Review series on sarcoidosis European Respiratory Journal

Imaging the inflammatory activity of sarcoidosis

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Keywords:
¹⁸F-FDG PET/CT, high resolution CT, inflammation, sarcoidosis activity

Word count: 4017

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Abstract

Accurate assessment of pulmonary and extra pulmonary organ involvement in sarcoidosis is one of the great challenges for clinicians. This assessment includes the evaluation of symptoms, sarcoidosis activity in a specific organ and its functional consequences. In this review, radiological and nuclear techniques to image the inflammatory activity of sarcoidosis are described, in particular $^{18}$F-FDG PET/CT. The current use of this technique in clinical practice is explained, particularly in patients with persistent symptoms, stage IV disease and cardiac sarcoidosis.
Introduction

Sarcoidosis is a chronic granulomatous disease of unknown origin that can affect any organ. Organs most frequently affected include the lymphatic system, lungs, skin, peripheral and central nervous system, and eyes.[1] Involvement of the heart is rare, although a potentially life-threatening manifestation of the disease.[2, 3]

Accurate evaluation of pulmonary and/or extra pulmonary organ involvement of sarcoidosis remains one of the great challenges for clinicians. This evaluation includes the assessment of sarcoidosis activity in a specific organ and its functional consequences.[4]

In patients with chronic disease, fibrotic changes may occur in the affected organs. These patients in particular might benefit from immunosuppressive treatment to prevent further irreversible organ damage. It is most likely that this organ damage occurs in patients with ongoing inflammatory activity.

To optimise clinical decision making on type and/or dose of immunosuppressive drugs, it is of utmost importance to have markers that accurately reflect the degree of sarcoidosis activity throughout the body, and ideally at single organ level in case of involvement with symptomatic and/or functional consequences.[5] However, currently there are only a few serum biomarkers that can be used to monitor sarcoidosis activity. Since none of these markers is ideal, the need for further development in this field is desirable.

In the past decade nuclear imaging, particularly positron emission tomography (PET) with $^{18}$F-Fluorodeoxyglucose ($^{18}$F-FDG), has emerged as a potentially powerful tool to visualise the intensity and extent of inflammatory activity of sarcoidosis throughout the body. [6-8] Radiological and other nuclear techniques are available to assess disease activity. In this article, a review of the literature is given on radiological and nuclear imaging in sarcoidosis
and $^{18}$F-FDG PET/CT imaging in particular. Additionally, the current application of this technique in our clinical practice is described.
Radiological imaging

Conventional chest radiography

Over four decades ago Scadding presented a staging system for pulmonary sarcoidosis based on chest radiography. It is a purely descriptive system that uses the presence or absence of lymphadenopathy and parenchymal disease to stage pulmonary sarcoidosis. A major drawback of this system is that, although its provides some prognostic information, the radiographic findings in themselves, hardly differentiate between active inflammation and fibrosis or inactive disease.[1]

Only serial changes on chest radiography might reveal some information on pulmonary disease activity. Its value as a tool to visualise inflammation of sarcoidosis is therefore mainly based on retrospective analysis.

High resolution CT

HRCT is superior to conventional radiography in detecting nodules, early fibrosis and parenchymal distortion. Its high spatial resolution provides improved anatomic detail enabling assessment of fine parenchymal changes at the level of the secondary pulmonary lobule. With the advent of Multi Detector CT scanners volumetric scanning has become routine in many institutions and enables fast imaging of the whole lungs in one single breath hold. It has become a powerful tool in the diagnosis of diffuse parenchymal lung disease (DPLD). In the evaluation of suspected pulmonary sarcoidosis HRCT enables a more confident first choice diagnosis with better interobserver agreement when compared to conventional chest radiography.[9] However, the exact diagnostic and prognostic value of HRCT in pulmonary sarcoidosis is still in research.
There are several studies that have investigated the prognostic role of HRCT by evaluating disease changes over time with serial CT scanning. These studies, with relatively small number of patients, demonstrated that architectural distortion, honeycombing, traction bronchiectasis and large cysts are invariably irreversible, (micro)nodular disease is in most cases reversible but that ground glass, irregular linear opacities and interlobular septal thickening can be reversible but quite often are not and can progress to fibrosis.[10-15] Thus, evaluating the reversibility of disease by HRCT appears to be possible only in retrospect with serial data. However, some HRCT features might still have the potential to discriminate between reversible disease (active inflammation) and irreversible disease (fibrosis). Additionally, HRCT features may carry predictive information regarding the response to anti-inflammatory therapy or progress towards fibrosis though large scale HRCT scoring data are required including follow-up scans and clinical data like serial lung function of well-typed patient groups.
Nuclear imaging

