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## FULL PAPER

# Prognostic value of breast MRI characteristics before and during neoadjuvant endocrine therapy in patients with ER+/HER2- breast cancer

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**Objective:** To investigate whether BIRADS MRI characteristics before or during neoadjuvant endocrine therapy (NET) are associated with the preoperative endocrine prognostic index (PEPI) in ER+/HER2- breast cancer patients.

**Methods:** This retrospective observational cohort study included 35 ER+/HER2- patients with 38 tumors (3 bilateral cases) treated with NET. The pre- and midtreatment (after 3 months) MRIs were evaluated by two breast radiologists for BIRADS imaging characteristics, shrinkage pattern, and radiologic response. PEPI was used as end point. PEPI is based on the post-treatment surgical specimen's pT- and pN-stage, Ki67, and ER-status. Tumors were assigned PEPI-1 (good prognosis) or PEPI-2/3 (poor prognosis). We investigated whether pre- and midtreatment BIRADS characteristics were associated with PEPI.

**Results:** Median patient age was 65 years (interquartile interval [IQI]: 53, 70). 17 tumors (44.7%) were associated with good prognosis (PEPI-1), and 21 tumors (55.3%) with poor prognosis (PEPI-2/3). A larger reduction in tumor size after 3 months of NET was significantly associated with PEPI; 10 mm (IQI: 5, 13.5) in PEPI-1 tumors vs 4.5 mm (IQI: 3, 7;  $p = .045$ ) in PEPI-2/3 tumors. Other BIRADS characteristics, shrinkage pattern or radiologic response were not associated with PEPI.

**Conclusion:** Only a larger reduction in tumor size on MRI after 3 months of NET was associated with PEPI-1 (good prognosis) in ER+/HER2- breast cancer patients.

**Advances in knowledge:** MRI characteristics previously reported to be associated with prognosis during neoadjuvant chemotherapy are not necessarily associated with prognosis during NET in ER+/HER2- breast cancer patients.

## INTRODUCTION

Neoadjuvant treatment for patients with estrogen receptor-positive (ER+) human epidermal growth factor receptor 2-negative (HER2-) breast cancer includes neoadjuvant endocrine therapy (NET) and neoadjuvant chemotherapy (NAC). NET leads to similar rates of breast conserving surgery (BCS) and pathologic response rates compared to NAC in strong ER+ breast cancer patients.<sup>1</sup> However, NET has the advantage of being less toxic compared to NAC.<sup>1</sup>

About 50–70% of patients show a clinical response during NET.<sup>2</sup> In order to identify patients who will benefit from

NET, it is important to monitor the tumor during treatment to allow for therapy adjustment, e.g. expediting surgery or switching treatment regimen. Response monitoring during neoadjuvant treatment is mostly done using MRI because it is the most sensitive modality to assess tumor response.<sup>3</sup> Many studies have identified MRI characteristics during NAC that are associated with tumor response and prognosis,<sup>4–7</sup> whereas studies investigating MRI during NET are limited.<sup>8,9</sup>

The performance of MRI to predict response after NAC differs among the different immunohistochemical

subtypes.<sup>4,7</sup> Especially predicting response in ER+/HER2- breast cancer has proven to be difficult.<sup>4,7</sup> For example, change in tumor size on MRI during NAC was associated with response in triple negative (TN) and HER2+ breast cancer, but was not associated with response or prognosis in ER+ breast cancer.<sup>4,10</sup> Changes in apparent diffusion coefficient (ADC),<sup>6</sup> and tumor shrinkage pattern during NAC, however, did show an association with tumor response in ER+/HER2- breast cancer.<sup>5</sup>

Pathologic complete response (pCR) is typically used as surrogate endpoint of survival in neoadjuvant studies. However, pCR might not be suited for ER+ breast cancer, because the rate of pCR is low (about 10%), and is poorly associated with prognosis.<sup>11,12</sup> This might also explain the relatively poor performance of MRI to predict response in ER+/HER2- breast cancer. The preoperative endocrine prognostic index (PEPI) was developed as a surrogate endpoint of survival for ER+/HER2- breast cancer after NET, and might better predict survival than pCR in this subset of patients. PEPI is derived from the histopathological evaluation after NET. Patients are stratified in three prognostic groups (PEPI-1, PEPI-2, and PEPI-3) based on pT- and pN-stage, the Ki67 index, and ER-status.<sup>13,14</sup> PEPI-1 is associated with the best prognosis, and PEPI-3 is associated with the poorest. Patients with a PEPI-1 after NET have such a favorable

prognosis that adjuvant endocrine monotherapy might suffice, whereas patients with a PEPI-2 or PEPI-3 should be recommended adjuvant chemotherapy.<sup>13,14</sup> Prediction of PEPI before or during NET could allow for therapy adjustments in patients who are predicted to have a poor prognosis after NET (*i.e.* PEPI-2 or PEPI-3).

