Original Article

Detection of Axillary Lymph Node Involvement in Early-Stage Breast Cancer: Comparison between Staging ^{18}F-2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography–Computed Tomography Scans, Mammography, and Sentinel Lymph Node Biopsy

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Abstract

Aims: The aim of this study was to evaluate the role of ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography–computed tomography (PET-CT) scan in the detection of axillary lymph node (ALN) involvement and comparison with sentinel lymph node biopsy (SLNB) in operable early-stage breast cancer (EBC). **Settings and Design:** It is a retrospective analysis of staging PET-CT scan of EBC. **Methods:** A total of 128 patients with histopathologically proven breast cancer (BC) were included in the study. Preoperative mammography supplemented with ultrasonography and staging ^{18}F-FDG PET-CT scan was done for all patients. Surgery was done within 30 (mean ± standard deviation = 13.8 ± 10.5) days of staging. SLNB was performed in patients without PET-positive ALNs. All patients with positive sentinel nodes and PET-positive ALNs underwent axillary lymph node dissection (ALND). **Statistical Analysis Used:** The comparison between categorical variables was made by Chi-square/Fisher's exact test as applicable. For continuous variables comparisons, Student's *t*-test and one-way analysis of variance tests were used. **Results:** Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PET-CT scan for detection of ALN involvement were 41.7%, 93.2%, 92.1%, and 45.6%, respectively. Sensitivity, specificity, PPV, and NPV of mammography were 84.5%, 54.5%, 78.0%, and 68.6%, respectively. Sixteen out of 46 (34.7%) patients with negative ALNs in PET-CT scan finally showed involvement in histopathology report after SLNB resulting in upstage of the disease. The size of tumor deposits in sentinel nodes was significantly smaller than PET-positive ALNs (P = 0.01). Our observations correlate with the results of earlier studies published in the literature. **Conclusions:** ^{18}F-FDG PET-CT scan cannot substitute SLNB for ALN screening in EBC. The limitations are most marked in smaller and micrometastatic tumor deposits in ALNs and may be attributed to limitations of PET resolution. However, PET-positive nodes showed good specificity for disease involvement in our study. Therefore, ALND can safely be performed by omitting SLNB in such cases.

Keywords: *Axillary node, breast cancer, positron emission tomography–computed tomography, sentinel lymph node biopsy*

Introduction

Incidence

The incidence of breast cancer (BC) is increasing in India. The report of a population-based survey by the National Cancer Registry Program (2020) showed a significantly increased incidence of BC across the country.[1] However, 5-year overall survival in Stage I and II patients are 95% and 92%, respectively.[2] This clearly indicates that early diagnosis and adequate treatment can improve outcomes.

Surgery is the treatment of choice in early-stage breast cancer (ESBC). The recent trend of conservative surgery in BC is justified by the better quality of life without compromising the survival outcome. The American College of Surgeons Oncology Group Z0011 trial supports sentinel lymph node biopsy (SLNB) rather than conventional axillary lymph node dissection (ALND) in clinically node-negative BC,[3] as SLNB can reduce the complications of ALND such as lymphedema, paresthesia, and shoulder stiffness in a significant number of patients. SLNB is also established for the axillary staging of patients with larger (T3)

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tumors, where the standard approach is that patients with positive sentinel nodes should have ALND. However, in resource-constrained countries like India, SLNB is yet to gain its maximum popularity due to the logistic limitations of radiotracer supply and the restricted availability of technical expertise.[4]

This clinical scenario supports the role of imaging in the diagnosis of axillary lymph node (ALN) involvement before BC surgery. At present, ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography–computed tomography (PET-CT) scan has established its diagnostic supremacy for detection of distant metastasis,[5] although sensitivity for the diagnosis of ALN involvement was low in previous literature, especially for small and micrometastatic nodal involvement.[6]

In this context, we retrospectively evaluated the performance of staging ^{18}F-FDG PET-CT scan for diagnosis of ALN metastases in EBC, and compared with it with SLNB, considering histopathology as a reference standard.

