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Supplement Article

VI. FDG-PET as a biomarker in lymphoma: from qualitative to quantitative analysis

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Introduction

Metabolic imaging with [18] Fluorine Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) provides a simple imaging biomarker capable to evaluate the glucose metabolism in fluorodeoxyglucose (FDG)-avid lymphoma tumours before treatment and for response assessment. Therefore, ^{18}FDG-PET/CT has been very soon recognized as the more valuable imaging tool in FDG-avid lymphoma for response assessment by its property to image the residual metabolic activity irrespective of residual volume. The 2007 International Harmonized project criteria, the Deauvillle criteria in 2009, the Lugano classification and the recommendations of the International Conference on Malignant Lymphoma (ICML) imaging and clinical working groups in 2014 have set rules for harmonizing visual positron emission tomography (PET) reporting for response evaluation [1–4]. This was necessary for minimizing risk of reporting any residual uptake observed after treatment as an evidence of a residual tumour with resulting false positive studies. The interpretation key proposed by the ICML imaging group for both interim (iPET) and end of treatment PET (eotPET) is the Deauville 5-point scale (5P-S) using the classical visual assessment. However, it has been recommended by the group to investigate other quantitative approaches for response assessment.

Similarly, ICML recommendations encourage investigating the quantitative analysis of FDG-PET/CT at staging. Indeed, new treatments have improved outcome in the most frequent types of lymphoma, but classic prognostic factors fail to select the small percentage of patients with high risk of relapse and treatment failure. For those reasons, we need new prognostic and predictive factors, a precise determination of initial tumour burden and an accurate and early assessment of responsiveness to therapy. FDG-PET/CT is by nature a quantitative imaging technique from which new metrics to measure tumour burden can be derived such as total metabolic tumour volume (TMTV) and total lesion glycolysis (TLG). Integrative PET combined these quantitative biomarkers with clinical, biological and molecular information to build new indices for a better patient stratification and personalized therapy. Therefore, we are gradually moving from visual to quantitative FDG-PET/CT, ICML recommendations being a strong starting point.

FDG uptake in lymphoma [5]

Most lymphoma are FDG-avid, the FDG avidity depending on subtypes; the most common including Hodgkin lymphoma (HL), diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) are always avid at presentation. Mucosa-associated lymphoid tissue lymphomas, small lymphocytic lymphoma, extranodal marginal zone lymphoma and cutaneous lymphomas are variably FDG-avid. Importantly, the FDG avidity is not only related to tumour cells but also to the proportion of environmental cells, among which activated macrophages and mononuclear cells have a very high FDG uptake via glucose transporter 3 receptors. In HL tumour that contains 1% of HRS cells, FDG uptake is mainly because of the surrounding reactive cells in the microenvironment, which explains the very high metabolic activity observed. In contrast, in DLBCL that contains 90% of tumour cells, the FDG uptake is mainly because of the tumour component. These differences in the nature of FDG uptake between HL and DLBCL explain the differences in the response kinetics after treatment. The intensity of the FDG uptake is the result of the metabolic activity of the different components of the lymphoma tumours (neoplastic cells and environmental cells) and of their interrelations explaining the wide variations between the different types of lymphoma and differences in PET imaging kinetics under treatment.

This metabolic activity is usually expressed by the maximum Standard Uptake Value $(SUV)_{max}$, which expresses the SUV value of the point (strictly voxel) with the highest

tumour uptake for a given patient. From this metrics, other quantitative parameters can be obtained such as the TMTV, the TLG and as far as the response to treatment is concerned, the ΔSUV_{max}. The latter is in %; the reduction of SUV_{max} from baseline study to post treatment study.

