ORIGINAL ARTICLE

Multicenter Registry in the Japanese Cardiac Sarcoidosis Prognostic (J-CASP) Study: Baseline Characteristics and Validation of the Non-invasive Approach Using ^{18}F-FDG PET

Tomoaki Nakata, MD[1)], Kenichi Nakajima, MD[2)], Masanao Naya, MD[3)], Shohei Yoshida, MD[4)], Mitsuru Momose, MD[5)], Yasuyo Taniguchi, MD[6)], Yoshimitsu Fukushima, MD[7)], Masao Moroi, MD[8)], Atsutaka Okizaki, MD[9)], Akiyoshi Hashimoto, MD[10)], Takatoyo Kiko, MD[11)], Satoshi Hida, MD[12)] and Kazuya Takehana, MD[13)]

Received: March 9, 2022/Revised manuscript received: May 9, 2022/Accepted: May 15, 2022
J-STAGE advance published: June 30, 2022

Abstract

***Background*: Recent advances in cardiac modalities contribute to the guidelines on the diagnosis of cardiac sarcoidosis (CS) updated by the Japanese Circulation Society. The multicenter registry, Japanese Cardiac Sarcoidosis Prognostic (J-CASP) study tried to reveal recent trends of diagnosis and outcomes in CS patients and to validate the non-invasive diagnostic approach, including cardiac ^{18}F-fluorodeoxyglucose (FDG) study.**

***Methods/results*: Databases from 12 hospitals consisting of 231 CS patients (mean age, 64 years; female, 65%; LV ejection fraction, 47%) diagnosed by the guidelines with FDG positron emission tomography (PET) study were integrated to compile clinical information on the diagnostic criteria and outcomes. Cardiac ^{18}F-FDG uptake and magnetic resonance imaging (CMR) was positive identically in the histology-proven and clinically-diagnosed groups. The histology-proven group more frequently had reduce LV ejection fraction, myocardial perfusion abnormality and low-grade electrocardiogram (ECG) abnormality (P=0.003 to 0.016) than did the clinical group. During a 45-month period, the histology-proven group more frequently underwent appropriate implantable cardioverter-defibrillator (ICD) treatment (14% versus 4%, P=0.013) and new electronic device implantation (30% versus 12%, P=0.007) than did clinical group, respectively. There, however, was no difference in all-cause or cardiac mortality or in new hospitalization due to heart failure progression between them.**

***Conclusion*: The J-CASP registry demonstrated the rationale and clinical efficacies of non-invasive approach using advanced cardiac imaging modalities in the diagnosis of CS even when histological data were available.**

Keywords: Cardiac sarcoidosis, Diagnostic imaging, FDG PET, Guidelines, Multicenter registry, Prognosis
Ann Nucl Cardiol 2022: 8 (1): 42–50

Sarcoidosis is a systemic disease characterized by chronic inflammatory reactions together with granuloma formation and subsequent degenerative process localized in any organ throughout the body. Over the past decade, clinical interests in cardiac sarcoidosis (CS) have been increasing along with advances in imaging modalities and perception of

doi: 10.17996/anc.22-00153

1) Cardiology, Hakodate Goryoukaku Hospital, Hakodate, Japan
2) Department of Functional Imaging and Artificial Intelligence, Kanazawa University, Kanazawa, Japan
3) Department of Cardiology, Hokkaido University Hospital, Sapporo, Japan
4) Department of Cardiovascular Medicine, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan
5) Department of Diagnostic Imaging and Nuclear Medicine, Tokyo Woman's Medical University, Tokyo, Japan
6) Department of Cardiology, Hyogo Brain and Heart Center, Himeji, Japan
7) Department of Radiology, Nihon Medical University, Tokyo, Japan
8) Department of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan
9) Department of Radiology, Asahikawa Medical University, Asahikawa, Japan
10) Department of Cardiology, Sapporo Medical University, Sapporo, Japan
11) Department of Cardiology, Fukushima Medical University, Fukushima, Japan
12) Department of Cardiology, Tokyo Medical University, Tokyo, Japan
13) Division of Cardiology, Department of Medicine II, Kansai Medical University, Hirakata, Japan