$^{67}$Gallium scintigraphy

In vivo, Gallium-67 ($^{67}$Ga) acts like an iron analogue and binds to transferrin. In inflammatory lesions, $^{67}$Ga will subsequently bind to lactoferrin which is an important binding protein in polymorphonuclear leukocytes.[16]

During the first 24 hours after administration, $^{67}$Ga citrate is excreted by the kidneys. Subsequently, the hepatobiliary system will excrete the radiopharmaceutical. Due to the slow plasma clearance, a substantial amount of $^{67}$Ga citrate remains in the body and will be distributed to ‘lactoferrin rich’ tissues. This explains the activity in bone marrow, spleen, liver and lacrimal and salivary glands.

Several authors have described the sensitivity and specificity of $^{67}$Ga scintigraphy to diagnose sarcoidosis. In the majority of the studies, active disease is defined by the presence of symptoms in patients with biopsy proven sarcoidosis. In order to determine specificity, sarcoidosis is defined as inactive when patients did not have symptoms and chest radiography did not change. Sensitivity of $^{67}$Ga scintigraphy ranges between 60-90%, with a low specificity of approximately 50%.[6, 17-21]

However, negative $^{67}$Ga scintigraphy combined with normal ACE has a high negative predictive value.[22, 23]

$^{67}$Ga scintigraphy correlates with ACE values and clinically effective steroid therapy is associated with an improvement of $^{67}$Ga scintigraphy and decrease in ACE.[19, 23-25]

Rizzatto et al. assessed the predictive value of $^{67}$Ga scintigraphy, chest radiography and ACE in 382 patients.[26] $^{67}$Ga scintigraphy appeared to be more sensitive than chest radiography in detecting disease progression and improvement. Furthermore, uptake of $^{67}$Ga citrate was suppressed by the use of corticosteroids but to a lesser extent than ACE.
The "lambda" and "panda" signs in $^{67}$Ga scintigraphy are suggested to be a characteristic feature of sarcoidosis. Bilateral hilar activity combined with predominantly right sided active lymph nodes in the mediastinum represents the lambda sign. The panda sign is based on the symmetrical activity in the lacrimal and parotid glands. However, these signs have demonstrated a poor diagnostic sensitivity in biopsy proven sarcoidosis patients.[27-29] Furthermore, the panda sign can be found in patients with HIV, malignant lymphomas and Sjögren’s syndrome as well.

In general, $^{67}$Ga scintigraphy is performed with 185 MBq $^{67}$Ga citrate, resulting in an effective radiation dose of 18.5 mSv.[30, 31]

**Somatostatin receptor scintigraphy**

Somatostatin receptors are present in several cell types, for example activated macrophages.[32] There are 5 somatostatin receptor subtypes and in vitro autoradiography of histological biopsies of sarcoidosis revealed that the somatostatin receptor subtype 2 (sst$_2$) is expressed in epitheloid cells and giant cells.[33] Somatostatin receptor scintigraphy (SRS) is most frequently performed with Indium-111 ($^{111}$In) pentetreotide. Pentetreotide shows high affinity for the sst$_2$ receptor and might therefore be used in the imaging of sarcoidosis. In general, SRS is performed with 200 MBq $^{111}$In-pentetreotide resulting in an effective radiation dose of 10.8 mSv.[34] Planar whole body images and SPECT of the chest are performed 24 hours after injection.

