Visual Findings of ^{18}F -Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Patients with Cardiac Sarcoidosis

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Abstract

Objective The purpose of this study was to evaluate the cardiac sarcoidosis (CS) activity according to the classified visual uptake pattern using ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) and assess the uptake pattern based on the free fatty acid (FFA) levels.

Methods Nineteen CS subjects who underwent ^{18}F -FDG PET/CT examinations with heparin loading (HL) were recruited to evaluate their CS activity. The ^{18}F -FDG uptake in the heart was classified into five categories (“none,” “diffuse” and “diffuse at base,” regarded as stable CS, and “focal” and “focal on diffuse,” regarded as de novo or worsening CS). The subject data were compared with the ^{18}F -FDG PET/CT findings in 13 healthy volunteers. The FFA serum levels were assessed in 10 patients with CS and all volunteers.

Results The sensitivity and specificity of ^{18}F -FDG PET/CT with HL were 75% (6/8) and 73% (8/11), respectively. The major pattern of cardiac ^{18}F -FDG uptake was “diffuse at base.” Ten of the 32 subjects, including the control group, exhibited this pattern. The FFA serum levels before heparin administration were statistically significantly different between the patients with the “none” pattern and those with the “diffuse” and “diffuse at base” patterns. There were no significant correlations between the FFA serum levels after heparin administration and the ^{18}F -FDG uptake patterns.

Conclusion “Diffuse at base” is the major ^{18}F -FDG uptake pattern associated with inadequate physiologic ^{18}F -FDG suppression. This pattern should be carefully interpreted when examining the ^{18}F -FDG PET/CT images of CS patients. Additionally, increased FFAs levels associated with HL may not completely suppress the physiologic myocardial FDG uptake.

Key words: cardiac sarcoidosis, PET, heparin loading, free fatty acid, physiologic uptake

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Introduction

Cardiac sarcoidosis (CS) has an unfavorable prognosis and is known to cause cardiac death via congestive heart failure, ventricular tachyarrhythmia and advanced conduction disturbances (1-3). Cardiac involvement is especially prevalent in Japanese patients with sarcoidosis, with a reported frequency of 60% in an autopsy series, in contrast to 20% in a series reported from the United States (4, 5). Early

intervention using corticosteroids improves the left ventricular function and/or arrhythmias in some patients with CS (6, 7). Several imaging modalities, including ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) using visual or semi-quantitative analyses, have improved the diagnosis of CS, providing important therapeutic and prognostic advantages (8-14).

^{18}F -FDG PET is reportedly useful for screening for CS, since glucose metabolism in the inflammatory lesions is enhanced by the activity of macrophages (15). However, the

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physiologic ^{18}F -FDG uptake in the myocardium tends to fluctuate. In order to overcome this difficulty, heparin loading (HL) and/or long fasting are used to suppress glucose metabolism in the myocardium. HL and long fasting may affect the free fatty acid (FFA) serum levels and control the physiologic ^{18}F -FDG uptake in the myocardium. However, the effects in suppressing the physiologic ^{18}F -FDG uptake induced by HL or long fasting remain controversial (8, 10, 16-18). Consequently, few studies have mentioned the uptake patterns or image interpretations of the myocardial ^{18}F -FDG uptake in CS patients.

The purpose of this study was therefore to classify the visual patterns of ^{18}F -FDG PET/computed tomography (CT) using HL in patients with either stable CS or de novo or worsening CS and assess the ^{18}F -FDG uptake patterns based on the levels of metabolic markers, such as FFA.

