Original Article

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Correlation between 18F-FDG Positron-Emission Tomography 18F-FDG Uptake Levels at Diagnosis and Histopathologic and Immunohistochemical Factors in Patients with Breast Cancer

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ABSTRACT

Objective: In this study, we aimed to determine the correlation between pretreatment-staging 18F-FDG total body positron-emission tomography/computed tomography (PET/CT) maximum standardized uptake value (SUV_{max}) levels and histopathologic and immunohistochemical predictive and prognostic factors in patients with breast cancer.

Materials and Methods: One hundred thirty-nine women with breast cancer who were treated between 2009 and 2015 at our hospital and who had pretreatment-staging PET/CT were included in the study. SUV_{max} levels and histopathologic and immunohistochemical results were compared.

Results: The median age was 48 years (range, 29-79 years). The mean tumor diameter was 33.4 mm (range, 7-120 mm). The histology was invasive ductal carcinoma in 80.6% of the patients. In the univariate analysis, SUV_{max} levels were significantly higher in patients with invasive ductal carcinoma; in patients with a maximum tumor diameter more than 2 cm; patients who were estrogen, progesterone, and combined hormone receptor-negative, triple-negative patients, and in tumors with higher grades ($p<0.05$). In HER2-positive patients, SUV_{max} levels were higher even if it was not statistically significant. There was no correlation between lymph node metastases and pathologic stage. In multivariate analysis, tumor diameter was an independent factor.

Conclusion: SUV_{max} levels are correlated with known histopathologic and immunohistochemical prognostic factors. PET/CT could be useful in preoperative evaluation of patients with breast cancer to predict biologic characteristics of tumors and prognosis.

Keywords: Breast cancer, positron-emission tomography, 18F-FDG, predictive, prognosis

Introduction

Breast cancer is the most common cancer in women in Turkey and worldwide (1). Although it can be cured when diagnosed early, it is the cause of most cancer deaths in women (2). Breast cancer is a heterogeneous disease, and it is crucial to determine its prognosis and choose an optimal treatment option (3). Traditionally, the most significant prognostic factors are patient's age, size of the tumor, histologic grade, and number of involved axillary lymph nodes (4). The patient's condition at the time of diagnosis plays a vital role in choosing the therapeutic approach. Determining the patient's prognosis preoperatively is gaining more and more importance while the number of patients that receive neoadjuvant chemotherapy and breast-conserving surgeries increase (5). The most important contributions of diagnostic imaging methods in breast cancer can be early diagnosis, more accurate and intervention-free staging, and effectiveness in monitoring treatment and determining prognosis (6).

Positron-emission tomography (PET) is a non-invasive imaging method that uses positron-emitting isotopes. In recent years, it has been used increasingly frequently in clinics, especially in oncology (7). The most commonly used radiopharmaceutical, FDG tagged with fluorine-18 (18F-FDG) is a glucose analog whose FDG involvement in tissues is in proportion to the use of glucose; it is taken up into cells like glucose but cannot be metabolized (8). The maximum standardized uptake value (SUV_{max}) is a semi-quantitative indicator of 18F-FDG's involvement by lesions and this value is related to the number of living tumor cells (9).

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18F-FDG positron-emission tomography/computed tomography (18F-FDG PET/CT) is recommended in the current treatment guidelines for conditions such as locally-advanced breast cancer and metastatic disease (10). PET/CT helps determine extra-axillary regional lymph nodes and distant metastases in patients with newly-diagnosed breast cancer and can change staging and treatment (11). In pathologically-diagnosed breast cancer, it was found that preoperative 18F-FDG PET/CT screening could give sufficient information on tumor biology, prognosis, disease-free survival, and the patient's treatment (12). Turkey's Social Security Institution covers reimbursement of PET/CT scan for breast cancer staging, restaging, and evaluating the treatment response; the examination is commonly required before surgery. In this study, we aimed to determine the correlation between maximum SUV values gathered from PET/CT scans performed for staging patients with breast cancer and histopathologic and immunohistochemical predictive and prognostic factors.

