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Axillary staging with 18F-FDG PET/CT in early breast cancer: impact of tumor subtypes

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BACKGROUND: Breast cancer is one of the most common cancers in women globally. Axillary lymph node metastasis remains one of the most independent prognostic factors in breast cancer.

OBJECTIVE: Evaluate the diagnostic accuracy of 18F-FDG-PET/CT in detecting axillary lymph node metastasis based on immunohistochemical subtypes and its correlation with sentinel lymph node biopsy (SLNB) results.

DESIGN: A retrospective cohort

SETTING: Tertiary oncology center in Turkiye

PATIENTS AND METHODS: Patients diagnosed with early-stage invasive ductal breast cancer and who underwent preoperative F-18 fluorodeoxyglucose positron emission computed tomography (18F-FDG PET/CT) evaluation were included in the study. Patients were divided into five immunohistochemical subtypes: Luminal A, Luminal B HER2 (-) (human epidermal growth factor receptor 2), Luminal B HER2 (+), HER2 (+), and triple negative. SLNB and SUVmax (Maximum Standard Unit Value) results were compared.

MAIN OUTCOME MEASURES: Diagnostic accuracy of 18F-FDG PET/CT for detecting axillary metastasis was the primary outcome. Interrater reliability testing in determining the agreement between 18F-FDG PET/CT and SLNB was the secondary outcome.

SAMPLE SIZE: 248

RESULTS: The sensitivity, specificity, PPV, NPV and accuracy of 18F-FDG-PET/CT for detecting axillary metastasis were 62%, 92%, 88%, 71% and 77%, respectively. Cohen's Kappa coefficient (0.54) showed moderate agreement with SLNB ($P<.001$). Tumors with positive HER2 gene amplification [HER2 (+) and Luminal B HER2 (+) have higher sensitivity than other subtypes (Luminal A, Luminal B HER2 (-) and triple negative). HER2 gene amplification also increases the agreement between 18F-FDG-PET/CT and SLNB results.

CONCLUSION: 18F-FDG-PET/CT has a high specificity but low sensitivity for ipsilateral axillary metastasis in invasive ductal carcinoma. The presence of HER2 gene amplification can increase sensitivity and concordance with SLNB.

LIMITATIONS: Retrospective design and limited number of patients for each subtype.

CONFLICT OF INTEREST: None.

Breast cancer is the most common cancer in women globally and ranks second in cancer-related deaths.[1,2] The treatment and prognosis of breast cancer are dependent on the tumor size, grade, hormone receptor status, immunohistochemical characteristics, positivity of e-cadherin, lymphovascular and perineural invasion status, axillary lymph node involvement, and metastatic spread.[3,4] Axillary lymph node involvement (positivity) and subsequent dissection can increase risk of complications and morbidity after mastectomy or breast-conserving surgery. Therefore, determining axillary positivity before or during the surgery plays a crucial role in breast cancer management.

Sentinel lymph node biopsy (SLNB) is the standard method to demonstrate axillary lymph node involvement in early-stage breast cancer with clinically and radiologically negative axillary lymph nodes.[5] Previous studies have reported that SLNB is an adequate procedure in terms of disease-free survival, overall survival, and recurrence, but can produce false-negative results at varying rates.[5-7] Compared to axillary lymph node dissection, SLNB reduces the incidence of morbidities such as seroma, temporary or permanent lymphedema, paresthesia, and arm immobility.[8] However, while the majority of SLNBs performed for early-stage breast cancer are negative, positive results occur at a lower rate [approximately 80% negative vs. 20% positive).[9]

SLNB positivity may be influenced by the concurrent interplay of multiple clinicopathological factors. Data have shown that SLN metastasis does not significantly differ across breast cancer molecular subtypes. However, in Luminal A and Luminal B tumors, certain clinicopathological factors such as younger age, higher tumor grade, and larger tumor size, have been identified as significant predictors of SLN involvement.[10-12] Majid et al. reported that tumor size >20 mm, multifocality, and the presence of lymphovascular invasion were strongly associated with an increased risk of SLN metastasis.[13]

