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ORIGINAL ARTICLE

ADC of Diffusion-weighted MRI and SUV_{max} of ^{18}F-FDG-PET/CT: Correlation with Prognostic Factors and Distant Metastasis in Breast Cancer

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OBJECTIVE

We aimed to evaluate the relationship between apparent diffusion coefficient (ADC), maximum standardized uptake value (SUV_{max}), and prognostic factors in breast cancer (BC) and to investigate the contribution of these parameters in determining the distant metastases at the time of diagnosis in BC.

METHODS

The study included 209 patients with invasive BC at the time of initial diagnosis. Patients underwent whole-body ^{18}F-fluorodeoxyglocose positron emission tomography/computed tomography and breast magnetic resonance imaging including diffusion weighted imaging. Histologic grade (HG), histological type, human epidermal growth factor 2 (HER-2), Ki-67, estrogen receptor (ER), and progesterone receptor (PR) markers of the breast tumor were evaluated in pathological samples. Tumor-node-metastasis (TNM) staging was performed based on clinical, pathological, and imaging findings.

RESULTS

HER-2 positivity and PR positivity demonstrated a strong correlation with distant metastasis (p=0.00040 ve 0.00045). ER positivity was positively correlated with SUV_{max} (p=0.0001) and SUV_{max}/ADC_{mean} (p=0.006). PR was positively correlated with ADC_{mean} (0.028). SUV_{max} was correlated with the tumor size (p=0.008), TNM stage (p=0.022 and r=0.159), and HG (p<0.0001 and r=0.347).

CONCLUSION

Both SUV_{max} and ADC_{mean} are helpful parameters in determining prognosis in BC. HER-2 and PR positivity, and tumor size can be used as revealing and useful parameters in determining distant metastases.

Keywords: Apperent diffusion coefficient; breast cancer; diffusion-weighted magnetic resonance imaging; positron emission tomography.

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INTRODUCTION

Detection of the presence and spread of distant metastases in breast cancer (BC) is the most important prognostic factor for making a treatment plan. Although distant metastases are detected at the time of diagnosis in 5% of the patients diagnosed with BC, distant metastases occurring in years are the most frequently seen causes of mortality in BC patients.[1,2] Patients with poor prognostic factors without detectable metastatic lesions are supported by adjuvant chemotherapy and/or radiation because of the high risk of metastasis. New prognostic markers are needed to identify this patient group who will benefit from adjuvant therapies.[3,4]

^{18}F-FDG positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) and diffusion-weighted image (DWI) are imaging methods that give indirect information of the biological properties of cancer. Apparent diffusion coefficient (ADC) and maximum standardized uptake value (SUV_{max}) values measured from breast mass have the potential to be used as prognostic biomarkers.[5–13]

DWI is an magnetic resonance imaging (MRI) technique based on thermal energy-dependent random movements (Brownian motion) of water molecules in biological tissues, and its quantitative parameter is ADC. In high cellular malignant tissue, low ADC values are expected due to restricted fluid diffusion in the relatively decreased extracellular space and an increase in the nucleus/cytoplasm ratio.[11,12]

^{18}F-FDG-PET/CT is a widely used diagnostic method in the diagnosis, systemic staging, detecting recurrence and evaluation of response to treatment, as well as distinguishing malignant from benign lesions, which enables image acquisition by using high glucose metabolism in cancer cells and therefore increased FDG uptake.[4–7] FDG uptake is quantified as the SUV_{max}, and this numerical value is generally associated with the biological aggressiveness of the tumor. Although PET/CT has a high sensitivity ranged from 81 to 99 % in tumors above 2 cm in initial staging, studies have shown that diagnostic accuracy is quite limited in small tumors (<1 cm) which results in a false negative PET/CT.[7,14,15]

Many biological factors, including molecular subtypes, histologic grade (HG), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and Ki-67 and also age and axillary lymph node (LN) involvement, have been used to determine the prognosis.[16]

Studies are showing that ADC[11,12,16] and SUV_{max} [7–9] or both of these values[5,13,14] obtained from the primary tumor in BC have a significant relationship with pathological prognostic factors. In our study, we investigate the relationship between SUV_{max}, ADC values and prognostic factors and also the contribution of these parameters of the primary tumor to the prediction of distant metastasis in BC patients.

MATERIALS AND METHODS

Patient Selection

The institutional review board of Istanbul Training and Research Hospital approved this retrospective study (May 08, 2020-2279); the need for informed consent was waived. Between January 2016 and December 2017, 608 patients with invasive BC at the time of initial diagnosis who had verified by core needle or excisional biopsy were included. Within 3–30 days after the biopsy, 231 of these patients, underwent either whole-body ^{18}F-FDG-PET/CT and breast dynamic contrast-enhanced (DCE-MRI) including DWI for initial local and systemic staging. In excluded 23 patients, the interval was longer than 30 days between PET-CT and DCE-MRI. Two patients were excluded due to motion artifacts in MRI. Finally, 209 (207 females and 2 males) BC patients remained. 126 of these patients diagnosed distant metastasis on PET-CT.

