Original article

Quantitative and qualitative evaluation of the interim PET/CT in lymphoma treatment in the prediction of complete metabolic response

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ABSTRACT

Objective: To compare two different methods for the interpretation of interim PET/CT (PET/CT-i) in lymphomas, and to establish which one best predicts a complete metabolic response (CMR) in the PET/CT study at the end of treatment (PET/CT-et).

Materials and methods: Retrospective longitudinal analysis of the PET/CT studies for staging (PET/CT-s), PET/CT-i and PET/CT-et of 65 patients, 35 Hodgkin's lymphoma (HL) and 30 non-HL was performed. The PET/CT-i was performed between the second and fourth chemotherapy cycle. It was interpreted using two different criteria: qualitative criteria (5 point visual scale) and semiquantitative criteria (percentage difference between the lesion with more SUVmax in the PET/CT-s and PET/CT-i). We analyzed the likelihood of obtaining a CMR in the PET/CT-et according to the results obtained on the PET/CT-i with these two criteria.

Results: We obtained sensitivity (S), specificity (Sp), positive predictive values (PPV), negative predictive values (NPV) and likelihood ratio (LR) for the qualitative/semiquantitative method of 91%/80%, 76.2%/67%, 88.9%/83.3%, 80%/60.9% and 32%/7.8%, respectively, to predict a CMR in the PET/CT-et. There were no statistically significant differences between the LR of both methods (p = 0.1942).

Conclusion: We found clear differences in S, Sp, PPV and NPV between both interpretation criteria for the PET/CT-i to predict a CMR in the PET/CT-et. Nevertheless, we cannot confirm the superiority of the qualitative method over the semiquantitative method for this purpose as no statistically significant differences were found in their LR in our study.

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EVALUACIÓN CUANTITATIVA Y CUALITATIVA DE LA PET/TC A MITAD DEL TRATAMIENTO EN LINFOMAS EN LA PREDICCIÓN DE RESPUESTA METABÓLICA COMPLETA

RESUMEN

Objetivo: Realizar una comparación entre 2 métodos para la valoración de la PET/TC a la mitad del tratamiento (PET/TC-mt) en linfomas, y establecer cuál de ellos predice con mayor precisión una respuesta metabólica completa (RMC) en la PET/TC al final del tratamiento (PET/TC-ft).

Material y métodos: Análisis retrospectivo longitudinal de los estudios PET/TC de estadificación (PET/TC-s), PET/TC-mt y PET/TC-ft de 65 pacientes con linfoma, 35 linfoma de Hodgkin y 30 linfoma no Hodgkin. La PET/TC-mt fue realizada entre el segundo y cuarto ciclo de quimioterapia y se valoró utilizando 2 criterios de interpretación: criterio cualitativo (escala visual de 5 puntos), criterio semicuantitativo (porcentaje de diferencia entre el SUVmax de la lesión con mayor actividad metabólica en la PET/TC-e y la PET/TC-mt). Analizamos la probabilidad de obtener una RMC en la PET/TC-ft según la clasificación de la PET/TC-mt con estos 2 criterios.

Resultados: Obtuvimos valores de sensibilidad (S), especificidad (E), valor predictivo positivo (VPP), valor predictivo negativo (VPN) y razón de probabilidad (RP) para el método cualitativo/semicuantitativo de 91%/80%, 76.2%/67%, 88.9%/83.3%, 80%/60.9% y 32%/7.8%, respectivamente, para predecir un RMC en la PET/TC-ft. No encontramos diferencias estadísticamente significativas entre la RP del análisis cualitativo y semicuantitativo (p = 0.1942).

Conclusión: Encontramos claras diferencias en la S, E, VPP y VPN entre ambos métodos de valoración de la PET/TC-mt para predecir una RMC en la PET/TC-ft. Sin embargo, al no encontrar diferencias estadísticamente significativas en la RP, no podemos afirmar que el método cualitativo sea superior al semicuantitativo para este fin.

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Introduction

PET/CT with 18F-FDG has demonstrated to be a very useful technique in all the phases of the management and follow up of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).5,6 Despite the use of this technique still being under validation, it clearly provides greater aid than what has been obtained with these objectives with conventional methods.

