Digestive and Liver Disease 48 (2016) 975–983

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Evolving roles of cross-sectional imaging in Crohn's disease

Andrea Magarotto[a], Stefania Orlando[a], Marina Coletta[a], Dario Conte[a,b], Mirella Fraquelli[b], Flavio Caprioli[a,b,*]

[a] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Italy
[b] Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda, Ospedale Policlinico di Milano, Italy

ARTICLE INFO

Article history:
Received 29 February 2016
Accepted 21 May 2016
Available online 30 May 2016

Keywords:
Computed tomography
Crohn's disease
Magnetic resonance imaging
Ultrasound
Ultrasound elasticity imaging

ABSTRACT

The implementation of cross-sectional imaging techniques for the clinical management of Crohn's disease patients has steadily grown over the recent years, thanks to a series of technological advances, including the evolution of contrast media for magnetic resonance, computed tomography and bowel ultrasound. This has resulted in a continuous improvement of diagnostic accuracy and capability to detect Crohn's disease-related complications. Additionally, a progressive widening of indications for cross-sectional imaging in Crohn's disease has been put forward, thus leading to hypothesize that in the near future imaging techniques can increasingly complement endoscopy in most clinical settings, including the grading of disease activity and the assessment of mucosal healing or Crohn's disease post-surgical recurrence.

1. Introduction

In the last three decades cross-sectional imaging techniques have gained increasing relevance in the clinical management of inflammatory bowel diseases (IBD). Patients with Crohn's disease (CD), in particular, benefit from abdominal imaging, given the transmural nature of CD-related inflammation, which frequently associates with extra-mucosal involvement and intra-abdominal complications [1]. Moreover, CD often affects segments of the small bowel, which is less readily reachable by endoscopy than the large intestine. Traditionally, cross-sectional imaging has been employed in the diagnostic work-up of patients with suspected CD of the small intestine and in the detection of CD-related complications [2]; in such clinical contexts, excellent levels of diagnostic performance have been reported for bowel ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). In a recent systematic review [3] an overall per-patient sensitivity of 85% (95% CI, 83–87%) and 78% (95% CI, 67–84%) was reported for US and MRI, respectively, in the diagnosis of CD. The corresponding values of per-patient specificity were 98% (95% CI, 95–99%) and 85% (95% CI, 76–90%). More recently, a series of innovative applications has been proposed to expand the traditional role of cross-sectional imaging in CD, to include: the assessment of disease activity, the detection and grading of post-surgical relapses, the assessment of mucosal healing following biological therapy, and the calculation of cumulative CD-related bowel damage. Additionally, abdominal imaging techniques have been employed for the prediction of the therapeutic response to anti-tumor necrosis factor (TNF) drugs and the need for surgical intervention, and, lately, in the distinction of active inflammation from fibrosis in CD-affected areas. In this paper we offer a review of the evolving applications of imaging in CD, with a particular emphasis on the most recent technological advances in cross-sectional imaging.

2. Evaluation of disease activity

From a clinical perspective, the detailed knowledge of Crohn's disease inflammatory status constitutes an essential element to guide both medical and surgical management. Even if routinely used in therapeutic trials, clinical disease activity scores, including Crohn's Disease Activity Index (CDAI) and Harvey-Bradshaw Index (HBI), were found to poorly correlate with mucosal inflammation as assessed by endoscopy [4–7]. As a consequence of this, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) does no longer consider the resolution of symptoms alone as a therapeutic target in Crohn's disease [8], and the US Food and Drug Administration is moving from CDAI as a clinical trial endpoint in CD towards more objective measures of disease, such as the findings from endoscopy [9].

On the other hand, over the last few years, good levels of diagnostic performance have been reported for cross-sectional imaging

* Corresponding author at: Department of Pathophysiology and Transplantation, University of Milan, Via Francesco Sforza, 35, 20122 Milan, Italy. Tel.: +39 0255033368; fax: +39 0255033644.
E-mail address: flavio.caprioli@unimi.it (F. Caprioli).

http://dx.doi.org/10.1016/j.dld.2016.05.017
1590-8658/

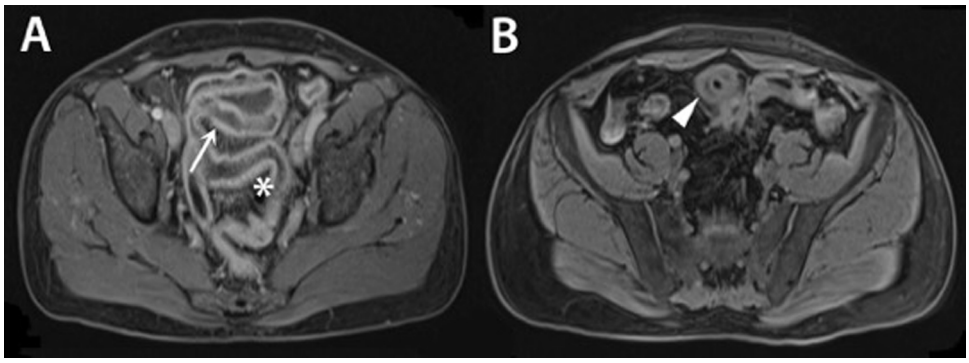

Fig. 1. Ileal Crohn's disease activity evaluated by magnetic resonance (MR) imaging. Axial T1-weighted MR images obtained after intravenous contrast injection, showing mural hyperenhancement (white arrow) and engorged vasa recta in the mesentery (comb sign) (white asterisk) in a representative patient with active Crohn's disease (panel A), and a thickened terminal ileum without significant contrast enhancement (white arrowhead) in a patient with fibrostenotic Crohn's disease (panel B).

techniques in the assessment of CD activity, as compared with surgical and/or endoscopic reference standards [10]. Importantly, several imaging parameters have been identified, which correlate with the presence of active intestinal inflammation: they have been employed for the calculation of imaging-based disease activity scores [10].

