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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 ¹⁸F-FDG PET in lymphoma. Particularly, with the integration of ¹⁸F-FDG PET in the clinical guidelines both in Europe and in the United States, it is irrefutable that ¹⁸F-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 ¹⁸F-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 ¹⁸F-FDG PET improved the accuracy of CT results by at least 30%. A false-positive result during therapy is a known shortcoming of ¹⁸F-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 ¹⁸F-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 ¹⁸F-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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