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Editorial

In Molecular Pursuit of Bone Metastasis by Fluciclovine PET

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Abstract

Diagnosing bone metastases with traditional anatomic modalities, such as MRI and CT, is limited by sensitivity, and conventional bone radiotracers are only indirect markers of cancer activity. Fortunately, molecular imaging is uniquely capable of providing radiotracers such as fluciclovine and radiolabeled choline, that actually target tumors in the bone. The merits of research in imaging osseous metastases in animal models using these radiotracers and the implications for future clinical translation are discussed.

Cancer metastasis, especially in the bone, is a dreaded development in the natural history of cancer usually carrying a grim prognosis and severe morbidity. Through efforts to understand the osseous phase of metastasis, strategies to treat and ultimately prevent tumor expansion need to be discovered. Radiolabeled imaging provides an exceptional vantage point with which to view bone metastases. Specifically, diagnosing bone metastasis with traditional anatomic modalities of MRI and CT is limited by their low sensitivity. Meanwhile, conventional bone radiotracers indirectly detect cancer leading to high false positive rates. Molecular imaging however, is uniquely suited to facilitate research by targeting specific functional pathways of malignancy. One such innovative radiotracer is fluciclovine, also known as anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC).(*1*) A leucine analog taken up by amino acid transporters, it has shown promise as a diagnostic tool for prostate cancer. Studies have demonstrated its capabilities in identifying metastatic tumor throughout the body including soft tissues and bone but the specific mechanisms of uptake have not been clearly established, especially in the skeletal milieu.

The article in this issue entitled "PET Tracer ^{18}F-Fluciclovine Can Detect Histologically Proven Bone Metastatic Lesions: A Preclinical Study in Rat Osteolytic and Osteoblastic Bone Metastasis Models" by Oka *et al*. (*2*) expands our insight into the bone metastatic niche and how it interacts with targeted radionuclides. This article provides novel information describing the histological characteristics of bone metastasis and how this relates to the uptake of the radiotracers- fluciclovine, fluorodeoxyglucose (FDG), choline and hydroxymethylene diphosphonate (HMDP), that have not been previously examined in the literature.

In this study, the investigators evaluated malignant osteoblastic and osteolytic models of metastasis and added bone trauma models to compare the impact of tumor and benign osseous remodeling on radiotracer activity with triple-tracer autoradiography. A breast cancer cell line was used for osteolytic lesions and a prostate cancer cell line was used for osteoblastic lesions, resulting in more clinically relevant bone lesions than are usually presented in bone models. A comprehensive

histological analysis was directed not only at the metastasis but also normal inflammatory cells, osteoblasts and osteoclasts as well as cells bearing amino acid transporters. This extensive histopathologic validation in bone highlights the interplay and overlapping nature of these cell types within metastases. Such data is difficult to obtain in clinical trials due to the difficulties in obtaining bone biopsies and, if obtained, are often of low diagnostic yield and thus animal models are important. Despite a plethora of publications on mechanisms of bone metastases, very few studies incorporate radiotracer detection.(*3*,*4*) Researchers have described the role of ^{18}F FDG and ^{18}F NaF activity in osteoblastic and osteolytic prostate cancer models, but rarely is this depth of histologic analysis found in the literature.(*5*)

Comparing the radioactive distribution of fluciclovine, FDG and choline in tumor and surrounding tissues revealed their relative abilities to identify bone disease and illustrates their distinct methods of action. FDG usually shows minimal uptake in prostate cancer, but radiolabeled choline has demonstrated benefit in tumor detection and, as the only other approved PET agent for prostate cancer imaging, was an intelligent selection for this trial. Unfortunately, a direct comparison between choline and fluciclovine is only reported in the osteoblastic model. Considering the similar indications between the two agents, evaluating choline's performance in the osteolytic model would have been worthwhile. Similarly, results for radiotracer detection of early osteolytic lesions were not matched by results in early osteoblastic lesions. With better sensitivity, ^{18}F NaF could have been substituted for HMDP, and would also have been more equivalent as a PET agent. However, these minor issues do not distract from an otherwise strong study.

The microenvironment of bone metastasis is a complex system. Despite low activity, fluciclovine's accumulation in osteolytic and osteoblastic tumors paves the way for future studies in other cancers with bone involvement. Furthermore, the potential for fluciclovine to detect early bone metastasis is very intriguing. Fluciclovine was recently approved by the FDA for imaging recurrent prostate cancer and therefore, proving additional applications for this agent would enable more rapid clinical translation. Monitoring therapy, including the effects of androgen deprivation, is an obvious prospect. Recognizing osteolytic tumor before characteristic appearances are seen on CT could highlight an opportunity for early intervention with precision therapy by targeted radionuclides armed with alpha and/or beta particles such as ^{223}Ra and ^{177}Lu. Clinical trials employing molecular radiotherapy in metastatic cancers are in their infancy, revealing an urgent unmet need for future investigations that can build upon the solid groundwork built by Oka and colleagues.(*2*)

References

1. Savir-Baruch B, Zanoni L, Schuster DM. Imaging of Prostate Cancer Using Fluciclovine. *PET Clin*. 2017;12:145-157.
2. Oka S, Kanagawa M, Doi Y, Schuster DM, Goodman MM, Yoshimura H. PET Tracer 18F-Fluciclovine Can Detect Histologically Proven Bone Metastatic Lesions: A Preclinical Study in Rat Osteolytic and Osteoblastic Bone Metastasis Models. *Theranostics* 2017; 7(7):2048-2064.
3. Dore-Savard L, Barriere DA, Midavaine E, et al. Mammary cancer bone metastasis follow-up using multimodal small-animal MR and PET imaging. *J Nucl Med*. 2013;54:944-952.
4. Kang WJ, Song EH, Park JY, Park YJ, Cho A, Song HT. (18)F-fluoride PET imaging in a nude rat model of bone metastasis from breast cancer: Comparison with (18)F-FDG and bioluminescence imaging. *Nucl Med Biol*. 2015;42:728-733.
5. Hsu WK, Virk MS, Feeley BT, Stout DB, Chatziioannou AF, Lieberman JR. Characterization of osteolytic, osteoblastic, and mixed lesions in a prostate cancer mouse model using 18F-FDG and 18F-fluoride PET/CT. *J Nucl Med*. 2008;49:414-421.