Advances in imaging of tuberculosis: the role of ^{18}F-FDG PET and PET/CT

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Purpose of review
To review the main applications, advantages and limitations of ^{18}F-FDG PET and PET/computed tomography (CT), and some other tracers in imaging of tuberculosis (TB).

Recent findings
In pulmonary TB, granulomas typically demonstrate increased ^{18}F-FDG uptake, and areas of active TB can be differentiated from old or inactive disease by dual time point imaging. However, standardized uptake value measurements are high in both TB and malignant lesions, with significant overlap that limits their usefulness. In extrapulmonary TB, ^{18}F-FDG PET detects more tuberculous lesions than CT, is of value in assessing response to tuberculostatic treatment, and helps in diagnosing spinal infection and identifying TB-related spondylitis; however, again, differentiation of malignant versus TB lymph node involvement is problematic. ^{18}F-FDG PET can also be considered a marker of disease status in patients with HIV and TB co-infection. Overall, evaluation of treatment response is potentially the most important clinical application of ^{18}F-FDG PET in TB, owing to its ability to distinguish active from inactive disease.

Summary
^{18}F-FDG PET and PET/CT may assist early diagnosis and facilitate differentiation between malignancies and TB, identification of extrapulmonary TB, staging of TB, and assessment of treatment response.

Keywords
fluorine-18 fluorodeoxyglucose, PET/computed tomography, tuberculosis

INTRODUCTION

Diagnosis of active pulmonary tuberculosis (TB) is a major challenge, especially in individuals with severe immunosuppression such as those co-infected with HIV. Such patients characteristically demonstrate an atypical radiographic pattern [1], for example middle and lower lung lobe involvement, absence of cavity formation, presence of lymphadenopathy and pleural effusions, or a miliary pattern, and occasionally they even have a normal chest X-ray.

[Fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET integrated with computed tomography (CT) is a noninvasive tool capable of early detection and assessment of disease involvement. Pulmonary and extrapulmonary TB involvement are assessed simultaneously, with time-saving and cost-saving implications. The most important role of ^{18}F-FDG PET in TB is probably its ability to assess early treatment response (when radiological features may remain unchanged), with consequent significant impact on patient management.

The use of ^{18}F-FDG is essentially based on its detection of increased glucose metabolism, which in TB is mainly due to increased macrophage and neutrophil activity. ^{18}F-FDG PET is unfortunately limited by its well documented lack of specificity and inability to clearly distinguish granulomatous disease from malignant involvement based on standardized uptake values (SUV_{max}) [2–4]. Furthermore, the value of dual time point imaging in this setting remains controversial [5–8].

Future developments are likely to include cyclotron-independent PET tracers, tracers linked with peptides or tuberculostatics, and improvements in the quantification of TB lesions. This article reviews

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KEY POINTS

- In extrapulmonary TB, ^{18}F-FDG PET detects more tuberculous lesions than CT, is of value in assessing response to tuberculostatic treatment, and helps in diagnosing spinal infection and identifying TB-related spondylitis.
- ^{18}F-FDG PET can differentiate active from inactive disease in patients with TB, and this is potentially an important clinical application in these patients.
- There is overlap in the standardized uptake values of TB and malignant lesions on ^{18}F-FDG PET, which limits its usefulness in distinguishing them.
- ^{18}F-FDG PET can be considered a marker of disease status in patients with HIV and TB co-infection.

the main applications, advantages and limitations of ^{18}F-FDG PET/CT in TB.

PULMONARY AND EXTRAPULMONARY TUBERCULOSIS

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.

TB granulomas consist of macrophages and lymphocytes, which demonstrate high levels of glucose uptake, resulting in lesions that are ^{18}F-FDG avid on PET imaging (Fig. 1). On activation, resting lymphocytes switch to glycolysis and increase their glucose uptake by approximately 20-fold over 24 h [9,10]. Unfortunately, these cannot reliably be differentiated from malignant lesions and false positives can also be due to other infective or inflammatory conditions.

Mycobacterium TB is divided into primary and postprimary TB on conventional imaging. Soussan *et al.* [11] identified two different patterns of TB on FDG PET scan: a pulmonary type with a more localized type of infection, and a lymphatic pattern of involvement associated with a more intense, systemic infection.

