Tuberculosis (TB) is currently the world’s leading cause of infectious mortality. Imaging plays an important role in the management of this disease. The complex immune response of the human body to Mycobacterium tuberculosis results in a wide array of clinical manifestations, making clinical and radiological diagnosis challenging. $^{18}$F-FDG-PET/CT is very sensitive in the early detection of TB in most parts of the body; however, the lack of specificity is a major limitation. $^{18}$F-FDG-PET/CT images the whole body and provides a pre-therapeutic metabolic map of the infection, enabling clinicians to accurately assess the burden of disease. It enables the most appropriate site of biopsy to be selected, stages the infection, and detects disease in previously unknown sites. $^{18}$F-FDG-PET/CT has recently been shown to be able to identify a subset of patients with latent TB infection who have subclinical disease. Lung inflammation as detected by $^{18}$F-FDG-PET/CT has shown promising signs that it may be a useful predictor of progression from latent to active infection. A number of studies have identified imaging features that might improve the specificity of $^{18}$F-FDG-PET/CT at some sites of extrapulmonary TB. Other PET tracers have also been investigated for their use in TB, with some promising results. The potential role and future perspectives of PET/CT in imaging TB is considered. Literature abounds on the very important role of $^{18}$F-FDG-PET/CT in assessing therapy response in TB. The use of $^{18}$F-FDG for monitoring response to treatment is addressed in a separate review.

Introduction

Tuberculosis (TB) is an infectious disease of pandemic proportions. In 2015, the World Health Organization estimated that there were 10.4 million new TB cases with 1.4 million deaths. Nearly 500,000 additional deaths occurred in patients with human immunodeficiency virus (HIV) and TB coinfection. Although the greatest burden of disease occurs in developing countries, developed countries are not spared from this menace. The HIV pandemic and the emergence of multidrug-resistant TB have been major impediments to control this infection.

The causative organism Mycobacterium tuberculosis (Mtb) is a complex acid-fast bacillus, which is relatively slow growing. The bacillus is able to survive in a harsh microenvironment within the patient in a quiescent state induced by a genetic program DevR regulon. A third of the world’s population is believed to harbor Mtb in this quiescent state, resulting in a latent TB infection (LTBI). Mtb is a successful pathogen with evidence of disease found in preserved bone tissue from 4000 BC. Mtb has been described as an obligate human pathogen because transmission of disease usually occurs from humans with fibro-cavitatory lung disease who expel the bacilli when they cough. Unlike humans, most animals succumb to the infection and die without developing the fibrosis and cavitation in the lung essential to transmission of the infection.
Risk Factors
The HIV pandemic, low socioeconomic circumstances with poor access to health care, overcrowding, smoking, and alcoholism are major drivers of the infection, especially in developing countries. Diabetes mellitus, end-stage renal failure, post-transplant states, lymphoma, and other conditions depressing host immune system are also important in the development of the infection. Health workers, patients in nursing homes, and prisoners are at greater risk of acquiring the infection. In developed countries, a large number of cases occur in migrants from endemic areas accounting for almost 50% of the cases seen.7-9

Transmission and Spectrum
TB is usually transmitted by the respiratory route. In the lung, *Mtb* may be completely cleared by the immune system, contained in a quiescent state or give rise to active infection.10 The outcome depends on the immune status of the host and results in a spectrum of TB states from no infection, latent through subclinical disease, to overt active disease.11,12

Interaction Between Host and *Mtb*
In patients with no previous exposure to *Mtb*, pattern recognition receptors expressed by macrophages, dendritic cells, and epithelial cells interact with *Mtb* ligands. This results in production of inflammatory cytokines and chemokines recruiting new cells to the site of infection and initiating granuloma formation by the innate immune system. The adaptive immune response usually occurs after approximately 4-6 weeks in humans, following the presentation of *Mtb* antigens by dendritic cells in lymph nodes. The innate immune system is less efficient in containing the infection and it has been suggested by some researchers to promote *Mtb* spread to other tissues.13 The adaptive immune system is predominantly a TH1-delayed type and offers the host protection against infection by sequestering *Mtb* in a granuloma, preventing it from spreading to other tissue with rapid bacillary killing occurring in the granuloma. The TB granuloma reaches structural and functional maturity after the acquisition of adaptive immunity. The early events of *Mtb* infection have been shown to influence the ultimate outcome, thus presenting potential targets for functional imaging to predict outcome at an early stage, which may be useful in the development of an effective vaccine or the development of successful interventional strategy against TB.13

Sites of Infection
Pulmonary disease is present in more than 80% of TB cases. TB can however affect any part of the body. It spreads to these organs by lymphatic, hematogenous, or direct extension from an infective focus. Extrapulmonary TB (EPTB) occurs in about 20% of cases, but can be seen in more than 50% of cases in immunosuppressed populations such as HIV.14,15 The presentation of active TB may be very variable. It may range from asymptomatic to severe disability as in Potts disease or 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 caused by the infection and to reduce the likelihood of transmission.

Diagnosis
Diagnosis of active TB can be challenging, and a high index of suspicion is required. The diagnosis of active pulmonary TB involves obtaining the appropriate history, eliciting relevant clinical signs, microbiologic evaluation for *Mtb*, and radiographic assessment of the thorax. Although microbiologic cultures are considered the gold standard for diagnosis, it may take as long as 8-10 weeks before results are available, and the yield has been reported by some authors to be as low as 80%.16 Microscopy results are available much earlier; however, this test suffers from a much lower diagnostic yield than culture. Moreover, in some populations such as children and very debilitated individuals, it may be impossible to get sputum samples for testing.17 Immunologic studies such as the tuberculin skin test (TST) and interferon gamma release assay (IGRA) can determine that a patient has been exposed to *Mtb* in the past but do not confirm the presence of active disease. The introduction of polymerase chain reaction assays, which are able to detect *Mtb* nucleic acid material, has improved TB diagnosis. A further advantage of these assays is their ability to detect nucleic acid sequences that suggest drug resistance. The sensitivity of these tests varies from 67% in sputum-negative patients with TB to 89% when used as an initial test in the diagnosis of TB.18 Imaging assumes a very important role in patients with suspected TB who are sputum negative, unable to produce sputum, or have EPTB.

Imaging
The chest X-ray is readily available in most parts of the world and relatively inexpensive compared with other imaging modalities and, in pulmonary TB, is the most common imaging modality used for the diagnosis of the infection. It plays a major role in the screening, diagnosis, and the response to the treatment of TB. The chest radiograph may be normal or show mild nonspecific changes in active TB.19 Chest CT is better at detecting and characterizing both subtle localized and disseminated parenchymal disease. It is also better in defining mediastinal lymphadenopathy. The diagnostic accuracy of chest X-ray in pulmonary TB has been reported to be 49% and chest CT 91%. High-resolution CT is particularly helpful in determining disease activity and revealing cavities and the presence of endobronchial spread.19,20

In EPTB, different imaging modalities are preferred for different sites of disease. CT for instance is useful for TB lymphadenitis and MRI is preferred for TB of the central nervous system and spondylodiscitis.

