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The added value of positron emission mammography in the assessment of the axillary lymph nodes of the pathologically proven breast cancer

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Abstract

Background The staging and management of patients with breast cancer are significantly influenced by the pathological state of the axillary lymph nodes (ALN). Thus, it is very desirable to have a differential diagnosis of metastatic ALN.

Purpose The aim of this research is to assess the effectiveness of non-invasive ALN staging using PEM versus traditional breast mammography and ultrasound in patients presenting with early-stage breast cancer. This study focuses on determining if PEM can reliably stage ALNs and potentially eliminate the need for more invasive methods.

Methods In a study involving 94 breast cancer patients, PEM was used to assess ALNs. The nodes were visually evaluated for positive or negative uptake, and further categorized as non-specific, indeterminate, or malignant based on their maximum uptake values. This classification was then compared with histopathological results.

Results There were a total of 94 breast cancer patients; the results from PEM demonstrated an ALN detection sensitivity of 83.3%. The specificity of PEM in this context was found to be 98.08%, and the overall accuracy rate was 91.49%. Additionally, the Positive Predictive Value (PPV) was calculated to be 97.2%, and the Negative Predictive Value (NPV) was 87.9%.

Conclusions The initial study has shown encouraging outcomes in terms of accurate lymph node assessment.

Keywords Positron emission mammography (PEM), Axillary lymph nodes, Breast cancer, PUVmax

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Background

Axillary lymph node involvement plays a crucial role in determining both the prognosis and the treatment approach for breast cancer patients [1]. Sentinel lymph node biopsy (SLNB) is generally the preferred method for staging in cases with clinically negative axillary nodes, while axillary lymph node dissection (ALND) is employed when there is evidence of metastasis [2].

Post-treatment lymphedema in breast cancer patients can detrimentally affect the function of the upper body and life quality, potentially worsening prognosis over time [3, 4]. National guidelines also recommend against exerting the arm on the same side as the treated breast to lessen the risk of developing breast cancer-related lymphedema, a concern that leads many women to adopt preventative measures [5, 6].

This underscores the necessity for a non-invasive technique for staging axillary lymph nodes. Positron emission mammography (PEM), a newer device dedicated to breast examination, affords a more refined metabolic scrutiny of dubious breast lesions and possesses the ability to uncover supplementary lesions [7, 8]. Its development aims to detect smaller breast cancers, making it a valuable supplement to mammography in breast cancer evaluation [8, 9]. PEM's imaging results are interpreted using a specialized BIRADS (Breast Imaging Reporting and Data System) classification [10, 11].

Methods

This study received approval from our institutional review board. We conducted a cross-sectional analysis of our database, which included 94 new patients who underwent PEM studies at our facility in 2021 and 2022. Initially, every patient was subjected to sonomammography. The treatment strategy for these patients was evaluated in multidisciplinary discussions, where a thorough review of clinical and imaging findings was conducted to determine the consensus on the necessity for additional imaging studies, such as histopathological examination and PEM. Three patients were omitted from the study due to previous surgical procedures, lack of complete clinical information, or unavailable imaging data (Figs. 1, 2, 3, 4, 5 and 6).

PEM examination

Patients were required to fast for a duration of 4 to 6 h prior to the FDG injection, with the aim of maintaining their glucose levels below 150 mg/dl. In the course of the imaging procedure, patients were placed in an upright stance, and the breast was meticulously positioned and compressed using transparent paddles, reflecting the arrangement typical in mammographic examinations. The administered dose of the radioactive substance, FDG, averaged around 0.154 mCi/kg, with the total volume used being approximately 3–5 ml, adjusted according to the patient's weight. Following the injection of the radiotracer, patients were required to rest in a calm

