Role of fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography in the evaluation of axillary lymph node involvement in operable breast cancer in comparison with sentinel lymph node biopsy

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ABSTRACT

Purpose: Role of (18 [F] fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose [FDG] positron emission tomography-computed tomography [PET-CT]) in the evaluation of axillary lymph node involvement in T1T2N0 breast cancer and compare results with sentinel lymph node biopsy (SLNB). **Methods:** A total of 37 patients of proven T1T2N0 breast cancer were included in the study. Patients with past history of breast surgery, T3T4 disease, uncontrolled diabetes mellitus and pregnant patients were excluded from the study. Pre-operative FDG PET-CT was performed followed by sentinel lymph node (SLN) biopsy with blue dye or combined technique. **Results:** SLN was identified in 32 of 37 patients with an identification rate of 86.48% (32/37). With combined technique SLN identification rate was 100% (6/6) while with blue dye alone; it was 83.8% (26/31). Among 37 patients, 16 had axillary metastases of which 12 had macrometastases and four had micrometastases detected by immunohistochemistry (IHC). Of 12 patients with axillary macrometastases, skip metastases were present in two patients in whom SLN was negative and in two patients SLN was not identified, but axillary dissection showed metastases. PET-CT had shown sensitivity, specificity, negative predictive value and positive predictive value of 56%, 90%, 73%, and 81.8%, respectively. IHC of SLN detected four patients with micrometastases upstaging the disease by 11% (4/37). **Conclusion:** Because FDG PET-CT has a high specificity in the evaluation of axillary lymph node involvement in T1T2N0 breast cancer patients according to the results of this study if FDG PET-CT is positive in axillary lymph nodes, axillary lymph node dissection may be considered instead of SLNB.

Keywords: Breast cancer, fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography, immunohistochemistry, sentinel lymph node biopsy

INTRODUCTION

Breast cancer is the most common cancer in females in western countries and in urban areas in India.[1] The axillary lymph node status is the most important prognostic factor for recurrence,

survival and for deciding systemic and loco regional treatment in breast cancer.[2,3] Axillary lymph node dissection (ALND) is considered to be the standard procedure to assess axillary lymph node status. It is associated with significant morbidity such as lymphedema and paresthesias (relative risk - 0.37) when compared with sentinel lymph node biopsy (SLNB).[4-6] The success of SLNB depends on identification rate and false negative rates. Lymphatic blockage is an important cause for failure to identify sentinel lymph node (SLN) and false negativity is due to skip metastases, which occur in 4-10% of cases.[7,8] Also SLNB requires expertise and special equipment (gamma probe for performing lymphoscintigraphy) which makes it difficult to be performed at all centers. Hence there is a need for less invasive techniques, with good accuracy and lesser complications to identify axillary

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involvement. One such development is the usage of positron emission tomography-computed tomography (PET-CT) for axillary assessment.

Malignant cells have increased glucose intake due to over expression of glucose transporter.[9] This concept is used in positron emission tomography (PET) scan in with fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose (FDG), a glucose analogue which shows increased uptake by cancer cells as compared with a normal cells.[10] However, PET alone has poor anatomical details, so PET-CT a hybrid technique has evolved in which fused images of PET and computed tomography (CT) are visualized, increasing the sensitivity of the test [Figure 1]. Initial studies showed high sensitivity for PET-CT for axillary assessment in breast cancer, but recent studies have shown that smaller tumor deposits may be missed in PET-CT.[11]

The false negative results with FDG PET-CT are seen in patients with low tumor burden and false positive may be due to other inflammatory conditions. Given the conflicting results reported in the literature, the role of PET-CT in axillary staging is questionable.[12] We performed a prospective study using pre-operative FDG PET-CT for axillary staging and comparing with SLNB and using conventional ALND as the reference standard.

