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Interim Fluorodeoxyglucose Positron Emission Tomography–Adapted Therapy Is Not an Efficient Approach to Improving Outcome in Early-Stage Hodgkin Lymphoma

TO THE EDITOR: We read with interest the recent article in *Journal of Clinical Oncology* by André et al,¹ which included 1,950 patients with early-stage favorable or unfavorable Hodgkin lymphoma who underwent interim fluorodeoxyglucose (FDG) positron emission tomography (PET) after two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Depending on the interim FDG-PET results, patients were randomly assigned to continuation of ABVD therapy with involved-field radiotherapy (IFRT); intensified therapy with escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) and IFRT; or de-escalated therapy with ABVD monotherapy without IFRT. After two cycles of ABVD, interim FDG-PET was positive in 18.8% of patients (13.0% with a favorable and 22.4% with an unfavorable risk profile). Treatment de-escalation in interim FDG-PET–negative patients was considered infeasible because of the higher relapse rate in patients treated without IFRT in both the favorable and unfavorable Hodgkin lymphoma subgroups. Unfortunately, subgroup analyses in interim FDG-PET–positive patients was not performed “because of their presumed common poor prognosis.”^{1(p1787)} The 5-year progression-free survival (PFS) rate was 77.4% in interim FDG-PET–positive patients treated with standard treatment, with 36 of 192 (18.8%) patients developing disease relapse during follow-up, whereas the 5-year PFS rate was 90.6% in interim FDG-PET–positive patients treated with escalated treatment, with 13 of 169 (7.7%) patients developing disease relapse during follow-up, resulting in a risk difference of 11.1%. André et al¹ concluded that classic European Organisation for Research and Treatment of Cancer prognostic factors (eg, erythrocyte sedimentation rate, B symptoms, age, and bulky disease) lose clinical relevance in the era of FDG-PET–adapted therapy. They also concluded that interim FDG-PET allowed for early treatment adaptation, but only for treatment intensification in interim FDG-PET–positive patients, whereas a negative interim FDG-PET result was not considered appropriate for omission of IFRT.

Although these results sound promising, we have several comments. First, André et al’s claim that a positive interim FDG-PET result guarantees a poor prognosis is untrue, because this statement was simply not supported by their own data. Note that patients with positive interim FDG-PET results had a good 5-year PFS of 77.4% and high 5-year overall survival of 89.3% following continuation of standard therapies.¹ Second, we do not agree with the authors’ statement that classic risk

factors lose clinical significance in the era of interim FDG-PET. In the negative interim FDG-PET group, there was a remarkable difference in PFS rates between patients with favorable (5-year PFS, 99.0%) and unfavorable (5-year PFS, 92.1%) risk profiles, despite the fact that patients with an unfavorable risk profile received more ABVD cycles. On the other hand, a subgroup analysis of favorable versus unfavorable cases in interim FDG-PET–positive patients was not performed. Consequently, it remains unknown whether treatment escalation is equally effective in these subgroups. The predictive value of interim FDG-PET in these subgroups has not been described previously, and omission of reporting these analyses results in a major loss of valuable available data. Third, we believe that an interim FDG-PET–adapted therapeutic approach is highly inefficient. Only 18.8% of patients will be positive at interim FDG-PET, who will all receive intensified therapy with escalated doses of BEACOPP. Of this subgroup, only 11.1% (risk difference in relapse rate) of patients will benefit from this treatment intensification. Consequently, only $0.188 \times 0.111 \times 100\% = 2.1\%$ of patients who undergo interim FDG-PET will benefit from this approach, because treatment de-escalation in interim FDG-PET–negative cases is considered infeasible. This high number of patients needed to scan would result in major increases in costs, radiation exposure, and patient discomfort. The outcome benefit of this approach is further nullified by the fact that the majority of cases in which first-line therapy fails can be cured by second-line therapies. This is reflected by the finding that, despite the large sample size and long minimum follow-up time, no benefit in overall survival ($P = .062$) was observed.¹ Note that the benefit of this approach will be even lower in the subgroup of favorable Hodgkin lymphoma, because of the lower incidence of interim FDG-PET–positive patients in this subgroup¹ and the presumption that it is not unlikely that prognosis is better in this subgroup even if standard, nonintensified therapy is applied. It is not unlikely that other cheap and readily available predictive biomarkers, such as the presence of two or more European Organisation for Research and Treatment of Cancer risk factors, will be able to provide comparable prognostic value and may consequently be better surrogates for deciding when to adapt treatment.

In conclusion, an interim FDG-PET–adapted therapeutic approach in early-stage Hodgkin lymphoma exposes all patients to more imaging-related ionizing radiation, subjects a considerable proportion (ie, all interim FDG-PET–positive patients) to intensified therapy, and will provide benefit to only a small minority of patients whose disease relapse will be avoided. Furthermore, overall survival is not improved, and health care costs will increase considerably. Therefore, interim FDG-PET–adapted therapy is not an efficient approach to improving outcome.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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No relationship to disclose

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No relationship to disclose