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REVIEW

HYBRID IMAGING IN INFLAMMATION AND INFECTION

Hybrid imaging in Crohn's disease: from SPECT/CT to PET/MR and new image interpretation criteria

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ABSTRACT

Crohn's disease is a chronic relapsing disease characterized by mucosal inflammation, lymphocytes infiltration and fibrotic strictures. Usually, the assessment of location, extension, inflammatory activity and severity of intestinal lesions is complex and invasive with endoscopic methods or histological and biochemical investigations. Thus, the diagnosis remains a challenge for the management of patients. Nuclear medicine techniques, in particular hybrid and molecular imaging, might offer a valid option for the evaluation and determination of the prognosis of the disease. Indeed, imaging methods provide a non-invasive, reproducible and quantitative analysis. An overview of the currently available multimodality imaging techniques in Crohn's disease are reviewed, with particular regard to positron-emission tomography/magnetic resonance and the choice of the best evaluation Score, explaining advantages and disadvantages of each one, with particular regard to their potential role for the assessment of disease activity and extent of inflammation in order to improve the diagnosis. We propose new interpretation criteria for PET/MR images.

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Key words: Crohn disease - Tomography, emission-computed, single-photon - Positron-emission tomography - Magnetic resonance imaging - Multimodal Imaging.

Inflammatory diseases are a heterogeneous class of diseases characterized by chronic inflammation of the target organ, often relapsing, invalidating and requiring life-long treatment. The so-called "aseptic chronic inflammatory diseases" include: autoimmune diseases, graft rejection, sarcoidosis, vasculitis, atherosclerosis and some degenerative diseases. In these patients, it is very important to try and achieve specific immunosuppression to extinguish the immune process with the aim of halting the disease, preventing or delaying complications and avoiding disease relapse, reducing to a minimum side effect by using specific immune therapies that block as selectively as possible the pathological mechanisms responsible for the disease.

New specific targeted therapies are being developed for several immune mediated diseases. Several clinical trials are being performed to assess the efficacy and safety of this approach. All of them, however, rely largely on the clinical assessment of the patients to evaluate the effect of treatment. An objective and reliable method to visualize directly the immune process underlying the individual disease would be valuable; specific diagnostic tests, furthermore, may allow the selection of patients to be treated.

Nowadays, nuclear medicine techniques are not often used for the diagnosis of chronic inflammatory diseases, but they do greatly contribute to the management and determination of the prognosis of the disease because of their high sensitivity. This is of paramount importance since, in most cases, therapeutic options are available and a prompt start to treatment may prevent disease or delay complications.

One of the most important steps in the study of autoimmune diseases has been the development of molecular nuclear medicine that, with the production of specific radiopharmaceuticals, has contributed to the identification of the immune process responsible for the individual disease. New molecular therapeutic agents provide to localize specifically target, block inflammatory reactions, obtaining information on disease activity, but also on the nature of the process and can, therefore, decide which treatment to start, when to start it and when to stop it or modify it.

Crohn's disease (CD) is characterized by a chronic mononuclear cell infiltration of the intestinal wall and hypertrophy of local lymphoid tissues.[1] Immune erosion of the intestinal wall may lead to severe complications of the affected bowel, such as stenosis and ulceration, which may require surgical resection. In over 70% of patients, relapse of the disease is noted within 1 year after the intervention. In the early relapse phase, symptoms are infrequent and non-specific and conventional barium X-ray examinations are negative. Since effective therapies are available, early diagnosis of relapse might allow prompt initiation of therapy to prevent the onset of complications and the need for further surgical resection.[2]

In CD, the detection of lymphocytes infiltrating the mucosa and sub-mucosa represents an important early marker of disease, together with the measurement of other serological/genetic/morphological/histological markers. As early as diagnosis can be made a specific early treatment can be started and the same markers can be often used for therapy follow-up. For histological examination, tissue specimens can be obtained from gut, although biopsies represent only a very minimal part of the gut and foci of disease could be present in parts of the gut not accessible to biopsy. Therefore, the opportunity to image gut inflammation, non-invasively, and disease activity is an important goal for nuclear medicine and radiology.

In this review, the current available multimodality imaging techniques were summarized, including single photon emission/computed tomography (SPECT), ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) and positron-emission tomography/magnetic resonance (PET/MR), with the aim to improve the diagnosis and staging of disease activity (Figures 1, 2).

Recent ECCO/ESGAR guidelines

The recent implementation of radiologic technique and imaging modalities for assessment of IBD has required an updated consensus document between the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) and the European Crohn's and Colitis Organisation (ECCO) in collaboration with EANM experts, in order to establish the diagnostic role

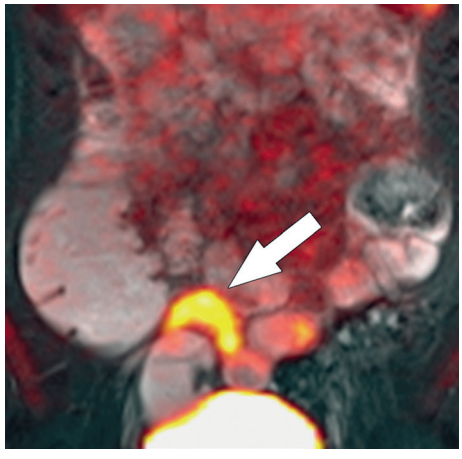

Figure 1.—Coronal slide of abdominal PET/MR in a patient with acute Crohn's disease showing active disease in the jejunal bowel loop of terminal ileum (arrow).

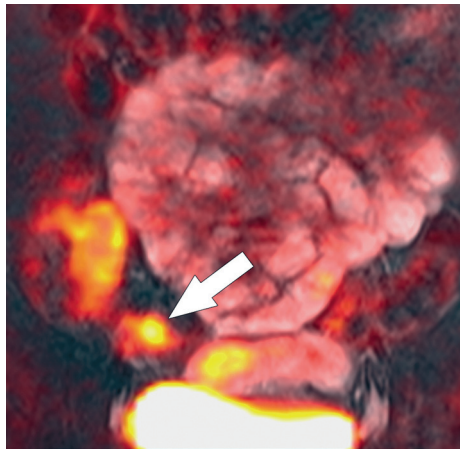

Figure 2.—Coronal slide of abdominal PET/MR in a patient with ileal Crohn's disease relapse. The arrow clearly shows the presence of active disease in a segment of terminal ileum.

of each of them. In this consensus document, the role the currently available imaging modalities, magnetic resonance imaging (MRI), computed tomography (CT), ultra-sonography (US), and nuclear medicine examinations, including hybrid imaging, has been re-evaluated. The sensitivity in the assessment of small and large bowel stenotic and penetrating lesions, of upper gastrointestinal (GI) tract lesions, of the global bowel damage, the accuracy in monitoring the therapeutic response, the assessment of colonic inflammation and complications, of perianal disease and urogenital, liver and biliary tract complications, has been separately discussed and reported for each modality, as well as the role for emergency situations and postoperative setting, with special attention to MRI.

