Value of \(^{18}\)F-FDG Accumulation in Mediastinal and Hilar Lymph Nodes on \(^{18}\)F-FDG PET/CT: Relation to Recurrence of Cardiac Sarcoidosis

Maruoka Y\(^1\), Baba S\(^1\), Isoda T\(^1\), Kitamura Y\(^1\), Nagao M\(^2\), Ide T\(^1\), Hiasa K\(^1\), Sasaki M\(^1\) and Honda H\(^1\)

\(^1\)Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
\(^2\)Tokyo Women’s Medical University, Tokyo, Japan

Abstract

Purpose: \(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG) accumulation in the left ventricular (LV) wall detects active myocardial inflammatory lesions in cardiac sarcoidosis (CS), but the significance of \(^{18}\)F-FDG accumulation in mediastinal and hilar lymph nodes (LNs) remains unclear. We investigated the association between CS recurrence and \(^{18}\)F-FDG accumulation in the mediastinal and hilar LNs, using positron emission tomography/computed tomography (PET/CT).

Materials and Methods: We retrospectively analyzed the records of 68 patients diagnosed with CS, who underwent \(^{18}\)F-FDG PET/CT before beginning treatment. The minimum follow-up period was 24 months. Patients were assigned to the recurrence (n=18) or no recurrence group (n=50) based on follow-up examinations. The \(^{18}\)F-FDG PET/CT maximum standardized uptake value (SUV\(_{\text{max}}\)) was measured in the LV wall, right ventricular (RV) wall, and mediastinal and hilar LNs. The association of CS recurrence was analyzed using Cox proportional hazards models. Recurrence-free survival (RFS) curves were made using the Kaplan-Meier method.

Results: In univariate analysis, sex, BNP, LVEF, and the SUV\(_{\text{max}}\) in the LV wall, RV wall, and mediastinal and hilar LNs were significant risk factors for CS recurrence. In multivariate analysis, only the SUV\(_{\text{max}}\) in the mediastinal and hilar LNs was a significant risk factor for CS recurrence. RFS rates were significantly higher in patients with an SUV\(_{\text{max}}\)>4.1 vs. \(\leq\) 4.1 (log-rank value=36.0, p<0.01).

Conclusion: The mediastinal and hilar LN SUV\(_{\text{max}}\) was an independent risk factor for CS recurrence after treatment. \(^{18}\)F-FDG accumulation in mediastinal and hilar LNs on \(^{18}\)F-FDG PET before treatment may be a useful biomarker to predict CS recurrence.

Keywords: Cardiac sarcoidosis; \(^{18}\)F-FDG PET; Lymph nodes; Recurrence-free survival

Abbreviations:

CS: Cardiac Sarcoidosis; LV: Left Ventricular; RV: Right Ventricular; LVEF: Left Ventricular Ejection Fraction; \(^{18}\)F-FDG: \(^{18}\)F-fluorodeoxyglucose; \(^{18}\)F-FDG PET: \(^{18}\)F-Fluorodeoxyglucose Positron Emission Tomography; LNs: Lymph Nodes; CT: Computed Tomography; JMHFW: Japanese Ministry of Health and Welfare; CRT: Cardiac Resynchronization Therapy; LVAD: Left Ventricular Assist Device; SUV: Standardized Uptake Value; SUV\(_{\text{max}}\): Standardized Uptake Value Maximum; VOI: Volume of Interest; NYHA: New York Heart Association; RFS: Recurrence-Free Survival; SD: Standard Deviation; ROC curve analysis: Receiver Operating Characteristic curve analysis

Introduction

Sarcoidosis is a disease of unknown etiology, characterized by the presence of non-caseating granulomas that can affect multiple organs. Cardiac involvement in sarcoidosis is associated with heart failure, ventricular tachyarrhythmias, conduction disturbances, and sudden cardiac death and is one of the leading causes of disease-related death [1-4]. Cardiac sarcoidosis (CS) may impair left ventricular (LV) [5] and right ventricular (RV) [6] function, and a low LV ejection fraction (LVEF) leads to poor prognosis [5]. Corticosteroid therapy is the mainstay of CS treatment [7,8], and its efficacy is about 50% [9,10]. Options for corticosteroid-refractory CS include immunosuppressant therapy and placement of an implantable cardiac defibrillator. However, recurrence of CS after these treatments is not rare and leads to a poor prognosis. Naruse et al. reported that 38% of CS patients experienced recurrent disease [11]. Therefore, it is clinically meaningful to evaluate the risk of recurrence of CS, although the risk factors remain unclear.