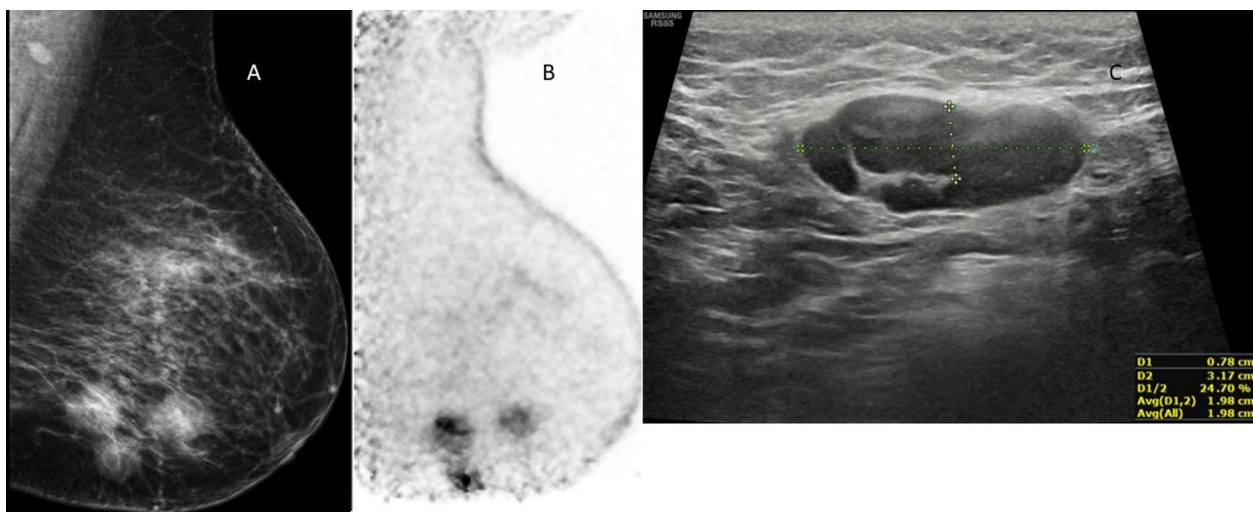


Fig. 1 A 75-year-old female presented with a complaint of a left breast lump. The images show **A** left MLO view, **B** left extended axillary view in PEM, and **C** left axillary ultrasound. There are irregular-shaped hyperdense lesions in the left breast's lower inner quadrant, identified as IDC in **A**, FDG avid lymph nodes which are not visualized in **B**, and an enlarged axillary lymph node with suspicious cortical thickening in **C**. The ultrasound displays the axillary lymph node with suspicious features. Pathology confirmed the lymph node's malignant nature. The PEM failed to detect the lymph node, likely due to technical issues as the patient was elderly and uncooperative