METHODS

This was a prospective study. Ethical committee approval was obtained from the institutional ethics committee. Thirty seven female patients who had histologically confirmed breast cancer on core needle biopsy with T1, T2 primary tumor without axillary node (N0) clinically and/or on ultrasonography were included in the study. A written informed consent is obtained from all the

Figure 1: (a-c) A 40-year-old pre-menopausal lady diagnosed as breast cancer had a lump located in left breast upper outer quadrant. Sagittal (a) positron emission tomography-computed image shows increased FDG uptake in left breast tumor and ipsilateral axillary lymph nodes. Pre-operative planar lymphoscintigraphy (b) image carried out with 99m-technetium sulphur colloid shows two lymph nodes in the axilla. Intraoperative sentinel lymph node biopsy performed by using Isosulphane blue dye (c) showing two lymphatic tracks and two blue nodes

patients. Patients with previously treated breast cancer, T3 and T4 lesions, previous history of tuberculosis of breast, male gender, uncontrollable diabetes mellitus and patients with clinically or sonographically detected lymph nodes were excluded from the study. All patients underwent pre-operative FDG PET-CT and SLN mapping.

18F-FDG PET-CT IMAGING

Pre-operative FDG PET-CT was performed in all patients within 2 weeks before surgery. The studies were acquired on a dedicated PET-CT scanner (Biograph 2, Siemens, Erlangen, Germany). All patients fasted for at least 4-h. Blood glucose was less than 140 mg/dl. A dose of 370 MBq (10 mC$_i$) of 18F-FDG was injected intravenously. The patients rested in a quiet room and after a 45-60 min 18F-FDG uptake period, PET-CT imaging was performed. No intravenous contrast agent was administered for the CT part of PET-CT. In the PET-CT system, CT acquisition was performed on spiral dual slice CT with a 130 Kvs, 60 m. As, slice thickness of 4 mm and a pitch of one. Image was acquired using a matrix of 512×512 pixels and pixel size of 1 mm. After CT, 3D PET acquisition was carried out for 2-3 min per bed position. PET data was acquired using matrix of 128×128 pixels with a slice thickness of 1.5 mm. CT based attenuation correction of the emission images was employed. PET images were reconstructed by iterative method ordered subset expectation maximization (two iterations and eight subsets). After CT acquisition, PET acquisition of the same axial range was performed with the patient in the same position. After completion of PET acquisition, the reconstructed attenuation corrected PET images, CT images and fused images of matching pairs of PET and CT images were available for review in axial, coronal and sagittal planes, as well as in maximum intensity projections and three dimensional cine mode. Later the images were analyzed by two experienced nuclear medicine physicians in consensus and maximum standardized uptake value (SUV$_{max}$) of the axillary nodes with an abnormal uptake was measured. Increased FDG uptake in a node with FDG uptake more than the background (mediastinal blood pool) was considered as positive.

SLN mapping and ALND

The study was started with the aim of performing combined technique for SLN identification. However, due to technical problems with gamma probe, only six patients underwent combined technique and for the rest isosulphane blue dye alone was used.

Radioisotope SLN mapping

Radioactive isotope (^{99m}Tc-sulphur colloid) of 200-300 microcurie in 0.1-0.2 ml normal saline was injected intradermally in the periareolar region before surgery and lymphoscintigraphy was performed using a large field view gamma camera with a high-resolution collimator. Static images were obtained using both anterior and lateral projections for 1-2 h following radiotracer injection. All the draining lymph nodes identified on lymphoscintigraphy were marked with indelible ink. If nodal
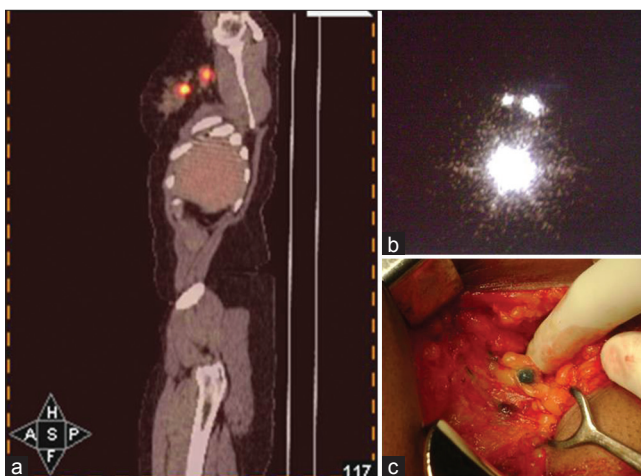
drainage was not identified after 60 min, the case was considered to be a failure. Prior to the performance of SLNB the background count (gamma count taken on the outer aspect of arm away from axillary lymphatic basin for 10 s) was noted. After raising the skin flaps gamma probe was used to localize the area of hot nodes. The lymph node was considered as hot node if the gamma probe count was 10 times more than background in 10-s duration.

