

Original article

## Relationship between primary tumour $^{18}\text{F}$ -FDG uptake and immunohistochemical and clinical prognostic parameters in breast carcinoma

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### ABSTRACT

**Objective:** The objective of this study was to investigate the relationship between level of  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) accumulation in primary breast tumour assessed by positron emission tomography/computed tomography (PET/CT) and histopathological and clinical prognostic factors.

**Material and methods:** A retrospective analysis was performed using the medical records of 58 female patients (age range: 31–86 years, mean age: 56) with biopsy of proven breast carcinoma, and who had undergone  $^{18}\text{F}$ -FDG PET/CT examination before chemotherapy/surgery. The  $^{18}\text{F}$ -FDG uptake of breast tumours was calculated as tumour to background ratio (TBR), which was compared with histopathological and clinical prognostic parameters.

**Results:** The histology of the breast tumour in the 58 patients was ductal type in 52 (90%), lobular in 4 (7%), and mucinous in 2 (3%). Tumour size was  $\leq 2$  cm in 31 (53%) patients, and  $> 2$  cm in 27 (47%). The levels of TBRs were not significantly different between the patients groups with tumours of 2 cm or less and greater than 2 cm ( $P=0.131$ ). No significant difference between levels of TBR was observed neither with regards to axillary lymph node involvement ( $P=0.065$ ) nor in terms of distant metastases ( $p=0.123$ ). No statistically significant difference was found in levels of TBRs between patients with c-erbB-2 receptor positive and negative ones ( $P=0.107$ ). Progesterone receptor (PR) expression was observed in 33 patients (57%), and 25 patients (43%) were PR negative. As regards progesterone receptor status, a statistically significant difference was observed in mean TBR levels between patients with and without progesterone receptor expression ( $P=0.020$ ). Oestrogen receptor expression was positive in 41 (71%) patients, and negative in 17 (29%) patients. The difference in the levels of TBRs between patients with and without oestrogen receptor expression was at the level of significance ( $P=0.050$ ).

**Conclusions:** It is concluded that  $^{18}\text{F}$ -FDG uptake correlates with progesterone negativity of the tumour. However, a significant association with clinical prognostic parameters and level of  $^{18}\text{F}$ -FDG uptake levels could not be demonstrated.

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### Asociación entre la captación de $^{18}\text{F}$ -FDG y las características inmunohistoquímicas y factores pronósticos en el cáncer de mama

### RESUMEN

**Objetivo:** El objetivo de este estudio fue investigar la asociación entre el nivel de captación de  $^{18}\text{F}$ -fluorodeoxiglucosa ( $^{18}\text{F}$ -FDG) en el tumor de mama primario, valorado mediante tomografía por emisión de positrones/tomografía computarizada (PET/TC) y correlacionarlo con los factores pronósticos histopatológicos y clínicos.

**Material y métodos:** Se analizaron retrospectivamente las historias clínicas de 58 mujeres (rango de edad: 31–86 años, edad media: 56 años) con biopsia de carcinoma de mama, que se sometieron a una exploración  $^{18}\text{F}$ -FDG PET/TC antes de la quimioterapia/cirugía. El grado de captación de  $^{18}\text{F}$ -FDG en los tumores de mama se calculó como el índice tumor/fondo (ITF) que se comparó con parámetros pronósticos histopatológicos y clínicos.

**Resultados:** La histología del tumor de mama en las 58 pacientes fue de tipo ductal en 52 (90%), lobular en 4 (7%) y mucinoso en 2 (3%). En 31 pacientes (53%) el tamaño del tumor fue  $\leq 2$  cm y en 27 (47%) fue  $> 2$  cm. Los niveles de ITF no fueron significativamente diferentes entre el grupo de pacientes con un tumor  $\leq 2$  cm y el grupo con tumor  $> 2$  cm ( $p=0,131$ ). No se observaron diferencias significativas entre los ITF ni

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con respecto a la afectación de los ganglios linfáticos axilares ( $p=0,065$ ), ni en términos de metástasis a distancia ( $p=0,123$ ). Tampoco hubo diferencias estadísticamente significativas en los niveles de ITF entre los pacientes con los receptores de c-erbB-2 positivos y negativos ( $p=0,107$ ). Treinta y tres pacientes (57%) presentaron receptores de progesterona positivos y en 25 pacientes (43%) eran negativos. Respecto al estado de los receptores de progesterona, se observó una diferencia estadísticamente significativa en los niveles medios de ITF entre pacientes con y sin la expresión del receptor de progesterona ( $p=0,020$ ). Los receptores estrogénicos fueron positivos en 41 pacientes (71%) y negativos en 17 (29%). Con relación a los receptores estrogénicos, la diferencia en el ITF entre los casos con receptores positivos y los negativos estaba en el nivel de significación ( $p=0,050$ ).

**Conclusiones:** Se concluye que la captación de  $^{18}\text{F}$ -FDG se relaciona con la negatividad de los receptores de progesterona del tumor. Sin embargo, no se demostró una asociación significativa con los parámetros pronósticos clínicos y el grado de captación de  $^{18}\text{F}$ -FDG.

