Measuring disease activity in Crohn's disease

Sara Onali, Emma Calabrese, Francesco Pallone

Gastrointestinal Unit, Department of Internal Medicine, University of Rome "Tor Vergata", Viale Oxford 81, 00133 Rome, Italy

Abstract

In the last few years the management of Crohn's disease (CD) has changed due to the introduction of new therapeutic agents that provide more alternative options in patients with severe diseases, introducing new concepts regarding treatment timing. At the moment, the absence of good predictors of disease outcome and a subclinical marker available to predict relapse during clinical remission are major problems in the management of CD. In recent decades, the evaluation of several variables has been proposed to address this issue, including disease behavior, clinical–endoscopic activity and intestinal damage. In particular, definition of mucosal restitution or healing after therapy has been proposed as a surrogate of efficacy and new goal of the therapy. Regarding this concept, several criticisms have been raised, such as the need to better define the role of mucosal healing in a transmural disease. In order to address this issue, new alternative techniques providing both extraluminal and luminal intestinal damage have been proposed, including ultrasonography, computed tomography and magnetic resonance imaging.

Key words: Crohn's disease—Mucosal healing—Crohn's disease activity—Monitoring disease

Crohn's disease (CD) is a heterogeneous condition with wide inter- and intra- individual variation in terms of type and severity of symptoms, occurrence of complications and responsiveness to medical treatment [1]. Such a clinical heterogeneity largely depends on the site(s), extent and type of the intestinal lesions as well as on what is called clinical behavior [2]. The course of the disease is usually remitting-intermittent and flares are characterized by clinical symptoms that may or may not be associated with either humoral and/or "visual" evidence of active inflammation. Thus, CD patients may be classified according to different variables including clinical symptoms, humoral abnormalities suggestive of active inflammation and gross changes as assessed by either endoscopy and/or imaging techniques.

The aims of medical treatment in CD patients have included controlling symptoms, preventing complications, meeting individual goals, and improving quality of life. In recent years, the introduction of new therapeutic agents capable of a powerful and effective control of intestinal inflammation has provided new management strategies in patients with moderate to severe disease [3]. The increasing availability of these drugs in different clinical settings has also offered the opportunity for redefining treatment's goals in these patients, from the control of clinical symptoms, possibly normalizing inflammatory markers, to the healing of gross lesions and preventing progression of structural bowel damage [4]. Thus, the need to properly assess disease activity/severity and carefully depict structural bowel changes to optimize indication, regimens and goals for the currently available drugs still exists.

Clinical activity

The assessment of what is called clinical activity depends on a number of heterogeneous clinical variables including subjective symptoms, quality of life, objective signs, and laboratory parameters expected to reflect inflammatory activity. Various scores have been proposed to assess the severity of clinical disease activity, and the composite-standardized and quantitative scores, such as the Crohn's Disease Activity Index (CDAI) or the Harvey–Bradshaw Index, are the most widely used either in clinical practice or as a primary outcome in clinical trial.

Although these indexes have addressed the issue of quantifying clinical judgement, they have left unsolved the measurement of intestinal inflammation activity [5].

CDAI includes eight parameters: number of liquid stools, abdominal pain, well being, abdominal mass, extraintestinal manifestations, use of anti-diarrheal drugs, body weight, and hematocrit values. A CDAI value > 150 defines active Crohn's disease, while a values < 150 indicate clinical remission. Improvements are defined as reduction in CDAI by 100 points or by 70 points

Correspondence to: Emma Calabrese; *email:* emma.calabrese@uniroma2.it; Francesco Pallone; *email:* pallone@med.uniroma2.it

in two consecutive evaluations [5]. Several criticisms of this metric have been raised. First, the parameters measured are relatively subjective, leading interobserver variability, and second, the calculation of CDAI is often time-consuming.

