

# The role of apparent diffusion coefficient values in the differential diagnosis of breast lesions in diffusion-weighted MRI

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## PURPOSE

We aimed to determine the apparent diffusion coefficients (ADCs) of focal breast lesions on diffusion-weighted magnetic resonance imaging (DW-MRI) and to evaluate whether ADC measurement can be used to characterize lesions as benign or malignant.

## MATERIALS AND METHODS

Fifty-one patients between the ages of 18–79 years (mean age, 48.5 years) with 51 histopathologically verified breast lesions were included in this study. The patients were examined with a 1.5 Tesla system using a bilateral phased-array breast coil. Spin-echo echo-planar imaging was used. The images were obtained with b values of 50, 400, and 800 s/mm<sup>2</sup>. The ADC values were calculated for breast lesions and for normal fibroglandular tissue. Receiver operating characteristics analyses were performed to find the threshold ADC values.

## RESULTS

The mean ADC was  $1.42 \pm 0.17 \times 10^{-3}$  mm<sup>2</sup>/s for normal fibroglandular tissue,  $1.9 \pm 0.45 \times 10^{-3}$  mm<sup>2</sup>/s for benign lesions, and  $0.86 \pm 0.26 \times 10^{-3}$  mm<sup>2</sup>/s for malignant lesions. The threshold ADC value to differentiate benign and malignant lesions was  $1.03 \times 10^{-3}$  mm<sup>2</sup>/s (sensitivity, 88.5%; specificity, 100%). With the ADC ratio (lesion to normal fibroglandular tissue), the threshold was 0.8 (sensitivity, 91.4%; specificity, 100%). The ADC value obtained from malignant lesions was statistically different from that of benign lesions ( $P < 0.001$ ).

## CONCLUSION

Diffusion-weighted imaging can be used to differentiate malignant and benign breast lesions.

**B**reast cancer is one of the leading causes of death from cancer in women (1). The use of magnetic resonance imaging (MRI) has a relatively short history for the diagnosis of breast lesions. Breast MRI—as a different diagnostic tool from mammography and ultrasonography (US)—can show tissue perfusion characteristics of the masses on breast parenchyma, as well as morphologic features, such as the contour, size, and shape of the breast lesions. Although conventional MRI sequences have an important role in the differential diagnosis of breast masses, this technology has a low specificity, thus requires the support of additional imaging techniques (2–4). Diffusion-weighted MRI (DW-MRI) is an active field of research in MRI. In addition to diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC) maps can be created, and quantitative measurements can be performed. Recent studies have shown a high accuracy rate in the differentiation between malignant and benign breast lesions using DW-MRI and ADC measurements (5–7). The measured ADC values were significantly lower in malignant lesions compared with benign lesions. Malignant breast tumors show a high amount of cellular structure (due to the intensity of the tumor tissue), resulting in low ADC values for these lesions (5–7).

The aim of this study was to evaluate the value of DWI and ADC values in the differential diagnosis of benign and malignant breast lesions.

## Materials and methods

### Patient selection

Patients with a suspicious mass diagnosed with mammography or US that were considered for a biopsy procedure were included in this prospective study.

The local ethics committee approved the study, and informed written consent was obtained from each patient.

Seventy patients who had a suspicious lesion on mammography or US according to Breast Imaging-Reporting and Data System (BI-RADS) criteria and who were recommended for biopsy procedure were included in the study. All patients had MRI prior to the biopsy procedure. DWI and ADC values were compared with the histopathology results (which were taken as gold standard). The patients who had general contraindications for magnetic resonance (MR) examination and contrast-medium injections, patients who rejected MR examination, patients who had cysts, patients who had noisy or nondiagnostic DWI examinations due to motion artifacts, and patients who refused to undergo a biopsy were excluded from the study. Nineteen of 70 patients were excluded from the study: 14 were excluded because their masses were found to be complicated cysts on MRI, two patients were excluded from the study because their DW-

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MRI sequences did not have diagnostic quality due to motion artifacts, and three were excluded because they did not accept a biopsy procedure. Hence, 51 (49 women, 2 men) patients were included in the study. The patients' ages varied between 18 and 79 years (mean age, 48.5 years).