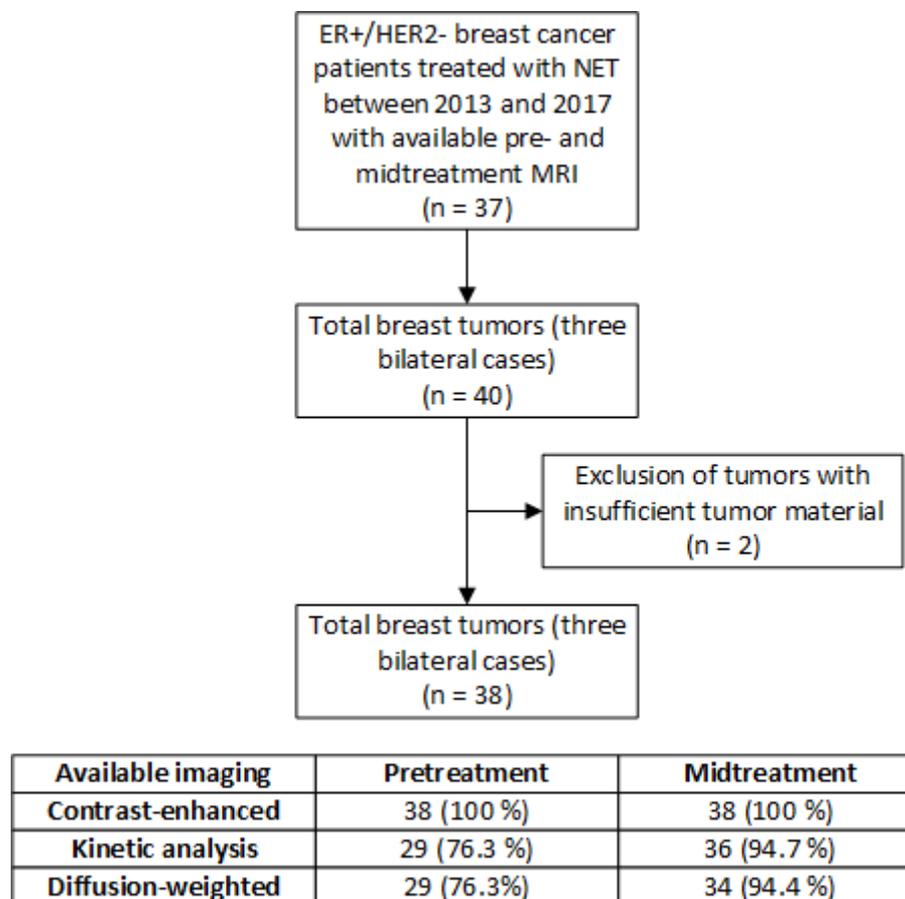
The aim of this study was to investigate whether MRI characteristics before and during NET were associated with PEPI after NET. We have focused on those characteristics that were previously associated with response or prognosis in NAC, namely: Breast Imaging Reporting and Data System (BIRADS) MRI characteristics, diffusion-weighted imaging (DWI) findings, and radiologic response.

## METHODS AND MATERIALS

### Patients and treatment

This retrospective explorative observational cohort study was approved by the institutional review board of the Antoni van Leeuwenhoek Hospital and the requirement for informed consent was waived. All patients diagnosed with pathologically proven ER+/HER2- breast cancer treated with NET between January 2013 and December 2017 with available pretreatment

Figure 1. Flowchart of inclusion and available imaging. Flowchart of patient inclusion and availability of imaging sequences at the different timepoints. ER+, estrogen receptor-positive; HER-, human epidermal growth factor receptor 2-negative; NET, neoadjuvant endocrine therapy.



and midtreatment (after 3 months) MRI were consecutively included ( $n = 37$ ; [Figure 1](#)). Three patients had a bilateral tumor. In total, 40 tumors were included in the study. NET was recommended to patients with strong ER+ ( $\geq 50\%$ ) / HER2- tumors where BCS could not be performed or to reduce the risk of involved surgical margins [e.g. in the case of an invasive lobular carcinoma (ILC)]. Additionally, there should be no indication for NAC for these patients: the tumor is  $\leq 30$  mm and there is  $\leq 1$  suspicious lymph node in combination with a low risk Mammaprint 70-gene signature (Agendia, Amsterdam, The Netherlands). In case of excess comorbidity (e.g. in cases where NAC or primary surgery at that time is expected to put excessive strain on the patient), NET is also recommended. The decision for NET is made during a multidisciplinary meeting. Tamoxifen (for pre-menopausal patients), aromatase inhibitors (AIs, for post-menopausal patients), or a sequential combination of both agents was recommended for a duration of 6–9 months. A breast tissue marker was placed before start of treatment for future localization of the tumor.<sup>7</sup> The midtreatment response MRI is performed after 3 months of NET: in case of unfavorable tumor response (*i.e.* stable or progressive disease), surgery is expedited or the endocrine therapy is switched.

#### MRI technique

MRI was performed before start and after 3 months of NET and included axial DWI and dynamic contrast-enhanced (DCE) imaging with patients in prone position ([Figure 1](#)). MRI was performed on a 1.5 T or a 3 T imaging unit (Achieva, Philips, Best, The Netherlands) with a dedicated 7- or 16-element SENSE breast coil (Philips, Best, The Netherlands).

DWI was performed using  $b$  values of 0, and 800 s/mm<sup>2</sup>;  $b$  values of 0, and 1000 s/mm<sup>2</sup>;  $b$  values of 0, and 1200 s/mm<sup>2</sup>; or  $b$  values of 0, 150, and 1500 s/mm<sup>2</sup>. The following imaging parameters were used: ratio of repetition time/echo time 5500/71 or 7000/90, flip angle 90°, voxel sizes 0.90 × 0.90 × 5 mm<sup>3</sup> or 0.99 × 0.99 × 5 mm<sup>3</sup>, and a field of view of 380 or 400 mm.

The DCE protocol consisted of an unenhanced three-dimensional  $T_1$  weighted fast field echo sequence with fat suppression before intravenous injection of gadolinium-containing contrast (0.1 mmol/kg, Dotarem, Geurbet, Villepinte, France), followed by five consecutive series of dynamic post-contrast images at 60 or 90 s intervals. Two sets of imaging parameters were used: acquisition time 60 or 90 s, ratio of repetition time/echo time 4.3/1.8 or 3.7/1.9, flip angle 10°, voxel sizes 0.62 × 0.62 × 2.3 mm<sup>3</sup> or 0.89 × 0.89 × 1.8 mm<sup>3</sup>, and a field of view of 400 mm ([Supplementary Material 1](#)). For nine patients, the pretreatment MRI was performed in the referring hospital.

#### MRI evaluation

Two dedicated breast radiologists (C.L. and G.W., with 18 and 30 years of experience) retrospectively reviewed the pre- and midtreatment MRIs. The radiologists independently interpreted the images and were blinded to the pathologic outcome. Only information regarding the laterality was made available in the case of bilateral tumors. Disagreements were overcome by reviewing the images in consensus.

