Comparative Evaluation of ^{18}F-FDG PET and ^{67}Ga Scintigraphy in Patients with Sarcoidosis

Yoshihiro Nishiyama[1], Yuka Yamamoto[1], Kotaro Fukunaga[1], Hiroyuki Takinami[2], Yasuyoshi Iwado[2], Katashi Satoh[1], and Motoomi Ohkawa[1]

[1]Department of Radiology, Faculty of Medicine, Kagawa University, Kagawa, Japan; and [2]Second Department of Internal Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan

^{67}Ga scintigraphy has been used for years in sarcoidosis for diagnosis and the extent of the disease. However, little information is available on the comparison of ^{18}F-FDG PET and ^{67}Ga scintigraphy in the assessment of sarcoidosis. The purpose of this study was to compare the uptake of ^{18}F-FDG and ^{67}Ga in the evaluation of pulmonary and extrapulmonary involvement in patients with sarcoidosis. **Methods:** Eighteen patients with sarcoidosis were examined. ^{18}F-FDG PET was performed at 1 h after injection of 185−200 MBq ^{18}F-FDG. ^{67}Ga whole-body planar and thoracic SPECT images were acquired 72 h after injection of 111 MBq ^{67}Ga. We evaluated ^{18}F-FDG and ^{67}Ga uptake visually and semiquantitatively using standardized uptake values (SUVs) and the ratio of lesion to normal lumbar spine (L/N ratio), respectively. The presence of pulmonary and extrapulmonary lesions was evaluated histopathologically or by the radiologic findings. **Results:** Five patients had only pulmonary lesions, 12 patients had both pulmonary and extrapulmonary lesions, and 1 patient had only an extrapulmonary lesion. Both ^{67}Ga planar and SPECT images detected 17 of 21 (81%) clinically observed pulmonary sites. The mean ± SD of the L/N ratio was 1.97 ± 1.09. ^{67}Ga planar images detected 15 of 31 (48%) clinically observed extrapulmonary sites. The mean ± SD of the L/N ratio was 1.17 ± 0.33. ^{18}F-FDG PET detected all 21 (100%) clinically observed pulmonary sites. The mean ± SD of the SUV was 7.40 ± 2.48. ^{18}F-FDG PET detected 28 of 31 (90%) clinically observed extrapulmonary sites. The mean ± SD of the SUV was 5.90 ± 2.75. **Conclusion:** The results of this clinical study suggest that ^{18}F-FDG PET can detect pulmonary lesions to a similar degree as ^{67}Ga scintigraphy. However, ^{18}F-FDG PET appears to be more accurate and contributes to a better evaluation of extrapulmonary involvement in sarcoidosis patients.

Key Words: ^{67}Ga scintigraphy; ^{18}F-FDG PET; sarcoidosis; extrapulmonary involvement

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Sarcoidosis is a multisystem inflammatory disease of unknown origin, characterized by the presence of noncaseating epithelioid cell granulomas in the affected tissue (*1*). Correct assessment of disease activity is critical for initiating an optimal management plan because a small percentage of patients may die without treatment soon after diagnosis, although most patients will have a self-limited course (*1*).

Traditionally, although ^{67}Ga has been used in scanning for the detection of sarcoidosis, it has serious limitations. First, patients must be injected with the radiolabeled material at least 48−72 h before image acquisition (*2*). Second, there is significant interobserver variability in the interpretation of ^{67}Ga scans (*3,4*). Third, although certain patterns noted on ^{67}Ga scans are considered to be unique to sarcoidosis (e.g., the λ-panda pattern), the overall sensitivity and specificity of ^{67}Ga vary significantly (*5,6*). Some researchers have reported that this tool is highly accurate, whereas others have failed to observe similar findings (*5,6*). Thus, at present, ^{67}Ga scanning is generally considered to have a limited role in the evaluation and management of sarcoidosis (*7*).

