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Diagnostic Performance of Semi-Quantitative Metabolic Parameters on ^{18}F-FDG PET/CT in the Axillary Staging of Breast Cancer Patients.

Mohamadien N[1] and Sayed M[1,2].

[1] Nuclear Medicine Unit, Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Assiut University, Egypt. [2] Department of medical imaging and Nuclear medicine, Almana General Hospital, Dammam, Kingdom of Saudi Arabia.

ABSTRACT:

Aim: The aim of the present study was to evaluate the diagnostic performance of semi-quantitative metabolic parameters on ^{18}F-FDG PET/CT; maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean), metabolic tumor volume (MTV), total lesion glycolysis (TLG), tumor to liver ratio (TLR), and tumor to mediastinum ratio (TMR) in the axillary staging of breast cancer (BC) patients. **Patients and methods:** One hundred fifty female patients with initially diagnosed BC were recruited in this retrospective study. A 3-D volume of interest (VOI) was drawn over the primary lesion to obtain metabolic PET parameters: SUVmax, SUVmean, MTV, TLG, TLR, and TMR. Additionally, the size and the SUVmax of the axillary lymph node (ALN) were measured. Histopathological examination of the ALN was considered the gold standard.

Results: One-hundred fifty female patients with mean age; 50.6 ± 12 years (range: 19 - 88 years). On a patient basis, histopathological examination revealed metastatic ALNs in 101 patients while 49 cases were negative for metastases, PET/CT successfully identified 74/101 "true positive" and 46/49 "true negative lesions" giving a sensitivity of 73.7 %, 93.9 % specificity with an overall accuracy of 80% (P<0.001). The mean age of patients with negative ALNs was insignificantly higher than that of the positive one. The median values of the aforementioned PET parameters were significantly higher in the ALN positive group. Apart from MTV the areas under the curve (AUCs) of all the PET parameters were superior to the AUC of the primary SUVmax and mean; so these parameters were better to predict ALN metastases.

Conclusion: The median values of the PET parameters; SUVmax, SUVmean, MTV, TLG, TLR, and TMR were significantly higher in patients with ALN metastases. Apart from MTV the rest of the PET parameters were superior to the primary SUVmax and mean in predicting ALN metastases.

Key Words: Breast cancer, Metabolic parameters, FDG-PET/CT, ALNM.

Corresponding Author: Mohamadien N. **E-mail**: *nsreen@aun.edu.eg.*

INTRODUCTION:

Breast cancer (BC) is the second common leading cause of cancer-related death among women [(1)]. The axilla represents the predominant lymphatic drainage pathway from the breast, while extra-axillary spread may occur in up to 56% of patients with BC including; the internal mammary chain, the inter-pectoral (Rotter's) space, the infra-clavicular area, the supraclavicular fossa and the breast itself [(2)].

The status of ALN metastases carries important prognostic and therapeutic implications in BC patients because it is highly associated with subsequent development of distant metastases [(3, 4)].

ALN staging is considered a crucial step in the treatment of BC [(5)]. Before the mid-1990s, ALN dissection (ALND) was the standard procedure for ALN staging however; it possesses a considerable morbidity and a higher rate of complications including lymphedema, restriction of shoulder movement, paresthesia and seroma [(6, 7)].

Sentinel lymph node biopsy (SLNB) became the standard procedure for ALN staging because it is less invasive and has less morbidity compared to ALND [(8)].

Assessment of nodal disease burden to guide treatment decision making can be achieved with axillary US, US-guided biopsy, and MRI [(9)].

^{18}F-FDG PET/CT has been widely used for diagnosis, staging, therapy monitoring, and detection of recurrence in patients with BC [(4)], additionally it is particularly useful for detection of extra axillary metastases [(10)].

Despite ^{18}F-FDG PET/CT is less sensitive than SLNB for the detection of nodal metastases, it has a higher specificity ranging from 95% to 100% allowing it to possibly substitute SLNB for some BC patients and hence reduce the complications [(3, 11)].

The aim of the present study was to evaluate the diagnostic performance of semi-quantitative metabolic parameters on ^{18}F-FDG PET/CT in ALN staging of BC patients.

