Original article

Standardized uptake value for $^{18}$F-fluorodeoxyglucose is correlated with a high International Prognostic Index and the presence of extranodal involvement in patients with Diffuse Large B-Cell Lymphoma

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A B S T R A C T

The aim of this study was to evaluate whether the maximum standardized uptake value (SUVmax) of $^{18}$F-Fluorodeoxyglucose (FDG) correlates with the International Prognostic Index (IPI) and the presence of extranodal involvement in patients with Diffuse Large B-Cell Lymphoma (DLBCL). Material and methods: 77 patients (age: 57.2 ± 18.5, 40 F, 37 M) with DLBCL who underwent FDG PET/CT for initial staging were included. SUVmax of the predominant lesions were compared to Ann Arbor stage, IPI scores, the presence of extranodal involvement and the number extranodal sites. Results: PET/CT detected nodal (n = 25) and extranodal involvement (n = 52) in all the patients. In 27 patients, extranodal disease could only be detected by PET. SUVmax of the predominant lesion in patients with extranodal disease was significantly higher than that of the patients who had only nodal disease (25 ± 12 vs. 15.3 ± 10 respectively, p = 0.001). SUVmax significantly correlated with IPI scores; the average SUVmax was significantly correlated with the IPI: Mean SUVmax of the predominant lesion was 13.9 ± 9.5 in patients with low risk (IPI = 0–1), 14.2 ± 8.8 in low-intermediate risk group (IPI = 2) whereas 26.6 ± 9.5 in high-intermediate risk group (IPI = 3) and 25 ± 13.6 in high risk group patients (IPI = 4–5) (p = 0.002). SUVmax was not correlated with clinical stage, the number of extranodal sites and serum LDH levels. Conclusion: FDG uptake correlates with IPI and the presence of extranodal involvement in DLBCL PET is a powerful method to detect extranodal disease in DLBCL. The correlation of SUVmax with these prognostic factors may highlight the importance of pretreatment FDG uptake as a metabolic marker of poor prognosis for patients with DLBCL.

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El valor estandarizado de captación de $^{18}$F-fluorodesoxiglucosa se correlaciona con un índice pronóstico internacional elevado y la presencia de afectación extranodal en pacientes con linfoma B difuso de células grandes

R E S U M E N

El objetivo de este estudio fue evaluar si el valor estandarizado de captación máximo (SUVmáx) de $^{18}$F-fluorodesoxiglucosa (FDG) se correlaciona con el índice pronóstico internacional (IPI) y la presencia de afectación extranodal en pacientes con linfoma B difuso de células grandes (LBDCG).

Material y métodos: Se incluyeron 77 pacientes (40 H, 37 M; edad: 57.2 ± 18.5 años) con LBDCG a los que se efectuó $^{18}$F-FDG PET/CT para la estadificación inicial. Se correlacionó el SUVmáx de las lesiones predominantes con el estadio Ann Arbor, las puntuaciones IPI y la presencia y número de sitios de afectación extranodal.

Resultados: La PET/TAC detectó afectación ganglionar (n = 25) y/o extranodal (n = 52) en todos los pacientes. En 27 la enfermedad extranodal fue solo detectada por la PET. El SUVmáx de la lesión predominante en los pacientes con enfermedad extranodal fue significativamente mayor que el de los pacientes que solo tenían enfermedad ganglionar (25 ± 12 frente a 15.3 ± 10, respectivamente; p = 0.001). El SUVmáx se correlacionó significativamente con el IPI: el SUVmáx medio de la lesión predominante fue de 13.9 ± 9.5 en pacientes con bajo riesgo (IPI = 0–1); 14.2 ± 8.8 en el grupo de riesgo bajo-intermedio (IPI = 2), por 26.6 ± 9.5 en el grupo de alto riesgo intermedio (IPI = 3) y, finalmente, 25 ± 13.6 en el grupo de pacientes de alto riesgo (IPI = 4–5) (p = 0.002). El SUVmáx no se correlacionó con el estadío clínico, el número de sitios extranigangliares ni los niveles de LDH en suero.

Conclusión: Una captación de FDG alta se correlaciona con IPI elevado y presencia de afectación extranodal en el LBDCG. La PET es un método poderoso para detectar enfermedad extranodal en LBDCG. La correlación del SUVmáx con estos factores pronósticos puede poner de manifiesto la importancia de la captación de FDG pretreatment como un marcador metabólico de pobre pronóstico en los pacientes con LBDCG.