The morphologic and kinetic features were evaluated according to the BIRADS.<sup>15</sup> The largest tumor in the breast was considered the index lesion. The size of the tumor was measured as its largest diameter in one of the three planes (sagittal, coronal, or axial) during initial enhancement (60–90 s post-contrast) and late enhancement (360–450 s post-contrast). In the case of a bilateral tumor, the index tumor of each breast was assessed independently. Kinetic features of the lesions were evaluated using DynaCAD (Invivo, Philips, Best, The Netherlands). After 3 months, the tumors were additionally evaluated on tumor shrinkage pattern, radiologic response, and the Response Evaluation Criteria in Solid Tumors (RECIST).<sup>16</sup> The shrinkage pattern classification was adapted from Fukada et al<sup>5</sup>; complete response (no visible tumor), concentric shrinkage; reduction of the largest diameter with disappearance of non-mass enhancement (residual foci of  $< 5$  mm were allowed), non-concentric shrinkage; if the shrinkage pattern couldn't be classified as concentric (e.g. decrease of intensity only, or diffuse decrease with non-mass enhancement), and stable or progressive growth ([Figure 2](#)).<sup>5</sup> The radiologic response was classified as; complete response (absence of pathological enhancement), partial response (partial disappearance of enhancement), and no response (stable or progressive disease). Lastly, the RECIST response categories included: disappearance of enhancing tumor was classified as complete response,  $\geq 30\%$  decrease in tumor size (initial enhancement) was classified as partial response,  $\geq 20\%$  increase in tumor size (initial enhancement) or the appearance of new lesions was classified as progressive disease, and if the shrinkage didn't qualify for partial nor progressive disease, the response was classified as stable disease.<sup>16</sup>

For the DWI assessment, the tumor was first identified on the DCE images and then localized on the DWI and the ADC maps. Both radiologists assessed the images for the presence of diffusion restriction in the tumor, which was defined as high signal intensity on the DWI combined with low signal intensity on the ADC maps.

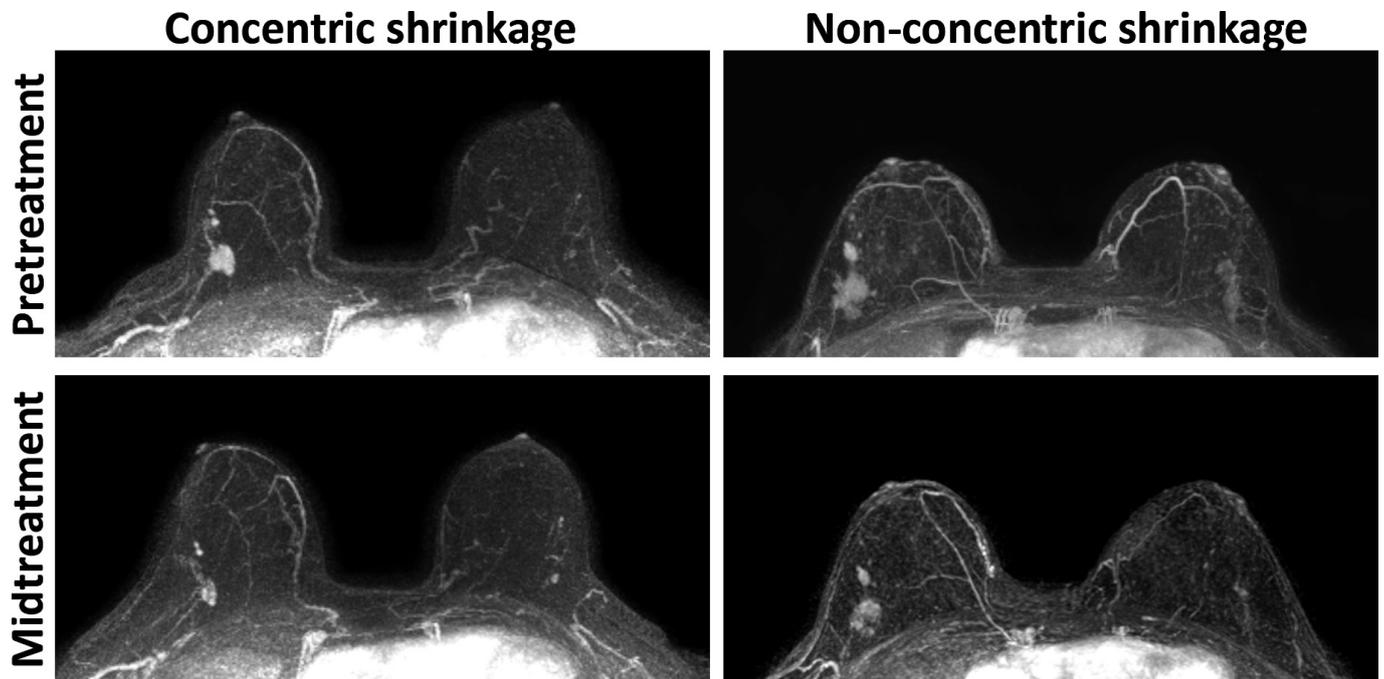
#### Pathologic response assessment

PEPI was used as endpoint.<sup>13,14</sup> PEPI is derived from the surgical specimen after NET and is based on: pT- and pN-stage, Ki67, and ER-status. Tumors are assigned risk points (0–12) based on these characteristics. The risk points stratify patients in one of three prognostic groups: PEPI-1 (0 points), PEPI-2 (1–3 points), and PEPI-3 (3 or more points) with distinct prognosis.<sup>13</sup> It is proposed that patients with PEPI-1 have such a favorable prognosis after NET that monotherapy with adjuvant endocrine therapy can suffice after surgery, whereas adjuvant chemotherapy should be considered for PEPI-2 and PEPI-3.<sup>13,14</sup> As both PEPI-2 and PEPI-3 should be considered for adjuvant chemotherapy, the a-priori decision to analyze PEPI-1 vs PEPI-2/3 was made, a method that was also adopted by a recent publication on the validation of PEPI.<sup>13</sup> Two patients were excluded due to insufficient tumor material in the surgical specimen to assess PEPI ([Figure 1](#)).