The high rate of negative SLNB results has led researchers to explore other diagnostic modalities for detecting axillary metastasis. The F-18 fluorodeoxyglucose positron emission computed tomography (18F-FDG-PET/CT) is widely used for patients with advanced stages of breast cancer to detect distant metastases or locally advanced diseases.[14] Some studies have shown that the 18F-FDG-PET/CT has high sensitivity and specificity for identifying axillary metastasis, while others indicate that 18F-FDG-PET/CT cannot replace SLNB.[15,16] There is considerable variability in baseline Maximum Standard Unit Value (SUVmax) in both primary breast tumors and axillary lymph nodes. A recent meta-analysis has shown that metabolic activity differs across breast cancer subtypes. Specifically, estrogen receptor-positive tumors exhibit significantly lower baseline SUVmax compared to human epidermal growth factor receptor 2 (HER2)-positive and triple-negative (TN) subtypes.[17]

This study aimed to evaluate the diagnostic accuracy, sensitivity, and specificity of 18F-FDG-PET/CT in detecting axillary lymph node metastasis and its correlation with SLNB results.

METHODS

Study design

This single center study is a retrospective analysis of prospectively collected data. Medical records of patients diagnosed with invasive ductal breast cancer who underwent 18F-FDG PET/CT between January 2015 and January 2021 at the Department of General Surgery, Kocaeli Derince Training and Research Hospital, Kocaeli, Turkiye were reviewed. Clinical, pathological, and imaging data were retrieved from the hospital's digital medical record system. The study was approved by the Derince Training and Research Hospital's Ethics Committee with the approval number 2021/34. Written informed consent was obtained from participants prior to the study.

Patient selection

Patients were included in the study based on the following criteria: 1) Age ≥ 18 years, 2) Histopathological diagnosis of invasive ductal carcinoma, 3) Underwent 18F-FDG PET/CT imaging as part of preoperative assessment, 4) Early-stage breast cancer at the time of diagnosis, 5) Underwent surgical treatment at our institution within the study period, 6) Availability of complete postoperative histopathology and imaging data. The exclusion criteria were: 1) Postoperative histopathological diagnosis other than invasive ductal carcinoma (e.g., lobular carcinoma, mixed subtypes), 2) Preoperative neoadjuvant chemotherapy prior to imaging or surgery, 3) Presence of distant metastatic disease at the time of diagnosis, 4) Diagnosis of any additional malignant disease during the study period, 5) Incomplete or missing key clinical, imaging, or pathology data.

Immunohistochemical and pathologic evaluation

The patients' immunohistochemical subtypes were determined according to the postoperative pathology reports. The tumor grade, estrogen receptor positivity, progesterone receptor positivity, and human epidermal growth factor receptor 2 (HER 2) positivity were

recorded from the reports and the data was used to divide patients into subtypes. The patients were divided into five immunohistochemical subtypes: Luminal A, Luminal B HER2 (-), Luminal B HER2 (+), HER2 (+), and TN [AUTHOR: define at first use]. Tumor grades, lymphovascular invasion, perineural invasion and perinodal involvement status were recorded from the pathology reports.

Sentinel lymph node biopsy (SLNB) and surgery

All patients underwent standard SLNB using methylene blue dye. The dye was prepared as a sterile solution and injected subcutaneously into the periareolar region following anesthesia induction. Following injection, the periareolar region was massaged for approximately 15 minutes. Blue-stained SLN were identified, excised, and evaluated via frozen section during surgery, in accordance with National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial and American College of Surgeons Oncology Group (ACOSOG) trials Z0010 and Z0011 guidelines.[18–21] Subsequently, the patients underwent modified radical mastectomy, simple mastectomy, or breast-conserving surgery with or without axillary lymph node dissection, based on the clinical and pathological indications.