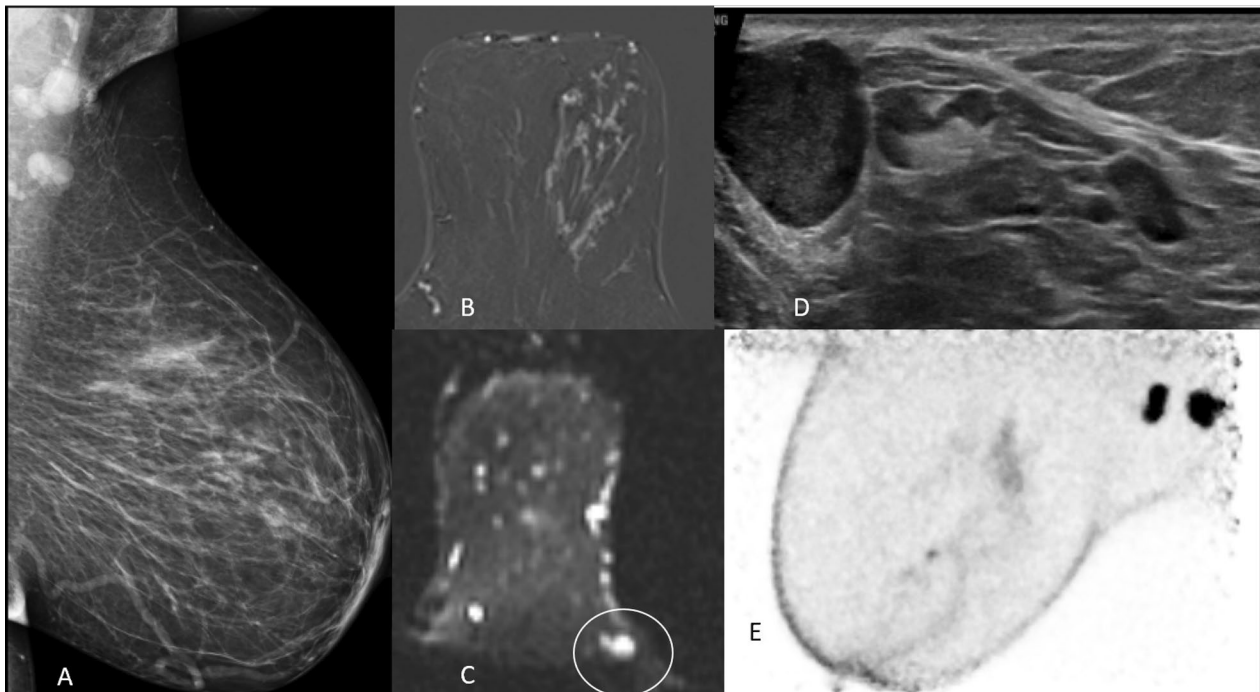


Fig. 2 A 64-year-old patient underwent screening sonomammography (**A** and **D**) revealing a focal linear asymmetry in the left breast UOQ noted by ultrasound, with a dilated duct containing echogenic content and an enlarged axillary lymph node with cortical thickening reaching 6 mm. MRI (**B** and **C**) showed an area of non-mass enhancement reaching the nipple, with (**C**) revealing an enlarged axillary lymph node with diffusion restriction (circled). PEM (**E**) showed multiple FDG avid left axillary lymph nodes, the largest measuring 2 cm, with PUV=3.5 and a lesion-to-background ratio (LTB) of 15.7. Histopathology confirmed IDC with major grade DCIS grade II

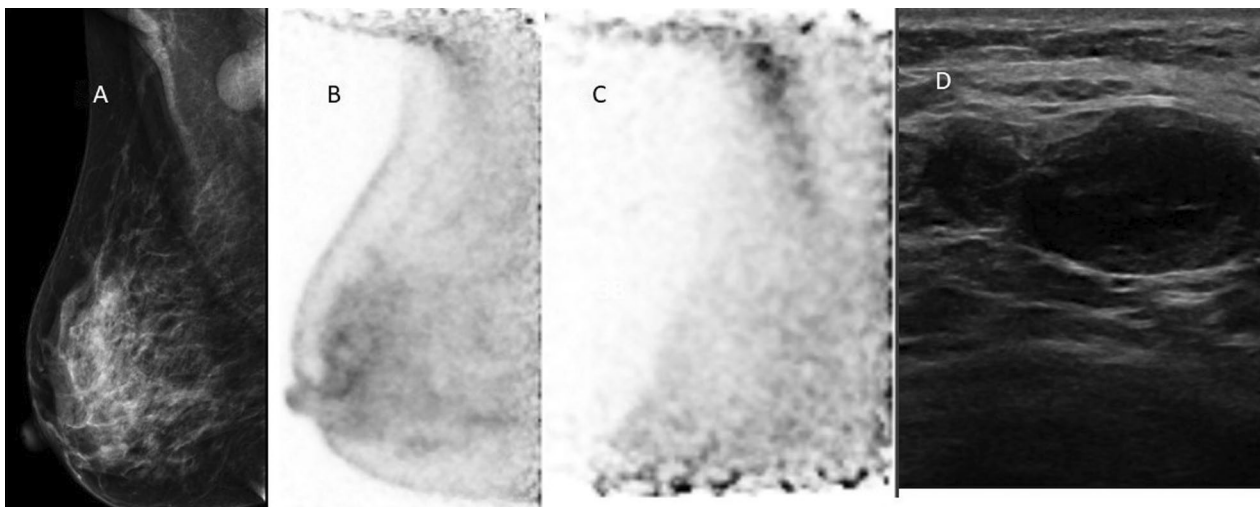


Fig. 3 A 56-year-old female presented with right breast swelling. Sonomammography (**A** & **D**) revealed focal asymmetry in the right breast with enlarged pathological lymph nodes. PEM (**B** & **C**) did not initially visualize avid lymph nodes, but adjusting the view revealed a few axillary focal avid FDG uptake lesions measuring about 12×10 mm, with PUVmax=2 and LTB=5.2, consistent with pathologically confirmed axillary lymphadenopathy

