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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 semiqualitative method for this purpose as no statistically significance differences were found in their LR in our study.

Evaluación cuantitativa y cualitativa de la PET/TC a mitad del tratamiento en linfomas en la predicción de respuesta metabólica completa

Palabras clave:
PET/TC
Linfoma
Respuesta precoz

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-e), 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).[1,2] 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 directly 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.[4,5] 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.[6–8]

Assessment of response at the end of treatment is one of the most usual applications of PET in HL and NHL.[9,10] 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.[9,10] 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 Store» (IPS) for HL and the «International Prognostic Index» (IPI) for DLBCL.[14–16] 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
Five-point scale for the visual evaluation of i-PET/CT.

1	No pathological activity exceeding the background activity.
2	Similar or greater pathological activity than that of the mediastinal pool.
3	Pathological activity of intermediate intensity between the mediastinal and hepatic pool.
4	Moderately increased pathological activity in relation to that of the hepatic pool.
5	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 ^{18}F-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.