high mortality risks due to progressive heart failure, lethal arrhythmias and sudden cardiac death (1, 2). The systemic assessment of localized sarcoidosis lesions, including heart, is not necessarily performed sufficiently because of the difficulties in the identification of active inflammatory reactions specific for sarcoidosis and of histological variations of the disease. Recent advances in cardiac imaging modalities have contributed to non-invasive and better diagnostic approaches in CS. In these contexts, the guidelines of Japanese Circulation Society (JCS) on CS (3, 4) were updated, highly valuing the efficacies of cardiac ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and cardiac magnetic resonance imaging (CMR) as major CS criteria. FDG PET imaging has been widely available and allowed an accurate systemic assessment of the disease activity in heart and other organs (5–7). Procedural recommendations on FDG PET were also published to improve the diagnosis reliability of FDG PET (8, 9). Histological assessment using endomyocardial biopsy is still important but the invasive nature of the procedure limits wide-spread use for early and precise diagnosis of CS and for monitoring subsequent treatment with corticosteroids or other immune-suppressants in a clinical setting. Histology of CS is one of minor criteria but not necessarily essential for the diagnosis in the updated JCS guidelines (3, 4). This is probably because the invasive procedure is sometimes difficult to be done safely and appropriately, depending on a clinical condition and necessity at each patient level. Furthermore, earlier data on CS were derived from small cohort studies and it was not revealed how CS patients were diagnosed and managed by using recent advanced imaging modalities, and the prognostic implications were not fully validated.

The Japanese Cardiac Sarcoidosis Prognostic (J-CASP) Study was designed as a multicenter registry of CS patients diagnosed by the updated JCS guidelines on CS. This study tried to reveal recent trends of diagnosis, clinical characteristics, treatment and prognosis of CS and to identify the values of the updated guidelines using retrospective, real-world data from 12 medical centers, focusing particularly on the clinical efficacy of a non-invasive approach with FDG PET at cardiology practice.

Methods

J-CASP study retrospectively compiled each database from 12 Japanese hospitals (Appendix I), initially consisting of consecutive 236 CS patients (Figure 1). The entry criteria for the J-CASP registry were as follows; patients were diagnosed as CS based on the 2015/2016 JCS guidelines criteria (Appendix II) (3, 4) and underwent FDG PET imaging. The definition of CS in the guidelines are as follows; a patient has two or more out of five major criteria (A to E), or has one major criteria and two of three minor criteria (F to H). In this study, 231 of 236 patients finally met the entry criteria but 5 patients without FDG data available were excluded (Figure 1). In addition to FDG data, the following clinical and outcome data were collected; pharmacological and/or non-pharmacological treatments at entry following the titration, and cardiac events such as all-cause of death, including cardiac and non-cardiac death, new hospitalization due to heart failure progression or lethal ventricular arrhythmias, new implantation of cardiovascular electronic device using cardioverter-defibrillator (ICD), device for cardiac resynchronization therapy (CRT) or their combination (cardiac resynchronization therapy-defibrillator: CRTD), and appropriate ICD therapy against lethal ventricular arrhythmias.

FDG PET study

In this registry, FDG PET data were essential for the entry to share the diagnostic trends and efficacy of this modality. ^{18}F-FDG was prepared by in-hospital cyclotron in 6 institutions or delivered from a radiopharmaceutical company. The administration dose of ^{18}F-FDG ranged from 2–7 MBq/kg and was determined in each institution. According to the recommendations for the diagnosis of cardiac sarcoidosis published by the Japanese Society of Nuclear Cardiology (8) and the European Association of Nuclear Medicine and the European Association of Cardiovascular Imaging (9), FDG PET-computed tomography (CT) was performed at a 12- to 20-hour fasting condition (≥18 hours in 72% of the patients) following a dietary control with a low-carbohydrate, high-fat and high-protein diet on the day before the study. The preparation for FDG PET imaging for the diagnosis for CS is critical to visualize FDG uptake specific for CS lesions by sufficiently suppressing physiologic uptake of FDG in normal myocardium (8, 9). Intravenous administration of unfractionated heparin of 50 IU/kg 15 min before application of PET trace was not routinely but additionally performed in four institutions, depending on a patient condition such as an insufficient fasting period less than 12 hours. PET reconstruction was performed with standard methods supplied by vendors, usually with a 3-dimensional ordered subset expectation maximization method, and X-ray CT based attenuation correction was applied.

Cardiac FDG uptake was evaluated visually by a nuclear cardiologist and/or nuclear medicine specialist in each medical center then classified as follows; focal, focal on diffuse, diffuse and no uptake. Focal and focal on diffuse uptakes were defined as a definitive myocardial uptake of FDG in this study (7, 8). The presence or absence of cardiac FDG uptake and the accumulation patterns were finally determined by 3 nuclear medicine physicians (KN and other 2 collaborators) in the core laboratory.

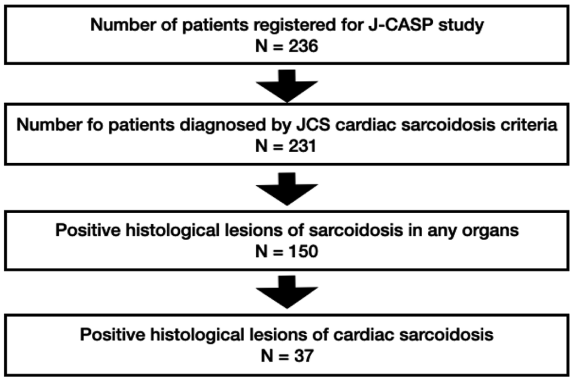

Figure 1 Diagnostic tree in the J-CASP registry based on the guidelines of Japanese Circulation Society (JCS) on cardiac sarcoidosis updated in 2015/2016.