Functional Imaging in Tuberculosis
Nuclear medicine imaging techniques such as PET and SPECT are increasingly gaining prominence in the evaluation of infection and inflammation such as TB.21,22 Hybrid imaging with...
PET/CT using $^{18}$F-FDG has been investigated for its usefulness in the management of TB. Active TB lesions contain activated macrophages and lymphocytes, which have high levels of glucose utilization. This creates an $^{18}$F-FDG signal on PET imaging forming the basis of $^{18}$F-FDG-PET imaging in TB. The findings from $^{18}$F-FDG-PET are complementary to CT; however, some studies have reported that $^{18}$F-FDG-PET detects more lesions than CT scan in TB. In evaluation of pulmonary TB, specifically with $^{18}$F-FDG-PET/CT, many scenarios have been evaluated (Table 1). These include:

- detection and assessment of lesion activity
- distinguishing active from inactive disease
- discriminating TB from malignant lesions
- identification of patterns of metabolic uptake in the lung parenchyma and thoracic nodes
- prediction of developing active TB from LTBI
- identification of the risk of developing active TB in patients with old healed TB lesions
- identification of subclinical TB
- assessing patients after a clinical cure of pulmonary TB
- monitoring response to TB chemotherapy
- differentiating pulmonary TB from non-tuberculous mycobacterial infections

**Assessment of Lesion Activity**

$^{18}$F-FDG has been known to be able to detect infectious foci for more than 2 decades. The usefulness of $^{18}$F-FDG-PET/CT in detection of infectious foci and lesion assessment was evaluated in a study involving 24 patients with bacterial, tuberculous, and fungal infections. This study, which included 8 patients with tuberculous infections, found $^{18}$F-FDG-PET was useful for assessing lesion activity in infections including TB. Subsequently, another study found a mean peak standardized uptake value (SUV) of 4.2 ± 2.2 in pulmonary tuberculomas lesions in 9 of 10 consecutive patients. A number of other studies have reported varying SUV max for pulmonary TB lesions ranging from less than 0.79 to more than 10. The differences in SUV max reported by different authors may be related to the different TB lesions studied (cavities, infiltrates, or granulomas), host responses, and the different virulence of Mtb in the various population groups studied. TB cavities are relatively avascular compared with other TB lesions and are more likely to have higher metabolic activity in their walls because of the Warburg effect (Fig. 1). Differences in ethnicity (African vs Eurasian) have been found to have different immune responses in TB. There is also a geographical difference in the distribution of the lineages of Mtb, with some lineages reportedly more virulent than others. Although the interactions of these factors in determining disease phenotype are poorly understood, ethnicity appears to be an important determinant of clinical disease phenotype irrespective of the Mtb lineage. The SUV max of TB lesions reflects disease activity, which depends on several factors including host factors such as immune status, race, comorbid clinical conditions, and Mtb virulence. The most effective use of SUV max and other metabolic metrics such as lean body mass corrected standardized uptake value in TB is comparing the SUV max of an identified lesion over time to assess disease activity in response to therapy. This assessment must be carefully correlated with the patient’s clinical history as a lesion may appear to progress after a patient with HIV-TB coinfection starts antiretroviral therapy while on TB treatment. This is because of immune reconstitution may cause inflammation with $^{18}$F-FDG uptake and could be misinterpreted as poor response to anti-TB chemotherapy on an $^{18}$F-FDG-PET/CT study.

**Distinguishing Active and Inactive Pulmonary Lesions**

Lesion activity as determined by $^{18}$F-FDG correlates with disease activity. In a study of 25 patients, $^{18}$F-FDG-PET was able to distinguish active from inactive pulmonary tuberculomas using dual time-point imaging. Active pulmonary tuberculomas had a higher SUV max at 1 and 2 hours and a greater increase in SUV max from the early to the late imaging compared with inactive pulmonary tuberculomas. The study found that using an SUV max of 1.05 for the 1-hour study, it was possible to separate active TB from inactive TB with a 100% sensitivity and specificity. Metabolic activity by $^{18}$F-FDG-PET/CT has been demonstrated in patients following treatment after a clinical cure who did not develop disease on follow-up. This may represent a state of equilibrium achieved after treatment where the immune system is able to contain replicating bacilli and prevent overt disease. Interpretation of metabolic activity in lesions with morphologic evidence of healed or old TB lesions must be carefully correlated with the patient’s clinical status. The absence of clinical symptoms of TB or elevated inflammatory markers of infection would favor a successful host immune response, whereas the presence of clinical symptoms or recent onset of immune suppression would tip the balance in favor of active TB.

**Distinction of Pulmonary TB From Malignant Pulmonary Lesions**

$^{18}$F-FDG is a nonspecific tracer accumulating in both inflammatory and malignant processes. Numerous authors have reported TB causing false-positive findings in patients being evaluated for malignancy. A very common clinical problem is the differentiation of a malignant from a benign pulmonary nodule. $^{18}$F-FDG-PET has been reported by some authors and reviews to be helpful for this clinical indication. $^{18}$F-FDG however does not reliably distinguish between TB and malignant lesions. This limits the role of $^{18}$F-FDG-PET/CT for this indication in regions where TB is prevalent. A study evaluated the use of dual time-point $^{18}$F-FDG-PET/CT in this setting for pulmonary lesions. The study assessed 30 patients with solitary pulmonary nodules: 14 had malignant lung lesions and 16 had benign lesions including 12 with pulmonary TB. The early, late, and percent change in SUV max could not distinguish benign from malignant lesions, although some discrimination was possible when the patients with TB were excluded from the analysis. The findings suggest that in TB endemic areas FDG-PET/CT is not helpful for reducing futile thoracotomies.
Table 1: Selected Published Studies Showing the Evolving Role of 18F-FDG-PET or PET/CT in TB Over the Years in Clinical Studies (Excluding Response Assessment)

<table>
<thead>
<tr>
<th>Year Published</th>
<th>Author</th>
<th>Journal</th>
<th>Feature of TB Evaluated</th>
<th>No of Patients With TB</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>Ichiya et al</td>
<td>Ann Nucl Med</td>
<td>Detection and lesion assessment</td>
<td>8</td>
<td>Determined TB showed 18F-FDG uptake</td>
</tr>
<tr>
<td>2000</td>
<td>Goo et al</td>
<td>Radiology</td>
<td>Lesion activity assessment</td>
<td>10</td>
<td>Assessed lesion activity of pulmonary tuberculomas</td>
</tr>
<tr>
<td>2008</td>
<td>Kim et al</td>
<td>Eur J Nucl Med Mol Imaging</td>
<td>Active versus inactive tuberculomas</td>
<td>25</td>
<td>Determined that 18F-FDG-PET/CT was able to differentiate active and inactive tuberculomas</td>
</tr>
<tr>
<td>2010</td>
<td>Sathekge et al</td>
<td>S Afr Med J</td>
<td>TB versus malignancy in pulmonary nodules</td>
<td>12</td>
<td>Unable to distinguish TB from malignancy</td>
</tr>
<tr>
<td>2012</td>
<td>Soussan et al</td>
<td>Eur J Radiol</td>
<td>Patterns of pulmonary TB</td>
<td>16</td>
<td>Identified 2 patterns reflecting the immunity of host</td>
</tr>
<tr>
<td>2012</td>
<td>Sathekge et al</td>
<td>Eur J Nucl Med Mol Imaging</td>
<td>Predictive value in response to therapy</td>
<td>20</td>
<td>Lymph node features at 4 months without a baseline predict patients who may respond to treatment</td>
</tr>
<tr>
<td>2013</td>
<td>Dong et al</td>
<td>Clin Nucl Med</td>
<td>TB pericarditis</td>
<td>5</td>
<td>Identified features distinguishing TB from idiopathic pericarditis</td>
</tr>
<tr>
<td>2013</td>
<td>Martin et al</td>
<td>HIV Med</td>
<td>TB diagnosed in HIV patients with FUO</td>
<td>8</td>
<td>TB and other causes of FUO could be correctly interpreted on PET/CT</td>
</tr>
<tr>
<td>2014</td>
<td>Jeong et al</td>
<td>J Korean Med Sci</td>
<td>Radiographic old healed TB lesions or LTBI</td>
<td>76†</td>
<td>18F-FDG uptake was associated with factors predicting risk of active TB</td>
</tr>
<tr>
<td>2014</td>
<td>Ghesani et al</td>
<td>Am J Respir Crit Care Med</td>
<td>Patient with LTBI</td>
<td>5*</td>
<td>18F-FDG may be useful to study the early event in LTBI</td>
</tr>
<tr>
<td>2016</td>
<td>Del Giudice et al</td>
<td>Biomed Res Int</td>
<td>Distinguishing TB from non-TB mycobacteria</td>
<td>6</td>
<td>Was of value in distinguishing TB from non-TB mycobacteria</td>
</tr>
<tr>
<td>2016</td>
<td>Esmail et al</td>
<td>Nat Med</td>
<td>Subclinical TB in LTBI</td>
<td>35*</td>
<td>Features to identify subclinical TB in patients with LTBI</td>
</tr>
<tr>
<td>2016</td>
<td>Malherbe et al</td>
<td>Nat Med</td>
<td>Patients after TB cure</td>
<td>50</td>
<td>Demonstrated the need for host immune response in keeping a disease-free state. May have a predictive value in determining relapse TB</td>
</tr>
<tr>
<td>2016</td>
<td>Wang et al</td>
<td>Medicine (Baltimore)</td>
<td>TB peritonitis</td>
<td>25</td>
<td>Identified imaging findings that suggested TB peritonitis or carcinoma in peritonitis</td>
</tr>
<tr>
<td>2016</td>
<td>Sun et al</td>
<td>PLoS One</td>
<td>TB pleuritis</td>
<td>30</td>
<td>The addition of CT findings to PET uptake improved the specificity of the study</td>
</tr>
<tr>
<td>2016</td>
<td>Gambhir et al</td>
<td>J Neurol Sci</td>
<td>TB meningitis</td>
<td>10</td>
<td>18F-FDG-PET/CT plays a complementary role to MRI in intracranial lesions and detected extracranial TB</td>
</tr>
<tr>
<td>2017</td>
<td>Lefebvre et al</td>
<td>Nucl Med Biol</td>
<td>TB lymphadenitis</td>
<td>18</td>
<td>Early confirmation of TB by 18F-FDG-PET/CT-guided biopsy. Detected unknown sites of lymphadenitis and extranodal TB.</td>
</tr>
<tr>
<td>2017</td>
<td>Bassetti et al</td>
<td>Skeletal Radiol</td>
<td>Tb spondylodiscitis</td>
<td>10</td>
<td>Determined that 18F-FDG-PET/CT was useful in differentiating TB from pyogenic spondylodiscitis</td>
</tr>
</tbody>
</table>

