Original Article

Eur J Breast Health 2024; 20(1): 45-51
DOI: 10.4274/ejbh.galenos.2023.2023-10-6

Does F-18 FDG-PET/CT Have an Additional Impact on Axillary Approach in Early-Stage Breast Cancer?

Burak Çelik[1], Medine Boge[2], Ece Dilege[1]

[1]Department of General Surgery, Koç University School of Medicine, İstanbul, Turkey
[2]Department of Radiology, Koç University School of Medicine, İstanbul, Turkey

ABSTRACT

Objective: Breast cancer (BC) is a significant health concern and one of the most diagnosed cancers in women, both in Turkey and globally. Despite advances in the management of BC, axillary lymph node involvement remains a significant consideration for treatment planning, local recurrence, and prognosis. We aimed to evaluate the contribution of F-18 fluorodeoxyglucose-positron emission tomography/computed tomography (F-18 FDG-PET/CT) in detecting axillary lymph node metastasis compared to ultrasound (US).

Materials and Methods: Eighty patients who were diagnosed with stage I and II BC and underwent US and F-18 FDG-PET/CT scans before surgery were enrolled in this study. Those who did not undergo F-18 FDG-PET/CT imaging, patients with distant metastases at the time of diagnosis and patients with micrometastases in the axilla were excluded from the analysis. Imaging results of the status of axillary lymph nodes were verified with the final pathology report of axillary lymph nodes.

Results: The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of F-18 FDG-PET/CT for the detection of ipsilateral axillary lymph node metastases were 75%, 77.27%, 72.97%, 79.07%, and 76.25%. The corresponding values for US were 72.22%, 81.82%, 76.47%, 78.26%, and 77.50%, respectively. When US finding is negative or suspicious in axillary lymph node evaluation, the accuracy of F-18 FDG-PET/CT for the detection of ipsilateral axillary lymph node metastases were 65.38%, 83.33%, 70.83%, and 79.55%, respectively.

Conclusion: This study found that F-18 FDG-PET/CT does not provide an additional advantage over US in assessing the axilla in early-stage disease.

Keywords: Breast cancer; lymph node metastasis; axillary staging; positron emission tomography; ultrasound

Cite this article as: Çelik B, Boge M, Dilege E. Does F-18 FDG-PET/CT Have an Additional Impact on Axillary Approach in Early-Stage Breast Cancer? Eur J Breast Health 2024; 20(1): 45-51

Key Points

- Metastatic involvement of axillary lymph node remains significant for treatment planning, local recurrence, and prognosis of breast cancer.
- F-18 FDG-PET/CT did not provide an additional advantage over US in assessing the axilla in early-stage disease.
- US examination by an experienced breast radiologist is sufficient for evaluating the axillary lymph nodes.

Introduction

Breast cancer (BC) is a significant health concern and one of the most diagnosed cancers, and the second leading cause of cancer-related deaths in women both in Turkey and globally. BC accounts for one out of every four female cancers (1). Despite advances in the management of BC, axillary lymph node involvement remains the most important prognostic factor, and has importance for treatment planning, local recurrence, and prognosis. Over the past two decades, the increased morbidity associated with axillary surgery has prompted extensive research efforts. This has resulted in a shift towards more personalized treatments, as exemplified by the American College of Surgeons Oncology Group Z0011 clinical trial (ACOSOG Z0011) (2) and ongoing trials aimed at eliminating the need for surgical axillary staging. Currently, no single ideal imaging method exists for accurately staging the axilla.

The AMAROS trial included patients with clinically negative axillary lymph nodes and T1 or T2 stage BC with micro- or macro-metastatic sentinel lymph node biopsy (SLNB). Axillary lymph node dissection (ALND) and axillary radiotherapy arms showed comparable results regarding local recurrence and survival outcomes (3).

Corresponding Author:
Burak Çelik; bcelik@kuh.ku.edu.tr

Received: 28.10.2023
Accepted: 07.12.2023
Available Online Date: 27.12.2024

©Copyright 2024 by the Turkish Federation of Breast Diseases Societies / European Journal of Breast Health published by Galenos Publishing House.

Prospective ongoing studies, such as SOUND (Sentinel node v Observation after axillary UltrasouND), INSEMA (Intergroup Sentinel Mamma study), and BOOG 2013-08 (Borstkanker Onderzoek Groep) are focused on evaluating the safety of omitting SLNB in breast conserving surgery (BCS) for patients with clinically negative axillary nodes. The SOUND trial is a prospective randomized multicenter study, and its objective is to compare the outcomes of SLNB versus observation (no axillary surgery) in patients with early BC, smaller than 2 cm, low-grade, biologically favorable tumors, and a negative preoperative axillary ultrasound (US) finding. In this clinical trial, where patients with small BC and negative axillary lymph nodes on US, omitting axillary surgery demonstrated non-inferiority in terms of disease-free survival compared to SLNB (4).

