Rev Esp Med Nucl Imagen Mol. 2016;35(3):152–158

Original article

Glycolytic activity in breast cancer using ^{18}F-FDG PET/CT as prognostic predictor: A molecular phenotype approach

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ARTICLE INFO

Article history:
Received 5 May 2015
Accepted 5 August 2015
Available online 27 October 2015

Keywords:
Breast cancer
^{18}F-FDG PET/CT
Molecular phenotypes
Prognosis
Disease free status
Disease free survival
Overall survival

ABSTRACT

Aim: To explore the relationship between basal ^{18}F-FDG uptake in breast tumors and survival in patients with breast cancer (BC) using a molecular phenotype approach.
Material and Methods: This prospective and multicentre study included 193 women diagnosed with BC. All patients underwent an ^{18}F-FDG PET/CT prior to treatment. Maximum standardized uptake value (SUVmax) in tumor (T), lymph nodes (N), and the N/T index was obtained in all the cases. Metabolic stage was established.

As regards biological prognostic parameters, tumors were classified into molecular sub-types and risk categories. Overall survival (OS) and disease free survival (DFS) were obtained.

An analysis was performed on the relationship between semi-quantitative metabolic parameters with molecular phenotypes and risk categories. The effect of molecular sub-type and risk categories in prognosis was analyzed using Kaplan–Meier and univariate and multivariate tests.
Results: Statistical differences were found in both SUVT and SUVN, according to the molecular sub-types and risk classifications, with higher semi-quantitative values in more biologically aggressive tumors. No statistical differences were observed with respect to the N/T index.

Kaplan–Meier analysis revealed that risk categories were significantly related to DFS and OS. In the multivariate analysis, metabolic stage and risk phenotype showed a significant association with DFS.
Conclusion: High-risk phenotype category showed a worst prognosis with respect to the other categories with higher SUVmax in primary tumor and lymph nodes.

Actividad glicolítica en el cancer de mama mediante ^{18}F-FDG PET/TC como predictor pronóstico: aproximación del fenotipo molecular

Palabras clave:
Cáncer de mama
^{18}F-FDG PET/TC
Fenotipos moleculares
Pronóstico
Estado libre de enfermedad
Supervivencia libre de enfermedad
Supervivencia global

RESUMEN

Objetivo: Analizar la relación entre la captación basal de ^{18}F-FDG en tumores mamarios y la supervivencia en pacientes con cancer de mama (CM) bajo la aproximación del fenotipo molecular.
Material y métodos: Este estudio prospectivo y multicentrico incluyó 193 mujeres diagnosticadas de CM. Todas las pacientes fueron sometidas a una ^{18}F-FDG PET/TC previa al tratamiento. Se obtuvo el SUVmax en el tumor (T), ganglios linfáticos (N) así como el índice N/T en todos los casos. Además se determinó el estadio metabólico.

Atendiendo a los factores biológicos pronósticos, los tumores fueron clasificados en subtipos moleculares y categorias de riesgo. Se obtuvo tanto la supervivencia global (SG) como la supervivencia libre de enfermedad (SLE).

Se estudió la relación entre los parámetros metabólicos semicuantitativos con los fenotipos moleculares y las categorías de riesgo. Se analizó el efecto del subtipo molecular y las categorías de riesgo en el pronóstico mediante análisis de Kaplan–Meier y test uni y multivariantes.
Resultados: Se encontraron diferencias estadísticamente significativas en tanto el SUVT como el SUVN, deacuerdo a los fenotipos moleculares y las categorías de riesgo, con valores mayores en los tumores biológicamente más agresivos. No se observaron diferencias con respecto al índice N/T.

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http://dx.doi.org/10.1016/j.remn.2015.08.001

El análisis de Kaplan–Meier reveló que las categorías de riesgo se relacionaron de forma significativa con la SG y SLE. En el análisis multivariante, el estadio metabólico y la categoría de riesgo mostraron asociación significativa con la SLE.
Conclusion: La categoría de alto riesgo manifestó un peor pronóstico con respecto a las otras categorías, con mayores valores de SUVmax tanto en el tumor primario como en ganglios linfáticos.

