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Determining the axillary nodal status with four current imaging modalities including ^{18}F-FDG PET/MRI in newly diagnosed breast cancer: A comparative study using histopathology as reference standard

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Abbreviations

^{18}F-FDG	^{18} F-fluorodeoxyglucose
AUC	Area under the Curve
CI	Confidence Interval
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
ROC	Receiver operating characteristics
SUV	Standardized uptake value

Abstract

Purpose: To compare breast magnetic resonance imaging (MRI), thoracal MRI, thoracal ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/MRI and axillary sonography for the detection of axillary lymph node metastases in women with newly diagnosed breast cancer.

Materials and Methods: This prospective double-center study included patients with newly diagnosed breast cancer between March 2018 and December 2019. Patients underwent thoracal (^{18}F-FDG PET/)MRI, axillary sonography, and dedicated prone breast MRI. Datasets were evaluated separately regarding nodal status (nodal^{+} vs. nodal^{-}). Histopathology served as reference standard in all patients. The diagnostic performance of breast MRI, thoracal MRI, thoracal PET/MRI and axillary sonography in detecting nodal positive patients was tested by creating receiver-operating-characteristic curves (ROC) with a calculated area under the curve (AUC). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were calculated for all four modalities. A McNemar test was used to assess differences.

Results: 112 female patients (mean age 53.04 ± 12.6 years) were evaluated. Thoracal PET/MRI showed the highest ROC-AUC with a value of 0.892. The AUC for breast MRI, thoracal MRI and sonography were 0.782, 0.814 and 0.834, respectively. Differences between thoracal PET/MRI and axillary sonography, thoracal MRI and breast MRI were statistically significant (PET/MRI vs. axillary sonography, p=0.01; PET/MRI vs. thoracal MRI, p=0.02; PET/MRI vs. breast MRI, p=0.03). PET/MRI showed the highest sensitivity (81.8%, 36/44) (95%-CI: 67.29-91.81%) while axillary sonography had the highest specificity (98.5%, 65/66), 95%-CI: 91.84-99.96%).

Conclusion: ^{18}F-FDG PET/MRI outperforms axillary sonography, breast MRI and thoracal MRI in determining the axillary lymph node status. In a clinical setting, the combination of ^{18}F-FDG PET/MRI and axillary sonography might be considered to provide even more accuracy in diagnosis.

Key words: breast cancer; axillary lymph node metastasis; PET/MRI; oncological imaging

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, representing about 25% of all cancers in women (*1*). Initial treatment strategies and patients' prognosis are fundamentally based on tumor biology and tumor stage. Typically, the axillary lymph nodes are the first site of nodal metastatic disease in invasive breast cancer (*2*). The ability to distinguish between nodal positive and nodal negative status in both, pre- and posttherapeutic situations is crucial to provide an appropriate and individualized therapeutic concept for the axilla and to determine prognosis (*3*). So far, sentinel lymph node biopsy or sentinel lymph node excision were regarded as the gold standard for axillary staging in early breast cancer (*4*), but different surgical axillary procedures like targeted lymph node excision or targeted axilla dissection have been proposed as favorable alternatives to deescalate invasive procedures like axillary dissection (*5*). However, these invasive procedures can cause morbidity such as infection, hematoma and patients´ discomfort. At the time of initial diagnosis, about 25-40% of early breast cancer stages show axillary nodal metastatic disease (*6,7*), which means that for about 60-75% of the patients with early stage breast cancer any kind of axillary intervention represents overtreatment. Therefore, a non-invasive imaging method for discriminating between nodal positive and nodal negative axillary status is desirable to avoid unnecessary biopsies prior to therapy and to facilitate therapy planning.

Different imaging modalities are available for the initial staging of breast cancer patients. Over the last years, breast magnetic resonance imaging (MRI), axillary sonography, and computed tomography (CT) have become well established in this regard (*8,9*). Yet, so far, no imaging modality has proven to be accurate enough to replace invasive procedures for determining the correct nodal status (*10,11*). While ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) -imaging can reliably display increased glycolytic activity of metastatic tissue, MRI offers high anatomic resolution and soft tissue contrast images. Hence, hybrid ^{18}F-FDG PET/MRI might serve as an excellent combined imaging modality for locoregional staging compared to conventional imaging such as ultrasound, breast MRI or CT (*12*).

The aim of our study was to compare thoracal ^{18}F-FDG PET/MRI, breast MRI, thoracal MRI, and axillary sonography with regard to their ability to determine the correct axillary nodal status in patients with primary breast cancer, using histopathology as the reference standard.

MATERIAL AND METHODS

Patients

The local ethics committees (study number 17-7396-BO and study number 6040R) approved this prospective, double-center study. All patients signed a written informed consent form prior to enrolment. Patients with newly diagnosed, therapy naive breast cancer with elevated risk for distant metastases between March 2018 and December 2019 were included in this study, fulfilling the following criteria: 1) newly diagnosed, treatment-naive T2-tumor or higher T-stage or 2) newly diagnosed, treatment-naive triple-negative tumor of every size or 3) newly diagnosed, treatment-naive tumor with molecular high risk (Ki67>14% or G3 or her2-overexpression). Contraindications to MRI or MRI contrast agents, breast-feeding or pregnancy or former malignancies in the last 5 years were exclusion criteria. 45 of the 112 patients were reported before (*13*). In contrast to the prior publication, we investigated further imaging modalities as breast MRI and sonography for axillary nodal staging instead of the comparison of MRI, PET/MRI and bone scintigraphy for N- and M-staging.

