

# Diagnostic performance of [<sup>18</sup>F]FDG PET in staging grade 1-2, estrogen receptor positive breast cancer

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## Research article

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# Abstract

## Background

Accurate staging of early breast cancer (BC) patients is essential for tailored treatment. Currently, the preferred imaging modality for staging is positron emission tomography with [<sup>18</sup>F]Fluorodeoxyglucose (FDG PET) combined with a diagnostic computed tomography (CT) scan of the thorax/abdomen. However, FDG PET might be insufficient for detection of malignant lesions in grade 1–2, estrogen receptor positive (ER+) BC, due to its low metabolic activity. The main aim of this study was to retrospectively investigate the diagnostic accuracy of FDG PET in this patient population.

## Methods

74 patients diagnosed with grade 1–2, ER+ clinical stage IIB/III or locoregional recurrent BC were included. Suspect tumor lesions detected on conventional imaging (mammography, ultrasound, magnetic resonance imaging, diagnostic CT, bone scintigraphy) and FDG PET were confirmed with pathology or follow-up. FDG PET-positive lesions were (semi)quantified with standardized uptake values (SUV) and total lesion glycolysis (TLG), and these FDG PET parameters were correlated with pathological features such as histological subtype, grade, ER, PR and HER2 expression and mitotic activity index.

## Results

Pre-operative imaging identified 155 lesions that were pathologically verified. Based on pathology, 115/155 (74.2%) lesions identified on FDG PET were classified as true positive, i.e. malignant (in 67 patients) and 17/155 (10.8%) lesions as false positive, i.e. benign (in 9 patients); 7/155 (4.5%) as false negative (in 7 patients) and 16/155 (10.3%) as true negative (in 14 patients). FDG PET incorrectly staged 16/70 (22.9%) patients: 3/70 (4.3%) were downstaged whereas 13/70 (18.6%) were upstaged. SUV did not help to discriminate between true- and false positive lesions (median SUV<sub>max</sub> 4.23, IQR: 2.54–6.37 vs. 3.07, IQR: 2.14–5.58,  $P=0.44$  respectively). For true positive lesions, FDG uptake correlated with histological subtype, showing higher uptake in ductal carcinoma compared to lobular carcinoma ( $P<0.05$ ).

## Conclusion

Within this study FDG PET inadequately staged 22.9% of grade 1–2, ER+ BC cases. Incorrect staging can lead to inappropriate treatment choices, potentially affecting survival and quality of life. Prospective studies investigating novel radiotracers are urgently needed.

## Trial registration

retrospectively registered.

## Background

Breast cancer (BC) is the most frequently diagnosed malignancy among women worldwide.<sup>1</sup> In the Netherlands, 16.000 women are newly diagnosed with BC annually, most of whom have stage I (40.4%) or stage II (32.6%) disease, whereas 9.6% patients have stage III and 4.6% stage IV.<sup>2</sup> For stage IIB/III (advanced T-stage disease often with nodal involvement) or locoregional recurrent disease, curative treatment generally consists of surgery, radiotherapy and (neoadjuvant or adjuvant) systemic therapy (i.e. chemo-, endocrine and targeted therapy).<sup>3</sup> In case of metastatic disease without curative options, burdensome locoregional as well as systemic therapy should be avoided in order to maintain quality of life. On the other hand, identification of oligometastatic disease may improve the chance of (prolonged disease free) survival by including these sites in the local therapy plan.<sup>4</sup> Therefore, accurate pre-operative staging is essential to identify locoregionally affected lymph nodes and (distant) metastases as it will affect treatment choices.

The initial work-up for BC includes physical examination, mammography, ultrasound and magnetic resonance imaging (MRI) of the breast and axilla, to assess the extent of locoregional disease.<sup>3</sup> Standard staging procedures detect (distant) metastases in approximately 7% and 8–21% of clinical stage IIB and III patients, respectively, and in 33% of those presenting with locoregional recurrences.<sup>5,6,7</sup> Furthermore, 10–25% will develop recurrences within 2 years, suggesting at least in part missed (occult) metastases at presentation.<sup>8</sup> According to (inter)national guidelines staging is often performed with 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography accompanied by a low-dose CT scan for attenuation correction (FDG PET). In addition to this, a diagnostic computed tomography (CT) scan of the thorax and abdomen is often performed.<sup>3,9</sup> For primary staging of clinical stage II/III BC, the sensitivity and specificity of FDG PET to identify lymph node involvement and distant metastases is 63–100% and 98–100%, respectively<sup>5,10</sup> and in recurrent disease it is 90% and 81%, respectively.<sup>11</sup>

However, FDG uptake of BC can be quite variable, due to various underlying biological features.<sup>10–17</sup> FDG uptake is often lower in lobular BC (vs ductal BC)<sup>14,15,17</sup>, in low-intermediate grade (vs high grade)<sup>11–17</sup> tumors and in ER-positive tumors compared to triple negative (ER-/PR-/HER2-).<sup>10,12,14–16,19–21,22</sup> Alternatively, triple negative BC (ER-/PR-/HER2-), a more aggressive phenotype, shows higher FDG uptake than ER+/PR + and HER2- BC.<sup>19</sup> Thus, these biological factors can affect the FDG-avidity of lesions potentially limiting the accuracy of FDG PET/CT for staging of grade 1–2, ER + BC.<sup>15</sup>

