PET/CT and dedicated PET in breast cancer: Implications for classification, staging, and response monitoring
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PART TWO | HANGING BREAST PET/CT

Response monitoring of primary tumor and axillary metastases
Sequential 18F-FDG PET/CT for early prediction of complete pathological response in breast and axilla during neoadjuvant chemotherapy

Submitted
Purpose
To investigate the value of combined primary tumor and axillary node response monitoring with sequential PET/CTs during neoadjuvant chemotherapy (NAC) for predicting pCR, taking the breast cancer subtype into account.

Methods
Two hundred and ninety PET/CTs were performed in consecutive 107 patients at baseline (PET/CT1, n=107), after two to three weeks of chemotherapy (PET/CT2, n=85), and after six to eight weeks (PET/CT3, n=98). The relative SUVmax change (from baseline) of the tumor, the lymph node, a combination of both (after logistic regression), and the change of the highest SUVmax per scan (either tumor or lymph node) were determined and their associations with complete pathological response of tumor and lymph node (pCR) after completion of NAC were assessed using receiver operating characteristic (ROC) analyses.

Results
A pCR was seen in 17 (65%) HER2-positive, 1 (2%) ER-positive/HER2-negative, and 16 (52%) triple negative tumors. The areas under the ROC curves (ROC-AUC) for the prediction of pCR in HER2-positive tumors with PET/CT at week 3 were 0.61 for the relative change in the tumor, 0.67 for the combination of the change in tumor and node, and 0.72 for the change of highest SUVmax per scan. At week 8 these were 0.59, 0.42, and 0.64, respectively. In triple negative tumors the ROC-AUCs with PET/CT at week 2 were 0.76, 0.84, and 0.76, respectively. At week 6 these values were 0.87, 0.93, and 0.88, respectively.

Conclusion
In triple negative tumors a PET/CT after six weeks (three courses) appears optimally predictive of pCR; in HER2-positive tumors neither PET/CTs at week 3 nor at week 8 seem useful. A combination of the change in SUVmax of both breast and axilla correlates best with pCR.
INTRODUCTION

Primary systemic therapy or neoadjuvant chemotherapy (NAC) is increasingly employed in the treatment of breast cancer.\textsuperscript{1} Compared with adjuvant chemotherapy, treatment with NAC resulted in similar survival.\textsuperscript{2} A major advantage of NAC is a reduction in tumor size. As a result, more patients can be offered breast-conserving surgery and initially unresectable tumors may become operable.\textsuperscript{3,4} Another advantage of NAC is the possibility to monitor response to chemotherapy. Complete absence of tumor cells in the surgery specimen (complete pathological response, pCR) of breast and axilla is associated with a favorable prognosis and is regarded as a highly desirable outcome of NAC, particularly in triple negative and human epidermal growth factor receptor 2 (HER2)-positive tumors.\textsuperscript{5} Response monitoring during NAC provides an opportunity to switch the chemotherapeutic regimen in an attempt to increase pCR rates in cases of an unfavorable response.\textsuperscript{6} Magnetic resonance imaging (MRI) for response monitoring has been shown to be valuable, but is dependent on the breast cancer subtype.\textsuperscript{7} As MRI visualizes anatomical change that requires time to occur, it is not particularly effective after only one course of chemotherapy.

The use of 18F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) is valuable for regional and distant staging in breast cancer.\textsuperscript{8-10} Further, several studies have reported promising results for the prediction of pCR to NAC with PET/CT.\textsuperscript{11-17} We and others have demonstrated that the accuracy of PET/CT response monitoring during NAC depends on the breast cancer subtype.\textsuperscript{18,19} Since sequential PET/CTs visualize the change in glucose metabolism of the tumor, it is hypothesized that response prediction with PET/CT could be performed early. This has been demonstrated previously, in some trials already after the first course of NAC.\textsuperscript{13,14,16,19} Accurate prediction of response to NAC at an early time-point is highly desirable, since administration of ineffective treatment can be limited and unnecessary drug toxicity may be decreased.\textsuperscript{20} Furthermore, more courses of effective chemotherapy can be administered before surgery, increasing the likelihood of achieving a pCR and possibly avoiding the necessity of adjuvant chemotherapy. As patient series reported in the literature have been relatively small and/or heterogeneous, no robust cut-off point for the selection of responders or non-responders has been established yet.\textsuperscript{17} In addition, the optimal time-point for response monitoring with PET/CT remains unknown, since most recent studies performed only a single PET/CT during NAC for response prediction.\textsuperscript{15,16,19} PET/CT visualizes both the breast and the axilla, enabling response monitoring of primary tumor as well as lymph node metastases. Response monitoring of primary tumor or axilla with PET/CT has been studied separately, but the combination of breast and axilla and its association with pCR of both breast and axilla has not been described.\textsuperscript{11-17,19,21} The aim of this analysis was to assess the accuracy of sequential PET/CTs early during NAC to detect response in relation to breast cancer subtype. We emphasized on the value of combined breast and axilla response monitoring for prediction of pCR of breast and axilla.
PATIENTS AND METHODS

