


# Hybrid $^{18}\text{F}$ -FDG PET/MRI might improve locoregional staging of breast cancer patients prior to neoadjuvant chemotherapy

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## Abstract

**Purpose** Our purpose in this study was to assess the added clinical value of hybrid  $^{18}\text{F}$ -FDG-PET/MRI compared to conventional imaging for locoregional staging in breast cancer patients undergoing neoadjuvant chemotherapy (NAC).

**Methods** In this prospective study, primary invasive cT2-4 N0 or cT1-4 N+ breast cancer patients undergoing NAC were included. A PET/MRI breast protocol was performed before treatment. MR images were evaluated by a breast radiologist, blinded for PET images. PET images were evaluated by a nuclear physician. Afterwards, a combined PET/MRI report was written. PET/MRI staging was compared to conventional imaging, i.e., mammography, ultrasound and MRI. The proportion of patients with a modified treatment plan based on PET/MRI findings was analyzed.

**Results** A total of 40 patients was included. PET/MRI was of added clinical value in 20.0% (8/40) of patients, changing the treatment plan in 10% and confirming the malignancy of suspicious lesions on MRI in another 10%. In seven (17.5%) patients radiotherapy fields were extended because of additional or affirmative PET/MRI findings being lymph node metastases ( $n = 5$ ) and sternal bone metastases ( $n = 2$ ). In one (2.5%) patient radiotherapy fields were reduced because of fewer lymph node metastases on PET/MRI compared to conventional imaging. Interestingly, all treatment changes were based on differences in number of lymph nodes suspicious for metastasis or number of distant metastasis, whereas differences in intramammary tumor extent were not observed.

**Conclusion** Prior to NAC, PET/MRI shows promising results for locoregional staging compared to conventional imaging, changing the treatment plan in 10% of patients and potentially replacing PET/CT or tissue sampling in another 10% of patients.

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**Keywords** Breast cancer · PET/MRI · Neoadjuvant chemotherapy · Locoregional staging

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## Introduction

Accurate locoregional staging prior to neoadjuvant chemo- and immunotherapy (NAC) in breast cancer patients is important to determine prognosis and to define an individual surgical and radiotherapy treatment plan after NAC. Standard staging imaging at breast cancer diagnosis is performed with full-field digital mammography (FFDM) and ultrasound (US). In a neoadjuvant setting, various international guidelines recommend

magnetic resonance imaging (MRI) to monitor response to treatment [1–3].

Locoregional staging prior to NAC (pre-NAC) remains challenging. Primary tumor diameter often differs between imaging modalities. Studies have proven MRI to be the most accurate modality for measuring tumor extent, particularly in a neoadjuvant setting [3–6]. The number and location of lymph node metastases, which are important indicators for clinical decision-making and determining locoregional recurrence (LRR) risk, cannot be assessed adequately prior to NAC. Schipper et al. have shown that US cannot accurately assess the number of lymph node metastases, with a reported NPV of just 50% to differentiate between one and three and four or more axillary lymph node metastases [7].

Previous studies have shown fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) positron emission tomography (PET)/ computed tomography (CT) is of added value in nodal staging [8–15]. PET/CT shows lymph node metastases in the internal mammary chain (IMC) and periclavicular area that are not detected on conventional imaging. The number of axillary lymph nodes suspicious for metastases is often higher on PET/CT compared to conventional imaging [8–11]. The specificity of PET/CT for axillary lymph node metastases is around 96%, compared to about 78% on US and breast MRI [16–18].

Since MRI is most suitable for soft tissue imaging, like breast and possible lymph node morphology, and PET has the advantage of showing increased metabolic uptake in lymph node (and distant) metastases, a combined approach in the form of hybrid PET/MRI may potentially provide improved locoregional breast cancer staging. With this complementary diagnostic information, both breast and nodal status could be determined more accurately prior to NAC within a single scan.

The purpose of this study was to assess the added clinical value of hybrid  $^{18}\text{F}$ -FDG PET/MRI (PET/MRI) compared to conventional imaging (i.e. FFDM, US and MRI) for locoregional staging prior to NAC in breast cancer patients.