Although there is data that FDG uptake (usually expressed as standard uptake value (SUV)) is lower in low grade ER + BC than in the other BC and that staging might be suboptimal<sup>23,24</sup>, no study has specifically investigated the extent of how this affects staging of BC. Therefore, the primary aim of this study was to retrospectively investigate the diagnostic performance of FDG PET in staging patients with grade 1–2, ER + BC. Secondary aims were to study whether level of tracer uptake in the primary tumor was associated with accuracy of staging, and to investigate which histopathological features might predict the accuracy of FDG PET.

## Materials And Methods

# Patient population

In this retrospective study we included women  $\geq 18$  years with histologically proven ER+, grade 1–2, clinical stage IIB/III or locoregional recurrent BC, treated at the Amsterdam UMC (VUmc) and The Netherlands Cancer Institute-Antoni van Leeuwenhoek (NKI-AvL) in the Netherlands between 2008–2016 and 2014–2015, respectively, with follow-up visits for at least 18 months. All patients underwent FDG PET/CT for staging. Patients with other malignancies in the last five years prior to diagnosis or (recurrent) BC were excluded.

Prior to inclusion, patients provided written informed consent, except when it was not possible to approach them for consent due to various reasons (e.g. death or no contact details available). The study was approved by the local Medical Ethics Committee of the VUmc (no.: 2017.382).

## Imaging procedures

According to standard of care, patients underwent mammography, ultrasound and MRI of the breast and axilla for locoregional staging. Patients at VUmc underwent an additional diagnostic CT scan of the thorax/abdomen and at both centers bone scans were performed if indicated (i.e. 'conventional imaging'). FDG PET scans were performed using Gemini TF-64 or Ingenuity TF-64 PET/CT scanner at VUmc and Gemini TF-16 or Gemini TF-Big Bore 16 (Philips Medical Systems) at AvL, according to the guidelines of the European Association of Nuclear Medicine (EANM).<sup>25</sup> Patients were administered 3.5 MBq/kg FDG at VUmc, and 190–240 MBq (according to the body mass index) at AvL.<sup>25</sup> All patients underwent a low-dose CT scan for attenuation correction, followed by PET scan (skull vertex to mid-thigh) at 60 min post-injection, with 2 min per bed position.

## Histopathology

According to standard of care, the biopsy of the primary tumor was used to evaluate histological subtype, grade (according to the Bloom-Richardson grading system), ER, PR, HER2 expression and mitotic activity. Compliant with Dutch guidelines ER-/PR-positivity on immunohistochemistry (IHC) was established if  $\geq 10\%$  of cell nuclei were immunoreactive, and HER2 was classified positive with 3+ or 2+ and amplified.<sup>3</sup> Mitotic activity was defined as the number of mitoses per 2 mm<sup>2</sup>. Suspect locoregional or distant lesions visible on conventional imaging and/or FDG PET that were decisive for therapy choices were verified by core needle biopsy and/or fine-needle aspiration cytology.

Pathological reports of lymph node resection were classified as follows: in case of presence of malignant cells: pathologically verified malignant lymph node. After neo-adjuvant therapy: in case of fibrosis compatible with complete response: pathologically verified malignant lymph node before neo-adjuvant treatment. In case of no malignant cells or fibrosis by cytology and/or histology: benign lymph node.

## Patient-based analysis

The patient-based outcomes consisted of determining the stage of disease at baseline and at the end of follow-up. Stage of disease was determined at clinical presentation together with conventional imaging and subsequently by FDG PET together with pathological confirmation.

## **Lesional analysis: qualitative and semi-quantitative FDG PET readings**

Conventional imaging was performed  $\leq$  5 weeks before or after FDG PET. Clinically relevant lesions suspicious for malignancy on any imaging modality were included in this analysis, with a maximum of 5 largest lesions per tissue type in case of distant metastases. Included lesions were either pathologically confirmed as benign or malignant (group A) or, in case of absent/inconclusive pathology, verified by additional imaging and/or follow-up for 18 months after primary diagnosis (group B). Based on these data, we classified lesions as: true positives (= malignant lesions suspect on FDG PET), true negatives (= benign lesions not suspect on FDG PET), false positives (= benign lesions suspect on FDG PET) and false negatives (= malignant lesions not suspect on FDG PET). In case of multiple axillary lymph nodes on FDG PET only those which were pathologically proven malignant, were included in group A.

Quantitative analysis was performed using in-house developed software (Accurate tool, version 04092018, R. Boellaard).<sup>26</sup> This analysis only included lesions visible on FDG PET. Volumes of interest (VOIs) were semi-automatically defined using 50% thresholds of peak standardized uptake values ( $SUV_{peak}$ ) adapted for local background<sup>26</sup> and verified by radiologists. For each VOI we determined:  $SUV_{max}$ ,  $SUV_{mean}$ ,  $SUV_{peak}$  and total lesion glycolysis (TLG). In addition, for primary breast lesions, VOIs were manually defined on the low-dose CT scans to calculate anatomical volumes. The correlation between these FDG PET parameters and various histopathological features of the primary tumor was assessed to investigate whether histopathological features predicted the accuracy of FDG PET.

