The role of the PET scan in the management of sarcoidosis

Rémy L.M. Mostard[a], *Marinus J.P.G. van Kroonenburgh*[b], *and Marjolein Drent*[c]

Purpose of review
It is important to gain knowledge and understanding about the appropriate use of PET scan in the management of sarcoidosis patients. This means that, in view of the radiation dose and costs, defining appropriate indications for PET scanning in sarcoidosis patients is vital.

Recent findings
PET has been shown to be a very sensitive technique for the assessment of inflammatory activity in sarcoidosis by detecting and quantifying the degree of inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body.

Summary
PET is not indicated in the standard workup, but can be of great value to complement more routinely used techniques. On the basis of the current findings, PET offers added value in sarcoidosis patients with unexplained persistent disabling symptoms. PET appears especially helpful in those persistently symptomatic patients without serological signs of inflammatory activity, in patients with radiologic signs of fibrosis and in the detection of active cardiac sarcoidosis. The use of PET to assess the extent of disease can uncover a suitable location for biopsy to obtain histological evidence for the diagnosis or to explain the (mainly extrathoracic) symptoms. Furthermore, the detection of unexpected organ involvement may offer prognostic value.

Keywords
inflammatory activity, organ involvement, PET, prognosis, sarcoidosis

INTRODUCTION

Sarcoidosis is a multisystemic disease characterized by cellular immunity activity with formation of noncaseating granuloma in various organ systems [1]. The diagnosis is usually based on consistent clinical features and histological evidence of noncaseating epithelioid cell granulomas. The clinical course of sarcoidosis is extremely variable [2]. Assessment of inflammatory activity is helpful to monitor the course of the disease and guide therapeutic strategies, but establishing the presence of inflammatory activity can be a challenge for clinicians. In recent years, PET has been shown to be a very sensitive technique to assess the inflammatory activity in sarcoidosis by detecting and quantifying the level of inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body [3–7]. This means that a technique has become available that is able to evaluate the presence of inflammatory activity in each organ system. It is important to gain knowledge and understanding about the appropriate use of this new technique in clinical practice. This means that, in view of the radiation dose and costs, defining appropriate indications for PET scanning in sarcoidosis patients is vital.

^{18}F-FLUORODEOXYGLUCOSE PET

In general, studies on PET in sarcoidosis use fluoride 18-fluorodeoxyglucose (^{18}F-FDG), which is the most

[a]Department of Respiratory Medicine, Atrium Medisch Centrum, Heerlen, [b]Department of Nuclear Medicine, Maastricht University Medical Centre and [c]Department of Interstitial Lung Diseases, Hospital Gelderse Vallei Ede, Maastricht University, FHML, Maastricht, The Netherlands

Correspondence to Rémy L.M. Mostard, MD, PhD, Department of Respiratory Medicine, Atrium Medisch Centrum, Henri Dunantstraat 5, P.O. Box 4446, 6401 CX Heerlen, The Netherlands. Tel: +31 455766666; e-mail: r.mostard@atriummc.nl

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KEY POINTS

- PET is a sensitive method to assess the inflammatory activity and the extent of disease in sarcoidosis.
- PET appears especially helpful in those persistently symptomatic patients without serological signs of inflammatory activity, in patients with radiologic signs of fibrosis and in the detection of active cardiac sarcoidosis.
- The use of PET to assess the extent of disease can uncover a suitable location for biopsy to obtain histological evidence for the diagnosis or to explain the (mainly extrathoracic) symptoms.

commonly used PET radiotracer worldwide because of its availability, the relatively long half-life and its high uptake in inflammatory disorders and malignant lesions. The increasing use of combined PET/computer tomography (CT) scans enables a more accurate localization and attenuation correction. Furthermore, this combined technique makes it possible to study morphological and metabolic changes together.

