

Which of the fluorine-18 fluorodeoxyglucose positron emission tomography/computerized tomography parameters are better associated with prognostic factors in breast cancer?

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Abstract

The aim of the present study is to evaluate the relationship between the immunohistochemical and histopathological prognostic factors and the metabolic fluorine-18 fluorodeoxyglucose positron emission tomography/computerized tomography (PET/CT) parameters in breast cancer.

A total of 94 female patients diagnosed with primary breast cancer (median age: 54.5 years, 94 lesions with size >15 mm) who underwent PET/CT imaging before any treatment were enrolled to this retrospective study. Maximum and average standardized uptake values (SUVmax and SUVavg), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and tumor/liver uptake ratio (TLR) of the primary tumors were calculated and compared between various histopathological and immunohistochemical prognostic factor groups.

All metabolic parameters were associated with clinical T stage, metabolic M stage, and nuclear grade. The MTV, TLG, and TLR were significantly higher in patients with suspected lymph node metastasis. There were significant differences according to estrogen receptor and human epidermal growth factor-2 status in the metabolic values other than MTV. In case of progesterone receptor, there were significant differences in the metabolic characteristics except for the MTV and TLG values. The Ki-67 labeling index was moderately correlated with SUVmax, SUVavg, and TLR. All metabolic characteristics except MTV were significantly higher in triple negative breast cancer compared with the other molecular subtypes.

The results of the present study suggest that the TLG and TLR values have stronger associations with several prognostic factors in breast cancer (BC) compared with other metabolic parameters.

Abbreviations: BC = breast cancer, CT = computerized tomography, ER = estrogen receptor, F-18 FDG PET/CT = fluorine-18 fluorodeoxyglucose positron emission tomography/computerized tomography, HER2 = human epidermal growth factor-2, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, LumA = Luminal A, LumB = Luminal B, MTV = metabolic tumor volume, PET/CT = positron emission tomography/computerized tomography, PR = progesterone receptor, ROI = region of interest, SUV = standardized uptake value, SUVavg = average standardized uptake value, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis, TLR = Tumor/liver uptake ratio, TN = triple negative, VOI = volume of interest.

Keywords: breast cancer, fluorodeoxyglucose positron emission tomography, prognosis

1. Introduction

Breast cancer (BC) is the most common type of malignancy, and the second leading cause of cancer related deaths among women.^[1]

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Preoperative BC staging is crucial to choose the optimal treatment. In order to determine the prognosis, treatment response, and estimated survival of the disease accurately, various factors such as clinical TNM staging; tumor size; histological type and grade; estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER2) status; proliferation rate (mitosis number, Ki-67 index); lymphatic invasion status; axillary nodal involvement; and metastasis should be evaluated.^[2] The tumor location, age, menopausal status, tumor grade, and p53 and BRCA gene mutations are the other important factors that facilitate therapy management and prognosis estimation in BC.^[3]

The fluorine-18 fluorodeoxyglucose positron emission tomography/computerized tomography (F-18 FDG PET/CT) is performed in patients with BC for staging, detection of recurrence, and estimation of prognosis.^[4] The metabolic evaluation of BC with F-18 FDG PET/CT has been reported in many studies in recent years.^[5–7]

The standard uptake value (SUV), a metabolic parameter defined as the level of F-18 FDG uptake in cancer cells with in vivo glucose hypermetabolism, is crucial for predicting the prognosis. However, the primary tumor SUVmax, which is the

most commonly used parameter in the metabolic evaluation of breast cancer, may not accurately reflect the total glucose metabolism in a tumor. This is especially true for quantitative measurements such as the total lesion glycolysis (TLG) and metabolic tumor volume (MTV), which help to better understand the distribution of the F-18 FDG uptake in heterogeneous tumor masses such as the BC.^[5,6] Several authors have reported that various factors such as body weight, plasma glucose level, length of the uptake period, and partial volume effects influence the SUV parameters.^[8–10] So, several methods have been used to correct the SUV parameters. Since the liver SUV value was reported to be relatively constant regardless of the correction method used,^[8] it was thought that at least some of the problems could be eliminated by using the ratio of the tumor SUV to the SUV of the reference region in the liver.^[11,12] According to some authors, TLR could be used as an alternative in the estimation of prognosis and to treatment response.^[12,13]

