ORIGINAL RESEARCH

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Relation Between Primary Tumor Suv$_{max}$ Value, Ki-67 Proliferation Index and Axillary Metastasis in Patients with Triple Negative Breast Cancer

Triple Negative Meme Kanserli Hastalarda Primer Tümör Suv$_{maks}$ Değeri, Ki-67 Proliferasyon İndeksi ve Aksiller Metastaz Arasındaki İlişki

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Abstract

Objective: The aim of our study was to determine the relationship between fluorodeoxyglucose (FDG) uptake, expressed as SUV$_{max}$ of the primary tumor in F-18 FDG positron emission tomography/computed tomography (PET/CT) for staging in triple-negative breast cancer (TNBC) patients, and axillary lymph node (LN) metastasis and Ki-67 expression.

Method: A total of 136 female TNBC patients who underwent F-18 FDG PET/CT imaging at our unit between July 2021 and March 2024 were retrospectively evaluated. Data on age, histopathology, hormone receptor status, Ki-67 levels, tumor location (right/left), the largest diameters of the tumor and axillary LN, axillary LN metastasis status, presence and site of distant metastasis, T stage, and clinical stage were recorded. SUV$_{max}$ values of the primary breast lesions and metastatic axillary LNs were documented.

Results: The mean age of the patients was 51.42±13.14 years (range: 23-86). Axillary LN metastasis was present in 95 patients (69.85%), and distant metastasis was detected in 24 patients (17.65%). No significant differences were observed between patients with and without axillary LN metastasis in terms of age, Ki-67, tumor size, tumor SUV$_{max}$, or T stage. Tumor and metastatic axillary LN sizes were positively correlated with SUV$_{max}$ values. However, no correlation was found between Ki-67 and tumor size, tumor SUV$_{max}$, axillary LN size, or axillary LN SUV$_{max}$ values.

Conclusion: In TNBC, there is no relationship between the SUV$_{max}$ value of the primary tumor in staging F-18 FDG PET/CT and axillary LN metastasis or the Ki-67 proliferation index. As expected in aggressive

Öz

Amaç: Çalışmamızın amacı, triple negatif meme kanseri (TNMK) hastalarında evreleme F-18 florodeoksiglikoz (FDG) pozitron emisyon tomografisi/bilgisayarlı tomografide (PET/BT) primer tümörün SUV$_{maks}$ olarak tanımlanan FDG tutulumu ile aksiller lenf nodu (LN) metastazı ve Ki-67 ekspresyonu arasındaki ilişkiyi belirlemektir.

Yöntem: Temmuz 2021-Mart 2024 tarihlerinde birimimizde F-18 FDG PET/BT görüntülemesi yapılmış olan TNMK tanılı 136 kadın hasta retrospektif olarak değerlendirildi. Hastaların yaşları, histopatolojileri, hormon reseptör durumları, Ki-67 seviyeleri, tümör lokasyonları (sağ/sol), tümör ve aksiller LN'lerinin en büyük çapları, aksiller LN metastaz durumları, uzak metastaz varlığı ve yeri, T evreleri, klinik evreleri, primer tümör ve metastatik aksiller LN'lerin SUV$_{maks}$ değerleri kayıt edildi.

Bulgular: Hastaların ortalama yaşı 51,42±13,14 yıl (aralık: 23-86) idi. Doksan beş (%69,85) hastada aksiller LN metastazı, 24 hastada (%17,65) uzak metastaz mevcut idi. Aksiller LN metastazı olan ve olmayan hastalar arasında yaş, Ki-67, tümör boyutu, tümör SUV$_{maks}$ veya T evreleri açısından anlamlı bir fark izlenmedi. Tümör ve aksiller LN boyutları SUV$_{maks}$değerleri ile pozitif korelasyon gösterdi. Ki-67 ile tümör boyutu, tümör SUV$_{maks}$ değeri, aksiller LN boyutu veya aksiller LN SUV$_{maks}$ değerleri arasında bir korelasyon bulunamadı.