## **Clinical implications on treatment plan**

We investigated the impact of incorrect lesion identification by FDG PET. Pathological outcome of surgically resected axillary lymph nodes were retrospectively compared to lymph nodes identified on FDG PET, excluding patients that had progressive disease during neo-adjuvant therapy. We postulated that without progression, any additional pathologically verified malignant node in the resection specimen compared to baseline FDG PET, should be classified as false negative on FDG PET. In case this would lead to stage migration of the N-stage, from N1 to N2, such patients would require an axillary lymph node dissection according to current guidelines instead of sentinel node/marked node resection.<sup>3</sup>

Similarly, the number of distant metastases are relevant for the treatment plan. In case of oligometastatic disease ( $< 4$  lesions) local treatment with curative intent can be considered, whereas in case of extensive disease ( $\geq 4$  distant metastases) a palliative option will prevail. We compared the distant lesions on FDG PET to the number of distant metastases confirmed through pathological verification and/or additional imaging at baseline and during the follow-up period.

## **Statistical analysis**

Statistical analysis was performed using SPSS Statistics 22.0 (IBM Corp.). Accuracy was measured at patient and lesional level, separate for groups A and B. The difference between FDG PET parameters ( $SUV_{max}$ ,  $SUV_{peak}$ ,  $SUV_{mean}$  and TLG) across the different categories in the two groups (true positives, false positives and false negatives, group A and B) was assessed using the Kruskal-Wallis test. The association between tracer uptake in the primary tumor and accuracy of staging was assessed by using the Mann-Whitney U test. The association between histopathological features of the primary tumor and accuracy of staging was assessed by using a chi-square test or an Mann-Whitney U test. The association between semi-quantitative FDG PET parameters and histopathological features of the primary tumor was investigated using a mixed model analysis with an intercept on patient level. Results were considered significant for a  $P$ -value  $< 0.05$ .

## Results

## Patients

Seventy-four patients (37 from each center) with a median age of 49 years (range: 28–94) were included. Most patients presented with clinical stage IIB (48.6%) or III (47.3%) BC (Table 1). FDG PET/CT was performed after primary surgery in four patients, and prior to surgery ( $n = 6$ ) or systemic treatment ( $n = 58$  neo-adjuvant and  $n = 6$  palliative) in the remaining 70 patients.

Table 1  
Patient characteristics

	N (%) or median (range)
<b>Age at diagnosis (y)</b>	49 (28–94)
<b>Clinical stage at presentation</b>	36 (48.6)
IIB	35 (47.3)
III	3 (4.1)
Locoregional recurrence	
<b>Histological subtype*</b>	57 (77.0)
Ductal	17 (22.7)
Lobular	1 (1.3)
Micropapillary	
<b>Grade</b>	7 (9.5)
1	67 (91.5)
2	
<b>ER receptor</b>	74 (100.0)
Positive	
<b>PR receptor</b>	13 (17.6)
Negative	61 (82.4)
Positive	
<b>HER2neu receptor</b>	65 (87.8)
Negative	9 (12.2)
Positive	

\* One patient with multifocal BC presented with 2 lesions in the breast, each having a different histological

subtype.

\*\* These patients directly underwent surgery before (n = 4) or after the FDG PET scan (n = 6) or received

endocrine treatment for metastatic disease (n = 5) or locoregional recurrence (n = 1) after FDG PET imaging.

	N (%) or median (range)
<b>Treatment received</b>	58 (78.4)
<b>Neo-adjuvant therapy</b> (after FDG PET imaging)	- 53 (91.4)
yes	- 5 (8.6)
- chemotherapy	16 (21.6)
- endocrine therapy	65 (87.8)
no**	- 4 (6.2)
<b>Surgery</b>	- 61 (93.8)
- yes	9 (12.2)
- before FDG PET imaging	69 (93.2)
- after FDG PET imaging	2 (2.7)
- no	3 (4.1)
<b>Adjuvant therapy</b>	
- yes	
- no	
- unknown	
* One patient with multifocal BC presented with 2 lesions in the breast, each having a different histological subtype.	
** These patients directly underwent surgery before (n = 4) or after the FDG PET scan (n = 6) or received endocrine treatment for metastatic disease (n = 5) or locoregional recurrence (n = 1) after FDG PET imaging.	

## Patient-based analysis

In 67% (47/70) the FDG PET stage was identical to the clinical stage at baseline and in 10% (7/70) FDG PET correctly upstaged patients (Table 2). However, of the remaining 16 patients, 3 were incorrectly downstaged and 13 were incorrectly upstaged. Four patients underwent staging with FDG PET after surgery as they had stage IIB or III disease post-surgery: 1 of these patients had an additional suspect breast lesion on FDG PET, and subsequent mastectomy showed multifocal breast cancer.