Echocardiographic assessment

Based on the American Society of Echocardiography recommendations, two-dimensional echocardiography was performed and evaluated by experienced echocardiographers with a commercially available ultrasound machine equipped with a 2.5-MHz variable frequency transducer from parasternal long-axis and apical four-, three- and two-chamber views at a left lateral decubitus position. In addition to visual evaluation of regional wall motion and thickness, left ventricular (LV) regional wall motion, end-diastolic diameter (LVDd; mm) and ejection fraction (LVEF, %) were evaluated using a standard technique.

Myocardial perfusion imaging

Myocardial perfusion single-photon emission computed tomography (SPECT) imaging was performed at rest or stress/rest conditions after an intravenous injection of ^{99m}Tc-labeled tetrofosmin or sestamibi (～370–740 MBq) with an electrocardiogram (ECG)-gated mode. A single- or two-head gamma camera equipped with a low-energy, parallel-hole collimator was used to collect data at 180 or 360 degrees using a step and shoot method (3–6-degree/step). Long-axis and short-axis SPECT images were reconstructed then visually and qualitatively evaluated myocardial perfusion abnormality in each hospital.

Histological examination

A histology of myocardial tissue biopsy is defined as one of minor, but not major, criteria for the CS diagnosis in the updated guidelines (Appendix II) (3, 4). This examination was performed when this examination was clinically indispensable, possible and acceptable for a patient. Histology of sarcoidosis was defined typically as non-caseating epithelioid granulomas together with monocyte infiltration, while fibrosis with a non-definitive or mild inflammatory cell infiltrations was considered to be atypical or less active lesions of sarcoidosis. Histology was also used for the differentiation from other cardiac diseases. This study included 150 patients with histology-proven sarcoidosis lesions in any organ. Out 40 patients who had undergone endomyocardial biopsy, 37 patients had histologically-proven CS (Figure 1).

Research ethics and statistics

In accordance with the “Declaration of Helsinki”, the J-CASP study was designed and was approved by each institutional ethical committee after reviewing in 12 participant institutions listed in Appendix I. The registry of each hospital data started under the compliance with data protection regulations. A final CS diagnosis for each patient was established by reviewing all available clinical, imaging and pathological data listed in the updated guidelines (Appendix II) then the pooled database was constructed by medical statistical scientists in the core laboratory.

Continuous variables are shown as mean ± standard deviation. The mean differences between 2 groups and the prevalence of variables were compared using one-way analysis of variance with t test and 2 × 2 contingency table analysis with Pearson statistics, respectively. A p value less than 0.05 was considered statistically significant. All data were analyzed using the SAS statistical package JMP version 12 (SAS Institute, Cary, NC, USA).

Results

J-CASP study analyzed data from 231 patients who were finally confirmed to have CS based on the updated guidelines and cardiac FDG PET dataset (Figure 1); a mean age of 64 years and 65% female and the mean follow-up interval of 45 months (Table 1). Oral glucocorticoid was prescribed in 178 (78%) patients. Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers and/or beta-blocking agents for the heart failure management were used in 125 (55%) and 144 (63%), respectively. Histological lesion of sarcoidosis in any organ was found in 150 (65%) patients and 37 (16%) patients had histologically-proven CS. The remaining 194 patients therefore were diagnosed by the other criteria in the guideline (Appendix II, Figure 1).

A further analysis was performed by dividing CS patients into two groups; histologically-proven CS and clinically-diagnosed CS groups (Table 1). The histological CS group more frequently took oral glucocorticoid and beta-blocking agents for the heart failure management and tended to use angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers than did the clinical group. Cardiovascular electronic device was used in 53 (23%) patients (34 for ICD and 19 for CRTD) at entry identically in both groups. Compared to the clinical CS group, the histological CS group had more reduced LVEF (49 ± 16 versus 40 ± 11 %, P=0.0011) but had nearly identical LVDd (52 ± 9 versus 55 ± 9 mm, P=0.062), respectively. Table 2 compares the prevalence of major and minor criteria other than histology for the diagnosis of CS