PET/MRI and breast MRI

All (^{18}F-FDG PET)/MRI examinations were performed in supine body position from head to mid-thigh on an integrated 3.0 Tesla PET/MRI scanner (Biograph mMR, Siemens Healthcare GmbH, Erlangen, Germany) about 60 minutes after intravenous injection of a body weight-adapted dose of ^{18}F-FDG (4 MBq/kg bodyweight). Patients fasted for 6 hours prior to examination and blood glucose levels were ensured to be below 150 mg/dl before ^{18}F-FDG was injected.

Just before the whole-body imaging was carried out, each patient underwent a dedicated breast MRI in head-first prone position on the same integrated 3.0 Tesla PET/MRI scanner. For imaging protocol details, see Kirchner *et al.* (*14*). Thoracal sections of whole-body (PET)/MRI were evaluated for axillary nodal status, hereinafter referred to as „^{18}F-FDG thoracal PET/MRI" and „thoracal MRI".

PET/MRI and MRI image analysis

Images were analysed independently and in random order by two experienced radiologists with extensive experience in hybrid imaging (J.M. and J.K.) as well as a nuclear medicine specialist (W.F.) using an OsiriX Workstation (Pixmeo SARL, Bernex, Switzerland) with a reading intermission of 4 weeks to avoid recognition bias. Discordant readings were resolved in collective consensus reading. In every patient and modality the axillary lymph node status was rated as either nodal positive or nodal negative. Morphologic features for the diagnosis of lymph node metastases MRI were: (a) short-axis diameter >10 mm, (b) irregular margin, (c) inhomogeneous cortex, (d) perifocal oedema, (e) absent fatty hilum, (f) asymmetry in comparison to contralateral site, (g) contrast media enhancement and (h) blurred nodal border (*15*). In PET/MRI, a tracer-uptake above the direct background and the surrounding lymph nodes was considered as a sign of malignancy. To measure SUVmax and SUVmean, a manually drawn region of interest was placed around the respective lymph node. Readers were blinded to patient identity, history and results of local and distant metastasis but aware of the diagnosis of breast cancer.

Axillary sonography

Axillary sonography was performed by a gynecologist with multiple years of experience in breast- and axillary ultrasound, each per centre. No regular second assessment was done by a second reader. An Acuson S2000 system (Siemens Healthcare GmbH, Erlangen, Germany), a SuperSonic Imagine Aixplorer (Toshiba Medical Systems GmbH, Neuss, Germany) and an Aplio

MX SSA-780A System (Toshiba Medical Systems GmbH, Neuss, Germany) each with a linear array transducer of 5 to 12 MHz were used. Lymph nodes were regarded as suspicious, mostly with indication for biopsy, when (a) cortical thickness was greater than 3 mm, (b) the cortex was lobulated or (c) the hilum was decreased or absent (*16,17*).

Reference standard

Histopathology served as reference standard in every patient and was used to evaluate the nodal status (nodal positive vs. nodal negative). If available, axilla dissection or sentinel lymph node biopsy prior to systemic therapy were used as reference standard. If no sufficient pretherapeutic sampling was available, sentinel lymph node excision or axilla dissection after neoadjuvant systemic therapy were used as surrogate reference standard. Herein, additional histological preparations were evaluated, using focal fibrosis or focal necrosis as an indirect indication for previously vital lymph node metastases (*18,19*).

Statistics

Statistical analysis was performed using SPSS Statistics 26 (IBM Corp., Chicago, IL, USA). A p-value <0.05 was considered as statistically significant. Data are presented as mean±standard deviation. The diagnostic performance of breast MRI, thoracal MRI, thoracal PET/MRI and axillary sonography in detecting nodal positive patients was tested by creating receiver-operating-characteristic (ROC) curves with a calculated area under the curve (AUC). A McNemar test was used to assess AUC differences between thoracal PET/MRI and axillary sonography, thoracal MRI and breast MRI and between axillary sonography and thoracal MRI, respectively. In addition, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated for breast MRI, thoracal MRI, thoracal PET/MRI and axillary sonography. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were defined as: Sensitivity - true positive/(true positive+false negative); Specificity - true negative/(true negative+false positive), positive predictive value - true positive/(true positive+false positive); negative predictive value – true negative/(true negative+false negative); Accuracy – (true negative+true positive) / (true negative+true positive+false negative+false positive) (*20*). To compare SUVmax values between false positive and correct positive lymph nodes in thoracal PET/MRI a student's t-test was used.

RESULTS

Patient population and Reference standard

A total of 112 women (mean age 53.04 ± 12.6 years) were prospectively included in this study (Fig. 1). For patient demographics and primary tumor characteristics see table 1. In every patient, a complete set of breast MRI, thoracal MRI and PET/MRI were available. Axillary sonography was available in a total of 108 patients. In all patients ^{18}F-FDG was used as tracer (mean activity 247.7 ± 53.52 MBq).