The ECCO-ESGAR document has further confirmed the well-known diagnostic accuracy of CT and US, also outlining the relative pros and cons. Certainly, US has a more limited coverage and lower accuracy than MRI and CT in exploring the entire length of the small or large bowel. On the other hand, although CT is very accurate for assessing the main features of IBD, repeated CT examinations may expose patients to an increased life-time radiation-induced cancer risk, particularly children and young adults. Repeated controls in CD patients should be performed with radiation-free techniques, such as US and MRI.

Nuclear medicine procedures, especially white blood cells (WBCs) scintigraphy, can be considered as an alternative to cross-sectional imaging for evaluation of disease activity and extension or complications in specific situations, with the main limitation of the radiation exposure and the poor anatomic detail. PET/CT preliminary studies with FDG were poorly specific for inflammation and for assessing disease activity. The document has also outlined that CT, US and small bowel follow-through (SBFT) are generally more available and less expensive than MRI and scintigraphy or hybrid imaging.[3-5]

Hybrid imaging

Radiolabeled WBCs using both ^{111}Indium (^{111}In)-oxine or ^{99m}Tc-HMPAO are the nuclear medicine gold standard to detect several inflammatory and infective diseases. The presence of WBCs in the inflamed intestinal mucosa is the hallmark of CD and it is the reason why WBCs scintigraphy could also be applied in this specific clinical condition in particular in the optic of monitoring disease's activity.[6-10] For these patients WBCs scintigraphy allows the evaluation of areas of bowel that cannot be explored with colonoscopy and it could represent a non-invasive procedure not only for diagnosis but also for follow-up and therapy monitoring. That could be extremely important for the children. Planar images, however, are burdened by the physiologic visualization of bowel after three hours, in particular for ^{99m}Tc-HMPAO, that can result in a false positive scan. Moreover, the poor spatial resolution, tissue attenuation and in particular the lack of anatomical landmarks that led to the inability to correctly localize the pathological focus of uptake have always been the great disadvantages of planar images.

The fusion of functional information, provided by scintigraphic imaging, with anatomic detail, provided by a radiological device, could overcome these limitations. With the advances in the field of technologies and the development of hybrid imaging, the way to make imaging has been widely transformed.[11] Hybrid imaging is characterized by the integration of radionuclide imaging and a CT scan. These two modalities can be coregistered or acquired separately and then fused *a posteriori.* In the second case, however, artefacts in the orientation and alignment of the images could negatively influence the result so this modality is strictly dependent by the ability of the operator. Hybrid imaging offers several advantages over planar images in particular considering that it provides an accurate fusion of functional and anatomical data enabling to a precise localization of the suspicious foci in a single imaging session that does not require any change in patient position. This is extremely important in the optic of sparing time and in particular, for CD, if we consider the movements of the bowel and so it would be desirable to coregister the CT and the SPECT. The use of X-ray tube of CT scan, is important not only for the anatomical data but also for the attenuation correction of images that improves the diagnostic accuracy.

The appeal to the combination of SPECT or a PET and a CT-scan is nowadays exploited in several fields and it often represents an undeniable diagnostic tool in different diseases. In the specific clinical setting of CD, a SPECT/CT could improve the diagnostic accuracy of

planar images acquired with WBCs scan in particular considering the physiologic visualization of bowel after 3 hours post injection that could be misinterpreted as pathologic uptake in a segment.

[^{18}F]-FDG PET is a non-invasive, three-dimensional imaging technique that exploits the higher uptake of FDG, a structural analogue of 2-deoxyglucose, by cells with active glucose metabolism such as tumor and infectious cells. These cells, overexpressing different isotypes of glucose transporters (GLUT), trap FDG by phosphorylation, producing a greater signal than background. The activity in the region of interest might be quantified using a standardized uptake value (SUV), based on the activity in the target tissue, the injected dose and the subject's weight. As well as SPECT, also PET may be integrated with CT, combining the physiological accuracy and functional data of PET and the anatomical information of CT in order to improve the spatial and temporal resolution, detection and provide attenuation correction of PET.[12-14]

In CD setting, PET/CT is revealed very useful and feasible to assess extent, location and inflammatory activity in the bowel, especially when conventional imaging cannot be performed or severe disease cases or strictures in the bowel prevent a complete endoscopy. Furthermore, PET/CT might be of particular importance for pediatric use due to its easy administration of FDG, non-invasive and fast procedure to acquire images.[15-17]

Recently the industries are developing new PET tomographs integrated with a MRI that seem to represent the future in diagnosis and follow-up of this disease, especially for being radiation-free for CD patients who need repeated imaging sessions over time during chronic disease.