Sonuç: TNMK'de evreleme F-18 FDG PET/BT'den edilen primer tümör SUV$_{maks}$ değeri ile aksiller LN metastazı veya Ki-67 proliferasyon indeksi arasında bir ilişki yoktur. Agresif malignitelerde beklenildiği gibi, primer

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Abstract

malignancies, primary tumor size was correlated with tumor SUV_{max} and metastatic axillary LN size, while metastatic axillary LN size was correlated with axillary LN SUV_{max}.

Keywords: 18F-fluorodeoxyglucose, axillary lymph node, Ki-67, positron emission tomography, triple-negative breast cancer

Öz

tümör boyutu, tümör SUV_{maks} ve metastatik aksiller LN boyutu ile, aksiller LN boyutu ise aksiller LN SUV_{maks} değeri ile korelasyon göstermiştir.

Anahtar kelimeler: 18F-fluorodeoksiglukoz, aksiller lenf nodu, Ki-67, pozitron emisyon tomografisi, triple negatif meme kanseri

Introduction

Breast cancer, characterized by its various molecular subtypes, is one of the most common malignancies among women (1,2). Triple-negative breast cancer (TNBC) is a subtype accounting for approximately 10-15% of all breast cancers, and is defined by the lack of expression of human epidermal growth factor receptor 2 (HER2), estrogen receptors (ER), and progesterone receptors (PR) (2). This feature makes it a clinically distinct and more challenging entity due to poor prognosis, high mortality risk, and aggressive course with metastases (3), which are largely associated with the inefficacy of targeted treatments in the absence of receptors (1,4).

In breast cancer patients, primary tumor size, axillary lymph node (LN) involvement, and distant metastases play crucial roles in determining treatment strategies and prognosis (5). Ki-67, an indicator of tumor proliferation, is widely used as a pathological marker in numerous malignancies, including certain breast cancer subtypes (6). Ki-67 is utilized in other breast cancer subtypes; however, its prognostic significance in TNBC remains unclear (7).

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography [F-18 fluorodeoxyglucose, positron emission tomography/computed tomography (FDG PET/CT)] is frequently employed in the imaging of breast cancer. Its uses include initial staging of large and locally advanced breast cancers, assessing response to neoadjuvant systemic therapy, detecting distant metastases, identifying locoregional or metastatic recurrences, restaging after treatment, planning radiotherapy, and determining prognosis (8-11). FDG uptake in primary lesions is primarily influenced by histological subtype, receptor status, Ki-67 proliferation index, and tumor size (8). The most commonly used method for quantifying F-18 FDG uptake is the maximum standardized uptake value (SUV_{max}), which reflects the highest FDG uptake in the region of interest (12). Primary TNBC lesions are known to exhibit higher SUV_{max} values compared to other subtypes, and available data demonstrate correlations between SUV_{max}, size, and Ki-67 in TNBC (8,9,13-17).

We aimed to investigate the relationship between FDG uptake, expressed as SUV_{max} of the primary tumor, and axillary LN metastasis, and Ki-67 expression in patients with TNBC.

Materials and Methods

Patient Selection

Patients with a diagnosis of breast cancer who underwent F-18 FDG PET/CT imaging in our nuclear medicine department between July 2021 and March 2024 were retrospectively evaluated. Patients with a histopathological diagnosis of TNBC were examined for inclusion. Those without a histopathological diagnosis, subjects who had undergone surgery or treatment for primary malignancy, and patients with other malignancies were excluded.

Collected data included histopathology, hormone receptor status, Ki-67 levels, tumor side (right/left), largest diameters of the tumor and axillary LN, axillary LN metastasis status, distant metastasis status and location, T stage, and clinical stage. Tumor staging was conducted based on the American Joint Committee on Cancer (AJCC) 8^{th} edition TNM classification system (18). Maximum standardized uptake values (SUV_{max}) derived from F-18 FDG PET/CT for the breast tumor (tumor SUV_{max}) and axillary LN (LN SUV_{max}) were recorded.

