

Combined use of ^{18}F -FDG PET/CT and MRI for response monitoring of breast cancer during neoadjuvant chemotherapy

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Abstract

Purpose To explore the potential complementary value of PET/CT and dynamic contrast-enhanced MRI in predicting pathological response to neoadjuvant chemotherapy (NAC) of breast cancer and the dependency on breast cancer subtype. **Methods** We performed ^{18}F -FDG PET/CT and MRI examinations before and during NAC. The imaging features evaluated on both examinations included baseline and changes in ^{18}F -FDG maximum standardized uptake value (SUVmax) on PET/CT, and tumour morphology and contrast uptake kinetics on MRI. The outcome measure was a (near) pathological complete response ((near-)pCR) after surgery. Receiver operating characteristic curves with area under the curve (AUC) were used to evaluate the relationships between patient, tumour and imaging characteristics and tumour responses.

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Results Of 93 patients, 43 achieved a (near-)pCR. The responses varied among the different breast cancer subtypes. On univariate analysis the following variables were significantly associated with (near-)pCR: age ($p=0.033$), breast cancer subtype ($p<0.001$), relative change in SUVmax on PET/CT ($p<0.001$) and relative change in largest tumour diameter on MRI ($p<0.001$). The AUC for the relative reduction in SUVmax on PET/CT was 0.78 (95 % CI 0.68–0.88), and for the relative reduction in tumour diameter at late enhancement on MRI was 0.79 (95 % CI 0.70–0.89). The AUC increased to 0.90 (95 % CI 0.83–0.96) in the final multivariate model with PET/CT, MRI and breast cancer subtype combined ($p=0.012$).

Conclusion PET/CT and MRI showed comparable value for monitoring response during NAC. Combined use of PET/CT and MRI had complementary potential. Research with more patients is required to further elucidate the dependency on breast cancer subtype.

Keywords Breast cancer · Neoadjuvant chemotherapy · Positron emission tomography · Magnetic resonance imaging · Response monitoring

Introduction

Neoadjuvant chemotherapy (NAC), also referred to as ‘pre-operative’ or ‘primary systemic’ therapy, is the standard treatment for locally advanced breast cancer. NAC has several advantages. First, by reducing the size of the tumour, it may allow breast-conserving surgery instead of mastectomy in about 16 % [1] up to 37 % [2] of all patients. Second, monitoring the effects treatment during NAC enables adaptation of the treatment in case of an unfavourable tumour response. Third, NAC offers an excellent platform for

translational research, since the molecular characteristics of breast cancer can be directly related to chemosensitivity.

Results from several studies have demonstrated superior disease-free survival in patients who achieve a pathological complete response (pCR) [3, 4]. Hence, achieving pCR is an important treatment objective, particularly in triple-negative tumours and tumours positive for human epidermal growth factor receptor 2 (HER2) [3]. In theory, response monitoring during treatment may help to predict which patients will achieve the desired pCR at a time when a change of chemotherapy regimen would still be practical. With this strategy 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 have suggested an improvement in outcome after treatment modification during NAC [5–7]. Dynamic contrast-enhanced MRI is frequently used to evaluate the effects of treatment, but its predictive value is not perfect and it performs relatively poorly in oestrogen receptor (ER)-positive/HER2-negative disease [8–10]. This limitation has led to the investigation of other imaging strategies. In this context, the role of ^{18}F -FDG PET/CT is under investigation. Promising but varying results have been reported [11–13], but the patient populations studied have been relatively small and/or heterogeneous.

PET/CT visualizes changes in glucose metabolism, whereas contrast-enhanced MRI depicts changes in morphology and perfusion. The rationale behind the possible complementary value of PET/CT and MRI for monitoring tumour response is based on this difference in visualization of underlying tumour characteristics. If this complementary value could be exploited effectively, new strategies might be developed to improve the accuracy of evaluating response during NAC.

The value of breast cancer response monitoring using either PET/CT or MRI alone has been previously reported. The performance of each of these techniques was shown to differ markedly among breast cancer subtypes [10, 14, 15]. Moreover, several investigators have reported higher baseline FDG uptakes in triple-negative tumours than in tumours of other breast cancer subtypes [14, 16].

