



Updates on ^{18}F -FDG-PET/CT as a clinical tool for tuberculosis evaluation and therapeutic monitoring

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Abstract: Tuberculosis (TB) is currently the world's leading cause of infectious mortality. The complex immune response of the human body to *Mycobacterium tuberculosis* (*M.tb*) results in a wide array of clinical manifestations, thus the clinical and radiological diagnosis can be challenging. ^{18}F -fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) scan with/without computed tomography (CT) component images the whole body and provides a metabolic map of the infection, enabling clinicians to assess the disease burden. ^{18}F -FDG-PET/CT scan is particularly useful in detecting the disease in previously unknown sites, and allows the most appropriate site of biopsy to be selected. ^{18}F -FDG-PET/CT is also very valuable in assessing early disease response to therapy, and plays an important role in cases where conventional microbiological methods are unavailable and for monitoring response to therapy in cases of multidrug-resistant TB or extrapulmonary TB. ^{18}F -FDG-PET/CT cannot reliably differentiate active TB lesion from malignant lesions and false positives can also be due to other infective or inflammatory conditions. ^{18}F -FDG PET is also unable to distinguish tuberculous lymphadenitis from metastatic lymph node involvement. The lack of specificity is a limitation for ^{18}F -FDG-PET/CT in TB management.

Keywords: Tuberculosis (TB); latent tuberculosis (latent TB); treatment response; fluorine-18 fluorodeoxyglucose (^{18}F -FDG); positron emission tomography and computed tomography (PET and CT)

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Introduction

The *Mycobacterium tuberculosis* (*M.tb*) is a relatively slow growing complex acid-fast bacillus. *M.tb* is able to survive in harsh microenvironments within patients in a quiescent state. After exposure to *M.tb*, an estimated 20–25% of the subjects become infected. One-fourth of the world's population is latently *M.tb*-infected and approximately 3–5% of these infected individuals will progress towards developing active tuberculosis (TB) disease during their

lifetime (1). Pulmonary disease is present in more than 80% of TB cases; while extrapulmonary TB (EPTB) occurs in about 20% of cases, but can be seen in more than 50% of cases in immunosuppressed populations such as in HIV patients (2). TB can spread by lymphatic, hematogenous, or direct extension from an infective focus. The presentation of active TB can be very variable, may range from asymptomatic to life threatening as in TB meningitis. Early and accurate diagnosis of TB with early initiation of treatment is important to minimize the morbidity and

mortality and to reduce the likelihood of transmission.

Active TB lesions contain activated macrophages and lymphocytes, which have high levels of glucose utilization. ^{18}F -fluorodeoxyglucose (^{18}F -FDG) uptake reflects cell glycolysis and is found in activated macrophages and lymphocytes, both of which are prominent in TB and other granulomatous inflammatory processes, as well as in neoplastic cells. The rate of uptake is reported as a standardized uptake value (SUV), the regional radioactivity concentration divided by the total injected radiotracer dose and adjusted to the patient weight. This creates ^{18}F -FDG signal on positron emission tomography (PET) which forms the basis of ^{18}F -FDG-PET imaging for TB. Lesion activity as determined by ^{18}F -FDG correlates with disease activity. The SUVmax (the maximum standardized uptake value after radiotracer administration) of TB lesions also depend on several factors including host factors such as immune status, comorbid clinical conditions, and *M.tb* virulence. ^{18}F -FDG-PET scan with/without computed tomography (CT) component can play a very important role in TB patients' management, and particularly so for those who are sputum negative, unable to produce sputum, or have EPTB (3-5). The lack of specificity is a limitation for ^{18}F -FDG-PET/CT, therefore ^{18}F -FDG-PET/CT scan must be interpreted taking the patient's clinical information into account. This paper reviews the current understanding of ^{18}F -FDG-PET/CT's application in TB patients' management. In this article, for standardization, the term ' ^{18}F -FDG-PET/CT' is used. However, while ^{18}F -FDG-PET/CT allows the spatial distribution of metabolic activity in the body to be aligned with anatomic image provided by CT, when the CT component is not available, in some cases ^{18}F -PET imaging alone may also provide sufficient information for TB care.

^{18}F -FDG-PET/CT for pulmonary TB

Soussan *et al.* (6) proposed two patterns of TB based on ^{18}F -FDG-PET appearance, the lung pattern and the lymphatic pattern. The lung pattern relates to restricted infection, patients have predominantly pulmonary symptoms with a parenchymal involvement, with ^{18}F -FDG uptakes on lung consolidation with or without cavitation surrounded by micronodules. Mediastino-hilar lymph nodes can be slightly enlarged with moderate uptake (Figures 1,2). The lymphatic pattern relates to a systemic infection, patients tend to have predominantly systemic and have extra-thoracic involvement, mediastino-hilar lymph nodes can be more enlarged and with higher uptake

than in the lung pattern (Figure 3). TB pleural effusions showing ^{18}F -FDG avidity may also be observed and in some instances can be the only manifestation of the disease.

TB cavities are relatively avascular compared with other TB lesions and are more likely to have higher metabolic activity in their walls (Figure 4).

The determination of pulmonary tuberculoma activity may be essential for treatment options, however, diagnosis of active pulmonary tuberculoma is problematic. In this aspect ^{18}F -FDG-PET/CT may play an important role. Kim *et al.* (7) reported that dual time-point imaging ^{18}F -FDG-PET/CT was able to distinguish active from inactive pulmonary tuberculomas. Active pulmonary tuberculomas had a higher SUVmax at 1 and 2 hours and a greater increase in SUVmax from the early to the late imaging compared with inactive pulmonary tuberculomas, with $\% \Delta \text{SUVmax}$ (percentage change in SUVmax) as a potent predictor for differentiation of tuberculomas' activity (7).

However, ^{18}F -FDG is a nonspecific tracer accumulating in both inflammatory and malignant processes. SUV measurements from both tuberculous and malignant lesions can be high with significant overlap (Figures 5,6). Numerous authors reported ^{18}F -FDG uptake does not reliably distinguish between TB and malignant lesions (8-10). Goo *et al.* (8) found a mean peak SUV of 4.2 ± 2.2 in pulmonary tuberculomas in 9 of 10 consecutive patients. Sathekghe *et al.* (10) reported a study evaluated the use of dual time-point ^{18}F -FDG-PET/CT, and concluded that SUV measurement was not useful in characterizing lesions as granulomatous or malignant. However, in countries and regions where TB and infections are not endemic, the probability of malignancy in association with positive ^{18}F -FDG-PET findings is high (90% if the patient is older than 60 years); likewise, the probability of malignancy in association with negative ^{18}F -FDG-PET findings is low (<5%) (11).