18F-FDG PET/CT Imaging

All patients fasted for at least 6 hours prior to the PET/CT. Those with blood glucose levels >200 mg/dL were excluded from imaging to minimize variability in 18F-FDG uptake. Imaging was performed 1 hour after intravenous injection of 18F-FDG at a dose of 1.2 mCi/kg (44.4 MBq/kg) using a GE Discovery 690, 64-slice PET/CT scanner. Whole-body scans (cranio-caudal) in 3D mode, with axial, coronal, and sagittal reconstructions were obtained. Image slices were thinned up to 3.3 mm for detailed analysis. An experienced nuclear medicine specialist evaluated all scans to reduce interobserver variability. The maximum standardized uptake value (SUVmax) was calculated using the following formula: SUVmax = (Measured activity concentration [kBq/mL] × Body weight [kg]) / Injected activity [kBq]

Statistical analysis

All statistical analyses were conducted using R version 4.2.1 (*https://www.r-project.org/*). Categorical variables were presented as frequencies and percentages (n, %). Normality of distribution for continuous variables was visually assessed using histograms and statistically using the Shapiro–Wilk test. Continuous variables that were not normally distributed were summarized as medians with interquartile ranges (25th and 75th percentiles). For group comparisons, categorical variables were analyzed using the Chi-square or Fisher's exact test, depending on cell counts. Non-normally distributed continuous variables were compared using the Mann–Whitney U test. Differences between groups were evaluated using Student's T-test for normally distributed continuous variables (e.g., age). To evaluate the diagnostic performance of SUVmax in predicting axillary lymph node metastasis, receiver operating characteristic (ROC) curve analysis was performed. The Youden Index was used to determine the optimal cut-off value that maximized sensitivity and specificity. The corresponding area under the curve (AUC) values were calculated to assess overall test performance, and 95% confidence intervals (CIs) were computed using DeLong's method for ROC analysis. Diagnostic test characteristics — including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy — were calculated using standard 2×2 contingency tables. The 95% confidence intervals for these proportions were estimated using the Wilson score method, which provides reliable interval estimates for binomial data. Intra-rater reliability for image interpretation was assessed using Cohen's kappa (κ) coefficient, with the following interpretation: ≤0: no agreement 0.01–0.20: slight 0.21–0.40: fair 0.41–0.60: moderate 0.61–0.80: substantial 0.81–1.00: almost perfect agreement. A two-tailed P value < .05 was considered statistically significant.

RESULTS

A total of 248 patients were included in the study. All patients were females and the mean age was 55.4 (26–86 years). All patients had invasive ductal carcinoma. In 138 (55.6%) patients, tumors were left-sided; in 110 (44.4%), they were right-sided. Tumor localization was most common in the upper outer quadrant (143, 57.9%), followed by upper inner quadrant (34, 13.7%), lower outer quadrant (23, 9.2%) and lower inner quadrant (10, 4.0%). Twenty-one (8.4%) of the patients had multicentric tumors, 15 (6.0%) patients had retroareolar tumors, and two (0.8%) patients had occult tumors. More than half of the patients had 2.1-5.0 cm tumors (n=150, 60.4%); 78 (31.4%) had 1.1-2.0 cm tumors; 17 (6.8%) had 0.6-1.0 cm tumors; and three (1.4%) patients had 0.5 cm or less tumors. The number of patients according to the clinical tumor (cT) stage were 97 (39%) patients for cT1 and 151 (61%) patients for cT2.

