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RESEARCH

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Positron emission mammography (PEM): a potentially promising one-stop shop for local staging of ILC

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Abstract

Background Invasive lobular cancer (ILC) has a high propensity for multiplicity, along with a high probability of incomplete surgical excision. Due to its insidious proliferative pattern, it tends to be clinically silent and radiologically elusive. We assess the performance characteristics of PEM in the detection and local staging of ILC.

Methods A retrospective study evaluated a total of 193 patients who underwent PEM examination, including 44 patients with ILC. Image analysis of PEM examinations included morphological criteria, uptake pattern, lesion to background ratio (LTB) and maximum PEM uptake value (PUV max) assessment. The findings were correlated with the histopathological results.

Results PEM showed high performance in surgical planning and detection of additional ILC lesions with sensitivity of 90.6% and specificity 82%. The mean PUV max and LTB of ILC lesions were significantly different from those of benign lesions and IDC lesions. The cutoff average LTB and PUVmax values to differentiate ILC from benign lesions were ≥ 3.3 & ≥ 2.2, respectively.

Conclusions The inclusion of PEM provides a functional image that can improve the diagnostic accuracy of the conventional studies, decreasing the rates of false results and improving the detection of multicentric ILC lesions identification and their differentiation from other benign breast lesions.

Advance in knowledge PEM is a promising new imaging technique that further improves the pretherapeutic assessment of ILC and facilitates the assessment of patients with renal impairment.

Keywords Invasive lobular carcinoma, PEM, PUV max and LTB

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Background

Invasive lobular cancer (ILC) is the second most common type of breast cancer s1.

Due to its infiltrative growth, subtle mammographic findings are more common in ILC than in the other invasive carcinomas. Thus, ILC lesions exhibiting similar density to breast parenchyma may be missed in mammography; hence, mammography sensitivity for ILC has been reported to vary from 57 to 79% [1, 2].

It also has a high incidence of multifocal, multicentric and contralateral disease, with the extent of disease often being underestimated [3, 4], making ILC more prone to

incomplete surgical excision and subsequent re-excision than other histological types of breast cancer [5].

After breast conservation surgery, incomplete excision of ILC ranges from 12 to 60%, leading to re-excisions or even mastectomy [6]. So, preoperative imaging workup is critical [2, 7].

Positron emission mammography (PEM) is a new breast-dedicated device that obtains a more accurate metabolic evaluation of suspicious breast lesions and detection of additional lesions [8, 9]. It has been developed for detecting smaller breast cancer, so it can be used as an adjunct to mammography in breast cancer assessment [10, 11]. PEM images are interpreted according to a functional BI-RADS (Breast Imaging Reporting and Data System) class [12].

The aim of this study, therefore, was to assess the performance characteristics of PEM in detection and proper evaluation of ILC extensions compared to conventional imaging modalities and evaluation of its efficacy to evaluate the suitability for breast conservative surgery (BCS) and influences the rate of re-excisions and the rate of mastectomies.

Methods

Patients

Our institutional review board approved this study. A retrospective review of the database of all 208 PEM studies for new patients was performed in 2021 and 2022 at our institute.

All patients underwent an initial sonomammography revealing a BIRADs IV lesion that requires further assessment. Patient management was discussed in multidisciplinary meetings where clinical and imaging findings were evaluated and a consensus decision was taken to perform further imaging, including PEM and histopathological assessment.

Out of the 208 patients, 15 patients were excluded due to prior surgical intervention, incomplete clinical data and/or incomplete or unavailable imaging. A total of 44 patients with ILC, 108 with invasive ductal carcinoma (IDC) and 41 with benign breast lesions were included in the study.

PEM examination

Patients were asked to fast for 4–6 h, and serum glucose levels should be below 150 mg/dl before the administration of FDG. Patients were seated upright, and the breast was gently stabilized between clear compression paddles with positioning similar to mammography. The average dose for the radioactive material was about 0.154 mCi/kg of FDG with a total amount of about 3–5 ml of FDG during the muscle rest. However, the dose varied depending on the patient's weight. After injecting the radiotracer, the patients had to rest quietly for 45–90 min before commencing imaging. About 12 images of each breast for each CC (craniocaudal) and MLO (mediolateral oblique) views were obtained. Additional axillary views for axillary lymph node evaluation were also obtained.