Patients
Patients with invasive breast cancer >3cm and/or at least one tumor-positive axillary node (stage II-III breast cancer) received NAC in our institute within one of several prospective trials studying different chemotherapeutic regimens. Since September 2008 patients were recruited for an additional imaging study, assessing the value of PET/CT for response monitoring during NAC. Patients with at least two PET/CT examinations (one at baseline and one during NAC), quantifiable tumor FDG uptake at baseline, and undergoing surgery after NAC were included in this analysis. The institutional board approved this study and informed consent was obtained from all patients.

Histopathological analysis
Core biopsies from the primary tumor were used for determination of the histological type, grade, and for immunohistochemical stainings. Estrogen receptor (ER) and progesterone receptor (PR) were considered positive when at least 10% of tumor cells showed staining. Samples were scored as HER2-positive when either a strong membrane staining (3+) was observed or if chromogenic in situ hybridization revealed amplification in samples with moderate (2+) membrane staining. Tumors were classified in three groups according to their receptor status: HER2-positive, ER-positive/HER2-negative, and triple negative. Grade was determined using modified Bloom-Richardson criteria.

Treatment
Neoadjuvant chemotherapy was administered as previously described. Briefly, HER2-positive tumors were treated with paclitaxel, trastuzumab, and carboplatin (PTC), administered weekly in three cycles of eight courses. In weeks seven and eight of each cycle only trastuzumab was given. HER2-negative tumors were treated with six courses of cyclophosphamide and doxorubicin (AC) in a dose-dense schedule (every two weeks). Conform institutional guidelines, based on consensus in a multidisciplinary meeting, chemotherapy could be switched to a (hypothetically) non-cross-resistant regimen (two-weekly capecitabine and docetaxel; CD). A switch was based on patient’s preference, drug toxicity, or MRI response monitoring. Further, inclusion of triple negative tumors in chemotherapeutic trials could lead to treatment modification (cyclophosphamide, thiotepa, and carboplatin; CTC).

PET/CTs were performed at baseline in all patients, after three and eight courses in HER2-positive tumors (after three and eight weeks), and after one and three courses in HER2-negative tumors (after two and six weeks). After NAC, all patients underwent breast-conserving or ablative surgery and a lymph node dissection in case of initial node-positivity.

18F-FDG PET/CT
After preparation with a six-hour fasting period and with a blood glucose level <10 mmol/l, an FDG dose of 180-240 MBq was given intravenously, depending on body mass
index. Using a whole body PET/CT scanner (Gemini TF, Philips, Cleveland, USA), a PET/CT was acquired after a resting period of 60 ± 10 min. A PET scan (3.00 min per bed position) of the thorax was performed with the patient in prone position, with hanging breasts and the arms above the head, with image reconstruction to 2x2x2 mm voxels. PET acquisition was preceded by a low-dose CT (2 mm slices). Subsequently, as a staging procedure, a standard supine whole body PET/CT was performed. During NAC only the hanging breast PET/CT was repeated for response monitoring using similar time interval after FDG injection, patient positioning, and acquisition as at baseline.

**Image reading**

A panel of three experienced reviewers (BK, WV, RVO) evaluated the images. FDG uptake was measured with maximum standardized uptake values (SUVmax), obtained by generating a 3D region of interest (ROI) based on region-growing procedures. In case of low tumor-to-background ratio, rendering an automated ROI generation unreliable, the SUV was derived from a manually drawn 3D volume of interest. In case of a complete metabolic response on the second or third PET/CT, the same ROI location of the PET/CT at baseline was used for calculation of SUVmax (i.e. background value in the breast at the site of the tumor).

**Response assessment of the primary tumor**

One consultant breast pathologist (JW) revised all surgery specimens regarding pathological response. Tumor response was assessed dichotomously. A pCR was defined as complete absence of residual tumor cells in the breast and the axilla, irrespective of the presence of in situ carcinoma. All specimens involving residual vital tumor cells (either in the breast or the axilla), including patients with only a few scattered cells (i.e., “near complete response”), were defined as incomplete remissions (non-pCRs).