## Materials and methods

### Patient selection and study design

This prospective single center study was approved by the institutional review board. Informed consent was waived by the institutional review board. Women with biopsy-proven primary invasive breast cancer with a tumor larger than 2 cm (cT2-4 N0) and/or a

pathologically confirmed lymph node metastasis (cT1-4 N+) undergoing NAC between February 2015 and June 2016 were consecutively considered for inclusion [19]. Exclusion criteria were pregnancy, presence of distant metastases at diagnosis or contra-indications for PET/MR imaging (such as known allergies for the contrast agents used or severe claustrophobia).

Conventional pre-NAC imaging consisted of FFDM and US of the suspicious breast lesion(s) and ipsilateral axilla. Breast cancer diagnosis and initial cTNM-classification were based on conventional imaging combined with pathology of pre-treatment core needle biopsies. If suspicious axillary lymph nodes were visualized, US-guided core needle biopsy of the most suspicious lymph node was performed. Reports of all conventional imaging exams and pathology reports were written in accordance with the Dutch Breast Cancer Guidelines [3].

After the decision to start NAC by a multidisciplinary tumor board in a newly diagnosed breast cancer patient, a PET/MRI breast protocol was performed prior to treatment initiation. Results concerning clinical tumor status (cN) and clinical nodal status and metastatic status (cN) on PET/MRI were compared to cT and cN status based on FFDM, US and MRI (the MR images made with PET/MRI were first interpreted separately, blinded for PET images). The percentage of patients with a modified treatment plan based on PET/MRI findings was analyzed.

### Hybrid $^{18}\text{F}$ -FDG PET/MRI protocol

Blood glucose levels had to be <10 mmol/l after a fasting period of at least 4 h. All PET/MR images were obtained after intravenous injection of a bodyweight adapted  $^{18}\text{F}$ -FDG dose (2 MBq/kg bodyweight) followed by a resting period of 45–60 min. All scans were performed from diaphragm to top of the humeral head on the same 3.0 T Biograph mMR integrated PET/MRI system (Siemens Healthcare, Erlangen, Germany) using a dedicated bilateral 16-channel breast radiofrequency coil (Rapid Biomedical, Rimpf, Germany) while patients were placed in a prone position and with both arms above their head.

The MR imaging protocol consisted of a two-dimensional T2-weighted turbo spin-echo sequence without fat suppression, a diffusion weighted imaging (DWI) sequence with fat suppression and a dynamic contrast enhanced T1-weighted sequence with fat suppression. As contrast agent, Gadobutrol (Gadovist®, Bayer Health Care, Germany) was used. It was automatically injected through a catheter in the antecubital vein

at a 0.1 mmol/kg bodyweight, followed by a saline flush.

Parameters used for T2-weighted imaging consisted of a 340 mm field of view (FOV), a voxel size of  $0.9 \times 0.8 \times 3.0$  mm, 46 slices, 6410 milliseconds repetition time (TR), 83 milliseconds echo time (TE), 5 min 28 s acquisition time, turbo factor 11 and 80 degrees flip angle in transverse plane. For DWI a 320 mm FOV, voxel size of  $1.7 \times 1.7 \times 4.0$  mm and 24 slices were used and b-values 50, 400, 800 and  $1000 \text{ s/mm}^2$  were acquired. For T1-weighted imaging, a 340 mm FOV,  $0.9 \times 0.9 \times 1.2$  mm voxel size, 128 slices, 10 degrees flip angle, 4.77 milliseconds TR, 1.78 milliseconds TE and 9.02 min acquisition time for a normal size breast were used. Magnetic resonance images were assessed by a dedicated breast radiologist with seven years of experience, blinded for PET results, using the descriptors of the American College of Radiology MRI BI-RADS lexicon [20].

The PET scanner has an axial FOV of 258 mm. All PET images were iteratively reconstructed and automatically attenuation corrected with the implemented 4-compartment model attenuation map ( $\mu$ -map). All PET images (one bed position) were acquired within 11 min of the initial activity measurement. PET images were evaluated by a dedicated nuclear medicine physician with four years of experience. A lesion was characterized as malignant if it showed a focally increased FDG uptake compared to the surrounding breast tissue. After initial separate assessment, both imaging specialists performed a consensus reading of both PET and MRI images and a combined conclusion was drawn.