The Harvey–Bradshaw Index or "simple index" proposed a 1-day index scoring from 0 to 15, and correlated imperfectly with the CDAI [6, 7]. Although these scores are useful to quantify disease activity, they often result relatively low in patients with fistulizing CD, making them inappropriate for assessing the activity of draining fistulas. Thus in 1995, Perianal Disease Activity Index (PDAI) was developed to score this special condition. It includes five elements: discharge, pain, restriction of sexual activity, type of perianal fistula, and degree of induration [8].

In clinical practice, another important point used to determine the activity of disease is the assessment of quality of life, which represents a major concern both for physicians and CD patients. To assess quality of life, the most commonly used score is IBDQ. It includes 32-items with four domains (bowel function, emotional status, systemic symptoms, and social function). Total score ranges from 32 to 224, with higher scores indicating better quality of life. The IBDQ is extensively used as a secondary endpoint in clinical trials and shows a good correlation with CDAI ($P > 0.001$) [9].

Disease behavior

In spite of the heterogeneous phenotype of the disease, in 1998 the Vienna classification identified three subgroups of patients according to disease behavior: B1, purely inflammatory (nonpenetrating, nonstricturing); B2, fibrostenotic; and B3, penetrating [10]. Based on the Vienna Classification, patients were assumed to show different patterns of evolution. In 2002, Louis and Cosnes [11, 12] independently demonstrated that most patients with CD had a nonpenetrating nonstricturing phenotype at diagnosis, but progressed to stricturing and penetrating lesions over the long term. They demonstrated that the natural history of CD is a dynamic process, leading to irreversible bowel damage in the large majority of patients.

Age at diagnosis, risk factors (including appendectomy, familial history of inflammatory bowel disease, and smoking), compliance and lifestyle significantly influence the clinical course of the disease. An early onset of Crohn's disease or a familial history of inflammatory bowel disease may be associated with a more aggressive course, with extensive intestinal lesions including the upper gastrointestinal tract, and with responsiveness to corticosteroids and immunomodulatory drugs [13].

Endoscopic activity

Ileocolonoscopy represents a fundamental procedure for diagnosis and monitoring disease outcomes. During an endoscopy in CD, different mucosal characteristics may be observed as erythema, swelling, nodularity, strictures, aphthous ulcerations, and variable size and depth of lesions. To assess the severity of endoscopic inflammation, the Crohn's Disease Endoscopic Index of Severity (CDEIS), the Simplified Endoscopy Score (SES-CD), or, in the postoperative setting, and the Rutgeerts' score were developed, at the beginning, for clinical trials to assess the efficacy of new drugs and are now routinely used in clinical practice [14–16]. CDEIS is based on the recognition of elementary lesions (non-ulcerated lesions, superficial, and deep ulcerations), associated with the appreciation of their surface in five segments (ileum, right colon, transverse, left colon and sigmoid, and rectum) [15]. This score is considered the gold standard for quantifying endoscopic severity, but due to its complexity, is poorly used in clinical practice. For this reason a simplified index (SES-CD), has been proposed showing good correlation with the aforementioned one [16, 17].

In the last few years, the goal of achieving improvement of mucosal damage or healing has become a therapeutic outcome, and these endoscopic scores have been used to address this issue.

Studies by the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID) have shown that endoscopic pattern severity (assessed by the CDEIS) correlated poorly with clinical (assessed by the CDAI) and biological activity (assessed by C-reactive protein measurement) [18]. Furthermore, clinical improvement is not always associated with the healing of mucosal lesions in CD. However, endoscopic severity may have an impact on the long-term course of the disease. A retrospective study has shown a more aggressive clinical course with an increased rate of penetrating complications and surgery in CD in those patients exhibiting deep and extensive ulcerations at colonoscopy. Among the 102 patients included in the study, 53 had severe endoscopic lesions at index colonoscopy, defined as extensive and deep ulcerations covering more than 10% of the mucosal area of at least one segment of the colon. Patients with severe endoscopic lesions needed significantly more colonic resections than patients without severe lesions (relative risk 5.43, 95% CI: 2.64–11.18) [19]. In a Norwegian clinical trial, the efficacy of therapies in CD was normally assessed by the improvement in clinical activity (defined by a decrease of the CDAI) and the assessment of endoscopic improvement was not usually performed. One of the reasons for this was that we had no definition for "mucosal healing" and we didn't know if, in a transmural disease, the healing of the surface of the abdominal wall alone could represent a good marker of drugs efficacy. However, there is growing evidence that obtaining mucosal healing during therapy is an indirect sign of the effectiveness of a drug [20].

