Predictive Efficacy of Interim Positron Emission Tomography/ Computed Tomography (PET/CT) for the Treatment of Aggressive Lymphoma

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The prognostic value of whole-body positron emission tomography/computed tomography (PET/CT) with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) shortly after the onset of induction chemotherapy or mid treatment could help to predict long-term clinical outcomes in patients with Hodgkin's or Non-Hodgkin's lymphoma. However, FDG is not a tumor-specific substance, and it may accumulate to the point of being detected in a variety of benign conditions or at physiologic anatomical sites, which may give rise to false-positive interpretation. In an attempt to standardize the reporting criteria for interim PET/CT, the First International Workshop on Interim PET in Lymphoma suggested visual response criteria with the Deauville five-point scale, and the standardized uptake value (SUV) has been investigated in comparison with this visual system. A quantitative approach using the measurement of maximal SUV (SUVmax) or the reduction rate of SUVmax ($\triangle$SUVmax) might be more appropriate in early-response PET/CT for reducing false-positive rates or for decreasing interobserver variability in interpretation. In this review, the predictive efficacy of PET/CT is discussed for the treatment of aggressive lymphoma, especially in terms of an interim PET/CT-based prognostic model.

Key Words: *Prognosis; Lymphoma; Non-Hodgkin; Positron-emission tomography*

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INTRODUCTION

Whole-body positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) is a functional imaging modality used for staging and monitoring in the treatment of malignant lymphoma and has a higher sensitivity and specificity than conventional imaging. Residual abnormalities following chemotherapy, which result from the development of fibrosis or tumor necrosis, are seen in up to 64% of lymphoma patients.[1-3] Conventional imaging, especially computerized tomography (CT), cannot reliably help in the differentiation between active tumors and fibrosis or necrosis.[4-7] These limitations have restricted the predictive value of conventional CT concerning the clinical outcome of non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL).

PET/CT may be a more accurate tool than conventional imaging for assessing treatment effects, correctly identifying patients with residual disease, and predicting therapeutic outcomes. Furthermore, FDG uptake is a tool used to predict the therapeutic response during or after the course of treatment. Several studies have demonstrated the prognostic value of post-therapeutic FDG-PET or PET/CT in malignant lymphoma.[8,9] Moreover, higher relapse rates and lower rates of event-free survival are observed in PET-positive than in PET-negative patients.[10-12] FDG-PET or PET/CT images can predict increased risk of treatment failure during or after primary chemotherapy. However, because FDG is not a tumor-specific substance, it may accumulate to the point of being detected in a variety of benign conditions, which may give rise to false-positive results. A correlation with findings on anatomical imaging such as

CT is important for identifying changes resulting from primary chemotherapy. Thus, interim FDG-PET/CT has emerged as a powerful predictive method of assessing HL and NHL.

The predictive value of interim PET scans appears to be positively correlated with the International Prognostic Index (IPI), which is used to predict treatment outcome for NHL, and the International Prognostic Score, which is used for HL. Recent studies have demonstrated that FDG-PET/CT, shortly after the initiation of induction chemotherapy or mid treatment, can predict long-term clinical outcomes in patients with HD or NHL.[9,13-16] These studies categorized patients by PET-positive or PET-negative results on the basis of visual analysis, and subsequently compared the rates of relapse and progression-free or failure-free survival. The present review describes the role of PET/CT, especially interim PET or a PET/CT-based prognostic model, in the treatment of aggressive lymphoma.

STANDARD CRITERIA FOR INTERIM PET/CT

In an attempt to standardize the reporting criteria for interim PET/CT, the First International Workshop on Interim PET in Lymphoma suggested visual response criteria with use of the Deauville five-point scale (5-PS), and the standardized uptake value (SUV) has been investigated in comparison with this visual system.[17] The use of a quantitative approach with the measurement of maximal SUV (SUVmax) or the reduction in SUVmax ($\triangle$SUVmax) might be more appropriate in early-response PET/CT for reducing false-positive rates and for decreasing the interobserver variability in interpretation.[18,19] However, $\triangle$SUVmax only partially reports on the tumor response because it reflects the changes in metabolic activity per representative tumor slice and not overall tumor activity. Metabolic tumor volume (MTV), which is defined as the volume of tumor tissue with increased FDG uptake, has been reported as an important independent prognostic factor that compensates for the deficiencies of SUV-based assessment in maliagnancies.[20-22] SUV can only represent metabolic extent with the dependence of SUVmax on the whole dimension of target lesions, whereas MTV represents the amount of high metabolic tumor cells with the volumetric estimation of active tumor burden.

1. Visual assessment by deauville 5-point scores
Patients were classified with 5-PS by interim PET/CT analysis based on the Deauville criteria as follows[17]: 1, no uptake; 2, uptake $\leq$ mediastinum; 3, uptake $>$ mediastinum but $\leq$ liver; 4, uptake moderately increased compared to the liver uptake at any site; 5, markedly increased uptake compared to the liver at any site and/or new sites of disease (Table 1). Interim PET/CT images were graded as negative or positive by comparison with initial PET/CT. Grades 1 through 3 were considered as negative and grades 4 and 5 as positive.[23] This grading process is independent of the size of the residual tumor.

