Abstract

Purpose: The purpose of this narrative review is to describe the clinical applications of advanced computed tomography (CT) and magnetic resonance (MRI) techniques in patients affected by Crohn's disease (CD), giving insights about the added value of artificial intelligence (AI) in this field.

Methods: We performed a literature search comparing standardized and advanced imaging techniques for CD diagnosis. Cross-sectional imaging is essential for the identification of lesions, the assessment of active or relapsing disease and the evaluation of complications.

Results: The studies reviewed show that new advanced imaging techniques and new MRI sequences could be integrated into standard protocols, to achieve a reliable quantification of CD activity, improve the lesions' characterization and the evaluation of therapy response. These promising tools are: dual-energy CT (DECT) post-processing techniques, diffusion-weighted MRI (DWI-MRI), dynamic contrast-enhanced MRI (DCE-MRI), Magnetization Transfer MRI (MT-MRI) and CINE-MRI. Furthermore, AI solutions show a potential when applied to radiological techniques in these patients. Machine learning (ML) algorithms and radiomic features prove to be useful in improving the diagnostic accuracy of clinicians and in attempting a personalized medicine approach, stratifying patients by predicting their prognosis.

Conclusions: Advanced imaging is crucial in the diagnosis, lesions' characterisation and in the estimation of the abdominal involvement in CD. New AI developments are promising tools that could support doctors in the management of CD affected patients.

Manuscript:

Introduction

Crohn's disease (CD) is a chronic relapsing granulomatous disease affecting 100-300 per 100,000 people in Western EU and USA [1]. It is characterized by transmural inflammation of bowel walls and by skip lesions that may be found in any segment of the gastro-intestinal (GI) tract (particularly the terminal ileum and adjacent colon, 50% of patients) [2].

The diagnosis of CD is based on a combination of clinical presentation, blood tests and endoscopic, radiologic, histologic findings; a single gold standard is missing [3].

The small bowel is one of the most common areas affected by inflammation in CD, so much of it is beyond the reach of standard ileo-colonoscopic evaluation, making the assessment of the disease, from endoscopic evaluation alone, incomplete (in 30% of patients) [4,5]. Heterogeneous bowel involvement and skip lesions contribute to sampling errors on biopsy, resulting in the underestimation of disease presence and severity (endoscopy misses submucosal disease in up to 57%) [6].

Cross-sectional imaging is complementary to ileo-colonoscopy, it can visualize the intramural or proximal small bowel inflammation and extra-mural lesions (fistulas and abscesses) being an essential tool for the characterization of lesions (distribution, activity and severity) and disease response to therapy [7–9].

The main aim of this review is to describe the clinical applications of advanced CT and MRI techniques in CD patients, compared to standard imaging and giving insights about the added value of artificial intelligence in this field. We focused on how the new advanced imaging techniques could overcome the limits of qualitative standard imaging, providing reliable quantitative biomarkers of CD activity, insights on lesions' characterisation and guiding disease management and follow-up.

Radiological imaging: standard practice

ECCO and ESGAR scientific societies jointly elaborated a consensus to establish standards for imaging in inflammatory bowel disease (IBD) using MRI, CT and US [7–9].

Ultrasonography is considered a first-line diagnostic modality in the evaluation of patients with suspected CD [7–13]. It is an accurate tool for the evaluation of bowel motility, wall thickening, stenosis, vascularization (color-doppler examination), abscesses and fistulas [10,13]. Its advantages are the accessibility, the absence of ionizing radiations and being well tolerated by patients [13]. The multicentre METRIC trial highlighted the high sensitivity of both MRE and US in the evaluation of the small bowel disease. However, the sensitivity of MRE for small bowel disease extent (80%) and presence (97%) resulted significantly greater than that of US (respectively, 70% and 92%) [14].

One of the main limitations of US is its limited ability to explore the small bowel, in relation to overlying structures [13].

Instead, CTE and MRE are able to examine the entire bowel wall, to detect both the intestinal pattern of involvement and complications [15]. This is particularly advantageous, in populations of patients who cannot be assessed endoscopically (e.g., primarily small intestinal involvement). Several studies have shown that CTE and MRE have comparable accuracies for assessing active inflammatory CD (sensitivity and specificity, respectively, 85–95%) [16–18]. For these reasons we focused, this radiological standard practice chapter, on CT and MRI imaging.

Both CTE and MRE differ from routine abdominal CT and MRI by using large volumes of a hyperosmolar oral neutral contrast-agent and intravenous administration of spasmolytics, which reduce enteric peristalsis (i.e., Buscopan®). Indeed, the bowel distention is crucial for the proper visualization of the bowel wall and the mesenteric veins [19].

MRE is preferred in young patients, in upper GI disease, in penetrating disease, and in patients who require steroids, biologics, and surgery. In fact, repeated CTE studies over time, lead to levels of diagnostic radiation exposure that might increase cancer risk [20,21]. This technique has demonstrated an high correlation between mucosal healing at endoscopy and transmural healing at imaging, with improved outcomes when detected (sustained clinical remission and reduced rates of surgery and hospitalization) [22–24].

Severity indices using MRE have already been proposed and validated to determine response to therapy (e.g., Magnetic Resonance Index of Activity–MaRIA score); however, no CT-based severity score has yet been developed.

MSCTE

Due to poor accessibility in some countries, time consuming and high cost of MRE, multi-slice computed tomography enterography (MSCTE), has become a popular and widely available, imaging technique to rapid evaluation of small bowel CD activity, complications [15] or postoperative recurrence in a semi-quantitative manner [25]. Contrast-enhanced imaging is initiated during the period between enteric and portal phases of enhancement, which is 45−70 seconds after beginning the injection of intravenous contrast.