^{18}F-FDG-PET/CT

All the patients were imaged using an FDG-PET/CT scanner with 16-multi-detector CT (mCT 20 ultra HD LSO PET/CT, (Siemens molecular imaging, Hoffmann Estates, Illinois, USA).

Patients were fasted for at least 6 h before the PET-CT procedure and all the patients' blood glucose levels measured below 150 mg/dL. All patients were administered intravenously with ^{18}F-FDG radiopharmaceutical, calculated from 0.15 mCi/kg based on their body weight. Following the injection, the patients were rested in the half-lying position for 50–60 min in a silent room. At the end of the rest period, combined image acquisition began unenhanced CT scan (3.5 mm slice thickness, 120 kV tube and up to 80 mA s) and subsequent 3D mode PET scan (5–7 bed positions, 3 min per bed position) between vertex and upper femur at the supine position.

1.5-Tesla Breast MRI

The MRI were acquired in the prone position, using a 1.5-Tesla scanner (Signa HDi; GE Healthcare, Milwau-

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kee, WI) with a dedicated bilateral breast phased-array coil. Before the examination, a catheter was placed through the antecubital vein to the patients. Standard protocol with contrast and DWI sequence was used in all examinations.

MR imaging protocol included axial, coronal, and sagittal turbo spin-echo T2 weighted (3D) sequence with 2 mm slice thickness and 1 mm slice spacing, axial fat-suppressed T2 sequence with slice thickness 2 mm and slice thickness 3 mm (fat suppression technique was the short-tau inversion recovery), axial DWI sequence with single-shot EPI; b value = 0 and 800 s/mm^2 with 3 mm slice thickness and slice spacing; after pre-contrast T1-weighted axial 3D dynamic gradient echo fat suppressed images, a bolus of 0.1 mmol/L per kilogram of body weight contrast agent gadoterate meglumine and 20 mL saline injection was administered with an automated contrast injector. In the post-contrast phase, six phased axial T1-weighted 3D dynamic gradient-echo fat-suppressed consecutive serial images were obtained with a maximum of 60-second intervals. Post-processing, maximum-intensity projection, subtraction, and ADC maps were obtained. All lesions were seen and evaluated at MRI.

Imaging Analysis

All ^{18}F-FDG-PET/CT images were analyzed by two nuclear medicine physicians with 5 and 10 years of experience in PET/CT. The readers were blinded to the histopathologic diagnosis and had any knowledge of other quantitative imaging data. The volume of interest (VOI) was determined as the area where FDG uptake was most intense on the relevant primary breast tumor, and FDG uptake was semiquantitatively analyzed in this area. SUV_{max} was considered the voxel with the highest SUV in the VOI examined and was used to measure and record uptake.

Two radiology physicians with 5 and 12 years of experience in breast MRI evaluated ADC maps retrospectively. The readers had no knowledge of histopathologic diagnosis and quantitative imaging data. On the ADC map, multiple uniform circular 20 mm^2 region of interests placed within the primary breast tumor. ADC measurements were made only from a solid portion of the tumor and dynamic contrast-enhanced images were used as a reference to avoid measuring from cystic, hemorrhagic, or necrotic areas. The average of the ADC values was calculated and noted as ADC_{mean}.

Figures 1 and 2 show the symbolic images of the ADC and the SUV_{max} measurement.

Histological Evaluation

In all patients, first the histological grade (HG) and type of the tumor were determined in the pathology specimens obtained by core needle biopsy or surgery. Subtyping was made according to the markers ER, PR, HER-2, and Ki-67 with immunohistochemical tests. The ER and PR results were determined to be positive according to the proportion of positively stained cell nuclei was higher than 10% and negative when less than 10%. HER-2 expression was determined with fluorescence *in situ* hybridization. Score +2 and +3 are defined as positive. If the Ki-67 proliferation index was over 15%, it was considered positive and below 15% was considered negative. LN status was evaluated mainly with the imaging techniques and also fine-needle aspiration and sentinel LN biopsy. TNM staging of all the patients was evaluated with initial imaging, biopsy, and pre-treatment clinical staging.

Statistical Analysis

Statistical analyzes were performed using IBM SPSS Statistics 25.0 (Armonk, NY: IBM Corp.) package program. Normality assumption of quantitative data was checked by Shapiro–Wilk test. Since the normality assumption was not provided, the Mann–Whitney U test and the Kruskal–Wallis test were used for assessing the relationship between SUV_{max}, ADC_{mean}, SUV_{max}/ADC values, and the clinicopathological parameters. Dunn test for pairwise comparison and Bonferroni correction was applied to the results. Correlation of quantitative data with each other (SUV_{max}, ADC, SUV_{max}/ADC) or with HG and clinical stage was evaluated with Spearman's Rho correlation coefficient. Logistic regression analysis was used to develop a model that can predict the presence of distant metastasis in the patient with prognostic factors and imaging data, variables with $p<0.10$ in univariate logistic regression analysis and variables considered to be clinically significant were evaluated by multiple logistic regression analysis.

