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Evaluation of Response to Steroid Therapy for Cardiac Sarcoidosis Using Volumetric Analysis of ^{18}F-FDG PET/CT

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Abstract

Background: The purpose of this study was to investigate the utility of total lesion glycolysis (TLG) in ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to predict the response to steroid therapy for cardiac sarcoidosis (CS).

Methods: Thirty-six patients with clinically suspected CS who had undergone ^{18}F-FDG PET/CT were retrospectively analysed. Of the 36 patients, 21 were diagnosed as having CS according to Japanese Ministry of Health and Welfare guidelines and divided into 12 responders and 9 non-responders after steroid therapy by the mean follow-up period of 19 months. SUVmax and total lesion glycolysis (TLG) for the left ventricle (LV) on ^{18}F-FDG PET/CT were compared between responders and non-responders using the Wilcoxon test. The predictability of response to steroid therapy was analysed using receiver operating characteristic curve analysis.

Results: TLG for the LV wall was significantly higher in non-responders [1082 ± 715 g (mean ± SD)] than in responders (452 ± 385 g, p=0.02), while there was no difference in the SUVmax for the LV wall between the two groups (responders 8.6 ± 2.3 vs. non-responders 11.4 ± 3.8). Use of an optimal TLG cut-off of 1070 g differentiated responders from non-responders with a sensitivity of 100%, a specificity of 55.6%, an accuracy of 81.0% and area under the curve of 0.80.

Conclusion: The non-responders to steroid therapy for CS showed a high level of TLG on ^{18}F-FDG PET/CT. TLG of ^{18}F-FDG PET/CT can be a predictor of response to steroid therapy in CS.

Keywords: Cardiac sarcoidosis; Steroid therapy; Prediction; ^{18}F-FDG PET; Total lesion glycolysis

Abbreviations: CS: Cardiac Sarcoidosis; ^{18}F-FDG PET: ^{18}F-Fluorodeoxyglucose Positron Emission Tomography; SUV: Standardized Uptake Value; MV: Metabolic Volume; TLG: Total Lesion Glycolysis; AV block: Atrioventricular Block; ECG: Electrocardiogram; LV: Left Ventricle; JMHW guideline: Japanese Ministry of Health and Welfare Guideline; CRT: Cardiac Resynchronization Therapy; LVAD: Left Ventricle Assist Device; SUVmax: Maximum Standardized Uptake Value, VOI: Volume of Interest; RBBB: Right Bundle Branch Block; VT: Ventricular Tachycardia; PVC: Premature Ventricular Contraction; LVEF: Left Ventricle Ejection Fraction; SD: Standard Deviation; ROC curve analysis: Receiver Operating Characteristic Curve Analysis

Introduction

Sarcoidosis is a multisystem disease of unknown aetiology characterised by the presence of noncaseating granulomas that can affect different kinds of organs. Cardiac involvement in sarcoidosis is associated with heart failure, ventricular tachyarrhythmia, conduction disturbances, or sudden cardiac death and it is one of the major causes of disease-related death [1-4]. Steroid therapy is the mainstay of treating cardiac sarcoidosis (CS) [5,6] and its efficacy in general is about 50% [7,8]. Corticosteroid-refractory CS patients require a change of therapeutic strategy, such as additional administration of immunosuppressants or placement of implantable cardiac defibrillators and have a poor prognosis [6].

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is valuable for the diagnosis and detection of active inflammatory lesions in CS [9-11]. The utility of ^{18}F-FDG PET for the prediction of the therapeutic effect for CS or for the risk assessment of adverse events including sudden death has also been investigated [9,12,13]. On ^{18}F-FDG PET, the standardized uptake value (SUV) has been widely used as a quantitative index of the degree of ^{18}F-FDG uptake. In some studies of malignant disease, metabolic volume (MV) and total lesion glycolysis (TLG) were measured using the SUV of ^{18}F-FDG PET/CT [14] and their prognostic significance has been reported [15-19]. Recent papers have reported metabolism-perfusion imaging to predict disease activity in CS with rubidium-FDG PET [20] or the usefulness of quantitative interpretation of ^{18}F-FDG PET in CS patients [21]. However, the association between the responses to steroid therapy for CS patients and MV or TLG in ^{18}F-FDG PET remains unclear. The purpose of this study was to investigate the utility of TLG in ^{18}F-FDG PET/CT to predict the response to steroid therapy of CS [22].