SPECT/CT papers using radiolabeled WBC or mAb antigranulocytes

A meta-analysis performed by Annovazzi *et al.* on 120 papers published from 1984 to 2005 on 4388 patients revealed that autologous leukocytes labeled with both ^{99m}Tc and ^{111}In show higher diagnostic accuracy compared with monoclonal antibodies, barium studies, ultrasound and CT.[18] The sensitivity and specificity of WBC scan however depends on the acquisition protocols and by the activity of the disease. In quiescent phases this examination seems to be less sensitive. Regarding the acquisition protocols, the best imaging time is still debated. The higher diagnostic accuracy seems to be obtained within 3 hours post injection [8] because the accumulation of radiolabeled autologous leucocytes in inflamed mucosa is very high at this time point, however the presence of physiological visualization of bowel, expression of excretion of ^{99m}Tc-HMPAO, can give false positive results. A "squat" view in addition to anterior and posterior views can be useful in some cases in order to distinguish bladder from bowel.[7] Li *et al.*[7] in 1992 compared ^{99m}Tc-HMPAO and ^{111}In labeled WBCs in a large cohort of patients affected by CD. They acquired only planar images after 2 hours post injection with fixed counts. Using a five-point scale of uptake in order to evaluate the inflammatory activity, comparing the bowel uptake with bone marrow and spleen, they found similar results in terms of sensitivity, specificity, diagnostic accuracy, positive predictive value and negative predictive value between ^{99m}Tc and ^{111}In (^{99m}Tc sensitivity 96%, specificity 97%, accuracy 97%, PPV 97%; NPV 96%. ^{111}In sensitivity 96%, specificity 97%, accuracy 97%, PPV 98%, NPV 96%). Becker *et al.* obtained similar findings reporting a sensitivity of 96%, a specificity of 97% and a diagnostic accuracy of 98% in discriminating inactive from active inflammation in bowel segments.[19, 20] Aydin *et al.* performed WBCs scan at three-time point (1, 2 and 4 hours post injection) and they found better results after two hours. This time point seems to represent a good compromise between image quality and the risk to have false positive results.[21] Some other authors explore the utility of SPECT in the quantification of inflammatory bowel activity expressed as a fraction of bone marrow uptake (SPECT Score) comparing these data with colonoscopy or surgery. They found a correlation between SPECT Score and CD activity index (CDAI), biochemical indexes of flogosis [22] and clinical parameters.[23]

As previously described, the limitations of planar images can be overcome by the integration with SPECT, or better with SPECT/CT, in order to improve the diagnostic performance of WBCs scan. Several papers are available in literature on the possible role of SPECT and SPECT/CT [20-25] in the evaluation of IBD reporting promising results. The added value of SPECT and SPECT/CT over planar images, include a more detailed visualization of the lesions and a better localization in the segments of bowel as summarized in Table I.[22-28, 30]

TABLE I.—*Radiopharmaceuticals used for SPECT imaging of CD.*

Ref.	Radiopharmaceutical	Modality	Added value of hybrid over planar images
Biancone *et al.*[24]	^{99m}Tc-WBCs	SPECT (2 h p.i.)	SPECT provides a more detailed visualization of CD lesions than planar images. This technique provides a maybe better discrimination between bowel and bone marrow uptake, thus being particularly useful for assessing lesions in the pelvis
Hillele *e al.*[25]	^{99m} Tc-WBCs	SPECT (1 h p.i.)	SPECT improves inter-operator variability and provides a correct of the extent of active disease
Weldon *et al.*[22, 23]	^{99m} Tc-WBCs	SPECT (1.5-2 h p.i.)	Provides non-invasive quantification of bowel activity in both large and small bowel
Mota *et al.*[26]	^{99m} Tc-WBCs	SPECT (30 min-2 h p.i.)	Could be useful to determine inflammatory activity in asymptomatic patients
Filippi *et al.*[27]	^{99m} Tc-WBCs	SPECT/CT (na)	Provides better anatomic detail in pelvic region useful for the detection of perianal fistula.
Kerry *et al.*[28]	^{99m} Tc WBCs *vs*. ^{99m}Tc LeukoScan	SPECT (4 h p.i.)	Improves both sensitivity and specificity. However, ^{99m}Tc LeukoScan is not useful for imaging IBD
Charron *et al.*[30]	^{99m} Tc LeukoScan	SPECT (2-4 h p.i.)	Improves sensitivity

Considering the complex labeling process of WBCs that requires qualified personnel, adequate laboratory and instrumentation and blood manipulation, some authors explored the possible role of antigranulocyte antibodies in alternative to WBC scintigraphy.[26-29] Kerry *et al.*, compared ^{99m}Tc-WBCs with ^{99m}Tc Leukoscan, a monoclonal Fab antibody fragment that recognizes specific glycoproteins on granulocyte surface, in 22 patients affected by IBD.[26] Sensitivity and specificity of WBCs after 2 hours post injection was 87% and 86%, higher than Leukoscan. The sensitivity of monoclonal antibodies increases with time from injection and it reaches a maximum at 4 hours (73% for planar images and 87% for SPECT). The specificity decreases with time from 100% after 2 hours to 57% after 4 hours for both planar and SPECT images suggesting to acquire Leukoscan at an earlier time after injection in order to improve the specificity, however at this time point the sensitivity was very low (40%) because it very difficult to distinguish pathologic uptake from physiologic visualization of bowel at early phases. Stokkel *et al.* also compared WBC and Leukoscan in 6 patients with IBD showing only a slight intestinal uptake in 50% of patients and the site did not correspond to the ones seen at WBCs scans and at endoscopy.[27]

From this analysis emerges that data available in literature seem to support the use of WBCs scan also in this clinical condition whereas the utility of antigranulocyte scintigraphy for imaging IBD is very limited.[26-29]

Several studies have been published on the use of radiolabeled IL2 in patients with CD for the detection of bowel-infiltrating lymphocytes.[30-32] In a comparative study between ^{99m}Tc-IL2 and ^{99m}Tc-HMPAO granulocytes, in patients with inactive CD, the two radiopharmaceuticals, in most cases, accumulated in different areas, indicating that they can detect different types of inflammation, namely the lymphocytic infiltration in inflamed areas and the granulocytic infiltration in infected areas due to mucosal damage.[33] Both radiopharmaceuticals were characterized by high negative predictive values, but ^{99m}Tc-IL2 was also characterized by a better correlation with time to relapse.[34] The use of ^{99m}Tc-anti-TNFα has also been tested in CD for therapy decision-making and biological therapy follow-up, but the uptake of this radiopharmaceutical in the gut wall has been shown to be minimal and not to correlate with the response to therapy.[35] These radiopharmaceuticals highlights the importance of hybrid imaging (SPECT/CT) for the precise localization of affected areas.