Materials and Methods

A total of 139 patients with breast cancer who underwent radiotherapy and preoperative PET/CT scan for clinical staging in our hospital between September 2009 and December 2015 were enrolled in the study. All patients were histopathologically-diagnosed as having breast cancer. Patients who underwent excisional biopsy, patients who had surgery elsewhere, patients who received neoadjuvant chemotherapy, patients who had distant metastasis, and those with no FDG involvement in tumor in their PET/CT scan were excluded from the study. Our study was carried out retrospectively, and permission was obtained from the local ethics committee and the hospital management to reach archived files. Written consent was given by all patients for PET/CT scans, surgery, and radiotherapy.

For the PET/CT scan, after at least 4-hour fasting, the patients with blood sugar value under 200 mg/dL were given intravenous 0.15 mCi/kg 18F-FDG compound and were advised to rest in a calm setting without speaking or chewing. After approximately 60 minutes, emission and transmission imaging was taken on a PET camera (Siemens Biograph TruePoint 2008A) from the skull base to the upper part of the femur for whole body images in eight bed positions, every position for three minutes. Consecutive 0.5-cm thick sections were prepared on axial, coronal, and sagittal planes of the regions within the scope of the image using the reconstruction method. Furthermore, maximum intensity projection (MIP) images were assessed. A 50 mL oral contrast agent was used for image capture. SUV_{max} was calculated as the rate of maximum activity intensity in lesion based on the dose of FDG injected per kilo. After the staging examinations were completed, the patients underwent mastectomy or breast-conserving surgery (BCS) and sentinel lymph node biopsy (SLNB) or axillary dissection. The histopathologic and immunohistochemical data were recorded from the patients' pathology reports. Histologic type, maximum tumor diameter, histologic grade, nuclear grade, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status, number of analyzed lymph nodes, status of lymph node metastasis, and number of metastatic lymph nodes were recorded for each patient.

Statistical analysis

The descriptive analyses and numeric data are presented as mean±standard deviation. The comparison of the SUV_{max} values and histopathologic and immunohistochemical factors was performed using the Mann-Whitney U test and Kruskal-Wallis test. Multiple regression analysis test was used for multivariate analyses. P 0.05 was considered statistically significant. Statistical analyses were completed using SPSS version 20.0 (IBM, Armonk, NY).

Results

A total of 139 patients were included in the study. The patients' clinical and pathologic characteristics are shown in Table 1. All of the patients were women. The median age was 48 years (range, 29 to 79 years). The mean values of SUV_{max} were 6.22±4.2 (range, 0.78-25.56) for the primary tumors and 4.26±2.8 (range, 1-13.6) for the lymph nodes. In the PET/CT reports, the mean tumor diameter was 24.6±11.8 mm (range, 10-100 mm). There was no FDG involvement in lymph nodes in 83 (59.7%) patients according to the PET/CT scans.

Twenty-eight patients (20.1%) underwent BCS and SLNB; 21 patients (15.1%) underwent BCS and AD; 71 patients (51.1%) mastectomy and AD; and 19 patients (13.7%) had mastectomy and SLNB. The histology was invasive ductal carcinoma for 112 patients (80.6%), 16 (11.5%) had invasive lobular carcinoma, and 11 patients (7.9%) had other histologic subtypes (medullary carcinoma in four patients (2.9%), mixed carcinoma in four patients (2.9%), papillary carcinoma in one patient (0.7%), tubular carcinoma in one patient (0.7%), and cribriform carcinoma in one patient (0.7%). The mean tumor diameter was 33.4 mm (range, 7-120 mm, SD 17.5). The mean number of mitoses in 18 and 35 patients whose number of mitoses and Ki-67 values were present in their pathology reports was 12.2 (range, 1-34) and 31% (range, 1%-80%), respectively. For T-stages, 28 patients (20.1%) had T1, 92 patients (66.2%) had T2, and 19 patients (13.7%) T3 disease. Tumor multifocality was discovered in 32 patients (23%) and multifocal tumors were found in the PET/CT scans of 12 patients (8.6%), which was evaluated using the highest SUV_{max} value. Eighty-five patients (62.2%) had pathologic lymph node metastasis. The mean number of dissected lymph nodes was 20±14 (range, 1-53, including sentinel lymph nodes). N-staging was as follows: 54 patients (38.8%) were N0, 53 patients (38.1%) were N1, 13 patients (9.4%) were N2, and 19 patients (13.7%) were N3. Micrometastasis was reported for five patients with N1 lymph node staging (N1mi: 5 patients). The mean number of metastatic lymph nodes was 7.2 (range, 1-45). Comparing FDG involvement in the lymph nodes and pathologic lymph node metastasis in the PET/CT scans, PET/CT was found false positive in 9 patients (6.5%), and false negative in 38 patients (27.3%). Histologic grades were grade 1 for 7 patients (5.0%), grade 2 for 54 patients (38.8%), and grade 3 for 78 patients (56.2%). On the other hand, nuclear grades were distributed as grade 1 for one patient (0.7%), grade 2 for 39 patients (28.1%), and grade 3 for 99 patients (71.2%). ER was positive in 106 patients (76.3%), and PR was positive in 97 patients (69.8%). When the estrogen and/or progesterone receptors were analyzed together, the hormone receptors in 109 patients (78.4%) were found positive. HER2 was positive in 47 patients (33.8%), and those whose results could not be obtained through immunohistochemical methods went through a fluorescence in situ hybridization (FISH). The results of 11 (7.9%) patients were triple-negative (ER, PR, and HER2 negative). The patients' distribution based on pathologic stage was as follows: 17 patients (12.2%) were stage IA, 2 patients (1.4%) were stage IB, 43 patients (30.9%) were stage IIA, 34 patients (24.5%) were stage IIB, 25 patients (18%) were stage IIIA, and 18 patients (12.9%) were stage IIIC.

