Fact Sheet About Interim and End-of-Treatment ^{18}F-FDG PET/CT in Lymphoma

TO THE EDITOR: A recent article by Moghbel et al. (*1*) concluded that the available data largely support the indispensable role that ^{18}F-FDG PET/CT imaging has come to play across the many stages of treatment and subtypes of disease encompassed by lymphoma. However, and unfortunately, several important facts that shed a different light on the role of ^{18}F-FDG PET/CT in the response assessment of lymphoma were not mentioned in their article.

The first of these facts is the spatial resolution of PET. Whole-body PET images have a typical spatial resolution of 6–9 mm. Residual lymphoma deposits with a size well below this spatial resolution are missed by PET. This is exemplified by several findings. First, ^{18}F-FDG PET/CT is commonly negative, whereas concomitant bone marrow biopsy (which assesses the bone marrow at a microscopic level) is positive (*2*). Second, a relatively high proportion of patients with curable lymphoma histologies who are treated with curative intent develops disease relapse during follow-up (*3,4*), which underlines that acquiring an ^{18}F-FDG PET/CT–negative status is not synonymous to cure. Third, lymphoma patients receiving palliative chemotherapy not infrequently have a negative ^{18}F-FDG PET/CT scan, although this merely means that the macroscopic tumor bulk has disappeared but that microscopic disease is still present. Similarly, patients with indolent, incurable ^{18}F-FDG–avid lymphomas who are treated with noncurative chemotherapy not infrequently acquire an ^{18}F-FDG PET/CT–negative status. Fourth, additional radiation therapy in chemotherapy-treated patients with a negative end-of-treatment ^{18}F-FDG PET/CT scan has been shown to significantly reduce relapse rates (*5*), again indicating that ^{18}F-FDG PET/CT can never exclude residual disease.

Another important fact not mentioned in the article of Moghbel et al. is the nonspecificity of ^{18}F-FDG. A recent metaanalysis showed that the majority (55.7%) of lesions that are ^{18}F-FDG–avid during and after therapy for lymphoma prove to be false-positive on biopsy because of inflammatory changes (*6*). Remarkably, histopathologic data on the nature of ^{18}F-FDG–avid lesions on interim PET in Hodgkin lymphoma are still completely lacking (*6*).

A third fact not mentioned is the poor methodology of observational interim and end-of-treatment ^{18}F-FDG PET/CT studies. The areas under the summary receiver-operating-characteristic curve were reported to be 0.877 for interim ^{18}F-FDG PET/CT in predicting treatment failure in Hodgkin lymphoma, and 0.651 and 0.817 for ^{18}F-FDG PET/CT in predicting treatment failure and death in diffuse large B-cell lymphoma, by two recent metaanalyses (*7,8*). However, the studies on this subject suffered from numerous methodologic flaws. One important methodologic concern in these studies is that they used only follow-up ^{18}F-FDG PET/CT (instead of histopathologic confirmation) as the reference standard for treatment failure (*7,8*) However, false-positive post-treatment ^{18}F-FDG PET/CT results are common (*6*). As a result, the value of ^{18}F-FDG PET/CT in predicting treatment failure is probably considerably overestimated. The same applies to death, since positive ^{18}F-FDG PET/CT results without histopathologic confirmation may (incorrectly) initiate additional intensive therapies, with associated morbidity and mortality. With regard to the predictive value of end-of-treatment ^{18}F-FDG PET/CT, Moghbel et al. referred to older metaanalyses by Zijlstra et al. (*9*) and Terasawa et al. (*10*) and mention this test to be reliably prognostic. However, Moghbel et al. failed to mention that the studies these metaanalyses included also used follow-up ^{18}F-FDG PET or PET/CT as the reference standard, thus introducing the same serious bias. Of note, although the value of end-of-treatment ^{18}F-FDG PET/CT is considerably overestimated (*3,4,6*), it is widely used in clinical practice for treatment decisions, often without histopathologic confirmation.