**Statistical methods**

Accuracy of response assessment of final pathological response by PET/CT2 and PET/CT3 was assessed using four receiver operating characteristic (ROC) analyses. The first analysis assessed the value of the primary tumor SUVmax change. The second assessed the association between changes in SUVmax of axillary lymph nodes and response at final pathology in patients with FDG-avid tumor-positive nodes on PET/CT1. Patients without baseline axillary SUVmax data (based on tumor-negative nodes or false-negative axillary PET/CT) were excluded from this analysis. The third analysis combined SUVmax changes of the primary tumor and axillary node in a logistic regression, the linear predictor of which was entered into the ROC analysis. Finally, the highest SUVmax per scan (either in the tumor or in the lymph node) and its relative change during NAC were calculated as proposed in the PERCIST algorithm. The area under the ROC curve (ROC-AUC) was calculated for the different cohorts. Confidence intervals (CI) were determined using the DeLong method and presented as 95% confidence intervals.
RESULTS

A total of 290 PET/CTs were performed in 107 stage II-III breast cancer patients; all patients underwent baseline PET/CT, 85 patients underwent a PET/CT after 2 to 3 weeks, and 98 patients underwent a PET/CT after 6 to 8 weeks. Baseline characteristics of the 107 included patients are presented in Table 1.

A pCR was found in 34 (32%) of 107 patients: 17 (65%) of 26 HER2-positive, 1 (2%) of 50 ER-positive/HER2-negative, and 16 (52%) of 31 triple negative tumors (Table 2). Because only a single patient with an ER-positive/HER2-negative tumor achieved pCR, this group could not be analyzed in detail.

HER2-positive disease

The ROC analysis for primary tumor SUVmax change at week 3 (after three courses) indicated a poor association with pCR, yielding an ROC-AUC of 0.61 (95% CI 0.33-0.89). This was 0.67 (0.43-0.92) for the combination of primary tumor and axilla SUVmax change (using a logistic model) and 0.72 (0.50-0.96) for the change in highest SUVmax values. The ROC-AUC for change in axillary SUVmax in patients with FDG-avid tumor-positive nodes was 0.74 (0.51-0.97).

Table 1  Baseline characteristics of 98 patients.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median</th>
<th>Range</th>
</tr>
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<td></td>
<td>47</td>
<td>25 - 68</td>
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<table>
<thead>
<tr>
<th>T-stage prior to NAC (MRI)</th>
<th>ct1</th>
<th>ct2</th>
<th>ct3</th>
<th>ct4</th>
</tr>
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<tbody>
<tr>
<td>cT1</td>
<td>9 (8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT2</td>
<td>66 (62%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT3</td>
<td>24 (22%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT4</td>
<td>8 (7%)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>N-stage prior to NAC (FNA/SLNB)</th>
<th>cN0</th>
<th>cN1</th>
<th>cN2</th>
<th>cN3</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0</td>
<td>18 (17%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN1</td>
<td>61 (57%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN2</td>
<td>2 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN3</td>
<td>26 (24%)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

| Multifocal or multicentric (MRI) | 34 (32%) |

<table>
<thead>
<tr>
<th>Subtype</th>
<th>HER2-positive</th>
<th>26 (24%)</th>
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<tbody>
<tr>
<td></td>
<td>ER-positive/HER2-negative</td>
<td>50 (47%)</td>
</tr>
<tr>
<td></td>
<td>Triple negative</td>
<td>31 (29%)</td>
</tr>
</tbody>
</table>

Abbreviations: NAC, neoadjuvant chemotherapy; MRI, magnetic resonance imaging; FNA, fine needle aspiration; SLNB, sentinel lymph node biopsy; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor.
In general, ROC analyses of the week 8 scans (after 8 courses) generated relatively worse associations. The ROC-AUC for primary tumor SUVmax change was 0.59 (0.34-0.85) and was 0.42 (0.18-0.66) for the logistic model of primary tumor and axilla SUVmax change. They were 0.63 (0.36-0.89) for axillary SUVmax change and 0.64 (0.38-0.90) for the change in highest SUVmax values. ROC curves are presented in Figure 1.