The molecular subtypes, which are among the factors that cause heterogeneity in BC, have unique characteristics and may affect the treatment choice and response to a given therapy protocol. According to the St. Gallen Consensus recommendations, the breast cancer patients are divided into 5 molecular subtypes: luminal A (LumA), luminal B/human epidermal growth factor receptor 2 (HER2) negative (LumB–), luminal B/HER2 positive (LumB+), HER2 positive (HER2+), and triple negative (TN) BCs.^[14]

In the present study, metabolic parameters of the primary tumor (SUVmax, SUVavg, MTV, TLG, and TLR) obtained by F-18 FDG PET/CT imaging were compared among cases diagnosed with LumA, LumB–, LumB+, HER2+, and TN subtype BCs. Furthermore, the metabolic parameters of the primary tumor were compared according to histopathological and immunohistochemical prognostic factors.

2. Patients and methods

2.1. Ethics approval and consent to participate

This study was approved by the Scientific Research Ethics Committee of Eskişehir Osmangazi University Medical Faculty (protocol number, 80558721/46) and informed consent was waived because of the retrospective design.

2.2. Patients

Consecutive BC patients who underwent whole body F-18 FDG PET/CT examinations in the Department of Nuclear Medicine, Eskişehir Osmangazi University Medical Faculty before any operation and/or other therapeutic interventions between August 2015 and December 2017 were enrolled. The exclusion criteria were as follows: history of chemotherapy for BC before the PET/CT examination, any missing data, and male sex.

When BC was multifocal or multicentric, the largest tumor was selected. Before the PET/CT imaging, all patients underwent clinical tumor staging, physical examination, mammography, ultrasonography, and core needle biopsy. The largest diameter of each lesion included in the present study required to be >15 mm (measured on the CT images of the PET/CT examination) to minimize the partial volume effect in F-18 FDG uptake. The following were the exclusion criteria: absence of histopathological or immunohistochemical study parameters.

The clinical tumor stage was determined using conventional methods such as physical examination, mammography, ultrasonography, and magnetic resonance imaging (MRI), whichever was available. The patients were divided into 4 groups according to the clinical T stage of the primary tumor. To determine the metabolic N stage, lymph nodes were evaluated visually and those with an F-18 FDG uptake higher than physiological were defined as positive. With respect to other organs, a high F-18 FDG uptake which could not be explained by physiological uptake was considered positive for a distant metastasis. The patients were also divided into 3 groups according to the nuclear grade of the primary tumor.

2.3. F-FDG PET/CT acquisition and image interpretation

All of the patients were asked to fast for at least 4 hours and the blood glucose level needed to be <200 mg/dL before the examinations for which a Siemens Biograph LSO 6PET/CT scanner (IL) was used. The median duration of the scans was 61 minutes (range, 56–93 minutes) after the intravenous administration of 229.4 to 436.6 MBq (6.2–11.8 mCi) F-18 FDG according to the body weight (3.7 MBq/kg). Acquisition of computed tomography (CT) was performed on a 4-slice spiral CT using a slice thickness of 5 mm (120–150 kV, 80 mA). After the transmission scan, three-dimensional PET acquisition was obtained by 6 to 8 sessions of 3 minutes bed position. The CT images were used for attenuation correction of PET/CT data. The PET images were reconstructed using an iterative method (ordered subset expectation maximization: 2 iterations, 8 subsets) and a 5 mm filter. After PET acquisition, the CT images, reconstructed PET images, and fused image pairs of matching PET and CT were reviewed in the axial, coronal, and sagittal planes and in projections of maximum intensity in the 3D cine mode.