Kwekkeboom et al. performed SRS in 46 sarcoidosis patients and demonstrated active lesions in 97% of the disease locations imaged by conventional chest radiography.[35] Additional thoracic and extra thoracic lesions were found but several other extra thoracic lesions were not properly demonstrated. Lebtahi et al. compared SRS with $^{67}$Ga imaging in 18 patients and found that SRS revealed significantly more sarcoidosis lesions at the clinically involved sites.
than $^{67}$Ga imaging (82% and 64%, respectively).[36] Although SRS demonstrated additional extra thoracic sites that were not suspected clinically, still 40% of the known extra thoracic lesions were not diagnosed. SRS seems therefore sensitive in the assessment of active thoracic sarcoidosis but the presence of extra thoracic disease can be missed.

$^{18}$F-FDG PET

Fluorine-18 fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) is widely used in the imaging of malignant tumours. An increased glucose metabolism of malignant cells causes the accumulation of $^{18}$F-FDG. Once $^{18}$F-FDG is transported through the cell membrane into the cytosol, it is phosphorylated by hexokinase. Here, the $^{18}$F-FDG is metabolically trapped as $^{18}$F-FDG-6-phosphate. Glucose transporters (GLUT) across the cell membrane account for the transport of $^{18}$F-FDG into the cell. In malignant cells, the expression of mainly GLUT-1 is responsible for $^{18}$F-FDG accumulation.[37-40] Activated leukocytes express the GLUT-1 transporter as well.[38] Consequently, $^{18}$F-FDG PET can be used in leukocyte mediated processes, like inflammatory lesions.

In 1994, the use of $^{18}$F-FDG PET in sarcoidosis was first reported by Lewis and Salama.[41] Although autoradiographic studies of sarcoid lesions are missing, the accumulation of $^{18}$F-FDG in macrophages and CD$^+$ T lymphocytes may explain the in vivo imaging of this granulomatous process.[42, 43]

$^{18}$F-FDG PET and $^{67}$Ga scintigraphy

Nishiyama et al. compared $^{18}$F-FDG PET and $^{67}$Ga scintigraphy retrospectively in 18 patients.[20] Histology was used as the gold standard. Sensitivity for the detection of thoracic disease was 100% for $^{18}$F-FDG PET and 81% for $^{67}$Ga scintigraphy while extra thoracic lesions were adequately observed in 90% and 48%, respectively. In a similar study, Prager et
al. reported a significantly higher, overall detection rate for $^{18}$F-FDG PET.[21] Thoracic
disease was found in 96% of the patients. $^{67}$Ga scintigraphy revealed thoracic abnormalities in
88%. Nineteen extra thoracic locations were found in $^{18}$F-FDG PET and 12 in $^{67}$Ga
scintigraphy.

In a prospective evaluation of both techniques, the overall sensitivity to detect active
sarcoïdosis in histologically proven sarcoïdosis was 97% for $^{18}$F-FDG PET and 88% for $^{67}$Ga
scintigraphy. Significantly more active lesions in the mediastinum, hila and extra pulmonary
regions were detected by $^{18}$F-FDG PET, mainly due to lymph node and spleen involvement.
Furthermore, inter observer agreement was considerably higher in $^{18}$F-FDG PET.[44]

Compared to $^{18}$F-FDG PET, $^{67}$Ga scintigraphy is less sensitive in detecting active sarcoïdosis
lesions, its radiation dose is three times higher and acquisition is 24 h after administration of
the radiopharmaceutical. In addition, $^{67}$Ga scintigraphy cannot guide in predicting disease
outcome.[45-47] Therefore, $^{67}$Ga scintigraphy is no longer the preferred nuclear imaging
technique in the assessment of sarcoïdosis activity. If conventional activity markers are unable
to demonstrate active disease though active sarcoïdosis is suspected, $^{18}$F-FDG PET is
recommended.

