The Role of Axillary SUV_{max} in ^{18}F-FDG PET/CT in Predicting the Number of Axillary Metastases of Breast Cancer

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ABSTRACT

Objective: To investigate the role of positron emission tomography/computed tomography (PET-CT) in determining the maximum number of axillary lymph node metastasis (ALNM) detectable in sentinel lymph node biopsy (SLNB).

Study Design: Observational study.

Place and Duration of the Study: Sivas Cumhuriyet University Faculty of Medicine, Turkiye, from January 2015 to August 2021.

Methodology: A total of 104 breast cancer patients who underwent surgery after a PET-CT scan were examined. A receiver operating characteristic (ROC) analysis was utilised to determine optimal cut-off values for the standardised uptake values of the primary tumour ($pSUV_{max)}$ and axillary lymph nodes ($nSUV_{max)}$ in the presence of ALNM and the presence of more than two ALNMs.

Results: The presence of more than two ALNMs was associated with $pSUV_{max,}$ $nSUV_{max,}$ LVI, and the number of LNs detected on PET-CT. In the ROC analysis, for the ability to predict more than two ALNMs in SLNB/axillary lymph node dissection (ALND), cut-offvalues were calculated as 4.65 for $pSUV_{max}$ (AUC=0.669, sensitivity=66.7%, specificity=62%, PPV=0.482, NPV=0.800, p=0.006) and 1.75 for $nSUV_{max}$ (AUC=0.838, sensitivity=81.8%, specificity=88.7%, PPV= 0.676, NPV=0.913, p<0.001).

Conclusion: Low sensitivity, NPV, and accuracy values that limit the use of PET-CT in preoperative axillary evaluation can be increased by targeting the criterion of more than two ALNMs. Thus, PET-CT can be used more effectively in axilla management.

Key Words: *Breast cancer, Positron emission tomography, SUV_{max} values, Axillary lymph node, ACOSOG Z0011.*

How to cite this article: Karabacak U, Turkan H, Coskun G, Mollaoglu MC, Hasbek Z, Karadayi K. The Role of Axillary SUV_{max} in ^{18}F-FDG PET/CT in Predicting the Number of Axillary Metastases of Breast Cancer. *J Coll Physicians Surg Pak* 2023; **33(04)**:374-379.

INTRODUCTION

Breast cancer is the most common cancer and the leading cause of death in women.[1] Treatment of breast cancer is multidisciplinary and initial staging is critical for an appropriate treatment plan. One of the many methods used for staging is positron emission tomography (PET-CT). Besides local staging, PET-CT has the advantage of scanning the whole body and detecting extra-axillary lymph nodes (LN) bone and distant organ metastases.[2] PET-CT is based on the principle of cancer cells having a more active glucose metabolism than other tissues. To assess the glucose metabolism of tissues, the uptake of the [18F] fluorodeoxyglucose ([18F] FDG) molecule is measured, the standardised uptake value (SUV) is calculated, and the primary tumour and its metastases are evaluated.[3-5]

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Received: September 29, 2022; Revised: March 02, 2023; Accepted: March 21, 2023
DOI: https://doi.org/10.29271/jcpsp.2023.04.374

Today the primary goal of breast cancer surgery is to conserve the breast and avoid axillary lymph node dissection (ALND) if possible. Sentinel lymph node biopsy (SLNB) has become a routine procedure in the historical development of surgery to limit the indication of axillary dissection and to reduce the associated morbidities.[6] Recent studies have shown that ALND can be avoided by considering the number of metastatic LNs detected and some accompanying criteria, even if there is metastasis in SLNB.[7,8] Thus, the number of metastatic lymph nodes gained importance in axilla management. The aim of this study was to investigate the role of the axilla SUV_{max} value in PET-CT and the number of possible metastatic lymph nodes.

METHODOLOGY

Patients who were operated for breast cancer in Cumhuriyet University Surgical Oncology Clinic, between January 2015 and August 2021 were analysed retrospectively. Demographic findings, operative notes, stages, pathology, and PET-CT results were searched from clinical records. Exclusion criteria were the absence of preoperative PET-CT or the inaccessibility of PET-CT images, having undergone diagnostic surgical excision before PET-CT, having a different cancer history, and

receiving neoadjuvant chemotherapy. One hundred and four consecutive patients who met these criteria were included in the study.