RESULTS

The detailed characteristics of the patients included in the study are shown in Table 1.

Comparison of Groups According to the Presence of Distant Metastasis

In the comparison of metastatic and non-metastatic groups, clinicopathologic factors and quantitative imaging data were compared in univariate analysis, and those with $p<0.1$ were evaluated by logistic regres-

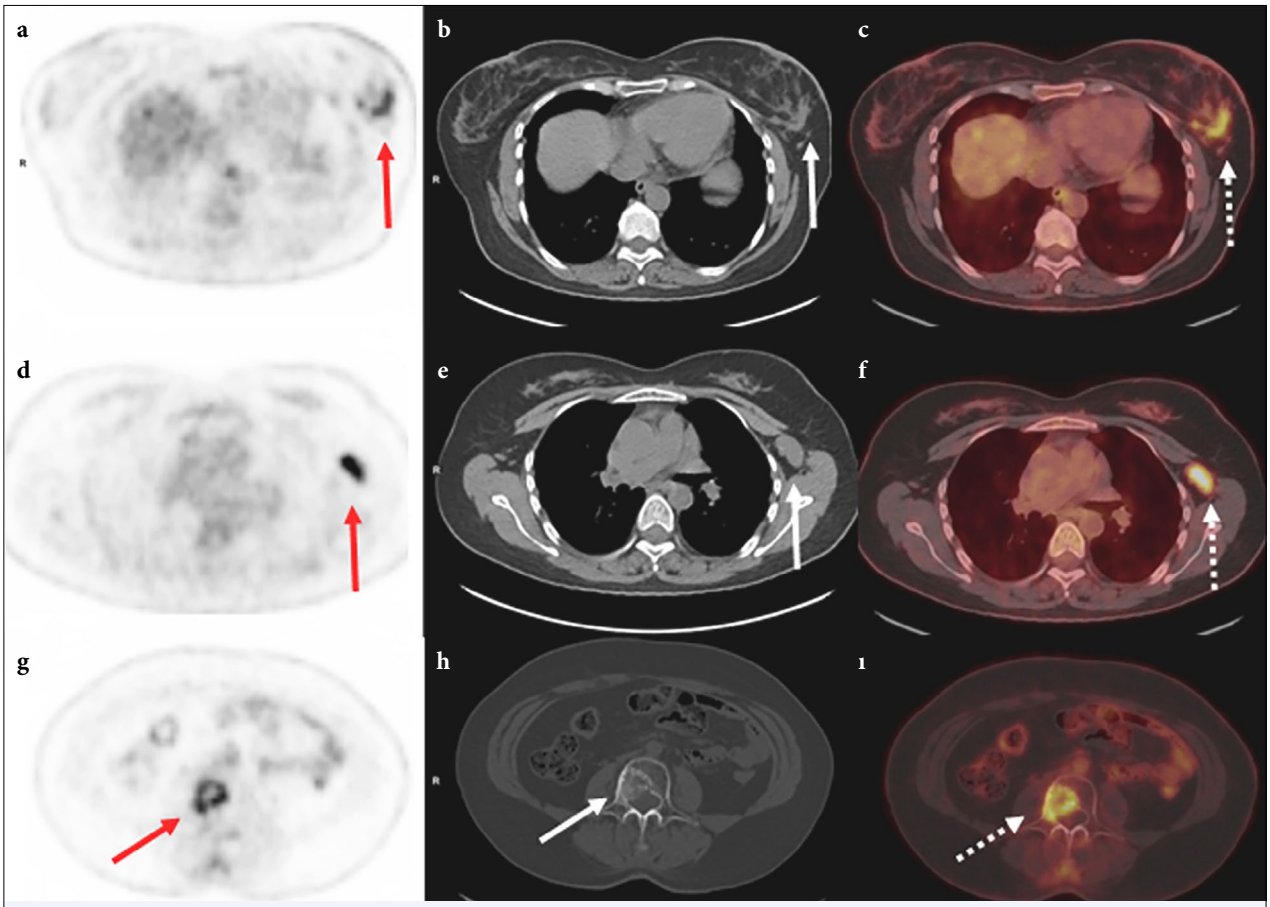

Fig. 1. 47 years old woman with Luminal B type invasive mucinous breast cancer, histologic grade 3, Immunohistochemical staining revealed ER+, PR+, HER-2 -, and Ki-67 %65, stage 4 with bone metastases. On ^{18}F-FDG-PET/CT images, a primary tumor (SUV_{max}:11.9) of approximately 5 cm in diameter is observed in the upper outer quadrant of the left breast (first row). Multiple metastatic lymph nodes (SUV_{max}:11.6) are seen on axillary sections (second row). There is an osteolytic metastatic lesion (SUV_{max}:12.3) in the L3 vertebral body (third row).
ER: Estrogen receptor; PR: Progesterone receptor; HER-2: Human epidermal growth factor receptor 2; ^{18}F-FDG-PET/CT: ^{18}F-FDG positron emission tomography/computed tomography; SUV: Standardized uptake value.