It is very important to know the true extension of the disease since this has a direct influence on treatment planning and determines the prognosis of the patients. In the staging of lymphomas, several studies have demonstrated that PET/CT allows detection of the disease at a lymph node level with greater precision than CT.3 This is mainly due to its capacity to detect disease in lesions less than 1 cm in size which would probably be classified as negative with conventional techniques. Moreover, PET/CT has a greater sensitivity for the detection of extranodal disease (i.e. the liver, spleen, bone marrow and muscle). The sensitivity of PET for the detection of nodal and extranodal disease has been described to be 92–100% and 74–78%, respectively.5,6 This technique therefore allows the staging classification to be closer to reality than that obtained by CT,3 with which the detectability is generally 15% lower than that achieved with PET.

Pretreatment evaluation with PET has led to a change in the stage of lymphoma in approximately 5–15% of the patients and, thus, a change in treatment strategy in 10–20% of the patients on comparison with the conventional staging method by CT.5,6

Assessment of response at the end of treatment is one of the most usual applications of PET in HL and NHL.5,6 The use of PET in this setting has been widely accepted. Indeed, in 2007 the working group of the «International Harmonization Project» (IHP) developed recommendations for the criteria of response to treatment in aggressive malignant lymphomas, recognizing the value of PET in identifying patients without residual disease and including the negativity of PET (complete metabolic response) in the definition of complete remission.6,7 This is due to the capacity of PET with 18F-FDG to distinguish between viable lymphoma cells and necrosis or fibrosis in residual masses after treatment.

These recommendations also suggest the use of visual evaluation for the interpretation of the end of treatment studies while quantitative and semiquantitative methods such as SUV are not as useful for this proposal. Recent studies have confirmed the superiority of these IHP criteria in the end of treatment assessment of both HL and NHL.11,12 With respect to interim PET/CT (i-PET/CT), many studies have supported this technique as a powerful prognostic tool to predict metabolic response at the end of treatment, progression-free survival (PFS) and global survival (GS), particularly in HL and diffuse large B-cell lymphomas (DLBCL).13 Some studies have even demonstrated that this capacity of prediction of PFS and GS is greater than that of other well-established clinical prognostic parameters such as the «International Prognostic Score» (IPS) for HL and the «International Prognostic Index» (IPI) for DLBCL.14,15 In addition, early, reliable prediction of response to treatment may have a positive influence on the global treatment outcome. That is, if the sensitivity to chemotherapy or immunotherapy can be assessed early during treatment, early changes may also be made in the treatment strategies. In this context, a patient with a positive i-PET/CT could receive a more intensive treatment, which could improve the possibility of achieving complete remission at the end of treatment. On the other hand, a patient with a negative i-PET/CT could benefit from less intensive and, therefore, less toxic treatment to thereby avoid possible, harmful secondary effects.

It is therefore of great importance to have precise, assessment criteria for i-PET/CT which reflect the power of the prediction of metabolic response at the end of treatment, the PFS, and the GS of this technique.

Table 1

| No pathological activity exceeding the background activity. |
| Similar or greater pathological activity than that of the mediastinal pool. |
| Pathological activity of intermediate intensity between the mediastinal and hepatic pool. |
| Moderately increased pathological activity in relation to that of the hepatic pool. |
| Markedly increased pathological activity in relation to that of the hepatic pool. |

To date, different evaluation methods have been used for i-PET/CT. On the one hand we have the qualitative or visual assessment of i-PET/CT which is the simplest and most widely used method for the evaluation of response to treatment. According to this, a 5-point scale was recommended by the «1st International Workshop on Interim PET in Lymphomas»13 in which different scores have been assigned based on the uptake of the lesions related to a standard reference score (Table 1). This is currently the qualitative method recommended and most commonly used in clinical trials.

On the other hand, several studies have evaluated the use of quantitative or semiquantitative analysis of i-PET/CT. At present SUV is the semiquantitative method most frequently used since it is not invasive and is easy to calculate.17,18 Indeed, some studies have presented evidence suggesting that this could further improve the prognostic value of i-PET/CT.19 However, the technical aspect of the calculation of the SUV does not have sufficient support and further clinical evidence demonstrating that the SUV is better than visual analysis in the prediction of the outcome of lymphomas is necessary.10,20 Furthermore, the best cut-off point for the reduction of the SUV between the staging study and mid-treatment remains to be defined.21

Taking the discrepancy between the use of these methods into account, the main objective of this study was to compare these two methods in the evaluation of i-PET/CT and establish which method provides greater reliability in the prediction of complete metabolic response at the end of treatment.

