FDG-PET/CT in Inflammatory bowel disease – Is there a future?

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Key Points
- FDG-PET/CT has shown promise in inflammatory bowel disease with generally good sensitivity and specificity in various settings, but its overall role is controversial
- Many issues remain unresolved and there is no consensus on imaging protocol in the literature – more studies with stringent methodology are needed
- Combining FDG-PET with CT or MR enterography yields more information than either exam alone
- At present the most promising roles are assessment of early treatment response and stricture characterization, whereas general use in the initial diagnostic workup should be reserved for equivocal cases.

Synopsis

FDG-PET/CT has potential in inflammatory bowel disease – the literature generally presents good sensitivity and specificity in various settings. At present, the most promising roles are assessment of early treatment response and stricture characterization, whereas general use in the initial diagnostic workup should be reserved for equivocal cases for the time being. However, it is challenging to image the moving and physiologically active bowel with FDG and the available literature is far from ideal; studies are generally small, and methodologies are highly variable with regards to imaging parameters, clinical features, treatment regimen, and reference standards. Thus, several issues remain unclarified, and further data is needed to make firm conclusions on the role of FDG and PET/CT in inflammatory bowel disease.

INTRODUCTION

Crohn’s disease (CD) and ulcerative colitis (UC) belongs to the group of chronic inflammatory bowel diseases. The etiology is unknown, but is thought to arise from a dysregulated interaction between the gut microbiome and the mucosal immune system in a genetically predisposed individual.

In CD, the inflammation is transmural and granulomatous, the distribution is typically segmental, and the entire gastrointestinal tract may be involved – from mouth to anus. Most frequently, the disease is located to the terminal ileum and right colon (ileocecal CD). In approximately one third of patients, the disease is located to the small intestine, and one third has CD restricted to the colon.

In contrast to CD, UC is restricted to the colon, the inflammation is extending from the rectum and the inflammation is submucosal and non-granulomatous.

Clinically, CD and UC are both characterized by recurrent disease activity and a strong tendency to relapse after remission has been achieved with medical treatment or surgical resection. A small proportion of patients experience continuous disease activity. Current guidelines for diagnosing CD and UC suggest ileocolonoscopy with multiple biopsies from the terminal ileum and each colonic segment as the first diagnostic examination. However in the case of CD, irrespective of the findings at ileocolonoscopy, further investigations are recommended to establish the location and extent of any CD in the upper small bowel. Furthermore, the disease pattern of recurrence and relapse as well as the assessment of treatment response necessitates repeated exams.

Ileocolonoscopy is regarded the gold standard for diagnosing CD located in the colon and terminal ileum. However, the examination is invasive, associated with patient discomfort and a small risk of colonic perforation. Furthermore, a complete ileocolonoscopy is not always possible. Thus, the need for non-invasive, patient friendly and reliable exams is in great demand. In recent years, technological
advances have improved non-invasive modalities especially for diagnosing CD. The main modalities are magnetic resonance imaging (MRI), computed tomography (CT), ultrasound, and capsule endoscopy. The latter modalities have all been showed in numerous studies to have a rather good sensitivity and specificity in terms of finding Crohn’s lesions in the small bowel. The latter cross-sectional modalities are rather good, but they are not perfect and their results is primarily founded on structural changes — although contrast enhancement, doppler measurements and diffusion waited MRI does give some clues about vascular status, and hereby an indirect sign of inflammation.

Positron emission tomography using the radioactive glucose analogue 18F-fluorodeoxyglukose (FDG-PET) has been available for decades and since it has been combined with CT or MRI it is now a days a very well established tool in many fields especially oncology. In the field of IBD it is not yet a well-established procedure, and in the recent European guidelines FDG-PET is not recommended for diagnostics in IBD due to lack of evidence. However, FDG-PET is unlike the structural/anatomical exams (CT, MRI, bowel ultrasound and capsule endoscopy) a functional test of metabolic activity. Combining FDG-PET with either CT or MRI produces a non-invasive imaging modality combining a metabolic assessment of pathophysiological processes with precise morphological correlation. This combination has been shown to be useful in the field of IBD diagnostic.

The purpose of this review was to present the current status on the use of FDG-PET/CT in IBD based on available literature.