*Patients with positive QuantiFERON test.
†Patients with radiographic evidence of old healed TB.
differentiate TB from malignant pulmonary lesions. To improve the ability to differentiate TB from malignancy, other PET tracers have been used, alone or in combination with $^{18}$F-FDG, with mixed results (Table 2).

**Patterns of Thoracic TB on FDG-PET/CT**

TB has been classically divided into primary and post primary disease based on the time elapsed since infection was acquired, site of infection in the lung, and pathology of the TB lesions. Using $^{18}$F-FDG-PET/CT, 2 distinct patterns of TB were identified in 1 study. These patterns were a predominantly lung pattern and a predominantly lymphatic pattern. The study examined 16 patients with pulmonary TB and 9 were found to have the lung pattern and 7 had the lymphatic pattern. Patients with the lung pattern presented with predominantly pulmonary symptoms and had predominantly parenchymal lung involvement (Fig. 1). The parenchymal lung involvement was usually consolidation with or without cavitation surrounded by micronodules. The mediastinal and hilar nodes in the patients with the lung pattern were only moderately enlarged with moderate $^{18}$F-FDG uptake. In the lymphatic pattern, patients had predominantly systemic symptoms and all patients had EPTB. Mediastinal and hilar lymph nodes were significantly larger and metabolically more active than those in patients with the lung pattern (Figs. 2, 6, 8, and 10). This pattern of metabolic activity is in keeping with newer insights into TB by biomolecular studies, which show that the radiographic appearance depends more on the host immunity rather than on the time of acquisition of infection to the development of disease. Patients with relatively intact immune function develop the lung pattern, whereas those with a compromised immune system are more likely to develop the lymphatic pattern.
**Prediction of Developing Active TB in LTBI**

One area of clinical importance in the global effort to control TB is to identify patients with LTBI who are at risk of developing active disease. TB is a spectrum ranging from LTBI to active disease. It is important to identify patients with subclinical TB and those with LTBI who are at risk of progressing to active TB. 18F-FDG-PET/CT was used to identify reactivation risk in cynomolgus macaques with LTBI. The test predicted the risk of reactivation TB with a 92% accuracy. In comparison with animals that did not reactivate, factors that were found to predict reactivation TB included:

- higher total lung 18F-FDG avidity
- higher SUV max of the most intense LTBI granuloma present
- larger size of the largest LTBI granuloma
- higher cumulative 18F-FDG avidity on metabolically active mediastinal lymph nodes
- more extrapulmonary sites of LTBI

In humans, a study suggested a similar role for 18F-FDG-PET/CT in patients with radiological evidence of old healed TB lesions, but with no clinical evidence of active infection. Nearly 80% of the patients had a positive TST or IGRA test, indicating they had LTBI. High 18F-FDG uptake in the old TB lesions correlated with risk factors for progression to active TB.

**PET/CT in Old Healed TB Lesions**

Old healed TB with radiographic lesions suggestive of TB sequelae without clinical or microbiological evidence of active TB is one of the strongest risk factors for subsequent development of active TB. Old healed TB usually presents on chest X-ray and CT scan as pulmonary nodules in the upper lobes or hilar regions with fibrotic scarring and volume loss. There may also be evidence of bronchiectasis or pleural scarring with no radiographic evidence of active disease such as tree-in-bud pattern. In a study involving 63 patients with radiological features suggestive of old healed TB lesions, 9 patients had increased 18F-FDG uptake with an SUV max of 1.5 or more in the old healed lesions. Higher 18F-FDG uptake was associated with patients’ age, history of previous TB, and extent of old lesions, which are known risk factors for development of active TB.

**PET/CT in Subclinical TB**

18F-FDG-PET/CT identified 10 patients with a subclinical TB infection from among 35 patients with HIV and LTBI in 1 study. The patients were asymptomatic, anti-retroviral naive HIV-1 positive, with CD4 counts ≥350 and positive QuantiFERON Gold in tube test. Patients who had infiltrates, fibrotic scars, and active nodules on CT were more likely to progress and thus considered to have subclinical TB. These lesions were not detected on plain radiographs and were often 18F-FDG avid. Patients with normal lung parenchyma or those with discrete nodules that did not have FDG uptake were considered to have LTBI with no evidence of subclinical TB. These patients were followed up for 6 months. Out of the 10 patients with subclinical disease, 4 required treatment for active TB compared with none in the 25 with no evidence of subclinical disease. The study suggests that 18F-FDG-PET/CT can be used to identify patients with subclinical TB. This is particularly important in patients with HIV-TB coinfection who...
are at risk of TB immune reconstitution syndrome, which may be fatal when antiretroviral therapy is initiated without recognizing the subclinical TB.

**PET/CT in Patients After Achieving a Clinical Cure**

Persistent metabolic activity in patients who had achieved a clinical cure for pulmonary TB has been reported in literature. In this study, \(^{18}\)F-FDG-PET/CT findings at 1 year after completion of anti-TB chemotherapy were compared with scans that were done 6 months after they had started anti-TB therapy. Fifty patients who had achieved a clinical cure for TB after 6 months of treatment were evaluated. Eight of these 50 patients relapsed within 2 years of completion of treatment. Three of the 8 relapsed after the 1-year post treatment scan, whereas the rest relapsed earlier. Only 32% of patients had complete resolution of the lesions seen on the earlier scan irrespective of structural abnormalities still present. The study also noted that 34% of the patients had a mixed response, which was defined as at least 1 new lesion or more intense \(^{18}\)F-FDG-avid lesion on the 1-year post-treatment scan compared with the scan at 6 months of therapy. The remaining 34% had improved scans where at 12 months, there was decrease in \(^{18}\)F-FDG avidity in all lesions seen on the 6-month scan but with persistent activity in one or more lesions higher than the background or reference structure. The 3 patients who developed recurrent TB after 1 year had a mixed response. None of the patients who had complete resolution of lesions on the 1-year scan was diagnosed with recurrent TB in the 2-year follow-up period. These findings suggest that \(^{18}\)F-FDG-PET/CT may have some predictive value for developing recurrent TB following a cure. Furthermore, the study found a mixed response in 28% of patients who had a durable cure defined by the authors as the absence of a relapse of TB in the period in which these patients were followed up after completion of treatment. The study also identified mRNA of *Mtb* from the sputum and bronchoalveolar lavage samples of patients who had a durable cure. This suggests TB treatment

