Rev Esp Med Nucl Imagen Mol. 2012;**31(6)**:308–314

Original Article

^{18}F-FDG semi-quantitative parameters and biological prognostic factors in locally advanced breast cancer

A.M. García Vicente[a,*], Á. Soriano Castrejón[a], F. Relea Calatayud[b], V. Muñoz Madero[c], M.J. Molina Garrido[d], A.A. León Martín[e], J.M. Cordero García[a], J.P. Pilkington Woll[a], I. Chacón López-Muñiz[f], A. Palomar Muñoz[a]

[a] *Nuclear Medicine Department, University General Hospital, Ciudad Real, Spain*
[b] *Pathology Department, University General Hospital, Ciudad Real, Spain*
[c] *Surgery Department, Provincial Hospital, Toledo, Spain*
[d] *Oncology Department, Virgen de la Luz Hospital, Cuenca, Spain*
[e] *Investigation Unit, University General Hospital, Ciudad Real, Spain*
[f] *Oncology Department, Virgen de la Salud Hospital, Toledo, Spain*

ARTICLE INFO

Article history:
Received 16 November 2011
Accepted 14 December 2011
Available online 19 March 2012

Keywords:
Locally advanced breast cancer
FDG
PET/CT
Prognostic factors

ABSTRACT

Aim: To analyse the correlation between ^{18}F-FDG uptake assessed by PET/CT in locally advanced breast tumours and histopathological and immunohistochemical prognostic factors.
Material and methods: Thirty-six women with breast cancer were prospectively evaluated. PET/CT was requested in the initial staging previous to adjuvant chemotherapy (multicentric study).
All the patients underwent an ^{18}F-FDG PET/CT with a dual-time-point acquisition. Both examinations were evaluated qualitatively and semiquantitatively with calculation of SUVmax values in PET-1 (SUV-1) and in PET-2 (SUV-2) and the percentage variation of the standard uptake values (retention index) between PET-1 and PET-2.

Clinical and metabolic stages were assessed according to TNM classification. The biological prognostic parameters, such as the steroid receptor status, *p53* and *c-erbB-2* expression, proliferation rate (Ki-67), and grading were determined from tissue of the primary tumour. Metabolic and biological parameters were correlated.
Results: A positive relationship was found between semiquantitative metabolic parameters and biological parameters. SUV-1 and SUV-2 values did not show significant statistical correlation ($p < .05$) except for the clinical tumour size.
About the biological parameters, retention index showed the best results with positive and significant relation ($p < .05$) with estrogen and progesterone receptor status and Ki-67. Isolated SUV values did not show significant relation to these parameters.
Conclusion: Retention index showed the best relation with biological parameters compared to isolated SUVmax values. These data suggest that SUV change over time is a prognostic marker.

Parámetros semicuantitativos de ^{18F}FDG y factores pronósticos biológicos en el cáncer de mama localmente avanzado

Palabras clave:
Cáncer de mama localmente avanzado
FDG
PET-TC
Factores pronósticos

RESUMEN

Objetivo: Analizar la correlación entre la captación de ^{18F}FDG valorada por la PET-TC en cáncer de mama localmente avanzado y factores pronósticos histopatológicos e inmunohistoquímicos.
Material y métodos: Se valoraron prospectivamente 36 mujeres con cáncer de mama. La PET-TC fue requerida en la estadificación previamente al tratamiento quimioterápico (estudio multicéntrico).
A todas se les realizó una PET-TC con ^{18F}FDG en 2 fases. Ambas fueron valoradas cualitativa y semicuantitativamente con cálculo del SUVmax en la PET-1 (SUV-1) y en la PET-2 (SUV-2) así como el índice de retención.

Los estadios clínicos y metabólicos fueron evaluados siguiendo la clasificación TNM. Se determinaron los parámetros biológicos pronósticos del tumor primario, como el estado de los receptores esteroideos, la expresión del *p53* y c-*erbB-2*, el índice de proliferación (Ki-67) y el grado histológico. Los parámetros biológicos e histológicos fueron correlacionados.
Resultados: Se encontró una relación positiva entre los parámetros metabólicos semicuantitativos y los biológicos. Los valores de SUV-1 y SUV-2 no mostraron una correlación estadísticamente significativa excepto para el tamaño clínico tumoral.

* Corresponding author.
E-mail addresses: angarvice@yahoo.es, amgarcia@sescam.jccm.es (A.M. García Vicente).

2253-654X/$ – see front matter
doi:10.1016/j.remn.2011.12.001

Acerca de los parámetros biológicos, el índice de retención mostró los mejores resultados con relación positiva y significativa ($p < 0,05$) con el estado de los receptores estrogénicos y progestágenos y el Ki-67. Los valores aislados del SUV no mostraron relación significativa con esos parámetros.
Conclusión: El índice de retención mostró la mayor relación con los parámetros biológicos comparados con los valores aislados de SUVmax. Estos datos sugieren que el cambio del SUV es un marcador pronóstico.