$^{18}$F-FDG PET/CT

It might be suggested that a combined imaging modality of $^{18}$F-FDG PET and CT is even
more sensitive than PET alone. Braun et al. retrospectively evaluated $^{18}$F-FDG PET/CT in 20
patients, both new and previously diagnosed sarcoïdosis.[6] This technique correctly
demonstrated 78% of the biopsy proven locations, with a 100% sensitivity for thoracic and
sinonasal disease. Skin lesions were the main reason for the decreased overall sensitivity,
probably explained by the skin thickness, causing difficulties in granuloma detection. In 12
patients, $^{67}$Ga scintigraphy was previously performed, with a correct detection of biopsy
proven lesions in 58%. Sensitivity of thoracic and sinonasal disease was 71% and 75%, respectively.

Teirstein et al. retrospectively analyzed 188 $^{18}$F-FDG PET/CT scans in 137 patients and demonstrated that this technique exhibits adequate sites for diagnostic biopsy. In 51 patients, $^{18}$F-FDG PET/CT was repeated to evaluate the effect of corticosteroids. Overall, the improvement seen by $^{18}$F-FDG PET/CT correlated well with changes in symptoms and clinical findings, although limited data have been provided.[8]

Quantifying metabolic activity by $^{18}$F-FDG PET/CT

Maximum SUV ($SUV_{\text{max}}$) is a semi-quantitative tool to measure disease activity. However, it only represents the maximum amount of activity in one pixel, corrected for the patients body weight and injected dose of the radiopharmaceutical. In oncology, $SUV_{\text{max}}$ has proven to be a reliable predictor of disease outcome. The difference in $SUV_{\text{max}}$ before and after chemo(radiotherapy) as well as the residual $SUV_{\text{max}}$ has shown to correlate with survival in several types of malignancy.[48-51]

In contrast with sarcoidosis, tumours are well-delineated processes. The pulmonary abnormalities in sarcoidosis can be diffuse as well as focal and appear in one or more lobes. Therefore, an increased metabolic activity with an $SUV_{\text{max}}$ of 3 involving all lobes might be more relevant than one small focal lesion with an $SUV_{\text{max}}$ of 10. So not only the amount of metabolic activity is relevant, the extent is of great importance as well.

Quantifying the total amount of metabolic activity in one organ might have great clinical value. One might suggest that the total amount of activity in the lung parenchyma correlates with the degree of deterioration in PFT in the future. To date, studies correlating quantified FDG uptake with clinical outcome have not been performed.
Prognostic value of $^{18}$F-FDG PET in sarcoidosis

Little is known about the prospective value of $^{18}$F-FDG PET in sarcoidosis. The metabolic activity in the lung parenchyma correlates with the number of neutrophils in broncho-alveolar lavage (BAL) fluid.[52] The number of neutrophils in BAL fluid is known to be associated with a worse outcome in sarcoidosis, which might suggest that metabolic activity in the lung parenchyma imaged by $^{18}$F-FDG PET might be correlated with a poorer prognosis as well.[53, 54]

In one study, lung parenchymal activity imaged by $^{18}$F-FDG PET was correlated with pulmonary function tests (PFT) after 12 months.[55] A significant decrease in diffusion capacity of the lung for carbon monoxide (DLCO) was found in 11 untreated patients with diffuse parenchymal activity. All patients showed stage II/III sarcoidosis on chest radiography. No change in vital capacity (VC) or forced expiratory volume (FEV$_1$) could be observed.