All surgeries were started with 5cc isosulfan blue injection for SLNB. It was aimed to sample at least three LNs during SLNB. ALND was not applied in the absence of metastasis. The criteria considered for ALND were detection of metastases in frozen section examination of sentinel lymph node (SLN), failure to identify SLN, and detection of metastases in unstained but suspicious-looking LNs. Thus, the pathological evaluation of the axilla was optimal. For each patient, primary tumour ($pSUV_{max}$) and axillary LN ($nSUV_{max}$) SUV_{max} values in preoperative PET-CT; the number of LNs detected on PET-CT (those without FDG uptake or pathological appearance are also included.); the types of surgery applied to the breast and axilla; pathological type; the number of LN metastases detected during SLNB or ALND; histologic grade; T stage; N stage; lymphovascular invasion (LVI); perineural invasion (PNI); Ki-67; estrogen receptor (ER); progesterone receptor (PR); and HER-2 status were examined.

PET/CT imaging was performed with a combined PET/CT scanner (Discovery 600 PET/CT GE Medical Systems, USA). Each patient fasted for at least six hours before imaging. After ensuring that blood glucose was <180 mg/dL, approximately 0.14 mCi/kg ^{18}F-FDG was administered intravenously one hour before image acquisition. Attenuation correction of PET images was performed with the CT data. The CT scan was performed first and right after the CT acquisition, a standard PET imaging protocol was taken from the cranium to the mid-thigh with an acquisition time of three min/bed in 3-D mode. All PET studies were acquired in 3-D mode. CT images were acquired with 70 mA, 120 kV, and an axial slice thickness of 2.5 mm. CT and PET images were matched and fused into transaxial, coronal, and sagittal images. The data were transferred *via* the Digital Imaging and Communications in Medicine protocol to a processing workstation (AW Volume Share5 GE Medical Systems S.C.S, France). Then, the visual and semi-quantitative analyses were performed, respectively. For PET images, an adaptive threshold setting of 42% of the maximum lesional metabolic activity was used, and the ROI was placed within the tumour while avoiding the peripheral area. The standardised uptake value (SUV) was calculated using the following formula: [Activity of ROI (mCi / ml) × Bodyweight (gram)] ÷ Injected dose (mCi).

The Kolmogorov–Smirnov test was used to compare the distribution of random sample. A chi-square test was used to compare categorical variables. The independent samples t-test was used to compare the normally distributed data, and the Mann-Whitney U-test was used to compare the data that were not normally distributed. ROC analysis was used to determine the cut-off values of $pSUV_{max}$ and $nSUV_{max}$ for any number of axillary lymph node metastasis (ALNM) and more than two ALNMs. Binary logistic regression analysis with univariate and multivariate models was used to examine the risk factors affecting more than two ALNMs. Backward Wald method was used to include independent risk factors in the multivariate model. Analysis results were presented as mean±standard deviation and median (minimum–maximum) for quantitative data and frequency (percent) for categorical data. Data were analysed with IBM SPSS V23. All p-values lower than 0.05 were considered statistically significant.