PET with ^{18}F-FDG is a well-established functional imaging technique for diagnostic oncologic imaging that provides data on glucose metabolism in lesions (*8*). However, ^{18}F-FDG PET allows the visualization not only of the malignant cells but also of the inflammatory cells (*9,10*). Lewis and Salama first observed ^{18}F-FDG uptake in sarcoid lesions in 2 patients (*11*). Increased ^{18}F-FDG accumulation in patients with sarcoidosis was subsequently reported by multiple other groups (*12–14*).

To our knowledge, with the exception of a sporadic case report, the literature contains no data on the potential advantages of ^{18}F-FDG PET over ^{67}Ga scintigraphy in the detection of granulomatous sites in patients with sarcoidosis. Therefore, the aim of this study was to compare ^{18}F-FDG PET and ^{67}Ga scintigraphy in the evaluation of pulmonary and extrapulmonary involvement in patients with sarcoidosis.

MATERIALS AND METHODS

Patients

The research study protocol was approved by the University Hospital Institutional Review Board. Written informed consent was obtained from each patient before entry into the study.

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For correspondence or reprints contact: Yoshihiro Nishiyama, MD, Department of Radiology, Faculty of Medicine, Kagawa University, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan.

E-mail: nisiyosi@kms.ac.jp

Eighteen consecutive patients with sarcoidosis (6 men, 12 women; mean age, 58.8 y; age range, 29−82 y) who underwent both ^{18}F-FDG PET and ^{67}Ga scintigraphy between February 2003 and December 2005 were retrospectively selected. Except for heart, the sarcoidosis was diagnosed by histologically proven noncaseating epithelioid granuloma on transbronchial hilar or mediastinal lymph node biopsy in 6 patients, scalene node biopsy in 2 patients, skin biopsy in 2 patients, and gastric biopsy in 1 patient. According to The Japanese Ministry of Health and Welfare's *Guideline for Diagnosis of Cardiac Sarcoidosis* described in Table 1 (*15*), 7 patients were diagnosed as having cardiac sarcoidosis. Of these 7 patients, the sarcoidosis was diagnosed by histologically proven noncaseating epithelioid granuloma on transbronchial hilar or mediastinal lymph node biopsy in 5 patients, scalene node biopsy in 1 patient, and skin biopsy in 1 patient. Pulmonary involvement was assessed by chest radiographic imaging, including CT findings. Extrapulmonary involvement was considered present if ocular, skin, muscle, lymph node, or other extrapulmonary manifestations of sarcoidosis were documented. The serum angiotensin-converting enzyme level was measured. None of the patients was receiving corticosteroids at the time of the study or had received them within the previous 3 mo. No patient showed evidence of diabetes mellitus.

^{18}F-FDG PET and Reconstruction

All patients were instructed to fast for at least 5 h before PET. Unfractionated heparin (50 IU/kg) was preadministered intravenously to all patients with cardiac sarcoidosis in an attempt to reduce physiologic ^{18}F-FDG uptake by the myocardium (*16*). To obtain a consistent effect, injection of ^{18}F-FDG was performed 15 min after administration of heparin. Serum glucose levels were measured at the time of ^{18}F-FDG administration. Patients were instructed not to speak or chew after ^{18}F-FDG administration to avoid unwanted artifacts.

All ^{18}F-FDG PET examinations were performed with an ECAT EXACT HR+ camera (Siemens/CTI Inc.). This camera acquires 63 planes simultaneously over a 15.5-cm field of view. In-plane resolution was approximately 4.6 mm, with an axial resolution of approximately 3.5-mm full width at half maximum. Images were acquired in 3-dimensional mode. A transmission scan was obtained using a ^{68}Ge rod source for the purpose of attenuation correction. The emission scan began at 60 min after injection of 185−200 MBq ^{18}F-FDG. Seven or 8 bed positions were used to scan from the skull base to the midthighs. PET images were reconstructed with ordered-subsets expectation maximization (OSEM) using 2 iterations and 8 subsets.