Sixteen patients with parenchymal activity and treated with immunosuppressive therapy, showed a significant increase in VC, FEV$_1$ and DLCO. Chest radiography demonstrated stage I in 9 patients and stage II/III in 6 patients. This finding suggests that $^{18}$F-FDG PET is able to assess the potential functional improvement that can be achieved if immunosuppressive therapy is applied. Conversely, 16 untreated patients without parenchymal activity did not show any change in PFT. In these patients, stage 0 was seen in one patient, stage I in 9 and stage II/III in 6 patients. These findings might suggest that the absence of metabolic activity imaged by $^{18}$F-FDG PET justifies a policy of watchful waiting.

The prognostic value of dual-time point PET imaging in persistent pulmonary involvement was evaluated by Umeda et al.[47] PET images were obtained at 60 min and 180 minutes after injection and Standardized Uptake Value (SUV) was measured. The retention of SUV was expressed as the SUV retention index (RI-SUV) and was correlated with changes on
chest CT after one year. In addition, initial $^{67}$Ga uptake was correlated as well as sIL-2R. The diagnostic accuracy of RI-SUV was significantly higher than early SUV or $^{67}$Ga uptake. Furthermore, sIL-2R showed a significant correlation with RI-SUV, but not with early SUV, which is in line with previous results.[7]

However, a prospective study with large numbers of patients to demonstrate the exact predictive role of $^{18}$F-FDG PET/CT is lacking.

$^{18}$F-FDG PET/CT acquisition

The patient fasts for at least six hours, preceded by a carbohydrate restricted diet for at least 24 h. Before the intravenous injection of $^{18}$F-FDG, 5 mg of diazepam is administered to reduce muscle activity and accumulation of $^{18}$F-FDG in brown fat. In order to reduce radiation exposure and accelerate $^{18}$F-FDG excretion by the kidneys, 20 mg of furosemide will be injected intravenously. Subsequently, $^{18}$F-FDG is administered based on the patients’ body weight with a maximum of 400 MBq. Sixty minutes after administration of $^{18}$F-FDG, low dose CT is performed from the subinguinal region to the head. Low dose CT is used for attenuation correction but also to optimize localisation when interpreting the images. Emission scan will be performed from the subinguinal region to the head with an acquisition time of 2½ minutes per bed position. In our clinic, a Philips Gemini Time of Flight $^{18}$F-FDG PET/CT is used. Reconstruction is performed in accordance with the 3D-RAMLA protocol applying 4 iterations with a 144 x 144 matrix.[56]

Radiation dose

Radiation dose of $^{18}$F-FDG PET is approximately 5.8 mSv for the first generation, standalone PET scanners. In the current PET/CT systems, the administered $^{18}$F-FDG activity is reduced and based on the patients bodyweight in accordance with the European guidelines.[57] A
bodyweight of 80 kilograms results in an effective radiation dose of 3.8 mSv.[30] More accurate disease location can be achieved by the concurrently obtained whole body CT, also performed for attenuation correction. This low dose CT adds approximately 2.9 mSv to the radiation dose.[58]

Even though $^{18}$F-FDG PET/CT is a non-invasive technique, it should be applied with care in evaluating sarcoidosis activity. $^{18}$F-FDG PET/CT is more expensive than other available tests and radiation exposure should not be ignored. Frequent repetition of $^{18}$F-FDG PET/CT is therefore not recommended.
18F-FDG PET/CT and MRI in cardiac sarcoidosis

Evaluating the presence of active sarcoidosis lesions in the myocardium is challenging, though crucial since this is one of the major causes of sarcoidosis related deaths.[59] Clinical involvement of the heart is reported in 5% of the sarcoidosis patients in the US, but autopsy studies have shown myocardial granuloma formation in at least 25% of the patients.[60] Incidence strongly varies with race and is most common in Japan.

In the early nineties, the Japanese Ministry of Health and Welfare (JMHW) has published diagnostic guidelines to assess the presence of cardiac sarcoidosis.[61] However, this guideline has not been validated and is now fairly outdated since more recently developed techniques, like 18F-FDG PET/CT and MRI, are not incorporated.