^{18}F -FDG-PET/CT for extrapulmonary TB

Although pulmonary TB is the most common presentation of the disease, TB can spread to virtually any tissue or organ of the body by haematogenous or lymphatic dissemination or contiguity (Figures 7-9). The most frequently reported EPTB affect sites include lymph nodes, pleura, musculoskeletal, gastrointestinal and genitourinary tract (12-16). The risk of *M.tb* infection and EPTB increases with advancing immunosuppression. Although definitive diagnosis and exclusion of active TB infection

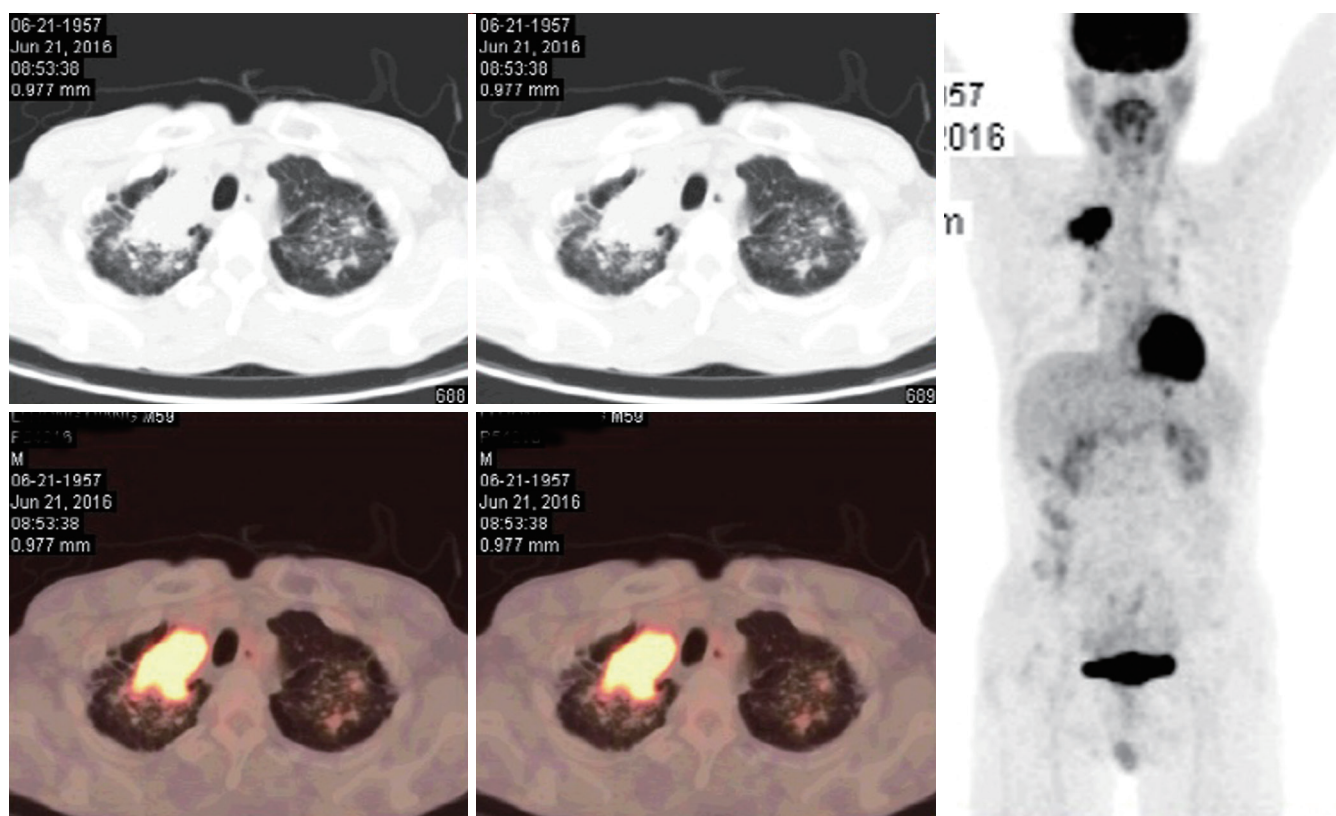


Figure 1 Pulmonary tuberculosis (a lung pattern) in a 59-year-old man. Axial CT (upper row) and axial PET/CT (lower row) and coronal PET (right one) images show intense FDG uptake in the right lung lesions and slight FDG uptake in left lung lesions. Slight FDG uptake in the mediastino-hilar lymph nodes uptake is also observed. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

by microbiology and histology is always recommended, ^{18}F -FDG PET/CT may contribute an earlier diagnosis. ^{18}F -FDG PET detects more EPTB lesions than CT. ^{18}F -FDG-PET/CT is particularly helpful when there is multisite involvement, and some sites of the disease may be unsuitable for biopsy such as in the skeleton or the pancreas. Stelzmueller *et al.* (17) reported more suspicious findings were delineated by ^{18}F -FDG PET than by CT, and the morphological changes as shown by CT did not match with hypermetabolic tissue as shown by ^{18}F -FDG PET in a variety of patients.

Musculoskeletal TB frequently involves the spine (Figure 7). Failure to identify and treat these areas of involvement in a timely manner may lead to serious complications such as vertebral collapse and spinal compression. ^{18}F -FDG-PET has several potential advantages including a high sensitivity in lesion detection and the fact that image quality is not affected by metal artefacts.

The most common site of EPTB involvement is the lymph nodes, and at least some of them which may be missed on CT scans (Figure 10) (1). However, differentiation of malignant versus TB lymph node involvement is problematic (1). It has also been reported that HIV-related lymphadenopathy may show metabolic uptake that may be difficult to distinguish from TB lymphadenitis (18). Moreover, intense ^{18}F -FDG uptake can be seen in some non-malignant lymphadenopathies such as sarcoidosis, toxoplasmosis and non-specific inflammatory lymphadenopathy.

^{18}F -FDG-PET/CT of subclinical TB infection

TB can be a spectrum of infection states, with transition from latent infection to active disease involving a subclinical phase of disease during which pathology evolves before symptomatic presentation. Autopsy studies in persons died

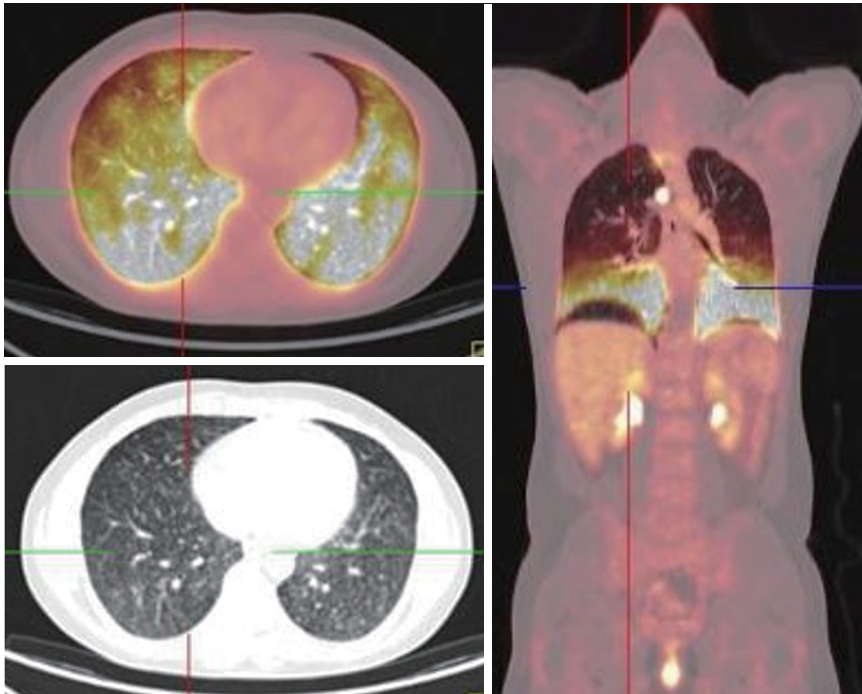


Figure 2 Axial CT and axial and also coronal FDG PET/CT images in a 42-year-old man show military pulmonary involvement in the lower lobes of both lungs (a lung pattern). FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