Considering these studies, the presence or absence of lymph node involvement in BC and its accurate determination at the time of diagnosis still cannot be reliably achieved. Although US is known to be the most reliable, easily accessible, and cost-effective modality for interpreting lymph node status, its sensitivity can be compromised due to its operator-dependent nature. F-18 fluorodeoxyglucose-positron emission tomography/computed tomography (F-18 FDG-PET/CT) is recommended for imaging in cases of locally advanced disease and primarily for detecting distant metastasis (5). It is also utilized in cases of uncertainty regarding axillary lymph node involvement (6). Our study aimed to evaluate the contribution of F-18 FDG-PET/CT in detecting axillary lymph node metastasis compared to US.

Materials and Methods

Study Design

This study retrospectively evaluated the imaging and pathology reports of 80 BC patients treated at Koç University Hospital, Breast Surgery Clinic, between June 2015 and March 2023. Stage I and II BC patients who had undergone initial diagnostic US and F-18 FDG-PET/CT scans were enrolled. This study was approved by the Koç University Institutional Review Board (2023.252.IRB1.081).

The staging of BC was done according to the 8th edition of the American Joint Committee on Cancer staging system (7). Data were collected from medical records, including operative notes, radiology, nuclear medicine, and pathology reports. Patients were initiated on treatment with neoadjuvant chemotherapy (NAC) or upfront surgery based on their clinical stage and immune phenotype. Clinical lymph node status by imaging was compared with the pathological assessments of surgically removed lymph nodes, either by SLNB or ALND. In patients who underwent NAC, in case of pathological complete response, the signs of response to therapy in the lymph node (LN) were reported, and those patients were assigned as LN positive.

US is the method of choice to evaluate the axillary lymph nodes. When there was suspicion of lymph node metastasis, fine needle aspiration biopsy (FNAB) was performed. Patients with micrometastatic LN were excluded from the study to minimize bias, as none of the imaging modalities used are intended to diagnose micrometastasis. Radiological evaluation of the axillary lymph nodes was compared with the final surgical pathology results (Figure 1). The US and F-18 FDG-PET/CT assessments were blinded to the findings of the other modality.

US Protocol

Preoperative axillary US was performed by a breast radiologist experienced in breast imaging using GE Logiq E10 and GE Logiq S8 machines (GE Healthcare, Milwaukee, Wisconsin, USA), which were equipped with high-frequency matrix linear transducers at a frequency range of 6 to 15 MHz. Bilateral axillary regions were scanned using an orthogonal direction along the axillary artery from the lower axilla to the junction of the axilla and upper arm, as well as the retro-pectoral area.

Suspicious axillary lymph nodes (ALNs) were identified based on the detection of one or more of the following US features: cortical thickness greater than 3.0 mm, focal cortical lobulation, irregular or round shape, markedly hypoechoic or heterogenous cortex, loss of fatty hilum and increased peripheral blood flow or abnormal cortical blood flow (nonhilar flow) on Doppler US.

For all identified suspicious ALNs during the preoperative axillary US, US-guided fine needle aspiration (FNA) or core-needle biopsy was recommended. The same breast radiologist performed the FNA procedure using a 22-gauge needle with a freehand technique. Each lymph node was aspirated at least twice. Immediately after aspiration, all FNA samples were evaluated at the bedside to obtain rapid cytological results. A fully automatic method was utilized, using 14 or 16-gauge needles for core-needle biopsies.

F-18 FDG-PET/CT Protocol

All patients refrained from eating for at least four hours before the PET study. The F-18 FDG-PET/CT scan was conducted 60 minutes after administering 0.8–1 mCi/kg of F-18 FDG if the blood glucose was <11 mmol/L, and the resulting images, spanning from the head to the proximal calf, were reconstructed using Q-clear time-of-flight and point-spread function data. No contrast agent containing iodine was used during the CT scan. The standardized uptake value (SUV) was determined by adjusting for the injected FDG dose and the patient's body weight. All F-18 FDG-PET/CT examinations were retrieved from the electronic archive system and assessed using a GE Healthcare AW workstation in Milwaukee, Wisconsin, USA. The F-18 FDG-PET/CT images were taken from the head to the proximal thighs. Before obtaining the PET images, a helical CT was performed with the person breathing shallowly, using a low-dose CT protocol to create an attenuation map. ALNs were evaluated visually and deemed positive when the F-18 FDG uptake level exceeded that of the adjacent ALN and the reference background. The ALN's morphological characteristics and dimensions were examined and documented. The PET signal revealed that ALN displaying basal physiological lymphatic uptake was classified as negative. The SUV_{max} was identified as the highest SUV value within the region of interest, delineated over the most intense area of F-18 FDG accumulation in the ALN for each patient.