The patients underwent four types of surgical procedures: 114 (45.9%) had BCS+SLNB (breast conserving surgery + SLNB), 70 (28.2%) had BCS+AD (BCS + axillary dissection), 46 (18.5%) had MRM [modified radical

mastectomy), and 18 (7.4%) had simple mastectomy + SLNB. A total of 108 (43.5%) patients had Luminal B HER2 (-); 52 (21.0%) patients had Luminal A; 38 (15.3%) patients had Luminal B HER2 (+); 30 (12.1%) patients had triple negative; and 20 (8.1%) HER2 (+) tumors. The pathological stages following surgical treatment were as follows: 40 (16.3%) patients had stage 1; 107 (43.1%) had stage 2a; 60 (24.1%) had stage 2b; and 41 (16.5%) had stage 3a cancer.

Univariate analyses of the negative and positive axilla groups showed that grade 2 tumor (66.1%) incidence was higher in all groups (*P*=.004) (**Table 1**). Grade 1 tumors were more common in Luminal A group (36.5%). Luminal B HER2 (+) and Luminal B HER2 (-) groups had a higher incidence for grade 2 tumors (71.1% and 69.4%, respectively). Grade 3 tumor incidence was highest in the TN group and lowest in Luminal A group (26.7% and 3.90%, respectively). Lymphovascular invasion was more common in Luminal B HER2 (+) and HER2 (+) groups (63.2% and 55.0%, respectively); and least common in the TN group (26.7%) (*P*=.019).

Tables 2 and 3 show the sensitivity, specificity, PPV, NPV, accuracy of 18F-FDG-PET/CT for detecting axillary metastasis and its agreement with SLNB. Axillary evaluation of HER2 (+) tumors with 18F-FDG-PET/CT showed 85% of accuracy, 88% PPV, 83% NPV, and a good agreement with SLNB (Kappa coefficient: 0.69, *P*<.005). In Luminal A tumors, 18F-FDG-18F-FDG-PET/CT had 71% accuracy, 90% PPV, 67% NPV, and a fair agreement with SLNB (Kappa coefficient: 0.38, *P*<.003). The 18F-FDG-PET/CT showed 76% accuracy, 97% PPV, 67%NPV, and a moderate agreement with SLNB in Luminal B HER2 (-) tumors (Kappa coefficient: 0.55, *P*<.001). In Luminal B HER2 (+) tumors, 18F-FDG-PET/CT showed 85% accuracy, 83% PPV, 80% NPV, and a good agreement with SLNB (Kappa coefficient: 0.63, *P*<.001). In TN tumors, 18F-FDG-PET/CT showed 80% accuracy, 90% PPV, 75% NPV, and moderate agreement with SLNB (Kappa coefficient: 0.59, *P*=.001). In all patients, the sensitivity, specificity, PPV, NPV, and accuracy of 18F-FDG-PET/CT for detecting axillary metastasis were 62%, 92%, 88%, 71%, and 77%, respectively. Cohen's Kappa coefficient (0.54) showed moderate agreement with SLNB (*P*<.001).

To further evaluate the diagnostic performance of 18F-FDG PET/CT in detecting axillary lymph node metastasis, an ROC curve analysis was performed for each immunohistochemical subtype (**Figure 1**). The AUC was highest in Luminal B HER2-positive tumors (AUC=0.85; 95% CI: 0.73–0.97) and HER2-positive tu-

Table 1. Histopathologic features according to the immunohistochemical subtypes.

	Luminal A	Luminal B HER2 (-)	Luminal B HER2 (+)	HER 2 (+)	Triple negative	Total	*P* value
	n=52	n=108	n=38	n=20	n=30	n=248	
Grade							
1	19 (36.5)	23 (20.4)	5 (13.2)	4 (20.0)	2 (6.60)	53 (21.7)	
2	31 (59.6)	75 (69.4)	27 (71.1)	11 (55.0)	20 (66.7)	164 (66.1)	.004
3	2 (3.90)	10 (10.2)	6 (15.7)	5 (25.0)	8 (26.7)	31 (12.2)	
Lymphovascular invasion							
Absent	31 (59.6)	50 (46.3)	14 (36.8)	9 (45.0)	22 (73.3)	126 (50.8)	.019
Present	21 (40.4)	58 (53.7)	24 (63.2)	11 (55.0)	8 (26.7)	122 (49.2)	
Perinodal involvement							
Absent	47 (90.4)	89 (82.4)	29 (76.3)	16 (80.0)	24 (80.0)	205 (82.6)	.427
Present	5 (9.62)	19 (17.6)	9 (23.7)	4 (20.0)	6 (20.0)	43 (17.4)	
Perineural invasion							
Absent	41 (78.8)	62 (57.4)	26 (68.4)	12 (60.0)	23 (76.7)	164 (66.1)	.053
Present	11 (21.2)	46 (42.6)	12 (31.6)	8 (40.0)	7 (23.3)	84 (33.9)	