Table 1 Clinical characteristics in 231 patients at entry

	Total	Histology-proven CS	Clinically diagnosed CS	P-value
Number	231	37 (35%)	194 (65%)	
Age (years old)	64 ± 11	61 ± 9	64 ± 11	0.11
Gender (female)	150 (65%)	24 (65%)	126 (65%)	0.99
Follow-up period (months)	45 ± 33	52 ± 27	44 ± 33	0.20
LVEF (%)	47 ± 15	40 ± 11	49 ± 16	0.0011
Medications at entry				
Glucocorticoids	178 (78%)	35/36 (97%)	143/192 (74%)	0.0025
ACE-I/ARB	125 (55%)	25/36 (69%)	100/192 (52%)	0.055
β-blocker	144 (63%)	30/36 (83%)	114/193 (59%)	0.0057
Other anti-arrhythmic agent	46 (20%)	10/36 (28%)	36/192 (19%)	0.22
Implanted electronic device at entry	53 (23%)	11 (30%)	42 (22%)	0.16
ICD	34 (15%)	6 (16%)	29 (15%)	
CRT	0 (0%)	0 (0%)	0 (0%)	
CRTD	19 (8%)	5 (14%)	13 (7%)	

Values are shown as mean ± one standard deviation. ACE-I: angiotensin-converting enzyme inhibitor, ARB: angiotensin-receptor blocker, CRT: cardiac resynchronization therapy, CRTD: cardiac resynchronization therapy-defibrillator, CS: cardiac sarcoidosis, ICD: implantable cardioverter-defibrillator, LVEF: left ventricular ejection fraction.

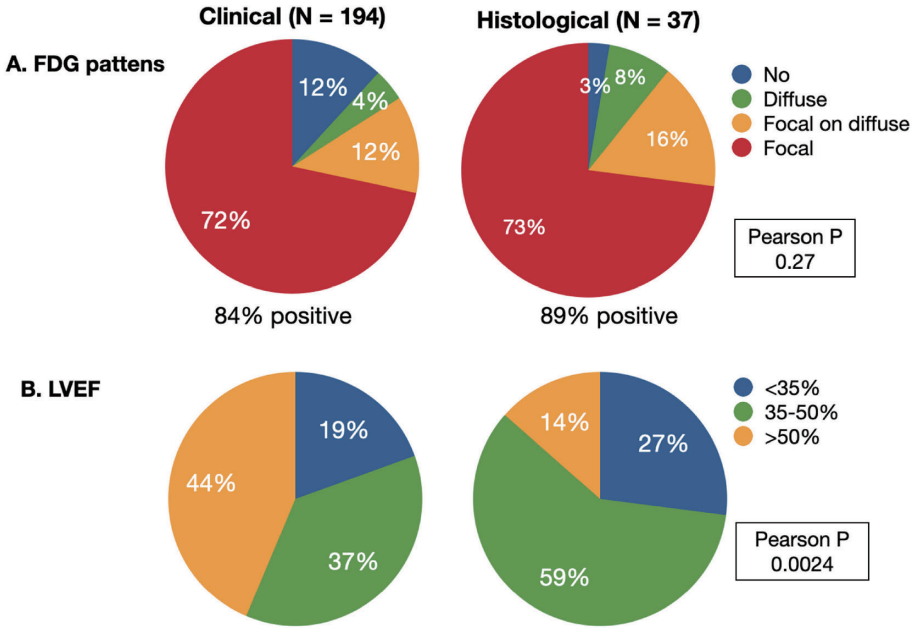

Figure 2 Distributions of myocardial FDG uptake patterns and ranges of left ventricular ejection fraction (LVEF).

between the groups. A high positivity of cardiac FDG uptake was observed identically in the clinical and histological CS groups (83% versus 89%, P=0.38) together with the similar uptake patterns; focal and focal on diffuse patterns were 72% and 12% for the clinically-diagnosed group and 73% and 16% for the histology-proven group, respectively (Figure 2A). There was no significant difference in the manifestations of delayed gadolinium enhancement in CMR (59% versus 66%, P=0.44), high-grade ECG abnormalities (68% versus 56%, P=0.18) or abnormal wall thinning (65% versus 60%, P=0.56) between the histology-proven and clinically-diagnosed CS groups, respectively. The histologically-proven group more frequently had LVEF less than 50% or regional wall motion abnormality (Table 2 and Figure 2B), myocardial perfusion SPECT abnormality and low-grade ECG abnormalities, but less frequently had positive FDG uptake in lymph mode than

Table 2 Prevalence of the major and minor criteria based on the Japanese Circulation Society guidelines on cardiac sarcoidosis updated in 2015/2016 in the histology-proven and clinically diagnosed cardiac sarcoidosis groups

	Histology-proven CS (n=37)	Clinically diagnosed CS (n=194)	P-value
Major criteria			
A. ECG abnormality[*1]	25 (68%)	108 (56%)	0.18
B. Abnormal wall thickness in IVS /free wall[*2]	24 (65%)	116 (60%)	0.56
C. LVEF <50% or regional wall motion abnormality[*2]	34 (92%)	132 (68%)	0.003
D. Positive ^{18}F-FDG findings in heart	33 (89%)	162 (83%)	0.40
E. Delayed enhancement on Gd-enhanced CMR	22 (59%)	128 (66%)	0.44
Minor criteria			
F. Low-grade ECG abnormality[*3]	31 (84%)	122 (63%)	0.014
G. Myocardial perfusion defect on SPECT	25 (68%)	89 (46%)	0.016