sion tests in multivariate analysis. Tumor size, HER-2 overexpression, and PR positivity were determined as independent variables affecting the presence of metastasis in multivariate analysis (Table 2).

Distant metastasis was present in 83 (39.7%) of the patients. There was no significant difference in mean age, histopathological diagnosis, HG, ADC_{mean}, SUV_{max}, SUV_{max}/ADC_{mean}, and molecular subtypes between metastatic and non-metastatic groups ($p>0.05$). The distribution of ADC_{mean}, SUV_{max} ve SUV_{max}/ADC_{mean} values of the metastatic and non-metastatic groups did not differ significantly ($p>0.05$) (Table 3).

Univariate analysis showed that a large tumor size (>2 cm) was significantly correlated with the presence of distant metastasis ($p<0.005$). Immunohistochemistry receptor positivity was present for HER-2, ER, and PR and p values between metastatic and non-metastatic groups were p=0.0004, 0.803, and 0.00045, respectively. HER-2 positivity and PR positivity demonstrated a strong correlation with distant metastasis. There was no difference for molecular subtypes (luminal A, luminal B, triple-negative, and HER2) and a high Ki-67 index between metastatic and non-metastatic groups (Table 4).

Correlation of SUV_{max} and ADC_{mean}

The mean SUV_{max}, ADC_{mean}, and SUV_{max}/ADC_{mean} values were 12.16±8.54 (range, 1.6–52.5), 962±206×10^{-6} mm^2/s (range, 464–1980×10^{-6}), and 0.13±0.009, respectively. There was no correlation between ADC_{mean} and SUV_{max} (correlation coefficient r=−0.017, p=0.805).

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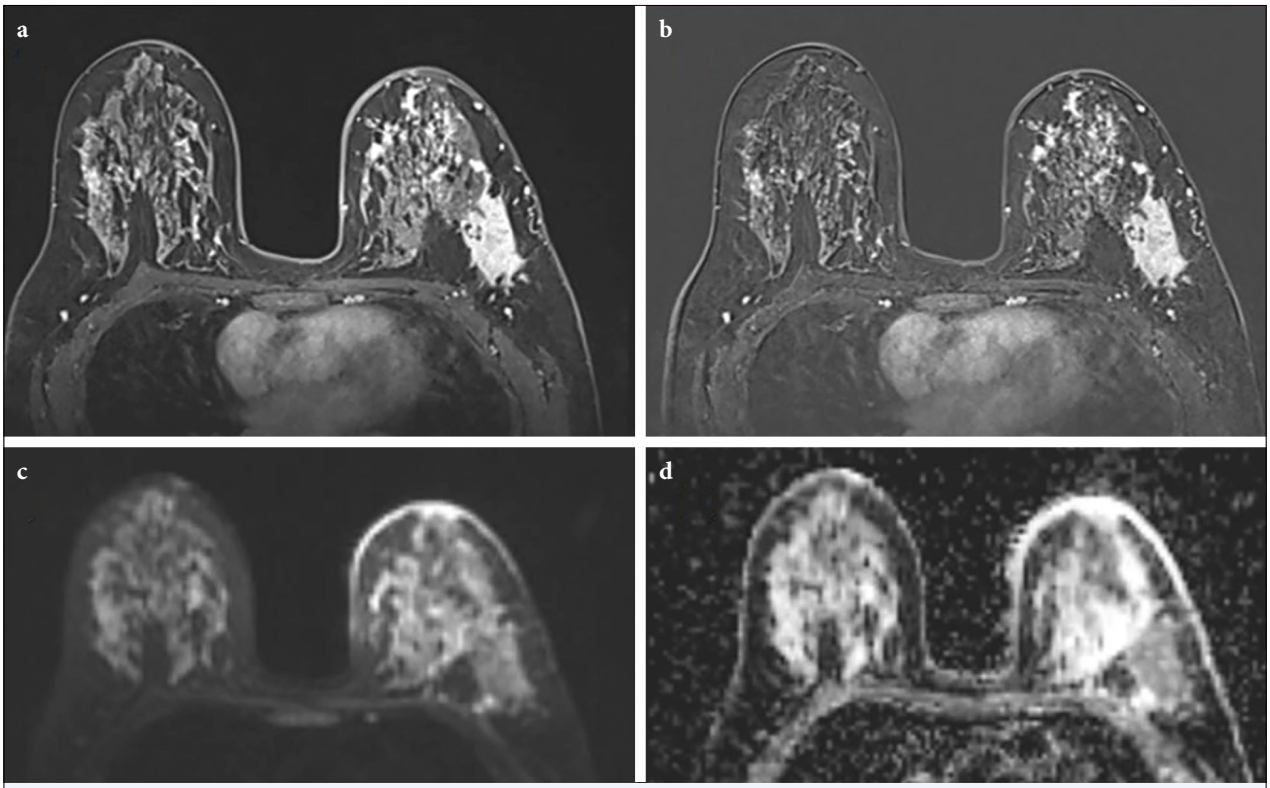