#### Statistical analysis

Summary statistics are reported as median [interquartile interval (IQI)]. The inter-rater agreement for categorical variables was

Figure 2. Shrinkage pattern. Examples of a concentric shrinkage pattern (left column) and a non-concentric shrinkage pattern (right column). The tumor in the right column shows a diffuse decrease after 3 months of NET (a non-concentric shrinkage pattern). This patient also showed segmental enhancement in the lateral upper quadrant of the left breast. This proved to be a complex sclerosing lesion at biopsy. The definitions of shrinkage pattern were adapted from Fukada et al<sup>5</sup>. NET, neoadjuvant endocrine therapy.



calculated using Cohen's  $\kappa$ . For continuous variables, the mean difference with limits of agreement, based on Bland–Altman analysis, and the intraclass correlation coefficient (ICC; two-way random-effects, absolute agreement, single rater) were calculated with 95% confidence intervals (95% CI).<sup>17</sup> Cohen's  $\kappa$  was interpreted as:  $<0$ , poor agreement;  $0.01$ – $0.20$ , slight agreement;  $0.21$ – $0.40$ , fair agreement;  $0.41$ – $0.60$ , moderate agreement;  $0.61$ – $0.80$ , substantial agreement;  $0.81$ – $1$ , almost perfect agreement<sup>18</sup>; and the ICC was interpreted as:  $<0.5$ , poor reliability;  $0.5$ – $0.75$ , moderate reliability;  $0.75$ – $0.9$ , good reliability;  $>0.9$ , excellent reliability.<sup>17</sup> The results after the consensus readings were used to investigate whether BIRADS characteristics on MRI before and after 3 months of NET were associated with the PEPI-groups. Statistical differences for categorical variables were calculated using Fisher's exact test, the Mann–Whitney  $U$  test for unpaired continuous variables, and the Wilcoxon signed-rank test for paired continuous variables. Statistical analyses were performed using R v. 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed  $p < .05$  was considered to represent statistical significance.

## RESULTS

### Patient cohort

Table 1 summarizes patient, tumor, and treatment characteristics. The pre- and midtreatment MRI of 35 patients and 38 tumors (3 bilateral cases) were evaluated. The median age at diagnosis was 65 years (IQI: 53, 70). Clinical stage was mostly Stage I (26.3%) or II (60.5%), there was one clinical Stage 0 (ductal carcinoma *in situ* in a bilateral case) and four cases of clinical Stage III (10.5%). Pretreatment Ki67 was similar between the PEPI-groups.

Patients received NET for a median duration of 7.4 months (IQI: 6.6, 7.9), and BCS could be performed in 31 patients (81.6%). At histopathological evaluation 17 tumors (44.7%) were associated with a good prognosis, or PEPI-1, whereas 21 patients (55.3%) were associated with a relatively poor prognosis, or PEPI-2/3.

### Inter-rater agreement

The inter-rater agreement for the BIRADS characteristics are summarized in Table 2. Most BIRADS characteristics show fair to moderate agreement, although the inter-rater agreement of the subclassifications for (non)mass shape and enhancement characteristics were poor. The mean inter-rater difference in pretreatment tumor size was  $-3.68$  mm with limits of agreement between  $-27.7$  mm and  $20.3$  mm, similarly, the mean difference in midtreatment tumor size was  $0.3$  mm with limits of agreement between  $-22.5$  mm and  $23.0$  mm (Figure 3). Large disagreements in tumor size were in cases when the radiologists disagreed about the focality of the tumor (*i.e.* the index lesion in a unifocal versus a multifocal tumor), or in the case of non-mass enhancement. The inter-rater agreement for tumor size at early enhancement was moderate with an ICC of  $0.68$  (95% CI:  $0.50, 0.80$ ;  $p < .001$ ) for pretreatment tumor size, and  $0.70$  (95% CI:  $0.53, 0.81$ ;  $p < .001$ ) for midtreatment tumor size.

### Associations between BIRADS characteristics and PEPI-groups

Tumor size at initial or late enhancement on pretreatment imaging was not significantly different between the PEPI-groups ( $p = .803$  and  $p = .162$ ) nor after 3 months of NET ( $p = .953$  and  $p = .517$ ). The change in tumor size at initial enhancement, after 3

Table 1. Patient, treatment and tumor characteristics

		All tumors ( <i>n</i> = 38)	PEPI-1 ( <i>n</i> = 17) Good prognosis	PEPI-2/3 ( <i>n</i> = 21) Poor prognosis
Age (years)				
Median (IQI)		65 (53, 70)	66.5 (54, 71)	60 (49.5, 69.5)
Laterality	Unilateral	32 (84.2 %)	13 (76.5 %)	19 (90.5 %)
	Bilateral	6 (15.8 %)	4 (23.5 %)	2 (9.5 %)
Tumor histology	DCIS	1 (2.6 %)	1 (5.9 %)	0 (0 %)
	IDC	22 (57.9 %)	11 (64.7 %)	11 (52.4 %)
	ILC	11 (28.9 %)	3 (17.6 %)	8 (38.1 %)
	Mixed IDC/ILC	4 (10.5 %)	2 (11.8 %)	2 (9.5 %)
Clinical stage	0	1 (2.6 %)	1 (5.9 %)	0 (0 %)
	I	10 (26.3 %)	8 (47.1 %)	2 (9.5 %)
	II	23 (60.5 %)	7 (41.2 %)	16 (76.2 %)
	III	4 (10.5 %)	1 (5.9 %)	3 (14.3 %)
Tumor grade	1	7 (18.9 %)	5 (31.2 %)	2 (9.5 %)
	2	24 (64.9 %)	7 (43.8 %)	17 (81 %)
	3	6 (16.2 %)	4 (25 %)	2 (9.5 %)
	Unknown	1	1	0
ER-percentage (IQI)				
Median (IQI)		100 (97.5, 100)	100 (100, 100)	100 (95, 100)
PR-percentage (IQI)				
Median (IQI)		80 (25, 92.5)	70 (45, 97.5)	80 (3, 90)
Ki67 (%)				
Pretreatment (IQI)		10 (5, 20)	11.3 (3, 20)	10 (5, 16.3)
Posttreatment (IQI)		2 (1, 5)	1 (1, 2)	5 (1, 10)
Duration of NET (months)				
Median (IQI)		7.4 (6.6, 7.9)	7.6 (6.8, 8.6)	7.0 (6, 7.7)
Therapy	AI	26 (68.4 %)	12 (70.6 %)	14 (66.7 %)
	Tamoxifen	8 (21.1 %)	2 (11.8 %)	6 (28.6 %)
	Combination	4 (10.5 %)	3 (17.6 %)	1 (4.8 %)
Surgery	BCS	31 (81.6 %)	15 (88.2 %)	16 (76.2 %)
	No BCS	7 (18.4 %)	2 (11.8 %)	5 (23.8 %)