The images were visually assessed by 2 experienced nuclear medicine specialists. Areas of abnormally intense tracer uptake were recorded. When a multifocal disease was present, a region of interest (ROI) analysis was carried out for the largest tumor visible on PET for a semiquantitative analysis of metabolic activity. The SUV value was calculated using the following formula: activity concentration (Mbc/mL)/(injected dose [MBq]/body weight [g]). The pixel with the highest FDG uptake within the ROI was used as the SUVmax value and the average FDG uptake of the pixels was defined as the SUVavg value. For the assessment of volume-based PET/CT parameters, a 3D volume of interest (VOI) was drawn over the primary tumor lesion using a commercial software (Syngo. Via, Siemens Medical Solutions, Chicago, IL) and the MTV was defined as the region confined by 42% isocontour of the maximum PET voxel of the lesion. The TLG was calculated by multiplying the MTV by the SUVavg within the VOIs of the primary tumor (TLG = SUVavg × MTV [cm³]). The tumor to liver uptake ratio (TLR) was defined as the ratio of the primary tumor SUVmax to liver SUVavg. The liver SUVavg was calculated by drawing a circular 3 cm diameter ROI over the relatively homogenous intense slice of normal liver parenchyma on the PET images.

2.4. Histopathological analysis

The diagnosis of primary BC and histopathological analysis were performed using tissue samples obtained by a tru-cut or fine-needle aspiration biopsy before the PET/CT examinations.

Nuclear grade and histological type were determined using formalin-fixed and paraffin-embedded 5 μ m tumor tissue sections stained with haematoxylin and eosin. The ER and PR were considered positive if tumors showed moderate or high positivity (2 or 3+) for at least 10% of the tumor cells assessed using ER and PR antibodies. The HER2 status was considered positive when the membrane immunostaining was 3+ or when it was 2+ and HER2 gene amplification was present according to fluorescence in-situ hybridization analysis. For the Ki-67 expression, the percentage of positively nuclear-stained cells was determined and counted according to the recommendations of the international Ki-67 in BC Working Group. The Scarff Bloom Richardson classification system was utilized for histopathological staging.^[15]

The subtypes of BC were defined according to the recommendations of the 12th International Breast Conference, and immunohistochemical surrogates were as follows^[14]:

- (1) LumA: ER (+) and/or PR (+), HER2 (-), and a Ki67 of <14%.
- (2) LumB-: ER (+) and/or PR (+), HER2 (-), and a Ki67 of \geq 14%.
- (3) LumB+: ER (+) and/or PR (+), HER2 (+), and any Ki67 index.
- (4) HER2+: ER (-), PR (-), HER2 (+).
- (5) TN: ER (-), PR (-), HER2 (-).

2.5. Statistical analysis

The IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY) was used for statistical analysis. The normality of distribution of the continuous data was analyzed using Shapiro Wilk test. Continuous data were expressed as median and categorical data as frequency and percentage. The Mann-Whitney *U* and Kruskal Wallis tests were used to compare continuous data with skewed distribution between 2 and >2 groups, respectively. Spearman correlation analysis was used to assess the relationship between continuous data. A $P < .05$ was used for the cut-off for statistical significance.

3. Results

A total of 94 female BC patients with a median age of 54.5 years (range, 28–78 years) were enrolled. The characteristics of the study population are summarized in Table 1. None of the included patients had any missing data. The associations between the clinicopathological factors and metabolic parameters are presented in Table 2.

The median value of all metabolic parameters in invasive ductal carcinoma (IDC, 70 patients, 74.5%) tended to be higher than that in the other subtypes (24 patients, 25.5%; 5 neuroendocrine carcinomas, 5 mucinous carcinomas, 4 invasive lobular carcinomas [ILCs], 3 solid papillary carcinomas, 2 medullary and tubular carcinomas and 1 apocrine carcinoma, 1 glycogen-rich type carcinoma, 1 cribriform carcinoma) but the difference between the groups was not significant (Table 2).

According to the clinical T groups, there were 25 (26.6%) patients in the T1c group, 52 (55.3%) patients in the T2 group, 11 patients (11.7%) in the T3 group, and 6 patients (6.4%) in the T4 group. The median value of the metabolic parameters gradually increased along with the clinical T stage ($P < .001$ for each metabolic parameter). The greatest differences were between the T1c and T3 groups.

Table 1

The characteristics of the patients.