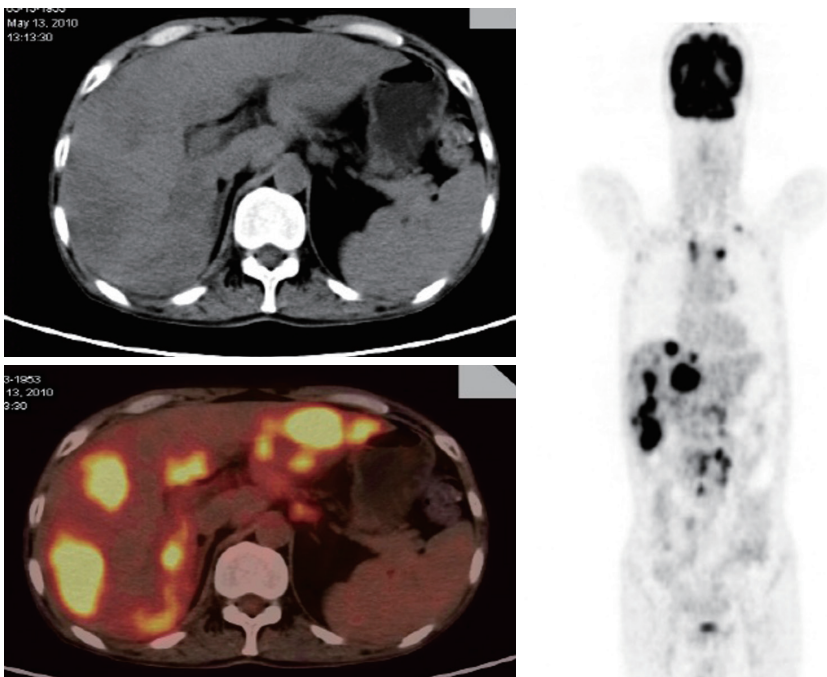


Figure 3 Disseminated tuberculosis (a lymphatic pattern) in a 57-year-old man. Multiple liver tuberculous lesions observed on axial CT image (upper row) show intense FDG uptake on axial PET/CT (lower row) and coronal PET (right one) images. FDG uptake in mediastino- retroperitoneal lymph nodes is also seen. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

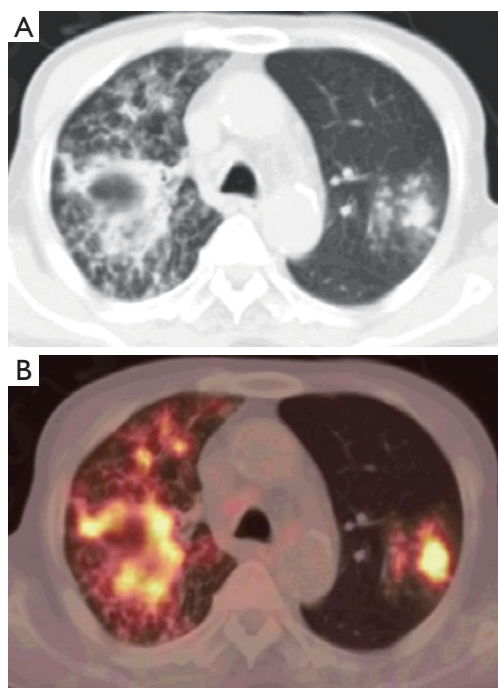


Figure 4 Pulmonary tuberculosis in a 61-year-old man. Axial CT (A) and axial ^{18}F -FDG-PET/CT (B) show multiple FDG-avid pulmonary lesions. There is a consolidation with central cavitation-peripheral FDG concentration and central cold areas in the right lung suggesting an active disease. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

from causes other than TB frequently showed evidence of minimally active disease. Population screening and prevalence surveys also identified asymptomatic patients by either imaging abnormalities consistent with TB or sputum culture positive for *M.tb* (19). These concepts have been validated by recent animal studies (20,21). In certain individuals a robust acquired immune response may eliminate infection completely while in others a quiescent infection remains with some mycobacteria persisting in non-replicating form (21,22). In a small proportion of patients, the immune response keeps active infection of replicating mycobacteria at the sub-clinical level, while in other patients, active inflammation and TB replication.

The restriction of the bacilli inside granulomas give rise to a latent TB infection (LTBI), defined by no visible symptoms of disease, but dormant and yet alive bacilli in the host. LTBI is not simply a state of bacterial stasis, but rather a state of dynamic bacterial and immunological equilibrium. It has been observed in mouse models that a subpopulation

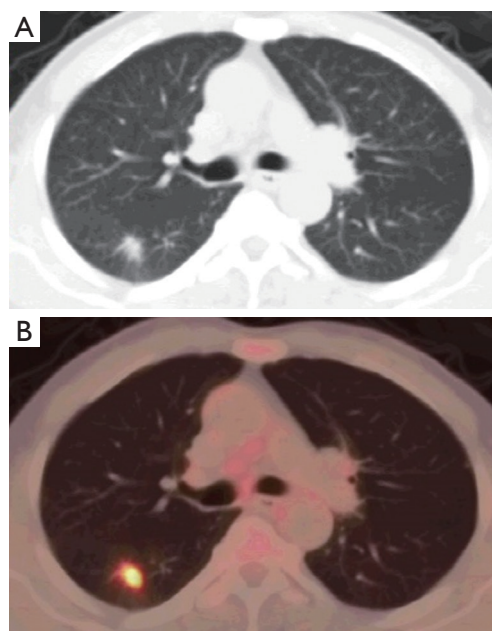


Figure 5 Pulmonary tuberculoma in a 59-year-old man. A nodule in right lower lobe with high FDG uptake observed on axial CT (A) and axial PET/CT (B) images mimics a lung cancer. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

of bacteria continues to replicate, although the size of the bacterial population remains stable (23). In addition, *M.tb* may accumulate mutations during latency (24). LTBI comprises a reservoir for new disease and ongoing *M.tb* transmission within communities. Two studies in TB endemic regions of Taiwan and Korea reported that a small percentage of “normal” subjects who underwent whole-body ^{18}F -FDG-PET scanning demonstrated increased ^{18}F -FDG uptake in mediastinal lymph nodes (25,26). LTBI state might last for the entire life span of the individual or progress to active TB by reactivation of the existing infection with a lifetime risk of 5–10% (27). HIV causes a sharp increase in the number of LTBI patients who progress to active disease (3,5).

