



Meme Kanserinde ADC Değerleri ile Histopatolojik Prognostik Faktörler Arasındaki İlişkinin Değerlendirilmesi

Relationship Between ADC Values and Histopathological Prognostic Factors in Breast Cancer

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Öz

GİRİŞ ve AMAÇ: Meme kanserinde difüzyon MR, lezyonun morfolojisi yanında, metabolik aktivitesi hakkında da bilgi vermektedir. Patolojik prognostik faktörler meme kanserli olgularda tedavi protokolünü ve sağ kalımı etkilemektedir. Bu çalışmada amacımız, meme kanserli olgularda ADC değerleri ile patolojik prognostik faktörler arasında ilişkinin değerlendirilmesidir.

YÖNTEM ve GEREÇLER: Kliniğimizde, meme kanseri tanısı ile preoperatif olarak Meme MR tetkiki yapılan 33 olgu retrospektif olarak değerlendirildi. 33 olguda toplam 44 malign kitle vardı. Tüm olguların post-operatif patoloji sonuçları elde edildi. Post-op histopatolojik spesmenlerde tümör çapı, aksiller lenf nodu durumu, histolojik grade klasik prognostik faktörler olarak ve östrojen reseptör durumu, progesteron reseptör durumu moleküler prognostik faktörler olarak değerlendirilmiştir. Difüzyon meme MR özellikleri ile klasik ve moleküler histopatolojik prognostik faktörler arasındaki ilişki Mann Whitney U test, Kruskal Wallis test and Spearman korelasyon analizi kullanılarak değerlendirildi.

BULGULAR: ADC değerleri, aksiller lenf nodu tutulumu 3'den az olan olgularda (N1) aksiller lenf nodu tutulumu 4 ve/veya daha fazla olan olgulara (N2-N3) göre anlamlı düzeyde yüksek bulundu (p=0,011; p=0,010; p<0,05).

TARTIŞMA ve SONUÇ: Sonuç: Düşük ADC değerleri lenf nodu tutulumuyla ilişkiliydi.

Anahtar Kelimeler: Difüzyon, Meme Kanseri, Manyetik Rezonans Görüntüleme

Abstract

INTRODUCTION: To evaluate the relationship between ADC values and histopathological prognostic factors in breast cancer patients. Materials and Methods A total of 33 female breast cancer patients with preoperative breast MRI image were retrospectively evaluated. There were a total of 44 malignant masses in 33 patients.

METHODS: In postoperative evaluation of histopathological specimens, conventional prognostic factors used were the tumor diameter, axillary lymph nodes and histological grade, and the molecular prognostic factors used were estrogen and progesterone receptor expression, C-erb-B2. In diffusion MR with a b-value of 1000s/mm² and 1500 s/mm², the relationship between apparent diffusion coefficient (ADC) and conventional and molecular histopathological prognostic factors was evaluated by using statistical methods such as Mann Whitney U test, Kruskal Wallis test and Spearman correlation analysis.

RESULTS: ADC was significantly lower in patients with 4 and/or more axillary lymph nodes involvement (N2-N3) compared to those with <3 axillary lymph nodes involvement (p=0.011; p=0.010; p<0.05).

DISCUSSION and CONCLUSION: Lower ADC values are related with axillary lymph node involvement.

Keywords: Diffusion, Breast Neoplasm, Prognosis

INTRODUCTION

Breast cancer is the most common of the cancer-related mortality in females following the lung cancer (1). Breast cancer is a heterogeneous disease with different molecular properties, biological behaviors, clinical courses and prognosis (1-2). Breast MRI images can give information about morphologic and dynamic properties of the lesion and is usually used for the lesions that could not be evaluated with other imaging methods, in the evaluation of multicentricity and bilaterality, in identifying the recurrent-residual lesions and for differentiation of the lesions such as scar tissue, fat necrosis and granulation tissue (3,4). The use of diffusion MRI in the breast is increasing in recent years, because it gives information about the morphology as well as microstructural characteristics of the lesion. In malignant lesions, diffusion restriction increases and ADC-value decreases with the increased b-value.