Pulmonary tuberculosis

The lungs are the most common site for TB and most patients present with pulmonary complaints. Goo *et al.* [12] studied 10 consecutive patients with histopathologically proven pulmonary TB and 10 tuberculomas. Nine of these granulomas demonstrated uptake of ^{18}F-FDG on PET with a mean maximal standardized uptake value (SUV_{max}) value of 4.2 ± 2.2 (SD). The study showed that pulmonary

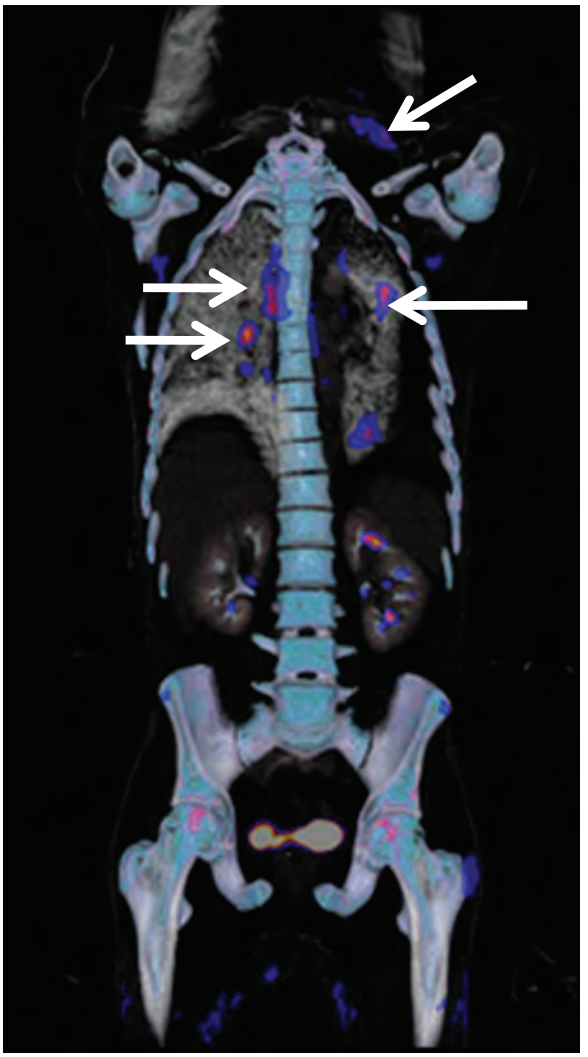

FIGURE 1. The figure shows tuberculosis lymphadenitis. ^{18}F-FDG-fused PET/CT coronal view. Arrows indicate ^{18}F-FDG uptake in left supraclavicular, right hilar and mediastinal nodes, and uptake in the left lung parenchyma compatible with active disease.

tuberculoma usually causes an increase in ^{18}F-FDG uptake.

Kim *et al.* [13] evaluated the potential role of dual time point imaging with ^{18}F-FDG PET in the differentiation of active pulmonary tuberculoma. A total of 25 consecutive patients with pulmonary tuberculoma were included and PET/CT imaging was performed at 60 min and 120 min postinjection. Early (E) and delayed (D) SUV_{max} values as well as %Delta SUV_{max} values were obtained in all patients. Active tuberculoma showed statistically significantly higher values of $SUV_{max}E$ (active $= 2.3 \pm 0.75$, 0.75, inactive $= 0.79 \pm 0.15$), $SUV_{max}D$ (active $=$ 2.48 ± 0.79, inactive $= 0.75 \pm 0.13$) and %Delta SUV_{max} (active $= 8.07 \pm 7.77$, inactive $= -3.83 \pm 6.59$)

6.59) compared with inactive tuberculoma. When a $SUV_{max}E$ of 1.05 was used as the cutoff, sensitivity, and specificity were 100 and 100%. These results suggest that areas of active TB can be differentiated from old or inactive disease by imaging at two time points, which would also be of value in the evaluation of treatment response and follow-up.