In patients with LTBI, treatment is recommended for persons deemed to be at high risk of developing active disease (28). The preferred treatment is isoniazid daily for 9 months (29). The ability to identify those with LTBI at greatest risk of progression and provide targeted preventive therapy is important. Using ^{18}F -FDG PET/CT scan in 35 asymptomatic, antiretroviral-therapy-naive and HIV-

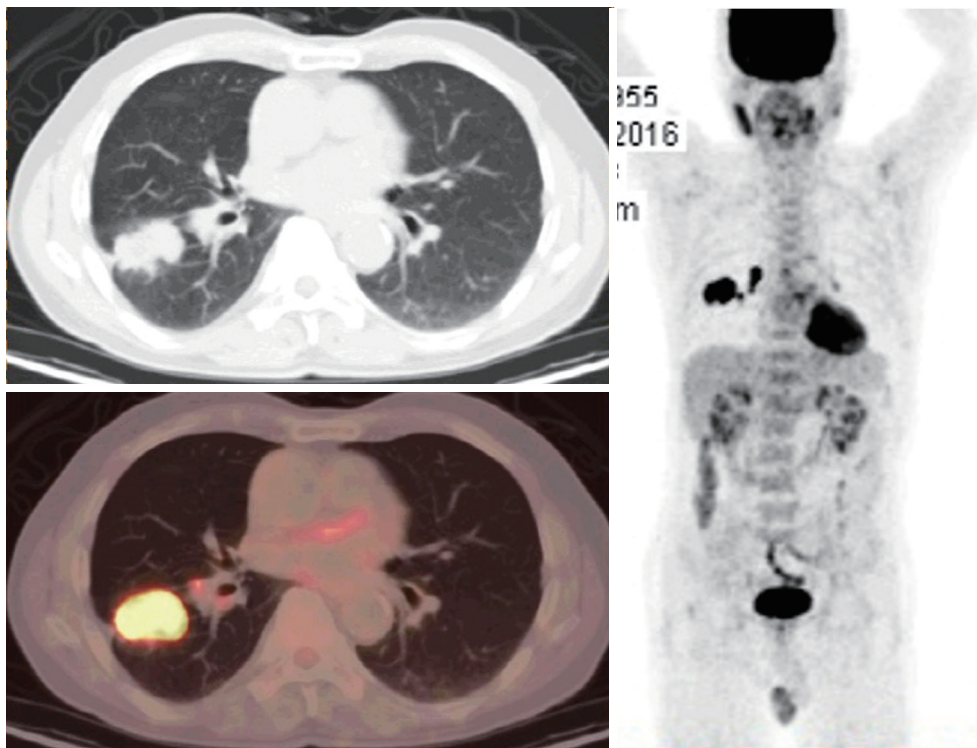


Figure 6 ^{18}F -FDG-PET/CT in a 61-year-old man with TB. A mass in the right lower lobe observed on axial CT image with intense FDG uptake on axial PET/CT and coronal PET images mimics a lung cancer. There are high uptake in the hilar lymph nodes, cervical lymph nodes and also bilateral parotid glands. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

infected adults with latent TB, Esmail *et al.* (30) identified ten individuals with pulmonary abnormalities suggestive of subclinical active disease who were substantially more likely to progress to clinical disease. These ten subclinical active disease subjects had an initial negative screen for active TB by sputum culture, chest X-ray and symptom screening, while PET/CT showed either infiltrates and/or fibrotic scars or active nodules, and were significantly more likely to have ^{18}F -FDG uptake within mediastinal lymph nodes; whereas the 25 participants with either normal lung parenchyma or discrete small nodules only showed no evidence of subclinical pathology. There were otherwise no significant differences in clinical characteristics between participants who did or did not have evidence of subclinical TB. Moreover, Ghesani *et al.* (31) reported five cases who were asymptomatic, had normal chest radiographs, and positive QuantiFERON gold assays. Four of the participants had positive ^{18}F -FDG-PET/CT scans involving mediastinal lymph nodes. None of the participants had ^{18}F -FDG uptake in the lungs. None of the ^{18}F -FDG-avid nodes met the radiological criteria for an enlarged lymph node. The

patient who had no ^{18}F -FDG uptake had a calcified lung granuloma and calcified hilar nodes noted on CT. Uptake in the mediastinal and hilar lymph nodes regressed during isoniazid prevention therapy (*Figure 11*) (31).

^{18}F -FDG-PET/CT of clinically cured TB

Currently there is no absolute measure of a sterilizing cure for TB. The current standard treatment period of 6 months was determined by acceptable rates of treatment failure and disease recurrence after discontinuation of chemotherapy (32). *M.tb* may persist in lung tissue for years after culture negativity has been achieved through anti-TB treatment. Malherbe *et al.* (33) described an international study involving 113 HIV-negative patients with ^{18}F -FDG-PET/CT scans acquired at different time points before, during, and after anti-TB therapy. On completion of therapy, the study found that patients who had achieved a clinical cure had different patterns of ^{18}F -FDG uptake. In some patients, there was complete resolution of metabolic activity in lesions that were seen at baseline; in others, most

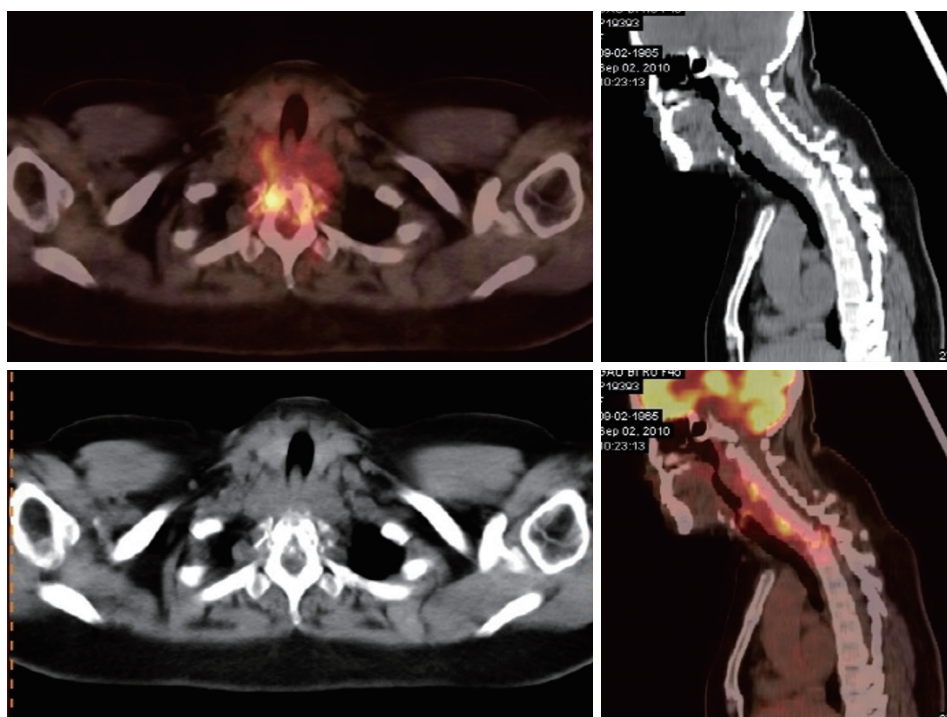


Figure 7 Axial and sagittal CT images and also axial and sagittal ^{18}F -FDG-PET/CT images in a 45-year-old woman with tuberculous spondylodiscitis and vertebral bone destruction. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