Several studies in patients with proven sarcoidosis showed that the extent of involvement and quantification of inflammatory activity can be more accurately assessed by ^{18}F-FDG PET than with ^{67}Gallium scintigraphy [5,6,8]. Apart from its value for assessment of inflammatory activity, ^{18}F-FDG PET is therefore also useful to identify occult and reversible granulomas in patients with sarcoidosis (Fig. 1) [4]. In addition, ^{18}F-FDG PET has several practical advantages over ^{67}Gallium scintigraphy as it is less time-consuming, the interobserver agreement is higher and the radiation exposure lower [6].

USE OF PET SCAN IN THE DIAGNOSTIC WORKUP OF SARCOIDOSIS

PET is not a technique of first choice and certainly not suitable for screening purposes in sarcoidosis, but, if used on a proper indication, it can be of added value to the more routinely used techniques like lung function testing, chest radiography (CXR), high-resolution computed tomography (HRCT) and serological inflammatory marker analysis [9,10▪,11▪]. To determine when PET scanning can be of added value, it is necessary to take into account the clinical question on one hand and the patient population on the other hand. Clinical questions include assessment of inflammatory activity or of extent of disease. Patient populations can be subdivided in to patients with suspected sarcoidosis, patients with newly diagnosed sarcoidosis and sarcoidosis patients with persistent disabling symptoms.

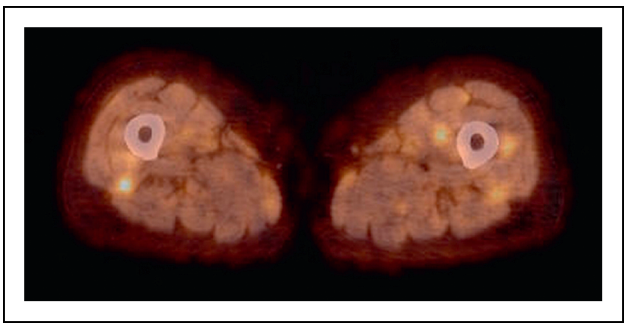

FIGURE 1. PET/CT image of a sarcoidosis patient showing multiple foci with increased FDG uptake in the muscles of the lower extremities. FDG, fluorodeoxyglucose.

In patients with suspected sarcoidosis, apart from those with Löfgren's syndrome, histological evidence of noncaseating epithelioid cell granulomas is desirable. If routine diagnostic procedures like bronchoscopy with transbronchial biopsy and bronchoalveolar lavage (BAL) do not provide sufficient evidence for the diagnosis, performing a PET scan can uncover a suitable location for biopsy to obtain histological evidence for the diagnosis. Two large cohort studies demonstrated that PET established the presence of previously unknown sites of active disease [4,11▪].

The presence of inflammatory activity can be regarded as highly likely in patients with newly diagnosed acute, symptomatic sarcoidosis [3,12]. The very high sensitivity of PET for assessment of inflammatory activity could therefore be established in such patient populations [3,5,6]. Hence, performing a PET in patients with newly diagnosed acute, symptomatic sarcoidosis is not necessary for the assessment of inflammatory activity. Nevertheless, evaluation of the extent of disease can be of value in this patient population to provide an explanation for the (mainly extrathoracic) symptoms.

Unlike acute sarcoidosis [3,12], assessment of inflammatory activity in sarcoidosis patients with persistent disabling symptoms that cannot be explained with the results of routine investigations, including the absence of lung functional or chest radiographic deterioration, remains a challenge to the clinicians. In these patients, it is often complicated to differentiate between reversible and irreversible disease. The assessment of inflammatory activity by clinical and radiographic features can be complicated as organ involvement beyond the scope of the used diagnostic tools might be missed [4,9]. Symptoms like arthralgia or fatigue can be nonspecific and difficult to objectify [13,14]. Furthermore, symptoms like coughing and dyspnoea might be related to ongoing inflammatory activity as well as to end-stage disease, that is,

pulmonary fibrosis [10▪], but it is often hard to differentiate between (partially) reversible and irreversible disease in these patients. It is important to be informed about the presence or absence of inflammatory activity in those patients, as fibrosis itself is irreversible. In general, patients with fibrosis without ongoing inflammatory activity are thus supposed not to benefit from immunosuppressive treatment [15,16].