The inflammatory lesions of CS are known to accumulate \(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG), making \(^{18}\)F-FDG PET a useful modality for diagnosis in patients suspected to have this disease. Further, reports indicate its utility for the detection of active myocardial inflammatory lesions [12-14] and the assessment of therapeutic effects following treatment in patients with CS [15]. In addition to the utility of \(^{18}\)F-FDG PET for the prediction of therapeutic effect in CS, its use for the assessment of the risk for adverse events, including sudden death, has also been investigated [12,15,16]. Recent studies indicate that
metabolism-perfusion imaging (rubidium-FDG PET) predicts disease activity in CS [17] and that 18F-FDG accumulation in the LV and RV wall on 18F-FDG PET predicts the clinical impact of CS [6,18,19].

Mediastinal and hilar lymph nodes (LNs) are common sites of involvement in sarcoidosis [1]. However, no reports focus on the clinical significance of 18F-FDG accumulation in mediastinal and hilar LNs in CS. Inflammation in the thoracic cavity is associated with high 18F-FDG accumulation in the mediastinal and hilar LNs. Therefore, we hypothesized that mediastinal and hilar LNs are also affected by the CS disease process. Moreover, there are no well-established risk factors for recurrent CS. The purpose of this study was to investigate the association between the recurrence of CS and 18F-FDG accumulation in the mediastinal and hilar LNs and in the LV and RV walls in patients with CS.

Methods

Patients

This study was approved by our institutional review board and written informed consent from each patient was obtained. We retrospectively evaluated the medical records of 111 consecutive patients that raised suspicion of CS who underwent 18F-FDG PET-computed tomography (CT) between January 2010-December 2014. Patients diagnosed with CS based on the 2006 Japanese Ministry of Health and Welfare (JMHW) guidelines [20,21] were included. Our exclusion criteria were: 1. high blood glucose level (>150 milligrams per deciliter (mg/dL)), and 2. No uptake or diffuse-type uptake of 18F-FDG in the LV myocardium [21].

Following patient selection, 68 patients were available for our analysis and their characteristics are shown in Table 1. All patients were initially treated with prednisolone, 30 mg per day. In 2 of the 68 patients, the steroid was discontinued due to side effects and the immunosuppressives were used instead. The response to treatment was determined by the consensus of two cardiologists. The patients who did not demonstrate a stabilization of clinical symptoms and improvement of cardiac function after steroid therapy were treated with immunosuppressant therapy, cardiac resynchronization therapy (CRT), or an LV assist device (LVAD).

| Variables                                      | No recurrence (n=50) | Recurrence (n=18) |
|------------------------------------------------|---------------------|------------------|
| Age (years old)                                | 58 ± 11             | 63 ± 11          |
| Sex                                            | Men/women           |                  |
|                                               | 30/20               | 3/15             |
| NYHA class                                     | II/III              |                  |
|                                               | 41/9                | 13/5             |
| Myocardial histopathological diagnosis         | Positive/negative   |                  |
|                                               | 14/36               | 7/11             |
| Follow-up period (month)                       | 36 ± 5              | 35 ± 8           |
| BNP (pg/mL)                                    | 257 ± 320           | 487 ± 414        |
| Electrocardiographic abnormalities             | Atrioventricular block | 31/50 (62%)  |
|                                               | Right bundle branch block | 17/50 (34%)    |
|                                               | Left bundle branch block | 5/18 (28%)     |
|                                               | Left axis deviation  | 14/50 (28%)      |
|                                               | Premature ventricular contraction | 29/50 (58%)    |
|                                               | Ventricular tachycardia | 3/50 (6%)       |
| Echocardiography abnormalities                 | Interventricular septum wall thinning | 40/50 (80%)   |
|                                               | Regional wall motion abnormality | 44/50 (88%)   |
|                                               | Ventricular aneurysm  | 2/50 (4%)        |
|                                               | Regional wall thickening | 5/50 (10%)    |
|                                               | LVEF (%)             | 50 ± 15          |

Data are mean ± SD or number of patients.