The aim of the present study was to investigate the complementary value of the combined use of PET/CT and MRI for monitoring response during NAC. In this context, the differences among breast cancer subtypes were also considered.

Patients and methods

Patient selection

From September 2008 we included patients who were scheduled to receive NAC in a prospective single-institution study

of response monitoring. All patients had primary invasive breast cancer of at least 3 cm in diameter and/or at least one tumour-positive axillary lymph node. The institutional review board approved this study and written informed consent was obtained from all patients.

Pretreatment pathology

Three core biopsies from the primary tumour were taken before NAC to determine the histological type and for immunohistochemical staining. All biopsies were reviewed by an experienced breast pathologist (J.W.). Samples were scored as positive for ER and progesterone receptor (PR) on immunohistochemistry when at least 10 % of the tumour cells showed staining. Samples were scored as HER2-positive when either strong membrane staining (3+) was observed on immunohistochemistry or if chromogenic *in situ* hybridization revealed amplification of the HER2 gene. We categorized breast cancer subtypes as HER2-positive (ER and PR either positive or negative), ER-positive/HER2-negative, and triple-negative (ER-negative, PR-negative and HER2-negative). Grade was determined using the criteria of Bloom and Richardson with modification [17].

Treatment

Patients with HER2-positive tumours were treated with a trastuzumab-based regimen consisting of paclitaxel (70 mg/m²/week), trastuzumab (2 mg/kg/week) and carboplatin (AUC 3 mg.h/ml/week; PTC) in three cycles of 8 weeks. In week 7 and 8 of each course only trastuzumab was given [18]. Patients with HER2-negative tumours began NAC with three courses of ddAC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² on day 1, every 14 days, with PEG-filgrastim on day 2). In the context of a larger study, three courses of docetaxel and capecitabine (docetaxel 75 mg/m² on day 1, every 21 days, and capecitabine 2×1,000 mg/m² on days 1–14; DC) were administered when an ‘unfavourable response’ was detected by MRI evaluation after the three initial courses. When a ‘favourable response’ was achieved, three further courses of ddAC were administered. The findings from this neoadjuvant programme have been reported previously [19]. Criteria for favourable and unfavourable MRI responses have been published elsewhere [20]. According to institutional guidelines, based on consensus in a multidisciplinary meeting, the chemotherapy regimen was changed to a theoretically noncross-resistant regimen in patients with an unfavourable response [20] after three courses. The second-line regimen consisted of capecitabine (850 mg/m² twice daily orally on days 1–14) and docetaxel (75 mg/m² intravenously on day 1; CD). Three courses were given, every

3 weeks. After NAC, all patients underwent breast-conserving surgery or a mastectomy.

PET/CT and MRI

Tumour response was monitored with both PET/CT and MRI. PET/CT and MRI examinations were performed before the start of chemotherapy (baseline examinations), and repeated at the end of the first of three 8-week courses of chemotherapy for HER2-positive tumours and after three of six cycles of chemotherapy for HER2-negative tumours (interim examinations). For the PET/CT scans, patients were prepared with a 6-h 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 scan was performed after a resting period of 60±10 min using a whole-body PET/CT scanner (Gemini TF; Philips, Cleveland, OH). With the patient in prone position (“hanging breast” configuration identical to positioning for MRI), a PET scan (3 min per bed position) of the chest was performed with image reconstruction to 2×2×2 mm voxels. PET acquisition was preceded by a low-dose CT scan (40 mAs, 2-mm slices). Subsequently, as a baseline staging procedure, a standard supine whole-body PET/CT scan (1.30 min per bed position, 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 a similar acquisition, time after FDG injection and patient positioning as those used in baseline imaging. All PET/CT examinations in the current study were performed using the same scanner. A panel of experienced readers (B.K., W.V. and R.V.O.) evaluated the images. We have described this procedure previously in more detail [14].

MRI was performed with a 3.0-T scanner (Achieva, Philips, Best, The Netherlands) using a dedicated seven-element SENSE breast coil. Both breasts were simultaneously imaged in prone orientation. An unenhanced coronal 3-D THRIVE SENSE T1-weighted sequence was acquired. A bolus (15 mL) of gadolinium-containing contrast agent (Dotarem 0.5 mmol/ml; Guerbet; Aulnay-sous-Bois, France) was administered intravenously at 3 mL/s using a power injector followed by a bolus of 30 mL of saline solution. Subsequently, five consecutive series were acquired with a voxel size of 1.1×1.1×1.1 mm. The following scanning parameters were used: acquisition time 90 s, TR/TE 4.4/2.3 ms, flip angle 10°, FOV 360 mm.