Materials and Methods

Patients

Thirty-six consecutive patients with clinically suspected CS who

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had undergone ^{18}F-FDG PET/CT for diagnosis between January 2010 and December 2013 were retrospectively analysed. The entry criteria were as follows: (1) atrioventricular (AV) block on electrocardiogram (ECG) or left ventricular (LV) wall motion abnormality and septal wall thinning on echocardiography; or (2) histologically proven sarcoidosis in lung, muscle and other organs. The exclusion criteria were as follows: (1) known coronary artery disease, myocarditis, valvular heart disease, or cardiomyopathies other than CS; and (2) high blood glucose level (>150 mg/dL). This retrospective study was approved by the institutional review board and the requirement for written informed consent was waived.

A total of 36 patients were classified into two groups of CS patients and non-CS patients based on 2006 Japanese Ministry of Health and Welfare (JMHW) guidelines [22,23]. The patients' characteristics are shown in Table 1. In all patients, an ^{18}F-FDG PET/CT examination was performed to make the diagnosis before treatment. In CS patients, the treatment started with prednisolone 30 mg per day. Twelve months after initiation of steroid therapy, the response was determined by the consensus of two cardiologists. CS patients in whom the corticosteroid dose could be tapered due to stable clinical symptoms or improved cardiac function were defined as responders. CS patients who required additional immunosuppressant or placement of cardiac resynchronization therapy (CRT) or a LV assist device (LVAD) because of unstable symptoms or progression of cardiac dysfunction were defined as non-responders. All responders were maintained on 5 mg to 10 mg of prednisolone per day and had no recurrence of CS during follow-up, which ranged from 17 months to 45 months (mean, 25 months). ^{18}F-FDG PET/CT was again performed for 17 of 21 CS patients to evaluate active lesions after initiation of steroid therapy (mean, 8 months).

^{18}F-FDG PET/CT Imaging

In each patient, 185 MBq of ^{18}F-FDG was intravenously administered after 18-hr fasting. ^{18}F-FDG PET/CT with an intravenous injection of heparin (50 IU/kg) 15 min before ^{18}F-FDG injection was performed. Scans of the heart were conducted 60 min after ^{18}F-FDG administration. ^{18}F-FDG PET/CT images were obtained using an integrated PET/CT scanner Discovery STE (GE Medical Systems, Milwaukee, WI). The PET scanner comprised 24 ring detectors consisting of 560 BGO crystals (4.7 × 6.3 × 30 mm). All emission scans were performed in 3-dimensional mode with 128×128 matrices (5.47 × 5.47 × 3.27 mm) and the acquisition time per bed position was 10 min. The PET images were reconstructed using the ordered-subset expectation-maximization method (VUE Point Plus) with 2 full iterations of 28 subsets and full-width at half maximum was 5.2 mm. A low-dose 16-slice CT (tube voltage, 120 kV; effective tube current, 30-250 mA) that covered from the vertex to the proximal thigh was performed for attenuation correction and for determining the precise anatomic location before acquisition of the PET image. The CT scan was reconstructed by filtered back projection into 512 × 512 pixel images with a slice thickness of 5 mm to match the PET scan.

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

Maximum SUV (SUVmax), MV and TLG in ^{18}F-FDG PET imaging were measured by the available software (Multi-Modality Tumor Tracking) in a dedicated workstation (IntelliSpace Portal 6, Philips Medical Systems, Milpitas, CA). SUV was obtained from each pixel as pixel activity (injected dose/body weight). A spherical volume of interest (VOI) corresponding to the entire LV wall was manually drawn and ^{18}F-FDG uptake except for the LV wall was excluded. SUVmax for the VOI was automatically calculated. Then, an SUV of 4.0 for the LV wall was determined as a low cut-off threshold. The volume for the LV wall with SUV ≥4.0 was then measured as MV. TLG was calculated by dividing the MV by the mean SUV in the MV.

