

Heterogeneity in metastatic breast cancer ^{18}F -fluoroestradiol uptake – clinically actionable, biologically illuminating?

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Metastatic breast cancer from an estrogen receptor positive (ER+) primary tumor is rarely cured, but patients often live for many years with their disease (1). A wide range of therapy regimens are available, including endocrine therapy, cytotoxic chemotherapy, and molecularly targeted agents. Without established guidelines, clinicians and patients are looking for biomarkers to direct sequencing or combining of these therapies.

Metastatic disease may have vastly different characteristics compared to a treated primary tumor, but contemporaneous biopsies may yield inadequate tissue (2) and may not represent the patient's full tumor burden.

In this issue of the *Journal of Nuclear Medicine*, Nienhuis et al. [CITE] demonstrate the potential contribution of molecular imaging to assessment of metastatic breast cancer, as they document ^{18}F -fluoroestradiol (^{18}F -FES) SUVmax (standardized uptake value of the hottest pixel) for 1617 lesions in 91 patients. Nienhuis et al. interpret their results (shown graphically in Fig. 1) as indicating that 36% of patients have site-to-site heterogeneity of disease, with both ^{18}F -FES positive and ^{18}F -FES negative lesions. Applying agglomerative hierarchical cluster analysis to imaging-detected disease characteristics (number of ^{18}F -FES positive lesions, percentage of ^{18}F -FES positive lesions, average ^{18}F -FES SUVmax, number of bone lesions, number of lung lesions, etc. – see Supplemental Fig. 2), the 91 patients are partitioned into 3 groups primarily based on tumor ^{18}F -FES avidity, number of tumors, and tumor location. These results and small differences by lesion type in average geometric mean ^{18}F -FES uptake lead the authors to conclude that “ ^{18}F -FES uptake is heterogeneous between tumor lesions .. and is influenced by anatomical site.” The manuscript provides valuable data on an

important topic, but further consideration is required to determine the role of ^{18}F -FES PET/CT imaging in metastatic breast cancer.

The first potential role of ^{18}F -FES PET/CT is to address the clinical dilemma of treatment selection and sequencing for metastatic breast cancer. The Nienhuis et al. study suggests several clinical predictions, such as that patients with any ^{18}F -FES negative lesion are unlikely to respond to endocrine therapy, and that patients with visceral disease are unlikely to respond to endocrine therapy. These straightforward hypotheses were evaluated but not strongly supported in a similar patient population (3). In that study, clustering based on tumor aggressiveness (measured by ^{18}F -fluorodeoxyglucose uptake) and average ^{18}F -FES uptake was robust to internal cross-validation and identified three groups with median progression-free survival ranging from 3.3 to 26.1 months. The clustering described by Nienhuis et al. [CITE] could have more clinical impact if additional clinical features were considered, such as prior exposure to different therapy types, and time between primary and metastatic diagnosis. In general, biomarkers should be assessed in the context of standard prognostic variables (4). The authors also propose background (normal tissue) correction for normalization of tumor ^{18}F -FES uptake measures, but this would require additional reader effort and add another source of measurement error. Studies EAI142 (NCT02398773) and IMPACT-MBC (NCT01957332) are ongoing to observe relationships between ^{18}F -FES uptake and response to endocrine therapy, but prospective biomarker-driven trials (5) are required to determine the role of ^{18}F -FES PET measures in clinical practice.

The second potential role ^{18}F -FES PET/CT is to inform development of new therapies that target the estrogen receptor, and to contribute to research into the mechanisms for development of metastatic disease. ^{18}F -FES PET may be used for pharmacodynamic monitoring of estrogen receptor blockade in both preclinical (6,7) and clinical (8,9) studies. For broader insights into disease development Nienhuis et al. [CITE] interpret their results as indicating that site-to-site heterogeneity within patients is an important consideration for metastatic breast cancer therapeutic development. Kurland et al. (10) examined similar lesion level data and concluded (from patterns of ^{18}F -FES uptake quite comparable to those in the Nienhuis et al. Fig. 1) that site-to-site heterogeneity could be attributed largely to measurement error, and that co-occurrence of lesions with extremely high and extremely low uptake was uncommon. This interpretation was supported by subsequent analysis in which progression-free survival was predicted by patient-level averages rather than characteristics defined by site-to-site heterogeneity (3). Differences in ER expression have been documented to occur between primary and metastatic disease (11,12), among different contemporaneous metastatic sites (13), and intratumorally (14). Understanding clonal evolution in response to multiple lines of treatment is clearly of fundamental interest for metastatic breast cancer, but other sources of information and extensive preclinical studies are required to provide context to the findings of clinical ^{18}F -FES PET/CT. Researchers with expertise in molecular imaging and genomic analyses should coordinate their efforts for optimal discovery.

A part of enabling effective cross-disciplinary collaboration in metastatic breast cancer is better nomenclature for “heterogeneity” to distinguish among patterns with

very different implications for clinical practice and basic research. When a group of patients treated as homogeneous by clinical guidelines (metastatic breast cancer from an ER+ primary tumor) has different average response to endocrine therapy based on a different classifier (such as PET/CT imaging), this indicates that breast cancer is a **heterogeneous disease**. The term inter-patient heterogeneity refers to the same phenomenon, but suggests (while not addressing) within-patient disease heterogeneity, either over time or in synchronous disease. ^{18}F -FES PET imaging has great promise for contributing to classification of patients with metastatic breast cancer in this manner. Second, **site-to-site heterogeneity**, different measurements for different tumors within the same person, is also detectable by ^{18}F -FES PET, but the existence of lesions with uptake somewhat above and somewhat below a pre-specified threshold does not necessarily yield actionable information. Finally, **intratumoral heterogeneity**, variability of measures within a single tumor, is of great relevance for understanding tumor biology (15), and at some level can be assessed by PET imaging (16,17).

In summary, the Nienhuis et al. study [CITE] supports prior findings that ^{18}F -FES PET imaging can help in clinically relevant classification of patients with metastatic breast cancer from an ER+ primary tumor, and presents correlative studies in normal tissue to guide further development of ^{18}F -FES uptake measures. The statement that uptake is “influenced” by the site of metastasis requires further study to evaluate possible clinical impact or biological insight; the number of evaluable visceral tumors was relatively small, and low sensitivity of CT to bone lesion identification could lead to an artefactual over-representation of bone lesions with higher ^{18}F -FES uptake. We look

forward to the future development of ^{18}F -FES imaging and the treatment of metastatic breast cancer.

DISCLOSURES

No potential conflicts of interest relevant to this article exist.

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