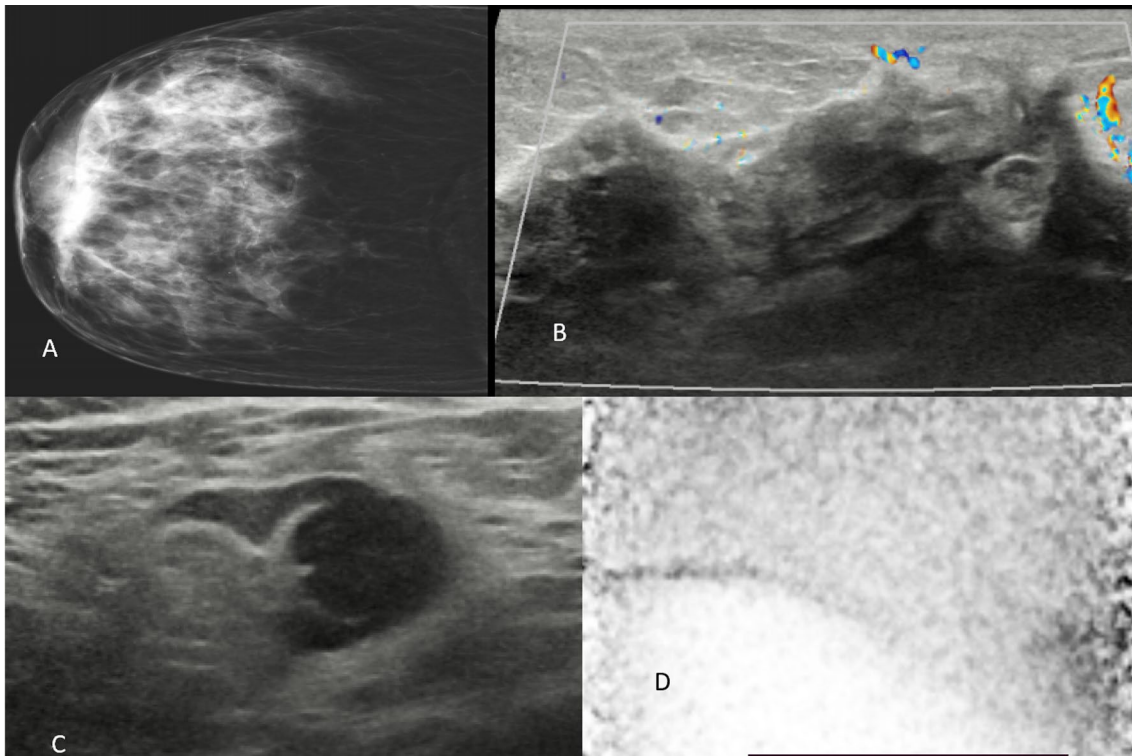


Fig. 4 A 68-year-old female presented with induration in the right breast's retroareolar area. Sonomammography (**A & B**) revealed retroareolar asymmetry with grouped and scattered microcalcifications extending to the upper quadrants. Ultrasound corresponded to large areas of altered echogenicity in the upper quadrants and retroareolar region, suggesting mass formation with prominent ducts extending to the LOQ. There was associated areolar thickening. **C** Axillary ultrasound revealed an enlarged axillary lymph node with a thickened cortex and effaced hilum. PEM (**D**) did not visualize avid lymph nodes. The PEM matched the pathology in this case with a pathologically proven negative axilla, showing mixed IDC and ILC