Low-dose CTE

Techniques to reduce dose of radiation exposure during diagnostic CT scanning, have been implemented using changes in both software and hardware, to maintain image quality. Low-dose CTE, using a model-based iterative reconstruction (MBIR), was found to be noninferior to the two standard-dose CTE techniques (filtered back-projection and adaptive statistical iterative reconstruction, ASIR images) in the detection of CD activity (sensitivity =85-94% and specificity=84-97%). A significant reduction in radiation exposure was noted with MBIR (mean [± SD] reduction, 3.30 ± 3.17 mSv) versus standard-dose imaging (7.16 ± 4.61 mSv; $p < 0.001$) [26].

CTE findings: semi-quantitative evaluation of activity

In routine radiological practice, visual assessment of mural hyperenhancement and wall thickening, lumen stenosis, haziness of the surrounding mesenteric fat and engorged vasa recta ("comb sign", CTE detecting sensitivity=80%–100%) have been well described and correlate with active inflammation [7–9,27,28].

Wall thickness and mural attenuation

Asymmetric segmental mural hyperenhancement and wall thickening, have a moderately high sensitivity and specificity for small bowel CD; they correlate significantly with histologic and endoscopic findings of inflammatory CD [29].

The wall thickening is measured in the thickest portion of the most distended segment or in the site of most severe inflammation; it can be classified as mild (3−5 mm), moderate (5−9 mm) or severe (≥10 mm) [15,30].

Increased attenuation on contrast-enhanced scans is a predictive but nonspecific sign with a morphologic pattern of hyperenhancement that can be: asymmetric (mesenteric border), stratified or homogeneous/symmetric [15]. The stratified (bi/tri-laminar) inner-wall hyperenhancement can be due to submucosal oedema, intramural fat deposition or inflammatory infiltration. This intramural fat deposition indicates chronicity, and it is unrelated to the presence of inflammation; on the other hand intramural oedema indicates active inflammation [15].

Measurements of terminal ileum attenuation are reported to have the highest sensitivity (90%) for predicting the presence of active inflammatory CD, compared with a sensitivity of 80% for visual assessment of mural hyperenhancement [30–32]. The main limitation of this HU quantitative evaluation is that it is subject to technical (KeV) and patient factors (cardiac status, patient weight, intravenous contrast iodine concentration rate, injection rate and timing). However, the presence of intramural fat or haemorrhage may underestimate or overestimate the degree of enhancement.

MRE

MRE allows high contrast resolution and multiplanar capability, without exposing patients to ionizing radiation and enabling the accurate assessment of small bowel CD activity and extraluminal/extraintestinal disease manifestations [33].

The MRE standard protocol typically consists, firstly, of a coronal single-shot fast/turbo spin-echo (ssFSE/ssTSE) sequence as an anatomic overview [34]. Next, coronal fast imaging with steady-state free precession (SSFP) images, contrast enhanced and unenhanced fat-suppressed 3-D T1-weighted breath-hold gradient-echo coronal images. Fat-suppressed T1-weighted axial images, after i.v. contrast administration, are acquired for multiplanar correlation. Axial fat-suppressed T2-weighted images are useful to highlight the bowel wall oedema and the inflammatory changes in the adjacent fat (figure 1) [35].

The main drawbacks of MRE compared to CTE are: the longer scanning time, the higher dependence to patients' compliance and the lower spatial resolution.

RM findings: well established criteria

The characteristic findings of CD active inflammation, in MR, are: ulcerations, asymmetric wall thickening (mesentery side >3 mm) (figure 1), strictures with or without upstream dilatation (figure 3), mesenteric lymphadenopathies, fat wrapping, mesenteric vascular engorgment- "comb" sign (figure 2), mucosal hyperenhancement on T1-weighted postcontrast imaging, mural oedema (increased signal intensity at T2-weighted -figure 3- and restricted diffusion on DWI-MRI), transmural or trilaminar enhancement, fistulas and abscesses (in penetrating disease) [15,34,36].

Figure 1. Fat infiltration and histologic specimen.