### MRI

All MRIs were obtained using a 1.5 Tesla MR (Magnetom Symphony, Siemens Healthcare, Erlangen, Germany) with a four-channel CP Breast Array coil. Conventional sequences of routine breast MRI were performed for all patients. The sequences used for the conventional MRI sequences were axial fat-suppressed T2-weighted (TR/TE, 4180/72 ms; slice thickness, 3 mm; matrix, 340×512), axial T1-weighted (TR/TE, 542/13 ms; slice thickness, 3 mm; matrix, 340×512), and contrast-enhanced three-dimensional dynamic fat-suppressed axial T1-weighted fast low-angle shot sequences (TR/TE, 4.4/1.6 ms; flip angle, 12°; slice thickness, 1 mm; matrix, 320×512). One precontrast sequence was followed by six postcontrast sequences for the dynamic contrast-enhanced images, and subtraction images were also obtained. Each of the six contrast-enhanced sequences took 56 s. Gadoterate meglumine (Dotarem®, Laboratoire Guerbet, Roissy, France) or gadobutrol (Gadovist®, Bayer Healthcare, Berlin, Germany) were used as contrast media. The contrast media was given intravenously over 20 s by an automatic MR-compatible injector. The doses were 0.2 mmol/kg for gadoterate meglumine and 0.1 mmol/kg for gadobutrol. Subtraction of the contrast-enhanced dynamic images was used as a standard. The precontrast images were removed from the corresponding postcontrast images on the basis of the pixels, and the subtracted series were obtained.

The DWIs that formed the basis of our study were performed prior to contrast-enhanced examination. The DW-MRI sequences were performed with a two-dimensional echo-planar imaging (EPI) sequence (TR/TE, 8200/95 ms; flip angle, 90°; slice thickness, 3.5 mm; matrix, 192×192; signal average, 4) in the axial plane. The sensitizing diffusion gradients were in three ortho-

nal planes with three different b values (b=50, 400, 800 s/mm<sup>2</sup>). The ADC map images were created automatically by the system. The ADC values were calculated according to the following formula:  $ADC=1/(b_2-b_1)\times\ln(S_1/S_2)$  where the S1 and S2 values were the signal intensities at the b values of b1=50 and b2=800 s/mm<sup>2</sup>, respectively.

### Lesion assessment

This study considered the ADC measurement values, the presence and extent of the breast lesions that showed abnormal contrast enhancement and the diffusion restriction of the lesions on the corresponding DWIs. The differences between the ADC values of the reference group lesions (malignant histopathology) and the control group lesions (benign histopathology) were investigated.

All lesions were evaluated by two radiologists (first author and second author) with three and 14 years of experience in breast MRI, respectively. The readers were blinded to the mammography, US, and final histopathological results. Contrast-enhanced images were used as reference images in evaluating the mass on DWI and ADC images because they had better resolution. The lesions were evaluated according to the BI-RADS MR lexicon for their shapes, margins, signal intensity, and contrast enhancement patterns. The DW-MRIs were analyzed to observe any restriction of diffusion in the lesions, and the ADC maps were used for ADC measurements. Each lesion was evaluated on T2-weighted and contrast-enhanced images; the enhanced part of the lesion was preferred for evaluation on the corresponding DW-MRI; the region of interest (ROI) was placed manually on the corresponding area of the ADC map. The ROI was placed in the solid portion of the tumors, and necrotic or cystic components were excluded from the measurement area. In addition, the ADC values of the contralateral normal breast tissue were measured to obtain the ADC ratio value for each patient. A standard 5 mm diameter circular ROI was used.