Imaging analysis

Image analysis was retrospectively performed in consensus by a radiologist with 12 years of experience in breast imaging. The reader was blinded to the lesion's definitive histopathological examination reports.

The assessed morphologic criteria were shape (oval, round, irregular), margin (circumscribed, not circumscribed), uptake pattern (mass, non-mass or both), number (single, multifocal and multicentric), LTB (lesion to background ratio), and PUVmax values (maximum PEM uptake value) were measured for index lesions only, as some additional lesions were too small.

Since PEM was performed as diagnostic examination, additional lesions were detected on PEM, either ipsilaterally or contralaterally, and eventually confirmed by histology or imaging follow-up. Lesions assigned a BI-RADS 3 or lower and stayed negative on 6-month follow-up were considered as negative.

Multifocal and multicentric breast cancers are defined as the presence of two or more tumors within the same breast. If the distance between the lesions is ≤ 5 cm, it is multifocal, and when the distance is >5 cm, it is multicentral.

Our study aims for guiding further surgical management; the additional suspicious lesions were confirmed by ultrasound second look and biopsy. PEM sensitivity and specificity in detection and characterization of involvement of more than one quadrant and bilaterality in preoperative assessment of ILC was correlated with biopsy results and/or post-surgical histopathological results.

Statistical analysis

Data analysis was performed with commercially available software (IBM SPSS Statistics for Windows version 24.0.2). Data were summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. The determination of the optimal LTB and PUV max threshold value for differentiating high-risk lesions from benign lesions was performed by the receiver operating characteristic (ROC) curve. Sensitivity, specificity and likelihood ratios were calculated at different cutoff values with a 95% confidence interval. P values ≤ 0.05 were considered statistically significant. Statistical evaluation was performed

with the Chi-squared and the Fisher exact test for categorical variables.

Results

The ILC patients' ages ranged from 35 to 72 years (mean age: 52 ± 10 years), and all patients were females. All patients underwent sonomammography and PEM, while only 32 underwent CEDM (contrast-enhanced digital mammography). Flow chart of enrolled patients is illustrated in (Fig. 1).

Qualitative assessment

The study included 44 patients with pathologically proven ILC with a total of 46 ILC index lesions and 53 satellite ILC lesions. One index lesion was detected by sonomammography only; it was in the axillary tail which is a blind area of the PEM detector.

In the two patients with bilateral pathologically proven ILC, bilateral index lesions were detected in sonomammography, CEDM and PEM.

In the 44 patients of ILC, a total of 33 lesions that were proven to be of benign nature either via histopathological correlation or via follow-up were also detected. Diagnostic performance of sonomammography, CEDM and PEM is detailed in (Table 1) (Fig. 2).

The maximal diameter of index lesion ranged from 0.6 to 15 cm, with an average of 5.4 cm.

Out of the 53 ILC lesions, 6 false-positive lesions were detected, pathologically proven 4 cases of high-risk lesions, 1 case of inflammatory process and 1 case of fat necrosis.

Out of a total of 23 multicentric lesions, PEM findings enforced by histopathological confirmation successfully changed the surgical management of 10 patients from breast conservative surgery due to the ILC being larger or the disease being multifocal or both. Surgical pathological results confirmed the presence of multicentric ILC disease in 7 out of the 10 cases.

One patient with suspected multicentric disease on PEM was overtreated due to patient choice of mastectomy without biopsy.

