

FOCUS ISSUE: CARDIAC SARCOIDOSIS – FROM THE CME SESSION AT 63rd SNMMI ANNUAL MEETING – REVIEW ARTICLE

Japanese Guidelines for Cardiac Sarcoidosis

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Abstract

For patients with sarcoidosis involving organs, those with cardiac lesions have especially poor prognosis. Among sarcoidosis patients, those in Japan have higher rates of cardiac involvement of sarcoidosis (CS) than do those in other countries. Therefore, the Japanese medical community has put great efforts into managing CS patients and has developed research activities. In this regard, the Japanese Ministry of Health & Welfare (JMHW) issued CS diagnostic guidelines in 1993 and these have been widely used around the world. The Japanese Circulation Society updated its nuclear medicine guidelines in 2010 and recommended using nuclear imaging to diagnose CS. In 2012 JMHW approved insurance reimbursement for ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) and since then ¹⁸F-FDG PET has been used in clinical practice for the diagnosis of CS in Japan. In 2014 the Japanese Society of Nuclear Cardiology recommended using ¹⁸F-FDG PET imaging in the diagnosis of CS.

Keywords: Cardiac involvement, Japanese Society of Nuclear Cardiology, Sarcoidosis, Tomography
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Among issues for sarcoidosis patients in Japan is the relatively high incidence of cardiac involvement, similar to the case in Scandinavian countries (1). Cardiac-involvement sarcoidosis (CS) has an extremely poor prognosis, and careful management is required. In this regard, the Japanese medical community has put great effort into the care of CS patients and has done substantial research (2, 3).

Hiraga et al. first published Japanese Ministry of Health and Welfare (JMHW) guidelines for the diagnosis of CS in 1993 (4). These guidelines were modified by the joint committee of the Japan Society of Sarcoidosis and Other Granulomatous Disorders and the Japanese College of Cardiology in 2006 (5).

The Japanese Circulation Society (JCS) updated its guidelines for nuclear cardiology in 2010 (6). These JCS guidelines include indications for the use of nuclear medicines to diagnose CS. In January 2006, the Japanese Ministry of

Health and Welfare was consolidated with the Ministry of Labour and became the Japanese Ministry of Health, Labour and Welfare (JMHLW). The JMHLW has approved ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) for detecting inflammatory myocardial regions in CS (7, 8). So far, Japan is the only country to have approved reimbursement for ¹⁸F-FDG PET in the diagnosis of CS. This JMHLW approval triggered an increase in the use of ¹⁸F-FDG PET for CS diagnosis in clinical settings. The Heart Rhythm Society (HRS) expert consensus on the diagnosis of CS also includes ¹⁸F-FDG PET (9).

Given the JMHLW's approval to fund insurance reimbursement, the Japanese Society of Nuclear Cardiology (JSNC) has decided to develop guidelines regarding the standardization of ¹⁸F-FDG PET procedure, on the assumption that ¹⁸F-FDG PET will be widely used in the diagnosis of CS (10). This

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Table 1 Japanese Guidelines and Recommendations

Name	Date issued	Direction
JMHW clinical guidelines	1993	Diagnosis of cardiac involvement of sarcoidosis Major diagnostic criteria include ⁶⁷ Ga uptake
JCS guidelines for cardiac nuclear medicine (6)	2012	⁶⁷ Ga scintigraphy: Diagnosis and clinical evaluation (Class 2a)
JSNC recommendation for ¹⁸ F-FDG PET for cardiac sarcoidosis (10)	2014	Standard approaches for fasting ¹⁸ F-FDG PET imaging for diagnosis of CS

Table 2 Japanese Ministry of Health, Labour, and Welfare's approval of use of SPECT and PET in nuclear cardiology

Test	Date of approval	Indication
¹⁵ O-labeled gas	1996	Diagnosis of heart disease
¹⁸ F-fluorodeoxyglucose	March 8, 2002	Diagnosis of viability (in case of difficult to diagnosis myocardial viability using myocardial SPECT)
	March 5, 2012 (Additional approval)	Detection of inflammatory myocardial regions in cardiac-involvement sarcoidosis
¹³ N-ammonia	March 5, 2012	Diagnosis of ischemic heart disease when other tests are not able to make diagnosis

review provides an overview of the Japanese guidelines for the diagnosis of CS.