PATIENTS AND METHODS:

One hundred fifty female patients with pathologically proven BC were enrolled in this retrospective study after approval by the Institutional Review Board and waving of consent. Patients were referred for initial staging with PET/CT scanning prior to surgery. ALN staging was evaluated after axillary clearance or SLNB.

Patients who underwent surgical excision of their primary lesion or received neoadjuvant therapy, uncontrolled diabetics, and pregnant females were excluded.

Positron emission tomography/computed tomography scanning protocol: Fasting for 4-6 h and blood glucose <180 mg/ dl before the study was confirmed in all participants. ^{18}F-FDG was injected intravenously in a peripheral vein at a 0.1 mCi/kg dose, and scans were acquired approximately 45-60 min post-injection.

Imaging was performed using a Siemens; Biograph Horizon 3 ring PET/CT system. PET/CT (Biograph mCT Flow, Siemens Healthcare, Erlangen, Germany), combining Lutetium oxyorthosilicate (LSO)-based PET crystals and 16-slice CT components. An imaging field of view from the base of the skull to the mid-thighs with the arms raised above the head whenever possible was used; otherwise the arms were positioned beside the patient's body.

The CT scan was obtained before the emission acquisition as a single sweep. Slice thickness was 3 mm with a pitch of 0.9 and a tube voltage of 120 kV.

The tube current range; 50 - 100 mAs that was automatically modulated according to the patient’s body mass index to achieve good image quality.

CT data were used for image fusion and the generation of the CT transmission map. No intravenous contrast media was used.

PET emission data were acquired in a three-dimensional mode, using continuous table motion (CTM) acquisition mode with an average table speed of 0.9 mm/Second.

The imaging data were reconstructed using a point spread function and a time-of-flight algorithm (TrueX + time-of-flight, UltraHD-PET), with 2 iterations and 21 subsets. A Gaussian filter with 5 mm full-width half-maximum was applied to the reconstructed images.

Non contrast low-dose CT was used for attenuation correction and anatomical mapping, a. Transaxial, coronal, sagittal, and fused images were analyzed on manufacturer's workstation (Syngo.via, Siemens Healthcare).

Data Interpretation: PET/CT images were interpreted by an experienced nuclear medicine physician blinded to the patients' clinical and pathology data. The gold standard for the evaluation of PET/CT findings was the histopathological examination.

The primary lesion was visually evaluated for the presence of uptake and quantitatively assessed by drawing a 3-D volume of interest (VOI) over the most intense lesion to obtain the following metabolic parameters; the mean and maximum standardized uptake values (SUVmean & SUVmax), metabolic tumor volume (MTV) and total lesion glycolysis (TLG).

Tumor to normal ratio was calculated by dividing the SUVmax of the primary lesion by the SUVmax of the liver and mediastinum to obtain tumor to liver ratio and tumor to mediastinum ratio (TLR and TMR), respectively.

Any ALN showing higher FDG uptake than the mediastinal blood pool considered positive on PET/CT and therefore positive for metastases, additionally we reported semi-quantitative data in the form SUVmax by drawing VOI over the concerned ALN.

Any focal abnormal increased FDG uptake at any part of the body not explained by clinical relevant alternative or with characteristic CT findings was considered positive for distant metastases.

Statistical analysis: Data were analyzed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, IL, USA)*. Descriptive statistics: Means, standard deviations, medians and IQR were calculated. Test of significances: Independent sample t-test was used to compare means. Mann Whitney-U test was used to compare the medians.

Receiver operating characteristic (ROC) analysis was performed to examine which metabolic parameters reflect nodal disease better. Uni- and Multivariate logistic regression analysis was conducted to detect the independent predictors of ALN metastases. *P*-value less than 0.05 was considered significant.

RESULTS:

One-hundred fifty female patients with pathologically proven BC were enrolled in this retrospective study. The mean age were 50.6 ± 12 years (range: 19-88 years). Most tumors were located in the left side (81/150), 66 in the right one and 3 cases had bilateral lesions. The median size of the primary lesion was 2.6 cm (range: 0.8-8.8 cm).