We preferred to include lesions equal to or larger than 10 mm in diameter to avoid incorrect measurement results. We made a single measurement

for lesions less than 1.5 cm and three different measurements for lesions over 1.5 cm in size. We also took into consideration the lowest (minimum) ROI measurement. We calculated the ADC ratio of the mass to the contralateral normal breast tissue for each patient. The diagnostic performance of the ADC values in the differentiation of lesions was evaluated by calculating the area under the receiver operating characteristics (ROC) curve (AUC) and optimal cutoff values.

### Statistical analysis

For continuous variable; ADC values were given as mean±standard deviation. The ADC values between malignant and benign groups were compared using Student's t test. One way ANOVA test was used for comparisons of diagnostic subgroups and when P value was found significant, as the Posthoc test Tukey multiple comparisons test was used to detect which group was significant. The sensitivity, specificity, and positive predictive value (PPV) were assessed. The ROC analysis was performed to distinguish between the threshold ADC values of the benign and malignant lesions.  $P < 0.05$  was considered statistically significant. The statistical analysis was performed using a commercially available software (Statistical Package for Social Sciences, version 15.0, SPSS Inc., Chicago, Illinois, USA).

### Results

There were 51 solid lesions detected in 51 patients. Sixteen lesions were diagnosed as benign and 35 lesions as malignant. The histopathological diagnoses were performed using tru-cut needle biopsy in 23 patients and excisional biopsy in 28 patients. The histopathological types of these lesions are shown in Table 1. The lesion sizes ranged from 10 to 70 mm (mean, 29.6±17.1 mm). The mean lesion size of the 16 (30.8%) benign lesions was 28.1±18.7 mm, and the mean lesion size of the 35 (67.3%) malignant lesions was 30.4±16.6 mm.

The mean ADC value of all benign lesions was  $1.9\pm 0.45\times 10^{-3}$  mm<sup>2</sup>/s, and mean ADC value of all malignant lesions was  $0.86\pm 0.26\times 10^{-3}$  mm<sup>2</sup>/s. The mean ADC ratio values of the mass/normal breast tissue were  $0.6\pm 0.14$  in

**Table 1.** Distribution of benign and malignant lesions

Diagnosis	Type of lesion	Number of lesions
Malignant	Invasive ductal carcinoma	25
	Invasive lobular carcinoma	1
	Ductal carcinoma <i>in situ</i>	3
	Invasive mixed carcinoma	5
	Medullary carcinoma	1
Benign	Fibroadenoma	7
	Abscess	1
	Atypical ductal hyperplasia	1
	Intraductal papilloma	1
	Fat necrosis	3
	Stromal degeneration	1
	Postoperative granulation	2

**Table 2.** The ROC analysis of the ADC values of the breast masses and the ADC ratio values

Classification variable	ADC	ADC ratio
	Diagnose	Diagnose
Sample size	51	51
Positive group (malignant)	35	35
Negative group (benign)	16	16
Disease prevalence (%)	68.6	95
Area under the ROC curve	0.974	0.993
Standard error	0.0182	0.00699
95% confidence interval	0.886 to 0.999	0.917 to 1.000
Z statistic	26.028	70.547
P (Area=0.5)	< 0.001	< 0.001

ADC, apparent diffusion coefficients; ADC ratio, mass to normal breast tissue ADC ratio values; ROC, receiver operating characteristics.

the malignant lesions and  $1.3 \pm 0.25$  in the benign lesions. The difference between the ADC and ADC ratio values of the benign and malignant lesions was statistically significant ( $P < 0.001$  for both the ADC and ADC ratio values). Malignant and benign lesions could be distinguished from each other using a threshold ADC value of  $1.03 \times 10^{-3} \text{ mm}^2/\text{s}$  with 88.5% sensitivity, 100% specificity, and 100% PPV. The threshold ADC ratio of the mass/normal fibroglandular tissue was 0.8 with 91.4% sensitivity, 100% specificity, and 100% PPV. The AUC was 0.974 for the ADC and 0.993 for the ADC ratio values (Table 2, Fig. 1). There was a statistically significant difference between the ADC and ADC ratio values

of fibroadenomas and invasive ductal carcinomas when compared diagnostic subgroups that consisting of fibroadenomas, invasive ductal carcinomas and other lesions ( $P < 0.001$ ).