This study received approval from the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (decision no: E-96317027-514.10-248478655, date: 10.07.2024). All diagnostic and therapeutic procedures were conducted in accordance with national guidelines and the Declaration of Helsinki. All patients provided informed consent for the procedures.

18F-FDG PET/CT Procedure

An Ingenuity TF 64 scanner (Philips medical systems, USA) was used to perform 18F-FDG PET/CT scans, with whole-body CT settings of 113 mAS, 120 kV and 4-mm section thickness (low dosage). The European Association of Nuclear Medicine version 2 ruleset was the basis for

image acquisition and evaluation (19). All patients were instructed to fast for 6 hours before scanning, and blood glucose was confirmed to be <150 mg/dL for each patient at the time of injection. 18F-FDG was administered intravenously as a standard dose of 3-4 MBq/kg. Patients were taken to the scanner after an interval of around 50 minutes (spent resting in a relaxed position) following intravenous 18F-FDG (3-4 MBq/kg) administration. PET imaging covered the same transverse field of view and employed 3 minutes of acquisition time per bed examined. Attenuation correction was based on CT images, and both corrected and non-corrected images were analyzed through maximum intensity projection as well as cross-sectional views in transaxial, coronal, and sagittal planes. Routine evaluations included checks for image quality, alignment accuracy, and potential artifacts.

Image Interpretation

The images were reviewed by two nuclear medicine physicians with over 10 years of expertise. The SUV_{max} was defined as the maximum SUV from a single voxel in an automated volume of interest that was defined as an is contour of 40% of the maximum reported signal intensity, in the area of a suspected lesion.

Pathological Evaluation

All tissue samples were examined by immunohistochemistry (IHC), and all samples negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 were included. ER-, PR-, and HER2- were defined as ER less than 1%, PR less than 1%, and a score of 0-1+ in HER2 IHC or IHC 2+ and negative silver *in situ* hybridization, respectively. Sections were lightly counterstained with hematoxylin. Sections obtained from LN tissue were used as a positive control for proliferating cells. The evaluation of Ki-67 immunostaining was performed in an area with a high cellular presence. All epithelial cells exhibiting nuclear staining, regardless of intensity, were considered positive. Approximately 500 nuclei were counted on each slide. Proliferative activity was assessed as the ratio of Ki-67 stained nuclei in the sample. Fine-needle aspiration cytology (FNAC) was conducted using a needle and a plastic syringe, guided by ultrasound. Following the FNAC procedure, the aspirates were promptly fixed in 95% ethanol. All FNAC smears were then stained using the Papanicolaou method without additional immunostaining and were evaluated routinely by a pathologist for diagnostic assessment.

Statistical Analysis

Statistics were performed using SPSS version 25.0 (IBM, Armonk, NY, USA) with the classical p-value threshold, considered significant if $p<0.05$. Categorical data were summarized using n and column (dependent) percentages and were analyzed by employing the appropriate chi-square tests or the Fisher-Freeman-Halton test. Histograms and Q-Q plots were used to estimate the presence or absence of normal distribution in numerical data, with deviation from the identity line defined as absence of normality. Descriptive statistics for numerical data included mean ± standard deviation or median (25^{th} percentile-75^{th} percentile) depending on normality or non-normality of the distribution. Between groups analysis of continuous variables was performed using Student's t-test or Mann-Whitney U test, depending on the normality of the distribution. Correlation results were based on Spearman's rho.

Results

We included 136 patients with TNBC into the study; the mean age was 51.42±13.14 years (range 23-86). All patients were diagnosed with invasive ductal carcinoma. Among these subjects, 95 (69.85%) had axillary LN metastasis and 24 (17.65%) had distant metastasis. Other data, including detailed tumor characteristics, are summarized in Table 1.