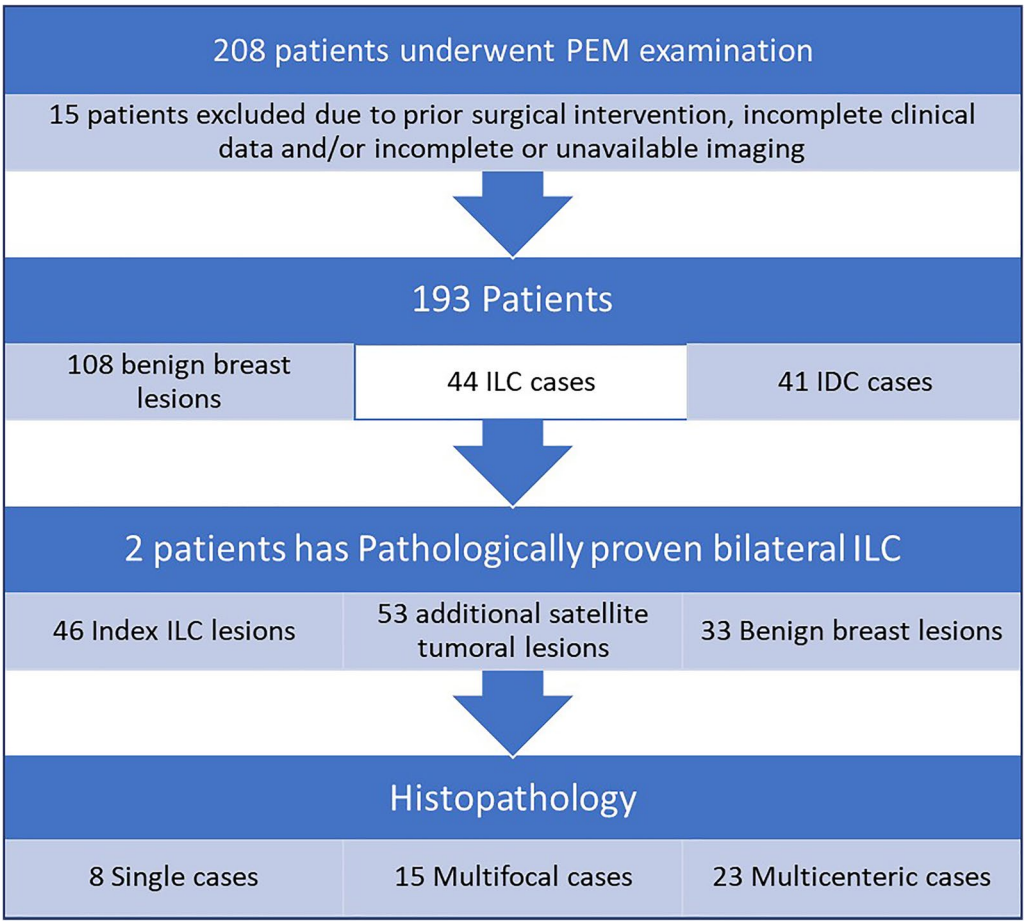

Fig. 1 Flowchart for enrolled and eligible participants in the study

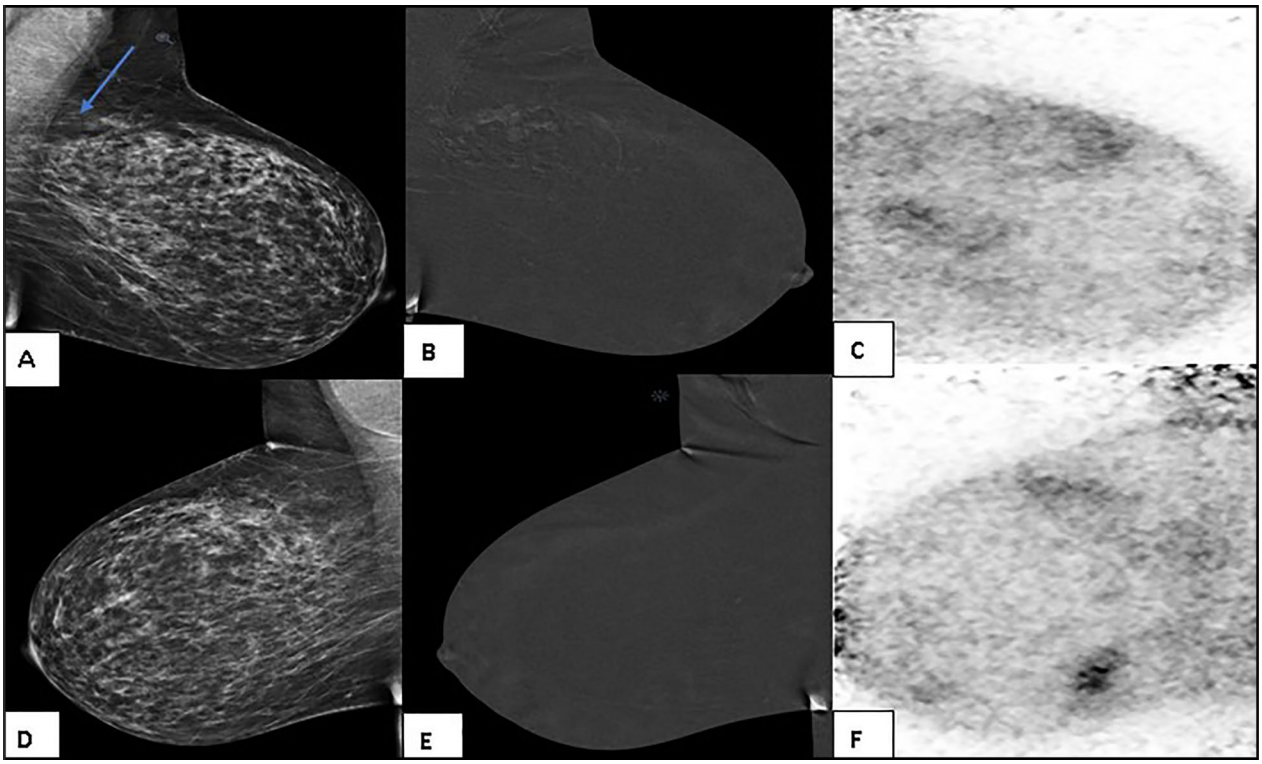

Fig. 2 A 48-year-old patient underwent screening sonomammography (**A** and **D**) that revealed left breast UOQ focal asymmetry (arrow) with underlying parenchymal distortion indicating further CEDM assessment. CEDM (**B** and **E**) revealed left breast UOQ focal non-mass enhancement and no right breast-enhancing masses. PEM (**C** and **F**) revealed left breast UOQ FDG avid non-mass lesion with PUV max (1.5) and LTB (2.5), left LOQ focal non-mass lesion showing intermediate FDG uptake with PUV max (1.36) and LTB (2.3) and right LOQ focal non-mass FDG avid uptake with PUV max (1.7) and LTB (3.4). Left breast lesions proved to be lobular carcinoma and right breast lesion proven to be PASH on histopathological correlation

Only two patients (4.5%) of the overall population needed a reoperation after the initial surgery.

Quantitative assessment

The cutoff average LTB value to differentiate ILC from benign lesions was > 3.3 with sensitivity 93.3% and specificity 95.1%, and the cutoff PUV max was > 2.2 with sensitivity 95.6% and specificity 97.6% ($P < 0.001$).

The mean PUV max and LTB of ILC lesions were 3.1 and 4.54, respectively. Benign and ILC lesions revealed significantly different mean PUV max and LTB values ($P < 0.001$) (Fig. 3).

