J of Nuclear Medicine Technology, first published online November 10, 2017 as doi:10.2967/jnmt.117.198663

Non-oncologic Applications of PET/CT and PET/MR in Musculoskeletal, Orthopedic, and Rheumatologic Imaging: General Considerations, Techniques, and Radiopharmaceuticals

Running title: PET in Musculoskeletal and Rheumatologic Imaging

Authors

Ali Gholamrezanezhad[1, 2]

Kyle Basques[3]

Ali Batouli[4]

Mojtaba Olyaie[4]

George Matcuk[1]

Abass Alavi[5]

Hossein Jadvar[6]

1. Division of Musculoskeletal Imaging. Department of Radiology. Keck School of Medicine. University of Southern California (USC). CA. USA

2. **Corresponding author:** Division of Musculoskeletal Imaging. Department of Radiology. Keck School of Medicine. University of Southern California (USC). 1520 San Pablo Street, Los Angeles, CA 90033. Phone: +1(443)839-7134. Email: a.gholamrezanezhad@yahoo.com

3. Division of Musculoskeletal Imaging. Department of Radiology. University Hospitals of Cleveland. Case Western Reserve University. Cleveland. OH. USA.

4. Department of Radiology. Allegheny General Hospital. Pittsburgh. PA. USA.

5. Division of Nuclear Medicine. Department of Radiology. Hospital of the University of Pennsylvania, Philadelphia, PA. USA.

6. Division of Nuclear Medicine. Department of Radiology. Keck School of Medicine. University of Southern California (USC). CA. USA.

Abstract
Positron Emission Tomography (PET) is often underutilized in the field of musculoskeletal imaging, with key reasons including the excellent performance of conventional musculoskeletal MRI, the limited spatial resolution of PET, and the lack of reimbursement for PET for non-oncologic musculoskeletal indications. However, with improvements in PET/CT and PET/MR imaging over the last decade as well as an increased understanding of the pathophysiology of musculoskeletal diseases, there is an emerging potential for PET as a primary or complementary modality in the management of rheumatologic and orthopedic patients. Specific advantages of PET include the convenience of whole body imaging in a single session, the relative resilience of the modality in the imaging of metallic implants compared to CT and MRI, the ability to evaluate deep joints not amenable to palpation, and the potential for improved specificity of diagnosis with novel radiopharmaceuticals. In this review, we discuss multiple radiopharmaceuticals and technical consideration of PET/CT and PET/MRI that can be employed in imaging of non-tumoral bone and soft tissue disorders. Both PET/CT and PET/MR hold significant promise in the field of musculoskeletal imaging, and with further radiopharmaceutical development and clinical research, these hybrid modalities can potentially transform the current management of patients with orthopedic and rheumatologic disease.

Key words: Positron Emission Tomography, PET/CT, PET/MR, Rheumatoid Arthritis, Septic Arthritis, Osteomyelitis, Inflammation, Polymyalgia Rheumatica, FDG

Introduction
Positron emission tomography (PET) was introduced four decades ago and has rapidly become the standard of care for the diagnosis and monitoring of a wide range of diseases, particularly in the field of oncology. In addition, as a metabolic and molecular imaging modality, PET has significantly advanced our understanding of normal human physiology as well as pathophysiology (1, 2). PET is now most commonly used as a hybrid modality, typically combined with computed tomography (CT) or magnetic resonance imaging (MRI) for better anatomic localization and attenuation correction purposes (3, 4, 5).

Despite the widespread application of PET/CT and PET/MR for oncologic purposes, the role of PET imaging in musculoskeletal disorders, especially non-oncologic applications, has not been widely appreciated. PET has traditionally been underutilized in musculoskeletal imaging for several reasons, such as the limited spatial resolution of PET and the excellent performance of musculoskeletal MRI, a modality that does not utilize ionizing radiation. However, with improvements in PET/CT and PET/MR imaging over the last decade as well as increased understanding of the pathophysiology of musculoskeletal diseases,

there is an emerging potential for PET as a primary or complementary modality in the management of rheumatologic and orthopedic patients. In fact, the low metabolic activity of osseous and tendinous structures is an advantage for detecting pathology of skeletal system, because of the low physiologic background activity leading to higher target to background ratio in imaging of these disease processes. In this review, we discuss the technical details as well as different radiopharmaceuticals of PET/CT and PET/MR imaging for the management of non-neoplastic musculoskeletal diseases.

PET Radiopharmaceuticals

PET is a powerful molecular imaging technique in which positron emitting radiotracers are administered to a patient and then subsequent imaging visualizes the in vivo distribution and kinetics of that radiotracer. Multiple PET radiopharmaceuticals have been developed that interact with biological systems, including radiotracers studying glucose, amino acid, and nucleotide metabolism, cellular receptors and transporters, and bone and cell turnover metabolites, among others.