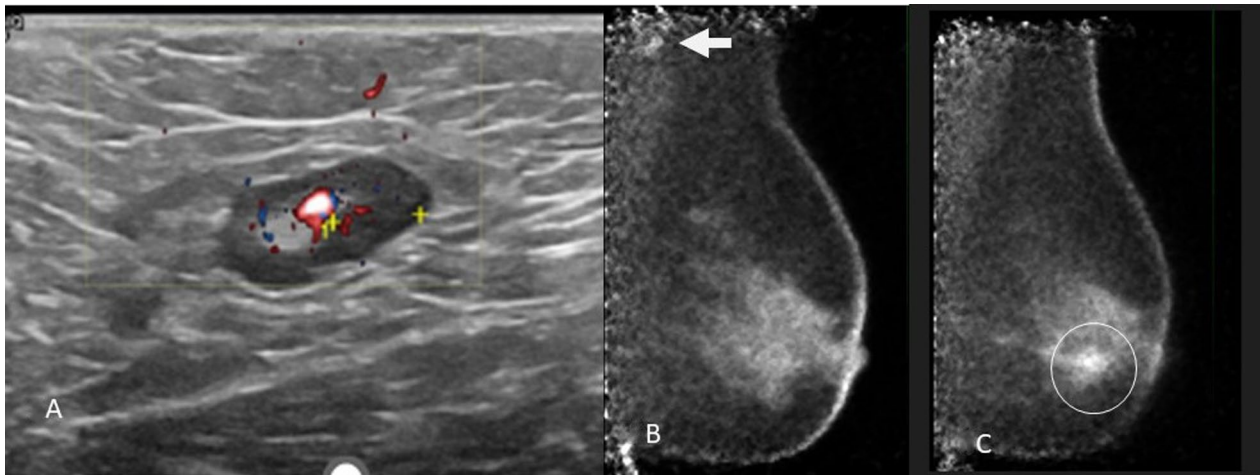


Fig. 5 A 55-year-old female complained of a left breast lump. Ultrasound **A** showed an enlarged oval left axillary lymph node with focal cortical thickening and hilar lymph node vascularity (low suspicion/indeterminate). PEM **B** revealed a solitary avid axillary lymph node with a PUV max of 1.5 and LTB of 2.7 (arrow) and **C** a left breast UIQ para-areolar FDG avid irregular mass measuring about 2 × 1 cm with a PUV max of 2.4 and LTB of 5.2 (circle). Pathology confirmed IDC

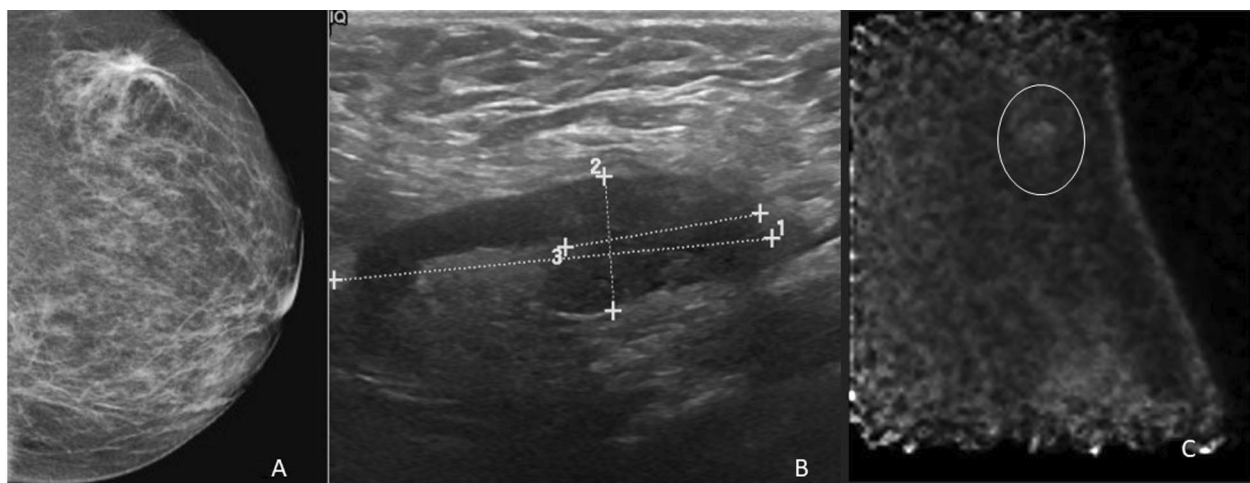


Fig. 6 A 50-year-old female presented with a complaint of a left breast lump. Sonomammography **A & B** showed focal asymmetry with distorted parenchyma in the left UOQ/axillary tail and an enlarged left axillary LN. PEM **C** revealed a low metabolic FDG avid axillary lymph node with a PUV max of 0.7 and LTB of 2.3. Pathology confirmed ILC. Pathologically proven ILC with positive surgical lymph node matching the ultrasound results. However, as it was low metabolic FDG avid at PEM, it was considered indeterminate (circle)

state for 45 to 90 min before the imaging process began. The procedure involved taking approximately 12 images per breast from both mediolateral oblique (MLO) and craniocaudal (CC) views. Special axillary views were also obtained to examine the axillary lymph nodes.

Imaging analysis

Image analysis was performed retrospectively, with agreement achieved by a radiologist possessing 12 years of expertise in breast imaging. Throughout the evaluation, the radiologist remained unaware of the final histopathological findings of the lesions to guarantee an impartial review.

The evaluation criteria focused on classifying the uptake as either positive (detected) or negative (non-detected). Detected lymph nodes were further categorized based on the data collected on maximum PUV (Positron Uptake Value) into three distinct groups: indeterminate, benign, and malignant.