### Imaging analysis and staging

To determine clinical tumor (cT) stage on conventional imaging, number of breast lesions (unifocal or multifocal) and size (largest diameter of the largest malignant breast lesion in one view) were measured on FFDM and US. For clinical nodal (cN), staging number and location of suspicious lymph nodes were determined on US. Characteristics of a suspicious axillary lymph node on US included diffuse cortical thickening, focal cortical mass and/or thickening and loss of the fatty hilum [21].

To determine cT-stage on MRI, also a number of breast lesions and tumor size were assessed on MRI. To determine size on MRI, the largest diameter of the largest breast lesion proven to be malignant was measured on the T1-weighted MRI sequence at peak enhancement (i.e., first dynamic phase after contrast injection) in one view. For determining cN-stage, number

and location of suspicious lymph nodes were assessed on MRI. The following criteria were considered suspicious: irregular margins, inhomogeneous cortex, perifocal edema, absent fatty hilum, asymmetry, and absence of chemical shift artifacts [22–24].

To determine cT-stage on PET/MRI, the diameter of the tumor was measured on MRI, as described above, as diameters are not clinically measured on PET. Therefore, tumor size was always the same on MRI and PET/MRI. Yet, uni- or multifocality was determined on both modalities (pathologically proven malignant hotspot on PET or pathologically proven suspicious lesion on MRI). For determining cN-stage, number and location of suspicious lymph nodes were assessed on both modalities. A lymph node was characterized as malignant on PET if an abnormal focal FDG accumulation was present in combination with high visual uptake intensity (VUI) compared to background tissue, as recommended by the European Association of Nuclear Medicine [17, 25].

If any distant metastasis was detected in the FOV of any imaging modality (a lesion outside the breast tissue and lymph nodes like a bone or lung) and also proven PET positive and/or pathologically confirmed malignant, patients were considered M1, if not they were considered M0.

### Treatment

Neoadjuvant chemotherapy generally consisted of four cycles of 3-weekly doxorubicin and cyclofosamide, followed by four cycles of 3-weekly docetaxel in case of an ER+ and/or HER2 overexpressed tumor, or 12 cycles of weekly paclitaxel in case of a triple negative tumor. In patients with HER2 overexpressed tumors, trastuzumab was added. After NAC, breast conserving surgery (BCS) or mastectomy and surgery of the ipsilateral axilla (sentinel lymph node biopsy in case of N0 and axillary lymph node dissection in case of N+) was performed. Postoperative radiotherapy of the breast was always performed after BCS. Chest wall and periclavicular irradiation were performed when patients had a cN1 ( $\geq 4$  suspicious nodes), cT1-2ypN+, c/ypT3N+, c/ypT4 or c/ypN2–3 status. Solitary chest wall irradiation was performed in case of irradical breast surgery. The internal mammary chain (IMC) was irradiated in case of a PET-positive or a pathologically proven tumor-positive lymph node in IMC.

**Table 1** Baseline characteristics

Median age in years [range]		50 [32–69]
Grade	1	4 (10.0%)
	2	19 (47.5%)
	3	16 (40.0%)
	Unknown	1 (2.5%)
Subtype	HER2+	12 (30.0%)
	ER/PR+, HER2-	19 (47.5%)
	Triple negative	9 (22.5%)
Histology	Invasive carcinoma NST	38 (95.0%)
	Invasive lobular carcinoma	2 (5.0%)

ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor, NST = no special type

**Results**

A total of 40 women with primary invasive breast cancer treated with NAC were consecutively included. One patient had to be excluded because she did not fit into the scanner due to her size. All PET/MR images were acquired before initiation of NAC and 4–28 days (median 10 days) after primary diagnostic conventional imaging and biopsy procedures. Baseline characteristics are shown in Table 1. In eight out of 40 patients (20%, of which two distant metastases) PET/MRI was of added clinical value. In four out of 40 patients clinically relevant lesions (one distant metastasis) found on PET/MRI, but not on MRI or conventional imaging, lead to treatment plan changes (Table 2 and Appendix Table 3). In

another four out of 40 patients PET/MRI confirmed malignancy of suspicious lesions on MRI (one distant metastasis), thereby potentially replacing PET/CT or tissue sampling.