**Figure 1**
PET/CT ROC analyses for breast (Breast) and axilla (Axilla) SUVmax change detecting pCR, the linear predictor of these two variables combined in a logistic regression (Logistic), and finally the change in the highest SUVmax (tumor or axilla) at each scan (Max) for HER2-positive tumors. The solid line presents the accuracy after 3 weekly courses in 21 patients (pCR n=14), whereas the dashed line presents the accuracy after 8 weekly courses in 25 patients (pCR n=17). Areas under the curves:

**PET/CT2:**
- Breast: 0.61 (95% confidence interval (CI) 0.33-0.89)
- Axilla: 0.74 (0.51-0.97) (2 patients without PET/CT1 axillary data excluded)
- Logistic regression: 0.67 (0.43-0.92)
- Highest SUVmax: 0.72 (0.50-0.96)

**PET/CT3:**
- Breast: 0.59 (95% CI 0.34-0.85)
- Axilla: 0.63 (0.36-0.89) (2 patients without PET/CT1 axillary data excluded)
- Logistic regression: 0.42 (0.18-0.66)
- Highest SUVmax: 0.64 (0.38-0.90)
Triple negative disease
A more obvious discrimination of response with PET/CTs during NAC was found in triple negative tumors. The relative change in SUVmax of the primary tumor and axillary nodes on PET/CT at week 2 (after one course) generated an ROC-AUC of 0.76 (0.55-0.96) and 0.74 (0.47-1.00), respectively, whereas the combination of primary tumor and axilla SUVmax change yielded an ROC-AUC of 0.84 (0.65-1.00). The ROC-AUC for highest SUVmax change was 0.76 (0.56-0.97).

Even more obvious associations of changes on PET/CT and pCR were found in triple negative tumors at week 6 (after three courses). The ROC-AUC for SUVmax change of primary tumor and axilla were 0.87 (0.73-1.00) and 0.86 (0.73-1.00), respectively. The change in highest SUVmax generated an ROC-AUC of 0.88 (0.74-1.00), increasing to 0.93 (0.82-1.00) for the combination of primary tumor and axilla in a logistic model (see Figure 2).

ER-positive/HER2-negative disease
Since only a single patient achieved pCR of breast and axilla combined, we performed a limited sensitivity analysis to compare PET/CT2 and PET/CT3 in this subgroup with (near)pCR of the breast as a reference standard; this was achieved by 7 of 50 patients. Looking at the relative decrease in SUVmax of the primary tumor only, ROC-AUC was 0.61 (0.37-0.86) for PET/CT2 and 0.87 (0.69-1.00) for PET/CT3 in predicting (near)pCR.
PET/CT ROC analyses for breast (Breast) and axilla (Axilla) SUVmax change detecting pCR, the linear predictor of these two variables combined in a logistic regression (Logistic), and finally the change in the highest SUVmax (tumor or axilla) at each scan (Max) for triple negative tumors. The solid line presents the accuracy after 1 course (2 weeks) in 25 patients (pCR n=13), whereas the dashed line presents the accuracy after 3 courses (6 weeks) in 28 patients (pCR n=14). Areas under the curves:

PET/CT2:
- Breast: 0.76 (95% CI 0.55-0.96)
- Axilla: 0.74 (0.47-1.00) (8 patients without PET/CT1 axillary data excluded)
- Logistic regression: 0.84 (0.65-1.00)
- Highest SUVmax: 0.76 (0.56-0.97)

PET/CT3:
- Breast: 0.87 (95% CI 0.73-1.00)
- Axilla: 0.86 (0.73-1.00) (7 patients without PET/CT1 axillary data excluded)
- Logistic regression: 0.93 (0.82-1.00)
- Highest SUVmax: 0.88 (0.74-1.00)
Table 2  ER-status, number of patients undergoing PET/CT2 and PET/CT3, and final pathological responses of primary tumor, axillary nodes, and primary tumor and axillary nodes combined, stratified by subtype.