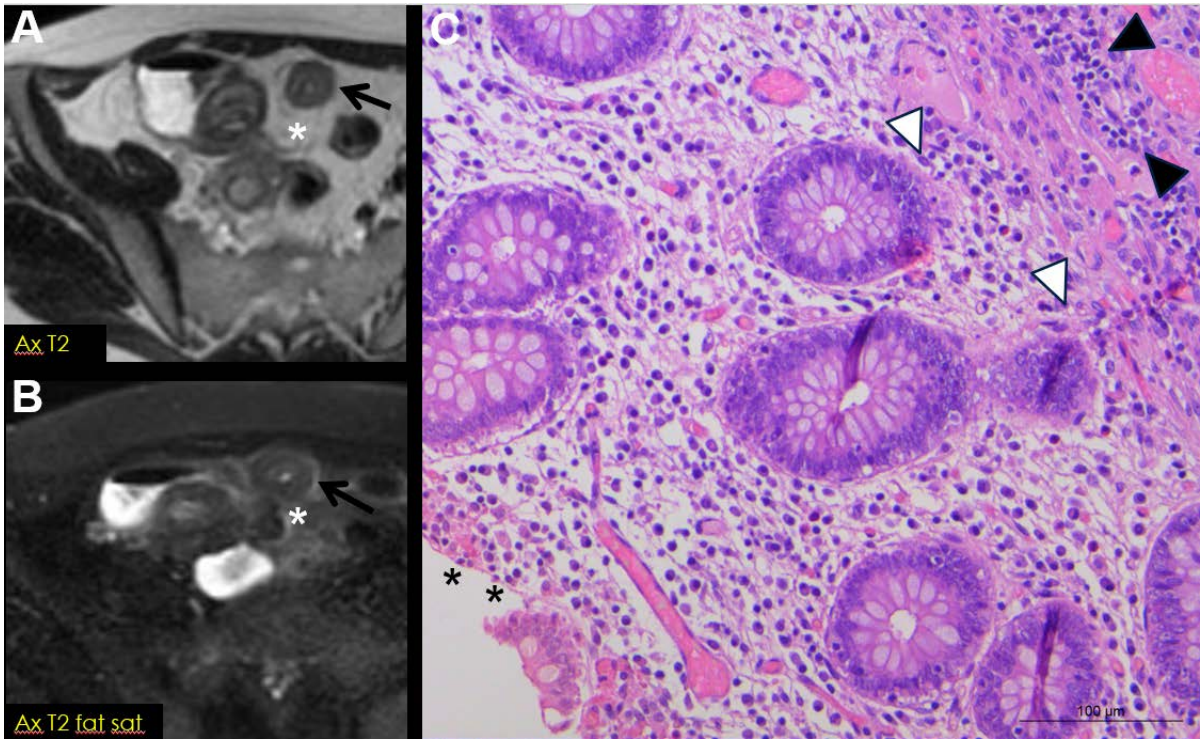

Figure 1: Axial T2-w image (**A**) shows an area of bowel wall thickening (black arrow). Axial fat sat T2-w image (**B**) images helped in distinguish fat infiltration (white asterisk) from wall oedema (black arrow) – not visible in **A**; **C**, the H&E stain shows highly inflamed colon mucosa in CD and severe changes of the glandular architecture. On the left, the mucosa shows erosions, with absence of the superficial enterocytes and loss of the enteric barrier (black asterisks). On the right, plasmacell aggregates are found in between the basal crypts and the muscularis mucosae (white arrowheads). The inflammatory infiltrate is also found beneath the muscularis mucosae (black arrowheads), a typical feature of CD (transmural inflammation).

Figure 2. Comb sign and histologic specimen.

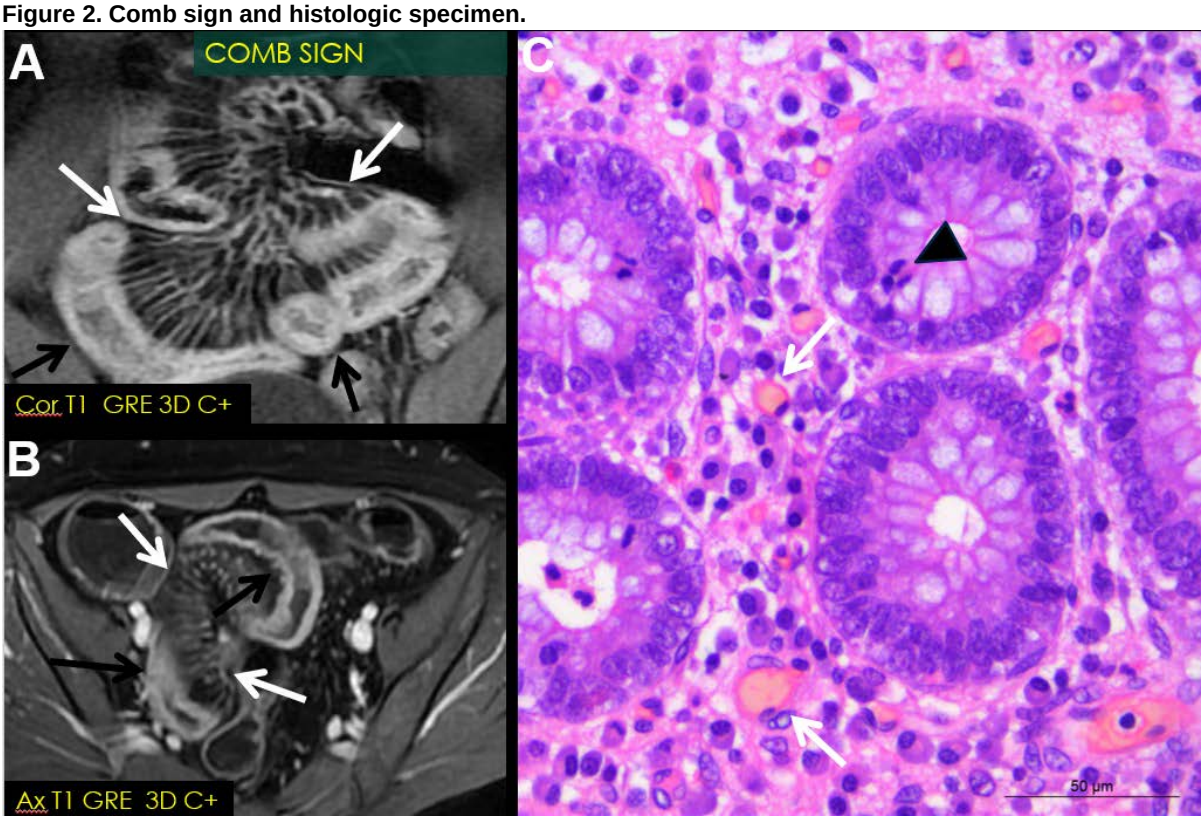

Figure 2: Coronal (**A**) and axial (**B**) contrast-enhanced T1-w images show multiple high-signal intensity parallel lines suggesting increased mesenteric vascularity (comb sign) in an area where bowel wall thickening (black arrows) is detected; **C** the relative H&E specimen of colon mucosa shows a marked increase in small capillaries in the lamina propria of the inflamed mucosa (white arrows). Capillaries are found in between the crypts, showing focal lymphocytic infiltration (black arrowhead) into the crypt wall (cryptitis).

Figure 3. Mural hyperintensity on T2-weighted images and histologic specimen.