In a series by Sathekge *et al.* [14] aimed at assessing the diagnostic accuracy for the differentiation of benign from malignant solitary pulmonary nodules, 12 patients with active lung TB were included. When compared with the series by Goo *et al.* [12] and Kim *et al.* [13], SUV_{max} values and %Delta SUV_{max} in lung tuberculoma were found to be higher. ^{18}F-FDG SUV_{max} values and %Delta SUV_{max} values were not significantly different in benign and malignant lesions. These findings are in agreement with the data reported by Chen *et al.* [15], who included a selected group of patients with an initial mean ^{18}F-FDG PET SUV of less than 2.5. A study by Kaneko *et al.* [16▪] evaluated the retention indices of tuberculous and nontuberculous lesions and found that these were high in both types of lesions with no statistically significant differences. A recent case series by Heysell *et al.* [17▪▪] suggested a role for quantitative ^{18}F-FDG PET in the diagnosis of active TB infection in which conventional methods are unavailable or unreliable.

The aforementioned results demonstrate that SUV measurements from both tuberculous and malignant lesions tend to be high with significant overlap. SUV measurements are therefore not useful in characterizing lesions as granulomatous or malignant.

Pleural effusions, which may show ^{18}F-FDG or ^{68}Ga-citrate (Fig. 2) avidity, may also be observed and in some instances may be the only manifestation of the disease, usually unilateral with septations, especially in adult-onset primary TB. Shinohara *et al.* [18] recently reported a case of asymptomatic primary TB pleurisy, which demonstrated intense uptake similar to that seen in mesothelioma.

Extrapulmonary tuberculosis

The AIDS epidemic has led to a higher incidence of TB, with changed disease patterns and increases in disseminated and extrapulmonary involvement. Extrapulmonary TB may affect any organ and is an AIDS-defining condition indicative of stage 4 disease in adults [19,20]. The most frequently reported affected sites include lymph nodes, pleura, musculoskeletal, gastrointestinal and genitourinary tract [21,22]. Despite recent advances, the diagnosis of extrapulmonary involvement remains problematic, as obtaining tissue or fluid for analysis from these sites is not always possible and is invasive. The correct assessment of the disease extent is important when deciding on the correct treatment regimen. ^{18}F-FDG PET studies done on TB patients have demonstrated that PET detects more tuberculous lesions, especially extrapulmonary, than CT.

The potential impact of dual-phase ^{18}F-FDG PET versus routine staging was evaluated by Sathekge *et al.* [14] in 16 TB patients. In nine patients, 18 sites of lymph node involvement were identified on both early and delayed images. Nine out of 18 sites of lymph node involvement, occurring in five patients, were missed on CT. In four of these five patients, the sites of lymph node involvement were the only sites of extrapulmonary TB identified. Sites of osseous involvement ($n = 4$) and joint involvement ($n = 3$) were identified on both CT and PET, and ^{18}F-FDG PET imaging did not result in alterations of treatment planning in any of the patients studied. Furthermore, it was found that ^{18}F-FDG PET cannot differentiate malignant lymph node involvement from lymph node involvement by TB: the median SUV_{mean} values of involved lymph node basins were 6.5 (range, 3.4–9.2) for TB and 8.0 (range, 2.5–20.1) for malignancy [14].

Although ^{18}F-FDG PET is clearly unable to distinguish tuberculous lymphadenitis from metastatic lymph node involvement based on the SUV, certain patterns of lymph node tracer distribution provide

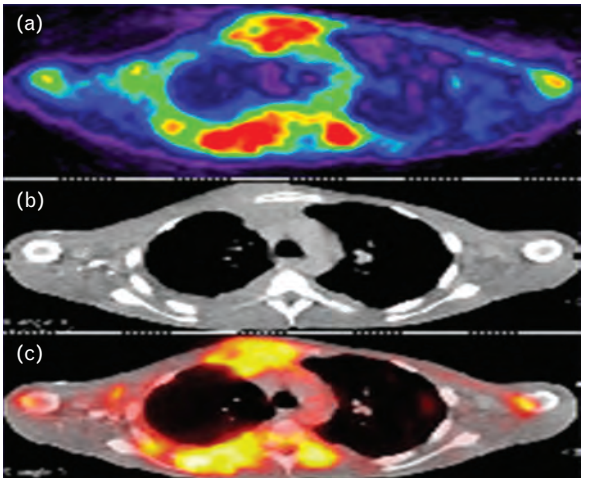

FIGURE 2. A 28-year-old man with a large right-sided pleural effusion and mycobacterium tuberculosis on pleural fluid analysis. Dual-time point imaging was performed at 60 min and 120 min following ^{68}Ga-citrate injection (224 MBq, IV) and IV contrast. (a) Transaxial section shows intense tracer accumulation in the anterior chest wall and posterior thickened pleura on the right. (b) Corresponding transaxial computed tomography (CT) section. (c) PET/CT-fused transaxial section showing the changes.