In our current practice, JMHW criteria are still used. However, echocardiography and 67Ga scintigraphy are replaced by CMR and 18F-FDG PET/CT, respectively. The principles and advantages of these two techniques will be discussed below.

Cardiac Magnetic Resonance Imaging (CMR) has become an important modality for the detection and functional evaluation of cardiac disease. Several studies have shown the value of gadolinium-diethylenetriaminepenta-acetic acid (DTPA) T1 and T2 weighted imaging for diagnosing cardiac sarcoidosis.[62, 63] However, the role of CMR in discriminating active from inactive, i.e. fibrotic, lesions in the myocardium has been insufficiently investigated.

Most patients with evidence of cardiac sarcoidosis receive an Implantable Cardioverter Defibrillator (ICD) or pacemaker to prevent sudden death caused by ventricular tachyarrhythmia or conduction blocks. After implantation of the device, these patients are no longer suitable for CMR. With the advent of MRI-conditional pacemakers and ICD devices undoubtedly more data on disease reversibility will become available. To date, study results
on disease reversibility and imaging of active disease are limited. However, it has been shown that after steroid treatment both contrast enhancement and later on T2 signal intensity can disappear suggesting that these imaging findings reflect active disease.

Mammalian metabolism depends on glucose and fatty acids.[64] ¹⁸F-FDG uptake in the myocardium is therefore a merely physiologic process. Several methods have demonstrated to reduce this physiologic uptake of ¹⁸F-FDG, i.e. the use of unfractionated heparin, prolonged fasting or a carbohydrate restricted diet for at least 24 h prior to scanning.[65-70] The latter has been proven to be the most effective method. Only fat and proteins are allowed while all carbohydrates, including vegetables, should be avoided.

When the intake of carbohydrates is limited, fatty acids will be used and physiologic uptake of ¹⁸F-FDG is reduced. Without any physiologic uptake in the myocardium, only pathologic processes, like active granulomas, will become evident. This is the basis of imaging active cardiac sarcoidosis with ¹⁸F-FDG PET/CT.

At this time, a limited number of studies evaluating the use of ¹⁸F-FDG PET/CT in cardiac sarcoidosis is available.

In a current meta-analysis, ¹⁸F-FDG PET/CT of 164 sarcoidosis patients was compared to the JMHW guidelines. A sensitivity of 89% and specificity of 78% was found for ¹⁸F-FDG PET/CT in the detection of active cardiac sarcoidosis.[71] Physiologic myocardial uptake was reduced by the use of the three aforementioned methods.

Figure 1 shows the ability of CMR to demonstrate sarcoidosis in the myocardium while ¹⁸F-FDG PET/CT provides information about the activity of these lesions. The presence of sarcoid lesions in the myocardium might give rise to the implantation of a cardioverter.
defibrillator, while the presence of active granulomas support treatment with immunosuppressive drugs.

In Figure 2, a flowchart shows the authors approach of patients suspected of having cardiac sarcoidosis. First, CMR, Holter monitoring and $^{18}$F-FDG PET/CT preceded by a carbohydrate restricted diet are performed. Modified JMHW criteria are discussed by the pulmonologist, cardiologist, nuclear medicine physician and radiologist. In these modified criteria, CMR and $^{18}$F-FDG PET/CT are incorporated, the latter replacing $^{67}$Ga scintigraphy.

In patients with cardiac sarcoidosis based on CMR, an ICD is implanted when ventricular arrhythmias are inducable during electrical stimulation of the ventricle. Active cardiac sarcoidosis is suggested when active cardiac lesions on $^{18}$F-FDG PET/CT match CMR. Then immunosuppressive therapy is started.

In case $^{18}$F-FDG PET/CT shows active sarcoidosis without increased $^{18}$F-FDG uptake in the myocardium, but with an abnormal CMR, immunosuppressive treatment is started as well. The resolution of current $^{18}$F-FDG PET/CT systems is approximately 5 mm.[72, 73] Smaller, though relevant cardiac sarcoidosis lesions might therefore be missed.