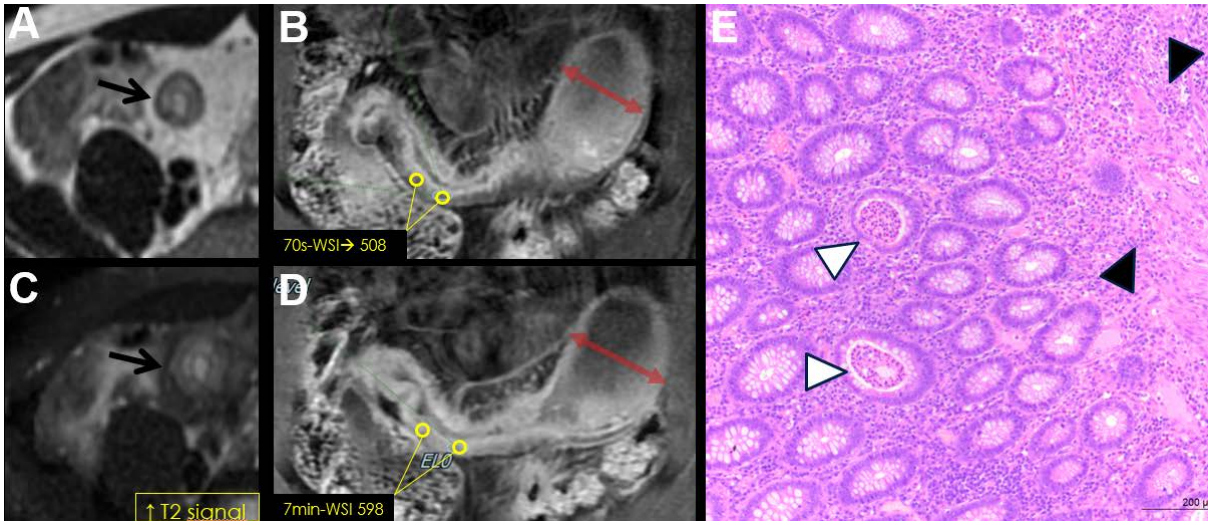

Figure 3: **A**-**D**, MRE demonstrate stenosis of distal ileum at T2-w and fat sat T2-w images (respectively **A** and **C**) and 70 seconds and 7 minutes after contrast-medium injection (respectively **B** and **D**). The findings were pathologically confirmed after surgery. **E**, H&E stain, two large crypt abscesses are observed in the inflamed

mucosa (white arrowheads); on the right, the muscularis mucosae is diffusely infiltrated by lymphocytes and plasmacells (black arrowheads), a feature suggestive for a transmural inflammation, a typical finding in CD.

Generally, severe inflamed segments are characterized by wall thickening≥10 mm and deep fissuring ulcers, resulting in submucosal oedema (hyperintense on fat-saturated T2-w images); submucosal fat deposition can simulate mural oedema (on non-fat-suppressed T2-weighted sequences) [34].

The engorgement of the vasa recta, or "comb sign," is best visualized on SSFP or postcontrast T1-weighted fat-suppressed imaging; these sequences also show reactive mesenteric lymphadenopathy well (figure 2).

Chronic fibrotic strictures occur in 30% of patients with CD, are generally hypointense on both T1-weighted and T2-weighted sequences, lack oedema and surrounding hyperemia, and enhance less than segments of active inflammation [34]. The strictures can contain variable proportions of inflammatory and fibrotic tissue due to co-existing repeated inflammation and reparative damage. However, the evidence of small bowel strictures without radiological findings of active inflammation does not predict the presence of tissue fibrosis [37].

Contrast enhanced (CE)-MRI and fibrosis detection

Chronic inflammation leads to fibrosis deposition, firstly in the submucosa and subserosa and later involving all the layers of bowel wall. Quantification of active inflammation versus fibrosis is challenging: actually, no technique is sufficiently accurate to assess the degree of fibrosis in a stricture, to guide clinical decisions.

Rimola et al. [38] showed that inflammation and fibrosis always co-exist and we can only try to assess, with MRI, which is predominant; in fact this technique resulted accurate for detecting severe fibrosis in CD lesions. They evaluated the signal intensity at submucosa at 70 s and 7 min after gadolinium injection concluding that the percentage of relative contrast enhancement (RCE) gain is a reliable MRI parameter for discriminate between mild–moderate from severe fibrosis deposition (RCE >24%, sensitivity=94% and specificity=89%) [38]. This could be explained by the fact that fibrosis deposition is associated to a reduced number and diameter of the vessels, compared to the normal mucosa. Fibrosis leads to a delayed diffusion of contrast

agent into the extravascular space, so the peak of enhancement is reached later than in predominantly inflammatory lesions.

MRI scores: quantification of CD activity

Validated and reproducible MRE indices for the quantification of CD activity are increasingly used, but only in clinical trials [39].

The main limitation is their complexity which precludes their use in clinical standard practice; actually, there is no standardization on the score to be used [9].

The most common scoring systems used can be divided in: scores including DWI evaluation, the Clermont score (CS) and the Nancy score [40]; scores not including DWI, the Magnetic Resonance Index of Activity (MaRIA) and its simplified version (sMaRIA), the Crohn's Disease MRI Index (CDMI) also called "the London score" and its extended version (extended London score) [41].

The best validated MRE activity scoring system is the MaRIA, which takes into account small bowel wall thickness, relative contrast enhancement, oedema, and ulceration on a bowel segment [42]. This score has shown high performance for detecting active inflammation (MaRIA$\geq$7) compared with endoscopy (correlate closely with Crohn's disease index of severity, CDEIS and Simple Endoscopic Score for Crohn's Disease, SES-CD) and a moderate concordance with Harvey-bradshaw index (HBI). A segmental decrease in MaRIA score on MRE has been associated with endoscopic mucosal healing [23,43,44]. The main drawbacks of this score is that the assessment is time-consuming and not evaluates the length of disease involvement.

