The War Is Opened: PSMA vs. $^{64}CUCL_2$ vs. Choline PET/CT

TO THE EDITOR: I have read with great interest the paper by Piccardo et al. (*1*) and the editorial by Ceci et al. (*2*) recently published in your journal.

After a careful analysis of the published data, some comments seem necessary.

First, a specific ^{18}F-choline acquisition protocol would improve the detection of recurrent prostate cancer, either for prostatic fossae or for lymph nodes. PET acquisition at only 20 min after ^{18}F-choline injection, as reported by the authors (*2*), cannot be considered as a standard. In a recent review, 21 of 29 (72%) studies that focused on ^{18}F-choline PET or PET/CT reported a late (after 60 min) whole-body scan, whereas only 8 of 29 (28%) reported acquisition at 10–15 min after tracer injection (*3*). In our recent experience (*4*) in 75 patients who underwent both an early static and a late whole-body acquisition, we found that in the case of low prostate-specific antigen levels (<2 ng/mL), early ^{18}F-choline PET/CT scans detected recurrent disease in prostatic fossae in 15 subjects. Conversely, late images were positive in only 4 patients. Therefore, in the case of prostatic fossae recurrence, a specific acquisition protocol would be useful to improve the detection rate up to 70%. Furthermore, Oprea-Lager et al. (*5*) reported that a single-time-point SUV measurement 30 min after injection was a reasonable alternative for predicting the enlarged pelvic lymph nodes. However, no dedicated European guidelines are currently available for ^{18}F-choline PET/CT examination.

Second, the authors did not report any data about $^{64}CuCl_2$ acquisition (early; after 4 h; or late, after 24 h) for the interpretation of the images. This information would be useful for the repeatability of the study and also for understanding the correct scheduling of patients.

Third, the comments by Ceci et al. (*2*) are mainly focused on the comparison between $^{64}CuCl_2$ and prostate-specific membrane antigen (PSMA)–based radiopharmaceuticals. Because most of the available data about PSMA-directed PET use ^{68}Ga-PSMA-11—a radiopharmaceutical agent with a urinary excretion—there is a loss of information for prostatic fossae recurrence. A study performed by Uprimny et al. (*6*) reported that when early (after 4–8 min) and late (after 60 min) ^{68}Ga-PSMA-11 PET/CT were used, an early ^{68}Ga-PSMA-11 scan was able to identify the presence of prostatic fossae recurrence in 50 patients, with a gain of detection rate more than 50% than late acquisition. Again, the acquisition protocol is useful for the correct interpretation of PET/CT findings.

In our opinion, the comparison between $^{64}CuCl_2$ and ^{68}Ga-PSMA-11 or ^{18}F-fluciclovine is mandatory, however:

- A specific endpoint should be drawn, in order to assess the impact on the patients' management and consequent survival rather than only detection rate.
- A final pathology as a gold standard should be recommended in order to solve the problematic gap between imaging and the pure biochemical recurrence and to prove the new tracers' reliability. However, it should be recalled that salvage lymph node dissection is still experimental and transrectal ultrasound–guided biopsy of the vescico-urethral anastomosis is no longer recommended by the European Association Urology (EAU) and National Institute for Health and Care Excellence (NICE) guidelines.

However, although $^{64}CuCl_2$ has a long half-life, its image resolution is significantly better than that of ^{11}C and ^{68}Ga (*7*). This characteristic has an important benefit in the identification of small areas of prostate cancer recurrence, particularly in the case of local recurrence after radical prostatectomy.

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Role of ^{18}F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring: Addition to the Expert Consensus

TO THE EDITOR: Although the joint Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the American Society of Nuclear Cardiology (ASNC) expert consensus (*1*) document has provided a comprehensive review on the role of ^{18}F-FDG PET/CT in cardiac sarcoid (CS) detection and therapy monitoring, we would like to highlight a few additional points that would warrant the authors' consideration.

Regarding patient preparation for the CS ^{18}F-FDG PET/CT, the expert panel recommended the preferred option being for the patient to consume at least 2 high-fat (>35 g), low-carbohydrate (<3 g) meals the day before the study and then fast for at least 4–12 h. We adopted a 72-h high-fat, high-protein, very-low-carbohydrate (HFHPVLC) diet preparation, with satisfying results (*2*). Our

