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^{18}F-FDG positron emission tomography: potential utility in the assessment of Crohn's disease

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Abstract

Computed Tomography Enterography (CTE) and Magnetic Resonance Enterography (MRE) are currently the dominant imaging tests used in the assessment of patients with Crohn's disease. More recently, the possibility of utilizing F-18 fluorodeoxyglucose (18F-FDG) Positron Emission Tomography (PET) or PET/CT has been explored in several preliminary studies. 18F-FDG PET appears to enable reliable detection of moderate to severe inflammation in bowel segments involved by Crohn's disease. Perhaps more importantly, 18F-FDG PET has the potential to provide a noninvasive, quantitative measure of inflammation that dynamically reflects changes in Crohn's disease activity. If 18F-FDG PET proves useful in monitoring responses to medical therapy within a few days of therapy initiation, an important new role for imaging in the management of patients with Crohn's disease could emerge.

Key words: Crohn's disease—Positron emission tomography—Computed tomography

Crohn's disease is an inflammatory bowel disease of incompletely understood etiology; however, the complex interactions of host immunity and normal bacterial flora in the gastrointestinal tract are increasingly thought to play an important role in the pathogenesis of this typically progressive and incurable disease [1]. The prevalence of Crohn's disease is estimated to be 26.0–298.5 cases per 100,000 persons in North America and the annual incidence is estimated at 3.1–14.6 cases per 100,000 person-years [2].

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After a diagnosis of Crohn's disease, two-thirds of patients are, on average, in clinical remission, while one-third are suffering from moderate-to-severe activity disease [3]. The natural history of the disease often progresses to include strictures, fistulas, and abscesses. Up to 80% of patients will require surgical management at some point in their lives [4, 5]. Unfortunately, surgery is not curative, with almost all patients eventually recurring and 20–70% requiring repeat surgery [6, 7].

Crohn's disease has a predilection for ileocolonic involvement, although any portion of the gastrointestinal tract may be involved, often with skip areas of relatively normal bowel separating diseased segments. Interestingly, the anatomic distribution of diseased bowel segments tends to change little over time, with a change in distribution being noted in only 10–15% of patients 10 years after diagnosis [8].

Conventional imaging in Crohn's disease

Indications for imaging tests in patients with known or suspected Crohn's disease include helping to establish a diagnosis, determining the extent and distribution of disease, evaluating potential complications, guiding percutaneous therapies, and assessing disease activity in terms of inflammation. The diagnosis of Crohn's disease is based on the constellation of clinical history, laboratory tests, imaging findings, endoscopy findings, and pathology results. Imaging findings that are particularly suggestive of Crohn's disease include involvement of the terminal ileum with or without colonic involvement, evidence of transmural disease, greater severity along the mesenteric border of bowel loops, presence of skip areas, fibrofatty proliferation, and fistulizing disease including perianal fistulas.

Fluoroscopic barium studies such as the small-bowel-follow-through and enteroclysis provided the foundation

for diagnostic imaging of Crohn's disease before the development of computed tomography enterography (CTE) and magnetic resonance enterography (MRE). Barium studies are effective in identifying abnormal bowel segments based on mucosal ulcerations, fissuring, and cobblestoning, as well as the presence of stricturing and tethering of bowel loops. Fistulas can be identified as can obstruction with proximal dilation. Most extraluminal abnormalities are inferred by the appearance of separation of bowel loops or extrinsic mass effect.

Computed tomography enterography and more recently MRE have largely supplanted the fluoroscopic techniques because of their robust capability in identifying all of the above findings as well as providing detailed visualization of the bowel wall and extraenteric findings [9–12]. Mural thickening, mural enhancement with or without stratification, abscesses, hyperemia, fibrofatty changes, and even other associated findings, such as cholelithiasis, urolithiasis, cholangitis, and sacroiliitis, are all demonstrated with CTE or MRE. This multifaceted assessment including superior morphologic detail assures a continued important role for CTE and MRE in the diagnosis of Crohn's disease.

One of the most important roles of imaging in patients with significant symptoms, either at the time of initial diagnosis or during a clinical flare of known Crohn's disease, is the detection of complications that may contraindicate colonoscopy or direct further clinical management. CTE and MRE are the ideal imaging modalities for detecting abscesses, localizing the abscesses in relation to specific bowel loops, determining the feasibility of percutaneous management, and guiding percutaneous interventional radiology procedures. CTE and MRE are also very useful in ruling out bowel obstruction or confirming strictures. In addition to assessing the complications of Crohn's disease, CTE and MRE provide the anatomic detail of distribution and extent of disease required for reaching decisions to intervene surgically and for surgical planning.

