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
Combined use of 18F-FDG PET/CT and MRI for response monitoring of breast cancer during neoadjuvant chemotherapy: initial results in 93 patients

Submitted

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Purpose
To investigated the complementary value of positron emission tomography with computed tomography (PET/CT) and MRI in predicting pathological response during neoadjuvant chemotherapy (NAC) of breast cancer. Furthermore we studied the role of breast cancer subtype in this context.

Methods
An 18F-FDG PET/CT and an MRI were performed at baseline and during NAC. After NAC all patients underwent surgery. MRI interpretation included lesion morphology at baseline and patterns change in morphology, tumor size, and contrast uptake kinetics. The 18F-FDG maximum standardized uptake value (SUVmax) of the primary tumor was measured at baseline PET/CT and during treatment. Tumor response after surgery was classified as (near) complete pathological response ((near)pCR) or non-complete response (non-pCR). The former was defined as complete absence of invasive residual tumor or only a small number of scattered tumor cells. The latter was defined as any residual invasive tumor that not satisfied the criteria for a (near) pCR. Statistical analyses, including receiver operating characteristic (ROC) curves, with area under the curve (AUC), were employed to identify imaging factors associated with pathological response.

Results
Forty-three of 93 patients (46%) achieved a (near)pCR. At multivariate analysis the following factors were significantly associated with pathological response: relative reduction in SUVmax on PET/CT, AUC: 0.78 (95% confidence interval (CI) 0.68-0.88), and relative reduction in largest tumor diameter of initial enhancement on MRI, AUC: 0.81 (CI 0.72-0.91). The AUC increased to 0.86 (CI 0.79-0.94) in the final multivariate model with MRI and PET/CT combined, compared to PET/CT alone (p=0.044), and compared to MRI alone (p=0.096). We observed a dependency on breast cancer subtype, but limited statistical power disabled their incorporation in advanced analyses at this stage.

Conclusion
MRI and PET/CT show complementary potential to predict response during NAC, but more research in a larger group of patients is needed.
INTRODUCTION

Neoadjuvant chemotherapy (NAC) is currently the standard treatment for locally advanced breast cancer. NAC has several advantages. First, by reducing the tumor load it may enable breast-conserving surgery (BCS) instead of mastectomy in about 16% of all patients. Second, monitoring of the treatment effect during NAC enables adaptations in cases of an unfavorable tumor response. Third, NAC offers an excellent platform for translational research, since the molecular characteristics of breast cancer can be directly related to chemo-sensitivity.

Results from several studies demonstrate superior disease-free survival in patients who achieve pathological complete response (pCR). This finding emphasizes the benefit of achieving pCR, particularly in triple negative and human epidermal growth factor receptor 2 (HER2)-positive tumors. Response monitoring during treatment may distinguish between patients with a favorable and those with an unfavorable outcome. Early and accurate prediction of the response to NAC is desirable, since administration of ineffective treatment can be limited, unnecessary drug toxicity may be decreased, and more cycles of effective chemotherapy can be administered before surgery. Moreover, some studies suggest an improvement in outcome after treatment modification during NAC.

Dynamic contrast-enhanced magnetic resonance imaging (MRI) is frequently used to evaluate the treatment effect, but its predictive value is far from ideal and it performs particularly poorly in estrogen receptor (ER)-positive/HER2-negative disease. This limitation has led to the investigation of other imaging strategies. In that context the role of 18F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) is subject of research. Up till now, promising but varying results have been reported. Furthermore, studied patient populations were relatively small and/or heterogeneous.

PET/CT visualizes the change in glucose metabolism, whereas contrast-enhanced MRI depicts changes in morphology and perfusion. Theoretically, this difference in visualization of underlying tumor function may provide complementary information to monitor tumor response when both modalities are combined. If this complementary value can be exploited effectively, new strategies can be developed to improve the accuracy of evaluating response during NAC.