The time-consuming aspect was partially overcome by the development of a simplified version (sMaRIA) [45].

Advanced MRI imaging for CD

Diffusion weighted imaging (DWI) MRI: qualitative and quantitative evaluation

DWI is an MRI technique, sensitive to the random movement of water molecules in fluids inside body tissues. The impedance of water molecule diffusion is affected by the extent of

tissue cellularity and the presence of intact cell membranes; it can be quantitatively assessed using the apparent diffusion coefficient (ADC) value [46].

The accuracy of DWI-MRE for the evaluation of inflammation in CD was shown to be noninferior to CE-MRE [47], although was very heterogeneous and likely overestimated in some studies [48]. The obvious advantage of DWI-MRE, compared to CE-MRE, is the reduction of the acquisition time, costs, and contrast-related risks [47,49,50].

Although the high and noninferior sensitivity, its main limitation is the high rate of false positives (up to 40%); for this reason DWI-MRE, can only be performed as an additional sequence and cannot replace the other sequences.

ADC and CD activity

The ADC is calculated at different diffusion-weightings (b values), and it is used for qualitative and quantitative evaluation of CD lesions, in combination with T2-weighted and CE-T1-weighted images. Diffusion hyperintensity, on an intermediate b value (500–600 s/mm^2), reduction of the ADC (apparent diffusion restriction) has been associated with bowel wall inflammation and less commonly with mural fibrosis [51,52].

Quantitative grading of CD mucosal inflammation is possible by mapping the ADC value in the bowel wall; it correlates with the HBI and has been shown to have a strong negative correlation with the SES-CD [53].

Qualitative grading of disease severity on DWI correlate with faecal calprotectin levels; higher levels are associated with greater extent of bowel with abnormal signal on DWI [54].

ADC diagnostic performance, in identifying active versus inactive disease, has been shown to improve in combination with DCE-MRI, or with qualitative MRE findings as part of the Clermont or Nancy scores [55,56].

Both CS and MaRIA showed high agreement for the detection of small bowel active CD (respectively, MaRIA >7, Clermont >8,4) but not for colonic disease [57].

The assessment is time-consuming and the ADC makes the CS difficult to reproduce, since the evaluation of the ADC is not a standardized process. Time consuming limitation was partially

overcome by Nancy score, in which DWI technique does not require fasting and the intake of a bowel preparation [58].

The sMaRIA score and the Nancy score are easy to use and are not time-consuming; according to the metanalysis by D'amico et al. seem to be the most suitable for the use in clinical practice [41].

Dynamic Contrast-enhanced (DCE)-MRI: quantification of CD activity

DCE-MRI is a perfusion MRI technique, based on dynamic T1-weighted imaging during injection of a gadolinium-based contrast agent. The main aim is the quantification of tissue vascular properties and to assess RCE in the bowel wall.

Two of DCE-MRI parameters are the wash-in (Ktrans) and the wash-out constants (Kep) that allow an estimation of perfusion (mL/min/100 g tissue). Another advantage of DCE-MRI is the higher temporal resolution than the 3D T1-weighted pre- and postcontrast acquisitions used for clinical interpretation. These DCE-MRI parameters were found to be elevated in inflamed versus normal bowel segments, in patients with active versus inactive CD [59] and moderately correlate with changes in c-reative protein (CRP) and HBI [60].

In conclusion, these perfusion parameters could be promising for evaluation of CD activity and for assessment of treatment response [61–63].

Magnetization Transfer Magnetic Resonance (MT-MRI): quantification of fibrosis

MRE and CTE, cannot be used to estimate accurately the amount of fibrosis in damaged bowel segments, due to the mixed (inflammation and fibrosis) histologic nature of most strictures [37,64].

Magnetization Transfer Magnetic Resonance (MT-MRI) provides a continuous measurement (MTR, 0–100%) generated by dipolar and exchange interactions between mobile water protons and immobile ones bound to macromolecules (e.g., collagen). Due to magnetic and exchange couplings between water and collagen, water magnetization is indirectly saturated resulting in signal intensity loss. As the amount of collagen in a tissue increases, there is greater signal loss and increasing MT effect or MTR.

Preliminary studies suggest that MT-MRI can be used to detect bowel wall fibrosis and distinguish inflamed-nonfibrotic from inflamed-fibrotic segments [65,66]. Fang et al. [65] showed that MT-MRI combined with conventional MRI improves the differentiation of fibrotic from inflammatory components of small bowel strictures. They found a significant correlation between histologic fibrosis scores and MTR ($p<0.001$), enabling to distinguish mild from moderate-to-severe fibrosis with a sensitivity of 91% and a specificity of 92%.

Motility Magnetic Resonance Imaging (CINE-MRI): quantification of motility

CINE-MRI consists in acquiring repeated images at the same anatomical location over a period of time (usually 15–20 s in breath-hold) [67]. This technique enables a real-time observation of intestinal motion, based on the proposed relationship between inflammatory activity and hypomotility. However, not only inflammatory but also fibrotic lesions leads to reduced motility [68–70].

CINE-MRI , limited to research use, allows quantification of motility and a further examination of the poorly distended loops. In fact, it is possible a dynamic assessment of bowel motility and the distinction between a fixed stricture and transient luminal narrowing [34]. Studies have found that the grade of motility correlates with clinical scores (e.g., HBI) [71,72], and could be used as a marker of inflammatory activity [68–70]. Menys et al. [73] found that quantification of terminal ileal motility had a 92% sensitivity and 71% specificity for active disease, confirmed on biopsy, with noninferior performance against the more involved MaRIA score.

Moreover, initial studies suggest that motility is better to predict early response to treatment than MRI activity scores, measuring the change in motility before and after therapy. Plumb et al. [74] showed that equivalent or higher motility, after 12 weeks of anti-TNFa treatment, was a predictor of treatment response.