18F-FDG is by far the most common radiotracer used in clinical PET imaging. Its biodistribution follows the pattern of in vivo glucose metabolism, with increased glucose metabolism typically associated with neoplastic and inflammatory pathologies. Increased 18F-FDG uptake is indeed seen in both neoplastic cells as well as cellular elements of inflammation, such as macrophages, fibroblasts, neutrophils, and capillaries (6, 7). 18F-FDG continues to be widely used due to its availability and low cost, as well as the wealth of evidence and years of experience demonstrating its clinical utility. However, 18F-FDG imaging suffers from the disadvantage of relatively limited specificity. While this is a major limitation in the imaging evaluation of neoplastic disorders, probably is not of a major issue in the imaging approach to non-neoplastic disorders of the musculoskeletal system, where the diagnosis of diseases mainly relies on non-imaging clinical and serologic findings. In fact, in these cases, the high sensitivity of 18F-FDG can be an advantage to identify mild and clinically silent stages of the disease.

18F-sodium fluoride (18F-NaF) is an FDA approved positron emitting radiotracer used as a marker of osteoblastic activity. The main advantage of this radiotracer is that its uptake by bone marrow is minimal and the radiotracer activity almost exclusively originates from the cortical bone. Uptake of 18F-NaF in the skeletal system is flow dependent and consists of fast chemisorption on hydroxyapatite crystals, forming fluoroapatite. 18F-NaF PET is a highly sensitive imaging probe for the detection of osseous metastases and other non-neoplastic bone lesions, such as traumatic (Fig. 1) and metabolic pathologies (8). Uptake of 18F-NaF by osteoblastic lesions is up to 10 times higher than uptake by normal bone, leading to excellent image contrast. Contrast is further improved by the fact that 18F-NaF does not bind to plasma protein and thus has fast renal excretion and therefore low background activity. It has been shown that 18F-NaF PET/CT

offers a higher sensitivity than MRI in the detection of osteoblastic bone lesions (9, 10). Combining 18F-NaF PET with MRI is a powerful approach that incorporates the high sensitivity of PET and the robust specificity of MRI for early diagnosis and accurate post-treatment follow-up of osteoblastic lesions (11).

Several other PET radiotracers are being studied for use in the musculoskeletal system. There has been increased interest in developing radiotracers with increased specificity compared to 18F-FDG and 18F-NaF, as well as radiotracers using more short-lived positron emitting radioisotopes that take advantage of newer PET equipment to limit radiation exposure and reduce image acquisition time (12).

- 68Ga-citrate and 68Ga-transferrin were originally used for tumor imaging, but have recently been studied for possible imaging of inflammation and infection in the musculoskeletal system (13). 68Ga has a half-life of 68 minutes, with high blood pool activity and liver and bone uptake, but low soft-tissue activity. It binds to lactoferrin, which is present in high concentrations in neutrophils and abscess fluid as well as in siderophores produced by different infectious microorganisms (12, 14). In clinical studies, these agents have been successful in detecting the infection site as early as 30 minutes post injection, but current protocols allow 60 minutes after injection to reduce background activity and improve image quality. High background activity in the thorax and upper abdomen may interfere with detecting thoracic and upper abdominal lesions; therefore, 68Ga-citrate and 68Ga-transferrin are most useful for lower abdominal and extremity infection sites. Imaging with these 68Ga agents is not only useful for the initial diagnosis of infection, but also for surgical planning, treatment monitoring (Fig. 2), and for differentiating prosthetic infection from aseptic loosening of a prosthesis (15).
- 68Ga-DOTA-Sialic acid-binding immunoglobulin-like lectin-9 (68Ga-Siglec-9) is a PET radiotracer introduced for the assessment of synovitis and in vivo imaging of inflammation. Siglec-9 is a leukocyte ligand of vascular adhesion protein-1 (VAP-1), which, during inflammatory processes, rapidly translocates from the intracellular space to the endothelial surface of cells, including vessels in human rheumatoid synovium (16). This is an important step in the regulation of leukocyte migration to sites of inflammation (20). However, as a PET radiotracer, 68Ga-Siglec-9 is somewhat nonspecific and not only detects vascular adhesion protein-1 in the vasculature at sites of inflammation, but also in cancer tissues (17). 18F-labeling of Siglec-9 peptide has also been performed in the preclinical setting (18, 19).
- 89Zr-labeled rituximab has been introduced as radiotracer for non-invasive B-cell imaging by PET/CT (20). This is a specific radiotracer for B-cell imaging, the CD20+ B-cell count in lymph nodes of subjects underwent 89Zr-rituximab PET imaging correlated positively with quantitative lymph node PET data. B cells are key players in the pathogenesis of autoimmune

inflammatory arthropathies, such as RA and SLE. 89Zr-rituximab has been successfully employed in identifying potential responders prior to treatment (Fig. 3) (20).