At the end of follow-up (after 18 months), 81.4% were disease-free (Suppl. Table 1). Of 67 patients who were diagnosed with locoregional disease at baseline, 3 developed metastases during follow-up. One patient had stage III by FDG PET at baseline; during follow-up multiple bone metastases were diagnosed

after 12 months. The second patient had multiple FDG-avid mediastinal lymph nodes which were classified as reactive lymph nodes (no biopsy/cytology performed), and 17 months later she developed pathologically proven liver metastases (without growing mediastinal nodes). The third patient had enhanced uptake in parasternal and paratracheal lymph nodes (no biopsy/cytology performed), which were interpreted at baseline as reactive lymph nodes probably due to esophagitis; 9 months later she presented with mastitis carcinomatosa, growing parasternal lymph nodes and liver metastases.

## Lesional analysis

In group A, 155 lesions were pathologically verified prior to neo-adjuvant therapy and primary surgical treatment (breast: 86, locoregional lymph nodes: 58, distant: 11; Suppl. Table 2A). Visual analysis of FDG PET correctly classified 115/155 (74.2%) lesions as malignant, and 16/155 (10.3%) as benign. FDG PET incorrectly categorized 24/155 (15.5%) lesions: 7/155 (4.5%) lesions in 7 patients were malignant but showed no uptake whereas 17/155 (11.0%) lesions in 9 patients (5 with 1 lesion, 2 with 2 lesions, and 2 with 4 lesions) were benign but showed enhanced uptake (Fig. 1). On this, pathologically confirmed lesional basis, FDG PET had a sensitivity and specificity of 94.3% and 48.4%, respectively.

Group B consisted of 112 lesions (Suppl. Table 2B). FDG PET classified 61/112 (54.5%) and 8/112 (7.2%) lesions as true positives and true negatives, respectively. Forty-three (43/112, 38.4%) lesions were classified incorrectly: 12/112 (10.8%) malignant lesions showed no uptake whereas 31/112 (27.7%) lesions showed enhanced uptake reported as suspect but were benign. On this, with imaging/follow up confirmed lesional basis, FDG PET had a sensitivity and specificity of 83.6% and 20.5%, respectively.

Results of groups A and B taken together (Suppl. Table 2C) yielded a sensitivity and specificity of 90.3% (95% CI 85.3–93.7%) and 33.3% (23.5–44.8%), respectively. Misclassification by FDG PET mostly involved axillary lymph nodes and bone, respectively (Suppl. Table 3).

A similar lesion-based analysis was performed for conventional imaging, including the diagnostic CT scan (Suppl. Table 4), showing high sensitivity and low-moderate specificity rates of 95.9% and 15.2% and 80.8% and 66.7% for group A and B, respectively. Outcomes of conventional and FDG PET imaging were also combined together for group A (Suppl. Table 5), showing that conventional imaging alone identified 23 additional suspect lesions of which 7 were malignant. FDG PET alone identified 10 other suspect lesions of which 5 were malignant.

Quantification of visually identified lesions on FDG PET did not improve discrimination between true and false positives lesions (Fig. 2, Suppl. Table 6 and Suppl. Figures 1 and 2), in either group (A and B). Since  $SUV_{max}$  highly correlated with other SUV-parameters ( $R^2$  range: 0.88–0.92), only  $SUV_{max}$  data are reported.

## Correlation between FDG PET parameters and histopathology

FDG uptake in the primary tumor was not associated with the accuracy of FDG PET staging ( $P=0.67$ ). Ductal carcinoma had a higher SUV<sub>peak</sub> and SUV<sub>mean</sub> than lobular carcinoma ( $P<0.05$ ), and HER2 + tumors had a significantly higher TLG compared to HER2- tumors ( $P<0.05$ ). (Suppl. Table 7). The % ER positivity correlated with TLG ( $P<0.05$ )

## Implications for the plan

In summary, in 22/74 (29.8%) patients, the treatment plan based solely on FDG PET imaging would have been incorrect. In total, 65/74 (87.8%) patients underwent surgical resection, in 34/65 patients (52.3%) surgery included also axillary lymph node dissection. No patient on neo-adjuvant therapy had progressive disease during treatment. Pathological analysis of axillary specimens classified 143 of 346 lymph nodes as malignant whereas 203 were benign (Suppl. Table 8). Since it is impossible to match each lymph node in the pathology specimen with their location on imaging, we compared the numbers of suspicious nodes on FDG PET with malignant nodes in the specimen. 83/143 (58.0%) malignant lymph nodes in 16 patients were classified as false negatives on FDG PET. In 7 patients, diagnosed with N1-stage disease on FDG PET, axillary lymph node dissection showed N2-disease (Suppl. Table 9). In 2 patients with one malignant node on FDG PET, 1 or 2 additional nodes were identified when the axillary lymph node dissection was performed. Additionally, FDG PET falsely identified N3 disease (infraclavicular lymph node) in one patient, whereas in one case N3 disease (intramammary lymph node) was missed. In the remaining patients FDG PET showed the same number or less affected lymph nodes than the resection specimen, the latter most likely due to the effect of neo-adjuvant systemic treatment. As neo-adjuvant treatment affects lesions size, no correlation between FDG PET positivity and size of the lymph node metastasis could be made.