When CMR is abnormal but $^{18}$F-FDG PET/CT does not show any increased activity, no immunosuppressive therapy will be started.
Current use of $^{18}$F-FDG PET/CT in clinical practice

$^{18}$F-FDG PET/CT should not be used in the standard work-up of all sarcoidosis patients. However, when appropriately indicated, application of $^{18}$F-FDG PET/CT can provide valuable information and optimize patient treatment. In our opinion, $^{18}$F-FDG PET/CT might be useful in the following situations (Table 1):

1. $^{18}$F-FDG PET/CT can guide the clinician to obtain histological proof of sarcoidosis. Biopsy from metabolic active lesions is more likely to yield the diagnosis than biopsy from inactive lesions.

2. In sarcoidosis patients with persistent symptoms and slightly increased or even normal biomarkers, $^{18}$F-FDG PET/CT might help to demonstrate sites of ongoing disease activity (Figure 3). Mostard et al. evaluated $^{18}$F-FDG PET/CT in 89 patients with unexplained, persistent and disabling symptoms and found that $^{18}$F-FDG PET/CT demonstrated active lesions in 73%. In 20% of these patients, serum markers of activity were normal.

3. $^{18}$F-FDG PET/CT is helpful in the detection of active cardiac sarcoidosis. As described previously, MRI is able to demonstrate cardiac involvement and might give rise to the implantation of a cardiac defibrillator. $^{18}$F-FDG PET/CT on the other hand, reveals the activity state of the cardiac lesions and helps indicating whether immunosuppressive treatment should be started or adjusted.

4. In patients with long standing and symptomatic pulmonary sarcoidosis or signs of fibrosis, the clinician might be challenged to prove the presence of active disease and decide on the usefullness of (additional) immunosuppressive therapy. Retrospective analysis of $^{18}$F-FDG PET/CT in symptomatic patients with stage IV disease, revealed persistent parenchymal disease activity in 14 out of 15 patients. In addition, patients with increased metabolic activity in the lung parenchyma show a significant increase in VC and DLCO after
treatment.[55, 75] These findings suggest that $^{18}$F-FDG PET/CT is able to demonstrate the potential functional improvement that can be achieved even when fibrosis, *i.e.* end stage disease, is present. Figure 4 illustrates this potential role of $^{18}$F-FDG PET/CT in one patient of this particular population.
Future perspective

Predicting the effect of immunosuppressive therapy might be of great value, particularly in expensive treatment like anti TNF-α. Anti TNF-α drugs can be labelled with 99m-Technetium (99mTc) and scintigraphy prior to therapy might predict whether this specific treatment will be successful. In rheumatoid arthritis, scintigraphy with 99mTc-labelled infliximab demonstrated a significantly higher activity in the affected joints than in those who were not affected.[76] Studies evaluating the role of 99mTc labelled anti TNF-α scintigraphy in sarcoidosis are lacking, although the success in other TNF mediated diseases suggests a promising technique.

Since 18F-FDG PET/CT is a whole body technique, active granulomas could be detected in one single study. Consequently, this technique might be able to determine the total granuloma load in sarcoidosis patients.

But not only the total amount of active disease is relevant, also quantification of the inflammatory mass per organ might help the clinician to titrate immunosuppressive therapy on an individual base. Since 18F-FDG PET is nowadays combined with CT, the target organ is easier to delimitate and the sum of activity in the organ of interest can be calculated. Although future studies are undoubtedly warranted to correlate quantification with functional outcome, and to proof this concept.

Although available in only a few hospitals worldwide, PET/MRI is the latest hybrid imaging technique. Since MRI compatible leads and devices have become available, repetitive CMR could be performed in patients with cardiac sarcoidosis. Combining the high sensitivity of 18F-FDG PET with the exact anatomical localization of MRI has great potential in the detection and follow-up of patients with cardiac sarcoidosis.[77] Although promising, to date, no such studies have been performed.