ECG data analysis

Resting 12-lead ECG or 24 h ECG monitoring was analysed by cardiologists blinded to ^{18}F-FDG PET data. According to the JMHW guidelines, right bundle branch block (RBBB), AV block, left-axis deviation, ventricular tachycardia (VT), premature ventricular contraction (PVC) (grade 2 in Lown's classification) and abnormal Q or ST-T changes were defined as abnormal.

Echocardiography data analysis

All patients underwent transthoracic or transesophageal echocardiography and their data were analysed by cardiologists blinded to ^{18}F-FDG PET data. According to the JMHW guidelines, abnormal wall motion, regional wall thinning or thickening and dilatation of the left ventricle were defined as abnormal. The LV ejection fraction (LVEF) was also measured by analysis of the LV end-diastolic and end-systolic dimensions using M-mode or B-mode echocardiography.

Major adverse cardiac events during follow-up

Patients were examined by cardiologists in our hospital at least every 3 months for a mean follow-up period of 25 months (17 months to 45 months). The primary endpoint was major adverse cardiac events consisting of cardiac death or heart failure hospitalization for CRT or LVAD.

Statistical analysis

Continuous data are expressed as means ± standard deviation (SD). Comparisons of LVEF, SUVmax, MV and TLG between responders and non-responders were analysed by the Wilcoxon test. The ability of SUVmax, MV and TLG to differentiate CS patients from non-CS patients and to predict the response to therapy was analysed by receiver operating characteristic (ROC) curve analysis. Comparisons of parameters between pre- and post-steroid therapy were performed using paired *t*-tests. Survival curves of patient subgroups were created by the Kaplan-Meier method to clarify the time-dependent, cumulative event-free rate and were compared using the log-rank test. The tests were performed using JMP® (version 9.0.2; SAS Institute, Cary, NC) statistical software. A p value of less than 0.05 was considered significant.

Results

Comparison of ^{18}F-FDG PET measurements between CS and non-CS patients

On the basis of the JMHW guidelines, 21 of the 36 patients were diagnosed as having CS and the other 15 patients were diagnosed as not having CS (non-CS patients). CS and non-CS patients' characteristics are shown in Table 1. The SUVmax, MV and TLG were significantly greater for CS patients than for non-CS patients (p<0.01; Table 2).

Diagnostic capability of CS patients by ^{18}F-FDG PET measurements

ROC curve analysis revealed that the optimal SUVmax was 5.3 for differentiating CS patients from non-CS patients, with an AUC of 1.0, 100% accuracy (36/36), 100% sensitivity (21/21) and 100% specificity (15/15). The optimal MV and TLG thresholds were 4 cm^3 and 16 g for differentiating CS patients from non-CS patients, with an AUC of 0.99

	CS patients (n=21)	Non-CS patients (n=15)
Age (years)	61 ± 11	59 ± 14
Sex (male/female)	7 / 14	5 / 10
Diabetes	1 (%)	0 (0%)
Electrocardiographic abnormalities	--	--
Atrioventricular block	13 (62%)	1 (7%)
Left bundle branch block	2 (10%)	3 (20%)
Right bundle branch block	10 (48%)	2 (13%)
Left axis deviation	3 (14%)	0 (0%)
Premature ventricular contraction	10 (48%)	5 (33%)
Ventricular tachycardia	2 (10%)	1 (7%)
Abnormal Q wave	5 (24%)	0 (0%)
ST-T abnormalities	3 (14%)	2 (13%)
Echocardiography abnormalities	--	--
Interventricular septum wall thinning	11 (52%)	5 (33%)
Regional wall motion abnormality	21 (100%)	10 (67%)
Ventricular aneurysm	3 (14%)	1 7(%)
Regional wall thickening	4 (19%)	0 (0%)
Left ventricular ejection fraction (%)	40 ± 12*	57 ± 10
Extra cardiac sarcoidosis	19 (90%)	5 (33%)
Lymph node	19 (90%)	5 (33%)
Lung	9 (43%)	5 (33%)
Eye	8 (38%)	3 (30%)
Liver	4 (19%)	1 (7%)
Spleen	4 (19%)	1 (7%)
Skin	2 (10%)	0 (0%)
Bone	0 (0%)	1 (7%)