The body mass index (BMI) ranges from 17.8-48 Kg/m^2 with a median of 29.4 Kg/m^2. The Ki-67 index ranges from 0-95 %. PET/CT detected positive FDG uptake in 77 axillary and 26 extra-axillary sites (including internal mammary, mediastinal, supraclavicular and abdominal sites). Regarding distant metastases it was detected in 25 patients at 38 sites; 20 at the bone, 12 at the lung and 6 at the liver.

Diagnostic performance: On patient basis histopathological examination revealed metastatic ALN in 101 patients while 49 cases were negative for metastases, PET/CT successfully identified 74/101 true positive and 46/49 true negative lesions ***(Figures 1 – 3)*** with overall accuracy of 80% as described in ***Table (1)*****.**

Quantitative evaluation: The mean age of the negative ALN group was insignificantly higher than that of the positive one. The median tumor size and BMI were higher among the positive ALN group (*P*-value= 0.002 and 0.962 respectively).

The median values of all PET parameters; SUVmean and max of the primary lesion, SUVmax of ALNs, TLG, MTV, TMR and TLR were significantly higher in the nodal positive group. Patients, tumor characteristics and axillary nodal status are illustrated in ***Table (2)*****.**

As all the PET parameters were significantly associated with ALN metastases, the ROC analysis was performed to determine the best parameter which predicts LN metastases better ***(Figure 4)***.

Apart from MTV, the areas under the curve (AUCs) of all the parameters were superior to the AUC of the primary SUVmax and mean; this means that these parameters predict LN metastases better than the primary SUV, ***(Table 3)***.

Table (1): Diagnostic performance of ^{18}F-FDG PET/CT in predicting ALN metastases.

Diagnostic parameter	Value	*P*-value
Sensitivity	73.7 %	<0.001
Specificity	93.9 %	
PPV	96.1 %	
NPV	63 %	
Accuracy	80 %	
LR+	1.1 %	
LR-	0.28 %	

PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

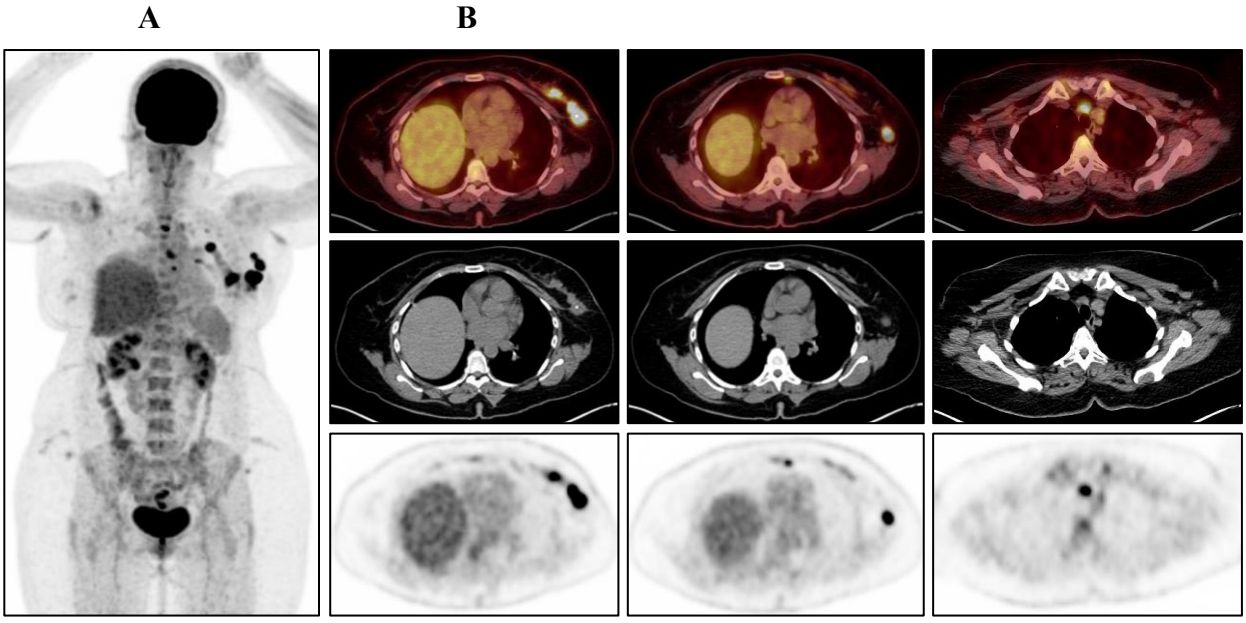

Figure (1): ^{18}F-FDG PET/CT scan of a 50-yeasr-old female with invasive ductal carcinoma of the left breast: (A) maximum intensity projection, (B) trans-axial PET/CT fusion images (top), corresponding CT (middle) and trans-axial PET images (lower row) showed multifocal intense ^{18}F-FDG avid lesions at the upper outer quadrant of the left breast, associated with intense hypermetabolic metastatic left axillary, left internal mammary (middle column), and mediastinal (right column) lymph nodes. (True positive axillary node).

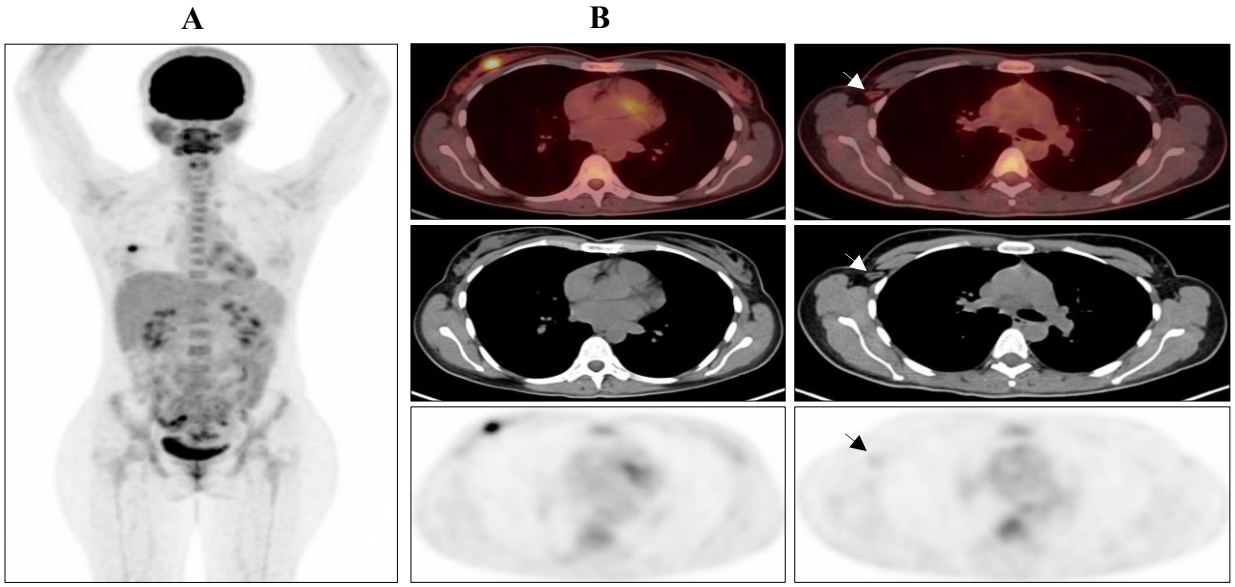

Figure (2): ^{18}F -FDG PET/CT scan of a 34-years-old female with invasive ductal carcinoma of the right breast: (A) maximum intensity projection, (B) trans-axial PET/CT fusion images (top), corresponding CT (middle) and trans-axial PET images (lower row) show ^{18}F -FDG avid irregular mass at the upper outer quadrant of the right breast about 1.5 ×1.2 cm with SUV max 7.69. A prominent right axillary lymph node (arrowed) shows low-grade metabolic activity less than mediastinal blood pole, probably reactive. Sentinel lymph node biopsy confirmed the reactive nature of this lymph node (True negative axillary node).