These measurements require, as is required for visual analysis, a standardization of the acquisition of the data, a proper calibration of the equipments and of the reconstruction methods. In addition, they require a harmonization of the methods used for computation. They must be reproducible between observers and from one centre to another. The major clues are biological (incorrect timing of the acquisition) or due to human errors (versatile use of different acquisition or reconstruction parameters, incorrect reporting of injected activity and erroneous localization of the involved sites). Indeed, in many countries, the equipments are strictly controlled by manufacturers and health agencies. To minimize errors, it is preferable to use parameters obtained from relative rather than from absolute measurements.

FDG-PET/CT for response assessment: qualitative and quantitative analysis

The response to treatment has been evaluated with FDG-PET/CT at interim (iPET) and at the end of treatment (eotPET). iPET is usually performed after the first chemotherapy cycles (2–4). The first large studies in DLBCL and advanced HL suggested that iPET performed after two cycles was a good predictor of outcome separating fast responders from slow responders. iPET was an independent predictor from prognostic scores (IPI and IPS) and might be considered as a surrogate marker of chemosensitivity. Subsequent studies have reported major differences in the prognostic value of iPET in DLBCL as well as in HL. Actually, at this time, iPET was reported visually when the residual uptake was higher than a fixed reference background, which could be the nearby background, the mediastinal blood pool or the liver according to the studies. Consequently, for the same residual uptake, increasing the background turns a PET positive to a PET negative, which explains the conflicting results. Deauville criteria (DC) have defined a common set of criteria for iPET by grading with a 5-point scale (5P-S) the level of residual uptake according to different levels of background. Therefore, it is a semi quantitative approach. The threshold of positivity was set for a residual uptake higher than the liver background (grade 4 of the scale). Using these criteria, the prognostic value of iPET has been confirmed in advanced HL and DLBCL. Consequently, the ICML groups have recommended DC for iPET reporting but also to report eotPET. The advantage is to use one single method for both time points. Indeed, the DC have been successfully used for reporting eotPET in DLBCL and in high tumour burden FL [6].

The Lugano classification has set four levels of response using 5P-S, which are the following: complete metabolic response (CMR), partial metabolic response (PMR), stable disease (SD) and progressive metabolic disease (PMD). At interim or end treatment, CMR is defined for scores 1–3 under standard treatment setting, the level of positivity above the liver. The relatively high residual uptake because of the generalized use of more aggressive therapy, which can be observed at interim and end treatment, explains the level chosen for positivity. Although the Lugano classification is easy to use, there is some difficulties when the level of the residual uptake is close to the uptake of the reference region or when it is necessary to compare the intensity of a residual uptake to that of the baseline tumour to classify a residual uptake within the PMR, SD or PMD categories. Indeed, the eye is sensitive to contrast and not to differences in intensity. For this reason, it is recommended to read the scan using an SUV scale allowing to 'score' in a more objective/quantitative way the residual site.

The ΔSUV_{max} technique has many advantages over the visual PET reporting. It describes the kinetics of tumour destruction missed by the visual analysis, which only reflects the response to treatment at a specific time point. It is more reproducible to quantify uptake variations. The superiority of this quantitative approach for iPET reporting has been confirmed in DLBCL and in HL resulting in a decrease of false positive cases and in an increase of the positive predictive value compared with visual analysis. In a prospective trial including 853 new diagnosed aggressive lymphoma patients (605 with DLBCL), iPET after two cycles reported with the ΔSUV_{max} was highly prognostic of time to treatment failure (TTF) and overall survival (OS)[7]. A reduction of SUV_{max} by 66% was the best cut-off to separate responders from non-responder patients. ΔSUV_{max} method as visual analysis requires a basal PET and a strict adherence to the guidelines recommendations.

FDG-PET/CT quantitative parameters at staging

It is now recognized that FDG-PET/CT scan is the most accurate staging technique in HL and FDG-avid NHL with an increased sensitivity for nodal and extranodal disease without loss of specificity compared with CT. Quantitative parameters obtained from FDG- PET obtained at staging are now under investigation.