In patients with breast cancer, recent studies have been found in the literature on the relationship between the data obtained from preoperative breast MRI and the prognostic factors determined on postoperative evaluation of pathological specimens. These studies have particularly studied the morphological features on conventional breast MRI and have reported similar results (1,5,6). Although the relationship between the diffusion breast MRI and histopathological prognostic factors was studied in recent years (2,7-11). Some studies have reported that diffusion MRI images can be used to differentiate and to characterize the benign and malignant breast lesions and that ADC values may be associated with prognostic factors (2,7-11).

The purpose of the present study was to evaluate the relationship between ADC values and conventional (tumor size, axillary lymph node involvement, histopathological grade, multifocal disease and lymphovascular invasion) and molecular (estrogen and progesterone receptors, Her-2) prognostic factors for breast cancer.

METHODS

Ethics committee approval was received from the İstanbul Kartal Dr. Lütfi Kırdar Education and Research Hospital Scientific Research and Science Board with the decision dated 05.02.2013 and numbered 8951337/1009/123 for the study.

Patients

The consecutive patients with a diagnosis of invasive breast cancer in whom preoperative MRI had been obtained were included in the study. We excluded patients with only in situ tumors in the study. Also in order to avoid any alteration in tumor tissue due to histology or grading, the patients in whom MRI was obtained during/after neoadjuvant chemotherapy were excluded from the study. A total of 33 female breast cancer patients were included in the study. There were a total of 44 malignant masses in 33 patients.

Breast MRI imaging protocol

Breast MR imaging was performed on a 1.5T imager (Intera, Philips Medical Systems, Best, The Netherlands) with a dedicated double breast four-channel surface coil and bilateral scans. Before the examination, a needle for intravenous administration of contrast agent was placed in cubital vein. Patient was placed in a comfortable prone position. Transverse T2-weighted fat suppressed spin echo sequence (TE/TR 110/7548 ms; inversion delay SPAIR 80 ms; flip angle 90°; FOV 380x380mm², acquired voxel size 1.06x1.74x3.0 mm³, reconstructed voxel size 0.94x0.94x3.00 mm³, total acquisition time 242s) was performed before administration of contrast material. DWI axial sequence: TR, 8000ms; TE, 82ms; 116x123 matrix; thickness, 4mm; FOV, 32cm; parallel acquisition factor: 2.0; and NEX, 2. DWI was acquired before dynamic sequences, with a spin-echo echoplanar imaging (EPI) sequence in the axial plane. Sensing diffusion gradients were applied sequentially in the x, y and z directions, with b values of 0, 1000 and 1,500 s/mm². A transverse three-dimensional high-resolution T1-weighted sequence (TE/TR 110/7548 ms; inversion delay SPAIR 80 ms; flip angle 90°; FOV 380x380mm², acquired voxel size 1.06x1.74x3.0 mm³, reconstructed voxel size 0.94x0.94x3.00 mm³, total acquisition time 242s) was performed before administration of contrast material. DWI axial sequence: TR, 8000ms; TE, 82ms; 116x123 matrix; thickness, 4mm; FOV, 32cm; parallel acquisition factor: 2.0; and NEX, 2. DWI was acquired before dynamic sequences, with a spin-echo echoplanar imaging (EPI) sequence in the axial plane. Sensing diffusion gradients were applied sequentially in the x, y and z directions, with b values of 0, 1000 and 1,500 s/mm². A transverse three-

dimensional high resolution high-resolution T1-weighted fast gradient echo fat-suppressed sequence [TE/TR 2.4/4.6 ms; inversion delay spectral presaturation attenuated by inversion recovery (SPAIR) 90ms; flip angle 10°; FOV 360x360 mm², acquired voxel size 0.9x0.9x2.5 mm³, reconstructed voxel size 0.83x0.83x2.50mm³, total acquisition time 60s] was performed before administration of contrast agent, followed by repeat performance of this same sequences at 0, 1, 2, 3, 4, 5 and 6 min. After administration of contrast agent. Postcontrast three-dimensional T1-weighted fast gradient echodynamic MR images were acquired after administration of 0.1mmol/kg GD-DTPA (gadolinium diethylene triamine-pentaacetic acid dimeglumine). Contrast medium was injected with a 10s timing delay into the antecubital vein with an 18-20G needle at a flow rate of 2ml/s followed by a flush of 20ml of saline-solution.