AI, Aromatase inhibitor; BCS, Breast conserving surgery; DCIS, Ductal carcinoma in situ; ER, Estrogen receptor; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma; IQI, Interquartile interval; NET, Neoadjuvant endocrine therapy; PEPI, Preoperative endocrine prognostic index; PR, Progesterone receptor.

Patient, treatment and tumor characteristics. Unless otherwise specified data are number of tumors, with percentages in parentheses.

months of treatment, decreased in both PEPI-groups. However, a larger reduction in tumor size was observed in tumors that ended up being a PEPI-1 (good prognosis) at histopathological evaluation. Tumor size decreased on average in PEPI-1 by 10 mm (IQI: 5, 13.5) compared to an average decrease of 4.5 mm (IQI: 3, 7;  $p = .045$ ; [Figure 4](#)) in PEPI-2/3. No other BIRADS characteristics of the pretreatment MRI or the midtreatment MRI were significantly associated with PEPI ([Supplementary Material 2](#)). Background parenchymal enhancement (BPE) decreased in all patients, but was not associated with PEPI ( $p = .770$ ). Lastly,

shrinkage pattern ( $p = .578$ ), radiologic response ( $p = .483$ ), and RECIST ( $p = .790$ ) were also not associated with PEPI ([Table 3](#)). All three patients with a complete radiologic response were diagnosed with an ILC. Two of these patients with a radiologic complete response had a PEPI-2/3 (poor prognosis) at histopathological evaluation and in both patients BCS could not be performed. These patients had involved surgical margins at pathology after attempting BCS, and underwent a mastectomy afterwards. Two examples of the pre- and midtreatment MRIs are shown in [Figures 5 and 6](#).

Table 2. Inter-rater agreement for BIRADS characteristics, DWI, shrinkage pattern, and radiologic response of pretreatment and midtreatment MRI during NET

	Inter-rater agreement	
	Pretreatment	Midtreatment
Fibroglandular tissue	0.482 (0.260, 0.705)	0.440 (0.208, 0.672)
Background parenchymal enhancement	0.681 (0.502, 0.859)	0.298 (0.030, 0.566)
Presence of mass	0.713 (0.459, 0.968)	0.684 (0.458, 0.911)
Mass – Shape	0.090 (-0.077, 0.257)	0.095 (-0.086, 0.276)
Mass – Margin	0.292 (-0.063, 0.646)	0.486 (0.085, 0.886)
Mass – Internal enhancement	0.193 (0.029, 0.358)	0.289 (0.041, 0.538)
Presence of non-mass enhancement	0.612 (0.357, 0.867)	0.469 (0.189, 0.750)
Non-mass – Distribution	-0.236 (-0.427, -0.045)	0.158 (-0.124, 0.440)
Non-mass – Internal enhancement	0.441 (-0.034, 0.916)	0
Kinetics – Early enhancement	0.482 (-0.110, 1.000)	0.519 (0.294, 0.744)
Kinetics – Late enhancement	0.482 (0.120, 0.844)	0.449 (0.204, 0.694)
Presence of diffusion restriction	0.889 (0.676, 1.000)	0.422 (0.139, 0.705)
Shrinkage pattern		0.517 (0.308, 0.725)
Radiologic response		0.670 (0.428, 0.912)

95% CI, 95% confidence interval; DWI, Diffusion weighted-imaging; NET, Neoadjuvant endocrine therapy. Data are Cohen's  $\kappa$  (95% CI).

### Association between DWI and PEPI-groups

Pretreatment DWI was available for 29 tumors, and midtreatment DWI for 34 tumors. There was no significant difference between the presence of diffusion restriction assessed qualitatively on pretreatment imaging ( $p = .622$ ) nor at the midtreatment imaging ( $p = .314$ ) between the PEPI-groups (Supplemental Materials 2).

## DISCUSSION

In this study, we investigated whether pre- or midtreatment BIRADS characteristics, kinetic, and DWI findings, on MRI were associated with prognosis (on the basis of PEPI) after NET in ER+/HER2- breast cancer patients. We found that only a larger

reduction of tumor size after 3 months of NET was more strongly associated with PEPI-1 (good prognosis) than with PEPI-2/3 (poor prognosis) in our patient cohort, although tumor size measurements suffered from large inter-rater variability, especially in case of multifocal masses or non-mass enhancement.

Research on the use of MRI during NET is limited. For NAC, however, several characteristics and changes on MRI associated with response or prognosis have been identified in ER+/HER2-tumors, *e.g.* a concentric shrinkage pattern was associated with improved survival.<sup>5</sup> In our study, shrinkage pattern was not associated with prognosis on the basis of PEPI after NET. On the other hand, changes in tumor size at initial and late enhancement were

Figure 3. Two Bland-Altman plots showing the interrater agreement of pretreatment tumor size (a) and midtreatment tumor size (b) in mm at initial enhancement on MRI.

