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PSMA-Based Detection of Prostate Cancer Bone Lesions with ^{18}F -DCFPyL PET/CT: A Sensitive Alternative to $^{99\text{m}}\text{Tc}$ -MDP Bone Scan and Na^{18}F PET/CT?

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Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy in men.¹ Although a large proportion of patients diagnosed with PCa will be cured by definitive local therapy (i.e. radical prostatectomy or radiation therapy), many will go on to develop metastatic disease. The sensitive detection of metastatic sites is of critical importance, as there is growing evidence that patients with a limited number of disease foci may benefit from directed treatment such as stereotactic ablative radiation.^{2–4}

Bony metastases from PCa are most often imaged with planar whole body bone scan utilizing the radiotracer $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP). Efforts at improving the sensitivity and specificity of this modality have included the introduction of single-photon emission computed tomography (SPECT) alone or in combination with X-ray computed tomography (SPECT/CT), which provides tomographic images with enhanced anatomic localization and lesion characterization.^{5–7} Further, the improved spatial resolution and intrinsic ability to quantify findings on positron emission tomography (PET) has also

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come to the forefront of imaging bone metastases in the form of Na¹⁸F PET/CT, which has been found to improve both sensitivity and specificity for the evaluation of bone metastases relative to ^{99m}Tc-MDP bone scan.^{8–10}

An alternative to ^{99m}Tc-MDP and Na¹⁸F is ¹⁸F-DCFPyL, a small molecule inhibitor of prostate specific membrane antigen (PSMA) that has been shown to have high uptake at sites of metastases in patients with advanced PCa.¹¹ A single case report with a similar PSMA-targeted agent noted correlation between Na¹⁸F PET/CT and the PSMA ligand prior to therapy with ²²³Ra.¹² In this report, we compare the sensitivity of ^{99m}Tc-MDP bone scan, Na¹⁸F PET/CT and ¹⁸F-DCFPyL PET/CT for detecting sites of osseous metastases in a single patient with progressive castration resistant PCa.

Case Report

The patient is a 45-year-old gentleman who had first presented approximately two years prior to the time of PET imaging with an elevated prostate-specific antigen (PSA) level of 39 ng/mL and suspected clinically localized PCa. Transrectal biopsy demonstrated PCa in every core up to Gleason 5+4=9. As the patient had no definitive evidence of metastasis on conventional imaging, he proceeded to undergo a radical retropubic prostatectomy, demonstrating extraprostatic extension, seminal vesicle invasion and positive bilateral pelvic lymph nodes. Post-prostatectomy his PSA was 10.5 ng/mL and he subsequently received treatment with leuprolide and docetaxel, resulting in PSA response to 1.0 ng/mL. The patient then enrolled in a series of clinical trials and received, in succession, Sipuleucel-T, anti-PD-L1 therapy, and enzalutamide, with persistent elevations in PSA as high as 15.6 ng/mL but decreasing to 1.0 ng/mL on enzalutamide. At this point in his treatment course, the patient was imaged with whole-body planar ^{99m}Tc-MDP bone scan, Na¹⁸F PET/CT, and ¹⁸F-DCFPyL PET/CT. Imaging with ¹⁸F-DCFPyL PET/CT was done after Institutional Review Board approval under the auspices of an exploratory investigational new drug application (eIND #121064). The imaging protocol used for whole body imaging with ¹⁸F-DCFPyL PET/CT has been previously described.¹³

Figure 1 includes an anterior projection whole body ^{99m}Tc-MDP bone scan image, an anterior maximum intensity projection (MIP) image from the Na¹⁸F PET scan, and an anterior MIP from the ¹⁸F-DCFPyL PET scan. For ^{99m}Tc-MDP and Na¹⁸F, the normal biodistribution is predominantly bone, with some uptake and excretion within the kidneys and bladder. For ¹⁸F-DCFPyL, the normal biodistribution includes the lacrimal glands, salivary glands, liver, spleen, proximal small bowel, kidneys, and bladder. Unlike the other two modalities, the ¹⁸F-DCFPyL scan demonstrates uptake in lymph nodes as well as bone lesions; the sites of abnormal radiotracer uptake within lymph nodes have been color-coded red in part (D) so as to emphasize the comparable lesions in bone, which remain black.