**cT-stage: Breast tumor size and focality**

On conventional imaging, mean tumor size was 33 mm and one patient had a multifocal tumor. After MR imaging, four patients had a multifocal tumor (all pathologically proven) and mean tumor size on MRI was 37 mm. Hybrid PET/MRI did not find additional multifocal tumors meaning that clinical tumor stage, based on the size of the primary tumor measured only on MRI (not on PET) and number of breast lesions (multifocality, measured on both MRI and PET), did not differ from MRI alone (Table 2 and Appendix Table 3). Hence, PET/MRI did not provide diagnostic advantages compared to MRI alone for breast tumor staging, nor did it result in treatment plan changes.

**cN-stage: Number and location of suspicious lymph nodes**

According to conventional imaging, 12 out of 40 patients were considered cN0 and 28 patients cN+. In six out of 40 patients, lymph node status changed based on PET/MRI findings. In these six patients number and location of lymph node hotspots on PET, combined with their morphology on MRI, resulted in confirmation of diagnosis and change in treatment plan.

**Table 2** Locoregional cTNM staging with number of suspicious axillary lymph nodes (0, ≤3, >3) based on conventional imaging and changes due to PET/MRI

cTN(# of suspicious axillary lymph nodes)M			
No. of patients per stage based on FFDM, US and MRI		No. patients with stage changes based on PET/MRI	
2	cT1N1(≤3)Mx		
2	cT1N1(>3)Mx	1	cT1N1(≤3)
10	cT2N0(0)Mx	2	cT2N0(0)M1*, cT2N2b(0)Mx
5	cT2N1(≤3)Mx	1	cT2N1(>3)Mx
7	cT2N1(>3)Mx	1	cT2N3bMx
1	cT2N3b(>3)Mx		
4	cT3N0(0)Mx	1	cT3N2b(0)Mx
3	cT3N1(≤3)Mx		
5	cT3N1(>3)Mx	2	cT3N3b(>3)Mx, cT3N3c(>3)M1*
1	cT4N0(0)Mx		
<b>Total</b>	<b>40</b>	<b>8</b>	

\*Sternal bone metastasis

In three patients, MRI showed an enlarged IMC node. PET/MRI confirmed malignancy of this node by showing focally enhanced FDG-uptake in the IMC node in these patients, making additional PET/CT imaging or tissue sampling superfluous. In another patient a suspicious IMC node with focally enhanced FDG-uptake was seen. No suspicious IMC node was described on MRI at first. The final combination of PET information with MRI morphology completed diagnosis and changed the treatment plan. In all four patients the IMC was incorporated in the radiotherapy field.