Statistical Analysis

The obtained findings in the study were evaluated using the SPSS, version 26 (IBM Inc., Armonk, NY, USA). Descriptive statistical methods, such as mean, standard deviation, median, minimum, and maximum values are used for quantitative variables, while qualitative variables are presented using frequency and percentage. The normality of the data was assessed using the Shapiro-Wilk test and Box Plot graphs. Diagnostic screening tests (sensitivity, specificity, positive predictive value, negative predictive value, and accuracy), the McNemar test, and the Kappa agreement level were used to compare qualitative data. Receiver operator curve (ROC) curve area was used to evaluate the US and F-18 FDG-PET/CT results for predicting pathological outcomes. The results were evaluated at a 95% confidence interval, with a significance level of $p<0.05$.

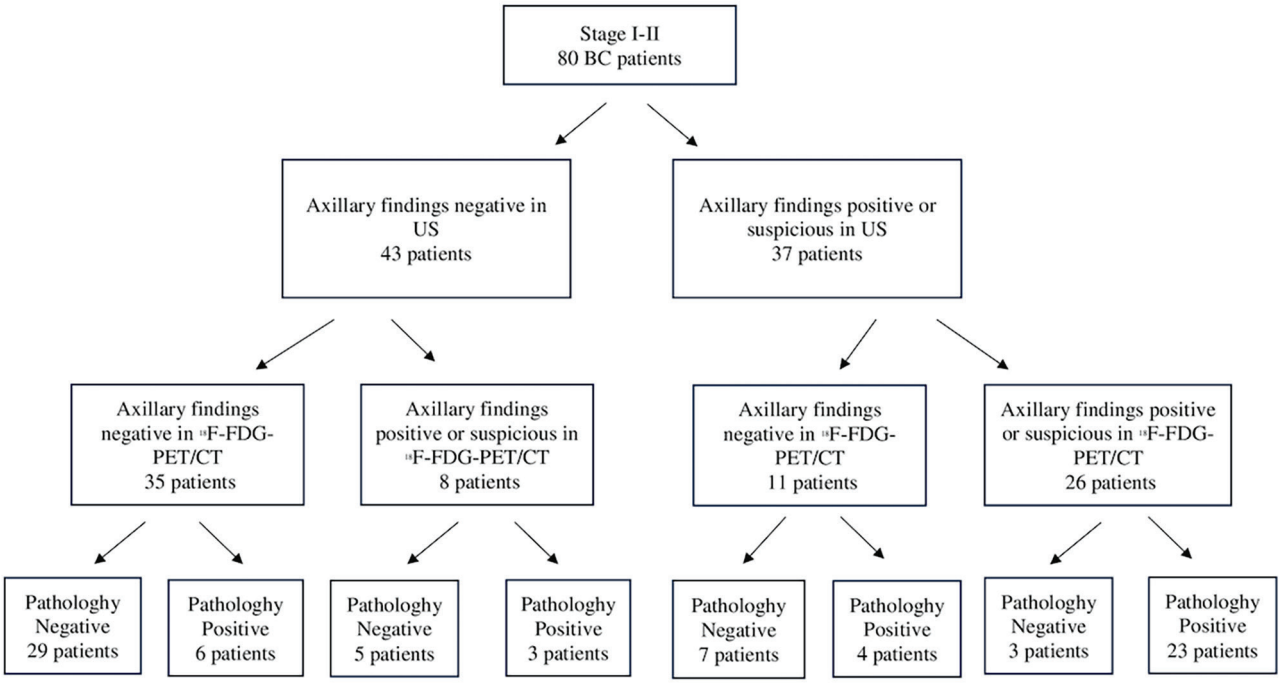

Figure 1. Study chart

F-18 FDG-PET/CT: F-18 fluorodeoxyglucose-positron emission tomography/computed tomography; US: Ultrasound; BC: Breast cancer

Sensitivity is defined as the ability of the test to correctly identify individuals with the condition among true positive cases. Specificity is defined as the ability of the test to correctly identify individuals without the condition among true negative cases.

Positive predictive value (PPV) is defined as the conditional probability of the individual having the condition when the test result is positive (indicating the presence of the disease) while the negative predictive value (NPV) is defined as the probability of the individual being free of the condition when the test result is negative (indicating the absence of the disease).

The κ (Kappa) value is used to assess the level of agreement beyond chance between two raters or methods. The interpretation of κ values helps determine the strength of agreement, ranging from poor to very good.

