^{18}F-Fluoroestradiol PET to Predict the Response to Neoadjuvant Treatment of Luminal Breast Cancer

TO THE EDITOR: Chae et al. (*1*) prospectively investigated the ability of pretreatment ^{18}F-fluoroestradiol PET/CT to predict the pathologic response to neoadjuvant therapy in postmenopausal women with estrogen receptor–positive breast cancer. Of 25 evaluated patients, 12 received neoadjuvant chemotherapy and 13 neoadjuvant endocrine therapy. In the former group, the 2 patients with ^{18}F-fluoroestradiol–negative tumors and none of the 10 patients with ^{18}F-fluoroestradiol–avid tumors achieved a pathologic complete response ($P = 0.02$). In the latter group, all 13 patients had ^{18}F-fluoroestradiol–avid uptake, but none achieved a pathologic complete response. No difference in pretreatment SUV_{max} between responders and nonresponders was observed in either group. However, using the Miller–Payne grading system to define response, 5 of 7 neoadjuvant chemotherapy patients with a baseline SUV_{max} of less than 7.3 achieved a pathologic response, whereas none of the 5 neoadjuvant endocrine therapy patients with an SUV_{max} of less than 7.3 were responders ($P = 0.03$). In agreement with another study (*2*), these results suggest that patients with low tumor ^{18}F-fluoroestradiol uptake at baseline are more likely to be treated with neoadjuvant chemotherapy than with neoadjuvant endocrine therapy. In patients with a high baseline tumor SUV_{max}, Chae et al. observed no difference in pathologic response, whatever the treatment group. For these tumors with high ^{18}F-fluoroestradiol uptake, a second PET examination could potentially be helpful to measure the change in SUV under treatment, in the same way as is sometimes done with ^{18}F-FDG imaging (*3*). This could increase the predictive value of ^{18}F-fluoroestradiol imaging. In the metastatic setting, among 16 patients treated with fulvestrant, baseline ^{18}F-fluoroestradiol PET was unable to predict the response (*4*). When a second examination was performed a few weeks after the start of treatment, the change in tumor ^{18}F-fluoroestradiol uptake was significantly larger in patients having clinical benefit from fulvestrant than in patients with progressive disease ($P = 0.025$) (*4*). Another research possibility would be the use of ^{18}F-FDG imaging in addition to ^{18}F-fluoroestradiol PET. In estrogen receptor–positive breast cancer, recent studies suggested that ^{18}F-FDG uptake measured at a single time point before neoadjuvant chemotherapy (*5*) or before initial surgery (*6*) was associated with patient survival. A pilot study evaluated the value of ^{18}F-fluoroestradiol and ^{18}F-FDG imaging together in predicting the response of various breast cancer phenotypes to neoadjuvant chemotherapy. The ratio of ^{18}F-fluoroestradiol SUV to ^{18}F-FDG SUV showed great value in predicting the response ($P = 0.002$) (*2*). However, the small number of patients in this study ($n = 18$) was a limitation. Moreover, luminal tumors were mixed with estrogen receptor–negative breast cancer. In the metastatic setting, the recent study from Kurland et al. showed that information from baseline ^{18}F-fluoroestradiol and ^{18}F-FDG imaging can be used together to separate patients into 3 groups with different prognoses (*7*).

In conclusion, although the study from Chae et al. suggests that baseline ^{18}F-fluoroestradiol PET could be of interest to predict the response to neoadjuvant therapy in estrogen receptor–positive breast cancer patients, the predictive value seems to have some limitations. Performing a second ^{18}F-fluoroestradiol PET examination during treatment or complementing the ^{18}F-fluoroestradiol examination with a ^{18}F-FDG PET examination could potentially improve the predictive power and deserves to be evaluated prospectively in a large study.

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REPLY: We thank Dr. David Groheux for the great summary and thoughtful comments regarding our paper (*1*). He suggested that even though ^{18}F-fluoroestradiol PET/CT could be of interest in the prediction of response to neoadjuvant therapy, a second ^{18}F-fluoroestradiol PET/CT examination during treatment or additional ^{18}F-FDG PET/CT could potentially improve the prediction of baseline ^{18}F-fluoroestradiol PET/CT.

Estrogen receptor–positive tumors are less responsive to chemotherapy, and the survival benefits are relatively modest. The current National Comprehensive Cancer Network guideline recommends that neoadjuvant endocrine therapy alone may be offered to those with strongly hormone receptor–positive tumors (*2*). However, there are currently no reliable biomarkers that will predict whether neoadjuvant endocrine therapy or neoadjuvant chemotherapy will offer more effective downstaging for a given patient with estrogen receptor–positive

breast cancer (*3*). We still need drug- or regimen-specific response predictors with clinically useful predictive accuracy (*4*).

