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Diagnostic accuracy of FDG-PET-CT to predict axillary lymph node response after neo-adjuvant chemotherapy in lymph node-positive breast cancer patients

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Abstract

Background In certain cases, some institutions use fluorodeoxyglucose positron emission tomography combined with CT (FDG-PET-CT) scans to assess response to neo-adjuvant chemotherapy (NAC) in lymph node-positive breast cancer (cN+), to determine the extent of surgery and subsequently radiotherapy. In this study, we assessed the diagnostic accuracy of FDG-PET-CT to determine the axillary response to NAC using the histopathology results as the golden standard.

Methods Between 2016 and 2022, all women with cN+ breast cancer receiving NAC and axillary surgery were retrospectively identified. Patients who underwent pre- and post-NAC staging with FDG-PET-CT were included. Excluded were patients with previous ipsilateral breast cancer, occult breast cancer or bilateral breast cancer. The histopathology lymph node results from surgery were used to calculate the diagnostic accuracy of FDG-PET-CT for detecting axillary lymph node metastases post-NAC.

Results Seventy-five patients were included. Forty-one patients (55%) had histologically proven axillary metastatic disease at the response evaluation after NAC, although FDG-PET positivity was only apparent in nine of these patients. There was a sensitivity of 22% (95% CI 11–38%) for FDG-PET-CT in detecting axillary lymph node metastases after NAC and a specificity of 94% (95% CI 80–99%). The positive predictive value was 82% (95% CI 48–98%) and the negative predictive value (NPV) was 50% (95% CI 37–63%).

Conclusions FDG-PET-CT scans have a low sensitivity and NPV to identify residual disease after NAC, indicating that these scans are unlikely to aid in decision making. Omission of post-NAC FDG-PET-CT should be considered in lymph node response evaluation unless other clinical indications with no other alternative.

Keywords Breast cancer, Axillary lymph nodes, Radiotherapy, FDG-PET-CT scan, Diagnostic accuracy

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Background

Worldwide, breast cancer is the most commonly diagnosed malignancy in women [1]. The mainstay of treatment is surgery with adjuvant therapy including chemo, hormonal and radiotherapy. The aims of neo-adjuvant chemotherapy (NAC) include de-escalating surgery and potentially achieving pathological complete response (pCR) [2, 3]. Typically, axillary lymph node dissection (ALND) is recommended when lymph node metastases are clinically suspected [4]. However, recent developments have focused on identifying patients in whom ALND can be safely omitted [5]. The targeted axillary dissection (TAD) procedure was developed to optimize axillary staging by marking the largest positive lymph node prior to NAC in combination with the sentinel lymph node biopsy technique [6, 7]. During surgery, both the marked and sentinel nodes are excised and their pathology is analyzed. Depending on the results, either ALND, adjuvant radiotherapy or no further axillary therapy is offered. Despite these developments, there remains interest in alternative methods of response evaluation. Highly sensitive non-invasive methods are warranted to minimize false-negative rates, potentially allowing avoidance of unnecessary invasive procedures in post-NAC node-negative patients, those with complete response. Additionally, highly specific methods could help identify candidates for adjuvant treatment options such as radiotherapy boosts [8–10].

Fluorodeoxyglucose positron emission tomography combined with a CT scan (FDG-PET-CT) is used in breast cancer staging to assess the degree of axillary lymph node metastases and screen for distant metastases [11–14]. However, FDG-PET-CT scans have also been used as a method of response evaluation after NAC [15–17]. Although it remains uncertain whether FDG-PET-CT scans are diagnostically accurate enough after NAC. The current Dutch guidelines, revised in 2017 [14], do not advice routine response evaluation after NAC using FDG-PET-CT scans. The guidelines do state that it can be considered to assess for the response of in-accessible lymph-nodes, such as internal mammary nodes, to assess for potential radiotherapy (boosts) [14]. On the other hand, FDG-PET-CT scans in addition to the TAD procedure lead to higher costs, as well as the generation and supplying of radiotracers have specifically a high contribution to the carbon footprint of a department [18, 19]. The aim of this study is to assess the diagnostic accuracy of the FDG-PET-CT scan as response evaluation of lymph nodes after NAC in breast cancer patients with initially clinically positive axillary lymph nodes.