Imaging plays at least one other major role in patients with Crohn's disease: the noninvasive assessment of disease activity. Imaging findings that confirm active disease (active inflammation) may indicate a severity of disease greater or less than expected based on clinical evaluation, thus affecting therapeutic management decisions. CTE and MRE findings, such as mural thickening, mural or mucosal hyperenhancement, fat-stranding, and hyperemia of the vasa recta, have been shown to correlate with active inflammation on pathology [10–13]. These findings have been particularly useful in assessing disease activity at the time of initial diagnosis of Crohn's disease or during significant clinical flares of established disease. The lack of specificity of CTE and MRE findings with respect to active inflammation has received less attention in the literature. Nevertheless, several studies have noted that mural thickening and even contrast hyperenhancement can be present in the absence of active inflammation or during clinical remission [14–16]. Findings that offer greater specificity for the presence of active inflammation may include a striated enhancement pattern of the bowel wall, fat-stranding in the adjacent mesenteric fat, and gross findings of abscess or active fistulas. With respect to MRE, it should be noted that special techniques such as diffusion weighted imaging, spectroscopy, and other sequences, may prove useful in the future, but remain to be fully explored in Crohn's disease. Finally, there is a lack of data to indicate that CTE or MRE findings can be used for assessing changes in disease activity over short time intervals, such as days to weeks, rather than months to years after initiation of therapy.

The capability of noninvasively confirming and, more importantly, quantifying inflammatory activity in bowel segments involved with Crohn's disease may become an increasingly important role for imaging. The medical management of Crohn's disease has shifted toward an emphasis on the early use of immunomodulator therapies, such as 6-mercaptopurine, which reduce the need for steroids, and biologic therapies, such as infliximab, that target tumor-necrosis-factor [17]. Unlike steroids, the immunomodulators and biologics reduce the rates of clinical and endoscopic relapse, promote mucosal healing, and decrease the need for surgery, at least in the short term [7, 17]. The new biologics, however, are expensive and may cost more than $20,000 per year of treatment in the U.S. [18]. Also of concern is the possibility of an increased risk of lymphoma, other malignancies, or serious infections resulting from the use of these drugs [19, 20]. For these reasons, the ability to noninvasively monitor response to therapy soon after initiating therapy with these drugs could be beneficial.

Positron emission tomography in Crohn's disease

Several nuclear medicine tests have been used in the evaluation of patients with inflammatory bowel disease including various radiolabeled autologous leukocyte techniques. Because of the complexity of the labeled leukocyte techniques, potential false positives and radiation dose considerations, positron emission tomography (PET) using F-18 fluorodeoxyglucose (^{18}F-FDG) is attracting increasing attention [21]. ^{18}F-FDG PET has proven to be effective in imaging a wide variety of other infectious or inflammatory conditions [22].

Several studies, some in adult populations and others in pediatric populations, evaluating the performance of ^{18}F-FDG PET in detecting bowel segments with active Crohn's disease confirmed by histopathology have reported sensitivities ranging from 85% to 98% and specificities ranging from 50% to 89% [23–26]. Dedicated PET/CT scanners have more recently been employed in

studies of patients with Crohn's disease and other inflammatory bowel diseases. One of the first studies using ^{18}F-FDG PET/CT and ileocolonoscopy-pathology correlation in 22 adult patients found that, although sometimes missing mild inflammation, 100% of bowel segments with deep ulceration, fissuring, or strictures were ^{18}F-FDG-avid [27]. This study, performed without oral or intravenous (IV) contrast material, noted that in some bowel segments with increased ^{18}F-FDG uptake on PET and mural thickening on CT, no abnormality was seen on endoscopy. The implication raised was that ^{18}F-FDG PET, although scored as false positive in these cases where endoscopy and superficial biopsies were considered the gold standard, may be able to identify mural inflammation missed by endoscopy with mucosal biopsies. In this study, ^{18}F-FDG uptake correlated well with clinical disease activity as measured by the Crohn's Disease Activity Index, the Crohn's Disease Endoscopy Index of Severity, and serum C-reactive protein.

A pediatric study using ^{18}F-FDG PET/CT reported a sensitivity of 82% and specificity of 97% for detecting active disease as confirmed on endoscopic biopsies [28]. In this study, also performed without oral or IV contrast material, CT was not found to contribute diagnostically, other than helping to localize abnormal bowel segments. The ^{18}F-FDG PET or PET/CT studies focusing on pediatric populations have noted the advantages of this relatively simple, fast, and noninvasive test for evaluating children with inflammatory bowel disease.

The focus of most investigations using ^{18}F-FDG PET or PET/CT in the assessment of inflammatory bowel disease has been on the detection of disease and the correlation of ^{18}F-FDG uptake with degree of inflammation. ^{18}F-FDG PET alone lacks the anatomic detail to provide meaningful assessment of disease morphology and most of the clinically important complications. We have described a case, however, where ^{18}F-FDG uptake, as viewed on fused PET/CTE images, enabled the diagnosis of an enterocolic fistula that was missed on CTE alone and could not have been diagnosed on PET alone [29]. In retrospect the fistula was visible but very subtle on CTE, and later confirmed at surgery.