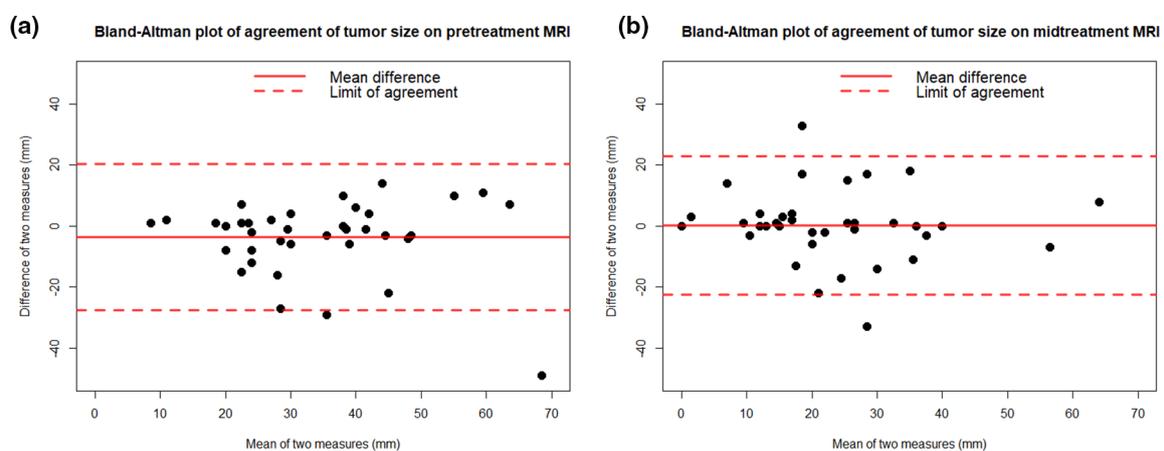
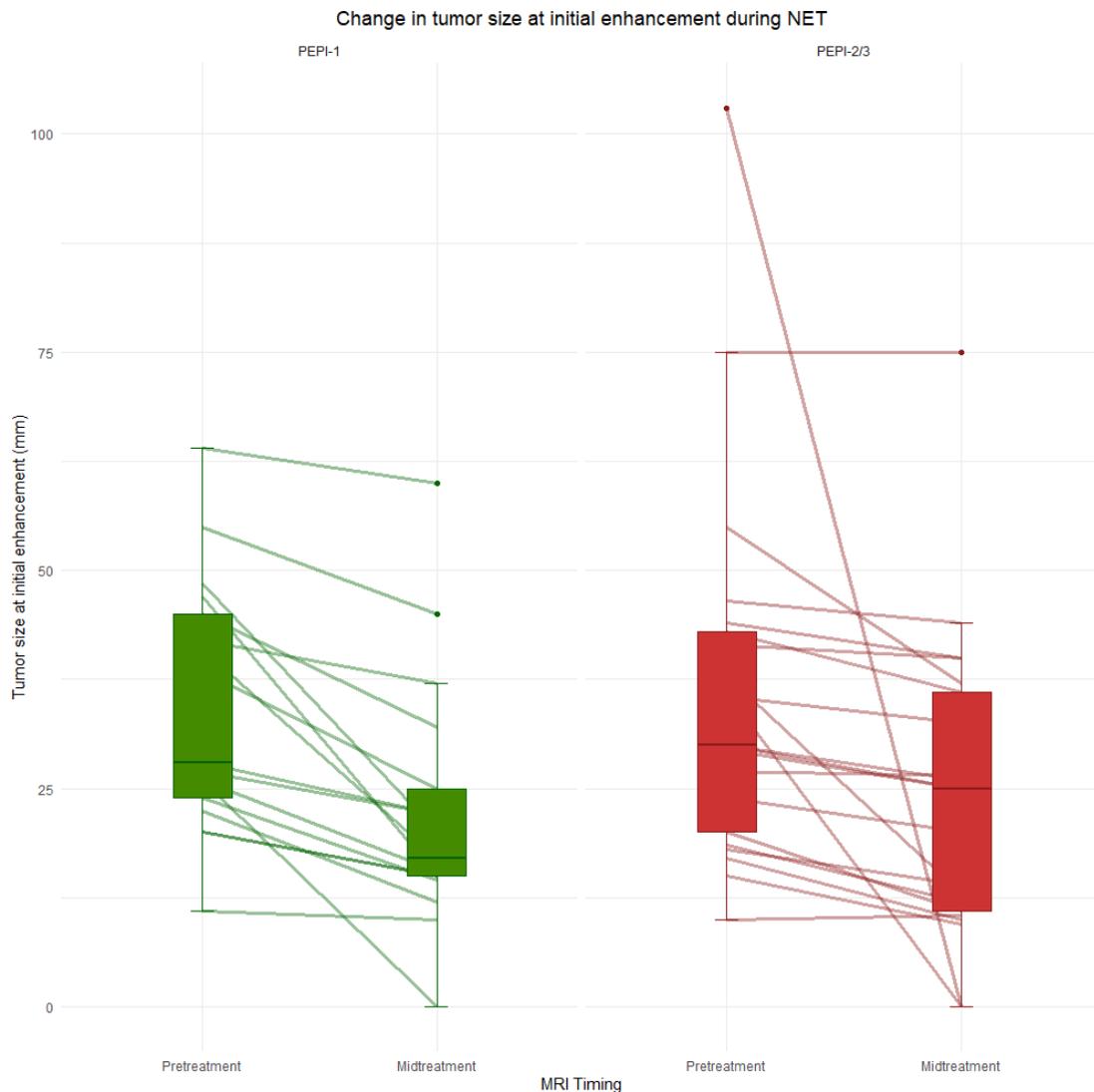


Figure 4. Change in tumor size at initial enhancement during NET. Tumor size at initial enhancement before start of NET and after three months of NET. Change in tumor size was associated with PEPI after NET ( $p = .045$ ). However, tumor size decreased on average in both PEPI-groups: it decreased by 10 mm (IQR: 5, 13.5) in PEPI-1 (good prognosis) vs 4.5 mm (IQR: 3, 7) in PEPI-2/3 (poor prognosis). IQR, interquartile interval; NET, neoadjuvant endocrine therapy; PEPI, preoperative endocrine prognostic index.