Methods

Patient selection

This retrospective study was performed in a non-academic, large teaching hospital treating 400–500 breast cancer patients per year. All patients with breast cancer and clinically positive axillary lymph nodes (cN+), treated with NAC and who underwent the TAD procedure between 2016 and 2022 were reviewed. Only patients undergoing response evaluation by FDG-PET-CT scans were retrospectively included in our study. Patients with a history of breast cancer in the same breast, bilateral breast cancer, inflammatory or occult breast cancer, and deviations from protocol (such as iodine seed displacement or if no NAC was given) were excluded. Patients with oligo-metastatic disease are eligible in our institution for curative treatment, including local, axillary and metastatic surgery and radiotherapy, as supported by the Dutch breast cancer guidelines [14, 20, 21] and thus were included in our study if meeting all other inclusion criteria. The study was approved by its institutional commission (20251107, Isala Lokale Haalbaarheid Commissie).

TAD procedure and neo-adjuvant chemotherapy

The diagnosis of breast cancer and axillary lymph node metastasis was made by mammography, ultrasound, biopsy of the primary tumor and fine needle aspiration of axillary lymph nodes. Subsequently, tumor size was measured using magnetic resonance imaging (MRI) and ultrasound. FDG-PET-CT scans were used to stage primary breast cancer in clinical N+ or T3+ breast cancers prior to NAC and to look for FDG uptake in the primary tumor, internal mammary lymph nodes, axillary nodes and potential distant metastases. As part of the TAD procedure, radioactive iodine (I-125) seeds were placed under ultrasound guidance by a breast radiologist to mark the most prominent metastatic axillary lymph node. After the placement of the I-125 seeds, all patients received NAC, which was administered according to national protocols. These NAC regimens included Adriamycin/Cyclophosphamide/Paclitaxel, 5-Fluorouracil/Epirubicin/Cyclophosphamide with Trastuzumab/Pertuzumab or Paclitaxel/Carboplatin/Trastuzumab/Pertuzumab.

FDG-PET-CT acquisition

After receiving NAC, patients received an evaluation PET-FDG-CT scan to assess the response of axillary lymph nodes and, if applicable, distant (oligo-)metastases. Before the revision of the current Dutch breast cancer guidelines in 2017, which advised against the routine application of response FDG-PET-CT scans, its usage was much more broadly applied [14]. During the last few years of the study period, response FDG-PET-CT scans were considered in our institution in patients with cN3+,

oligo metastatic disease and in patients with contraindications to other assessment methods.

Patients were administered F18-FDG using a quadratic dose to weight scheme in which the average patient was administered 2.35 MBq/kg according to European Association of Nuclear Medicine guidelines [22]. Fasting of 6 h before administration of F18-FDG and 1 h of rest after injection was required. Patients were scanned on two different PET-scanners: (1) Philips Vereos Digital PET-CT, (2) Philips Ingenuity TF PET-CT. Image reconstructions were done according to EARL-1 standards [23]. Additionally high-resolution reconstructions were made at a 2 mm reconstruction. Both reconstructions were used for visual interpretation of FDG-PET-CT, while measurements were only done using EARL-1 reconstructions. Every scan was reviewed by a dedicated nuclear medicine physician and a radiologist. Lymph nodes were counted as positive depending on a combination of size, morphology on CT scan and Standardized Uptake Value (SUV) compared to the liver bed and blood pool. The results of these were discussed for every individual patient in a multi-disciplinary meeting, with at least a radiologist, nuclear medicine physician, breast surgeon, oncologist, radiotherapy physician and pathologist present, to confirm the findings and advise on further treatment, including the surgical procedure.

Surgery

For the primary surgery, patients underwent either mastectomy or lumpectomy, depending on response to NAC, tumor size, location, and ratio of tumor volume to breast volume. For axillary surgery, the marked axillary node was identified using a gamma probe and subsequently removed. If more than one lymph nodes were clinically positive, based on the clinical examination, ultrasound test and FDG-PET-CT scan during the staging process, the sentinel node was also excised by using patent blue injection to locate the node. In principle, at least a total of three to four lymph nodes were sampled [7].