Metastatic disease was missed by FDG PET in 2 patients: one patient had multiple bone metastases and the other patient had a lung metastasis. In 8 other patients false positive lesions were identified in the liver, thyroid, bone and lymph nodes located in the neck, mediastinum and inguinal region (Suppl. Table 5).

## Discussion

To our knowledge, this is the first study assessing the diagnostic performance of FDG PET in patients with stage IIB/III or LRR, grade 1–2, ER + breast cancer. In this study, the sensitivity of FDG PET for disease staging was 77.1%. Previous studies have reported sensitivity of up to 100% for primary breast cancer<sup>14,27</sup> and 81–97% for restaging of LRR<sup>14</sup>, each for all types of breast cancer combined. In addition, as expected previous studies have shown that FDG PET outcomes affected the treatment plan in 6.5–13% of patients with primary breast cancer.<sup>10,14</sup> These data reinforce the importance of additional imaging modalities next to the conventional imaging to obtain the correct stage which is essential for an adequate treatment plan. In our case the treatment plan was correctly adapted by FDG PET in 7/70 (10%) patients, but in 16/70 (23%) patients FDG PET would have led to an incorrect treatment plan (Table 2).

Thus, our results support the hypothesis that FDG PET is insufficient for (re)staging of grade 1–2 ER + breast cancer.

## TNM lesion detection

When looking into more detail to detection of individual lesions, this study shows that the sensitivity and specificity of FDG PET for lesion detection (pre-operatively) was 94.3% and 48.8% (group A)/83.6% and 20.5% (group B), respectively in patients with grade 1–2, ER + BC. Differentiation of lesion detection based on the type of lesion (i.e. primary breast lesions, locoregional lymph nodes and distant metastases), showed that FDG PET accurately detects primary breast tumors (83/87 (95.4%). Our data are in line with a prospective study that showed similar detection rate of BC lesions when comparing FDG PET/CT with MRI (95% vs 100%,  $P=1.0$ ).<sup>28</sup> However, compared to other conventional imaging techniques such as MRI, it is known that FDG PET has less sensitivity and less accuracy for determining the size of the tumor and to assess the presence of multifocal disease.<sup>14</sup> For locoregional lymph nodes, previous studies have shown that micrometastases are suboptimally detected with FDG PET(CT).<sup>29,30</sup> However, in current clinical practice, it is essential to identify all affected nodes before neo-adjuvant treatment as only extensively affected axillary lymph nodes (i.e.  $\geq N2$ -disease/'bulky' disease) remaining after neo-adjuvant systemic treatment will in general require axillary lymph node dissection. In case of N1-disease (1–3 affected lymph nodes) at diagnosis and response on neo-adjuvant treatment, resection of the sentinel node(s) and marked node is deemed sufficient when followed by locoregional radiotherapy.<sup>3</sup> In our study, 26/96 (27.1%) axillary lymph nodes were incorrectly identified: 3.1% of the axillary lymph nodes were identified as false negatives and 24.0% as false positive nodes (Suppl. Table 3). These incorrect identified nodes could potentially change the N-stage and eventually the locoregional treatment, making it even more important that these nodes are correctly identified.

In case of distant metastases, FDG PET(CT) is known to have a high yield as shown in inflammatory and stage II/III BC.<sup>14,31–34</sup> In this study, distant metastases were identified in 7/70 patients (10%), which is at the lower end from what would be expected from literature for stage IIB/III/LRR.<sup>5,6,7</sup> In 4 patients FDG PET confirmed the suspicion of metastases as seen on conventional imaging and in 3 patients metastatic lesions were correctly identified on FDG PET alone. However, FDG PET also missed lung and bone metastases in 7 patients. Distant metastases were mainly located in extra-axillary lymph nodes, lung and bone. FDG PET lacks sensitivity for detection of (small) lung nodules (due to partial volume effect and respiratory movement) and identifies osteoblastic lesions suboptimally (often showing low or no FDG uptake in these lesions).<sup>14,35</sup> In our study, most of the lung lesions were small (range: 4–11 mm) and therefore correct identification of these might have been hampered by partial volume effect, however, the low grade, ER + breast cancer subtype might also have played a role. Most of the bone lesions included in this study were osteolytic and also for these lesions applies that the specified low grade, ER + breast cancer subtype might have affected its identification on PET.