Previously, we have shown the value of breast cancer response monitoring using PET/CT alone and MRI alone. Response monitoring was strongly dependent on breast cancer subtype in those reports. The aim of the present study was to investigate the complementary value of a combined use of PET/CT and MRI to monitor response during NAC. In line with our previous research we furthermore studied the role of breast cancer in this context.
PATIENTS AND METHODS

Patient selection
Since September 2008 we consecutively included patients who were eligible for NAC, in a prospective single-institution NAC trial. In this trial different regimens of NAC and the role of breast imaging in this context were investigated. The patients were women with primary invasive breast cancer >3 cm and/or at least one tumor-positive node. The institutional review board approved this study and written informed consent was obtained from all patients.

Pre-treatment pathology
A core biopsy from the primary tumor was taken before NAC to determine the histologic type and to perform immunohistochemical staining. All biopsies were reviewed by an experienced breast pathologist (JW). Samples were scored as positive for estrogen receptor (ER) and progesterone receptor (PR) by immunohistochemistry (IHC) when at least 10% of the tumor cells showed staining. Samples were scored as HER2-positive when either a strong membrane staining (3+) could be observed by IHC or if chromogenic in situ hybridization revealed amplification of HER2 in samples with moderate (2+) membrane staining at IHC. We categorized breast cancer subtypes into HER2-positive (ER and PR may be positive or negative), ER-positive/HER2-negative-, and triple negative (ER, PR-, and HER2-negative). Grade was determined using modified Bloom-Richardson criteria.\textsuperscript{15}

Treatment
Patients with HER2-positive tumors were treated with a trastuzumab-based regimen consisting of paclitaxel, trastuzumab, and carboplatin (PTC) in three courses of 8 weeks. In week seven and eight of each course only trastuzumab was given. Patients with HER2-negative tumors were treated with six courses of cyclophosphamide and doxorubicin (AC), administered in a dose-dense schedule (every two weeks). In case of an unfavorable response after three courses, chemotherapy was typically switched to a theoretically non-cross-resistant regimen consisting of capecitabine (twice daily on days 1-14) and docetaxel (on day 1) (CD).\textsuperscript{16} Courses were repeated every 3 weeks. After NAC, all patients underwent breast-conserving surgery or mastectomy.

PET/CT and MRI
Baseline and interim tumor response monitoring was done using MRI and PET/CT. Interim MRI and PET/CT were performed at the end of the first of three 8-week courses of primary chemotherapy for HER2-positive tumors after and 3 of 6 cycles of primary chemotherapy for HER2-negative tumors.
For PET/CT patients were prepared with a six-hour fasting period. Blood glucose levels were required to be <10 mmol/l. An FDG dose of 180-240 MBq was given intravenously, depending on body mass index. The PET/CT was acquired after a resting period of 60 ± 10 minutes using a whole body PET/CT scanner (Gemini TF, Philips, Cleveland, USA).
With the patient in prone position a PET scan (3 min per bed position) of the chest was performed with image reconstruction to 2x2x2 mm voxels. PET acquisition was preceded by a low-dose CT (40 mAs, 2 mm slices). Subsequently, as a baseline staging procedure, a standard supine whole body PET/CT (1.30 min per bed position and 5.0 mm CT slices) was performed from the base of the skull to the upper half of the femora. During NAC, only the breast PET/CT was repeated for response monitoring using similar acquisition, time interval after FDG injection, and patient positioning as those used at baseline imaging. A panel of experienced readers (BK, WV, and RVO) evaluated the images using orthogonal multiplanar reconstructions and simultaneous display of PET, CT, and fused PET/CT images. First, the primary tumor was qualitatively assessed. Moderate or intense FDG uptake was considered sufficient for response monitoring with PET/CT. FDG uptake was measured using maximum standardized uptake values (SUVmax), obtained by generating a 3D region of interest (ROI) based on region-growing procedures. In case of a low tumor-to-background ratio, rendering an automated ROI generation unreliable, the SUVmax was derived from a manually drawn volume of interest. In case of a complete metabolic response on the second PET/CT (increased FDG uptake at baseline, no increased FDG uptake on the second examination), the same ROI location of the PET/CT at baseline was used for calculation of SUVmax (i.e., the background value in the breast at the original site of the tumor was taken). Relative changes in SUVmax between both PET/CTs were calculated for analytic purposes.