Materials and Methods

Subjects and criteria for the CS activity

Nineteen patients diagnosed or re-diagnosed as having either a history of CS or de novo CS according to the criteria of the Japanese Society of Sarcoidosis and Other Granulomatous Disorders Guidelines were selected from among a population of subjects who underwent ^{18}F -FDG PET/CT imaging at our hospital from April 2005 to March 2008 (17, 19). Five patients with CS were newly diagnosed, and the other 14 patients had a history of treatment for CS. The diagnosis of worsening sarcoidosis was made by two cardiologists with 35 and 25 years of experience, respectively, because it is difficult even with the new criteria to evaluate the current sarcoid activity, especially in patients with a history of treatment for CS. The observers also empirically determined whether treatment for CS should be initiated based on the findings of various examinations, including electrocardiograms (ECGs), echocardiography, measurement of the angiotensin-converting enzyme level in the serum, imaging results of nuclear medicine and/or magnetic resonance imaging and patient symptoms, etc. None of the patients had severe symptoms from extracardiac sarcoidosis, such as progressive dyspnea during daily life activities due to lesions of pulmonary sarcoidosis. Thirteen patients were being treated with a maintenance dose of corticosteroids, and one patient had received methotrexate. Two patients had well-controlled diabetes mellitus. All patients had undergone coronary angiography at least once in their clinical history, and the absence of significant stenosis of the coronary arteries was confirmed.

The serum levels of angiotensin-converting enzyme, brain natriuretic peptide and C-reactive protein were measured within two weeks of the ^{18}F -FDG PET/CT examinations in all patients. The FFA serum levels before and after heparin administration were obtained in 10 patients with cardiac sarcoidosis and all volunteers. Standard 12-lead ECG and/or Holter ECG monitoring to check for arrhythmia was per-

formed. The left ventricular ejection fraction (LVEF) was calculated using two-dimensional echocardiography according to the area-length formula.

Thirteen healthy volunteers (11 men and two women, mean age: 50.9 y; range: 33-76 y) without cardiac disease were studied to obtain normal ^{18}F -FDG uptake patterns for the visual analysis and reference values for the standardized uptake value (SUV) for cardiac uptake on the ^{18}F -FDG PET/CT images obtained using HL. The mean serum blood glucose level at the time of the ^{18}F -FDG PET/CT examination was 103 ± 11.7 mg/dL. The study protocol was approved by the Institutional Review Board. Written or oral informed consent was obtained from all subjects.

^{18}F -FDG PET/CT technique

After the patients had fasted for more than 12 hours, their blood glucose level was measured. We preadministered 50 IU/kg of unfractionated heparin (UFH) intravenously in all patients and the 13 control subjects. In order to obtain a consistent effect, ^{18}F -FDG was injected 15 minutes after the administration of UFH. Subsequently, a dose of 185-370 MBq (5-10 mCi) of ^{18}F -FDG was administered. One hour after the injection, ^{18}F -FDG images were acquired twice, once for the heart and once for the whole body from the vertex to the upper thigh. The studies were performed using combined PET/CT tomography images (Siemens Biograph Sensation 16, Siemens, Munich, Germany). Emission scans were acquired first for 10 minutes per bed position for the heart, followed by acquisition for the whole body for three minutes per bed position. The PET data were reconstructed using an ordered-subset expectation maximization algorithm (4 iterations, 8 subsets). The CT data were used for attenuation correction and anatomic localization of extracardiac sarcoidosis. Unenhanced CT images were acquired at a slice thickness of 5 mm at 60 mAs and 120 kVp with a 0.5-second tube rotation time.

Analyses of ^{18}F -FDG PET/CT

Visual analysis of CS

We evaluated the degree of CS using visual methods for adding a new visual pattern. The method involved the classification of the ^{18}F -FDG PET/CT images into uptake patterns based on the fusion images: "none," "diffuse," "focal" and "focal on diffuse," as defined in previous studies (10). Additionally, as shown in Fig. 1, we added a new category: "diffuse at base," defined as a mild or moderate uptake that circumscribed over one-third of the area on the basal side of the LV. The "none" and "diffuse" patterns were respectively observed in four and five of the 13 healthy volunteers in whom the uptake of ^{18}F -FDG was examined using the heparin protocol. The "diffuse at base" pattern was newly classified as normal because this pattern was observed in the remaining four of the 13 healthy volunteers. For the abnormal variations, we visually localized the site of ^{18}F -FDG uptake in patients exhibiting "focal" or "focal on diffuse" patterns.

Figure 1. Five uptake patterns observed using ^{18}F -FDG PET/CT imaging. The top images are maximum intensity projection, the middle images are coronal slices, and the bottom images are transaxial slices through the heart.

The tests were conducted by one experienced nuclear medicine physician with 32 years of experience and one experienced radiologist with nine years of experience in radiology/nuclear medicine. Any initial differences in their interpretations were resolved by consensus.