It has been shown that the SUV_{max} value was linked to the lymphoma aggressiveness and that an $SUV_{max} > 10$ was the best cut-off to discriminate aggressive from indolent lymphoma with 81% specificity. In patients with a clinical or histological suspicion of transformed lymphoma, the SUV_{max} value can be used to guide the site to biopsy.

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The SUV_{max} has been explored as a prognosticator but except in MCL in a short series of patients, its prognostic value has not been established. In contrast, several series have shown that the TMTV was predictive of outcome. TMTV measures the total metabolic volume of the viable fraction of local tumours, which gives an estimate of the total metabolic tumour burden. Various methods of TMTV measurement have been used in various types of lymphoma. Recently, a method using a fixed SUV_{max} thresholding with a 41% SUV_{max} threshold as recommended by the European Association of Nuclear Medicine (EANM) for TMTV measurement in solid tumour has been developed in patients with HL and DLBCL showing good reproducibility [8]. The computed volume gives an index of TMTV linked to the portion of the tumour with maximal metabolic activity. In a small series of patients with HL baseline, TMTV was predictive of PFS and DSS, patients with large volume having poorer outcome. The presence of a bulky tumour of $\geq$10 cm does not retain significance in predicting PFS in multivariate analysis in contrast to TMTV. In 114 newly diagnosed DLBCL patients, a baseline MTV $\geq$550 cm^3 was an independent pre-therapy prognostic factor and predicted negatively the overall survival (3-year OS = 60% vs OS = 87% in the group with MTV $<$550 cm^3). MTV appeared more relevant than the bulk. In 108 patients with nodal presentation of peripheral T-cell lymphoma, it has been shown recently that TMTV was an independent predictor of outcome.

Integrative FDG-PET

This is a holistic approach combining the qualitative or quantitative imaging parameters with clinical and biological data with the aim to improve the patient risk stratification.

With this perspective baseline, TMTV has been combined with early PET response evaluated at two cycles in HL and DLBCL. Different risk categories could be individualized by this combination: fast responder patients with a low initial volume with an excellent outcome, slow responder patients with a large volume and a poor outcome and an intermediate category. In a series of 147 DLBCL patients, the integration of TMTV with iPET results split the group of iPET + ve patients (DS = 4–5) in two categories according to the TMTV: patients with a good outcome with TMTV $<$400 cm^3 (5-year PFS = 95%) and patients with a poor outcome with TMTV $\geq$400 cm^3 (5-year PFS = 29.7%) [9]. To the same end, in DLBCL, some studies have tried to defined new predictive models by combining PET data with gene expression profiling (GCB/ACB) or expression of relevant biomarkers in tumour cells (BCl2). In 57 patients with DLBCL, the GCB/ABC combined with IPET after 3–4 cycles separated two risk groups: a good risk group (patients with fast response of GCB subtype) and a bad risk group (all ABC patients and patients GCB slow responders). In 91 DLBCL patients treated with R-CHOP, BCL2 protein expression and BCL2 gene alteration combined with early PET/CT response after two cycles was significantly predictive of PFS and OS and improved risk stratification [10]. The same approach was investigated in a large group of 310 patients with advanced-stage HL treated with ABV. Agostinelli reported that the presence of different markers in the accessory cells (CD68KP-1 and PD1) and in RS cells (STAT-1) split iPET-negative patients in two groups: iPET- negative with a low molecular risk profile and a good outcome and iPET-negative patients with a high molecular risk profile and a poor outcome [11]. A recent study has proposed in 102 patients diagnosed with extranodal natural killer/T-cell lymphoma a new risk model combining the post treatment PET Deauville score and the Epstein-Barr virus DNA positivity that was significant associated with progression free survival [12].

Conclusions

The 2014 ICML recommendations have opened the field to investigate the added value of quantitative analysis of FDG-PET/CT. Although first results are convincing, the methods of measurement should be harmonized to assess the clinical value of these quantitative parameters in multicenter trials.

Conflict of interest

The authors have no competing interest.

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