MRI was performed with a 3.0-Tesla scanner (Achieva, Philips, Best, The Netherlands) using a dedicated 7-elements Sense breast coil. Both breasts were simultaneously imaged in prone orientation. An unenhanced coronal 3D thrive sense T1-weighed sequence was acquired before the administration of contrast agent. Subsequently, five consecutive series were acquired after the intravenous administration of contrast. A bolus (14 ml) of gadolinium containing contrast agent was administered intravenously at 3 mL/s using a power injector followed by a bolus of 30 ml of saline solution. These series were acquired with a voxel size of 1.1x1.1x1.1 mm. The following scanning parameters were used: acquisition time 90 s TR/TE: 4.4/2.3; flip angle 10°; FOV 360 mm.

A viewing station that permitted simultaneous viewing of two series reformatted and linked in three orthogonal directions was used for the interpretation of the breast MRI. The viewing station displayed all image series (unenhanced and contrast enhanced), subtraction images at initial, and at late enhancement, and maximum intensity projection of both breasts. The subtraction images were also color coded, representing different rates and curve types of enhancement. The largest tumor diameter was assessed in the three reformatted planes (sagittal, axial and coronal) at initial and late enhancement. The results were reported by a radiologist experienced in breast MR imaging (CL).

**Post surgery pathology**

All surgery specimens were reviewed by an experienced breast pathologist (JW). Pathological response to chemotherapy was assessed dichotomously (i.e., presence or absence of viable residual disease in the surgery specimen). Response at pathology was classified as (near) complete pathological response ((near)pCR) or non-complete
response (non-pCR). The former was defined as complete absence of invasive residual disease or only a small number of scattered tumor cells. The latter was defined as presence of vital invasive tumor cells. A pCR was defined as complete absence of residual invasive tumor cells at microscopy. Residual in situ carcinoma was not incorporated in the definition of residual disease.

Statistics

Relative change in FDG-SUVmax was calculated using the equation:

\[
\frac{\text{SUV}_{\text{interim PET/CT}}}{\text{SUV}_{\text{baseline PET}}} \times \frac{\text{SUV}_{\text{baseline PET}}}{100}
\]

Relative change in size on MRI was calculated using the equation:

\[
\frac{\text{Largest diameter}_{\text{interim MRI}}}{\text{Largest diameter}_{\text{baseline MRI}}} \times \frac{\text{Largest diameter}_{\text{baseline MRI}}}{100}
\]

SPSS (version 20·0; SPSS Chicago, Ill) was used for all analyses. Univariate analyses were done using Student T-tests for normally distributed variables and Mann Whitney-U for the non-normally distributed ones. Multivariate binary logistic regression was performed using backward step-wise feature selection with probability to enter 0.05 and probability to remove 0.10. The following features were entered in the multivariate analysis: age, baseline SUVmax on PET/CT, baseline largest tumor diameter of initial and late enhancement on MRI, relative change in SUVmax on PET/CT, relative change in largest tumor diameter of initial and late enhancement on MRI. Receiver operating characteristics (ROC) curve analyses with area under the curve (AUC) measurement were employed to investigate associations between patients, tumor, and imaging characteristics and the tumor response at pathology after surgery. In addition these associations were studied separately for the different breast cancer subtypes.

RESULTS

The mean age of the 93 women was 47.8 years. The vast majority of the tumors (91%) were invasive ductal cancers. The baseline characteristics of the cohort are presented in Table 1. Forty-three patients (46%) achieved a (near)pCR, whereas 50 (54%) had residual disease (non-pCR) (Table 2). There was a higher rate of (near)pCR in HER2-positive and triple negative tumors compared with ER-positive/HER2-negative tumors: 76%, 68% and 13%, respectively (p<0.001) (Table 3).
| Table 1 Baseline characteristics of 93 included patients. |
|---|---|
| Age (years) | 47.8 (25.8-68.1) |
| **T-stage before NAC** |  |
| cT1 | 7 |
| cT2 | 58 |
| cT3 | 23 |
| cT4 | 5 |
| **N-stage before NAC** |  |
| cN0 | 13 |
| cN1 | 52 |
| cN2 | 2 |
| cN3 | 26 |
| **Histologic type** |  |
| Invasive ductal carcinoma | 85 |
| Invasive lobular carcinoma | 7 |
| Adenocarcinoma NOS | 1 |
| **Type of lesion on MRI** |  |
| Mass | 42 |
| Multifocal | 28 |
| Diffuse | 23 |
| **SUVmax on baseline PET/CT** |  |
| HER2-positive | 6.0 (2.3-11.1) |
| ER-positive/HER2-negative | 6.2 (2.4-18.7) |
| Triple negative | 11.6 (4.5-47.3) |
| **Clinical subtype** |  |
| HER2-positive | 25 |
| ER-positive/HER2-negative | 40 |
| Triple negative | 28 |
| **Chemotherapy regimen** |  |
| AC | 43 |
| PTC | 25 |
| AC and CD | 19 |
| AC and CTC | 4 |
| AC and PTC | 1 |
| CD | 1 |