Introduction

Preoperative prediction of patient prognosis is becoming increasingly important because more and more women with breast cancer are given neoadjuvant chemotherapy with the aim of downstaging their disease and increasing the feasibility of breast-conserving surgery.

^{18}F-FDG (FDG) uptake may provide important clinical and biological information that can be of prognostic significance. In addition it has been proposed that dual-time-point FDG-PET may improve the sensitivity and accuracy of FDG-PET in assessing patients with primary breast cancer.[1]

The biological characteristics of the tumours are considered important prognostic factors in patients with breast cancer and may influence glucose metabolism as detected by PET.[2]

Patients with locally advanced breast tumours have a worse prognosis due to the lymph node involvement and a higher incidence of distant metastases. Thus, following the recommendation of NCCN Task Force Report, FDG PET/CT is indicated in locally advanced tumours and is not recommended in stages I and II because of the low prevalence of metastatic disease and the high rate of false positives.[3]

The aim of this prospective analysis was to determine the possible correlation between FDG uptake and well established prognostic markers in women with locally advanced breast cancer.

Material and methods

This prospective and multicentric study (Investigation project, grant: 2009/40) was approved by the review boards of the seven enrolled hospitals. Written consent was obtained from all patients.

Patients

From October 2009 to December 2010, all patients with the following inclusion criteria were studied: large (stage IIB) and/or locally advanced breast cancer (IIIA–IIIC) with indication of neoadjuvant chemotherapy. Exclusion criteria were clinical stage IV, previous surgery to the breast or axilla or administration of a previous treatment.

All patients underwent digital mammography, breast ultrasonography and FDG PET/CT before receiving neoadjuvant chemotherapy.

Tumour histology and biological parameters were evaluated by the core needle biopsy before neoadjuvant chemotherapy.

Patients fasted for at least 4 h before the FDG administration and had blood glucose levels less than 160 mg/dl at the time of injection.

Image acquisition and analysis

FDG PET/CT was performed in a reference hospital, following a standardized protocol, in three-dimensional (3D) mode, 3 min/bed position with a dedicated whole-body PET/CT machine, placed in our reference centre for the study. Transmission scans were performed for all patients to provide attenuation correction with CT. The PET section thickness was 3.8 mm. Iterative reconstruction and scatter correction of image were done.

All the patients underwent PET/CT with a dual-time-point acquisition. The first examination was performed as whole-body images from head to thigh 60 min after intravenous administration of approximately 370 MBq of ^{18}F-FDG (PET-1). The second examination imaged the chest only, with acquisition of one or two bed positions 3 h after FDG administration (PET-2).

Both examinations were evaluated qualitatively and semiquantitatively with calculation of SUVmax values in PET-1 (SUV-1) and in PET-2 (SUV-2). The percentage variation of the standard uptake values (retention index, RI) between PET-1 and PET-2 was obtained attending to the formula: $RI = (SUV\text{-}2 - SUV\text{-}1/SUV\text{-}1) \times 100$.

PET/CT images were interpreted by two nuclear medicine specialists blinded to the patients record. If the interpretation differed, consensus was reached with the help of a third physician.

The SUVmax of the breast cancer was measured by manually marking a cubical volume of interest (VOI) around the tumour.

Clinical and metabolical sizes of the primary tumour were established attending the biggest diameter assessed by morphological techniques (digital mammography and breast ultrasonography) and the maximum diameter of the lesion in the axial delayed PET imaging respectively.

The metabolical N status was visually evaluated in axilla and in internal mammary, supra and infraclavicular regions. A lymph node with a detectable metabolism, higher than background activity in adjacent fat that increasing in the delayed PET/CT was considered positive.

Clinical and metabolical stages were determined according to the American Joint Committee on Cancer (AJCC) 7th edition by clinical examination, mammogram and ultrasonography (clinical stage) and FDG PET/CT (metabolical stage) in all the patients.[4] An example is shown in Fig. 1.

The presence or absence of metastatic disease was evaluated in FDG PET/CT.

Prognostic factors

In breast tumours there are several prognostic factors in different phases of validation. In Table 1 are referred prognostic factors attending to their importance and clinical evidence.

- Category 1 prognostic factors had showed their utility in the treatment and prognosis.
- Category 2 prognostic factors are pending of validation by statistical studies but are well biologically and clinically studied.
- Category 3 factors have not been studied enough to demonstrate their prognostic value.

Table 1
Prognostic factors in breast cancer classified by categories of evidence.

Category 1	Axillary involvement, grade and histological type of tumour, mitotic rate, ER/PR expression.
Category 2	C-erb-B2, proliferation markers (MIB-1), vascular invasion and p53.
Category 3	Microvascular density, ploidia, GERF, TGFα, bcl-2, pS2 and D catepsine.