Data presented as n (%). Significant at *P*<.05. HER2: Human epidermal growth factor receptor 2

mors (AUC=0.82; 95% CI: 0.59–0.99), indicating excellent discriminative ability in these subgroups. The PET/CT also demonstrated solid performance in the TN and Luminal B HER2-negative subtypes, with AUCs of 0.79 and 0.80, respectively. The Luminal A group had the lowest AUC (0.68; 95% CI: 0.54–0.83), reflecting limited sensitivity in this subtype.

DISCUSSION

Axillary nodal staging is a critical component of breast cancer treatment, since it is the most important independent prognostic factor, with overall survival linked to the number of positive axillary lymph nodes.[22] However, factors like genetic heterogeneity makes the tumors' behaviors widely different. As a result, new diagnostic and treatment modalities are needed. Some studies suggest that 18F-FDG-PET/CT is sufficient for detecting axillary metastasis and performing an axillary dissection, while others demonstrated no additional diagnostic value of 18F-FDG-PET/CT.[23-28] Therefore, in this study, we aimed to find the accuracy of 18F-FDG-PET/CT in detecting ipsilateral axillary metastasis in breast cancer according to the immunohistochemical subtypes. We also aimed to see if there is an agreement between SLNB results and SUVmax values.

The 18F-FDG-PET/CT is used as a prevalent imaging modality in many cancer types for detecting metastatic diseases, staging and evaluating the response to treatment, etc. In some studies, the sensitivity of 18F-FDG-PET/CT varies based on the tumor burden and proves insufficient in detecting axillary micrometastases.[26,27] It has been also shown that 18F-FDG-PET/CT has moderate sensitivity, high sensitivity, and pooled diagnostic accuracy up to 77.3%.[28,29] Due to these limitations, 18F-FDG-PET/CT is not recommended as a primary method for axillary staging. The sensitivity and specificity of 18F-FDG-PET/CT are naturally influenced by the threshold of cut-off SUVmax values. According to a study by Udea et al, decreasing the SUVmax threshold can lead to a specificity of 100%, but with a decreased 36% sensitivity.[30] Kim et al also suggested that lowering the SUVmax value threshold to <1.05 can increase sensitivity up to 100%, but false negatives are omitted in the study.[31] We found the diagnostic accuracy of 18F-FDG-PET/CT 77% and sensitivity being 62% when the SUVmax value >1.95 f1or all patients.

The current literature suggests that false positive rates can be reduced using the SUVmax analyses.[32,33] According to Ozer et al, the mean SUVmax value of axilla is 1.939 times higher in patients with metastatic axillary lymph nodes than those without axillary metastasis (*P*=.001). Also, the cut-off value of SUVmax is >1.1

Table 2. ROC analyses and the level of agreement between axillary metastasis (Axilla SUV max) and 18F-FDG-PET/CT.