- 11C-methionine is used for PET imaging of amino acid metabolism. It was originally utilized to try to distinguish neoplastic from inflammatory lesions (12, 21). However, it was subsequently found to accumulate in both categories of lesions. Currently, the radiotracer is being studied for the imaging of musculoskeletal infectious and inflammatory processes (22). Soft tissue and bone uptake of 11C-methionine is relatively low in the extremities, making it a promising radiotracer for evaluation of limb musculoskeletal infections, particularly in pediatric and adolescent population (12, 23).
- 11C-PK11195 is a radiolabeled form of PK11195, a specific ligand for the peripheral benzodiazepine receptor (PBR), which is highly expressed on activated mononuclear phagocytic cells (12, 24). This radiotracer has primarily been investigated for the diagnosis of neuroinflammation (25), but more recent work has proposed a role in non-neurological inflammation, such as inflammation of vascular structures and periprosthetic soft tissues in animal models (26-27).
- 1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-5-iodouracil (FIAU) has been found to be a substrate for bacterial thymidine kinase (TK). (124)I-FIAU has been tested in humans as an infection imaging radiotracer (28, 29).
- 18F-labeled leukocytes have been shown to be effective in the diagnosis of various infectious and inflammatory pathologies. The underlying mechanism of labeled leukocyte imaging is based on chemotaxis exerted on activated leukocytes by chemo-attractants, resulting in cell-bound radionuclide trafficking from the blood pool compartment to the lesion. The use of 18F labeling is facilitated by the particular avidity of inflammatory cells for 18F-FDG (30, 31).
- Integrin avb3 has been suggested as a target for imaging of angiogenesis, as it is expressed on activated endothelial cells. 18F-galacto-RGD has been introduced as a radiotracer for PET imaging of Integrin avb3 expression. While it is mainly studied for oncologic applications, some authors have suggested that it can be also employed for the evaluation of inflammatory disorders (32).

Several other radiotracers, such as 11C-choline, 11C-tyrosine, and 18F-fluorothymidine have also been studied for PET imaging of musculoskeletal system (32); however, their main applications were study of neoplastic disorders, which is beyond the scope of this review.

Imaging protocol

A detailed discussion of PET/CT and PET/MR imaging protocols is beyond the scope of this manuscript. Generally, when 18F-FDG PET is performed, it is

recommended to image the patient 60 minutes after injection of radiotracer. However, several modifications in imaging protocol have been employed to increase the specificity of 18F-FDG PET for non-oncological indications.

Dual time point PET imaging has been suggested for the diagnosis of osteomyelitis. It has been shown that dual time point imaging with 18F-FDG is more accurate than single time point scanning in the differentiation of benign lesions from malignant neoplastic pathologies (33, 34). Sahlmann et al. demonstrated that, similar to inflammatory processes in other locations, dynamic dual time point 18F-FDG PET elicits a characteristic pattern in chronic osteomyelitis that differentiates it from neoplastic pathologies. In chronic osteomyelitis, the SUV(max) between 30 and 90 minutes post-injection scans remains stable or decreases, with a median decrease of 6%, while in malignant lesions, the SUV(max) and SUV(mean) between 30 and 90 minutes post-injection both increase (33).

Brown et al. also tested this hypothesis on an experimental rabbit model of post-surgical osteomyelitis to distinguish between acute infection and sterile post-surgical inflammation (35). In their study, image acquisition was performed 7 and 14 days after surgical intervention with continuous PET image acquisition for 90 minutes following 18F-FDG administration. However, their findings were not promising and they concluded that in the complicated clinical context of acute post-surgical and post-traumatic inflammation versus infection, the diagnostic accuracy of 18F-FDG PET is limited. This is mainly because of the fact that increased glucose utilization is the main basis of PET imaging and this type of hypermetabolism is generally characteristic of all inflammatory processes, including infectious pathologies, but not specific to any type of them. This conclusion was concordant with what was previously stated by Kälicke et al. in a clinical study on 21 patients with suspected osteomyelitis. They concluded that PET is not able to differentiate between postsurgical reactive changes and further infection in early postoperative phase (36).

Quantitative PET imaging

Quantification of the metabolic data obtained from PET images offers several benefits in the diagnostic management of diseases, including assessment of response to therapy in serial and follow-up imaging. Several methods of quantification have been proposed that are categorized into semiquantitative measures and absolute quantitative analysis. Semiquantitative methods include measures such as standardized uptake value (SUV), corrected SUV for factors such as lean body mass (SUV_{LBM} or SUL), target to background ratio, and other variants. They are routinely used in the daily clinical practice of nuclear medicine as simple, but practical and objective indicators of metabolic activity of the lesion. However,

these semiquantitative measures are prone to inter-reader and intra-reader variability (37).

