Inability of Fluorodeoxyglucose Positron Emission Tomography to Detect Viable Hodgkin Lymphoma During and After Treatment

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Published in:
Journal of Clinical Oncology

DOI:
10.1200/JCO.19.02780

Publication date:
2020

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TO THE EDITOR:

The HD16 trial described by Fuchs et al[1] aimed to determine whether fluorodeoxyglucose positron emission tomography (FDG-PET) scans after 2 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) might help predict individual outcomes and guide treatment. Of the 1,007 patients included, FDG-PET after 2 cycles of ABVD revealed a Deauville score (DS) of 1 or 2 in 667 patients (66%), a DS of 3 in 218 (22%), a DS of 4 in 122 (12%), and a DS of 5 in 0 (0%). Using a conservative threshold, patients with a DS of 1 or 2 were randomly assigned to an additional 20 Gy of radiation therapy or no further treatment, whereas all patients with a DS of ≥ 3 were treated with an additional 20 Gy of radiation therapy. In the 328 patients with a DS of 1-2 treated with ABVD and radiation therapy, 15 (4.6%) had a tumor event, whereas in the 300 patients treated with ABVD only, 29 (9.7%) had a tumor event. In the 218 patients with a DS of 3 treated with ABVD and radiation therapy, 13 (6.0%) had a tumor event, whereas in the 122 patients with a DS of 4 treated with ABVD and radiation therapy, a tumor event occurred in 17 patients (13.9%). Of all 74 tumor events in all groups combined, 7 (9.5%) were classified as early progression occurring within 3 months of treatment, 17 (23.0%) as an early relapse within 1 year of treatment, and 50 (67.6%) as a late relapse occurring $>$ 1 year after treatment. When only considering the patients treated with ABVD and radiation therapy, the 5-year progression-free survival (PFS) rate of patients with a DS of 1-2 (93.2%) was not very different from that of patients with a DS of ≥ 3 (88.4%). However, when a DS of ≥ 4 was used as the cutoff value, the predictive value improved. The 5-year PFS rate of patients with a DS ≤ 3 (93.1%) was significantly different from that of patients with a DS of ≥ 4 (80.9%). Fuchs et al[1] concluded that an FDG-PET with a DS of ≥ 4 indicates a high risk of treatment failure, and that radiation therapy in patients with low DS cannot be omitted without a clinically relevant loss of tumor control.

We would like to add some remarks to the discussion. First, we do not agree with Fuchs et al[1] that a DS of ≥ 4 indicates a high risk of treatment failure, because 80.9% of these patients were still disease free 5 years after standard treatment. As a result, FDG-PET results are not likely to be useful for risk-adapted treatment approaches, because the vast majority of patients with a DS ≥ 4 cannot benefit from treatment intensification. Furthermore, second-line therapies were able to cure the majority of patients in whom first-line therapy failed (only 1 Hodgkin lymphoma–related death in all patients with a DS of ≥ 4), further undermining the potential benefit of FDG-PET–adapted treatment escalation in these patients. Second, FDG-PET after 2 cycles of ABVD failed to detect the majority of patients with viable residual lymphoma. Note that only 17 (23.0%) of all 74 tumor events occurred in patients with a DS of ≥ 4, whereas 57 tumor events (77.0%) occurred in patients with a DS ≤ 3. Third, the end-of-treatment evaluations failed to detect residual viable lymphoma in a high proportion of patients. Note that in 67.6% of patients, the relapsed lymphoma was detected $>$ 1 year after treatment, which indicates that determining disease status within a short time frame after treatment is not feasible using current treatment evaluation methods.

As a result of the limited spatial resolution of PET scanners, residual viable lymphomatous cells cannot be excluded.[2] This has been demonstrated by multiple studies showing a high number of disease relapses in patients with negative end-of-treatment FDG-PET examinations.[3] The low sensitivity of FDG-PET to detect residual lymphoma explains why trials applying treatment de-escalation (ie, omitting radiation therapy) in Hodgkin lymphoma homogeneously showed a loss of tumor control in patients treated with chemotherapy alone.[1,4,5] Furthermore, even patients with Hodgkin lymphoma treated with palliative intent and patients with indolent, noncurable but baseline FDG-avid non-Hodgkin lymphomas frequently acquire an FDG-PET–negative status, but this does not equal cure.

In conclusion, FDG-PET cannot exclude residual viable lymphoma, cannot be used to inform patients about their prognosis, cannot be used to guide treatment, and cannot be used as an outcome measure of therapeutic trials. Therefore, the use of FDG-PET scans during and after treatment in patients with Hodgkin lymphoma seems unjustified.

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

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.02780.

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DOI: https://doi.org/10.1200/JCO.19.02780; Published at ascopubs.org/journal/jco on January 30, 2020.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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