*1. High-grade AV block (including complete AV block) or fatal ventricular arrhythmia (e.g., sustained VT and VF).
*2. Echocardiographic findings of basal thinning of the ventricular septum (IVS) or abnormal ventricular wall anatomy such as ventricular aneurysm, regional wall thickening or motion abnormality.
*3. Ventricular arrhythmias such as non-sustained VT, multifocal or frequent premature ventricular contraction (PVC), bundle branch block, axis deviation or abnormal Q waves.
AV: atrioventricular, CMR: cardiac magnetic resonance imaging, CS: cardiac sarcoidosis, ECG: electrocardiogram, FDG: fluorodeoxyglucose, Gd: gadolinium, LVEF: left ventricular ejection fraction, SPECT: single-photon emission computed tomography, VF: ventricular fibrillation, VT: ventricular tachycardia.

Table 3 Outcomes in the histology-proven and clinically diagnosed CS groups during a follow-up

	Histology-proven CS (n=37)	Clinically diagnosed CS (n=194)	P-value
All-cause mortality	2 (5%)	7 (4%)	0.60
Cardiac and non-cardiac death			0.71
Cardiac / non-cardiac death	1 (3%) /1 (3%)	2 (1%) / 5 (3%)	
New hospitalization due to HF progression	6 (16%)	26 (13%)	0.19
New hospitalization due to LVA	6 (16%)	17 (9%)	0.17
New implantation of electronic device	14 (38%)	28 (14%)	0.0007
ICD/CRT/CRTD	5 (14%) /0/9 (24%)	12 (6%) /1(0.5%) /15 (8%)	
Appropriate ICD treatment against LVA	5 (14%)	7 (4%)	0.013

CRT: cardiac resynchronization therapy, CRTD: cardiac resynchronization therapy-defibrillator, CS: cardiac sarcoidosis, HF: heart failure, ICD: implantable cardioverter-defibrillator, LVA: lethal ventricular arrhythmias.

did the clinically diagnosed group: 34 (92%) versus 132 (68%), P=0.003; 25 (68%) versus 89 (46%), P=0.016; and 31 (84%) versus 122 (63%), P=0.014; and 19 (51%) versus 149 (77%), P=0.001; respectively. During a 45-month interval, the histology-proven group more frequently underwent appropriate ICD treatment against lethal arrhythmic events (14% versus 4%, P=0.013) and new electronic device implantation (38% versus 14%, P＝0.007) than did clinically-diagnosed group, respectively (Table 3). There, however, was no difference in all-cause or cardiac mortality or new hospitalization due to heart failure progression between the groups. Figure 3 compares positive rates of myocardial ^{18}F-FDG uptake between groups with and without reduced LVEF in histology-proven and clinically diagnosed cardiac sarcoidosis patients and between groups with and without cardiac electronic device implantation. Although histologically diagnosed CS patients without reduced LVEF tended to have a greater positive ^{18}F-FDG uptake (94%) than others, there was no significant difference in the positive rate between them.

Discussion

The J-CASP registry revealed the diagnostic and prognostic trends of 231 CS patients diagnosed by the CS guidelines updated by using advanced cardiac imaging and is likely to support the effective diagnostic performance of the non-invasive diagnostic approach with FDG PET.

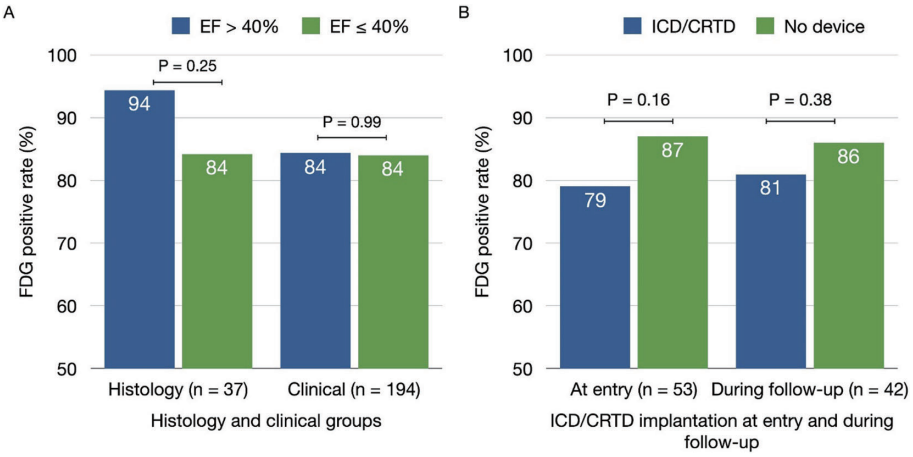

Figure 3 Comparison of positive rates of myocardial ^{18}F-FDG uptake between groups with and without LVEF of 40% or less in histology-proven and clinically diagnosed cardiac sarcoidosis patients (A) and between groups with and without cardiac electronic device implantation at entry or newly during a follow-up (B).