Image Interpretation

Breast MRI images were evaluated by two radiologists having at least 5 years of experience in breast MR imaging. The greatest diameter of the tumor was considered for statistical analysis. The place of circle ROI (region of interest) was determined by the consensus of two radiologists. A single ROI with 5-10 mm² was manually drawn around the borders of the target lesion on the b=1,000 and 1500s/mm² DWI. Care was taken to avoid apparent necrotic or cystic components by referring to other MRI images [13-19]. We obtained two ADC map (b-1000 and b-1500) and we compared them.

Pathological examination

Histopathological evaluation was performed by two pathologists having at least 5 years of experience in breast histopathology. Conventional prognostic factors were determined as tumor size, axillary lymph node involvement, multicentricity, histological and nuclear grades, and lymphovascular invasion. On the other, molecular prognostic factors were ER/PR expression, C-erb-B2.

All areas of the preparation were evaluated in the tumor cell for ER and PR, expression. Only the stained areas limited to the nuclei are considered as positive. The intense-, normal-, and weak stained cells were multiplied by 3, 2 and 1 respectively to calculate a total score with a maximum of 300 points. Those with a score of <30 were considered as negative.

Characteristic membranous (Chicken-Wire) staining was considered as positive for C-erb-B2. The cells with no staining or weak staining in <10% of the cells were scored as 0=negative, those with weak staining in >10% cells were 1+(negative), those with weak-moderate staining in >10% cells were 2+(unclear), those with moderate-intense staining in <30% cells were 2+(unclear), and those with moderate-intense staining in >30% cells were 3+ (strongly positive).

Estrogen and progesterone receptors were determined as positive or negative, and C-erb-B2 protein (Her-2/neu) was determined as negative, unclear or strongly positive.

Histological grade was determined by using modified Bloom-Richardson-Elston system which includes the nuclear polymorphism, tubule formation and mitosis parameters. Each parameter was scored from 1 to 3 obtain a total score.

Tubule formation was scored as atubule formation of >75%(=1), 10-75%(=2) or <10%(=3).

Nucleus size was scored as follows: 1=equal to the normal ductus epithelium, 2=medium-sized, and 3=large nucleus.

Mitosis was scored on 10 bba (X400 magnification, 0.186 mm²:2/3) as a mitosis count of 0-7(=1), 8-14(=2) or >14(=3).

Nuclear grade was determined according to modified Black system as follows: for nucleus diameter, 1=small, 2=medium and 3=large; for nucleus shape, 1=regular and 2=irregular; for pleomorphism, 1=low, 2=medium and 3=high; for nucleus, 1=not distinguished, 2=distinguished and 3=clear. Nuclear grade was grade I for a total

score of 4-6, grade II for 7-8 and grade III for 9-11.

Statistical analysis

Statistical analysis was performed by using NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). In addition to the descriptive statistics (mean, standard deviation, median, frequency and ratio), Mann Whitney U test was used for the two –group comparison of quantitative parameters with no normal distribution. For the comparison of three or more groups with no normal distribution, Kruskal Wallis test was used, followed by Mann Whitney U test to determine the group responsible from the difference. Spearman correlation analysis was used to evaluate the association between the parameters. Statistical significance set at $p < 0.01$ and $p < 0.05$.

RESULTS

A total of 33 female breast cancer patients who had a preoperative breast MRI image were included in the study. Study patients aged 37-76 years with a mean age of 53 years. There were a total of 44 malignant masses in 33 patients.

Histologic Analysis

The pathology report was invasive ductal carcinoma in 40 patients (91%), invasive lobular carcinoma in 3 (6.8%) and ductal carcinoma in situ with an invasive component in 1(2.2%).