So, quantification of motility may possibly be used as a marker of inflammatory activity and as a predictor of treatment response, as part of a new follow-up protocol.

One of the main drawback of motility MRI is the potential time added to a routine investigation due to additional breath holds needed [67].

Advanced CT imaging for CD

DECTE

Dual-energy CT (DECT) is based on data acquisition at two different energy settings; it combines morphological and multiple quantitative parameters evaluation.

DECT scanners can obtain images of quality and diagnostic accuracy comparable to conventional single-energy CT, reducing radiation exposure and contrast media doses, offering unique advantages in the diagnosis and evaluation of activities in CD patients (especially in the younger) [75–79].The acquisition of data with different spectra of photons in one single CT acquisition, allows material decomposition analysis: the basis for spectral CT [80–82]. The most used spectral applications are: mono-energetic images and Iodine concentration.

Virtual mono-energetic images (VMI)

The mono-energy application allows to choose one or more energy levels (keV) producing VMI. Compared to conventional single-energy abdominal CT, low-energy VMI showed an improved signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) on contrast-enhanced scans, particularly in obese patients [83,84]. Low keV VMI accentuate iodine-enhanced structures (the attenuation increases as the mean energy of the photons decreases) without increasing image noise, decreasing the amount of injected contrast media and improving the image contrast of normal blood supply vessels. It makes possible to clearly distinguish between an inflamed and a normal intestinal tissue (figure 4) [85–87].

Figure 4. Increased attenuation of CD lesions on VMI at low KeV.

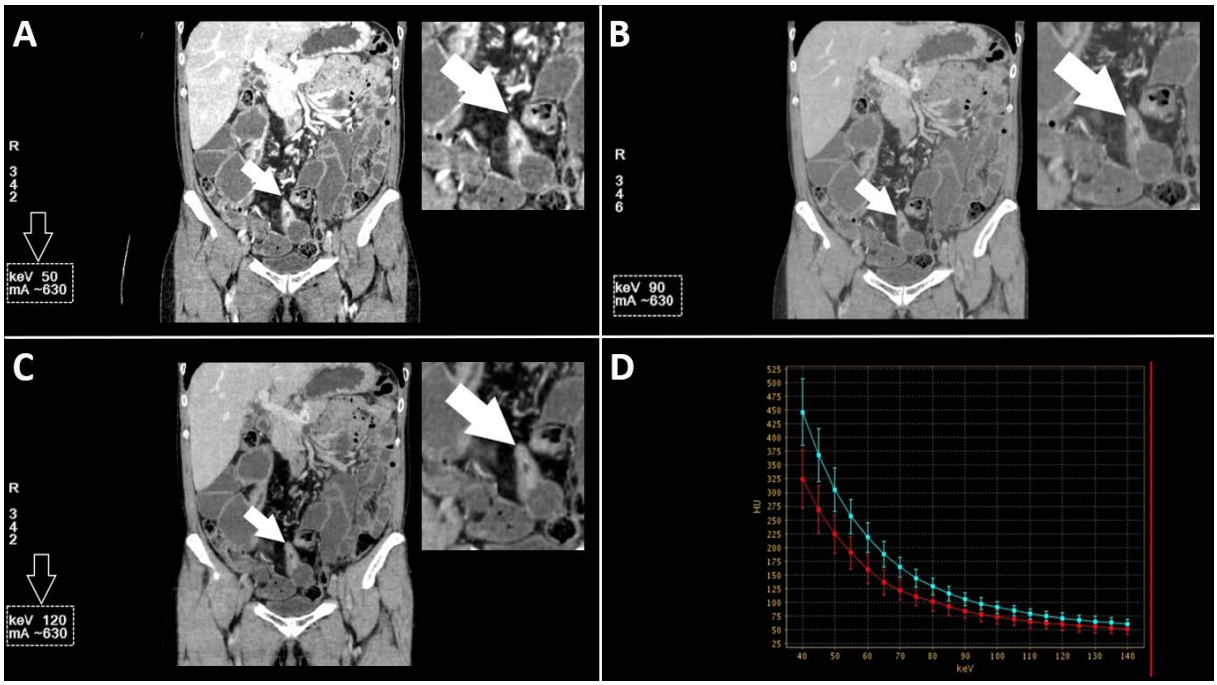

Figure 4: A 46-year-old woman with active CD. **A-C** Virtual mono-energetic images (VMI) respectively acquired at 50 KeV (A), 90 KeV (B), 120 KeV (C), (white open arrows). Segmental enhancing small bowel wall thickening and stricturing (white arrows) is well demonstrated, suggesting active CD. Note that lesion conspicuity is the best on VMI at 50 KeV due to the high contrast of iodine**;** a decrease in energy, in the range approaching the K-edge of iodine (33 KeV), causes markedly increased attenuation of iodine enhanced structures. **D,** the graph depicts the change of HU curve at variation of KeV.

Chen et al. [88], have proposed the combined use of VMI at 60 keV and conventional CTE at 120 keV to improve the efficiency of CD diagnosis; the overall imaging quality at 60 keV were higher, so they considered it to be the best energy level.

Iodine concentration images (iodine maps)

DECT post-processing techniques can decompose contrast-enhanced images into iodine image that only show iodine (iodine maps) [80]. Iodine maps could quantitatively evaluate the contrast enhancement of a CD lesion, with high accuracy and regardless of acquisition parameters [89]. Iodine concentration (IC) or density (ID) is a feature of Iodine Quantification, most commonly defined by the units mg/mL; it can be applied in the different scan phases (e.g., arterial or venous). The absolute IC, on iodine images, may provide a more consistent, quantitative evaluation of iodine content in a particular voxel compared to HU conventional attenuation measurements which considers both the tissue density and iodine amount.

