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

Deauville criteria predicts outcome in Hodgkin lymphoma, particularly considering the high specificity of this imaging modality.

However, we strongly disagree with this conclusion. First, the fact that posttreatment ^{18}F-FDG PET had a sensitivity of only 25% indicates that most patients who are not cured actually have negative posttreatment ^{18}F-FDG PET findings. This is due to the limited spatial resolution of PET, as a result of which residual disease can never be excluded (*4*), as has been shown by several studies (*5*). The diagnostic performance of a test comprises both sensitivity and specificity. Any test with such a low sensitivity can generate a high specificity if the threshold to define positivity is simply raised. The combination of the very low sensitivity and the generally good prognosis of patients with Hodgkin lymphoma underlines that the number of patients needed to be scanned in order to detect one case of residual disease is actually quite high. ^{18}F-FDG PET scans are expensive, are not available in all institutions, provide ionizing radiation, and cause discomfort to the patient. Furthermore, according to the study of Bakhshi et al. and several other studies (*6*), the false-positive rate of posttreatment ^{18}F-FDG PET is actually very high. This applies to both the Revised International Workgroup criteria and the Deauville criteria, with false-positive rates of 85.7% and 66.7%, respectively, in the study by Bakhshi et al. (*1*). Awareness of this high false-positive rate is of the utmost importance, because it may result in unjustified initiation of second-line therapies and erroneous prognostication (if biopsy confirmation of ^{18}F-FDG–avid lesions is not possible), lead to a high number of unnecessary conformational biopsies, and cause unnecessary patient anxiety. The fact that an early ^{18}F-FDG PET–based detection of residual disease has not been proven to improve patient outcome further nullifies the need to acquire posttreatment ^{18}F-FDG PET scans (*7*).

In conclusion, interim ^{18}F-FDG PET fails to predict outcome in Hodgkin lymphoma, and posttreatment ^{18}F-FDG PET scans have a strikingly low sensitivity for the detection of residual disease. Furthermore, most ^{18}F-FDG–avid lesions seen on posttreatment ^{18}F-FDG PET scans appear to be false-positive findings. Therefore, neither interim nor posttreatment ^{18}F-FDG PET predicts outcome in Hodgkin lymphoma.

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REPLY: In reply to Adams et al., we would like to state that our study assessed the prognostic significance of interim and posttreatment PET with low-dose CT (PET/CT) in pediatric Hodgkin lymphoma in comparison to conventional imaging (*1*). In a disease with high cure rates, the purpose of evaluation with PET/CT is to identify high-risk patients and potentially prevent overtreatment of low-risk patients.

In our study, we found the sensitivity of posttreatment PET/CT and contrast-enhanced CT (CECT) to be equally low; however, the specificity of PET/CT was significantly high as compared with CECT (76.4% vs. 95.7%). This finding was also observed in a previously reported study by Furth et al. on pediatric Hodgkin lymphoma (*2*), establishing the fact that although PET/CT may not detect minimal residual disease, PET/CT can reasonably rule out active disease as compared with CECT. In our study, false-positive posttreatment findings were present in 21.8% of patients on CECT, as compared with 3.9% of patients on PET/CT; hence, PET/CT in effect may alleviate unnecessary patient anxiety about the presence of residual disease in an otherwise curable disease.

In the study cited by Adams et al. (*3*), the metaanalysis of the proportion of false-positive posttreatment PET/CT findings in adults with lymphoma also showed a high false-positive rate, 23.1%; however, unlike our study, comparison with conventional imaging was not done. In our study, if only posttreatment CECT had been used for response assessment, 23.6% of the patients would have required additional further evaluation with biopsy or (if biopsy was not possible) follow-up imaging to rule out disease. This percentage is higher than that for PET/CT; by use of the Deauville criteria, 5.8% of patients were PET/CT-positive after treatment. In contrast to the conclusion of Adams et al., posttreatment PET/CT can decrease unnecessary invasive procedures and patient anxiety when compared with CECT because of the better specificity of PET/CT. This observation was also reported in a cost-effectiveness analysis of posttreatment PET/CT in a study by Cerci et al. (*4*).

On the basis of two large studies that evaluated the role of PET/CT in Hodgkin lymphoma using the Deauville criteria, posttreatment PET/CT is more valuable in detecting primary refractory disease than in predicting relapse (*5,6*). In those studies, 60% of patients with positive interim PET/CT findings had primary refractory disease at the end of treatment, suggesting that PET/CT identified primary refractory disease (disease unresponsive to first-line chemotherapy) better than it identified patients with minimal residual disease who would relapse. Response to salvage chemotherapy and long-term outcome differ between these two scenarios (*7*). This also explains the inferior survival observed in our patients with positive PET/CT findings after treatment and underscores the utility of PET/CT in identifying primary refractory disease rather than predicting relapse.

We agree that routine use of PET/CT for response evaluation is not mandatory. However, in patients with risk factors for poor