Data are mean ± SD or number of patients;
CS: Cardiac Sarcoidosis;
*P<0.01 vs. non-CS patients.

Table 1: Patient characteristics.

	CS patients (n=21)	Non-CS patients (n=15)
^{18}F-FDG accumulation of LV wall	--	--
SUVmax	9.8 ± 3.3*	2.8 ± 1.0
Metabolic volume (cm^3)	127 ± 101*	8 ± 2
Total lesion glycolysis (g)	722 ± 623*	35 ± 9
Fasting blood glucose (mg/dL)	97 ± 15	99 ± 12

Data are mean ± SD or number of patients;
^{18}F-FDG: ^{18F}-Fluorodeoxyglucose; PET: Positron Emission Tomography; CT: Computed Tomography; CS: Cardiac Sarcoidosis; LV: Left Ventricle; SUVmax: Maximum of Standardized Uptake Value.
*P<0.01 vs. non-CS patients.

Table 2: Comparison of ^{18}F-FDG PET/CT measurements between CS and non-CS patients.

and 0.99, 97% (35/36) and 97% (35/36) accuracy, 100% (21/21) and 100% (21/21) sensitivity and 93% (14/15) and 93% (14/15) specificity, respectively.

Comparison of ^{18}F-FDG PET measurements and LVEF between responders and non-responders

Of the 21 CS patients, 12 patients were responders to steroid therapy and the other 9 were non-responders. MV and TLG were significantly greater for non-responders than for responders (182 ± 112 cm^3 vs. 85 ± 69 cm^3; p=0.03, 1082 ± 715 g vs. 452 ± 385 g; p=0.02), respectively (Figure 1). No significant differences in LVEF (responder's 42% ± 13% vs. non-responders 37% ± 10%) and SUVmax (responders 8.6 ± 2.3 vs. non-responders 11.4 ± 3.8) were noted between the responders and non-responders.

Predictability of response to steroid therapy in CS patients

ROC curve analysis revealed that the optimal SUVmax was 8.0 for predicting non-responders, with an AUC of 0.69, 66.7% accuracy (14/21), 58.3% sensitivity (7/12) and 77.8% specificity (7/9). The optimal MV and TLG thresholds were 190 cm^3 and 1070 g for predicting non-responders, with an AUC of 0.79 and 0.80, 81% (17/21) and 81% (17/21) accuracy, 100% (21/21) and 100% (21/21) sensitivity and 56% (5/9) and 56% (5/9) specificity (5/9), respectively.

Comparison of ^{18}F-FDG PET measurements between before and after therapy

In CS responders, SUVmax (8.4 ± 1.8 vs. 3.8 ± 1.0), MV (69 ± 50 cm^3 vs. 2 ± 3 cm^3) and TLG (346 ± 281 g vs. 10 ± 16 g) were significantly greater at pre-therapy than at post-therapy (Figure 2). In non-responders, there were no significant differences in SUVmax, MV and TLG between the two conditions.

Representative ^{18}F-FDG PET images at pre and post-steroid therapy for non-responders and responders are presented in Figures 3 and 4.