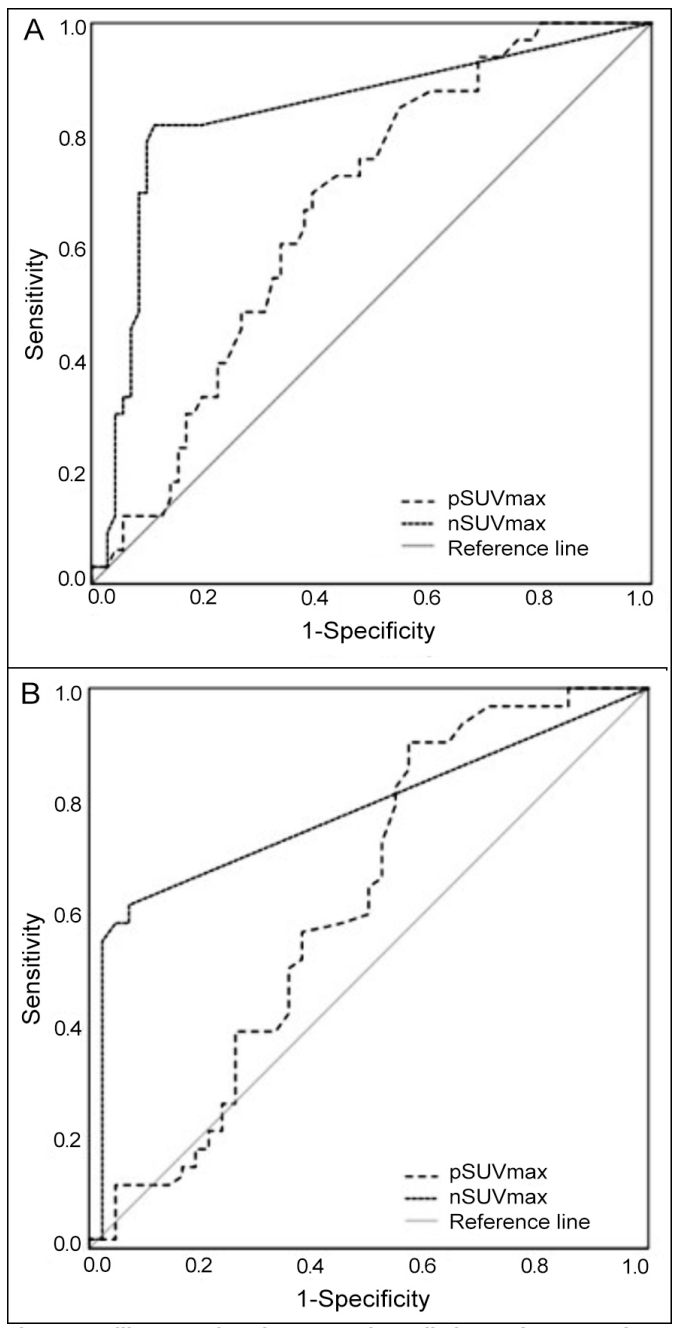

Figure 1: Axillary Lymph Node Metastasis Prediction Performance of PET-CT. (A) ROC curve of $pSUV_{max}$ and $nSUV_{max}$ to predict the presence of any number of ALNM. (B) ROC curve of $pSUV_{max}$ and $nSUV_{max}$ to predict the presence of more than 2 ALNMs. $pSUV_{max}$: Primary tumour maximum standardised uptake value, $nSUV_{max}$: Nodal maximum standardised uptake value, ALNM: Axillary lymph node metastasis, PET-CT: Positron emission tomography, ROC: Receiver operating characteristic.

RESULTS

The characteristics of the enrolled patients and the association with ALNM are summarised in Table I. ALNM was detected as a result of SLNB or ALND in 62 (59.6%) of 104 patients included in the study. Thirty-three patients (32%) had more than two ALNMs. The median value of $pSUV_{max}$ without ALNM was 3.8 (1-16), while the median of those with ALNM was 5 (1.9-18, p=0.042). The median value of $nSUV_{max}$ without ALNM was 1.0 (1-13.8), while the median of those with ALNM was 2.2 (1-14.7, p<0.001).

In the univariate model, it was shown that the risk of having more than two ALNMs during SLNB or ALND increased with the increase in $nSUV_{max}$ and $pSUV_{max}$ values, being grade 2, LVI and the number of LNs detected on PET-CT. In the multivariate model, LVI and detection of more than one LN on PET-CT were shown to be independent predictive values for detecting more than two ALNMs during SLNB or ALND (Table II).

To predict any number of LN metastases detected in SLNB or ALND, in the ROC analysis, the area under the curve at 4.05 cut-off value for $pSUV_{max}$ 0.618 and the area under the curve at 1.25 cut-off value for $nSUV_{max}$ 0.776 were calculated (Table III, Figure 1A). In the ROC analysis for the ability to predict more than two ALNMs in SLNB or ALND, the area under the curve at 4.65 cut-off value for $pSUV_{max}$ 0.69 and the area under the curve at 1.75 cut-off value for $nSUV_{max}$ 0.838 were calculated (Table III, Figure 1B).