The ADC values of the lesions and normal breast tissue measurements ranged from 0.52 to  $2.66 \times 10^{-3} \text{ mm}^2/\text{s}$  and from 1.11 to  $1.79 \times 10^{-3} \text{ mm}^2/\text{s}$ , respectively. The lowest ADC value ( $0.52 \times 10^{-3} \text{ mm}^2/\text{s}$ ) was in invasive-mixed carcinoma; the highest ( $2.66 \times 10^{-3} \text{ mm}^2/\text{s}$ ) was found in postoperative changes. The mean ADC value of all benign lesions was  $1.9 \pm 0.45 \times 10^{-3} \text{ mm}^2/\text{s}$ , and this mean ranged from 1.14 to  $2.66 \times 10^{-3} \text{ mm}^2/\text{s}$ . Of all benign lesions, intraductal papilloma had the lowest ADC value ( $1.14 \times 10^{-3} \text{ mm}^2/\text{s}$ ),

and postoperative granulation tissue had the highest ADC value ( $2.66 \times 10^{-3} \text{ mm}^2/\text{s}$ ). The ADC values ranged from 0.52 to  $1.2 \times 10^{-3} \text{ mm}^2/\text{s}$  in malignant lesions, and the mean ADC value for these lesions was  $0.86 \pm 0.26 \times 10^{-3} \text{ mm}^2/\text{s}$ . The highest ADC value of all primary malignant lesions ( $1.2 \times 10^{-3} \text{ mm}^2/\text{s}$ ) was in medullary carcinoma, and the lowest ADC value ( $0.52 \times 10^{-3} \text{ mm}^2/\text{s}$ ) was in invasive-mixed carcinoma. The mean ADC values of the 25 cases of invasive ductal carcinoma were  $0.83 \times 10^{-3} \text{ mm}^2/\text{s}$ , and that of the seven cases of fibroadenoma were  $1.72 \times 10^{-3} \text{ mm}^2/\text{s}$ .

The mean ADC ratios of the mass/normal breast tissue were  $0.6 \pm 0.14$  in the malignant lesions and  $1.3 \pm 0.25$  in the benign lesions. The lowest mass/normal breast tissue ADC ratio value (0.38) was found in invasive ductal carcinoma, and the highest ratio (1.78) was found in abscesses. The mean ADC ratio of mass/normal breast tissue was 0.57 among 25 invasive ductal carcinoma cases and 1.27 among seven fibroadenoma cases.

There were no benign lesions that had ADC or ADC ratio values under the threshold values of  $1.03 \times 10^{-3} \text{ mm}^2/\text{s}$  and 0.8, respectively ( $n=16$ ). Although the ADC values of four lesions from a total of 35 malignant lesions were over or equal to the threshold value  $1.03 \times 10^{-3} \text{ mm}^2/\text{s}$  (Fig. 2), they had malignant characteristics according to the BI-RADS MR lexicon on conventional MR images (false negatives) (Figs. 3, 4). Three of these four patients also had higher ADC ratio values than the threshold. One of these four lesions had an ADC ratio value lower than the threshold (Fig. 4). The histopathological findings of these lesions were one medullary carcinoma (Fig. 3), two invasive ductal carcinoma (Fig. 4), and one mixed-invasive carcinoma. The ADC values of all other malignant masses were below the threshold value.

## Discussion

There is a direct relationship between ADC values and tumor cellular structure. Cellular organization of the tumor can be evaluated with DW-MRI and is currently one of the most important indicators of cellularity (4–12).

