Original article

**18**F-FDG-PET/CT in the surveillance of patients with lymphoma: Detection of asymptomatic recurrences


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**ABSTRACT**

**Aim:** To assess the diagnostic accuracy of 18F-FDG-PET/CT in detecting asymptomatic recurrences in patients with lymphoma. To define uptake patterns of recurrence indicative of recurrence.

**Material and methods:** Those patients with lymphoma who fulfilled the following inclusion criteria of clinical complete remission and negative PET/CT study were included retrospectively and longitudinally. Conventional surveillance of these patients was performed only by 18F-FDG PET/CT following a standardized procedure. Pathologic locations (supra- and infradiaphragmatic) and their character (single or multiple) were analyzed in order to determine reliable metabolic patterns of recurrence. The final diagnosis was established by histopathological analysis or clinical follow-up greater than 8 months.

**Results:** A total of 199 explorations belonging to 106 patients with lymphoma were included. Of these patients, 59 had Hodgkin’s lymphoma and 47 non-Hodgkin’s lymphoma. There was suspicion of relapse from the metabolic point of view in 27 of the PET/CT scans. Of these, 14 (10 patients) were false positive (FP), and 13 (8 patients) true positive. The remaining studies were true negative, no false negatives being detected. The pattern most frequently related to recurrence was infradiaphragmatic lymph node involvement while most of the FP had isolated supradiaphragmatic involvement. Sensitivity, specificity, PPV, NPV and diagnostic accuracy of PET/CT parameters for the study were 100%, 92%, 48%, 100% and 93%, respectively.

**Conclusion:** 18F-FDG-PET/CT is a sensitive technique in the detection of asymptomatic recurrences in patients with lymphoma during their follow-up. Multiple character and infradiaphragmatic locations were the patterns that best correlated to the diagnosis of recurrence.

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**PET-TAC con 18F-FDG en el seguimiento de pacientes con linfoma: detección de recidivas asintomáticas**

**Resumen**

**Objetivos:** Determinar la rentabilidad diagnóstica de la PET-TAC con 18F-FDG en la detección de recidivas asintomáticas en pacientes con linfoma. Definir patrones de captación indicativos de recidiva.

**Material y métodos:** Se incluyeron de forma retrospectiva y longitudinal pacientes afectos de linfoma con los siguientes criterios de inclusión: remisión completa clínica con estudio PET-TAC negativo. Se realizó seguimiento convencional de estos pacientes únicamente mediante PET-TAC con 18F-FDG según técnica estándar. Se analizaron las localizaciones patológicas (supra e infradiaphragmáticas) y su carácter (único o múltiple) con vistas a determinar patrones metabólicos fidedignos de recidiva. El diagnóstico final se estableció por análisis histopatológico o seguimiento clínico-radiológico superior a 8 meses.

**Resultados:** Se incluyeron 199 exploraciones correspondientes a 106 pacientes, 59 afectados de linfoma de Hodgkin y 47 de linfoma no Hodgkin. Veintisiete estudios fueron indicativos de recidiva desde el punto de vista metabólico. De ellos 14 fueron falsos positivos (FP), 10 pacientes y 13 verdaderos positivos, 8 pacientes. El resto de los estudios fueron verdaderos negativos y no se detectaron falsos negativos. El patrón más frecuentemente relacionado con recidiva fue la afectación adenopática infradiaphragmática mientras que la mayoría de los FP posiblan afectación supradiaphragmática aislada. Los parámetros de sensibilidad, especificidad, VPP, VPN y exactitud diagnóstica por exploración fueron de: 100%, 92%, 48%, 100% y 93% respectivamente.

**Conclusión:** La PET-TAC con 18F-FDG es una técnica sensible en la detección de recidivas asintomáticas de pacientes con linfoma durante el seguimiento. El carácter múltiple y las localizaciones infradiaphragmáticas fueron los parámetros mejor correlacionados con el diagnóstico de recidiva.