Absolute quantitative techniques employ various mathematical models on PET data, including nonlinear regression and Patlak-Gjedde graphical analysis and may require dynamic or parametric whole-body PET image acquisition. In dynamic image acquisition, time series of PET data are dynamically acquired, which enables simulation of physiologic processes through tracer kinetic modeling. The models may employ region of interest (ROI)-based kinetic analysis or voxel-based kinetic modeling (37), the detail of which is beyond the scope of this review. More sophisticated techniques for the quantification of PET data have allowed for specialized applications such as static and dynamic 18F-NaF PET quantification of tracer plasma clearance (K(i)) in osteoporosis. Compartmental and non-compartmental machine learning models have already been tested in animal models (38), and there is great potential in utilizing quantitative PET to better understand biologic systems.

PET/CT versus PET/MR

The hybrid modality of PET/CT has become widely used and widely available since its introduction, with major advantages of combining modalities, including improved anatomic localization and better attenuation correction. PET/CT is currently the standard of care for most clinical applications of PET imaging.

Technological advances during the past decade, including development of digital detector technology that is not disturbed by the magnetic field, has allowed the development of PET/MR. This consists of a whole-body MR imaging, such as Dixon sequences, that can now be acquired in a reasonable timeframe. PET/MR, as a hybrid modality, provides several advantages over PET/CT, particularly with respect to evaluation of the musculoskeletal system. For example, the lower ionizing radiation exposure of PET/MR compared with PET/CT is particularly important for pediatric population and young adults who may need repeated follow-up imaging studies for an extended period. In these cases, PET/MR can save patients a significant amount of radiation (1).

More importantly, PET/MR provides higher soft tissue contrast than PET/CT, which is crucial for appropriate diagnosis of ligamentous, tendinous, and muscular pathologies (1, 2). In addition, as MRI with multi-sequence multi-parametric protocoling is usually required for the diagnostic work-up of these soft tissue pathologies, PET/MR can potentially serve as a “one-stop shop” for patient workup, where both a diagnostic MRI of the pertinent anatomy as well as a whole body PET/MR can be performed during the same imaging session.

In some applications, PET/MR can be superior to PET/CT in its more accurate co-registration and better MR imaging–based motion correction of PET data compared to PET/CT (1). Although no head-to-head comparisons of PET/CT and PET/MR have been reported for musculoskeletal applications, currently available PET/MR machines generally provide image quality comparable to PET/CT

(3, 4, 5). In addition, no significant negative effects of the PET hardware on MR image quality and machine functionality have been identified.

However, PET/MR does have some disadvantages in the evaluation of musculoskeletal pathologies compared to PET/CT. For example, PET/CT continues to feature better attenuation correction than PET/MR. PET/CT is also much more widely available and is lower in cost. PET/MR scanners are not only more expensive, but also the image acquisition time is generally longer, which further results in higher cost. MR imaging of extremities also often needs special coils, such as those for knees, wrists, etc. These coils are often an additional expense and third-party coils are not necessarily 'PET-friendly'. Also, some patients have contraindications for MR imaging, including patients with permanent pacemakers, intra-aortic balloon pumps, and left and right ventricular assist devices, while these patients can be safely images by PET/CT.

There are also differences in the quantification of 18F-fluorodeoxyglucose (18F-FDG) uptake/metabolic activity using the measure of Standardized Uptake Value (SUV). While SUV can be used in PET/MR, these values are scanner-dependent and not entirely comparable to the quantitative values obtained from PET/CT. MRI also is relatively weak in the evaluation of cortical bone compared to CT, though newly introduced techniques such as ultra-short TE sequences may help to overcome this. However, such sequences also have their own drawbacks, including artifacts at larger field of view and longer image acquisition time (2, 39, 40). No experience with these sequences on PET/MR has been published and more investigation to confirm the usefulness in PET/MR imaging for musculoskeletal applications is warranted.

Advances in both PET/CT and PET/MR techniques continue to be made. At present, the two are considered comparable for most clinical applications, though evidence is building that PET/MR may be superior for certain applications including the confident diagnosis of osteomyelitis (41). PET/CT remains the more commonly performed exam due to its availability and lower cost (42).

Future Perspectives

Multiple PET radiotracers have been developed with potential applications in the musculoskeletal system, as discussed above. Many of these radiotracers have only been tested in animal models, but there are many promising opportunities for future human clinical trials using agents that have favorable diagnostic performance and safety profiles.

The use of hybrid PET/MR is rapidly evolving in the diagnostic management of different disorders, with the major advantage of combining the morphological information of MRI and functional information of PET (43, 44). PET/MR in the management of musculoskeletal disorders is currently a hot topic for investigation, with scarce reports of its use in non-oncological applications. The combination of 18F-FDG PET or other more specialized radiotracers with novel MRI sequences tailored for the musculoskeletal system raises numerous exciting possibilities.