TABLE 1. Visual assessment based on a five-point scale

1. No uptake
2. Uptake $\leq$ mediastinum
3. Uptake $>$ mediastinum but $\leq$ liver
4. Uptake moderately increased compared to the liver at any site
5. Uptake markedly increased compared to the liver at any site or/and new sites of disease

2. Quantitative assessment based on SUVmax
Patients were classified by the quantitative analysis of ^{18}F-FDG uptake changes based on the percentage reduction of SUVmax between the initial and interim PET/CT. On axial, coronal, or sagittal coregistered PET/CT slices, simple circular regions of interest (ROIs) were placed so as to cover the lesion or background. SUV measurements were corrected for body weight according to the following standard formula[24]:

Mean ROI activity (MBq/mL)/[injected dose (MBq)/body weight (kg)]

For each PET dataset, the maximum SUV (SUVmax) was defined as the highest SUV among all hypermetabolic tumor foci. The SUVmax reduction rate ($\triangle$SUVmax) was calculated as follows:

$$\triangle SUVmax\ (\%)=100\times[SUVmax\ (initial)-SUVmax\ (interim)]\ /SUVmax\ (initial)$$

If all lesions had disappeared on interim PET, ROIs were drawn in the same area on the interim PET as on the baseline PET.

3. Quantitative assessment based on MTV2.5
Patients were classified by the quantitative analysis of metabolic volume changes based on the percentage of MTV reduction ($\triangle$MTV) between initial and interim PET/CT. To define the exact tumor margins around the target lesions, SUV2.5 was used as in previous reports, which means that the tumor volume area in PET/CT was delineated by a circle encompassing regions with an SUV cutoff value of 2.5.[21,25] MTV2.5 was measured by use of the AW Volume Share™ workstation on the fused PET/CT images.[22] The active MTV2.5 was measured in a 3-D manner by selecting volume of interest (VOI) on the axial image, and the size of the VOI was manually regulated on the corresponding coronal and sagittal images to include entire active tumors. The SUVmax and the sum of the tumor volumes in all hypermetabolic tumor foci were computed automatically by the program. The MTV2.5 reduction rate ($\triangle$MTV 2.5) was calculated by use of the same formula as for the SUVmax reduction rate.

INTERIM PET/CT FOR THE TREATMENT OF DIFFUSE LARGE B CELL LYMPHOMA

Patients with diffuse large B cell lymphoma (DLBCL) are stratified into prognostic groups according to the IPI or molecular profiling.[26,27] These therapeutic measures make it possible to predict survival after chemotherapy and to alter therapeutic strategies in groups with a poor risk classification, referred to as "risk-adapted therapy." Since the addition of the anti-CD20 monoclonal antibody, rituximab, to CHOP, the therapeutic outcomes of these patients have improved. The use of rituximab for the treatment of DLBCL has changed the prognostic risk groups based on the IPI, which is referred to as the revised IPI.[28] However, there are still 20% to 40% of patients who will not be cured with R-CHOP, and the failure of R-CHOP chemotherapy might be associated with a less effective response to salvage chemotherapy.[29] Therefore, there is a continuous effort to improve immune-chemotherapy and to determine which patients have a poor prognosis based on their response to treatment.

Despite the prognostic value of interim PET/CT response, which has important implications for response-adapted therapy in DLBCL, an optimal extension of the use and standardized definition of interim PET/CT is still being investigated (Table 2). The pitfalls of interim PET/CT interpretation may be related to the definition of positivity without concern for tumor physiology or anatomical variations. Aggressive NHLs have different clinical features with multifocal, noncontinuous involvement at diagnosis and involve both nodal and extranodal sites simultaneously compared with other solid malignancies. The prognostic significance of early PET scans after the first or second cycle of chemotherapy may be associated with false determination owing to tracer uptakes by inflammatory or infectious lesions.[30-32] Quantitative SUV-based assessment at the time of early treatment response has been shown to increase the predictive value of interim PET over visual assessment or to be equivalent to visual assessment for determining midtherapy response.[18,33-35] However, the quantitative assessment of SUVmax in the early response period has several drawbacks for defining positivity in cases of interobserver interpretation, for considering volumetric changes in the tumor during chemotherapy, and for interpreting minimal residual uptakes or physiologic anatomical FDG uptakes.