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Introduction

Up to 50% of aggressive non-Hodgkin’s lymphoma (NHL) and 30% of Hodgkin’s lymphomas recur after first-line treatment.1

The importance of early detection of recurrences is the initiation of early treatment, even when the tumor load is low, which may improve survival of the patients.2

There is no agreement about which method should be used in the detection of recurrences and most choose a combination of clinical exploratory data helped by morphological imaging techniques. It is also known that most recurrences are detected by the patient or by the clinician,3 since clinical symptoms are generally present in 80% of the cases before recurrence is diagnosed, especially in the HL,4 only 6% of recurrences prior to development of symptoms in patients with large cell lymphoma being documented.5

The PET-CT study with 18F-FDG is a highly effective technique in staging, both initial as well as when there is suspicion of recurrence. It has high effectiveness in the evaluation of response to treatment in patients with lymphoma.6 However, there are few works that have analyzed the role of PET-CT study in the usual follow-up of patients with complete remission, some of them describing an important rate of false positives.7,8 Therefore, the role of this technique in the follow-up has yet to be determined.9

Since patients with lymphoma account for one-third of the requests for PET-CT studies with 18F-FDG in our setting and belong to half of the patients during the normal follow-up, we performed a retrospective analysis of these cases to determine the diagnostic yield of this technique in the detection of asymptomatic recurrences.

In addition, based on the background of the high number of falsely positive studies described in the previous literature,9,10 we analyzed the metabolic patterns in those cases in which disease was subsequently confirmed in order to define those that were the most reliable to predict recurrence.

Material and methods

Patients affected by lymphoma with the following criteria were retrospectively included: complete clinical remission (CCR) with negative PET-CT study.

Conventional follow-up of these patients was performed only by PET-CT with 18F-FDG according to the standard technique, using a hybrid equipment.1† The PET-CT was requested with a periodicity of twice a year in the first 5 years after the diagnoses, for any type of lymphoma, and yearly in the following years until the 10th year in aggressive lymphomas and 15 years in indolent ones.

A whole body scan was acquired (from the skull base to the upper third of the lower limbs), initiating acquisition with the low dose CT transmission study (120 kV, 80 mA) without intravenous contrast, followed by the tridimensional mode (3D) emission study at a time of 3 min per field.

The PET images were reconstructed using the CT images for the attenuation correction and after using an iterative reconstruction algorithm. The images were evaluated by at least two expert nuclear medicine physicians independently, visualizing the PET, CT and fused images in axial, coronal and sagittal projection. In case of disagreement, a third specialist entered into the evaluation.

A study was classified as positive and indicative of recurrence when at least one lesion was seen with metabolic rate superior to the reference background activity, that was not explained by reactive-inflammatory phenomena, or a finding with doubtful interpretation in which its nature could not be defined (reactive-inflammatory versus tumor).

Reactive-inflammatory was defined as a finding consistent with single or multiple abnormal lymph nodes localized in laterocervical territories, or inguinal or mediastinic ones that had not undergone variation in their uptake patterns compared to previous PET-CT studies.1,11

Regarding the bony uptakes, we classified the asymmetric ones with focal character as positive, as reported by other authors.1,12

Pathological localizations, both lymph node and in solid organs, as well as their character (single or multiple) were analyzed. The lymph node localizations were classified into supra- and infradiaphragmatic.

Age over 45 years for HL and over 60 years for NHL were analyzed as independent prognostic factors according to international recommendations.13,14 Furthermore, other data were obtained such as stage of the previous disease at the last line of treatment and before obtaining complete clinical remission (CCR), NHL type (high or low grade) and time since the end of the treatment and the diagnoses of recurrence.

The patterns of metabolic involvement were related with the final diagnoses in order to determine reliable recurrence patterns. In addition, the correlation of recurrence was analyzed with the type of lymphoma, age at diagnosis, and stage in the total group of patients and separately by types of lymphoma.

In inferential statistics, the comparison of two or more proportions was performed using the chi-square technique. The Student’s t test was used for comparison of means.

The SPSS statistical program for analysis of data (version 18.0 for Windows) was used.

The final diagnosis was established by histopathological analysis or clinical–radiological follow-up greater than 8 months. Those patients with absence of diagnostic confirmation were excluded.

The studies were classified as:

- True positive (TP): positive study with histopathologically or clinically demonstrated recurrence, detected by other techniques within the 6 months following the study.
- True negative (TN): negative study without histologically or clinically demonstrated recurrence in the 6 months of follow-up.
- False positive (FP): positive study without demonstrated recurrence.
- False negative (FN): negative study with demonstrated recurrence.

A total of 199 examinations in 106 patients, 57 males and 49 females, with mean age on diagnoses of 43 years, were analyzed.

Fifty-nine patients had a previous diagnosis of HL and 47 of NHL (27 high-grade). Table 1 shows the distribution of patients by stages at the time of diagnosis of the disease.

Results

Twenty-seven PET-CT studies were positive, multiple lymph node localizations being seen in 17 cases. Of these, 13 were TP in 8 patients, determining the detection of 7% asymptomatic recurrences in the total number of patients evaluated. The remaining studies (14) were FP, which accounts for 52% of the total positive studies and corresponded to 10 patients. No case of recurrence was detected with negative PET-CT during the follow-up.