The mean PUV max and LTB in benign lesions (1.560 and 2.58, respectively) were significantly lower than those of ILC lesions; however, mean PUV max and LTB values in IDC lesions (4.1 and 5.75, respectively) were significantly higher than those of ILC lesions $P < 0.001$ (Fig. 4).

Discussion

At present, breast cancer is the most common malignant tumor in women worldwide [13]. Invasive lobular carcinoma is the second most prevalent type of breast carcinoma with an incidence rate of 5% and 15% with high propensity for multifocal manifestation of disease [4].

Diagnosis and assessment of ILC has always been challenging and problematic, as it tends to be clinically silent and radiologically elusive in many cases. Surgical outcomes for patients with early-stage ILC remain worse than the surgical outcomes for patients with IDC, with higher rates of positive margins and increased need for repeat operations and completion mastectomies [14].

The role of imaging in the evaluation of breast lesions is undeniable, because an early detection and accurate diagnosis of multiple breast cancers is of paramount importance for deciding the extent of surgical procedures for adequate clearance of the tumor, ensuring a lower rate of advanced metastatic disease at diagnosis and a longer overall survival [8, 15].

Formerly the standard way to assess suspicious lesions included sonomammography and image-guided needle biopsy, with limitations including underestimation in patients with dense parenchyma, small lesions and patients with ILC that presents as subtle