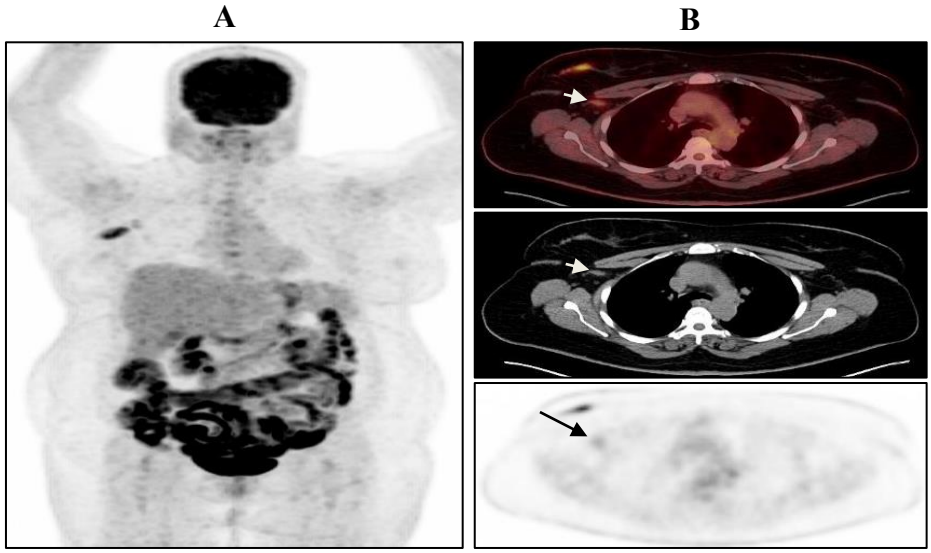

Figure (3): ^{18}F-FDG PET/CT scan of a 58-years-old female with invasive lobular carcinoma, Grade 2 of the right breast: (A) maximum intensity projection, (B) trans-axial PET/CT fusion images (top), corresponding CT (middle) and trans-axial PET images (lower row) show ^{18}F-FDG avid soft tissue lesion at the upper outer quadrant of the right breast about 3.6 x 1.3 x 1.8 cm with SUV max 5.5. Mildly FDG avid enlarged right axillary lymph node (arrowed) with thickened cortex and SUV max about 2 “suspicious node”. Sentinel lymph node biopsy show reactive nature of this lymph node (False positive axillary node).

Table (2): Patients, tumor characteristics and its correlation with PET parameters.

Parameter		Total (n=150)	Node negative (n=49)	Node positive (n=101)	*P*-value
Age in years: mean ± SD		50.6 ± 12	52.2 ± 12.2	49.86 ± 12.3	0.267**
Tumor size in cm: Median (IQR)		2.6 (1.6)	2.5 (1.4)	2.9 (1.8)	0.002*
BMI: median (IQR)		29.4 (9)	28 (10)	29.6 (9)	0.962*
Primary. SUVmax: Median (IQR)		7.9 (9)	5.7 (6)	8.9 (12)	<0.001*
Primary. SUVmean: Median (IQR)		4.6 (6)	3 (4)	5.8 (7)	0.001*
Axillary SUVmax: Median (IQR)		4.8 (8.3)	1.6 (1.4)	6.6 (9)	<0.001*
MTV: median (IQR)		6.1 (10.7)	4.7 (6)	7.3 (12)	0.006*
TLG: median (IQR)		28.1 (66)	15 (28)	38.5 (93)	<0.001*
TLR: median (IQR)		2.4 (3.5)	1.9 (2)	3.4 (5)	<0.001*
TMR: median (IQR)		3.9 (5)	2.6 (3)	4.6 (6)	<0.001*
ER status:	Negative Positive	40 110	9 (18.4%) 40 (81.6%)	31 (30.7%) 70 (69.3%)	0.109#
PR status:	Negative Positive	53 97	13 (26.5%) 36 (73.5%)	40 (39.6%) 61 (60.4%)	0.116#
HER2 neu:	Negative Positive	89 61	34 (69.4%) 15 (30.6%)	55 (54.5%) 46 (45.5%)	0.081#
T-stage:	I& II III& IV	99 51	49 (100%) 0 (0%)	50 (49.5%) 51 (50.5%)	<0.001#
N-stage by PET:	Negative Positive	73 77	46 (93.9%) 3 (6.1%)	27 (26.7%) 74 (73.3%)	<0.001#
M-stage:	0 1	125 25	49 (100%) 0 (0%)	76 (75.2%) 25 (24.8%)	<0.001#
Histologic type:	IDC ILC Mucinous	135 14 1	40 (81.6%) 8 (16.3%) 1 (2.1%)	95 (94.1%) 6 (5.9%) 0 (0%)	0.04#
Molecular subtype:	Luminal A Luminal B HER2 overexpression Triple negative	41 80 7 22	17 (34.7%) 26 (53.1%) 2 (4.1%) 4 (8.1%)	24 (23.8%) 54 (53.5%) 5 (4.9%) 18 (17.8%)	0.309#
Grade:	Low (I& II) High (III)	103 47	35 (71.4%) 14 (28.6%)	68 (67.3%) 33 (32.7%)	0.611#
Ki-67 level:	Low (<14%) High (≥14 %) Not assessed	15 86 49	8 (16.3%) 25 (51%) 16 (32.7%)	7 (6.9%) 61 (60.4%) 33 (32.7%)	0.081#
Extra-axillary LN:	Absent Present	124 26	46 (93.9%) 3 (6.1%)	78 (77.2%) 23 (22.8%)	0.012#