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*Figure 2* Twenty-five-year-old woman with HIV presented with night sweats but no pulmonary symptoms. \(^{18}\)F-FDG-PET/CT allowed early diagnosis of TB by directing biopsy. The study illustrates importance of imaging in a patient who could not produce sputum. If patient was able to produce sputum, it may have been sputum negative as there is little parenchyma lung involvement. It also demonstrates the predominantly lymphatic pattern that has been described in \(^{18}\)F-FDG-PET/CT.
may not eradicate all the bacilli, and that the immune system of the host is important in maintaining a disease-free state after TB treatment and clinical cure. This implies that patients may still have metabolically active lesions on completion of anti-TB treatment, thus $^{18}$F-FDG-PET/CT finding must not be interpreted in isolation but must be correlated with other clinical data.

**Differentiation of TB and Non-Tuberculous Mycobacteriosis**

TB and non-tuberculous mycobacteria may have a similar presentation. Microscopy may isolate acid-fast bacillus in both diseases. The differentiation of the 2 entities is by culture or polymerase chain reaction. This differentiation is important as treatment is different. The role of $^{18}$F-FDG-PET/CT in distinguishing TB from non-tuberculous mycobacteriosis is not clearly established. An early study found slightly higher albeit insignificant mean SUV max of $5.15 \pm 1.56$ for non-TB mycobacteriosis compared with $4.96 \pm 1.61$ for pulmonary TB lesions. A subsequent investigation found the opposite. The mean SUV max of TB lesions was $10.07 \pm 6.45$, which was significantly higher than the non-tuberculous mycobacteriosis, which was $3.59 \pm 2.32$. The difference in the results of these 2 investigations could be caused by differences in the subtypes of non-tuberculous mycobacteriosis strains or to the type of pulmonary lesions that were evaluated. Because of differences in factors affecting metabolic activity in these pulmonary lesions, SUV alone cannot be used to distinguish one entity from the other.

**Other PET Tracers in Pulmonary TB**

Several PET tracers have been used in the evaluation of pulmonary lesions suspected to be TB usually in an attempt to distinguish TB from malignancy (see Table 2). These tracers include:

- gallium-68 citrate
- carbon-11 choline and fluorine-18 labeled choline derivatives
- fluorine-18 fluoro-L-thymidine
- gallium-68 alfatide
- gallium-68 prostate-specific membrane antigen
- fluorine-18 fluoro-misonidazole

**Gallium-68 Citrate**

PET/CT with gallium-68 (68Ga) tracers has increased considerably over the last few years. Ga68 is obtained from a generator, is readily available, relatively inexpensive, and easy to label. In a study to evaluate the use of Ga68 citrate PET/CT in TB, a mean SUV max of $3.99 \pm 2.88$ for pulmonary TB lesions was found. In another study, Ga68 citrate PET detected more EPTB lesions than did CT. Ga68 citrate is believed to accumulate in inflammatory lesions by nonspecific and specific transferrin dependent and independent mechanisms similar to Ga67 citrate. Ga68 citrate PET/CT may be a useful alternative to FDG-PET/CT for assessing TB; however, further studies are required. Figure 3 illustrates the use of Ga68 citrate in a patient with TB-HIV coinfection demonstrating TB lymphadenitis.

**C11- and F18-labeled Choline Derivatives**

Choline is a precursor for biosynthesis of the cell membrane. There is increased uptake of choline in cells with increased turnover. A study evaluated the uptake rates of $^{18}$F FDG and C11 choline in lung cancer, pulmonary TB, and atypical mycobacterial infection in relation to lesion size. The study included 97 patients with lung cancer, 14 untreated patients with TB, and 5 patients with untreated atypical mycobacterial infection. For tumors larger than 1.5 cm in diameter, the uptake of the tracers in the 3 pathologies was distinct. Lung cancer showed high uptake with both tracers. TB showed high FDG uptake but low choline uptake. Atypical mycobacterial infection showed low uptake for both tracers. This suggests that performing dual-tracer imaging with FDG and choline derivatives may improve the specificity of FDG for differentiating TB from malignancy and from atypical mycobacterial infections. In the literature, the use of $^{18}$F FDG and an F18 fluoroethylcholine to distinguish TB from malignancy has been reported.

**F18 Fluoro-L-Thymidine**

F18 fluoro-L-thymidine (FLT) is incorporated into nucleic acid-like thymidine, and imaging thus reflects cell proliferation. The difference in mechanisms of uptake of FDG and FLT has been investigated for their value in distinguishing benign from malignant lesions. In a multicenter trial to evaluate the role of FLT in assessment of pulmonary lesions in 55 patients, 16 patients had pulmonary TB, 16 had malignancy, and 23 had other benign conditions. FDG was more sensitive (87.5%) than FLT (68.75%), whereas FLT was more specific (76.92%) than FDG (58.97%) for differentiating benign and malignant lesions. A combination of the 2 tracers, however, yielded a sensitivity of up to 100% and a specificity of 89.74%. The best separation of TB, malignancy, and other benign lung lesions was achieved by using the ratio of FLT to FDG uptake. A ratio of less than 0.4 was more likely to be TB or other benign disease, whereas a ratio between 0.4 and 0.9 suggested a malignant process. A ratio above 0.95 suggested benign, non-TB disease. Using these cutoff values, the accuracy of differentiating TB from other diseases can be improved.

**Ga68 Alfatide**

Ga68 alfatide is a PET tracer that images angiogenesis. There is abundant neovascularization in tumor lesions driven by the high metabolic demand of cancer cells compared with TB granulomas. In TB granulomas, there is a sharp decrease in microvessel density from the edge of the lesion to the avascular center. It is this difference between malignant lesions and TB that is exploited in Ga68 alfatide imaging. A study compared the diagnostic potential of $^{18}$F FDG and Ga68 alfatide II in the differentiation of TB and non–small cell lung cancer (NSCLC). This study included 34 patients: 13 with pulmonary TB and 21 with NSCLC. The SUV max and SUV...
mean of Ga68 alfatide for NSCLC were $3.83 \pm 0.22$ and $2.29 \pm 0.20$, respectively, which was significantly higher than the values for TB, which were $2.90 \pm 0.23$ and $1.75 \pm 0.14$, respectively. The authors concluded that Ga68 alfatide was superior to F18 FDG in distinguishing of NSCLC from pulmonary TB. These findings suggest a potential role for noninvasive distinction of TB from malignancy by PET/CT using PET tracers that image angiogenesis; however, validation with larger studies is needed.

**Ga68 Prostate-specific Membrane Antigen**

In patients with prostate cancer, the differentiation of lung metastasis from other lesions may be a problem. A study evaluated the role of Ga68 prostate-specific membrane antigen (PSMA) in this differentiation. The study assessed 89 pulmonary lesions in 45 patients. Pulmonary lesions were classified based on histopathology and response to hormone deprivation therapy. The study found 76 lesions to be metastatic prostate cancer, 7 primary lung cancers, 2 TB, and 4 lesions of unknown etiology. Ga68 PSMA uptake was demonstrated in 2 proven active TB lesions. The SUV max of the TB lesions was 7.8 and 2.5, and the mean SUV max was $4.4 \pm 3.3$ and $5.6 \pm 1.6$ in prostate metastasis and primary lung cancer, respectively. Ga68 PSMA may also accumulate in old lesion of patients with TB who have achieved a clinical cure probably related to post-inflammatory changes (Fig. 4). These data suggest that Ga68 PSMA cannot be used to discriminate TB from malignant disease in the lungs.