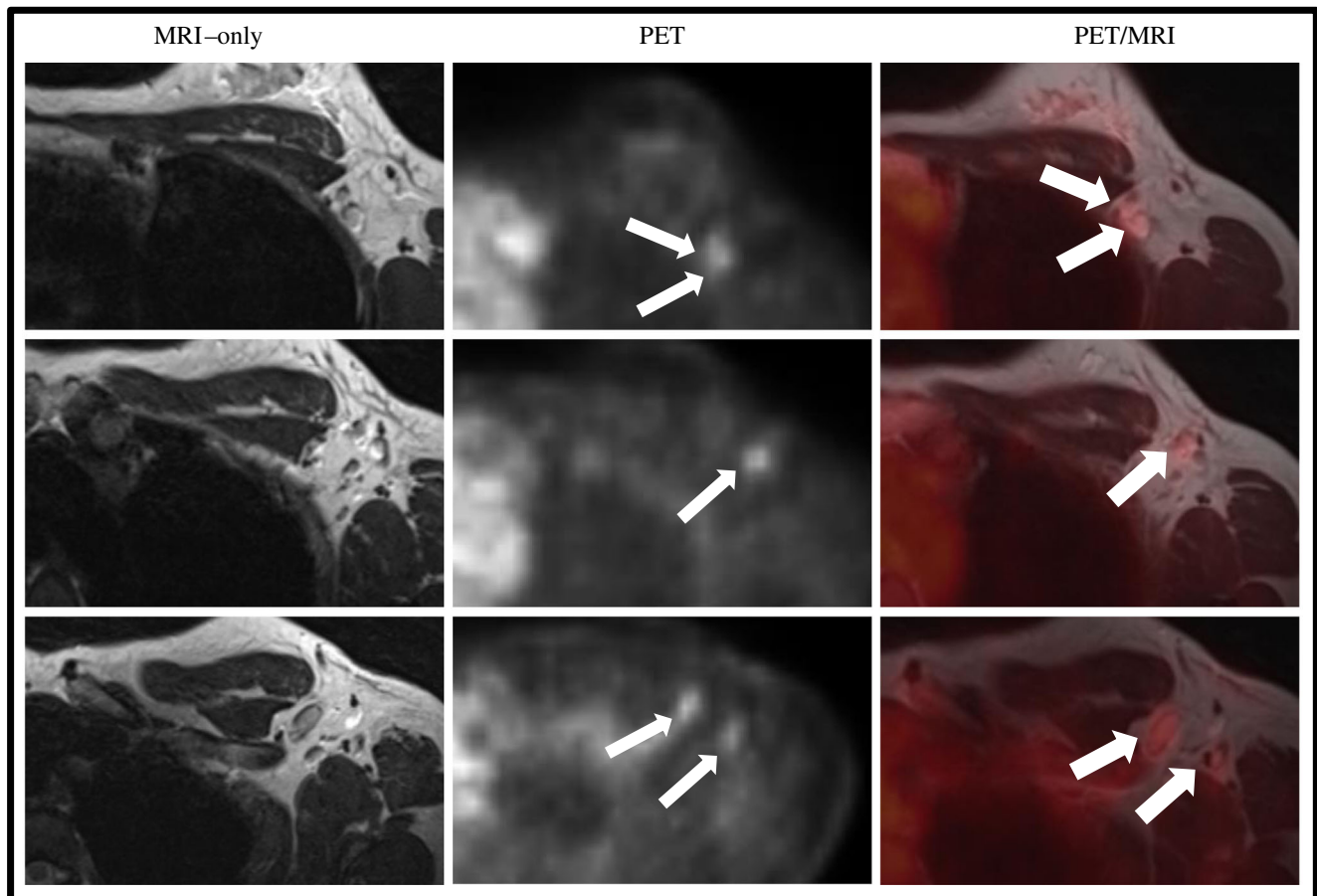
One patient had five axillary FDG hotspots suspicious for lymph node metastases on PET/MRI, whereas initially only two were seen on US (of which one was proven to be malignant by tissue sampling) and no lymph nodes suspicious for metastases were described on MRI alone. Combining PET information with MRI, all five lymph nodes were marked as suspicious for metastases. As a consequence, chest wall and

periclavicular area were added to the radiotherapy field. Image examples are shown in Fig. 1.

One patient had three axillary lymph nodes suspicious for metastases on PET/MRI compared to more than three on US and MRI. Final clinical decision by the multidisciplinary tumor board was to consider three lymph nodes to be suspicious for metastases. The chest wall and periclavicular area were, therefore, excluded from the radiotherapy field. Images are shown in Fig. 2.

#### Additional findings – Distant metastases

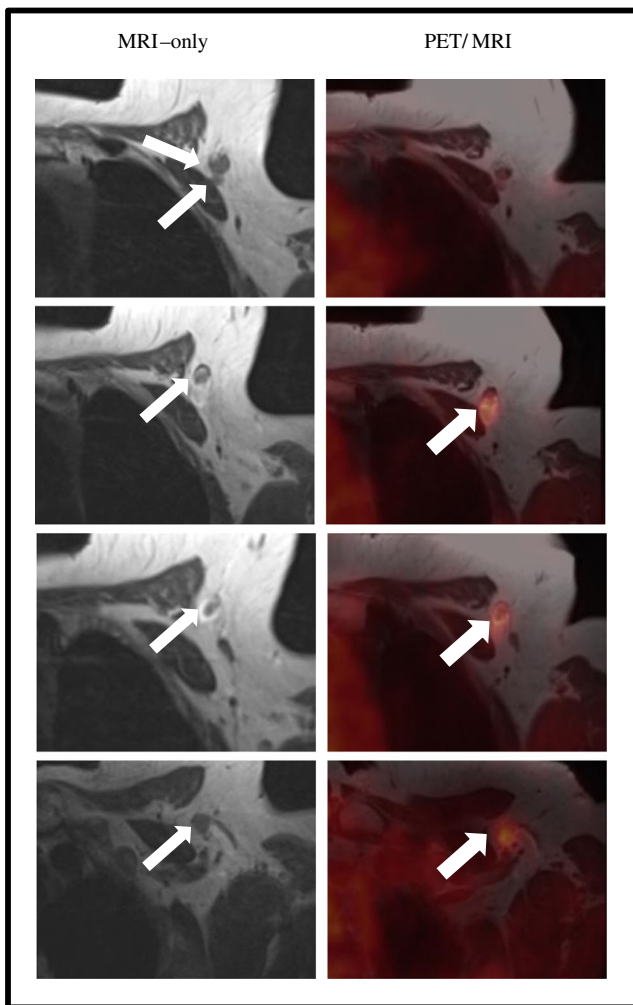
PET/MRI confirmed and changed metastatic status in two patients. In both cases a sternal bone metastasis was found. In one patient a sternal bone abnormality was detected by the radiologist on MRI. PET/MRI confirmed malignancy by showing focally enhanced FDG-uptake of this bone abnormality, making additional PET/



