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 90.0%, 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.

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

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 de 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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Introduction

Breast cancer is the first cause of cancer-related mortality in the female population of the United States and other developed countries. 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. 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 and patients with pCR of lymph node could avoid unnecessary axillary lymph node dissections (ALNDS). Patients with complete pathological response (pCR) have significantly higher disease-free and overall survival rates than non-responders (non-pCR). However, only 3–27% of treated patients achieve pCR. 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. 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). The accuracy of PET-CT in predicting responses to neoadjuvant therapies has been investigated prospectively in several studies. However, only a few 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 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.

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/m²) 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 administered 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 adjuvant endocrine treatment. Finally all the patients with positive axillary lymph nodes pretreatment, with T3-T4 tumors or wich had conservative surgery recieved adjuvant radiotherapy.

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 18F-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 mAs, 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™ 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 millilitre)/injected activity (in megabecquerels)/body weight (in kilograms).
Response evaluation

Metabolic response was evaluated by comparing relative changes in SUVmax (ΔSUVmax). The SUVmax on the PET-CT images obtained after completion of NAC was compared with those obtained from the baseline study. To combine the information of the locoregional disease (T+N), the SUVmax of the lesion (tumor or abnormal lymph nodes) with the highest uptake was used. Background FDG uptake was subtracted to the pretreatment and baseline SUVs, therefore a complete response on PET-CT implied a ΔSUVmax of 100.

The breast background uptake was determined by drawing a 2-cm circular ROI in an area of normal breast tissue, which was confirmed by reviewing either prior mammograms or corresponding CT images. Care was taken to ensure that none of the abnormal FDG uptake was included in the background ROI.

Reference standard

The study of the specimen of the breast lesion and affected lymph nodes obtained in surgery was the standard of reference. Pathologic response to NAC (pCR or non-pCR) was evaluated by one of two pathologists (each with more than 15 years of experience).

RCB was calculated as a continuous index according to the MD Anderson Calculator (available in Internet: http://www.mdanderson.org/breastcancer_RCB) combining the following parameters: Primary Tumor Bed Area (mm) × (mm), Overall Cancer Cellularity (as percentage of area (%)), Percentage of Cancer that is in situ Disease (%), Number of Positive Lymph Nodes, Diameter of Largest Metastasis (mm). According to the Symmans classification patients were classified into four groups: pathologic complete response (pCR) and three RCB classes (RCB-I, RCB-II and RCB-III).

Statistical analysis

Quantitative parameters are expressed as mean ± 1 standard deviation (SD). Quantitative parameters that do not follow a normal distribution are expressed as median and range (IQR).

To identify an optimal threshold for the prediction of the pCR, a ROC analysis was performed by incrementally increasing cut-off values of the ΔSUVs and recalculating corresponding true-positive and false-negative rates. Area under the curve (AUC) with 95% confidence interval (CI), standard error (SE), sensitivities and specificities were assessed. The Mann–Whitney test was used to compare SUVs between the RCB classes. A 5% significance level was accepted by the tests. Data processing and analysis were performed with the SPSS v.15.0.

Results

Clinical-pathologic characteristics

Fifty-eight patients signed the informed consent for multidisciplinary management. Fifteen patients were excluded from the analysis for the following reasons: 4 had metastasis on the first PET-CT, 3 patients could not receive NAC and/or surgery due to their medical condition and the second PET-CT was not performed in 8 patients due to different reasons decided by the Breast Cancer Committee of our hospital. Finally, a total of 43 patients were included in this study. All the patients received Docetaxel 100 mg/m² every 21 days and 10 patients (23.3%) whose tumors expressed HER2 receptors also received Herceptin®. Patient and tumor characteristics are shown in Table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
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<tr>
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<tr>
<td>Premenopausal</td>
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<tr>
<td>Postmenopausal</td>
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<tr>
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<tr>
<td>II A</td>
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</tr>
<tr>
<td>II B</td>
<td>19</td>
<td>44.2%</td>
</tr>
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<td>II B</td>
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<tr>
<td>III</td>
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<tr>
<td>Histological type</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<td>23.3%</td>
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Tumor and axillary/supraclavicular lymph node pathologic complete response

Fourteen (32.6%) of the 43 breast tumors examined during surgery showed a pCR.

