Post-ABVD biopsy results, and not post-ABVD FDG-PET results, predict outcome in early-stage Hodgkin lymphoma

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Conflict of interest

The authors have no competing interests.

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Post-ABVD biopsy results, and not post-ABVD FDG-PET results, predict outcome in early-stage Hodgkin lymphoma

We read with interest the recently published article by Milgrom *et al* (2017) entitled '*Early-stage Hodgkin lymphoma outcomes after combined modality therapy according to the post-chemotherapy 5-point score: can residual pet-positive disease be cured with radiotherapy alone?*'. Their study included 174 patients with early-stage (I-II) Hodgkin lymphoma treated with ABVD (doxorubicin, bleomycin, vincristine; dacarbazine; median 4 cycles, range 2–6) followed by an ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan. Patients were treated with additional radiation therapy (RT) regardless of FDG-PET findings. The prognostic value of post-ABVD FDG-PET results according to the

Deauville criteria and several quantitative FDG-PET biomarkers (table IV in Milgrom *et al*, 2017) was evaluated. After ABVD therapy, 5-year progression-free survival (PFS) was 100% (0 relapses/98 patients) in patients with Deauville scores of 1–2, 97% (2/65) for a Deauville score of 3, 83% (1/8) for a Deauville score of 4 and 67% (1/3) for a Deauville score of 5. Three of 11 (27·3%) patients with positive FDG-PET results (i.e. Deauville score ≥4) underwent biopsy of residual FDG-avid lesions. FDG-PET results were false-positive in 2/3 (66%), with biopsy showing no lymphoma, whereas biopsy revealed residual lymphoma in 1/3 (33%) cases. This particular patient developed disease relapse during follow-up. On the other hand, none of the FDG-PET metrics was able to differentiate between relapsing and non-relapsing patients. The results were compared with a very selective group (inclusion criteria for this cohort not clearly described in the methods section) of 15 Hodgkin lymphoma patients treated with additional salvage chemotherapy and autologous stem cell transplantation (ASCT). Of these 15 patients, 13 had undergone post ABVD biopsy, with 13 of these biopsies (100%) showing residual lymphoma, highly contrasting the results of the other cohort, in which biopsy showed no lymphoma in the majority of cases. Despite intensive treatment with ASCT, 6/15 (40%) Hodgkin lymphoma patients developed disease relapse during follow-up. Comparison between these two cohorts revealed FDG-PET metrics to be more or less similar in both groups (table III in Milgrom *et al*, 2017), despite the clearly different prognosis of patients included in these two cohorts. Moreover, despite Milgrom *et al*.'s statement that the 15 patients treated with intensive therapies all suffered from stable or progressive disease, the reduction in FDG-PET metrics in this cohort was notable (Table III in Milgrom *et al*, 2017). On the other hand, a strong significant difference ($P < 0{\cdot}001$) between these two cohorts was the presence of a post-ABVD lymphoma-positive biopsy (table III in Milgrom *et al*, 2017). The authors concluded that a positive post-ABVD FDG-PET scan was associated with inferior PFS, but the majority of patients with positive FDG-PET results were considered to be curable with RT alone.

However, we disagree with their interpretations. First, we believe the conclusion of Milgrom *et al* (2017) overestimates the value of FDG-PET. Note that only 4 cases of disease relapse occurred, of whom 2 (50%) had negative post-ABVD FDG-PET results (Deauville score 3). One case of relapse in a patient with positive post-ABVD FDG-PET results (Deauville score 4) occurred 5 years after treatment [figure 1 (Milgrom *et al*, 2017)], which strongly suggests that this is not the same disease but a lymphoma *de novo*, further reducing the predictive value of post-ABVD FDG-PET. Second, we believe the title of their article does not reflect their findings, in which they report FDG-avidity to be synonymous to residual lymphoma ('*can residual PET-positive disease be cured with radiotherapy alone?*') despite their finding that 2/3 (66%) of cases of residual FDG-avid lesions appeared to be false-positive when biopsy was performed. Note that the high false-positive rate at response evaluation scans in Hodgkin lymphoma has be reported before (Adams & Kwee, 2016, 2017), with inflammation being responsible for FDG-avidity in the majority of cases. The fact that post-ABVD FDG-PET results alone have a low positive predictive value (PPV) in predicting disease relapse, and biopsy results do clearly predict a dismal prognosis, suggest that false-positive results are common at post-ABVD FDG-PET scans.