HUs at conventional CT are also dependent on acquisition potential, on the energies of the x-rays used, injection flow rate [90] and patient size. These do not need to be considered when

interpreting the dual-energy–derived ID values; consequently, IC is a more reproducible and reliable measure than traditional HU [91,92].

Normalized IC (NIC) is calculated based on the equation NIC = IC lesion/IC reference (the reference most commonly being the aorta). The main point of normalization is to reduce technical or physiological variabilities within the tissue of interest due to varying cardiac output and phase times.

IC and CD

ID has been shown to be a surrogate marker of perfusion in a variety of abdominal imaging applications [93,94]. Active inflammation is linked with more blood perfusion and accompanying IC, and thus the iodine map on DECTE can clearly indicate the activity of CD.

Several studies proved that NIC can be used for quantification and objective evaluation of CD activity: it correlates strongly with clinical scores (e.g., Crohn's Disease Activity Index, CDAI), evidence-based radiologic signs of CD, endoscopic scores (e.g., , SES-CD), making possible to distinguish normal from pathologic segments as well as discrimination between active and remission lesions [95–101].

Furthermore, NIC correlation with histologic scores of inflammation was reported to be significantly higher in the gut segments that had active inflammation of any amount at histologic examination, compared with segments without inflammation. Unfortunately, NIC was not able to distinguish between different histologic grades of inflammation (mild, moderate, or severe) [101].

Collectively, these studies suggested that mean NIC at DECTE could be an accessible non-invasive cost-effective biomarker of CD activity.

The main limitation is the extreme heterogeneity between these studies, in terms of different DECTE brands and protocols (IC normalization, IQ scan phase, ROI placement, reference standards). Limited literature precludes to reach clinically robust threshold for the use of IC in daily clinical practice, because different hardware and algorithms are used by the different vendors and users.

Artificial intelligence and CD

AI applications in CD aim at improving patients' health outcomes. In this setting, AI is proving to be a useful tool for the diagnosis as well as for the prediction of disease activity, symptom severity, and treatment response [102].

ML models can extract useful information from existing patient data, on which they are trained to predict the outcomes for new patients [103]. This is particularly useful for patients' management, given the disease's multifactorial characteristics, which makes diagnosis and long-term monitoring difficult. Gut microbiota composition, genomic, molecular, endoscopic, imaging and histologic data, as well as clinical and laboratory biomarkers are some of the informations on which a ML model can be trained on [104–108].

As concerns imaging, advanced radiological techniques as MRE or CTE represent important diagnostic tools for evaluating the extent of IBD, particularly with regard to small bowel evaluation which is out of reach of endoscopic examination and in characterizing intestinal strictures [109].

Analysis of bowel MRI is challenging due to the complex structure of the bowel wall. Furthermore, subjectivity, interobserver variation and non-standardized reporting have always been challenging issues when applying imaging modalities in clinical practice.

A systematic review conducted by the Stenosis Therapy and Anti-Fibrotic Research Consortium (STAR) revealed that stricture classifications vary widely among radiological examinations, which are not precise enough to be used in everyday practice to discriminate inflammation from fibrosis-related lesions and state their severity [110]. In this setting, some authors investigated the role of Computer aided analysis based on AI techniques (like deep learning- DL- or radiomics) to overcome such obstacles.

Radiomics, DL and AI in general are revolutioning almost every field of radiology. As for IBD, automation could be useful for reducing interobserver variability, detecting and classifying bowel lesions based on disease activity/severity and stratifying patients more objectively [111].

DL and artificial neural networks (ANNs) replicate human brain neural networks for finding patterns associated with a particular diagnosis or outcome and can be applied to structured data as well as images. True 3D analysis of MREs is also important for more consistent

measurement of disease activity. Recent developments in computer-aided diagnosis for semiautomated bowel wall thickness measurement [112] and AI using active and semi-supervised learning for segmentation of affected bowel regions in CD, based on a small training set of annotated imaging [113], has the potential to streamline the research and clinical workflow in the evaluation of CD.

ML and advanced imaging

Many studies in literature focus on the application of ML models for using clinical and laboratory data to predict CD progression, patients' prognosis and treatment response [114–119].

As per their applications in the radiological field, authors are more and more experimenting ML tools applied to CTE and MRI images of patients affected by CD, obtaining encouraging data - which suggest that useful information can be extracted from radiological examinations [120]. At the moment, the main applications of AI in radiology for CD include [121]: automatic detection and segmentation of CD typical lesions, assessment of disease activity, detection of intra and extra- intestinal complications and patients' stratification based on disease severity.

Indeed, while at the beginning studies focused mostly on the detection and segmentation of CD lesions at imaging, the research in this field will expand more and more towards the extraction of novel patterns and radiological features that could predict disease trajectory, patients' prognosis and treatment response [120].

Automatic detection and segmentation of CD typical lesions

The detection and segmentation of a CD lesion by a ML model include its automatic individuation and contouring in the images. As for MRE examinations, Mahapatra et al. extracted features related to shape and intensities from MRE images and merged them with ML models to individuate and segment inflammation lesion in 26 MRE examinations [122]. Their model showed a sensitivity > 90% and a specificity >75% in lesion detection.

They then tried, in another study [113], to merge semi-supervised learning (SSL) and active learning (AL) for the same purposes (automatic detection and segmentation) in the same dataset, achieving greater classification accuracy than with the fully supervised technique. Indeed, through SSL, they trained their model with few labelled and many unlabelled findings

to generate probability maps. Through AL, they selected those voxels which would have led to maximum improvement in model's performance.

For what concerns CTE examinations, Binu et al. developed ML and DL algorithms for the detection of inflammation related lesions [123], comparing their performances with sections segmented by radiologists. Both approaches reached an AUC > 0.89. For assessing wall thickness, they then developed, in a following study, a semi-automated model [112] which showed similar agreement with each annotator compared to inter-annotator agreement [112].