Materials and methods

A retrospective, longitudinal analysis was made of all the PET/CT with 18F-FDG performed in patients with lymphoma in our department during the period from January 2007 to March 2011. We included all the patients in whom a staging study had been obtained mid-treatment, from the 2nd to the 4th cycle, and at the end of treatment.

In all the cases the patients had fasted during the 4 h prior to the administration of an i.v. dose of 370 MBq (10 mCi) of 18F-FDG, with previous glycemia control not greater than 200 mg/dl in any case. Thereafter, the patients underwent a period of relative rest of approximately 60 min after which we initiated the acquisition of images.

The study included the base of the cranium to the upper third of the upper limbs, initiating the acquisition with the transmission study with low dose CT (120 kV, 80 mA) without i.v. contrast followed by a tridimensional emission study (3D) at a time of 3 min per field. The PET images were reconstructed using the CT images for the correction of attenuation and after applying the iterative reconstruction algorithm. The images were evaluated independently by at least 2 experts in nuclear medicine, visualizing the PET, CT and fusion images in axial, coronal and sagittal projections. In the case of disagreement, a third specialist was called in.
Interpretation of the images

Evaluation of the staging studies (s-PET/CT)

Any increase in metabolic activity in a non-physiological site which could not be explained by an infectious or inflammatory process was classified as pathological. The SUVmax of the lesion with greatest metabolic activity was obtained.

Evaluation of the interim PET/CT (i-PET/CT) studies

The i-PET/CT was performed between the 2nd and 4th chemotherapy cycles, closest to the following and furthest from the previous cycle. The images were analyzed using 2 different interpretation criteria. On the one hand, we used qualitative criteria and, on the other hand, a semiquantitative method:

A. Qualitative method – we used the 5-point visual scale recommended by the «1st International Workshop on Interim PET in Lymphoma» (Table 1). For practical purposes, a value ≤3 was considered negative while a value ≥4 was considered positive (Fig. 1).

B. Semiquantitative method – we used the percentage of difference of the SUVmax (%ΔSUVmax) between the lesion with greatest metabolic activity in the s-PET/CT study and the lesion with greatest metabolic activity in the i-PET/CT, independently of the localization of each (Fig. 2), so that:

\[ \% \Delta \text{SUV}_{\text{max}} = \left( \frac{\text{SUV}_{\text{max}}(\text{PET-e}) - \text{SUV}_{\text{max}}(\text{PET-mt})}{\text{SUV}_{\text{max}}(\text{PET-e})} \right) \times 100 \]

A study with a %ΔSUVmax ≥ 83% (value obtained by ROC analysis) was considered negative while a %ΔSUVmax < 83% was deemed positive.

Evaluation of the studies at the end of treatment (et-PET/CT)

All the studies were carried out at least 3 week after the last cycle of chemotherapy. The et-PET/CT was classified according to the IHP recommendations (Table 2). These guidelines recommend a purely visual evaluation, using the activity of the mediastinal pool as a background reference to define a PET/CT as positive or negative in residual lesions >2 cm in the greatest transverse diameter, independently of the localization. A larger or normal-sized lesion presenting activity over the surrounding background should be considered as positive. The guidelines also include specific criteria to define the positivity of lesions localized at a hepatic, splenic, and bone marrow level.

Analysis of the results

According to the results obtained with the qualitative method in i-PET/CT we calculated the statistical values of sensitivity (S), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) as well as the ratio of probability (RP) to achieve complete remission in the et-PET/CT.

The RP measured the likely probability of a concrete result (positive or negative) according to the presence of absence of disease. It is clinically useful and does not depend on prevalence, in contrast to the S, Sp, PPV and NPV thereby allowing its use as an index of comparison between different tests for the same diagnosis.