Based on the reference standard, 44 patients (39%) were nodal positive, while 68 (61%) patients were nodal negative. In 57 of 112 patients histological samples were taken before systemic therapy (31 axillary core-needle biopsies, 20 sentinel lymph node excisions, 6 axilla dissections), whereas 55 samples were taken right after neoadjuvant systemic therapy (50 sentinel lymph node excisions, 5 axilla dissections).

Diagnostic performance

Of all imaging modalities tested, thoracal PET/MRI showed the highest ROC-AUC with a value of 0.892 (95%-Confidence Interval (CI): 0.801-0.953) (Figure 2 and Table 2). The areas under the curve for breast MRI, thoracal MRI and axillary sonography were 0.782 (95%-CI: 0.674-0.871), 0.814 (95%-CI: 0.718-0.904) and 0.834 (95%-CI: 0.740 - 0.920), respectively.

We found that PET/MRI had the highest sensitivity (81.8% (36/44), 95%-CI: 67.29-91.81%), while breast MRI had the lowest sensitivity (61.4% (27/44), 95%-CI: 45.50-75.64%) of the four imaging modalities. On the other hand, axillary sonography had the highest specificity (98.5 % (65/66), 95%-CI: 91.84-99.96%), while breast MRI as well as thoracal PET/MRI had the lowest specificity (each 95.6% (65/68), 95%-CI: 87.64-99.08%). With 96.7% (29/30) (95%-CI: 80.39-99.51%) axillary sonography entailed the best positive predictive value, whereas breast MRI showed the weakest positive predictive value (90.0%, 27/30); 95%-CI: 74.37-96.54 %). Thoracal PET/MRI offered the best negative predictive value with 89.0 % (65/73) (95%-CI: 81.25-93.84%). Instead, breast MRI offered the weakest negative predictive value (79.3 %, 65/82) (95 %-CI: 72.42-84.77 %). Overall, thoracal PET/MRI showed the best diagnostic accuracy (90.18%, 101/112) (95%-CI: 83.11-94.99 %) (see Tables 3 and 4, for an example see Fig. 3 and Fig. 4). Differences between PET/MRI and axillary sonography (p=0.01), thoracal MRI (p=0.02) and breast MRI (p=0.03) were statistically significant, whereas differences between axillary sonography and thoracal MRI were non-significant (p=0.68).

According to the reference standard, 8/44 nodal-positive patients (18.2%) were missed in thoracal PET/MRI, these patients were rated false negative in the other three imaging modalities as well. Four of these patients received primarily operative therapy. Latency time between imaging and histopathological sampling was 39.25 ± 4.38 days in these 4 patients. The remaining 4 patients received neoadjuvant chemotherapy and latency time between imaging and start of chemotherapy was 18.25 ± 5.54 days.

Axillary sonography showed only one false positive rating and the highest specificity. This patient was rated false positive as well in breast MRI, thoracal MRI and thoracal PET/MRI (see Fig. 5). Thoracal PET/MRI showed 3 false positive ratings, in two of which the primary tumor had previously been marked by a clip. These false positive lymph nodes showed a significantly lower

SUVmax compared to correctly positive lymph nodes (3.73 ± 0.75, range 3.0 – 4.5 vs 6.31 ± 3.96, range 2.6 – 17.7, $p = 0.002$)

DISCUSSION

In this study, we compared four state-of-the-art imaging modalities regarding their diagnostic performance in determining the axillary nodal status of 112 patients with newly diagnosed breast cancer. The results indicate the superiority of thoracal ^{18}F-FDG PET/MRI in comparison to thoracal MRI, prone breast MRI, and axillary sonography. While ^{18}F-FDG PET/MRI offers the highest sensitivity, accuracy, and ROC-AUC for detecting locoregional lymph node metastases, axillary sonography is the imaging modality with the highest specificity.

Correctly identifying the nodal status is crucial in patients with newly diagnosed breast cancer, because it's a major factor for choosing the optimal treatment strategy (*21-24*). Until some years ago, complete axillary dissection was the standard for axillary staging and at the same time a procedure to achieve regional control (*25*). Since various studies have shown the equality of sentinel lymph node biopsy to axillary dissection for staging purposes, sentinel lymph node biopsy or equivalent procedures have evolved as the standard for patients with a clinically low-risk of axillary nodal metastases (*26-28*).

Our results are in line with other studies, as they underscore that breast MRI has a minor role in evaluating the axillary nodal status of breast cancer. This is mostly due to the limited field-of-view of breast MRI using dedicated breast coils that do not allow a complete assessment of the axillary region. Despite the introduction of more advanced MRI sequence protocols or lymph node specific contrast agents, so far, data have remained insufficient from a oncologic perspective (*29*).

Sonography comes with the advantage of low costs and wide accessibility, but the quality of the examination is depending on the skill and experience of the examiner. Our data yield a high specificity (98.5%) but limited negative predictive value (83.8%) of axillary ultrasound. This drawback of axillary ultrasound has also been described by Farrell *et al.*, who reported the high specificity of 100%, but the risk of underestimating the number of affected lymph nodes (*30*).