Table 1: Baseline characteristics of the patients.

18F-FDG PET/CT Imaging

In each patient, a low-carbohydrate and high-fat diet [22] was started 24 hours before 18F-FDG injection and it was continued for 6 hours. After an 18-hour fast, 4 MBq/kg of 18F-FDG was then administered intravenously [23]. Cardiac scanning was started 60 minutes after the injection of 18F-FDG. 18F-FDG PET/CT images were generated using a PET/CT instrument equipped with 24 ring detectors consisting of 560 BGO crystals (4.7 mm × 6.3 mm × 30 mm) (Discovery STE; GE Medical Systems, Milwaukee, WI, US). The acquisition time per bed position in the emission scans was 10 minutes. The PET image matrix size was 128 mm × 128 mm (5.47 mm × 5.47 mm × 3.27 mm). For image reconstruction, the ordered subset expectation maximization method (VUE Point Plus) with 2 iterations and 28 subsets was used. The full-width at half maximum was 5.2 mm. A 16-slice scan (tube voltage, 120 kV; effective tube current, 30 mA to 250 mA) was performed for the purpose of attenuation correction before the PET image scans were started. The CT scan images were 512 × 512 matrices and had a slice thickness of 5 mm. The PET/CT fusion images were obtained using GENIE-Xeleris workstation software (GE Medical Systems, Milwaukee, WI).

Image evaluation

The 18F-FDG PET image standardized uptake value (SUV) maximum (SUVRmax) was measured in the LV wall, RV wall, and mediastinal and hilar LNs [6,21]. The SUV was obtained from each pixel as pixel activity (injected dose/body weight). A spherical volume

Citation: Maruoka Y, Baba S, Isoda T, Kitamura Y, Nagao M, et al. (2017) Value of 18F-FDG Accumulation in Mediastinal and Hilar Lymph Nodes on 18F-FDG PET/CT: Relation to Recurrence of Cardiac Sarcoidosis. J Mol Genet Med 11: 284. doi:10.4172/1747-0862.1000284

J Mol Genet Med, an open access journal
ISSN: 1747-0862

Volume 11 • Issue 3 • 1000284
of interest (VOI) corresponding to the LV wall, RV wall, and mediastinal and hilar LNs was manually drawn, and the highest pixel value was determined as the SUV\(_{\text{max}}\).

**Analysis of CS recurrence**

All patients were followed up by cardiologists at our institution at least every 3 months after discharge. The minimum follow-up period was 24 months, and \(^{18}\)F-FDG PET was performed at least every 6 months during this time. Patients in recurrence group had an interim \(^{18}\)F-FDG PET at 3 months to demonstrate resolution. Physicians performed blood tests, ECG, echocardiography, and \(^{18}\)F-FDG PET when they suspected a recurrence of CS. A CS recurrence was judged based on a myocardial focal-type or diffuse-on-focal-type uptake findings on \(^{18}\)F-FDG PET as well as clinical symptoms with New York Heart Association (NYHA) class or more and cardiac dysfunction (EF<50%) [21], and the patients presented with arrhythmia were also defined as a recurrence. The patients were divided into recurrence and no recurrence groups according to their SUVs using the optimal cutoff values and recurrence-free survival (RFS) between the groups.