Isosulphane blue dye SLN mapping

A test dose of 4 ml of 1% isosulphane blue dye (lymphazurin 1%; US Surgical Corp., Norwalk, CT, USA) was injected in the subareolar region and 1 ml injected in the breast parenchyma in the peritumoral region toward the axillary side of the lump. After 5-10 min of blue dye administration, a small incision 2-3 cm long was given along the skin crease between axilla and breast centered at the anterior axillary fold. After raising the skin flaps, blue stained lymphatic tracks were meticulously searched and traced toward axilla. The blue stained lymph node to which a blue stained lymphatic tract leads was considered as SLN and resected.

Reference standard

All patients underwent a complete ALND. Nodes detected either as hot node or blue node or both were considered to be sentinel node and resected and sent for detailed pathological examination by paraffin fixation processing and immunohistochemistry (IHC) using pan-cytokeratin antibody (Dakopatts, Carpinteria, CA, USA). Non-SLNs were stained only with hematoxylin and eosin staining.

Statistical analysis

The general clinic-pathological characteristics of the patients in the study were analyzed. The diagnostic accuracy of PET-CT scan was compared with the final histology of the nodes using following diagnostic indices: Sensitivity, Specificity, Positive and negative predictive values and accuracy.

RESULTS

We studied 37 patients with biopsy proven breast carcinoma. Table 1 describes the clinico-pathological characteristics of the patients:

Reference standard (ALND)

A total of 16 patients had axillary lymph node metastases of which 12 patients had macrometastases and four patients had micrometastases detected on IHC, there by upstaging the disease in 10.8% (4/37).

FDG PET-CT

The sensitivity of PET-CT in detecting axillary metastases was 56.2% (9/16); specificity was 90.4% (19/21); positive predictive value was 81.8% (9/11); negative predictive value was 73% (19/26) and accuracy was 75.6% (28/37). The Likelihood ratio for a positive test was 5.9 and Likelihood ratio for negative test was 0.4. There were no patients with positive internal mammary lymph nodes detected in PET-CT. PET-CT was

false negative in seven patients (43.7%) and false positive in two patients (9.5%). PET-CT was negative in all four patients with micrometastases detected by IHC [Table 2].

The characteristics of seven patients in whom PET-CT was falsely negative is given in Table 3. The mean SUV_{max} in node positive patients in our study was 6.6 (range 2.3-13.7) and the mean SUV_{max} in node negative patients was 6.7 (range1.3-14.5) [Figure 1a]. The SUV_{max} of axillary lymph nodes varied from 0.5 to 8.2 [Table 4]. With a SUV_{max} of ≥ 0.5, the sensitivity and specificity of PET-CT

Table 1: Clinico-pathological characteristics of the patients

Characteristics	Variable
Menopausal status	
Postmenopausal	24
Premenopausal	13
Age (years)	
Mean±SD	50.5±13.5
Range	26-83
Tumor size (cm)	
Mean±SD	2.7±1.0
Range	1.00-3.8
Histology	
Invasive ductal	34
Lobular	2
Secretory	1
Location of tumor	
Upper outer quadrant	18
Upper inner quadrant	8
Lower inner quadrant	4
Lower outer quadrant	5
Central subareolar	2
SLN count with gamma probe	
Mean±SD	3158±1024.2
Range	798-11002
Number of axillary lymph nodes dissected	
Mean±SD	15.4±3.4
Range	6-27
SUV_{max} of primary tumor	
Mean±SD	6.7±3.7
Range	1.3-14.5
SUV_{max} of lymph node	
Mean±SD	1.2±2.3
Range	0.5-8.2