In our study, ^{18}F-FDG PET/MRI demonstrated the best diagnostic performance in detecting nodal positive patients compared to the other modalities (ROC-AUC of 0.892). Previous PET/MRI studies in primary breast cancer showed conflicting results regarding the nodal staging: while Botsikas *et al.* and Grueneisen *et al*. found an equal or superior diagnostic performance for MRI alone compared to PET/MRI (*31,32*), van Nijnatten *et al*. showed an added value of dedicated axillary PET/MRI compared to MRI alone (*33*). Further studies even indicated that PET/MRI could lead to treatment changes or replace invasive sampling compared to conventional staging with MRI, ultrasound or full-field digital mammography (*12*). In our study, ^{18}F-FDG PET/MRI still missed about 18% of the nodal positive patients, while at the same time, it had the best negative predictive value of all imaging modalities (89 %), emphasizing its high reliability in excluding malignancy in locoregional lymph nodes.

The highest specificity, on the other hand, was achieved by axillary sonography, which only depicted one false positive finding, whereas PET/MRI lead to 3 false positive ratings. Two of these 3 false positive patients had clip-marking of the primary tumor before, pointing to a reactive FDG-uptake of these lymph nodes.

False positive lymph nodes showed a significant lower SUVmax than correct positive lymph nodes. However, as SUVmax ranges from both groups overlapped and the number of false positive lymph node was very low, there is no reliable SUVmax cut-off.

There are limitations to this study. Most importantly, some samples were taken after neoadjuvant systemic therapy and therefore had to be evaluated retrospectively, taking into account indirect histopathological indicators for metastasis such as focal post-therapeutic fibrosis or necrosis (*18,19*). Furthermore, several samples were taken as a percutaneous biopsy, only representing a part of a lymph node. In contrast to lymph node excision, this also bears a small residual risk of missing out tumor cells. Furthermore, the prospective study design intended axillary sonography to be the first examination, as it was conducted in the same session with breast sonography and histopathological sampling of the primary tumor to ensure accordance with the patient inclusion criteria. Therefore (PET/)MRI examinations were often performed after clip-marking of the breast, which may have caused reactive axillary lymphadenopathy. Therefore, the number of false-positive findings in (PET/)MRI might be artificially increased.

Our data suggest 1) that ^{18}F-FDG PET/MRI provides the highest overall diagnostic performance, 2) the use of ^{18}F-FDG PET/MRI to exclude metastatic spread to axillary lymph nodes, and 3) the use of axillary sonography to confirm the diagnosis of suspected nodal positivity.

Consequently, future workflows should consider performing ^{18}F-FDG PET/MRI as a “searching tool” before clip-marking of the primary tumor, if applicable in clinical workflow, and to add axillary sonography afterwards to specify findings. If both imaging modalities show a positive nodal status, it could be taken into consideration to even dispense axillary histopathological sampling. Although tissue pathology will be the final determiner of the N-stage, knowledge of the higher sensitivity of PET/MRI compared to the other modalities will help in the growing field of targeted biopsy in the future. However, further prospective studies would be needed to investigate the potential replaceability of sampling by this approach.

Disclosure

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Conflicts of interest: Wolfgang P. Fendler is a consultant for Endocyte and BTG, and he received fees from RadioMedix, Bayer, and Parexel outside of the submitted work. No other potential conflicts of interest relevant to this article exist.

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

Informed consent: Informed consent was obtained from all individual participants included in the study.

KEY POINTS

Question: Does thocaral ^{18}F-FDG PET/MRI show a better diagnostic performance than thoracal MRI, breast MRI and axillary sonography?

Pertinent findings: Thoracal ^{18}F-FDG PET/MRI shows highest sensitivity (81.8%) and highest ROC-AUC (0.892) in assesing axillary nodal status, while axillary sonography is the most specific imaging modality (specificity 98.5 %) in detecting axillary lymph node metastases.

Implications for patient care: PET/MRI could be used to exclude axillary metastatic disease and axillary sonography could be added afterwards to specify findings, if PET/MRI shows nodal involvement.