TABLE 1
Guideline for Diagnosis of Cardiac Sarcoidosis from The Japanese Ministry of Health and Welfare (*15*)

Histologic diagnosis group
Cardiac sarcoidosis is diagnosed when histologic analysis of operative or endomyocardial biopsy specimens demonstrates epithelioid granuloma without caseating granuloma
Clinical diagnosis group
In patients with histologic diagnosis of extracardiac sarcoidosis, cardiac sarcoidosis is diagnosed when item (a) and 1 or more of items (b–e) are present:
(a) Complete right bundle branch block, left-axis deviation, atrioventricular block, ventricular tachycardia, premature ventricular contraction (>grade 2 in Lown's classification), or abnormal Q or ST–T change on electrocardiogram or Holter electrocardiogram
(b) Abnormal wall motion, regional wall thinning or thickening, or dilatation of left ventricle on echocardiogram
(c) Perfusion defect on ^{201}Tl myocardial scintigram or abnormal accumulation on ^{67}Ga-citrate or ^{99m}Tc-pyrophosphate myocardial scintigram
(d) Abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed ejection fraction of left ventricle
(e) Interstitial fibrosis or cellular infiltration over moderate grade in endomyocardial biopsy even if findings are nonspecific

^{67}Ga Imaging and Reconstruction

^{67}Ga scintigraphy was performed at 72 h after injection of 111 MBq ^{67}Ga-citrate. Imaging was performed with a large-field-of-view γ-camera (Prism 2000; Picker International) with medium-energy and a general-purpose collimator. Twenty-percent windows were placed symmetrically around each of the 3 main photo peaks of ^{67}Ga (93, 184, and 296 keV). Whole-body imaging was performed with both anterior and posterior view images at a speed of 15 cm/min. The spot images were obtained by collecting 300,000−500,000 counts at the preset time of 5 min. Thoracic SPECT was performed on all patients except for 1 patient with an extrapulmonary lesion. SPECT was performed on a 64×64 matrix at 120° at 30 s each over a range of 360°. Transverse, coronal, and sagittal sections were reconstructed. SPECT images were reconstructed with OSEM using 2 iterations and 12 subsets.

^{18}F-FDG PET and ^{67}Ga Image Interpretation

Two experienced nuclear physicians retrospectively reviewed attenuation-corrected transaxial, coronal, sagittal, and 3-dimensional PET images using a dedicated computer workstation (Siemens/CTI, Inc.). The same nuclear physicians retrospectively reviewed ^{67}Ga planar and SPECT images using another dedicated computer workstation (FX; Shimadzu). Readers were unaware of CT scan findings and accompanying reports, although they knew the diagnosis of sarcoidosis. ^{67}Ga images were read before ^{18}F-FDG PET images, with an interval of several days between interpretations. Images were evaluated independently and, in the case of disagreement, the final decision was made by consensus.

Pulmonary and extrapulmonary involvement on conventional evaluation, on ^{18}F-FDG PET, or on ^{67}Ga scintigraphy was evaluated. For visual analysis, in the mediastinum/hilum, focal radioactivity that was greater than the surrounding background mediastinal activity was interpreted as spread of sarcoidosis. Focal increases in radioactivity seen in locations unaccounted for by the normal biodistribution of the agent were interpreted as pulmonary parenchyma and spread of extrapulmonary disease. The increased accumulation in the salivary glands was identified by tracer uptake greater than that in the normal nasopharynx. For the analysis of sarcoidosis involvement, evaluation was done using 2 sites: pulmonary and extrapulmonary. The pulmonary site included mediastinal/hilar lymph nodes and pulmonary parenchyma. The extrapulmonary site included nonpulmonary lesions. Bilateral organs—including salivary glands, cervical or supraclavicular lymph nodes, axillary lymph nodes, paraaortic lymph nodes, inguinal lymph nodes, and

muscles—were considered as only 1 organ site (even when the extent was unilateral) for sarcoidosis involvement. Multiple lesions in the skin were defined as a single lesion.