# Association between FDG PET parameters and histopathology

Quantification of FDG uptake only showed a trend for higher SUV<sub>max</sub> and TLG values in malignant (true positive) lesions compared to false positives and false negatives. However, no specific threshold for malignancy could be determined, as has been described in other studies.<sup>36,37</sup> The histological subtype however, correlates with FDG uptake, with ductal BC having higher FDG uptake compared to lobular BC. This is in accordance with other studies and can probably be explained by a lower tumor cell density, a low level of GLUT1 expression, diffuse infiltration of surrounding tissue and a decreased proliferation rate in lobular BC, eventually resulting in lower FDG uptake.<sup>16,18,19</sup>

We did not observe a difference in FDG uptake between grade 1 and grade 2 tumors. In literature it is known that grade 3 tumors have significantly higher FDG uptake than grade 1–2 tumors but no information is available regarding the correlation between FDG uptake and grade 1 and 2 tumors separately.<sup>11–17</sup> Regarding the receptor status, we found that the % ER positivity and HER2 status correlated with TLG. No correlations could be found between the PR status and FDG uptake. Previous studies have been somewhat contradictory about this: a few studies have shown that there is no correlation between hormone receptor status (positive or negative) and FDG uptake<sup>13,38</sup> whereas others have shown that FDG uptake is affected by hormone receptor status.<sup>12,14–16,19–21</sup> These studies do not take the expression levels of ER and PR separately and in combination into account, which may be essential to identify the relation with FDG uptake. For HER2, no correlation could be found between its status (positive/negative) and FDG SUV which is consistent with other studies.<sup>15,16,21</sup> However, HER2 status did correlate with TLG, but we could not confirm this from other studies as they did not include TLG in their analyses.

We did not find a correlation between FDG uptake and the mitotic activity index (mean ± standard deviation: 3.1 (± 4.1); range: 0–19), probably as we only included tumors which are expected to be less metabolically active than other subtypes of breast cancer. Studies including more metabolically active tumors, identified by a higher Ki-67 expression, have reported higher FDG uptake.<sup>16,39</sup>

## Limitations

Due to the retrospective set-up of this study not all clinical, imaging, and pathology data were available for all patients. We had access to all the FDG PET/CT scans, but the scans of other imaging modalities were not always present. In those cases, the available report of the radiologist was used to compare lesions on the different imaging modalities. Furthermore, of the 267 lesions investigated, 155/267 lesions were pathologically verified (reference method), whereas for 112/267 lesions only additional imaging and/or follow-up data were available, which precludes a definitive diagnosis regarding these lesions. However, our separate analyses for both groups yielded results in a similar range, supporting the chosen approach. For the visual analysis we also included all axillary lymph nodes, benign or malignant, as verified according to the pathology report. However, in case of multiple avid lymph nodes on the FDG PET

scan it can be difficult to match the exact lymph node that was pathologically proven benign or malignant to the correct lesion on the scan. In that case it was assumed that the lesion that is most avid on the scan is also most likely the one of which biopsy or cytology is performed and this lesion could also be quantified. Of the remaining lesions only the number of affected lymph nodes were taken into account in the analysis.

## Scientific implications

Imaging with FDG PET/CT for patients with grade 1–2, ER + BC can potentially lead to incorrect staging. In search for alternative methods to improve staging, imaging based on the ER which is independent of metabolic activity might be of interest. Several clinical studies have shown that 16 $\alpha$ -[<sup>18</sup>F]-fluoro-17 $\beta$ -estradiol ([<sup>18</sup>F]FES) PET/CT has overall high sensitivity (84%) and specificity (98%) rates<sup>40</sup>, making it an interesting ER-targeting PET tracer to compare with FDG for staging of patients with grade 1–2, ER + BC.

## Conclusion

The data presented in this study shows that FDG PET imaging inadequately staged 22.9% of grade 1–2, ER + BC cases. This can lead to incorrect staging and subsequently to inappropriate treatment choices, potentially affecting survival and quality of life. Prospective studies investigating novel radiotracers are urgently needed to improve current imaging staging procedures.

## Abbreviations

BC Breast cancer

CT Computed tomography

EANM European association of Nuclear Medicine

ER Estrogen receptor

HER2 Human epidermal growth factor receptor 2

FDG [<sup>18</sup>F]Fluorodeoxyglucose

FES 16 $\alpha$ -[<sup>18</sup>F]-fluoro-17 $\beta$ -estradiol

IHC Immunohistochemistry

MRI Magnetic resonance imaging

PET Positron emission tomography

PR Progesterone receptor

SUV Standardized uptake value

TLG Total lesion glycolysis

VOI Volume of interest

## Declarations

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been performed in accordance with the Declaration of Helsinki and it has been approved by the Medical Ethics Review Committee of the VUmc. Informed consent was obtained from participants included in the study, except when it was not possible to approach them for consent due to various reasons (e.g. death or no contact details available).

### CONSENT FOR PUBLICATION

Participants included in this study provided consent for publication.

### AVAILABILITY OF DATA AND MATERIALS

The data supporting the conclusions of this article is included within the article.

### COMPETING INTERESTS

The authors declare that they have no conflict of interest.

- R. Iqbal: declares that she has no conflict of interest.
- L.H. Mammatas: declares that she has no conflict of interest.
- T. Aras: declares that she has no conflict of interest.
- W.V. Vogel: declares that he has no conflict of interest.
- T. van de Brug: declares that he has no conflict of interest.
- D.E. Oprea-Lager: declares that she has no conflict of interest.
- H.M.W. Verheul: declares that he has no conflict of interest.
- O.S. Hoekstra: declares that he has no conflict of interest.
- R. Boellaard: declares that he has no conflict of interest.
- C.W. Menke-van der Houven van Oordt: declares that she has no conflict of interest.