Other interesting possibilities that are being explored in CD, are the use of radiolabeled antibiotics for direct imaging of bacterial presence in the damaged gut mucosa,[36] or new radiopharmaceuticals for imaging endothelial activation as an early marker of vascular inflammation in CD.[37]

Role of [^{18}F]-FDG PET/CT

Several groups have evaluated the use of PET in CD, summarized in Table II.[38-55] A first study backs to 1999 where Skehan *et al.*[38] performed [^{18}F]-FDG PET in 25 pediatric patients with suspected IBD, 15 of whom with CD, using endoscopy with biopsy and SBFT as reference standards. They found an overall sensitivity of

TABLE II.—*Radiopharmaceuticals used for PET imaging of CD.*

Ref	Modality	Advantages	Disadvantages	Radiological burden issue
Lemberg *et al.*[39]	PET	Useful diagnostic adjunct to endoscopy, no bowel preparation, low radiation exposure, non-invasive	Low specificity, small group of patients	1.3 mSv with PET compared with an estimated 20 mSv with small bowel study
Loffler *et al.*[40]	PET	Fast, non-invasive, low radiation exposure, semi-quantitative analysis, high sensitivity	NA	Effective dose: 3-7 mSv for children
Skehan *et al.*[38]	PET	Useful technique for the detection of intestinal inflammation in children, adjunct to colonoscopy and barium studies	NA	Single patient effective dose: 1.3 mSv
Holtmann *et al.*[41]	PET *vs*. hydro-MRI *vs*. colonoscopy	High sensitivity and specificity, complementary to colonoscopy for stenoses identification, non-invasive	Small group of patients, limited comparison with endoscopic data in some studies	Better combine PET and MRI than CT because its significant radiation exposure
Neurath *et al.*[42]	PET *vs*. hydro-MRI *vs*. GAB	Higher sensitivity than MRI and GAB and same good specificity, non-invasive	NA	NA
Berthold *et al*.[43]	PET *vs*. PET/CT	CT additional anatomical information	No description of negative predictive value	The exposure of a PET-CT is not higher than of a PET-scan (estimated 3-7 mSv)
Bettenworth *et al.*[44]	PET/CT	Non-invasive	Glucose uptake quite variable, pathologic findings not always differentiable	Injected FDG activities and x-ray radiation doses of the CT scanner were reduced to the necessary minimum
Jacene *et al.*[46]	PET/CT	Sensitive qualitative analysis, correlation with histology	Small group of patients	NA
Lapp *et al.*[47]	PET/CT	Clinically useful in suspected and known CD patients for clinical decision-making	Small group of patients	NA
Louis *et al.*[48]	PET/CT	High sensitivity, good specificity, good correlation with clinical and biological parameters	Higher radiation exposure than MRI	10 mSv (0.1 mSv for the CT scout view, 4.5 mSv for the CT, and 5.7 mSv for the 18F-FDG study) not allowed a frequent use
Meisner *et al.*[49]	PET/CT	CT essential for accurate CD analysis, non-invasive	Small group of patients	NA
Russo *et al.*[51]	PET/CT	Correlation with clinicopathological markers, high sensitivity and modest specificity, assessment of early pharmacodynamic response	False positive due to deeper bowel layers, small group of patients	Total radiation dose for both scans: 11.2 mSv, optimized to lowest radiation exposure
Saboury *et al.*[50]	PET/CT	Correlation with clinical, endoscopic, and lab indices of disease activity, detection and characterization of the anatomic location and the degree of inflammation in the bowel	Lack of follow-up scan, not included small intestine and extra-intestinal lesions, small group of patients	NA
Das *et al*.[52]	PET/CT enteroclysis	High sensitivity and resolution, unique scanning session, low radiation exposure	nasal and abdominal discomfort, lack of an endoscopic evaluation of the small intestine, lack of follow-up	Less radiation exposure than barium studies/enteroclysis (12 15 mSv: (BMFT/ enteroclysis 3 mSV and CT abdomen 10 mSV)
Lenze *et al.*[45]	PET/CT *vs*. MR enteroclysis and transabdominal Ultrasound	High sensitivity, no bowel preparation	Less sensitive than MR-enteroclysis in detecting strictures in the duodenum/ proximal jejunum	8 mSv (18FDG-PET below 7 mSv, low-dose CT ¼ 1 mSv), less than a barium enema (15 mSv)
Ahmadi *et al.*[53]	PET/CT enterography	Non-invasive, additive to CTe, less time-consuming, no bowel preparation	Small group of patients	7 mCi- 4 mSv, similar to the radiation exposure from a small bowel series
Groshar *et al.*[54]	PET/CT enterography	Reduced background activity, better definition	Small group of patients, only one radiological interpretation	NA
Shyn *et al.*[55]	PET/CT enterography *vs*. CT enterography	Therapy monitoring, anatomical characterization, correlation with histopathology grading of inflammation and serum C-reactive protein	Small group of patients	Effective dose: for the first 4 patients range 13.9-23.9 mSv; for the last 9 patients range 6.5-11.5 mSv

81%, specificity of 85% and, when colonoscopy was limited, PET localized further inflammatory areas in the proximal large bowel. Authors concluded that PET is a useful technique in children and it may be used an adjunct to colonoscopy and barium studies when they are unsuccessful. Several years later, the same group confirmed that PET identified active inflammatory disease in 81.5% of CD patients, according to endoscopic results. Therefore, it does not have to replace conventional studies, but to be an alternative and further investigation, considering the significant radiation exposure as limiting factor too.[39] Also Loffler *et al.*[40] performed FDG-PET in 23 pediatric patients, 17 of whom with CD, obtaining a sensitivity and specificity equal to 98% and 68% with histology as standard of reference, 92% and 65% with endoscopy as standard of reference, respectively. They considered PET as a fast, non-invasive imaging method with low radiation exposure that allows the assessment of disease activity in children at an early stage.

Another group evaluated the accuracy of FDG-PET to assess inflammation non-invasively in 43 CD patients, considering ileocolonoscopy and hydromagnetic resonance imaging (hydro-MRI) as reference standards. Results showed that PET might be comparable to hydro-MRI for the assessment of the proximal ileum, complementary to colonoscopy to identify the nature of stenosis with high sensitivity and specificity, suggesting PET as a promising non-invasive technique for clinical management of CD.[41] The same group compared PET to hydro-MRI and antigranulocyte scintigraphy (GAB) in 59 patients with active CD, 28 of whom colonoscopy was performed. PET had the highest sensitivity (85%) than hydro-MRI (67%) and GAB (41%), while a specificity equal to 89% comparable to hydro-MRI (93%), but not to GAB (100%). Authors concluded that PET allowed the non-invasive detection of inflamed gut segments in CD with high sensitivity and specificity.[42] A comparison between PET and PET/CT has been demonstrated by Berthold *et al.*[43] in 23 children and adolescents, 19 of whom with CD, using endoscopy with biopsy and histology as gold standard. CT provided additional anatomical information, although in this study only PET was able to locate the activity in the gut segments. However, FDG detected extra intestinal inflammation, contributing to diagnosis and to determinate the extent and degree of high-grade inflammation, especially in those parts of the small bowel that are not accessible to endoscopy.