**Fig. 1** Images of a patient with no lymph nodes suspicious for metastases on MRI (T2w sequence is shown in the left column) and five axillary FDG hotspots suspicious for lymph node metastases on PET (small

arrows, middle column). Adding PET information to MRI, resulted in five lymph nodes marked as suspicious for metastases (big arrows, right column)





**Fig. 2** Images of a patient with three axillary lymph nodes suspicious for metastases on PET/MRI (big arrows, right column) compared to five on MRI-only (small arrows, left column). Combining PET information with MRI, resulted in three lymph nodes marked as suspicious for metastases

CT imaging or tissue sampling superfluous. In the other patient the bone lesion was not described in the MRI report at first. In both cases a hotspot on PET combined with morphologic information on MRI completed diagnosis. In retrospect, the bone metastasis of the second patient was visible as a subtle abnormality on T2-weighted MR images. In both patients the treatment plan was adjusted. In both cases a whole body PET/CT was acquired consecutively and did not show other distant metastases. Both patients are being treated curatively (oligometastatic breast cancer), and the sternal bone will be additionally irradiated.

## Discussion

Accurate pre-NAC staging in breast cancer patients is important as it reflects prognosis and determines treatment plan after NAC. This study demonstrated the added clinical value of hybrid PET/MRI compared to conventional imaging and MRI for locoregional staging prior to NAC in breast cancer patients. For tumor staging, PET/MRI was not of added value compared to MRI alone. However, in 10% of patients PET/MRI detected nodal or distant metastases, which were not detected on MRI or conventional imaging modalities. In another 10% it confirmed malignancy of lesions characterized as probably malignant on MRI, making additional PET/CT imaging or tissue sampling redundant. The treatment plan was adjusted in all these patients.

Considering cT-stage, a recent study by Grueneisen et al. found that both PET/MRI and MRI enable better determination of breast tumor extent in comparison to PET/CT [26]. Similar to our results, PET/MRI did not provide diagnostic advantages for breast tumor staging compared to MRI alone. These results underline the importance of breast MRI for primary tumor staging of breast cancer patients.

Regarding cN-stage, Grueneisen et al. looked at axillary lymph node involvement. PET/MRI, MRI and PET/CT allowed for a correct positive or negative axillary nodal status in 86%, 80% and 88%, respectively ( $p > 0,05$ ) [26]. Similar to our results, PET shows best results for axillary lymph node staging. On the contrary, Taneja and colleagues showed a lower sensitivity on PET (60%) than on MRI (93.3%) for detection of axillary lymph nodes with PET/MRI [27]. A possible explanation for the lower PET detection rate is that PET/MRI scans in the study of Taneja might have been made during NAC treatment (this was not specified). Since previous research demonstrated that PET shows response to NAC treatment earlier than MRI [28], a PET/MRI scan made during NAC treatment might no longer show lymph node metastases on PET, due to early metabolic response, while remaining suspicious on MRI.