SLN: Sentinel lymph node, SUV_{max}: Maximum standardized uptake value, SD: Standard deviation

Table 2: Comparison of PET-CT with SLN, ALND, and IHC

Number of patients	PET-CT	SLN	Rest of axilla (ALND)	IHC
16	Negative	Negative	Negative	Negative
4	Negative	Negative	Negative	Positive
3	Negative	Not identified	Negative	Not done
2	Positive	Not identified	Positive	Not done
3	Positive	Positive	Positive	Positive
3	Positive	Positive	Negative	Positive
2	Negative	Positive	Negative	Positive
2	Positive	Negative	Negative	Negative
1	Positive	Negative	Positive	Negative
1	Negative	Negative	Positive	Not done

PET-CT: Positron emission tomography-computed tomography, SLN: Sentinel lymph node, ALND: Axillary lymph node dissection, IHC: Immunohistochemistry

Table 3: Characteristics of patients with false negative PET-CT

Case no	Age	Tumor size	Site of tumor	Tumor SUV$_{max}$	SLN (H and E)	SLN (IHC)	Rest of axilla	No. positive nodes	Histopathology of primary tumor
1	62	2.50	Lt. UIQ	9.5	Positive	+	-	2	Lobular carcinoma
2	36	1.50	Rt. UOQ	4.7	Negative	+	-	1	IDC
3	67	2.50	Rt. UOQ	4.6	Negative	+	-	1	IDC
4	38	3.8	Lt. UOQ	13.7	Not identified	-	+	1	IDC
5	48	2.00	Lt. LOQ	3.3	Positive	+	-	1	Secretory carcinoma
6	61	1.8	Lt. UOQ	3.4	Negative	+	-	1	IDC
7	62	1.7	Lt. UOQ	2.3	Negative	+	-	1	IDC

SUV$_{max}$: Maximum standardized uptake value, UIQ: Upper inner quadrant, UOQ: Upper outer quadrant, LOQ: Lower outer quadrant, IDC: Invasive ductal cancer, Rt.: Right, Lt.: Left, H and E: Haematoxylin and eosin staining, IHC: Immunohistochemistry, SLN: Sentinel lymph node, PET-CT: Positron emission tomography-computed tomography

Table 4: Results of the ROC curve with respect to SUV$_{max}$ of the axillary lymph nodes

SUV$_{max}$ of nodes	Sensitivity	Specificity	PPV	NPV	FP	FN
0.000	1.000	0.000	0.500	–	21	0
0.500	0.563	0.905	0.855	0.674	2	7
0.800	0.500	0.905	0.840	0.644	2	8
0.900	0.500	0.952	0.913	0.656	1	8
1.000	0.500	1.000	1.000	0.667	0	8
2.300	0.438	1.000	1.000	0.640	0	9
4.500	0.375	1.000	1.000	0.615	0	10
5.800	0.250	1.000	1.000	0.571	0	12
6.000	0.188	1.000	1.000	0.552	0	13
7.300	0.125	1.000	1.000	0.533	0	14
8.200	0.063	1.000	1.000	0.516	0	15

SUV$_{max}$: Maximum standardized uptake value, PPV: Positive predictive value, NPV: Negative predictive value, FP: False positive, FN: False negative, ROC: Receiver operative characteristic

Figure 2: Receiver operating characteristic curve plotting true positive (sensitivity) versus false positive fraction (1-specificity), with respect to SUV$_{max}$ of the axillary lymph nodes

were 56.2% and 90.4% respectively. The area under the curve was 0.7 [Figure 2].

