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Reply: Interim PET in Hodgkin lymphoma: is it so useless?

Running title: Interim PET useless in Hodgkin lymphoma?

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We thank Meignan et al. (*1*) for their interest in our recently published article "Fact sheet about interim and end-of-treatment ^{18}F-FDG PET/CT in lymphoma" (*2*), in which we document the limitations and low necessity of interim ^{18}F-FDG PET/CT imaging in lymphoma. Although Meignan et al. (*1*) seem to agree with us that interim ^{18}F-FDG PET/CT has low clinical value in *non-Hodgkin* lymphoma (*2-4*), they disagree on the value of interim ^{18}F-FDG PET/CT in *Hodgkin* lymphoma, which we will therefore discuss in this reply.

Hodgkin lymphoma is usually divided in early- and advanced-stage disease, which are treated differently, and have a different prognosis. Studies have shown that the value of interim ^{18}F-FDG PET/CT for predicting outcome is not homogeneous in these different disease entities. In early-stage Hodgkin lymphoma the value of interim ^{18}F-FDG PET/CT can be considered low: patients with positive interim ^{18}F-FDG PET/CT scans have been reported to have a generally good progression-free survival (PFS, range: 30%-100%) and an excellent overall survival (OS, range: 85.2%-100%) after standard, non-intensified therapies, with the majority of studies reporting long-term PFS estimates higher than 80% (*5*). Consequently, it has to be concluded that the far majority of patients with positive interim ^{18}F-FDG PET/CT scans remains disease-free after finishing non-intensified treatment, and that second-line and third-line therapies can cure the majority of patients in whom first-line therapy fails. This seriously questions whether early treatment intensification based on interim ^{18}F-FDG PET/CT results is justified. Preliminary data from the not yet published randomized EORTC/LYSA/FIL H10 trial (*6*) showed interim ^{18}F-FDG PET/CT positive patients treated with intensified regimens (2×ABVD + 2×BEACOPP$_{esc}$ + radiation therapy [RT]) to have a better PFS than those treated with standard therapy (3× ABVD

+ RT) (5-year PFS 91% vs. 77%), but OS was not significantly different between these two groups (*6*), supporting our aforementioned statement. On the other hand, although the relapse rate of early-stage Hodgkin lymphoma patients with negative interim ^{18}F-FDG PET/CT results treated with standard therapies is low from an absolute point of view (*7-9*), it is actually high considering the generally good prognosis (long-term PFS≈93% (*10*)) of these patients, which underlines that a negative interim ^{18}F-FDG PET/CT result cannot reliably exclude residual disease (*11*). Although randomized studies applying interim ^{18}F-FDG PET/CT based treatment de-escalation (*7,8*) have shown that interim ^{18}F-FDG PET/CT negative patients have a generally good outcome after being treated with less intensive therapies, this is more likely a reflection of the generally good prognosis of the disease rather than thanks to the negative predictive value (NPV) of interim ^{18}F-FDG PET/CT (*12*). Note that from a relative point of view, disease relapse occurs much more frequently in patients treated with de-escalated therapies than in those who continue standard therapy regimens despite negative interim ^{18}F-FDG PET/CT results (hazard ratios of up to 9.36 have been reported (*7,8,12*)). Considering the low positive predictive value (PPV) and low NPV, it remains very questionable whether an interim ^{18}F-FDG PET/CT based therapeutic approach is justified in early-stage Hodgkin lymphoma. This is not at least due the fact that several other, cheap and easily available biomarkers (for example the EORTC, GHSG, and NCCN risk models (*13*)) have shown to have prognostic value in this disease, equaling those of interim ^{18}F-FDG PET/CT, which may be a better surrogate for risk adapted trials. Note that ^{18}F-FDG PET/CT scans are expensive, expose patients to potentially harmful ionizing radiation, provide patient discomfort and are not available in all institutions (particularly in non-Western countries). Therefore, it is not unlikely that interim FDG-PET is useless in early-stage Hodgkin lymphoma.