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Introduction

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common subtype of NHL and represents 25–35% of all cases with non-Hodgkin Lymphomas (NHL). DLBCL is an aggressive subtype which should be immediately diagnosed and treated. Extranodal involvement and associated constitutional symptoms are more common in DLBCL compared to indolent lymphomas and indicate a more aggressive phenotype with lower survival rates. In order to determine patients with high risk, clinical prognostic factors are described and defined as the International Prognostic Index (IPI). In addition to its value in risk stratification, IPI is also used in predicting response to treatment. IPI includes advanced age (>60 years), advanced stage of disease (stage III and IV), presence of extranodal involvement (more than 1 site), elevated serum lactate dehydrogenase (LDH) levels, and poor performance status according to Eastern Cooperative Oncology Group (ECOG ≥ 2).

18F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) is a well-recognized diagnostic tool used for staging and monitoring response to therapy in NHL. FDG PET and PET/CT have been shown to be more accurate than conventional CT in staging lymphomas, particularly in showing extranodal involvement and residual disease after treatment. NCCN recommends the routine use of FDG PET/CT on initial staging of patients with DLBCL.

In a large oncology practice, tumor FDG uptake, expressed as SUVmax, is recognized as a parameter of aggressive tumor behavior that predicts a worse prognosis. Today it is well known that aggressive tumors tend to have higher levels of FDG uptake while less aggressive tumors tend to have lower levels of FDG uptake. Similarly, authors have demonstrated that aggressive NHL subtypes show higher FDG uptake compared to indolent lymphoma subtypes and the intensity of FDG uptake in PET may help to distinguish between indolent and aggressive NHL subtypes. More recently, authors have reported worse overall survival in patients with DLBCL who have higher FDG uptake on pretreatment PET.

In this study, we investigated the association of SUVmax as a metabolic marker for poor prognosis with clinical poor prognostic factors such as IPI scores and with the presence of extranodal involvement in a homogenous group of patients with DLBCL.

Material and methods

Between January 2009 and April 2012, all patients with biopsy proven DLBCL and who underwent FDG PET/CT for initial staging in our institution (n=77) were enrolled in this retrospective study. The group included 37 men and 40 women, with an age range of 14–93 years (average, 57.2±18.5 years). The classification of NHL was performed based on the 4th edition of WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues published in 2008. Patients with prior diagnosis of another malignant disease were excluded from the study.

Clinical risk scores

For the calculation of International Prognostic Index (IPI), one point was counted for each of the following: age >60 years, Ann Arbor stage III or IV, extranodal involvement > 1 site, LDH above the upper limit of normal and poor performance status according to Eastern Cooperative Oncology Group (ECOG >2). Risk groups were defined as low (0–1 points), low-intermediate (2 points), high-intermediate (3 points), and high risk (4–5 points).

PET/CT imaging

PET/CT imaging was performed by an integrated PET/CT scanner (Siemens Biograph 6 – True Point PET/CT systems; Siemens, Chicago, IL, USA). Patients were fasted for at least 6 h prior to injection of 5.3 MBq/kg (144 μCi/kg) 18F-FDG. The blood glucose levels were less than 150 mg/dl in all patients at the time of the FDG injection. PET/CT imaging was performed 60 min after FDG injection. Unenhanced CT images were acquired for attenuation correction from the skull vertex to distal thigh using 3 mm slice thickness and calculated effective mAs due to patient weight. The PET and CT images were reviewed on a workstation (Leonardo, Siemens Medical Solutions, Erlangen, Germany) in all standard planes along with maximum-intensity-projection images and were analyzed visually and quantitatively by two reviewers experienced in interpreting PET/CT scans. Findings were recorded by consensus.

PET-positive findings were defined as visually evaluated nodal or extranodal lesions with focal or diffuse accumulation of FDG higher than background or mediastinal blood pool. In all patients, areas of abnormal FDG uptake were identified and SUV of measurable pathological tissue was determined. For each PET dataset, the lesion with the most intense FDG uptake among all foci was carefully identified by interpreters and defined as the predominant lesion in consensus. The maximum standardized uptake value (SUVmax) was used to quantify FDG uptake. SUVmax was calculated using the following formula:

\[
SUV_{\text{max}} = \frac{C_{\text{max}} \times TBW/I}{A}
\]

(Cmax: activity concentration in the voxel of highest tumor activity (Bq/ml), TBW: total body weight (kg), IA: injected activity (kBq)).

