Original article

Considering the Relationship between Quantitative Parameters and Prognostic Factors in Breast Cancer: Can Mean Standardized Uptake Value be an Alternative to Maximum Standardized Uptake Value?

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Abstract

It was aimed to investigate the correlation between maximum standardized uptake value (SUVmax), mean standardized uptake value (SUVmean), and retention index (RI), which represents the quantitative evaluation of the uptake of ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) used in positron emission tomography (PET) and clinicopathologic as well as biologic prognostic factors. Forty-one women with breast cancer who were histopathologically diagnosed were included in this study. Neoadjuvant chemotherapy was applied to all patients before PET/computed tomography (CT). After FDG injection, PET/CT screening was applied within the 1st h (PET-1) and in the 2nd h (PET-2). SUVmax, SUVmean, SUVmax RI, and SUVmean RI of every image were calculated qualitatively and semiquantitatively. The correlation between quantitative and semiquantitative PET parameters and biologic as well as clinicopathologic prognosis factors was evaluated. Statistically, significant positive correlation was found between lymph nodes (LNs), which were evaluated by clinical picture, clinical stage as well as histopathologically and quantitative PET parameters (SUVmax1, SUVmax2, , RImax, SUVmean1, SUVmean2, RImean) ($P < 0.05$). While statistically significant correlation with RImax was detected only by LN (histopathological), correlations with RImean were detected by clinical picture, clinical stage, metabolic stage, and LN (histopathological). Statistically, significant correlation was found between RImax and estrogen receptor in patients who were histopathologically diagnosed with invasive ductal carcinoma ($n = 34$) ($P < 0.05$). We detected correlations between biologic and clinicopathologic prognostic factors and SUVmax as well as SUVmean values in breast carcinoma. SUVmean values may provide important knowledge when the correlation between prognostic factors and PET parameters is investigated even if they are not used routinely.

Keywords: Breast cancer, prognostic factors, semiquantitative positron emission tomography parameters

Introduction

Breast cancer is the most common malignancy in women and the second leading cause of cancer-related deaths worldwide.[1] Prognostic parameters include the presence and number of axillary lymph nodes (LNs) involved, estrogen/progesterone receptor (ER/PR) status, Ki-67 staining index, C-erbB2 overexpression, p53 level, histological type and grade, and distant metastases.[2]

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Several methods are utilized to estimate the total amount or proportion of fluorodeoxyglucose (FDG) uptake in tumor tissues. Positron emission tomography (PET) scanning has been designed to measure the *in vivo* concentration of the radioactivity in kBq/ml.[3] Although PET/computed tomography (CT) can also be effectively used for the diagnosis, staging, and follow-up of the patients with breast cancer, the FDG uptake intensity has also been shown to be associated with certain clinical and biological indices of prognosis. In this regard, previous studies have established the prognostic values: maximum standardized uptake value (SUVmax), late SUVmax, and retention index (RI).[4-7] These studies have focused on the utility of several quantitative PET parameters such as mean standardized uptake value (SUVmean) and SUVpeak in addition to SUVmax, particularly during the assessment of the response to the treatment.[8] Higgins *et al*. studied PET/CT before radiotherapy (RT) at head and neck tumors, and they analyzed the relationship of SUVmax, SUVmean, and total lesion glycolysis values with disease-free survival (DFS), locoregional control, and distant metastasis-free survival. In their study, they found a positive relationship between the increasing SUVmean value and inferior DFS. In conclusion, they showed that SUVmean could be a useful prognostic factor as an FDG-PET parameter.[9] Some studies on breast cancer have shown that there is a positive correlation between biological and clinical prognostic markers and early SUVmax, late SUVmax, and RI. In our study, we investigated the relationship between SUVmean values (early SUVmean, late SUVmean, RI) and clinical and biological prognostic factors in addition to SUVmax values.

Methods

Patients

This study has been approved by the Inonu University School of Medicine Ethics Committee, Malatya. All persons gave their informed consents before their containment in the study. All patients were diagnosed with breast cancer by histopathological examination, and then, they underwent PET/CT imaging between April 2013 and December 2013 in the Inonu University Faculty of Medicine nuclear medicine department.

A total of 41 women (age range: 51.85 ± 15.4 years) with newly diagnosed breast cancer as documented by biopsy results were included in the study. Thirty-four patients had invasive ductal carcinoma (83%), 4 had invasive lobular carcinoma, 1 had medullary carcinoma, 1 had tubular carcinoma, and 1 had cribriform carcinoma of the breast. Patients who had undergone chemotherapy and/or RT or had total mastectomy were excluded from the study. Mammography, breast ultrasound, and PET/CT examination were performed in all participants. Histopathological diagnoses and biological parameters were assessed through sampling with gross needle biopsy.