^{18}F-FDG PET measurements and major adverse cardiac events

After initiation of steroid therapy, 5 of 21 CS patients had implantation of CRT (after 2 ± 1 month) and 1 patient had implantation of LVAD (after 1 month). Event-free rates had no significant difference between patients with SUVmax<8.0 and ≥8.0 (Log-rank value=0.30, p=0.58). On the other hand, MV<190 cm^3 and TLG<1070 g had significantly lower event-free rates than those with ≥ 190 cm^3 (Log-rank value=9.93, p<0.01) and ≥1070g (Log-rank value=9.93, p<0.01), respectively (Figure 5).

Discussion

Our results demonstrated that all of the SUVmax, MV and TLG in LV wall on ^{18}F-FDG PET were significantly higher in CS patients than in non-CS patients and had high diagnostic capability for CS. In our study, 18 h fasting before ^{18}F-FDG injection was performed, which have been known as a useful method to inhibit physiological myocardial uptake [23]. On diagnostic performance of CS, it was suggested that the SUVmax in LV wall was no less effective than both MV and TLG in the condition of sufficient suppression of physiological myocardial uptake.

On the contrary, the MV and TLG had significantly higher predictive value for the response to steroid therapy and adverse cardiac events than the SUVmax. That suggests that the response to steroid therapy in CS patients is associated with the extent as well as the degree of active inflammation in the LV wall before therapy. We think that MV or TLG is associated with the extent of active inflammation in CS, as well as the extent or volume of malignant tumour. Therefore, MV or TLG is superior to SUVmax in predicting the response to steroid therapy. In addition, after steroid therapy, the responders showed almost no remaining MV and TLG, while non-responders had no significant decrease of either. The assessment of MV and TLG in the LV wall after treatment for CS can clarify the presence or absence of continuing active inflammation. That suggests that ^{18}F-FDG PET is a helpful tool for evaluation after, as well as before, steroid therapy for CS.

The most important factor is the determination of the lower cut-off of myocardial uptake in the process of calculating TLG. In the present results, the mean SUVmax for LV in non-CS patients was 2.8. A previous 18 h fasting ^{18}F-FDG PET study showed a SUVmax of 4.2 for active inflammatory myocardium in CS [24]. The present ^{18}F-FDG PET protocol involved 18 h fasting and heparin loading to suppress

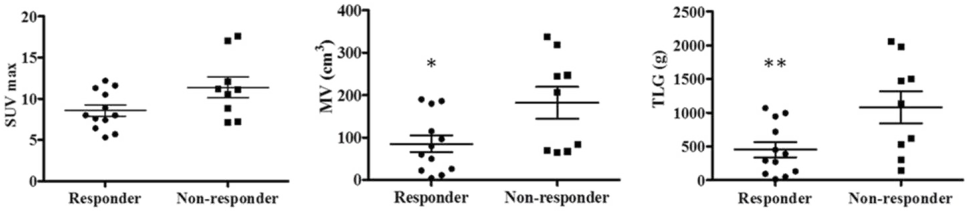

Figure 1: The box-and-whisker plot of ^{18}F-FDG PET measurements in responders and non-responders. The boxes represent the 25% to 75% range with bisecting lines showing the median value and the horizontal lines represent the 10% to 90% range. SUVmax (*left*) of the LV wall shows no significant difference between responders and non-responders. The MV (*centre*) of the LV wall is significantly higher in non-responders than in responders. *P=0.03. TLG (*right*) of the LV wall is significantly higher in non-responders than in responders. **P=0.02.