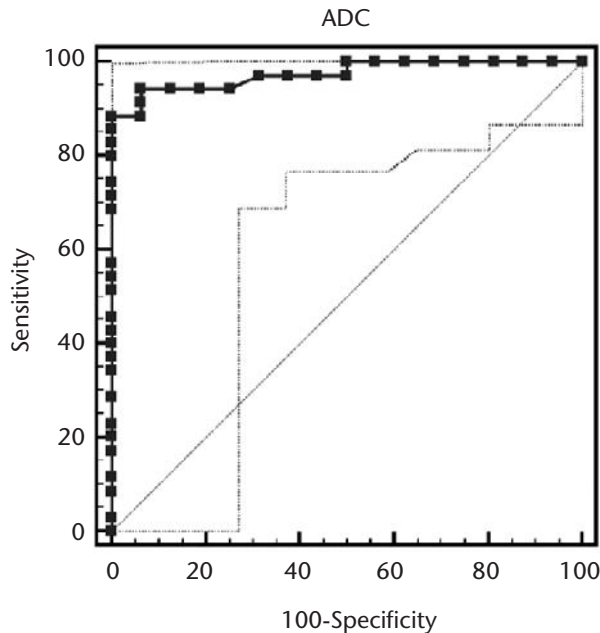
Breast MRI is increasingly used for the detection, diagnosis, and staging of breast cancer (4, 13). In addition to conventional MRI, DWI has been reported as a useful technique for the discrimination between benign and malignant breast lesions (7, 9, 10). We believe that DWI has a potential role in

improving the diagnostic performance of breast MRI.

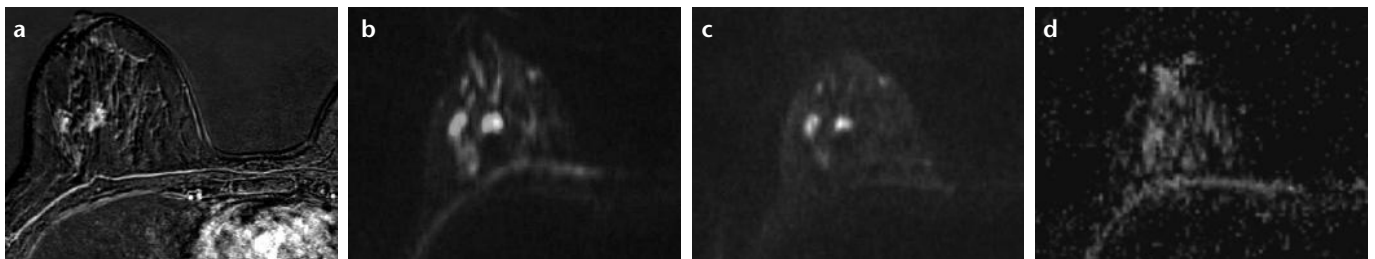
Our findings show that a quantitative analysis of ADC values can be used to distinguish malignant focal breast lesions from benign lesions. We have taken into account the lowest ADC value obtained from a lesion using dif-

ferent ROIs. Studies have shown that a minimum ADC value has a higher sensitivity and specificity compared with mean ADC values, especially in heterogeneous lesions (14–16). However, the ratio of the ADC value of the mass to the ADC value of breast tissue shows a higher sensitivity. This increased sensitivity can eliminate the possible effect of measurement differences between different subjects with varying breast tissues. Park et al. (17) recommend that the ADC values of breast lesions must be compared with that of normal fibroglandular tissue because the ADC value is variable with the gradient factor  $b$ . ADCs were determined using linear regression analysis and analysis of the natural log of the signal intensity versus the gradient factor  $b$  (18). Gimi et al. (19) and El Khauli et al. (5) reported that adding ADC ratio values to conventional MR data improved the diagnostic performance of the MRI. El Khauli et al. (5) used the term “normalized ADC” instead of “ADC ratio”.