Predictive markers are used as indicators of the likely benefit of a specific treatment before it begins, without the need for follow-up marker studies. Clinical validation of the ability of ^{18}F-fluoroestradiol PET/CT to predict a beneficial response in subjects and to differentiate responders from nonresponders can be based on a single neoadjuvant endocrine therapy arm. However, given the evidence regarding the efficacy of neoadjuvant chemotherapy for estrogen receptor–positive disease, a comparison of neoadjuvant chemotherapy versus neoadjuvant endocrine therapy is required (*5*). That is to say, to establish the medical utility of ^{18}F-fluoroestradiol PET/CT as a predictive biomarker of response to neoadjuvant endocrine therapy, a randomized clinical trial demonstrating that ^{18}F-fluoroestradiol PET/CT distinguishes a subset of patients who benefit from neoadjuvant endocrine therapy from those who do not would be required (*6*). In this study, we focused on the ability of the functional heterogeneity of ^{18}F-fluoroestradiol PET/CT–determined estrogen receptor status to predict the pathologic response to neoadjuvant chemotherapy and neoadjuvant endocrine therapy in randomized postmenopausal patients with estrogen receptor–rich breast cancer. ^{18}F-fluoroestradiol PET/CT was used as a stratification factor. We classified patients into groups based on their ^{18}F-fluoroestradiol PET/CT status and compared the two treatments separately in the two marker groups. This approach may be useful for demonstrating the clinical utility of ^{18}F-fluoroestradiol PET/CT as a predictive marker. Our study indicated that there may be an interaction between ^{18}F-fluoroestradiol uptake status and treatment (*7*). ^{18}F-fluoroestradiol PET/CT has potential clinical implications in the selection of either neoadjuvant chemotherapy or neoadjuvant endocrine therapy in postmenopausal women with estrogen receptor–rich breast cancer.

We agree with Dr. Groheux that tumors with high ^{18}F-fluoroestradiol uptake may need a second ^{18}F-fluoroestradiol PET/CT examination during treatment or additional ^{18}F-FDG PET/CT to improve the ability to predict the response to neoadjuvant endocrine therapy. A second ^{18}F-fluoroestradiol examination as a surrogate or pharmacodynamic marker for outcome may more accurately predict clinical benefit from fulvestrant than baseline ^{18}F-fluoroestradiol values; however, this requires an additional follow-up study. It should also be determined whether and how PET-guided response assessment can be used to modify treatment. ^{18}F-FDG uptake may be a prognostic marker that provides information on patient outcome regardless of neoadjuvant chemotherapy or neoadjuvant endocrine therapy. ^{18}F-FDG PET/CT is most likely to be therapeutically relevant if it can identify patients who have a poor prognosis with neoadjuvant endocrine therapy (*6*). Additional study is needed to determine whether neoadjuvant chemotherapy alone or neoadjuvant chemotherapy combined or administered sequentially with neoadjuvant endocrine therapy improves outcome in patients with high ^{18}F-FDG uptake.

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Neither Posttreatment PET/CT Nor Interim PET/CT Using Deauville Criteria Predicts Outcome in Pediatric Hodgkin Lymphoma

TO THE EDITOR: With interest we read the article by Bakhshi et al. (*1*) that was recently published online ahead of print. Their study aimed to assess the value of interim ^{18}F-FDG PET (after 2 cycles of chemotherapy) and posttreatment ^{18}F-FDG PET in predicting treatment failure, event-free survival, and overall survival. The study prospectively included 57 patients with early- or advanced-stage Hodgkin lymphoma treated with doxorubicin, bleomycin, vinblastine, and dacarbazine with or without additional radiation therapy. ^{18}F-FDG PET scans were interpreted according to both the Revised International Workgroup criteria (*2*) and the Deauville criteria (*3*). Interim ^{18}F-FDG PET, according to either the Revised International Workgroup criteria or the Deauville criteria, had no value in predicting event-free survival or overall survival. End-of-treatment ^{18}F-FDG PET, interpreted according to the Revised International Workgroup criteria, was positive in only 7 patients and had a sensitivity of 25% and specificity of 88% in predicting treatment failure. This group of 7 patients included 4 patients with progressive disease according to end-of-treatment ^{18}F-FDG PET, 3 of whom (75%) had false-positive findings (2 biopsy-confirmed and 1 determined by follow-up imaging), and 3 patients with partial remission according to end-of-treatment ^{18}F-FDG PET, all 3 of whom (100%) were considered to have false-positive findings as determined by follow-up imaging. According to the Deauville criteria (which apply a higher threshold to determine positivity), only 3 of 52 patients (5.8%) were considered positive at end-of-treatment ^{18}F-FDG PET. Two of these 3 cases (66%) were considered false-positive. Bakhshi et al. (*1*) concluded that posttreatment ^{18}F-FDG PET using the