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Original article

Basal ^{18}F-FDG PET/CT in follicular lymphoma: A comparison of metabolic and clinical variables in the prognostic assessment☆

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ABSTRACT

Aim: To analyze the relationship of clinical variables related to prognosis and tumor burden, with metabolic variables obtained in the staging ^{18}F-FDG PET/CT, and their value in the prognosis in follicular lymphoma (FL).
Methods: 82 patients with FL, a ^{18}F-FDG PET/CT at diagnosis and a follow-up for a minimum of 12 months, were retrospectively enrolled in the present study. Clinical variables (Tumor grade, Follicular Lymphoma International Prognostic Index (FLIPI) and Tumor burden) were evaluated. Metabolic variables such as SUVmax in the highest hypermetabolic lesion, extralymphatic locations, number of involved lymph node locations, bone marrow (BM) involvement, PET stage and diameter of the biggest hypermetabolic lesion, were analyzed in order to establish a PET score and classify the studies in low, intermediate and high metabolic risk. Clinical and metabolic variables (included metabolic risk) were compared. The relation among all variables and disease-free survival (DFS) was studied.
Results: The 28% of patients had a high-grade tumor. The 30.5% had FLIPI risk low, 29.3% intermediate y 40.2% high. The 42.7% presented a high tumor burden.
The PET/CT was positive in 94% of patients. The tumor grade did not show significant relation with metabolic variable. FLIPI risk and tumor burden showed statistical relations with the SUV max and the PET score ($p < 0.008$ and $p = 0.003$ respectively). With respect to DFS, significant differences were detected for the PET stage and FLIPI risk ($p = 0.015$ and $p = 0.047$ respectively). FLIPI risk was the only significant predictor in Cox regression analysis, with a Hazard Ratio of 5.13 between high risk and low risk.
Conclusion: The present research highlights the significant relation between metabolic variables obtained with FDG PET/CT and clinical variables although their goal as an independent factor of prognosis was not demonstrated in the present work.

Valor de la ^{18}F-FDG PET/TC basal en el linfoma folicular: comparación de las variables metabólicas y clínicas en la valoración pronóstica

Palabras clave:
Linfoma folicular
Estadificación
^{18}F-FDG PET/TC
PET-TC Score
Pronóstico
Riesgo metabólico

RESUMEN

Objetivo: Analizar la relación entre las variables clínicas relativas al pronóstico y la carga tumoral y las variables obtenidas en la ^{18}F-FDG PET/TC de estadificación, así como su valor pronóstico para el linfoma folicular (LF).
Métodos: Se realizó un estudio retrospectivo de 82 pacientes con LF, ^{18}F-FDG PET/TC en el momento del diagnóstico y seguimiento mínimo de 12 meses. Se evaluaron las variables clínicas (grado tumoral, Índice pronóstico internacional para el linfoma folicular (FLIPI) y carga tumoral). Se analizaron las variables metabólicas tales como SUVmax en las lesiones más hipermetabólicas, localizaciones extralinfáticas, número de localizaciones ganglionares afectas, afectación de la médula ósea, estadio PET y diámetro de la lesión hipermetabólica de mayor tamaño, a fin de establecer una puntuación PET y clasificar los estudios en riesgo bajo, medio y elevado. Se compararon las variables clínicas y metabólicas (incluyendo el riesgo metabólico) y se estudió la relación entre todas las variables y la supervivencia libre de enfermedad (SLE).

☆ The results of this study have not been presented neither published before.

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Resultados: El 28% de los pacientes tenían un tumor de alto grado. El 30,5% tenía un riesgo bajo de FLIPI, el 29,3% un grado intermedio y el 40,2% un riesgo elevado. El 42,7% presentó una elevada carga tumoral.

La PET/TC fue positiva en el 94% de los pacientes. El grado del tumor no reflejó una relación significativa con la variable metabólica. El riesgo de FLIPI y la carga tumoral guardaron relaciones estadísticas con SUVmax y la puntuación PET ($p < 0,008$ y $p = 0,003$, respectivamente). Con respecto a la SLE, se detectaron diferencias significativas para el estadio PET y el riesgo FLIPI ($p = 0,015$ y $p = 0,047$, respectivamente). El riesgo FLIPI fue el único factor predictivo significativo en el análisis de regresión, con un cociente de riesgo instantáneo (HR) de 5,13 entre alto y bajo riesgo.

Conclusión: La presente investigación resalta la considerable relación entre las variables metabólicas obtenidas con FDG PET/TC y las variables clínicas, aunque su objetivo como factor independiente de pronóstico no ha sido demostrado en el presente estudio.

