The Ongoing Misperception That Labeled Leukocyte Imaging Is Superior to ^{18}F-FDG PET for Diagnosing Prosthetic Joint Infection

TO THE EDITOR: With interest we read the review article by Palestro (*1*) on radionuclide imaging of musculoskeletal infections. Palestro claims that labeled leukocyte imaging is the radionuclide test of choice for diagnosing prosthetic joint infection. On the basis of our longstanding experience, we strongly disagree with this statement and believe it should be rectified.

First, Palestro failed to describe the numerous disadvantages of labeled leukocyte imaging, which include its complexity, high costs, associated potential hazards due to the direct handling of blood products, and considerable radiation burden (*2,3*). ^{18}F-FDG PET imaging is practically superior, because it is routinely available in developed countries, provides a completed examination within 1 h after ^{18}F-FDG administration (rather than 24 h for labeled leukocyte imaging), is safe (lack of pathogens in the final product based on existing Food and Drug Administration records), and provides images with significantly higher spatial resolution than that of conventional planar scans (*2,3*).

Second, evidence-based data indicate that the diagnostic value of ^{18}F-FDG PET is at least equal to that of labeled leukocyte imaging. A systematic review and metaanalysis that was based on 14 studies with a total of 838 lower-extremity prostheses reported ^{18}F-FDG PET to have pooled sensitivity and specificity of 86% and 86%, respectively (95% confidence intervals, 82%–90% and 83%–89%, respectively), for the detection of prosthetic hip or knee joint infection (*4*). Another more recent prospective study, which included the largest number of lower-extremity prostheses so far (n = 221) and had a subgroup comparison with labeled leukocyte/bone marrow imaging (n = 88), reported ^{18}F-FDG PET to have a sensitivity, specificity, positive predictive value, and negative predictive value of 81.8%, 93.1%, 79.4%, and 94.0%, respectively, for hip prostheses and 94.7%, 88.2%, 69.2%, and 98.4%, respectively, for knee prostheses (*5*). In patients who underwent both ^{18}F-FDG PET and labeled leukocyte/bone marrow imaging, there was a trend (P = 0.0625) toward a higher sensitivity for ^{18}F-FDG PET in hip prostheses, whereas other comparisons did not show any significant differences between the two imaging modalities (*5*). Thus, evidence indicates that the diagnostic performance of ^{18}F-FDG PET in detecting infection in painful hip and knee prostheses is sufficiently high for routine clinical application and not inferior to labeled leukocyte imaging. Interestingly, Palestro argues that comparative investigations of ^{18}F-FDG and bone or labeled leukocyte imaging are contradictory. He supports this statement with outdated data that were published by his own research group in 2004 (*6*). That particular study enrolled only 59 patients with lower-extremity prostheses, and images were acquired with a coincidence PET machine. On the basis of suboptimal data generated with this instrument, the authors claimed that ^{18}F-FDG imaging was less accurate than labeled leukocyte/marrow imaging (*6*). By now, it is well established that coincidence PET systems provide images of substantially lower quality than today's standards. Therefore, their claim is totally unjustified. We should mention that recent consensus guidelines do not include leukocyte/bone marrow imaging for detection of infection in painful joints.

In conclusion, ^{18}F-FDG PET, and not labeled leukocyte imaging, should be regarded as the imaging modality of choice for the detection of prosthetic joint infection, as supported by the available evidence and the considerable practical advantages of ^{18}F-FDG PET over conventional methods.

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REPLY: In their letter, Kwee et al. state that, on the basis of practical advantages and available data, ^{18}FDG PET, not labeled leukocyte imaging, should be the imaging test of choice for detecting prosthetic joint infection. There are indeed practical advantages to ^{18}F-FDG, and I addressed them in the article (*1*). These advantages, however, are meaningful only if the performance of ^{18}F-FDG is at least comparable to that of labeled leukocyte imaging. Kwee et al. argue that, on the basis of the results of a metaanalysis and recently published data, ^{18}F-FDG is comparable to labeled leukocyte imaging for diagnosing prosthetic joint infection. A review of the literature, however, reveals rather striking inconsistencies in the results reported for ^{18}F-FDG, both alone and in combination with bone or labeled leukocyte imaging. This is in striking contrast to the consistently excellent results that have been reported for labeled leukocyte/marrow imaging over more than 3 decades. Thus, it is difficult to argue convincingly that ^{18}F-FDG is comparable to, and therefore should replace, labeled leukocyte imaging for diagnosing prosthetic joint infection.

There are some additional points that warrant discussion. As Kwee et al. correctly note, I did not address the disadvantages of labeled leukocyte imaging in the article. I assumed, perhaps mistakenly, that after more than 30 y of publications on labeled leukocyte imaging, it was unnecessary to reiterate the already well-known shortcomings of the procedure and that better use could be made of the allotted space.