DISCUSSION

Multidisciplinary protocols including surgery, radiation therapy, chemotherapy, targeted therapy and endocrine therapy are used in the treatment of breast cancer.[9] Which combination of these treatments will be used is determined by the stage of the disease and its molecular subtype. Staging is based on tumour size, axillary lymph node involvement, and the presence of distant metastases. Axillary lymph node involvement alters both the treatment plan and the prognosis.[10] In clinical practice, the axilla is routinely evaluated with USG, and if metastasis is suspected, a fine needle aspiration biopsy or trucut biopsy from the LN is performed.[11,12] Some studies reported that USG and PET-CT are nearly equal in axillary evaluation.[13,14] However, Davidson *et al.* utilised PET-CT to detect 18% of true positive lymph node metastases in patients with no suspicious findings in the axilla on USG.[15] Similarly, Riegger *et al.* demonstrated that PET-CT was significantly more accurate than USG in detecting axillary breast cancer metastasis.[16]

In one of the earliest studies on the role of PET-CT in axillary staging, Veronesi *et al*. evaluated 236 clinical node-negative patients to compare PET-CT and SLNB. PET-CT findings were positive in 43 patients, with 38 being classified as true positives with pathological confirmation. However, 65 patients had axillary metastasis in SLNB. Many metastases could not be detected by PET-CT.[17] In their study including 137 patients with early-stage breast cancer, Kim *et al.* reported the mean $nSUV_{max}$ value in patients with ALNM to be higher than those without ALNM and found a cut-off value of ≥3.85 (sensitivity 50%, specificity 100%, and PPV 100%) for the presence of metastasis and <1.05 (sensitivity 100%, specific 33%, NPV 100%) for the absence of metastasis.[18] Many other studies on the performance of PET-CT in detecting breast cancer-related axillary metastases have produced inconsistent results (sensitivity 24–82%, specificity 91–100%, PPV 63–100%, NPV 53–94% accuracy 78–94).[14,18-23] When this study and the other studies mentioned are considered together, the lack of a definite SUV_{max} cut-off value, as well as its low sensitivity and NPV, is the limiting factor for PET-CT axilla evaluation. The presence of involvement in PET-CT has a clear value, but the absence of involvement does not appear to imply that there is no metastasis in the axilla.

Today, it has been proven that axillary dissection is not required in every patient with SLNB metastasis. Many studies have shown that when patients are chosen based on the specific criteria, there is no significant difference in axillary recurrence and survival rates between those who received ALND and those who received direct or tangential radiotherapy to the axilla. In fact, less arm oedema was reported in the radiotherapy groups than in the ALND groups.[17,24] The ACOSOG Z0011 study is one of the most important studies that has changed the way medical professionals think about the axilla in recent years.[8] The study included 891 patients who had breast-conserving surgery for a T1 or T2 invasive breast tumour, did not have palpable LNs in the axilla, and were on an adjuvant systemic therapy plan that included tangential whole-breast irradiation. All patients had one or two metastatic LNs in their SLNB. Only SLNB was performed in 446 patients and ALND in 445 patients. They revealed that there was no significant difference in 10-year overall survival or local recurrence rate and that the SLNB-only group had less arm morbidity.

The number of metastatic lymph nodes, as well as the presence of metastases in SLNB, have become critical in planning surgical treatment. The authors were unable to find another study in the literature that attempted to predict the number of metastatic LNs that can be found in SLNB using PET-CT. In this study, the $nSUV_{max}$ cut-off value was calculated as 1.75 for the presence of more than two ALNM (sensitivity 81.8%, specificity 88.7%, PPV 67.6%, NPV 91.3%, accuracy 86.5%, p<0.001) (Table III, Figure 1B). In the univariate analysis, a relationship between $pSUV_{max,}$ $nSUV_{max,}$ LVI, and the number of LNs detected on PET-CT was discovered for the presence of more than two ALNMs, whereas in the multivariate analysis, a relationship between LVI and the number of LNs detected on PET-CT was discovered (Table II). In the study by Kim *et al.* detect the presence of any number of metastases, a very low $nSUV_{max}$ cut-off value was calculated for the absence of metastases, while a high value was calculated for the presence of metastases. The metastasis status of patients who fall between 1.05 and 3.85 $nSUV_{max}$ is uncertain.[18] In the present study, for the presence of ALNM, the $pSUV_{max}$ optimal cut-off value was 4.05, and the $nSUV_{max}$ optimal cut-off value was 1.25 (Table III, Figure 1A). The cut-off value of 1.75, which the authors found for more than two ALNMs conditions, is exactly in the uncertain area in terms of metastasis in Kim *et al*.'s study. The authors think that this result is remarkable.

Table I: Patient characteristics.