With the advent of immunosuppressants, and especially anti-TNF therapy, mucosal healing rates increased
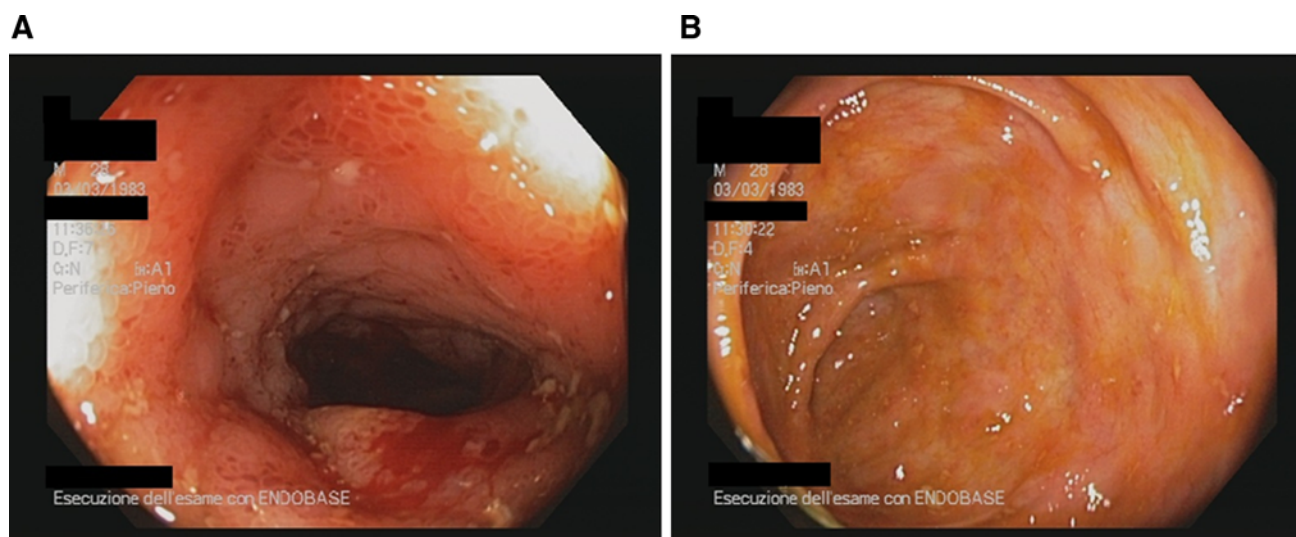
Fig. 1. Mucosal healing in a 20-year-old CD patient after 12 months of biological therapy. **A** Shows ulcers in the terminal ileum. **B** Shows mucosal healing in the same area after anti-TNF-α antibodies therapy.

considerably, and emerging evidence suggests that these therapies will not only reduce disease activity, but might also affect long-term complication rates.

In the endoscopic sub-study of the ACCENT I study, patients treated with scheduled maintenance therapy with infliximab had superior rates of mucosal healing, and those who maintained complete mucosal healing over 1 year had a lower rate (but the difference was not significant) of hospitalizations and surgeries [21]. Recently, a study of mucosal healing in a cohort of Leuven CD patients under long-term treatment with infliximab was reported. In this study, 214 patients had a colonoscopy before and a second one within months after starting infliximab. Mucosal healing (complete or partial) was observed in 68% of the 183 initial responders. Mucosal healing was associated with a significantly lower need for major abdominal surgery during long-term follow-up (14.1% major surgeries in patients with mucosal healing vs 38.4% in patients without mucosal healing, $P < 0.0001$) [22].