Results

One male and 79 females, a total of 80 patients, were enrolled in this study. The mean ± standard deviation age was 55.38±14.05 years, and the median was 55 (range: 27–86). The clinical T-stage distribution was as follows: cT1, 42 (51.3%) patients; cT2, 38 (47.5%) patients; and cT3, 1 (1.3%) patient. The clinical N stage distribution was as follows: cN0, 53 (66.3%) patients and cN1 27 (33.8%) patients. The clinical stage distribution was as follows: 1A, 33 (40.9%) patients; 2A, 26 (32.5%) patients; and 2B, 21 (26.2%) patients. Among them, 65 (81.3%) patients were diagnosed with histopathological proven ductal carcinoma, 10 (12.5%) with lobular carcinoma or mixed histology, 2 (2.5%) with mucinous carcinoma, 2 (2.5%) with micropapillary carcinoma, and 1 (1.3%) with tubular carcinoma. Twenty-three (28.8%) patients received NAC before surgery, while 57 (71.2%) patients underwent upfront surgery. In the subtype analysis, 59 (73.6%) patients were HR+/HER2-, 14 (17.5%) patients were HR-/HER2+, and 7 (8.8%) patients were HR-/HER2-. Of 80 patients, 30 underwent SLNB followed by ALND, while SLNB was performed on the remaining 50. The results were analyzed based on these procedures.

According to preoperative US, axillary lymph node involvement was negative in 53.8% (n=43) of patients, suspicious in 31.3% (n=25) of patients, and positive in 15% (n=12) of patients. Preoperative F-18 FDG-PET/CT revealed negative axillary lymph node involvement in 57.5% (n=46) of patients, suspicious involvement in 12.5% (n=10) of patients, and positive involvement in 30% (n=24) of patients. On US examination, there was one metastatic lymph node in 30% (n=24) of the patients, 2 in 13.8% (n=11) of the patients, and 3 in 2.5% (n=2) of the patients. In the F-18 FDG-PET/CT examination, there was one metastatic lymph node in 25% (n=20) of the patients, 2 in 15% (n=12) of the patients, 3 in 1.3% (n=1) of the patients, and 4 in 1.3% (n=1) of the patients (Table 1). FNAB was performed on 25 (31.25%) out of 80 patients, revealing carcinoma metastasis in 18 (22.5%) cases and yielding negative results in 7 (8.75%) cases. The remaining 55 (68.75%) patients did not undergo FNAB.

Axillary evaluation by US was true-negative (TN) in 34 (45.0 %) patients, true-positive (TP) in 27 (33.8%) patients, false-negative (FN) in 9 (11.3%), and false-positive (FP) in 10 (12.5%) patients. Kappa correlation level between US and axillary lymph node pathology results was 52.1% and found to be statistically significant (Kappa coefficient: 0.521; p = 0.001 (Table 2).

Axillary evaluation by F-18 FDG-PET/CT was TN in 36 (45%) patients, TP in 26 (32.5%) patients, FN in 10 (12.5%) patients, and FP in 8 (10%) patients. Kappa correlation level between F-18 FDG-PET/CT and axillary lymph node pathology results was 54.3% and found to be statistically significant (Kappa coefficient: 0.543; p = 0.001) (Table 2).

Axillary evaluation by US and F-FDG-PET/CT both were TN in 29 (47.5%) patients, TP in 23 (37.7%) patients, FN in 6 (9.8%) patients

Table 1. Distribution of descriptive characteristics

Age	Mean ± SD	55.38±14.05
	Median (Min-Max)	55 (27–86)
Histopathological type	Invasive ductal carcinoma	65 (81.3)
	Invasive lobular carcinoma/ mixt	10 (12.5)
	Mucinous carcinoma	2 (2.5)
	Micropapillary carcinoma	2 (2.5)
	Tubular carcinoma	1 (1.3)
Subtype	Luminal A (ki-67<20%)	37 (46.3)
	Luminal B (ki-67>20%)	22 (27.5)
	HER2 +	14 (17.5)
	Triple negative	7 (8.8)
Neoadjuvant chemotherapy	None	57 (71.3)
	Given	23 (28.8)
Clinical T stage	T1	41 (51.3)
	T2	38 (47.5)
	T3	1 (1.3)
Clinical N stage	N0	53 (66.3)
	N1	27 (33.8)
Stage	IA	33 (41.3)
	IIA	26 (32.5)
	IIB	21 (26.3)
Evaluation of axilla in US	Negative	43 (53.8)
	Suspicious	25 (31.3)
	Positive	12 (15.0)
Metastatic lymph node number in US	None	43 (53.8)
	1	24 (30.0)
	2	11 (13.8)
	3	2 (2.5)
Evaluation of axilla in F-18 FDG-PET/CT	Negative	46 (57.5)
	Suspicious	10 (12.5)
	Positive	24 (30.0)
Metastatic lymph node number in F-18 FDG-PET/CT	None	46 (57.5)
	1	20 (25.0)
	2	12 (15.0)
	3	1 (1.3)
	4	1 (1.3)
Axillary lymph node pathology	Negative	44 (55.0)
	Positive	36 (45.0)