Many authors investigated on the role of [^{18}F]-FDG PET/CT for the assessment of inflammation in adult and pediatric patients with CD, where the CT scan provided better anatomical details, improving the diagnostic accuracy of PET. After a preclinical study, Bettenworth *et al.*[44] performed PET/CT in 25 patients with histologically diagnosed Crohn's colitis. PET/CT showed positive findings in 88% of extensive ulcerations, but only in 50% of superficial epithelial lesions, concluding that PET/CT is a non-invasive and promising translational method, but the intestinal glucose uptake is variable and pathologic segments are always not distinguishable from regular ones. The same group compared [^{18}F]-FDG PET/CT, MR-enteroclysis and trans-abdominal ultrasound in order to evaluate the best non-invasive imaging method for the detection and differentiation of inflammatory and fibromatous stenosis in CD, using endoscopy and histology as reference standards. Detection and differentiation rates of three methods were not so different to consider them statistically significant. However, a combination between trans-abdominal ultrasound and PET/CT or MR-enteroclysis led to a 100% detection rate of strictures.[45] Jacene *et al.*[46] preoperatively investigated the accuracy of PET/CT in CD patient with obstructive symptoms in comparison to postoperative histopathological analyses of these lesions. Findings showed that FDG is taken up by different lesions, including inflammatory lesions, fibrotic strictures and muscle hypertrophy. Thus, a qualitative PET analysis is quite sensitive, but a semi-quantitative analysis could help the identification of patients with active inflammation, using the maximum lean standardized uptake value (SUL_{max}). Another group studied the clinical utility of PET/CT in 7 patients, 4 of whom with CD, indicating PET/CT as a useful imaging method in diagnosis, management and clinical decision-making of patient with known or suspected CD.[47] The accuracy of PET/CT has been demonstrated by Louis *et al.*[48] in a prospective study which includes 22 patients with active CD. They found that PET/CT detected 35 of 48 endoscopically affected segments with a sensitivity and specificity of 72.9% and 55.3%, respectively. Furthermore, severe endoscopic lesions, such as deep ulcers and strictures, were detected by PET/CT with 100% of sensitivity, suggesting a direct proportion between

sensitivity and significant endoscopic lesions. Globally, PET/CT Score well correlated with clinical parameters, endoscopy and biological activity of CD. Also, Meisner *et al.*[49] conducted a pilot study using PET/CT for the assessment of disease activity in 12 patients with IBD, 7 of whom with CD. Results showed that PET/CT was positive in 59.4% of analyzed regions with 81.3% of correlation between PET activity and clinical disease activity, demonstrating PET as a non-invasive technique to identify active inflammatory regions in CD. The feasibility and potential clinical utility of [^{18}F]-FDG PET/CT for the assessment of CD activity was investigated in a study performed by Saboury *et al.*[50] 22 subjects underwent PET/CT followed by ileocolonoscopy in order to correlate the imaging scan results with clinical and endoscopic parameters. PET/CT detected 15 additional segments compared to those visualized by endoscopy and all global PET parameters were significantly correlated to standard clinical Scores (CDAI), allowing a new quantitative analysis of regional and global CD activity using PET imaging too. Recently, Russo *et al.*[51] evaluated the role of [^{18}F]-FDG PET/CT as a marker of progression of inflammatory activity and its response to anti-TNF therapy in 22 patients with CD. For PET/CT, the sensitivity and specificity were respectively 88% and 70%, the SUV showed significant cross-sectional and longitudinal correlation with clinicopathological markers like C-reactive protein and Harvey-Bradshaw Index. Authors concluded that their study is a first investigation to comprehend the role of [^{18}F]-FDG PET/CT in the early pharmacodynamic response and it needs larger and further studies.

Other authors studied the CD activity combining [^{18}F]-FDG PET with CT enteroclysis or CT enterography (CTe). Das *et al.*[52] included in a prospective study 17 patients, 9 of whom with CD, using PET/CT enteroclysis in order to obtain both morphological and functional details. PET/CT enteroclysis detected 50 segments of small and large intestine with a significantly higher detection rate than barium studies and colonoscopy, respectively 16 and 17 segments. Furthermore, this imaging technique detected also extra-intestinal abnormalities and differentiated the active form of disease from the fibrostenotic form, resulting as a non-invasive, feasible and promising technique. Ahmadi *et al.*[53] examined the role of combined [^{18}F]-FDG PET/CTe in active CD. CTe identified 48 abnormal small bowel segments as well as PET, confirmed by correlation between CTe Score and SUV_{max}, suggesting a similar sensitivity of both imaging method and PET may provide additional information to CTe diagnostic data, determining inflammation degrees in abnormal small bowel segments. Also, Groshar *et al.*[54] performed [^{18}F]-FDG PET/CTe in 28 patients with known or suspected CD in order to correlate the CTe Score and SUV_{max} for the assessment of the grade and severity of inflammation in abnormal segments. Results showed the detection of 85 abnormal segments in 22 patients, while 6 subjects had no abnormal segments, with a good directly proportional correlation between SUV_{max} and CTe measurements of mural thickness and enhancement, concluding that SUV_{max} might be a reliable parameter to quantify CD activity. Finally, Shyn *et al.*[55] compared [^{18}F]-FDG PET/CTe with CTe alone with the purpose of evaluating the diagnostic efficacy of two imaging methods in 13 patients with CD, measuring different parameters such as CTe Severity Score, SUV_{max}, simplified endoscopic Score, and clinical parameters correlated with pathology inflammation grade. In 3 patients, PET detected active inflammation and an enterocolonic fistula, not revealed by CTe alone. Then, SUV_{max} was strongly correlated to disease activity, suggesting that PET/CTe might improve the detection and grading of active inflammation in CD patients.