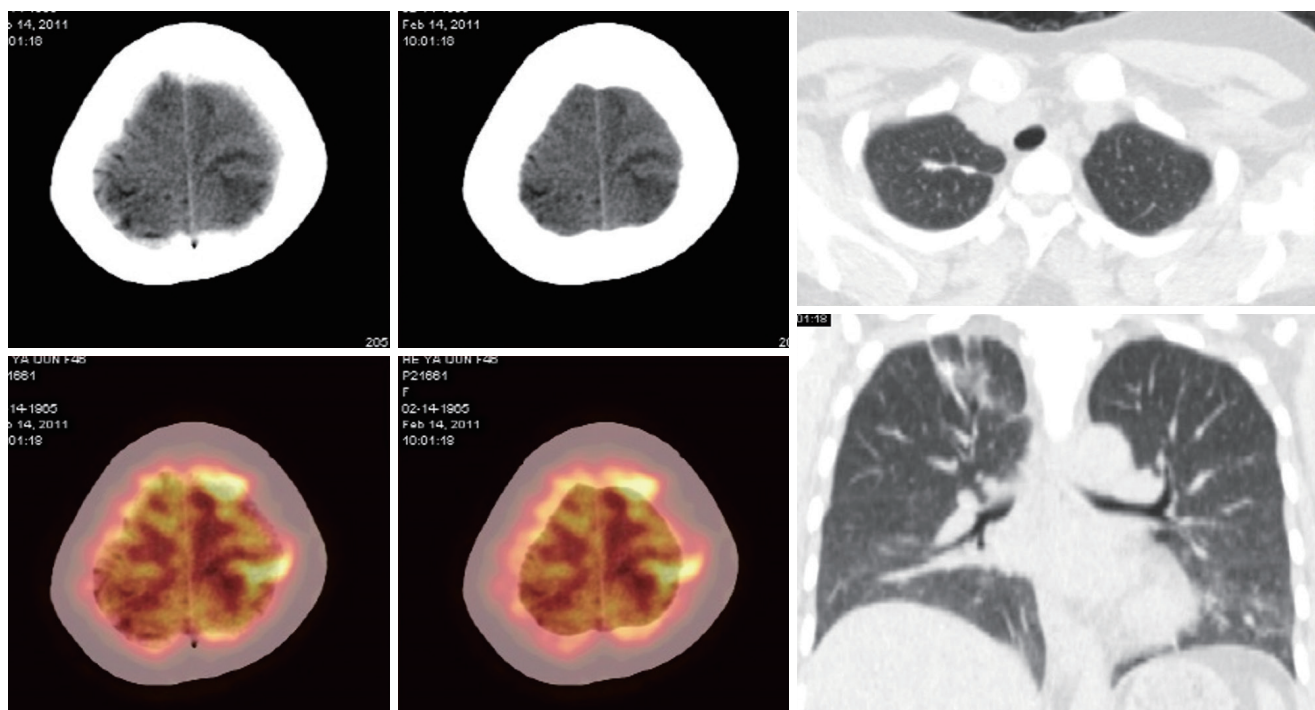


Figure 8 Axial and coronal CT and also axial ^{18}F -FDG-PET/CT in a 47-year-old woman show tuberculosis involving lung, brain, and meninges. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

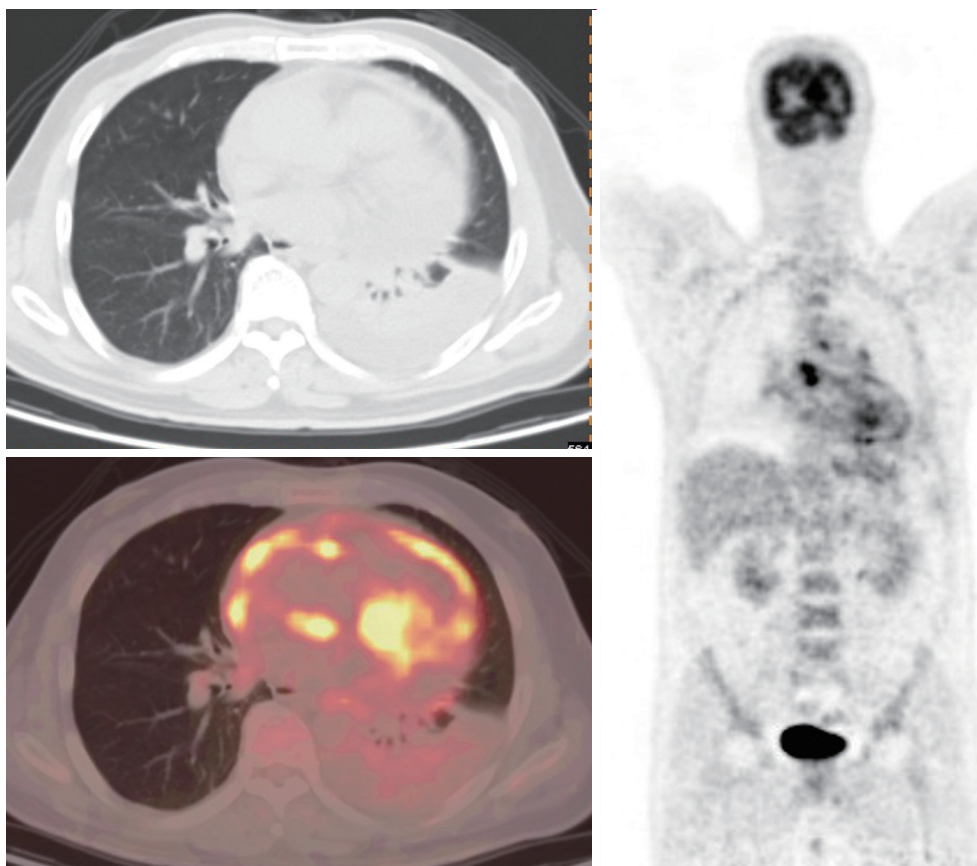


Figure 9 Axial CT and axial ^{18}F -FDG-PET/CT and coronal PET images in a 48-year-old woman with tuberculous pericarditis. Slight FDG uptake in the mediastinal lymph nodes is also noted. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

of the lesions resolved, with a few just above background or reference structure. In some others, however, some lesions were more intense than the baseline scan or new lesions appeared in patients who achieved and sustained a clinical cure. These dynamic patterns were found after anti-TB treatment and even a year later, regardless of drug sensitivity, sustained culture conversion or clinical cure. The new TB lesions may be due to differential response of the various TB lesions and microevolution in subpopulations of *M.tb* in patients. These findings present a challenge in interpretation of end-of-treatment ^{18}F -FDG scans. Viable *M.tb*, with the potential to elicit a host response, often persists even after clinically curative treatment.