study included 215 ^{18}F-FDG PET/CT tests from 207 patients with biopsy-proven sarcoidosis and clinical suspicion for CS between July 2014 and December 2015, the largest patient cohort to undergo CS ^{18}F-FDG PET/CT so far. On the basis of diet preparation protocol, we categorized the patients into 2 groups. Group 1 patients had a 24-h or less pre–^{18}F-FDG PET/CT HFHPVLC diet, whereas group 2 patients had a 72-h HFHPVLC diet before ^{18}F-FDG PET/CT. All patients had a HFHPVLC breakfast 4 h before scheduled ^{18}F-FDG PET/CT. We found that the 72-h HFHPVLC diet protocol achieved complete suppression of physiologic myocardial ^{18}F-FDG uptake in 86.7% (167/193) of patients, with only 3.6% (7/193) of patients with failed suppression and indeterminate for CS. In contrast, only 50% (6/12) of patients in group 1 had complete suppression of myocardial ^{18}F-FDG uptake and were negative for CS, and 41.7% of patients (5/12) had failed suppression and indeterminate for CS. The high incidence of failed suppression in the 24-h HFHPVLC diet protocol is in keeping with the authors' statement that "nonspecific myocardial uptake may be observed in up to 20% of patients despite various dietary preparations." Because our data showed that the 72-h HFHPVLC diet protocol surpassed the 24-h diet preparation approach, with high patient compliance and physician stratifications, we would recommend and encourage the authors and other investigators to verify this simple and straightforward protocol in their practices.

As for interpretation for cardiac PET, the authors prefer to have both rest myocardial perfusion study and cardiac ^{18}F-FDG PET. We agree that a concurrent rest myocardial perfusion study can somewhat increase diagnosis confidence in CS (*3*). However, decreased perfusion at rest is not specific nor sensitive for CS diagnosis; many CS can have normal or even increased perfusion. Our experience also showed that, with optimal suppression of physiologic myocardial ^{18}F-FDG uptake, the rest myocardial perfusion study or reorientation/reconstruction of cardiac ^{18}F-FDG PET/CT images might not be needed (*4,5*). The authors recommended interpretation of concurrent myocardial perfusion and ^{18}F-FDG PET images mainly based on the data from Brigham and Women's Hospital, which included 118 patients over a 5-y period who underwent <24-h HFHPVLC diet followed by a fast of at least 3 h before ^{18}F-FDG PET and ^{82}Rb myocardial perfusion PET (*6*). As we commented about their data before (*2*), the diffuse myocardial ^{18}F-FDG uptake that was defined as normal perfusion was probably due to failed suppression, thus indeterminate for CS. The focal on diffuse pattern of myocardial ^{18}F-FDG uptake, which was interpreted by the Brigham and Women's Hospital group as areas of inability to suppress ^{18}F-FDG from normal myocardium versus diffuse inflammation, was instead categorized into abnormal metabolism and PET-positive. This description actually reflected the nature of indeterminate for CS in this focal on diffuse pattern. We think the focal increased tracer uptake in the focal on diffuse pattern is mainly due to physiologic papillary muscular uptake, rather than CS. Thus the focal on diffuse pattern is probably due to suboptimal suppression and should be counted as diffuse and nondiagnostic for CS. In our study (*2*), all the patients underwent the same ^{18}F-FDG PET/CT imaging protocol on the same scanner with a time span of 1.5 y. We classified cardiac ^{18}F-FDG uptake as none and ring-like diffuse at base (negative for CS); focal (positive for CS); and diffuse (indeterminate for CS). We found that this classification renders CS ^{18}F-FDG PET/CT interpretation very straightforward and easy to follow, with high interobserver agreement among senior radiology residents and radiology and nuclear medicine attending physicians. In our study, all the positive CS had concordant cardiac MRI findings wherever MRI was available, and both positive and negative CS had consistent results on available follow-up ^{18}F-FDG PET/CT scans. Furthermore, the indeterminate rate (including both focal on diffuse and diffuse patterns) is very low in the 72-h HFHPVLC diet group. On a different note, we want to echo the authors' opinion that, given the high incidence of coexisting thoracic and extrathoracic sarcoidosis, the field of view of ^{18}F-FDG PET/CT should be from the skull base to thigh, or at least include both chest and abdominal organs to better evaluate the extent of sarcoidosis disease (*7*).

We appreciate the joint SNMMI–ASNC expert panel's comprehensive review. Nonetheless, imaging of CS remains challenging. Long-term prospective multicenter clinical trials are required to further validate the optimal PET imaging protocol.

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Reply: Role of ^{18}F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring: Addition to the Expert Consensus

We thank Dr. Lu and Dr. Sweiss for their comments on the "Joint SNMMI–ASNC Expert Consensus Document on the Role of ^{18}F-FDG PET/CT in Cardiac Sarcoid Detection and Therapy Monitoring" (*1*). In their letter to the editor (*2*), the authors describe a 72-h high-fat, high-protein, very low-carbohydrate (HFHPVLC) diet (*3*) for patient preparation before ^{18}F-FDG PET/CT for cardiac sarcoidosis and recommend that others verify what they consider to be a simple and straightforward protocol. They cite their experience and publication that included 12 scans with a 24-h or less HFHPVLC dietary preparation and 193 scans with a 72-h