Introduction

In breast cancer (BC), it has been previously described that even for two patients who share the same staging based on anatomical features, the disease entities at the molecular level could be different; thus further stratification of the patient according to the biological behavior of the cancer cells seems reasonable.[1] For that reason, biological subtypes have gained widespread acceptance due to differences in presentation, response to treatment and prognosis.[2]

Tumor cells in the vast majority of BC have significantly increased glycolysis and therefore utilize the administered ^{18}F-fluorodeoxiglucose (FDG) to a greater extent than the normal cells.[3] Therefore ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) can discriminate aggressive forms of BC from indolent ones. Due to the remarkable heterogeneity of the disease, various aspects of ^{18}F-FDG uptake can be shown according to tumor biology.[4]

Summarizing, the intensity of ^{18}F-FDG accumulation in BC cells may vary with the extent of the disease, tumor differentiation, histological subtypes, and different biological prognostic parameters. Based on that, connection between BC glycolytic metabolism and prognosis have been reported, although the experience is limited.[4,5]

The aim in the present work was to study the relations between the ^{18}F-FDG uptake in primary tumor and lymph nodes under a molecular phenotype perspective and study their implications in the patient's outcome.

Material and Methods

This prospective and multicentre study was approved by the local ethics committee of our institution and Investigation Board and included 7 hospitals. The Institutional Review Boards in each hospital approved the protocol of this study.

Patients

Written informed consent was obtained from all patients. Between September 2009 and September 2013 patients with LABC who underwent staging by ^{18}F-FDG PET/CT prior to any treatment or surgical procedure were evaluated. The inclusion criteria were newly diagnosed unilateral or bilateral BC with clinical indication of neoadjuvant chemotherapy (NC). The exclusion criteria were the presence of metastasis confirmed by other methods previous to the request of an ^{18}F-FDG PET/CT.

All the patients were imaged using digital mammography, ultrasonography and some of them magnetic resonance imaging.

Based on the stage and tumor biology patients underwent NC or surgery, following by adjuvant treatment. Palliative chemotherapy was administered in non-operable cases.

After follow up, the patient status was established classifying as disease free status or no disease free status in case of death, stable disease, recurrence or progression. Disease-free survival (DFS) was defined as the time, in months, from the date at initial staging to tumor recurrence or death from any cause. Overall survival (OS) was defined as the time, in months, from the date at initial staging to death from any cause or the date of censoring at the last follow-up.

FDG-PET/CT imaging

Patients fasted for at least 4 h before the PET examination and had blood glucose levels less than 160 mg/dl at the time of FDG injection. PET/CT was performed on the same dedicated PET/CT equipment (Discovery DSTE-16 s, GE Medical Systems) located in a reference hospital. The whole-body images were acquired from head to thigh 60 min after intravenous administration of approximately 8.89 mmol/L of ^{18}F-FDG, 3 min/bed position. Transmission scans were performed for all patients to provide attenuation correction with CT with acquisition parameters for the CT of 120 kV, modulated 120 mA. The PET and CT section thickness was 3.8 mm. Iterative reconstruction and scatter correction of image was done.

Imaging assessment

Visual assessment, image interpretation, and data analysis were performed independently by two nuclear medicine physicians in consensus. They were aware of the patient's clinical history, which was provided by the referring physician, but were blinded to the results of other imaging studies.

For the visual assessment, an increased uptake of ^{18}F-FDG with intensity higher than the surrounding tissues and not explained by physiological processes was considered positive for tumor. The same criterion was used in the evaluation of hypermetabolic axillary or extra-axillary lymph nodes and distant lesions.

Volumes of interest (VOIs) were placed manually over the most intense areas on primary breast tumor (T) and lymph nodes (N) on attenuation-corrected images. Analysis was based on measuring the maximum ^{18}F-FDG uptakes in both locations, the standard uptake value (SUVmax).

The SUVmax within the VOIs of interest was obtained and calculated as follows: SUVmax = maximum activity concentration in VOI (MBq/g)/[injected dose (MBq)/body weight (g)]. Furthermore the SUV max N/T index was established (SUVmax N/SUVmaxT).

Metabolical stages were determined according to the classification of the American Joint Committee on Cancer (AJCC) 7th edition.[6] Metabolic size of the lesions was established in PET images considering the greatest diameter in any projection. N stages were metabolically established. In case of distant hipermetabolic lesions, non-explained by physiological or inflammatory processes, patients were classified as stage IV.

Histopathological analysis

The histopathological analysis was performed on specimens obtained by gross-needle aspiration biopsy and surgical procedures. The determination of tumor type (four main groups: infiltrating ductal carcinoma, infiltrating lobular carcinoma, lobular carcinoma "in situ" and ductal carcinoma "in situ") and the histopathological grading (1. Well differentiated; 2. Moderately differentiated; 3. Poorly differentiated) were performed on formalin