**Statistical analysis**

Continuous data are expressed as the mean ± standard deviation (SD). Comparisons of LVEF and the \(^{18}\)F-FDG PET SUV\(_{\text{max}}\) in the LV wall, RV wall, and mediastinal and hilar LNs pre-treatment between the recurrence and no recurrence groups were analyzed using the Wilcoxon test. The Spearman correlation test was used to assess correlations between two values. The ability of the SUV\(_{\text{max}}\) in the LV wall, RV wall, and mediastinal/hilar LNs to differentiate the recurrence from the no recurrence group and to predict recurrence after therapy was analyzed by receiver operating characteristic (ROC) curve analysis. In patients with recurrence, comparisons of the SUV\(_{\text{max}}\) in the LV wall, RV wall, and mediastinal and hilar lymph nodes before treatment and after recurrence were performed using paired t-tests. We applied univariate and multivariate Cox proportional hazard models to analyze the prediction of recurrence of CS. Covariates included age, sex, New York Heart Association (NYHA) class, brain natriuretic peptide (BNP), LVEF, and \(^{18}\)F-FDG PET measurements. Survival curves of patient subgroups were created using the Kaplan-Meier method to clarify the time-dependent, cumulative recurrence-free rate and compared using the log-rank test. The tests were performed using JMP statistical software (version 10.0; SAS Institute, Inc., Cary, NC, USA). A p value of less than 0.05 was considered significant.

**Results**

**Comparison of \(^{18}\)F-FDG PET measurements between the recurrence and no recurrence groups**

CS recurrence occurred in 18 patients. The 18 CS patients with recurrence were followed for 25 to 49 months (median follow-up, 36 months) and the 50 CS patients without recurrence were followed for 24 months to 52 months (median follow-up, 34 months). The SUV\(_{\text{max}}\) results in the LV and RV walls and mediastinal and hilar LNs pre-treatment were significantly higher in the recurrence group than in the no recurrence group (8.6 ± 3.8 vs. 5.1 ± 2.7, p<0.0001, 3.8 ± 3.2 vs. 1.8 ± 1.0, p=0.01, 8.6 ± 4.6 vs. 2.8 ± 1.1; p<0.0001, respectively) (Table 2).}

**Table 2:** The difference in \(^{18}\)FDG-PET measurements between patients with and without recurrence of CS.

| Variables                  | No recurrence (n=50) | Recurrence (n=18) |
|----------------------------|----------------------|-------------------|
| SUV\(_{\text{max}}\)       |                      |                   |
| LV wall                    | 5.1 ± 2.7            | 8.6 ± 3.8**       |
| RV wall                    | 1.8 ± 1.0            | 3.8 ± 3.2*        |
| Mediastinal/hilar LNs      | 2.8 ± 1.1            | 8.6 ± 4.8**       |

\(^{18}\)FDG-PET=\(^{18}\)fluorodeoxyglucose positron emission tomography; SUV\(_{\text{max}}\)=maximum of standardized uptake value.

\(*p<0.05\) vs. patients without recurrence; \(**p<0.0001\) vs. patients without recurrence.

**Correlations between \(^{18}\)F-FDG accumulation in mediastinal/hilar LNs and myocardium**

There was a significant positive linear correlation between the SUV\(_{\text{max}}\) in the mediastinal and hilar LNs and the LV wall (r=0.70, p<0.0001) and between the SUV\(_{\text{max}}\) in the mediastinal and hilar LNs and the RV wall (r=0.71, p<0.0001).

**Correlations between LVEF and \(^{18}\)F-FDG PET parameters**

There was a significant inverse linear correlation between the LVEF and SUV\(_{\text{max}}\) in the LV wall (r=-0.38, p=0.001) and between the LVEF and the SUV\(_{\text{max}}\) in the RV wall (r=-0.25, p=0.04). However, there was no significant correlation between the LVEF and the SUV\(_{\text{max}}\) in the mediastinal and hilar LNs (r=0.21, p=0.09).