Histopathological procedure

All excised lymph nodes were analyzed for pCR or residual metastases. An ALND was recommended if there were more than three clinically positive axillary lymph nodes at initial staging, based on clinical examination, ultrasound and the staging FDG-PET-CT scan, and there were histopathological residual metastases in any of the excised axillary lymph nodes. This was either at the same time as the surgery using a frozen section or as a secondary ALND after the initial surgery, if no frozen section was conducted.

The lymph nodes were halved, embedded in paraffin and subjected to haematoxylin and eosin staining. Macrometastases were defined as tumor deposits larger than 2.0 mm. Micrometastases were defined as tumor deposits larger than 0.2 mm but not larger than 2.0 mm, and isolated tumor cells were defined as cell clusters or single cells with no single cluster larger than 0.2 mm. pCR was defined as no micro-, macrometastases or isolated tumor cells in any of the axillary nodes.

Radiotherapy

Radiotherapy was administered according to national Dutch protocols [14]. Radiotherapy techniques were updated during the study. In 2016, intensity-modulated radiotherapy (IMRT) for radiotherapy planning was used, and from 2021 onwards a combination of IMRT and volumetric-modulated arc therapy (VMAT) was used. Axillary radiotherapy was recommended if there were histopathological residual tumor-positive axillary lymph node(s) after NAC, or if there were more than three positive axillary lymph nodes prior to NAC. All patients with positive internal mammary lymph nodes on pre-NAC FDG-PET-CT scans received radiotherapy to the internal mammary region. Radiation dose to the lymph node regions, internal mammary and/or axillary, was 15 times 2.67 Gy or 20 times 2.17 Gy and was administered after surgery. The schedule depended on whether or not a boost dose was given to the lumpectomy cavity. If the FDG-PET-CT scan for determination of the response to NAC remained positive for internal mammary lymph nodes, an additional radiotherapy boost to the positive internal mammary node was given of 20×0.5 Gy (total boost dose 20×2.67 Gy).

Data collection

Data on patient demographics, treatment, FDG-PET-CT scans, pathology results, recurrences and mortality were collected. From the staging and response evaluation FDG-PET-CT scans, the number of positive axillary and internal mammary lymph nodes as well as the maximum Standard Uptake Value (SUVmax) of the primary tumor and axillary lymph nodes were recorded. The histopathological and receptor status of the breast cancer and the number of axillary lymph nodes with isolated tumor cells, micro- and macrometastases were collected from the pathology results. Receptor types of breast cancer were defined as either (1) Estrogen (ER) and/or progesterone (PR) positive and Human Epidermal growth factor Receptor 2 (HER2) positive, (2) ER and/or PR negative and HER2 positive, (3) ER and/or PR positive and HER2 negative, (4) or triple negative. A HER2 heterogeneity result was considered negative for the purpose of data recording.

Statistical analysis

All data analyses were performed using Stata version 17.0. The sensitivity, specificity, positive predictive value

Table 1 Patient and tumor characteristics ($N=75$)

Clinical tumor stage before NST	*53 (46–63)*
T1	12 (16%)
T2	33 (44%)
T3	19 (25%)
T4	11 (15%)
Clinical lymph node stage before NST	
N1	30 (40%)
N2	16 (21%)
N3	29 (39%)
Clinical metastatic stage before NST	
M0	59 (79%)
M1	16 (21%)
Tumor histopathology[1]	
Invasive carcinoma of no special type	68 (91%)
Lobular carcinoma	3 (4.0%)
Metaplastic carcinoma	2 (2.7%)
Mixed invasive and lobular carcinoma	1 (1.3%)
Receptor and immune status	
HR+/HER2+	11 (15%)
HR–/HER2+	13 (17%)
HR+/HER–	38 (51%)
Triple negative	13 (17%)
Grade	
I	1 (1.3%)
II	34 (45%)
III	36 (48%)
Undefined	4 (5.3%)