**F18 Fluoromisonidazole**

F18 fluoromisonidazole (FMISO), a PET tracer that images hypoxia, has been used to study tumor biology in malignant cells. Hypoxia induces the accumulation of hypoxia-inducible factor 1 alpha, which synergistically increases
collagenase activity resulting in lung destruction and cavitation. The pathogenesis of TB is complex with hypoxia playing a key role both in LTBI and in active disease. Five patients with pulmonary TB were imaged with F18 FMISO and demonstrated tracer accumulation in TB consolidation and around pulmonary cavities. Blood vessels are usually scanty or absent in TB cavities. F18 MISO demonstrated heterogeneous levels of hypoxia in TB lesions within the same patient. The findings were consistent with pathologic findings that determined there was considerable variation in the TB lesions found in the same patient. This study suggests that F18 FMISO and other hypoxia tracers may help improve our understanding of TB pathogenesis and probably help in the development of therapeutic interventions by identifying susceptible lung tissue before irreversible damage occurs.

**Extrapulmonary TB**

TB can affect any part of the body, and there have been several reports and studies on 18F-FDG-PET/CT in TB. Lymph nodes, the pleura, abdomen, skeleton, and central nervous system are commonly affected sites. Imaging plays an important role in the early diagnosis of EPTB.

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**Figure 4** Patient being assessed for prostate cancer with Ga68 PSMA. Tracer uptake noted in the apex of the left upper lobe. Patient had just completed treatment for pulmonary TB, which involved the left upper lobe. CT findings were more in keeping with post-infective changes. Ga68 PSMA is unable to distinguish tuberculosis from metastatic lung cancer, but CT features and history increased specificity of the study.
**TB Lymphadenitis**

TB lymphadenitis is the most common site of EPTB. The disease may be localized or generalized. FDG has been shown to demonstrate both the pattern and the site of disease in various reports. \(^{79,80}\) \(^{18}F\)-FDG-PET/CT usually shows metabolic activity in a matted group of lymph nodes, which may have a central area of hypometabolism depending on the degree of caseous necrosis (Fig. 5). \(^{15}\) FDG-PET identified more lesions than CT in some studies. \(^{24,25}\) The clinical usefulness of \(^{18}F\)-FDG-PET/CT in TB lymphadenitis was evaluated in 1 study. \(^{42}\) This study included 18 patients: 13 with disseminated lymphadenitis and 5 with localized disease. Initial evaluation by \(^{18}F\)-FDG-PET/CT allowed rapid confirmation of TB diagnosis by guiding biopsy in 5 patients. \(^{18}F\)-FDG-PET/CT also detected unknown extranodal sites in 9 patients. Among the patients with disseminated nodal disease, \(^{18}F\)-FDG-PET/CT detected TB lymphadenitis in 10 patients who had not been previously detected by conventional imaging. This study demonstrates that \(^{18}F\)-FDG-PET/CT allows an accurate pre-therapeutic lymph node mapping, detecting previously undiagnosed TB lymphadenitis and also helps in early TB confirmation.

Different studies have been conducted to help distinguish or find features favoring one etiology over another. Dual-time-point imaging with \(^{18}F\)-FDG-PET/CT was not helpful for differentiating TB from other conditions including sarcoidosis, HIV lymphadenopathy, and lymphoma. Ga68 alfatide PET/CT was found to be useful in the differentiation of lymphadenopathy because of NSCLC and TB lymphadenitis in 1 study; however, validation in larger studies is still needed. \(^{61}\) Figure 6 demonstrates extensive TB lymphadenitis in a patient with TB-HIV coinfection; the nodes responded to anti-TB therapy.

**TB Pleuritis**

Pleural TB is the second most common site of EPTB. Pleural involvement occurs in up to 30% of TB cases in some high-burden TB endemic areas. \(^{81}\) One study evaluated the role of \(^{18}F\)-FDG-PET/CT for distinguishing benign from malignant pleural effusions. \(^{90}\) The study included 176 patients with pleural effusion, 108 with malignant effusion and 68 with benign effusions, including 30 with tuberculous effusions. Combining the PET and CT characteristics of the pleura on the \(^{18}F\)-FDG-PET/CT scan, the study determined the specificity for benign lesions to be 92.6%. PET-FDG was useful for detecting malignant lesions but lacked sensitivity, whereas CT was useful in excluding malignant involvement of the pleura. Twenty-five (83.3%) of the 30 patients with TB were correctly classified as benign using \(^{18}F\)-FDG-PET/CT with 5 falsely classified as malignant. Seventeen (56.7%) of the patients with TB demonstrated FDG uptake; however, based on CT pattern, 12 of these were diagnosed as benign on the \(^{18}F\)-FDG-PET/CT findings. Patterns on FDG-PET/CT found that correctly identified TB as a benign effusion were:

- encapsulated effusion irrespective of the \(^{18}F\)-FDG uptake
- no or slight pleural thickening with no \(^{18}F\)-FDG uptake
- no or slight pleural thickening with diffuse \(^{18}F\)-FDG uptake

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\(^{118}\) A.O. Ankrah et al.
• no or slight pleural thickening with diffuse $^{18}$F-FDG uptake at costodiaphragmatic recesses

Patterns on FDG-PET/CT because of TB that led to falsely characterizing the effusion as malignant were:

• no pleural thickening with multiple nodular $^{18}$F-FDG uptake
• nodular pleural thickening with nodular $^{18}$F-FDG uptake
• irregular pleural thickening with diffuse $^{18}$F-FDG uptake

The study suggests that $^{18}$F-FDG-PET/CT was useful in distinguishing malignant from benign pleural effusions, including those caused by TB. The CT findings of $^{18}$F-FDG-PET/CT were very important in improving the specificity of the study. In the evaluation of the pleura on $^{18}$F-FDG-PET/CT, TB pleuritis should be included in the differential diagnosis in the proper clinical setting. Figure 7 demonstrates TB pleuritis, which may be limited involving part of the pleura or generalized involving the whole pleura.

Abdominal TB
Abdominal TB generally affects the lymph nodes, peritoneum, ileocecal valve, colon, liver, spleen, and adrenal gland. Solid viscera are affected to a greater extent than the gastrointestinal tract. Abdominal TB may be difficult to diagnose, as the clinical features are usually nonspecific and related to the area of interest. On $^{18}$F-FDG-PET/CT imaging, it may present at multiple sites and may mimic malignancy.

Abdominal TB Lymphadenitis
The lymph nodes demonstrate metabolic activity on $^{18}$F-FDG-PET, which cannot be distinguished from most other causes of abdominal lymphadenopathy. Findings on $^{18}$F-FDG-PET/CT may vary depending on the site. The abdominal nodes may be focal or generalized. Literature has reported cases of obstructive jaundice because of TB lymphadenitis blocking the common bile duct. In 1 case of abdominal TB evaluated with $^{18}$F-FDG-PET/CT, the $^{18}$F-FDG-avid lymph node noted on $^{18}$F-FDG-PET/CT was suspected to be a pancreatic malignancy, and histology was needed to establish the diagnosis. TB lymphadenitis of the abdomen may appear in isolation or as a part of a generalized TB lymphadenitis on $^{18}$F-FDG-PET/CT.

TB Peritonitis
The role of $^{18}$F-FDG-PET/CT in peritoneal thickening and ascites of undetermined significance has been evaluated. $^{18}$F-FDG-PET/CT was found to be useful for distinguishing malignant and benign causes of peritoneal disease. However, in both peritoneal thickening and ascites, distinction of TB peritonitis from peritoneal carcinomatosis by $^{18}$F-FDG-PET/CT was more challenging compared with other benign causes of peritoneal disease. Features distinguishing TB peritonitis from peritoneal carcinomatosis on $^{18}$F-FDG-PET/CT were investigated in 1 study. This study included 76 patients: 25 with peritoneal TB and 51 with peritoneal carcinomatosis. The study determined that findings on $^{18}$F-FDG-PET/CT more consistent with TB peritonitis were:

• involvement of more than 4 regions of the peritoneum
• string beads appearance of $^{18}$F-FDG uptake
• smooth uniform thickening of the peritoneum

FDG-PET/CT findings favoring peritoneal carcinomatosis were:

• dominant distribution in the pelvis or right subdiaphragmatic area
• clustered $^{18}$F-FDG uptake
• focal $^{18}$F-FDG uptake
• irregular peritoneal thickening and nodules.