In advanced-stage Hodgkin lymphoma, results on the predictive value of interim ^{18}F-FDG PET/CT are less consistent. Two studies by Gallamini et al. (*14,15*) reported interim ^{18}F-FDG PET/CT to have an excellent PPV and NPV. Patients with positive interim ^{18}F-FDG PET/CT results had a dismal PFS of 12.8% and 28%, whereas patients with negative interim ^{18}F-FDG PET/CT results had an excellent PFS of 95% in both studies after finishing standard ABVD therapy (*14,15*). However, both studies suffered from a major methodological flaw: only a very small minority of cases of disease relapses was histologically confirmed, and relapse was documented by means of follow-up imaging in the majority of cases (*14-17*). Note that posttreatment and follow-up ^{18}F-FDG PET/CT studies suffer from a strikingly high number of false-positives, as has been reported in several lymphoma subtypes (*18-21*), including Hodgkin lymphoma (*22*). Consequently, the studies by Gallamini et al. (*14,15*) are methodologically seriously biased. Note that the predictive value of interim ^{18}F-FDG PET/CT was generally lower in other comparable studies (*23*) and that 2 recent studies (*24,25*) including advanced-stage lymphoma as part of their patient population showed interim ^{18}F-FDG PET/CT to have minor or no value at all in predicting prognosis. As already reported in our fact sheet (*2*) and repeated by Meignan et al. (*1*), 3 recent studies (*26-28*) on treatment intensification in interim ^{18}F-FDG PET/CT positive patients were published, all lacking a randomized control arm treated with non-intensified treatments. Consequently, the true benefit of treatment intensification in these patients could not be assessed. In addition, comparisons with historical studies that suffered from inadequate methodology and heterogeneous results are futile (*23*). Note that we individually criticized all these 3 studies for these issues (*29-31*). On the other hand, multiple, recently published, large-scale studies (*16,26-28*) unambiguously showed that (in contrast to the studies by Gallamini et al. (*14,15*)) actually a high proportion of the large group of negative interim ^{18}F-FDG PET/CT patients develops disease relapse during follow-up, which means that a negative

interim ^{18}F-FDG PET/CT result cannot exclude residual disease. In other words, the majority of relapses occurs after a negative interim ^{18}F-FDG PET/CT result (*16,26-28*). This concern should be taken into account when interpreting the results of the (not yet published) study by Casasnovas/Meignan et al. (*32*) on treatment de-escalation in interim ^{18}F-FDG PET/CT negative patients, which is the only randomized study yet available claiming that ^{18}F-FDG PET/CT based treatment de-escalation is feasible (except the minor changes in treatment as performed by Johnson et al. (*26*) who omitted bleomycin in interim ^{18}F-FDG PET/CT negative patients without a significant increase in relapse rate).

In conclusion, interim ^{18}F-FDG PET/CT is not justified in early-stage Hodgkin lymphoma. The value of positive interim ^{18}F-FDG PET/CT results in advanced-stage Hodgkin lymphoma is not well established due to methodological issues in historical studies, and a lack of a control/randomization arm in recent ^{18}F-FDG PET/CT adapted trials. On the other hand, the majority of disease relapses in advanced-stage Hodgkin lymphoma occurs in the large group of interim ^{18}F-FDG PET/CT negative patients, which underlines that residual disease cannot be excluded and that treatment de-escalation in these patients is highly questionable. Except for the currently not yet published results of the AHL2011 LYSA Study performed by Casasnovas/Meignan et al. (*32*), there is no data that confirms that treatment de-escalation in interim ^{18}F-FDG PET/CT negative advanced-stage Hodgkin lymphoma is feasible. Therefore, there is currently no convincing evidence to support interim ^{18}F-FDG PET/CT in routine clinical care in both early- and advanced-stage Hodgkin lymphoma, neither for prognostication, nor for treatment adaptation.

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