*F-18 FDG-PET/CT: F-18 fluorodeoxyglucose-positron emission tomography/computed tomography; US: Ultrasound; T: Tumor; N: Nodal; HER2: Human epidermal growth factor receptor 2; SD: Standard deviation; Min-Max: Minimum-Maximum

and FP in 3 (4.9%) patients. Kappa correlation level between US and F-18 FDG-PET/CT and both axillary lymph node pathology results was 70.3% and found to be statistically significant (Kappa coefficient: 0.703; p = 0.001) (Table 2).

The sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG-PET/CT for detecting ipsilateral axillary lymph node metastases were 75%, 77.27%, 72.97%, 79.07%, and 76.25%. The corresponding values for the US were 72.22%, 81.82%, 76.47%, 78.26%, and 77.50%, respectively. When US finding was negative or suspicious in axillary lymph node evaluation, the accuracy of F-18 FDG-PET/CT for the detection of ipsilateral axillary lymph node metastases were 65.38%, 83.33%, 70.83%, and 79.55%, respectively. In predicting axillary lymph node metastasis, the area under the ROC curve for F-18 FDG-PET/CT was 0.77 (77%), with a standard error of 5.5%. This finding was statistically significant (p = 0.001), indicating that the ROC curve for F-18 FDG-PET/CT is a reliable predictor of axillary lymph node metastasis. Also, in predicting axillary lymph node metastasis, the area under the ROC curve for the US test was 0.761 (76.1%), with a standard error of 5.6%. This finding was again statistically significant (p = 0.001), indicating that the ROC curve for the US test was a reliable predictor of axillary lymph node metastasis. When comparing these areas pairwise, no statistically significant difference was found between the predictive abilities of USG and ^{18}F-FDG-PET/CT tests in predicting axillary lymph node pathology (p = 0.871). When US is negative or suspicious in axillary lymph node evaluation, the area under the ROC curve for F-18 FDG-PET/CT was 0.744 (74.4%), with a standard error of 6.5%.

Discussion and Conclusion

In BC treatment, axillary staging continues to be important in determining the treatment approach. The nodal staging process typically involves various imaging studies, such as US and magnetic resonance imaging (MRI).

US is widely used as a prevalent imaging modality in assessing the axillary region in BC. It offers the advantages of being non-intrusive, economically efficient, and without ionizing radiation exposure. US facilitates comprehensive characterization of axillary lymph nodes, encompassing their dimensions, configuration, and structure. Additionally, it can identify noteworthy attributes, such as aberrant lymph node morphology, augmented cortex thickness, diminishment of adipose hilum, and heightened vascularity, potentially suggestive of metastatic engagement. Conversely, F-18 FDG-PET/CT synergistically amalgamates functional insights from PET with anatomical data garnered from CT. The combination of F-18 FDG-PET/CT furnishes insights into the metabolic vitality of tissues, offering utility in identifying metastatic pathology. The modality is proficient in identifying regions characterized by heightened glucose metabolism, a trait often linked to highly active neoplastic cells. F-18 FDG-PET/CT exhibits superiority over traditional staging modalities, such as physical examination and conventional imaging, when detecting metastatic afflictions within the axillary region. Nevertheless, it is imperative to acknowledge that the use of F-18 FDG-PET/CT could be constrained in its capacity to identify micrometastasis within the axillary lymph nodes. The potential inadequacy of F-18 FDG-PET/CT in detecting axillary lymph node metastases arises when dealing with either a limited count of lymph nodes or nodes of diminutive dimensions. In the investigation conducted by Segaert et al. (8), it was observed that F-18 FDG-PET/CT exhibited diminished sensitivity in accurately assessing axillary involvement in surgically treatable BCs characterized by a limited tumor burden within the breast. ^{18}F-FDG-PET/CT alone is not recommended as the primary imaging method for routine staging of axillary lymph nodes in BC patients. This is due to its limited sensitivity in detecting axillary metastases, which has been observed to range from 37% to 85% (9, 10).