All images were assessed according to a previously described procedure [20, 21] by a radiologist (C.L.) experienced in breast MRI. In brief: 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 MR images. The viewing station displayed all image series (unenhanced and contrast-enhanced), comprising subtraction images at initial enhancement (90 s after contrast agent injection), at late enhancement (450 s after contrast agent injection) and maximum intensity projections of both breasts. The subtraction images were also colour-coded, representing different rates and shapes of enhancement curves. These colour codes were categorized from red (initial enhancement ≥100 % with washout late enhancement) to green (initial enhancement <100 % with persisting late enhancement). In accordance with Kuhl et al. [22], we categorized the enhancement curves as type 1, 2 and 3, where type 1 represented a persisting shape, type 2 a plateau and type 3 a wash-out enhancing shape. The largest tumour diameter was assessed in the three reformatted planes (sagittal, axial and coronal) at initial and late enhancement.

Postsurgery pathology

The surgical resection specimens were assessed according to EUSOMA (European Society of Breast Cancer Specialists) guidelines [23, 24] by an experienced breast pathologist (J.W.). Complete absence of residual invasive tumour cells irrespective of carcinoma in situ was defined as pCR. A small number of scattered tumour cells left on microscopy was considered near pCR. A combination of both near pCR and pCR was classified as (near-)pCR. The presence of viable residual disease in the resection specimen due to tumour progression, stable disease or partial response to NAC, was classified as non-pCR. Pathological response was assessed dichotomously: (near-)pCR versus non-pCR. Radiographs of the specimens were obtained and the pathologist had access to the presurgery breast images. Axillary response was not evaluated in the current study.

Statistics

The relative change in maximum standardized uptake value (SUV_{max}) was calculated using an equation comparable to that used by Hatt et al. [25]:

$$\left(\frac{\text{SUV}_{\text{max}} \text{ interim PET/CT} - \text{SUV}_{\text{max}} \text{ baseline PET/CT}}{\text{SUV}_{\text{max}} \text{ baseline PET/CT}} \right) \times 100\%$$

The relative change in tumour size on MRI was calculated using the equation:

$$\left(\frac{\text{Largest diameter interim MRI} - \text{Largest diameter baseline MRI}}{\text{Largest diameter baseline MRI}} \right) \times 100\%$$

With these equations, a negative value indicates a reduction, a value of zero no change, and a positive value tumour progression on imaging. For example, the relative change of a tumour with an SUVmax of 12 at the start of treatment and a value of 3 during treatment would be -75% (i.e. 75 % reduction).

SPSS (version 20.0; SPSS Chicago, Illinois) was used for all analyses. Univariate analyses were done using Student *t* test for normally distributed continuous variables and the Mann Whitney *U* test for nonnormally distributed variables. Multivariate binary logistic regression was performed using backwards step-wise feature selection with a probability for entry 0.05 and a probability for removal 0.10. Features that were significant in the univariate analysis ($p \leq 0.05$) were entered in the multivariate analysis.

Receiver operating characteristics (ROC) curve analysis with area under the curve (AUC) measurement were used to investigate relationships between patient, tumour characteristics and imaging characteristics and the tumour response on pathology after surgery. In addition, these relationships were studied separately for the different breast cancer subtypes (HER2-positive, ER-positive/HER2-negative and triple-negative).

Results

Included in the study were 93 women with breast cancer of stage 2 or higher. Their mean age was 47.8 years (25.8–68.1 years). The vast majority of the tumours (91 %) were invasive ductal cancers. The baseline characteristics of the cohort are presented in Table 1.

Of the 93 patients, 43 (46.2 %) achieved a (near-)pCR and 50 (53.8 %) had residual disease (non-pCR) as shown in Table 2.