The correlation between the PET/CT SUV_{max} values and the patients' clinical and pathologic factors is demonstrated in Table 2. For uni-

Table 1. Patient and tumor characteristics

Characteristics	Number	%	Characteristics	Number	%
Age	Median age 48±10.2 years (range, 29-79)		Histologic grade		
Aged <45 years	51	36.7	1	7	5.0
Aged ≥45 years	88	63.3	2	54	38.8
SUV_{max} values	6.22±4.2 (range, 0.78-25.56)		3	78	56.2
PET/CT lymph node SUV_{max} values	4.26±2.8 (range, 1-13.6)		Nuclear grade		
PET/CT tumor diameter	24.6±11.8 mm (range, 10 mm-100 mm)		1	1	0.7
PET/CT lymph node involvement			2	39	28.1
Positive	56	40.3	3	99	71.2
Negative	83	59.7	Estrogen receptor		
Operation type			Negative	33	23.7
BCS+SLNB	28	20.1	Positive	106	76.3
BCS+AD	21	15.1	Progesterone receptor		
Mastectomy+SLNB	19	13.7	Negative	42	30.2
Mastectomy+AD	71	51.1	Positive	97	69.8
Histopathologic diagnosis			Hormone receptor (ER and/or PR +)		
Ductal carcinoma	112	80.6	Negative	30	21.6
Lobular carcinoma and others	27	19.4	Positive	109	78.4
Tumor diameter	33.4 mm±17.5 (7 mm-120 mm)		HER2		
T-stage			Negative	92	66.2
1	28	20.1	Positive	47	33.8
2	92	66.2	Triple-negative		
3	19	13.7	Yes	128	92.1
N-stage			No	11	7.9
0	54	38.8	Pathologic stage		
1	53	38.1	IA	17	12.2
2	13	9.4	IB	2	1.4
3	19	13.7	IIA	43	30.9
			IIB	34	24.5
			IIIA	25	18.0
			IIIC	18	12.9

SUVmax: maximum standardized uptake value; PET/CT: Positron-Emission Tomography/Computed Tomography; BCS: breast-conserving surgery; SLNB: Sentinel Lymph Node Biopsy; AD: axillary dissection; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2

variate analyses, the patients' age, histologic subtype, maximum tumor diameter, existence of lymph node metastasis, histologic grade, nuclear grade, ER, PR, combined hormone receptor hormone receptor, HER2 condition, triple-negative results, and pathologic stage were compared.