Table 2. The level of agreement between US, F-18 FDG-PET/CT, both US and F-18 FDG-PET/CT and axillary lymph node pathology results

	True positive	True negative	False negative	False positive	Kappa	*p*
US	27 (33.8)	34 (42.5)	9 (11.3)	10 (12.5)	**52.1**	**1.000**
F-18 FDG-PET/CT	26 (32.5)	36 (45.0)	10 (12.5)	8 (10.0)	**54.3**	**0.815**
US/F-18 FDG-PET/CT both	23 (37.7)	29 (47.5)	6 (9.8)	3 (4.9)	**70.3**	**0.648**

Mc Nemar test; *F-18 FDG-PET/CT: F-18 fluorodeoxyglucose-positron emission tomography/computed tomography; US: Ultrasound

Table 3. ROC analysis and diagnostic scans of US, F-18 FDG-PET/CT, and F-18 FDG-PET/CT findings when US negative or suspicious

	Diagnostic scan					ROC curve		*p*
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy	Area	95% confidence ınterval	
F-18 FDG-PET/CT	75.00	77.27	72.97	79.07	76.25	0.770	0.662–0.879	0.001
US	72.22	81.82	76.47	78.26	77.50	0.761	0.652–0.871	0.001
F-18 FDG-PET/CT (US negative or susp.)	65.38	83.33	70.83	79.55	76.47	0.744	0.616–0.871	0.001

*F-18 FDG-PET/CT: F-18 fluorodeoxyglucose-positron emission tomography/computed tomography; US: Ultrasound; ROC: Receiver operator curve

FNAB is a crucial procedure for the assessment of axillary lymph nodes in BC patients. It is used for preoperative staging and effectively detects metastatic involvement in axillary lymph nodes. Its high sensitivity, accuracy, and minimally invasive nature make it a valuable tool for initial axillary staging and decision-making regarding further surgical interventions. The meta-analysis of 35 studies conducted by Houssami and Turner (11) showed the sensitivity and specificity of US alone at 61.4% (51.2–79.4%) and 82% (76.9–89%), respectively, and US with FNAB at 79.6% (74.1–84.2%) and 98.3% (97.2–99%), respectively. The PPV and NPV of US with FNAB was 100% and 67.4% (60–76.2), respectively.

The sentinel lymph node (SLN), often the initial node within the lymphatic basin to receive drainage from a specific anatomical territory, assumes immunological responsibility for the associated area. SLNs have a comparatively modest false negative rate of 5 to 10% and a heightened sensitivity rate ranging from 90 to 95% in identifying malignancy within the lymph node basin (12). SLNB, utilizing either dye contrast material or preferably radioisotopes, has gained widespread acceptance as the preferred invasive method for assessing lymph nodes.

Despite studies reporting high sensitivity and specificity rates in detecting axillary lymph node involvement using F-18 FDG-PET/CT, this technique is not accurate enough to replace the currently accepted methods for axillary staging. The limited spatial resolution of F-18 FDG-PET/CT may result in false-negative results, particularly for microscopic metastases that cannot be reliably detected (5, 6).

A study including 90 patients was conducted by Riegger et al. (13) and also compared F-18 FDG-PET/CT and US as non-invasive imaging techniques for detecting axillary lymph node metastases, using US as the reference standard. The sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG-PET/CT for detecting axillary lymph node metastases were 54%, 89%, 77%, 74%, and 75%, respectively. For US, it was 38%, 78%, 54%, 65%, and 62%, respectively. F-18 FDG-PET/CT was significantly more accurate than US for detecting axillary lymph node metastases (p = 0.019). The findings indicated that while F-18 FDG-PET/CT appeared more accurate than US, it demonstrated a sensitivity like that of US in detecting axillary lymph node metastases. Consequently, it was not recommended as a substitute for SLNB. However, F-18 FDG-PET/CT did prove effective in identifying unexpected loco-regional extra-axillary lymph node metastases that were not previously detected. Another study by Aukema et al. (14) also supported the utility of F-18 FDG-PET/CT as an additional imaging tool for assessing extra-axillary lymph node metastases, significantly impacting patient management. These findings highlight the potential advantage of F-18 FDG-PET/CT in evaluating regional lymph nodes, particularly in specific locations such as the internal mammary and supraclavicular lymph nodes. Another recent study by Aktaş et al. (15) also compared the sensitivity, specificity, PPV, NPV, and accuracy of F-18 FDG-PET/CT, US, and MRI in 336 patients. The results of US for detecting ALN metastases were 83%, 62%, 59.2%, 54.8%, and 79.1%, respectively. For MRI, these values were 86.1%, 75%, 68.5%, 51.6%, and 85.3%, respectively, and for F-18 FDG-PET/CT, they were 78%, 53%, 56.2%, 51.4%, and 72.5%, respectively. Kappa correlation levels between ALN positivity and US, MRI, and F-18 FDG-PET/CT results were 67.3%, 77.5%, and 60.5%, respectively.