Tumor size ranged from 4 to 50 mm with a mean size of 20.00 ± 10.94 mm. Tumor size was < 2 cm in 52.3% of the patients ($n=23$) and 2-5cm in 47.7%($n=21$).

Prognostic factors are summarized in Table 1. As a histological grade, there were 7 patients (15.9%) with grade 1, 13(29.5%) with grade 2, and 24(54.6%)with grade 3 lesions.

In 23of the 44 lesion (52.3%), one or more lymph node involvement was found at histopathologic examination. Of the cases, 47.7%($n=21$) had no

axillary lymph node, 22.7%($n=10$) had 1-3, 20.5% ($n=9$) had 4-9 and 9.1% ($n=4$) had more than 9 axillary lymph nodes. Lymph node involvement is summarized in Table 1.

In our series, 88.6% of the tumors were (39/44) ER-positive and 68.2% (30/44) were PR-positive. Thirty-two lesions showed negative (0,1+) c-erbB-2 protein findings, and 12 patients showed positive findings (2+,3+). The median percentage of K6-67 expression was 14.0%.

ADC Value Analysis

The mean ADC-1000 value of all malignant lesions was $0.96 \times 10^{-3} \text{mm}^2/\text{s}$ (range $0.58-1.90 \times 10^{-3} \text{mm}^2/\text{s}$, SD $0.21 \times 10^{-3} \text{mm}^2/\text{s}$). The mean ADC-1500 value of all malignant lesions was $0.80 \times 10^{-3} \text{mm}^2/\text{s}$ (range $0.51-1.60 \times 10^{-3} \text{mm}^2/\text{s}$, SD $0.18 \times 10^{-3} \text{mm}^2/\text{s}$) (Figs.1,2).

There was no significant correlation between the ADC value and conventional prognostic factors of age, tumor size and histologic/nuclear grades. Relation between ADC values and Prognostic Factors are summarized in Table 1. However, there was a statistical difference between axillary lymph node involvement and ADC 1000 and ADC 1500 values (ADC 1000 $p=0.017$; $p < 0.05$; ADC 1500 $p=0.019$; $p < 0.05$). Namely, according to the two-group comparisons, there was no significant difference in ADC -1000 and ADC-1500 values between patients with no axillary lymph node involvement compared to those with 1-3 lymph nodes involvement ($p < 0.05$). Although ADC-1000 value in patients with no axillary lymph node involvement was higher compared to those with 4-9 or > 9 axillary lymph node involvement, it did not reach statistical significance (ADC 1000 $p=0.055$; $p=0.053$; $p > 0.05$; ADC 1500 $p=0.063$; $p=0.075$; $p > 0.05$). ADC-1000 and ADC-1500 values in patients with 1-3 axillary lymph node involvement was significantly higher compared to those with 4-9 or > 9 axillary involvements (ADC 1000 $p=0.011$; $p=0.010$; $p < 0.05$; ADC 1500 $p=0.014$; $p=0.016$; $p < 0.05$). There was no significant difference in ADC-1000 and ADC-1500 values between patients with 4-9 axillary involvement and those with > 9 axillary involvements($p > 0.05$).

There was no significant correlation between the ADC value and molecular prognostic factors, including ER, PR, c-erbB-2.