Methods

This was a retrospective study conducted in a tertiary care cancer hospital in eastern India. The waiver of institutional review board approval was obtained vide memo number EC/WV/TMC/10/20.762 histopathologically proven BC patients underwent staging ^{18}F-FDG PET-CT scan in our institution between January 2016 and December 2018. Digital mammography complemented with two-dimensional ultrasonography (USG) was performed in all cases. One hundred and fifty-eight ESBC patients were found eligible for upfront surgery. Among them, 128 patients had surgery for BC in our institution within 30 days of the staging scan and were included in the study [Chart 1]. Clinical data were retrieved from the electronic record system of the hospital. Patients with a past history of cancer, bilateral BCs, nonavailability of images, or clinical data in the archive were excluded from the study.

^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography–computed tomography scan

A staging ^{18}F-FDG PET-CT scan was performed after histopathological confirmation of BC in all cases included in our study. Fasting blood sugar level <160 mg/dL was ensured before the ^{18}F-FDG injection. 10–12 mCi ^{18}F-FDG was injected after at least 4 h of fasting. Compulsory waiting for 45 min in a quite ambient environment was ensured for all patients. Scans were obtained in a 16 slice nontime of flight dedicated PET-CT scanner (Discovery IQ, GE, NYSE). CT scan from the base of the skull up to the mid-thigh level was performed after intravenous administration of nonionic low osmolar iodinated contrast agent (Omnipaque, GE, NYSE) if not clinically contraindicated. CT images were obtained with 120–140 Kvs, automated mAs, a slice thickness of 3 mm, and a pitch of one. Images were acquired using a matrix

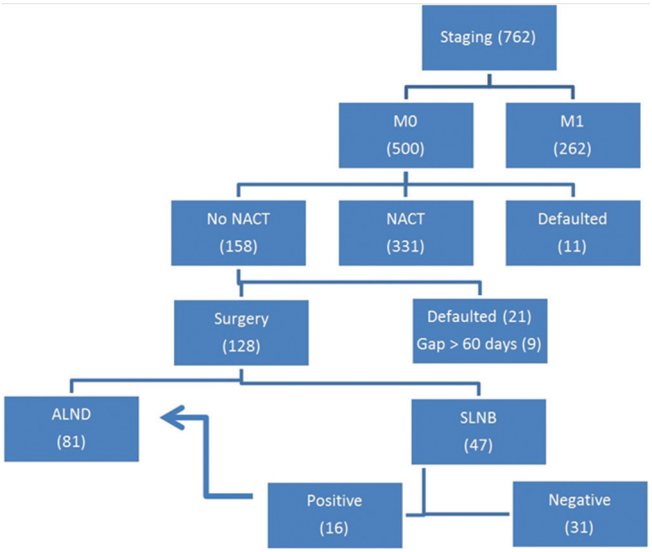

Chart 1: Flowchart of our study population. M0: Nonmetastatic, M1: Metastatic, NACT: Neoadjuvant chemotherapy, ALND: Axillary lymph node dissection, SLNB: Sentinel lymph node biopsy

of 512 × 512 and a pixel size of 1 mm. Three-dimensional PET scan of the same region was performed in six-bed positions with 2–3 min acquisition time per bed position, 128 × 128 image matrix, and 1.5 mm slice thickness. All PET-CT images were analyzed by two nuclear medicine physicians of at least 10 years of experience in BC imaging. Image interpretation was done in dedicated workstation (ADW version 4.5, GE, NYSE). ALNs were characterized by short-axis diameter (SAD) and maximum standardized uptake value (SUV_{max}).