		ALNM		Total	p-value
		Absence (n=42) n (%)	Presence (n=62) n (%)		
Age*		58,7 ± 12,2	56,0 ± 11,5	57,1 ± 11,8	0,243
Histological grade	1	14 (33)	13 (21)	27 (26)	
	2	22 (53)	34 (55)	56 (54)	
	3	6 (14)	15 (24)	21 (20)	0,257
T-stage	1	15 (36)	10 (16)	25 (24)	
	2	26 (62)	44 (71)	70 (67)	
	3	1 (2)	6 (10)	7 (7)	
	4	0 (0)	2 (3)	2 (2)	0,054
N-stage	0	40 (95)	0 (0)	40 (39)	
	1	2 (5)	36 (58)	38 (36)	
	2	0 (0)	18 (29)	18 (17)	
	3	0 (0)	8 (13)	8 (8)	<0,001
LVI	Absence	35 (83)	24 (39)	59 (57)	
	Presence	7 (17)	38 (61)	45 (43)	<0,001
PNI	Absence	31 (82)	33 (56)	64 (66)	
	Presence	7 (18)	26 (44)	33 (34)	0,009
Ki-67	Low (<14%)	14 (33)	18 (29)	32 (30)	
	High (≥14%)	28 (67)	44 (71)	72 (70)	0,641
ER	Negative	7 (17)	14 (23)	21 (20)	
	Positive	35 (83)	48 (77)	83 (80)	0,461
PR	Negative	9 (21)	19 (31)	28 (27)	
	Positive	33 (79)	43 (69)	76 (73)	0,298
HER-2	Negative	28 (67)	47 (76)	75 (72)	
	Positive	14 (33)	15 (24)	29 (28)	0,308
Pathological type	Invasive breast carcinoma of no special type	30 (71)	55 (89)	85 (82)	
	Invasive lobular carcinoma	5 (12)	2 (3)	7 (6)	
	Cribriform carcinoma	3 (7)	2 (3)	5 (5)	
	Invasive papillary carcinoma	3 (7)	2 (3)	5 (5)	
	Neuroendocrine carcinoma	1 (3)	1 (2)	2 (2)	0,249
Number of LN detected on PET-CT	0	31 (74)	16 (26)	47 (45)	
	1	6 (14)	18 (29)	24 (23)	
	>1	5 (12)	28 (45)	33 (32)	<0,001
Operation method	BCS	31 (74)	22 (35)	53 (51)	
	Mastectomy	11 (26)	40 (65)	51 (49)	<0,001
Type of axillary surgery	SLNB	32 (76)	3 (5)	35 (34)	
	SLNB+ALND	4 (10)	24 (39)	28 (27)	
	ALND	6 (14)	35 (56)	41 (39)	<0,001
More than 2 ALNM	No	42 (100)	29 (47)	71 (68)	
	Yes	0 (0)	33 (53)	33 (32)	<0,001

**Mean Value ± Standard Deviation, ALNM: Axillary lymph node metastasis, LVI: Lymphovascular invasion, PNI: Perineural invasion, ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor 2, LN: Lymph node, PET-CT: Positron emission tomography, BCS: Breast conserving surgery, SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection.*

Table II: Uni- and multi-variate logistic regression analysis for more than two axillary lymph node metastases.

		Univariate OR (%95 CI)	p	Multivariate OR (%95 CI)	p
Age		1,005 (0,97 - 1,041)	0,791		
$pSUV_{max}$		1,118 (1,004 - 1,246)	0,042		
$nSUV_{max}$		1,535 (1,222 - 1,927)	<0,001		
Histologic grade	1	Reference			
	2	3,721 (1,132 - 12,224)	0,030		
	3	2,875 (0,711 - 11,619)	0,138		
LVI (Absence)		7,969 (3,084 - 20,591)	<0,001	5,783 (1,372 - 24,375)	0,017
PNI (Absence)		2,037 (0,84 - 4,939)	0,115		
Ki-67 (<14)		1,278 (0,513 - 3,185)	0,599		
ER (Negative)		0,542 (0,202 - 1,454)	0,224		
PR (Negative)		0,412 (0,167 - 1,015)	0,054		
HER-2 (Negative)		0,762 (0,296 - 1,961)	0,573		
Number of LN Detected on PET-CT	0	Reference			
	1	8,8 (2,102 - 36,847)	0,003	4,318 (0,677 - 27,541)	0,122
	>1	25,667 (6,537 - 100,784)	<0,001	17,544 (2,707 - 113,724)	0,003

Backward Wald method was used to include independent risk factors in the multivariate model. OR: Odds ratio, CI: Confidence interval, $pSUV_{max}$: Primary tumour maximum standardised uptake value, $nSUV_{max}$: Nodal maximum standardised uptake value, LVI: Lymphovascular invasion, PNI: Perineural invasion, ER: Estrogen receptor, PR: Progesterone receptor, HER-2: Human epidermal growth factor receptor 2, LN: Lymph node, PET-CT: Positron emission tomography.

