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18-FDG-PET in a patient cohort suspected for cardiac sarcoidosis: Right ventricular uptake is associated with pathological uptake in mediastinal lymph nodes.

Running head: PET in CS: cardiac and lymph node uptake

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Abstract

Introduction: In up to 65 % of cardiac sarcoidosis patients, the disease is confined to the heart. Diagnosing isolated cardiac sarcoidosis is challenging due to the low sensitivity of endomyocardial biopsy. If cardiac sarcoidosis is part of biopsy-confirmed systemic sarcoidosis the diagnosis can be based on cardiac imaging studies. We compared the imaging features of patients with isolated cardiac FDG-uptake on positron emission tomography with those who had findings indicative of systemic sarcoidosis.

Materials and methods: 137 consecutive cardiac FDG-PET/CT studies performed on subjects suspected of having cardiac sarcoidosis were retrospectively analyzed.

Results: 33 patients had pathological left ventricular FDG-uptake and 12 of these also had pathological right ventricular uptake. 16/33 patients with pathological cardiac uptake had pathological extracardiac uptake. 10/12 patients with both LV- and RV-uptake had extracardiac uptake compared to 6/21 with pathological LV-uptake without RV-uptake. SUVmax values in the myocardium were higher among patients with abnormal extracardiac uptake. The presence of extracardiac uptake was the only imaging-related factor that could predict a biopsy indicative of sarcoidosis.

Conclusion: Right ventricular involvement seems to be more common in patients who also have findings suspective of systemic sarcoidosis, compared to patients with PET findings indicative of isolated cardiac disease.

Introduction

Sarcoidosis is a multisystem granulomatous inflammatory disorder that can affect any organ system. The disease typically manifests in the lungs, often as asymptomatic hilar lymph node enlargement. The most common presentation is symmetrical hilar adenopathy, which is encountered in approximately 95 % of patients with lung sarcoidosis.[1] Middle mediastinal or prevascular lymph nodes are involved in approximately 50 % of patients with pulmonary sarcoidosis.[2] Unilateral hilar lymph node enlargement or mediastinal node enlargement without hilar adenopathy indicates an alternative aetiology.[3] Pulmonary sarcoidosis is often an incidental finding when imaging is performed to investigate other symptoms or diseases. Sarcoidosis patients should be screened for cardiac involvement because of the potential life-threatening consequences of the disease. Sudden cardiac death has been shown to be a potential initial manifestation of CS.[4-6] The recommended initial screening evaluations include patient medical history, ECG and echocardiography. However, only 40-50 % of patients with cardiac involvement at autopsy had clinically evident cardiac disease during their lifetimes.[7]

Due to the difficulty of diagnosing CS, epidemiological literature on the topic is limited. CS has traditionally been diagnosed using the guidelines issued in 2006 by the Japanese Ministry of Health and Welfare (JMHW) and revised by Japan Society of Sarcoidosis and Other Granulomatous Disorders. The revised criteria were proposed by the Heart Rhythm Society in 2014.[8] According to both guidelines, CS can only be diagnosed via direct confirmation by endomyocardial biopsy (EMB) or based on a previous diagnosis of systemic sarcoidosis combined with clinical and imaging findings indicating cardiac involvement. Given that the sensitivity of EMB is low, many patients with probable CS do not fulfil the current diagnostic criteria.[9]

Cardiac ^{18}fluorodeoxyglucose positron emission tomography/computerized tomography (18FDG PET/CT) (later referred to as PET) has been used to identify active cardiac inflammation, with a sensitivity and specificity of 89 % and 78 %, respectively.[10] In the revised JMHW guidelines Ga-scintigraphy was included as a major criteria to demonstrate myocardial inflammation. Due to low sensitivity of Ga-scintigraphy the JMWH has since approved substituting it with FDG-PET. The demand for cardiac imaging has increased because it has been suggested that CS should be excluded in patients under the age of 55 years with unexplained dilated cardiomyopathy, second or third degree atrioventricular (AV) block or persistent ventricular tachycardia (VT).[8,11]

In a previous study of 110 Finnish CS patients, CS was diagnosed by direct EMB in 50 % of the patients and by biopsy from another affected site combined with cardiac imaging findings suggesting sarcoid involvement in the other 50 % of the patients.[12] Seventy-one of the 110 patients had clinically isolated cardiac sarcoidosis, e.g., no clinical signs or history suggesting extracardiac disease. However, PET showed metabolically active mediastinal lymph nodes in 71 % of these patients. In a study by Simonen et al., it was found that confirmed CS FDG-avidity of mediastinal lymph nodes was caused by granulomatous inflammation in all patients from whom a biopsy was obtained.[13] Mediastinal lymph node biopsy serves as an alternative to histologically diagnosed sarcoidosis when an EMB is negative despite a strong clinical suspicion of CS. This fact may increase the true clinical sensitivity of PET compared to the figures reported previously, many of which are based on cardiac uptake patterns only.[10]

Our aim was to study the association between pathological extracardiac and cardiac FDG uptake.