Conclusion

With the increased investigation of PET in the musculoskeletal system, measuring the diagnostic performance and clinical outcomes of modalities using PET will continue to be of great importance, particularly in the pediatric population, where ionizing radiation exposure will always remain a drawback. Comparisons with competing modalities that use less or no ionizing radiation must be performed to ensure appropriate care.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Andersen KF, Jensen KE, Loft A. PET/MR Imaging in Musculoskeletal Disorders. *PET Clin*. 2016; 11: 453-63.
2. Bashir U, Mallia A, Stirling J, Joemon J, MacKewn J, Charles-Edwards G, et al. PET/MR in Oncological Imaging: State of the Art. *Diagnostics (Basel)*. 2015; 5: 333-57.
3. Giraudo C, Raderer M, Karanikas G, et al. 18F-Fluorodeoxyglucose positron emission tomog- raphy/magnetic resonance in lymphoma: comparison with 18F-fluorodeoxyglucose positron emission tomography/computed tomography and with the addition of magnetic resonance diffusion-weighted imaging. *Invest Radiol*. 2016; 51: 163–9.
4. Platzek I, Beuthien-Baumann B, Langner J, et al. PET/MR for therapy response evaluation in malignant lymphoma: initial experience. *MAGMA*. 2013; 26: 49–55.
5. Platzek I. (18)F-Fluorodeoxyglucose PET/MR Imaging in Lymphoma. *PET Clin*. 2016; 11: 363-73.
6. Kubota K1, Ito K, Morooka M, Minamimoto R, Miyata Y, Yamashita H, Takahashi Y, et al. FDG PET for rheumatoid arthritis: basic considerations and whole-body PET/CT. *Ann N Y Acad Sci*. 2011; 1228: 29-38.
7. Matsui T, Nakata N, Nagai S, Nakatani A, Takahashi M, Momose T, et al. Inflammatory cytokines and hypoxia contribute to 18F-FDG uptake by cells involved in pannus formation in rheumatoid arthritis. *J Nucl Med*. 2009; 50: 920-6.
8. Tarnawska-Pierścińska M, Hołody Ł, Braziewicz J, Królicki L. Bone metastases diagnosis possibilities in studies with the use of 18F-NaF and 18F-FDG. *Nucl Med Rev Cent East Eur*. 2011; 14: 105-8.
9. Pampaloni MH, Nardo L. PET/MR radiotracer beyond ^{18}F-FDG. *PET Clin*. 2014; 9: 345-9.
10. Mosavi F, Johansson S, Sandberg DT, et al. Whole- body diffusion-weighted MRI compared with (18) F-NaF PET/CT for detection of bone metastases in patients with high-risk prostate carcinoma. *AJR Am J Roentgenol*. 2012; 199: 1114–20.

11. Ouvrier MJ, Vignot S, Thariat J. State of the art in nuclear imaging for the diagnosis of bone metastases. *Bull Cancer*. 2013; 100: 1115-24.
12. Nielsen OL, Afzelius P, Bender D, Schønheyder HC, Leifsson PS, Nielsen KM, et al. Comparison of autologous (111)In-leukocytes, (18)F-FDG, (11)C-methionine, (11)C-PK11195 and (68)Ga-citrate for diagnostic nuclear imaging in a juvenile porcine haematogenous staphylococcus aureus osteomyelitis model. *Am J Nucl Med Mol Imaging*. 2015; 5: 169-82.
13. Nanni C, Errani C, Boriani L, Fantini L, Ambrosini V, Boschi S, et al. 68Ga-citrate PET/CT for evaluating patients with infections of the bone: preliminary results. *J Nucl Med*. 2010; 51: 1932-6.
14. Kumar V, Boddeti DK, Evans SG, Angelides S. (68)Ga-Citrate-PET for diagnostic imaging of infection in rats and for intra-abdominal infection in a patient. *Curr Radiopharm*. 2012; 5: 71-5.
15. Kumar V, Boddeti DK. (68)Ga-radiopharmaceuticals for PET imaging of infection and inflammation. *Recent Results Cancer Res*. 2013; 194: 189-219.
16. Virtanen H, Autio A, Siitonen R, Liljenbäck H, Saanijoki T, Lankinen P, et al. 68Ga-DOTA-Siglec-9--a new imaging tool to detect synovitis. *Arthritis Res Ther*. 2015; 17: 308.
17. Aalto K, Autio A, Kiss EA, Elima K, Nymalm Y, Veres TZ, et al. Siglec-9 is a novel leukocyte ligand for vascular adhesion protein-1 and can be used in PET imaging of inflammation and cancer. *Blood*. 2011; 118: 3725-33.
18. Li XG, Autio A, Ahtinen H, Helariutta K, Liljenbäck H, Jalkanen S, et al. Translating the concept of peptide labeling with 5-deoxy-5-[18F]fluororibose into preclinical practice: 18F-labeling of Siglec-9 peptide for PET imaging of inflammation. *Chem Commun (Camb)*. 2013; 49: 3682-4.
19. Li XG, Helariutta K, Roivainen A, Jalkanen S, Knuuti J, Airaksinen AJ. Using 5-deoxy-5-[18F]fluororibose to glycosylate peptides for positron emission tomography. *Nat Protoc*. 2014; 9: 138-45.
20. Bruijnen S, Tsang-A-Sjoe M, Raterman H, Ramwadhdoebe T, Vugts D, van Dongen G, et al. B-cell imaging with zirconium-89 labelled rituximab PET-CT at baseline is associated with therapeutic response 24 weeks after initiation of rituximab treatment in rheumatoid arthritis patients. *Arthritis Res Ther*. 2016; 18: 266.
21. Zhao S, Kuge Y, Kohanawa M, Takahashi T, Zhao Y, Yi M, Kanegae K, Seki K, Tamaki N. Usefulness of 11C-methionine for differentiating tumors from granulomas in experimental rat models: a comparison with 18F-FDG and 18F-FLT. *J Nucl Med*. 2008; 49: 135-41.
22. Roivainen A, Parkkola R, Yli-Kerttula T, Lehikoinen P, Viljanen T, Möttönen T, et al. Use of positron emission tomography with methyl-11C-choline and 2-18F-fluoro-2-deoxy-D-glucose in comparison with magnetic resonance imaging for the assessment of inflammatory proliferation of synovium. *Arthritis Rheum*. 2003; 48: 3077-84.