Preliminary studies incorporating fully diagnostic CTE protocols into the performance of ^{18}F-FDG PET/CT scans provide further insight into the diagnostic strengths and weaknesses of ^{18}F-FDG PET in comparison with CTE, and the potential value of a combined PET/CTE approach [29–31]. A retrospective study without endoscopic or histologic correlation found that in 41 PET/CTE scans with 48 abnormal bowel segments on CTE, ^{18}F-FDG PET was positive in 79% [31]. ^{18}F-FDG PET did not detect disease in any bowel segment not regarded as abnormal on CTE. The crucial point of emphasis is that this study merely focused on detection of diseased bowel segments, and not necessarily on detection of active inflammation. We conducted a prospective pilot study with endoscopic and histopathologic correlations and found that the combined ^{18}F-FDG PET/CTE did not detect diseased bowel segments that were not already evident on CTE alone [29]. CTE alone and combined PET/CTE both detected 100% of bowel segments with more than mild disease activity; the specificity was 90%. These findings illustrate the excellent sensitivity of CTE alone in detecting diseased bowel segments, with or without active inflammation, in patients with Crohn's disease (Fig. 1). The key question remaining is which of these tests can prove to be the most useful in detecting and quantifying disease activity.

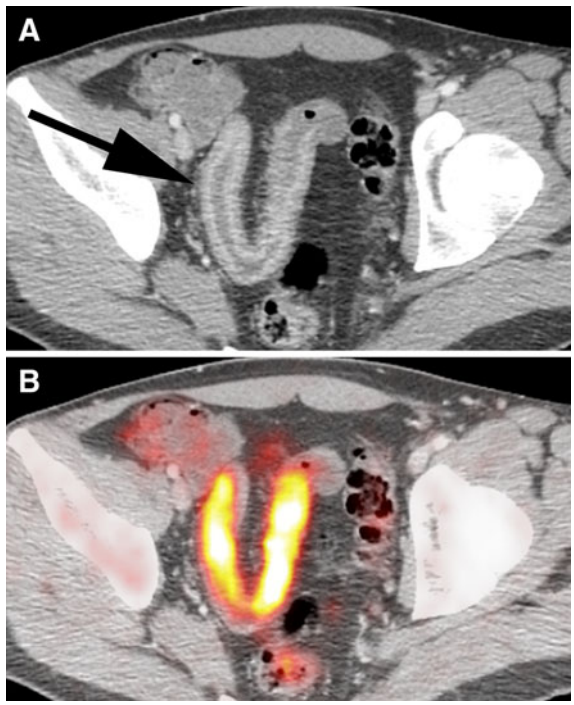

Fig. 1. The CT enterography portion (**A**) of this combined PET/CTE scan demonstrates mural thickening, mucosal enhancement in a stratified pattern (*arrow*), and mild hyperemia of the vasa recta with fibrofatty proliferation. The PET portion (**B**) of the PET/CTE scan confirms active inflammation based on intense ^{18}F-FDG uptake in this small bowel segment.

Quantifying Crohn's disease activity

Endoscopic assessment including pathology analysis of biopsy specimens is the generally accepted gold standard for determining disease activity, but is invasive and limited in its ability to evaluate the entire bowel wall deep to the mucosa. A surrogate marker for therapeutic modification of disease outcomes in Crohn's disease is more complex to define and select, but currently is often based on endoscopic assessment of mucosal healing [7]. A surrogate marker for disease modification should correlate with actual clinical outcomes, such as disease progression or the need for surgical intervention. Patient

