Interim FDG-PET in lymphoma, a questionable practice in hematology

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Lymphoma is the sixth most frequently occurring malignancy in the Western world, accounting for 4.8% of all malignancies [1]. Lymphomas are treated with (immuno)chemotherapy or radiation therapy (RT), either as monotherapy or as combined modality treatment. Historically, treatment response evaluation was only applied after treatment, varied widely among institutions, and comprised several assessments such as the evaluation for the presence of B-symptoms, laboratory examinations, biopsies of residual masses, lymph nodes or bone marrow, liver and spleen assessment using laparotomy, and various imaging studies such as x-rays, gallium, and computed tomography (CT) scans [2]. In 1999 the International Workshop Criteria (IWC) [2] were published in order to standardize response criteria in non-Hodgkin's lymphoma. These criteria mainly relied on tumor shrinkage during therapy as assessed by CT by comparing the long-axis diameters before and after treatment [2]. In the first years of the millennium, ¹⁸F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) gradually entered the clinical arena, and several studies were published evaluating the prognostic value of FDG-PET scans after treatment. However, end-of-treatment FDG-PET scans were uniformly adopted in 2007 when

integrated into the response criteria of the International Harmonization Project (IHP) [3, 4]. The 2014 Lugano criteria [5, 6] and 2016 refinement of the Lugano criteria [7] not only promote performing FDG-PET scans after treatment, but also during treatment, also known as interim FDG-PET. These examinations are also promoted by other guidelines such as the guidelines of the European Society of Oncology (ESMO) [8, 9] and the National Comprehensive Cancer Network (NCCN) [10, 11], and the value of these examinations are hyped at conference meetings [12–14]. Consequently, interim FDG-PET scanning is adopted worldwide at numerous institutions, and thousands of lymphoma patients undergo an interim FDG-PET evaluation every year.

In the present issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Lazarovici et al. [15] report the results of an important trial. Their study included 36 patients with primary mediastinal B-cell lymphoma (PMBCL) who underwent interim FDG-PET after four cycles of immunochemotherapy. Patients with positive interim FDG-PET results according to non-specified criteria underwent histological restaging. Scans were retrospectively scored according to the Deauville criteria [6]. After four cycles of immunochemotherapy, 17 patients had positive interim FDG-PET results; two patients had a Deauville score of 2, one patient had a Deauville score of 3, and 14 patients had a Deauville score of 4. All these FDG-PET positive patients underwent histological restaging, 15 by means of surgical debulking, and two by means of CT-guided core biopsy. Histological examination revealed 16/17 positive interim FDG-PET scans to be false-positive, resulting in a false-positive rate of 94.1%. False-positive results were caused by inflammatory necrosis/fibrosis in 15 cases and silicosis in one case. During a median follow-up of 48.5 months, 2/17 (11.8%) of patients with positive interim FDG-PET results and 3/19 (15.8%) of patients with interim FDG-PET negative

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results developed disease relapse. Lazarovici et al. [15] concluded that a positive interim FDG-PET result does not reflect active disease in the vast majority of cases. Furthermore, they concluded the relapse rate to be similar between interim FDG-PET positive and negative patients, and that interim FDG-PET should be used with caution in PMBCL.

The study by Lazarovici et al. [15] is the first study that explicitly describes the false-positive rate in interim FDG-PET positive PMBCL patients. However, several prior studies have assessed the false-positive rate of positive interim FDG-PET results in aggressive non-Hodgkin's lymphoma using histological restaging as reference standard (Table 1). In 2010, a study by Moskowitz et al. [16] included 98 patients with advanced-stage aggressive non-Hodgkin's lymphoma (70 with diffuse large B-cell lymphoma [DLBCL] and 28 with PMBCL) who underwent interim FDG-PET after treatment with four cycles of R-CHOP. Patients with negative interim FDG-PET results received three additional cycles of ifosfamide, carboplatin, and etoposide (ICE), whereas patients with positive interim FDG-PET results underwent histological restaging. Patients with (false) positive interim FDG-PET results, but negative biopsies were treated equally as those with negative interim FDG-PET results, whereas patients with positive interim FDG-PET results and biopsies containing

residual lymphomatous deposits were treated with intensified therapies consisting of three additional cycles of ICE, rituximab and high-dose therapy and autologous stem cell transplantation. After four cycles of R-CHOP, 97 patients underwent interim FDG-PET, which was positive in 38 cases (39.2%). In line with the results of Lazarovici et al. [15], biopsy revealed a very high false-positive rate of 33/38 (86.8%). Patients with positive interim FDG-PET, but negative histological restaging results had a similar outcome as those with negative interim FDG-PET results ($P = 0.146$). Moskowitz et al. [16] concluded that interim FDG-PET results do not predict outcome in patients with DLBCL/PMBCL. Another prospective study by Casasnovas et al. [17] included 98 patients with DLBCL. Interim FDG-PET was performed after four cycles of immunochemotherapy and was positive in 42/98 (42.9%) according to the IHP criteria. In 10/42 (23.8%) restaging biopsy was performed, which was false-positive in 8/10 (80%) of cases. A survival analysis on the prognostic value of false-positive interim FDG-PET results was not reported. Cox et al. [18] included 73 patients with DLBCL and 12 with PMBCL who underwent interim FDG-PET after three cycles of R-CHOP or six cycles of R-MACOP-B. 24/85 (28.2%) had positive interim FDG-PET results according to the IHP criteria, of whom seven underwent restaging

Table 1 Proportion of histopathologically proven false-positive interim FDG-PET results