useful clues regarding diagnosis and management. Lymph nodes with central attenuation and peripheral enhancement are suggestive of TB involvement and are associated with nonresponse to tuberculostatics. In a series of 24 patients, using a cut-off value of five or more lymph node basins identified on a pretreatment ^{18}F-FDG PET scan, treatment responders and nonresponders to first-line tuberculostatic treatment could be differentiated with an accuracy of 0.88 (area under the receiver operating characteristic curve) [23].

Dong *et al.* [24▪] recently evaluated retrospectively the role of FDG-PET in differentiating acute tuberculous ($n = 5$) from idiopathic pericarditis ($n = 10$). Pericardial thickness as well as the SUV_{max} measured here and in the mediastinal-clavicular and supraclavicular lymph nodes were used. The authors found that the mean SUV_{max} of the mediastinal-clavicular and supraclavicular lymph nodes were significantly higher in those with TB pericarditis, and that knowledge of this pattern could be used to expedite diagnosis and treatment.

Musculoskeletal involvement is also seen often, frequently affecting the spine (most series report around 50% spinal involvement) [22]. Multiple vertebral bodies and disc spaces may be involved and diagnosis of spinal involvement is often difficult due to the lack of specific morphological imaging findings. Failure to identify and treat these areas of involvement in a timely manner may lead to serious complications such as vertebral collapse, spinal compression, and spinal deformity. According to a recent review by Skaf *et al.* [25], '^{18}F-FDG PET is a promising technique for diagnosing spinal infection and has several potential advantages over other imaging modalities' (p. 8). These include a high sensitivity in lesion detection and the fact that image quality is not affected by metal artefacts [26,27]. The procedure can be completed in a single session and is characterized by high sensitivity and superior image resolution compared with single-photon-emitting tracers. In addition, a recent study found that ^{18}F-FDG PET/CT is more effective than MRI in distinguishing between tuberculous and pyogenic spondylitis [28]. Another recent review by Rivas-Garcia *et al.* [29] on the image findings in Pott's disease emphasizes the role of advanced imaging such as ^{18}F-FDG-PET in the assessment of lesion extent, as a guide to biopsy, to assist in surgery planning, and to contribute to follow-up evaluation.

Kim *et al.* [30] investigated the use of ^{18}F-FDG PET in the detection and differentiation of TB spondylitis and pyogenic spondylitis. They included 23 consecutive patients with suspected spondylitis and made use of dual time point imaging at 60 and 120 min postinjection. Analysis of SUV_{max} (early and delayed), as well as the percentage change between the two time points, did not reveal any statistically significant differences between the conditions. This suggests that dual time point imaging with ^{18}F-FDG PET is not helpful in distinguishing spondylitis caused by mycobacterium TB infection from other infective causes.

Gratz *et al.* [31] also investigated the use of ^{18}F-FDG PET in 16 patients with suspected spondylitis, employing a target to background ratio in order to differentiate osteodegenerative changes from infective changes, and found that a lower ratio (<1.45) was associated with the former. The authors concluded that ^{18}F-FDG PET/CT was superior to MRI and conventional nuclear medicine imaging (with ^{67}Ga-citrate and ^{99m}Tc-MDP).

These findings highlight the potential role of FDG PET/CT in demonstrating lesion extent, in detecting additional lesions missed on morphological imaging, and in serving as a guide for biopsy with aspiration for culture.

CO-INFECTION WITH HIV

In patients with HIV and TB co-infection, early diagnosis of TB is of the utmost importance, as initiation of highly active antiretroviral therapy (HAART) has to be delayed in order to first treat the TB. Pulmonary TB presentation in an HIV-positive patient (especially where the CD4 cell count is low) is different from that in an HIV-negative patient in that the expected findings of consolidation, cavitation, and apical involvement are less frequently seen. Functional imaging by means of ^{18}F-FDG PET may be helpful in reaching a diagnosis here. In the case in which typical morphological features of TB are absent, the intensity and pattern of FDG uptake may suggest the diagnosis in this clinical setting.

