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Original article

Predictive value of PET-CT for pathological response in stages II and III breast cancer patients following neoadjuvant chemotherapy with docetaxel

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ABSTRACT

Purpose: To prospectively study the value of PET-CT with fluorine-18 fluorodeoxyglucose (FDG) to predict neoadjuvant chemotherapy (NAC) response of locoregional disease of stages II and III breast cancer patients.
Material and methods: A written informed consent and approval were obtained from the Ethics Committee. PET-CT accuracy in the prediction of pathologic complete response (pCR) after NAC was studied in primary tumors and lymph node metastasis in 43 women (mean age: 50 years: range: 27–71 years) with histologically proven breast cancer between December 2009 and January 2011. PET-CT was performed at baseline and after NAC. SUVmax percentage changes (ΔSUVmax) were compared with pathology findings at surgery. Receiver-operator characteristic (ROC) analysis was used to discriminate between locoregional pCR and non-pCR. In patients not achieving pCR, it was investigated if ΔSUVmax could accurately identify the residual cancer burden (RCB) classes: RCB-I (minimal residual disease (MRD)), RCB-II (moderate RD), and RCB-III (extensive RD).
Results: pCR was obtained in 11 patients (25.6%). Residual disease was found in 32 patients (74.4%): 16 (37.2%) RCB-I, 15 (35.6%) RCB-II and 2 (4.7%) RCB-III. Sensitivity, specificity, and accuracy to predict pCR were 90.9%, 90.6%, and 90.7%, respectively. Specificity was 94.1% in the identification of a subset of patients who had either pCR or MRD.
Conclusion: Accuracy of ΔSUVmax in the locoregional disease of stages II and III breast cancer patients after NAC is high for the identification of pCR cases. Its specificity is potentially sufficient to identify a subgroup of patients who could be managed with conservative surgery.

Valor predictivo de la PET-TC en la respuesta a la quimioterapia neoadyuvante en el cáncer de mama en estadios II y III

Palabras clave:
Cáncer de mama
Quimioterapia neoadyuvante
PET-TC

RESUMEN

Objetivo: Estudiar de forma prospectiva el valor de la PET-TC con fluor-18-desoxiglucosa (FDG) para predecir la respuesta a la quimioterapia neoadyuvante (NAC) de la enfermedad locoregional en pacientes con cáncer de mama en estadios II y III.
Material y métodos: Se obtuvo un consentimiento informado por escrito y la aprobación del Comité Ético. Se estudió la precisión de la PET-TC para predecir la respuesta completa patológica (pCR) tras la NAC en los tumores y en los ganglios de 43 mujeres (edad media: 50 años; rango: 27–71 años) que presentaban cáncer de mama diagnosticado por histología entre diciembre del 2009 y Enero del 2011. Los estudios PET-TC se realizaron al diagnóstico y tras la NAC. Los cambios en el porcentaje del SUVmax (delta-SUVmax) se compararon con los hallazgos de la anatomía patológica de la pieza quirúrgica. Se realizaron análisis de Característica Operativa del Receptor (ROC) para discriminar entre pCR y no-pCR en la enfermedad locoregional. En las pacientes que no alcanzaron la pCR, se investigó si el delta-SUVmax podía identificar de forma precisa las siguientes categorías de carga tumoral residual: RCB-I (enfermedad mínima residual (MRD)), RCB-II (moderada RD), y RCB-III (extensa RD).
Resultados: Se obtuvo pCR en 11 pacientes (25,6%). Se encontró enfermedad residual en 32 pacientes (74,4%): 16 (37,2%) RCB-I, 15 (35,6%) RCB-II y 2 (4,7%) RCB-III. La sensibilidad, especificidad y precisión para predecir la pCR fueron 90,9%, 90,6%, y 90,7%, respectivamente. En la identificación del subgrupo de pacientes con pCR o MRD la especificidad fue del 94,1%.

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Conclusión: El delta-SUVmax identifica con elevada precisión la pCR en la enfermedad locoregional de las pacientes con cáncer de mama en estadios II y III tras la NAC. La especificidad es potencialmente suficiente para identificar un subgrupo de pacientes que podrían ser candidatas a cirugía conservadora.