Assessment of disease activity and definition of complications

Some authors showed how AI can extract noninvasive biomarkers of disease severity, activity and treatment response CTE and MRI [112,120,124–127].

As concerns studies focused on MRE, Holland et al., developed a DL model on MRE images to stratify patients and grade disease severity (no disease- mild- moderate - severe) in their series of 170 patients [124], achieving an F1 score of 0.83. In particular, they observed that the accuracy of their model was optimal (100%) in the detection of severe cases, becoming lower in the discrimination of mild from moderate disease. They also observed a high concordance with the MaRIA score.

Lamash et al. developed a 3D processing tool based on a convolutional neural network (CNN) that allowed the segmentation of small bowel tracts and the extraction of quantitative information about lesions' activity on MR examinations of pediatric CD patients [125].

Schuffler et al. also developed a model which semi-automatically extracted MR features - like bowel wall thickness and bowel contrast enhancement - for the determination of CD severity. In their series, they proved that their model's performances were comparable to selected MRI activity scores, but – as for Pulayert's – it was more objective and reproducible.In their series, Pulayert et al. developed and validated the VIGOR score for ileo-colonic CD, which combined semiautomatic measurement of MRI features with radiologists' evaluation of MR images. Their score proved to be as accurate as conventional MRI activity scores, but with the advantage of being more objective and reproducible for disease and treatment monitoring, overcoming the problem of the inter-reader variability [126].

As for studies focused on CTE, Stidham and coworkers [112], compared their semi-automated model's and radiologist's performances in the assessment of small bowel CD lesions in their series of 138 CTE examinations. The model and the two radiologists involved in the study showed comparable performances in the measurement of maximum bowel wall thickness (BWT-max), maximum small bowel dilation diameter (DIL-max), and minimum lumen diameter (LUM-min). The model was also able to depict bowel strictures with the criteria of upstream dilation, showing an AUC of 0.857), which was higher (up to 0.917) if another criteria of stricture without upstream dilation was taken in consideration.

A recent study by Meng et al. put in comparison radiologists' evaluation, radiomics and deep learning models for the of intestinal fibrosis in CD affected patients at CTE. Specifically, they developed and validated a CTE-based deep learning model for characterizing bowel fibrosis which proved to be better than radiologists, and not inferior but more time-saving compared to the radiomics model [127].

Stratification of patients

Furthermore, Konikoff et al. [128] developed a ML model that predicted clinically relevant findings at CT in patients with CD in the emergency department with an AUC of 0.774, thus allowing a stratification of patients on the base of their risk of having CD complications at imaging. In this setting, they aimed at developing a tool for suggesting proper indications for CT scans, reducing their number thus avoiding radiation and contrast material exposure while identifying high-risk patients.

Radiomics and advanced imaging

Radiomics represent a promising tool that could help radiologists in clinical decision-making and patient-phenotyping, allowing a better assessment of disease severity. Indeed, through texture analysis, many quantitative features might be extracted from radiological examinations, which could be inserted into ML models to predict preferred outcomes, towards a "personalized medicine" approach [129].

In the gastrointestinal field, radiomics proved to be a helpful technique facilitating radiologists to be more accurate in diagnosing small bowel, colon, rectal cancer, and other lesions [130–133], in predicting gene signatures [134],in the assessment of treatment response [130–132] and in the detection of fibrosis in paediatric patients with CD [135].

However, a limited number of studies focused on the diagnosis of CD [112,136]. In this setting, authors mainly focused on how radiomics could help in: diagnosis of CD [137], definition of disease severity and complications [138–140], assessment of response to therapy [141–143].

Diagnosis of CD

The added value of radiomics features has been evaluated in the differential diagnosis of CD and UC [137]. For this purpose, Li et al. developed a nomogram based on CT radiomics features combined with clinical variables, reaching an AUC of 0.8846 on the test set.

Definition of disease severity and complications

The evaluation of disease severity at imaging is essential for the management of patients, but it is limited by inter-reader variability. In their recent study, Ding et al tried a more objective and reproducible approach at MR examination, stratifying CD severity in terminal ileum through the extraction of radiomics, obtaining comparable results to MaRIA scores assigned by senior radiologist [138]. Li et al.[139] built a CTE-based radiomic model for the identification of fibrosis in CD patients, which achieved satisfying performances among 3 distinct institutions in the discrimination between none–mild and moderate–severe fibrosis, considering different bowel segments with inflammatory lesions of various severity. Furthermore, their model outperformed the radiologist's interpretation, grading the various fibrotic lesions.

In their series, Kurowski et al. [140], showed that radiomics features' heterogeneity of visceral adipose tissue is higher in patients with CD compared with controls, which could be an alarm of disease severity in paediatric CD.

Assessment of response to therapy

Recently, radiomics has proved to be a useful tool not only in assisting radiologists in the diagnosis and staging of CD, but also in the assessment of the response to therapy. As for studies focused on MRE, some authors developed and validated MRI-based radiomics nomogram for the detection of secondary loss response to infliximab in their series of patients with CD [141], while others [142], built various MRE-radiomics based ML model for the prediction of response to immunosuppressive treatment in CD patients, achieving AUCs that ranged from 0.71 to 0.99. Other authors focused on CTE examination [143] , building a CTE-

based radiomics nomogram to predict loss of response of infliximab in patients with CD, which showed good performances and a following clinical benefit.

Conclusions

Advanced imaging plays an important role in diagnosis, lesions' staging and characterization of disease complications in CD patients. In this setting, recent AI developments can support clinicians in improving diagnostic accuracy as well as in the stratification of patients through the prediction of their prognosis, towards a personalized medicine approach.

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