Age

Age was significantly associated with (near-)pCR ($p=0.033$) as shown in Table 2. Of the 43 patients with (near-)pCR and of the 50 patients with non-pCR, 28 (65.1 %) and 27 (54 %), respectively, were younger than 50 years ($p=0.28$). This distribution, however, varied among the different breast cancer subtypes: of the patients with a HER2-positive, ER-positive and triple-negative tumour who achieved (near-)pCR 8 of 19 (59.7 %, $p=0.55$), 2 of 5 (40 %, $p=0.63$) and 17 of 19 (89.5 %, $p=0.001$), respectively, were younger than 50 years.

PET/CT

SUVmax on interim PET/CT and relative change in SUVmax on PET/CT were significantly associated with (near-)pCR ($p=0.007$ and <0.001 , respectively; Table 2). Residual disease was found on pathology in 21 of 58 tumours (36.2 %) with $\geq 50\%$ reduction in SUVmax and in 5 of 19 tumours (26.3 %) with $\geq 80\%$ reduction in SUVmax.

MRI

The largest tumour diameters at initial as well as late enhancement were significantly associated with (near-)pCR ($p < 0.001$ for both). Accordingly, there was a significant association between relative change in largest tumour diameter at both initial and late enhancement and (near-)pCR ($p < 0.001$ for both; Table 2). Of 93 tumours, 23 (24.7 %) showed a reduction of 75 % or more in largest tumour diameter at initial enhancement on interim MRI. Of these 23 tumours, 20 (87.0 %) achieved a (near-)pCR on pathology.

Of the 43 tumours with a (near-)pCR, 18 (42 %) had no residual enhancement on the interim MRI, 9 (21 %) had a type 1 curve, 14 (33 %) a type 2 curve, and 2 (5 %) a type 3 curve. Of the 50 tumours with a non-pCR, 3 (6 %) had no more enhancement on the interim MRI, 5 (10 %) a type 1 curve, 29 (58 %) a type 2 curve, and 13 (26 %) a type 3 curve.

Breast cancer subtypes

There was a higher rate of (near-)pCR in HER2-positive and triple-negative tumours than in ER-positive tumours: 76.0 %, 67.9 % and 12.5 %, respectively ($p < 0.001$). Typical responses to NAC for various breast cancer subtypes are shown in Fig. 1.

Figure 2 shows the relationship between relative changes on PET/CT and MRI in relation to pathological response in various breast cancer subtypes. For HER2-positive tumours, a 100 % reduction in largest tumour diameter on MRI was associated with a wide range of relative changes in SUVmax on PET/CT (-85 to -15%). For ER-positive/HER2-negative tumours (near-)pCR was never achieved at relative reductions in SUVmax on PET/CT less than 40 %, independent of the reduction in largest tumour diameter on MRI.

Table 1 Characteristics of the 93 patients

| Characteristic | HER2-positive (n=25) | ER-positive/HER2-negative (n=40) | Triple-negative (n=28) | p value |
|--|----------------------|----------------------------------|------------------------|---------|
| Age (years), median (range) | 47 (29–61) | 48 (29–64) | 45 (26–68) | 0.409 |
| Tumour stage prior to NAC, n (%) | | | | |
| T1 | 3 (12) | 2 (5) | 2 (7) | 0.462 |
| T2 | 12 (48) | 25 (63) | 21 (75) | |
| T3 | 9 (36) | 10 (25) | 4 (14) | |
| T4 | 1 (4) | 3 (8) | 1 (4) | |
| Node-stage prior to NAC, n (%) | | | | |
| N0 | 0 | 6 (15) | 7 (25) | 0.054 |
| N1 | 16 (64) | 23 (58) | 13 (46) | |
| N2 | 0 | 0 | 2 (7) | |
| N3 | 9 (36) | 11 (28) | 6 (21) | |
| Stage, n (%) | | | | |
| 2 | 10 (40) | 22 (55) | 17 (61) | 0.464 |
| 3 | 14 (56) | 16 (40) | 11 (39) | |
| 4 ^a | 1 (4) | 2 (5) | 0 | |
| Histology, n (%) | | | | |
| Invasive ductal cancer | 21 (84) | 37 (93) | 27 (96) | 0.133 |
| Invasive lobular cancer | 4 (16) | 3 (8) | 0 | |
| Other type | 0 | 0 | 1 (4) | |
| Baseline SUVmax on PET/CT, median (range) | 6 (2–11) | 6 (2–19) | 12 (5–48) | <0.001 |
| Largest diameter on MRI (mm), median (range) | | | | |
| Initial enhancement | 46 (12–123) | 40 (16–115) | 39 (16–88) | 0.380 |
| Late enhancement | 41 (9–123) | 36 (14–87) | 34 (16–64) | 0.386 |
| Type of lesion on MRI, n (%) | | | | |
| Mass | 7 (28) | 16 (40) | 19 (68) | 0.018 |
| Multifocal | 8 (32) | 16 (40) | 4 (14) | |
| Non-mass | 10 (40) | 8 (20) | 5 (18) | |