The differences showed statistical significance, and the authors concluded that $^{18}$F-FDG-PET/CT is useful for distinguishing TB peritonitis and peritoneal carcinomatosis. In the evaluation of the peritoneum for TB by $^{18}$F-FDG-PET/CT, the specificity of the study can be improved by interpreting...
the site and distribution of metabolic uptake with CT characteristics. Figure 9 shows a case of TB peritonitis with smooth thickening diffuse FDG uptake and involvement of more than 4 areas of the peritoneum (Fig. 8).

**Hepatic TB**

Hepatic TB shows $^{18}$F-FDG uptake, which is indistinguishable from other pathology such as metastatic disease. $^{18}$F-FDG uptake may be solitary, multiple, or even diffuse (figure shows focal hepatic uptake).$^{86,87}$ Intense diffuse $^{18}$F-FDG uptake in the liver has also been described under various names such as “hot liver” or “hepatic superscan”.$^{88,89}$ Hepatic superscan has also been described in other conditions such as lymphoma, breast cancer, and even infectious mononucleosis. In the reported cases of TB hepatic superscan in the literature, there was no focal liver lesion seen on CT.

**Other Sites of Abdominal TB**

$^{18}$F-FDG-PET or PET/CT in TB of adrenal, pancreatic, jejunal, splenic, renal, and common bile duct TB have all been described in literature (Fig. 9 demonstrates adrenal and splenic TB and Figure 11 shows splenic TB).$^{90-94}$ In all these cases, $^{18}$F-FDG accumulation was noted in the TB lesions. $^{18}$F-FDG-PET/CT is able to accurately stage infection, usually demonstrating other sites of infection, which may have been previously undiagnosed. In some case of TB, there is no pulmonary involvement, with the abdomen being the only site of disease. $^{18}$F-FDG-PET/CT usually detects such abdominal lesions that are confirmed on biopsy to be TB. For lesions in areas that have a high physiological $^{18}$F-FDG uptake, such as the kidney, dual-time-point imaging may be useful for clearly defining the TB lesions.$^{92}$

**Musculoskeletal TB**

Musculoskeletal TB is a common form of EPTB accounting for about 10% of cases. Musculoskeletal TB usually has an insidious presentation over a long time, making the diagnosis elusive.$^{95}$ $^{18}$F-FDG-PET/CT may help in early diagnosis and start of therapy to prevent complications such as vertebral collapse.

**TB Spondylitis and Spondylodiscitis**

Spondylitis is the most common form of skeletal TB occurring in about 50% of cases. In a case-controlled retrospective study with $^{18}$F-FDG-PET/CT, TB spondylodiscitis had higher SUV max compared with pyogenic spondylodiscitis (12.4 vs 7.3) with SUV max above 8 giving the highest specificity.$^{43}$ In another study, it was found that $^{18}$F-FDG uptake in the spleen was significantly higher in pyogenic spondylitis compared with TB spondylitis. Optimal semiquantitative indices that suggested a pyogenic etiology over TB were determined. An SUV max greater than 1.49 in the spleen, a spleen liver ratio more than 0.95, and a spleen bone marrow ratio of greater than 0.89 favored a pyogenic spondylitis.$^{96}$ MRI is the preferred imaging of choice in spondylodiscitis because of its ability to provide excellent anatomic information of the epidural space and spinal cord.$^{97}$ TB spondylitis usually affects more than 1 vertebra, which may be contiguous or not and may be complicated by vertebral collapse (Fig. 10). $^{18}$F-FDG-PET/CT in TB may be complementary to MRI by assessing the burden of disease of TB in addition to the excellent morphological evaluation provided by MRI. $^{18}$F-FDG-PET/CT has been shown to be superior to other nuclear medicine techniques such as Tc-99m diphosphonate or Ga67 citrate in the evaluation of spondylitis.$^{98}$ Figure 10 demonstrates spinal TB involving contiguous vertebrae and demonstrating the importance of $^{18}$F-FDG in early diagnosis.

**TB Arthritis and Osteomyelitis**

TB arthritis usually presents as a monoarthritis, which may affect 1 joint and usually involves the knee or hip.
18F-FDG-PET demonstrates increased uptake in the synovium, which is not distinguishable from other causes of arthritis. The intense joint uptake may be discovered incidentally in a patient being evaluated for other pathology. In the absence of a high index of suspicion, TB arthritis may initially be misdiagnosed as another non-TB arthritis. TB osteomyelitis occurs less frequently than arthritis. Isolated TB osteomyelitis in the absence of associated arthritis is rare. The femur, tibia, and small bones of hands and feet are usually involved. The CT component may determine bone destruction, sinus formation, and sequestrum with intense 18F-FDG uptake present; however, these are not specific to TB and may frequently mimic metastatic disease.

TB of the Heart

TB Pericarditis

TB pericarditis is more prevalent in TB endemic areas, with idiopathic pericarditis occurring more frequently in non-TB endemic areas. TB pericarditis was shown to be useful in the management of TB pericarditis. In 1 study, the usefulness of 18F-FDG-PET/CT in differentiating acute tuberculous pericarditis from idiopathic pericarditis was evaluated. This study included 15 patients: 5 with TB and 10 with idiopathic pericarditis. It was determined that the mean SUV max of FDG uptake of the pericardium was higher for TB pericarditis than idiopathic pericarditis, 13.5 versus 3. The study also found a higher pericardial thickness in patients with TB pericarditis, 5.1 mm versus 3.4 mm. Mediastinal and cervical lymphadenopathy were identified in both groups. The 18F-FDG uptake in the lymph nodes of patients with TB pericarditis was significantly higher than in those with idiopathic pericarditis (5.3 vs 2.8). There was no difference, however, in the lymph node size between these 2 groups. The authors concluded that PET/CT was useful for differentiating acute tuberculous pericarditis and idiopathic pericarditis. These findings must be validated in a larger study. 18F-FDG-PET/CT may reveal previously undiagnosed sites of TB when evaluating patients with known TB pericarditis. A case of TB pericarditis is demonstrated in Fig. 11.

TB of the Myocardium

Literature has reported cases of myocardial tuberculoma and TB myocarditis. Because of the physiologic myocardial uptake of 18F-FDG, proper preparation of patient is important.
when TB of the myocardium is suspected. The myocardium shows intense $^{18}$F-FDG uptake in TB myocarditis. The findings may mimic cardiac sarcoidosis.

**TB of the Central Nervous System**

**TB Meningitis**

In TB meningitis, $^{18}$F-FDG-PET/CT has been reported to help assess the burden of disease. In 1 study, the role of $^{18}$F-FDG-PET/CT in determining the disease burden in 10 patients with TB meningitis was evaluated. $^{18}$F-FDG-PET/CT was compared with MRI, chest X-ray, and abdominal ultrasound. $^{18}$F-FDG-PET/CT determined additional extracranial lesions in vertebrae, spinal cord, and lymph nodes, which had not been detected on conventional imaging. For intracranial lesions, $^{18}$F-FDG-PET/CT confirmed the findings of MRI in 6 cases and detected an additional lesion in 1 case. In 3 patients, $^{18}$F-FDG-PET/CT did not detect the lesions seen on MRI. $^{18}$F-FDG-PET/CT may have a complimentary role to MRI in the detection of cranial lesions. $^{18}$F-FDG-PET/CT is also useful for the detection of extracranial site of disease in TB meningitis.