Table 2 shows the description of the pathological findings by PET-CT.

Of all the patients, histological confirmation was only obtained in 5.

With regard to distribution of the metabolic findings in the 13 TP studies (8 patients), 4 revealed supra- and
Half of the patients with recurrence underwent a PET-CT study before verifying or considering the diagnosis of recurrence. Specifically, two PET-CT studies were performed on three patients and three studies on one patient (Fig. 1).

With regard to the interpretation of the metabolic findings, 8 out of the 17 FP studies were doubtful in the initial evaluation. On the contrary, only one TP was doubtful. If the doubtful PET-CT studies had been excluded from the study, classifying them as negative, the number of FP would have decreased to 6, increasing the positive predictive value (PPV) from 48 to 68%.

The metabolic findings in the studies classified as FP consisted in supra-diaphragmatic involvement in 5 patients with lymph node territory involvement. In the FP group, the abnormal findings reduced their metabolic rate or spontaneously normalized in subsequent PET-CT scans in all the cases except for three, two of which showed metabolic stability of the lesions and one progression (Fig. 2). In only two cases, the benignness was confirmed by biopsy corresponding to non-specific lymphadenitis and follicular hyperplasia, respectively (Fig. 3).

Table 3 shows the statistical diagnostic parameters for studies in patients analyzed. Evaluating the lymph node localizations affected in supra- and infradiaphragmatic as a whole, as well as the infradiaphragmatics or supradiaphragmatics individually, it was found that the likelihood of suffering disease when these are affected was 83%, 93% and 36%, respectively.

The multiple character and infradiaphragmatic localizations were the best parameters correlated with the recurrence diagnoses, although the supra- and infradiaphragmatics were also correlated with statistical significance ($p < 0.05$).

Analyzing the results according to type of lymphoma, no statistical significance was found between stage and age on diagnoses, although the groups of advanced stage on diagnoses (stages III and IV) had an increased likelihood of recurrence. There was also greater likelihood of recurrence in the group of patients with NHL versus those with HL and in the patients with advanced stages, although these relations were not statistically significant.

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Analyzing the total of the sample with regard to the type of lymphoma, stage and age on diagnoses, a relation was found between greater likelihood of recurrence and prognoses, determined by age on diagnoses ($p < 0.05$). There was also greater likelihood of recurrence in the group of patients with NHL versus those with HL and in the patients with advanced stages, although these relations were not statistically significant.
In our case, only two patients with recurrence had high grade NHL, which corroborates this fact. However, the results regarding the FP rate are very unequal with levels ranging from less than 1 to 55%. Rhodes et al., analyzing a group of 41 children in complete remission, found 41 and 63% FPs for NHL and HL, respectively, this being similar to our results. On the contrary, in other groups, including patients with suspicion of recurrence, they found a superior prevalence of disease with recurrence rates of up to 31% in the patients.

The different results found in the studies conducted up to now are probably due to the different criteria used to determine the positivity of the PET and in the patient screening.

The FDG is not a specific tumor compound, so that physiological and not tumoral conditions may give rise to focal deposits causing FP. This reduces the diagnostic accuracy and in some cases entails unnecessary biopsies. In our case, only two patients with FP studies were subjected to biopsy. A relevant fact is that the next PET-CT study showed complete or partial resolution of the findings in most of the patients, two cases showed metabolic stability in two isolated bone lesions. Only one showed progression, so that a biopsy was performed, with a result consistent with reactive follicular hyperplasia. Thus, when there are metabolic findings in single, non-accessible localizations or in areas not affected at the time of diagnosis, the best option may be to maintain an expectant attitude.

High grade lymphomas, due to their rapid growth, generally cause early symptoms. Therefore, detection of the relapse is mostly clinical and more difficult by imaging techniques during a routine follow-up. Precisely in our sample, it was demonstrated that 1/8 of the patients with recurrence had high grade NHL, which corroborates this fact.

With regard to the evaluation of the PET studies, most of the authors do not use semi-quantitative parameters in the classification and state that the SUV calculation does not offer relevant information, the analysis of the metabolic function based on localization and extension being more important. In a previous work, the most reliable patterns of recurrences were defined as those coinciding with localization prior to the treatment, multiple and infradiaphragmatic localizations. These same authors state that patients with uptake in one localization should be managed conservatively. Others have defined that the extension of the positivity of the PET is clearly related with recurrence.