JMHW guidelines for the diagnosis of cardiac sarcoidosis

Guidelines for the diagnosis of cardiac sarcoidosis were first published by Hiraga et al. in 1993 (Table 1) (4). These guidelines were modified by the joint committee of the Japan Society of Sarcoidosis and Other Granulomatous Disorders and the Japanese College of Cardiology in 2006 (Table 1) (5). These modified guidelines stipulate the following: A histopathological or clinical diagnosis of sarcoidosis in organs other than the heart is essential, and the following cases should be diagnosed as cardiac sarcoidosis: 1) cases histopathologically diagnosed as positive for cardiac sarcoidosis on the basis of myocardial biopsy (histopathologically diagnosed group) and 2) cases with clinical findings indicating characteristic cardiac abnormalities including principal and secondary signs and symptoms (clinically diagnosed group) (Table 1 and Table 2). In the histopathologically diagnosed group, the positivity rate for detection of cardiac sarcoidosis may be low owing to sampling errors in myocardial biopsy. Hence, in actual clinical settings, the number of cases in the clinically diagnosed group may be higher than in the histopathologically diagnosed group. Upon diagnosis of cardiac sarcoidosis, it is important to determine the disease activity in order to develop a treatment strategy, assess severity, predict prognosis, and tailor steroid therapy. Nuclear imaging is useful in detecting inflammation. ⁶⁷Gallium (⁶⁷Ga) imaging has been used for this purpose, but ⁶⁷Ga imaging has low diagnostic sensitivity owing to its low image resolution. Given this circumstance, ¹⁸F-FDG PET has been used to diagnose cardiac sarcoidosis.

JCS guidelines for nuclear medicine in the diagnosis of cardiac sarcoidosis

The Japanese Circulation Society (JCS) has issued and updated guidelines for the clinical use of cardiac nuclear medicine since 1991. JCS nuclear cardiology guidelines, similar to ACC/AHA clinical guidelines, aim to facilitate patient management in clinical settings. The most recent update was conducted in 2011 and a digest version was published in 2012 (6). In these JCS guidelines, ⁶⁷Ga has a class 2a indication for diagnosis and clinical evaluation in patients with cardiac sarcoidosis. However, the latest JCS guidelines did not include ¹⁸F-FDG PET for the diagnosis of CS.

JSNC recommendations for ¹⁸F-FDG PET in cardiac sarcoidosis

JMHLW approved the clinical use of ¹⁸F-FDG PET for detection of inflammatory myocardial regions in CS and also approved reimbursement for ¹⁸F-FDG use in 2012 (Table 2) (7, 8). Since the time of this approval, many nuclear medicine physicians, radiologists, and cardiologists have applied ¹⁸F-FDG PET to detect cardiac lesions in CS in clinical settings. However, there has been no standard approach for fasting ¹⁸F-FDG PET imaging to detect CS lesions that includes patient preparation, data acquisition, and image interpretation. In this regard, Dr. Yoshio Ishida chaired the JSNC committee, which aimed to establish a standard approach for ¹⁸F-FDG PET imaging (10). The recommendation addresses mainly 3 areas of concern: patient preparation, data acquisition, and image interpretation. A detailed treatment of each of these subjects is provided by other authors in this issue of *Annals of Nuclear Cardiology* and therefore this article will only briefly

summarize these areas.