Clinical implications

This study enrolled 231 patients in whom FDG PET data were available, including 150 patients who had sarcoidosis histology in any organ and 37 with myocardial histology compatible with CS. A histological evidence for CS is still a gold standard. In the updated guidelines, however, histology is defined as one of minor criteria and is not necessarily mandatory for the diagnosis when patients meet the major and other minor diagnostic criteria (Appendix II) (3, 4). The histology-proven and clinically diagnosed CS groups had a similar prevalence of the major criteria and identical findings on positivity and uptake patterns of FDG and delayed gadolinium-enhancement in myocardium. The high positivities of cardiac FDG uptake (89% for the histological CS and 83% for the clinical CS), indicate the high diagnostic reliability of this method and the updated guidelines even when cardiac histology is not available. Besides the invasiveness of endomyocardial biopsy, a histological finding is sometimes non-specific or non-diagnostic, probably depending on an activity and severity of the disease and on technical issues such as a biopsy site, resulting in a limited clinical use and a low diagnostic accuracy (10). The non-invasive approach using FDG PET study has great advantages in terms of the safety, ability of systemic assessment, repeatability and easy access at clinical practice to the invasive one. Thus, the non-invasive diagnostic strategy of the updated guidelines in combination with recent cardiac modalities has a clinically reliable diagnostic performance, enhancing clinicians' opportunity and ability to identify CS patients more precisely.

There was a lack of data using a large cohort of CS patients on cardiac complications, diagnostic values of recent cardiac imaging modalities, advanced implantable electronic devices, and prognostic values of the recently updated guidelines. Identification of life-threatening arrhythmias is one of important clinical issues in CS patients not only for an early detection of cardiac involvement of sarcoidosis but also for the management throughout the clinical course (1, 2). The histology-proven group had more increased lethal arrhythmic events than did clinical CS group, while histologically diagnosed CS patients without reduced LVEF tended to have a greater positive ^{18}F-FDG rate than did those without. There, however, was no significant difference in a positive rate of myocardial ^{18}F-FDG uptake between groups with and without reduced LVEF or between groups with and without cardiac electronic device implantation. Thus, a positivity itself of myocardial ^{18}F-FDG uptake is not necessarily related closely to LV dysfunction or to cardiac electronic device treatment. Nevertheless, it is likely that cardiac ^{18}F-FDG PET imaging can identify active CS lesion prior to manifestation of LV dysfunction or independently of the present or future necessity of cardiac electronic device treatment due to advanced heart failure and/or lethal arrhythmias.

The increased arrhythmic events in the histology-proven group may be related to depressed cardiac function but is possibly elucidated by the selection bias. The endomyocardial biopsy may have been more likely to be indicated for patients at high clinical risks necessary for aggressive treatment with drugs and implantable cardiovascular electronic devices. The histology-proven and clinically diagnosed CS groups had nearly identical over-all and cardiac mortalities. From these findings, the aggressive treatment effectively might have functioned in the histology-proven group, reducing the mortality to the level at which the clinically-diagnosed group had. In addition, the non-invasive diagnostic approach is likely to identify CS patients without a significant underestimation of cardiac mortality risks when compared to the invasive approach using endomyocardial biopsy.

FDG PET study

Irrespective of myocardial histology data available, a high prevalence of cardiac FDG positivity was demonstrated in this population, indicating the high diagnostic performance of cardiac FDG PET study and non-invasive diagnostic approach based on the updated CS guidelines. Cardiac FDG uptake in patients with suspected or known sarcoidosis is presumed to represent active inflammation in myocardium necessary for anti-inflammatory or immunosuppressive drug treatment (11–13). In this study, the FDG positivity in lymph mode in the histologically-proven group was less frequent than that in the clinically diagnosed group. Besides the selection bias, this study cannot precisely elucidate reasons of the different rate in the positive FDG findings between the groups. Nevertheless, several clinical speculations can be offered. First, more initiative diagnostic approach using myocardial biopsy may have contributed to earlier detection of FDG-positive sarcoidosis lesion prior to systemic involvement of sarcoidosis, including lymph nodes, during the disease process. Second, there may be some patient group which is more likely to have cardiac involvement than that in lymph node. This possibility is also supported by the presence of isolated cardiac sarcoidosis. When compared to lymph node involvement, excluding bilateral swelling in hilar lymph nodes observed in patients with typical lung sarcoidosis, cardiac involvement may be more easily suspected clinically due to symptoms, arrhythmias or cardiac dysfunction. Thus, it is important to recognize not only the possible discrepant manifestation between cardiac and non-cardiac involvement of sarcoidosis lesion but also the diagnostic necessity of FDG imaging for systemic screening of sarcoidosis lesion independently of biopsy approach.