When the SUV_{max} values were compared based on age, the SUV_{max} values in patients aged less than 45 years were found statistically significantly high (p=0.04). The comparison based on histopathology was performed in groups as ductal carcinoma, lobular carcinoma, and others, and the SUV_{max} values in ductal carcinoma were found statistically significantly high (p=0.04). The SUV_{max} values were also statistically significantly higher in patients with tumor diameters more than 2 cm (T2, T3 tumors), compared with patients whose tumor diameters were 2 cm or less (T1 tumors) (p=0.02). There was no statistically significant difference between the SUV_{max} values of the patients with and without lymph node metastasis (p=0.24). As histologic grade and nuclear grade increased, the tumor SUV_{max} values became statistically significantly higher (p=0.001 and p=0.004, respectively). The patients with negative ER, PR, and hormone receptors had statistically significantly higher SUV_{max} values (p>0.001). Although patients with positive HER2 had higher SUV_{max} values, there was no statistically significant difference (p=0.308). The triple-negative patients had statistically significantly higher SUV_{max} values than those with negative HER2 (p= 0.05). The only finding in the multivariable analysis was that tumor diameter was an independent prognostic factor.

Table 2. Correlation between clinical and pathologic prognostic factors and SUV_{max} values

Variable	Comparison	Number	SUV_{max} (Mean±SD)	p
Age (years)	<45 years	51	6.9±0.6	0.04
	≥45 years	88	5.8±0.4	
Histopathologic diagnosis	Ductal carcinoma	112	6.6±0.4	0.04
	Lobular carcinoma and others	27	4.7±0.8	
Tumor diameter	≤2 cm (T1)	28	4.5±0.8	0.02
	>2 cm (T2-T3)	111	6.7±0.4	
Lymph node involvement	Negative	54	6.6±0.6	0.24
	Positive	85	5.9±0.5	
Histologic grade	1	7	3.3±1.5	0.001
	2	54	5.4±0.6	
	3	78	7.0±0.5	
Nuclear grade	1	1	5.7±4.2	0.004
	2	39	5.2±0.7	
	3	99	6.6±0.4	
ER	Negative	33	8.7±0.7	<0.001
	Positive	106	5.4±0.4	
PR	Negative	42	8.0±0.6	<0.001
	Positive	97	5.4±0.4	
Hormone receptor	Negative	30	8.9±0.7	<0.001
	Positive	109	5.5±0.4	
HER2	Negative	92	5.9±0.4	0.308
	Positive	47	6.8±0.6	
Triple-negative	No	128	6.1±0.4	0.05
	Yes	11	7.2±1.3	
Pathologic stage	IA	17	5.1±1.0	0.352
	IB	2	3.7±2.9	
	IIA	43	6.4±0.6	
	IIB	34	6.9±0.7	
	IIIA	25	6.1±0.8	
	IIIC	18	6.2±0.9	

SUV_{max}: maximum standardized uptake value; HER2: human epidermal growth factor receptor 2; ER: estrogen receptor; PR: progesterone receptor

Discussion and Conclusion

In the univariate analyses in our study, we found that the SUV_{max} values in young patients (aged less than 45 years) who had an invasive tumor diameter larger than 2 cm, negative hormone receptors, and triple-negative tumors were significantly higher as histologic and nuclear grades increased.

The survival rates of breast cancer are worse in young patients (aged <40 years) compared with elderly patients, and the multivariate analyses show that young age is an independent indicator of poor prognosis (13). Breast cancer at a young age progresses more aggressively; in a study with 185 premenopausal women with breast cancer, the number of those with negative ER and PR aged <35 years, the number of those with lymphatic and vascular invasion and pathologic grade 3 tumors were considerably high (14). In a retrospective evaluation with 1398 women with early-stage breast cancer, age, for those aged under 35 years, was shown as a strong and independent prognostic factor that determines relapse, distant metastasis, and mortality (15). In previous studies, there was no relationship found between age and SUV_{max} values; however, the SUV_{max} values in the young patients were higher in our study (16-18).

Similar to previous studies, 18F-FDG involvement was higher in patients with invasive ductal carcinoma (17, 19, 20). This relationship may be related to the low density of tumor cells in lobular carcinomas,

low GLUT1 (glucose transporter 1) expression, low proliferative index, and diffuse infiltrative growth pattern (16, 20-22).