<table>
<thead>
<tr>
<th></th>
<th>HER2-positive (n=26)</th>
<th>ER-positive/HER2-negative (n=50)</th>
<th>Triple negative (n=31)</th>
<th>Total (n=107)</th>
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<td><strong>ER</strong></td>
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<tr>
<td>Negative</td>
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<td>0</td>
<td>31 (100%)</td>
<td>47 (44%)</td>
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<tr>
<td>Positive</td>
<td>10 (38%)</td>
<td>50 (100%)</td>
<td>0</td>
<td>60 (56%)</td>
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<tr>
<td><strong>PET/CT2 performed</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5 (19%)</td>
<td>11 (22%)</td>
<td>6 (19%)</td>
<td>22 (21%)</td>
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<tr>
<td>Yes</td>
<td>21 (81%)</td>
<td>39 (78%)</td>
<td>25 (81%)</td>
<td>85 (79%)</td>
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<tr>
<td><strong>PET/CT3 performed</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1 (4%)</td>
<td>5 (10%)</td>
<td>3 (10%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Yes</td>
<td>25 (96%)</td>
<td>45 (90%)</td>
<td>28 (90%)</td>
<td>98 (92%)</td>
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<td><strong>Chemotherapy</strong></td>
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<td>31 (62%)</td>
<td>22 (71%)</td>
<td>53 (50%)</td>
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<tr>
<td>CD</td>
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<td>1 (2%)</td>
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<td>1 (1%)</td>
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<tr>
<td>AC-CD</td>
<td>0</td>
<td>18 (36%)</td>
<td>5 (16%)</td>
<td>23 (21%)</td>
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<tr>
<td>AC-CTC</td>
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<td>0</td>
<td>4 (13%)</td>
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<td>PTC</td>
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<td>26 (24%)</td>
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<tr>
<td><strong>Primary tumor</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No complete pathological response</td>
<td>9 (35%)</td>
<td>45 (90%)</td>
<td>12 (39%)</td>
<td>66 (62%)</td>
</tr>
<tr>
<td>Complete pathological response</td>
<td>17 (65%)</td>
<td>5 (10%)</td>
<td>19 (61%)</td>
<td>41 (38%)</td>
</tr>
<tr>
<td><strong>Axillary nodes</strong></td>
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<td></td>
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<tr>
<td>No complete pathological response</td>
<td>3 (12%)</td>
<td>38 (76%)</td>
<td>13 (42%)</td>
<td>54 (50%)</td>
</tr>
<tr>
<td>Complete pathological response</td>
<td>23 (88%)</td>
<td>2 (4%)</td>
<td>10 (32%)</td>
<td>35 (33%)</td>
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<td>cN0 before NAC</td>
<td>0</td>
<td>10 (20%)</td>
<td>8 (26%)</td>
<td>18 (17%)</td>
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<td><strong>Primary tumor and nodes combined</strong></td>
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<tr>
<td>No complete pathological response</td>
<td>9 (35%)</td>
<td>49 (98%)</td>
<td>15 (48%)</td>
<td>73 (68%)</td>
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<tr>
<td>Complete pathological response</td>
<td>17 (65%)</td>
<td>1 (2%)</td>
<td>16 (52%)</td>
<td>34 (32%)</td>
</tr>
</tbody>
</table>

Abbreviations: HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; NOS, not otherwise specified; AC, cyclophosphamide and doxorubicin; CD, capecitabine and docetaxel; CTC, cyclophosphamide, thiotepa, and carboplatin; PTC, paclitaxel, trastuzumab, carboplatin.
Figure 3  Scatter plots showing the relative change in highest SUVmax (tumor or node) and primary tumor size in HER2-positive (left column), ER-positive/HER2-negative (middle column), and triple negative (right column) tumors on PET/CT2 (upper row) and PET/CT3 (lower row). Non-responders (non-pCR) are indicated with a downwards triangle, responders (pCR) with a upwards triangle.
DISCUSSION

This study demonstrates that PET/CT response monitoring during NAC appears to be informative, depending on the breast cancer subtype. In HER2-positive tumors, associations between PET/CT2, PET/CT3, and pCR could not be demonstrated, but results were slightly better for PET/CT2 than for PET/CT3. In triple negative tumors pCR was more accurately predicted by PET/CT, with the largest discriminative power between pCR and non-pCR for PET/CT3. From this study no robust conclusions could be drawn regarding accuracy of PET/CT in predicting pCR of breast and axilla in ER-positive/HER2-negative tumors. However, PET/CT3 seemed superior to PET/CT2 in predicting (near) pCR. Further, this study suggests that a combined analysis of changes in SUVmax in the primary tumor and the axillary nodes improves the ability to discriminate early between tumors that will or will not achieve a pCR at final pathology.