Positron emission tomography/computed tomography imaging procedures

FDG injection was administered after at least 4 h of fasting and when the fasting blood glucose was below 200 mg/dl. Routine PET/CT scanning (PET1) was performed for 1 h after FDG injection at a dose of 370 MBq, with a late scan (PET2) obtained in approximately 2 h after injection. The second scan involved only breast region at 1 or 2 bed positions. The PET/CT images (Siemens, Biograph mCT, Milwaukee, USA) were acquired between the head and thigh in the standard 3D mode with 10–22 bed positions, with a 3-min acquisition time per position, while the patients were holding their arms above their head. The image cross-sections were 3.8 mm thick. Iterative reconstruction and image scatter correction were performed. SUVmax and SUVmean for PET1 and PET2 images were recorded. RI values representing the percent change in each quantitative PET parameter (i.e., SUVmax, SUVmean) were calculated according to the following formula: RI = (SUV2 − SUV1/SUV1) ×100.

PET/CT images obtained for each patient were assessed by two separate nuclear medicine specialists. SUVmax and SUVmean measurements were performed manually by drawing the volume of interest around the breast tumor tissue.[10] The greatest diameter of the lesion was estimated using the clinical and metabolic dimensions of the primary tumor, morphological imaging modalities (i.e., digital mammography and breast ultrasound) and PET/CT images. Metabolic LN assessments with PET1 and PET2 involved axillary, internal-mammarian, supraclavicular, and infraclavicular LNs. The increase in the metabolism of LNs was assessed on the basis of elevated metabolic activity against the background. Metabolic and clinical staging were based on clinical examination, breast ultrasound (clinical stage), PET/CT (metabolic stage) as suggested by the American Joint Committee on Cancer.[11] The presence of distant metastases was evaluated using PET/CT.

Histopathological examination

Histopathological assessment was based on the gross needle aspiration cytology and surgical specimens. Five-micrometer-thick cross-sections from tissue samples fixed with formaldehyde and embedded in paraffin blocks were prepared and stained with hematoxylin and eosin for the determination of the following tumor types and histopathological grades. Primary antibodies for ER and PR in the paraffin-embedded samples were examined. C-erbB2 and proliferation index were

determined using Ki-67 antibodies. A cutoff value of 10% was used for nuclear immunostaining to differentiate between PR-positive or PR-negative tumors. C-erbB2 was considered positive when more than 30% of tumor cells had complete membrane immunostaining (3+) or when fluorescence *in situ* hybridization showed her2 gene amplification, despite a complete membrane immunostaining in <30% of the tumor cells (2+). Final LN (N) status (i.e., negative or positive) was determined histopathologically or by sentinel node biopsy.

Statistical analysis

All statistical tests were two-sided with a significance level of $P < 0.05$. SPSS 18.0.1 (SPSS Inc., Chicago) for Windows was used for all analyses. All semiquantitative data were expressed in terms of mean ± standard deviation. The Spearman's rank-order correlation coefficient was used to measure the association between SUVmax and the numerical prognostic variable, and the association between SUVmax and categorical measures was assessed by Mann–Whitney U-test and Kruskal–Wallis test (clinical markers and molecular biomarkers).

Results

Early and late SUVmax estimates in 41 primary lesions showed an increased late SUVmax in 34 patients and a decrease in 6 patients, with no change in a single case. FDG-PET parameters of the patients are presented in Table 1.

Despite higher readings with regard to quantitative PET parameters among patients with a histopathological diagnosis of invasive ductal cancer ($n = 34$) as compared to those with lobular cancer ($n = 4$), the difference was not statistically significant. The average SUVmax1 and SUVma × 2 in patients with invasive ductal carcinoma were 7.9 ± 3.9 and 9.9 ± 5.1, respectively, while SUVmean1 and SUVmean2 were 4.5 ± 2.2 and 5.7 ± 2.8, respectively. Among four patients with invasive lobular carcinoma, SUVmax1 and SUVmax2 were 8.5 ± 4.0 and 12.8 ± 5.4, respectively, with the corresponding SUVmean1 and SUVmean2 of 4.8 ± 2.4 and 7.0 ± 3.0, respectively. However, there was a statistically significant increase in RImax and RImean in patients with invasive ductal carcinoma as compared to those with invasive lobular carcinoma ($P < 0.01$ and $P < 0.02$, respectively) [Table 2].