SEROLOGICAL INFLAMMATORY MARKERS AND PET RESULTS

Various studies have investigated the value of individual serological inflammatory markers for assessing disease activity [12,17–21]. Several studies found that neopterin and soluble interleukin-2 receptor (sIL-2R) levels were significantly elevated in progressive, and thus active, disease [12,19]. Keijsers *et al.* [3] showed that elevated angiotensin-converting enzyme (ACE) and sIL-2R levels correlated with the positive PET findings, though the reported sensitivity of these markers was low. Neopterin levels were not evaluated in this latter study. Among the serological inflammatory parameters evaluated in another study, positive sIL-2R showed the strongest association with PET positivity in a population of patients with persistent disabling symptoms [9]. Nevertheless, combining the results of serological inflammatory markers (ACE, sIL-2R and neopterin) increased the sensitivity for detecting inflammatory activity without false-positive results in that study. The positive predictive value of the combined serological inflammatory markers for the presence of inflammatory activity on PET appeared to be excellent, though the negative predictive value was moderate. It can therefore be concluded that PET appears to offer added value in assessing the inflammatory activity in patients with persistent symptoms in the absence of signs of serological inflammatory activity.

PULMONARY INVOLVEMENT

CXR is the most commonly used radiologic imaging technique to evaluate patients with pulmonary sarcoidosis. In general, patients with a lower CXR stage according to the Scadding at presentation are more likely to experience resolution of the CXR abnormalities [22,23]. However, the CXR stage does not clearly correlate with the level of dyspnoea, lung function tests or 6-min walk distance [22–24]. Moreover, one major issue concerning the radiographic staging system has been interobserver variability and lack of appropriate definitions of changes in time, as a result of which it has limited applicability in individual patient assessments, including treatment decisions [23]. No clear relation exists between CXR stages and PET findings either [9,10▪].

The presence and extent of parenchymal abnormalities on HRCT have been found to correlate with respiratory functional impairment in sarcoidosis [25,26]. However, HRCT is a morphological imaging technique that provides only indirect information on the underlying metabolic changes. Follow-up CT studies in patients with pulmonary sarcoidosis have shown that nodular opacities represent potentially reversible findings [27,28]. With regard to parenchymal consolidations, however, it is not possible to differentiate between fibrotic or granulomatous components in the consolidations on the basis of HRCT findings. Because of preexisting major abnormalities, radiological features are frequently of limited value for the assessment of inflammatory activity in sarcoidosis patients with fibrotic disease.

Achieving a reliable comparison of results requires a standardized scoring system of abnormal findings on HRCT and PET. Several studies found that the intrareader and interreader reliability of a semiquantitative HRCT scoring system described by Oberstein *et al.* [29] was good, and the HRCT features of this scoring system were associated with respiratory functional impairment in sarcoidosis [25]. The interobserver agreement of simple PET scoring systems proved to be very good [6,9]. A recent study demonstrated that the severity of pulmonary involvement as assessed by HRCT features and lung function parameters correlated with the PET activity in sarcoidosis [10▪]. The semiquantitative HRCT scoring system that was used in this study appeared to offer a better ability to identify patients with positive pulmonary PET findings than the traditionally used radiographic staging system introduced by Scadding. It is also important to emphasize that a proportion of the patients with normal CXR findings (stage 0) as well as the majority of patients with signs of fibrosis on CXR (stage IV) or HRCT had positive pulmonary PET findings. An example of a sarcoidosis patient with signs of pulmonary fibrosis and positive pulmonary PET findings is shown in Fig. 2.

