Spatially discordant uptake within prostate cancer bone metastases on ^{18}F-Sodium Fluoride and Prostate Specific Membrane Antigen (^{18}F-PSMA) PET/CT scans

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Background: Molecular imaging targeting Prostate-Specific Membrane Antigen (PSMA) has recently been shown to be a sensitive method of detecting metastatic prostate cancer, however, its colocalization of uptake with traditional bone imaging agents has not been examined. The purpose of this study is to compare the spatial concordance of ^{18}F-NaF PET/CT and ^{18}F-PSMA-targeted PET/CT agents within prostate cancer bone metastases.

Methods: Prostate cancer patients with known bone metastases were enrolled on consecutive clinical trials comparing utility of PSMA-targeted PET/CT (^{18}F-DCFBC or ^{18}F-DCFPyL) and ^{18}F-NaF PET/CT. For pelvis and spinal lesions detected by both radiotracers, regions-of-interest (ROIs) derived by various thresholds of uptake intensity were compared spatially between tracers using overlap volume (ratio of overlapping volume to minimum ROI volume). Spatial colocalization of radiotracers was correlated with uptake characteristics and disease (castration) status at the time of imaging.

Results: The study included 149 lesions in 19 patients. Qualitatively, lesions exhibited a heterogeneous range of spatial concordance between PSMA and NaF uptake from completely matched to completely discordant. Quantitatively, overlap volume decreased as a function of tracer intensity ($p<0.05$ between sequential testing of gradient-based, 60%-SUV_{max}, 70%-SUV_{max}, and 80%-SUV_{max} ROIs). This finding varied by disease status, where lesions from patients with castration-sensitive disease showed high spatial concordance while lesions from patients with castration-resistant disease demonstrated more frequent spatial discordance. High registration accuracy was achieved (ICC=0.93), allowing for voxel-based assessment demonstrating regions defined exclusively by PSMA uptake had lower CT density compared to regions defined by both PET tracers and visible sclerotic regions by CT ($p<0.001$). All quantitative findings occurred with no-to-weak correlation with maximum uptake and volume characteristics ($\rho \leq 0.4$).

Conclusion: Traditional models of prostate cancer bone metastasis assume direct interactions between prostate cancer cells and osteoblasts resulting in a sclerotic lesion seen on radiographs and bone scans. As metastatic prostate disease in the bone progresses to castration-resistant status, a greater discordance in regions of high uptake between NaF PET and PSMA PET is observed. This may indicate a possible phenotypic shift from tumor growth dependent on bone remodeling to one that permits metastatic growth independent of osteoblastic activity. This observation may have implications for effectiveness of radionuclide therapy such as ^{223}Ra in which uptake in sites of bone turnover may not coincide with regions of highest cancer activity.

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