HR, hormone receptor; HER2, human epidermal growth factor receptor 2; AC/PAC, adriamycin/cyclophosphamide/paclitaxel; FECTPE/PCTPE, 5-fluoroucacil/epirubicine/cyclofosfamide with trastuzumab/pertuzumab; PTCP: paclitaxel/carboplatin/trastuzumab/pertuzumab

[1]One patient with unknown tumor histopathology result

Table 2 Treatment details ($N=75$)

Neo-adjuvant chemotherapy regimen	
AC/PAC	41 (55%)
FECTPE/PCTPE	2 (2.7%)
PTCP	22 (29%)
AC/PAC + Carboplatin	6 (8.0%)
Other	4 (5.3%)
Primary operation type	
Breast conserving surgery	51 (68%)
Mastectomy	24 (32%)
Axillary lymph node surgery	
No ALND	58 (77%)
Primary ALND	13 (17%)
Secondary ALND	4 (5.3%)
Axillary lymph nodes histopathology	
Positive	41 (55%)
Negative	34 (45%)
Solely macrometastases	34 (45%)

AC/PAC, adriamycin/cyclophosphamide/paclitaxel; FECTPE/PCTPE, 5-fluoroucacil/epirubicine/cyclofosfamide with trastuzumab/pertuzumab; PTCP, paclitaxel/carboplatin/trastuzumab/pertuzumab

Table 3 Summary of FDG-PET-CT parameters

	Initial scan SUVmax	**Response scan SUVmax**
	Median (IQR 1–3)	**Median (IQR 1–3)**
Primary tumor		
HR+/HER2+ ($n=11$)	10.1 (7.9–13.3)	2.1 (1.9–2.8)
HR–/HER2+ ($n=13$)	6.9 (5.4–10.3)	2.0 (1.8–2.4)
HR+/HER2– ($n=38$)	6.7 (5.0–10.0)	2.2 (1.9–2.9)
Triple negative ($n=13$)	11.7 (7.1–15.2)	2.3 (2.0–3.3)
*Axilla**		
HR+/HER2+ ($n=11$)	9.4 (8.0–13.3)	1.4 (1.2–2.0)
HR–/HER2+ ($n=13$)	6.2 (5.6–8.4)	1.3 (1.1–1.7)
HR+/HER2– ($n=38$)	7.3 (3.8–10.8)	1.5 (1.2–2.0)
Triple negative ($n=13$)	8.0 (5.6–13.7)	1.7 (1.3–2.0)

*Based on the lymph node with the highest activity

(PPV), and negative predictive value (NPV) of the FDG-PET-CT scans for response evaluation to detect axillary positive lymph nodes were calculated using the pathology results of the surgically removed axillary lymph nodes as the reference standard. Both micro-, macrometastases and isolated tumor cells were considered pathologically positive lymph nodes. As a subgroup analysis, sensitivity, specificity, PPV, and NPV were also calculated for the detection of macrometastases only in the axillary lymph nodes to see if there is diagnostic value in detecting macrometastases only.

Results

A total of 351 patients with lymph node-positive breast cancer received the TAD procedure between January 2016 and December 2022, out of which 75 patients who received a response FDG-PET-CT scan were included in this study. The mean age was 53 years (IQR: 46–63). The largest group of patients ($n=33$) had a cT2 tumor at time of diagnosis and 16 patients had distant metastases. Thirteen patients had triple negative breast cancer and 24 patients had HER2 positive breast cancer. Most patients had invasive carcinoma of no special type ($n=68$). Patient and tumor characteristics are presented in Table 1. All patients received NAC before undergoing definitive surgery with the TAD procedure. The majority of patients ($n=51$) received breast conserving surgery. A median of three lymph nodes (IQR: 2–6) were removed during all axillary procedures. Treatment details are given in Table 2.