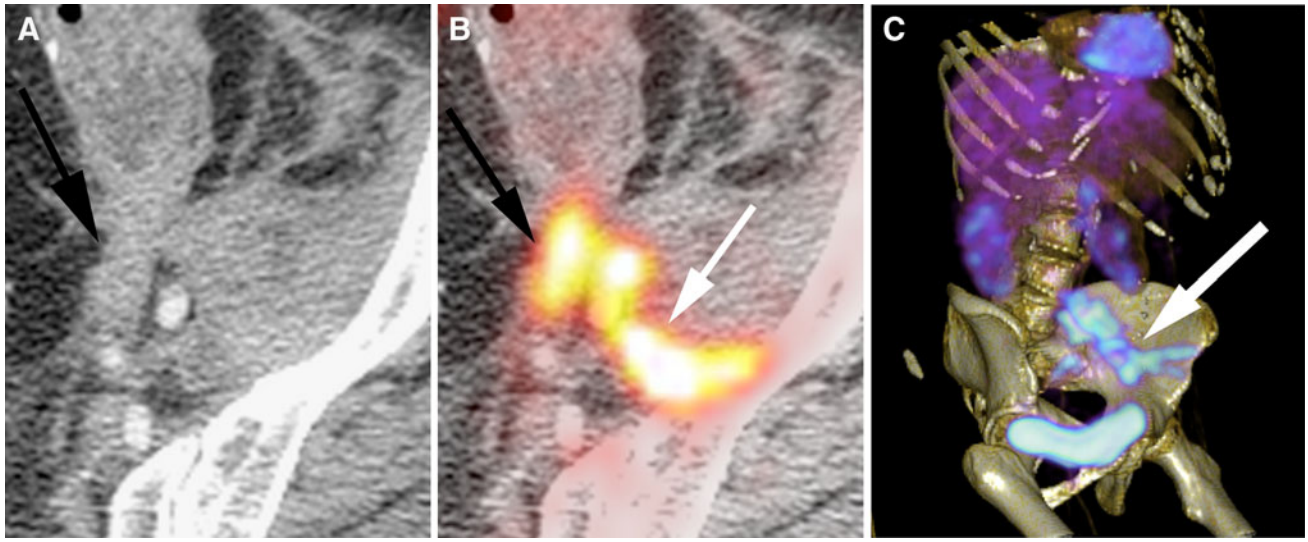

Fig. 2. In this patient with previous bowel resection for Crohn's disease, the CTE portion of the PET/CTE scan (**A**) fails to demonstrate mucosal or mural hyperenhancement (*arrow*) in a short segment of thickened small bowel. The PET portion of the scan (**B**) clearly reveals intense ^{18}F-FDG uptake not only in the inflamed small bowel segment (*black arrow*), but also in a fistula (*white arrow*) extending into the iliopsoas muscle. A volume-rendered PET/CTE image (**C**) was helpful in surgical planning for resection of the small bowel segment and complex fistula (*arrow*).

symptoms can be quantified using clinical tools but have shown relatively poor correlation with disease activity as confirmed on endoscopy [32, 33]. Serum C-reactive protein has proven to be the most useful systemic marker of inflammation in patients with Crohn's disease, although it has not shown consistent correlation with endoscopic findings [34, 35]. There is also interest and research activity directed at the use of gene array analysis in assessing disease activity, although these tests remain to be validated and have not entered the realm of clinical practice [35]. An obvious question for consideration is: can molecular imaging provide a robust, noninvasive surrogate marker for disease activity and therapeutic modification of disease course?

Among the available imaging tests, the major advantage of ^{18}F-FDG PET in the imaging assessment of patients with Crohn's disease appears to be its accurate assessment of disease activity. ^{18}F-FDG uptake in inflammatory conditions has been shown to reflect the aggregation of acute and/or chronic inflammatory cells characterized by increased metabolic activity and glucose utilization [36]. As such, ^{18}F-FDG uptake is a relatively direct and quantifiable indicator of inflammation, unlike the less specific signs used to gauge inflammation on CTE or MRE exams. Nevertheless, as outlined above, single time-point studies using CTE or MRE have found reasonable correlations of imaging findings with disease activity.

One PET/CT study that compared bowel wall thickness on unenhanced CT with ^{18}F-FDG uptake on PET found that ^{18}F-FDG uptake correlated with severe disease on endoscopy better than did bowel thickening [27]. In our study comparing CTE alone with ^{18}F-FDG PET/CTE, the correlation of ^{18}F-FDG uptake with inflammation as graded by pathology was better, on a per-patient basis, than the composite CTE score, although CTE performed better on a per-bowel-segment analysis [29]. ^{18}F-FDG uptake correlated well with serum C-reactive protein levels whereas CTE score did not. In addition, we found that ^{18}F-FDG uptake clearly identified active inflammation in two of the 13 patients, for whom CT only demonstrated mural thickening without more specific features of active inflammation (Fig. 2). What has not adequately been addressed to date, however, is the ability of imaging tests to accurately monitor disease activity changes over short periods of time.

We are not aware of published studies that have systematically evaluated the ability of CTE or MRE to dynamically monitor disease activity during the first few weeks after initiation of medical therapy for Crohn's disease. The few studies that have reviewed imaging tests at more than one time-point have often compared tests separated by many months or even years. The same is true for ^{18}F-FDG PET, for which only one study has evaluated ^{18}F-FDG PET scans performed at two time-points [37]. This study demonstrated that a significant decrease in ^{18}F-FDG uptake on follow-up scans correlated with improved clinical symptoms in five patients; however, the scans were performed at an average of 437 days apart. Our clinical experience with CTE and MRE suggests that the imaging features used for assessing active inflammation in Crohn's disease, such as mural thickening and contrast enhancement, tend to change very slowly over time. It seems likely that mor-

phologic features of Crohn's disease as depicted on CTE and MRE will change much more slowly than the actual degree of inflammatory cell aggregation and activity occurring on the cellular level. The disconnect between metabolic changes revealed by ^{18}F-FDG PET with morphologic changes evident on CT is a common theme in oncologic imaging studies focused on therapy monitoring [38].

There is a reason to believe that ^{18}F-FDG PET may be able to provide a much more effective dynamic marker of inflammatory disease activity, which more closely parallels response to therapy. Many oncologic studies have demonstrated that changes in semi-quantitative measurements of ^{18}F-FDG uptake correlate well with response to chemotherapy and biologic agents within as little as 24 h after initiation of therapy [38, 39]. The same concept of short-term monitoring of targeted therapies using ^{18}F-FDG PET for inflammatory diseases is only beginning to be investigated. A recent study assessing response to infliximab therapy in 16 patients with rheumatoid arthritis found that decreases in ^{18}F-FDG uptake 2 weeks following initiation of therapy correlated well with disease activity scores at 14 and 22 weeks, whereas C-reactive protein and erythrocyte sedimentation rate did not [40]. If future investigations demonstrate a similar capability of ^{18}F-FDG PET in monitoring therapy for Crohn's disease, then the potential for early modification of expensive, potentially harmful, yet ineffective therapies could be realized.