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Figures

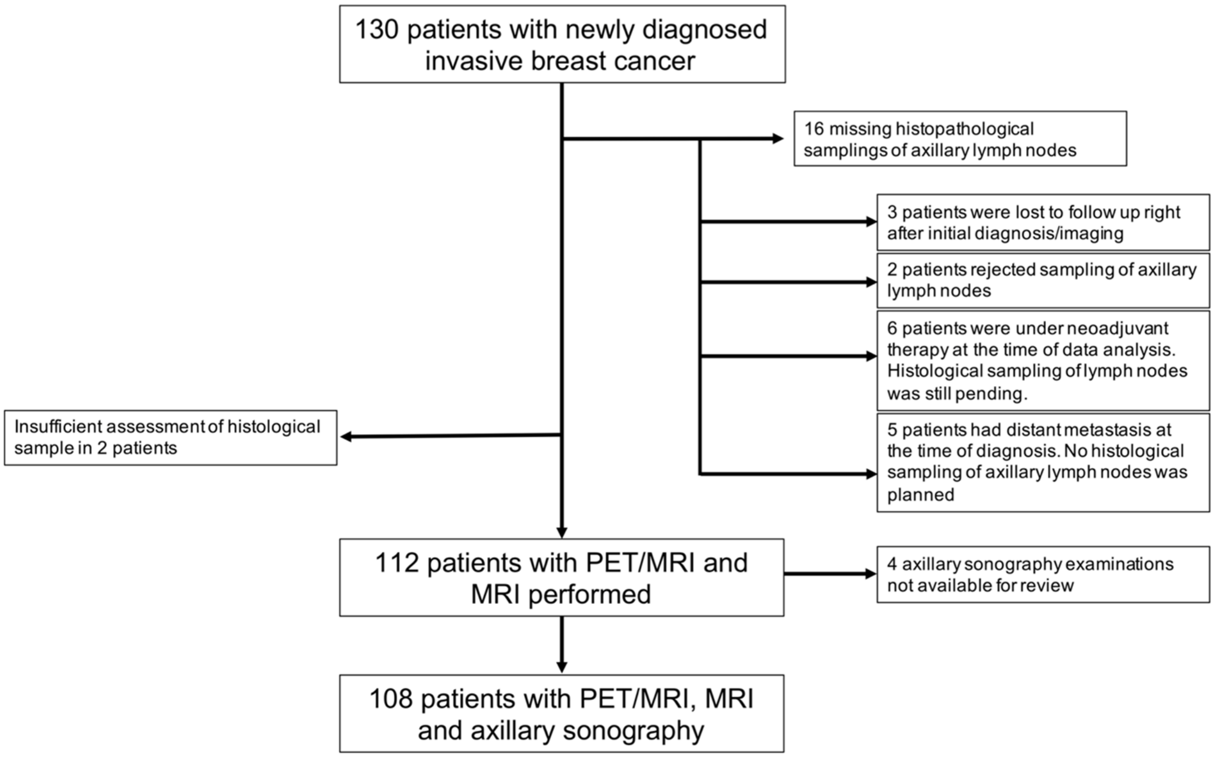


Figure 1. STARD-Diagram. Initial number of patients and reasons for exclusion.

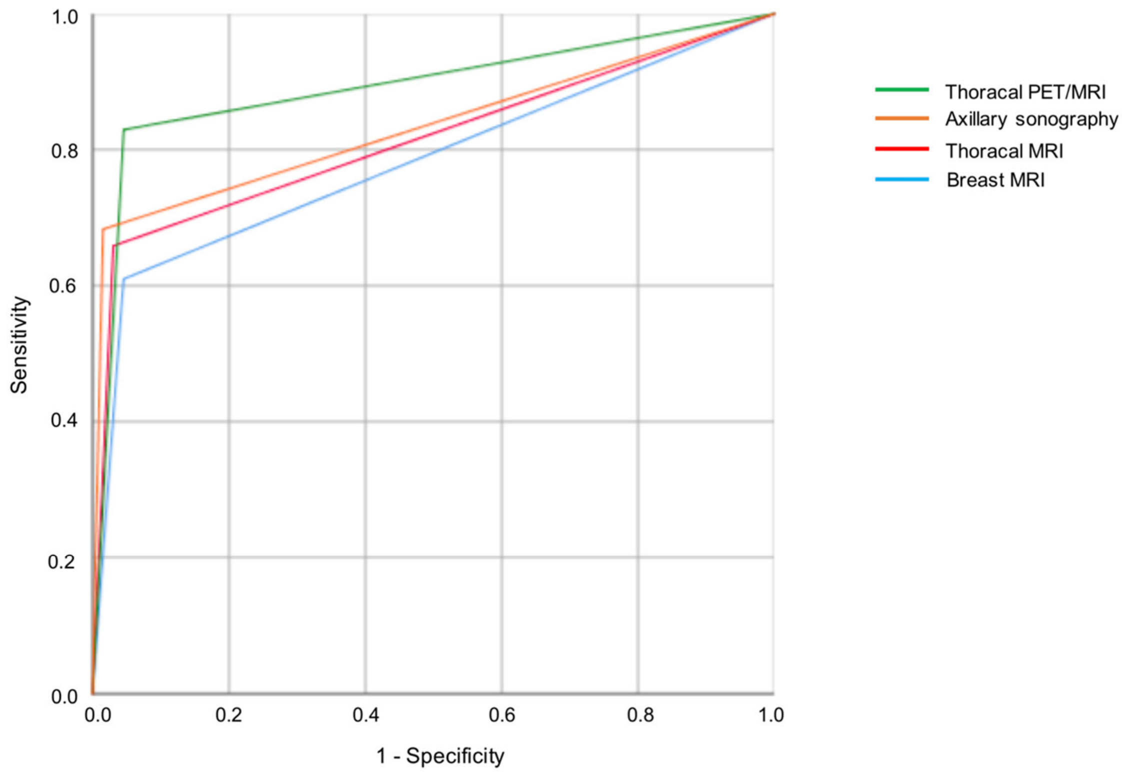


Figure 2. Receiver operating characteristic curve for diagnostic performance of detecting axillary lymph node positiviy comparison between thoracal PET/MRI (green), axillary sonography (orange), thoracal MRI (red) and breast MRI (blue).