Fig. 2. Same patient. (a) Post-contrast T1 weighted axial image shows high intensity left upper outer quadrant lesion. (b) Post-contrast subtraction image. (c) Axial diffusion-weighted image with b value of 800 shows restricted diffusion in a 5 cm mass. (d) ADC map shows restricted diffusion (ADC_{mean}: 830×10^{-6} mm^2/s).
ADC: Apparent diffusion coefficient.

Relationships between Prognostic Factors, SUV_{max}, ADC_{mean} and SUV_{max}/ADC_{mean}

Univariate analysis showed that SUV_{max} and SUV_{max}/ADC_{mean} were significantly correlated with large tumor size (p=0.008 and p=0.002), Ki67 status (p<0.0001, p<0.0001). In terms of hormone receptor status; ER positivity was positively correlated with high SUV_{max} (p=0.0001) and SUV_{max}/ADC_{mean} (p=0.006). PR was positively correlated with ADC_{mean} (0.028). HER-2 positivity had no significant correlation (p>0.1) with SUV_{max} and ADC_{mean} (Table 5).

The relationships between clinical stage and HG, ADC_{mean}, SUV_{max}, and SUV_{max}/ADC_{mean} were evaluated with Spearman's Rho coefficient. SUV_{max} and SUV_{max}/ADC_{mean} had a positive significant association with the clinical stage (p=0.022 and r=0.159) and HG (p<0.0001 and r=0.347) (Fig. 3). However, ADC_{mean} had no significant correlation with clinical stage and HG. When histopathological subtypes were evaluated, IDC had higher SUV_{max} and SUV_{max}/ADC_{mean} values compared to invasive lobular carcinoma (ILC) (p=0.048).

DISCUSSION

The association between the SUV_{max}, ADC_{mean}, and pathologic prognostic factors in BC was analyzed previously.[5,13,14,17,18] In the current study, we also evaluated the effect of these parameters to the presence of distant metastasis in the initial diagnosis of BC and there is no previous study on this subject.

Relationships between SUV_{max} and ADC_{mean}

Our study with 209 invasive BC showed no correlation between SUV_{max} and ADC_{mean}. Similar to our study, many of the studies evaluating this relationship were also found no correlation between ADC_{mean} and SUV_{max}.[14,17,18] In contrast, few previous studies[5,13] showed that SUV_{max} and ADC_{mean} were inversely correlated. Among these studies, only Kitajima et al.[5] had a larger sample size (214 IDC patients) compared to our study and in that study, ADC_{mean} showed a weak inverse correlation with SUV_{max}.

In the study of Baba et al.[17] including malignant and benign breast tumors, a linear inverse correlation was found between SUV_{max} and ADC_{mean}. However, no

Table 1 Patient characteristics

	n=209	100%
Patients		
Female	207	99
Male	2	1
Mean age (years)	51.3±11.9	
Mean lesion diameter (mm)	34.4±17.8	
Tumor diameter <2cm	43	20.6
TNM Stage		
Stage I	4	1.9
Stage II	54	25.8
Stage III	68	32.6
Stage IV	83	39.7
Histopathology		
IDC	179	85.6
ILC	10	4.8
Other	20	9.6
Histologic grade		
Well-differentiated	17	8.1
Moderately differentiated	108	51.7
Poorly differentiated	84	40.2
Immunohistochemistry		
HER-2 positivity	72	34.4
ER positivity	163	78
PR positivity	77	36.8
Molecular subtypes		
Luminal A	40	19.2
Luminal B	127	60.8
Triple-negative	21	10
HER-2 type	21	10
Ki-67 ≧14%	168	80.4
Axillary lymph node metastasis	178	85.2

TNM: Tumor node metastasis classification; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; HER-2: Human epidermal growth factor receptor 2; ER: Estrogen receptor; PR: Progesterone receptor

correlation was observed when only malignant tumors were considered. Another finding determined by the author is that very high ADC values and high SUV_{max} do not show an inverse correlation in mucinous tumors and may affect the statistics. In these studies, we thought that differences between study subjects; sample size, histopathological subtypes, the inclusion of benign and *in situ* cases, may cause differences in the SUV_{max} and ADC_{mean} correlation results.