**Predictability of recurrence after treatment in patients with CS with \(^{18}\)F-FDG PET parameters**

ROC curve analysis revealed that the optimal SUV\(_{\text{max}}\) thresholds for predicting recurrence of CS in the LV wall, RV wall, and mediastinal and hilar LNs were 6.4, 2.4, and 4.1, with an AUC of 0.82, 0.69 and 0.93, accuracy of 76% (52/68), 81% (55/68) and 91% (62/68), sensitivity of 83% (15/18), 56% (10/18) and 94% (17/18), and specificity of 74% (37/50), 90% (45/50) and 90% (45/50), respectively (Figure 1).

**RFS analysis with Cox proportional hazards model**

In univariate analysis, the \(\chi^2\) and the hazard ratio to predict recurrence of CS were 1.96 and 0.69 for age, 5.90 and 0.54 for sex, 0.82 and 0.75 for the NYHA class, 11.0 and 0.43 for BNP, 7.31 and 0.50 for...
LVEF, 10.3 and 0.41 for the LV wall SUV\textsubscript{max}, 5.54 and 0.43 for the RV wall SUV\textsubscript{max}, and 20.6 and 0.24 for the mediastinal and hilar LN SUV\textsubscript{max}, respectively. In multivariate analysis, the \(\chi^2\) and the hazard ratio to predict recurrence of CS were 0.20 and 0.87 for age, 2.56 and 0.64 for sex, 0.89 and 0.64 for the NYHA class, 2.36 and 0.56 for BNP, 3.60 and 0.50 for the LVEF, 0.014 and 0.95 for the LV wall SUV\textsubscript{max}, 0.31 and 0.78 for the RV wall, and 7.69 and 0.34 for the mediastinal and hilar LN SUV\textsubscript{max}, respectively (Table 3).

**Figure 1:** Predictability of risk for cardiac sarcoidosis (CS) recurrence after treatment, using receiver operating characteristic (ROC) curve analysis. ROC curves demonstrating the ability of the maximum standardized uptake value (SUV\textsubscript{max}) to predict CS recurrence are shown for the left ventricular (LV) wall (left), right ventricular (RV) wall (center), and mediastinal and hilar lymph nodes (LNs) (right). The areas under the curve for SUV\textsubscript{max} in the LV wall, RV wall, and mediastinal and hilar LNs were 0.82, 0.69, and 0.93, respectively.

**Table 3:** Recurrence relation factor after treatment of CS.

| Characteristics | Variables | Univariate analysis | Multivariate analysis |
|-----------------|-----------|---------------------|-----------------------|
|                 |           | \(\chi^2\) | Hazard ratio | \(p\) | \(\chi^2\) | Hazard ratio | 95% CI | \(p\) |
| Age (years old) | \(\geq 54\) vs.<54 | 1.96 | 0.69 | 0.17 | 0.2 | 0.87 | 0.46-1.65 | 0.66 |
| Sex | Men vs. women | 5.9 | 0.54 | 0.02 | 2.56 | 0.64 | 0.36-1.11 | 0.11 |
| NYHA class | III vs. II | 0.82 | 0.75 | 0.37 | 0.89 | 0.64 | 0.26-1.62 | 0.35 |
| BNP (pg/mL) | \(\geq 133\) vs.<133 | 11 | 0.43 | 0.0009 | 2.36 | 0.56 | 0.26-1.18 | 0.13 |
| LVEF (%) | \(<45\) vs. \(\geq 45\) | 7.31 | 0.5 | 0.007 | 3.6 | 0.5 | 0.25-1.06 | 0.07 |

18F-FDG PET measurement

| Characteristics | Variables | Univariate analysis | Multivariate analysis |
|-----------------|-----------|---------------------|-----------------------|
|                 |           | \(\chi^2\) | Hazard ratio | \(p\) | \(\chi^2\) | Hazard ratio | 95% CI | \(p\) |
| SUV\textsubscript{max} of LV wall | \(\geq 6.4\) vs.<6.4 | 10.3 | 0.41 | 0.0013 | 0.014 | 0.95 | 0.44-2.12 | 0.91 |
| SUV\textsubscript{max} of RV wall | \(\geq 2.4\) vs.<2.4 | 5.54 | 0.43 | 0.019 | 0.31 | 0.78 | 0.32-1.89 | 0.58 |
| SUV\textsubscript{max} of mediastinal/hilar LNs | \(\geq 4.1\) vs.<4.1 | 20.6 | 0.24 <0.0001 | 7.69 | 0.34 | 0.16-0.73 | 0.0058 |