previously not associated with response in ER+/HER2- tumors during NAC,<sup>4</sup> but a larger reduction in tumor size was associated with PEPI-1 (good prognosis) in this study. In our study, BPE decreased in all patients, a known effect of endocrine therapy,<sup>19</sup> but was not associated with PEPI. However, a low pretreatment BPE was previously reported to be associated with a reduction in tumor size after NET.<sup>8</sup> Additionally, changes in contralateral parenchymal enhancement, a quantitative measure of the delayed enhancement of healthy breast tissue, during NET were predictive of PEPI.<sup>20</sup> Lastly, Reis et al, have reported a high correlation between residual disease size on MRI and pathology after NET and recommend the use of MRI for response monitoring during NET. Similar to our study, however, several patients (7 out of 35) were discordantly classified as complete responders on MRI with residual disease at pathology.<sup>9</sup>

As NET is increasingly recommended as an alternative for NAC in ER+/HER2- breast cancer patients,<sup>21</sup> it is important to identify

accurate pre- or midtreatment methods to determine whether NET will be effective to allow for therapy adjustments in patients who are unlikely to experience benefit. As we report in this study, it is likely that MRI characteristics associated with a favorable prognosis after NAC are not necessarily associated with a favorable prognosis after NET. This could be due to differences in tumor biology (high proliferation vs low proliferation) or differences in treatment mechanisms (cytotoxic vs antiproliferative). Additionally, differences in findings compared to NAC studies could also be attributed to the differences in endpoints (pCR vs PEPI).

Although pCR is typically used as a surrogate endpoint in neoadjuvant breast cancer studies, it is poorly associated with prognosis in ER+/HER2- breast cancer.<sup>11,12</sup> Therefore, PEPI might be a more suitable surrogate endpoint for ER+/HER2- patients after NET, as PEPI stratifies patients in groups with distinct prognoses, and was validated in independent cohorts.<sup>13,14</sup>

Table 3. Shrinkage pattern and radiologic response at midtreatment MRI during NET

		PEPI-1 (n = 17) Good prognosis	PEPI-2/3 (n = 21) Poor prognosis	p
Shrinkage pattern	Complete response	1 (5.9%)	2 (9.5%)	.578
	Concentric	8 (47.1%)	6 (28.6%)	
	Non-concentric	6 (35.3%)	7 (33.3%)	
	No shrinkage	2 (11.8%)	6 (28.6%)	
Radiologic response	Complete response	1 (5.9%)	2 (9.5%)	.483
	Partial response	14 (82.4%)	13 (61.9%)	
	No response	2 (11.8%)	6 (28.6%)	
RECIST	Complete response	1 (5.9%)	2 (9.5%)	.790
	Partial response	7 (41.2%)	6 (28.6%)	
	Stable disease	9 (52.9%)	13 (61.9%)	
	Progressive disease	0	0	

NET, Neoadjuvant endocrine therapy; PEPI, Preoperative endocrine prognostic index; RECIST, Response evaluation criteria in solid tumors. Shrinkage pattern and radiologic response at midtreatment MRI during NET.

A larger reduction of tumor size was associated with improved prognosis after NET (PEPI-1), however, tumor size decreased on average in both PEPI-groups during treatment. Additionally, although the tumors were measured by experienced radiologists, measurements suffered from large inter-rater variability. Although the limits of agreement included clinically meaningful thresholds ( $\pm 20$  mm), this was mostly due to disagreement of the index tumor (in case of multifocal masses) and in tumors with non-mass enhancement. The agreement in radiologic response was substantial between the radiologists. Remarkably, three patients showed a radiologic complete response, two of whom had a poor prognosis (PEPI-2/3) at histopathological evaluation, a similar observation made by Reis et al.<sup>9</sup> All three patients were diagnosed with an ILC, which are known to grow diffusely

without significant desmoplastic reaction (*i.e.* show non-mass enhancement), and are often ill-defined on imaging.<sup>22,23</sup> Response assessment based solely on changes in tumor size should be done with care, especially in the case of ILC. Automatic quantitative analysis tools could aid the radiologists in response assessment during NET, and also decrease inter-rater variability.

Our study has some limitations. Firstly, this exploratory study was retrospective, with a relatively small and heterogeneous cohort of 35 patients (38 tumors), which limits the power to detect small effects. However, for a NET MRI study, this is a large sample. Secondly, NET is a relatively new treatment option and the patient selection is not as clear-cut compared to NAC, which leads to a heterogeneous cohort treated with NET for varying

Figure 5. The images of a 68-year-old patient with a T1N0 IDC (Grade: 2, ER: 100 %, PR: 60 %) of the left breast. On the pre-treatment images (top row), a unifocal mass enhancing lesion with rim enhancement of 20 mm is visible. In the kinetic analysis (middle row), only a minimal part of the lesion shows wash-out (red), the vast majority of the tumor shows cumulative contrast enhancement (blue). The ADC map (right row) shows diffusion restriction in the rim of the lesion. After 3 months of AI, the size of the mass decreased to 15 mm (largest diameter). Enhancement and diffusion restriction are still present but significantly reduced. This patient was considered a radiologic partial responder. At histopathological evaluation, the specimen was assigned a PEPI-1 (good prognosis). ADC, apparent diffusion coefficient; AI, aromatase inhibitor; DCE, dynamic contrast-enhanced; DWI, diffusion weighted-imaging; ER, estrogen receptor; IDC, invasive ductal carcinoma; PR, progesterone receptor; PEPI, preoperative endocrine prognostic index.