^a In the patients with stage 4 disease a solitary metastasis was detected on the baseline PET/CT scan. These patients were treated with curative intention

For triple-negative tumours, (near-)pCR was related to a relative reduction in SUVmax on PET/CT as well as a relative reduction in largest tumour diameter at initial and late enhancement on MRI (Table 3 and Fig. 2).

Multivariate analysis

In the multivariate analysis, relative change in SUVmax on PET/CT, relative change in largest tumour diameter at late

Table 2 Results univariate analysis of patient and imaging characteristics in relation to pCR

| Characteristic | Non-pCR (n=50) | | (Near-)pCR (n=43) | | p value |
|---|----------------|------|-------------------|------|---------|
| | Mean | SD | Mean | SD | |
| Age (years) | 48.8 | 10.1 | 44.2 | 10.3 | 0.033 |
| SUVmax baseline PET/CT | 8.3 | 5.3 | 10.5 | 8.6 | 0.29 |
| Largest diameter on MRI (mm) | | | | | |
| Initial enhancement | 49.2 | 27.8 | 47.2 | 23.8 | 0.696 |
| Late enhancement | 42.2 | 23.5 | 40.0 | 19.7 | 0.629 |
| Relative reduction in SUVmax on PET/CT (%) | 41.4 | 23.5 | 64.4 | 18.6 | <0.001 |
| Relative reduction in largest diameter on MRI (%) | | | | | |
| Initial enhancement | 26.4 | 27.3 | 67.1 | 34.0 | <0.001 |
| Late enhancement | 36.5 | 34.2 | 79.1 | 32.8 | <0.001 |