Our results were in agreement with these statements, since all the patients diagnosed finally of recurrent had multiple-type infradiaphragmatic involvement.

### Table 3

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Sp: specificity; S: sensitivity; NPV: negative predictive value; PPV: positive predictive value.

**Discussion**

Different studies, analyzing the effectiveness of the PET with FDG in the detection of recurrences, have found low specificity in both HL and NHL. This points to the need for histological verification of a positive PET result, since at least one-third of these patients may have benign conditions.

On the other hand, high sensitivity of the metabolic image has been confirmed on detecting preclinical relapses, even 9 months before the histological confirmation on diagnosing disease in symptomatic patients with erroneous radiological studies, and in the diagnosis of second neoplasms. In addition, the high negative predictive value determines that a recurrence is very unlikely when the PET is negative has been described. However, the different results found in the studies conducted up to now are probably due to the different criteria used to determine the positivity of the PET and in the patient screening.

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Our results were in agreement with these statements, since all the patients diagnosed finally of recurrent had multiple-type infradiaphragmatic involvement.
At present, there is no consensus about which follow-up method to use. The guidelines of the NCCN (National Comprehensive Cancer Network) recommend a routine follow-up with imaging techniques in patients with HL in remission after first line treatment. However, on the contrary, three cost-effective retrospective studies have argued against imaging techniques in the follow-up of asymptomatic patients.

On the other hand, the routine study is not effective alone since it only detects recurrences in 11% of the cases. However, when combined with the clinical aspects, they have been defined as the most cost-effective follow-up tools.

The interest in the early detection of recurrence stems from the importance of diagnosing the disease when it shows low tumoral burden since early treatment in these cases has demonstrated improvement in survival. In our sample, half of the patients with recurrence required at least one additional PET-CT study after the first suspicion, showing progression of the findings in all the cases with changing pattern, in two of them consistent with the resolution of some lesions with appearance of other new ones.

With regard to the periodicity of the follow-up studies, and given that most of the recurrences occur in the first three years, the use of imaging studies could be justified, especially in high risk patients. In this context, the following conditions have been defined as high risk: patients with advanced stage on diagnosis, elderly age at the time of the diagnosis and existence of residual masses in the first 24 months after the treatment. In our casuistics, we observe that 6/8 patients with recurrence demonstrated advanced stages on diagnosis and in the same number of cases, the recurrence was detected in the first year of follow-up. We did not observe any relation between the rest of the parameters and the appearance of recurrence. Other authors advocate a more conservative management, reserving the PET for when there is suspicion of radiological recurrence, symptoms or new abnormal lymph nodes detected in the examination.

Few works have analyzed the role of the imaging techniques in the routine follow-up of patients with asymptomatic lymphoma. As far as we know, only two works have analyzed the conventional CT scan, finding an asymptomatic recurrence rate of between 5.7 and 20% of the cases. With regard to the PET-CT, most of the works include patients with clinical suspicion of recurrence in their casuistics. This introduces a screening bias and reduces the reliability in the detection of asymptomatic recurrences by the said technique.

In addition, a limiting factor was the absence of histological confirmation in all the localizations. This is a common determinant of many studies, since for ethical reasons it is impossible to obtain them. That is why a reference standard based on all the available evidence derived from the remaining techniques and clinical history was used instead of them and we consider that it is a valid method, given the prolonged follow-up time in all of the cases. The limited number of histological confirmations, 5 in the 18 patients with positive PET-CT studies, explains the fact that new PET-CT studies were requested to verify the existence or absence of the malignant pathological process.

The inclusion of doubtful studies within the positive ones could have increased the FP rate, although we consider that it was necessary, at least in this preliminary evaluation, to consider them in this way in order to avoid false negatives. On the other hand, the results obtained on these FP offered valuable information to us, since recurrence during the follow-up was not demonstrated in any patient with a single lymph node localization. Furthermore, when supra-diaphragmatic lymph node involvement was found, even if it is multiple, it was linked to low likelihood of recurrence. Given the limited rate of patients with recurrence, it may be risky to generalize these results. However, we consider them to be very representative and we will increase the case samples for their verification.

Conclusions

The PET-CT study with 18F-FDG is a sensitive technique in the detection of asymptomatic recurrences in patients with lymphoma. Although the PPV is limited, especially in single pathological localizations, multiple and infradiaphragmatic lymph node involvement was highly predictive of recurrence in our series of patients.

Conflict of interests

The authors declare they have no conflict of interests.

References