All three imaging studies were centrally reviewed by experienced nuclear medicine readers (SPR and MSJ) and a consensus was reached as to sites of abnormal uptake suspicious for osseous metastatic disease. In all, 89 bone lesions were identified on at least one modality. Planar ^{99m}Tc-MDP bone scan revealed 12 suspicious sites, Na¹⁸F demonstrated 39 suspicious sites, and ¹⁸F-DCFPyL was notable for 87 suspicious sites of abnormal

radiotracer uptake within the bones. Assuming all 89 lesions to be true positive would yield a sensitivity of 13.5% for bone scan, 43.8% for Na¹⁸F PET/CT and 97.7% for ¹⁸F-DCFPyL PET/CT. Lesions that were occult on ^{99m}Tc-MDP bone scan and Na¹⁸F PET/CT but were apparent with ¹⁸F-DCFPyL included lesions entirely within the marrow cavity of the affected bone (Figure 2) as well as subtle sites of abnormal cortical-based uptake (Figure 3).

Discussion

We directly compared ^{99m}Tc-MDP bone scan and Na¹⁸F PET/CT to an ¹⁸F-labeled PSMA-targeted PET radiotracer for the detection of bone lesions in metastatic PCa. The sensitivity for bone lesions with ¹⁸F-DCFPyL appears to be markedly higher than the sensitivity of these traditional bone imaging modalities. This preliminary observation may be a result of the difference in the biological mechanism of the radiotracers—whereas ^{99m}Tc-MDP and Na¹⁸F localize on the basis of bony reaction in response to the presence of metastatic disease, ¹⁸F-DCFPyL binds directly to tumor cells. Thus, early lesions or those centered within the marrow cavity, which have not caused a bony reaction may only be visible with ¹⁸F-DCFPyL PET/CT. This apparent improved sensitivity is particularly important in regards to the comparison with Na¹⁸F PET/CT, which is considered by many to be the standard for diagnosing osseous metastatic disease and has demonstrated an ability to profoundly impact the management of PCa patients.¹⁰ If these findings can be confirmed in a larger patient cohort, the approach to imaging PC patients with suspected metastatic disease to the bone will need to be re-thought. A previous report with a similar agent also suggested at least similar sensitivity between Na¹⁸F PET/CT and PSMA-targeted PET/CT.¹²

An obvious limitation of this work is that histopathologic proof of the bone lesions identified on any of the modalities is lacking and was beyond the scope of this observational report. Larger, prospective studies comparing ^{99m}Tc-MDP bone scan, Na¹⁸F PET/CT and ¹⁸F-DCFPyL PET/CT with clinical and imaging follow-up are needed to definitively assess if PSMA-targeted ¹⁸F-DCFPyL PET/CT truly has enhanced sensitivity for bone metastases.

Conclusions

The results from this case report are highly encouraging that PSMA-targeted PET/CT with small molecules such as ¹⁸F-DCFPyL may offer improved sensitivity for the detection of early/subtle bone metastatic disease relative to either ^{99m}Tc-MDP bone scan or Na¹⁸F PET/CT. These findings warrant confirmation in a larger study.

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Clinical Practice Points

1. Imaging of bone metastases in prostate cancer has traditionally involved planar ^{99m}Tc -MDP bone scan with or without the use of supplemental tomographic imaging. More recently, Na^{18}F PET/CT has been found to have improved sensitivity and specificity for sites of osseous metastatic involvement.
2. PSMA is a cell surface enzyme that is highly expressed in prostate cancer and has been explored as a target for prostate cancer imaging.
3. In this case report, we found that PSMA-based PET/CT with the small molecule ^{18}F -DCFPyL detected a large number of bony lesions that were occult on ^{99m}Tc -MDP bone scan and Na^{18}F PET/CT.
4. PSMA-targeted PET/CT may offer improved sensitivity by binding directly to tumor cells, as opposed to localizing to sites of bony reaction.
5. This preliminary finding should be further explored in larger studies.

Figure 1.

(A) Anterior projection whole body planar ^{99m}Tc -MDP bone scan, (B) anterior view of the MIP from the Na^{18}F PET, (C) anterior view of the MIP from the ^{18}F -DCFPyL PET, and (D) anterior view of the MIP from the ^{18}F -DCFPyL PET with sites of abnormal radiotracer uptake within lymph nodes masked with a red overlay. Note the increasing number of visible lesions with Na^{18}F PET relative to ^{99m}Tc -MDP bone scan and with ^{18}F -DCFPyL PET relative to either of the other two modalities.

Figure 2.

(A) Axial fused ^{18}F -DCFPyL PET/CT and (B) axial fused Na^{18}F PET/CT images through the proximal thighs demonstrating a lesion with intense ^{18}F -DCFPyL uptake in the marrow space of the left femur that is occult with Na^{18}F (red arrowheads).

Figure 3. (A) Axial fused ^{18}F -DCFPyL PET/CT and (B) axial fused Na^{18}F PET/CT images through the C5 level of the cervical spine with a lesion in the right lateral mass that is clearly visible with ^{18}F -DCFPyL but demonstrates no uptake on the Na^{18}F scan (red arrowheads).