	Cutoff value	AUC (%95 CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Kappa value
All patients	1.95	0.79 (0.73-0.84)	62	92	88	71	77	0.54
HER 2 (+)	2.1	0.82 (0.59-0.99)	78	91	88	83	85	0.69
Luminal A	1.95	0.68 (0.54-0.83)	39	97	90	67	71	0.38
Luminal B HER2 (-)	2.35	0.80 (0.72-0.88)	59	98	97	67	76	0.55
Luminal B HER2 (+)	1.65	0.85 (0.73-0.97)	79	84	83	80	85	0.63
Triple negative	2.25	0.79 (0.62-0.96)	64	94	90	75	80	0.59

SUVmax: Maximum Standard Unit Value; HER2: human epidermal growth factor receptor 2

Table 3. Distribution of SUVmax values in node-negative vs. node-positive patients and proportion of patients with confirmed metastasis when SUVmax exceeds the subtype-specific threshold.

Subtype	SUVmax (Negative)	SUVmax (Positive)	Cutoff SUVmax	PPV > Cutoff (%)	*P* value
All Patients	0.00 (0.00–1.40)	2.60 (1.00–5.75)	1.95	88.4	<.001
Luminal A	0.00 (0.00–1.40)	1.40 (0.00–2.50)	1.95	90.0	.003 / .017
Luminal B HER2 (–)	0.00 (0.00–1.17)	2.80 (1.05–6.05)	2.35	97.1	<.001
Luminal B HER2 (+)	0.00 (0.00–1.20)	2.80 (1.90–7.95)	1.65	83.3	<.001
HER2 (+)	1.00 (0.00–1.73)	3.40 (2.30–4.30)	2.10	87.5	.005 / .014
Triple Negative	0.00 (0.00–1.50)	2.90 (1.77–4.68)	2.25	90.0	.001 / .006

SUVmax: Maximum Standard Unit Value; HER2: human epidermal growth factor receptor 2; PPV: positive predictive value.