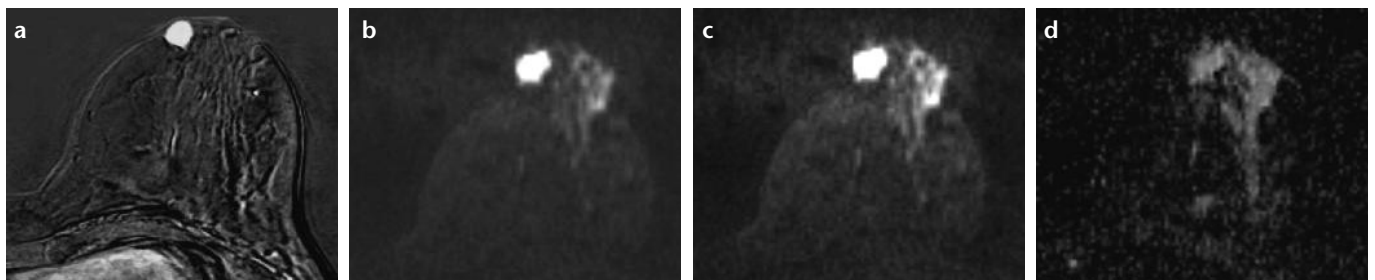
Both the mean minimum ADC and ADC ratio values of breast lesions showed a statistically significant difference ( $P < 0.001$ ) between malignant and benign lesions in our study. The lesions could be distinguished from each other using a threshold ADC val-



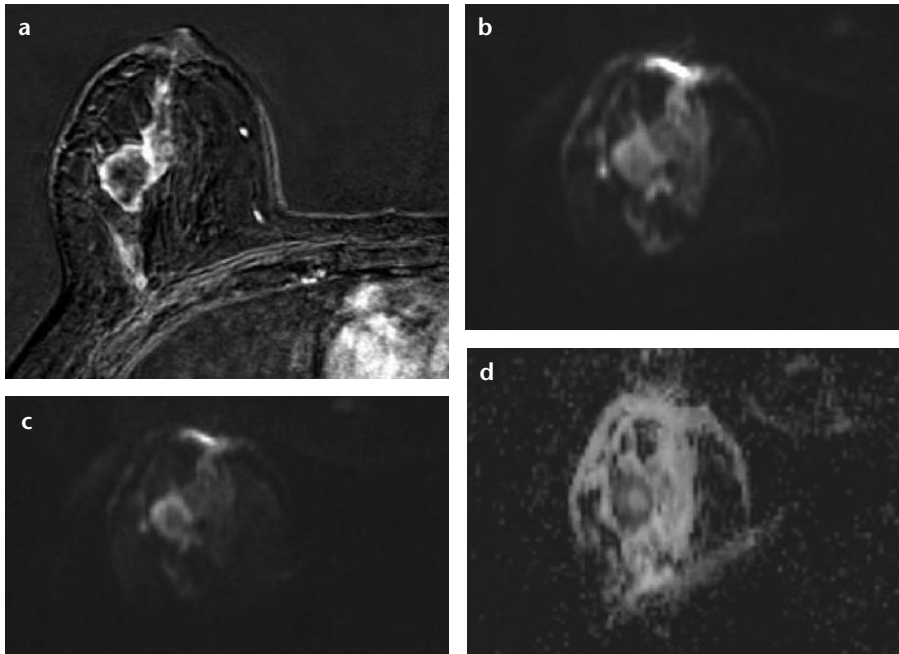
**Figure 1.** The ROC analysis of the ADC values. High sensitivity and specificity can be observed.



**Figure 2. a–d.** A 31-year-old female patient with a histopathological diagnosis of invasive ductal carcinoma. Spiculated margin of the lesion with a 12 mm diameter can be observed on an axial T1-weighted contrast-enhanced MRI (a). The tumor is multifocal, and the second focus has identical findings. The DWIs at  $b=400$  s/mm<sup>2</sup> (b) and at  $b=800$  s/mm<sup>2</sup> (c) clearly demonstrate this lesion. The ADC was  $0.91 \times 10^{-3}$  mm<sup>2</sup>/s, and the ADC ratio was 0.72 on the corresponding area (d).