Next to differentiating between a positive or negative axillary nodal status, our study showed the importance of evaluating the exact number of positive axillary lymph nodes and the involvement of extra-axillary lymph nodes (IMC and periclavicular area) with PET/MRI. The pre-NAC presence of lymph nodes suspicious for metastases in the IMC, axilla (>3 tumor-positive

nodes) or periclavicular area are important determinants for the extent of radiotherapy fields and for risk of LRR. This cannot be accurately determined pre-NAC with conventional staging techniques, as described by Schipper et al. [7], or in post-NAC surgery specimens due to pre-treatment.

This study suggests that approximately 1 in 13 patients treated with NAC may harbor undetected lymph node metastases (including axillary, periclavicular and IMC nodes) when they do not undergo a pre-NAC PET/(MRI) scan. Patients with undetected lymph nodes in the IMC or periclavicular area treated with conventional tangential fields in case of BCS, only receive low scatter doses in these areas, leaving these nodes (partially) untreated.

Extended nodal US imaging could be considered an alternative to PET/MRI. However, US imaging of the IMC is labor-intensive, operator dependent and no hard evidence favoring it can be found in the literature [11, 29]. Furthermore, research has shown US is not suited to differentiate between  $>3$  or  $\leq 3$  axillary tumor-positive axillary nodes and that it is body composition dependent [7]. Finally, PET/MRI can show focally enhanced FDG uptake in morphologically normal lymph nodes. PET/MRI may, therefore, be superior for locoregional N-staging, potentially changing prognosis and treatment plan.

Finally, all included patients were M0 at diagnosis. Our results suggest that 2/40 patients treated with NAC have sternal bone metastases, of which 1/40 would remain undetected when they do not undergo a pre-NAC PET/(MRI) scan. Studies from the 1980's indicate that 1.9–2.4% of breast cancer patients have solitary sternal bone metastases, compared to 5% in our study [30, 31]. The latter might be higher due to the higher risk population with patients receiving NAC in our study. Nevertheless, similar to the undetected lymph node metastases, these sternal bone metastases will only receive low radiotherapy scatter doses in case of BCS or chest wall irradiation, leaving them (partially) untreated.

Since current guidelines advise additional PET/(CT) imaging or tissue sampling for suspicious lymph/metastatic nodes on MRI or conventional imaging, PET/MRI functioned as a diagnostic confirmation tool instead of PET/CT or tissue sampling in 10% of our patients. For example, all IMC nodes were also visible on MRI (one in retrospect). Future research focusing on the MRI characteristics determining malignancy of metastatic (IMC) nodes may replace PET imaging or tissue

sampling. The value of IMC radiation in terms of breast cancer recurrence and (cardio)toxicity remains debatable. As Aukema et al. suggested, a patient-tailored radiotherapy field around the PET-positive node instead of the whole IMC might be a solution in the future.

One of the limitations of our prospective study is its small sample size. If selection bias occurred, our small sample size may over- or underestimate the magnitude of the added value of PET/MRI for locoregional staging prior to NAC. Since patients were included consecutively, risk for selection bias was minimized. Furthermore, as patients in this study were treated with NAC, axillary surgery was performed after neoadjuvant treatment. A pathologist cannot reliably determine the pre-NAC number of lymph node metastases in a post-NAC surgical sample [32]. We do know that PET specificity for axillary lymph nodes is 94% [17]. Therefore, it is safe to assume that the PET-positive nodes were tumor-positive and patients were correctly upstaged [11].

In conclusion, pre-NAC hybrid PET/MRI shows promising results for locoregional breast cancer staging when compared to FFDM, US and MRI alone. For staging the primary tumor, PET/MRI is equally as good as MRI. For locoregional N and M-staging, PET/MRI is of added clinical value, detecting nodal and distant metastases not detected as such on MRI or conventional imaging modalities and thereby changing the treatment plan in 10% of patients. In another 10% of patients, PET/MRI made additional PET/CT imaging or tissue sampling superfluous by confirming malignancy of suspicious lesions on MRI.