More recently, in a prospective clinical study, Baert et al. [23] provide evidence that complete mucosal healing can lead to significantly higher steroid-free remission rates through 2 years in patients with CD.

Future research should continue to explore the value of mucosal healing (Fig. 1). Some authors have suggested that transmural healing might be a superior end-point, although correlations between mucosal and transmural healing have not yet been studied.

It is well known that postoperative recurrence after ileo-colonic resection is a feature of CD. Ileocolonoscopy currently represents the gold standard for assessing CD recurrence. Rutgeerts et al. [24, 25] demonstrated that endoscopic recurrence after curative ileo-colonic resection is observed in almost 73% of patients at 1 year and

in almost 90% of patients at 3 years, even in the absence of overt symptoms. Severe endoscopic recurrence, assessed by Rutgeerts score (i2) is observed in about one-third of patients at 3 months and in almost two-thirds of patients 6 months after surgery [25]. The severity of endoscopic lesions has been found to be predictive of symptomatic and early clinical relapse, being associated with a more aggressive course of the disease. Patients with less severe endoscopic lesions according to Rutgeerts' score (< 5 aphtoid ulcers at anastomosis site), have a lower risk of clinical recurrence risk at 9% compared with 100% risk at 4 years for patients with more severe endoscopic recurrence (Rutgeerts' score i2 or greater). Ileocolonoscopy by using Rutgeerts' score is recommended within the first year after surgery to make a decision regarding postoperative treatment, especially in high risk patients [25].

Based on these data, evolution of mucosal healing is becoming more and more used in clinical practice as a therapeutic goal. However, one might argue that a commonly accepted definition of mucosal healing is still lacking. Moreover, endoscopic evaluation of mucosal changes does not take into consideration the transmural nature of CD, thus leading to the need of new diagnostic tools of integrating endoscopy.

Conventional radiology and new alternative techniques

Although ileocolonoscopy represents the gold standard technique to evaluate ileo-colonic CD, it presents some limitations. It is sometimes incomplete due to individual anatomy and the examinations have shown several drawbacks related to the procedure's invasiveness and discomfort, as well as the risk of bowel perforation and it cannot be useful in patients with upper lesions or fibro-

stricturing disease. Over the last few years, alternative techniques, including ultrasonography (US), in particular, ultrasonography with oral contrast ingestion (Small Intestine Contrast Ultrasonography, SICUS), computed tomography (CT) and magnetic resonance imaging (MRI) have been increasingly used for the evaluation of patients with CD. The choice between imaging techniques is often determined by local availability and expertise.

Regarding the role of US in monitoring CD, no standardized scores of disease damage and activity are available so far. Some findings, compatible with CD activity, are generally considered, including bowel wall thickness, small bowel dilation, bowel stricture, complications of disease as fistulae, mesenteric enlargement, and abscesses identified [26–28]. Disease location and disease activity are the main factors influencing the accuracy of US regarding the diagnosis of CD. The highest values were found for anatomic areas easily accessible by US, such as the terminal ileum and left colon. The principal advantage of this technique is being a widely available, minimally invasive and an ionizing radiation-free tool.

Recent data suggest that the sensitivity of US for the detection of disease activity ranged from 63% to 100%, with specificity in the range of 77–100%. Overall sensitivity was 85% (95% CI 79–89%) and specificity 91% (95% CI 87–95%) [29, 30].

More recently, SICUS performed after the ingestion of 375 mL (range 250–500 mL) of oral contrast solution consisting of polyethylene glycol (PEG) has been proposed for detecting small bowel lesions in patients with suspected or known CD (>95%) [27]. SICUS findings compatible with CD recurrence include an increased bowel wall thickness, thus providing the view of extraluminal small bowel lesions. In a prospective longitudinal study, we recently reported that SICUS may represent an alternative non-invasive technique useful for assessing CD recurrence after ileo-colonic resection [31].