Patient preparation: fasting time and diet modification

The most important issue with fasting ^{18}F -FDG PET/computed tomography (CT) imaging for diagnosis of CS is to reduce or remove physiological myocardial ^{18}F -FDG uptake (11). Three different approaches to suppressing physiological ^{18}F -FDG uptake have been employed. Within these approaches, a longer fasting time has been shown to be quite important (12, 13). The JSNC committee realized the importance of a fasting period of longer than 18 hours. However, during our data review, we could find only limited data to support the usefulness of fasting for longer than 18 hours. In this regard, the JSNC recommendation for fasting time was 12 hours. The final meal prior to ^{18}F -FDG administration may also play an important role in modifying cardiac metabolism. A low-carbohydrate diet may simply reduce the glucose energy source to the myocardium and may remove physiological FDG uptake (13, 14). A high-fat meal may be used to shift myocardial metabolism from glucose metabolism to fatty acid metabolism (15). Both approaches may be used to reduce physiological FDG uptake. However, by 2012 only one institution had reported the usefulness of a high-fat meal for fasting ^{18}F -FDG PET imaging. Therefore, the JSNC committee included only the low-carbohydrate diet in its recommendations for ^{18}F -FDG PET preparation.

Another possible approach to reducing physiological ^{18}F -FDG uptake is to use unfractionated heparin. Unfractionated heparin actually increases plasma free fatty acid (FFA) concentration (16) and is believed to shift myocardial metabolism from glucose to fatty acid. However, this possibility has not been proven. Since the first study involving a relatively large population in the detection of CS using ^{18}F -FDG PET used heparin (17), many facilities have used heparin in clinical practice. Heparin has some serious side effects and therefore there are some concerns with using it (18). Therefore, the JSNC committee did not include heparin administration as part of its preferred preparation. Further, the committee issued a precaution regarding heparin use and pointed out the importance of further evaluations in that regard.

^{18}F -FDG data acquisition

Although most of the FDG PET studies for detecting CS used 2D data acquisition, the current PET/CT scanners use 3D data acquisition. Data from 3D acquisition was limited at that time although there were some guidelines for ^{18}F -FDG PET/CT in oncology (19). Based on the previously issued guidelines, the committee recommended an ^{18}F -FDG dose ranging from 111 to 259 MBq (2-5 MBq/kg) for 3D data acquisition.

Image acquisition should begin 60 minutes after FDG administration, similar to the case for ^{18}F -FDG PET viability study (10, 20). Given the importance of cardiac involvement in sarcoidosis, it would be preferable to have cardiac spot scans for up to 10 minutes. Both hands should be raised during data acquisition.

^{18}F -FDG image interpretation

When examining ^{18}F -FDG PET imaging, it is important to consider common sites of cardiac lesions in sarcoidosis. The most common site is the left ventricular free wall followed by the intraventricular septum (21). In cases of conduction abnormality, it is quite important to look at the intraventricular septum (22).

The diagnostic criteria for ^{18}F -FDG PET imaging are based on of the those defined within a previous study by Ishimaru et al. (17). Negative uptake includes no FDG uptake in the myocardium, identified as “none”, and diffuse homogenous ^{18}F -FDG uptake, identified as “diffuse”.

Positive uptake includes a focal uptake pattern. Considering the granuloma formation of sarcoidosis, the focal pattern is consistent with pathophysiology. There were some discussions among committee members about including the “focal and diffuse” pattern showing false positive uptake. There were some concerns that this pattern may be associated with insufficient patient preparation. However, in patients with heart failure, myocardium sometimes shifts from metabolizing predominantly fatty acids to metabolizing predominantly glucose. In this regard, some CS patients with poor LV function may have diffuse ^{18}F -FDG uptake and thus this pattern should be positive.

Conclusions and future directions

This JSNC recommendation is the first to propose a standardized approach to ^{18}F -FDG PET imaging for detecting cardiac sarcoidosis. This recommendation has contributed to CS diagnosis in clinical practice. In this regard, recent JCS cardiac sarcoidosis guidelines included ^{18}F -FDG PET imaging as one of the major diagnostic criteria. In addition, since the publication of this recommendation, a significant amount of data has been published. In light of these recent data, this JSNC recommendation should be updated.

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Conflicts of interest

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