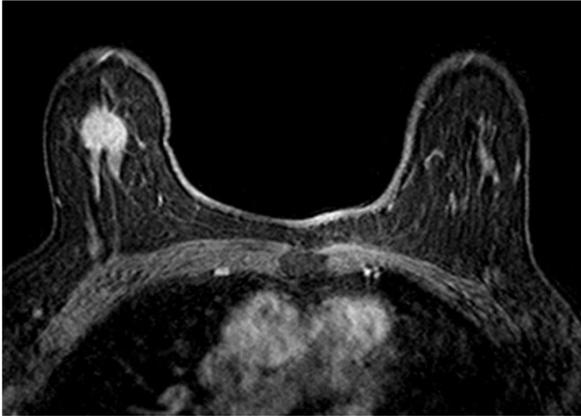


Fig. 1a

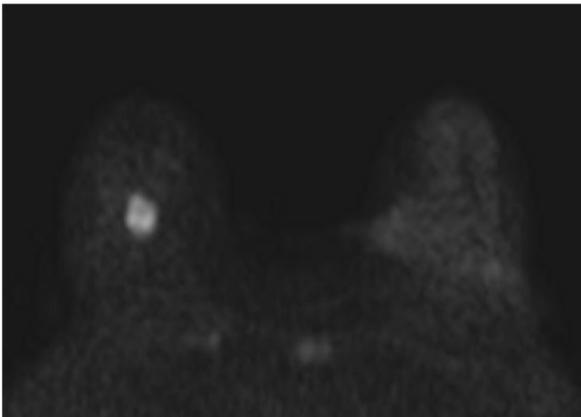


Fig. 1b

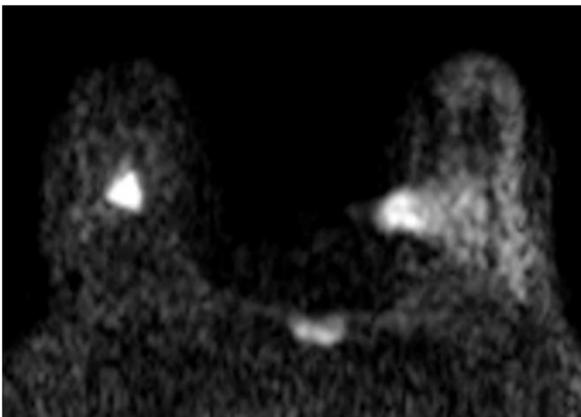


Fig. 1c

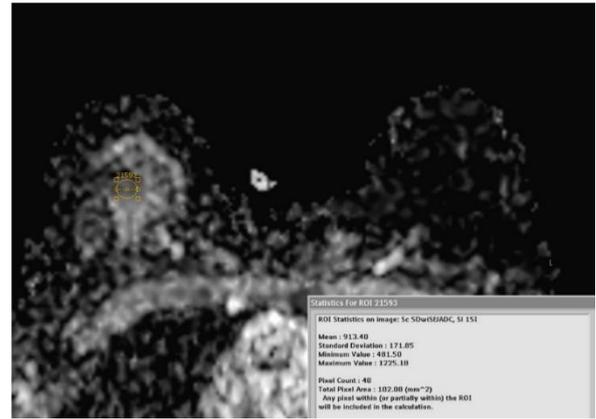


Fig. 1d

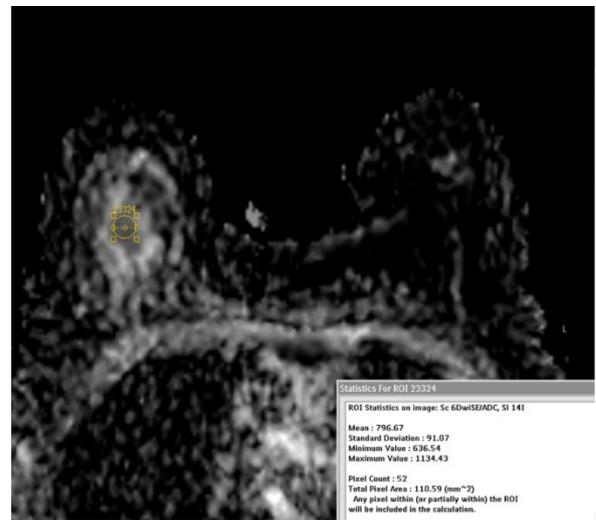


Fig. 1e

Figure 1. A 50-year-old woman with breast cancer, diagnosed as invasive ductal carcinoma, histological grade 2, ER (-), PR (+), C Erb B2 3 (+). T1 weighted axial contrast enhanced images (a) shows mass with spiculated margins in the right breast. High signal intensity was detected in the right breast on b1000 and b1500 DWI (b, c). The ADC value was found to be $0.91 \times 10^{-3} \text{mm}^2/\text{s}$ on ^{1000}ADC map (d), $0.79 \times 10^{-3} \text{mm}^2/\text{s}$ on ^{1500}ADC map (e).