NYHA: New York Heart Association; BNP: Brain Natriuretic Peptide; LVEF: Ejection Fraction in Left Ventricle; 18F-FDG PET: 18F-Fluorodeoxyglucose Positron Emission Tomography; SUV\textsubscript{max}: Maximum Standardized Uptake Value; RV: Right Ventricle; LN: Lymph Nodes

RFS rates were significantly higher in patients with a mediastinal and hilar LN SUV\textsubscript{max}<4.1 than in those with an SUV\textsubscript{max} \(\geq 4.1\) (log-rank value=27.9, \(p<0.0001\)) (Figure 2).

**Comparison of the SUV\textsubscript{max} in the LV wall, RV wall, and mediastinal/hilar LNs before and after treatment in CS patients with recurrence**

18F-FDG PET was performed at the time that recurrence was diagnosed in all 18 cases. There was no significant difference in the SUV\textsubscript{max} in the LV wall (8.6 \pm 3.9 vs. 6.7 \pm 2.7, \(p=0.06\)) or the RV wall (3.8 \pm 3.3 vs. 2.5 \pm 1.8, \(p=0.08\)) between the pretreatment and disease recurrence examinations. In contrast, the SUV\textsubscript{max} in the mediastinal and hilar LNs was significantly lower before-treatment than after recurrence (8.5 \pm 4.6 vs. 4.0 \pm 2.0, \(p<0.01\)) (Table 4).

Representative 18F-FDG PET images before treatment and at the time recurrence was diagnosed are presented in Figure 3.

**Discussion**

Our results demonstrate that the SUV\textsubscript{max} in the LV wall, RV wall and mediastinal and hilar LNs before treatment in the recurrence group were significantly higher than the corresponding SUV\textsubscript{max} results in the no recurrence group. Additionally, our multivariate
analysis indicates that the high SUVmax in mediastinal and hilar LNs was a significant risk factor for recurrence of CS after treatment. Significant correlations in the SUVmax between the mediastinal and hilar LNs and the LV and RV walls were observed, whereas there was no significant correlation between the SUVmax in the mediastinal and hilar LNs and the LVEF. The disease progression of sarcoidosis leads to decreased mediastinal involvement and increased parenchymal involvement. Aysun Yakar et al. reported that in sarcoidosis without cardiac involvement, mediastinal LN18F-FDG accumulation decreases as the disease progresses [24]. We hypothesize that cardiac sarcoidosis with highly remaining 18F-FDG accumulation in mediastinal and hilar LNs implies a high degree of sarcoidosis activity. 18F-FDG accumulation in the mediastinal and hilar LNs may be associated with the degree to which CS is refractory and not directly reflect cardiac dysfunction.

LV and RV wall SUVmax values were not independent risk factors for CS recurrence. A possible explanation on 18F-FDG accumulation in the LV wall is the passage from the active inflammatory phase to the chronic phase. CS in chronic phase does not necessarily show as high 18F-FDG accumulation in LV wall as in active inflammatory phase because of fibrosis of myocardium. Thus, it might to be difficult to evaluate disease progression of CS only by mean of SUVmax values of 18F-FDG accumulation in LV wall. With respect to 18F-FDG accumulation in RV wall, a recent study reported that increased RV 18F-FDG accumulation reflects RV pressure overload or pulmonary hypertension [25].