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The data presented in this study was obtained according to standard of care.

### AUTHORS' CONTRIBUTIONS

- RI: concept, design, data acquisition, data-analysis and interpretation, drafting and revision of the manuscript.
- LHM: data acquisition, interpretation and revision of the manuscript.
- TA: data-analysis and interpretation and revision of the manuscript.
- WVV: data acquisition, interpretation and revision of the manuscript.
- TvdB: data-analysis and revision of the manuscript.
- DEO: critical review and revision of the manuscript.
- HMWV: critical review and revision of the manuscript.
- OSH: design, critical review and revision of the manuscript.
- RB: design, critical review and revision of the manuscript.
- CWM: concept, design, data acquisition, data interpretation and critical review and revision of the manuscript.

All authors read and approved the final manuscript.

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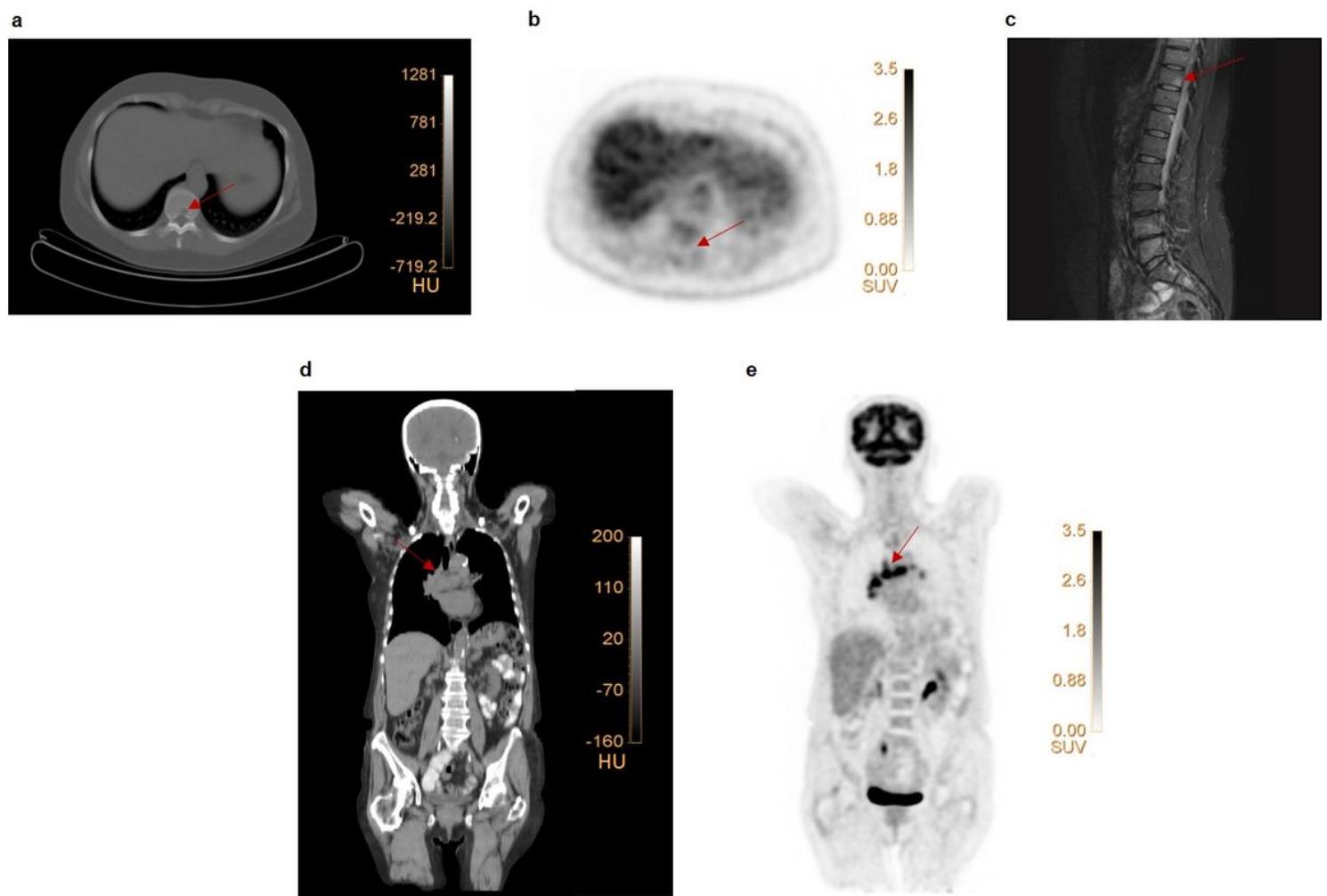
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## Tables

Due to technical limitations, table 2 is only available as a download in the Supplemental Files section.