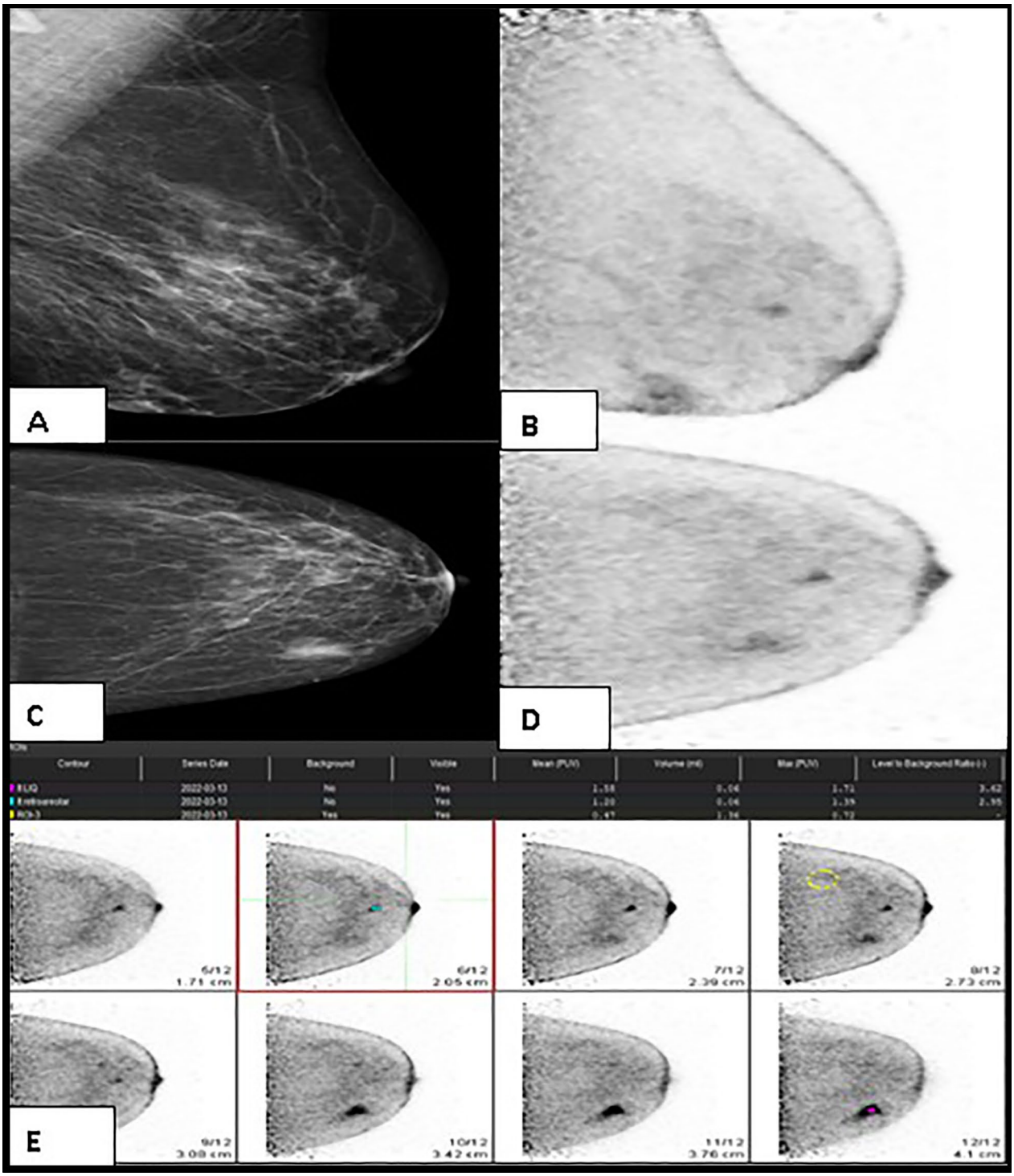

Fig. 3 A 64-year-old patient underwent screening sonomammography (**A** and **C**) that revealed left breast LOQ ill-defined dense lesion infiltrating the skin with ultrasound revealed suspicious lesion (not illustrated). PEM (**B**, **D** and **E**) revealed left breast LIQ skin-infiltrating FDG avid irregular mass (Arrow) with PUV max = 1.71 with LTB = 3.6. Another retro-areolar FDG avid smaller lesion is seen with PUV max 1.4 and LTB of about 3. Second-look ultrasound-detected suspicious looking nodule with histopathology-proven multicentric ILC