OPTIMIZING THE SCAN
Besides the general issues with 4-6 hours fasting and refraining from strenuous physical activity for 24 hours before the exam, there is no definite consensus on patient preparation prior to FDG-PET of the bowel; the different studies utilized different protocols which to a high degree was dependent on whether FDG-PET was combined with CT or MRI. Several factors need to be addressed, amongst others peristalsis, indigenous bacterial flora, and active mucosal lining can all result in increased physiological FDG uptake, that may hamper visual interpretation of FDG PET bowel uptake and potentially lead to inaccurate recording of standardised uptake value (SUV) measurements. Torihara et al. highlighted this issue as a possible confounder of bowel activity in a study of 61 participants without known bowel disease: the frequency of foci with uptake equal to or higher than the liver was notable, i.e. 10% of examined segments exclusively in the colon.

One possible way to reduce intense physiologic bowel uptake arising from peristalsis is administration of the antispasmodic drug N-butylicopolamine (eg. Buscopan), a drug commonly used in radiology to reduce motion artefacts of the bowel during MRI. In a study from 2008, Emmott et al.
improved accuracy of FDG-PET reporting by significantly reducing artefacts in the bowel during FDG-PET by injection of 20 mg Buscopan 1 minute before FDG administration 11, whereas Miraldi et al. reduced artifacts through colon cleansing with an isosmotic solution taken the evening prior to examination 12.

Some protocols suggest improving interpretation by optimizing bowel distention, e.g. water as a negative CT negative contrast agent 13, or mannitol like in most MRI exams 14. Zhang et al. found oral negative contrast agent and hypotonic bowel preparation decreased the physiological intake of FDG, increased the distention of the gastrointestinal tract with an overall improvement of image quality 15.

Finally, it is well-known that the widely used anti-diabetic metformin may diffusely increase FDG uptake in the small bowel and colon, albeit through unknown mechanisms. The effect is significantly reduced if the drug is stopped for 3-5 days before the exam. 16

PET PERFORMANCE

FDG has been available for almost 50 years now 17, and combined with PET is has become part of the recommended diagnostic workup strategy in most malignant diseases and dementia over the last two decades 18. Routine application has also increased within the field of infectious and inflammatory diseases, especially in whole-body ailments like fever of unknown origin and large-vessel vasculitis 19. The use of FDG-PET in the field of IBD is however not as well founded. Although the first case report on the subject was published more than 20 years ago 20, the evidence and potential role of FDG-PET in IBD remains controversial.

In terms of diagnostics in IBD, an important distinction is between primary diagnosis and monitoring disease activity; some studies are available on primary diagnosis in patients with Suspected IBD, but the main focus in the literature are on monitoring. This is perhaps not surprising as the abovementioned physiologic uptake may conceal true positive lesions as well as give rise to false positive findings. Also, as the final diagnosis is based on histopathology, endoscopy is required anyway. It would however be desirable with a non-invasive imaging method with a more physiologic approach as an adjunct to the mainstay morphologic modalities for surveillance purposes.

FDG-PET in patients suspected of IBD.

In 1997, Bicik et al. reported on the use of FDG-PET in 7 patients with suspected IBD using endoscopy and histology as the gold standard 20. They showed high PET activity in areas with macroscopic disease as well as in areas of active inflammation on biopsy in the absence of macroscopic disease in 6 of 7 patients (2 UC and 4 CD). The authors concluded FDG-PET might be a useful tool as a noninvasive means to identify active inflammation in IBD.
Perhaps not surprising, the potential of PET as a non-invasive primary diagnostic has been explored in pediatric settings. In 1999, Skehan et al. reported the use of FDG-PET in 25 pediatric patients (mean age 13) with suspected IBD; colonoscopy and/or small bowel series was gold standard. A total of 18 patients were identified with IBD – 15 with CD and 3 with UC. FDG-PET correctly identified 60 of 79 (76%) possible regions with sensitivity for identifying inflammation of 71% and a specificity of 81%, whereas the overall patient-based values were 81% and 85%, respectively. The authors concluded that FDG-PET could be a useful adjunct if conventional studies are technical unsuccessful. However, in a significant proportion of patients colonoscopies were incomplete and PET detected more proximal lesions in 80%. A retrospective study from 2006 by Loeffler et al. included 23 pediatric patients with suspected IBD of which 17 cases had CD and 2 cases had UC as the final diagnosis. Of the 23 patients 18 had a corresponding colonoscopy within 10 days of the FDG-PET, albeit no colonoscopy completion rate or inclusion criteria were reported. The overall sensitivity of FDG-PET was 98% (57/58) and the specificity was 68% (40/59) when compared with histology. When compared with endoscopy there was a sensitivity of 90% and a specificity of 75%. The author’s reported the FDG-PET was even more accurate in the small intestine.