The median measured SUVmax was respectively for the primary tumor and axillary lymph nodes 8.0 (IQR 5.5–13.5) and 7.9 (5.0–11.4) for the initial FDG-PET-CT scan and 2.2 (IQR 1.9–2.9) and 1.4 (IQR 1.2–1.9) for the response scan. Details per hormone receptor subtype are given in Table 3. The prevalence of positive axillary lymph node(s) on histopathology after the TAD procedure was 55% ($n=41$). As seen in Table 4, nine of these 41

Table 4 Two by two table for axillary lymph node detection

		Axillary lymph nodes histopathology		
		Positive for metastases	**Negative for metastases**	**Total**
FDG-PET-CT scan	Positive uptake	9 (12%)	2 (2.7%)	11 (15%)
	Negative uptake	32 (43%)	32 (43%)	64 (85%)
	Total	41 (55%)	34 (45%)	75 (100%)

patients showed positive axillary lymph node(s) on their response evaluation FDG-PET-CT scans resulting in a sensitivity of 22% (95% CI 11–38%). Two of the patients with negative axillary lymph nodes on histopathology had positive axillary lymph node(s) on their response evaluation FDG-PET-CT scans (specificity 94%; 95% CI 80–99%). The PPV for the FDG-PET-CT scan to detect positive axillary lymph nodes was 82% (95% CI 48–98%) and the NPV was 50% (95% CI 37–63%). Additionally to the positive axillary lymph nodes, in twenty patients positive internal mammary lymph node(s) were found on their primary staging FDG-PET-CT scan and none of them had remaining positive internal mammary lymph nodes on their response FDG-PET-CT scan.

In the subgroup analysis, there were 34 patients (45%) with macrometastases in axillary lymph node(s) on histopathology, of which nine patients had positive uptake on their response evaluation FDG-PET-CT scan. For the detection of axillary lymph node macrometastases only, the response evaluation FDG-PET-CT scans showed a specificity of 95% (95% CI 84–99%) and a sensitivity of 26% (95% CI 13–44%). The PPV was 82% (95% CI 48–98%) and NPV was 61% (95% CI 48–73%).

Discussion

Whilst finding a high specificity of 94%, we show in our study that the sensitivity and NPV for FDG-PET-CT scans are limited, with only 22% of positive lymph nodes after NAC being identified by this scan and a NPV of 50%. Even in the subgroup analysis for detecting only macrometastases in the axillary lymph nodes, the sensitivity and NPV were, subsequently, only 26% and 61%. Suggesting that the usefulness of response FDG-PET-CT scans, in order to measure for lymph node metastases after NAC, is limited even in the current limited applications. Especially with procedures such as the TAD procedure having high accuracies for evaluating post-NAC response in the axilla.

Whilst previous studies have evaluated FDG-PET-CT scans for axillary response in breast cancer [24], our study uniquely used the TAD procedure as a reference reflecting developing clinical practice. Our study found that FDG-PET-CT scans after NAC have a low sensitivity and high specificity of detecting residual axillary metastases. These results are consistent with results of previous studies. A meta-analysis by Samiei et al. [24] reported that all currently used imaging modalities, such as ultrasound, MRI and FDG-PET-CT, have limitations in accurately assessing axillary lymph node metastases after NAC using sentinel long node biopsy or ALND as the reference. Their meta-analysis showed, with a total of 209 FDG-PET-CTs included, a sensitivity and specificity of 38% (95% CI 18%-61%) and 86% (95% CI 77%-93%) for detecting residual axillary disease, similar to the sensitivity of 22% (95% CI 11–38%) and specificity of 94% (95% CI 80–99%) in our study. One study by Koolen et al. [25] performed an early FDG-PET-CT scan, two to three weeks after starting NAC, to predict axillary PCR. They found a sensitivity of 48% and specificity of 95%, again lacking in finding axillary lymph node metastases. Even in our case using the TAD procedure, the combination of the sentinel node procedure and marking the axillary lymph node, as the gold standard shows lymph node response evaluation by FDG-PET-CT scans after NAC is not accurate.

Our results show the FDG-PET-CT scans fail to detect axillary metastases after NAC. The sensitivity of FDG-PET-CT scans depends on the FDG uptake, which in turn depends on the metabolic activity of the tumor and its metastases [26, 27]. NAC causes the malignant breast cancer cells, including the metastases in the lymph nodes, to die and thus reducing tumor activity [28]. Tumor size is positively linked to its detection by the FDG-PET-CT scan [29]. Lymph node metastases are already smaller than the main tumor and a partial response can cause the metabolic activity of metastases in the lymph nodes to become too small to be detected, whilst still having true malignant cells [30–32]. Thus causing the FDG-PET-CT scan to show a false negative after NAC but also having a high specificity.