Semi-quantitative analysis of CS

The second method involved measuring the maximum SUV (maxSUV) of the PET/CT images. In order to exclude the presence of sarcoidosis in the lungs and/or the physiologic uptake of ^{18}F -FDG (e.g., brown adipose tissue, aortic wall, pulmonary hilum or lymph nodes), regions of interest (ROIs) were tightly drawn on the PET/CT images over all segments, referring to the CT images and defined using a software program (4DM SPECT). In each group (de novo or worsening CS, stable CS and control), the maxSUV, standard deviation (SD) of the maxSUV and coefficient of variation (COV) of the maxSUV were calculated for each of the 17 myocardial segments modeled using the previously reported method (14), based on a scientific statement issued by the American Heart Association, to enable comparisons between the groups.

Therapeutic analysis of ^{18}F -FDG PET

Follow-up PET/CT images were obtained to survey the changes in uptake after the patient achieved a stable physi-

cal condition. We evaluated the therapeutic effect using the same protocol as that for the visual analysis in the diagnostic analysis of the change from an abnormal pattern ("focal" or "focal on diffuse") to a normal pattern ("none," "diffuse," "diffuse at base").

Statistical analysis

The sensitivity and specificity were calculated using standard formulas. Unpaired *t*-tests were used to examine differences (e.g., in the maxSUV) between the groups. Fisher's exact test was used to compare the diagnostic performance of ^{18}F -FDG PET/CT. When a one-way analysis of variance indicated a difference between the groups, comparisons of the lesions with a normal pattern were made using the Tukey statistic. The proportional investigator agreement and Cohen's kappa were calculated by the two nuclear medicine physicians. A *p* value of <0.05 was considered to be significant. The analyses were performed using the SPSS version 14.0 software program for Windows.

Results

Patient characteristics

Eight patients were diagnosed as having de novo or worsening CS and 11 patients were diagnosed as having stable

Table 1. Patient Characteristics and Laboratory Data

Characteristic	Patients with de novo or worsening CS lesions (n=8)	Patients with stable CS lesions (n=11)
Age at diagnosis (y)		
Median (Range)	57 (37-75)	60 (47-83)
Sex (no.)		
Men:Women	2:6	2:9
State of treatment (no.)		
Initial	5	0
Recurrence	3	11
Diagnostic criteria of cardiac sarcoidosis (no.) in the Japanese Ministry of Health and Welfare Guidelines		
Histological diagnosis group	2	3
Clinical diagnosis group	6	8
Symptoms at PET examination (no.)		
Dyspnea	6	7
Palpitation	5	4
Others	1	2
Serum C-reactive protein (<0.3 mg/dL)		
Average ($\pm$ SD)	0.17 ($\pm$ 0.25)	0.35 ($\pm$ 0.63)
Serum ACE (<25 U/mL)		
Average ($\pm$ SD)	17.1($\pm$ 10.0)	13.7($\pm$ 7.6)
Serum BNP (<18.4 pg/mL)		
Average ($\pm$ SD)	394.1 ($\pm$ 401.7)	301.4 ($\pm$ 378.7)
Involved organs of sarcoidosis (no.)		
Heart	8	11
Lymph node	6	7
Lung	4	7
Eye	3	6
Muscle	2	0
Spleen	2	0
Skin	4	1
Echocardiogram		
Thinning of basal wall (no.)	2	9
LVEF (%)		
Median (Range)	49 (33-73)	36 (14-68)
ECG finding at PET examination (no.)		
Pacemaker rhythm	4	6
AVB	2	0
BBB	2	2
Frequent PVC	0	2
Others	1	1
Implanted PM (no.)	4	7

CS: cardiac sarcoidosis, ECG: electrocardiogram, LVEF: left ventricular ejection fraction, PM: pacemaker, ACE: angiotensin-converting enzyme, BNP: brain natriuretic peptide, CRP: C-reactive protein
 Serum ACE greater than the normal range (<25 U/mL); Serum BNP greater than the normal range (<18.4 pg/mL),
 AVB: atrioventricular block, BBB: bundle branch block, PVC: premature ventricular contraction