SLN mapping

Of 37 patients scheduled for SLNB, six patients underwent combined technique and the rest 31 patients underwent blue dye alone due to technical problems. Out of six patients studied with combined technique (pre-operative lymphoscintigraphy, intraoperative gamma probe and blue dye), the identification rate of hot SLN was 100% (six out of six cases). The mean number of hot SLN identified was two (range: 1-4). Of 37 patients studied with blue dye, a single blue stained SLN was identified in nine cases, two nodes in 13 cases, three nodes in four cases, four nodes in four cases, five nodes in one and seven nodes in one patient. The identification rate of SLN was 100% with combined technique and 83.8% (26/31) with blue dye alone. Overall SLN was identified in 32 out of 37 cases (86.4%). The hot SLN were found in six out of six cases (100%) in which gamma probe was used. Blue SLN was found in 32 out of 37 cases (86.4%) as a whole and 26 out of 31 cases (83.8%) where it was the only method of SLN mapping [Figure 1b and c]. Thus, the use of combined technique helps in better identification of sentinel node.

Of 37 patients, SLN was identified in 32 with an identification rate of 86.4% (32/37). Sixteen patients had axillary lymph node metastases of which SLN had metastases in 12 patients (four
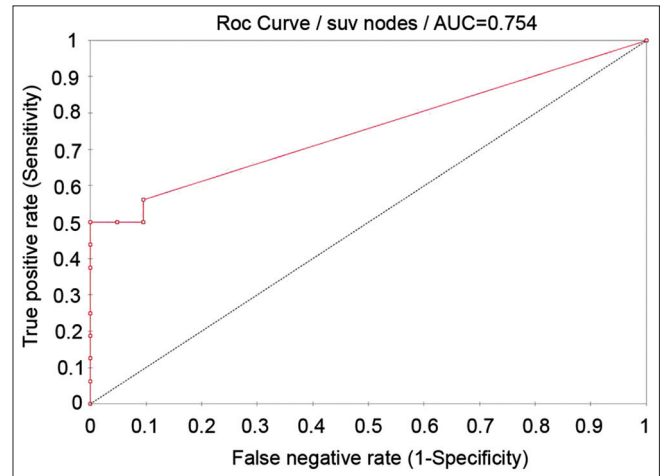
micrometastases and eight macrometastases), two patients had skip metastases in non-SLN and in two out of five patients in whom SLN was not identified had axillary lymph node metastases. The sensitivity of SLNB was 85.7% (12/14), false negative was 14.3% (2/14), negative predictive value was 90% (18/20) and diagnostic accuracy of SLN in detecting axillary metastases was 93.7% (30/32). Out of 12 patients in whom SLN was detected four had micrometastases and eight had macrometastases, which was accurately predicted by SLNB. Nine patients had metastases confined only to SLN of which five had macrometastases and four had micrometastases [Figure 3a-d]. Three patients had metastases in both SLN and non-SLN.

Comparison of PET-CT and SLNB

FDG PET CT was positive for lymph node metastases in three patients (8.1%; 3/37) in whom SLNB was not useful. Of the three patients, SLN could not be identified in two patients, but PET-CT was positive and in one patient with skip metastases (SLN was negative) PET-CT showed the disease in axilla. Sixteen patients had axillary lymph node metastases of which 12 patients had macrometastases and four patients had micrometastases detected on IHC, there by upstaging the disease in 10.8% (4/37). The size of the positive lymph nodes in all patients was less than 1 cm on histopathological examination. All patients with SLN micrometastases detected on IHC were missed by PET-CT.
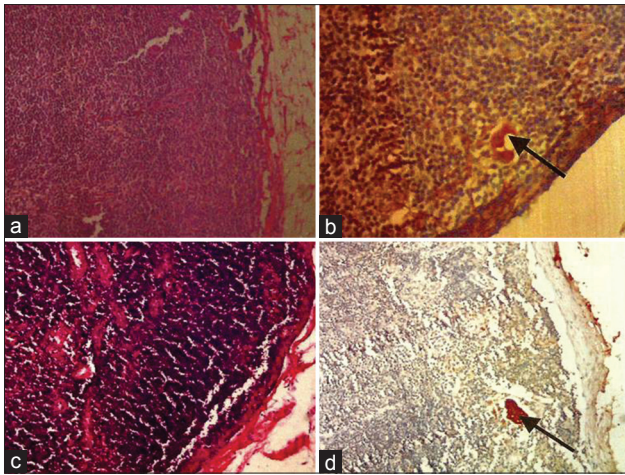
Figure 3: (a-d) A 50-year-old female with breast cancer underwent sentinel lymph node biopsy. Routine H and E, at ×40 (a) and ×100 (c) showed no metastasis. Immunohistochemistry staining of the same node using pancytokeratin antibody shows micrometastases (arrow) at ×40 (b) and ×100 (d)