In 2007, Das et al. made an effort to improve the CT part of the PET-CT by combining the PET with CT enteroclysis. Of the 17 patients included in the study 15 of had an ileocolonoscopy and all had other radiologic evaluation as per standard of care, i.e. the gold standard was endoscopy, radiology, or both. The final diagnoses included CD (n=9), intestinal tuberculosis (n=5), tropical sprue (n=2), and celiac disease (n=1), and no subgroup analyses was performed with CD alone. They concluded that PET-CT enteroclysis as a single investigation detects a significantly higher number of lesions both in the small and large intestine in comparison to that detected by conventional barium and colonoscopy combined together. Also, this was the first study to report extra-intestinal findings (i.e. sacroiliitis and lymphadenopathy) and suggest this to be a potential advantage of whole-body PET over conventional imaging.

FDG-PET in patients with known IBD

Whereas the evidence for the use of FDG-PET in the primary diagnostic setting is rather scarce, the use in patients with known disease is better studied. Again, the early studies were stand-alone PET.

Starting in 2002, Neurath et al. studied the use of FDG-PET in a prospective setup, with 59 (+12 controls) patients with chronic active CD, using colonoscopy (28/59), MRI or antigranulocyte scintigraphy in comparisons. For the detection of inflamed segments of the small and large bowel segments, PET was found to have a sensitivity of 85%, higher than Hydro-MRI (41%) and antigranulocyte scintigraphy (67%), with a specificity of 89% compared with 93% and 100% for Hydro-MRI and
antigranulocyte scintigraphy, respectively. Neurath et al. concluded that FDG-PET appeared to be a reliable noninvasive tool for simultaneous detection of inflamed areas in the small and large bowel of patients with CD. It is however worth considering that sensitivity and specificity was based on only 28 (45%) with colonoscopy (45/127 lesions) and 24/127 lesions detected with PET were in areas inaccessible to endoscopy and thus not further classified.

In 2005, Lemberg et al. enrolled 65 children in the first and to date only prospective case-control study; 55 children (aged 7-18 years) with newly diagnosed IBD (n=37) or symptoms suggestive of recurrent disease (n=18), and as controls 10 children with recurrent abdominal pain (aged 8-15 years). All had PET scans, and the results were compared with small bowel follow-through with pneumocolon and/or colonoscopy. They found 38 patients had CD and 17 had UC. In patients with CD, compared to colonoscopy PET correctly identified the presence of inflammation in one segment in 90% of cases with a specificity of 50%, although the study was limited by the poor intubation rate of the terminal ileum. In the patients with UC PET identified inflammation in at least 1 bowel segment correctly in 14/17 cases leading to a sensitivity of 81% when compared with colonoscopy. Furthermore, PET was correctly without evidence of inflammation in children with recurrent abdominal pain. Lemberg et al. concluded that PET may not be able to replace conventional studies, but give a noninvasive tool for identifying and localizing active intestinal inflammation in children with IBD. However, several caveats pertain to this study: Several issues may have contributed to the rather poor sensitivity, e.g. a gap between PET and reference standards of as much as 62 days together with anti-inflammatory treatment being initiated may have inadvertently lead to false-negative findings. Furthermore, three fibrotic stenosis not detected by PET were also considered false-negative, although FDG is not taken up by metabolically inert fibrosis in contrast to inflammatory stricture. On the other hand, colonoscopies were only sufficient in half of the patients and inflammatory lesions proximal to the colonoscopies were classified as false-positive which may have contributed to the poor specificity.