Parameters	n
Number of patients	94
Age	
Median (range)	54.5 (28–55)
Histology	
IDC	70 (74.5%)
ILC	4 (4.3%)
Other	20 (21.2%)
Grade	
I	23 (24.5%)
II	35 (37.2%)
III	36 (38.3%)
Clinical T stage	
T1c	25 (26.6%)
T2	52 (55.3%)
T3	11 (11.7%)
T4	6 (6.4%)
Metabolic axillary lymph node status	
Positive	25 (26.6%)
Negative	69 (73.4%)
Metabolic M stage	
M0	86 (91.5%)
M1	8 (8.5%)
Molecular subtypes	
Luminal A	19 (20.2%)
Luminal B HER2(-)	31 (33%)
Luminal B HER2(+)	29 (30.8%)
HER2(+)	9 (9.6%)
Triple negative	6 (6.4%)

HER2=human epidermal growth factor receptor 2, IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma.

All of metabolic parameters were significantly higher in the 8 patients with suspected distant metastasis according to the PET/CT findings (3 patients had liver, 3 patients had bone, 1 patient had lung, and 1 patient had both bone and lung metastasis) compared with those without metastasis. The patients with suspected axillary nodal involvement had significantly higher median MTV, TLG, and TLR values compared with those without nodal involvement. They also tended to have higher median SUVmax and SUVavg values but these differences were not statistically significant. The median value of each metabolic parameter was significantly higher in patients with higher nuclear grade.

The ER-negative patients had significantly higher median SUVmax, SUVavg, TLG, and TLR compared with ER-positive patients (P values=.001, .007, .024, and .002, respectively). The median MTV value tended to be higher in ER-negative patients compared with ER-positive patients but the difference was not significant. The HER2-negative patients had significantly higher median SUVmax, SUVavg, TLG, and TLR values than the HER2-positive patients (P values=.001, .002, .036, and .001, respectively). The median MTV value tended to be higher in HER2-negative patients compared with HER2-positive patients but the difference was not significant. The PR-negative patients had significantly higher median SUVmax, SUVavg, and TLR values than the PR-positive patients (P values=.012, .046, and .028, respectively). The median MTV and TLG values tended to be higher in PR-negative patients compared with PR-positive patients but the differences were not significant.

Table 2**Associations between clinicopathological factors and metabolic parameters.**

Prognostic factors (N)	SUVmax median	SUVavg median	MTV median	TLG median	TLR median
Histology					
IDC (70)	6.79	3.58	6.62	25.53	2.69
ILC (4)	4.47	3.15	5.24	18.11	1.71
Other (20)	5.51	2.68	6.56	21.00	2.37
<i>P</i> value	<u>.625</u>	<u>.657</u>	<u>.855</u>	<u>.952</u>	<u>.523</u>
Clinical T stage					
T1c (25)	4.86	2.64	2.35	6.22	2.92
T2 (52)	7.23	3.63	7.32	27.41	3.6
T3 (11)	13.86	5.16	59.85	264.16	8.81
T4 (6)	12.16	4.81	45.39	296.19	7.76
<i>P</i> value	<.001	<.001	<.001	<.001	<.001
Metabolic axillary lymph node status					
Positive (25)	5.12	3.3	3.98	12.13	1.66
Negative (69)	6.03	3.4	6.48	24.75	1.88
<i>P</i> value	<u>.128</u>	<u>.108</u>	.02	.003	<.001
Metabolic M stage					
M0 (86)	5.91	3.43	6.22	17.49	2.19
M1 (8)	10.69	5.08	19.14	111.07	4.06
<i>P</i> value	.023	.014	.023	.009	.015
Nuclear grade					
I (23)	3.61	2.34	6.7	18.63	1.57
II (35)	7.15	3.59	13.25	56.74	2.84
III (56)	10.66	4.41	22.9	136.34	4.1
<i>P</i> value	<.001	<.001	.002	<.001	<.001
ER status					
Positive (80)	5.24	3.41	6.5	18.37	2.16
Negative (14)	10.09	4.72	16.28	52.79	4.11
<i>P</i> value	.001	.007	<u>.115</u>	.024	.002
PR status					
Positive (67)	5.12	3.32	6.48	18.01	2.07
Negative (27)	7.7	3.99	6.6	24.75	3.06
<i>P</i> value	.012	.046	<u>.219</u>	<u>.076</u>	.028
HER2 status					
Positive (56)	4.99	3.13	6.47	15.70	1.79
Negative (38)	8.41	4.21	7.92	30.25	3.37
<i>P</i> value	.001	.002	<u>.272</u>	.036	.001
Molecular subtypes					
Luminal A (19)	3.15	1.57	4.54	6.33	1.18
Luminal B (HER2 -) (31)	6.46	3.65	6.85	26.32	1.88
Luminal B (HER2 +) (29)	7.99	4.03	6.77	29.25	3.06
HER2 + (9)	9.89	4.89	9.08	40.32	3.9
TN (6)	10.45	4.59	25.81	98.06	4.81
<i>P</i> value	<.001	<.001	<u>.251</u>	.006	<.001

Underline indicates statistically insignificant.