Available data suggest that HIV binding to resting CD4 T lymphocytes causes them to home from the blood into lymph nodes, and that they are induced into apoptosis via secondary signals through the homing receptors [32]. Clinically, this correlates to generalized, peripheral lymphadenopathy (with characteristic morphology) that precedes tissue involution and results in the loss of superficial lymph nodes in the later stage of disease [33].

Various studies on animal models have been conducted to determine whether FDG PET/CT can identify activated lymphoid tissues, and whether this pattern may reflect the extent of simian immunodeficiency virus infection. Within a few days after primary infection by intravenous, intrarectal, or intravaginal routes, FDG PET imaging revealed a

distinct pattern of lymphoid tissue activation centered on axillary, cervical, and mediastinal lymph nodes. Increased tissue FDG uptake preceded fulminant virus replication at these sites, suggesting that a diffusible factor of host or viral origin was responsible for lymphoid tissue changes [34,35].

Scharko *et al.* [34] evaluated FDG PET findings in 15 patients infected with HIV-1. They observed distinct lymphoid tissue activation in the head and neck during the acute phase, a generalized pattern of peripheral lymph node activation at the mid-phase and involvement of abdominal lymph nodes during the late stages. This suggests that lymphoid tissue activation follows a predictable sequence. This was confirmed by Sathekge *et al.* [36], who in addition demonstrated that the FDG signal derived from PET imaging in patients with HIV not only correlates with viral load but is also inversely related to the CD4 cell count. Knowledge of the CD4 cell count and the viral load can therefore be used to predict whether lymph node involvement is likely due to retroviral disease or whether other disorder (such as lymphoma or metastatic disease) is more likely.

EVALUATION OF TREATMENT RESPONSE

This is potentially the most important clinical application of ^{18}F-FDG PET/CT in TB (Fig. 3). Morphological changes often take significantly longer than molecular changes to manifest, and it is in this context that PET may have a role, emphasizing the need for further evaluation.

In developing countries, multidrug-resistant and extensively drug-resistant TB has serious consequences, and monitoring of therapy is thus essential. A major advantage of PET is the ability to quantify ^{18}F-FDG uptake, allowing assessment of response to therapy at an early stage of the disease and change/modification of treatment in nonresponders [37].

TB treatment regimens can be complex in the settings of co-infection with HIV, where a high possibility of development of immune reconstitution inflammatory syndrome exists and where high levels of drug resistance occur. Treatment duration may need to be between 3 and 9 months, and PET might provide an objective measure of treatment response and the required duration.

Studies involving TB infection models in animals have demonstrated a clear correlation