Relationships between SUV_{max} and Prognostic Factors

In our study, the relationships between SUV_{max} and ADC_{mean} values of primary breast tumor and clinicopathological prognostic factors were evaluated. We observed that high SUV_{max} was correlated with tumor size, ER, Ki-67, high HG, advanced TNM stage, histological subtype, and molecular subtype. These results are similar to previously published studies; SUV_{max} had a positive correlation with tumor size and high HG.[13,17,18] Contrary to our study, there is also a study showing that there is no relationship between HG and SUV_{max}.[19]

IDC is the most common type of invasive BC and the second most common tumor type is ILC. We observed a significant difference between SUV_{max} of the two groups of histologic types in line to previous studies.[20,21]

Higher SUV values were seen in tumors with a triple-negative hormonal profile in the current study, a finding consistent with the previous studies.[7,14,17] The majority of triple-negative tumors (80%) are the intrinsic basal type and this molecular subtype is associated with a poor prognosis due to the lack of hormonal markers used in targeted hormonal therapy.[14,17]

Ki-67 proliferation index is a marker of high mitotic activity and is useful for evaluating the degree of cellularity. Our study confirms a highly significant positive relationship between Ki-67 and enhanced glycolysis as determined by the measure of SUV_{max}, as observed previously.[14,20] Our study also demonstrated a strong correlation between ER negativity and high SUV_{max} values. SUV_{max} showed no significant correlation with HER-2 overexpression and PR positivity, as observed previously.[7,13,14,20,22,23]

Axillary LN positivity was not correlated with SUV_{max}. This finding was consistent with a previous study[17] but inconsistent with other studies.[13,18] However, our study had a larger sample size of all these studies.

Relationship between ADC and Prognostic Factors

In many studies comparing ADC in malignant and benign lesions of the breast, significantly lower ADC values and diffusion restriction were observed in malignant lesions. *In vivo*, perfusion is also important factor as microscopic motion that affects ADC. Increasing microvessels due to tumor angiogenesis in malignant lesions may cause an increase in ADC due to the perfusion effect.[24] Studies are showing that ER positivity causes high tumor cellularity and ER positivity causes low ADC values due to decreased intra-tumor perfusion by blocking the angiogenic pathway.[25,26]

In our study, we found a significant association between the low ADC values and ER positivity which is consistent with many of the previous studies.[11,18,24,27–30] We also observed a significant association between low ADC for PR-positive carcinomas as compared to PR-

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Table 2 Multiple logistic regression analysis for distant metastasis

	Favourable	Unfavourable	p	Exp(B)	Lower 0.95	Upper 0.95
Tumor size	≦2 cm	>2cm	0.02	2.75	0.17	6.47
HER-2 Status	Negative	Positive	0.0001	4.87	0.91	17.3
Histologic grade	1,2	3	0.067	3.97	2.46	9.66
PR status	Negative	Positive	0.014	2.32	1.18	4.54

HER-2: Human epidermal growth factor receptor 2; PR: Progesterone receptor

Table 3 Comparison of the ADC_{mean}, SUV_{max} and SUV_{max}/ADC_{mean} depending on distant metastasis

Distant metastasis	n	%	ADC_{mean}	SUV_{max}	SUV_{max}/ADC_{mean}
Absent	126	60.3	974±218	11.30±7.57	0.012±0.08
Present	83	39.7	944±187	13.48±9.74	0.014±0.011
p			0.352	0.09	0.06

SUV: Standardized uptake value; ADC: Apparent diffusion coefficient

Table 4 Comparison of the prognostic factors depending on the distant metastasis

Distant metastasis	Axillary LN metastasis		PR (+)		High Ki-67		Tumor >2cm		HER-2 (+)		ER (+)		HT**		High HG***	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Absent	95	76	31	24.6	100	79.3	92	72.2	23	18.2	99	78.5	105	83.3	59	47.6
Present	83	100	46	55.5	68	81.3	74	91.5	49	59	64	77.1	74	89.1	47	57.8
p	*		**0.00045**		0.64		**0.005**		**0.0004**		0.803		0.502		0.102	

*: Axillary LN metastasis was present in all of the 83 metastatic patients and it was unavailable to statistically compare between the two groups; **: Histopathologic type (HT) was evaluated in two groups: IDC and other type; ***: Histologic grade (HG): Grade 1 and 2 were defined as low grade, grade 3 was defined as high grade. IDC: Invasive ductal carcinoma; LN: Lymph node; PR: Progesterone receptor; HER-2: Human epidermal growth factor receptor-2; ER: Estrogen receptor

negative cancers (p=0.028). No relationship was found between Ki-67 and ADC values, supporting the similar studies.[25,30] HER-2 overexpression is associated with poor prognosis which is accompanied by angiogenesis and cellularity. Because of the increased cellularity, it can be expected low ADC values in HER-2 positive cases.[31] But in most of the studies investigating the relationship between ADC and HER-2, no correlation was found in line with our study.[11,18,28]