To provide the most accurate measurement of SUVmax, volume of interest (VOI) was created large enough to maintain tumor inside the boundaries, and maximum care was accomplished to avoid “spill-in” from adjacent structures with intense FDG uptake. In addition, to minimize the partial volume effect, only lesions larger than 20 mm in short axis size were evaluated as described in previous studies.

For all patients, we collected the following parameters known to have prognostic value in non-Hodgkin Lymphoma: age, Ann Arbor stage, performance status according to ECOG, IPI, serum LDH levels. Patients’ informed consents to examination were obtained before PET/CT imaging and this study was approved by the ethics committee of our institution.

Statistical analysis

The differences between SUVmax according to Ann Arbor clinical stage and IPI scores were analyzed by Kruskal Wallis test. The differences in SUVmax according to the presence of extranodal involvement were analyzed by Mann Whitney U test. A value of \( p < 0.05 \) was considered to be statistically significant.

Results

Clinical Ann Arbor stages of the patient population were as follows: stage I: 3 patients, stage II: 28 patients, stage III: 18 patients and stage IV: 28 patients. In all patients, involved nodal regions and/or extranodal areas were clearly identified by PET/CT. To exclude misdiagnosis, PET findings were proved to be positive by histopathological verification in selected cases where extranodal disease was detected in gastrointestinal system, in bones and bone marrow without any radiological abnormalities detected on CT. In patients with visceral involvement, PET findings were correlated with ultrasound and/or Magnetic Resonance Imaging (MRI).
In patients with central nervous system involvement, both MRI and flow cytometry were performed to prove diagnosis.

The comparison of SUV\textsubscript{max} on pretreatment PET with clinical factors is given in Table 1.

The average of SUV\textsubscript{max} of the predominant lesion did not correlate with clinical Ann Arbor stages (Table 1). Patients were grouped with Ann Arbor stage as patients with stage 1–2 disease and patients with advanced stage disease (stage 3–4). Even though there was a slight increase in SUV\textsubscript{max} in patients with advanced stage disease (18.7 ± 12.8 in patients with stage 1–2 disease vs. 23.4 ± 11.9 in patients with stage 3–4 disease), the difference was not significant in statistical analysis \( (p = 0.3) \).

PET/CT detected extranodal involvement in 52 patients (Fig. 1). The most common site of extranodal involvement was bones (n:12) followed by the lungs, liver, gastrointestinal system (n:9) and bone marrow (n:6). Twenty-four patients had one site of extranodal involvement whereas 28 patients had more than one extranodal involved site. In 27 patients, extranodal involvement was detected only by PET. The corresponding CT slices of the involved regions failed to show lymphomatous involvement in these patients. The most common site where CT failed to detect extranodal disease was the bone (n:9), muscle (n:2), followed by the gastric wall (n:4), liver (n:4) and abdominal viscera (small intestine n:1, adrenal gland n:1, pancreas n:2).

The average of SUV\textsubscript{max} of the predominant lesion was compared according to the presence of extranodal involvement. We observed that SUV\textsubscript{max} was significantly higher in patients with extranodal disease than patients who had only nodal disease \((25 ± 12 \text{ vs. } 15.3 ± 10 \text{ respectively, } p = 0.001)\) (Fig. 2). However, SUV\textsubscript{max} did not correlate with the number of extranodal sites.

Finally, SUV\textsubscript{max} of the predominant lesion was compared among clinical risk groups defined by IPI. The average SUV\textsubscript{max} of the most active lesion on PET/CT was 13.9 ± 9.5 in patients with low risk, 14.2 ± 8.8 in low-intermediate risk group, 26.6 ± 9.5 in high-intermediate risk group and finally, 25 ± 13.6 in high risk group patients. We observed that SUV\textsubscript{max} significantly related to IPI scores, such that, patients with high-intermediate and high risk groups according to IPI scores had significantly higher FDG uptake compared to patients with low and low-intermediate risk, \( p = 0.002 \) (Fig. 3).