For the semiquantitative method we first established the %ΔSUVmax with the best S and Sp value using ROC curves (Fig. 3). Once this cut off point had been determined, we calculated the S, Sp, PPV, NPV and RP to achieve complete metabolic response in
Fig. 2. (A) s-i-et-PET/CT studies in a patient with DLBCL. The lesion with the greatest metabolic activity in the s-PET/CT had a SUVmax of 44. The lesion with the greatest metabolic activity in the i-PET/CT had a SUVmax of 4.6. The %ΔSUVmax between these 2 lesions was of 89% and was therefore considered as a negative study mid-treatment. The et-PET/CT was considered as complete metabolic response. (B) s-i-et-PET/CT studies in a patient with HL. The lesion with the greatest metabolic activity in the s-PET/CT had a SUVmax of 12.1. The lesion with the greatest metabolic activity in the i-PET/CT had a SUVmax of 10. The %ΔSUVmax between these 2 lesions was of 17%, and was, thus, considered a positive study mid-treatment. The et-PET/CT was considered as metabolic stability.

Table 3
Descriptive analysis of the population studied.

<table>
<thead>
<tr>
<th></th>
<th>Number (%)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>37 (56.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>28 (43.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>44.9</td>
<td>16–86</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>35 (53.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>30 (46.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High grade</td>
<td>23 (76.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low grade</td>
<td>7 (23.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>8 (12.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ii</td>
<td>22 (33.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iii</td>
<td>12 (17.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>iv</td>
<td>23 (35.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since last study cycle and i-PET/CT (days)</td>
<td>18</td>
<td>15–45</td>
<td></td>
</tr>
<tr>
<td>SUVmax in s-PET/CT</td>
<td>18.6</td>
<td>3.8–44</td>
<td></td>
</tr>
<tr>
<td>SUVmax in i-PET/CT</td>
<td>2.7</td>
<td>0.7–11.9</td>
<td></td>
</tr>
<tr>
<td>%ΔSUVmax s-PET/CT vs. i-PET/CT</td>
<td>83.8</td>
<td>17–97</td>
<td></td>
</tr>
<tr>
<td>Glycemia* (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s-PET/CT</td>
<td>93.1</td>
<td>64–197</td>
<td></td>
</tr>
<tr>
<td>PET/CT</td>
<td>96.8</td>
<td>67–184</td>
<td></td>
</tr>
<tr>
<td>PET/CT</td>
<td>93.2</td>
<td>60–180</td>
<td></td>
</tr>
</tbody>
</table>

* No statistically significant differences were found between the glycemia level of the patients in each study.

The et-PET/CT according to the obtainment of a %ΔSUVmax ≥ the established cut off point.

The χ² method was used to establish possible statistically significant differences between the values obtained by the two methods.

Results

We analyzed the s-PET/CT, i-PET/CT and et-PET/CT of 65 patients (195 studies) with lymphoma: 35 HL and 30 NHL. Table 3 shows a descriptive analysis of the study population.

On evaluation with the semiquantitative method, the cut off for the %ΔSUVmax with the best S, Sp values in the ROC curves was 83% (Fig. 3). This means that a %ΔSUVmax ≥ 83% between the s-PET/CT and the i-PET/CT predicts complete metabolic response in the et-PET/CT with a S, Sp, PPV and NPV of 80, 67, 83.3 and 60.9%, respectively. The RP for this method was 7.8. This means that it is 7.8 times more probable to obtain complete metabolic response in the et-PET/CT when there is a negative i-PET/CT (%ΔSUVmax ≥ 83%) than when this study is positive (%ΔSUVmax < 83%) (Table 4).

With respect to the qualitative method, a negative i-PET/CT was found to predict complete metabolic response in the et-PET/CT with a S, Sp, PPV and NPV of 91, 76.2, 88.9 and 80%, respectively. The RP for this method was 32. This means that it is 32 times more probable to obtain complete metabolic response in the et-PET/CT with a negative i-PET/CT (score ≤ 3 in the 5-point scale) than when this study is positive (score ≥ 4 in the 5-point scale) (Table 4).

No statistically significant differences were observed between the RP of the semiquantitative and the qualitative methods (p = 0.1942) to predict complete metabolic response in the et-PET/CT.

Discussion

Numerous studies have demonstrated that PET/CT with 18F-FDG at the end of treatment is highly predictive of disease-free survival (DFS) and GS in aggressive HL and NHL with or without residual masses in the CT. Thus a negative PET at the end of treatment is highly indicative of a greater DFS while a positive PET indicates a shorter time free of disease.