**Figure 3. a–d.** A 37-year-old female patient with an intensely enhanced lesion with a 13 mm diameter and lobulated margin on T1-weighted contrast-enhanced MRI (a). The DWI at  $b=400$  s/mm<sup>2</sup> (b) and at  $b=800$  s/mm<sup>2</sup> (c) clearly demonstrates this high-signal lesion. An ADC map (d) shows non-restricted diffusion within the lesion. The ADC was  $1.20 \times 10^{-3}$  mm<sup>2</sup>/s, and the ADC ratio was 0.87 on the corresponding area with a histopathologic diagnosis of medullary carcinoma. These unexpectedly high ADC and ADC ratio results were attributed to the central necrosis of the lesion.



**Figure 4. a–e.** A 44-year-old female patient with invasive ductal carcinoma. An axial T1-weighted contrast-enhanced image (a) clearly shows the 24 mm diameter lesion. The lesion has a large necrotizing area and a rim-like enhancing pattern. The DWIs at  $b=400$  s/mm<sup>2</sup> (b) and at  $b=800$  s/mm<sup>2</sup> (c) demonstrate the high-signal lesion with greater contrast on the corresponding localization of the contrast-enhanced parts. Diffusion restriction is clearly observed on the ADC map (d). The ADC was  $1.15 \times 10^{-3}$  mm<sup>2</sup>/s, and the ADC ratio was 0.71 for the corresponding area. This unexpectedly high ADC result was attributed to the large necrotizing area of the lesion.

ue of  $1.03 \times 10^{-3}$  mm<sup>2</sup>/s with 88.5% sensitivity, 100% specificity, and 100% PPV. The threshold ADC ratio value of mass/normal fibroglandular tissue was 0.8 with 91.4% sensitivity, 100% specificity, and 100% PPV. The AUC was 0.974 for ADC and 0.993 for ADC ratio values. These sensitivity and specificity rates are higher than those given in the literature (4, 5, 16). A reason for this finding can be attributed to our preference in using the minimum ADC value and ADC ratio measurements, while the mean ADC value was evaluated in many studies in the literature (14–16).

Four of 35 malignant lesions showed false negative ADC values, and three of these showed false negative ADC ratios though they all had malignant characteristics according to the BI-RADS MR lexicon on conventional MR images. One of these lesions showed medullary carcinoma upon histopathological analysis, and three of these lesions were invasive ductal carcinoma (one of which was mixed type). Medullary carcinoma may show false negative findings in MR, and central necrosis is a common feature of this carcino-

ma (20). The lesion had a lobulated margin and showed a central necrosis that we believe resulted in higher ADC values. Two of the three other lesions were small (10 and 13 mm), and the last lesion had a large necrotizing area.

There are some limitations to DW-MRI. Echoplanar DWI, the most common image acquisition scheme used for DWI, can result in image distortion due to eddy currents. Geometric distortion, signal loss, and image-blurring artifacts in EPI are caused by magnetic field inhomogeneities (6, 7, 12). These artifacts could impair ADC measurements (4, 6, 17). Incorrect measurement values could be obtained if the circle is placed on an incorrect localization (especially in lesions with large necroses or small sizes). Susceptibility changes occur at sharp transitions between different tissue types (such as tissue-fat interfaces). The EPI sequence is very sensitive and especially so in breast imaging because of the large surrounding fat tissue. As the b value increases, susceptibility artifacts can become more apparent and problematic (2, 6, 7). The use of a high imaging bandwidth, a spin echo-based