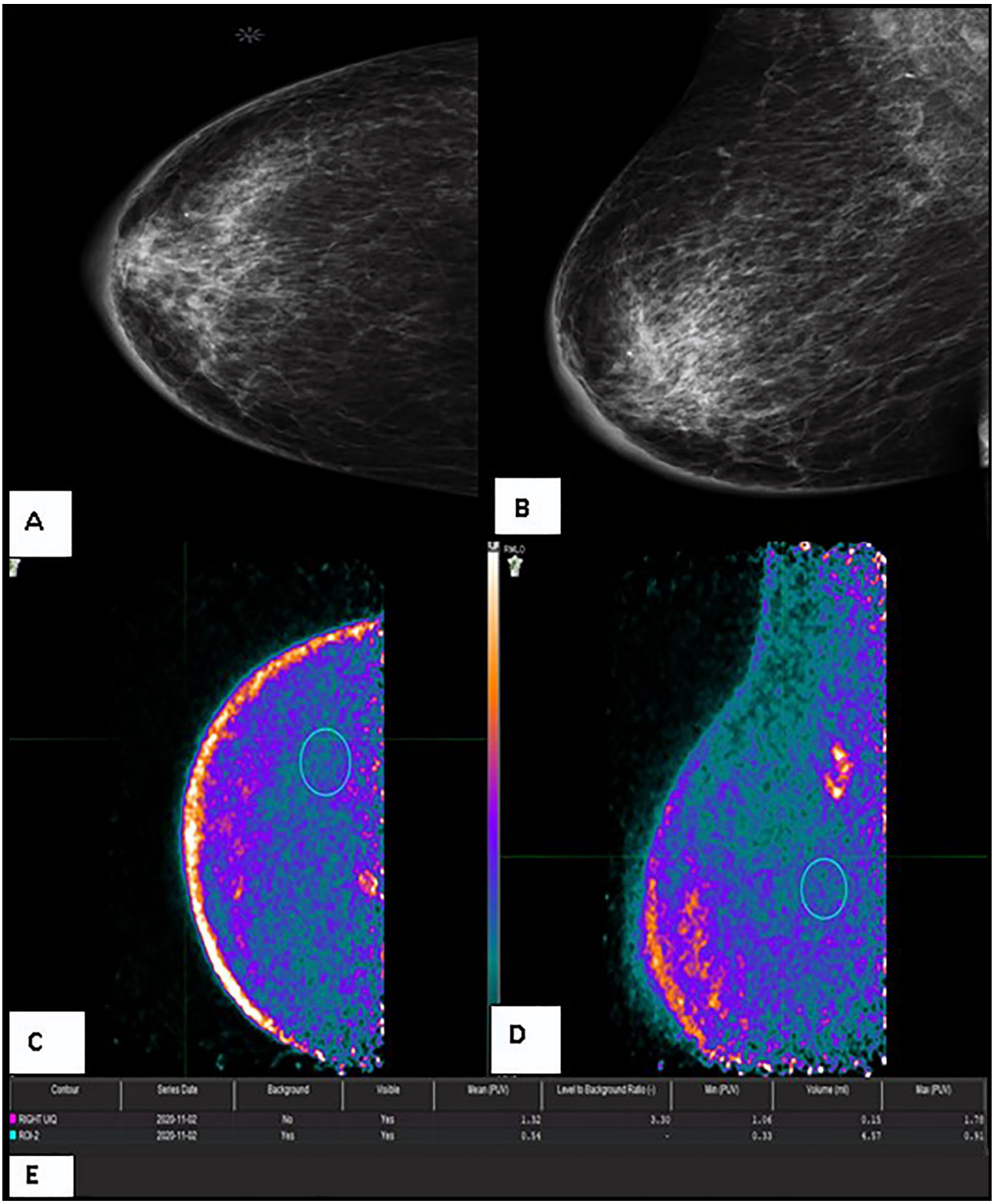

Fig. 4 A 56-year-old female presented with right breast swelling. Sonomammography (**A** and **B**) revealed right breast diffuse edema pattern and skin thickening yet with no definite masses, lymph node biopsy proved adenocarcinoma of breast origin warranting further assessment. PEM (**C** and **D**) revealed right breast diffuse skin and nipple/areola complex FDG activity with PUV max = 2.5 & lesion to back ground (LTB) = 4.8. Right breast deeply seated mass with avid FDG uptake, PUV = 1.8 and LTB = 3.3 is noted. Histopathology proved ILC

Table 1 Diagnostic performance of different imaging modalities

Detection of modality	Multicentric lesions			Any additional ipsilateral ILC foci	
	Sonomammography	CEDM	PEM	Sonomammography	PEM
Sensitivity (%)	60.9	81.2	91.3	66	90.6
Specificity (%)	74	75	87	72.7	81.8
PPV (%)	70	76.5	87.5	79.55	88.9
Accuracy (%)	67.4	78.1	89	68.6	87.2

Ipsilateral additional lesions assessment was not feasible in CEDM as MDT requests of biopsy assessment were decided upon PEM results

architectural distortion, focal asymmetry or shows no abnormalities at all [16].