ER=estrogen receptor, HER2=human epidermal growth factor receptor 2, IDC=invasive ductal carcinoma, ILC=invasive lobular carcinoma, MTV=metabolic tumor volume, PR=progesterone receptor, SUVavg=average standardized uptake value, SUVmax=maximum standardized uptake value, TLG=total lesion glycolysis, TLR=tumor/liver ratio, TN=triple negative.

There were moderate and positive correlations between the Ki67 labeling index and the SUVmax ($P < .001$, $r = 0.507$), SUVavg ($P < .001$, $r = 0.479$), and TLR values ($P < .001$, $r = 0.445$); and weak and positive correlations between the Ki67 labeling index and MTV ($P = .042$, $r = 0.210$) and TLG values ($P = .001$, $r = 0.331$).

All of the metabolic parameters except MTV significantly differed according to the molecular subtype and patients in the HER2+ and TN groups had the highest values in this regard (Table 2). The greatest differences in the median SUVmax, SUVavg, MTV, TLG, and TLR values were observed between the LumA and TN groups (P values: $<.001$, $.003$, $.251$, $.078$, and $.001$, respectively), but the difference was not statistically significant for MTV and TLG values. Also, there were marked

differences in the SUVmax, SUVavg, MTV, TLG, and TLR values between the LumA and HER2+ groups (P values: $<.001$, $<.001$, $.251$, $.038$, and $.001$, respectively), but the difference was not significant for the MTV value.

4. Discussion

Breast cancer is a heterogeneous type of malignancy because several factors affect its behavior and prognosis.^[14] Because of this heterogeneity, the optimal treatment and expected response to treatment may vary substantially for each patient.^[14]

F-18 FDG PET/CT may give relevant information about the metabolism, diagnosis, and prognosis of BC.^[16] Several studies have suggested a correlation between the clinicopathological

features of BC, which are important prognostic factors, and the metabolic parameters obtained by PET/CT.^[5,6,17,18]

The SUV values, which are quantitative measures of FDG uptake by tumors, are routinely used in clinical practice and SUVmax is the most widely used one. However, the SUVmax value does not reflect the total glucose metabolism in a tumor. Recently, different quantitative measurements such as MTV and TLG have drawn interest due to better assessment of the volume, shape, and heterogeneity of the tumor.^[5,6] The MTV value is calculated by various software applications in the literature using different threshold values such as 40%,^[19] 42%,^[20] and 50%^[6] of the SUVmax of the primary tumor. In solid tumors such as BC, 42% of the SUVmax of the tumor as a threshold value may be more effective in demonstrating tumor glycolytic activity.^[21,22] Therefore we used this threshold in the present study. Several reports indicate that MTV and TLG are more useful for evaluating tumor prognosis.^[6,23,24]

The SUVmax value may be affected by the glucose level, body weight, duration after injection, size of the ROI, and resolution of the scanner. The SUVmax value also has other limitations for representing the glucose metabolic rate of tumors such as its susceptibility to the impact of noise, partial volume effect, image resolution, and definition of the VOI and it is a single-voxel value representing the most intense FDG uptake in the tumor.^[25,26] Therefore, the SUVmax value may not be an adequate surrogate for the metabolic rate of the tumor, and there is need to further explore other potential metabolic parameters that can predict prognosis. The mediastinal vessels and normal liver tissue are the most commonly used parameters for individual background activity.^[27] Paquet et al^[8] reported that SUV_{liver} is relatively constant regardless of which correction method was used. It has been suggested that at least some of the problems can be eliminated by using the ratio of tumor SUV to the SUV of the reference region in the liver.^[11,12] In the current study, we used the SUV_{liver} to represent individual normal uptake. Normalization of the SUVmax value using normal liver uptake may reduce the effect of individual bias.