We found no significant differences between patients with and without axillary LN metastasis in terms of age, lesion side, Ki-67, largest tumor diameter, tumor SUV_{max}, and T stage (Table 2).

The frequency of stage T2 was significantly lower in patients with distant metastasis than in other patients ($p=0.026$). We found no significant differences between patients with and without distant metastasis in terms of age, lesion side, Ki-67, tumor largest diameter, tumor SUV_{max}, axillary LN metastasis, axillary LN largest diameter and axillary LN SUV_{max} (Table 3).

The largest tumor diameter was positively correlated with tumor SUV_{max} ($r=0.397$, $p<0.001$) and the axillary LN largest diameter ($r=0.271$, $p=0.001$). The axillary LN's largest diameter was positively correlated with the axillary LN SUV_{max} ($r=0.783$, $p<0.001$). There were no significant correlations between Ki-67 and largest tumor diameter, tumor SUV_{max}, largest axillary LN diameter, axillary LN SUV_{max} (Table 4).

Table 1. Summary of age and tumor characteristics

Age (n=136)	51.42±13.14
Side (n=136)	
Right	53 (38.97%)
Left	83 (61.03%)
Ki-67 (%) (n=122)	70 (50-80)
Tumor largest diameter, cm (n=136)	3.0 (2.2-4.4)
Tumor SUV_{max} (n=136)	16.6 (9.35-23.0)
Axillary LN metastasis (n=136)	95 (69.85%)
Axillary LN largest diameter, cm (n=136)	1.50 (0.00-2.22)
Axillary LN SUV_{max} (n=136)	5.20 (0.00-11.10)
Distant metastasis (n=136)	24 (17.65%)
Distant metastasis location (1) (n=136)	
Bone	11 (8.09%)
Lung	9 (6.62%)
Liver	7 (5.15%)
Brain	1 (0.74%)
T stage (n=136)	
T1b	3 (2.21%)
T1c	27 (19.85%)
T2	84 (61.76%)
T3	22 (16.18%)

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile-75^{th} percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables (1). Patients may have multiple metastases.
LN: Lymph node, SUV_{max}: Maximum standardized uptake value

Discussion

Poor prognosis and treatment challenges are typical for TNBC; there are few assessment tools that can contribute to patient management (4). Our analysis of SUV_{max} values obtained from staging F-18 FDG PET/CT images aimed to identify potential relationships with metastases (axillary LN or distant) and Ki-67 proliferation index. Our results showed that the size of the main tumor was positively correlated with the size of the metastatic LNs and LN SUV_{max} values. However, neither the axillary LN metastasis status nor the Ki-67 proliferation index was associated with the SUV_{max} value of the primary tumor.

In the present study, SUV_{max} and the largest diameter values of the primary tumor were found to be similar in patients with and without axillary LN metastasis. These results add to the available literature concerning different breast cancer subtypes, which have mostly reported the lack of relationships between the SUV_{max} of the primary lesion and axillary LN metastasis (9,14,20). In contrast, a study by Jung et al. (21) including 428 patients with all breast cancer subtypes, found significantly higher SUV_{max} values for primary tumors in patients with axillary LN metastasis compared to those without (4.93±3.32 vs. 3.22±2.78). Similarly, in a study of 671 patients with invasive breast cancer, higher preoperative primary tumor SUV_{max} values were detected in patients with axillary LN metastasis. However, when the same patients were stratified by molecular subtypes, TNBC patients with and without axillary LN metastasis were found to

Table 2. Summary of age and tumor characteristics with regard to axillary LN metastasis

