Letter to the Editor

Clinical Cancer Research

FDG PET and FES PET Predict PFS on Endocrine Therapy—Response

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We thank Drs. Mammatas, van Helden, Verheul, and Menke-van der Houven van Oordt for their interest in our work, and for their comments on our article. Specifically, the authors of the letter expressed concern that the analysis contradicted prior work by our group and others (1, 2) predicting response to endocrine therapy using ^{18}F-fluoroestradiol (FES) uptake alone, without the need for quantitative assessment of ^{18}F-fluorodeoxyglucose (FDG) PET. A key difference between these prior efforts and the current article is that our primary endpoint was progression-free survival (PFS). Response is a common endpoint for identifying activity in a novel treatment, or discrimination of a novel biomarker. PFS is a preferred endpoint for later trials due to its more direct relationship to patient outcomes (3). More so than response, PFS will reflect both aggressiveness of the underlying disease and response to therapy. Our results suggest that pretherapy FDG uptake is a strong predictor of disease aggressiveness, consistent with prior work (4), and that low pretherapy FDG uptake predicts a more indolent disease course, independent of ER expression. As such, stratification by pretherapy FDG uptake considerably adds to the predictive value of FES PET. The authors of the letter suggested that endocrine resistance due to extensive prior exposure could explain the study's lack of predictive value for FES uptake alone. However, over half of our patients had no prior endocrine therapy for metastatic disease, so as a cohort, they were no more heavily pretreated than for other studies. Potential relevant markers directly related to endocrine resistance (such as ESR1) were not measured in either the current or prior studies.

The second concern raised by the authors of the letter was that the patient-level summaries of FES and FDG uptake used information only from the 3 most FDG-avid lesions, potentially neglecting important FES-negative lesions. Our analysis evaluated both FES and FDG uptake for all lesions and explicitly evaluated summary measures that focused on identifying patients with FES-negative disease, either by quantitative measures (with a minimum FDG SUV) or by qualitative assessment (Table 2). To reply to the authors' specific concern, we assessed the presence or absence of any lesion(s) with FES SUV_{max} (weighted by kg not lean body mass) $\leq$1.5 or 1.54 (the two thresholds mentioned; ref. 5). We found that 24 of 84 (29%) patients had at least 1 lesion with FES $SUV_{max} \leq 1.5$, and 26 of 84 (31%) had at least 1 lesion with FES $SUV_{max} \leq 1.54$. One of the proposed classifiers in Table 2 was the presence of any aggressive, FES-negative lesion (17/84, 20%, with presence of any lesion FES $SUL_{mean} \leq 1$ and FDG $SUV_{max} > 5$). Removing the FDG uptake restriction, the number of participants with any lesion FES $SUL_{mean} \leq 1$ was 53/84 (63%). Kaplan–Meier survival curves for these FES-only measures as predictors of PFS are shown in the figure below.

In addition, FES $SUV_{max} \leq 1.54$ did not predict inferior PFS (log-rank test $P = 0.65$), nor did absence of FES uptake by qualitative assessment (Fig. 1D in the article, $P = 0.95$). The measure with a minimum FDG uptake for "FES negative" lesions was more promising (Fig. 1C in the article, log-rank $P = 0.07$). As described in the article, the summary measures using values from up to 3 lesions were motivated by previous analysis of an overlapping patient cohort, which concluded that average uptake for a limited number of lesions provided "a reasonable summary of synchronous ER expression for most patients" (6).

Our analysis acknowledges that within-person interlesion variation may exist and be clinically important in a minority of patients. However, our focus is on a clinical approach that can apply to the large population of patients with advanced breast cancer who are deciding among endocrine-based and chemotherapy-based treatment regimens based on current disease characteristics. Our analysis used a machine-learning technique (recursive partitioning) with internal cross-validation to identify the most promising predictors of PFS in our patient cohort. These findings were consistent both with prior research supporting FES PET as a predictor of response to endocrine therapy (1, 2), and with characterization of a sizeable minority of patients with ER^+ metastatic breast cancer whose disease is indolent and who are likely to remain stable on endocrine therapy (7).

We disagree with the authors of the letter that the results of our study indicated a diminished utility of FES PET in guiding endocrine therapy compared with FDG PET. Rather, our results support the added benefit of FDG PET when combined with FES PET measures in predicting disease course for patients with metastatic breast cancer from ER-expressing primary tumors treated with endocrine therapy. It is not surprising that a combination of imaging markers that can assess both likelihood of response to endocrine therapy (FES) and disease aggressiveness (FDG) does a better job of predicting PFS than either alone. Our analysis supports the utility of multiparametric molecular imaging, but clearly indicates a need for further study and prospective validation.

Disclosure of Potential Conflicts of Interest

D. Mankoff is a consultant/advisory board member for Blue Earth Diagnostics. No potential conflicts of interest were disclosed by the other authors.

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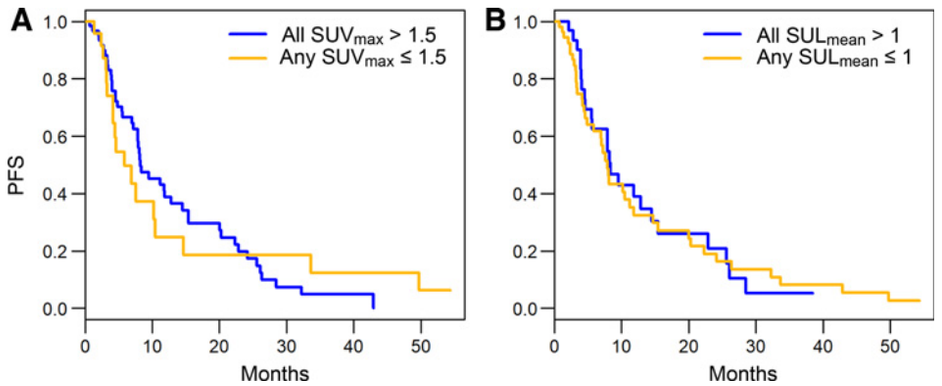

Figure 1.
Models predicting PFS by FES PET measures alone (without FDG PET). **A,** Absence (60/84) or presence (24/84) of any lesion with FES $SUV_{max} \leq 1.5$ does not predict PFS (log-rank test $P = 0.84$). **B,** Absence (31/84) or presence (53/84) of any lesion with FES $SUL_{mean} \leq 1.0$ does not predict PFS (log-rank test $P = 0.83$).

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