*Hybrid-PET/CT*

The introduction of combined hybrid PET-CT opened up new possibilities and in 2007, two such studies were published. One included both UC and CD, the other only CD, both was compared with colonoscopy. In the study by Meisner et al. PET activity was seen in 13/24 (52%) regions in patients with UC and 19/32 (59.4%) regions in patients with CD. There was high correlation between PET activity and disease activity as determined by colonoscopy, disease activity indices, and radiology (in UC 23/24 (96%); in CD 26/32 (81%))

24. It is worth mentioning, though, that PET only assessed the ileocolonic area although CD may affect the entire GI-tract. In the study by Louis et al. 22 patients with active CD was included. All had colonoscopy,
although in 5 cases strictures caused colonoscopy to be incomplete. A total of 48 lesions was found at colonoscopy and PET-CT found 35 of the affected segments, leading to a sensitivity and specificity of 73% and 55%, respectively, in terms of finding endoscopic visible lesions. They found sensitivity to be improved in cases with severe endoscopic lesion. Also, CT found signs of inflammation in PET-positive areas not detected by endoscopy, which raises the possibility that the poor specificity due to false-positive scans may be incorrectly low if some of these lesions were in fact true positives.

The focus on optimizing scan and the value of combining FDG-PET with CT was investigated by several groups in 2010. Groshar et al. published the use of FDG-PET and CT enterography (CTE) in 28 patients with known or suspected CD. They found good correlation between SUVmax and mural thickness and a significant difference between SUVmax in normal vs. abnormal segment. The study also illustrated the challenge with colonoscopy – 63% of patients with a normal colonoscopy exhibited abnormal segments on CTE.

In a retrospective study Ahmadi et al. evaluated 41 PET/CTE scans of patients with known CD. Here 38 of 48 abnormal bowel segments on CTE had increased FDG uptake. FDG-PET did not identify additional segments not identified by CTE, but abnormal segments on CTE without increased FDG uptake were associated with failure of medical therapy (P=0.001) – hence the authors conclude that this might help identify patients at high risk of failing medical treatment.

In a prospective study by Shyn et al. with 13 known CD patients CTE and PET-CTE was compared, using endoscopy (n = 7) or surgery (n = 6) as reference. The combined 18F-FDG PET/CTE did not detect diseased bowel segments that were not already evident on CTE alone. CTE alone and combined PET/CTE both detected 100% of bowel segments with more than mild disease activity; the specificity was 90% - thus, FDG was better at detecting moderate-to-severe lesions than mild lesions. The combined scan also discovered an enterocolonic fistulae that otherwise would have been missed.

In a publication from Das et al. FDG-PET is combined with CT-colonography in 15 patients with active UC using colonoscopy as reference standard. There was a good correlation between SUVmax and endoscopic activity level when compared (κ = 55.3%, p =0.02). Six patients had a one-to-one correlation between PET and endoscopy activity grades, and in seven patients FDG-PET/CT revealed extra-intestinal findings. The authors did not elaborate on colonoscopy success rate, and incomplete colonoscopy could explain the discrepancies.

Finally, Holtmann et al. compared FDG-PET/CT to MRI in 43 patients using colonoscopy as reference standard. In a total of 241 segments 80 showed endoscopic activity, and 72 (sensitivity 90% and specificity 92.6%) and 53 (sensitivity 66% and specificity 99%) was detected by FDG-PET and MRI.
respectively. In 2012, Treglia et al. published a meta-analysis of 7 studies enrolling a total of 219 patients. They found a pooled per-segment sensitivity of 85% and specificity of 87%.

**Structures**

One of the troublesome issues when treating patients with CD is obstructive disease, since strictures that are primarily of inflammatory nature can be treated with medicine, whereas primarily fibrotic strictures is only treatable with surgery. Several studies have tried to utilize FDG-PET to establish the underlying etiology of strictures in order to predict the right treatment strategy. Thus, the abovementioned study by Holtmann also focused on stenosis in a subset of patients. They employed stand-alone PET only, but confirmed inflammation in 16/17 stenoses with one false-negative finding.