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## Introduction

$^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography/computed tomography (PET/CT) is a widely used diagnostic modality in oncologic imaging. Reflecting their glucose hypermetabolism, uptake of  $^{18}\text{F}$ -FDG by breast cancer cells and the ability of  $^{18}\text{F}$ -FDG PET/CT in visualizing the primary tumor both in primary and recurrent settings has been shown in breast carcinoma.<sup>1</sup> Apart from primary tumor diagnosis, accurate staging of patients with breast carcinoma is also required for planning the optimal therapy.  $^{18}\text{F}$ -FDG PET/CT has been reported to be more accurate than conventional imaging methods in initial and recurrent staging of breast cancer.<sup>2</sup>

As well as preoperative determination of tumor extent, prognosis stratification is also essential in patients with breast carcinoma. Several biological and clinical prognostic factors related to breast carcinoma have been described in the literature such as estrogen (ER) and progesterone receptor (PR) status, expression of the proto-oncogene c-erbB-2, axillary nodal status, size of the primary tumor and presence of metastases.<sup>3,4</sup> Among these, determination of ER and PR status in tumor cells is important for appropriate hormone therapy. Hormone sensitive breast cancer is less aggressive than hormone resistant one and overall, the median survival in patients with ER positive tumors is longer than for patients with ER negative breast cancer.<sup>5</sup> Absence of PR is independent predictor of poor response and is associated with higher recurrence rates and shorter survival time.<sup>6</sup> Overexpression of c-erbB-2 receptor is associated with increased mitogenesis, invasiveness and determination of c-erbB-2 receptor is useful for selecting patients with advanced breast cancer for the therapy with therapeutic antibodies like trastuzumab.<sup>7</sup>

It has been reported that,  $^{18}\text{F}$ -FDG PET/CT can also be used to assess the proliferative activity/or biological aggressiveness of malignant tissue by calculating the level of  $^{18}\text{F}$ -FDG uptake in primary breast tumors.<sup>2</sup> Pretherapeutic overview of the entire body and evaluation of the tumor proliferation rate, which will help to stratify patients according to risk for recurrence and to tailor the aggressiveness of therapy for an individual patient with  $^{18}\text{F}$ -FDG PET/CT in a single examination, is a challenging approach. The probable relationship between  $^{18}\text{F}$ -FDG uptake expressed as SUV and other clinical and biologic prognostic factors in breast carcinoma were investigated previously and some positive and statistically significant differences were found between SUV and clinicopathological parameters such as high tumor size, presence of axillary lymph node metastases, ER and PR negativity.<sup>2-4,8</sup> In all of these studies, standardized uptake value (SUV) was used as the quantitative analysis and the association of SUV and other prognostic factors were investigated. The aim of this study was to evaluate the possible correlation between proliferative activity of primary tumor and other biologic and clinical

prognostic markers in breast carcinoma by using a different quantitative method of tumor to background ratio (TBR), with  $^{18}\text{F}$ -FDG PET/CT.

## Material and methods

### Patients

Files of patients with breast carcinoma, who underwent  $^{18}\text{F}$ -FDG PET/CT examination between October 2012 and May 2016, were retrospectively reviewed. Of these, 58 female patients (age range: 31-86 years, mean age: 56) with biopsy proven breast carcinoma who were examined with  $^{18}\text{F}$ -FDG PET/CT before any initial therapy and surgery, were enrolled to the study. Patients with bilateral breast cancer or patients in whom  $^{18}\text{F}$ -FDG PET/CT was performed after surgery or neoadjuvant/primary chemotherapy, were excluded from the study.

This study was approved by the local ethics committee of our faculty (meeting date: 13.04.2016 decision number: 2016/122) and written informed consent was obtained from all patients.

### *$^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography scanning procedure*

Images from the skull base to the midthigh were acquired in 8 or 9 bed positions with an acquisition time of 2 minutes per bed position with integrated  $^{18}\text{F}$ -FDG PET/CT scanner (Biograph mCT, Siemens, Germany). Patients were advised to fast for at least 6 hours and 370 MBq of  $^{18}\text{F}$ -FDG was injected to the patients whose blood glucose level was <200 mg/dl. PET/CT studies were performed 1 hour after the administration of the radiopharmaceutical. The CT part of the integrated scan was carried out without contrast enhancement by using 16 slice CT with the acquisition parameters of 190 mA, 5 mm slice thickness and 140 kV. Right after the CT imaging, PET scan was performed without changing the position. The CT data were used for the attenuation correction of PET scanning.

### *Image analysis and quantification*

Acquired images of  $^{18}\text{F}$ -FDG PET/CT were analysed on Siemens Syngo via PET/CT workstation. For axillary involvement, lymph nodes showing  $^{18}\text{F}$ -FDG uptake without fatty hilum were considered as metastatic. Any lesion showing  $^{18}\text{F}$ -FDG accumulation in sites different from the primary tumor and axillary region presenting radiological aspects of metastases, were regarded as distant metastases. Tumor-to-background ratios (TBRs) were calculated in all breast tumors for semiquantitative analysis of tumor  $^{18}\text{F}$ -FDG uptake. For this purpose, a region of interest was drawn around the site of the primary breast lesion. For background uptake, a

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