Strictures and the need for surgery

One of the vexing problems in the management of patients with Crohn's disease is determining whether narrowed bowel segments are predominantly inflammatory in nature and likely to respond to medical therapy, or predominantly fibrotic in nature and unlikely to respond to medical therapy. In the latter case, patients often require surgical resection, which as mentioned above, is not curative, and if repeated resections are required then such resections can lead to short bowel syndrome [4, 5, 41].

Initial attempts at characterizing strictures using ^{18}F-FDG PET have suggested that lower levels of ^{18}F-FDG uptake may correlate with predominantly fibrotic strictures that are unlikely to respond to medical therapy and thus more likely to require surgical resection [31, 42, 43]. However, the suggested standardized uptake value (SUV) thresholds for separating surgical from non-surgical disease have been quite varied. In our small series, we were not able to confirm a relationship between SUV values in strictures and the need for surgical resection [29]. The problem in using ^{18}F-FDG PET as a marker of fibrosis may be the assumption of an inverse correlation of fibrosis and inflammation, when, in fact, active inflammation is present to varying degrees in most obstructive strictures.

Perhaps a more direct approach to this problem would be the development of PET probes directed at fibrosis or fibrogenesis itself. In this regard, studies are beginning to elucidate the steps leading to fibrostenosis in Crohn's disease, which may in turn suggest molecular targets for imaging with PET. The exact mechanisms of fibrogenesis are not fully understood, but they appear to involve multiple processes including fibroblastic activity, inflammation, cytokine activity, and genetic factors [44]. For example, certain isoforms of transforming growth factor beta (TGF-β), while possessing anti-inflammatory properties, may stimulate fibrogenesis [41]. Conversely, tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine with inhibitory effects on fibrogenesis. Other than growth factors and cytokines, potential targets for PET probes, which could be considered include type III collagen, fibronectin, fibroblasts, and other yet to be determined targets [45]. If achieved, accurate, noninvasive characterization of strictures as reversible or irreversible has the potential to significantly improve the clinical management of patients with severe Crohn's disease.

Practical considerations in performing ^{18}F-FDG PET or PET/CT

The ^{18}F-FDG PET or PET/CT scan protocols used for the assessment of patients with Crohn's disease will differ in some respects from the protocols used for oncologic indications. Since the patient population affected by Crohn's disease often includes younger patients, it is important to consider the possibility of pregnancy in the women of childbearing age. The blood glucose level is checked, as with oncology patients, to detect hyperglycemia that may reduce the sensitivity of the scan. Patients fast for 4–6 h before the scan, but are allowed to drink water. The dose of ^{18}F-FDG PET is an important consideration in this population of patients who may face decades of medical imaging tests. We demonstrated that a weight-based dose of 3.3 MBq/Kg (0.09 mCi/Kg) was sufficient for diagnostic PET imaging in patients with Crohn's disease [29]. For a 70-kg patient this would correspond to an estimated effective dose of 4.4 mSv, compared to an estimated annual background dose in the U.S. of 3.5 mSv [46]. The uptake period between the IV administration of ^{18}F-FDG and the initiation of PET scanning is 60 min. If CTE is incorporated into the PET/CT protocol, then the patient should drink approximately 1350 ml of a refrigerated neutral oral contrast agent, such as VoLumen (Bracco Diagnostics, Inc., Princeton, NJ), for 45–60 min during the ^{18}F-FDG uptake period.

Scanning is limited to the abdomen and pelvis, to include the dome of the diaphragm through the upper thighs. Including the perianal region is helpful for detecting perianal fistulas (Fig. 3). When performing