For lesions visualized on ^{18}F-FDG PET, regions of interest (ROIs) were placed over the entire ^{18}F-FDG–avid lesion including the largest amount of radioactivity. The standardized uptake value (SUV) was calculated by using the following formula:

$$SUV = c_{dc}/(d_i/w),$$

where c_{dc} is the decay-corrected tracer tissue concentration (in Bq/g), d_i is the injected dose (in Bq), and w is the patient's body weight (in g). The maximal SUV value in the lesion ROI was calculated. For lesions visualized on ^{67}Ga scintigraphy, ROIs were placed over the entire ^{67}Ga-avid lesion (L) including the largest amount of radioactivity and the normal lumbar spine (N) on the planar image. The mean values of the ROIs (total counts/total pixels) were calculated, and the ratio of the lesion to normal lumbar spine (L/N ratio) was obtained.

^{18}F-FDG PET and ^{67}Ga scintigraphy findings were compared with the results of biopsy or clinical−radiologic follow-up as the reference standards. A hypermetabolic ^{18}F-FDG or ^{67}Ga lesion was considered true-positive for sarcoidosis involvement if proven by biopsy or if resolved after corticosteroid therapy on follow-up ^{18}F-FDG PET, ^{67}Ga scintigraphy, or other imaging.

Statistical Analysis

For statistical comparison of data obtained from ^{18}F-FDG PET, ^{67}Ga planar imaging, and SPECT, the Fisher exact test was used. Results were considered to be statistically significant if the probability P of a first-degree error was <0.05.

RESULTS

The median time interval between ^{18}F-FDG PET and ^{67}Ga scintigraphy was 6.6 d (range, 2−20 d). The mean ± SD blood glucose level at the time of ^{18}F-FDG injection was 101.6 ± 11.7 mg/dL (range, 82−123 mg/dL).

Twenty-one pulmonary involvements (17 mediastinal/hilar lymph node and 4 pulmonary parenchyma) were identified in 17 of the 18 patients (Table 2). Eleven pulmonary involvements had histologic verification and the remaining 10 were correlated with clinical−radiologic follow-up. ^{18}F-FDG or ^{67}Ga pulmonary uptake in these 10 lesions was decreased after corticosteroid therapy. All 17 mediastinal/hilar lymph nodes had bilateral involvement. The prevascular region was not involved and calcification was not present on CT in all patients with pulmonary involvement. All 21 pulmonary involvements were visually identified with ^{18}F-FDG PET. The mean ± SD of the SUV was 7.40 ± 2.48. Thirteen mediastinal/hilar lymph nodes and 4 pulmonary parenchymal involvements were visually identified with both ^{67}Ga planar imaging and SPECT. The mean ± SD of the L/N ratio was 1.97 ± 1.09. Neither ^{18}F-FDG PET nor ^{67}Ga scintigraphy showed any false-positive results in the pulmonary area. No significant difference in the detection of pulmonary involvement was found between ^{18}F-FDG PET, ^{67}Ga planar imaging, and ^{67}Ga SPECT.