PET/MR in IBD advantages and disadvantages

Hybrid PET/MR scanners are the most advanced, clinically approved devices available for *in-vivo* diagnostic imaging. They acquire simultaneously (coacquisition) or sequentially metabolic data from PET and functional and morphologic information from MR.[56, 57]

In the setting of coacquisition, the PET and MR components of this hybrid technology simultaneously image the same body region, allowing a nearly complete spatial and temporal matching of PET and MR data. This spatial and temporal matching is not achievable by sequential PET/MR scanners neither by PET/CT, with the latter being limited by the necessarily asynchronous acquisition of the PET events and the CT data.[56]

The matching of the PET and MR data translates into the possibility of exploring a queried lesion, for example a thickened bowel loop, with a large array of PET and functional MR (fMR) biomarkers that include, among

others, SUV_{max}, metabolic volume, apparent diffusion coefficient (ADC), volume transfer coefficient (Ktrans). This would be precluded, due to bowel peristalsis and patient movements, in the case of sequentially acquired PET and MR scans.

Secondarily PET/MR coacquisition may symbiotically overcome some limitations of each modality taken apart. In fact, MR provides anatomic information that may improve PET-based quantification; this on the other side might be employed for *in vivo* validation of several functional MR techniques.[58] Moreover, serially acquired high temporal resolution MR data can track and quantitate patient motion allowing for MR-assisted PET motion correction with subsequent reduction in PET related motion artefacts, noise, blurring, and increased contrast.[58, 59]

Another important advantage of PET/MR compared to PET/CT is the reduced radiation burden to the patient. PET/MR allows a 20% reduction in radiation exposure compared to PET/CT, when the CT component is used for attenuation correction only, or up to 60-73% in the case the CT part is employed both for attenuation correction and for producing diagnostic quality CT images.[60, 61]

The geometry of the PET components of the PET/MR scanners, with the resultant increased sensitivity in the center of the PET field of view (FOV), allows reducing activity to up to 30-50% of that required for comparable quality PET from PET/CT.[62]

Moreover, the lengthier times required to acquire MR sequences might be used to prolong PET acquisition, improving the quality of the PET images and/or allowing a lower activity. In a phantom study, increasing bed position time by a factor of 8, from 2 minutes to 16 minutes, allowed reducing to 1/8 (12.5%) the injected activity with PET images displaying same signal to contrast ratio as those obtained from 100% activity while using 2 minutes per bed position.[63]

A major disadvantage of PET/MR compared to PET/CT relies in its limits in quantifying the attenuation exerted by body tissues on the gamma-rays. While in PET/CT the density of the tissues, as measured by CT Hounsfield units, may be used to compute the linear attenuation correction (LAC), this is not the case of PET/MR where the signal intensity of the tissue does not have any direct relations with the LAC. Several techniques have been employed to address this issue, the most effective being tissue segmentation/decomposition and atlas based methods; however, the problem has not been resolved yet.

Another potential disadvantage of PET/MR, compared to PET/CT, is the lengthier acquisition time (23-30 minutes for a Crohn's PET/MR protocol *versus* 12-15 minutes for a Crohn's PET/CT study), with MR acquisition being the time limiting factor. However, to take advantage of the potentialities offered by PET/MR, neither PET nor MR quality must be compromised.

Most of the research efforts in clinical PET/MR have been deployed in neuroimaging and oncologic imaging. In selected indications, PET/MR has been proven advantageous over PET/CT, and also over PET and MR performed separately. For example, it improves staging of central nervous system cancers, detection of satellite brain lesions, residual disease, and evaluation of intra-tumoral heterogeneity.[64-68] In oncologic body imaging PET/MR has been demonstrated to be superior to PET/CT and also to MR in several respects, including evaluation of liver, peritoneal, bone, and lymph node metastases, and whole body staging of different primary cancers; moreover, it can also provide insights into the tumor biology, as in the case of breast cancer.[69-78]

PET/MR has enormous potentialities also in the evaluation of CD. However, it has been rarely used in this disease, with only two research manuscripts available in the literature.[42, 48, 79-81]

PET/MR might increase the diagnostic confidence in assessing patients affected by Crohn's disease. It has been shown that MR enterography, PET/CTe, and PET/MR enterography had similar accuracy in detecting areas affected by CD. However, PET/MR enterography provided additional clinically relevant information due to its increased accuracy in assessing extra-luminal manifestations of the disease, that were associated with higher need for stoma (P=0.022), and also distant localization (P=0.002).[80]

PET/MR enterography was also useful in assessing the dominant nature of strictures. Strictures constitute one of the most important clinical challenges in CD. They occur in about 11% of patients at presentation, and their prevalence increases over time. Moreover, they represent a major cause of morbidity in CD.[45, 82, 83]

While several medical options are available for predominantly inflammatory strictures, the fibrotic ones need to be treated more invasively, by surgery or mechanical dilatation. This pivotal information, however,

is not usually available to the clinicians, due to the limits of current techniques, even in the case of endoscopic biopsy. Therefore, patients are usually treated conservatively first, and in the case of failure, a surgical approach is pursued.[45, 82, 83]

In two very recent PET/MR studies focused on this very specific topic, with surgical pathology as standard of reference, it was found that PET/MR could be useful to differentiate between fibrotic and inflammatory strictures.

PET/MR enterography was more accurate in detecting fibrosis compared with PET/CTe (P=0.043) and with MR enterography (P=0.024).[80]

Among the different PET/MR biomarkers that were investigated, the best discriminator between fibrosis and active inflammation was the hybrid PET/MR enterography biomarker ADC*SUV_{max}, that at a cut-off of less than 3000, was associated with accuracy, sensitivity, and specificity of 71%, 67%, and 73%, respectively.[81]

Due to the possibility to coacquire PET and MR, the technique may potentially benefit from the synergism between the extremely high sensitivity of PET in detecting active lesions (sensitivity 84.5-100%) and the superior anatomic layout, high signal to noise ratio, and functional information provided by MR. The authors of the current study retrospectively investigated the performance of PET/MR *versus* PET alone and *versus* MR alone in assessing active inflammation in CD patients. Of 43 consecutive patients who had undergone PET/MR for CD between December 2012 and July 2016, 32 patients underwent abdominal surgery within 8 weeks from the PET/MR. At the time of the study, operative surgical records were available for 21 of them and they constituted our study population.

Patients fasted for at least 6 hours before PET/MR acquisition. Two hours before scanning they were asked to start drinking at least two liters of a negative polyethylene-glycol based oral contrast solution. Between 80 and 90 minutes before acquisition, FDG at a 40% activity of that suggested by EANM guidelines was injected. Finally, five minutes before the start of the PET/MR acquisition, 20 mg of Joscine N-butilbromure were injected intravenously. Scans were acquired with a simultaneous PET/MR scanner (mMR, Siemens, Erlangen, Germany) starting from mid-thighs upward to the diaphragm. Two body coils (12 channels) were combined to cover the entire abdomen.