Whilst the histopathology results from the TAD procedure were used as a gold standard for the FDG-PET-CT scan, the heterogenous group of 75 patients limits firm conclusions. Our patient cohort was a selected cohort with in general more advanced disease including those with N+ or T3 breast cancer at primary diagnosis reflecting the current application of response FDG-PET-CT scans. This usage has shifted during the study period due to national guideline update. In the earlier years, it was common to offer a response FDG-PET-CT scan for any cN+ patients whilst in the last few years in our institution it was narrowed down to mostly cN3+ or cM+ patients, clinical suspicion of tumor progression, or contraindications for MRI. Additionally, since the study period standard care keeps on developing, such as triple-negative breast cancer patients now receiving immune checkpoint inhibitors [33]. The cohort has a mix of triple negative, hormone positive and HER2+ positive breast cancer

patients, while the cohort numbers were too low to conduct sub-group analyses per receptor type. Previous literature has shown the luminal type (ER+ and/or PR+ receptor positive) breast cancer tumors have the lowest baseline FDG uptake whilst HER2+ and triple negative have the highest FDG uptake [34–36] . This is also seen in our study with the triple negative breast cancers having the highest axillary and primary tumor FDG uptake at baseline and response. The hormone receptor positive and HER2– group is known to have lower uptake while also being the biggest group in our cohort, which especially after neo-adjuvant therapy could mean an underestimation of positive nodes by FDG-PET-CT scans resulting in even lower negative predictive value and higher positive predictive value compared to if subtype analyses were possible. Despite the heterogeneity, the cohort of patients reflects the clinical practice of the last years in our institution and shows the inaccuracy of using response FDG-PET-CT scans for response evaluation of lymph nodes.

Although Dutch national guidelines do not recommend routine response evaluation after NAC, they are still used for various reasons. One given reason in the guidelines is less accessible nodes such as internal mammary nodes, due to invasive biopsies, having a higher risk of complications such as bleeding or pneumothoraxes [37]. But the low sensitivity and PPV of the FDG-PET-CT scans to detect residual axillary lymph node metastases suggest they are unlikely to contribute in decision making regarding inaccessible nodes after NAC. In our cohort none of the 20 patients with initial positive internal mammary lymph nodes were positive on their response scan and subsequently none of them received a radiotherapy boost to the internal mammary region. Decisions regarding treating potential positive internal mammary lymph nodes such as radiotherapy boosts could instead be based on other factors such as visible macroscopic nodes on the radiotherapy planning CT scan [38, 39]. Contrary to this the high specificity of response FDG-PET-CT scans indicate it could be applied to identify patients with a high likelihood and burden of residual axillary malignancy where the TAD procedure could be omitted and an ALND can be offered directly. Even if response FDG-PET-CT scans are used for other reasons, such as contradictions for MRI or clinical suspicion of tumor progression, caution should be taken with the results of the lymph nodes, as they likely are underestimating the metastases after NAC when negative. Whilst the high specificity indicates a high likelihood of residual axillary metastases.

Conclusions

The response FDG-PET-CT scans showed a low sensitivity and NPV for detecting residual metastases in axillary lymph nodes after NAC, using the histopathology results from the TAD procedure as a gold standard. This diagnostic inaccuracy of lymph node response FDG-PET-CT indicate that they are unlikely to be useful in decision making. Importantly, FDG-PET-CT scans are associated with high costs, complex logistics and a high environmental impact. Combined with the limited clinical value, omission of response FDG-PET-CT scans should be considered unless other clinical indications.

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Author contributions
All authors contributed to the study conception and design. KK. R. and JJ. N. wrote the main manuscript text. IM. N. aided in the statistical analysis. All authors reviewed and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
. The study was approved by its institutional commission (20251107, Isala Lokale Haalbaarheid Commissie).

Consent for publication
Not applicable.

Competing interest
The authors declare no competing interests.

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