23. Harris SM, Davis JC, Snyder SE, Butch ER, Vavere AL, Kocak M, Shulkin BL. Evaluation of the biodistribution of 11C-methionine in children and young adults. *J Nucl Med*. 2013; 54: 1902-8.
24. Pugliese F, Gaemperli O, Kinderlerer AR, Lamare F, Shalhoub J, Davies AH, et al. Imaging of vascular inflammation with [11C]-PK11195 and positron emission tomography/computed tomography angiography. *J Am Coll Cardiol*. 2010; 56: 653-61.
25. Cagnin A, Gerhard A, Banati RB. In vivo imaging of neuroinflammation. *Eur Neuropsychopharm*. 2002; 12: 581-6.
26. Pugliese F, Gaemperli O, Kinderlerer AR, Lamare F, Shalhoub J, Davies AH, et al. Imaging of vascular inflammation with [11C]-PK11195 and positron emission tomography/computed tomography angiography. *J Am Coll Cardiol*. 2010; 56: 653-61.
27. Ren W, Muzik O, Jackson N, Khoury B, Shi T, Flynn JC, et al. Differentiation of septic and aseptic loosening by PET with both 11C-PK11195 and 18F-FDG in rat models. *Nucl Med Commun*. 2012; 33: 747-56.
28. Bettegowda C, Foss CA, Cheong I, Wang Y, Diaz L, et al. Imaging bacterial infections with radiolabeled 1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-iodouracil. *Proc Natl Acad Sci USA*. 2005; 102: 1145-50.
29. Diaz LA Jr, Foss CA, Thornton K, Nimmagadda S, Endres CJ, Uzuner O, et al. Imaging of musculoskeletal bacterial infections by [124I]FIAU-PET/CT. *PLoS One*. 2007; 2(10): e1007.
30. Dumarey N. Imaging with FDG labeled leukocytes: is it clinically useful? *Q J Nucl Med Mol Imaging*. 2009; 53: 89-94.
31. Rini JN, Palestro CJ. Imaging of infection and inflammation with 18F-FDG-labeled leukocytes. *Q J Nucl Med Mol Imaging*. 2006; 50: 143-6.
32. Al-Ibraheem A, Buck AK, Beer AJ, Herrmann K. Alternative PET Tracers in Musculoskeletal Disease. PET Clin. 2010; 5(3): 363-74.
33. Sahlmann CO, Siefker U, Lehmann K, Meller J. Dual time point 2-[18F]fluoro-2'-deoxyglucose positron emission tomography in chronic bacterial osteomyelitis. *Nucl Med Commun*. 2004; 25: 819-23.
34. Tian R, Su M, Tian Y, Li F, Li L, Kuang A, Zeng J. Dual-time point PET/CT with F-18 FDG for the differentiation of malignant and benign bone lesions. *Skeletal Radiol*. 2009; 38: 451-8.
35. Brown TL, Spencer HJ, Beenken KE, Alpe TL, Bartel TB, Bellamy W, et al. Evaluation of dynamic [18F]-FDG-PET imaging for the detection of acute post-surgical bone infection. *PLoS One*. 2012; 7: e41863.
36. Kälicke T, Schmitz A, Risse JH, Arens S, Keller E, Hansis M, et al. Fluorine-18 fluorodeoxyglucose PET in infectious bone diseases: results of histologically confirmed cases. *Eur J Nucl Med*. 2000; 27: 524-8.
37. Houshmand S, Salavati A, Hess S, Werner TJ, Alavi A, Zaidi H. An update on novel quantitative techniques in the context of evolving whole-body PET imaging. *PET Clin*. 2015; 10: 45-58.