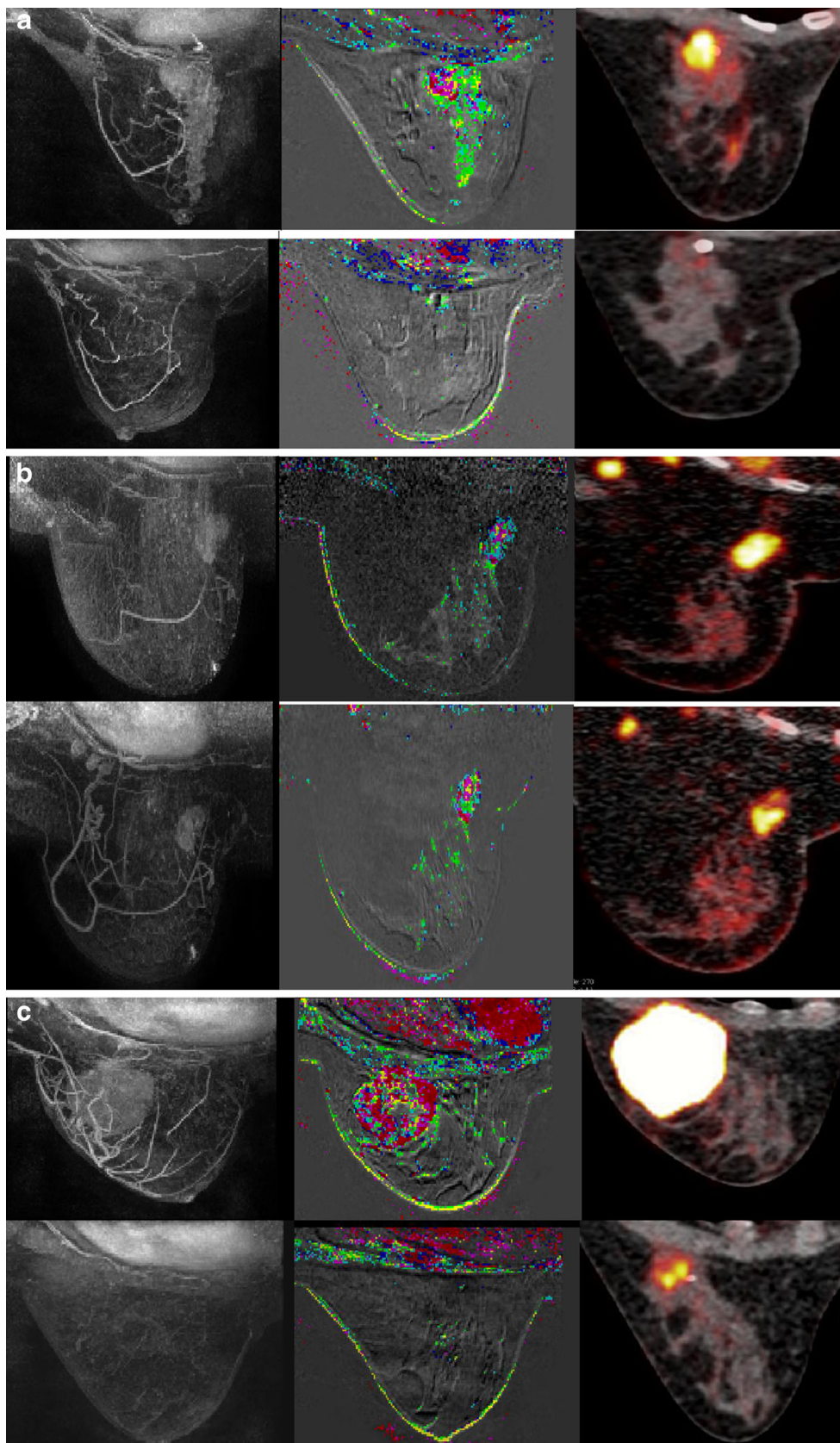


Fig. 1 Typical examples of images obtained in patients with tumours of various breast cancer subtypes. **a** A 39-year-old woman with a HER2-positive tumour showing a good response on MRI and PET/CT and complete response on final pathology. **b** A 36-year-old woman with an ER-positive/HER2-negative tumour showing a moderate response on MRI and PET/CT and Residual disease on final pathology. **c** A 32-year-old woman with a triple-negative tumour showing a good response on MRI and PET/CT and complete response on final pathology. Maximum intensity projection MR images (*left*), MR subtraction images colour-coded for time-vs.-intensity curve type (*centre*), and SUV on PET/CT (*right*). The images in the *upper rows* were obtained prior to treatment and the images in the *lower rows* during treatment. The colour codes on the subtraction images reflect contrast uptake kinetics: *red to green* initial enhancement $\geq 100\%$ with washout late enhancement to initial enhancement $< 100\%$ with persisting late enhancement

enhancement on MRI and breast cancer subtype retained significant associations with (near-)pCR. The results of the multivariate analysis are presented in Table 4.

ROC-curve

The AUC was 0.78 (95 % confidence interval, CI, 0.68–0.88) for the relative reduction in SUV_{max} on PET/CT and 0.79 (CI 0.70–0.89) for the relative reduction in tumour diameter at late enhancement on MRI. The AUC increased to 0.90 (CI 0.83–0.96) in the final multivariate model with PET/CT, MRI and breast cancer subtype combined ($p=0.012$).

Discussion

We explored the potential complementary value of PET/CT and contrast-enhanced MRI for monitoring the response of breast cancer to NAC. We identified changes in imaging features during NAC that were associated with the

Table 3 Results univariate analysis reduction in SUV_{max} on PET/CT and largest diameter of tumour enhancement on MRI in relation to pathological response in various breast cancer subtypes

| Breast cancer subtype | Non-pCR (%) | | (Near)pCR (%) | | p value |
|--|-------------|----|---------------|----|---------|
| | Mean | SD | Mean | SD | |
| Reduction in SUV_{max} on PET/CT | | | | | |
| HER2-positive | 69 | 16 | 59 | 21 | 0.29 |
| ER-positive/HER2-negative | 37 | 24 | 62 | 15 | 0.013 |
| Triple-negative | 40 | 11 | 70 | 15 | <0.001 |
| Reduction in largest diameter at initial enhancement on MRI | | | | | |
| HER2-positive | 74 | 30 | 84 | 22 | 0.45 |
| ER-positive/HER2-negative | 21 | 21 | 30 | 43 | 0.44 |
| Triple-negative | 17 | 17 | 60 | 32 | <0.001 |
| Reduction in largest diameter at late enhancement on MRI | | | | | |
| HER2-positive | 77 | 26 | 92 | 19 | 0.22 |
| ER-positive/HER2-negative | 35 | 33 | 51 | 45 | 0.47 |
| Triple-negative | 16 | 22 | 74 | 36 | <0.001 |