### Discussion

DLBCL is an aggressive subtype of NHL. Extranodal involvement is more frequently seen in DLBCL compared to most NHL subtypes and indicates a more aggressive phenotype. In this study, we evaluated the association of SUV\textsubscript{max} with Ann Arbor stages, serum LDH levels, IPI scores and the presence of extranodal disease in patients with DLBCL. We observed that pretreatment FDG uptake correlated both with the presence of extranodal involvement and with high IPI scores in patients with DLBCL.

The routine use of FDG PET during the past decade in the visualization of metabolically active tumor cells has become important in the assessment of lymphoma patients, with FDG PET having clear advantages over contrast enhanced CT. FDG PET/CT is now the imaging modality of choice for staging, evaluating treatment response and follow-up in Hodgkin disease and most NHLs. The integration of FDG PET/CT into clinical oncology practice provided important contribution to the detection of extranodal disease in lymphoma patients.

In this study, PET was able to detect 27 of 52 patients with extranodal involvement without any significant findings on the

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**Table 1**

Comparison of SUV\textsubscript{max} on pretreatment PET with clinical factors.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>( n )</th>
<th>SUV\textsubscript{max}</th>
<th>( p )</th>
</tr>
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<tbody>
<tr>
<td>Extranodal disease</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No sites</td>
<td>25</td>
<td>15.3 ± 10</td>
<td></td>
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<tr>
<td>1 site</td>
<td>24</td>
<td>23.8 ± 13.3</td>
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<tr>
<td>&gt;1 sites</td>
<td>28</td>
<td>25.4 ± 11</td>
<td></td>
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<tr>
<td>IPI</td>
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<tr>
<td>Low risk (0–1)</td>
<td>17</td>
<td>13.9 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Low-intermediate risk (2)</td>
<td>14</td>
<td>14.2 ± 8.8</td>
<td>0.02</td>
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<tr>
<td>High-intermediate risk (3)</td>
<td>19</td>
<td>26.6 ± 9.5</td>
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<tr>
<td>High risk (4–5)</td>
<td>28</td>
<td>24.9 ± 13.6</td>
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<tr>
<td>Ann Arbor stage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>I–II</td>
<td>31</td>
<td>19 ± 12.8</td>
<td>0.14</td>
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<tr>
<td>III–IV</td>
<td>45</td>
<td>23.3 ± 11.7</td>
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<td>LDH levels</td>
<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>32</td>
<td>19.8 ± 13.6</td>
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<tr>
<td>Elevated</td>
<td>45</td>
<td>22 ± 11.9</td>
<td>0.3</td>
</tr>
</tbody>
</table>

IPI: international prognostic index. LDH: lactate dehydrogenase.

\( p \) value indicates the significance between SUV\textsubscript{max} according to the presence of extranodal involvement.
Combining cervical: diaphragm uptake corresponding occurs.

Fig. 2. Figure demonstrates a comparison of FDG uptake with respect to the presence of extranodal involvement. In column A, maximum intensity projection (MIP) image of a patient with stage II disease is presented. Hypermetabolic lymph nodes with biopsy proven DLBCL are seen on bilateral cervical and right axillary region with SUVmax (cervical): 14.82 and SUVmax (axillary): 7.23. Note that the patient does not have extranodal disease. On the contrary, column B demonstrates the MIP image of a patient with stage IV DLBCL, who has multiple sites of extranodal involvement (column C). Column C demonstrates the CT and fused PET/CT images. In column C, pathological FDG uptake attributable to bilateral adrenal lesions which have invasion to left kidney can be clearly seen (SUVmax: 38.7). In addition, multiple lymph nodes on both sides of the diaphragm (SUVmax: 24.9) are noted.

corresponding CT images of the PET/CT scan. Of these, 9 patients had bone lesions negative on CT but positive on PET. We observed that PET significantly contributed to the detection of extranodal sites especially in patients with bone involvement because radiological findings may not be seen until an overt bony destruction occurs.

The use of FDG PET/CT in predicting outcome for lymphoma patients has been investigated by several groups either by SUV analysis or by visual interpretation. It is known that standardized uptake value, as a semi-quantitative measurement of FDG uptake, provides intrinsic molecular-biological information of tumors. Strong evidence from a growing number of research studies demonstrated that SUVmax is highly correlated with aggressive behavior of the tumor and worse prognosis for the patient. Authors have demonstrated that aggressive NHL show higher FDG uptake compared to indolent lymphoma subtypes which have better clinical outcomes and longer overall survival rates. In addition, SUVmax has been shown to be a useful predictor of the proliferation potential in NHL. In our patient group, Ki 67 proliferation index results was available in 22 patients.