Jacene et al. tried predicting the need for surgical intervention in obstructive CD by FDG PET/CT in 17 patients scheduled to undergo surgical resection due to obstructive symptoms. Twelve of 13 patients who underwent surgery had pathologic correlation with the predominant histopathology being inflammation (n=5), fibrosis (n=4), and muscle hypertrophy (n=3), but in all patients there was significant overlap of the histological features. Of the 12 patients, ten were considered to have active inflammation by visual assessment of PET-CT. When a cut-off value was applied to maximum standardized uptake value corrected for lean body mass (SULmax), a value of > 8 predicted inflammation with a sensitivity of 60% and a specificity of 100%. SULmax was also significantly higher in severe vs. mild-to-moderate inflammation, and no patient with predominantly fibrotic or muscle hypertrophic stenosis has SULmax values > 8. The authors concluded that stenosis in CD usually comprise a continuum of inflammation, fibrosis, and muscle hypertrophy, and although FDG-PET could not consistently differentiate between active inflammation, fibrotic stricture and muscular hypertrophy it may help clinicians decide on treatment strategy with the combination of visual/qualitative and semi-quantitative assessment.

In a prospective setting, Lenze et al. compared the diagnostic accuracy of MRI, FDG-PET/CT and ultrasound. No single modality was superior compared to the others for detection and differentiation of strictures in 30 CD patients with 37 CD-associated strictures (22 inflamed, 12 mixed, and 3 fibrostenotic), but a combined diagnostic approach using FDG-PET/CT or MRE combined with ultrasound resulted in a 100% detection rate of symptomatic strictures requiring interventions. However, there were only three patients with fibromatous strictures in the study and the gold standard was an unvalidated scoring system combining endoscopy and histology rather than surgical specimen as in other studies.

**Response evaluation**
As functional test of metabolic activity FDG-PET may help predict response to treatment faster and more reliable than conventional cross sectional imaging.

In 2010, Spier et al. conducted a small pilot study on 5 IBD patients (3 CD and 2 UC) with FDG-PET before and after treatment. Each patient had five bowel segments scored (0–3) for FDG uptake with the liver as reference. After an average of 437 days (range 77–807) the post treatment PET/CT scan was performed. All patients showed significantly improved physician global assessment scores (p=0.004). The total PET score of all segments was 32 pretreatment and 14 posttreatment (p<0.01). Of 11 pretreatment active segments, nine (82%) segments became either inactive or displayed decreased activity, while two showed no change (p<0.001). The authors concluded that FDG-PET score decreased with successful treatment of inflammation in active IBD and correlated with symptom improvement. However, several severe caveats pertain to the study; the study included only patients with colonic disease, treatment regimens differed and the gap between pre-treatment and post-treatment scan was long and highly variable.

In 2016, Russo et al. assessed the utility of FDG-PET as a marker of progression of inflammatory activity and its response to treatment in patients with CD. Twenty-two patients with known active CD and scheduled to start anti–tumor necrosis factor alpha (TNFa) treatment were recruited prospectively to undergo FDG-PET scanning pre-treatment and 12 weeks post-treatment. All 22 patients’ index scans were used to assess sensitivity and specificity against a reference standard MRI measure (MaRIA). The sensitivity and specificity of FDG PET were 88% and 70%, respectively, which correlated well with previous studies. Of the 22 patients included, 17 completed the post-treatment scan and SUV-based PET results correlated significantly with C-reactive protein and Harvey-Bradshaw Index in cross-sectional and longitudinal analyses. There were significant differences in clinical responders compared to non-responders in terms of reduction in SUV-related measures. Surprisingly, there were very poor correlations to fecal calprotectin, which is one of the standard tools in the follow-up of CD patients. The authors concluded FDG-PET might be useful for longitudinal monitoring of inflammatory activity in CD.

In 2017, Epelboym et al. studied the possibility of utilizing low dose FDG-PET to predict treatment response to anti-TNFa treatment in 8 patients with known CD. All patients had clinically active CD and were planned to start biologic treatment. An index FDG-PET was performed within a week before the first dose of anti-TNFa, and the second scan was performed after 2 weeks before the second dose of anti-TNFa. A positive-response scan was characterized as one with at least 30% decrease of FDG activity in the most FDG-avid bowel loop. Of eight enrolled patients, seven displayed a decline in FDG avidity at 2 weeks. Five of them were determined to have a clinical response and to be in steroid-free remission at weeks 8, 26, and 52. However, 2 of the 7 patients with reduced FDG activity were determined to not have a
clinical response but did display an interval decline in the biochemical inflammatory marker CRP at 8 weeks. One patient with no decrease in FDG avidity did not display any clinical or biochemical response, and no steroid-free remission at any follow-up time points of anti-TNFα therapy following the first FDG-PET. The study was limited by size, but it does shown that low-dose FDG-PET/CT has the potential to monitor early treatment response and predict clinical response in patients with active CD prior to a second dose of anti-TNF therapy. Further and larger studies are needed to make more firm conclusions on whether a lack of PET response prior to second dose predicts anti-TNFα failure in patients with CD.