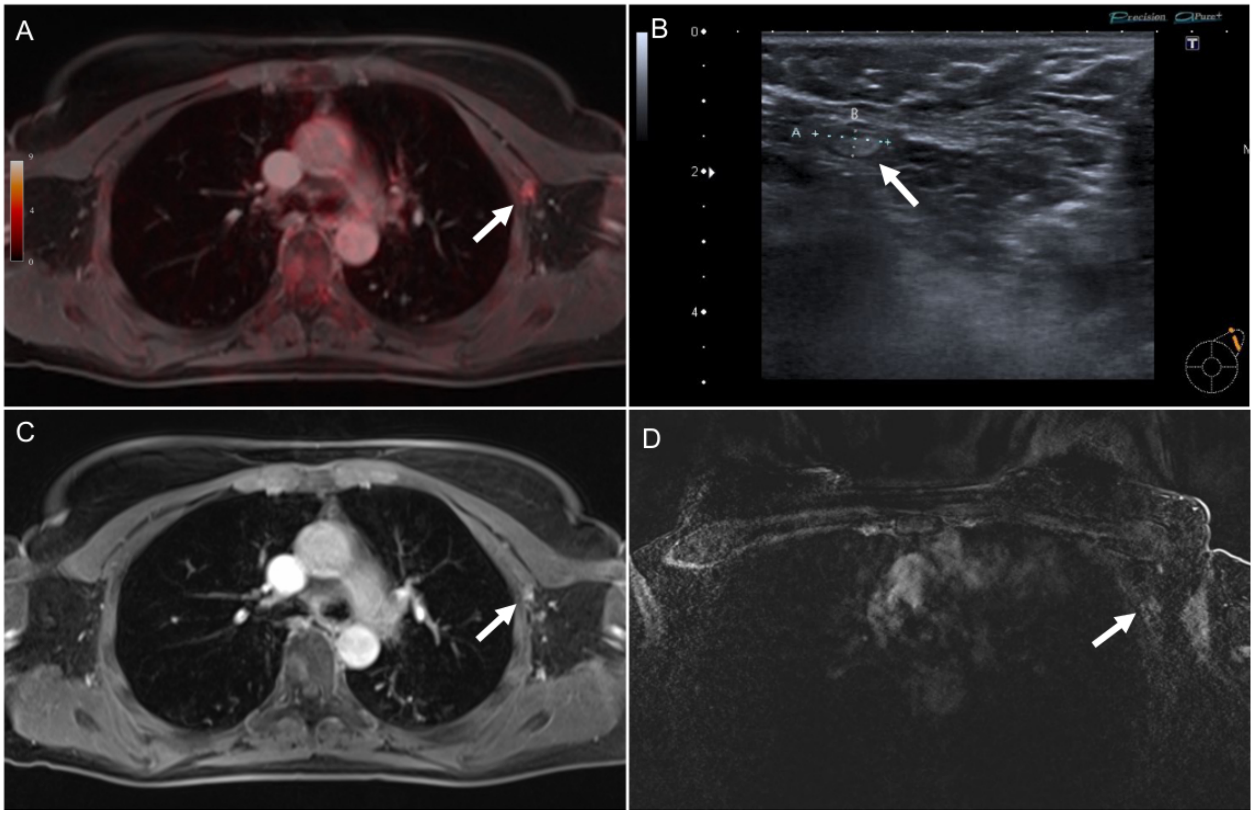


Figure 3. Pathologically confirmed axillary lymph node metastasis that was correctly identified in ^{18}F-FDG PET/MRI (A) because of its tracer-uptake above the background (SUVmax 4.7). This lymph node was rated false negative in axillary sonography (B), thoracal MRI (C) and breast MRI (D).