In a recent systematic review, Panes and colleagues reported that ultrasonography is an accurate technique for diagnosis of suspected CD and for evaluation of disease activity (sensitivities 0.84, specificity 0.92). It is widely available and non-invasive, but its accuracy is lower for disease proximal to the terminal ileum [29]. Contrast-enhanced US could classify severity significantly better than Doppler-US signal and measurement of mural thickening ($P < 0.001$) [32, 33].

In the last few years, CT and MRI competed with conventional radiologic techniques such as small bowel follow through (SBFT). CT offers a fine mucosal detail, cross-sectional imaging techniques and permits the complete evaluation of both luminal and extraluminal structures [34]. CT and MRI have greatly improved the detection of structural small bowel lesions in CD [35–37]. High quality images have made it possible to visualize the precise location of lesions, bowel wall involvement, fat or mesenteric changes around the gastrointestinal tract, and the presence of strictures, fistulas, and abscesses. An exact topography of CD lesions is possible [36].

CT has demonstrated over 80% sensitivity and specificity for detecting bowel segments affected by CD and a high specificity (90%) and sensitivity (70–80%) for extraluminal complication [36]. In addition, CT can easily be standardized, and images can be read centrally, thus improving intra-observer disagreement. However, the main drawback of CT is the risk of repeated radiation exposure associated with the need for follow-up studies, particularly in younger patients [38].

There are very few studies comparing the diagnostic accuracy of MRI and CT in CD, but no significant differences in sensitivity, specificity, and accuracy were observed regarding CD location, extent and bowel wall enhancement [35]. However, MR was significantly superior to CT in detecting strictures [35]. The role of MRI in CD was recently investigated by Rimola and colleagues [29, 39–41]. The accuracy of MRI in the diagnostic workout of patients with suspected CD was evaluated in several studies [39–43]. Overall sensitivity and specificity of MRI for the diagnosis of CD, were 78% (95% CI 67–84%) and 85% (95% CI 76–90%), respectively. As with US, in addition to wall thickness, consideration of other changes that are associated with disease activity, such as wall enhancement after injection of MRI contrast, and the presence of edema, increase the sensitivity of MRI for diagnosing CD. Several studies have evaluated the accuracy of MRI in the assessment of activity in the terminal ileum and/or the colon. Pooled results determining accuracy of MRI for the assessment of disease activity show a sensitivity of 80% (95% CI 77–83%) and specificity of 82% (95% CI 78–85%) [29].

In a recent study, Rimola et al. [39] validated MRI findings as predictors of active and severe CD and provided a quantitative Magnetic Resonance Index of Activity (MaRIA). In this study, 48 patients with clinically active ($n = 29$) or inactive ($n = 19$) CD disease, underwent MRI and ileocolonoscopy as a gold standard, by using CDEIS score. A regression model was created using the wall thickness, relative contrast enhancement, presence of edema and ulcers. Estimation of activity in each segment using this regression model, correlated with CDEIS ($P < 0.001$, $r = 0.798$) [39].

The introduction of novel imaging techniques has increased the accuracy in defining changes in bowel structure. These tools can be used to quantify damage, to measure disease progression over time, and to assess the impact of treatment strategies in the progression of CD. In the same vein, recently the Crohn's Disease Digestive Damage Score (The Lemann score) was proposed [44]. The aim of this score is to measure cumulative tissue damage based on a comprehensive assessment of struc-

tural bowel damage, including stricturing lesions, penetrating lesions (fistulas and abscesses), and surgical resection. The index score takes into account damage location, extent, and severity. To evaluate damage extent, the digestive tract is divided into segments based on their clinical relevance, frequency of involvement, feasibility of defining limits to one given segment, and the Montreal Classification of disease. For each segment, severity is scored on an ordinal scale ranging from 0 (normal) to 3 (maximal) for stricturing lesions, penetrating lesions, and surgical resection or bypass of bowel. The final score varies from zero (no digestive damage) to a theoretical maximum value corresponding to complete resection of the digestive tract. This score is based on independent ordinal variables describing lesions (strictures, penetration by ulcers, fistulas and abscess, and surgical resection of bowel) in each segment for the four CD locations. The Lemann score should provide a better measurement of the severity of structural bowel damage and may be used to measure bowel damage progression with repeated assessments. The slope of the curve of digestive damage could be taken into account for decision-making, independent of damage severity.