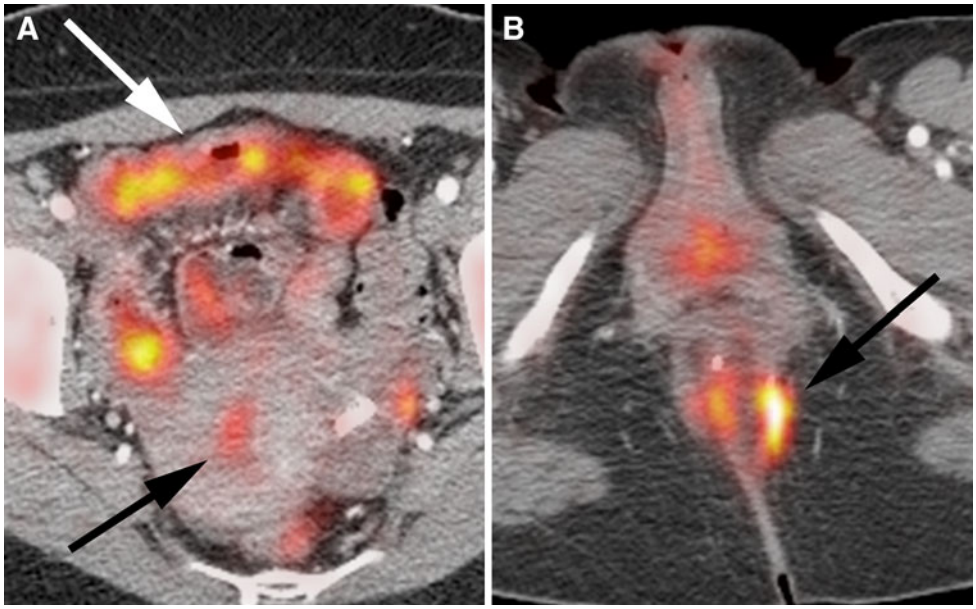

Fig. 3. A female patient with active Crohn's disease underwent PET/CTE (**A**) confirming active disease in multiple pelvic small bowel segments (*white arrow*). Physiologic activity within the endometrial cavity (*black arrow*) is easily distinguished from bowel activity on fused images. Other sites of inflammation are also detected by PET/CTE (**B**) such as the perianal fistula (*arrow*) containing a surgical seton.

PET/CTE, the CTE acquisition is used for attenuation correction of the PET scan, and no additional CT acquisition is needed. In choosing the mA and kVp for the CT acquisition, it is important to use the lowest settings compatible with a diagnostic scan. Most PET/CT scanners are capable of automatic tube current modulation, and the use of this option is recommended. Automatic tube current modulation enables the operator to choose a minimum image quality level or maximum noise level, which the scanner maintains, while automatically minimizing the dose [47].

Further dose reductions from the diagnostic CT component of PET/CT scans are likely to be realized, as adaptive statistical iterative reconstruction algorithms are incorporated into PET/CT scanners. The blending of iterative reconstruction algorithm images with standard filtered back projection images has been shown, in one study, to allow a 50% dose reduction during CT colonography, while maintaining diagnostic image quality [48]. For PET/CT protocols performed without oral or IV contrast material, or when a recent CTE or MRE has already been performed, further reductions in mA may be possible. If the CT portion of the PET/CT is obtained only for the purpose of attenuation correction of the PET images, then the tube current can be reduced to as little as 10 mA. This approach could be considered for therapy monitoring protocols when the short-interval follow-up scan is obtained only for the purpose of quantifying changes in ^{18}F-FDG uptake.

The CT acquisition is obtained before the PET acquisition during a single end-tidal breath-hold. This level of breath-hold tends to minimize respiratory misregistration of breath-hold CT images from PET images acquired during quiet, continuous breathing. For CTE protocols, approximately 80–150 ml of non-ionic contrast material containing 300–370 mgI/ml is injected at 3–5 ml/sec and with a 70 s scan delay.

PET acquisitions are usually obtained with 3–5 bed positions, beginning at the bottom of the pelvis and finishing at the top of the diaphragm. PET acquisitions may require 1–5 min per bed position depending on the scanner, patient size, and ^{18}F-FDG dose. Longer acquisitions may improve overall image quality, but may increase the probability of bowel motion during the scan.

Transaxial PET and CT images should be reconstructed at the same interval, for example, 3 mm or less. The PET and CT image slice thicknesses do not have to be identical, as long as the reconstruction intervals are identical. PET image thickness should not exceed 5 mm, and CT image thickness should not exceed 3 mm. Multiplanar reconstructions are very helpful, and, in the case of CT, they should be generated from 1 mm or thinner transaxial datasets. If the PET/CT workstation does not allow for optimal display of diagnostic CT images using a 512 × 512 matrix, then the CT portion can be further reviewed on a PACS workstation.

PET and PET/CT interpretation considerations

Increased physiologic ^{18}F-FDG activity can be seen anywhere along the gastrointestinal tract, which tends to be more pronounced in the ascending colon, anorectum, and stomach, but is also seen in the small bowel. Physiologic uptake can be mild or intense and explains some of the false-positive PET findings reported in patients with inflammatory bowel disease. In general, the more focal and intense the ^{18}F-FDG uptake, the less likely it is to be physiologic. Crohn's disease may involve long