 # Chi square test; *Mann Whitney-U test; **Independent sample t-test; SD, standard deviation; IQR, interquartile range; Axillary SUVmax, maximum standardized uptake value of axillary lymph node; TLG, total lesion glycolysis; TLR, tumor to liver ratio; Primary SUVmax, maximum standardized uptake value of the primary tumor; Primary SUVmean, mean standardized uptake value of the primary tumor; MTV, metabolic tumor volume; ER, Estrogen receptors; PR, progesterone receptors; HER2 neu, human epidermal growth factor receptor 2.

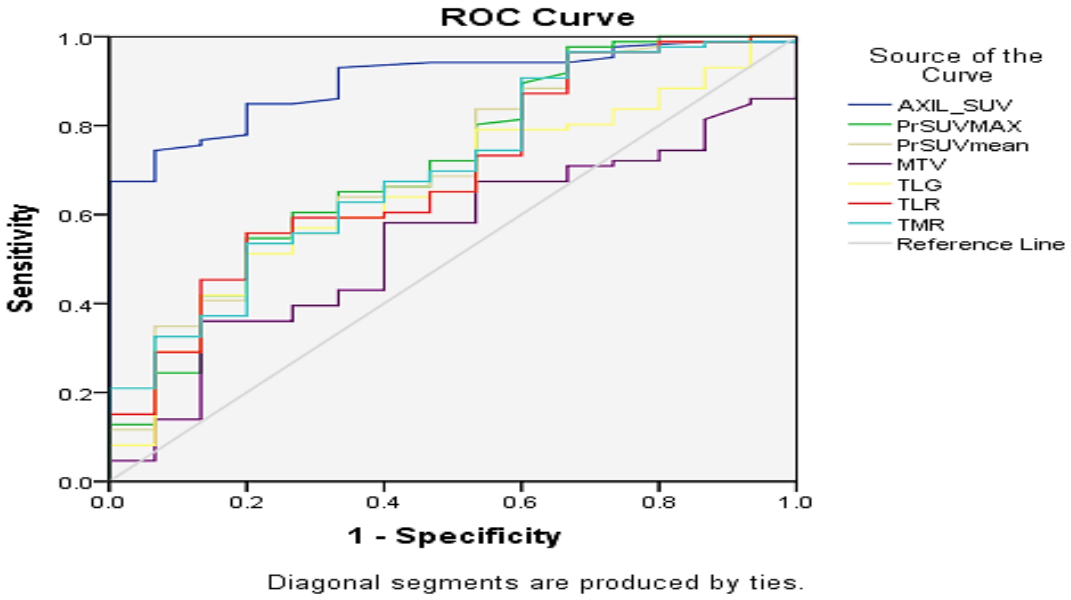

Figure (4): Association between semi-quantitative ^{18}F-FDG-PET/CT parameters and ALN status.

Table (3): AUCs of the quantitative parameters.