![Figure 2: Recurrence-free survival (RFS) curves of two groups classified by a cutoff value of 4.1 for the maximum standardized uptake value (SUVmax) in the mediastinal and hilar lymph nodes. RFS rates were significantly different between patients with SUVmax<4.1 (red) vs. ≥ 4.1 (blue).](image)

| Variables                  | SUVmax at diagnosis | SUVmax at recurrence |
|----------------------------|---------------------|----------------------|
| LV wall                    | 8.6 ± 3.8           | 6.7 ± 2.7            |
| RV wall                    | 3.8 ± 3.2           | 2.5 ± 1.7            |
| mediastinal/hilar LNs      | 8.5 ± 4.6           | 4.0 ± 2.0*           |

18F-FDG-PET=18F-fluorodeoxyglucose positron emission tomography; SUVmax=maximum of standardized uptake value; LV: Left Ventricle; RV: Right Ventricle

*p<0.05 vs. SUVmax at diagnosis

Table 4: The difference in 18F-FDG-PET measurement in patients with recurrence, between diagnosis and after recurrence.

![Figure 3: A 65-year-old female patient with recurrence 6 months after steroid therapy for cardiac sarcoidosis. Maximum intensity 18F-fluorodeoxyglucose positron emission tomography projection images before steroid therapy (left) and 6 months after steroid therapy (lower right) are presented. The left ventricular ejection fraction and maximum standardized uptake value (SUVmax) in the left ventricular (LV) wall, right ventricular (RV) wall, and the mediastinal and hilar lymph nodes (LNs) before treatment were 25%, 4.4, 1.6, and 5.5, respectively. The SUVmax in the LV wall, RV wall, and the mediastinal and hilar LNs at recurrence were 8.7, 1.8, and 2.5, respectively.](image)

All patients were maintained on a low-carbohydrate and high-fat diet for a period of 6 hours, followed by fasting for 18 hours before 18F-FDG injection. As this protocol is known to inhibit physiological myocardial uptake [22,23], we believe that our evaluation of myocardial 18F-FDG uptake here has sufficient validity.

The present study has several limitations. First, the median follow-up period was 31 months, so it lacks long-term follow-up data to confirm the outcomes of patients who responded to steroid therapy and showed no recurrence during this period. Second, the patients with CS who were analyzed were relatively few and recruited from a single center. Further studies are needed to confirm our hypotheses by evaluating the outcomes of patients with CS in multicenter studies with longer follow-up periods.

**Conclusion**

In conclusion, the 18F-FDG PET SUVmax in mediastinal and hilar LNs was a significant risk factor for recurrence of CS. 18F-FDG accumulation in mediastinal and hilar LNs may be a useful biomarker.
to predict CS recurrence and facilitate the clinical management of patients with CS.