Thirty patients had locoregional lymph node metastasis. Three of these patients could not be evaluated at surgery as SNB (Sentinel Node Biopsy) had been performed before NAC. Fig. 1 shows patient distribution according to lymph node response.

Locoregional pathologic complete response (pCR) and residual cancer burden (RCB)

Mean RCB was ±1474. Tumor distribution according to the Symmans classification is shown in Fig. 2.

Tumor complete response assessed by PET-CT

ROC analyses were performed to determine optimal cut-off values of ΔSUVs in order to better differentiate pCR and non-pCR patients after NAC. The ROC curves for the prediction of pCR are presented in Fig. 3.

At a cut-off value of 90.4%, positive predictive value (PPV) was 91.7% and tumor pathologic response was predicted with 90.7% accuracy (Table 2).

Fig. 1. Patient distribution according to lymph node response.
Lymph node complete response assessed by PET-CT

Lymph nodes were affected in 30 patients at diagnosis. Two criteria were used to define lymph node involvement. The first one was that lymph node metastasis was considered to exist if fine needle aspiration or lymph node biopsy were positive (20 patients; 67%). The second criterion was that the lymph nodes were clearly positive on the basal PET-CT with response on PET-CT after NAC and in absence of an inflammatory condition at diagnosis (10 patients; 33.4%). Six patients could not be evaluated by

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Value (%)</th>
<th>I.C. (95%)</th>
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<td>Specificity</td>
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</tr>
<tr>
<td>Accuracy</td>
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<td>80.8–100</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>91.7</td>
<td>71.9–100</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>90.3</td>
<td>78.4–100</td>
</tr>
<tr>
<td>Prevalence</td>
<td>32.6</td>
<td>17.4–47.7</td>
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<tr>
<td>Lymph node</td>
<td></td>
<td></td>
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<tr>
<td>Sensitivity 80</td>
<td>80</td>
<td>50.2–100</td>
</tr>
<tr>
<td>Accuracy</td>
<td>79.2</td>
<td>60.8–97.5</td>
</tr>
<tr>
<td>Positive predictive value</td>
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</tr>
<tr>
<td>Negative predictive value</td>
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<td>Prevalence</td>
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<tr>
<td>Locoregional</td>
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<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>90.9</td>
<td>69.4–100</td>
</tr>
<tr>
<td>Specificity</td>
<td>90.6</td>
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<tr>
<td>Accuracy</td>
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<td>Positive predictive value</td>
<td>76.9</td>
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<tr>
<td>Negative predictive value</td>
<td>96.7</td>
<td>88.6–100</td>
</tr>
<tr>
<td>Prevalence</td>
<td>25.6</td>
<td>11.4–39.8</td>
</tr>
</tbody>
</table>

Fig. 2. Tumor distribution according to the Symmans classification.

Fig. 3. Axial (a and c) CT and (b and d) PET-CT (a and b) at baseline and (c and d) after chemotherapy in a 42-year-old woman with HER2 invasive ductal carcinoma of the right breast. Baseline SUVmax were 32.1 and 6.3 on the tumor and the regional lymph nodes, respectively, with a ΔSUVmax in the locoregional disease of 100% (background uptake was substracted from the lesions SUVmax). After surgery, she was classified as RCB-0 according to the RCB classification.
PET-CT: three because SLB had been performed before NAC and consequently before the posttreatment PET, one because of important brown fat uptake which masked potential lymph node FDG uptake and two were not adequate for response monitoring of the lymph nodes as the lymph node SUVmax in the pretreatment PET scan was indistinguishable from that of the background. Twenty-four patients were finally included for analysis. Fig. 4 shows patient distribution according to pCR by PET-CT.

Three patients were thought to have complete response in the lymph nodes by PET-CT but residual disease was demonstrated by histology study (Fig. 4).

At a cut-off value $\Delta$SUVmax of 90.2% positive predictive value (PPV) was 72.7% and a pathological response in the lymph nodes was predicted with an accuracy of 79.2% (Table 2).

Locoregional pathological complete response assessed by PET-CT

An optimal cut-off value of 91.1% was found. At this cut-off value positive predictive value (PPV) was 76.9% and pathological response in locoregional disease was predicted with 90.7% accuracy (Table 2). One patient had pCR and post-treatment SUV was 1.3, this being higher than for the surrounding tissue. Therefore, she was classified as MRD on PET-CT. The pathology study showed an inflammatory component consisting of plasmocytes and focal presence of foam cells and hemosiderophages were found. Three patients were thought to have CR on PET and the pathology study showed two microscopic tumor focus (0.2 and 0.5 mm) in the first patient, a 2 cm lobular carcinoma in the second patient and a 3 cm grade I ductal carcinoma in the third patient. The first two patients were classified as RCB-I. Fig. 5 shows PET-CT images of a patient with tumor and axillary pCR.