Study (year)	Lymphoma subtype	Therapy before FDG-PET acquisition	FDG-PET criteria for positivity	No. of interim FDG-PET positive	Proportion of patients biopsied (%)	Proportion of false-positive results (%)	Histological findings of false-positive cases
Lazarovici et al. (2017) [15]	PMBCL	4× R-ACVBP or 4× R-CHOP or 4× R-COPADEM	Non-specified criteria	17/36 (47.2%) (2× DS of 2, 1× DS of 3 and 14× DS of 4)*	17/17 (100%)	16/17 (94.1%)	15× inflammatory necrosis/fibrosis 1× silicosis
Schoder et al. (2016) [19]	DLBCL: 51 PMBCL: 13 FL grade 3B: 1	4× R-CHOP	DS 4–5	21/65 (32.3%)	21/21 (100%)	19/21 (90.5%)	19× inflammation
Cox et al. (2012) [18]	DLBCL: 73 PMBCL: 12	3× R-CHOP or 6× R-MACOP-B	IHP	24/85 (28.2%)	7/24 (29.2%)	4/7 (57.1%)	4× inflammation/reactive
Casasnovas et al. (2011) [17]	DLBCL: 98	4× R-CHOP: 52 4× R-ACVBP: 50	IHP	42/98 (42.9%)	10/42 (23.8%)	8/10 (80%)	8× “no evidence of lymphoma”
Moskowitz et al. (2010) [16]	DLBCL: 98	4× R-CHOP	>local background activity with corresponding abnormality at CT	38/98 (38.8%)	38/38 (100%)	33/38 (86.8%)	33× inflammation

*A retrospective classification according the Deauville criteria was performed in this study

ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; CHOP cyclophosphamide, doxorubicin, vincristine, and prednisone; COPADEM methotrexate, cyclophosphamide, vincristine, doxorubicin, and prednisone; DLBCL diffuse large B-cell lymphoma; DS Deauville score; FL follicular lymphoma; IHP International Harmonization Project; MACOP-B methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; OS overall survival; PFS progression-free survival; PMBCL primary mediastinal B-cell lymphoma; R rituximab

biopsy. Four of seven (57.1%) positive interim FDG-PET scans were considered false-positive, with biopsy showing inflammation only. Finally, a study by Schoder et al. [19] included 51 DLBCL, 13 PMBCL, and one follicular lymphoma grade 3B patients treated with four cycles of R-CHOP followed by an interim FDG-PET scan. Twenty-one of 65 (32.3%) scans were classified positive with a Deauville score of 4 or 5. All 21 patients underwent histological biopsies, which were false positive in 19/21 (90.5%) cases, all showing inflammation. In summary, the results of Lazarovici et al. [15] are in line with previous studies showing a strikingly high false-positive rate and a lack of prognostic value of positive interim FDG-PET results.

The non-specificity of FDG-PET scans is well known, with FDG accumulating in many different malignant and benign tumors, and non-neoplastic conditions, particularly (therapy-induced) inflammation. Laboratory studies have already shown that tumor-associated FDG-avidity is not only due to accumulation in tumor cells, but also due to a major proportion of FDG-avid accessory non-neoplastic cells, for example macrophages and granulocytes [20]. Particularly Hodgkin's lymphoma is well known for this phenomenon, because the neoplastic Reed-Sternberg cells comprise no more than 0.1–1.0% of the pathological substrate and the far majority consists of associated inflammatory neutrophils, macrophages, eosinophils, mast cells, histiocytes, macrophages, B-cells, and natural killer cells [21]. Laboratory studies indicate that soon after treatment initiation (as soon as 4–6 days), an increase in apoptotic and necrotic tumor cell is followed by an influx of inflammatory, FDG-consuming cells [20]. On the other hand, after treatment initiation, tumor FDG uptake declines rapidly as soon as after 1 day, and there is no difference in tumor FDG uptake between FDG-PET scans 20 days after treatment and after the entire regimen [22]. Therefore, interim FDG-PET does not reflect the dose-response relationship of anti-lymphoma treatments, as has been shown by aforementioned studies showing virtually all FDG uptake at interim PET to be caused by inflammation [15–19].

The fact that a positive interim FDG-PET may represent inflammation rather than viable lymphoma and that interim FDG-PET results have no prognostic value at all, have major clinical and scientific consequences. First, there is no justification to perform interim FDG-PET scans in routine clinical care. Note that the results can cause anxiety when the patient is incorrectly informed that the lymphoma is not responding well to treatment. Furthermore, it may erroneously cause the treating physician to alter treatment. Drawbacks such as the high costs and exposure to ionizing radiation associated with excessive FDG-PET imaging should also be considered. Moreover, considering the high false-positive rate, performing biopsies of residual FDG-avid lesions at interim FDG-PET will have low value and result in additional costs, anxiety, and risks. Second, interim FDG-PET results cannot be used

for early assessment of the effectiveness of new therapies in ongoing or future therapeutic trials, and studies reporting interim FDG-PET results as outcome measure may not be valid. Finally, studies on treatment adaptation on the basis of interim FDG-PET results are likely in vain.

In conclusion, FDG-avidity at interim PET may represent (therapy-induced) inflammation rather than viable lymphoma and interim FDG-PET results may have no prognostic value. The hematology community has persistently overseen these findings and incorporated interim FDG-PET in guidelines on lymphoma, although the first results showing that interim FDG-PET may be infeasible were already published in 2010. Therefore, rectifying this misconception is needed and further research on interim FDG-PET is unlikely to be fruitful.

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Compliance with ethical standards

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