sequence, and a short time echo can reduce this artifact (6). Image distortion does not change the functional sensitivity of the diffusion (up to a certain limit) because the ADC map is created per pixels (7). Motion artifacts also can cause incorrect ADC measurements (4, 6). Two patients were excluded from our study because their DW-MRI sequences did not have diagnostic quality due to motion artifacts. EPI-DWI has low spatial resolution (2, 4, 6, 7). Small cancer foci may not be depicted in DWI. The higher signal-to-noise ratio afforded by imagers with higher magnetic field strength can be used to increase the spatial resolution of DWI, thereby allowing the detection and characterization of smaller lesions (6). Even under optimal circumstances, small lesions may not be visualized on ADC maps, and Kinoshita et al. (10) have reported that lesions <10 mm in diameter cannot be demonstrated using DWI. We preferred to include lesions equal to or greater than 10 mm in diameter to avoid incorrect measurement results (5). T2 shine-through and blackout effects, hemorrhage, necrosis, cystic lesions, or mucous-protein components may cause changes in signal intensity on DWIs (6, 21, 22). Non-mass-like enhancing lesions form large and noncompact lesions containing normal parenchyma within the tumor. Noninvasive ductal carcinoma, lobular carcinoma *in situ*, atypical ductal hyperplasia, papillomas, hormonal changes, and fibrocystic disease may show this type of enhancement (22). Although this type of lesion can cause incorrect ADC measurement, the ADC measurement values of three ductal carcinoma *in situ* and one intraductal papilloma in our study were correlated with their pathology. It is important to emphasize the need for high-quality DWIs and fat suppression to achieve reliable quantitative DW-MRI (6, 23). In necrotizing lesions, the peripheral enhancing viable tumor tissue is too thin for ROI application. We took this situation into consideration in the study and placed the ROI on the most enhanced and non-necrotizing part of the lesions on the ADC map.

If the selected b value is lower than 400 s/mm<sup>2</sup>, the image is affected by the water molecular diffusion, as well as the microcirculation and consequent-

ly the perfusion of the blood in the capillary (2, 4, 6). As expected, there is a marked increase in the number and size of capillary blood vessels in malignant tumors. Therefore, if a low b value is selected, perfusion effects in the ADC value will be pronounced in malignant lesions. This selection results in pseudo diffusion where the ADC and diffusion value is greater than normal breast tissue due to capillary perfusion (9). It has been reported that the DW-MRI with high b values are more reliable in differentiating between lesions, though signal loss is more severe (2, 6, 7). Bogner et al. (24) reported that using variable b values does not provide an advantage, and they reported the ideal b value as 850 s/mm<sup>2</sup>. We used three different b values (b=50, 400, 800 s/mm<sup>2</sup>) to suppress normal tissue as much as possible and to easily view hypercellular lesions. As the b value increased in our study, the diffusion weight of the examination also increased, and the malignant lesions appeared and were illuminated more clearly than the benign lesions. The signal intensity was low, but the lesion visibility was better, with a value of b=800 s/mm<sup>2</sup>.

The main limitation of the study was the small population and small male sample size. We think that new studies should validate ADC measurements using a larger group of patients. Further limitation to our study was that we did not take the menstrual cycle of the patients into consideration during the planning of the biopsy procedure. Although the ADC values of normal fibroglandular breast tissue demonstrate changes during menstruation, these changes are not statistically significant (25).

In conclusion, DW-MRI provides additional information regarding the characterization of breast lesions, and this information can help in the differential diagnosis. The examination is fast, easy, does not need contrast medium injection, and is a promising tool for reducing invasive breast interventions. One of the most important advantages of DW-MRI is a quantitative analysis with ADC measurements. This study showed that ADC ratio measurements and minimum ADC measurements has a potential role in improving the diagnostic performance of DW-MRI in the characterization of breast

lesions. Therefore, a more accurate prediction of lesion malignancy could be made by ADC measurements prior to histopathological sampling, given that the lesion is of the appropriate size. Although DW-MRI cannot be used alone in the differential diagnosis of breast lesions, it can be used in combination with conventional breast MRI.

#### Conflict of interest disclosure

The authors declared no conflicts of interest.

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