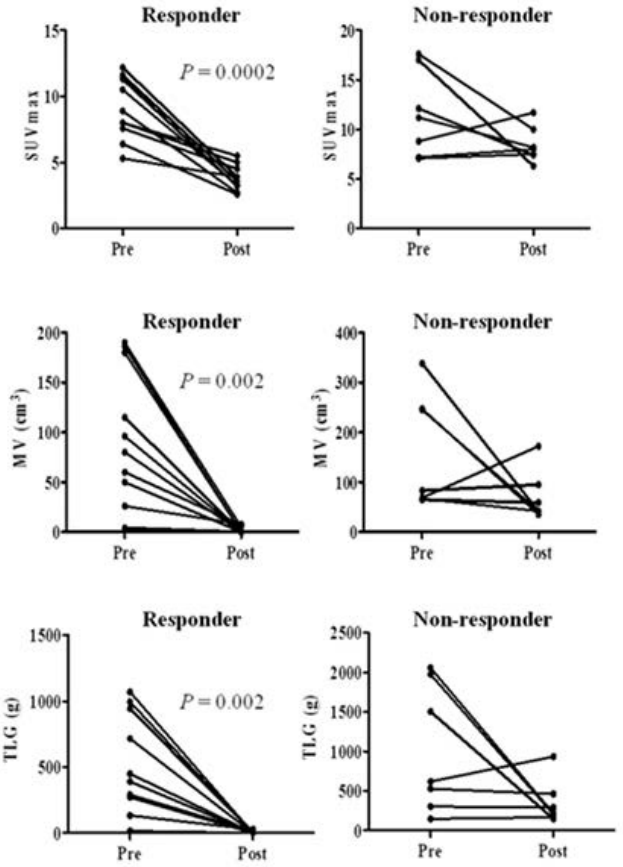

Figure 2: Comparison of ^{18}F-FDG PET measurements between before and after steroid therapy. The graphs of data points and fitted lines in ^{18}F-FDG PET measurements before and after steroid therapy are presented. In CS responders, SUVmax (*upper*), MV (*middle*) and TLG (*lower*) are significantly greater at pre-therapy than at post-therapy. In non-responders, there are no significant differences in SUVmax, MV and TLG between the two conditions.

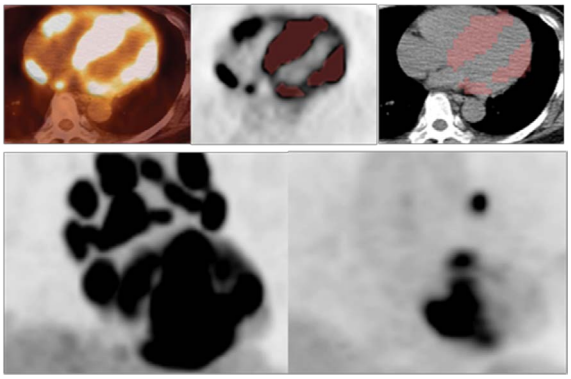

Figure 3: A 54-year-old female who was a non-responder to steroid therapy for CS. From ^{18}F-FDG PET/CT fusion images before steroid therapy (*upper left*), the volume of the LV wall with SUV ≥ 4.0 automatically extracted (*upper centre*) and displayed on the CT images (*upper right*). The SUVmax, MV and TLG in the LV wall before therapy are 17.6, 245 cm^3 and 1976 g, respectively. Maximum-intensity-projection image of ^{18}F-FDG PET/CT before steroid therapy (*lower left*) and 8 months after initiation of steroid therapy (*lower right*) are presented. After steroid therapy, the patient had continually unstable symptoms of heart failure and cardiac dysfunction and additional administration of methotrexate was performed. The post-therapy SUVmax, MV and TLG in the LV wall after steroid therapy are 10.0, 42 cm^3 and 282 g, respectively.