$\Delta$SUVmax correlation with RCB (residual cancer burden)

No correlation was found between baseline SUV and the RCB index. Negative correlation between $\Delta$SUVmax (Rho: $-0.661$; $p < 0.001$) and the RCB index was found. The relation between $\Delta$SUVmax and the RCB index is shown in Fig. 6.

Residual disease (RD): staging by PET-CT into RCB classes

No differences were found ($p < 0.310$) in the baseline SUVmax of locoregional disease according to the RCB classification (Table 3). Significant differences were found in the $\Delta$SUVmax of locoregional disease ($p < 0.001$), of the different RCB classes. Differences in

Fig. 4. Axial (a and c) CT and (b and d) PET/CT (a and b) at baseline and (c and d) after chemotherapy in a 44-year-old woman with triple negative invasive ductal carcinoma of the right breast showing no pCR. Decrease in the SUVmax from baseline was observed after chemotherapy from 17.6 and 24.9 on the tumor and the regional lymph nodes, respectively to 11 and 9.6. $\Delta$SUVmax in the locoregional disease was 44.2%. After surgery she was classified as RCB-II according to the RCB classification.
the ΔSUVmax between RCB-III and the other RCB classes could not be analyzed because of the small sample of patients (n = 2). Therefore classes II and III were grouped. Although we found differences between RCB-0 class and the RCB I-III classes (p < 0.001), no differences between RCB-I class and RCB II and III classes were found (p < 0.105).

### Diagnostic accuracy to differentiate between RCB-0 and I and RCB II and III classes

As patients with RCB-0 and RCB-I have the same prognosis and could be managed with breast-conserving surgery we investigated if there was a cut-off value at which there was high specificity to differentiate RCB-0 and RCB-I classes from RCB-II and RCB-III. An optimal cut-off value of 91.1% was found. At a cut-off value of 91.1%, PPV was 92.3% and pathological response in locoregional disease was predicted with 94.1% specificity (Table 4). Fig. 7 shows PET-CT images of a patient with tumor and axillary residual disease.

### Discussion

Previously, neoadjuvant treatment was only expected to benefit patients who required mastectomy due to an unfavorable
tumor–breast-size relationship, but who could be candidates for breast-sparing surgery if the tumor size could be reduced. This recommendation was developed at a time when pCR was a rare outcome. With recent improvement in treatment efficacy, this restriction is being revisited—especially for patients with triple-negative or HER2-positive tumors, as nowadays almost half will show pCR. High pCR rate still does not result in a higher rate of breast-sparing surgery. The establishment of diagnostic tools for a more reliable assessment of remaining tumor tissue would help to avoid unnecessary mastectomies. These tools could provide information to the multidisciplinary team as an aid to adopting the most adequate attitude such as additional preoperative medical treatments when the probability of obtaining pCR is low or to improve conservative rates when pCR is more probable. Treatment-response information is valuable in all patients, given that a pCR can improve an initially unfavorable prognosis and the lack of a pCR might indicate the need for a more intense surveillance program or to promote the development of new postsurgical treatment options.

In this study, we have demonstrated that, in our sample, ΔSUVmax could accurately predict pCR to NAC of breast cancer patients.