Several studies reported a lower F-18 FDG uptake in ILC compared with IDC.^[7,28] This finding is because of several factors including the lower density of tumor cells, lower proliferation rates, lower expression of GLUT1, and the diffuse infiltration of surrounding tissues by the tumor in ILCs.^[7,29] In the present study, all of the metabolic parameters obtained by F-18 FDG scanning were lower in ILCs than in other BC types. However, the difference was not significant because of the low number of patients with other BC types. Similar to our results, Higuchi et al^[30] did not report a significant association between the histological subtypes and the tumor SUVmax in their large scale study in 743 patients but the highest median metabolic values were observed in patients with IDC.

Tumor size is a well-known independent prognostic factor and a larger tumor size and poor histopathological differentiation are associated with a higher risk of metastasis in BC.^[31] Although several studies reported a positive correlation between the 18F-FDG uptake and tumor size,^[6] others did not find such relationship.^[5,7] The inconsistency between those studies may be due to the bias of partial volume effect. Groheux et al^[7] included only patients with tumors >2 cm to minimize this effect, and reported that SUVmax value was not associated with the size of the tumor. In the present study, patients with tumor size of <15 mm were excluded in order to eliminate the partial volume effect.

There was a significant association between the T stage of the primary tumor and the SUVmax, SUVavg, MTV, TLG, and TLR values. One of the strong prognostic factors in BC is the axillary lymph node involvement. While absence of such involvement is associated with a 10-year disease-free survival rate around 70% to 80%, this rate is approximately 30% for patients with axillary lymph node metastasis.^[32]

The relationship between the metabolic parameters and axillary node status is also a controversial topic. In the present study, the MTV, TLG, and TLR values were higher in the presence of suspected axillary lymph node involvement. However, the patients with and without axillary node involvement had similar SUVmax and SUVavg values. Similarly, Groheux et al,^[10] did not find a relationship between SUVmax or other metabolic parameters and the presence of axillary node positivity. On the other hand, Kajáry et al^[5] reported that the SUVmax, SUVavg, MTV, and TLG values of the tumor were associated with lymph node involvement.

The histological grade in invasive carcinomas is classified by tumor cell tubule structure, nuclear pleomorphism, and mitotic count according to Scarff–Bloom–Richardson criteria.^[15] Tumors with higher histological grade behave more aggressive than low-grade tumors.^[10] Previous studies reported a positive association between SUV values and nuclear grade.^[5,7] Similarly, in the present study the metabolic values increased in higher nuclear grades.

Estrogen receptor negative patients with BC have been reported to have a higher risk for tumor proliferation and progression.^[33] Cooper et al^[34] reported that loss of regional ER expression was present in the hypoxic regions of BC. Several studies reported that ER negativity was associated with the metabolic parameters.^[5,6,10]

Kaida et al^[6] reported that PR negativity was not associated with any of the volumetric parameters. Conversely, Groheux et al^[10] and Kajáry et al^[5] found an association between the increased volumetric parameters and PR negativity. In the present study, we observed a significant association between ER or HER2 status and all of the metabolic parameters except MTV. Similarly, PR negativity was significantly associated with the metabolic parameters except for MTV and TLG.

The HER2 oncoprotein promotes tumor growth and thus progression and is considered to be a poor prognostic marker associated with high recurrence and mortality.^[35] While several studies reported a significant association between the HER2 status and the metabolic parameters,^[5,36] others did not find such a relationship.^[7,28] In the present study, we observed a significant association between the HER2 status and each of the metabolic parameters except MTV.

The nuclear-associated antigen Ki-67 is expressed during cellular proliferation and its overexpression indicates a high proliferation rate of tumor cells and is considered an independent poor prognostic factor in BC.^[37] According to our results, the SUVmax of the tumor was best correlated with Ki-67 among the metabolic parameters.