The following coacquired PET/MR sequences were coacquired: coronal short time inversion recovery (STIR), axial T2w half Fourier acquisition single shot turbo spin echo (HASTE), coronal T1w Dixon, axial diffusion weighted imaging (DWI). The coacquisition of this part of the study is essential to ensure temporal and spatial matching of the MR and PET data. After completion of the above described coacquired sequences, the following stand-alone breath-hold MR sequences were obtained: coronal T2w HASTE, axial T1w dual gradient echo (GE), dynamic contrast enhanced T1w volumetric interpolated breath hold examination (VIBE). Data were sent to a dedicated workstation (SyngoVia, Siemens, Erlangen, Germany). PET images alone, MR images alone, and combined PET/MR images were randomly presented and analyzed at least 4 weeks apart. For standing-alone PET, PET images were assessed in the coronal and axial plane. For standing alone MR, coronal portal venous phase contrast enhanced VIBE, coronal STIR and coronal T2 weighted HASTE were assessed. For the combined PET/MR assessment, coronal and axial PET images, coronal portal venous phase contrast enhanced VIBE, coronal STIR and coronal T2 weighted HASTE were assessed. MR and PET images were evaluated both before and after coregistration and fusion.

The investigators were not aware of the surgical description but they were informed of the diagnosis of CD and of the occurrence of subsequent surgery.

For the analysis, the gastrointestinal tract was divided into five segments: stomach plus duodenum, jejunum, proximal ileum, distal ileus, and colon. Each segment was classified as acutely inflamed if it satisfied the following criteria, otherwise it was considered negative for acute inflammatory changes:

For PET, focally increased FDG uptake with SUV_{max} >4.

For MR, bowel wall enhancement, increased signal on T2 weighted/STIR images, and brisk post contrast enhancement.

For combined PET/MR images, coexistence of SUV_{max} ≥4 with at least one of the MR criteria reported above.

On the basis of the above criteria of the 105 segments evaluated in 21 patients: 66/105 segments were called positive on PET, 53/105 on MR, and 55/105 on PET/MR.

At surgery 59/105 segments were positive for active inflammation. The true positive segments (TP) were 54 in PET, 47 in MR, 52 in PET/MR; the true negative (TN) segments were 34 in PET, 40 in MR, and 43 in PET/MR; the false positive (FP) segments were in 12 in PET, 6 in MR, and 3 in PET/MR; the false negative segments were 5 in PET, 12 in MR, and 7 in PET/MR.

McNemar Test, with a p value of 0.05, was used to assess for statistical significance.

Sensitivity was 91.5% for PET, 80% for MR, and 88% for PET/MR. While PET was statistically significant more sensitive than MR (P=0.02), no statistically significant differences were found between the sensitivity of PET and PET/MR (P=0.48) neither between that of MR and PET/MR (P=0.08).

Specificity was 74% for PET, 87% for MR, and 93% for PET/MR. The higher specificity of MR and PET/MR, compared to PET, was statistically significant (P=0.04 and P=0.01 respectively). No statistically significant differences were found between specificity of MR and that of PET/MR (P=0.37).

Diagnostic accuracy was 84% per PET, 83% for MR, and 91% for PET/MR. The better accuracy achieved by PET/MR, compared to PET and MR, was statistically significant (P=0.02 and P=0.01 respectively), meanwhile no statistically significant differences were observed between overall accuracy of PET and MR.

In conclusion PET/MR proved to be more accurate than PET alone and MR alone, and more specific than PET alone. PET proved to be more sensitive than MR alone. Therefore, PET/MR might, while coupling the strengths of MR and PET, is capable to overcome some of their limitations and might improve the evaluation of active inflammatory changes in Crohn's disease patients.

The recently published MR Scores in CD (MaRIA *vs.* Clermont Scores and criticisms)

MRI, due to its high sensitivity for tissue inflammation, has been increasingly used to assess CD inflammation and activity during the last two decades.[84-93] Thus far, both MR-specific parameters (T1weigthed Gd-enhancement and T2weighted signal of the intestinal wall, T1-w pattern of Gd-enhancement, T2 mesenteric fat signal, curves of Gd-wall enhancement, DWI-ADC values) as well as morphologic ones (wall thickening, increased mesenteric vascularity or comb sign, mucosa ulcerations, increased local lymph nodes number-enhancement, intestinal complications. disease length) have been successfully correlated to biological, endoscopic or histological indexes inflammation.[86, 87, 89, 91, 92, 94, 95]

By arranging and integrating these parameters, several qualitative and quantitative Scores have been proposed, each one based on similar MRI parameters. Validated quantitative MRI activity Scores include the MaRIA and the Clermont Score.

The MaRIA (Magnetic Resonance Index of Activity) Score, proposed by Rimola *et al.*,[95] is based on the association of two morphologic parameters, *i.e.* wall thickening, mucosa ulcerations, and 2 MRI specific parameters, wall edema (assessed on T2w images only) and relative contrast enhancement or RCE (on T1w post Gd images); on the basis of a logistic regression analysis, all these parameters are linked by a mathematic formula, which is: 1.5*wall thickness + 0.02*RCE + 5*edema + 10*ulceration.

Hardonneau *et al.*[96] proposed the *Clermont* Score, very similar to the MaRIA, but substituting gadolinium injection with DWI (diffusion weighted imaging), by using the quantitative values of the ADC map as an alternative to the the Gd-injection. Authors conclude that Clermont Score (=1.646 × bowel thickness-1.321 × ADC+5.613 × edema+8.306 × ulceration+5.039) was highly correlated with the MaRIA (rho=0.99) in ileal CD, although not in colonic CD (rho <0.80).

Caruso *et al.*[97] recently compared the Clermont Score with the SES (Simple Endoscopic Score) MRE assessed active ileal disease in 31 patients (56.3%). In this study, the Clermont Score significantly correlated with the MaRIA Score (r=0.91; P<0.0001) and the Simple Endoscopic Score for CD (r=0.76; P<0.0001).[98, 99]

An activity Score only has been histologically validated thus far, although based on a limited number of patients,[100] proposed by Steward *et al*.[87] The study showed that mural thickness (coefficient 1.34 [95% CI: 0.36, 2.32], P=0.007) and T2 signal (coefficient 0.90 [95% CI: 0.24, 2.04] P=0.06) are best predictors of the histopathological acute inflammation Score (AIS=1.79+1.34*mural thickness+0.94*mural T2 Score).