Increased FDG uptake has also been observed in patients with idiopathic pulmonary fibrosis (IPF) [30,31]. All of the models proposed for the pathogenesis of pulmonary fibrosis involve a central role for fibroblasts, which are known to express glucose transporter-1 [30,32]. It could be speculated that the elevated FDG uptake in patients with fibrotic changes, including honeycombing, is a reflection of increased fibroblast metabolism and not because of inflammatory activity *sensu stricto* [30]. However, the majority of the sarcoidosis patients with fibrotic

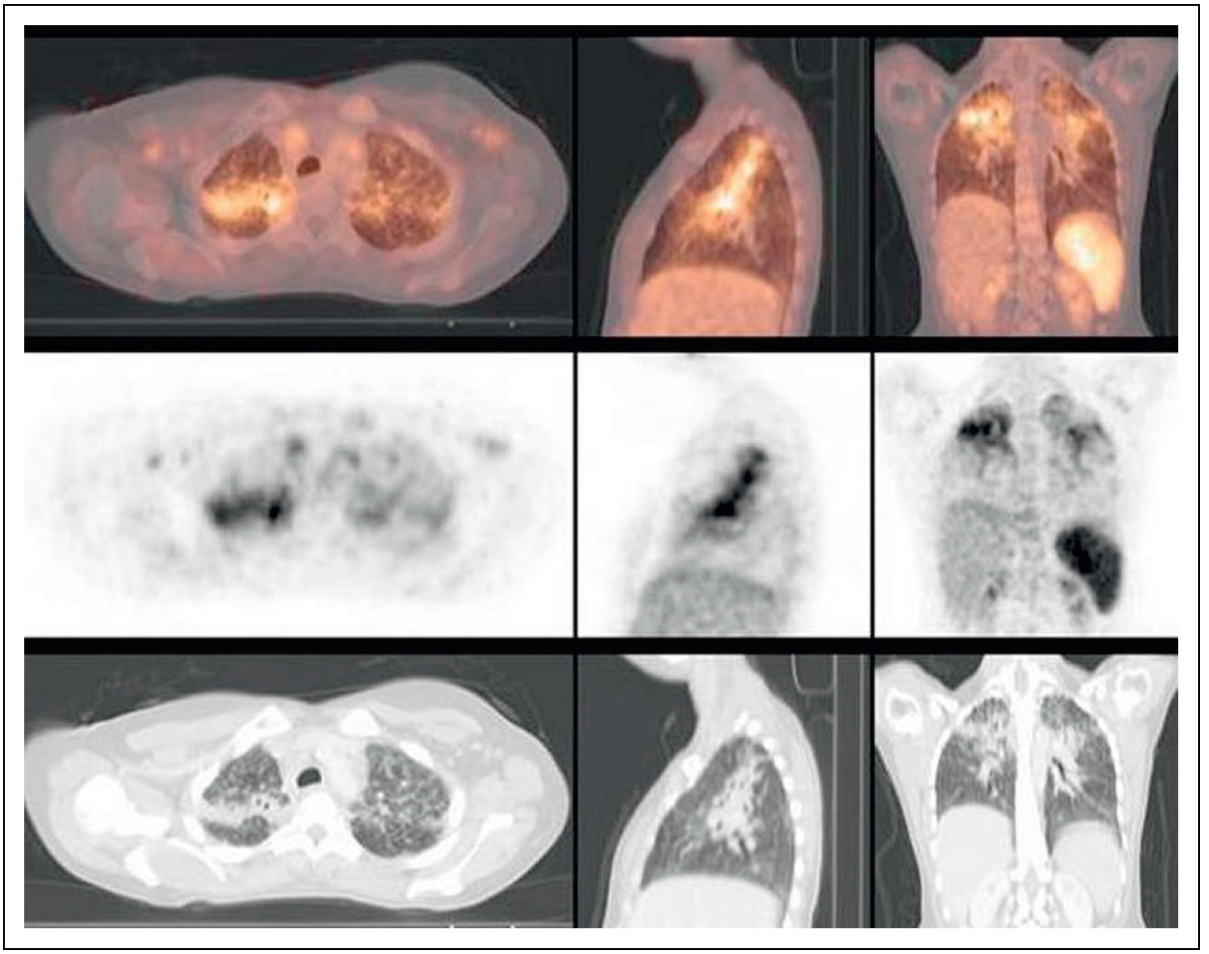

FIGURE 2. Sarcoidosis patient with signs of pulmonary fibrosis demonstrating ^{18}F-FDG PET activity. Top: transversal (left), sagittal (middle) and coronal (right) PET/CT fusion images showing that the increased FDG uptake in the pulmonary parenchyma corresponds to the parenchymal consolidations. The abdominal increased FDG uptake corresponds to the spleen. Middle: transversal (left), sagittal (middle) and coronal (right) PET images showing increased FDG uptake in the pulmonary parenchyma and in the spleen (coronal image). Bottom: transversal (left), sagittal (middle) and coronal (right) computed tomography (CT) images showing parenchymal consolidations with hilar retraction and architectural distortion of the pulmonary parenchyma. FDG, fluorodeoxyglucose.

changes in the above-mentioned study showed extrathoracic PET-positive findings (82%) and increased serological inflammatory markers (73%) [10▪]. Furthermore, the mean maximum standardized uptake values (SUV_{max}: 7.2 ± 4.1) in these patients were higher than the values reported by two studies with IPF patients [30,31] (0.99 ± 0.29 and 2.9 ± 1.1, respectively). These findings strongly suggest that PET-positive findings in sarcoidosis patients with CXR stage IV are related to inflammatory activity. The extrathoracic findings can be helpful to differentiate between sarcoidosis and other interstitial lung diseases like IPF in patients presenting with pulmonary fibrosis.