Sentinel lymph node biopsy

SLNB was performed using 2 ml of 1% methylene blue and 4–5 mCi 99 m-technetium nanocolloid if available injected intradermally in the peritumoral region in three to four divided doses. One ml (2.5 mg) indocyanine green (Aurogreen)-based SLNB was performed where nanocolloid was not available. Radioactive sentinel lymph nodes (SLNs) were identified using hand-held gamma probe (Europrobe3, Eurorad S. A2, Ettore Bugatti, 67201 Eckbolsheim – France). Fluorescent nodes were identified with an infra-red camera (Irillic.nm Pvt Ltd.). The nodes with maximum radioactivity at least ten times more than the background counts or visibly blue-stained nodes or fluorescent nodes or clinically suspicious nodes were considered SLNs and sent for frozen section examination. Frozen section analysis was performed as per the American Society of Clinical Oncology/College of American Pathologists guidelines. Immunohistochemistry was performed with an anti-cytokeratin antibody cocktail (cytokeratin AE1–AE3; Dako Corporation, Denmark). Macrometastasis was defined as a single focus of metastasis measuring >2 mm in a given lymph node. Micrometastasis

measured more than 0.2 mm, but not more than 2 mm. The presence of isolated tumor cell clusters was defined as single cells or small clusters of cells not larger than 0.2 mm and no more than 200 cells in a single cross-section. ALND was done in all patients with macrometastasis.

Statistical analysis

The data normalcy was checked by the Shapiro–Wilks test. The comparison between categorical variables was made by Chi-square/Fisher's exact test as applicable. For continuous variables comparisons, Student's *t*-test and one-way analysis of variance tests were used. All *P* values were two-tailed, and values <0.05 were considered significant. Diagnostic performance of the PET-CT scan was compared with the final histopathology report using sensitivity, specificity, and diagnostic accuracy. All statistical analyses were done in SPSS version 23 (IBM Corp, New York, USA).

Table 1: Clinicopathological characteristics of patients

Characteristics	Variables (%)
Age (years)	
Mean±SD	56.17±12.5
Range	27-80
Histology	
DCIS	3 (2.3)
IDC	108 (84.4)
ILC	8 (6.3)
Special	9 (7.0)
T stage	
I	15 (11.7)
II	85 (66.4)
III	28 (21.8)
Grade	
1	3 (2.3)
2	42 (32.8)
3	83 (64.8)
Primary tumor size (mm)	
Mean±SD	32.19±18.28
Median	30.0
Range	10-174
Axillary node SAD (mm)	
Mean±SD	9.25±5.04
Range	4-27
Median	7.5
Histopathological size of tumor deposit of axillary node (mm)	
Mean±SD	8.78±9.35
Median	6.5
Range	0-35
SUV_{max} primary tumor	
Mean±SD	7.93±6.29
Median	5.9
Range	2-35
SUV_{max} axillary node	
Mean±SD	3.10±6.27
Median	1.25
Range	0-36.7

SD: Standard deviation, SAD: Short axis diameter, SUV_{max}: Maximum standardized uptake value, DCIS: Ductal carcinoma *in situ*, IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma

Results

A total of 128 histopathologically proved carcinoma breast patients with clinically negative ALNs were included in our study. Patients' age was in normal distribution pattern. All patients had EBC and underwent upfront surgery within 30 (mean ± standard deviation [SD] = 13.8 ± 10.5) days of PET-CT scan. Table 1 shows the clinicopathological characteristics of the patients. Metabolic activity of ALNs neither had a linear correlation with the size of the node nor with the metabolic activity of primary breast lesions [Figure 1].

Reference standard

Following surgery, all patients had histopathological confirmation of ALNs. Eighty-one patients with positive ALNs in PET-CT scans had undergone ALND. Positive SLNB during surgery upstaged the disease in 16 patients and subsequently, ALND was performed. Thirty-one patients had negative frozen section biopsy of SLNs and did not have ALND [Chart 1].