CS. Table 1 summarizes the characteristics of the patients. The mean serum blood glucose and HbA1c levels at the time of the ^{18}F -FDG PET/CT examinations was 94 ± 0.9 mg/dL (range: 74-109 mg/dL) and 5.6% (range: 4.6-8.5%), respectively. The five patients with newly diagnosed CS were started on steroid therapy, and the dose of corticosteroids was increased in the four patients with suspected recurrence at the discretion of experienced physicians. Finally, eight of the nine patients treated with increased doses of corticosteroids or who started receiving corticosteroid treatment satisfied the criteria and were regarded as having “de novo or worsening CS.” In the remaining case involving an increased corticosteroid dose, the patient’s status was regarded as “stable CS” with a “diffuse” pattern, as the patient died of severe heart failure one month after the start of treatment, and an autopsy showed no evidence of de novo or worsening lesions in the heart. The remaining 10 patients treated without an increased corticosteroid dose were observed throughout

their clinical course for at least 12 months and received a reduced or constant dose of corticosteroids. Consequently, these patients were regarded as having “stable CS.”

FFA levels and ^{18}F -FDG PET/CT images

The FFA serum levels at before and after heparin administration were 0.70 ± 0.27 and 2.83 ± 0.95 , respectively, in the CS group. The FFA serum levels before and after heparin administration did not correlate with the ^{18}F -FDG uptake patterns in this group. In contrast, the FFA serum levels before and after heparin administration were 0.58 ± 0.34 and 2.65 ± 0.62 in the control group. Within the control group, the FFA serum levels measured before heparin administration were significantly different between the patients with the “none” pattern and those with the “diffuse” and “diffuse at base” patterns (Fig. 2). There were no significant correlations between the glucose or FFA serum levels before heparin administration and the ^{18}F -FDG uptake patterns.

Figure 2. Correlation with the FFA serum levels at pre-heparin administration and each FDG uptake pattern within the control group. The circles indicate the figures within each FDG uptake pattern.

Analyses of the ^{18}F -FDG PET/CT images

Table 2 shows the number of subjects with each of the five patterns determined using a visual-based analysis. In the visual analysis of the patients with de novo or worsening CS, the sensitivity of ^{18}F -FDG PET/CT was 75% (6/8). In the patients without deterioration, the specificity of ^{18}F -FDG PET/CT was 73% (8/11). The percentage of investigator agreement and Cohen's kappa were 84% (16/19) and 0.69, respectively.

Fig. 3 shows the average values of the maxSUV, SD and COV for the 17 segments in each of the three groups (control, de novo or worsening CS and stable CS) obtained using a semi-quantitative analysis. The average maxSUV values of the 17 segments in the control, de novo or worsening CS and stable CS groups were 3.53 ± 2.53 , 4.11 ± 1.45 and 3.45 ± 1.58 , respectively. The average maxSUV values of the 17 segments did not differ significantly between the three groups (Fig. 3a). The average SD of the 17 segments (Fig. 3b) and average COV of the 17 segments (Fig. 3c) were each significantly different between the de novo or worsening CS group and the control group. The average SD values of the 17 segments in the control, de novo or worsening CS and stable CS groups were 0.51 ± 0.30 , 1.43 ± 1.27 and 0.65 ± 0.39 , respectively. Meanwhile, the average COV values of the 17 segments in the control, de novo or worsening CS and stable CS groups were 0.16 ± 0.05 , 0.33 ± 0.20 and 0.20 ± 0.13 , respectively. In addition, the de novo or worsening CS group tended to have higher SD and COV values than the stable CS group, although the differences were not significant ($p=0.05$ and $p=0.08$, respectively).

Table 2. Subject Numbers of Visual Patterns of ^{18}F -FDG Heart Uptake

	None	Diffuse at base	Diffuse	Focal	Focal on diffuse
De novo or worsening CS (n = 8)	0	2	0	3	3
Stable CS (n = 11)	3	4	1	1	2
Control (n = 13)	4	4	5	0	0

CS: cardiac sarcoidosis

^{18}F -FDG PET/CT outcomes of the therapeutic analysis

In all patients with de novo or worsening CS, the ^{18}F -FDG PET/CT examinations were performed from four to 18 weeks (median: 7 weeks) after the augmentation of immunosuppression. The serum blood glucose levels obtained after the treatment ^{18}F -FDG PET/CT examinations were significantly increased compared to the pretreatment levels ($p < 0.05$; mean: 106 mg/dL, range: 78-126). In addition, the pre- and post-treatment serum ACE levels in the patients with de novo or worsening lesions were significantly decreased ($p < 0.05$; mean: 8.7 U/mL, range: 3.6-16.6), whereas the changes in the LVEF on echocardiography were not significant ($p=0.07$).