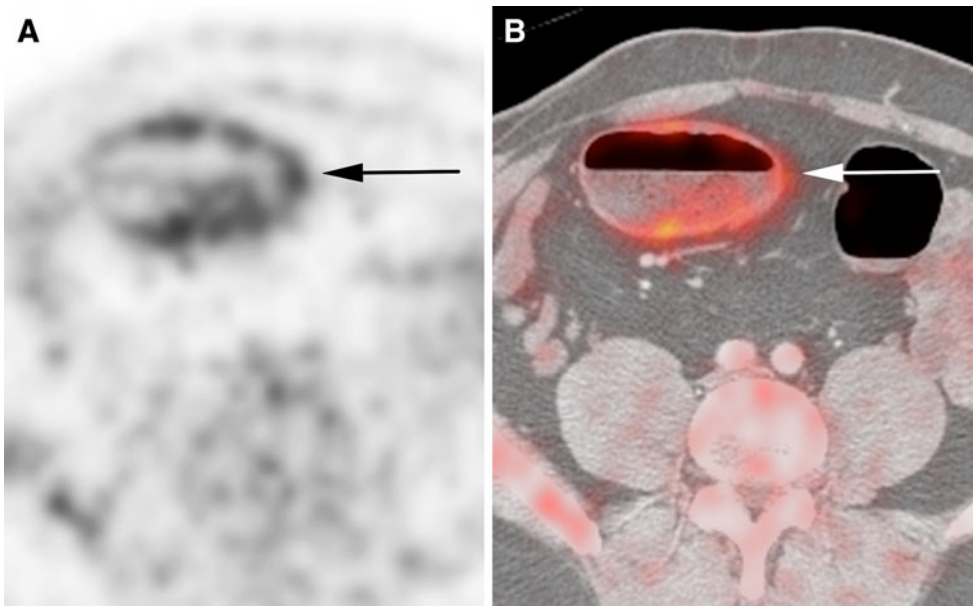

Fig. 4. The PET image (**A**) and corresponding fused PET/CTE image (**B**) from a patient with active Crohn's disease demonstrate an air-^{18}F-FDG fluid level (*black arrow*) confirming physiologic intraluminal ^{18}F-FDG activity, along with mural ^{18}F-FDG uptake (*white arrow*) reflecting inflammation in the bowel wall.

segments of bowel, but in many cases, the discrete segmental pattern of uptake along with the intensity of uptake enables confident delineation of the inflamed bowel. Of course, one of the significant advantages of the combined PET/CTE is that the CTE findings can facilitate the correct attribution of increased ^{18}F-FDG uptake to physiologic factors in normal bowel, or to active inflammation in diseased bowel.

Physiologic bowel uptake may not only reflect intramural or mucosal localization, but can also reflect intraluminal activity caused by swallowed salivary activity or activity secreted intraluminally by bowel mucosa (Fig. 4). The intake of a large volume of oral contrast material, as in a CTE protocol, may tend to dilute intraluminal ^{18}F-FDG activity and to minimize the intensity of physiologic bowel activity in some cases. Distention of bowel by a large volume of oral contrast material may also tend to minimize the apparent intensity of ^{18}F-FDG uptake in the bowel wall by reducing the pixel concentration of ^{18}F-FDG.

Shifting of bowel loops between the PET and CT acquisitions of a PET/CT scan can lead to misregistration of bowel such that ^{18}F-FDG uptake on PET images does not localize to the appropriate bowel loop on CT images (Fig. 5). In addition, when substantial misregistration of bowel loops is observed on PET/CT, one should consider the potential for significant artifactual decreases in SUV measurements, because of partial volume effects, in bowel loops that are moving during the PET acquisition itself. Interestingly, patients with severe Crohn's disease or prominent associated mesenteric fibrofatty proliferation often have bowel loops that become fixed in position within the abdomen or pelvis. This fixation of bowel loops in patients with relatively advanced Crohn's disease may actually insure optimal PET/CT image registration and accurate SUV measurements.

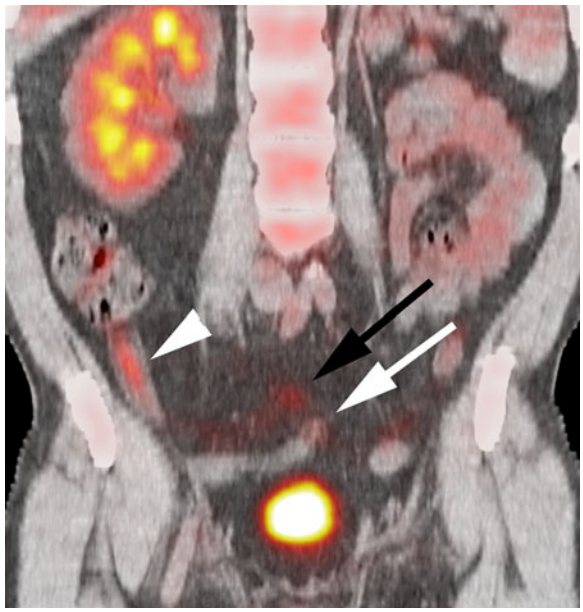

Fig. 5. A coronal PET/CT image from a patient with Crohn's disease demonstrates misregistration of a loop of small bowel as seen on CT (*white arrow*) and PET (*black arrow*). Shifting of bowel between PET and CT acquisitions, or during the longer PET acquisition, can lead to uncertainties regarding the presence and quantification of ^{18}F-FDG uptake in a particular bowel segment. The mildly inflamed terminal ileum (*arrowhead*) is well registered on PET/CT.