It is important to control carbon-hydrate intake and a blood sugar level before FDG PET study to suppress a physiological cardiac uptake of FDG as recommended previously (8, 9). In this study, 3 nuclear medicine specialists in the core laboratory visually evaluated cardiac FDG uptake by differentiating from non-cardiac, non-specific or physiological FDG uptake and identified a focal or focal on diffuse pattern of cardiac FDG uptake as positive (7, 8). Because of the retrospective nature of this study, cardiac FDG uptake was not quantitatively assessed using a standardized uptake value (SUV). Although SUV could be a biomarker of active inflammations in cardiac sarcoidosis lesions, cardiac SUV metrics is still controversial and has to be carefully interpreted. This is because the value per se is technically changeable depending on PET scanner, imaging protocol and reconstruction methods used, and because the cut-off value specific for CS and reproducibility are not sufficiently validated to correlate with the underlying pathophysiological and inflammatory intensity (9). In a multicenter study using a cardiac imaging modality, it is critical to optimize standardization of procedures and image interpretations.

CMR is another valuable tool for the diagnosis and prognostication of CS patients (12–14). This method may be more accessible and understandable for clinicians. This study, however, was not designed to separately determine the diagnostic and prognostic values by comparing with cardiac FDG uptake. There was no significant different in the positive rates of cardiac FDG uptake and delayed gadolinium-enhancement between the histology-proven and clinically diagnosed groups. Compared to the high positivity of cardiac FDG uptake in 195 (84%) patients, however, delayed gadolinium-enhancement was limited to 150 (65%) of CS patients. The difference in positivity between the imaging studies can be partially elucidated by the nature of the observational study design, entry criteria and patient population in this study. Gadolinium-enhancement per se reflects fibrotic lesions or degenerative process on the way to an inactive stage of sarcoidosis and the diagnostic value therefore highly depends on the etiology and activity of inflammatory reactions. In contrast, FDG accumulates in active inflammatory lesions and is changeable in response to immunosuppressive therapy. Thus, cardiac FDG PET and CMR can identify different pathological backgrounds of CS, indicating that not only the appropriate selection but also the combined use of the imaging techniques can contribute complementarily to non-invasive diagnosis and staging of the disease, to monitoring clinical course and response to treatments, and probably to predicting future outcomes in CS patients (14–16).

Limitations

The J-CASP study is still under way, and further detailed analysis and follow-up study are desirable to answer clinical questions unresolved here. This study retrospectively analyzed the pooled database consisting of 231 CS patients finally registered in the core laboratory. Despite the relatively large volume of CS patients, selection bias was not completely ruled out. Because of the study design, this non-interventional, observational study did not evaluate therapeutic effects of drugs used. It is still undetermined how cardiac FDG uptake assessed by uptake patterns or SUV can be a therapeutic target and a prognostic biomarker following immunosuppressive therapy specific for CS (11–13). The management of CS patients is generally complex and often requires a multidisciplinary approach, depending on the disease activity and severity of cardiac complications. Because histology has not only the importance but also limitations in the clinical setting (10, 14–16), a non-invasive approach in combination with cardiac FDG PET and/or CMR is expected to further contribute to the early and precise diagnosis and comprehensive management in patients with suspected or known CS. In

addition to economic evaluation, it is desirable to develop a more effective, acceptable non-invasive diagnostic strategy with a serial FDG PET protocol and to further update the CS guidelines to help clinicians optimize CS patient care at a multimodality era. A future prospective interventional study is also required to guide best practice how therapeutic strategy, including novel agents for immunosuppression and heart failure management, can improve clinical outcomes in relation to the risk-stratification using advanced cardiac imagings.

Conclusions

The J-CASP registry consisting of 231 CS patients revealed the nearly identical over-all and cardiac mortalities and manifestations of cardiac FDG uptake and delayed gadolinium enhancement in the histology-proven and clinically diagnosed CS groups. The findings support acceptable clinical efficacies of the updated CS guidelines and the rationale behind the non-invasive diagnostic strategy using advanced cardiac imaging modalities, particularly FDG PET, even if cardiac histology cannot be obtained.

Acknowledgments

The authors are particularly grateful to the staff of each nuclear medicine laboratory in the 12 participant hospitals, for their technical and clinical assistance. The authors also sincerely thank Shitaro Saito, MD and Zhuoqing Chen, MD in the Department of Nuclear Medicine (the core laboratory of the J-CASP study), Kanazawa University, Kanazawa, Japan, for their collaboration in the assessment of all the FDG PET images.

Sources of funding

None.

Conflicts of interest

None.

