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Prudence required when using ^{18}F-FDG PET as reference standard for lymphoma detection

Running title: ^{11}C-MET and ^{18}F-FDG PET in lymphoma

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With interest we read the article by Kaste et al. (*1*) entitled "*Comparison of ^{11}C-methionine and ^{18}F-FDG PET-CT for staging and follow-up of pediatric lymphoma*" that was recently published in the Journal. Kaste et al. (*1*) mention ^{18}F-FDG PET to be a valuable tool for staging and response monitoring in lymphoma, with a particular high sensitivity but limited specificity due to non-malignant etiologies that may mimic tumor uptake. Therefore, another tracer, ^{11}C-methionine (^{11}C-MET), was investigated and compared to ^{18}F-FDG for both staging and monitoring response to therapy after treatment in 21 pediatric patients (19 with Hodgkin lymphoma, 2 with diffuse large B-cell lymphoma [DLBCL]). At staging, 3 nodal groups demonstrated discordant metabolic activity, whereas all others were found to have concordant metabolic activity. Eight weeks after treatment, paired ^{18}F-FDG and ^{11}C-MET PET was available in 15 patients, of whom 14 (93.3%) had concordant ^{18}F-FDG PET and ^{11}C-MET PET results. In the remaining patient, metabolic activity was minimally discordant: ^{18}F-FDG PET had normalized, but the ^{11}C-MET PET study remained slightly positive. This particular patient remained well for more than 3 years from diagnosis without further treatment (i.e., false-positive end-of-treatment ^{11}C-MET PET). During follow-up, 3 patients developed disease relapse and 1 patient developed a secondary DLBCL (importantly, it was not reported how these events related to end-of-treatment ^{18}F-FDG and ^{11}C-MET PET results) and no deaths occurred. Kaste et al. (*1*) concluded ^{11}C-MET uptake to be elevated in most regions involved with lymphoma, both at baseline and at end-of-treatment.

However, we disagree with Kaste et al.'s (*1*) conclusion. Their claim that increased ^{11}C-MET uptake is observed in most regions involved with lymphoma cannot be determined by a comparison with staging and response assessment ^{18}F-FDG PET scans, due to a suboptimal sensitivity and specificity of this imaging modality. First, ^{18}F-FDG can accumulate in many

different other cancers, and several benign alterations, particularly infections and (therapeutic lesions) as already noted by Kaste et al. (*1*) themselves. Studies have also shown that tumor-associated ^{18}F-FDG uptake is not only due to viable tumor cells, but also due to a considerable proportion of non-neoplastic cellular elements (such as macrophages) (*2*). Particularly Hodgkin lymphoma is s an extreme example of this phenomenon, since malignant Reed-Sternberg tumor cells occupy only 0.1-1.0% of the pathological substrate, while the remainder of tissue consists of inflammatory cells . Also note that after start of chemotherapy, an increase in apoptotic and necrotic tumor fraction is followed by an early (4-6-days afterwards) influx of inflammatory cells that consume ^{18}F-FDG (*3*). Therefore, ^{18}F-FDG-avidity during or after treatment generally does not reflect lymphomatous tissue, as has already been shown by several studies that showed a high rate of biopsied false-positive FDG-avid residual lesions (*4*). On the other hand, negative ^{18}F-FDG PET results cannot exclude lymphomatous tumor involvement, particularly after treatment. This has been convincingly shown by several studies reporting absence of ^{18}F-FDG-avid bone marrow lesions in patients with lymphoma-positive bone marrow biopsies (*5*). Furthermore, anti-lymphoma therapy has been reported to reduce glucose uptake by malignant cells as a result of downregulation of glucose membrane transporters and/or hexokinase activity (*6*), generating false-negative results. Finally and most importantly, the spatial resolution of current PET systems is only 6-7 mm, as a result of which it cannot exclude presence involvement by small lymphomatous deposits (*7*). This hypothesis is supported by several findings such as the occurrence of disease relapse in large proportions of patients who acquired ^{18}F-FDG PET negative status (*8,9*), a lower relapse rate in patients with negative ^{18}F-FDG PET results after chemotherapy who were treated with additional radiation therapy compared to those who were treated with chemotherapy alone (*10*), and the fact that huge proportions of patients with incurable, indolent lymphomas treated with non-curative chemotherapy can acquire a negative

^{18}F-FDG PET status after therapy. However, the latter does by no means imply the absence of residual lymphomatous disease after treatment.

In conclusion, caution is warranted when using staging and (particularly) response assessment ^{18}F-FDG PET scans as reference standard for determining the presence or absence of lymphoma deposits throughout the body, since this test suffers from a non-negligible proportion of false-positives and false-negatives. Since Kaste et al. (*1*) reported ^{11}C-MET PET to closely match ^{18}F-FDG PET results, they should have concluded that the former appears to be equally good or bad as the latter in terms of lymphoma detection, rather than that ^{11}C-MET uptake is elevated in most regions involved with lymphoma.

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