Table 1: Statistical mean and standard deviation of quantitative parameters

	Number of patients	Statistics (mean)	SD
Age	41	51.8	15.4
Tumor size (cm)	41	3.1	1.6
SUVmax1	41	7.9	4.0
SUVmax2	41	9.9	5.2
SUVmax RI	41	31.4	73.2
SUVmean1	41	4.6	2.3
SUVmean2	41	5.8	2.9
SUVmean RI	41	0.2	0.2

SD: Standard deviation; SUV: Standardized uptake value; RI: Retention index

In terms of clinical T status, which signifies the tumor size, there was a significant increase in SUVmax2, SUVmean2, and RImean among T2 and T3 tumors in comparison with T1 tumors ($P < 0.02$, $P < 0.02$, and $P < 0.03$, respectively). A significant association was also observed between clinical T and semiquantitative PET parameters (i.e., SUVmax1, SUVmax2, SUVmean1, SUVmean2, and RImean). Histopathological N status also showed a significant association with all semiquantitative PET parameters (SUVmax1, SUVmax2, RImax, SUVmean1, SUVmean2, and RImean). SUVmean1 showed a significant correlation with clinical T status ($P < 0.03$) and histopathological N status ($P < 0.05$). There was a statistically significant positive correlation between SUVmean2 and clinical T status ($P < 0.009$) and histopathological N status ($P < 0.01$) [Table 3].

RImean also showed a significant correlation with the clinical T status ($P < 0.01$), clinical stage ($P < 0.03$), metabolic stage ($P < 0.02$), axillary metastasis ($P < 0.03$), and N status ($P < 0.01$). When a more homogenous grouping was done, an association between SUVmax1 and histopathological N status was observed in patients with invasive ductal carcinoma ($P < 0.04$). In addition, SUVmax2 was significantly associated with clinical T status ($P < 0.04$) and histopathological N status ($P < 0.01$). Similarly, significant associations were found between RImax and ER ($P < 0.04$) and late SUVmean and histopathological N status ($P < 0.03$) [Table 4].

Discussion

A number of different prognostic factors including age, histological type, histological grade, hormone receptor status, C-erbB2 amplification, proliferation index, presence of distant metastases, and axillary LN involvement are used for prognostic assessments in patients with breast cancer.[12] Previous studies have also established that the prognostic role of SUV has a value in breast cancer, with higher SUVmax values correlating with axillary LN metastasis in this group of patients.[13,14] FDG uptake has also been reported to be associated with the histological tumor type (lobular, ductal), the growth pattern of the tumor (nodular, diffuse), immunoreactivity, and MIB 1 monoclonal antibody which is a marker of tumor cell growth. On the other hand, no associations were detected between SUVmax and axillary LN involvement, tumor size, percentage of tumor cells, presence of inflammatory cells, histopathological

Table 2: Comparison of multiple semiquantitative positron emission tomography parameters (maximum standardized uptake values 1 and 2, maximum retention index, mean standardized uptake values 1 and 2, mean retention index) with qualitative clinical, pathologic, and biologic variables

	Patients number	Mean			
		SUVmax2 ±SD	RImax±SD	SUVmean2±SD	RImean±SD
Histologic type	38	*P*=0.29	*P*=0.01	*P*=0.36	*P*=0.02
Invasive ductal	34	9.9±5.1	0.3±79.4	5.7±2.8	0.2±0.2
Invasive lobular	4	12.8±5.5	0.5±19.6	7.0±3.0	0.5±0.2
Distant metastasis	41	*P*=0.17	*P*=0.93	*P*=0.27	*P*=0.48
Positive	30	9.3±5.4	0.3±84.1	5.5±3.0	0.2±0.2
Negative	11	11.5±4.7	0.2±28.6	6.4±2.5	0.3±0.2
Clinical T	41	*P*=0.02	*P*=0.08	*P*=0.02	*P*=0.03
T1	6	4.9±3.1	0.9±9.6	3.0±2.0	0.02±0.2
T2	29	10.2±4.9	0.4±85.1	6.0±2.7	0.2±0.2
T3	5	14.7±5.0	0.1±25.1	8.1±2.6	0.3±0.1
T4	1	8.2	0.2	4.0	0.1
Axillary LN metastasis	41	*P*=0.25	*P*=0.08	*P*=0.38	*P*=0.03
Positive	30	10.6±5.3	0.3±84.0	6.0±2.8	0.3±0.2
Negative	11	8.1±4.9	9.8±16.8	5.1±3.2	0.1±0.2

SD: Standard deviation; SUV: Standardized uptake value; RI: Retention index; LN: Lymph node

Table 3: Correlation of clinical and metabolic prognostic factors with semiquantitative metabolic parameters