pathological response after NAC in relation to breast cancer subtype. In the multivariate analysis a large relative reduction in SUV_{max} on PET/CT, a large relative reduction in the largest tumour diameter at late enhancement on MRI, and breast cancer subtype were independent markers for a (near-)pCR (Table 4). A combination of these features in 93 patients led to an increased AUC, suggesting an improved ability to differentiate between responders and nonresponders to NAC by applying both modalities in combination with knowledge of the breast cancer subtype.

Several studies have investigated PET/CT and MRI in the setting of NAC. These studies focused on comparison

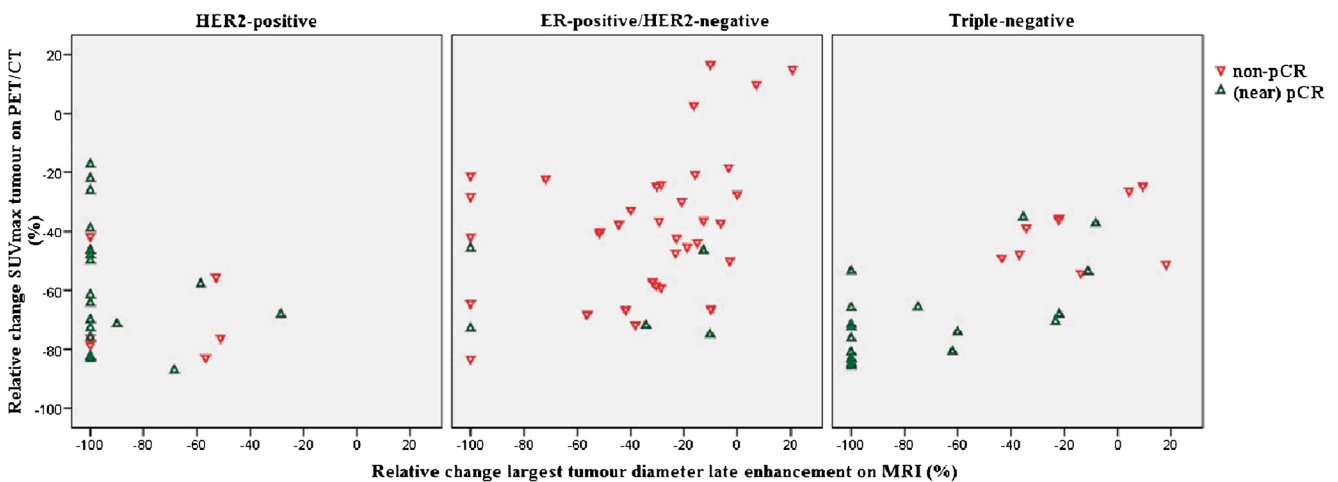


Fig. 2 Relationship between relative changes on PET/CT and MRI in relation to pathological response in various breast cancer subtypes (*red triangles* non-pCR, *green triangles* (near)pCR). A negative value

indicates a reduction, zero no change and a positive value tumour progression on imaging

Table 4 Results multivariate analysis of patient and imaging characteristics in relation to (near) pathological complete response

| Characteristic | Odds ratio | 95 % confidence interval | <i>p</i> value |
|---|------------|--------------------------|----------------|
| Age (years) | 0.959 | 0.902–1.020 | 0.188 |
| Relative reduction in SUVmax on PET/CT (%) | 0.970 | 0.941–1.000 | 0.047 |
| Relative reduction in largest diameter on MRI (%) | | | |
| Initial enhancement | 0.992 | 0.958–1.026 | 0.623 |
| Late enhancement | 0.974 | 0.956–0.993 | 0.006 |
| Breast cancer subtype | | | |
| HER2-positive | 1.0 | (Reference) | |
| ER-positive/HER2-negative | 2.166 | 0.420–11.173 | 0.356 |
| Triple-negative | 0.163 | 0.037–0.716 | 0.016 |