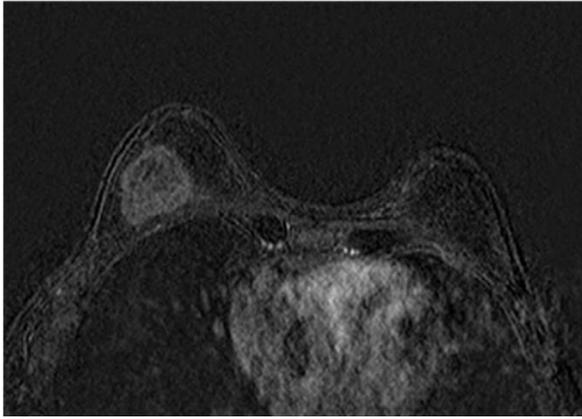


Fig. 2a

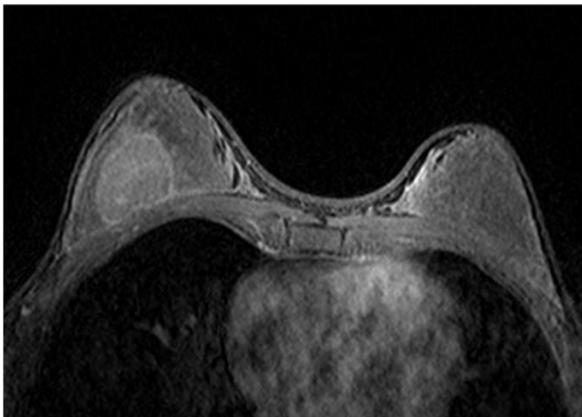


Fig. 2b

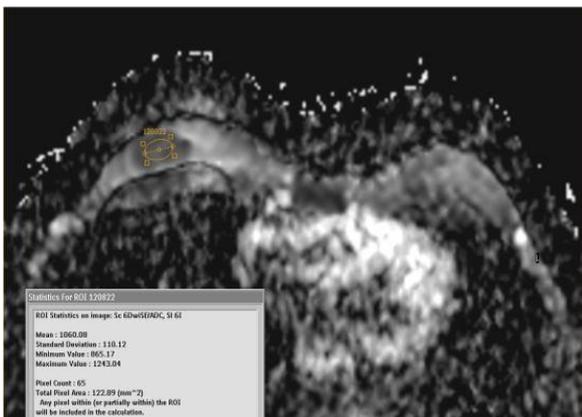


Fig. 2c

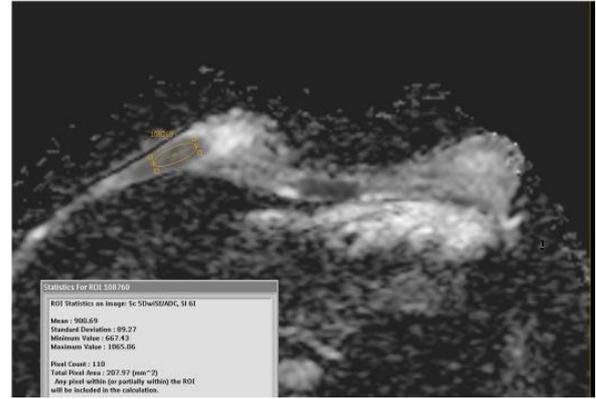


Fig. 2d

Figure 2: A 25-year-old woman with breast cancer diagnosed as invasive ductal carcinoma, histological grade 2, ER / PR (+), C Erb B2. T1 weighted axial contrast enhanced and subtraction (3-1) images (a, b) shows mass in the right breast. The ADC value was found to be $1 \times 10^{-3} \text{mm}^2/\text{s}$ on b1000 ADC map (c), $0.9 \times 10^{-3} \text{mm}^2/\text{s}$ on b1500ADC map (d).