Materials and methods

Study population

We retrospectively screened all cardiac PET studies performed in the Tampere University Hospital from August 2012 to September 2015. We excluded PET studies in which the clinical indication was not CS suspicion, the patient's clinical data could not be obtained or the PET study was performed to followup on previously diagnosed CS. Imaging studies were also excluded if the dedicated imaging protocol, as described below, was not followed precisely. Altogether, 137 PET examinations were analyzed for the present study. In our hospital, PET is routinely performed in the diagnostic workup of possible CS. The reason for a clinical suspicion of CS was one or more of the following: unexplained AV block (n=61), ventricular (n=39) or supraventricular (n=13) arrhythmia, unexplained dilated cardiomyopathy (n=27), an unexplained low ejection fraction on echocardiography (n=46), other echocardiographic findings suggestive of CS (n=53), or syncope (n=27). Symptoms and clinical findings were considered unexplained by the cardiologist after inconclusive routine studies, including clinical examination, ECG and echocardiography. Coronary angiography was performed in cases of clinical suspicion of coronary artery disease.

PET Imaging

All patients underwent an integrated PET/CT (Discovery STE 16, GE Healthcare, Milwaukee, WI, USA) examination. To minimize physiological myocardial FDG uptake, the patients were instructed not to consume any carbohydrates during the day before the imaging exam and to fast for 12 h before the FDG injection. The patients maintained a food diary during the prescribed diet. The patients were also instructed to avoid heavy physical exercise to minimize FDG uptake in skeletal muscle. Patient height and weight were measured before the administration of the radiopharmaceutical, and blood glucose levels were tested toconfirm level of <7 mmol/l. The

PET/CT images were acquired approximately 60 min after the intravenous injection of FDG using the Medrad® Intego PET infusion system (Bayer Medical Care Inc., Indianola, PA, USA). In our hospital, the activity injected is based on a patient's weight (3-3.2 MBq/kg). The imaging protocol has been described in more detail previously.[14]

Analysis of PET images

We classified the uptake pattern in the left ventricular (LV) myocardium according to the recommendations of the Japanese Society of Nuclear Cardiology (10) as 'none' (no activity exceeding normal blood pool activity), 'global diffuse' (uniform activity over the entire myocardium), 'focal' (focally increased spot(s) of activity, other regions inactive), 'focal on diffuse' (intense focal spot(s) of activity overlapping global myocardial activity) or 'diffuse non-global' (faint activity on at least two LV walls, but at least some areas of myocardium with no activity over normal blood pool activity). Diffuse non-global uptake is not mentioned in the Japanese Society of Nuclear Cardiology recommendations but was considered to be a similar physiological phenomenon to diffuse uptake. The uptake was called physiological if it was classified as none, global diffuse or diffuse non-global. Uptake was called pathological if it was classified as focal or focal on diffuse. We also classified the uptake in the right ventricle (RV) in a similar manner. The maximum standardized uptake value (SUVmax) in the heart was measured, and its location was determined. Extracardiac uptake in the lymph nodes was considered pathological if it exceeded that of the mediastinal blood pool. The areas inspected for possible pathological extracardiac uptake included lymph nodes in axillary, subclavicular, mediastinal, hilar and epigastric sites. Pathological FDG uptake in the lung parenchyma, liver, spleen and bone was also noted. Uptake in the liver, spleen and lung parenchyma was considered pathological if there were spots of metabolic activity exceeding the physiological uptake of the surrounding parenchyma. Bone marrow uptake was considered pathological if focal uptake exceeding that of the liver was

noted. The images were interpreted after patient anonymization and randomization. The images were separately interpreted by two experienced nuclear medicine physicians (HT, KS) blinded to all clinical data. In cases where the interpretation of LV uptake differed between the observers, a consensus was reached and used in further analyses.