Introduction

Breast cancer is the first cause of cancer-related mortality in the female population of the United States and other developed countries.[1] Multidisciplinary treatment, including neoadjuvant chemotherapy (NAC), is the most appropriate approach for stage II and III breast cancer patients. Recent improvement in NAC efficacy has implied increased pCR rates. However, the higher pCR rates in some breast cancer subtypes, as HER2 positive and Triple Negative tumors have not resulted in a higher rate of breast-sparing surgery.[2] Conservative surgery may be performed if an accurate method is found to depict residual disease. Tumors with pCR might undergo unnecessarily large tumor bed resections[3] and patients with pCR of lymph node could avoid unnecessary axillary lymph node dissections (ALNDs).[4] Patients with complete pathological response (pCR) have significantly higher disease-free and overall survival rates than non-responders (non-pCR).[5,6] However, only 3–27% of treated patients achieve pCR.[7] Residual disease (RD) after neoadjuvant treatment includes a broad range of responses from near pCR to frank resistance. Measuring the RD after NAC has been proposed as a way to improve the prognostic information that can be obtained from evaluating pathologic response.[8] Residual cancer burden (RCB) can be calculated as a continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size) for prediction of distant relapse-free survival (DRFS).[8] The accuracy of PET-CT in predicting responses to neoadjuvant therapies has been investigated prospectively in several studies. However, only a few[9–11] have evaluated response after treatment completion and have used pCR, a relatively robust endpoint, as reference. Potential utility of PET-CT in categorizing RD has not been studied.

It is of fundamental importance to combine metabolic information of all the disease, independently of location, since it helps decision-making, regarding the subsequent treatment of the patients. We used locoregional SUVmax as reference to evaluate response to NAC, that is, we combined uptake of the primary tumor with axillary/supraclavicular lymph node metastases. The PERCIST criteria[12] recommend an approach similar to ours to evaluate response to treatment in different types of tumors. As our aim was to study the accuracy of PET-CT performed within the clinical practice, we studied ΔSUVmax, this being the most widely used standard parameter.[12]

Consequently, the purpose of our study was to prospectively investigate the value of PET with fluorine-18 fluorodeoxyglucose (FDG) for NAC response in locoregional disease of patients with stages II and III breast cancer.

Material and methods

Patient eligibility

This study was conducted with the approval of the local Ethics Committee at our institution. All clinical stages II and III breast cancer patients who were candidates for docetaxel-based neoadjuvant treatment were prospectively included between December 2009 and August 2011. An informed consent was obtained prior to any study procedure. Patient diagnosis was obtained by mammography, ultrasonography and/or magnetic resonance (MR) imaging and by pathology diagnosis obtained by core needle biopsy (CNB). Eligibility criteria were as follows: histologically proved breast cancer without any history of treatment prior to the study, patient age >18 years, and adequate organ function. Exclusion criteria were: males, uncontrolled diabetes, pregnancy, or concomitant malignancy.

Neoadjuvant chemotherapy

Patients received between four and six cycles of Docetaxel (100 mg/m^2) every 21 days. Patients with HER-2 receptor-positive disease additionally received weekly trastuzumab (initial dose, 4 mg per kilogram of body weight; subsequent dose, 2 mg/kg). Surgical resection was performed after completion of NAC in all the patients. Antracycline-based adjuvant chemotherapy, endocrine, trastuzumab or locoregional radiotherapy were administrated if clinically indicated. Antracycline-based adjuvant chemotherapy was administrated when residual disease was found at pathology analysis of the surgical specimen. All the patients with positive RE or RP receptors recieved adyuvant endocrine treatment. Finally all the patients with positive axillary lymph nodes pretreatment, with T3-T4 tumors or wich had conservative surgery recieved adyuvant radiotheraphy.

PET/CT

Imaging was performed on a PET-CT equipment (Biograph; Siemens, Erlangen, Germany) with 3–4 mm theoretical spatial resolution with a 6-row detector CT. Patients fasted 6 h before PET imaging. In all patients, PET-CT images were acquired before and after neoadjuvant treatment from the top of the skull to the midthigh with their arms raised. Blood glucose level had to be less than 7 mmol/l before injection of 5 MBq/kg of ^{18}F-FDG. CT study was acquired after administration of 120 ml of intravenous contrast and delay of 50 s, with the following parameters: 120 kVp; 95 mA s, pitch of 1.5, section thickness of 5 mm. PET emission data were acquired in three-dimensional mode, followed by reconstruction using the iterative mode. Emission counts were collected over 3 min per table position. All CT images were reconstructed into a 512 × 512 matrix. These data were then converted into 511-keV-equivalent attenuation coefficients for attenuation correction. All PET-CT studies were performed at baseline and after completion of NAC.

Image interpretation

The PET and CT images in all standard planes were reviewed on the workstation (Syngo^{TM} software system; Siemens Medical Imaging, Forchheim, Bavaria, Germany). Two physicians trained in the interpretation of PET-CT studies (each with more than 7 years of experience) evaluated each study. There was consensus interpretation when needed. The Regions of Interest (ROIs) were placed manually over all the breast tumors, recording, above all, the affected lymph nodes and maximum standardized glucose's uptake values (SUVmax; maximum standardized uptake value). The SUV was calculated according to the following equation: SUV = maximal count times calibration factor (in kilobecquerels per milliliter)/injected activity (in megabecquerels)/body weight (in kilograms).