Data are presented as median (range) or number of patients. Abbreviations: T-stage, tumor stage; NAC, neoadjuvant chemotherapy; N-stage, locoregional lymph node stage; NOS, not otherwise specified; SUVmax: maximum standardized uptake value; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; AC: doxorubicin (adriamycin) and cyclophosphamide; CD: capecitabine and docetaxel; PTC: paclitaxel, trastuzumab, and carboplatin; CTC: carboplatin, thiopeta, and cyclophosphamide.
At univariate analysis the following variables were significantly associated with absence of pCR: age (p=0.033), tumor subtype (p<0.001), relative reduction in SUVmax on PET/CT (p<0.001), and relative reduction in largest tumor diameter on late and initial enhancement on MRI (both p<0.001) (Table 2). At multivariate analysis, relative reduction in SUVmax on PET/CT and relative reduction in largest tumor diameter of initial enhancement on MRI retained significant associations with (near)pCR.

Twenty-three of 93 tumors (25%) had a reduction in largest diameter of initial enhancement of 75% or more on interim MRI. Twenty of these 23 tumors (87%) achieved a (near)pCR at pathology. These results and other percentage of tumor reduction on MRI for both initial and late enhancement are shown in Table 4.

In 21 of 58 tumors (36%) with a 50% reduction in SUVmax, residual disease was found at pathology. This fraction reduced to 5 of 19 tumors (26%), when an 80% reduction in SUVmax had been found (Table 5). The AUC was 0.78 (95% confidence interval (CI) 0.68-0.88) for relative reduction in SUVmax on PET/CT and 0.81 (CI: 0.72-0.91) for relative reduction in tumor diameter of initial enhancement on MRI. This AUC increased to 0.86 (CI: 0.79-0.94) in the final multivariate model with MRI and PET/CT combined (p=0.044 compared with PET/CT, and p=0.096 compared with MRI).

In Figure 1 the relationship between relative changes in SUV max on PET/CT and relative changes in tumor largest diameter on MRI at initial enhancement with regard to pathology response is depicted. This is specified for the different breast cancer subtypes.
DISCUSSION

We explored the potential complementary value of contrast-enhanced MRI and PET/CT to monitor stage II-III breast cancer response to NAC. For this purpose, we identified features that were associated with pathological response after the completion of chemotherapy, the golden standard. At multivariate analysis, a large relative reduction in the largest tumor diameter at initial enhancement on MRI and a large relative reduction in SUVmax on PET/CT were independent markers for (near)pCR. A combination of these features in 93 patients led to an increased AUC of the ROC curves, suggesting an improved ability to differentiate between responders and non-responders during NAC.

As described in the introduction of this paper, PET/CT visualizes the change in glucose metabolism, and MRI changes in morphology and perfusion. The rationale behind the possible complementary value of PET/CT and MRI is based on this knowledge.

Several studies have been published recently with regard to PET/CT and MRI in the setting of NAC. These studies were focused on differences, rather than assessment of complimentary values.\textsuperscript{17-20} Moreover, studies were typically performed in relatively small patient groups. To our best knowledge no studies have been reported with a comparable design and size as the current study.
Controversies in NAC imaging studies

Some key issues in NAC imaging studies are currently under investigation. Lack of standardization across studies hampers generalization and comparison of study results. First, there is no consensus with regard to the optimal time point to perform the examination(s) during NAC. Usually, examinations are done at baseline, but the time points for the subsequent examination(s) vary: after the first cycle of NAC, halfway NAC, and sometimes after completion of NAC, shortly before surgery. The interim examinations in this study were done halfway the treatment.