	SUVmax1	SUVmax2	RImax	SUVmean1	SUVmean2	RImean
Clinical T						
r	0.37	0.44		0.32	0.40	0.36
P	<0.01	<0.003		<0.03	<0.009	<0.01
Clinical stage						
r		0.03				0.33
P		<0.04				<0.03
Metabolic stage						
r						0.34
P						<0.02
N (histopathological)						
r	0.46	0.46	0.31	0.30	0.40	0.36
P	<0.02	<0002	<0.04	<0.05	<0.01	<0.01
Axillary metastasis						
r						−0.34
P						<0.03

SUV: Standardized uptake value; RI: Retention index

Table 4: Correlation of clinical and biological prognostic factors with semiquantitative metabolic parameters (*n*=34 patients with invasive ductal cancer)

	SUVmax1	SUVmax2	RImax	SUVmean1	SUVmean2	RImean
Clinical T						
r		0.35				
P		<0.04				
N (histopathological)						
r	0.34	0.41			0.35	
P	<0.04	<0.01			<0.03	
Estrogen receptor						
r			−0.35			
P			<0.04			

SUV: Standardized uptake value; RI: Retention index

grade, steroid receptor status, and glucose transporter 1 expression.[5,15] However, in our study, there was a statistically significant association between certain PET parameters (SUVmax1, SUVmax2, RImax, SUVmean1, SUVmean2, and RImean) and LN metastasis [Table 3].

T stage is a parameter that indicates the tumor size.[16] Several previous studies reported no association between the SUVmax of the primary breast lesion and the tumor size while clinical T status had a significant impact on SUV1 in a study carried out by Garcia Vicente *et al*.[17] Moreover, in our study, SUVmax1, SUVmax2, SUVmean1, SUVmean2, and RImean had a significant association with clinical T. Clinical T status was associated with significant differences in SUVmax2, SUVmean2, and RImean. While SUVmax and RI had no association with metabolic T staging based on the assessment of PET images, there was a significant association between SUVmean2 and metabolic T staging ($P < 0.02$). There was a statistically significant association between the clinical stage and SUVmax2 ($P < 0.04$) and SUVmean2 ($P < 0.03$).

As compared with poorly differentiated tumors, well differentiated tumors had lower uptake previous data.[18] However, the differences between the groups did not reach a higher significance level as compared to the data reported by Avril et al. and Shimoda et al. On the other hand, in contrast with previous reports, RI showed a significant association.[5,7,19] In our patients with invasive ductal carcinoma, although the average SUVmax1-2 and SUVmean1-2 were lower as compared to patients with invasive lobular carcinoma, the differences were not statistically significant. However, in patients with invasive ductal carcinoma, a statistically significant difference was noted by decreasing SUVmax RI and SUVmean RI. In a study carried out by García Vicente *et al*., who investigated the association between biological prognostic factors and early SUVmax, SUVmax2, and RI, a significant association was found between RI and ER and PR.[20] Besides, in another study carried out by García Vicente *et al*., who investigated RI and biological prognostic parameters, no significant associations with estrogen and progesterone were observed as compared to a significant association between RI and C-erbB2.[20] In the study carried out by Kumar *et al*., ER, PR, and C-erbB2 had a significant correlation with the SUVmax of the primary lesion.[21] Mavi *et al*. reported an association between ER and SUVmax of the primary lesion while no effects were detected for PR status and C-erbB2.[22]

In our study, no significant associations were observed between estrogen and progesterone hormone receptors and SUVmax and SUVmean values. However, an assessment of the patients with invasive ductal carcinoma ($n = 34$) showed a significant correlation between ER and SUVmax RI ($P < 0.04$) in contrast with the absence of such association between C-erbB2 and semiquantitative PET parameters. Previous studies have reported that a second late imaging could increase the accuracy of PET/CT.[23-26] In addition, it is possible that the changes in dual time point SUV may yield higher diagnostic accuracy.[27] Several previous studies examined the association of late PET/CT imaging with metabolic and biological parameters. However, our literature search did not reveal any study that examined the association between biological/metabolic parameters SUVmean (early, late, RI). In our study, SUVmax and SUVmean were shown to be significantly associated with the clinical T, clinical stage, and N (pathological) status. Besides, while SUVmax had no predictive value in detecting metabolic axillary LN metastases, RImean showed a significant association. Previous studies showed an association between SUVmax1, SUVmax2, RI, and biological and clinical prognostic parameters in patients with breast cancer.[19,20] In contrast with the previous reports, our results suggested an association between biological and clinical prognostic parameters in breast cancer and SUVmean1, SUVmean2, and RImean. Due to its ability to provide whole body imaging in a single session, PET-CT has been successfully used to assess the extent of the disease in patients with breast cancer in recent years.

Conclusion

While assessing the relationship between clinical, biological prognostic factors and PET parameters, SUVmean values should also be considered in addition to SUVmax values.

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Conflicts of interest
There are no conflicts of interest.

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