In the present study, we observed that patients with extranodal disease had higher standardized uptake values compared to patients with only nodal involvement. The SUV rises with the increasing accumulation of FDG by tumor tissue, its proliferative activity and biological aggressiveness of the tumor. Recently, Kim et al. reported that combined assessment of volume and metabolism was predictive of survival in DLBCL patients who are treated with R-CHOP. On the other hand, extranodal disease indicates a more aggressive behavior of lymphoma with worse clinical outcomes. Thus, extranodal involvement is listed among the factors of IPI as a poor prognostic factor in patients with NHL. Authors have reported that overall survival was significantly reduced with the presence of extranodal involvement even in Rituximab era. Combining these facts, we considered that both the presence of extranodal disease and higher pretreatment FDG uptake in patients with extranodal involvement were in accordance.

In this study, we did not observe any association between SUVmax and clinical stage of patients as well as serum LDH levels. Current literature lacks evidence whether lesion SUVmax correlates with Ann Arbor stage of the patients with DLBCL. In addition, there is not enough knowledge in the literature that defines an association of serum LDH levels and FDG uptake in areas involved with lymphoma. Similar to our results, in few studies, authors reported that serum LDH levels were not correlated with lesion SUVmax in patients with NHL.

Fig. 3. The Boxplot graphic demonstrates the distribution of maximum SUVmax geometric means and confidence intervals in different risk groups as defined by IPI.
Today, researches on the clinical use of FDG PET/CT have been focused on better stratification of patient based risk factors in patients with aggressive lymphoma. In a group of patients with primary central nervous system lymphoma, Kawai et al. demonstrated that progression free survival and overall survival were significantly longer in patients with low to moderate FDG uptake than patients with high FDG uptake. More recently, the prognostic impact of FDG uptake on pretreatment PET is being pronounced. Chihara et al. reported that the 3-year progression free survival and overall survival was significantly shorter in patients with SUV ≥ 30 compared to patients with SUV < 30, independent of IPI. They did not find any association between high SUV and clinical characteristics such as IPI, clinical stage and the presence of extranodal involvement. However, one important limitation of this study was that the authors report they did not routinely control blood glucose level prior to FDG injection, which is inevitable for accurate and reliable calculation of SUVmax.

We assumed that combining metabolic data obtained by accurately acquired PET/CT may contribute to better define patient based risk factors especially in patients with DLBCL. In this study, we observed that pretreatment FDG uptake correlated with the presence of extranodal involvement and high IPI which are known as poor prognostic factors. To our knowledge, this study is the first to demonstrate the association of FDG uptake with clinical poor prognostic factors in patients with DLBCL.

Patients with DLBCL generally have a great variability in clinical presentation, response to treatment and prognosis. Thus, efforts have been augmented to identify the biological and clinical risk factors associated with poor prognosis. IPI is the accepted classification system to determine patients with high risk. Even though IPI has proved valuable for risk stratification, there is still variability in clinical outcome within individual risk groups. Evidence from clinical trials provided conflicting results for high risk patients in overall survival rates with high dose chemotherapy and stem cell transplantation. The current literature points out the need to determine patient specific and biologically based risk factors in order to provide more precise treatment strategies for treating high risk patients.

We consider that our study is limited by its retrospective design along with the lack of follow up data. We believe that information about progression free survival and overall survival would provide additional value to our paper from a clinical point of view. However, we consider that demonstration of metabolic aggressiveness of DLBCL by PET/CT on pretreatment work-up may provide important prognostic clues on the behavior of lymphomas along with clinical risk factors. We believe that further prospective studies on survival are warranted to confirm our observations.

In conclusion, our study indicates that high FDG uptake of predominant lesion on pretreatment PET/CT correlates with clinical poor prognostic factors. The findings of this study may highlight the importance of SUVmax on pretreatment PET. We consider that the variability in patient outcome within the individual risk groups may be overcome by combining IPI with metabolic data obtained by pretreatment PET. Further prospective studies may provide efficient use of SUVmax in combination with IPI to guide risk-adapted therapies in patients with DLBCL.

Conflict of interest

The authors declare no conflict of interest.

References