Variable	AUC (95% CI)	Cut-off	Sensitivity	Specificity	*P*-value
Axillary SUVmax	0.899 (0.834 - 0.964)	≥1.05	98.8	93.3	<0.001
Primary SUVmax	0.680 (0.592 - 0.768)	≥1.51	100	93.3	<0.001
Primary SUVmean	0.673 (0.584 - 0.762)	≥0.85	100	93.3	=0.001
MTV	0.639 (0.548 - 0.730)	≥2.66	86	93.3	=0.006
TLG	0.697 (0.611 - 0.783	≥2.64	100	93.3	<0.001
TLR	0.685 (0.599 - 0.771)	≥0.47	100	93.3	<0.001
TMR	0.683 (0.596 - 770)	≥0.92	98.8	93.3	<0.001

Axillary SUVmax, maximum standardized uptake value of axillary lymph node; TLG, total lesion glycolysis; TLR, tumor to liver ratio; TMR, tumor to mediastinum ratio Primary SUVmax, maximum standardized uptake value of the primary tumor; Primary SUVmean, mean standardized uptake value of the primary tumor; MTV, metabolic tumor volume.

In Univariate analysis tumor size (p=0.031), axillary SUVmax (p <0.001), primary SUVmean (p =0.001), primary SUVmax (p =0.001), MTV(p =0.031), TLG (p =0.022), TMR (p =0.001) and TLR (p 0.001) were associated with a higher probability of ALN metastases**,** while age of the patients, tumor grade, estrogen receptors (ER) status, progesterone receptors (PR) status, human epidermal growth factor receptor 2 (HER2) status, molecular subtype and Ki-67 index showed no significant association with ALN metastases. Those parameters showing statistical significance (P<.05) on univariate analysis were subjected for the multivariate analysis.

On multivariate analysis, only the axillary SUVmax [adjusted odds ratio (OR) = 0.071, 95% CI: 0.028 – 0.178, p = <0.0001] and TMR [adjusted odds ratio (OR) = 17.911, 95% CI: 1.045 – 306.947, P = <0.047] maintained independent significance in predicting ALN metastases ***(Table 4)***.

Table (4): Univariate and multivariate logistic regression analysis for axillary lymph node metastases.

Variable	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**
Age (<50 versus ≥50)	1.105	0.559-2.188	0.773			
Tumor size in cm	0.424	0.195-0.924	0.031			
Grade(low versus high)	0.824	0.391-1.739	0.612			
ER status	0.508	0.220-1.174	0.113			
PR status	0.551	0.260 – 1.165	0.119			
HER2 status	1.896	0.920-3.906	0.083			
Molecular subtypes (Non-luminal B versus Luminal B)	0.984	0.497-1.950	0.963			
Ki-level	0.359	0.117-1.095	0.072			
Axillary SUVmax	0.240	0.007-0.083	<0.001	0.071	0.028 – 0.178	0.000
Primary SUVmax	1.11	1.042-1.182	0.001			
Primary SUVmean	1.183	1.067-1.313	0.001			
MTV	1.043	1.004-1.083	0.031			
TLG	1.007	1.001-1.014	0.022			
TMR	1.249	1.098-1.1420	0.001	17.911	1.045 – 306.947	0.047
TLR	1.386	1.150-1.670	0.001			

ER, Estrogen receptors; PR, progesterone receptors; HER2, human epidermal growth factor receptor 2; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; TMR, tumor to mediastinum ratio; TLR, tumor to liver ratio.

DISCUSSION:

Mammography is still the most used modality for initial assessment of primary BC, usually complemented with ultrasonography for the evaluation of ALN involvement. Recently metabolic imaging with ^{18}F-FDG PET/CT is accepted as a standard care in many malignancies including BC [(12)].

ALN staging may be done somewhat reliably, yet the assessment of the internal mammary lymph and per-clavicular nodes remains a matter of debate; detection of axillary and extra-axillary nodal involvement using US is suboptimal and of lower accuracy than PET/CT [(13, 14)].

^{18}F-FDG PET/CT can be used for ALN staging in patients with early BC and may guide the surgeon to proceed for ALND rather than SLNB, yet this is not the role in all cases because of its low negative predictive value [(15, 16)].