Table 1. $^{18}$F-FDG PET/CT indications in sarcoidosis

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<th>Indications for $^{18}$F-FDG PET/CT in sarcoidosis</th>
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<td>- Obtaining histological proof of sarcoidosis</td>
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<td>- Determining the presence of active disease in symptomatic patients with normal conventional markers</td>
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<td>- Assessing the presence of active cardiac sarcoidosis, combined with CMR</td>
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<td>- Evaluating disease activity in symptomatic patients with longstanding sarcoidosis or stage IV disease</td>
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Figure 1.

MRI (a) and $^{18}$F-FDG PET/CT (b) of a 49-year old male with sarcoidosis and ventricular arrhythmias. MRI demonstrated a diffuse hypokinetic left ventricle with an ejection fraction of 35% and enhancement in T2 weighted images in the anterior, inferior and interventricular septal wall. $^{18}$F-FDG PET/CT after a carbohydrate restricted diet revealed that the majority of these lesions were still active. An ICD was implanted because of the arrhythmias and immunosuppressive therapy was started given the presence of active inflammation in the myocardium.
Figure 2.

Flowchart showing the approach of patients with cardiac sarcoidosis

1. Start on adjunct immunosuppressive therapy
2. Active cardiac involvement on FDG-PET/CT requiring CMR: start therapy
3. Active extracardiac sarcoidosis without cardiac involvement or normal CMR: start therapy
4. Normal FDG-PET/CT with abnormal CMR: no therapy
Figure 3.

Chest radiography (a) and $^{18}$F-FDG PET/CT (b and c) of a 67-year old female diagnosed with sarcoidosis 2 years before referral to our tertiary center. The use of 10 mg prednisone per day for 2 years, later combined with methotrexate had not prevented a serious decrease in pulmonary function. She suffered from severe dyspnoea on exertion and fatigue. At presentation, chest radiography revealed a diffuse nodular pattern with mild fibrotic changes predominating in the mid lobes without lymphadenopathy. Serum ACE and calcium were normal while sIL-2R was only slightly increased. $^{18}$F-FDG PET/CT however demonstrated severely increased metabolic activity in the lung parenchyma. Active lymph nodes were seen in the mediastinum, hila, upper abdomen and left inguinal region. Combined with PFT, 6-min walk distance (6-MWD), symptoms and findings, infliximab was started. After 6 cycles, the increase in FEV$_1$ was 11%, VC 21% and DLCO remained stable. Maximum distance during the 6-MWD showed an increase of 21%. Chest radiography and $^{18}$F-FDG PET/CT demonstrated improvement, most impressive by $^{18}$F-FDG PET/CT (bottom row). These findings show that $^{18}$F-FDG PET/CT is able to reveal the ongoing inflammatory activity of sarcoidosis thereby demonstrating the potentially reversible lesions.
Figure 4. A 40-year old male with progressive pulmonary sarcoidosis was treated with prednisone and methotrexate. After 2 years of treatment, pulmonary function tests remained stable. VC was normal, FEV₁ and DLCO were decreased. ACE and sIL-2R were normal. This patient was considered to have inactive disease with pulmonary scarring.

HRCT (a) showed a perihilar masslike consolidation with central traction brochiectasis, cystic changes and distortion of the lung parenchyma. No nodular disease was present and the changes were interpreted as being fibrotic without active disease. ¹⁸F-FDG PET (b) on the other hand showed increased metabolic activity in the lung parenchyma combined with active lymphadenopathy in hila and the mediastinum. Based on these findings, infliximab therapy was initiated. After 6 cycles, VC, FEV₁ and DLCO showed a considerable increase of 15%, 11% and 8% respectively. HRCT demonstrated a significant improvement (c) while only a slight metabolic activity remained visible by ¹⁸F-FDG PET (d).