**TB Brain Abscess and Intracranial Pathology**

PET/CT demonstrates $^{18}$F-FDG uptake in intracranial TB lesions. The high physiologic uptake in the brain may decrease the sensitivity of the detection of TB lesions. The corresponding CT may demonstrate a space-occupying lesion, which may have ring enhancement, although this is not specific to TB. The possibility of a TB brain abscess must be considered when $^{18}$F-FDG accumulates in the periphery of a ring-enhancing lesion in a severely ill or immunocompromised patient. $^{68}$Ga$^{68}$ alfaticide may be more useful than $^{18}$F-FDG in distinguishing brain metastasis because of NSCLC from TB brain abscess.

A study evaluated the use of C$^{11}$ methionine and $^{18}$F-FDG for distinguishing intracranial tuberculosis from malignancy. They noted better lesion detection and characterization with methionine; however, the tracer lacked specificity similar to $^{18}$F-FDG.

**Genital TB**

$^{18}$F-FDG-PET/CT was compared with ultrasound, MRI, and CT in women with genital TB in 1 series. The detection rate of FDG-PET/CT was similar to MRI and CT; however, the characterization of these lesions was less accurate with $^{18}$F-FDG-PET/CT. This suggests that $^{18}$F-FDG-PET/CT may be a useful noninvasive clinical tool in genital TB management.

**Ocular TB**

The diagnosis of ocular TB is challenging. Recent studies have suggested a role for FDG-PET/CT by looking for other sites...
of disease. In 1 study, 20 patients with a positive QuantiFERON test with various forms of uveitis were evaluated. FDG uptake in mediastinal nodes was detected in 9 patients, and PET-guided biopsy led to the diagnosis of TB in 2 patients. Algorithms have been developed where 18F-FDG-PET/CT has been suggested as part of the workflow for the diagnosis of patients with suspected ocular TB.

**Less Common Sites of TB**

Intense 18F-FDG uptake has been described in TB of the breast, the skin in erythema nodosum because of TB, and in a fistula-in-ano caused by TB. All these cases had intense 18F-FDG uptake, but imaging alone was insufficient to make the diagnosis. Scrofuloderma where TB lymphadenitis affects the skin may be demonstrated on 18F-FDG-PET/CT (Fig. 12).

**TB Mimicking Disseminated Malignancy**

18F-FDG-PET/CT may frequently reveal disseminated TB, which may mimic malignancy. Several cases have been reported in literature. Nuclear physicians must have a high index of suspicion of TB when interpreting 18F-FDG-PET/CT in TB endemic areas or migrants from such countries. Super 18F-FDG scan has been described in a case with high TB disease burden with diminished 18F-FDG uptake at physiologic sites.

**HIV and TB**

HIV and TB have a synergistic interaction. HIV causes an atypical presentation of TB with less pulmonary involvement and more systemic symptoms. TB is also very common in HIV and can cause the progression of HIV. HIV presents with lymphadenopathy, which depends on the stage of the HIV infection. The CD4 and viral load are important when interpreting 18F-FDG-PET scans in patients with HIV.

Lymphadenopathy in HIV progresses in a stepwise fashion usually beginning at the cervical followed by the axillary, mediastinal, and abdominal nodes in late the stages of the disease. In patients on antiretroviral therapy with suppressed viral loads, FDG-avid lymph nodes with concomitant TB are more likely caused by TB. However, as viral load increases, bilateral and symmetrical 18F-FDG-avid axillary nodes initially and then inguinal nodes as the viral load further increases is more likely to be because of HIV-related lymphadenopathy. In a prospective study, 18F-FDG-PET/CT in 20 HIV-positive patients with fever of unknown origin (FUO) was compared with PET/CT finding in HIV-positive patients without FUO. TB was the cause in 40% of the patients with FUO. The study found that all biopsies performed for focal 18F-FDG-avid central lymph nodes (mediastinal, internal mammary, para-aortic, and mesenteric nodes) corresponded to the cause of FUO. Biopsy of peripheral nodes (cervical, axillary inguinal, and iliac nodes) with SUV less than 4 was useless as it was nonspecific in determining the cause of FUO. In extra-nodal sites, focal 18F-FDG uptake always corresponded to cause of FUO. The study found high viral loads did not prevent correct interpretation of the 18F-FDG-PET/CT study. Another study used symmetry and metabolic metrics to distinguish HIV adenopathy and lymphoma. It is yet to be determined if using the metabolic metrics may improve the ability to distinguish TB from lymphoma and HIV-related lymphadenopathy. In HIV-TB coinfection, extranodal and central lymph nodal involvement
is more likely to represent TB than HIV-associated lymphadenopathy. Furthermore, for the evaluation of peripheral nodes, high SUV values favor TB as the cause of lymphadenopathy (more than 6 has been suggested), whereas nodes with SUV less than 4 are nonspecific. The finding of symmetrical peripheral (axillary, cercal, inguinal, and iliac) nodes with SUV less than 4 with benign features on the corresponding CT would be more in keeping with HIV-associated lymphadenopathy.

**Multidrug-resistant TB**

Imaging with thin-slice CT has shown differences in imaging findings between drug-sensitive and drug-resistant TB. Multiple cavities, nodules, bronchial dilatation bilateral involvement, and segmental or lobar consolidation are more frequently seen in drug-resistant than in drug-sensitive TB. 18F-FDG-PET/CT changes from baseline to as early as 2 months after the start of therapy were found to predict a good outcome in patients with MDR TB whose treatment lasted for 2 years. 18F-FDG-PET/CT in TB lymphadenitis in 20 HIV-positive patients was also found to predict outcome at 4 months of standard therapy in the absence of a baseline study. Nitroimidazole antibiotics have been shown to be effective against multidrug-resistant TB with newer analogs being developed for anti-tubercular activity. It is conceivable that PET-radiolabeled nitroimidazole compounds may play a role in detection of TB lesions containing multidrug-resistant
This is an important potential role as PET/CT may allow early in vivo detection of a TB lesion that is resistant to anti-TB therapy even when most other lesions are resolving. This would enable precision medicine and host-directed therapy to be applied in TB management.

The TB granuloma is a complex aggregate of immune cells that serves to protect the host by confining *Mtb* to the granuloma but also provides a niche in which the bacilli grow in a quiescent state and later spread in the host. The typical TB granuloma is the caseous granuloma, but non-necrotizing and fibrotic types may also occur. A caseous granuloma typically consists of a central core of *Mtb*-infected immune cells and caseous necrosis, which is surrounded by an aggregate of immune cells, usually differentiated macrophages, but may contain a few other cells such as dendritic cells. The granuloma usually has an outer layer of lymphocytes forming a follicular-like structure. The granuloma may contain a variable amount of fibrosis. TB granulomas are heterogeneous, varying from a protective, through a homeostatic, to a transmissive TB granuloma. Protective granulomas are well-defined hard granuloma where calcification and fibroblasts predominate with few or no neutrophils. Homeostatic granulomas have less fibrotic tissue and calcification with a small number of neutrophils in a center of caseous necrosis. There is an immune balance with dormancy and metabolic adaptation of *Mtb*. Transmissive granulomas have abundant

**Figure 12.** Eighteen-year-old HIV-negative female with scrofuloderma and splenic TB. Patient was diagnosed by isolation of *Mtb* from skin scrapings. 18F-FDG-PET/CT demonstrates focal uptake noted in the spleen, and a splenic abscess was also present. There is extensive bilateral para-aortic, common iliac, internal iliac, and external iliac TB lymphadenitis.
neutrophils, and necrosis predominates and allows reactivation, growth, and spread of Mtb to other parts of the body. TB granulomas are not static but can transform from one type to another by cell death, immune cell recruitment, and vascular and tissue remodeling. In both active and latent disease, a spectrum of granuloma can be present in the same individual, and these granulomas may progress or regress independently of other granulomas in the same host. Functional imaging of the granuloma to identify the type of granuloma present may allow the identification of TB granulomas that are transforming from protective to transmissive granuloma, and allow therapeutic interventions before morbidity, mortality, and the ability of host to transmit TB ensues. 