The sensitivity of FDG PET-CT for detection of ALN metastases depends on the FDG avidity of the primary tumor and the axillary tumor burden for example; in patients with aggressive histologic features a significantly higher proportion of metastases are detected [(17)].

We retrospectively studied 150 female patients with early BC, the overall accuracy of ^{18}F-FDG PET/CT was 80%.

The sensitivity, specificity, positive and negative predictive values were 73%, 93.9%, 96.1% and 63% respectively, these figures were similar to those reported by ***Song et al.,*** who studied the predictive value of ^{18}F-FDG PET/CT for ALN metastases in invasive ductal BC. The authors found 48.1 % sensitivity and 94.7 % specificity [(1)].

We encountered a total of 30 false readings in this study (3 positive and 27 negative). ***Liu et al.***, stated that cases with false negative PET tends to had significantly smaller and fewer tumor-positive ALNs than the true-positive patients. These results outlined the limitation of FDG PET in detection of ALN micro-metastases [(16)].

In addition to being a cancer non-specific imaging agent, FDG can be taken in benign conditions related to infection or inflammation, giving false-positive results, and these facts can interpret the three false-positive results in our study [(18)].

The median tumor size and BMI were higher among the positive nodal group; these figures were in line with those of ***Kim et al.*** and ***Tuzcu et al*** [(5,19)].

Similar to ours ***An et al***., and ***Can et al***., reported that the mean values of SUVmean and max of the primary lesion, TLG and MTV were significantly higher in the nodal positive group [20, 21]. Apart from MTV the AUCs of all the parameters were superior to the AUC of the primary SUVmax and mean; this means that these parameters have a higher and significant relationship with ALN metastases better than primary SUV, these results were in line with those of ***Kaida et al,*** [22].

SUVmax is the most commonly used metabolic parameter [23, 24]. However, it only represents the maximum value of a single voxel in the tumor and ignores the actual extent of metabolic abnormality and the heterogeneity in distribution of ^{18}F-FDG within a lesion. Furthermore, it may potentially be affected by several patient-related variables and technical parameters [25]. MTV and TLG as measures of tumor metabolic burden, have been reported to comprehensively reflect glucose uptake within the whole tumor, and were adopted as the optimal parameters for therapeutic evaluation by PET Response Criteria in Solid Tumors (PERCIST) [26]. Recent studies confirm the superiority of the prognostic value of MTV and TLG compared to SUVmax in various cancers [27, 28].

The use of tumor to normal (represented in liver or mediastinum) uptake ratio has emerged from the concept of lesion to normal(L/N) ratio used in brain imaging which was used before the introduction of SUV and these new parameters proved highly reproducible when performed in two PET scanners [29]. In this study we investigate the reproducibility of TLR and TMR in predicting axillary LN metastases and found that the median values of these parameters were significantly higher in patients with positive LN metastases as well as they were better than Primary SUVmax and mean in predicting ALN metastases.

In Univariate analysis tumor size, axillary SUVmax, primary SUVmean, primary SUVmax, MTV, TLG, TMR and TLR were associated with a higher possibility of ALN metastases**,** while age of the patients, tumor grade, ER, PR, HER2, molecular subtype and Ki-67 index showed no significant association with ALN metastases, similar to ours ***Song et al.,*** found that lymphovascular invasion, tumor size, SUVmax, and nodal FDG uptake were significantly associated with ALN metastases [1].

On multivariate analysis, only the axillary SUVmax and TMR maintained independent significance in predicting ALN status hence it can be considered the most important prognostic factor for predicting ALN metastases, those are in line with the results of ***Song et al.,*** [(1)], in contrast to ours ***An et al***., who found that lymph vascular invasion and MTV were the significant predictors of ALN metastases [(20)].

A potential Limitation of the current study was its retrospective single-center study design with a limited number of subjects. Further prospective multi-center studies in a larger group of patients, may be considered to validate our findings.

CONCLUSION:

The median values of the metabolic PET parameters; SUVmax, SUVmean, MTV, TLG, TLR and TMR were significantly higher in patients with ALN metastases. Apart from MTV the rest of the PET parameters were superior to the primary SUVmax and mean in predicting ALN metastases, this denotes that these parameters predict ALN metastases better than SUV of the primary lesions.

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