In 2017 Palatka et al. utilized FDG-PET to evaluate treatment response in 12 CD patients before and 1 year after Anti-TNFα treatment. All patients had colonoscopy as a reference. They describe a clearly visible difference in terms of inflammatory sites on PET. However, changes in the global PET score used to express activity of CD as a single number was not significantly different in various settings, except in a subgroup of patients with a high initial score. In clinical and endoscopic scores the change was significant. This corresponded to other studies where high initial activity on FDG-PET is a predictor of response. In this setup, the use of the PET-score was questionable since it only showed significant results in the subgroup with the most severe baseline inflammation, but the study was limited in size.

**Novel approaches – quantification and PET/MRI**

Despite the widespread acceptance of SUV-based parameters also among clinicians, it is well known to the nuclear medicine community that this methodology has its shortcomings; standardized protocols are pivotal to reduce the many potential pitfalls both technical and patient related and to this effect novel quantification methods are being explored.

In a publication from 2014, data from a prior prospective study were used to test the feasibility of novel volume-based quantification methods to measure more globally the degree of inflammation in CD based on FDG PET. To access global inflammation, all pathologic lesions has to be summed up in a single number and preferentially so by using partial volume corrected (PVC) value of total glycolysis in all lesions (i.e. total lesion glycolysis; TLC) by summing mean values of SUV. Thus, a global CD activity score (GCDAS) was calculated as the sum of PVC-TLG over all clinically significant FDG-avid regions in each subject. GCDAS significantly correlated with CDAI and fecal calprotectin ($r = 0.64$ and $r = 0.51$, respectively; $p < 0.05$). A drawback to this method is that it is time consuming and requires strictly standardized protocols.

Barry et al. showed in a study of 60 patients with known UC the correlation between MAYO score and FDG uptake. Rectal PET activity showed a significant correlation with the Mayo score ($k = 0.465$, $p < 0.001$), endoscopic subscore ($k = 0.526$, $p < 0.001$), histological score ($k = 0.496$, $p < 0.001$), and FC
(k = 0.279, p = 0.031). Extent evaluation by FDG PET-CT and colonoscopy showed a significant correlation (k = 0.582, p < 0.001).

Over the past few years attention has turned to the possible role of FDG-PET/MRI scanners, which has the potential to not only combine the good image qualities of MRI, a well-known tool in IBD, with the functional component of FDG-PET, but also to reduce the radioactive burden. In a prospective pilot study enrolling 21 patients with known CD, Domachevsky et al. found that adding apparent diffusion coefficient (ADC) and metabolic inflammatory volume (MIV) to MaRIA score resulted in an AUC of 0.92 (compared to MaRIA alone with an AUC of 0.63) resulting in 83% sensitivity and 100% specificity.

In another study on PET/MRI in 50 patients with known CD, Li et al. showed wall thickness and the comb sign to be the most important parameters for detecting segments with active inflammation of any type. In terms of quantification, SUVmax ratio from PET was the most important parameter for detecting severely inflamed segments with ulceration. Finally, in a recent paper, Li et al introduced a PET/MRI index defined as (0.87 × wall thickness) + (1.97 × edema) + (0.83 × ulceration) + (0.55 × SUVmax ratio) + 1.14. When PET/MRI index was compared to MaRIA score, sensitivity was comparable (0.855 vs 0.894 p > 0.05) but specificity was better with the PET/MRI Index, i.e. 0.933 vs. 0.711, P < 0.001, respectively. The author concluded the PET/MRI index to yield significantly improved specificity and diagnostic accuracy compared with conventional MR indices (MaRIA and the Clermont score).