Kwee et al. suggest that the issue of contradictory results for ^{18}F-FDG was based on one—in their opinion, flawed—investigation (*2*). To the contrary, contradictory results have been, and continue to be, reported for ^{18}F-FDG alone and in combination with bone or labeled leukocyte imaging. These results, both favorable and unfavorable, were summarized in my article (*1*).

Kwee et al. attribute the poor results of Love et al. (*2*) for ^{18}F-FDG to the use of coincidence detection rather than dedicated PET. A careful review of the literature, however, reveals investigations that used state-of-the-art PET or PET/CT to diagnose prosthetic joint infection, and their results for ^{18}F-FDG were no better, and in some cases were less satisfactory, than the results reported by Love et al. (*1–4*). Consequently, the argument that the data reported by Love et al. (*2*) are invalid, or flawed, because of the imaging device used is not tenable. Furthermore, this investigation was one of the very few in which the final diagnosis, in all cases, was based on histopathologic and microbiologic specimens obtained at the time of surgery (*2*).

Finally, Kwee et al. mention that recent consensus guidelines do not include leukocyte/marrow imaging for detecting prosthetic joint infection. One can presume that these guidelines do not include ^{18}F-FDG either, since Kwee et al. do not address this in their letter. According to the most recent revision of the American College of Radiology Appropriateness Criteria on imaging after total hip arthroplasty, labeled leukocyte/bone marrow imaging is the best imaging test for diagnosing infection (*5*).

In summary, given the inconsistent and at times contradictory results that have been reported for ^{18}F-FDG over more than 15 y of investigation, ^{18}F-FDG—its practical advantages notwithstanding—is not a suitable replacement for labeled leukocyte/marrow imaging for diagnosing prosthetic joint infection. For the moment, labeled leukocyte/marrow imaging is the best imaging test available for this indication.

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PET-Guided Stereotactic Irradiation of Prostate Cancer Lymph Node Metastases

TO THE EDITOR: We read with interest the study by Rauscher et al. reporting data about the short-axis diameter of prostate cancer lymph nodes detected by prostate-specific membrane antigen (PSMA) PET (*1*). The authors suggest that this imaging modality may be helpful for guiding salvage surgery (*1*). Such a paradigm is already being applied in radiation oncology, where noninvasive PET-guided salvage stereotactic body radiotherapy has entered routine clinical practice (*2*). Individual lymph nodes detected by choline or PSMA PET/CT can be irradiated in selected patients with oligometastatic prostate cancer. This avoids many of the risks associated with surgery, as well as the intraoperative challenge of locating a specific node. In keeping with Rauscher et al., our clinical impression was that the nodal metastases being detected with these scans were frequently under the 8- to 10-mm threshold in short-axis diameter used to identify nodes with a higher risk of being pathologic on conventional imaging (*3*). We therefore reviewed the plans of 46 PET-positive prostate cancer nodal metastases treated with salvage stereotactic body radiotherapy, 37 detected by choline and 9 by PSMA PET/CT. The median short axis on CT was 0.9 cm (range, 0.5–2.4 cm) for choline-detected nodes and 0.7 cm (range, 0.7–1.4 cm) for PSMA-detected nodes, with 10 of 37 (27%) and 24 of 37 (65%) choline-detected nodes and 5 of 9 (56%) and 7 of 9 (78%) PSMA-detected nodes having a short axis smaller than 8 and 10 mm, respectively. These results corroborate those of Rauscher et al. and indicate that nodal metastases identified by prostate cancer–specific PET imaging would frequently have been considered normal risk or low risk by size criteria alone (*1*). The median volume of choline- and PSMA-detected nodes was 1.3 cm^3 (range, 0.4–12.6 cm^3) and 0.6 cm^3 (range, 0.4–1.7 cm^3), respectively.

The authors mention the possibility of incorrectly allocating nodal fields in PET and surgical lymphadenectomy. Accurate targeting is also relevant in radiation oncology, especially when treating individual nodes as opposed to nodal regions. For example, if there are neighboring PET-negative nodes, it may not always be possible to differentiate the nodal metastasis on size or morphologic criteria. Therefore, coregistration of the diagnostic PET/CT scan with the radiotherapy-planning CT scan may be used to help identify the target node during treatment planning. In such situations it is important to verify the registration between the PET scan and the low-dose CT scan, to ensure that the region with enhanced uptake on PET corresponds to the correct node on CT and avoid possible misalignment of the PET and planning CT scans. A further challenge with small nodes can be good visualization on the imaging system (e.g., cone-beam CT) that is used to correctly position the node before irradiation. In our experience, if preset cone-beam CT options are not optimal, certain parameters (on the TrueBeam platform; Varian Medical Systems) may be adjusted by the user, improving image quality and facilitating accurate targeting.

Advances in diagnostic imaging are helping to drive new treatment options for patients and are enabling the detection of small metastases, with further reductions in the size threshold being likely (*4*). This is expected to present additional challenges to clinicians and to manufacturers of image-guided radiation therapy platforms that need to be able to accurately treat ever-smaller targets in the body.