Comparison of positron emission tomography–computed tomography scan and mammography

Diagnostic accuracy of mammography and PET-CT scan for the detection of ALNs involvement were compared in this study. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of

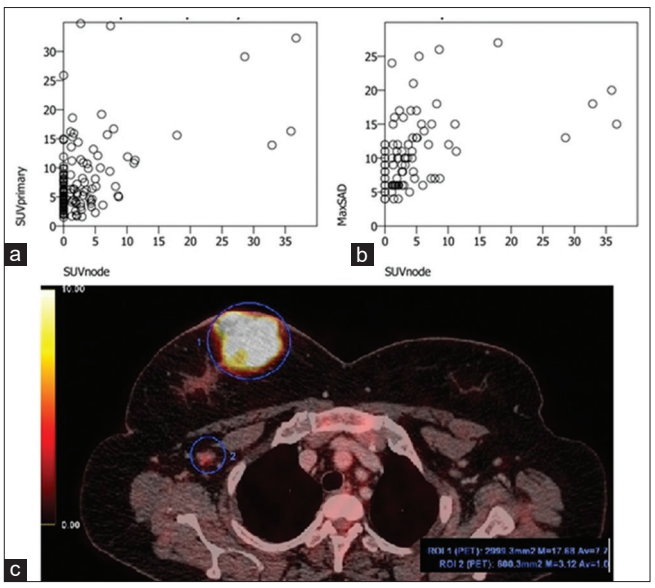

Figure 1: Scatterplot of (a) Metabolic activity of axillary lymph node versus metabolic activity of primary lesion, (b) Metabolic activity of axillary lymph node versus size of the axillary nodes (c) Axial section of fused PET CT image showing primary breast lesion (within blue circle 1) with marked metabolic activity and axillary lymph node (within blue circle 2) with minimal metabolic activity (SUVmax in inset). PET CT: Positron emission tomography–computed tomography

mammography were 84.5%, 54.5%, 78.0%, and 68.6%, respectively. Considering the SUV_{max} of ALNs of 3 or more as significant, PET-CT scan showed sensitivity, specificity, PPV, and NPV were 41.7%, 93.2%, 92.1%, and 45.6%, respectively. The area under the receiver operating characteristic curve was 0.76 [Figure 2]. Taking SAD more than 10 mm as significant morphological criteria for ALN involvement, the scans showed sensitivity, specificity, PPV, and NPV are 46.4%, 68.2%, 83.0%, and 42.3%, respectively. Increased metabolic activity of ALNs had better specificity for the detection of ALN involvement than mammography. However, the lymph nodal size showed no incremental value over the metabolic parameter for the detection of ALN involvement in our patient cohort.

Comparison of positron emission tomography–computed tomography scan and sentinel lymph node biopsy

A total of 46 patients without ALN involvement in PET-CT scans had undergone SLNB. SLNs were identified in all cases (identification rate 100%). Sixteen out of 46 (34.7%) patients had positive ALNs in the final histopathology report. For these 16 patients, the positive nodes had mean (± SD) SUV_{max} 1.14 (± 1.46). Thirty patients with negative SLNs had mean (± SD) SUV_{max} 0.38 (± 0.82). The difference of SUV_{max} between these two groups was statistically significant (P = 0.02). The mean SUV_{max} of PET-positive ALNs, false PET-negative ALNs, and SLNB-negative (true PET-positive) nodes are compared in Figure 3.

As per the histopathological report, the mean (± SD) diameter of tumor deposits of positive SLNs which were not detected by PET CT was 8.69 (± 6.03) mm, significantly smaller than the mean diameter of tumor deposits of the PET-positive nodes, which was 14.49 (± 8.59) mm (P = 0.01) [Figure 4].

Discussion

The involvement of ALN is the most important prognostic parameter for recurrence and survival in primary BC.[7,8] Involved ALNs are managed with ALND in EBC. It has significant postoperative morbidity. Noninvasive technique for effective preoperative screening of ALN has been in demand for long time. The latest National Comprehensive Cancer Network guideline recommends routine imaging evaluation of ALN and classifies the image-detected disease as "low tumor burden."[9] Mammography is the most commonly performed initial imaging modality for screening of breast pathology. It can identify enlarged ALN only to raise suspicion for metastasis [Figure 5]. However, mammography alone is not suitable for the evaluation of axilla in BC staging mainly because of poor spatial resolution.[10] In our study, mammography had 84.5% sensitivity and 54.5% specificity for nodal detection. USG increases sensitivity (range: 26%–76%) and specificity (range: 88%–98%) while using the morphological characteristics for the detection of nodal metastasis. However, there is no standard guideline or recommendation for USG evaluation of axilla in BC.[11]

