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Original article

Dual time point 2-deoxy-2-[^{18}F]fluoro-D-glucose PET/CT: Nodal staging in locally advanced breast cancer

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ABSTRACT

Aim: To assess dual time point 2-deoxy-2-[^{18}F]fluoro-D-glucose ^{18}FDG PET-CT accuracy in nodal staging and in detection of extra-axillary involvement.
Material and methods: Dual time point [^{18}F] FDG PET/CT scan was performed in 75 patients. Visual and semiquantitative assessment of lymph nodes was performed. Semiquantitative measurement of SUV and ROC-analysis were carried out to calculate SUVmax cut-off value with the best diagnostic performance. Axillary and extra-axillary lymph node chains were evaluated.
Results: Sensitivity and specificity of visual assessment was 87.3% and 75%, respectively. SUVmax values with the best sensitivity were 0.90 and 0.95 for early and delayed PET, respectively. SUVmax values with the best specificity were 1.95 and 2.75, respectively. Extra-axillary lymph node involvement was detected in 26.7%.
Conclusion: FDG PET/CT detected extra-axillary lymph node involvement in one-fourth of the patients. Semiquantitative lymph node analysis did not show any advantage over the visual evaluation.

PET-TC con 2-deoxi-2-[^{18}F]fluor-D-glucosa en doble fase: estadificación ganglionar en cáncer de mama localmente avanzado

Palabras clave:
[^{18}F] FDG PET-TC
Cáncer de mama localmente avanzado
PET en doble fase
Estadificación ganglionar

RESUMEN

Objetivo: Valorar la precision diagnóstica de la PET-CT con 2-deoxi-2-[^{18}F]fluor-D-glucosa [^{18}F] FDG en doble fase en la estadificación ganglionar y en la detección de afectación extra-axilar.
Material y métodos: Se realizó una [^{18}F] FDG PET-TC en doble fase a 75 pacientes. Se valoraron los ganglios linfáticos de forma visual y semicuantitativa. Se realizaron medidas del SUV y análisis ROC para calcular el valor de SUV max con la mejor precisión diagnóstica. Se evaluaron los niveles axilares y extra-axilares.
Resultados: La sensibilidad y especificidad del análisis visual fue del 87.3% y 75% respectivamente. Los valores de SUVmax con la mejor sensibilidad fueron de 0.90 y 0.95 para el PET en fase precoz y tardía respectivamente. Los valores de SUV max con la mejor especificidad fueron de 1.95 y 2.75 respectivamente. Se detectó afectación ganglionar extra-axilar en el 26.7%.
Conclusión: La PET-TC con FDG detectó afectación ganglionar extra-axilar en una cuarta parte de las pacientes. El análisis semicuantitativo no pareció aportar ninguna ventaja sobre la valoración visual.

Introduction

The presence of axillary lymph node metastases is the most important prognostic factor in breast cancer. No imaging technique currently available allows for an accurate evaluation of axillary lymph node involvement, and even though positron emission tomography (PET) with 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) is less sensitive than sentinel node biopsy for the detection of lymph node metastases, its specificity is high, ranging from 85% to 100%.[1]

For [^{18}F]FDG PET, a revision reported a sensitivity and specificity that ranged from 57 to 100% and 66 to 100%, respectively.[2] However the sensitivity depends on the high a priory likelihood of voluminous lymph node metastases and intrinsic tumour characteristics like grade and type.[3,4]

Locally advanced breast tumors have a higher incidence of axillary, extra-axillary involvement and distant metastases.[5]

Several studies have demonstrated that [^{18}F]FDG PET is superior to conventional diagnostic techniques in the detection of extra-axillary nodal metastases, particularly to the internal mammary

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lymph nodes.[6] The rate of detection is particularly high in patients in advanced stages (III or IV) of breast cancer.

In addition it has been proposed that dual-time-point [^{18}F]FDG PET may improve the sensitivity and accuracy of [^{18}F]FDG PET in assessing patients with primary breast cancer.[7] On the contrary this procedure seems not to improve the overall performance of standard PET in detecting axillary lymph node metastasis in breast cancer patients.[8]

The aim of this study was to evaluate the accuracy of dual time point [^{18}F]FDG-PET/computed tomography (CT), in nodal staging and in the detection of extra-axillary involvement and determine whether the use of a semiquantitative lymph node analysis has any advantage over the visual evaluation for the correct classification of lymph nodes in patients with locally advanced breast cancer.