Old healed TB usually presents on chest X-ray and CT scan as nodules with fibrotic scarring. These lung lesions often persist long after the end of successful treatment (33-35). It has been noted that latently infected persons who show evidence of fibrotic scarring are up to 15 times

more likely to develop disease (36). In a study involving 63 patients with radiological features suggestive of old healed TB lesions, 9 patients had increased ^{18}F -FDG uptake with a SUVmax of 1.5 or more in the old healed lesions (Figure 12) (37). These metabolically active old TB lesions do not necessarily represent active disease, but might reflect an equilibrium between the host's immune response and the replicating bacilli, and represent an increased risk of development of active TB.

The evidences above suggest that ^{18}F -FDG-PET findings must be carefully correlated with clinical data when interpreting end-of-therapy scans. High uptake of ^{18}F -FDG by PET may both represent ongoing active disease, or simply the host immune system activity that will ultimately prevail.

TB treatment monitoring by ^{18}F -FDG-PET

The slow growth of *M.tb* necessitates long therapy

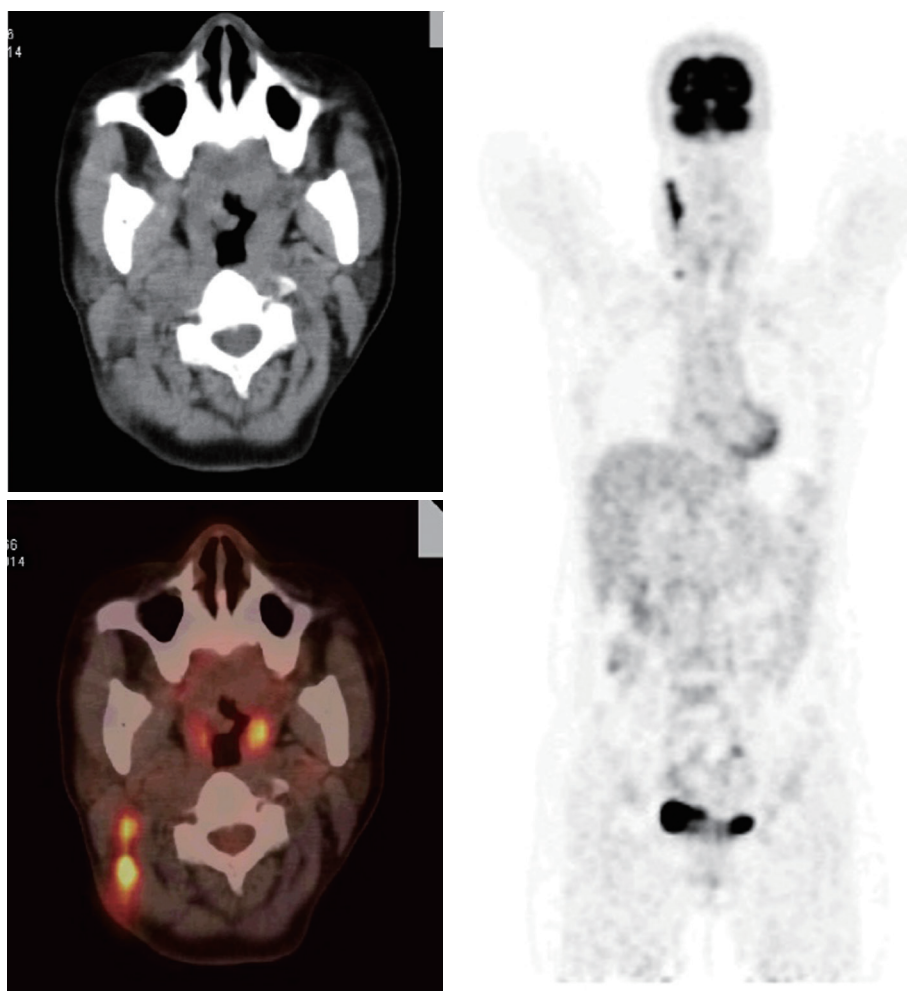


Figure 10 Axial CT, axial ¹⁸F-FDG-PET/CT and coronal PET images in a 48-year-old woman with tuberculosis involving cervical lymph nodes. FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

which renders treatment susceptible to failure due to non-adherence. Standard treatment duration for simple pulmonary or lymph node TB without resistance sign is 6 months according to WHO guidelines, with a relapse rate <5% (38). The treatment duration for EPTB is variable, and shortening treatment is also a major aim of anti-TB drug development. Early response assessment is a key element and particularly relevant for patients with no bacteriological proof and for patients with multi-drug resistant (MDR) or extensively-drug resistant (XDR) TB. Currently, response to treatment in patients with bacillus-positive TB is monitored principally by serial bacteriologic examinations, whereas responses in patients with bacillus-negative TB are usually monitored clinically or radiographically. Up to 20% of patients presenting with pulmonary TB are culture-

negative, and fluids for diagnostic analysis are unavailable in most EPTB patients. There is urgent need for biomarkers that allow rapid identification of patients who respond poorly to TB treatment (39,40). ¹⁸F-FDG-PET/CT for TB can assess early treatment response when radiological features may remain unchanged, with consequent significant impact on patient management (1,41,42). In a study cohort of 28 subjects with MDR-TB, Chen *et al.* (43) reported that selected imaging markers can be more sensitive than conventional sputum microbiology in distinguishing successful from unsuccessful treatment. ¹⁸F-FDG-PET/CT was the best method for early prediction of treatment results and long term outcome, with ¹⁸F-FDG-PET/CT at 2 months demonstrated 96% sensitivity for predicting treatment success and 79% specificity for predicting