	Axillary LN metastasis		
	No (n=41)	**Yes (n=95)**	**p**
Age	50.88±13.31	51.65±13.13	0.754†
Side			
Right	14 (34.15%)	39 (41.05%)	0.571§
Left	27 (65.85%)	56 (58.95%)	
Ki-67 (%)	75 (50-80)	62.5 (50-80)	0.086‡
Tumor largest diameter, cm	2.75 (2.0-4.0)	3.2 (2.3-4.5)	0.104‡
Tumor SUV_{max}	16.4 (8.6-22.7)	16.6 (9.8-23.1)	0.744‡
T stage			
T1b	1 (2.44%)	2 (2.11%)	0.182¶
T1c	11 (26.83%)	16 (16.84%)	
T2	26 (63.41%)	58 (61.05%)	
T3	3 (7.32%)	19 (20.00%)	

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile-75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. †: Student's t-test, ‡: Mann-Whitney U test, §: Chi-square test, ¶: Fisher-Freeman-Halton test, LN: Lymph node

Table 3. Summary of age and tumor characteristics with regard to distant metastasis

	Distant metastasis		
	No (n=112)	**Yes (n=24)**	**p**
Age	50.73±12.79	54.63±14.51	0.189†
Side			
Right	43 (38.39%)	10 (41.67%)	0.946§
Left	69 (61.61%)	14 (58.33%)	
Ki-67 (%)	70 (50-80)	70 (45-80)	0.611‡
Tumor largest diameter, cm	3.00 (2.26-4.20)	3.38 (1.97-5.84)	0.489‡
Tumor SUV_{max}	16.67 (9.35-22.80)	15.88 (8.30-30.83)	0.654‡
Axillary LN metastasis	76 (67.86%)	19 (79.17%)	0.395§
Axillary LN largest diameter, cm	1.32 (0.00-2.20)	1.81 (1.05-2.62)	0.092‡
Axillary LN SUV_{max}	4.85 (0.00-11.50)	6.15 (2.95-9.45)	0.598‡
T stage			
T1b	3 (2.68%)	0 (0.00%)	**0.026¶**
T1c	19 (16.96%)	8 (33.33%)	
T2	75 (66.96%)	9 (37.50%)*	
T3	15 (13.39%)	7 (29.17%)	

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25^{th} percentile-75^{th} percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. †: Student's t-test, ‡: Mann-Whitney U test, §: Chi-square test, ¶ Fisher-Freeman-Halton test, * Significantly different category, LN: Lymph node, SUV_{max}: Maximum standardized uptake value

Table 4. Correlations between Ki-67, diameters and SUV_{max} levels

		Tumor largest diameter, cm	Tumor SUV_{max}	Axillary LN largest diameter, cm	Axillary LN SUV_{max}
Ki-67 (%)	r	0.078	0.108	-0.139	-0.070
	p	0.390	0.238	0.126	0.442
Tumor largest diameter, cm	r		0.397	0.271	0.141
	p		<0.001	0.001	0.101
Tumor SUV_{max}	r			0.081	0.159
	p			0.350	0.064
Axillary LN largest diameter, cm	r				0.783
	p				<0.001

r: Spearman correlation coefficient, LN: Lymph node, SUV_{max}: Maximum standardized uptake value

have similar SUV_{max} values, consistent with our findings (22).

The lack of correlation between the high metabolic activity of primary tumors and axillary LN metastasis, in TNBC, a highly aggressive malignancy, remains unclear. However, unlike other subtypes, TNBC is suggested to be more prone to hematogenous spread rather than lymphatic spread (22,23). The lack of correlations between tumor SUV_{max} and axillary LN diameter or SUV_{max} values in our study provides indirect support for the literature data. Nonetheless, our correlation analyses revealed a positive relationship between largest tumor diameter, axillary LNs, and LN SUV_{max} values. This finding aligns with numerous studies in the literature, which have demonstrated that tumor size and SUV_{max} values increase in parallel in multiple subtypes of breast cancer (9,14-16,24). In a study by Arslan et al. (16), a similar positive correlation was attributed to the rapid growth of more aggressive tumors. Considering the aggressive nature of TNBC, our results provide additional evidence concerning the direct impacts on SUV_{max} and tumor growth.