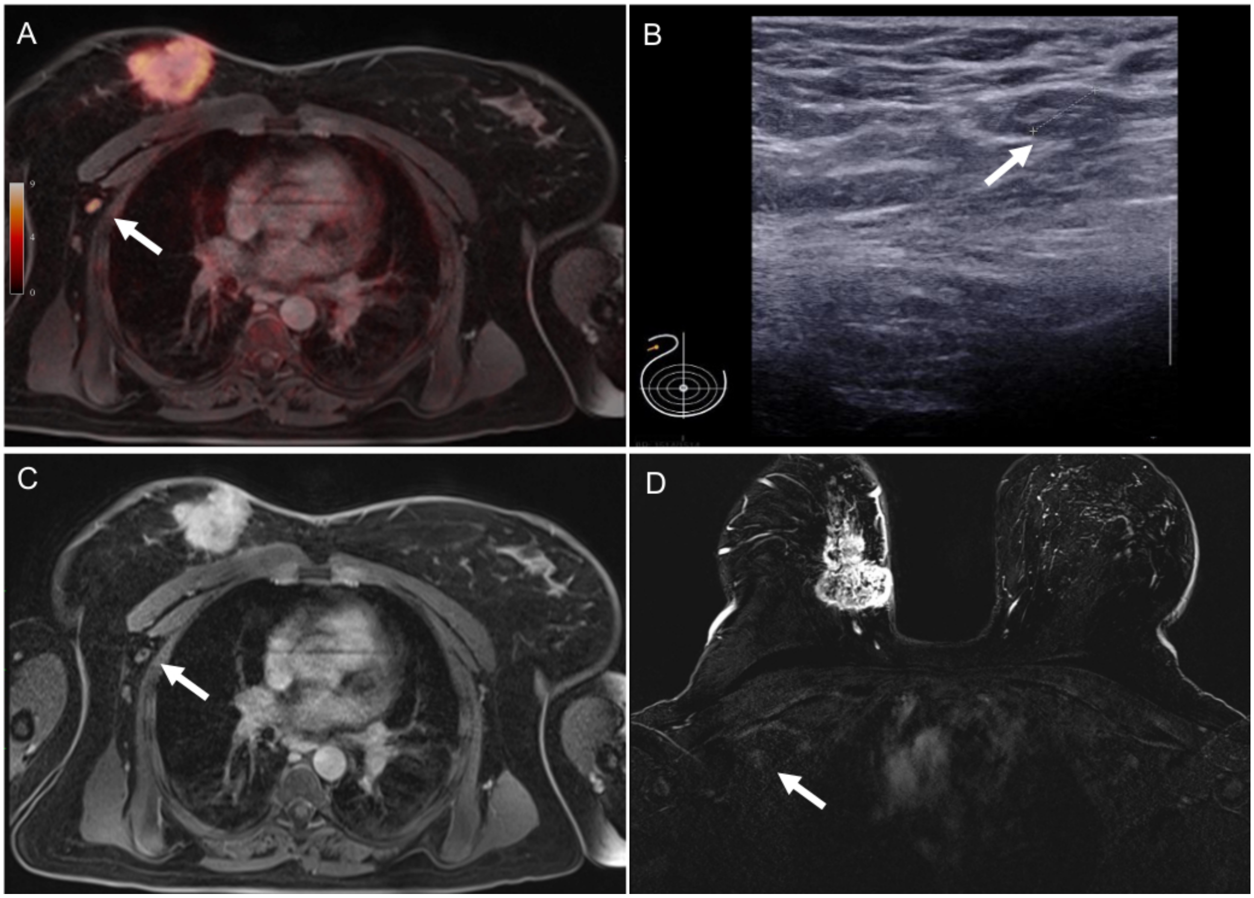


Figure 4. Pathologically confirmed axillary lymph node metastasis that was correctly identified in ^{18}F-FDG PET/MRI (A) because of its tracer-uptake above the background (SUVmax 4.3) and in axillary sonography (B) because of its cortical enlargement to 3.8 mm (short axis diameter 8 mm). This lymph node was rated unsuspicious in thoracal MRI (C) and breast MRI (C). Large primary is seen in the right breast.