Conclusions

In the last few years, the concept of CD as a progressive disease inducing cumulative structural damage has emerged. The need to develop an instrument, which should be able to assess cumulative structural bowel damage in CD patient's history, taking into account both the extent and severity of bowel lesions, including the phenotype's disease and previous surgery, is still lacking. Damage will be assessed based on the medical history, endoscopy, and other imaging techniques, chosen on the basis of the patient's characteristics. Development of this instrument should provide a better measurement of the severity of structural bowel damage and may be used to measure the disease progression with repeated assessments, identifying patients with severe damage who require rapid changes in therapy.

Conflict of interest   The authors have no relevant financial interests to disclose.

References

1. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, et al. (2010) The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol 105:289–297
2. Van Assche G, Dignass A, Panes J, et al. (2010) The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohns Colitis 4:7–27
3. Hanauer SB (2009) Positioning biologic agents in the treatment of Crohn's disease. Inflamm Bowel Dis 15:1570–1582
4. D'Haens GR, Fedorak R, Lemann M, et al. (2009) Endpoints for clinical trials evaluating disease modification and structural damage in adults with Crohn's disease. Inflamm Bowel Dis 15:1599–1604
5. Pallone F, Ricci C, Boirivant M, Montano S (1981) Measuring the activity of Crohn's disease. Ital J Gastroenterol 13:51–53
6. Sandler RS, Jordan MC, Kupper LL (1988) Development of a Crohn's index for survey research. J Clin Epidemiol 41:451–458
7. Harvey RF, Bradshaw JM (1980) A simple index of Crohn's-disease activity. Lancet 1:514
8. Irvine EJ (1995) Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. J Clin Gastroenterol 20:27–32
9. Irvine EJ, Zhou Q, Thompson AK (1996) The short inflammatory Bowel Disease questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT investigators. Canadian Crohn's relapse prevention trial. Am J Gastroenterol 91:1571–1578
10. Gasche C, Scholmerich J, Brynskov J, et al. (2000) A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis 6:8–15
11. Louis E, Collard A, Oger AF, et al. (2001) Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. Gut 49:777–782
12. Cosnes J, Cattan S, Blain A, et al. (2002) Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis 8:244–250
13. Biancone L, De Nigris F, Del Vecchio Blanco G, et al. (2002) Review article: monitoring the activity of Crohn's disease. Aliment Pharmacol Ther 16(Suppl 4):29–33
14. Hommes DW, van Deventer SJ (2004) Endoscopy in inflammatory bowel diseases. Gastroenterology 126:1561–1573
15. Mary JY, Modigliani R (1989) Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut 30:983–989
16. Daperno M, D'Haens G, Van Assche G, et al. (2004) Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 60:505–512
17. Cellier C, Sahmoud T, Froguel E, et al. (1994) Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. Gut 35:231–235
18. D'Haens G, Van Deventer S, Van Hogezand R, et al. (1999) Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. Gastroenterology 116:1029–1034
19. van Assche G, Vermeire S, Rutgeerts P (2010) Mucosal healing and anti TNFs in IBD. Curr Drug Targets 11:227–233
20. Froslie KF, Jahnsen J, Moum BA, et al. (2007) Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology 133:412–422
21. Hanauer SB, Feagan BG, Lichtenstein GR, et al. (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 359:1541–1549
22. Schnitzler F, Fidder H, Ferrante M, et al. (2009) Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis 15:1295–1301
23. Baert F, Moortgat L, Van Assche G, et al. (2010) Mucosal healing predicts sustained clinical remission in patients with early stage Crohn's disease. Gastroenterology 138:463–468 (quiz e410-461)
24. Rutgeerts P, Geboes K, Vantrappen G, et al. (1990) Predictability of the postoperative course of Crohn's disease. Gastroenterology 99:956–963
25. Rutgeerts P (2003) Strategies in the prevention of post-operative recurrence in Crohn's disease. Best Pract Res Clin Gastroenterol 17:63–73
26. Parente F, Greco S, Molteni M, et al. (2004) Oral contrast enhanced bowel ultrasonography in the assessment of small intestine Crohn's disease. A prospective comparison with conventional ultrasound, x ray studies, and ileocolonoscopy. Gut 53:1652–1657
27. Calabrese E, La Seta F, Buccellato A, et al. (2005) Crohn's disease: a comparative prospective study of transabdominal ultrasonography, small intestine contrast ultrasonography, and small bowel enema. Inflamm Bowel Dis 11:139–145
28. Maconi G, Parente F, Bollani S, et al. (1996) Abdominal ultrasound in the assessment of extent and activity of Crohn's disease:

clinical significance and implication of bowel wall thickening. Am J Gastroenterol 91:1604–1609

29. Panes J, Bouzas R, Chaparro M, et al. (2011) Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. Aliment Pharmacol Ther 34:125–145

30. Martinez MJ, Ripolles T, Paredes JM, et al. (2009) Assessment of the extension and the inflammatory activity in Crohn's disease: comparison of ultrasound and MRI. Abdom Imaging 34:141–148

31. Calabrese E, Petruzziello C, Onali S, et al. (2009) Severity of postoperative recurrence in Crohn's disease: correlation between endoscopic and sonographic findings. Inflamm Bowel Dis 15:1635–1642

32. Migaleddu V, Quaia E, Scano D, et al. (2008) Inflammatory activity in Crohn disease: ultrasound findings. Abdom Imaging 33:589–597

33. Migaleddu V, Scanu AM, Quaia E, et al. (2009) Contrast-enhanced ultrasonographic evaluation of inflammatory activity in Crohn's disease. Gastroenterology 137:43–52

34. Hara AK, Swartz PG (2009) CT enterography of Crohn's disease. Abdom Imaging 34:289–295

35. Fiorino G, Bonifacio C, Peyrin-Biroulet L, et al. (2011) Prospective comparison of computed tomography enterography and magnetic resonance enterography for assessment of disease activity and complications in ileocolonic Crohn's disease. Inflamm Bowel Dis 17:1073–1080

36. Goetz M, Neurath MF (2009) Imaging techniques in inflammatory bowel disease: recent trends, questions and answers. Gastroenterol Clin Biol 33(Suppl 3):S174–S182

37. Ippolito D, Invernizzi F, Galimberti S, et al. (2010) MR enterography with polyethylene glycol as oral contrast medium in the follow-up of patients with Crohn disease: comparison with CT enterography. Abdom Imaging 35:563–570

38. Peloquin JM, Pardi DS, Sandborn WJ, et al. (2008) Diagnostic ionizing radiation exposure in a population-based cohort of patients with inflammatory bowel disease. Am J Gastroenterol 103:2015–2022

39. Rimola J, Ordas I, Rodriguez S, et al. (2011) Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. Inflamm Bowel Dis 17:1759–1768

40. Rimola J, Ordas I, Rodriguez S, et al. (2011) Imaging indexes of activity and severity for Crohn's disease: current status and future trends. Abdom Imaging. doi:10.1007/s00261-011-9820-z

41. Rimola J, Rodriguez S, Cabanas ML, et al. (2011) MRI of Crohn's disease: from imaging to pathology. Abdom Imaging. doi:10.1007/s00261-011-9797-7

42. Maccioni F, Viscido A, Broglia L, et al. (2000) Evaluation of Crohn disease activity with magnetic resonance imaging. Abdom Imaging 25:219–228

43. Maccioni F, Viscido A, Marini M, et al. (2002) MRI evaluation of Crohn's disease of the small and large bowel with the use of negative superparamagnetic oral contrast agents. Abdom Imaging 27:384–393

44. Pariente B, Cosnes J, Danese S, et al. (2011) Development of the Crohn's disease digestive damage score, the Lemann score. Inflamm Bowel Dis 17:1415–1422