Thirty-one extrapulmonary involvements (10 lymph node, 7 heart, 6 muscle, 3 salivary gland, 3 skin, 1 spleen, and 1 stomach) were identified in 13 of the 18 patients (Table 2). Eight extrapulmonary involvements had histologic verification and the remaining 23 were correlated with clinical−radiologic follow-up. ^{18}F-FDG or ^{67}Ga extrapulmonary uptake in these 23 lesions decreased after corticosteroid therapy. Of the extrapulmonary involvements, 28 were visually identified with ^{18}F-FDG PET. The mean ± SD of the SUV was 5.90 ± 2.75. Fifteen extrapulmonary involvements were visually identified with ^{67}Ga planar scintigraphy. The mean ± SD of the L/N ratio was 1.17 ± 0.33. Two salivary gland involvements were visually identified with ^{67}Ga planar scintigraphy but not with ^{18}F-FDG PET. One stomach involvement was not visually identified with both ^{18}F-FDG PET and ^{67}Ga planar scintigraphy. Neither ^{18}F-FDG PET nor ^{67}Ga scintigraphy showed any false-positive results in the extrapulmonary area. No significant difference in the detection of extrapulmonary involvement was found between ^{18}F-FDG PET and ^{67}Ga planar scintigraphy.

Figure 1 illustrates ^{67}Ga scintigraphy and ^{18}F-FDG PET images of a patient with pulmonary and extrapulmonary sarcoidosis.

DISCUSSION

This study, although limited in the number patients, involves a direct comparison of ^{67}Ga scintigraphy and ^{18}F-FDG PET in the same sarcoidosis group. ^{18}F-FDG PET appears to be preferable in patients with sarcoidosis because of at least comparable and perhaps even better sensitivity of ^{18}F-FDG PET in addition to several practical advantages (less radiation exposure, shorter duration between injection and diagnosis).

Previous lymphoma studies suggest that ^{18}F-FDG PET should be used in place of ^{67}Ga scintigraphy because the former detects significantly more disease sites (*17*), defines active disease more accurately (*18*), and leads to improved detection of intraabdominal nodal disease (*19*). Compared with ^{67}Ga scintigraphy, ^{18}F-FDG PET has several advantages: Because of the favorable physical conditions of positron emitters, PET enables higher spatial resolution than do conventional nuclear medicine imaging techniques. This higher spatial resolution enables the acquisition of excellent-quality images within 2 h, whereas the acquisition of a ^{67}Ga scintigram can be performed 48−72 h after injection. Furthermore, the good image quality of ^{18}F-FDG PET enables the detection of even small lesions. In the future, ^{18}F-FDG PET might prove to be a sensitive marker of disease activity in sarcoidosis patients and replace ^{67}Ga scintigraphy as in case of lymphoma diagnosis.

In patients with pulmonary sarcoidosis, ^{18}F-FDG uptake of lung has been reported to be concordant with histopathologic activity of pulmonary sarcoidosis and was found to be decreased after high-dose steroid therapy (*14*). The

TABLE 2
^{18}F-FDG PET and ^{67}Ga Scintigraphy Findings in 18 Patients with Sarcoidosis