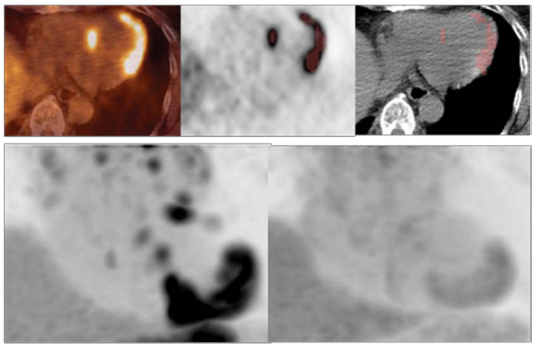

Figure 4: A 66-year-old male who was a responder to steroid therapy for CS. From ^{18}F-FDG PET/CT fusion images before steroid therapy (*upper left*), the volume of the LV wall with SUV ≥ 4.0 is automatically extracted (*upper centre*) and displayed on the CT images (*upper right*). The SUVmax, MV and TLG in the LV wall are 11.3, 50 cm^3 and 391 g, respectively. SUVmax is high, suggesting a non-responder. However, TLG could predict a responder. Maximum-intensity-projection images of ^{18}F-FDG PET/CT before steroid therapy (*lower left*) and 5 months after initiation of steroid therapy (*lower right*) are presented. The patient has improvement of heart failure and ^{18}F-FDG accumulation of the LV wall has almost disappeared. The SUVmax and TLG in the LV wall after steroid therapy are 3.2, 0 cm^3 and 0 g, respectively.

physiological myocardial ^{18}F-FDG uptake. According to these data, the lower cut-off of SUV for normal myocardium was determined and the TLG was calculated to represent the active inflammatory area. Our proposed method is a feasible and quantitative method to extract the active inflammatory lesion and suppress physiological myocardial uptake in CS.

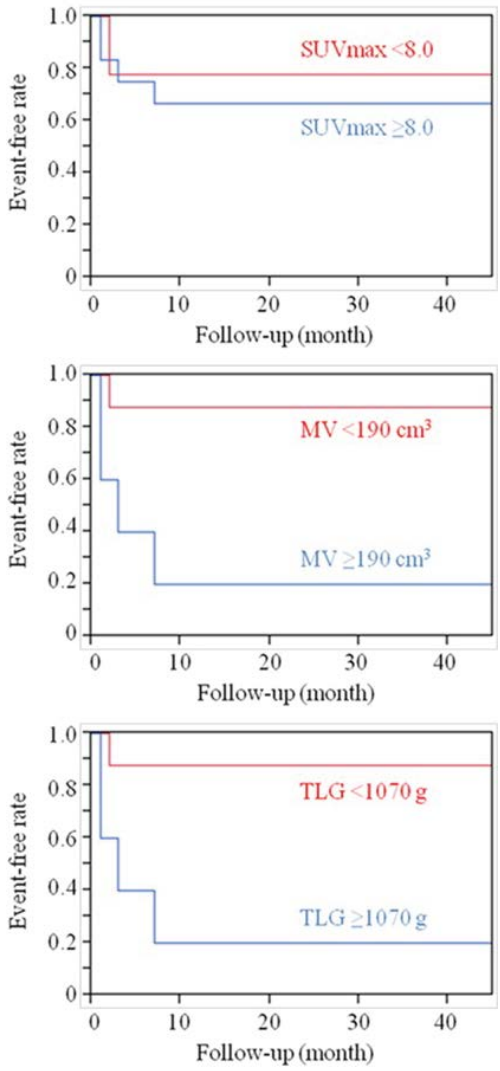

Figure 5: Event-free curves of two groups classified by cut-offs of SUVmax<8.0 and ≥8.0 (*upper*), MV<190 cm^3 and ≥ 190 cm^3 (*middle*) and TLG<1070 g and ≥1070g (*lower*). Event-free rates had no significant difference between patients with SUVmax<8.0 (in red) and ≥8.0 (in blue). MV<190 cm^3 (in red) and TLG<1070 g (in red) had significantly lower event-free rates than those with ≥ 190 cm^3 (in blue) and ≥1070g (in blue), respectively.

The present study had several limitations. First, the mean follow-up period was 25 months and the present study lacked long-term follow-up data to confirm the outcomes of responders to steroid therapy in CS. Second, the number of CS patients analysed in the present study was relatively small in a single centre. Further studies are needed to confirm our hypothesis by evaluating the outcomes of CS patients during long-term follow-up in multicentre studies.

Conclusion

In conclusion, TLG, which expresses metabolic and volumetric indices in ^{18}F-FDG PET, was significantly greater in non-responders than in responders to steroid therapy for CS. TLG is more useful than SUVmax in the prediction of the response to steroid therapy for CS and contributes to clinical management and determination of the therapeutic strategy in CS patients.

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