Collection of clinical data

Clinical data were retrospectively collected from the electronic medical record system of Tampere University Hospital, which contains information from 2008 onward. We collected demographic information, echocardiography findings, relevant diagnoses, symptoms and EMB findings.

Statistical methods

Statistical analyses were performed using IBM SPSS statistics version 22.0 (Armonk, NY, USA) and R software version 3.2.2. The chi-square test was used for dichotomous variables and a t-test was used for continuous variables to compare the results. Linear regression was used to assess independent predictors of positive biopsy findings in a multivariate model, including age, sex, and pathological LV, RV and extracardiac uptake.

Results

Results: Thirty-three of 137 (24 %) patients had pathological cardiac uptake. Of these 12 (36 %) had pathological uptake in both left and right ventricles. There were 29 of 137 (21 %) patients with pathological extracardiac uptake foci. Extracardiac uptake was significantly associated with pathological LV and RV uptake (Table 1, Figure 1). Patients with both pathological cardiac and extracardiac uptake had significantly higher SUVmax values in the myocardium compared to the patients with abnormal myocardial uptake but physiological extracardiac uptake (SUVmax 10.4 (S.D. 4.7) and 6.6 (S.D. 2.3), respectively, p-value 0.001).

Patients with uptake in both ventricles had pathological extracardiac uptake significantly more often than patients with physiological RV uptake ($p<0.001$). Ten of the 12 patients with pathological RV-uptake also had pathological extracardiac foci. Patients with pathological RV-uptake also had pathological extracardiac uptake more often than those with pathological uptake in the LV but not in RV (p-value 0.003, Table 3, Figure 1). Pathological myocardial uptake was associated with uptake in mediastinal and hilar lymph nodes but not with pathological uptake at other extracardiac sites (Table 2)

Patients with pathological extracardiac uptake were predominantly female, more often had a history of ventricular tachycardia and less often had a history of heart failure compared to the patients without pathological extracardiac uptake.

Biopsies from an extracardiac focus were obtained from 25 patients, which was indicative of sarcoidosis in 15 patients. In addition, 7 patients had a positive EMB. In a linear regression model, only extracardiac uptake, but not LV or RV uptake, predicted a positive biopsy overall (EMB or extracardiac). Out of 10 patients with both abnormal RV and extracardiac uptake, six had biopsy-confirmed sarcoidosis: 3 by EMB and 3 by extracardiac tissue biopsy.

Discussion

We found a significant association between pathological myocardial FDG uptake and pathological uptake in hilar and mediastinal lymph nodes. The association was especially strong in patients with pathological uptake in the RV free wall. Pathological myocardial uptake was stronger in patients who also had pathological extracardiac uptake. Extracardiac uptake was the only factor that could predict a positive biopsy finding for sarcoidosis.

A few studies have examined the association between cardiac and extracardiac FDG uptake in patients suspected for CS, but the results are somewhat contradictory. In a study by Kandolin et al., 71 % of patients with histologically verified CS had positive mediastinal lymph nodes on whole-body FDG-PET.[12] The percentage was the same even in patients without clinical or anamnestic extracardiac sarcoidosis. In our clinical population consisting of patients, who were suspected of having CS, 29 of 137 patients (21 %) had abnormal extracardiac FDG uptake. The low number of patients with pathological extracardiac uptake is due to the fact that only a small proportion of our population had sarcoidosis. In the study of Yokoyama et al., abnormal extracardiac uptake was observed in 54 % of the 92 FDG-PET studies performed on patients suspected of having CS.[15] In their population, there was a significantly higher proportion of biopsy-confirmed CS patients compared to our study cohort. Therefore, this discrepancy could simply indicate selective differences between the cohorts. In our study, a total of 33 patients had pathological cardiac uptake, and among these patients, 48 % had abnormal extracardiac FDG uptake. In the study of Patel et al., similar results were found. In their study, among patients with pathological myocardial uptake, 40 % also had pathological extracardiac FDG-positive foci.[16] On the other hand, Blankstein et al. reported that extracardiac FDG uptake was not significantly associated with pathological cardiac findings.[17] In that study, 118 PET studies were performed to assess myocardial inflammation or perfusion defects in patients suspected of having CS, and 27 % of 71 patients with pathological

uptake or perfusion defects had abnormal extracardiac uptake. However, the authors did not specifically report the number of patients with abnormal cardiac uptake who also had extracardiac uptake. Perfusion defects may be due to previously active inflammation that has since become inactive, which may possibly explain these differing results.