Table III: ROC analysis results of $pSUV_{max}$ and $nSUV_{max}$ values for axillary lymph node metastasis presence.

		Cut-Off	AUC (%95CI)	p	Sensitivity (%95 CI)	Specificity (%95 CI)	PPV	NPV	Accuracy
ALNM[a]	$pSUV_{max}$	>4,05	0,618 (0,5 - 0,736)	0,042	0,581 (0,458 - 0,704)	0,548 (0,397 - 0,699)	0,672	0,470	0,568
	$nSUV_{max}$	>1,25	0,776 (0,686 - 0,867)	<0,001	0,613 (0,492 - 0,734)	0,929 (0,851 - 1,007)	0,700	0,619	0,741
>2 ALNM[b]	$pSUV_{max}$	>4,65	0,669 (0,565 - 0,773)	0,006	0,667 (0,506 - 0,828)	0,62 (0,507 - 0,733)	0,482	0,800	0,635
	$nSUV_{max}$	>1,75	0,838 (0,746 - 0,93)	<0,001	0,818 (0,686 - 0,95)	0,887 (0,813 - 0,961)	0,676	0,913	0,865

[a]Presence of any number of axillary lymph node metastases, [b] Presence of more than 2 axillary lymph node metastases, ROC: Receiver operating characteristic, AUC: Area under the curve*, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, $pSUV_{max}$: Primary tumour maximum standardised uptake value, $nSUV_{max}$: Nodal maximum standardised uptake value.*

The study method was designed to investigate the relationship between the nSUVmax value on PET-CT and the number of metastatic LNs in patients with breast cancer. The retrospective and single-centre design, the small number of patients, and the application of ALND to some patients and SLNB to others can be considered as the limitations of this study. On the other hand, since metastasis was not observed in the SLNB, ALND was not performed in 35 (34%) of the 104 patients included in the study. Sixty-nine (66%) patients underwent ALND because of at least one metastasis in the SLNB or because the SLN could not be identified. In total, more than two ALNMs were detected in 33 of the patients (32%). No axillary recurrence was observed in the follow-up of only SLNB patients and the ALND rate is relatively high. Therefore, the study method was optimal for pathological evaluation and the metastatic LNs count of the axilla.

The ACOSOG Z0011 study demonstrates the importance of the number of metastases, but it should be noted that only patients who underwent breast-conserving surgery and were clinical node-negative were included in this study. In patients with suspected lymph node metastasis in clinical evaluation, there is no evidence yet that the SUV_{max} value in PET-CT can be used instead of trucut biopsy or that it can be treated as the ACOSOG Z0011 study. The authors' think that the relationship between the SUV_{max} value and the number of ALNM can take place in daily practice, supported by future randomised prospective studies. Targeting more than two ALNMs instead of at least one LN metastasis is seen to increase sensitivity and NPV and accuracy values that limit the use of PET-CT.

CONCLUSION

To avoid ALND in breast cancer patients, the number of metastases is as important as the presence of metastases in the SLNB. Low sensitivity, NPV, and accuracy values that limit the use of PET-CT in preoperative axillary evaluation can be increased by targeting the criterion of more than two ALNMs. Thus, PET-CT can be used more effectively in axilla management.

ETHICAL APPROVAL:

The study was approved by Sivas Cumhuriyet University Ethical Committee (Date: 21.09.2022 No. 2022-09/11).

PATIENTS' CONSENT:

Consent for the participation in the study was not obtained from patients as data were collected from medical record without disclosing the identity of participants.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

UK: Study conception and design.
UK, HT, GC, MCM: Acquisition of data.
UK, KK, ZH: Analysis and interpretation of data.
UK: Drafting of manuscript.
UK, KK, ZH: Critical revision.
All authors read and approved the final version of the manuscript to be published.

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