Ipsilateral axillary LN metastasis is the main predictor of long-term survival.[3,4] The presence of LN metastasis is very important in the decision to proceed with conservative therapy and ADC value would help staging of axillary LN non-inasively.[18] However, in the present study, ADC_{mean} was not correlated with LN metastasis in consistence with the previous studies.[17,18,24] A few studies with small sample sizes reported that a lower ADC_{mean} was associated with positive LN metastasis.[13,32]

Factors Affecting the Presence of Metastasis

In our study, tumor size, HER-2 overexpression, and PR positivity were determined as independent variables affecting the presence of metastasis in multivariate analysis.

Tumor size is a well-known and important prognostic factor of BC and increasing size of the breast tumor is associated with high metastatic potential and decreased overall survival.[4] Our study confirmed that the risk of distant metastasis is significantly higher in tumors larger than 2 cm, at the initial presentation.

The majority of BC cases are of the luminal-A subtype, which are hormone receptor-positive tumors (ER and/or PR) and these types of tumors are sensitive to hormonal therapies. However, cases with luminal BC constitute the majority of patients with distant metastases at the time of diagnosis and are frequently incurable. Recent studies revealed that invasiveness and metastasis of luminal BC are supported by the two isoforms of PR (PR-A and PR-B), in two different pathways. As a

Table 5 Associations of SUV_{max}, ADC_{mean}, and SUV_{max}/ADC_{mean} with clinicopathologic prognostic factors

	n	%	SUV_{max} Mean±SD	p	ADC_{mean} ($\times10^{-6}$) Mean±SD	p	SUV_{max}/ADC_{mean} Mean±SD	p
Tumor size								
≦2 cm	43	20.6	9.11±5.53	**0.0008**	1012±239	0.18	0.009±0.004	**0.002**
> 2cm	166	79.4	12.95±9.04		950±196		0.014±0.01	
ER status								
Positive	163	78	10.86±7.39	**<0.0001**	946±215	**0.012**	0.012±0.009	**0.006**
Negative	46	22	16.77±10.61		1021±161		0.016±0.011	
PR status								
Positive	77	36.8	13.14±8.65	0.103	923±204	**0.028**	0.015±0.011	**0.023**
Negative	132	63.2	11.59±8.46		985±205		0.012±0.009	
HER-2 status								
Positive	72	34.4	13.66±9.86	0.12	963±192	0.79	0.014±0.011	0.12
Negative	137	65.6	11.38±7.68		962±214		0.012±0.009	
Triple-negative								
Absent	188	90	10.13±5.91	**0.021**	932±236	0.077	0.012±0.010	0.091
Present	21	10	17.48±12.22		1055±160		0.017±0.012	
Ki-67 index status								
<14%	41	19.6	8.46±6.73	**<0.0001**	961±219	0.96	0.009±0.007	**<0.0001**
≧14%	168	80.4	13.06±6.73		963±204		0.0014±0.0010	
Histologic grade								
Grade 1	17	8.1	6.43±3.51	**<0.0001**	965±216	0.719	0.0084±0.006	**<0.0001**
Grade 2	108	51.7	10.75±5.66		653±202		0.0092±0.0057	
Grade 3	84	40.2	13.47±5.58		970±203		0.0013±0.009	
Histology								
IDC	179	85.6	12.63±8.83	**0.042**	952±195	0.055	0.013±0.010	**0.023**
ILC	10	4.8	6.81±3.75		986±196		0.007±0.005	
Others	20	9.6	10.66±6.7		1039±295		0.0011±0.007	
Axillary LN metastasis								
Absent	31	14.8	9.64±6.03	0.083	978±282	0.9	0.01±0.007	0.79
Present	178	85.2	12.60±8.85		960±192		0.013±0.010	
Stage								
I	4	1.9	4.32±3.20	**0.0022**	974±218	0.197	0.0078±0.005	**0.009**
II	54	25.8	8.96±3.68		968±227		0.009±0.007	
III	68	32.5	9.12±4.79		962±236		0.0011±0.007	
IV	83	39.7	11.30±5.75		758±135		0.0013±0.0009	

SUV: Standardized uptake value; ADC: Apparent diffusion coefficient; SD: Standard deviation; ER: Estrogen receptor; PR: Progesterone receptor; HER-2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; LN: Lymph node

result of these studies, PR-A has the main responsibility in promoting invasiveness and metastasis by suppressing estrogen/ER action. Overexpression of PR-A is associated with increased invasiveness of BC and decreased disease-free survival.[33,34] In our study, a highly significant positive correlation was found between PR positivity in the breast tumor and the presence of distant metastasis at the time of diagnosis.