There may be some alternative explanations for the association between abnormal FDG uptake in the RV and in mediastinal lymph nodes in addition to their vulnerability to sarcoid inflammation. Pulmonary hypertension has been shown to increase FDG uptake in the right ventricular free wall.[18] Hilar adenopathy in sarcoidosis has been associated with elevated pulmonary pressure.[19] Therefore, pulmonary hypertension and the consequent right ventricular workload could theoretically explain the association between abnormal FDG uptake in mediastinal lymph nodes and in the RV. However, pulmonary hypertension has been shown to occur in less than 10 % of patients with sarcoidosis.[20] Moreover, in the context of an increased workload, the uptake should be uniform rather than patchy as in our patients. In our cohort, 8 of 12 patients with abnormal RV uptake also had abnormal FDG uptake in hilar lymph nodes. Interestingly, in our study population, no patients had abnormal RV uptake without accompanying LV uptake. There are only a few case reports of isolated right ventricular CS and only one patient showed this pattern in the study of Manabe et al.[21-23] One could also speculate that cardiac sarcoidosis typically begins in the LV, which has the greatest myocardial mass of the heart chambers, and the right ventricle and mediastinal lymph nodes would then become involved later if inflammation starts to spread. This speculation could explain why the association was especially strong between abnormal extracardiac and RV uptake in our study.

Previously, Manabe et al. showed that patients with pathological RV uptake fulfil the JMWH criteria more often than those with uptake only in the LV.[22] This is consistent with our findings: 6 of 12 patients with RV uptake had biopsy-confirmed sarcoidosis compared to only 4 of 21 patients with LV uptake alone. As the diagnostic yield of EMB is low, extracardiac uptake foci provide an

alternative site for biopsy. Manabe et al. also showed that patients with RV uptake had more widespread pathological uptake in the LV, suggesting more widespread disease. All these findings seem to suggest that the inflammatory process is more widespread in patients with RV involvement, and one may speculate that sarcoidosis of the heart originates in the LV.

We did not find a statistically significant association between abnormal cardiac FDG uptake and non-hilar/mediastinal extracardiac uptake. The low statistical power due to the low number of extrathoracic FDG-avid foci may explain this result. On the other hand, PET results indicated lung sarcoidosis in 14 patients. Abnormal FDG uptake in the lung parenchyma was not associated with abnormal LV or RV uptake. Patients with known lung sarcoidosis may be promptly referred for PET when presenting with unspecific symptoms considered potentially cardiac in origin. This could lead to a selection bias toward imaging patients with less severe symptoms/findings if they have known lung sarcoidosis.

In our population, a positive tissue biopsy for sarcoidosis was obtained significantly more often from patients with extracardiac uptake than from those who had physiological extracardiac uptake. This finding was expected, as a tissue biopsy is easier to obtain from extracardiac sites compared to EMB. Seven patients had biopsy confirmation of sarcoidosis but physiological cardiac uptake on PET, which is most likely due to the inactive state of their sarcoid disease. As shown in our previous study, one patient with EMB-confirmed CS did not have any myocardial uptake on PET.[14] Such a finding may represent a patient with myocardial inflammation that has caused myopathy that has since become inactive and accordingly PET-negative.

Our results and the previous literature seem to suggest that truly isolated CS is often confined to the LV myocardium. According to the present diagnostic criteria, EMB is the only method to verify isolated CS. However, EMB is rarely obtained from the LV. Therefore, if the patients in our

population with pathological, isolated LV uptake truly have CS, then the present diagnostic criteria are insensitive for the diagnosis of isolated CS.

There are limitations in our study. Guidelines to select patients with suspected CS for PET imaging did not exist until very recently.[24] Our study population is relatively unselected, with most cases showing PET- or biopsy-negative results. However, this represents the true clinical situation. Our study population consists of Finnish patients representing Caucasians. Since the epidemiology of sarcoidosis is known to differ between populations, our findings may not be directly generalizable to other populations. In addition, the number of patients with biopsy-confirmed cardiac sarcoidosis in our population was relatively low. This limitation is evident in many of the available CS studies.

New knowledge gained

Right ventricular involvement seems to be more common in patients who have FDG-PET findings suggestive of systemic sarcoidosis compared to those with pathological findings confined to the heart.