Statistical analysis

The data analysis was conducted using the IBM SPSS Statistics for Windows, version 24.0.2, a commercially available software. Quantitative data were represented through means, standard deviations, medians, and ranges (minimum and maximum values). In dealing with categorical data, both frequency and relative frequency (%) were implemented. The identification of optimal threshold levels for LTB (lesion-to-background ratio) and PUV max (maximum Positron Uptake Value) for separating high-risk lesions from benign counterparts entailed employing the receiver operating characteristic (ROC)

curve methodology. At various cutoff points, specificity, sensitivity, and likelihood ratios were determined, with each calculation including a 95% confidence interval. The benchmark for deeming results statistically significant was determined to be *P*-values at or below 0.05. For categorical variables, statistical evaluations were carried out using the Fisher exact test and Chi-squared test.

Results

Within the study cohort, the age distribution extended from 27 to 69 years. All participants in the study underwent both sonomammography and PEM.

Qualitative assessment

This study encompassed 94 patients who were pathologically diagnosed with breast cancer. The findings revealed that PEM detected LNs in 42.5% of cases, while 57.5% remained undetected.

In terms of PEM criteria, the lymph nodes from all 94 cases were categorized into two groups: those with positive uptake (detected FDG activity within the lymph nodes), amounting to 40/94 cases, and those with negative uptake (non-detected FDG activity within the lymph nodes), totaling 54/94 cases. Upon analyzing the maximum PUV max data, it was found that 4 out of the 40 detected LNs were classified as non-specific by PEM. This led to a total of 58 LNs being considered negative or non-suspicious by PEM (54 non-detected plus 4 classified as benign based on PEM criteria). Conversely, 36 out of the 40 were deemed pathological (malignant) by PEM criteria.

Table 1 Accuracy measures of PEM in detection of axillary lymph nodes in relation to surgery

Criteria of Lymph node (PEM)	Pathology finding				Total	Sensitivity	Specificity	PPV	NPV	Accuracy
	Positive		Negative							
	No	%	No	%						
PEM positive	35	97.2	1	2.8	36	83.3	98.08	97.22	87.93	91.49
PEM Negative	7	12.1	51	87.9	58					
Total	42		52		94* (100%)					

* Statistically significant at $p \leq 0.05$

When comparing these results to the pathological findings, which served as the reference standard, it was discovered that 42 LNs were actually pathological and 52 were benign. Among the 36 LNs detected as suspicious by PEM, only 1 was found to be benign (inflammatory) upon pathological examination (a false positive), while the remaining 35 were confirmed as malignant (true positives). There were 4 cases identified as benign by PEM that were subsequently confirmed as malignant (false negatives) by pathology, specifically found to be invasive lobular carcinoma (ILC).

Furthermore, among the 54 LNs that PEM did not detect, 3 were later proven malignant by pathological analysis (false negatives), while the remaining 51 non-detected LNs were confirmed as benign (true negatives) by pathology, as detailed in Table 1.

Quantitative assessment

Receiver operating characteristic (ROC) analysis was conducted to evaluate the capability of PUVmax and LTB to detect lymph node involvement. The analysis determined optimal threshold values for the measures along with their sensitivity, specificity, and statistical significance.

The PUVmax metric demonstrated strong diagnostic accuracy at a cutoff value greater than 1.5, achieving 98.08% sensitivity and 83.3% specificity. The area under the PUVmax ROC curve equaled 0.929, reflecting highly significant discrimination ability ($P < 0.001$). In contrast, at a threshold of 2.6, LTB showed markedly inferior performance with 50% sensitivity and

low statistical significance ($AUC = 0.500, P = 0.868$), as detailed in Table 2.

Evaluating PEM uptake values in the axillary lymph nodes in breast cancer

The mean of the maximum PEM uptake value (PUVmax) in the studied lymph nodes was 2.27 ± 2.12 , with a range from 0.9 to 7.4. The mean of the maximum lesion-to-background ratio (LTB) was 6.5 ± 5.18 , with a range from 2.6 to 17.3.

Discussion

PEM, or positron emission mammography, represents a novel molecular imaging technique in breast imaging. Utilizing a radiotracer, it can detect various biological processes, including metabolic activities and cell proliferation, crucial in understanding cellular behaviors [12]. To date, there have been relatively few studies specifically dedicated to evaluating PEM’s effectiveness in axillary lymph node assessment. The majority of research and literature have predominantly concentrated on PEM’s role in evaluating breast lesions, with less emphasis on axillary lymph nodes.