			Pulmonary sites						Extrapulmonary sites				
				^{18}F-FDG		^{67}Ga planar		^{67}Ga SPECT,		^{18}F-FDG		^{67}Ga planar	
Patient no.	Age (y)	Sex	Lesion	Visual	SUV	Visual	L/N ratio	visual	Lesion	Visual	SUV	Visual	L/N ratio
1	63	F	Mediastinal/hilar LN	+	10.52	+	1.46	+	Salivary gland	−		+	1.11
			Pulmonary parenchyma	+	5.72	+	0.93	+	Supraclaviclar LN	+	5.67	+	1.27
									Muscle	+	4.51	+	0.88
2	69	F	Mediastinal/hilar LN	+	7.71	+	1.74	+	Axillary LN	+	3.76	−	
									Heart	+	11.64	+	1.10
3	42	M	Mediastinal/hilar LN	+	5.71	−		−	Heart	+	6.89	−	
									Muscle	+	3.26	+	0.95
4	42	M	Mediastinal/hilar LN	+	5.99	+	1.44	+	Heart	+	6.44	+	1.01
5	38	M	Mediastinal/hilar LN	+	5.52	+	1.88	+	Heart	+	5.03	−	
			Pulmonary parenchyma	+	4.33	+	0.89	+	Inguinal LN	+	4.79	−	
									Muscle	+	3.06	−	
6	29	M	Mediastinal/hilar LN	+	12.46	+	5.26	+	Salivary gland	−		+	1.98
									Supraclaviclar LN	+	7.62	+	1.14
									Paraaortic LN	+	7.06	−	
									Muscle	+	4.62	−	
7	51	F	Mediastinal/hilar LN	+	11.79	+	2.64	+					
			Pulmonary parenchyma	+	9.51	+	1.32	+					
8	69	M	Mediastinal/hilar LN	+	7.00	+	1.82	+					
9	64	F	Mediastinal/hilar LN	+	7.52	+	2.33	+					
			Pulmonary parenchyma	+	4.42	+	0.80	+					
10	70	F	Mediastinal/hilar LN	+	9.95	−		−	Muscle	+	5.51	−	
11	73	F	Mediastinal/hilar LN	+	6.63	+	3.58	+					
12	60	M	Mediastinal/hilar LN	+	8.73	+	2.05	+					
13	57	F	Mediastinal/hilar LN	+	4.12	+	1.47	+	Salivary gland	+	3.46	+	1.45
14	45	F	Mediastinal/hilar LN	+	9.63	+	2.25	+	Heart	+	9.84	+	1.00
									Supraclaviclar LN	+	6.98	+	1.38
									Paraaortic LN	+	6.71	+	1.64
									Inguinal LN	+	4.25	+	0.78
									Skin	+	2.87	−	
15	68	F	Mediastinal/hilar LN	+	7.66	−		−	Supraclaviclar LN	+	6.80	−	
									Heart	+	8.48	−	
									Skin	+	2.17	−	
16	68	F	Mediastinal/hilar LN	+	5.47	+	1.65	+	Heart	+	6.31	−	
									Muscle	+	3.01	+	0.80
17	82	F	Mediastinal/hilar LN	+	5.05	−		−	Inguinal LN	+	2.17	−	
									Skin	+	12.94	+	1.03
									Spleen	+	9.35	−	
18	40	F							Stomach	−		−	

LN = lymph node; + = abnormal uptake; − = no uptake.

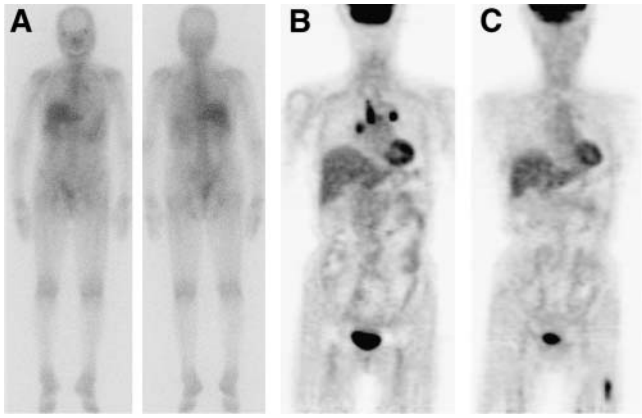

FIGURE 1. ^{67}Ga scintigraphy and ^{18}F-FDG PET images of 70-y-old woman with pulmonary and extrapulmonary sarcoidosis (patient 10 in Table 1). (A) Anterior and posterior ^{67}Ga whole-body images show no abnormal uptake. (B) ^{18}F-FDG PET image shows increased uptake at mediastinal and bilateral hila. (C) Increased uptake is also observed at left upper thigh on ^{18}F-FDG PET image.

ability to visualize ^{18}F-FDG accumulation by activated inflammatory cells makes PET a promising modality for the management of sarcoidosis. Some reports demonstrated that ^{18}F-FDG PET was superior to ^{67}Ga scintigraphy in evaluation of fever of unknown origin (*20,21*). These reports in combination with the results of the present study suggest that ^{18}F-FDG PET has the potential to become the single most-effective imaging modality in the evaluation of nonmalignant disorders.