The Ki-67 proliferation index is a commonly used prognostic factor in luminal breast cancer subtypes, where patients are classified into luminal A and B subgroups based on Ki-67 levels (25). However, no specific classification based on Ki-67 expression exists

for TNBC, and its prognostic role in this subtype remains inconclusive (26). A meta-analysis of 39 studies involving 7,716 TNBC patients reported that those with Ki-67 levels ≥40% had significantly higher recurrence and mortality risks compared to those with Ki-67 levels of <40% (7). That being said, a definitive prognostic cut-off for Ki-67 in TNBC has not been established. Notably, our patient population had exceedingly high Ki-67 values (70%, range: 50-80%), and therefore, which might have prevented the detection of significant variations in the evaluation of patients based on axillary LN metastasis. Despite the limited literature data in this respect, there exist several studies which have explored these relationships in patients with TNBC. For instance, similar to our results, Groheux et al. (27) found no correlations between the SUV_{max} of the primary lesion and Ki-67 levels in their study of 55 TNBC patients. There are studies in the literature reporting mild-to-moderate relationships in TNBC (9,17). Particularly notable is the study by Koo et al. (9), which described significantly higher SUV_{max} values in patients with ">20%" Ki-67 values compared to those with lower values. Again, the lack of association between these factors in the present study (especially FDG up-take) might be explained by the overwhelmingly elevated Ki-67 results throughout the study group. As mentioned before, one of the primary issues with Ki-67 assessment is the lack of standardization and significant interobserver variability. Factors such as human error, variations in the selection of tumor regions for evaluation, and the specific antibody used for detection can impact Ki-67 assessments (9).

Expanding upon the scope of studies on this topic, we also analyzed and compared patients with distant metastasis. The only significant difference between patients with and without distant metastasis was found to be T stage, which is an anticipated result. All other parameters, including Ki-67, tumor/LN SUV_{max}, and other tumor properties, were similar. Our findings in this context, which were obtained from a substantial group of patients, add new data to available literature by showing that these parameters are unassociated with distant metastasis. To our knowledge, there are no studies that have explored these parameters in the context of distant metastasis.

It is important to note that SUV_{max} reflects only the highest F-18 FDG uptake in the region of interest and does not represent the metabolic activity of the entire tumor. Glucose metabolism parameters, such as metabolic tumor volume and total lesion glycolysis, may have greater utility than other measurements in identifying malignancy or tumor characteristics (28). The primary limitation of our study, is the measurement of only SUV_{max} values for primary lesions and axillary LNs in F-18 FDG PET/CT, without considering additional parameters. Furthermore, the single-center, retrospective design, and the lack of significant differences regarding the majority of data are other limitations of the present study. Nonetheless, this study has examined patients with TNBC from various aspects, providing either provide additional evidence or new data for this field.

Conclusion

In TNBC patients, who have a worse prognosis and clinical course compared to other breast cancer subtypes, no relationship was found between the SUV_{max} value of the primary tumor obtained from staging F-18 FDG PET/CT and axillary LN metastasis or the Ki-67 proliferation index. Our data expand evidence in this regard and provide new data for distant metastasis, which also appears to be unassociated with the examined parameters.

Ethics

Ethics Committee Approval: This study received approval from the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (decision no: E-96317027-514.10-248478655, date: 10.07.2024). All diagnostic and therapeutic procedures were conducted in accordance with national guidelines and the Declaration of Helsinki.

Informed Consent: All patients provided informed consent for the procedures.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.V.T., E.A., G.U., Concept: Ö.V.T., E.A., Design: Ö.V.T., Data Collection or Processing: Ö.V.T., E.A., G.U., Analysis or Interpretation: Ö.V.T., Literature Search: Ö.V.T., Writing: Ö.V.T., G.U.

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