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#### Compliance with ethical standards

**Funding** This study was funded by an academic incentive from the Maastricht University Medical Center + .

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

**Informed consent** Informed consent was waived by the institutional research committee.

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## Appendix

**Table 3** Locoregional cTNM staging with tumor size and number of suspicious lymph nodes per imaging modality and changes due to PET/MRI staging

Patient	cT(size index tumor in mm)N(# of suspicious axillary lymph nodes)M		
	FFDM and US	MRI	Changes based on PET/MRI
1	cT2(50)N0(0)Mx	cT3(59)N0(0)Mx	
2	cT2(31)N1(1)Mx	cT3(53)N1(1)Mx	
3	cT2(25)N0(0)Mx	cT1(19)N0(0)Mx <sup>1</sup>	cT2N0M1
4	cT2(24)N1(1)Mx <sup>2</sup>	cT2(25)N0(0)Mx	
5	cT1m(13)N1(4)Mx <sup>3</sup>	cT1(13)N1(>4)Mx	
6	cT2m(42)N1(6)Mx	cT3m(70)N1(>4)Mx	
7	cT2(45)N0(0)Mx	cT3(72)N0(0)Mx	
8	cT3(63)N0(0)Mx	cT2(48)N0(0)Mx <sup>4</sup>	cT2N2bMx
9	cT ≥ 1 (20)N1(1)Mx <sup>5</sup>	cT3(68)N1(1)Mx	
10	cT2(38)N1(4)Mx	cT3(60)N1(3)Mx	cT3N3b(>3)Mx
11	cT2(28)N1(5)Mx	cT2(25)N1(4)Mx	
12	cT1(18)N1(2)Mx	cT2(27)N1(4)Mx	
13	cT2(30)N1(1)Mx	cT2(38)N1(1)Mx	
14	cT1(19)N1(4)Mx	cT1(17)N1(5)Mx	cT1N1(≤3)Mx
15	cT2(28)N0(0)Mx	cT2(24)N0(0)Mx	
16	cT ≥ 1(n.m.)N1(1)Mx	cT2m(37)N0(0)Mx	cT2mN1(>3)Mx
17	cT2(24)N0(0)Mx	cT2(27)N0(0)Mx	
18	cT2(22)N1(1)Mx	cT2(27)N1(1)Mx	
19	cT2(23)N0(0)Mx	cT1(18)N0(0)Mx	
20	cT2(22)N0(0)Mx	cT2(31)N0(0)Mx	
21	cT2(32)N0(0)Mx	cT2(29)N0(0)Mx	
22	cT3(78)N1(5)Mx	cT3(60)N1(5)Mx	
23	cT2(26)N1(1)Mx <sup>2</sup>	cT2m(22)N1(1)Mx	
24	cT3(58)N0(0)Mx	cT2(36)N0(0)Mx	
25	cT2(21)N1(2)Mx	cT1(15)N1(2)Mx	
26	cT3(60)N1(6)Mx	cT2(44)N0(0)Mx	
27	cT2(46)N1(1)Mx <sup>2</sup>	cT2(44)N1(1)Mx <sup>2,4</sup>	cT2N2b(0)Mx
28	cT1(16)N1(1)Mx	cT1(15)N1(1)Mx	
29	cT2(41)N0(0)Mx	cT3(58)N0(0)Mx	
30	cT2(29)N0(0)Mx	cT2(46)N1(1)Mx	
31	cT1(16)N1(2)Mx	cT2(45)N1(6)Mx	
32	cT3(59)N1(6)Mx	cT3(55)N1(5)Mx	cT3N3c(>3)M1
33	cT1m(20)N1(1)Mx	cT2(26)N1(1)Mx	
34	cT1(15)N1(≥2)Mx	cT2(25)N1(9)Mx	
35	cT2(30)N1(6)Mx	cT2(41)N3a(10)Mx	
36	cT2(30)N1(6)Mx	cT2(31)N1(6)Mx <sup>4</sup>	cT2N3b(>3)Mx
37	cT3(75)N1(1)Mx	cT3(60)N1(1)Mx	
38	cT1(18)N1(5)Mx	cT2(32)N1(6)Mx	
39	cT2(35)N3b(4)Mx	cT2(35)N3b(7)	
40	cT1(10)N1(1)Mx	cT1m(13)N1(1)Mx	

n.m. = not measurable

<sup>1</sup> Suspicious sternal node, <sup>2</sup> Lymph node biopsy negative, <sup>3</sup> Biopsy second lesion negative, <sup>4</sup> suspicious node internal mammary chain, <sup>5</sup> difficult to measure, at least 20 mm



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