To date, breast imaging is facing the challenge of running faster than breast cancer, in order to offer a personalized treatment and improve patient prognosis and overall survival. The application of molecular techniques and artificial intelligence may allow breast imaging to play a crucial role in breast cancer care, beyond the detection [16].

PEM is a new and advanced molecular breast imaging technique that, using a radio tracker, detects biological processes, including cellular behaviors performed for metabolism and cell proliferation [8].

PEM is believed to obtain a more accurate detection of small breast lesions, particularly in women with high breast density, thanks to the combination of an early metabolic evaluation provided by FDG high spatial resolution. Detection of sub-centimetric breast tumors might lead to the identification of multiple occult lesions that evade conventional diagnosis [11, 15].

According to our knowledge, there has been no dedicated study for assessment of PEM performance in ILC. The aim of our study was to assess the diagnostic performance of PEM to achieve better preoperative assessment as regards assessment of index lesion extension and detection of ipsilateral as well as contralateral additional ILC lesions.

Mammography is less sensitive in detecting ILC than IDC, which can be explained primarily due to its pathologic features, with wide sensitivity ranging from 57 to 81% compared to 63 to 98%, respectively [17]. In assessment of ILC lesions, CEDM reported sensitivity and specificity of 84.2% and 66.7% [18].

Our study revealed sonomammography sensitivity and specificity for detection of ILC additional lesions of 66% and 72.7%, respectively.

The addition of PEM to conventional imaging or clinical breast examination findings is associated with increased sensitivity, accuracy and negative predictive value in depicting breast lesions [19]. In our study, addition of PEM to sonomammography increased sensitivity of ILC detection from 66 to 90.6% and specificity from 72.7 to 81.8%.

Our results are in keeping with Toi, 2023, who revealed PEM pooled sensitivity and specificity of PEM of 85% and 79% [20].

In our study, one index lesion was not detected on PEM being axillary tail lesion. Similarly Kalles et al. and Caldarella et al. emphasized that despite the obvious advantages of PEM, interpretation of PEM scans can also be challenging, especially in lesions that are in proximity to the chest wall or in the axillary region because non-inclusion of the malignancy in the field of view can result in false-negative results [19, 21].

In the study PEM showed high performance in detection of ILC lesions with sensitivity and specificity of 90.6% and 81.8%, respectively, which is comparable to Hashimoto et al., Caldarella et al. and Kalinyak et al., who revealed PEM malignant lesions sensitivity of 89.2%, 85% and 92.8%, respectively. All the studies assessed different histopathological types of breast lesions [11, 19, 22].

However, Sueoka et al. reported a much lower sensitivity of PEM detecting additional ipsilateral lesions (62.1%) [15].

Schilling et al. stated that MRI (magnetic resonance imaging) revealed 90% sensitivity for detection of ILC which is similar to PEM sensitivity for detection of ILC lesions in our study, suggesting that the two modalities are comparable for ILC depiction [23].

The specificity of a PEM scan can be attenuated because of high FDG uptake in cases of innate hypermetabolism, like benign lesions, such as fibroadenomas, and acute or chronic inflammatory processes [21]. That agrees with our findings where Ipsilateral ILC detection sensitivity was 81.8% with 6 false-positive lesions including high-risk lesions, inflammatory changes and fat necrosis.

Preoperative staging of breast cancer has three main purposes: the measurement of the index lesion, the search for ipsilateral additional lesions and the screening for contralateral cancers [3, 16].

PEM may be used as an auxiliary or alternative imaging technique for diagnosing of patients who, for different reasons, cannot tolerate MRI [8].

In our study, a total of 21.7% (10 of 46 index lesions) had a successful change in their proposed operation from breast conservative surgery to mastectomy based on the additional multicentric lesion detection at PEM, that is comparable with the MRI performance in Moloney et al., where it showed a change in proposed operation at a total of 23.2% (16 of 70 cases) [3].

The final decision was left to the discretion of the surgeon and patient at consultation [3]. Similarly, in our study, one patient was overstaged and underwent mastectomy, due to patient choice of mastectomy without biopsy in a small breast. Two of our patients who underwent a reoperation with overall 93.4% (43/36 cases) were correctly staged on PEM.