Tumor diameter and axillary lymph node metastasis are the most vital clinical prognostic factors in breast cancer (4). Although a number of studies reported a positive correlation between tumor size and FDG involvement, some studies found no relationship (17, 23). In our study, we evaluated tumors in two categories as tumors with diameter of 2 cm or less, and those larger than 2 cm. FDG involvement was found higher as FDG involvement increased. In studies regarding the use of PET/CT in staging lymph nodes, it was stated that it could not be as sensitive, especially with patients with clinically-negative lymph nodes, and could not replace histopathologic examination (24-26). Zhang et al. (27) demonstrated that axillary lymph node staging was limited to 46% sensitivity in their study with 164 patients with breast cancer. There are also studies in the literature that reported a significant and positive correlation between PET/CT SUV values and lymph node metastasis (17, 23). However, there are studies that could not demonstrate a relationship between the condition of lymph node and FDG involvement (28). There was no statistically significant difference when the SUV_{max} values of the patients with and without lymph node metastasis were compared in our study, although the SUV_{max} values increased in patients with lymph node metastasis with higher N-stage. The fact that no relationship was found could be related to the high level of false negativity in PET/CT scans, late referral of patients with low grades, and the inadequacy of PET/CT scans in showing micrometastases.

Pathologic grade is one of the important predictive factors that shows tumor differentiation in breast cancer and the relationship between SUV values and histological grade is explained through high glucose metabolism in actively increasing tumors (5). The relationship between grade and PET/CT SUV values in patients with breast cancer has been reported (19). High-grade tumors were shown to have higher SUV values compared with low-grade tumors (29). In a study by Ueda et al. with 152 patients with breast cancer, the authors demonstrated that invasive tumor size, nuclear grade, and negative estrogen receptor were correlated with high SUV values in their multivariate analyses (17). In our study, we observed that the SUV values were statistically significantly higher as both histologic and nuclear grade increased. High SUV values could be an indication for high-grade and biologically-aggressive tumors.

Breast cancer is a heterogeneous disease that can be divided into histopathologic and molecular subtypes (30). According to gene-expression profiles, the first breast cancer subtypes were defined by Perou et al. (31). ER, PR, and HER2 gene expression features are significant determinants used routinely in newly-diagnosed breast tumors. Subtypes identified based on hormone receptors, HER2 status, and Ki-67 proliferative index give information on tumor biology and clinical behavior, and treatments including subtypes are recommended in guidelines (32, 33). Estrogen and progesterone receptors hold a crucial place in determining prognosis for patients with breast cancer and establishing whether they would benefit from hormonal therapy. HER2 status is an important predictive factor that determines whether the patients can start goal-directed therapy (trastuzumab) (34). Luminal A tumors (positive ER and PR, negative HER2, Ki-67 <1%) is the subtype with the best prognosis, triple-negative tumors show more biologically aggressive behavior (30, 35). In our study, negative ER and PR, positive HER2 and triple-negative patients had higher SUV_{max} values. High values of SUV have also been reported in patients with negative hormone receptors by previous researchers (17, 36). Basu et al. (37) stated that PET/CT sensitivity was 100% for patients who were triple-negative and these patients had higher FDG involvement compared with patients with positive hormone receptors, and the authors emphasized that PET/CT scanning of these tumors was important for determining tumor activity and treatment response.

Ki-67 is an indicator of the proliferation of cancer cells; however, its measurement and limit values change in different centers. In a study by Ito et al. (38) with 138 patients with invasive ductal breast cancer, the authors compared patients with Ki-67 values >14% and ≤14% and reported statistically significantly higher FDG involvement in patients with high Ki-67 values. In their comparison by number of mitosis, Ueda et al. (17) found the mean SUV values statistically significantly increased as the number of mitosis increased. In our study, no statistical comparison was performed because there was only a small number of patients whose number of mitosis and Ki67 index were reported. One of the limitations in our study is that the effects of SUV_{max} value on treatment results, local control, and survival were not investigated.

Our study demonstrates that SUV_{max} values are related to the recognized histopathologic and immunohistochemical prognostic factors in breast cancer. Predictability of predictive and prognostic factors before treatment is of importance in terms of deciding the therapeutic approach. In preoperative assessment of patients with breast cancer, PET/CT scanning is inadequate in examining axillary lymph nodes; however, it may prove beneficial in displaying the biologic characteristics and behavior of a tumor.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethic committee.

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

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