Reprint requests and correspondence:
Tomoaki Nakata, MD, PhD
Cardiology, Hakodate Goryoukaku Hospital, Hakodate, Japan
Clinical associate professor, Sapporo Medical University
Hakodate 040-8611, Hokkaido, JAPAN
E-mail: tnakata@sapmed.ac.jp

References

1. Okada DR, Smith J, Derakhshan A, Gowani Z, Misra S, Berger RD, et al. Ventricular arrhythmias in cardiac sarcoidosis. Circulation 2018; 138: 1253–64.
2. Kazmirczak F, Chen KA, Adabag S, von Wald L, Roukoz H, Benditt DG, et al. Assessment of the 2017 AHA/ACC/HRS guideline recommendations for implantable cardioverter-defibrillator implantation in cardiac sarcoidosis. Circ Arrhythm Electrophysiol 2019; 12: e007488.
3. The Japanese Circulation Society (JCS). Guidelines for the diagnosis and treatment of cardiac sarcoidosis (JCS 2016). Published on February 24, 2017 (https://www.j-circ.or.jp/cms/wp-content/uploads/2020/02/JCS2016_terasaki_h.pdf)
4. Terasaki, F, Yoshinaga K. New guidelines for diagnosis of cardiac sarcoidosis in Japan. Ann Nucl Cardiol 2017; 3: 42–5.
5. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, et al: The use of ^{18}F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. J Nucl Med 2012; 53: 241–8.
6. Genovesi D, Baucknehtt M, Altini C, Popescu CE, Ferro P, Monaco L, et al. The role of positron emission tomography in the assessment of cardiac sarcoidosis. Br J Radiol 2019; 92: 20190247.
7. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakaue S, Kamigaki M, et al. Focal uptake on ^{18}F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. Eur Heart J 2005; 26: 1538–43.
8. Kumita S, Yoshinaga K, Miyagawa M, Momose M, Kiso K, Kasai T, et al; Committee for diagnosis of cardiac sarcoidosis using ^{18}F-FDG PET, Japanese Society of Nuclear Cardiology. Recommendations for ^{18}F-fluorodeoxyglucose positron emission tomography imaging for diagnosis of cardiac sarcoidosis—2018 update: Japanese Society of Nuclear Cardiology recommendations. J Nucl Cardiol 2019; 26: 1414–33.
9. Slart RHJA, Glaudemans AWJM, Gheysens O, Lubberink M, Kero T, Dweck MR, et al. Procedural recommendations of cardiac PET/CT imaging: standardization in inflammatory-, infective-, infiltrative-, and innervation- (4Is) related cardiovascular diseases: a joint collaboration of the EACVI and the EANM: summary. Eur Heart J Cardiovasc Imaging 2020; 21: 1320–30.
10. Uemura A, Morimoto S, Hiramitsu S, Kato Y, Ito T, Hishida H. Histologic diagnostic rate of cardiac sarcoidosis: evaluation of endomyocardial biopsies. Am Heart J 1999; 138: 299–302.
11. Chareonthaitawee P, Beanlands RS, Chen W, Dorbala S, Miller EJ, Murthy VL, et al. Joint SNMMI-ASNC expert consensus document on the role of ^{18}F-FDG PET/CT in cardiac sarcoid detection and therapy monitoring. J Nucl Cardiol 2017; 24: 1741–58.
12. Vita T, Okada DR, Veillet-Chowdhury M, Bravo PE, Mullins E, Hulten E, et al. Complementary value of cardiac magnetic resonance imaging and positron emission tomography/computed tomography in the assessment of cardiac sarcoidosis. Circ Cardiovasc Imaging 2018; 11: e007030.
13. Fukushima K, Nagao M, Yamamoto A, Serizawa N, Ishizaki U, Suzuki A, et al. Discrepancy between significant fibrosis and active inflammation in patients with cardiac sarcoidosis: combined and image fusion analysis of cardiac magnetic resonance and ^{18}F fluorodeoxyglucose positron emission tomography. Eur J Hybrid Imaging 2019; 3: 9.
14. Tavora F, Cresswell N, Li L, Ripple M, Solomon C, Burke A. Comparison of necropsy findings in patients with sarcoidosis dying suddenly from cardiac sarcoidosis versus dying

suddenly from other causes. Am J Cardiol 2009; 104: 571–7.
15. Sohn DW, Park JB, Lee SP, Lee SP, Kim HK, Kim YJ. Viewpoints in the diagnosis and treatment of cardiac sarcoidosis: Proposed modification of current guidelines. Clin Cardiol 2018; 41: 1386–94.
16. Hulten E, Agarwal V, Cahill M, Cole G, Vita T, Parrish S, et al. Presence of late gadolinium enhancement by cardiac magnetic resonance among patients with suspected cardiac sarcoidosis is associated with adverse cardiovascular prognosis: A systematic review and meta-analysis. Circ Cardiovasc Imaging 2016; 9: e005001.