Conclusion

Patients with pathological myocardial FDG uptake had abnormal FDG uptake in mediastinal and hilar lymph nodes more often than patients with physiological cardiac uptake. Patients with both LV and RV uptake had FDG uptake in mediastinal and hilar lymph nodes more often than those with isolated LV uptake. SUVmax values in the myocardium were higher in the patients with abnormal extracardiac FDG uptake, suggesting that sarcoid inflammation in the heart is stronger and more widespread in patients with findings suggestive of systemic sarcoidosis.

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Table 1. Baseline variables and FDG-PET findings in patients with and without pathological extracardiac FDG uptake.

Variable	Pathological extracardiac FDG uptake (n=29)	No pathological extracardiac FDG uptake (n=108)	p-value
Female gender	19 (66 %)	40 (37 %)	0.006*
BMI	27.3 (4.2)	28.0 (5.9)	0.525
Age, years	44.1 (12.3)	44.2 (13.2)	0.97
History of:			
Ventricular tachycardia	21 (72 %)	54 (50 %)	0.035*
2nd or 3rd degree AV-block	14 (48 %)	42 (39 %)	0.241
Heart failure	8 (28 %)	59 (55 %)	0.01*
Pathological LV uptake	16 (55 %)	13 (12 %)	<0.001 *
Pathological RV uptake	10 (34 %)	2 (1,9 %)	<0.001 *
Extracardiac biopsy positive for sarcoidosis	11 (38 %)	4 (4 %)	<0.001 *
EMB or extracardiac biopsy positive for sarcoidosis	15 (52 %)	7 (7 %)	<0.001 *

The values represent n (%) for dichotomous variables and the mean (+/- SD) for continuous variables.

Abbreviations: BMI=Body mass index; EMB=endomyocardial biopsy; FDG-PET= ^{18}Fluorodeoxyglucose positron emission tomography; AV=atrio-ventricular; RV= right ventricle; LV= left ventricle

Table 2. Pathological uptake at different extracardiac sites in patients with myocardial uptake in both ventricles and in the left ventricle only.

Extracardiac uptake site	Pathological LV uptake with no RV uptake (n=21)	Pathological uptake in both ventricles (n=12)	p-value
Lung	3 (14 %)	3 (25 %)	0.374
Spleen	0 (0 %)	1 (8 %)	0.364
Hilar ln	6 (29 %)	8 (67 %)	0.039*
Mediastinal ln	6 (29 %)	8 (67 %)	0.039*
Axillary ln	0 (0 %)	0 (0 %)	
Subclavicular ln	0 (0 %)	1 (8 %)	0.364
Abdominal ln	1 (5 %)	0 (0 %)	0.636