between the two techniques rather than on the assessment of their complementary value [26–29]. Moreover, all studies were performed in relatively small patient groups, with the exception of the study by Tateishi et al. [30]. These authors compared MRI and PET/CT in 142 patients and observed a superior accuracy of the latter for predicting pCR to NAC. The potential impact of breast cancer subtype was, however, not reported. To our knowledge no studies have been reported with a design comparable to 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 for performing 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, after completion of half the NAC course and sometimes after completion of NAC shortly before surgery. The interim examinations in this study were done half way through the treatment. A previous study demonstrated that PET/CT is able to monitor therapy response after one cycle of chemotherapy, but it is less accurate than after completion of half the treatment [31]. Second, it is still under investigation which PET parameter correlates best with response to chemotherapy. The values of parameters such as SUVmean, SUVpeak and total lesion glycolysis are not yet properly validated [25, 32]. In the current study we decided to focus on SUVmax as the most straightforward and reproducible parameter, particular in patients with a good metabolic response. Another consideration was that most other studies have also used SUVmax. This enables generalization and comparison of results among studies.

Third, there is no consensus as to which threshold values should be employed for PET/CT or MRI to assess breast cancer response during NAC. The response criteria for solid tumours (RECIST) are widely applied and recently PERCIST

was proposed for PET/CT monitoring [33, 34]. Criteria for 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 was the relatively large CIs associated with a specific choice of threshold given the current number of our included patients. The AUC indicated, however, that PET/CT and MRI overall provide complementary information. Fourth, different end-points were used, and different definitions of pCR were applied in NAC studies [9, 35]. 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 [36]. In the current exploratory research, we primarily focused on the ability of interim PET/CT and MRI scans of the breast to detect changes in the primary tumour associated with response on pathology after surgery.

Current limitations and research prospects

There is emerging evidence that breast cancer subtype plays an important role in response monitoring during NAC. Loo et al. reported the relevance of breast cancer subtype in the accuracy of MRI in monitoring response during NAC [10]. In recent studies, Humbert et al. [16] and Koolen et al. [14] reported differences in SUV decrease on PET when stratifying according to breast cancer subtype. In the current study, for some breast cancer subtypes, response on final pathology was primarily associated with response on PET/CT, for others with response on MRI, and for still others with response according to both modalities. These effects can be considered a reflection of differences in the underlying tumour functions (changes in glucose uptake, morphology and perfusion) and to be related to the breast cancer subtypes that are affected by the treatment.

Although the number of patients in the current exploratory study was relatively large, stratification into subgroups of

breast cancer subtypes did not provide sufficient statistical power to address the impact of breast cancer subtype on response prediction with PET/CT and MRI. Particularly in the ER-positive/HER2-negative subgroup (the largest subgroup), the number of responders on final pathology was relatively small (5 of the 40, 12.5 %). Nevertheless, our exploratory analyses may generate hypotheses for further research.

In view of these findings, further research in a larger group of patients may enable us to address several subjects that emerged in this exploratory analysis. The relevance of breast cancer subtype will be studied more thoroughly in the context of the combined use of PET/CT and MRI. In particular, if the observed dependency of response on imaging on breast cancer subtype remains consistent in a larger group of patients, we will be able to establish cost-effective imaging strategies based on breast cancer subtype. These cost-effectiveness studies are currently ongoing. In addition, the observed relationship between a good response on interim MRI and (near-)pCR will be integrated in future studies. More precise cut-off values need to be established for SUVmax reduction on PET/CT, in both the breast and the lymph nodes, combined with cut-off values for size reduction on MRI.

There are indications that other MRI techniques such as diffusion-weighted imaging may be of additional value for monitoring response to therapy [37]. We plan to incorporate these analyses in our further research as well. All the above-mentioned efforts may eventually lead to improved patient-tailored treatment.

Conclusion

In this exploratory analysis, the combined use of interim PET/CT and MRI showed potential for improving the ability to predict final tumour response on pathology during NAC. Additional research in a larger group of patients is needed to further elucidate the dependency on breast cancer subtype.

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Conflicts of interest None.

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