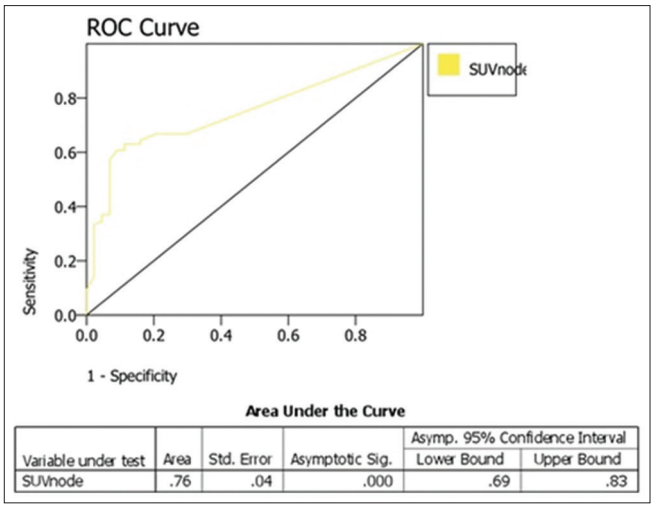

Figure 2: ROC curve plotting true positive (sensitivity) versus false positive fraction (1 specificity), with respect to SUV_{max} of the axillary lymph nodes. ROC: Receiver operating characteristic, SUV_{max}: Maximum standardized uptake value

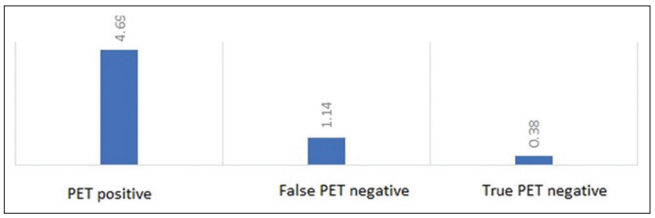

Figure 3: Comparison between mean SUV_{max} of PET-positive ALNs, false PET-negative ALN, and true PET-negative nodes. SUV_{max}: Maximum standardized uptake value, PET: Positron emission tomography, ALNs: Axillary Lymph Node

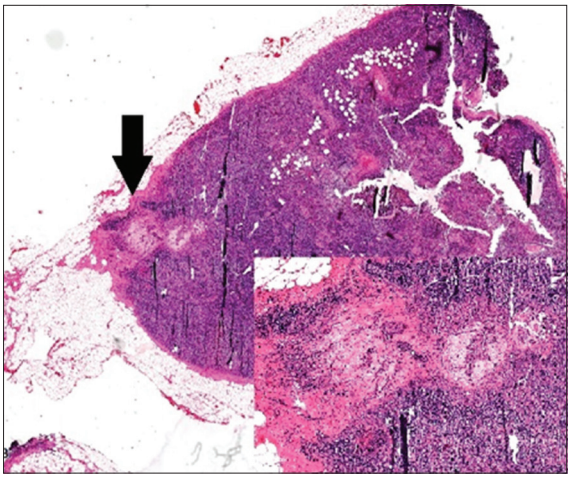

Figure 4: Sentinel lymph node biopsy on one patient with PET-negative axillary nodal disease in our study. Permanent section shows a focus of micro-metastasis (black arrow) H and E, ×40 with high power view of the micro-metastatic focus (H and E, ×400) in inset. PET: Positron emission tomography