In contrast, numerous studies have investigated the utility of PET CT in axillary lymph node assessment, revealing a pooled sensitivity of 63% and a pooled specificity of 94%. However, sensitivity rates reported in these studies have varied significantly, ranging from 20 to 100%. Such discrepancies in sensitivity and specificity across different studies could be attributed to variations in clinical populations and the methodologies employed in PET imaging and interpretation [13].

Table 2 Validity (AUC, sensitivity, specificity) for PUVmax and LTB in detection of L.Ns

	Best cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (%)	P-value
PUV _{max}	1.5	83.3	98.08	97.2	87.9	0.929	< 0.001
LTB	2.6	50	0	33.3	0	0.500	1.00

AUC area under a curve, p value probability value

NPV Negative Predictive Value, PPV Positive Predictive Value

For patients undergoing initial surgery or neoadjuvant chemotherapy, the decision-making process concerning axillary lymph node dissection or sentinel lymph node biopsy is greatly influenced by imaging assessments, which play a crucial role in guiding clinical decisions.

Ultrasound not only offers dependable morphological data but also plays a crucial role in guiding biopsies of suspicious nodes. In patients receiving neoadjuvant chemotherapy with confirmed nodal metastasis, performing targeted axillary dissection of the biopsy-proven metastatic node could potentially mitigate the issue of elevated false-negative rates observed with sentinel lymph node biopsy [13].

In their 2015 study, Maxwell and colleagues highlighted the efficacy of ultrasound in discerning nodal involvement. They emphasized that any nodal involvement suggested by imaging techniques necessitates verification via an ultrasound-guided biopsy. Furthermore, if imaging and biopsy collectively confirm nodal involvement, it is recommended to forego the sentinel lymph node procedure in favor of undertaking an axillary lymph node dissection. If there are no signs of axillary lymphadenopathy detected on imaging, the sentinel lymph node procedure is recommended when deemed appropriate.

The exploration of other imaging methods like PEM for axillary lymph node assessment is aimed at evaluating their potential to replace or supplement surgical procedures like SLNB. A meta-analysis encompassing 69 studies estimated the sensitivity of SLNB at 93%, with its specificity considered to be near 100%, owing to the reliance on histological examination [13].

In our study, we evaluated 94 axillary lymph node (LN) cases using PEM. These were divided into two categories: those with positive uptake (detected), numbering 40/94, and those with negative uptake (non-detected), totaling 54/94. According to the PEM criteria, 4 out of the 40 detected LNs were deemed non-specific, leading to a total of 58 LNs being classified as negative or non-suspicious (54 non-detected plus 4 benign based on PEM criteria), while 36/40 were identified as pathological (malignant) by PEM.

When juxtaposed with surgical pathological findings used as the gold standard, it was found that 42 LNs were pathological and 52 were benign. Out of the 36 LNs identified as suspicious by PEM, only 1 was later found to be benign (inflammatory) by pathology (a false positive), and 35 were confirmed as malignant (true positives). Additionally, 4 cases categorized as benign by PEM were later confirmed as malignant (false negatives) by pathology, specifically diagnosed as invasive lobular carcinoma (ILC).

Among the 54 LNs with negative uptake not detected by PEM, 3 were subsequently confirmed as malignant

by pathology (false negatives), while the remaining 51 non-detected LNs were confirmed as benign (true negatives). The effectiveness of PEM in our study showed a sensitivity of 83.3%, specificity of 98.08%, and an overall accuracy of 91.49%. The Positive Predictive Value (PPV) was 97.2%, and the Negative Predictive Value (NPV) was 87.9%.

The research conducted by Narayanan et al. in 2011 [14] along with Glass & Shah's study in 2013 [15] presented findings similar to ours concerning axillary lymph node evaluation, albeit in PET examinations. Glass and Shah [15] concluded that PEM is effective for detecting, characterizing, and determining the extent of primary breast disease, but they did not recommend it for axillary node staging. Narayanan et al. [14] reported that out of 19 axillary lymph nodes identified as suspicious, only 10 (53%) actually exhibited nodal metastatic disease.