Finally, the article does not mention the lack of a control arm in interim ^{18}F-FDG PET/CT–adapted trials. Given the poor methodology of the observational studies on interim and end-of-treatment ^{18}F-FDG PET/CT (which is, unfortunately, widely ignored), there is actually no sound scientific basis on which to perform interim ^{18}F-FDG PET/CT–adapted trials. Importantly, all interim ^{18}F-FDG PET/CT–adapted trials that have been performed so far (*1*) also suffer from a major flaw, namely the lack of a control arm. If escalated therapy is applied to only (a subgroup of) interim ^{18}F-FDG PET/CT–positive patients (and all interim ^{18}F-FDG PET/CT–negative patients receive standard therapy), any improvement in outcome in the former group may simply be due to the greater effectiveness of intensified therapy rather than being the merit of ^{18}F-FDG PET/CT–based patient selection. Similarly, if deescalated therapy is applied to only (a subgroup of) interim ^{18}F-FDG PET/CT–negative patients (and all interim ^{18}F-FDG PET/CT–positive patients receive standard therapy), any claim of noninferiority of this strategy compared with standard therapy in all patients with regard to outcome may simply be due to the generally good outcome of the entire population rather than being the merit of an ^{18}F-FDG PET/CT–based patient selection.

Given the aforementioned facts, it is our opinion that interim and end-of-treatment ^{18}F-FDG PET/CT has too quickly entered the clinical arena, without consideration of its intrinsic limitations and without a solid foundation of evidence.

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REPLY: The content of this letter to the editor from Adams and Kwee is not surprising because of these authors' long-known interest in denying the role of ^{18}F-FDG PET in lymphoma. Particularly, with the integration of ^{18}F-FDG PET in the clinical guidelines both in Europe and in the United States, it is irrefutable that ^{18}F-FDG PET has a well-recognized role in lymphoma management. In this letter, the authors' concerns and the validity of most of the points they have raised are clinically irrelevant.

More specifically, Adams and Kwee state that the spatial resolution of PET is not adequate to detect viable tumor deposits that measure below 6–9 mm. The authors do not appear to have realized the fact that imaging endpoints are surrogates for survival; therefore, they are not expected to detect every microscopic site of tumor. In our review article (*1*), we defend not that a negative ^{18}F-FDG PET finding translates to a 100% relapse-free survival but rather that it translates to a higher likelihood of a longer relapse-free survival. The better-known part of the equation is that a positive PET finding is associated with a high likelihood of residual disease presence—but again, not in 100% of cases. These likelihood scenarios give guidance to clinicians to better approach therapy algorithms. In the past, CT was the modality to be used as a guidance tool, and we all know that ^{18}F-FDG PET improved the accuracy of CT results by at least 30%. A false-positive result during therapy is a known shortcoming of ^{18}F-FDG PET, but biopsy is not a perfect method to evaluate response either because of the sampling errors and its invasive nature. Could the authors offer a noninvasive, practical modality to detect microscopic residual tumor? Alternatively, could they offer any data comparing microscopic residual disease with a negative PET result at the time of imaging to support their argument?

Adams and Kwee also wrongly state that the interim PET–adapted trials did not have a control arm. At least 3 clinical trials—H10 (*2*), HD16 (NCT00736320), and RAPID (*3*)—have control arms. In the RAPID trial, the PET-directed approach led to a 3-y progression-free survival of 95% in the radiation therapy arm and 91% in the non–radiation therapy arm (95% confidence interval, 0.84–2.97; $P = 0.16$) (*3*). Overall survival for 3 y was 97% in the involved-field radiation therapy arm and 99% in the non–involved-field radiation therapy arm, a result that was nonsignificant. In this trial, interim PET had an excellent negative predictive value. In a more detailed analysis, negative PET findings after 3 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) had an excellent prognosis without further treatment (3-y progression-free and overall survivals of 90.8% and 99.0%, respectively). In fact, these are excellent predictive values for an imaging test, considering the inherent resolution limits and also considering the absence of a comparable imaging modality to be a contender to PET.

Moreover, the authors' negative claim about end-therapy PET is entirely contrary to scientific evidence. End-therapy ^{18}F-FDG PET has the most established role for predicting survival. The authors can review the metaanalysis by Zhu et al. (*4*), as well as recent prospective data published by Mamot et al. (*5*), Martelli et al. (*6*), and González-Barca (*7*) et al.

Overall, Adams and Kwee's claims are based on flawed and incorrect assumptions and a lack of understanding of clinical trial designs and published study results. The oncologic community and the imagers do stand by the published ^{18}F-FDG PET data, particularly the end-therapy PET data, which showed a strong correlation between posttherapy PET status and survival. The results of large prospective trials are also emerging (NCT01856192, NCT01287741, and NTR1014), and some early results further support end-therapy PET as a good surrogate endpoint for progression-free survival (unpublished data). However, the mature results of large prospective datasets should also undergo meta-analysis for further validation of PET as a reliable surrogate for outcome.

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