Recently, three MRE-based indices have been correlated: the MaRIA, the Clermont and the London indi-

ces.[92-95, 98] According to the authors, the MaRIA Index has the best operational characteristics for detecting not only disease activity but also for grading severity, which supports its use in clinical studies and clinical practice.

Several MRI qualitative Scores for CD activity have been also proposed or published, as an alternative to quantitative ones.

Maccioni *et al.*[101] firstly proposed, in 2010, a qualitative MRI Score for CD activity (Qual-MRI-CDAS) based on the analysis, at the level of the most active intestinal segment affected by CD, of 5 different parameters, each one Scored 1-3 (absent-low: 1; definitely present: 2; markedly present: 3) on T1- T2 w images. These parameters include both morphological and specific MR parameters, as wall thickening, number of local enhanced lymph nodes, T2 weighted signal intensity of the wall, T2 weighted perivisceral fluid/fat edema, T1 weighted early (60 seconds) wall enhancement. The basic Score [84-99] was also corrected according to the extent of the disease and evidence of severe inflammatory complications, thus obtaining a good correlation (Spearman Test) was performed between with the Biological Activity (BA) (r=0.75), with the CD Endoscopic activity index (CDEIS) (r=0.86) and CD Activity index (CDAI) (r=0.75).

A similar Score was also proposed and validated by Prezzi *et al.*,[94] the so-called London Index or MR enterography global Score (MEGS). MEGS represents the evolution of a Score proposed initially by Steward *et al.*,[93] which included the sum of qualitative grades for segmental mural thickness, mural T2 signal (mural edema), mural contrast enhancement and perimural T2 signal. In order to better reflect the global burden of disease (*i.e.* beyond point estimates of segmental activity), the Score was expanded to include segmental disease length, evaluation of colonic haustral loss and evaluation of extra-enteric complications, such as enlarged mesenteric lymph nodes, abscesses and fistulae. MEGS has been validated prospectively against stool calprotectin, blood C-reactive protein (CRP) and the Harvey-Bradshaw Index, with satisfactory results.

The advantages of qualitative indexes rely on the easier application and more comprehensive assessment of the disease extent and severity; the main limitation is the subjectivity of the evaluation.

Undoubtedly, both, qualitative and quantitative Scores, to be correctly applied, strongly depend on the experience of the radiologist on MRE and CD imaging.

Interestingly, Rimola *et al.*[99] have recently proposed the characterization of both inflammation and fibrosis in CD lesions using MRI. To do this, they evaluated the already known unenhanced parameters of the Maria Score, (wall thickening, edema, ulcers) plus signal intensity at submucosa at 70 seconds and 7 minutes after gadolinium injection, stenosis, and pattern of enhancement in each phase of the dynamic study, and changes on this pattern over time. By adding those parameters, MRI was able to discriminate between mild-moderate and severe fibrosis deposition with a sensitivity of 0.94 and a specificity of 0.89.

Recently, three MRE-based indices have been correlated: the MaRIA, the Clermont and the London indices.[92-94, 98, 100] According to the AA, the three indexes have an overall high accuracy. The MaRIA index has the best operational characteristics for detecting not only disease activity but also for grading severity, which supports its use in clinical studies and clinical practice. The Clearmont has the advantage to be free from gadolinium injection. The London index was "somewhat better than the other two for classifying segments as active or inactive".

Finally, a recent study from Pendsé *et al.*,[100] suggest a possible use of DWI for a qualitative rather than quantitative evaluation of CD. The authors reported that "the quantitative measurement of ADC in bowel is often difficult due to the relatively thin bowel wall, given the typical image slice thickness (normal bowel wall 1-2 mm, typical DWI slice thickness 5-8 mm). Bowel peristalsis during image acquisition introduces further error".

In conclusion, an ideal MRI activity index Score still does not exist. The several available Scores are all valuable, some of them have been validated *versus* clinical and endoscopic Cd activity Scores, although none has been fully validated with histopathological specimens.

Our proposed interpretation criteria for PET/MR

When reading PET/MR in CD patients, at first, we evaluate the coronal reconstructed PET, coronal STIR, and coronal portal venous phase contrast enhanced VIBE, before and after having been coregistered and fused with PET. The assessment of this set of images is useful, in our experience, to rapidly identify potential segments of active disease, and grossly estimate the

inflammatory burden. Thereafter, all the other MR sequences are evaluated before and after fusion with PET.

At first, we focus our attention on PET to detect positive areas. We call a bowel loop as actively inflamed in the case of focally increased FDG uptake, with an SUV_{max}>4, in association with at least one of the following MR signs: wall thickening (>3 mm), mural edema as seen on T2 HASTE/STIR, engorgement of the vasa recta, intense contrast enhancement.

In the case a focal area of increased FDG uptake is not associated with any of the above MR signs, we consider that as PET false positive for active inflammation. Similarly, absence of marked FDG uptake in thickened and enhancing bowel loops, rules out, in our experience, active inflammation.

After these steps, we focus on the coronal portal venous phase VIBE and on the coronal T2weighted HASTE to search for areas of bowel distension that might point to potential strictures. If we identify a potential stricture we ensure that the findings persist on all the sequences and that there is a good coregistration of the PET and ADC maps to measure the corresponding $ADC*SUV_{max}$. In the case of $ADC*SUV_{max}$ values <3000 we classify that stricture as predominantly fibrotic.

Obviously, beside searching for areas of active inflammation and for strictures, we also assess the entire GI tract for stigmata of non-active and non-stricturing CD, in particular we rely on the MR sequences to detect lipomatous hypertrophy, pseudo-sacculations, and areas of bowel wall thickening. Last but not least we search for signs of sacroileitis.

Conclusions

From the present review, it is possible to note that the future to assess the CD activity is represented by the multimodality imaging, including SPECT/CT, PET/CT and PET/MR, provided there are more specific radiopharmaceuticals than FDG. The development of new radiopharmaceuticals for CD would result extremely important for the early diagnosis, therapy decision-making and therapy follow-up, using the best evaluation Score for the extent and activity of bowel inflammation, especially when endoscopic approach is not available.

All published Scores have some disadvantage and we propose a novel interpretation criteria for PET/MR images.

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