Assessment of disease activity through lung function tests requires evidence of progression between two measurements and so does not reflect the current status. Moreover, lung function testing cannot distinguish between reversible granulomatous lesions and irreversible fibrotic changes, and correlates only modestly with the level of dyspnoea reported by patients [23,33]. The assessment of the global lung burden as traditionally performed by lung function testing in combination with CXR abnormalities therefore appears to be insufficient for sarcoidosis patients with unexplained persistent disabling symptoms. A more accurate and global measure of both pulmonary and extrapulmonary disease may be achieved by the use of combined PET/CT in these patients.

PREDICTING THE PRESENCE OF PET POSITIVITY

As mentioned above, because of the excellent positive predictive value and moderate negative

predictive value of serological inflammatory marker testing for the presence of inflammatory activity on PET, this technique offers added value in assessing the inflammatory activity in sarcoidosis patients without serological signs of inflammatory activity [3,9]. In a recent study, a clinical prediction rule, based on sIL-2R levels and HRCT scoring results, was derived and internally validated [34▪]. This clinical prediction rule is useful to identify patients for whom there is a high probability that PET will show the presence of inflammatory activity. It has the potential to increase the cost-effectiveness of diagnostic investigation, as performing PET for the assessment of inflammatory activity is unnecessary in patients with a high predicted probability. An additional advantage is that the assessment of inflammatory activity could become more standardized. Future prospective studies are warranted to develop more sophisticated models, and the search for new inflammatory parameters should continue as well.

PROGNOSTIC VALUE OF PET-POSITIVE FINDINGS

Keijsers *et al.* [35] found that increased ^{18}F-FDG uptake in the pulmonary parenchyma correlated with the number of neutrophils and the $CD103^+CD4^+/CD4^+$ ratio in BAL fluid of sarcoidosis patients. Previously, an increase in the number of neutrophils in BAL fluid was found to be associated with an unfavourable outcome [12,36]. Another study showed that diffuse parenchymal activity in sarcoidosis patients, as imaged by ^{18}F-FDG PET, predicts a future deterioration of diffusion capacity for carbon monoxide when medical treatment is withheld [37]. The same study also found, however, that treatment with corticosteroids or immunosuppressive drugs improved lung function significantly.