## Figures



**Figure 1**

Examples of false negative and false positive lesions on FDG PET. a-c Patient with primary ER+ breast cancer with faint uptake in the primary tumor (SUV<sub>max</sub> 2.3). Low-dose CT (a) revealed a lytic lesion in the 10th thoracic vertebra (Th10) without enhanced FDG uptake (b). An MRI scan (c) revealed multiple

vertebral metastases (Th4, Th11, Th12, L4, L5), including the one at Th10. This lesion was classified as false negative on FDG PET. d-e. Patient with multiple mediastinal FDG avid, suspect lymph nodes. Coronal section of a low-dose CT-scan (d) and FDG PET scan (e). Endobronchial ultrasound guided-biopsy of 3 mediastinal lymph nodes showed reactive cells. These lesions were therefore classified as false positive on FDG PET.

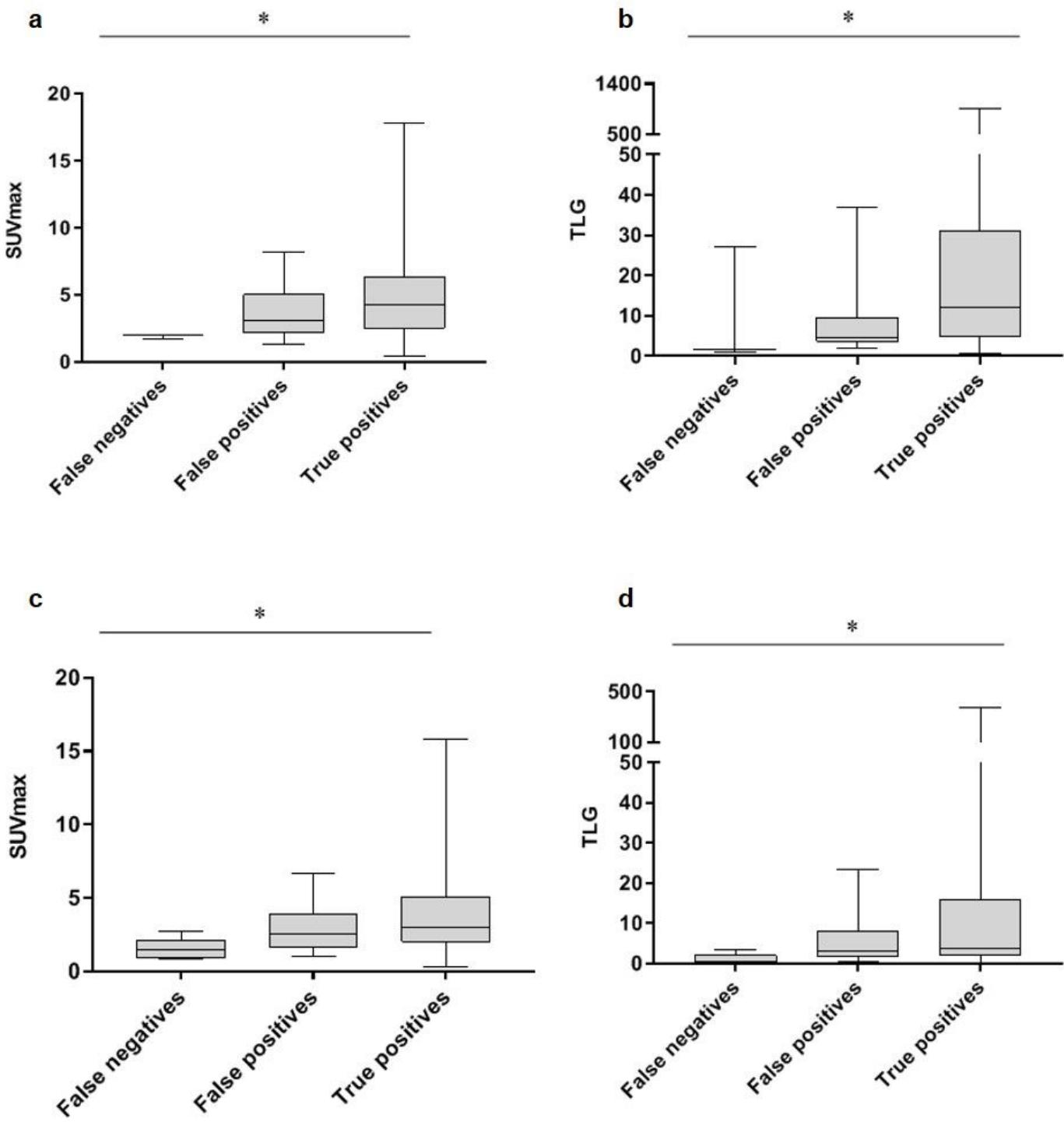


Figure 2

SUVmax and TLG show no significant differences between false and true positive lesions. Lesions were classified into 3 groups, i.e. false negatives, false positives and true positives; lesions have been verified with pathology (a/b) or additional imaging and/or follow-up (c/d). Similar results have been obtained for SUVpeak and SUVmean (Suppl. Fig. 1 and 2). \*P <0.05.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table2.png](#)
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