HER-2 oncoprotein is responsible for cancer development by stimulating cell proliferation. HER-2 also increased angiogenesis through up-regulation of vascular endothelial growth factor (VEGF) and increasing microvascular density of the tumor accompanied by increasing invasion and metastasis.[17,18,30] Our study showed that HER-2 overexpression of BC seen in 49 patients was positively and strongly associated with distant metastasis (Table 4). HG has been accepted as a prognostic factor for metastasis in the previous studies depending on tumor size.[4] In this study, HG was included in the multiple logistic regression analysis since $p<0.1$ in univariate analysis, but it was not an independent risk factor for the presence of distant metastases.

SUV_{max}/ADC_{mean} is a combination of these parameters and it was more accurate than either SUV_{max} and

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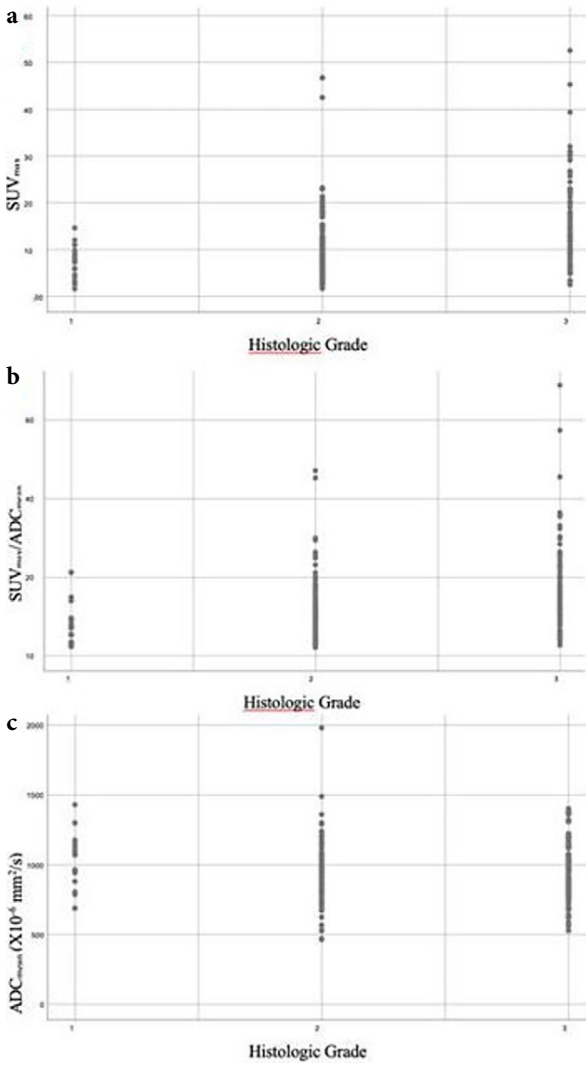

Fig. 3. Histogram plot demonstrated the relationships between HG, ADC_{mean}, SUV_{max}, and SUV_{max}/ADC_{mean}. In Spearman's Rho coefficient, SUV_{max} (a) and SUV_{max}/ADC_{mean} (b) had a positive significant correlation with HG ($p<0.0001$ and $r=0.347$), however, ADC_{mean} had no significant correlation ($p=0.719$) with clinical stage and HG (c).

HG: Histologic grade; ADC: Apparent diffusion coefficient; SUV: Standardized uptake value.

ADC_{mean} for demonstrating the relationships with prognostic factors. SUV_{max}/ADC_{mean} was previously used in the study of Baba et al.[17] and was found useful in differentiating benign from malignant breast tumors. In our study, this ratio did not differ significantly between patients with and without distant metastases (Table 3).

This study has some limitations. First, it was performed retrospectively in a single institution. Second, metastases were evaluated only at the time of diagnosis, and metastases developed during treatment and maintenance were not evaluated due to the short follow-up period.

Third, since FDG-PET/CT is only applied to advanced-stage BC patients in our center, the number of early-stage patients was relatively low.

CONCLUSION

Both SUV and ADC are helpful parameters in determining patient prognosis in BC. There was no correlation between SUV_{max} and ADC_{mean} as they are parameters based on different biological characteristics of the tumor, but both values have a complementary role in evaluating prognosis. When SUV_{max} and ADC_{mean} values were evaluated separately in pre-treatment imaging, they were not associated with the presence of metastases, but the SUV_{max}/ADC_{mean} ratio may be a helpful marker in predicting the presence of distant metastases. HER-2 positivity, PR positivity, and tumor size were found to be significantly associated with the presence of distant metastasis at the time of diagnosis. These findings may contribute to determining the metastasis potential of the tumor and selecting the most promising therapeutic approach in BC.

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