Several studies have reported promising results for PET/CT response monitoring during NAC.\textsuperscript{11-17} Up until now, the studied series of patients have been heterogeneous; only two papers have made a distinction between the clinical subtypes.\textsuperscript{18,19} Whereas Humbert et al have reported accurate response prediction in 37 HER2-positive tumors and poor distinction in 25 triple negative tumors,\textsuperscript{19} we found the exact opposite; accuracy was high in triple negative tumors, but suboptimal in HER2-positive tumors.\textsuperscript{18} Several explanations may exist for these conflicting results: the differences in patient numbers, timing of the scan, chemotherapeutic regimens, patient preparation, or scan acquisition protocols may all contribute. In the present study, using pCR of breast and axilla as outcome instead of (near)pCR of the breast only, does not change our previous findings that PET/CT response monitoring appears accurate in triple negative tumors, but less accurate in HER2-positive tumors.\textsuperscript{18} Part of our findings have been corroborated by Groheux et al, demonstrating accurate identification of complete responders in triple negative tumors after two courses of NAC.\textsuperscript{15}

The optimal time-point for PET/CT response monitoring during NAC has not yet been established. Many studies have used one fixed time-point for response monitoring with PET/CT;\textsuperscript{11,15,16,19} only a few recent studies have performed sequential PET/CTs.\textsuperscript{14,28} In a recent meta-analysis Wang et al stated that early response monitoring (after 1 or 2 courses) was more accurate than late (after 3 courses or later),\textsuperscript{17} although the latter consisted of end-of-treatment scans as well, which were generally less accurate. An important remark is that most studies used a chemotherapeutic regimen with four courses every three weeks.\textsuperscript{11-13,15,16,19,28} In our study, HER2-negative tumors were treated with a dose-dense schedule (every two weeks) and PET/CTs were performed after three courses (six weeks), which is the same relative time-point as after the second course in a three-week schedule. In HER2-positive tumors a relatively new schedule was used, consisting of weekly administrations of paclitaxel, trastuzumab, and carboplatin.\textsuperscript{22} Some authors have stated that response monitoring could be performed after the first course.\textsuperscript{13,14,16,19} Our results suggest that the efficacy of PET/CT to monitor response in triple negative tumors after one course may be suboptimal in comparison with the performance after three courses (six weeks). In HER2-positive tumors the early PET/CT...
seemed superior, although both PET/CT2 and PET/CT3 yielded poor to moderate associations.

Although detection of responders could be important for prognostication, it would also be valuable to detect non-responders at an early time-point. Our study shows that this is particularly useful with PET/CT3 in triple negative tumors (Figure 3). Changing the chemotherapy regimen at this point, based on the PET/CT response, could possibly lead to increased pCR rates (and improved survival).

A recently published large study by von Minckwitz and co-workers reported that a pCR in both breast and lymph nodes is a better discriminator between patients with favorable and unfavorable outcomes than a pCR or (near)pCR in the breast only. When using pCR of the breast only as outcome measure, further post-surgery adjuvant chemotherapy could still be considered in case of (extensive) nodal involvement after NAC. Based on our promising results regarding response monitoring in primary tumor as well as axillary nodes and the ability of PET/CT to visualize both regions in one scan, we hypothesized that assessment of FDG uptake in both breast and axilla would yield stronger associations with pCR in breast and axilla. Although the subgroups of breast cancer subtypes available for evaluation in this study were relatively small, we have shown the potential benefit of this combined approach. This might be a valuable addition to MRI response monitoring, in which axillary nodes are not adequately visualized.

It should be acknowledged that our results are preliminary findings from an early analysis. Even the relatively large patient group was insufficient to reveal some important aspects of response monitoring with PET/CT. The group of patients with ER-positive/HER2-negative tumors undergoing PET/CT evaluation and achieving a favorable pathological response was too small for more advanced statistical analysis. Nevertheless, PET/CT response in this group was variable (Figure 3), enabling differentiation based on PET/CT information, perhaps with other reference standards (for instance, survival). Further, it appeared useful for predicting (near)pCR, particularly with PET/CT3.

Since patients with insufficient baseline FDG uptake were not included in this analysis, some form of inclusion bias might have occurred. However, our baseline analysis in this cohort of patients showed that FDG uptake was sufficient for response monitoring in the majority of patients (95%), thereby excluding only a very small number of patients (particularly from the ER-positive/HER2-negative group).

In conclusion, PET/CT response monitoring during NAC is informative, but its performance is heavily dependent on the breast cancer subtype. In triple negative tumors, a PET/CT after one course (two weeks) seems relatively accurate, but a PET/CT after three courses (six weeks) appears optimal for response assessment. For HER2-positive tumors, neither a PET/CT after three nor a PET/CT after eight weekly courses was found to be accurately associated with pathological response. A combination of the change in FDG uptake of breast and axilla had the strongest association with pCR.
REFERENCES


24 Boellaard R, Oyen WJG, Hoeckstra CJ, et al. The Netherlands protocol for standardisation and