The poor predictive value of post-ABVD FDG-PET scans performed in early-stage Hodgkin lymphoma patients treated with ABVD and RT is well known. Radford *et al* (2015) included 565 patients with early-stage Hodgkin lymphoma treated with 3 cycles of ABVD followed by an FDG-PET scan. Positive FDG-PET results were found in 145/565 (25·6%) patients, and these patients were treated with only 1 additional cycle of ABVD and RT. Remarkably, 127/145 (87·6%) of these patients remained alive without disease progression and 3/145 (2·1%) died of causes other than lymphoma, resulting in a poor predictive value of only 10·3% for FDG-PET in predicting relapse during follow-up (Radford *et al*, 2015). Note that only 5/565 patients of the entire cohort (0·9%) had positive FDG-PET results and died due to persistent Hodgkin lymphoma (Radford *et al*, 2015), which underlines that only a very small proportion of patients can potentially benefit from early treatment intensification based on these FDG-PET results. Ciammella *et al* (2016) retrospectively evaluated 165 early-stage Hodgkin lymphoma patients treated with ABVD and RT with available post-ABVD FDG-PET scans. These scans were positive in only 23/165 (13·9%) when the Deauville criteria were applied. Of these 23 patients, only 4 suffered disease relapse after additional treatment with RT or intensified chemotherapy, resulting in a poor PPV of only 17·4% for post-ABVD FDG-PET.

In conclusion, studies applying biopsies of residual FDG-avid lesions at PET scans after ABVD therapy revealed false-positive results in an unacceptably high proportion of cases. Furthermore, a dismal prognosis is predicted by the presence of residual lymphoma in the biopsy specimen, rather than FDG-PET results, which further fuels the presumption that post-ABVD FDG-PET results are false-positive in a high proportion of cases.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Author contributions

Hugo J.A. Adams: study design, article writing, final approval of the manuscript. Thomas C. Kwee: study design, article writing, final approval of the manuscript.

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Conflicts of interest

None (all authors).

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Post-ABVD biopsy results, and not post-ABVD FDG-PET results, predict outcome in early-stage Hodgkin lymphoma: response to Adams and Kwee

We would like to thank Drs. Adams and Kwee for their thoughtful review of our paper (Milgrom *et al*, 2017). We assessed the outcomes of early-stage Hodgkin lymphoma (HL) patients according to the results of end of chemotherapy (eoc)-positron emission tomography (PET) scans that were performed after the completion of ABVD (doxorubicin, bleomycin, vincristine, dacarbazine) and before radiation therapy (RT) was given. We identified excellent outcomes for the cohort overall, consistent with the known favourable prognosis of early-stage HL patients. We focused our attention on patients who had a positive eoc-PET scan, defined as a Deauville 5-point score (5PS) of 4 or 5. Despite the persistent PET-positivity, these patients had achieved a significant partial response to ABVD. The majority of these cases were cured with RT alone, suggesting that appropriately selected patients with a post-ABVD 5PS of 4 or 5 may be salvaged with RT and thus spared intensive salvage chemotherapy and autologous stem cell transplantation (ASCT).

In response to our paper, Drs. Adams and Kwee have argued that 'post-ABVD biopsy results, and not post-ABVD FDG-PET results, predict outcome in early-stage Hodgkin lymphoma.' However, multiple groups have demonstrated the significant association between post-treatment PET results and risk of relapse (Cremerius *et al*, 2001; Naumann *et al*, 2001; Spaepen *et al*, 2001; Advani *et al*, 2007; Furth *et al*, 2009; Barnes *et al*, 2011). Therefore, we believe that Drs. Adams and Kwee meant to argue that 'post-ABVD biopsy results predict outcome *more accurately* than post-ABVD FDG-PET results.' As evidence, they cite their work, which shows that post-treatment PET scans may give false positive findings. We agree that a 5PS of 4-5 may represent a false positive result, as mentioned in our Discussion section. Although a biopsy is recommended to verify the presence of persistent disease, it may not be possible, particularly after a significant partial disease response, as was experienced by the patients in our cohort. In this setting, the small area of persistent ^{18}F-fluoro-2-deoxy-D-glucose