In a separate study by Berg et al. in 2006 [16], PEM demonstrated a sensitivity of 91%, specificity of 93%, Positive Predictive Value (PPV) of 95%, Negative Predictive Value (NPV) of 88%, and an overall accuracy of 92% yet for breast lesions not the axillary lymph nodes when interpreted alongside mammographic and clinical findings.

Concerning PUV measurements in our studied axillary lymph nodes, the mean maximum PEM uptake value (PUVmax) was 2.27 ± 2.12 , with a range from 0.9 to 7.4. However, the LTB results showed an insignificant *P*-value ($P=0.868$). This could be attributed to the absence of a normal reference for background uptake in the axilla, as opposed to the breast, complicating the interpretation of these values, as well as improper and difficult patient positioning.

According to Yamamoto et al., found that Youden's index, the cutoff point for differentiating benign from malignant breast lesions was set at 1.97 for PUVmax, yielding a specificity of 85% and a sensitivity of 76%. The cutoff for LTB (lesion-to-background ratio) for breast lesions was determined to be 2.62, with the same sensitivity and specificity [17]. Our study's outcomes are consistent with those reported by Toi in 2023 [18], demonstrating a comparable pooled sensitivity of 85% and specificity of 79% for PEM in breast cancer assessment.

Limitations

There are some limitations of the current study

There is a lack of substantial research on the effectiveness of positron emission mammography (PEM) in characterizing axillary lymph nodes in cases of breast cancer. This gap underscores the necessity for more

comprehensive studies to fully evaluate PEM's role and capabilities in this specific aspect of breast cancer diagnosis and treatment.

Aside from the obvious benefits of PEM technology, there are several limits to PEM scanning

In positron emission mammography (PEM), the use of FDG as a tracer is not exclusively specific to tumors, as benign conditions, particularly those involving inflammation or infection, can also exhibit uptake. This complicates the differentiation between benign and malignant processes. Another concern with PEM is its association with increased radiation exposure, which heightens the risk of inducing cancer in radiosensitive organs. Some examinations in our study were excluded due to inadequate axillary visualization in standard views, a limitation we attempted to address by employing extended axillary views. When correlating lymph node (LN) findings with histopathological data, results were accurate for invasive ductal carcinoma (IDC), but invasive lobular carcinoma (ILC) presented false negatives due to low uptake activity. Ductal carcinoma in situ (DCIS) cases aligned with pathology, showing negative results for LNs, and in benign cases, there was one instance of granulomatous mastitis (GM) falsely appearing positive on PEM due to high activity. Notably, the urinary bladder receives the highest radiation exposure during PEM, posing a significant cancer risk.

Conclusions

Preliminary study shows promising results for accurate lymph node assessment by PEM and characterization of the benign and malignant lymph nodes using the PUV max as reference standard with improved lesion detectability with 83.3% sensitivity 98.8% and sensitivity in assessing ALN status among patients presenting with breast cancer.

The clinical utility of non-invasive axillary lymph node (ALN) staging is via PEM, in comparison with alternative non-invasive modalities such as breast mammography and sonography, among patients with early-stage breast cancer. FDG PEM appears to be relatively accurate in the depiction of primary breast cancer.

Abbreviations

ALN	Axillary lymph nodes
ALND	Axillary lymph node dissection
BIRADS	Breast imaging and reporting data system
DWI	Diffusion-weighted imaging
FDG	Fluorodeoxyglucose
FN	False negative
FP	False positive
ILC	Invasive lobular carcinoma
LN	Lymph node
LTB	Lesion to background
MLO	Mediolateral oblique

MRI	Magnetic resonance imaging
NPV	Negative Predictive Value
PET-CT	Positron emission tomography-computed tomography
PPV	Positive Predictive Value
PUV	Positive uptake value
PEM	Positron emission mammography
ROC	Receiver operating characteristic
ROI	Region of interest
SLNB	Sentinel lymph node biopsy
TN	True negative
TP	True positive

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Author contributions

GH wrote the manuscript and is responsible for correspondence to journal. AH collected patient data and was responsible for image processing and collection of patient's images. GM and OM participated in the design of the study and performed the statistical analysis. MH and MM conceived of the study and participated in its design and coordination, and was responsible for the review of the draft from a clinical point of view. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed 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 the Institutional Review Board (IRB) of the National Cancer Institute, Cairo University, with ethical committee approval number 2302-308-057. Informed written consent was taken from all subjects.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests

No financial or non-financial competing interests.

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