Our study found similarities among all findings (sensitivity, specificity, PPV, NPV, and accuracy) of US and F-18 FDG-PET/CT. Our statistical analysis demonstrated that F-18 FDG-PET/CT did not contribute additionally when axillary lymph node status in US was

negative or suspicious (Table 3). US and F-18 FDG-PET/CT both increased the specificity (83.33%) compared to US (81.82%) alone but had no advantage in sensitivity (65.38%, 72.22%, respectively). When US and F-18 FDG-PET/CT evaluated the axillary lymph nodes both, we demonstrated that false negativity decreased from 11.3% to 9.8% compared to US alone. The accuracy of the modalities did not surpass one another. We observed that when lymph nodes are categorized as negative or suspicious by US, F-18 FDG-PET/CT scans had no added value on lymph node staging (Table 3).

Both US and F-18 FDG-PET/CT have utility in assessing the axillary region in individuals afflicted with BC. US, a widely employed imaging method, facilitates comprehensive elucidation of axillary lymph nodes. In contrast, F-18 FDG-PET/CT yields functional insights into tissue metabolic activity and has demonstrated its superiority over conventional staging techniques in detecting metastatic pathology. Nonetheless, F-18 FDG-PET/CT may exhibit limitations when detecting minuscule axillary lymph node metastases. The selection of the suitable imaging approach hinges on many considerations, encompassing the clinical context, resource availability, and unique patient attributes.

Fibroblast Activation Proliferation Inhibitor (FAPI) PET in BC has gained significant attention due to its potential in detecting primary and metastatic lesions. FAPI targets fibroblast activation protein (FAP), which is overexpressed in cancer-associated fibroblasts of several tumor entities, including BC (16). Studies have shown that FAPI PET/CT is superior to FDG PET/CT in detecting primary and metastatic lesions in various cancers, including BC, with higher tracer uptake (17). However, it is important to note that FAPI PET/CT may also have limitations, such as high physiological uptake in normal breast tissue, which can obscure primary tumors (18). In the context of FAPI PET, while it is gradually gaining acceptance, there is currently a lack of studies demonstrating its ability to reveal axillary metastasis.

F-18 fluoroestradiol (F-18 FES) PET/CT has emerged as a valuable tool in the staging and management of estrogen receptor (ER)-positive BC. Studies have shown that F-18 FES PET/CT is sensitive in monitoring regional estrogen binding in advanced and metastatic ER-positive BC, and its uptake quantitation correlates well with ER expression measured by immunohistochemistry (19). This demonstrates the potential of F-18 FES PET/CT in influencing staging and management decisions for ER-positive BCpatients. Furthermore, the comparison of diagnostic accuracy between F-18 FES and F-18 FDG-PET/CT for BC recurrence in patients with a history of ER-positive primary BC has been investigated. This comparison provided insights into the potential of F-18 FES PET/CT as an alternative or complementary imaging modality in specific clinical scenarios (20). While F-18 FDG-PET/CT remains an important imaging modality in BC staging, the emerging evidence suggests that F-18 FES PET/CT may offer specific advantages in certain clinical contexts. However, no published study has shown that it could play a decisive role in the axilla.

The retrospective design of this study is a limitation, as well as the limited number of patients; the F-18 FDG-PET/CT is not routinely recommended in the guidelines for early-stage cancer. On the other hand, the radiologist's expertise is a well-known factor affecting the accuracy of an US evaluation. If this study had been done in a group of patients evaluated by a non-breast specialist, an F-18 FDG-PET/CT scan might have been found superior to US. Subsequent investigation is warranted to ascertain the optimal utilization of these imaging modalities for axillary evaluation in BC patients.

When looking at the 5-year follow-up results published in SOUND trial, where axillary observation was noted in patients and disease-free survival was found to be non-inferior to those with SLN procedures (98%, 97.7% respectively, p: 0.024), it emphasizes once again the importance of accurate and comprehensive preoperative US assessment of the axilla (4).

In conclusion, this study has demonstrated that US performed by an experienced breast radiologist is sufficient for evaluating axillary lymph nodes accurately. F-18 FDG-PET/CT did not provide an additional advantage over US in assessing the axilla in early-stage disease.

Ethics Committee Approval: This study was approved by the Koc University Institutional Review Board (2023.252.IRB1.081, date: 10.03.2023).