Modified ver.

Cavities usually result in permanent loss in pulmonary function, and the cavity may provide a niche for other pathogens such as Aspergilla sp. to thrive. Because of the avascular nature of the lesion, the Mtb in such lesion may be exposed to sub-therapeutic dose during anti-TB treatment, promoting drug resistance. 18F-FDG-PET/CT is useful in the detection of cavities, demonstrating disease activity in old active lesion. PET/CT is also useful in detecting lesion activity for aspergilla occupying old cavities and may help monitor therapy for such lesions. The hypoxia tracer F18 MISO has been used to image these TB cavities and showed different degrees of hypoxia in different cavities in the same patient. This may help explain biology of such lesion and help in the development of therapeutic intervention in these lesions. 18F-FDG-PET/CT may also be useful to identify old healed cavities that are more likely to relapse. An 89Zr-labeled PET tracer has been found useful in detection of CD4 and CD8 cells T lymphocytes. This tracer may have a potential role in the assessment of TB of TB lesions that are at risk of cavitation before it occurs and may help develop strategies to prevent irreversible damage.

**Cavitary TB Lesions**

TB cavities occur in active TB and are usually associated with TB progression and transmission. Cavities occur more frequently in drug-resistant TB than in TB susceptible to first-line anti-TB agents. Cavities are avascular, with a selective absence of CD4 and CD8 T lymphocytes on the luminal surface. Cavities usually result in permanent loss in pulmonary function, and the cavity may provide a niche for other pathogens such as Aspergilla sp. to thrive. Because of the avascular nature of the lesion, the Mtb in such lesion may be exposed to sub-therapeutic dose during anti-TB treatment, promoting drug resistance. 18F-FDG-PET/CT is useful in the detection of cavities, demonstrating disease activity in old active lesion. PET/CT is also useful in detecting lesion activity for aspergilla occupying old cavities and may help monitor therapy for such lesions. The hypoxia tracer F18 MISO has been used to image these TB cavities and showed different degrees of hypoxia in different cavities in the same patient. This may help explain biology of such lesion and help in the development of therapeutic intervention in these lesions. 18F-FDG-PET/CT may also be useful to identify old healed cavities that are more likely to relapse. An 89Zr-labeled PET tracer has been found useful in detection of CD4 and CD8 cells T lymphocytes. This tracer may have a potential role in the assessment of TB of TB lesions that are at risk of cavitation before it occurs and may help develop strategies to prevent irreversible damage.

**LTBI**

18F-FDG-PET/CT has been reported to assess the risk of development of active TB by assessing lung inflammation in humans. Fully quantitative methods for assessing total lung inflammation with 18F-FDG-PET/CT, which correct for air and lung, have been described in the literature. Modified versions of these methods that would be practical in the clinical setting will be useful in assessing the risk of progression of LTBI. The core of most mature TB granulomas is necrotic and hypoxic. In LTBI, hypoxia was determined to be one of the factors that switched metabolism of Mtb to the quiescent state. Imaging with hypoxic tracers may be beneficial to assess the extent of disease LTBI and help understand the pathology. One study evaluated whether PET was able to evaluate the early events in LTBI in humans using 18F-FDG. Five people were recruited in the study. The participants were asymptomatic, had normal chest radiographs, and positive QuantiFERON gold assays. Four of the participants had positive PET scans involving mediastinal lymph nodes. None of the participants had FDG uptake in the lungs. The patient who had no FDG uptake had a calcified lung granuloma and calcified hilar nodes noted on CT. None of the 18F-FDG-avid

**Neutrophils in TB**

Neutrophils have been implicated in both host protection and inflammatory processes that cause damage in TB. High number of neutrophils in bronchoalveolar fluid has been shown to correlate with cavitary TB lesions. Neutrophils also correlate with a longer duration of smear positivity in patients with active TB. Neutrophils also portend a poorer prognosis and increased mortality in active disease. In TB granulomas, neutrophil infiltration is associated with an increase in the size of granulomas with disruption of the structure promoting spread of Mtb and neutrophils, resulting in disease progression from latent to active infection. Imaging modalities that are able to identify neutrophils in vivo may potentially impact the management of TB by identifying patients with LTBI at risk of progression.

64Cu PET/CT may be used to image both latent and active TB patients, providing a biomarker for progression of disease prognosis in patients with active TB.
nodes met the radiological criteria for an enlarged lymph node. This study suggests that 18F-FDG-PET/CT may be useful to study early events and probably the course of LTBI.

**TB and Fever of Unknown Origin**

18F-FDG-PET/CT has been found to be useful in the evaluation of patients with FUO, and TB is frequently a cause of the fever with or without HIV. More than 50% of patients with FUO were eventually diagnosed with TB by FDG-PET/CT in 1 series.

**TB and Children**

The use of 18F-FDG-PET/CT in TB in children does not differ from that in adults. The tissues of children are more radiosensitive, and modalities not using ionizing radiation would be preferred when imaging them. The use of PET/MRI may reduce radiation burden and offer advantages of FDG-PET in TB imaging for specific sites such as TB spondylitis.

**Other Preclinical PET/CT Imaging in TB**

In the preclinical setting, F18 sodium fluoride has been used in the detection of microcalcification that may occur in pulmonary TB lesions. A number of drug-labeled PET tracers have been evaluated in nonhuman primates such as C11-labeled rifampicin, isoniazid, and ethambutol. These studies were used to evaluate biodistribution of these drugs in the body. The biodistribution of F18 labeled pyrazinamide analog in a mouse model has also been studied.

**Conclusion and Future Perspectives**

PET/CT with 18F-FDG is useful in the management of patients with TB. In evaluation of patients with FDG-PET/CT, there has been an evolution from TB merely being a nuisance, causing false-positive studies in oncology patients, to a place where PET/CT is useful for evaluation of different aspects of the infection. 18F-FDG-PET/CT helps with the diagnosis of TB in patients with FUO and helps confirm the diagnosis of TB early by revealing site of biopsy in patients with suspected TB. The pre-therapeutic scan gives a metabolic map, staging the disease and revealing previously undiagnosed sites. 18F-FDG-PET/CT has been used to identify patients with subclinical TB. The use of lung inflammation as determined by 18F-FDG-PET/CT is increasingly finding a role in stratifying patients likely to develop TB. Available PET tracers are helping us understand the pathogenesis of the disease. The ability of PET/CT to image ligands or receptors on immune cells, allowing predominant cell types in TB lesions to be imaged, could potentially not only increase our understanding of the spectrum of lesions found in both LTBI and active TB, but allow personalized therapeutic intervention strategies based on the PET findings. A radiopharmaceutical that will be able to identify TB, distinguishing it from other pathologies, would make an impact in clinical practice, and several compounds are being evaluated. One such candidate is the modified trehalose analog. Trehalose is a non-mammalian disaccharide important for mycobacterial cell wall synthesis and virulence. Trehalose analogs have recently been explored with detectable tags in detection of mycobacteria with some promising results. To achieve the goals of the ‘End TB strategy’ of the World Health Organization, intensified research and innovation has been identified as one of the pillars and components. PET/CT imaging of TB is well positioned to have a major impact especially in the areas of research and in vitro assessment of new intervention strategies against the infection. The role of PET/CT imaging in TB is likely to evolve as new data about the role of PET/CT management in TB becomes available. Development of new tracers or repurposed old tracers may also play a significant role in management of TB in the near future.

**Conflict of Interest**

No conflicts of interests.

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**References**


Niselke M, Mayosi BM: Tuberculous pericarditis with and without HIV. Heart Fail Rev 18:367-373, 2013


126. Mahon RN, Hafner R: Applying precision medicine and immunotherapy advances from oncology to host-directed therapies for infectious diseases. Front Immunol 8:688, 2017


136. Eum SY, Kong JH, Hong MS, et al: Neutrophils are the predominant infected phagocytic cells in the airways of patients with active pulmonary TB. Chest 137:122-128, 2010