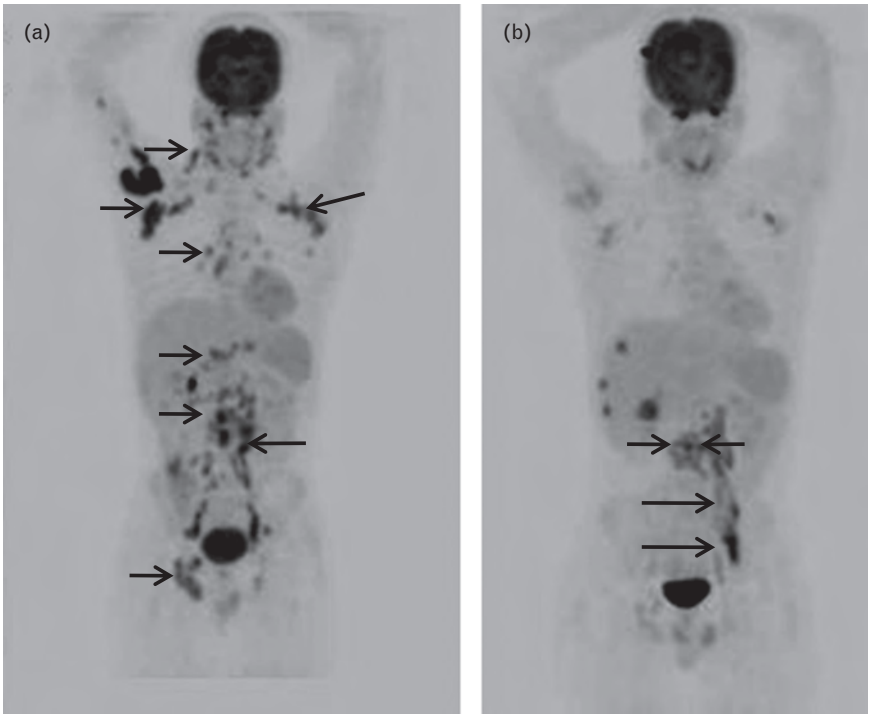

FIGURE 3. (a) The figure shows F-18-FDG PET scan in a patient with extensive pulmonary and nonpulmonary disease. Small arrows indicate F-18-FDG avid lymphadenopathy. (b) Tuberculosis response after 2 months of therapy. Good response with extrapulmonary lesions in the spine (small arrows) and psoas muscle (large arrows) lagging behind when compared with the lymph nodes.

between a decrease in ^{18}F-FDG lung accumulation and successful antibacterial treatment, thus highlighting the potential of quantitative ^{18}F-FDG PET/CT to evaluate treatment response [38].

Park *et al.* [39] have demonstrated that during anti-TB treatment, some bacillus-negative tuberculomas do not decrease in size and may even increase, making it difficult for physicians to decide whether or not to alter treatment regimens. Imaging with ^{18}F-FDG PET may be useful in this situation. If it demonstrates an increase in activity in the lesion, then it is likely that the tuberculoma is active and that treatment should be discontinued or changed. If the lesion shows a decrease in activity, it is likely that the tuberculoma is responsive to anti-TB treatment, and current treatment should be continued according to standard protocols [39]. Park *et al.*'s findings have been confirmed by others [40,41,42▪▪].

In addition, cancer patients receiving immunosuppressive therapy are at an increased risk for developing asymptomatic extrapulmonary disease. Although definitive diagnosis and exclusion of active TB infection by culture and histology is always recommended, ^{18}F-FDG PET/CT may contribute in reaching an earlier diagnosis [41].

It has been shown that the SUV_{max} of involved lymph node basins (both early and delayed) and the number of involved lymph node basins on pretreatment scans are significantly higher in nonresponders than in responders (respective *P* values of 0.03, 0.04, and 0.002) [37]. Using a cutoff of 5 or more involved lymph node basins, responders could be separated from nonresponders with a sensitivity, specificity, and positive and negative predictive value of 88, 81, 70, and 93%, respectively. Using a cutoff of 8.15 for the early SUV_{max} of lymph node basins and of 10 for the late SUV_{max} of lymph node basins, a comparable sensitivity of 88% came at the cost of a lower specificity: 73 and 67%, respectively [37].

The accuracy of these findings tends to be slightly lower when FDG PET imaging is performed at 4 months after treatment initiation, and a cutoff for SUV_{max} values of involved lymph nodes of 4.5 then appears more accurate. Under these circumstances, Sathekge *et al.* [23] found that lymph nodes responding to TB treatment could be differentiated from nonresponsive ones with a sensitivity and specificity of 95 and 85% (area under the curve: 0.96), respectively. The number of lymph nodes with rim enhancement and low central attenuation was significantly higher in nonresponders compared with responders.

Several other studies have confirmed the value of ^{18}F-FDG PET/CT in follow-up and evaluation of treatment response, especially in patients with extrapulmonary involvement and when drug resistance is prevalent [42▪▪,43–45].

OTHER PET TRACERS AND POTENTIAL APPLICATIONS

Although essentially beyond the scope of this review, it should be noted that various other PET tracers have been investigated for imaging of TB, including ^{11}C-choline [46–48], ^{18}F-FLT [49,50], and ^{68}Ga-citrate, with some promising results, for example prediction of the nature of a solitary pulmonary nodule with ^{11}C-choline.

CONCLUSION

In addition to early identification of extrapulmonary TB, staging of TB, and assessment of treatment response, there is an increasing clinical need for effective imaging to facilitate differentiation between malignancies and TB (which is particularly important for solitary pulmonary nodules); PET/CT may provide clinicians with this much-needed tool.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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