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ç., M.B., E.D.; Concept: B.Ç., E.D.; Design: B.Ç., E.D.; Data Collection and/or Processing: B.Ç.; Analysis and/or Interpretation: B.Ç., E.D.; Literature Search: B.Ç., M.B., E.D.; Writing: B.Ç., M.B., E.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30. (PMID: 31912902) [Crossref]
2. Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 2017; 318: 918-926. (PMID: 28898379) [Crossref]
3. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014; 15: 1303-1310. (PMID: 25439688) [Crossref]
4. Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, et al. Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial. JAMA Oncol 2023; 9: 1557-1564. (PMID: 37733364) [Crossref]
5. Rosen EL, Eubank WB, Mankoff DA. FDG PET, PET/CT, and breast cancer imaging. Radiographics 2007; 27(Suppl 1): 215-229. (PMID: 18180228) [Crossref]
6. Zhang X, Wu F, Han P. The role of (18)F-FDG PET/CT in the diagnosis of breast cancer and lymph nodes metastases and micrometastases may be limited. Hell J Nucl Med 2014; 17: 177-183. (PMID: 25526754) https://pubmed.ncbi.nlm.nih.gov/25526754/ [Crossref]
7. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. 8th ed. Springer Cham; 2017. https://link.springer.com/book/9783319406176 [Crossref]

8. Segaert I, Mottaghy F, Ceyssens S, De Wever W, Stroobants S, Van Ongeval C, et al. Additional Value of PET-CT in Staging of Clinical Stage IIB and III Breast Cancer. Breast J 2010; 16: 617-624. (PMID: 21070439) [Crossref]
9. Hodgson NC, Gulenchyn KY. Is there a role for positron emission tomography in breast cancer staging? J Clin Oncol 2008; 26: 712-720. (PMID: 18258978) [Crossref]
10. Veronesi U, De Cicco C, Galimberti VE, Fernandez JR, Rotmensz N, Viale G, et al. A comparative study on the value of FDG-PET and sentinel node biopsy to identify occult axillary metastases. Ann Oncol 2007; 18: 473-478. (PMID: 17164229) [Crossref]
11. Houssami N, Turner RM. Staging the axilla in women with breast cancer: the utility of preoperative ultrasound-guided needle biopsy. Cancer Biol Med 2014; 11: 69-77. (PMID: 25009748) [Crossref]
12. Faries MB, Bedrosian I, Reynolds C, Nguyen HQ, Alavi A, Czerniecki BJ. Active macromolecule uptake by lymph node antigen-presenting cells: a novel mechanism in determining sentinel lymph node status. Ann Surg Oncol 2000; 7: 98-105. (PMID: 10761787) [Crossref]
13. Riegger C, Koeninger A, Hartung V, Otterbach F, Kimmig R, Forsting M, et al. Comparison of the diagnostic value of FDG-PET/CT and axillary ultrasound for the detection of lymph node metastases in breast cancer patients. Acta Radiol 2012; 53: 1092-1098. (PMID: 23002144) [Crossref]
14. Aukema TS, Straver ME, Peeters MJ, Russell NS, Gilhuijs KG, Vogel WV, et al. Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer. Eur J Cancer 2010; 46: 3205-3210. (PMID: 20719497) [Crossref]
15. Aktaş A, Gürleyik MG, Aydın Aksu S, Aker F, Güngör S. Diagnostic Value of Axillary Ultrasound, MRI, and 18F-FDG-PET/ CT in Determining Axillary Lymph Node Status in Breast Cancer Patients. Eur J Breast Health 2022; 18: 37-47. (PMID: 35059590) [Crossref]
16. Giesel FL, Kratochwil C, Lindner T, Marschalek MM, Loktev A, Lehnert W, et al. 68 Ga-FAPI PET/CT: Biodistribution and Preliminary Dosimetry Estimate of 2 DOTA-Containing FAP-Targeting Agents in Patients with Various Cancers. J Nucl Med 2019; 60: 386-392. (PMID: 30072500) [Crossref]
17. Wang Q, Tang W, Cai L, Chen Y. Non-18F-FDG-Avid Intrahepatic Metastasis of Breast Cancer Revealed by 68Ga-FAPI PET/CT. Clin Nucl Med 2022; 47: 228-230. (PMID: 34653058) [Crossref]
18. Zhang Y, Zhou Y, Tian R, Su M. Physiological uptake characteristics of breast on 68Ga-FAPI-04 PET [Internet]. In Review; 2023 Jul [cited 2023 Dec 5]. Available from: https://www.researchsquare.com/article/rs-3167458/v1 [Crossref]
19. Liu C, Gong C, Liu S, Zhang Y, Zhang Y, Xu X, et al. 18F-FES PET/CT Influences the Staging and Management of Patients with Newly Diagnosed Estrogen Receptor-Positive Breast Cancer: A Retrospective Comparative Study with 18F-FDG PET/CT. Oncologist 2019; 24: 1277-1285. (PMID: 31337657) [Crossref]
20. Chae SY, Son HJ, Lee DY, Shin E, Oh JS, Seo SY, et al. Comparison of diagnostic sensitivity of [18F]fluoroestradiol and [18F]fluorodeoxyglucose positron emission tomography/computed tomography for breast cancer recurrence in patients with a history of estrogen receptor-positive primary breast cancer. EJNMMI Res 2020; 10: 54. (PMID: 32448947) [Crossref]