FDG uptake can be quantified using SUV. SUV measurements involve the placement of a region of interest over the anatomic structure and then recording either the average pixel value or maximum pixel value for

the region of interest. The maximum pixel value is often used because of its reduced dependence on precise placement or size of the region-of-interest. SUV is a semi-quantitative or relative measure of radiopharmaceutical activity in a selected volume relative to the total administered dose, normalized to a body parameter such as weight. The use of SUV ratios, for example, the ratio of bowel uptake to normal liver uptake may be useful in standardizing comparisons [27, 29]. From a practical point of view, quantifying inflammation with SUV parameters on PET may prove to be simpler and more reproducible than composite scores proposed for CTE [29].

Many factors affect the accuracy and reproducibility of SUV measurements. If PET/CT is to be used for monitoring response to therapy, then it is important to follow a very consistent protocol including scanning the patient on the same PET/CT scanner, using the same FDG dose, the same uptake period, and the same PET scan technique. PET/CT scanner quality control and calibration are critical. The patient should undergo a similar prep and have a similar blood glucose level. Neutral oral contrast will have no effect on CT attenuation correction of PET datasets and therefore will not alter SUV measurements. IV contrast enhancement can produce visible artifactual increases in FDG uptake when very concentrated, for example, in the aorta during the arterial phase. IV contrast enhancement of visceral organs or bowel, however, does not result in visually apparent increase in FDG uptake, but may have the potential to skew SUV measurements slightly higher, generally much less than 10% [49].

Increased FDG uptake in normal-sized or enlarged mesenteric lymph nodes is commonly observed in patients with Crohn's disease as with other inflammatory conditions of the bowel [29, 30]. FDG uptake may also be identified in associated inflammatory lesions, such as perianal fistulas, cholangitis, and sacroiliitis. Increased FDG uptake may occasionally be observed in segments of bowel known to be involved by Crohn's disease, but during apparent clinical remission and in the absence of symptoms [27, 50]. Whether or not such metabolic activity reflects chronic inflammation smoldering between active flares of disease and whether or not this finding may predict a shorter time interval to relapse remain to be determined (Fig. 6).

In summary, the precise role of ^{18}F-FDG PET in Crohn's disease remains to be determined; however, preliminary experience suggests that its key advantage will be in accurately and noninvasively quantifying disease activity. While ^{18}F-FDG PET does not seem to improve substantially on CTE or MRE in the detection and anatomic characterization of diseased bowel segments, it does seem to have the potential to better assess the presence and degree of inflammation. If ^{18}F-FDG PET is shown to be an accurate, dynamic marker of Crohn's disease activity over short intervals of time, then this would open the door for therapy-monitoring applications. The ability to confirm efficacy or lack of efficacy of an expensive drug, with potential significant side effects, within days to weeks of therapy initiation could have a significant impact on the clinical management of patients with Crohn's disease in the future. Moreover, the use of ^{18}F-FDG PET as a noninvasive biomarker of disease activity could find further utility in clinical trials assessing new targeted therapies for Crohn's disease.

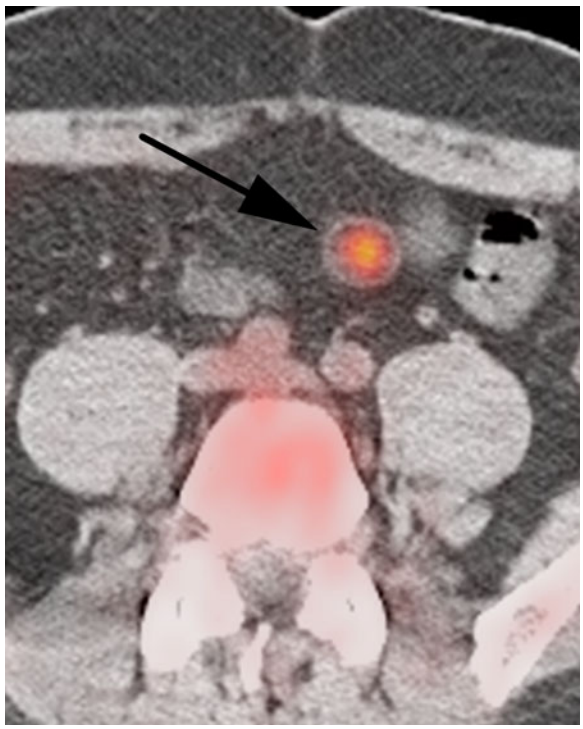

Fig. 6. A patient underwent PET/CT for the evaluation of adenoid cystic carcinoma of the head and neck; however, no ^{18}F-FDG -avid tumor was identified. The patient also had a history of Crohn's disease, in remission and without symptoms. A segment of small bowel (*arrow*) demonstrates intramural fat on CT consistent with chronic disease, but no CT findings to indicate active inflammation. The presence of focal-increased ^{18}F-FDG uptake within this segment is of uncertain significance in this patient with Crohn's disease in clinical remission.

Conflict of interest. None.

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