# Heterogeneity in Metastatic Breast Cancer $^{18}$F-Fluoroestradiol Uptake: Clinically Actionable, Biologically Illuminating?

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Metastatic breast cancer from an estrogen receptor (ER)–positive 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 combine these therapies. Metastatic disease may have vastly different characteristics compared with 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. (*3*) demonstrate the potential contribution of molecular imaging to assessment of metastatic breast cancer, as they document $^{18}$F-fluoroestradiol ($^{18}$F-FES) $SUV_{max}$ (SUV of the hottest pixel) for 1,617 lesions in 91 patients. Nienhuis et al. interpret their results (shown graphically in Fig. 1 (*3*)) 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. With the application of agglomerative hierarchical cluster analysis to imaging-detected disease characteristics (e.g., number of $^{18}$F-FES–positive lesions, percentage of $^{18}$F-FES–positive lesions, average $^{18}$F-FES $SUV_{max}$, number of bone lesions, number of lung lesions; Supplemental Fig. 2 of Nienhuis et al. (*3*)), 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 led the authors to conclude that "$^{18}$F-FES uptake is heterogeneous between tumor lesions . . . and is influenced by anatomic site." The article 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 (*4*). In that study, clustering based on tumor aggressiveness (measured by $^{18}$F-FDG uptake) and average $^{18}$F-FES uptake was robust to internal cross-validation and identified 3 groups with median progression-free survival ranging from 3.3 to 26.1 mo. The clustering described by Nienhuis et al. (*3*) 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 (*5*). 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 (*6*) are required to determine the role of $^{18}$F-FES PET measures in clinical practice.

The second potential role of $^{18}$F-FES PET/CT is to inform development of new therapies that target the ER and to contribute to research into the mechanisms for development of metastatic disease. $^{18}$F-FES PET may be used for pharmacodynamic monitoring of ER blockade in both preclinical (*7,8*) and clinical (*9,10*) studies. For broader insights into disease development Nienhuis et al. (*3*) 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. (*11*) examined similar lesion-level data and concluded (from patterns of $^{18}$F-FES uptake quite comparable to those in Fig. 1 of Nienhuis et al. (*3*)) 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 (*4*). Differences in ER expression have been documented to occur between primary and metastatic disease (*12,13*), among different contemporaneous metastatic sites (*14*), and intratumorally (*15*). 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"

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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-positive 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.* When this disease heterogeneity is referred to as interpatient heterogeneity, it invites parallels to the unrelated phenomenon of intrapatient heterogeneity, either over time or in synchronous disease. $^{18}$F-FES PET imaging has great promise for revealing disease heterogeneity in metastatic breast cancer from an ER-positive primary tumor. 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 prespecified 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 (*16*), and at some level can be assessed by PET imaging (*17,18*).

In summary, the Nienhuis et al. study (*3*) supports prior findings that $^{18}$F-FES PET imaging can help in clinically relevant classification of patients with metastatic breast cancer from an ER-positive 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 biologic insight; the number of evaluable visceral tumors was relatively small, and low sensitivity of CT to bone lesion identification could lead to an artifactual overrepresentation 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.

## DISCLOSURE

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## REFERENCES

1. Kwast AB, Voogd AC, Menke-Pluijmers MB, et al. Prognostic factors for survival in metastatic breast cancer by hormone receptor status. *Breast Cancer Res Treat.* 2014;145:503–511.
2. Amir E, Miller N, Geddie W, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. *J Clin Oncol.* 2012;30:587–592.
3. Nienhuis HH, van Kruchten M, Elias SG, et al. $^{18}$F-fluoroestradiol tumor uptake is heterogeneous and influenced by site of metastasis in breast cancer patients. *J Nucl Med.* 2018;59:1212–1218.
4. Kurland BF, Peterson LM, Lee JH, et al. Estrogen receptor binding ($^{18}$F-FES PET) and glycolytic activity ($^{18}$F-FDG PET) predict progression-free survival on endocrine therapy in patients with ER+ breast cancer. *Clin Cancer Res.* 2017;23: 407–415.
5. Altman DG, McShane LM, Sauerbrei W, Taube SE. Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK): explanation and elaboration. *PLoS Med.* 2012;9:e1001216.
6. Mandrekar SJ, An MW, Sargent DJ. A review of phase II trial designs for initial marker validation. *Contemp Clin Trials.* 2013;36:597–604.
7. Fowler AM, Chan SR, Sharp TL, et al. Small-animal PET of steroid hormone receptors predicts tumor response to endocrine therapy using a preclinical model of breast cancer. *J Nucl Med.* 2012;53:1119–1126.
8. Heidari P, Deng F, Esfahani SA, et al. Pharmacodynamic imaging guides dosing of a selective estrogen receptor degrader. *Clin Cancer Res.* 2015;21: 1340–1347.
9. Wang Y, Ayres KL, Goldman DA, et al. $^{18}$F-fluoroestradiol PET/CT measurement of estrogen receptor suppression during a phase I trial of the novel estrogen receptor-targeted therapeutic GDC-0810: using an imaging biomarker to guide drug dosage in subsequent trials. *Clin Cancer Res.* 2017;23:3053–3060.
10. van Kruchten M, de Vries EG, Glaudemans AW, et al. Measuring residual estrogen receptor availability during fulvestrant therapy in patients with metastatic breast cancer. *Cancer Discov.* 2015;5:72–81.
11. Kurland BF, Peterson LM, Lee JH, et al. Between-patient and within-patient (site-to-site) variability in estrogen receptor binding, measured in vivo by $^{18}$F-fluoroestradiol PET. *J Nucl Med.* 2011;52:1541–1549.
12. Aurilio G, Disalvatore D, Pruneri G, et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. *Eur J Cancer.* 2014;50:277–289.
13. Sighoko D, Liu J, Hou N, Gustafson P, Huo D. Discordance in hormone receptor status among primary, metastatic, and second primary breast cancers: biological difference or misclassification? *Oncologist.* 2014;19:592–601.
14. Avigdor BE, Beierl K, Gocke CD, et al. Whole-exome sequencing of metaplastic breast carcinoma indicates monoclonality with associated ductal carcinoma component. *Clin Cancer Res.* 2017;23:4875–4884.
15. Gyanchandani R, Lin Y, Lin HM, et al. Intratumor heterogeneity affects gene expression profile test prognostic risk stratification in early breast cancer. *Clin Cancer Res.* 2016;22:5362–5369.
16. Almendro V, Kim HJ, Cheng YK, et al. Genetic and phenotypic diversity in breast tumor metastases. *Cancer Res.* 2014;74:1338–1348.
17. Tixier F, Hatt M, Valla C, et al. Visual versus quantitative assessment of intratumor $^{18}$F-FDG PET uptake heterogeneity: prognostic value in non-small cell lung cancer. *J Nucl Med.* 2014;55:1235–1241.
18. O'Sullivan F, Roy S, Eary J. A statistical measure of tissue heterogeneity with application to 3D PET sarcoma data. *Biostatistics.* 2003;4:433–448.