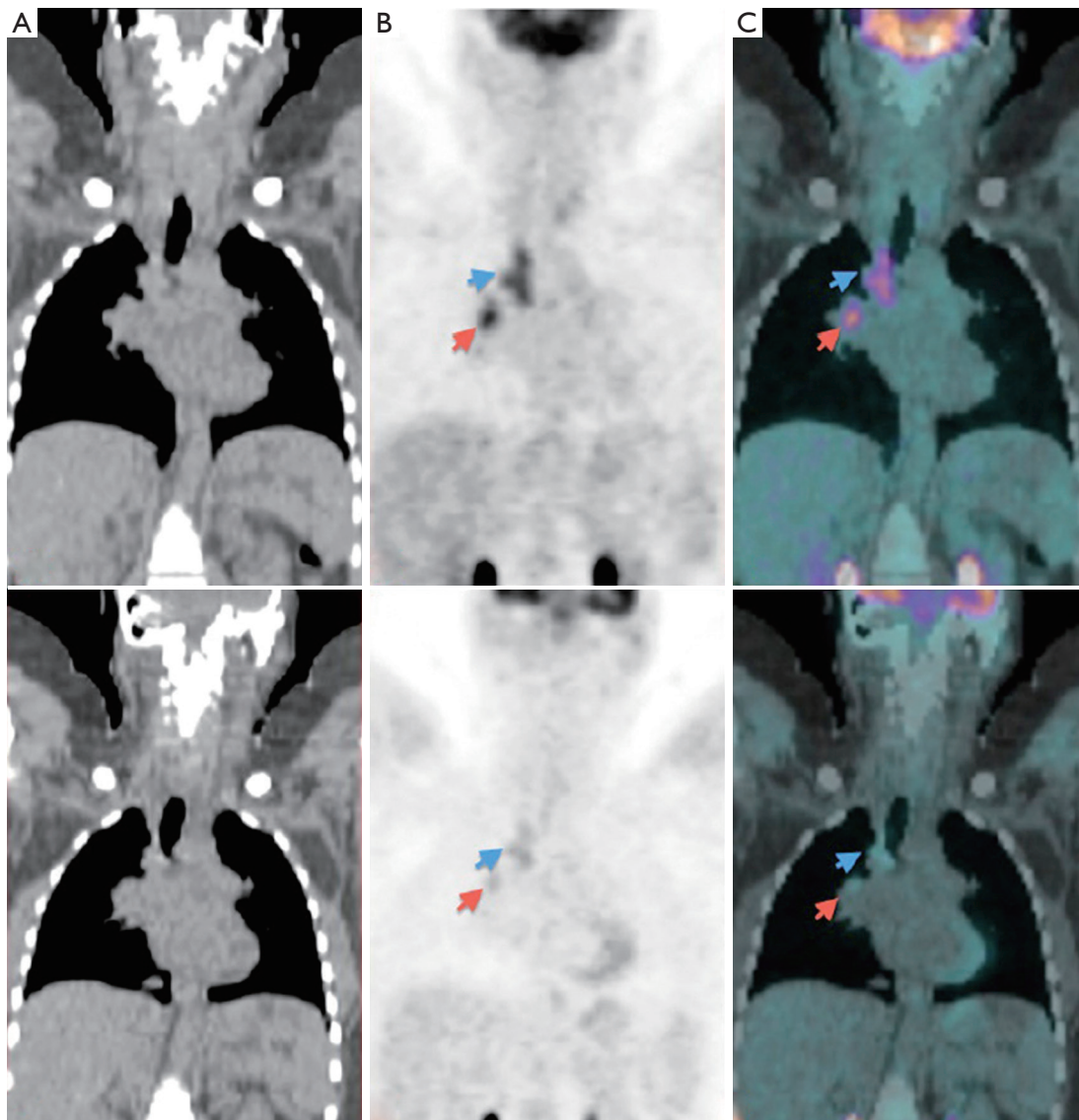


Figure 11 ^{18}F -FDG-PET/CT images of a 29-year-old woman who was the daughter of an active TB case and diagnosed with latent tuberculosis infection. (A) Coronal CT images. (B) Coronal PET images. (C) Coronal PET/CT fused images demonstrating FDG uptake in the right paratracheal region (blue arrow) and in the right hilar region (red arrow). Top panels are the initial study, and bottom panels are the study after 3 months of treatment with isoniazid demonstrating reduction in ^{18}F -FDG uptake. Reproduced with permission from (31). FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

treatment failure. Similar results were also accomplished by CT, but not until the 6 months scan (43).

Martinez *et al.* (44) reported ^{18}F -FDG PET/CT was used for therapeutic monitoring in 21 HIV-negative TB patients. They noted that lower SUVmax at month 1 of treatment is a marker for early improvement (Figure 13), and confirms a diagnosis of TB suspected on the basis of histological or clinical symptoms. If the SUVmax is higher

on repeated PET/CT, lack of adherence, drug resistance or a misdiagnosis should be considered. Stelzmueller *et al.* (17) reported that, in a cohort of 35 patients with pulmonary TB or EPTB, persistent ^{18}F -FDG PET/CT lesions in 15 patients and progressive lesions in four patients after a mean treatment duration of 16.1 months; and both components of ^{18}F -FDG PET and CT provided complementary information at initial evaluation and during follow-up.

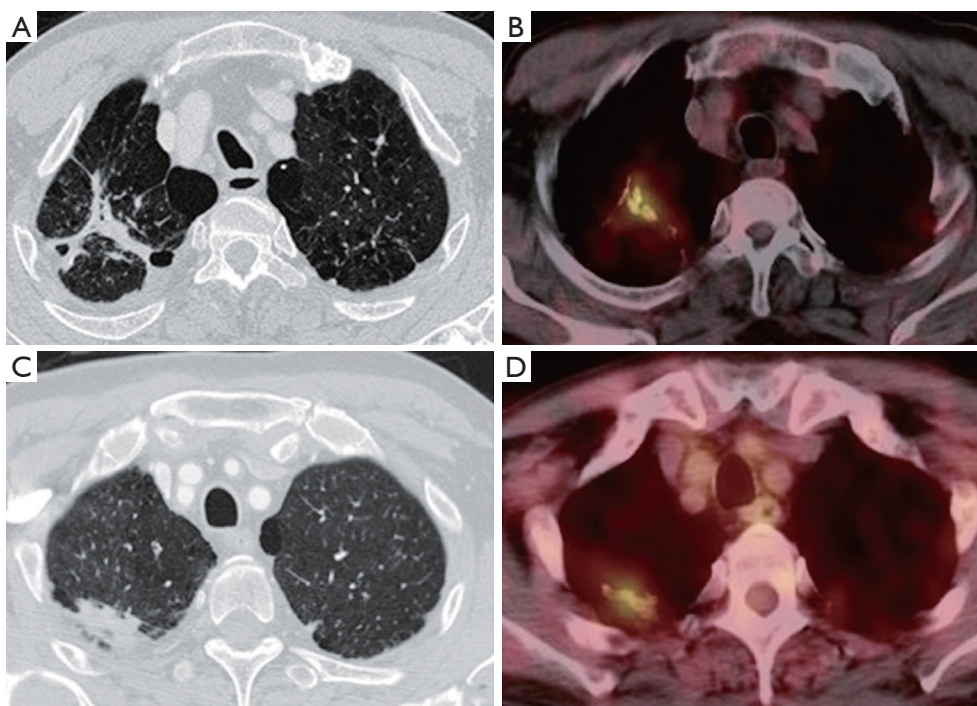


Figure 12 Axial chest CT and axial ^{18}F -FDG-PET/CT images of two subjects with old healed TB show high ^{18}F -FDG uptake. Fibrotic scar and calcified nodules suggesting old healed TB in the right upper lobe is observed on the chest CT (A) of a 76-year-old man without a history of TB. The SUVmax of the lesions was measured as 4.0 by ^{18}F -FDG PET/CT (B). Both the TST and IGRA were negative. Fibrotic scar and nodules in the right upper lobe are observed on the chest CT (C) of a 71-year-old man. He was treated for pulmonary TB 25 years earlier. The SUVmax of the lesions was measured as 2.2 by ^{18}F -FDG PET/CT (D). Both the TST and IGRA were positive. Reproduced with permission from (37). TST, tuberculin skin test; IGRA, interferon- γ release assay; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