Second, there is no consensus which threshold values should be employed using MRI or PET/CT to assess tumor response during NAC. The response criteria for solid tumor (RECIST) are widely applied to assess tumor response to therapy and recently the PERCIST...

Figure 1  Relationship between relative changes on PET/CT and MRI regarding pathological response for all cases and different breast cancer subtypes separately.
was proposed for PET/CT monitoring.\textsuperscript{21,22} Criteria for the response monitoring in breast cancer are not yet standardized, mainly due to varied chemotherapeutic regimens and differences in time-points for response monitoring across studies. In the current study, we employed ROC analysis based on continuous values rather than choosing a specific threshold value on the ROC curve. An important reason for this choice is the relatively large confidence intervals associated with a specific choice of threshold given the number of cases. The area under the curve indicates, however, that PET/CT and MRI overall may provide complementary information.

Third, different endpoints are used, and different definitions of pCR are applied in NAC studies.\textsuperscript{7,23} An international panel of representatives of breast cancer clinical research groups recommended that pCR should be based on histopathological assessment, including absence of invasive cancer in both breast and lymph nodes.\textsuperscript{24} In a large pooled analysis von Minckwitz et al. demonstrated the importance of this definition with respect to the prognosis (depending on breast cancer subtypes) of patients treated with NAC.\textsuperscript{2} In the current explorative research we primarily focused on the sensitivity of interim MRI and PET/CT to visualize changes in the primary tumor associated with response at pathology. A study involving monitoring of treatment response of lymph nodes and primary tumor using PET/CT and MRI may be an ideal setting to relate imaging findings to pCR (breast and lymph nodes). The application of PET/CT in the detection of lymph node metastases is reported in several studies, but is still subject of research.\textsuperscript{25–28} MRI is typically unable to visualize axillary lymph nodes effectively due to the design of the MR breast coils. Visualization of response of lymph nodes to chemotherapy using PET/CT is part of ongoing parallel research.

**Current limitations and research prospects**

There is emerging evidence that breast cancer subtypes play an important role in the response prediction during NAC. Loo et al. reported relevance of subtype in the accuracy of MRI to monitor response during NAC.\textsuperscript{9} In recent studies Humbert et al and Koolen et al reported differences in SUV decrease on PET when stratifying for breast cancer subtype.\textsuperscript{13,29} Although the number of patients in our study was relatively high, stratification into subgroups of breast cancer subtypes did not yet allow firm statistical analysis to address the impact of breast cancer subtype on response monitoring with PET/CT and MRI. Particularly in the ER-positive/HER2-negative subgroup (the largest subgroup), the number of responders at final pathology was relatively small (5/40, 13%) (Table 3). Nevertheless our explorative analyses may generate hypotheses for promising further research. Figure 1 depicts that for some tumors response at pathology is associated with response at PET/CT, for others with response at MRI, and for still others with responses according to both modalities. Apparently this is a reflection of the differences in the underlying tumor functions and related subtypes that are affected by the treatment. With regard to breast cancer subtypes Figure 1D suggests that there is no (near)pCR when the decrease in SUVmax on PET/CT is smaller than about 40% in ER-positive/HER2-negative tumors, but due to the abovementioned small numbers of responders this finding need to be interpreted with caution so far.
In this ongoing research we will expand the cohort to approximately 300 patients. The relevance of breast cancer subtype will then be studied more thoroughly in the context of the combined use of PET/CT and MRI. In our opinion the increase in AUC when combining PET/CT and MRI may become more explicit in this larger group of patients as well. Moreover the observed relationship between a good response at interim MRI and (near)pCR (Table 4) will be integrated in our future studies. We will also explore cut-off values for SUVmax reduction on PET/CT, in both the breast and the lymph nodes, combined with cut-off values in size reduction on MRI, in more detail. These efforts may eventually lead to an improved patient-tailored treatment.

In this explorative analysis, the combined use of interim MRI and PET/CT showed potential to improve the ability to predict final tumor response at pathology during NAC. The exact merits of this combined use for different subtypes of breast cancer may become more apparent in a larger group of patients.
REFERENCES


15. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer; a study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957; 11: 359–77.


25. Koolen BB, Valdés Olmos RA, Elkhuizen PHM, et