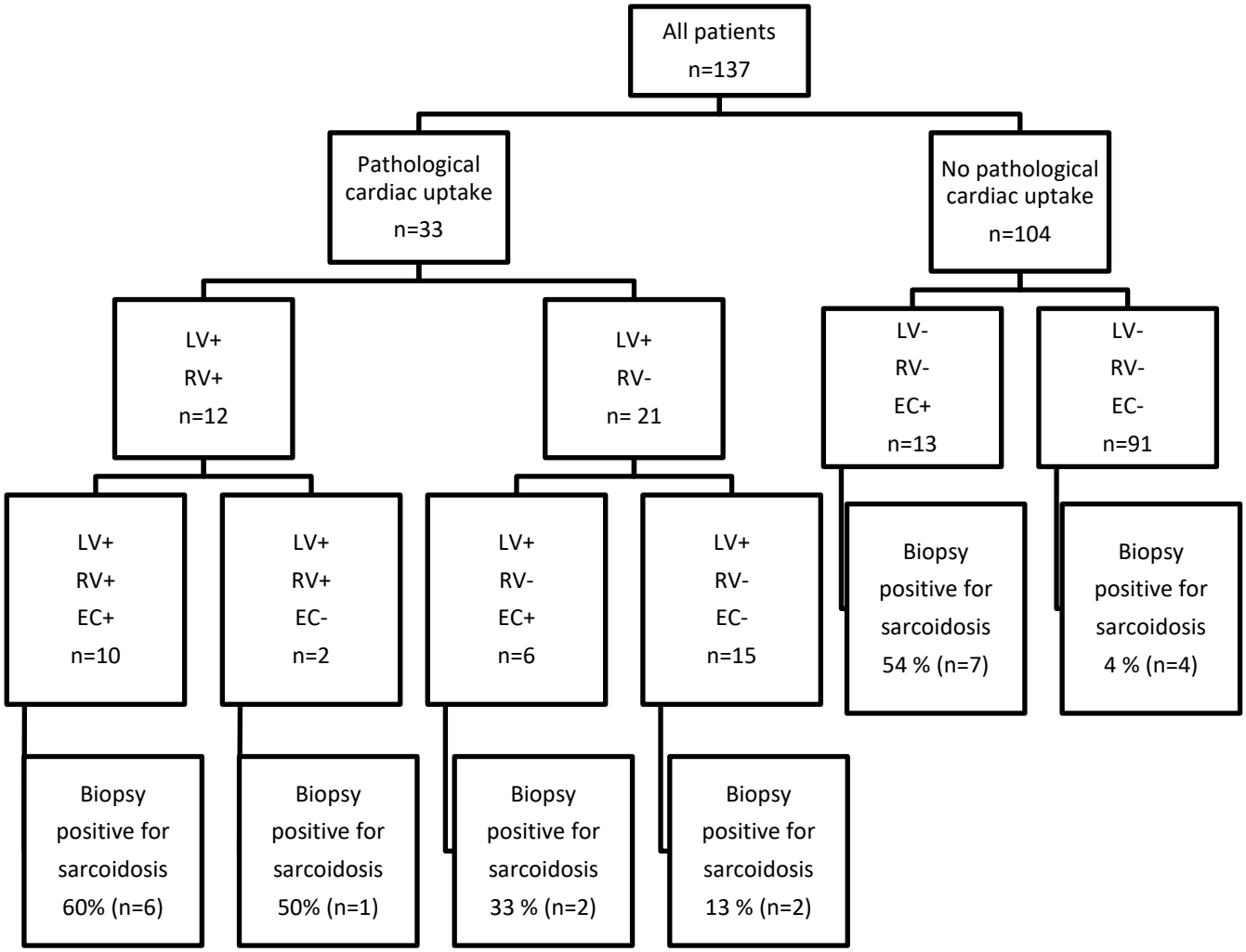
The values are n (%). Abbreviations: RV=right ventricle; LV=left ventricle; ln=lymph node

Table 3. Pathological extracardiac uptake at different sites in patients with and without pathological LV uptake, RV uptake and LV uptake without RV uptake (a, b and c, respectively).

3a			
Extracardiac uptake site	Pathological LV uptake (n=33)	Physiological cardiac uptake (n=104)	p-value
Lung	6 (18 %)	8 (7,7 %)	0.085
Spleen	1 (3 %)	4 (4 %)	0.652
Hilar ln	14 (42 %)	10 (10 %)	<0.001*
Mediastinal ln	14 (42 %)	9 (9 %)	<0.001*
Axillary ln	0 (0 %)	5 (5 %)	0.246
Subclavicular ln	1 (3 %)	4 (4 %)	0.652
Abdominal ln	1 (3 %)	5 (5 %)	0.554
3b			
Extracardiac uptake site	Pathological RV uptake (n=12)	Physiological RV uptake (n=125)	p-value
Lung	3 (25 %)	11 (9 %)	0.108
Spleen	1 (8 %)	4 (3 %)	0.372
Hilar ln	8 (67 %)	16 (13 %)	<0.001*
Mediastinal ln	8 (67 %)	15 (12 %)	<0.001*
Axillary ln	0 (0 %)	5 (4 %)	0.628
Subclavicular ln	1 (8 %)	4 (3 %)	0.372
Abdominal ln	0 (0 %)	6 (5 %)	0.571
3c			
Extracardiac uptake site	Pathological LV uptake with no RV uptake (n=21)	Physiological cardiac uptake (n=104)	p-value
Lung	3 (14 %)	8 (8 %)	0.273
Spleen	0 (0 %)	4 (4 %)	0.474
Hilar ln	6 (29 %)	10 (10 %)	0.029*
Mediastinal ln	6 (29 %)	9 (9 %)	0.020*
Axillary ln	0 (0 %)	5 (5 %)	0.628
Subclavicular ln	0 (0 %)	4 (4 %)	0.372
Abdominal ln	1 (5 %)	5 (5 %)	0.735

The values are n (%). Abbreviations: RV=right ventricle; LV=left ventricle; ln=lymph node

Figure 1. Patients divided into groups according to PET findings and the number of tissue biopsies positive for sarcoidosis.



Abbreviations: LV=left ventricle; RV=right ventricle; EC=extracardiac; + = pathological FDG uptake; - = no pathological FDG uptake