DISCUSSION

Breast cancer is a heterogenous disease characterized by varying molecular features, biological behavior, clinical course and prognosis (1-2). Therefore, it is important to identify the conventional and molecular prognostic factors in these patients in order to determine the appropriate therapy to increase the survival (19-20). There is evidence that the progression of malignant tumours does not depend exclusively on the cancer cells; it is also influenced by the tumour microenvironment. The tumour microenvironment is a complex system that includes tumour cells, stromal cells (such as adipocytes, fibroblasts, endothelial cells, and infiltrating immune cells), and extracellular matrix. Diffusion MR imaging has been shown to have potential in the detection and characterization of breast malignancies, based on its ability to characterize tissue microstructures (3,4,21,22). Microscopic movement is influenced by the molecular diffusion of the water and microcirculation of blood (23,28). On the other hand, diffusion of the water is influenced by cellularity, viscosity, intracellular and extracellular membrane permeability, active transportation, flow and structural arrangement (23,29,30). ADC is a measurable value and many previous studies have showed marked diffusion

restriction and lower ADC values in malignant lesions compared to benign lesions (24,25,28,29,31-35). Restricted diffusion and thus lower ADC values are due to high cellularity in cancer tissue, large-nuclei numerous macromolecular protein content and narrowed extracellular distance (27,31).

Many previous studies have showed a significant association between morphological and kinetic properties of the mass lesions on conventional breast MRI and several poor prognostic factors in breast cancer (1,6,36-38). More recent studies have reported that ADC value measured by Diffusion breast MRI is effective in identifying the cancer tissue and the menstruation-related changes in normal breast parenchyme (23). Malignant tumors show lower ADC values compared to benign lesions (23,29,39). In these studies, authors have also investigated the association between ADC value of the cancer tissue and prognostic factors for breast cancer. However, there are conflicting results in the literature about the association between ADC value on diffusion MRI and prognostic factors for breast cancer (7,9-11,23).

In our study, there was no significant correlation between the ADC value and conventional prognostic factors, including age, tumor size and histologic/nuclear grades. Another conventional prognostic factor, the axillary lymph node involvement is the most important factors used to predict the prognosis of breast cancer (36). In our study, ADC-1000 and ADC-1500 values were found to be significantly higher in patients with 1-3 axillary lymph node involvement (N1) compared to those with 4-9 (N2) and >10 (N3) axillary lymph node involvement. However, there was no significant difference in ADC-1000 and ADC-1500 values between the patients with no nodal involvement (N0) and N1 patients. Similarly, ADC-1000 and ADC-1500 values did not differ between patients with 4-9 and >9 axillary lymph nodes. According to the TNM staging system regardless of what is T (primary tumor), N2 and N3 patients (4 or more nodal involvement) are classified as stage 3 or more. As a result, lower ADC values found in N2 and N3 patients

compared N0 and N1 patients indicates its association with poor prognostic factors.

Similar to our results, Abdel Razek (9) and Paola Belli et al. (2) have also reported a correlation between low ADC values and positive axillary lymph nodes. On the other hand, in contrast to our results, Takashi Kamitani et al. (10) have found higher ADC values in patients with positive axillary lymph nodes. In the study by Sung Hun Kim et al. (23), ADC values were not correlated with lymph node involvement. This may be due to the fact that authors have included the subgroups of mucinous and medullar cancers which are usually associated with high ADC values. It has been already reported that ADC values are higher in mucinous and medullar cancer due to the inflammation associated with higher cellularity (18). There were no patients with mucinous or medullar cancer in our study. We included only the patients with invasive ductal and invasive lobular carcinoma as well as in situ carcinomas with an invasive component.

In our study, there was no significant correlation between the ADC value and molecular prognostic factors, including ER, PR, c-erbB-2. Similarly, Sung Hun Kim et al. (23) have found no correlation between ADC value and ER/PR expression. On the other hand, in the studies by Takashi Kamitani et al. (10) Laura Martincich et al. (7) and SY Choi et al. (11), ER expression was correlated with low ADC values. Similar to our study, SY Choi et al. (11), Sung hun Kim et al. (23) and Takashi Kamitani et al. (10) have also reported no correlation between C-erb-B2 and ADC values. However, Laura Martincich et al. (7) reported a correlation between low ADC values and negative C-erb-B2 values.