The use of SPECT considerably increases the accuracy of ^{67}Ga imaging in the staging of malignant lymphoma (*22*). In the present study, 17 of 21 pulmonary involvements were visually identified with both ^{67}Ga planar imaging and SPECT. In this study, ^{67}Ga SPECT appeared to offer no additional information. ^{67}Ga is known to be more sensitive for lesions in superficial location, such as skin and muscle regions (*22*). However, in our study, ^{67}Ga imaging was false-negative in 2 skin and 3 muscle lesions. This finding may, in part, be due to the characteristics of the studied patient population. Recently, whole-body SPECT has become possible (*23*). In the present study, only thoracic SPECT was performed. In this respect, further studies are needed to compare ^{18}F-FDG PET and whole-body ^{67}Ga SPECT in patients with sarcoidosis.

There are no standard, accepted approaches for the evaluation of suspected extrapulmonary sarcoidosis. Somatostatin analog scintigraphies (^{99m}Tc-depreotide, ^{111}In pentetreotide) represent a novel alternative to ^{67}Ga scintigraphy in extrapulmonary sarcoidosis (*2,3*). ^{201}Tl scintigraphy, which has been studied in cardiac sarcoidosis patients, frequently demonstrates heterogeneous cardiac uptake in patients without clinical disease (*24*). Recent studies have revealed that ^{18}F-FDG PET is a useful method for identification of cardiac sarcoidosis (*16,25*). Okumura et al. (*25*) compared ^{18}F-FDG PET with ^{67}Ga scintigraphy in 11 patients with cardiac sarcoidosis. The sensitivity of ^{18}F-FDG PET (100%) in detecting cardiac sarcoidosis was significantly ($P < 0.01$) higher than that of ^{67}Ga scintigraphy (36%). In our investigation of 7 patients with cardiac sarcoidosis, although the study group was small, all (100%) exhibited myocardial ^{18}F-FDG uptake and only 3 (43%) exhibited ^{67}Ga uptake in the heart. These results are similar to those obtained by Okumura et al. (*25*). Thus, ^{18}F-FDG PET seems to be a promising alternative to ^{67}Ga scintigraphy for evaluating the extent of extrapulmonary sarcoidosis. However, we evaluated even cardiac sarcoidosis using only whole-body ^{18}F-FDG PET. Neither cardiac ^{18}F-FDG PET nor perfusion PET was performed in this study. In this respect, further studies are needed to evaluate cardiac involvement.

The value of the data from the present study is limited by the retrospective nature of the study and the small number of sarcoidosis patients. Also, the results were not all proven by a histologic gold standard. It may be difficult to differentiate between physiologic and pathologic uptake, such as gastric uptake, by ^{18}F-FDG PET. The selection of patients with more severe disease is possible for performing both ^{18}F-FDG PET and ^{67}Ga scintigraphy instead of only one of these procedures. However, more extrapulmonary involvement was detected with ^{18}F-FDG PET than with ^{67}Ga scintigraphy, despite the fact that in most cases the field of view for ^{67}Ga scintigraphy was larger than that for ^{18}F-FDG PET. At the same time, PET is time-consuming for a whole-body survey from head to toe. However, a modern PET/CT hybrid scanner can greatly reduce the scanning time. Further evolution of PET scanner technology—including the PET/CT hybrid scanner, larger-field-of-view scanners, better detector material, and superior processing methods—should provide superior diagnostic performance. Further studies involving a larger number of patients are required to clarify further the clinical usefulness of ^{18}F-FDG PET and ^{67}Ga scintigraphy in sarcoidosis patients.

CONCLUSION

The results of this clinical study suggest that ^{18}F-FDG PET can detect pulmonary lesions to a similar degree as ^{67}Ga scintigraphy. However, ^{18}F-FDG PET appears to be more accurate and contributes to a better evaluation of extrapulmonary involvement in sarcoidosis patients.

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