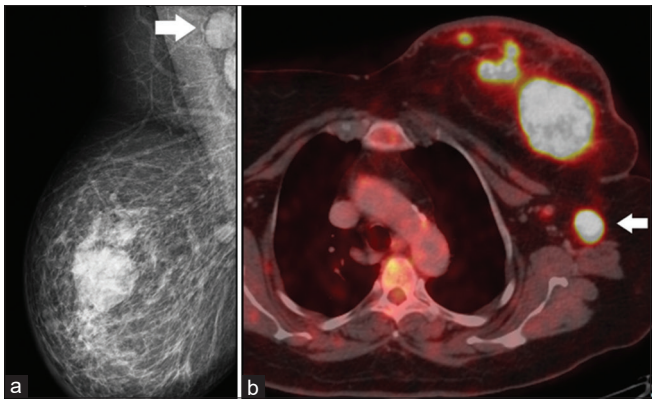

Figure 5: MLO view of mammography (a) and axial fused PET-CT image (b) of left breast show an enlarged metabolically active axillary node (white arrows). The node showed macrometastatic tumor deposit in histopathology report. MLO: Mediolateral oblique, PET-CT: Positron emission tomography–computed tomography

A meta-analysis showed variable sensitivity (ranging from 20% to 100%) with high specificity of PET-CT scan for detection of ALN involvement in BC.[12] An earlier study from India showed that sensitivity, specificity, PPV, and NPV of PET-CT scans are 52.6%, 90.4%, 81.8%, and 73%, respectively, in patients with clinically node-negative EBC.[6] Our results are similar with earlier studies conducted with an identical patient cohort with sensitivity, specificity, PPV, and NPV are 41.7%, 93.2%, 92.1%, and 45.6%, respectively. Specificity of PET-CT scan is high, but with sensitivity unacceptably low for a screening test.

An earlier study demonstrated noninferiority of PET-CT over CT scan for detection of ALN metastases in BC, with sensitivity, specificity, PPV, NPV, and accuracy of FDG PET/CT 58%, 92%, 82%, 77%, and 79% and of CT 46%, 89%, 72%, 71%, and 72%, respectively.[13] Our study shows metabolic activity of PET radiotracer alone was as accurate to detect axillary nodal metastasis as morphological criteria obtained from CT scan.

In our study, 16 out of 46 (34.7%) patients with PET-negative ALNs showed involvement of SLN in the final histopathology report. Similar identification rate was obtained in a previous study from the Indian subcontinent.[6] These false-negative nodes in PET-CT scan had either micrometastases or significantly smaller tumor deposits as compared to PET-positive ALNs. The observation is in agreement with the previous prospective multicenter trial by Wahl *et al*.[14] The limitation of spatial resolution of PET scanners to identify small nodal metastases has been described by Liu.[15] Superiority of the SLNB procedure for the detection of ALN micrometastasis was also described.

Limitations

Our study population was not suitable for subgroup analysis based on histopathological types, as the number of patients in some subgroups was inadequate. A meta-analysis done by Liang *et al*. showed greater sensitivity of magnetic resonance imaging (MRI) than PET-CT for the diagnosis of ALN involvement.[16] Our study does not include MRI although it has the potential for being noninvasive diagnostic investigation of choice. However, MRI is not a part of routine imaging modality in BC staging. In our study, only semi-quantitative metabolic parameter (SUV_{max}) of ALN from PET images was used to diagnose metastasis. The present research is focused on other imaging parameters as well. Radiomics is an evolving field in medical image analysis with help of various artificial intelligence and neural network tools. Effort has been made to develop a radiomic nomogram for preoperative prediction of ALN involvement in BC patients with help of radiomic and clinical features. Both nomogram and radiomic signature of MRI images showed satisfactory results for the prediction of the number of involved ALN.[17] Radiomic features of PET images also have prospective role. Our study did not evaluate the radiomic features of PET images of axillary lymph nodes.

Conclusions

Staging ^{18}F-FDG PET-CT scan is sufficiently specific to identify ALN involvement in EBC. Patients with PET-positive ALN can safely undergo ALND, omitting SLNB. However, PET-CT scan shows poor sensitivity. This is predominantly due to inadequate PET resolution for small and micrometastatic diseases in ALNs. Therefore, SLNB cannot be replaced with PET-CT scan as a screening tool for clinically axillary node-negative ESBC.

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Conflicts of interest

There are no conflicts of interest.

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