Although only a fraction of tumor cells are eradicated during the initial cycles of R-CHOP chemotherapy, it is at this point that the greatest rate of killing occurs.[13,31,36] This is therefore an appealing time point at which to assess changes in metabolic activity as a surrogate marker for tumor sensitivity to treatment. It is intuitive that this could allow meaningful prognostic information to direct changes in or escalation of therapy. However, immunochemotherapy may lead to inflammatory changes within the tumor bed, leading to frequent false-positive PET assessments and thereby significantly decreasing the positive predictive value.[37,38] Recent studies using the definition of visual or SUV-based assessments reported a low positive predictive value and a high negative predictive value in the treatment of DLBCL with immunochemotherapy. A low positive predictive value for visual or SUV-based assessments could make it difficult to intensify the treatment strategy because of concerns regarding over-treatment of a substantial portion of poor responders.[4,32,36,39] In addition, interobserver mismatches in the interpretation of interim scans according to different visual criteria should caution us regarding the use of interim PET in response-adapted treatment.[40] To compensate for these discrepancies and to better predict clinical outcomes, the combined evaluation of interim PET/CT response using visual, SUV-based, and MTV-based assessment may allow more differentiated prediction of individual prognosis in patients with DLBCL after the rituximab era.[41] However, no definitive information is currently available on the role of interim PET/CT regarding which assessment or which standardized criteria should be applied in DLBCL.

TABLE 2. Predictive power of interim PET/CT in DLBCL

Study	N	PET after	Criteria	2 years (PFS/EFS)	
				PET ($-$)	PET ($+$)
Jerusalem, 2000	28	3 cycles	Visual	62% (PFS)	0% (PFS)
Spaepen, 2002	70	3-4 cycles	Visual	85% (PFS)	4% (PFS)
Kostakoglu, 2002	17	1 cycle	Visual	85% (PFS)	15% (PFS)
Haioun, 2005	83	2 cycles	Semiquantitative	82% (EFS)	43% (EFS)
Mikhaeel, 2005	57	2-3 cycles	Visual	87% (PFS)	34% (PFS)
Lin, 2007*	92	2 cycles	△SUVmax	79% (EFS)	21% (EFS)
Itti, 2009*	80	4 cycles	△SUVmax	82% (EFS)	25% (EFS)
Moskowitz, 2010	98	4 cycles	Visual	90% (PFS)	79% (PFS)
Total	603	1-4 cycles		62-90%	0-79%

DLBCL: diffuse large B cell lymphoma, EFS: event-free survival, PET/CT: positron emission tomography/computed tomography, PFS: progression-free survival, △SUVmax: reduction rate in the maximal standardized uptake value.
*SUV-based quantitative analysis.

INTERIM PET/CT FOR THE TREATMENT OF PERIPHERAL T CELL LYMPHOMAS

Peripheral T cell lymphoma (PTCL) is a heterogeneous group of aggressive lymphomas. The T-cell phenotype itself is associated with unfavorable prognosis compared to B-cell phenotype lymphomas.[42] Although PTCL is chemosensitive to conventional regimens, the clinical outcomes have been uniformly disappointing. In particular, elderly patients generally have impaired bone marrow function, altered drug metabolism, comorbidities, and functional status impairment.[43] They frequently show intolerance and treatment-related complications with full-dose salvage chemotherapy[44-46] and may need to be frequently hospitalized during full courses of salvage chemotherapy. Although the prognostic role of interim PET/CT in PTCL is less well established than in DLBCL, some studies have suggested that the interim PET response may also be useful for predicting the outcome in PTCL. A retrospective study of mature T-cell and NK/T cell lymphoma reported that patients achieving interim PET/CT negativity showed improved 2-year progression-free survival and overall survival compared with those with interim PET/CT positivity.[47] Another retrospective study yielded similar results regarding the prognostic role of interim PET/CT.[48] In addition, the reviewer also reported that an analysis of 59 patients with PTCLs using interim PET/CT response based on 5-PS, $\triangle$SUVmax, and $\triangle$MTV2.5 after three and four courses of induction treatment had predictive value for progression-free survival; no significant difference was observed between the visual and quantitative assessments for predicting progression.[49] However, the major drawback of these reports was the lack of uniform and reliable criteria for interim PET interpretation. Data concerning the role of PET/CT in patients with PTCLs using interim assessment with FDG uptake are limited. T/NK cell lymphomas are mostly FDG avid, with higher uptake in more aggressive subtypes but lower uptake in cutaneous disease.[50,51] The advantage of using the baseline metabolic tumor parameters is the availability of prognostic information before treatment and thus allocation to the most optimal treatment intensity from the start. Song et al. measured MTV in extranodal NK/T-cell lymphoma patients and found that high MTV was correlated to poorer overall survival.[52] If confirmed in more studies including in other PTCL patients, quantitative PET/CT studies could be an alternative to visual PET/CT analysis for patients with PTCL. Therefore, prospective studies are needed to determine the optimal use of interim PET/CT in PTCLs, including the role of visual or quantitative assessment.

CONCLUSION

Interim PET/CT analysis has significant predictive value for disease progression and survival in the treatment of aggressive lymphoma, and poor responders according to interim PET/CT should be considered for an alternative

therapeutic plan or intensification of treatment. However, the visual assessment of interim PET/CT may make it hard to identify patients with poor prognosis as early as possible or to switch therapeutic modalities with intensification or stem cell transplantation for overcoming adverse clinical outcomes. Larger and prospective studies and harmonization of the criteria for interpreting interim PET/CT are needed to confirm the predictive efficacy in future clinical trials.

CONFLICT OF INTEREST STATEMENT

None declared.

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