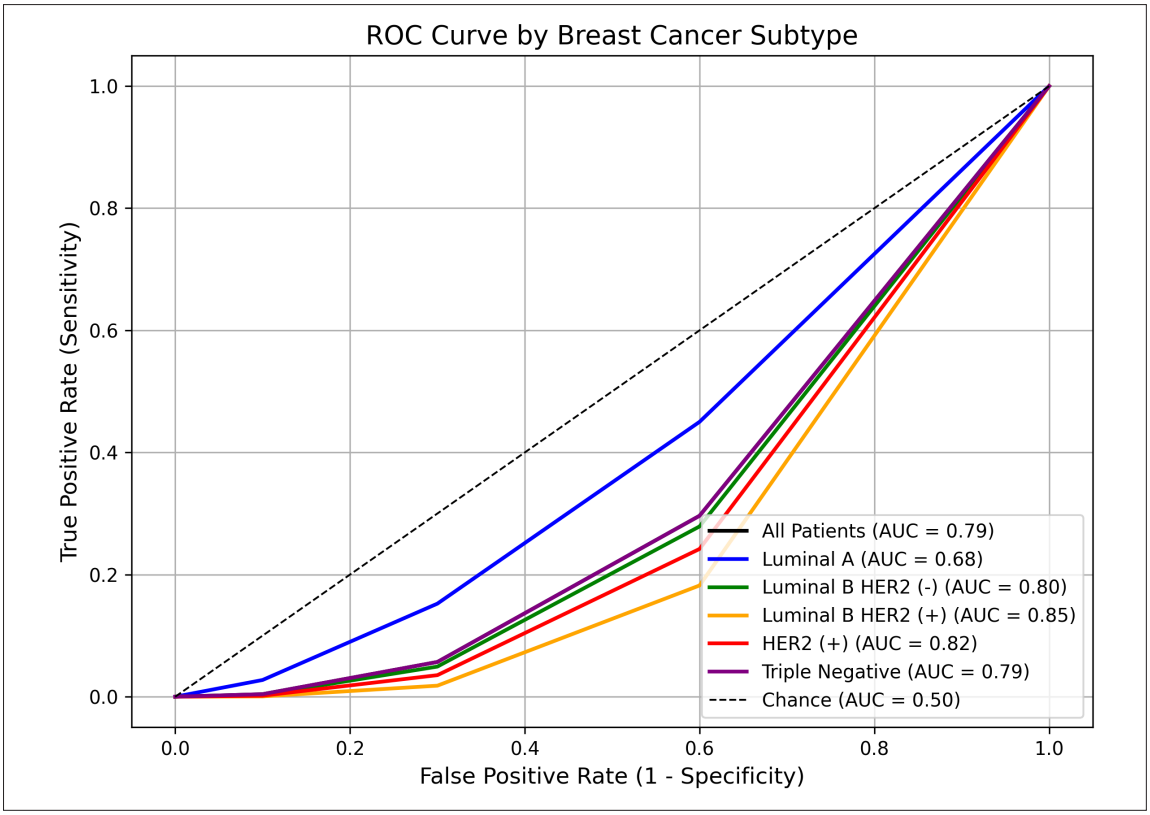

Figure 1. Receiver Operating Characteristic (ROC) curves by breast cancer subtype.

when distinguishing metastatic and non-metastatic axillary lymph nodes.[25] However due to suboptimal specificity and sensitivity rates, it is recommended that tumor biology also be considered in clinical decision making. In the same study, they have reported that TN tumors have higher SUVmax values than Luminal A and Luminal B tumors. Kajary et al also showed a significant correlation between tumor subtypes and volumetric parameters.[24] In our study, we calculated the cut-off SUVmax value for each biological subtypes and saw that sensitivity, specificity, PPV, NPV, and accuracy highly vary between subtypes (**Table 2**). For example, when Luminal B HER2 (-) and Luminal A groups had the highest specificity (98% and 97%, respectively), they had the lowest sensitivity for 18F-FDG-PET/CT in the detection of axillary metastasis (59% and 39%, respectively). Also, in Luminal A group SLNB and 18F-FDG-PET/CT had the lowest agreement.

In the current literature, the specificity of 18F-FDG-PET/CT is relatively high.[25-28] According to a systematic review by Kasem et al, the specificity was found to be 91.6% and they reported that it is consistent with a meta-analysis by Zang et al [specificity 91% (95% CI:87%-93%)].[28,34] In contrast, some studies suggest that 18F-FDG-PET/CT cannot be used routinely for axillary staging.[26,35] The most important argument behind this opposing view is that most studies did not compare the SUVmax values with the immunohistochemical status of the tumors.

According to a meta analysis by Liang et al, pooled sensitivity of 18F-FDG-PET/CT is 64%; however, comparative analyses suggest that prospective studies evaluating 18F-FDG-PET/CT tend to demonstrate higher pooled sensitivity and specificity than retrospective studies, likely due to more standardized protocols and reduced selection bias.[36] According to another meta-analysis by Han et al., several limitations—including small sample sizes, study heterogeneity, and the predominance of retrospective designs—may have contributed to an overestimation of 18F-FDG-PET/CT's diagnostic performance. Their subgroup analysis showed only a modest difference in sensitivity between prospective 18F-FDG-PET/CT studies (0.86; 95% CI: 0.70–1.00) and 18F-FDG-PET/Magnetic Resonance Imaging studies (0.78; 95% CI: 0.65–0.92), underscoring the need for cautious interpretation.[37]