Laidley et al. who assessed the MRI performance revealed slightly lower results in which 82 (87.1%) were correctly staged, 2 over staged and 4 under staged [24], and also in keeping Mann et al., where 41 of the 44 changes (88%) were later judged to be appropriate based on pathology [25].

As regards to quantitative assessment, ILC was found to have LTB uptake values between 2 and 7 which is in keeping with results in Mamaria, 2019 which showed values between 2.5 and 5, and this happens to be lower than IDC values in our study that was between 3 and 8.8 [13].

ILC lesions revealed lower mean PUV max than IDC, 3 and 4.2, respectively ($P < 0.001$), that is in keeping with multiple prior studies of Ueda et al., Gil-Rendo et al. and Fujii et al.; studies of PET-CT in breast cancer revealed PUV max of ILC 1.5, 2.6 and 2.25, respectively, and PUV max of IDC of 4.8, 4.24 and 3.44, respectively [26–28].

Mean PUVmax of 3.78 was identified in malignant tumors, while a mean PUVmax of 1.17 was reported in the glandular tissue of the healthy breast, with the difference being statistically significant ($P < 0.001$). Similarly, the mean ratio between tumor and healthy glandular tissue in breast cancer patients 3.15 was found to be significantly higher than the ratio for benign lesions 1.17 [22].

This is similar to our results where PUV and LTB of ILC lesions, 3.1 and 4.5, respectively, were significantly different from those of benign breast tissue, 1.560 and 2.58, respectively $P < 0.001$.

The cutoff point calculated by Youden's index for differentiating benign and malignant lesions was 1.97 for PUVmax, with a sensitivity of 76% and a specificity of 85%. The cutoff point was 2.62 for LTB (sensitivity 76%, specificity 85%) [29].

Our study showed similar results with higher sensitivity and specificity where the cutoff PUV max was > 2.2 with sensitivity 95.6% and specificity 97.6% and the cutoff average LTB value to differentiate ILC from benign lesions was > 3.3 with sensitivity 93.3% and specificity 95.1% and ($P < 0.001$).

Most ILC carcinoma is hormone receptor (HR)-positive, and human epithelial growth factor-2 (HER2) overexpression is negative [14], which is in keeping with our study where 97.8% of cases were HR positive and 95.7% were HER2 negative.

Breast cancer care is an ever-changing matter. A learning curve is needed, and skills are improving over years to obtain optimal results in terms of diagnosis, staging and response to treatment. Breast imaging should be performed using state-of-the-art equipment and protocols.

Limitations

The principal limitations of this study are:

- The retrospective study design.
- The preselection of cases resulted in a higher rate of multicentricity than usual as PEM was done for selected cases indicated after the MDT.
- No comparison between PEM and MRI in the same population as only 8 cases underwent both PEM and MRI.
- Currently, the application of PEM in clinical routine is limited, in comparison with the widespread availability of CEDM and MRI, and its cost-effectiveness in evaluating suspicious breast lesions has not been investigated: Further research on this topic could be helpful.

Its strengths are the accuracy of data collection and the reproducibility as imaging findings were correlated with histopathological results and follow-up.

Conclusions

In conclusion, the addition of PEM to conventional imaging is associated with increased sensitivity and accuracy in depicting breast lesions, local staging and surgical planning. Its diagnostic performance is superior to that of sonomammography. Its results are comparable to the published MRI results in an assessment of ILC, offering an acceptable alternative to MRI in patients who cannot tolerate MRI.

It is necessary to emphasize the importance of the correlation with mammography and ultrasound, as well as the clinical findings of each patient.

Abbreviations

BCS	Breast conservative surgery
BI-RADS	Breast Imaging Reporting and Data System
CC	Craniocaudal
CEDM	Contrast-enhanced digital mammography
HR	Hormone receptor

HER2	Human epithelial growth factor-2
ILC	Invasive lobular carcinoma
IDC	Invasive ductal carcinoma
LTB	Lesion to background ratio
MLO	Mediolateral oblique
MRI	Magnetic resonance imaging
PEM	Positron emission mammography
PET	Positron emission tomography
PUV max	Maximum PEM uptake value
ROC	Receiver operating characteristic

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Author contributions
SH wrote the manuscript and AM was responsible for correspondance to journal. AM collected patient data and was responsible for image processing and collection of patient's images. OM & AD participated in the design of the study and performed the statistical analysis. ST 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 2112–308-059. 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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