Introduction

Follicular lymphoma (FL) is one of the most common types of lymphoma. It accounts for approximately 20% of adult non-Hodgkin's lymphomas and 70% of indolent lymphomas. It is characterized by diffuse lymphoadenopathy, bone marrow (BM) involvement in 70% of patients, splenomegaly and less common, other extranodal sites of involvement.

Once the diagnostic is confirmed by biopsy, additional test are performed in order to obtain information about the tumor load and prognosis of the patient. The test includes blood test (complete blood cell, lactate dehydrogenase levels, uric acid levels, liver function tests, and creatinina) and imaging techniques [computed tomography (CT) scan and positron emission tomography (PET) scan].

Different treatment options are used for patient with FL due to the heterogeneous clinical course of FL, ranging from clinical monitoring to radiotherapy, chemotherapy, chemoradiotheraphy, monoclonal antibodies and/or autologous stem cell transplant.[1,2] Thus, in addition to adequate clinical assessment, a correct staging of FL patients is essential for establishing the best treatment protocol in order to avoid aggressive treatments, when unnecessary, and detect patients in whom a less intensive therapy would not be enough. Nowadays, the staging of FL is according to the Cotswolds modification of the Ann Arbor staging system,[3] which divides patients into groups (stage) based upon how much of the lymphatic system is involved at the time of diagnosis.

In addition, some prognostic tools for FL have been used. The best measures of prognostic are the tumor grade, FL international prognostic index (FLIPI), and tumor burden.[4] Regarding to tumor grade, the FL is classified in four grades: 1, 2, 3a and 3b and the differences in molecular genetics as well as clinical behavior suggest that FL Grade IIIb is an aggressive disease. The FLIPI assess five prognostic factors: age >60, stage III or IV, number of involved nodal areas >4, high level of serum lactate dehydrogenase, and hemoglobin <12 g/dl (low risk: 0–1 factors, intermediate risk: 2 factors, and high risk ≥3 factors). The tumor burden can be defined using the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria that evaluate: symptomatic splenomegaly, cytopenia, pleural effusion or peritoneal ascitis, B symptoms and single nodal site higher or equal to 7 cm, defining high tumor burden with at least one of the previously referred criteria.

Despite the utility of FLIPI risk and tumor grade for prognosis, the decision for treatment in FL patients is based on the assessment of the burden, aggressiveness of the tumor, age, general healthy and associated symptoms.

The impact of positron emission tomography/computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (FDG) on the staging and assessment of treatment response in potentially curable aggressive lymphomas is well established. Regarding to indolent lymphomas, the major impact of PET/CT is observed in FL.[5] The current literature suggests that initial staging of presumed early-stage FL with PET may change the management in a significant number of patients.[6] However, a limited experience exists with respect to PET and prognosis in FL.[7]

The aim of the present study was to analyze the relationship of clinical variables, associated with prognosis and tumor burden, with metabolic variables obtained in the staging ^{18}F-FDG PET/CT, and their value in the prognosis.

Methodology

A retrospective, longitudinal and multicentre study was performed evaluating all the studies FDG PET/CT performed in patients with FL from January 2007 to November 2013 referred from 9 hospitals.

Patients

Patients with a histologically proven FL, with a FDG PET/CT at diagnosis and a follow-up for a minimum of 12 months since the date of PET/CT, were enrolled in the present study. Patients with relapse or death within first year were included. This research was approved by the institutional review boards of our hospital.

The evaluation during the follow-up was carried out by means of clinical and hematological parameters during scheduled or unscheduled visits, on the basis of diagnostic imaging results (i.e., CT and/or PET/CT).

At the end of the treatment, 61 patients were assessed by PET/CT using the 2007 International Harmonization Project (IHP) criteria[8] and Deauville 5-point scale (5PS) criteria.[9] The rest were assessed by CT.

Clinical variables

Tumor specimen obtained from biopsy was assessed to classify the tumor in grades following the WHO classification of FL, from 1 to 3 based on increased numbers of centroblasts counted per high power field.[10] The biopsy was obtained from the site more accessible and it was not guided by PET results. Grade 3 tumors were classified as high histological grade, and grade 1 and 2 as low.

Prognostic factors as patient age, stage, number of involved lymph node areas, Ann Arbor stage, serum lactate dehydrogenase and hemoglobin levels were assessed to obtain the FLIPI risk.

High tumor burden FL was obtained following the Groupe dÉtude des Lymphomes Folliculares (GELF) criteria.[11]

Other parameters were collected as elevation of beta-2-microglobulin, and bone marrow involvement in biopsy.

After the follow up, disease-free survival (DFS) was defined as the time, in months, from the date of the end of chemotherapy to tumor recurrence or death from any cause or the date of censoring at the last follow-up.