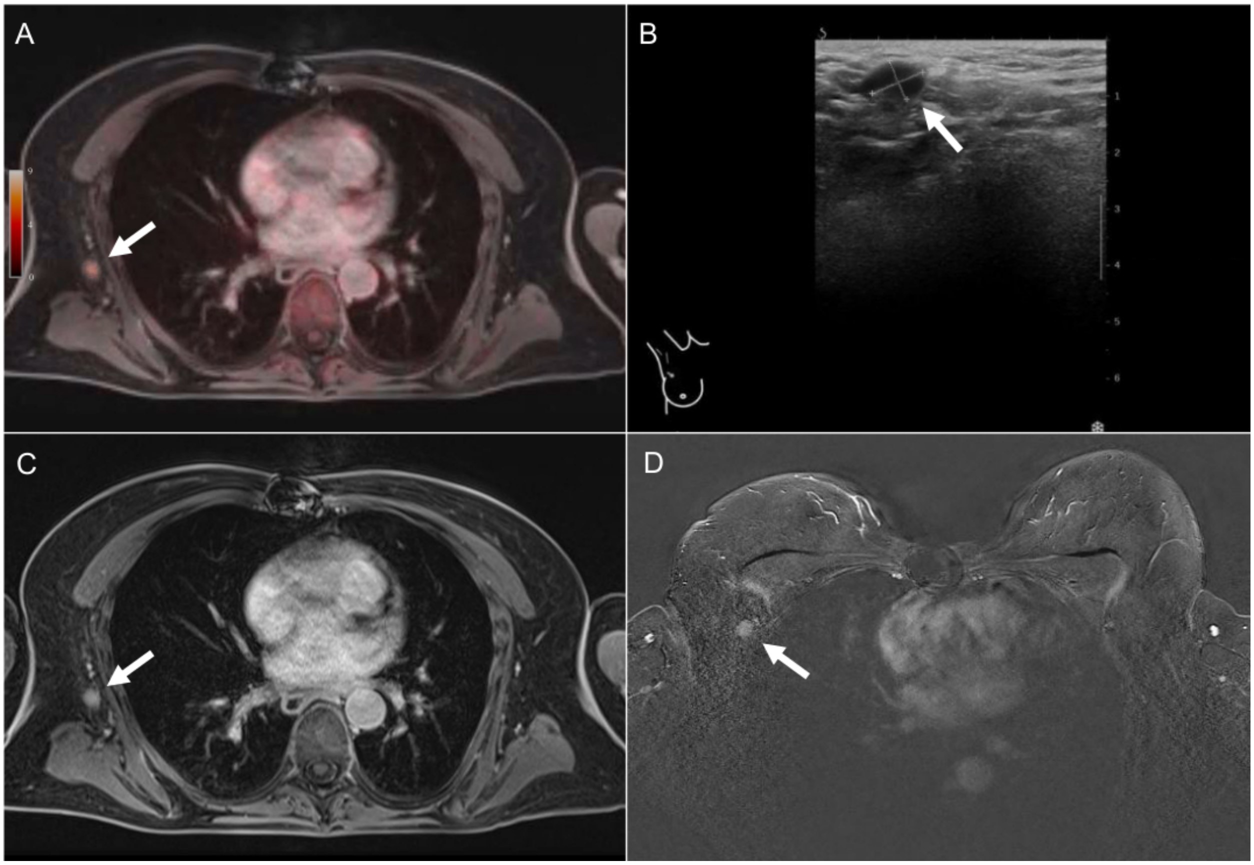


Figure 5. Suspicious right axillary lymph node in all imaging modalities. As no signs of malignancy were seen in histopathology, this patient was rated false positive in all modalities. (A) Thoracal PET/MRI: 9 mm lymph node with loss of fatty hilum, very slight perifocal oedema and FDG-Uptake slightly above the background (SUVmax 3.7). (B) Sonography: hypoechogenic lymph node with loss of fatty hilum (10 mm). (C) Thoracal MRI: 9 mm lymph node with loss of fatty hilum and very slight perifocal oedema. (D) Breast MRI: 8 mm lymph node with loss of fatty hilum and contrast-agent affinity.

Tables

Total patients		**112**
Sex		112 female
Mean age (± Standard deviation)		53.04 ± 12.6 years
Menopause status		
	pre	49
	peri	5
	post	58
Ki67		
	positive >14 %	98
	negative <14 %	14
Progesterone status		
	positive	87
	negative	25
Estrogen status		
	positive	89
	negative	23
HER2neu-expression		
	positive	31
	negative	81
Tumor grade		
	G1	6
	G2	58
	G3	48
Histology		
	NST	95
	Lobular invasive	10
	other	7
TNM staging		
T-stage	T1	39
	T2	64
	T3	6
	T4	3
N-stage	N0	74
	N1	25
	N2	5
	N3	8
M-stage	M0	108
	M1	4

Table 1. Patient demographics and primary tumor characteristics.

NST: Invasive carcinoma of no special type.

	Area under the Curve	95 % Confidence Interval
Thoracal PET/MRI	0.892	0.801 - 0.953
Axillary sonography	0.834	0.740 - 0.920
Thoracal MRI	0.814	0.718 - 0.904
Breast MRI	0.782	0.674 - 0.871

Table 2. Area under the curve for thoracal PET/MRI, axillary sonography, thoracal MRI, and breast MRI.

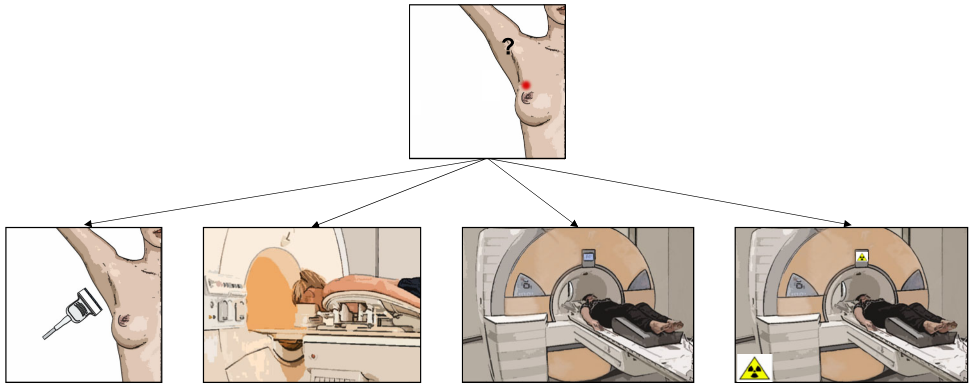
	positive		negative	
	correct	false	correct	false
Thoracal PET/MRI	39		73	
	36	3	65	8
Sonography	30		78	
	29	1	65	13
Thoracal MRI	30		82	
	28	2	66	16
Breast MRI	30		82	
	27	3	65	17

Table 3. Correct and false positive as well as correct and false negative findings of thoracal PET/MRI, axillary sonography, thoracal MRI and breast MRI.

		Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Thoracal PET/MR	%	**81.8**	**95.6**	**92.3**	**89.0**	**90.18**
	95% CI	67.29-91.81	87.64-99.08	79.72-97.34	81.25-93.84	83.11-94.99
Sonography	%	**69.1**	**98.5**	**96.7**	**83.3**	**87.04**
	95% CI	52.91-82.38	91.84-99.96	80.39-99.51	76.07-88.72	79.21-92.73
Thoracal MRI	%	**63.6**	**97.1**	**93.3**	**80.5**	**83.93**
	95% CI	47.77-77.59	89.78-99.64	77.83-98.24	73.58-85.94	75.79-90.19
Breast MRI	%	**61.4**	**95.6**	**90.0**	**79.3**	**82.14**
	95% CI	45.50-75.64	87.64-99.08	74.37-96.54	72.42-84.77	73.78-88.74

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of thoracal PET/MRI, axillary sonography, thoracal MRI and breast MRI.

Graphical abstract



	Axillary sonography	Breast MRI	Thoracal MRI	Thoracal PET/MRI
Diagnostic performance (Area under the Curve)	0.834	0.782	0.814	0.892

Supplemental Data

PET Images for Figures 3-5, respectively.