A meta-analysis evaluating the accuracy of 18F-FDG PET in predicting responses to neoadjuvant therapies was published in September 2011. It included five studies6–11,13,17 whose goal was to predict tumor response with pCR as a reference standard. In our study, specificity was higher (96.6%) than specificities found in previous studies (pooled specificity 84% (95% CI, 71–93%)). Although these studies had the same goal (pCR), it is difficult to compare the results mainly because the definition of pathologic response and timing of the PET–CT evaluation were different. An important point in our work that differentiates it from previous studies is that all our patients received the same administered treatment. Schneider-Kolsky et al. investigated whether drug sequence affects changes in the SUVmax on FDG-PET during NAC in women with locally advanced breast cancer. They showed that SUVmax uptake may be dependent on the drugs used. Using a ΔSUVmax with a cutoff of 75%, they observed 78% sensitivity and 62% specificity. We chose a higher ΔSUVmax reduction (90.4%) as we were looking for a high specificity. In this setting, high specificity has the greatest importance since, optimally, no cases should exist in which the PET–CT diagnoses CR and the pathology study shows residual disease. Jung et al. studied 66 patients before and after two NAC protocols. They obtained a sensitivity and specificity of 70% and 69.6%, respectively using a ΔSUV peak (SUVp) cutoff of 84.8%. One reason why our results appeared to be better could have been that we had more patients with pCR (32.6% vs 15.2%), although their patient sample was larger (n = 66) than ours (n = 43). Park et al. studied 50 patients with several treatment regimens and detected 100% sensitivity and 62.5% specificity. These authors attributed the low specificity to the small size of the tumors (more than 50% of the non-detected tumors were smaller than 1 cm). Berriolo-Riedinger et al. evaluated the accuracy of PET-CT to predict pCR after the first chemotherapy cycle. They found that with a 60% ΔSUVmax cutoff, specificity was 86%. We chose to perform the second PET-CT just before surgery as we wanted to minimize the time between the PET-CT performed for response evaluation and evaluation of the surgical specimens. Furthermore, the results of the second PET-CT would, in no way, affect the chemotherapy regimen. Choi et al. studied 41 patients before and after NAC. The area under curve to predict pCR was 0.72 (0.91 in our study). Thus, they concluded that PET-CT is not adequate to predict pCR. Their study differed from ours because they used changes in the SUVp to classify patients as responders and because patients received different treatment regimens. Similarly, as Jung’s study, the lower rate of tumors with pCR (7 (17%)) could have influenced their results. Our rate of pCR was probably higher because the study was performed in a clinical setting and patients not responding to treatment or progressing were not referred to perform the second PET-CT or did not have surgery, according to oncological criteria.

In 2012, Buchbender et al. analyzed if FDG-PET-CT could differentiate between breast cancer lesions with pCR and lesions without pathological complete response (npCR) after two cycles of NAC in 26 patients. They also stratified response in more than two categories but according to a different pathological scale (Sinn scoring system). The ROC analysis showed ΔSUVmax (%) of 66% as the best threshold to differentiate pCR and npCR. Although their study is also not comparable to ours because of the different methodology, especially regarding the different time-point of the second PET scan, they found a higher sensitivity (88% vs 78.6%) to predict pCR and lower specificity (89% vs 96.6%) than in our work. These differences could be partially explained due to the fact we commented before, that we were looking for a high specificity and consequently we chose higher ΔSUVmax reductions than in other studies. Other differences with our study are that different stages of the disease were included and different chemotherapeutic regimens were administered.

Also, in 2012 a new metaanalysis was published by Cheng et al. This metaanalysis included most of the previously analyzed studies in the meta-analysis of Wang et al. plus three additional ones, all of which had been published before September 2011. The conclusions where similar to those of Wang et al., showing a reasonable sensitivity of PET-CT and PET in evaluating response to NAC in patients with breast cancer, with a relatively low specificity. Additionally the combination of other imaging methods (MR, US, mammography) with PET-CT or PET is recommended.

In addition to that found in the current literature, our study shows that the ΔSUVmax has sufficient potential specificity to detect pCR in MRD patients in the clinical practice, which could therefore allow more patients to benefit from conservative surgeries. To the best of our knowledge, this is also the first study that combines both the ΔSUVmax of the tumors and the lymph nodes in this special setting. These findings are important because the goal of a diagnostic tool is to give information that help clinicians make decisions. Therefore, clinicians need a response endpoint that includes lymph node and tumor response. Our results could have a direct implication on clinical practice as the study was performed in a clinical setting using ΔSUVmax which is the most used parameter.

Our study has several limitations. In the first place, the sample was small and only included two cases of patients with high RCB (RCB-III). Consequently, differences could not be investigated with
this subgroup of patients. Secondly, not all patients had a lymph node biopsy on diagnosis, however the probability of lymph node involvement was high based on previously reported specificities of FDG PET-CT. 1,7

Our study, while important, demonstrates the need for additional prospective studies that would ideally include more patients in order to define what the role of PET-CT in the clinical setting is and to establish management protocols.

Conflicts of interest

The authors declare not to have any conflicts of interest.

References