PET/MRI has also been assessed for the evaluation of the aforementioned stenosis. In 2016, Catalano et al. compared MRI, FDG-PET and hybrid PET-MRI in terms of evaluating fibrotic strictures, using surgery as standard of reference. Combined PET-MRI was better than either exams alone. Best discriminator between fibrosis and active inflammation was the combined PET/MR enterography (MR-E) apparent diffusion coefficient × SUVmax cutoff of less than 3000, which was associated with accuracy, sensitivity, and specificity values of 0.71, 0.67, and 0.73, respectively. Pellino et al showed PET/CT-E, PET/MR-E, and MR-E were equally accurate in detecting CD sites in a study enrolling 35 patients with known CD. PET/MR-E was found more accurate in detecting fibrotic components compared with PET/CT-E [p = 0.043] and with MR-E (p = 0.024). In conventional MRI fibrosis was more frequently classified as inflammation compared with PET/MR-E (p = 0.019). After reviewing the PET-MR-E, 6/8 patients with predominantly inflammatory CD who received medical treatment remained surgery free (median follow-up of 9 (6-22) months).

**DISCUSSION AND FUTURE PERSPECTIVE**

Although FDG-PET/CT in IBD generally displays good sensitivity and specificity in different settings, many unanswered questions remain and more evidence is needed. With continuous improvement of MRI and
ultrasonography these modalities continue to be the standard of care in most parts of the world. Internationally, a more widespread use of PET/CT as a universal, first-line modality for routine clinical practice is limited by availability, cost, and an appreciable radiation burden. The latter is especially important in IBD patients since most are diagnosed at a young age and often require repeated scans; the radiation reducing potential of PET-MRI and improved state-of-the-art PET/CT scanners is promising in this respect. Nonetheless, if FDG and PET/CT is to have a role in the future, it needs to provide information not otherwise obtainable by MRI, ultrasound, or capsule endoscopy or as an adjunct in difficult cases. The available literature points towards several areas of potential, i.e. early response evaluation especially in the setting of biologic treatment, assessment of strictures to guide treatment strategy, and diagnosis of extra-intestinal disease. However, the literature is far from ideal; studies are generally small, with highly variable methodologies both with regards to PET/CT, clinical parameters, treatment regimen, and reference standards. Thus, direct comparison or pooling of data is severely hampered. Add to this the intrinsic challenges of imaging the bowel, a moving organ with intrinsic physiological activity and susceptible to the effect of several extrinsic factors. Perhaps novel PET tracers with different or complementary properties could become a future game changer, but until now none have been translated to human imaging.

With regards to reference standard, it is a striking feature of several studies that a significant proportion of included patients do not complete a full endoscopic examination (if such data are presented at all). A potential feature of PET/CT is the ability to detect disease proximal to endoscopy, but such lesions are often classified as false-positives or excluded from data analysis even though they may represent true positive findings. Perhaps we also need to realize that that a direct comparison between the morphologic and the functional modalities is far more difficult than usually appreciate with the dichotomous approach of most studies. Louis et al. ¹³ suggested that a large proportion of “false-positive” lesions on endoscopy may have contained sub-endoscopic features of activity either on histology or involving deeper bowel layers. This may be supported by a case report from Parbo et al. on a young boy with UC on anti-TNFα treatment who was clinically declining despite of a normal colonoscopy. CT showed only discretely thickened walls of the colon, and small bowel capsule endoscopy showed no signs of inflammation. FDG PET scan was performed and revealed avid FDG uptake in the entire colon. An additional colonoscopy only indicated light disease activity inconsistent with the clinical presentation. A total colectomy was performed and subsequent pathological examination of the colon showed multiple crypt abscesses under a healed mucosa ⁴⁶. This could also explain why FDG-PET in a study Rubin et al. found inflammatory activity in the colon despite negative endoscopic, histology, and symptom assessment in 4 of 10 patients with known UC ⁴⁷.
CONCLUSION

To answer to the question we pose in the title of this overview: Yes, we strongly believe there is a future role for FDG-PET/CT or FDG-PET/MRI in IBD. At present, most promising is the assessment of early treatment response and stricture characterization, whereas use for in the initial diagnostic workup should be preserved for equivocal cases for the time being. However, there is a dire need for structured, well-designed prospective studies with strict protocols for patient preparation, imaging and registration of clinical parameters and treatment regimens.

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