The molecular classification has indicated a molecular basis for the heterogeneity of BCs and unique features of different molecular subtypes and has provided important prognostic and predictive information to guide clinical decision-making. Targeting subcellular levels noninvasively, PET and SPECT imaging has become a promising way to identify BC subtypes and monitor treatment.^[23,38] As the fundamental molecular mechanisms of BC are better understood and future target therapies are

studied, more specific targets will be used for the research and development of novel imaging agents. The molecular subtypes of BC have unique properties and the optimal treatment may differ at the individual level.^[3]

In line with the St. Gallen consensus recommendations, the patients were divided into 5 groups according to their molecular subtypes, comprising patients with LumA, LumB-, LumB+, HER2, and TN.^[13] LumA, which is the most common subtype, shows low expression of cellular proliferation genes. The LumB subtype is associated with a more aggressive course, worse prognosis, higher histological grade, and higher proliferative index compared with LumA subtype. The HER2 gene promotes tumor growth and progression, and HER2-positive subtype is associated with higher recurrence and mortality rates. Trastuzumab targets the HER2 receptor and has improved survival outcomes in HER2 positive patients during the last decade.^[39]

Triple-negative BC, in particular the intrinsic basal type, is associated with a more aggressive course and poorer outcome than other subtypes.^[40] The TN phenotype has been reported to show higher F-18 FDG uptake than the LumA and LumB subtypes.^[7] Kajáry et al^[5] reported significant relationships between the volumetric parameters and biological subtypes, with the exception of MTV in TN cases. They concluded that the SUVmax value may reflect the tumor metabolism more accurately than the SUVavg, MTV, and TLG values. The findings of our study also suggest a similar association between the glycolytic phenotypes and molecular subtypes. All of the metabolic parameters except MTV were markedly lower in patients with LumA subtype and higher in those with TN BC.

Groheux et al^[7] reported a 1.3 times higher F-18 FDG uptake in premenopausal BC patients. According to Kim and Sung,^[41] the rate of FDG uptake in premenopausal patients tended to be higher than in postmenopausal patients. In the present study, the median values of metabolic parameters were higher in premenopausal patients than postmenopausal ones, but the difference was not significant ($P = .414$).

In the present study, unlike other similar studies we also examined the association of TLR with the prognostic factors in BC. The SUV value of the liver is relatively constant, and calculating the ratio of tumor SUVmax value to liver SUVavg may provide important and reliable information.^[8] The SUVmax value may be influenced from several aforementioned factors. In order to control for such confounders, the background ROI was obtained from the liver to calculate the SUVavg value (SUVliver).^[42] The use of TLR as an alternative approach to evaluate the prognosis and treatment response has been reported in several recent studies.^[9,13] Whereas the TLR value was associated with lymph node involvement and distant metastasis, the SUVmax did not have a relationship with these outcomes in the present study. Therefore, TLR value seems to be more informative than the tumor SUVmax in predicting axillary nodal involvement. On the other hand, the TLR and SUVmax values had similar associations with other prognostic factors.

An important limitation of the present study is the lack of standardized methods and definite cut-off values for calculating volumetric parameters in the literature.^[5,6,10,43] In solid tumors such as BC, 42% of the SUVmax of the tumor has been recommended as a threshold value to demonstrate the glycolytic activity by some authors.^[21,22] Therefore the threshold of 42% was used in the present study. There were no male BC patients and all of the patients underwent PET/CT examination before any chemotherapy, thus, the findings of the present study are not

generalizable to male patients and those underwent treatment before imaging. Histopathological validation for every metastatic site was not available for practical, ethical, and technical reasons. Since we did not aim to investigate postoperative pathology findings, we did not examine the pathological T, N, or M status of the patients. Therefore, we compared metabolic parameters with the clinical T stage and metabolic M and N stages. Moreover, this was a retrospective study and the number of patients in several subgroups was relatively low.

In the present study, compared with other metabolic parameters the TLG and TLR values were more strongly associated with most of the prognostic factors in BC including the lymph node involvement and distant metastasis, therefore, these markers may provide relevant information about tumor biology and behavior.

Author contributions

Author's contributions: Hasan Önner, Emre Entok, Murat Dinçer, Serdar Erkasap, Serap Işıksoy, and Funda Canaz were involved in the study design, implementation, data collection, manuscript preparation, and writing of the manuscript. Hasan Önner and Emre Entok participated in the data analysis and manuscript preparation. Murat Dinçer, Serdar Erkasap, Serap Işıksoy, and Funda Canaz worked in data analysis and preparation of the draft manuscript. All authors read and approved the final manuscript

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