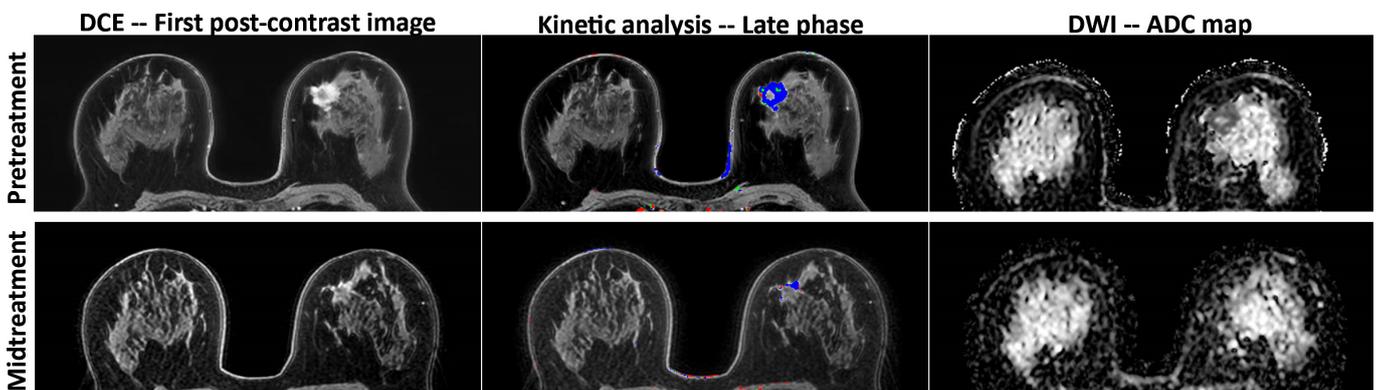
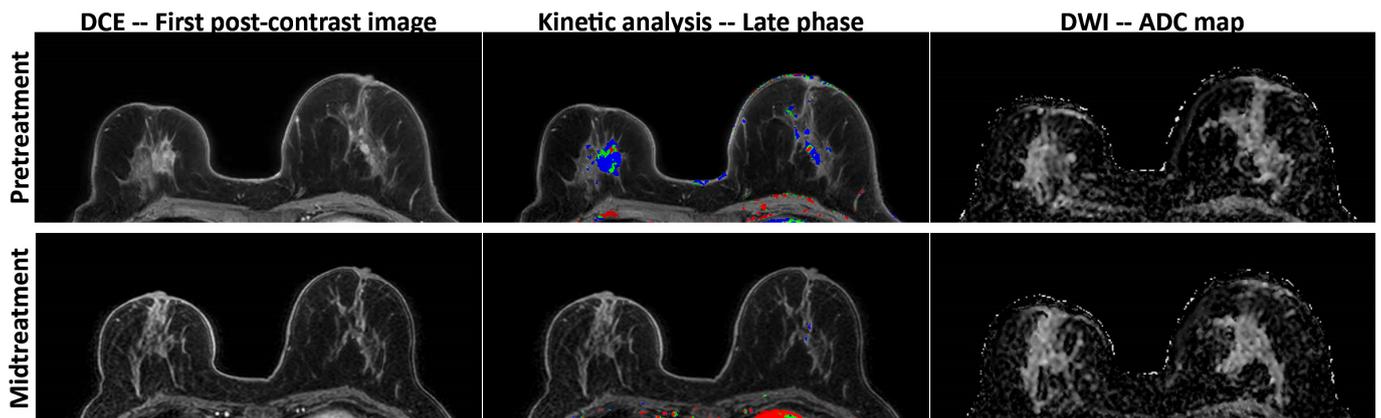


Figure 6. The images of a 71-year-old patient with a bilateral tumor. The right breast showed a T2N0 ILC (Grade: 2, ER: 100%, PR: 5%), and the left breast showed a DCIS (TisN0). The kinetic analysis showed some plateau and wash-out sections in both lesions. Diffusion restriction in the right lesion was noted. After 3 months of AI, the right lesion (ILC) showed no enhancement on the DCE and no diffusion restriction. The left lesion decreased in size, however, some sections of the lesion still showed cumulative enhancement on the kinetic analysis (shown in blue). The right lesion was considered a radiologic complete response (no pathological enhancement). However, at histological evaluation an invasive component of 25 mm was found in the surgical specimen. The lesion was assigned a PEPI-2/3 (poor prognosis). The left lesion was considered a partial responder after 3 months of NET, and was assigned a PEPI-1 (good prognosis) at histological evaluation (based on pathological complete response). ADC, apparent diffusion coefficient; AI, aromatase inhibitor; DCE, dynamic contrast-enhanced, DWI, diffusion-weighted imaging; DCIS, ductal carcinoma *in situ*; ER, estrogen receptor; ILC, invasive lobular carcinoma, PR, progesterone receptor; PEPI, preoperative endocrine prognostic index.



reasons (e.g. strong ER+ tumors vs excess comorbidity). Additionally, there are no guidelines for response evaluation during NET: the patient cohort might be the result of selection bias, where difficult to image tumors were evaluated with MRI as opposed to ultrasound. This could also explain the large inter-rater variability. Thirdly, differences in tumor response and change in BPE exist between AI and tamoxifen,<sup>1,19</sup> however, due to small sample size we could not further stratify the patient cohort into different treatment groups. Lastly, tumor ADC at DWI was reported to be associated with tumor response after NAC and survival in general,<sup>6,24</sup> however, due to the different *b*-value pairs used during the midtreatment imaging resulting in variability of ADC measurements,<sup>25,26</sup> we could not perform a quantitative ADC analysis. The results should be interpreted with this perspective in mind and should certainly be validated in a larger cohort.

In conclusion, larger reduction of tumor size after three months of NET was significantly associated with PEPI-1 (good prognosis) at histopathological evaluation. No other investigated breast MRI characteristics were associated with PEPI. Response monitoring based only on change in tumor size should, however, be done with care, because tumor size also decreased on average in patients with PEPI-2/3 (poor prognosis). Particularly, in the case of an ILC, multifocal tumor or non-mass enhancement, size measurements on MRI suffers from inter-rater variability. MRI characteristics previously reported to be associated with prognosis after NAC in literature were not associated with prognosis after NET in the current study. Radiologists must be aware that response evaluation on MRI differ between NET and NAC.

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