38. Cheng C, Heiss C, Dimitrakopoulou-Strauss A, Govindarajan P, Schlewitz G, Pan L, et al. Evaluation of bone remodeling with (18)F-fluoride and correlation with the glucose metabolism measured by (18)F-FDG in lumbar spine with time in an experimental nude rat model with osteoporosis using dynamic PET-CT. *Am J Nucl Med Mol Imaging*. 2013; 3: 118-28.
39. Chaudhry AA, Gul M, Gould E, Teng M, Baker K, Matthews R. Utility of positron emission tomography-magnetic resonance imaging in musculoskeletal imaging. *World J Radiol*. 2016; 8: 268-74.
40. Quick HH. Integrated PET/MR. J Magn Reson Imaging. 2014; 39: 243-58.
41. Signore A, Glaudemans AWJM, Gheysens O, Lauri C, Catalano OA. Nuclear Medicine Imaging in Pediatric Infection or Chronic Inflammatory Diseases. *Semin Nucl Med*. 2017; 47(3): 286-303.
42. Gholamrezanezhad A, Chirindel A, Subramaniam R. Assessment of Response to Therapy. In: PET-CT and PET-MRI in Oncology. A Practical Guide. Springer Science & Business Media (Heidelberg, Germany). 2012: 279-322. DOI: 10.1007/978-3-642-01139-9
43. Lee IS, Jin YH, Hong SH, Yang SO. Musculoskeletal applications of PET/MR. *Semin Musculoskelet Radiol*. 2014; 18: 203-16.
44. Chaudhry AA, Gul M, Gould E, Teng M, Baker K, Matthews R. Utility of positron emission tomography-magnetic resonance imaging in musculoskeletal imaging. *World J Radiol*. 2016; 8: 268-74.

Figure legends

Figure 1. A 67-year-old female with bilateral breast cancer underwent 18F-NaF PET/CT for the evaluation of osseous metastasis. There is a focus of intensely increased radiotracer uptake involving the right ischiopubic junction (A) corresponding to the healing fracture identified on low dose CT (B).