In the visual analysis, six of eight patients with de novo or worsening CS changed from an abnormal visual pattern to a near-normal visual pattern after treatment (Fig. 4, 5). In the remaining patients, the patterns changed from “diffuse at base” to inhomogeneous mixed patterns, including a near-normal appearance (Fig. 6).

Discussion

In this investigation, the “diffuse at base” pattern on the visual analyses of the ^{18}F -FDG PET/CT images using HL was found to require careful interpretation, including the possibility of recurrence.

The visual analysis had a relatively high sensitivity and specificity for distinguishing between de novo or worsening CS and stable CS, although the results of our study are not superior to those of previous studies (10, 12), which showed that ^{18}F -FDG PET had highest sensitivity (100%) and high specificity (over 80%). We speculate that these differences depend on the clinical condition of the patients. Our study included several patients with recurrent CS. Evaluating recurrent CS is difficult because a clear definition of recurrent CS has not yet been established. In a previous study, the most important finding for newly diagnosed CS using ^{18}F -FDG PET/CT was the detection of a heterogeneous uptake (10, 14). However, during the remission stage of CS, the affected myocardium has already been replaced by fibrous tissue, thus complicating the visual interpretation of an abnormal pattern.

Two patients with de novo or worsening CS and four patients with stable CS exhibited a “diffuse at base” pattern, although this pattern was regarded as normal in this study.

Figure 3. Semi-quantitative analysis showed the COV of maxSUV in myocardium FDG uptake in the average of 17 segments within each group. The circles indicate the figures within each group.

These observations suggest that “diffuse at base” is a common pattern for active CS granulomas and physiologic ^{18}F -FDG uptake in the heart. In contrast, the myocardial ^{18}F -FDG uptake in the volunteers was distributed homogeneously throughout the LV myocardium, with a relatively high uptake in the lateral and posterior walls at the base (17, 20-22). We surmise that this physiologic uptake pattern may mask CS lesions that frequently appear in the septal areas on the basal side. Additionally, the detection of this pattern suggests that HL may be limited in suppressing the physiologic ^{18}F -FDG uptake in the normal heart. In the control group, a lower FFA serum level before heparin administration tended to correlate with the inadequate suppression of the cardiac physiologic ^{18}F -FDG uptake. However, this tendency may not apply to patients with a damaged myocardium, such as those with CS. One reason for this finding is the modification of fibrotic tissue in the myocardium in cases of progressive CS. We speculate that the fibrotic changes associated with CS cause an inhomogeneous uptake pattern of ^{18}F -FDG, which confuses the visual inter-

pretation. In addition, our volunteer group did not include any subjects with a “focal” pattern, which occasionally appears on ^{18}F -FDG PET examinations (23). Empirically, a focal ^{18}F -FDG uptake frequently settles in the basal septal wall of the left ventricle. We believe that the presence of a “focal” pattern in this location may be explained by two possible mechanisms: the presence of true sarcoidosis lesions or a severe form of the “diffuse at base” pattern. However, this study included too small a number of subjects to confirm this hypothesis. Therefore, it remains unknown whether glucose tolerance abnormalities and lipid metabolic disorders influence the physiologic ^{18}F -FDG uptake in the damaged myocardium, and further studies of large numbers of subjects are required. In the present study, even in the control group, HL did not completely suppress the physiologic ^{18}F -FDG uptake in nine subjects with elevated serum FFA levels. In order to overcome these difficulties, the use of low carbonate meals and/or a longer fasting time may provide sufficient suppression of the cardiac physiologic uptake (8, 17). Therefore, this equivocal pattern “diffuse at

Figure 4. Newly diagnosed case with “focal” pattern of CS: a 50-year-old woman with arterioventricular block: MIP and axial images of ^{18}F -FDG PET/CT at pre-treatment. ^{18}F -FDG PET/CT showed “focal” pattern in the upper septal wall of heart, and lymph-nodes uptake in mediastinum. Eight weeks later from steroid therapy, ^{18}F -FDG PET/CT showed vague uptake with near “diffuse at base” pattern, and the arterioventricular block diminished.