Table 4
Values of S, Sp, PPV and RP for the semiquantitative and qualitative methods in the prediction of complete metabolic response in the et-PET/CT according to the results obtained in the i-PET/CT.

<table>
<thead>
<tr>
<th></th>
<th>S</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>RP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semiquantitative method (for a cut off of %ΔSUVmax ≥ 83%)</td>
<td>80%</td>
<td>67.0%</td>
<td>83.3%</td>
<td>60.9%</td>
<td>7.8</td>
</tr>
<tr>
<td>Qualitative method</td>
<td>91%</td>
<td>76.2%</td>
<td>88.9%</td>
<td>80%</td>
<td>32</td>
</tr>
</tbody>
</table>
The utility of this test is even have obtained other cut offs using ROC recommend

However, to date, different ongoing clinical studies are the main reason for the wide ranges in the literature published on this subject was the lack of uniformity mainly in aggressive HL and NHL.

Other studies have compared this method and a widely used semiquantitative method (∆SuVmax) in patients with DLBCL in the evaluation of the i-PET/CT, with results which pointed to the use of the latter as the best method for the interpretation of these studies always aimed at predicting complete metabolic response at the end of treatment, PFS and GS.

In our study we obtained a global S, Sp, PP and NPV of 80, 67, 83.3 and 60.9%, respectively with the use of the semiquantitative method. These results are comparable to those obtained in other studies except, perhaps, in the low Sp. This may be explained, in part, by the cut off point chosen to consider an i-PET/CT as positive or negative. Using analysis with ROC curves we decided that a %∆SuVmax ≥ 83% was a good cut off since it provides a good relationship between the S and the Sp (79.5 and 66.7%). A reduction in the cut off would have further reduced the Sp and obviously the S would have improved (Fig. 3).

Other studies have obtained other cut offs using ROC curves. In one of these studies, a %∆SuVmax ≥ 65.7% between the baseline and interim treatment studies (2 cycles) was established as the best cut off. With this value these authors obtained a precision of 76.1% to predict the DFS. The estimation of this DFS at 2 years was 21% for patients with a %∆SuVmax ≥ 65.7%, compared with 79% in patients with a %∆SuVmax ≥ 65.7%. With visual analysis the i-PET/CT had a precision of 65.2% to predict the DFS. The estimation of this DFS at 2 years was 21% for patients with a %∆SuVmax ≥ 65.7%, compared with 79% in patients with a %∆SuVmax ≥ 65.7%.

Nonetheless, several studies have compared this method and a widely used semiquantitative method (∆SuVmax) in patients with DLBCL in the evaluation of the i-PET/CT, with results which pointed to the use of the latter as the best method for the interpretation of these studies always aimed at predicting complete metabolic response at the end of treatment, PFS and GS.

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Nonetheless, several studies have compared this method and a widely used semiquantitative method (∆SuVmax) in patients with DLBCL in the evaluation of the i-PET/CT, with results which pointed to the use of the latter as the best method for the interpretation of these studies always aimed at predicting complete metabolic response at the end of treatment, PFS and GS.

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that the SUV and the visual analysis had a very similar prediction of the DFS when used after the 4th cycle of treatment.\textsuperscript{14}

Our S, Sp, PPV and NPV were 91, 76.2, 88.9 and 80\%, respectively using the visual method for the assessment of i-PET/CT. These results are better than those obtained by the previously cited study, albeit very similar to those obtained in other studies and also superior to those obtained by the semiquantitative method in our study. This indirectly supports the use of this method in the evaluation of response mid-treatment when the objective is to predict metabolic response at the end of treatment.

This affirmation is supported by other similar observational studies which included a greater casuistic of patients with aggressive NHL. These studies suggest that i-PET/CT evaluated visually may identify response early during chemotherapy, and that PET may predict the outcome of these patients.\textsuperscript{16,33,34} These studies also found a statistically significant difference in the DFS and OS between the group of patients with a positive i-PET/CT and a negative i-PET/CT ($p < 0.05$). In comparison with our study the results of 2 of these studies\textsuperscript{16,34} were obtained using visual criteria of binary response (positive/negative) in contrast to the 5-point visual scale which we used which is considered superior to the previous criteria. The third study also included the criteria of minimum residual disease (MRD). The MRD includes all the cases which are at the limit or are difficult to classify due to a low level of residual uptake (just above the surrounding background) where disease had previously been present. This problem disappears with the use of the 5-point scale. In this last study, the DFS at 5-years was 16.2, 59.3 and 88.8\% for positive i-PET/CT, MRD, and negative i-PET/CT, respectively.\textsuperscript{33}