PET also enables a more accurate clinical assessment of the prognostic factors by depicting organ involvement, like bone involvement, which is associated with a chronic course of the disease [15,38]. PET/CT appeared to be an excellent modality to detect bone or bone marrow involvement compared with more conventional modalities [39▪], suggesting that physiological changes precede morphological changes, which is a concept known from PET/CT in oncology [40]. Nevertheless, no clear data exist on the prognostic significance of PET/CT-positive osseous findings in sarcoidosis patients or on whether there is an increased risk of fracture at these sites [38]. However, as follow-up PET/CT after therapy showed improvement of the osseous involvement [39▪], PET/CT may play a role in monitoring the osseous involvement in sarcoidosis.

On the basis of the above findings, it is tempting to speculate that the distribution of increased FDG uptake has added prognostic value.

Detection of cardiac sarcoidosis is of utmost importance with respect to the prognosis, as this is a major cause of serious morbidity and mortality in sarcoidosis [41]. Fasting cardiac PET seems to be the most sensitive test for detecting active sarcoid lesions and their response to treatment, but there is no thoroughly evaluated diagnostic algorithm to screen for cardiac sarcoidosis [42▪▪,43]. However, the results of a recent study suggested that combined use of PET and cardiac MRI may provide optimal detection of cardiac sarcoidosis by differentiating active granulomatous inflammation from fibrous lesions [44▪▪].

IMPLICATIONS OF PET POSITIVITY FOR THERAPY

The indications for the treatment of individual patients depend on many factors, not just whether the patient is symptomatic but also whether there is evidence of significant involvement in vital organs. The presence of potential (partial) reversibility in patients with radiological signs of fibrosis may have therapeutic consequences [4]. Inflammatory activity can indicate persistent evolution of the disease and may therefore be a target for therapy. Deciding which sarcoidosis patients with fibrotic disease may benefit from pharmacological treatment remains a challenge to clinicians, as it is not always clear whether respiratory symptoms in these patients are a result of organ damage or because of ongoing inflammation or both. Careful consideration also needs to be given to the likely benefits of any therapy, set against the risk of adverse events, as adding the burden of medication like corticosteroids to disabled sarcoidosis patients with pulmonary fibrosis might harm them even further. To date, there is no medication with the proven capability of reversing fibrosis, but there is hope that treatment can arrest the fibrosis of reversible granulomas that persist among the fibrotic elements. Techniques that are purported to differentiate between fibrotic end-stage tissue and granulomatous tissue with inflammatory activity are therefore of importance. Several reports have demonstrated a significant reduction of FDG uptake after the initiation or modification of treatment in sarcoidosis patients [4,5,45,46]. An example of a pretreatment and posttreatment PET scan of a patient with sarcoidosis is shown in Fig. 3. Keijsers *et al.* [45] demonstrated that changes in PET imaging in a small cohort of sarcoidosis patients treated with infliximab considerably correlated with the clinical signs of improvement, including reduced fatigue.