Figure 5. Newly diagnosed biopsy proven case with “focal on diffuse” pattern of CS: a 64-year-old woman with severe heart failure (LVEF 33%): MIP, coronal image, and sagittal image of ^{18}F -FDG PET/CT at pretreatment showed “focal on diffuse” pattern in the heart, and mild uptake of lymph-nodes in mediastinum. After 6 weeks of steroid therapy, ^{18}F -FDG PET/CT showed vague uptake with near “diffuse” or “none” pattern, and the cardiac function was improved (LVEF 56%).

base” should be carefully interpreted when examining the ^{18}F -FDG PET/CT images of CS patients.

In the semi-quantitative analyses, our results showed that the COVs of the maxSUV values were significantly different between the de novo or worsening CS group and the control group. However, an outlier in the de novo or worsening CS group affected the results for SD. Meanwhile, it remains difficult to distinguish between de novo or worsening CS and stable CS based on the COV or SD of the maxSUV obtained using ^{18}F -FDG PET/CT. Tahara et al. showed that the COV of the mean SUV obtained using ^{18}F -FDG PET/CT is useful for assessing patients with CS treated with steroids (14). However, the authors did not mention whether their recruited subjects with CS were being treated for the

first time. We suspect that the COV of the SUV is affected by several different factors, including body fat, as well as the number of divided segments, ROIs and time of measurement after injection. In particular, recurrent CS cases have been previously treated with steroids, which often induce glucose intolerance. Although the serum glucose levels at the time of ^{18}F -FDG PET/CT were controlled within the normal range in our study groups, the results did not show any significant differences between the patients with de novo or worsening CS and those with stable CS.

An important limitation of this study is that the patients with worsening CS were defined according to their clinical background, as a clear definition of the disease activity in patients with recurrent CS has not yet been established. The

Figure 6. Recurrence case of “diffuse at base” pattern of CS: a 50-year-old woman with CS under maintenance dose of steroid. After exacerbation of atrioventricular block, she was administrated a loading dose of steroid. Remission period: one year before exacerbation, maximum intensity projection (MIP) of ^{18}F -FDG PET/CT shows mild uptake in the lungs and inhomogeneous “diffuse” uptake pattern in heart. A polar map of left myocardium shows main uptake at basal portion of anterolateral wall. Exacerbation period: MIP shows aggravated lesions in bilateral lungs and inhomogeneous “diffuse at base” uptake pattern. A polar map shows dominant uptake at inferolateral wall. Post-treatment period: After 1 month of loading dose of steroid, MIP shows disappearing uptake in both the lungs and slightly inhomogeneous “diffuse” pattern.

newest criteria are applicable for the diagnosis of CS only, not assessing the disease activity of CS. The CS patients without a disease activity satisfied the criteria, even after treatment. In order to overcome these difficulties, we applied the decisions of the experienced cardiologists as a gold standard. Certainly, their clinical decisions may be subjective. However, in this study, we believe that the specialists' decisions had a certain validity for evaluating the CS activity because both the clinical symptoms and laboratory data of the patients improved after treatment. To acquire objective results, it is necessary to develop robust criteria regarding CS recurrence in the near future. Another limitation is that the population size was small, particularly with respect to patients with de novo or worsening CS, as the study was performed at a single center and the majority of the patients were taking some type of medication. However, we are certain that ^{18}F -FDG PET/CT is the most effective means of detecting de novo or worsening CS, especially in patients with recurrence for whom there is no robust definition for diagnosis and/or those with a pacemaker who cannot be examined using alternative imaging modalities, such as cardiac magnetic resonance imaging. Further studies involving multicenter trials are therefore needed.

Conclusion

On visual analyses, the “diffuse at base” pattern should be carefully interpreted when examining the ^{18}F -FDG PET/CT images of CS patients. Furthermore, increased FFA levels in patients treated with HL may not completely suppress the physiologic myocardial FDG uptake.

The authors state that they have no Conflict of Interest (COI).

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