Material and methods

This prospective and multicentric study was approved by the local ethics committee of our institution and Investigation Board (2009/40) and includes 7 hospitals of our region. The Institutional Review Boards in each institution approved the protocol of this study.

Patients

Written informed consent was obtained from all patients. Seventy-five patients (all women; mean age 52.5, SD ± 11.8) were studied.

The inclusion criteria were newly diagnosed unilateral breast cancer with indication of neoadjuvant treatment (stage II or III), with histological confirmation of lymph node state by a previous fine-needle aspiration (FNA) or sentinel node biopsy (SNB), performed after the PET/CT study. The exclusion criteria were presence of distant metastasis confirmed by other methods previous to the request of a PET/CT.

All the patients were imaged using digital mammography, ultrasonography, as conventional diagnostic imaging (CDI), and [^{18}F]FDG PET/CT performed in a unique reference centre.

FDG-PET/CT imaging

Patients fasted for at least 4 h before the PET/CT examination and had blood glucose levels lower than 160 mg/dl at the time of injection. PET/CT was performed with a dedicated whole-body PET/CT machine following a standardized protocol in three-dimensional (3D) mode, 3 min/bed position.[9] 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 was done.

All the patients underwent dual time point imaging with an average interval time of approximately 120 min between the two phases. The first examination was performed as whole-body image from head to thigh 60 min after the 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 (PET-2).

Image interpretation

For visual interpretation images were displayed in three orthogonal projections and as whole-body maximum-pixel-intensity projection images. Two experienced nuclear medicine physicians, who were blinded to the conventional staging investigations, interpreted in consensus the [^{18}F] FDG PET/CT studies.

Metabolic images were considered positive if areas in the lymph node took up more FDG than the surrounding tissue in the early PET (PET-1) and kept or increased activity in delayed image (PET-2).

Homogeneously hypoechoic lymph nodes with a diameter of ≥1 cm in oval or round shape were defined by CDI as positive.

A combined assessment, metabolical and clinical attending the information of CDI, was performed considering it as pathologic if any technique showed signs of lymph node involvement.

The breast areas, supraclavicular and internal mammary lymph node chains were evaluated to establish the percentage of extra-axillary involvement.

Semiquantitative measurement of SUVmax was done on the axillary or extra-axillary focus with the highest abnormal FDG uptake in PET-1 (SUV-1) and PET-2 (SUV-2). The percentage difference in the SUVmax or retention index (RI) between SUV-1 and SUV-2 was calculated.

We obtained the short axial diameter of the lymph node with the greatest FDG uptake in each case using the CT portion of the PET. The lymph node with the highest FDG uptake was classified attending to its size in group 1 (short axial diameter <1 cm) or group 2 (short axial diameter ≥1 cm).

The clinical and metabolic N stages (cN and mN) were established according to the clinical exploration and the results of morphological imaging techniques and the recommendations of the American Joint Committee on Cancer (AJCC) 7th edition.[10]

Histopathological analysis

Histological confirmation of the suspicious lymph node, according to morphological imaging, was obtained by FNAB (fine needle aspiration *biopsy*) previous to PET/CT scan or sentinel node biopsy (SNB) after PET/CT scan.

Statistical analysis

All statistical tests were two-sided with a significance level of $p < 0.05$. SPSS 18.0.1 for Windows was used for all analyses.

All semiquantitative data were expressed in terms of mean ± SD.

Sensitivity, specificity, positive and negative predictive values (PPV, NPV) and accuracy of [^{18}F]FDG PET/CT imaging for lymph node staging were analyzed using standard statistical analyses. The 95% confidence intervals (CI) were calculated using the binomial distribution.

The results (mN) were related to the previous cN established attending to the clinical exploration and morphological imaging techniques. The integration of both imaging techniques (morphologic and metabolic) was evaluated considering as positive any lymph node that was positive with any technique.

The mean SUV-1 and SUV-2 values were obtained in group 1 and group 2 lymph nodes.

A ROC-analysis (receiver-operating characteristics) was performed, and the cut-off value was calculated as to obtain the best diagnostic test parameters to establish the lymph node involvement in PET-1 and PET-2.

The concordance between cN and mN was assessed (kappa index) classifying the results as: poor (<0.20), weak (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) and very good (0.81–1.00).

Results

Of the 75 patients, 63 had lymph node involvement confirmed by histopathology. Sixty-seven patients underwent FNAB guided by ultrasonography in the suspicious lymph node. The rest of cases were confirmed by SNP. Thus, the prevalence of lymph node involvement was high (84%).