As repeated assessments of disease activity are required during the course of Crohn's disease, radiation-free techniques (*i.e.* bowel US and MRI) have rapidly overtaken CT scanning for this clinical purpose, because of the emerging concern of cancer risk owed to diagnostic radiation exposure [3]. Still, it is worth mentioning that good diagnostic accuracy has been reported for CT scanning in the detection of active CD, as demonstrated by an overall sensitivity of 81% (95% CI, 77–86%), a specificity of 88% (95% CI, 82–91%), a likelihood ratio for positive results (LR+) of 6.75 and a likelihood ratio for negative results (LR−) of 0.22, as compared with endoscopy [3].

In a systematic review a pooled overall diagnostic accuracy of 91% (95% CI, 84–96%) has been reported for MRI in the identification of frankly active CD [10]. The corresponding figures for mild activity and remission were respectively 62% (95% CI, 44–79%) and 62% (95% CI, 38–84%). However, caution should be exercised in interpreting these results, as the analyzed studies were highly heterogeneous with regard to: patient selection criteria (known *vs.* suspected CD, consecutive *vs.* selected cohorts), MR protocols (bowel preparation, intravenous contrast, magnetic field strength) and reference standards for disease activity (colonoscopy, histopathology and intra-operative findings). Moreover, variable criteria for disease assessment (*i.e.* to define the positivity of the index test) have been considered, including: bowel wall enhancement, thickness, T2 hyperintensity, presence of ulceration and stenoses, cobblestoning, lymph node enlargement and extra-intestinal findings [10] (Fig. 1). In a prospective study wall thickness, relative contrast enhancement, presence of edema and ulcers at MR were identified as independent predictors of Crohn's disease endoscopic index of severity (CDEIS) in patients with ileocolonic CD [11]. Such parameters were subsequently confirmed in a validation cohort from the same Authors [12] and used to derive a quantitative magnetic resonance index of activity (MaRIA), by the formula:

$$\text{MaRIA(S)} = 1.5 * \text{wall thickness} + 0.02 * \text{RCE} + 5 * \text{edema} + 10 * \text{ulceration}$$

By using endoscopy as a reference standard, degrees of sensitivity of 81% and specificity of 89% (LR+ 7.36, LR− 0.21) have been reported for MaRIA in the grading of Crohn's disease activity [13]. In contrast, this index was found not to correlate with CDAI in a recent multicenter observational study [14], this further supporting the relative inadequacy of clinical indexes in the assessment of disease activity in patients with Crohn's disease.

Over the last few years several innovations have been introduced to MR imaging, with the intent of improving its diagnostic accuracy and tissue characterization capabilities. In this context, promising results have been recently shown by diffusion-weighted imaging (DWI)-MR. DWI is a novel form of MR imaging based upon the measurement of the random Brownian motion of water molecules within a voxel of tissue. Even if the relationship between histology and diffusion is complex, in general, densely cellular tissues or tissues with cellular swelling exhibit lower diffusion coefficients [15]. Therefore, this technique has been initially applied to the characterization of tumor masses and in cerebral ischaemia [15]. More recently, a potential application of DWI in grading tissue inflammation and evaluating inflammatory conditions, including CD, has been postulated [16]. The potential advantages of DWI-MR over standard MR in the study of the bowel include high contrast resolution and avoidance of gadolinium administration [16]. In a preliminary series, an excellent level of diagnostic accuracy of DWI-MR in the detection of active CD inflammation has been reported, with a sensitivity of 94.7% and a specificity of 82.4% (LR+ 5.38, LR− 0.06) with regard to endoscopic or surgical findings [17]. This was associated with very good levels of intra- and inter-rater reliability of the technique. Notably, DWI-MR without intravenous contrast did not prove inferior to standard contrast-enhanced MR in evaluating CD-related small-bowel inflammation in a very recent prospective non-inferiority study [18], thus confirming the data deriving from a retrospective series (Table 1) [19]. The recently reported excellent agreement between DWI-MR results and the MaRIA index further supports the usefulness of this technique in the study of CD inflammatory status [20]. However, it should be pointed out that a reduced ability of DWI-MR in detecting penetrating complications against standard MR has been described; if confirmed through larger prospective series, this issue can represent a potential limitation of this imaging technique in the diagnostic work-up of CD patients.

Thanks to a number of practical advantages, including reduced costs, high reproducibility and minimal invasiveness, bowel US has been considered as a valid alternative to both MRI and CT for the evaluation of disease activity in patients with CD [21–23]. Nonetheless, the widespread application of this technique has been initially hampered by concerns over levels of reduced accuracy in evaluating proximal small-bowel segments and significant inter-observer variability in reporting US parameters [22]. Additionally, some early studies failed to document a significant correlation between ultrasonographic findings and biochemical or clinical parameters of CD-related inflammation [21–23]. Such negative results can be explained by the adoption of increased bowel wall thickness (BWT) as the only US parameter of disease activity, while other factors,