Likewise, a retrospective analysis of 88 patients with HL studied after having received 2 or 3 cycles of chemotherapy with the ABVD scheme found a statistically significant difference in the DFS at 5 years between the group with a positive (39\%) and negative (92\%) i-PET/CT.\textsuperscript{35} These results were posteriorly confirmed in prospective studies carried out by Hutchings et al.\textsuperscript{36} Zinzani et al.,\textsuperscript{37} and Gallamini et al.\textsuperscript{38} In these 3 studies, almost all the patients (94–100\%) with a positive i-PET/CT had refractory disease or relapse within the first 2 years, while those who were i-PET/CT negative showed complete remission, with very few relapse (<6\%).

We also calculated the RP for each of the methods. As mentioned previously, the RP measures the probability of a concrete result (complete metabolic response at the end of treatment) according to the presence or absence of disease (positive or negative study mid-treatment). It is clinically useful and does not depend on the prevalence in contrast to the S, Sp, PPC and NPV, thereby allowing its use as an index of comparison between different tests for the same diagnosis. In our study we obtained an RP of 7.8 for the semiquantitative method. This means that it is 7.8 times more probable to obtain complete metabolic response in the et-PET/CT with a negative (%$\Delta$SUV\textsubscript{max} ≥ 83\%) than a positive (%$\Delta$SUV\textsubscript{max} ≤ 83\%) i-PET/CT. The RP for the visual method was 32. This means that it is 32 times more probable to obtain complete metabolic response in the et-PET/CT when the i-PET/CT is negative (score < 3 in the 5-point scale) than when this is positive (score ≥ 4 in the 5-point scale). Despite these clear differences between the 2 methods in favor of the visual scale, we did not obtain statistical significance between the RP of the two methods ($p = 0.1942$).

On the other hand, it should be taken into account that HL and NHL each have very different mechanisms of response. This hypothesis is based on the assumption that the cellular architecture and physiopathology of the neoplastic tissue is different in these 2 types of lymphoma. In HL, the neoplastic cells of Reed–Stemberg (RS) represent less than 1\% of the total cellularity of the neoplastic tissue while in NHL these cells contribute more than 90\% of the total of the cellular population. In HL, the non-neoplastic lymphomononuclear cells produce a network of cytokines which protect the RS cells in addition to being potentiators of the detector power of PET. This non-neoplastic cellular compartment is disactivated very early after treatment which is translated into what we know as «complete metabolic response» in the PET images. On the other hand, in DLBCL a progressive fraction of neoplastic cells is destroyed by chemotherapy which is predictive of the final response to chemotherapy. This means that in the PET images we see a progressive reduction in metabolic activity with the extent of this reduction being predictive of the final outcome. For these reasons, visual evaluation may be better to determine response in HL while semiquantitative assessment may be more appropriate for DLBCL. These results have been presented in only one study published by Meignan et al.,\textsuperscript{13} thereby making further studies necessary to confirm these results.

The results of our study reflect the potential prognostic power of i-PET/CT considering the attainment of complete metabolic response in the et-PET/CT as the final objective. This may create a bias in our results since some cases of complete metabolic response may not coincide with the clinical response. However, as mentioned previously, the large NPV of the et-PET/CT was included as a criterion of complete remission.\textsuperscript{9,10}

Finally, there may be another probable bias on having performed the analysis of the results considering the patients with HL and NHL as a single group when the current trend is to divide these patients into 2 groups since, as mentioned above, the response to chemotherapy differs in these 2 neoplasms. Nonetheless, the results obtained are very similar to those published by other series in which HL and NHL were studied independently.

**Conclusion**

In the present study we can state that the visual method for evaluation of i-PET/CT with the aim of predicting complete metabolic response in the et-PET/CT has a higher S, Sp, PPV and NPV than that obtained by the semiquantitative method used. Nonetheless, no statistically significant differences were found in the RP between the two methods and we cannot, therefore, affirm that the visual method is superior to the semiquantitative method used for this objective.

**Conflict of interests**

The authors declare no conflict of interests.

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