

Reply to H.J.A. Adams et al and C. Kobe et al

We thank Adams and Kwee¹ and Kobe et al² for their interest in our subsidiary analysis from the RAPID (Randomized Phase III Trial to Determine the Role of Fluorodeoxyglucose-PET Imaging in Clinical Stages IA/IIA Hodgkin Disease) trial.³ In this study, we demonstrate that individual positron emission tomography (PET) score is strongly associated with outcome. Patients with stage IA to IIA early-stage Hodgkin lymphoma (HL) with a PET score of 5 after three cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) had significantly worse outcomes, with 5-year event-free survival (EFS) and overall survival rates of 61.9% (95% CI, 41.1% to 82.7%) and 85.2% (95% CI, 69.7% to 100%), respectively, compared with 93.4% (95% CI, 91.0% to 95.8%) and 97.8% (95% CI, 96.4% to 99.2%) in patients with PET scores of 1 to 4.

Adams and Kwee¹ conclude rightly that a majority of patients with early-stage HL have reasonable outcomes without treatment escalation and highlight that the proportion of patients in our study with a PET score of 5 was low. However, we strongly disagree that these markedly inferior EFS and overall survival rates constitute reasonable outcomes for patients with a PET score of 5 treated with four cycles of ABVD and involved-field radiotherapy, particularly when the potential benefits of early treatment intensification have already been demonstrated by the H10 trial.⁴

Kobe et al² raise concerns that our results were biased by treatment differences. However, patients with a score of 5 had significantly higher risk than those with all other scores, including patients with a score of 3 or 4 who received identical treatment. The strong association between a score of 5 and inferior outcome is a robust finding, which remained after adjusting for treatment in patients with a score of 1 or 2 and excluding patients who did not receive radiotherapy.³

We thank Kobe et al² for highlighting inconsistencies in the definition of Deauville score 5 (DS5) and providing the opportunity to clarify the current internationally agreed recommendations.^{5,6} The 5-point scale was developed by our group⁷ and adopted as the preferred reporting method at the first international workshop in Deauville.⁸ A score of 5 was originally defined by us as “uptake markedly higher than the liver and/or new lesions.”^{7(p1826,3050-3051)} We chose to use three times the maximum liver uptake in RAPID,^{3,9} with appropriately rigorous quality control to ensure quantitative accuracy. The Deauville publication defined DS5 as “markedly increased uptake at any site and new sites of disease,”^{8(p1259)} but this was subsequently revised in line with our original definition, and the original

definition was used in validation studies^{10,11} and 2014 international guidance.^{5,6}

The decision-making scan in RAPID was not an end-of-treatment assessment for most patients.^{3,9} The 2014 guidance stated an interim score of 4 or 5 may represent chemotherapy-sensitive disease if “uptake has reduced from baseline”^{6(p3062)} but that the degree of reduction that predicted adequate response was “dependent on disease type, timing, and treatment given.”^{6(p3063)} We do not seek to redefine existing definitions of PET positivity, which apply primarily to end of treatment, but rather to provide important data where evidence is lacking regarding use of interim PET.

We appreciate concerns raised by Kobe et al² that our results should not be overinterpreted. We are conscious of the limitations of this exploratory analysis, clearly acknowledging that “relatively few patients had a PET score 4 with a small number of events.”³ We have not claimed outcomes to be equivalent for patients with scores of 1 to 3 and a score of 4; however, we did not observe a difference between these groups. Although EFS was inferior for patients with a score of 4 or 5 combined, this was driven almost entirely by events in patients with a score of 5. Patients with a score of 4 had good outcomes with ABVD and involved-field radiotherapy, with a 5-year EFS of 93.5% (95% CI, 84.9% to 100%). Treatment of patients with DS4 and nonbulky early-stage HL requires careful consideration in light of the H10 study,⁴ but our results highlight uncertainty regarding the need for treatment escalation in this group.³

Adams and Kwee¹ point out that most relapses occurred in patients with scores of 1 to 4 and conclude that these patients cannot benefit from PET-guided approaches. However, in the 93.4% (95% CI, 91.0% to 95.8%) of patients with PET scores of 1 to 4 who remained event free at 5 years, excellent outcomes were achieved with less-intensive treatment than with the prior standard of care and the H10 approach⁴ in patients with nonbulky stage I to IIA HL. We therefore believe that there are clear benefits with PET-guided treatment.

We thank Kobe et al² for acknowledging the importance of early PET response in risk-adapted treatment strategies and agreeing that our results are hypothesis generating. We also believe that our findings emphasize the need to re-evaluate clinical prognostic groupings. We hope this subsidiary analysis³ will assist in future trial designs and promote reporting of individualized PET scores using clear methodology to enable external validation, while supporting a need for treatment intensification in patients with DS5.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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