Lefebvre *et al.* (45) reported that of 18 patients with lymph nodes TB, ^{18}F -FDG PET/CT correctly identified cure in nine patients (no ^{18}F -FDG uptake on posttreatment PET scans) and treatment failure in two patients. However, it should be noted that, due to possible measurement error, a SUVmax variation of <20–25% may not be clinically meaningful (46).

Patients with noncavitary tuberculomas may have no symptoms, and their cultures may be negative. While the majority of pulmonary tuberculomas decrease in size by anti-TB treatment during and even after treatment, a transient enlargement during the early period of treatment can also be observed (47,48). Imaging with ^{18}F -FDG PET/CT may help for these cases. If the lesion shows a decrease in activity, tuberculoma is likely responsive to anti-TB treatment; on the other hand, if ^{18}F -FDG PET/CT demonstrates an increase in lesion activity, then a change of current treatment regimen should be considered.

For TB involvement in the lymph nodes, Sathekge *et al.* reported two studies where ^{18}F -FDG PET/CT provided prognostic information of distinguishing anti-TB treatment responders from nonresponders (49,50). In 2011, Sathekge *et al.* (49) reported a study on the relationship between the baseline severity and extent of lymph nodes TB as assessed by ^{18}F -FDG PET and response to treatment at 4 months. There were 24 consecutive HIV patients with newly diagnosed TB who strictly adhered to the treatment regimen, thus treatment failure could be considered a surrogate marker for MDR. It was found that SUVmax of involved lymph node bastions and number of involved lymph node bastions were significantly higher in nonresponders. In 2012, Sathekge *et al.* (50) further described 20 consecutive HIV patients where ^{18}F -FDG PET/CT scans performed at 4 months after TB treatment as recommended (51). It was found that SUVmax value was significantly higher in nonresponders. Note that FDG

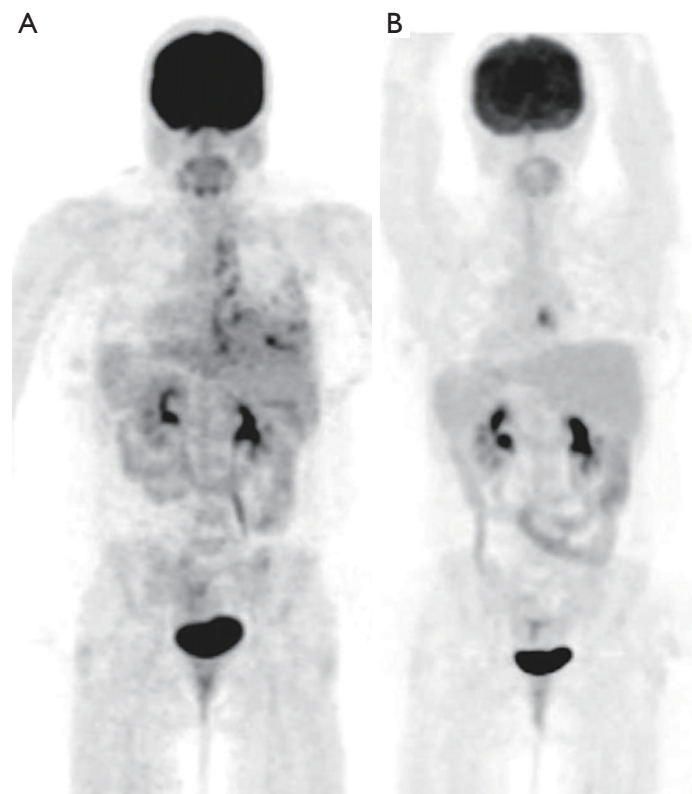


Figure 13 ^{18}F -FDG PET/CT in a 35-year-old woman with multidrug-resistant (MDR) tuberculosis before (A) and after (B) 1 month of anti-tuberculosis treatment. Regression of pulmonary and lymph node pathological foci are observed at the follow-up scan (B). Reproduced with permission from (44). FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

uptake by TB-involved lymph nodes of patients with HIV could be significantly higher than the uptake by TB-involved lymph nodes of HIV-negative patients (52), thus a different cut-off value may be applied in TB-infected HIV-negative patients to differentiate nonresponders from responders. Validation studies are also needed to confirm Sathekge *et al.*'s reports.

Patients with TB-HIV may start on anti-TB therapy and then later followed by antiretroviral therapy. This can cause increased inflammation in existing TB lesions because of immune reconstitution and may be misinterpreted as poor TB treatment response on imaging (3,53). A careful history taking and knowing the time of initiation of antiretroviral therapy are necessary to allow correct interpretation of ^{18}F -FDG-PET/CT images used to monitor anti-TB therapy.

Besides ^{18}F -FDG, other PET tracers have been investigated for imaging of TB, such as ^{11}C -choline, (^{18}F) fluoroethylcholine (^{18}F -FEC), 30-deoxy-30-(^{18}F)fluoro-L-thymidine (^{18}F -FLT), ^{68}Ga -citrate, (^{18}F) sodium fluoride

(^{18}F NaF) and radiolabeled anti-TB drugs (5). While some potentially promising results have reported, their clinical application has not been firmly established, and thus beyond the scope of the current review.

Conclusions

^{18}F -FDG-PET/CT not only is a useful clinical tool, it also help to understand the dynamics of pathophysiology and natural course of *M.tb* infection. ^{18}F -FDG-PET/CT is valuable in TB staging and locating EPTB, identifying patients with subclinical TB, and assessing early treatment response. However, ^{18}F -FDG-PET/CT is costly and involves radiation exposure, it does not need to be recommended to all patients with TB. Though its role in TB management is expanding, guidelines for the use of ^{18}F -FDG-PET/CT in TB clinical management have not been established. Currently the published case series mostly dealt with a few dozens of cases. Validation studies are required for many individual reports (54). There is a

strong need for creating and populating global repository of annotated images, where all existing observations, hypotheses and recommendations could be verified, with the help of machine learning, statistics and other data mining techniques (54-57). One up-and-coming project to consider is the TB Portals Program (<https://tbportals.niaid.nih.gov/>) (55). The current review supports the justification of the TB Portal collection of clinical images as well as clinical information.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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