Limitations of our study the relative inadequacy in the number of patients as well as lack of a standard b value for diffusion MRI, resulting in conflicting results in previous studies using different b values. Moreover, size of the tumor was <1cm in 7 and <2cm in 24 out of 44 lesions. In small lesions, 3T DW MRI is more effective than 1.5T MRI in identifying a lesion. Because we used 1.5T MRI in our study, the reliability is low for

small lesions. On the other hand, Marini et al. (29) have found that ADC values are lower in patients with invasive ductal carcinoma compared to those with other cancer types and we had 3 invasive lobular carcinoma patients in our series. Thus larger and homogeneous patient series are needed for future studies.

In conclusion, ADC value was found to be significantly lower in patients with N2 and N3 disease (axillary lymph node involvement of 4 or more) compared to those with N1 disease (axillary lymph node involvement < 3) according to TNM staging system. Despite the lacking the number of the study results of the present study suggest that low ADC value is correlated with lymph node involvement and thus with poor prognosis.

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The Authors declares that there is no conflict of interest.

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Tablo 1. Relation Between ADC Value and Prognostic Factors

Factors	Number of Lesions (n:44)	ADC 1000	p	ADC 1500	p
		Min-Max/Mean±SD/Median (X10 ⁻⁵ mm ² /s)		Min-Max/Mean±SD/Median (X10 ⁻⁵ mm ² /s)	
Axillary Lymph Node Metastasis					
Negative (-)	21(47.7%)	0,58-1,90/0,99±0,27/1,00	^a 0,017*	0,51-1,60/0,83±0,22/0,81	^a 0,019*
1-3 positive node (+)	10(22.7%)	0,89-1,30/1,04±0,14/1,00	^a 0,017*	0,68-1,00/0,87±0,11/0,87	^a 0,019*
4-9 positive node (+)	9(20.5%)	0,70-1,00/0,86±0,10/0,82	^a 0,017*	0,62-0,88/0,72±0,10/0,72	^a 0,019*
>9 positive node (+)	4(9.1%)	0,80-0,90/0,84±0,05/0,83	^a 0,017*	0,59-0,75/0,68±0,07/0,69	^a 0,019*
Histologic Grade					
Grade 1	7(15.9%)	1,00	^a 0,348	0,83	^a 0,442
Grade 2	13(29.5%)	0,90	^a 0,348	0,75	^a 0,442
Grade 3	24(54.6%)	0,95	^a 0,348	0,81	^a 0,442
Nuclear Grade					
Grade 1	3(6.8%)	1,10	^a 0,174	0,91	^a 0,370
Grade 2	20(45.5%)	0,90	^a 0,174	0,78	^a 0,370
Grade 3	24(47.7%)	0,93	^a 0,174	0,82	^a 0,370
Lymphovascular invasion					
(+)	21(47.7%)	0,99	^b 0,868	0,81	^b 0,814
(-)	23(52.3%)	0,90	^b 0,868	0,80	^b 0,814
Esrogen Receptor (ER)					
(+)	39(88.6%)	0,93	^b 0,456	0,79	^b 0,365
(-)	5(11.4%)	0,90	^b 0,456	0,82	^b 0,365
Progesterone Receptor (PR)					
(+)	30(68.2%)	0,90	^b 0,275	0,78	^b 0,512
(-)	14(31.8%)	1,00	^b 0,275	0,82	^b 0,512
C-erbB-2 Protein					
0	28(63.7%)	0,98	^a 0,710	0,80	^a 0,291
1+	4(9.1%)	1,00	^a 0,710	0,85	^a 0,291
2+	2(4.5%)	0,91	^a 0,710	0,63	^a 0,291
3+	10(22.7%)	0,90	^a 0,710	0,80	^a 0,291

^aKruskal-Wallis Test ^bMann-Whitney U Test *p<0,05