DISCUSSION

The most important prognostic factor for patients with breast cancer is axillary lymph node status. Until recently, ALND was the standard procedure and all the lymph nodes in the axilla were dissected. Although ALND is safe, it is associated with significant long-term morbidity. Clinical examination of the axilla is inaccurate in evaluating axillary lymph node involvement. The ultrasound scan has been reported to be a sensitive method of assessing axillary lymph node status. Baruah *et al*.[13] recently reported a study where they had triaged the patients for SLNB and ALND based on ultrasound guided fine needle aspiration cytology of the suspicious nodes by which axillary metastases were detected in 53% of patients.

Recent meta-analysis on PET-CT for assessing axillary lymph node in early invasive breast cancer showed pooled sensitivity of 63% and pooled specificity of 94%. Twenty six studies had been reviewed with sensitivity varying from 20 to 100% and specificity of 75-100%.[14] The sensitivity for picking micrometastases in this meta-analysis was 11%. The specificity is high in many studies, but the sensitivity varied. In a study published by Kim *et al*.[15] planned treatment based on PET-CT was reported. One hundred thirty-seven patients underwent PET-CT of which 27 had positive scans who underwent complete ALND directly and the rest 110 underwent SLNB followed by ALND, if they were positive. They had eight false negative scans and no false positive scan with an overall sensitivity of 77.1%, specificity of 100% and positive predictive value of 100% and accuracy of 94.2%. With this treatment plan, they had avoided unnecessary SLNB in 27 patients who had positive PET-CT scan. Veronesi *et al*.,[16] performed ALND if either PET – CT or SLNB was positive, with a PET-CT sensitivity of 37% and specificity of 96%.

In the present study, PET-CT scan had a sensitivity of 56.2% (9/16), specificity of 90.4% (19/21), positive predictive value of

81.8% (9/11) and negative predictive value of 73% (19/26) in detecting axillary lymph node metastases. The diagnostic accuracy of PET scan was 75.6%. Even though conceptually PET-CT may very well detect very small lesions, the present evidence suggests that for peripheral lymph node staging, its sensitivity rapidly declines below 5 mm size, even in tumors that are very avid for FDG.[17] Our results were similar to most of the other studies, which also showed high specificity for PET-CT scan. False negativity of PET scan was 43.7% (7/16; 3 macrometaastases and four micrometastases were not detected). This finding is also comparable with the results published in the literature; where in false negative rates have been reported to vary between 0 and 80%. The sensitivity of SLNB in a meta-analysis of 69 studies was 93% and specificity was 100%, which was significantly higher than sensitivity of PET-CT.[18] In four patients, SLNB was not useful (two patients in whom SLN was not identified and in two patients SLN was false negative), but PET-CT showed uptake in the axilla in three cases of the four. PET-CT was found to be useful in 8.1% (3/37) of patients in whom SLN could not identify metastatic spread to axilla. Hence, SLNB and PET-CT were complimentary in detecting axillary metastases in N0 axilla.

The limitation of our study was it's a small sample size. In addition for SLN mapping using radioisotope, we did not use single-photon emission computed tomography/CT imaging. The main reasons for higher FDG PET false negative results for axillary staging include the limited spatial resolution of the technique and fewer metabolically hyperactive cells in patients with micrometastases.

CONCLUSION

The sensitivity of PET CT in detecting small and micrometastases is low and hence it cannot be used as a substitute for SLNB. However, due to its high specificity, in patients with PET-CT positive nodes, ALND may be considered up head instead of SLNB. PET-CT may be used as a complimentary investigation along with SLNB to detect the patients with skip metastases. However, further studies are needed to consider this application of PET CT as few patients may undergo unnecessary axillary dissection because of false positivity.

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