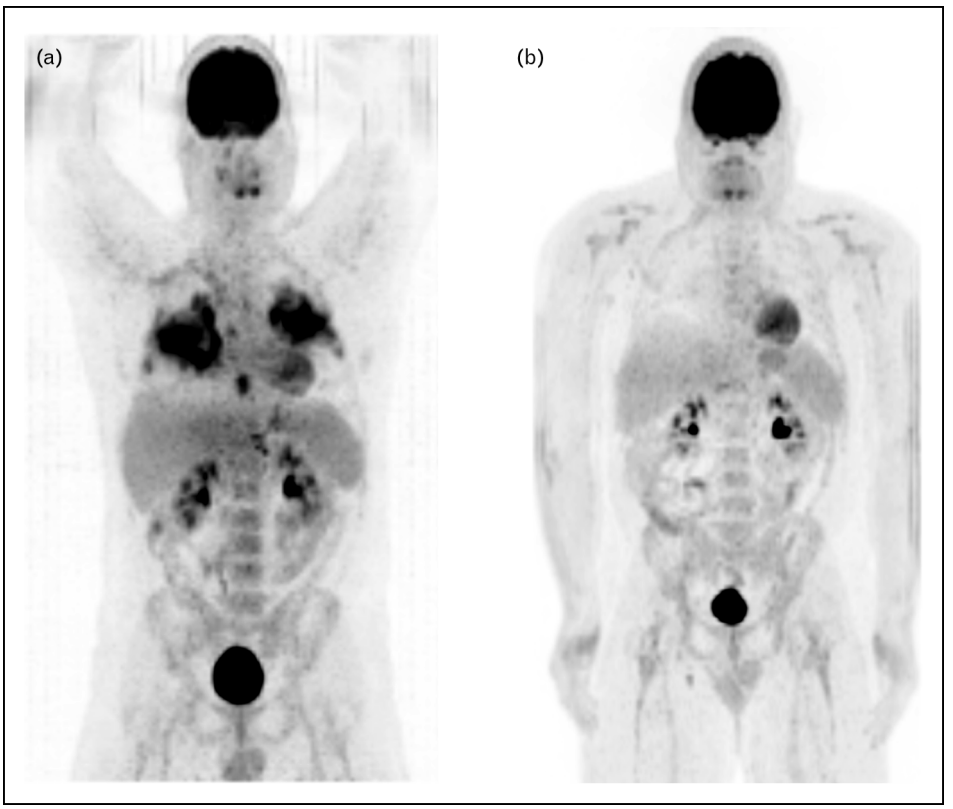

FIGURE 3. Pretreatment and posttreatment PET findings of a patient with sarcoidosis. (a) Coronal PET image showing pathologically increased FDG uptake in the pulmonary parenchyma and paraoesophageal lymph nodes. (b) Coronal PET image after therapy with infliximab showing resolution of the pathologically increased FDG uptake in the pulmonary parenchyma and paraoesophageal lymph nodes. FDG, fluorodeoxyglucose.

Teirstein *et al.* [4] described that the improvement of symptoms, conventional imaging findings and physiological data paralleled the therapy-related decrease in SUV_{max} as seen on the PET scans in most patients, including three patients with radiographic stage IV. A decrease in FDG uptake after therapy was also found in patients with refractory sarcoidosis treated with adalimumab [46]. PET/CT was repeated after a change in therapy in part of the sarcoidosis patients in a study on bone involvement as assessed by PET, and showed a decrease in the number of bone localizations and the SUV_{max}, respectively [39▪]. A recent study showed that positive PET results were a significant predictor of a change in therapy during follow-up [11▪]. However, because of the relatively short follow-up period, no conclusion could be drawn as to whether the decision to change the therapy altered the course of disease.

The value of PET in the follow-up of therapy is another topic of interest. It is still not clear how long therapy, including antitumor necrosis factor (TNF)-α agents, should be continued. Further studies are required to investigate whether PET, in addition to other clinical parameters, could be helpful in guiding the duration of treatment. If this is the case, PET could increase the cost-effectiveness and avoid long-term side-effects. On the basis of the above-mentioned results of studies with follow-up PET during treatment [4,45,46], a reduction in inflammatory activity can be presumed to have occurred in patients with clinical signs of improvement during treatment. Follow-up PET scans therefore seem unnecessary in these patients.

CONCLUSION

PET is a sensitive method to assess the inflammatory activity and the extent of disease in sarcoidosis. PET is not indicated in the standard workup, but can be of great value to complement more routinely used techniques. PET appears especially helpful in patients with unexplained persistent disabling symptoms in the absence of serological signs of inflammatory activity, in patients with radiologic signs of fibrosis and in the detection of active cardiac sarcoidosis. The use of PET to assess the extent of disease can uncover a suitable location for biopsy to obtain histological evidence for the diagnosis or to explain the (mainly extrathoracic) symptoms. Furthermore, the detection of extrathoracic involvement can offer prognostic value.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 583–584).

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This study demonstrated that PET/CT after a high-fat and low-carbohydrate diet is a sensitive tool, with a very good interobserver agreement, for the diagnosis of active cardiac sarcoidosis. Combined use of PET and cardiac magnetic resonance imaging may provide optimal detection of cardiac sarcoidosis by differentiating active granulomatous inflammation from fibrous lesions.

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