References

1. Iannuzzi MC, Rybicki BA, Teirstein AS (2007) Sarcoidosis. N Engl J Med 357: 2153-2165.
2. Rybicki BA, Major M, Popovich J, Malariak MJ, Iannuzzi MC (1997) Racial differences in sarcoidosis incidence: A 5-year study in a health maintenance organization. Am J Epidemiol 145: 234-241.
3. Doughan AR, Williams BR (2006) Cardiac sarcoidosis. Heart 92: 282-288.
4. Mehta D, Lubitz SA, Frankel Z, Wisnivesky JP, Einstein AJ, et al. (2008) Cardiac involvement in patients with sarcoidosis: Diagnostic and prognostic value of outpatient testing. Chest 133: 1426-1435.
5. Yazaki Y, Iose M, Hiroe M, Morimoto S, Hiramitsu S, et al. (2001) Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol 88: 1006-1010.
6. Manabe O, Yoshinaga K, Ohira H, Sato T, Tsujino I, et al. (2014) Right ventricular (18) F-FDG uptake is an important indicator for cardiac involvement in patients with suspected cardiac sarcoidosis. Ann Nucl Med 28: 656-663.
7. Dubrey SW, Falk RH (2010) Diagnosis and management of cardiac sarcoidosis. Prog Cardiovasc Dis 52: 336-346.
8. Sugisaki K, Yamaguchi T, Nagai S, Ohmori S, Takenaka S, et al. (2003) Clinical characteristics of 195 Japanese sarcoidosis patients treated with oral corticosteroids. Sarcoidosis Vasc Diffuse Lung Dis 20: 222-226.
9. Hiramitsu S, Morimoto S, Uemura A, Kato Y, Kimura K, et al. (2005) National survey on status of steroid therapy for cardiac sarcoidosis in Japan. Sarcoidosis Vasc Diffuse Lung Dis 22: 210-213.
10. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakae S, et al. (2005) Focal uptake on (18)F-fluorodeoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. Eur Heart J 26: 1538-1543.
11. Naruse Y, Sekiguchi Y, Nagami A, Okada H, Yamauchi Y, et al. (2014) Systematic treatment approach to ventricular tachycardia in cardiac sarcoidosis. Circ Arrhythm Electrophysiol 7: 407-413.
12. Ohira H, Tsujino I, Yoshinaga K. (2011) 18F-fluoro-2-deoxyglucose positron emission tomography in cardiac sarcoidosis. Eur J Nucl Med Mol Imaging 38: 1773-1783.
13. Yousef G, Leung E, Mylonas I, Nery P, Williams K, et al. (2012) The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: A systematic review and metaanalysis including the Ontario experience. J Nucl Med 53: 241-248.
14. Osborne MT, Hulten EA, Singh A, Waller AH, Bittencourt MS, et al. (2014) Reduction in 18F-fluorodeoxyglucose uptake on serial cardiac positron emission tomography is associated with improved left ventricular ejection fraction in patients with cardiac sarcoidosis. J Nucl Cardiol 21: 166-174.
15. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, et al. (2014) Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol 63: 329-336.
16. Isiguzo M, Brunken R, Tchou P, Xu M, Culver DA (2011) Metabolism-perfusion imaging to predict disease activity in cardiac sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 28: 50-55.
17. Ahmadian A, Brogan A, Berman J, Sverdlow AL, Mercier G, et al. (2014) Quantitative interpretation of FDG PET/CT with myocardial perfusion imaging increases diagnostic information in the evaluation of cardiac sarcoidosis. J Nucl Cardiol 21: 925-939.
18. Betensky BP, Tschabrunn CM, Zado ES, Goldberg LR, Marchlinski FE, et al. (2012) Long-term follow-up of patients with cardiac sarcoidosis and implantable cardioverter-defibrillators. Heart Rhythm 9: 884-891.
19. Mc Ardle BA, Birnie DH, Klein R, De Kemp RA, Leung E, et al. (2013) Is there an association between clinical presentation and the location and extent of myocardial involvement of cardiac sarcoidosis as assessed by 18F-fluorodeoxyglucose positron emission tomography? Circ Cardiovasc Imaging 6: 617-626.
20. Diagnostic standard and guidelines for sarcoidosis (2007) Jpn J Sarcoidosis Granulomatous Disord 27: 89-102.
21. Ishida Y, Yoshinaga K, Miyagawa M, Moroi M, Kodomo C, et al. (2014) Recommendations for (18) F-fluorodeoxyglucose positron emission tomography imaging for cardiac sarcoidosis: Japanese Society of Nuclear Cardiology recommendations. Ann Nucl Med 28: 393-403.
22. Harisankar CN, Mittal BR, Agrawal KL, Abrar ML, Bhattacharya A (2011) Utility of high fat and low carbohydrate diet in suppressing myocardial FDG uptake. J Nucl Cardiol 18: 926-936.
23. Morooka M, Moroi M, Uno K, Ito K, Wu J, et al. (2014) Long fasting is effective in inhibiting physiological myocardial 18F-FDG uptake and for evaluating active lesions of cardiac sarcoidosis. EJNMMI Res 4: 1.
24. Yakar A, Yakar F, Sezer M, Bayram M, Erdogan EB, et al. (2015) Use of PET-CT for the assessment of treatment results in patients with sarcoidosis. Wien Klin Wochenschr 127: 274-282.
25. Kluge R, Barthel H, Pankau H, Seese A, Schauer J, et al. (2005) Different mechanisms for changes in glucose uptake of the right and left ventricular myocardium in pulmonary hypertension. J Nucl Med 46: 25-31.