False negative rates of SLNB should be considered when staging the axilla. Important factors that can affect frozen section analysis and lead to false negative SLNB results include the tumor size, the size of the metastases in the SLN, and the presence of hormone receptor-negative tumor. [38,39] According to Wahl et al, patients with positive 18F-FDG-PET/CT could undergo immediate axillary dissection, while for those with negative 18F-FDG-PET/CT, SLNB is still the method of choice for axillary staging.[33] However, they also underline that in patients with only one tumor-associated lymph node, the average sensitivity was lower compared to those with multiple tumor-associated nodes (46%; *P*=.005). This observation suggests that 18F-FDG-PET/CT is less sensitive in patients with more limited tumor node involvement. In the same study, patients with false-negative axilla with 18F-FDG-PET/CT had fewer and generally smaller tumor-related lymph nodes compared to the patients with a true-positive axilla.[33] In addition to its low sensitivity, the 18F-FDG-PET/CT also has higher false negative rates compared to SLNB.[40] Whole-body 18F-FDG-PET/CT protocols have the potential to fail to detect axillary metastasis when small number of nodes are metastatic, because even though breast cancers have high glucose metabolic activity, they do not have an SUVmax as high as those in other cancers.[41,42] In another study by Aktas et al, 18F-FDG-PET/CT has similar results compared to other radiological modalities, and it was also emphasized that combining imaging methods may increase the accuracy of the diagnosis.[43]

In our study, we found results consistent with the literature in terms of sensitivity, specificity, and accuracy. We also achieved high specificity for the total patient group and each subtype. However, sensitivity for detecting ipsilateral axillary metastasis was lower across all groups. We also realized that tumors with positive HER2 gene amplification (HER2 (+) and Luminal B HER2 (+) have higher sensitivity than other subtypes [Luminal A, Luminal B HER2 (-) and triple negative]. Although the 18F-FDG PET/CT cannot replace SLNB in routine axillary staging due to its limited sensitivity, our findings suggest that it may serve as a valuable adjunct in specific clinical scenarios. In patients with HER2-positive tumors, where 18F-FDG PET/CT demonstrated higher sensitivity and concordance with SLNB, it may help guide preoperative decision-making or provide supportive evidence when SLNB is inconclusive or technically unsuccessful. Additionally, in settings where SLNB is not feasible or contraindicated, 18F-FDG PET/CT may offer a non-invasive alternative to assess axillary involvement, especially when interpreted alongside other clinical and pathological factors.

The retrospective design of this single-centered study and the limited number of patients for each immunohistochemical subtypes are the limitations of this study. Since it is a retrospective study, it has selection bias. Another limitation is that the small number of patients in each group prevents a reliable multivariate analysis. Prospective multi-centered studies with a large group of patients are needed to determine the true sensitivity and specificity of 18F-FDG-PET/CT. All 18F-FDG PET/CT images were interpreted by a single experienced nuclear medicine specialist. While this helped ensure consistency in image evaluation, it also introduced a potential source of subjectivity, as interobserver variability was not assessed. Future studies should consider blinded, dual-reader evaluations or interobserver concordance analyses to better assess the reliability of PET/CT interpretations. It should also be noted that the SLNB procedure in this study was performed using methylene blue dye only, without the use of a radioactive isotope tracer. Although methylene blue is a widely used and a cost-effective agent, it has been reported to have higher false-negative rates compared to the standard dual-tracer technique that combines a radiocolloid and dye. This could poten-

tially affect the accuracy of the SLNB results used as the reference standard in our study, and may influence the calculated sensitivity and concordance of 18F-FDG PET/CT.

In conclusion, 18F-FDG-PET/CT has high specificity (92%) but limited sensitivity (62%) for detecting ipsilateral axillary lymph node metastasis in patients with early-stage invasive ductal carcinoma. This suggests that 18F-FDG-PET/CT alone is not sufficiently sensitive to replace SLNB for routine axillary staging. However, diagnostic performance varied across molecular subtypes, with higher accuracy and agreement observed particularly in HER2 (+) and Luminal B HER2 (+) tumors. In these subgroups, 18F-FDG-PET/CT may provide useful preoperative information and help guide individualized management decisions. Given the retrospective, single-center design and limited subgroup sizes, caution is warranted in interpreting these findings. Larger, prospective, multicenter studies are needed to better define the role of 18F-FDG-PET/CT in axillary staging, particularly in the context of molecular subtypes and evolving surgical approaches.

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