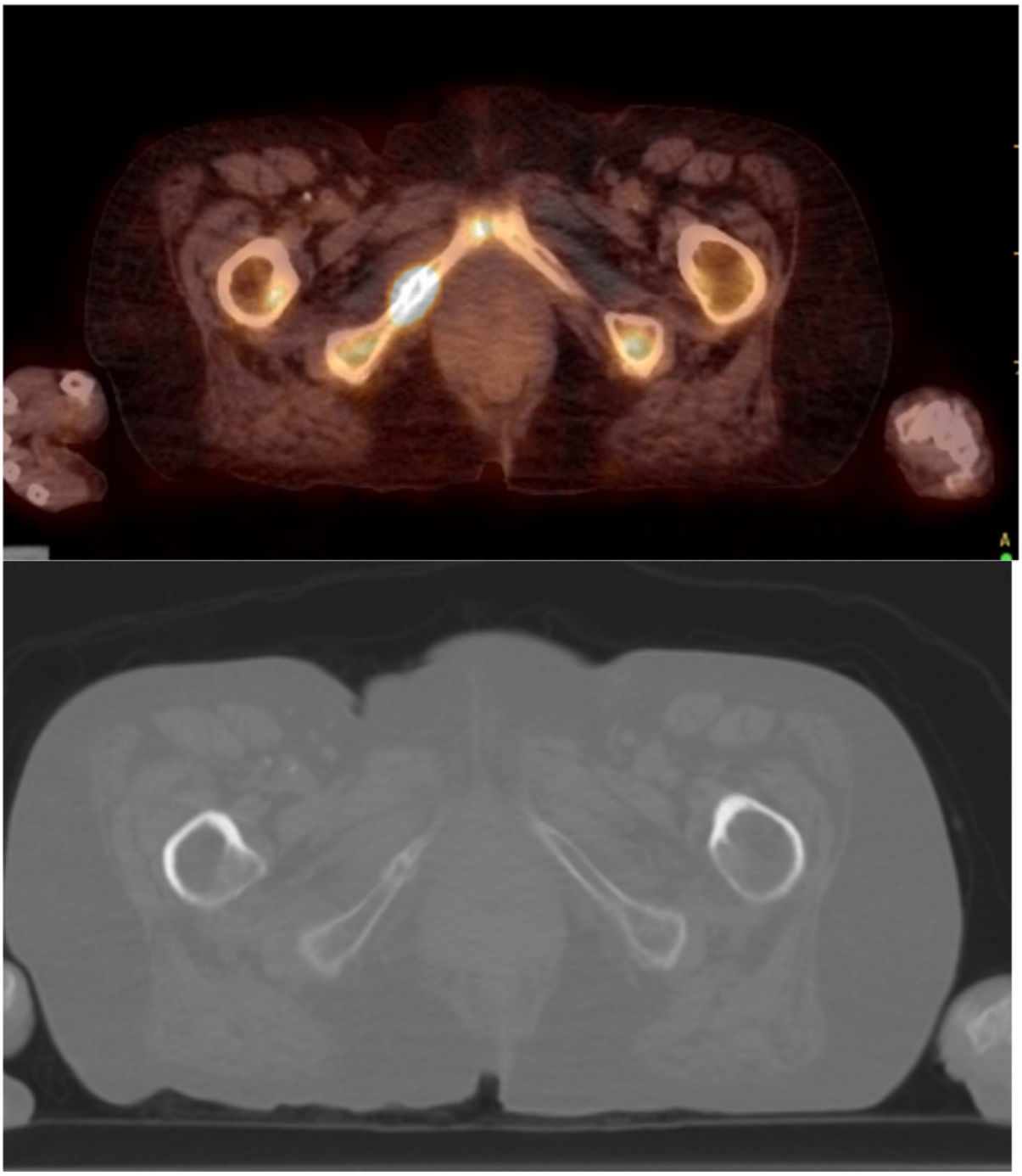

Figure 2. Comparison of pre- and post-treatment 68Ga-citrate PET/CT in a patient with acute osteomyelitis. Pre-therapy PET/CT shows increased radiotracer uptake involving the proximal tibia. Post-therapy PET/CT demonstrate no significant uptake, representing complete response to treatment. (Image reprinted with permission from Journal of Nuclear Medicine. The associated research was originally published in Journal of Nuclear Medicine. Nanni C, Errani C, Boriani L, Fantini L, Ambrosini V, Boschi S, et al. 68Ga-citrate PET/CT for evaluating patients with infections of the bone: preliminary results. J Nucl Med. 2010; 51: 1932–6. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.).

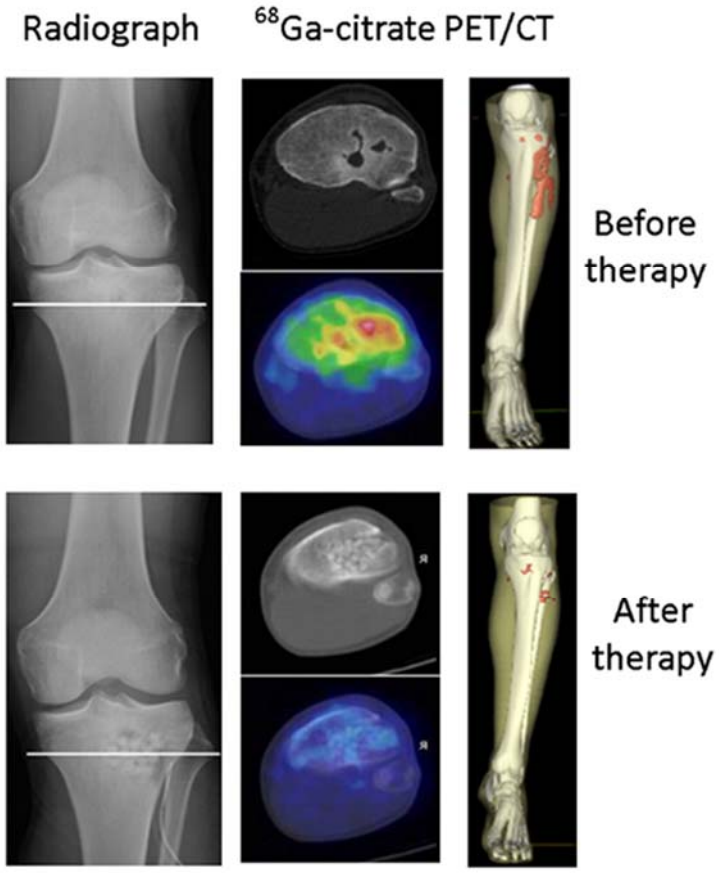

Figure 3. 89Zr-Rituximab PET/CT of a patient with active rheumatoid arthritis, demonstrating increased radiotracer uptake involving the left second metacarpophalyngeal joint as well as the right wrist (Image courtesy of Dr. J. van der Laken, Afdeling Reumatologie, VU Universitair Medisch Centrum, Amsterdam).