

# Four Different Apparent Diffusion Coefficient Measurement Methods in Breast Masses

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## ABSTRACT

**Objective:** To compare the effect of different quantification methods of ADC values in the evaluation of breast lesions and compare contralateral normal breast tissue ADC value by calculating ADC ratios.

**Study Design:** Descriptive study.

**Place and Duration of the Study:** Sisli Etfal Training and Research Hospital, Turkey, between February 2019 and December 2020.

**Methodology:** Two hundred and forty-six breast MRI scans with DWI of the patients with biopsy proven unilateral breast lesions were studied. ADC measurements were done by placing ROI. Two ADC values and two ADC ratios were obtained by different methods. The diagnostic accuracies of these four techniques were compared.

**Results:** Mean ADC values and ratios of benign and malignant lesions were statistically significant in all of four methods to quantify ADC ( $p < 0.001$ ). Highest positive value and negative predictive value, and diagnostic accuracy rates were achieved when the most restricted part ADC value was calculated. However; highest sensitivity rate and negative predictive value were achieved by calculating the ratio of darkest point ADC to contralateral breast tissue. Positive predictive value, negative predictive value, and diagnostic accuracy rate of calculated ADC values and ratios were higher when lesions were larger than the mean size ( $3.15 \text{ mm}^2$ ).

**Conclusion:** Highest diagnostic accuracy rate was obtained with most restricted part ADC value. Obtained ratios by calculating contralateral breast tissue ADC value did not improve the diagnostic accuracy rate. Positive and negative predictive values and diagnostic accuracy rates of ADC values and ratios increased as the lesion size increased.

**Key Words:** Breast mass, Diffusion weighted imaging, ADC value, ADC ratio, Normalised ADC.

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## INTRODUCTION

Diffusion-weighted imaging (DWI) has been used for the past two decades in the evaluation of breast masses. It was first utilised by Englander *et al.* and several studies have been published about this evolving technique.<sup>1-4</sup> These studies stated that DWI has superiority to conventional magnetic resonance imaging (MRI) in the differentiation of benign and malignant breast masses.<sup>5</sup> DWI is an MRI technique that uses the signal contrast that arises from the differences in Brownian motion of the water molecules.<sup>5,6</sup> In the human body; water molecules are found in intracellular and extracellular compartments. As extracellular water molecules freely diffuse, intracellular water molecules have relatively restricted diffusion.

DWI gives quantitative and qualitative data about the diffusion properties.<sup>6</sup> Restriction of water diffusion can be calculated by the apparent diffusion coefficient (ADC). It has been shown that malignant tumors have lower ADC values than benign tumors as they consist of more cell count and intracellular water.<sup>5,6</sup>

Several studies have been published for the diagnostic value of ADC values in the differentiation of breast tumors.<sup>1-3,5</sup> A meta-analysis based on 13,847 breast lesions (10,622 benign and 3,225 malignant) concluded that an ADC threshold of  $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$  can be used to differentiate benign lesions from breast cancer.<sup>5</sup> Various methods have been used to obtain ADC values by placing regions of interest (ROI) to the darkest point on the ADC map, to the whole lesion, and to multiple sites of the lesion and calculating the mean value.<sup>7-9</sup> In the study of McDonald *et al.*; it is stated that the ADC values of normal breast tissue were higher in patients with dense breast tissue on mammography.<sup>10</sup> However; there is no consensus on ADC measurement method.

This study was aimed to compare the effect of different measurement methods of apparent diffusion coefficient (ADC) values in the evaluation of breast lesions; and determine its diagnostic value in distinguishing benign/malignant lesions; and evaluate

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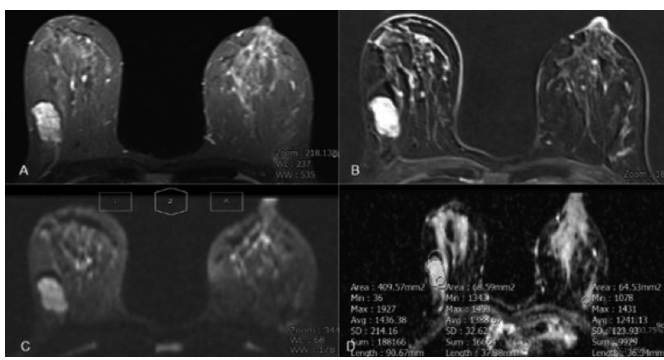
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the possible effect of contralateral normal breast tissue ADC value by calculating ADC ratios.

## METHODOLOGY

This study was conducted in Sisli Etfal Training and Research Hospital, Turkey, between February 2019 and December 2020. Three hundred and twenty-eight patients, who were admitted to breast radiology clinics for either screening or diagnostic purposes and had breast MRI with DWI between February 2019 and December 2020, were evaluated. Among them, female patients, who had breast tumors and undergone core biopsy, were included in the study. Exclusion criteria were male gender, patients who had biopsy proven bilateral breast cancer; patients who had breast biopsy of surgery history during six months before the MRI scan, patients who received chemotherapy or radiotherapy before the MRI scan, and patients with extensive artifacts in DWI, patients with implants, and patients whose core biopsy, excisional biopsy or postoperative histopathological reports could not be obtained.

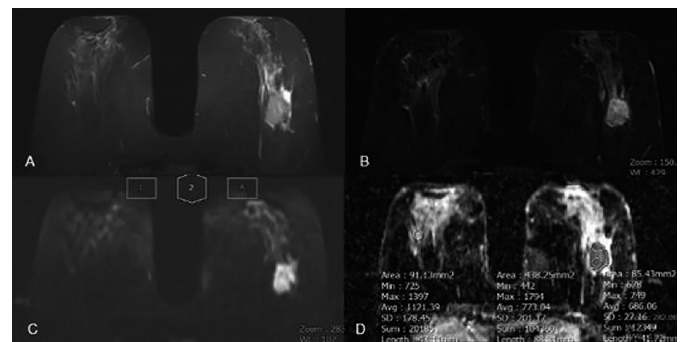
This study was conducted in accordance with the 1964 Helsinki Declaration and approved by the Ethics Committees of the Hospital. Since the study was retrospective, informed consent by patients was waived. MRIs were acquired using 1.5 Tesla Siemens scanner (Avanto, Erlangen Germany). In premenopausal women, imaging was performed within 7-14 days of the cycle to prevent possible effects of the menstrual cycle on ADC. Patients were positioned in prone position. Conventional MRI protocol was applied as T1 weighted fast spin echo axial sequence (TR = 650, TE = 112, Matrix 448 × 224, FOV = 320×320 mm, NEX = 1, Thickness = 3.0 mm) and pre- and post-contrast T1 weighted three-dimensional fat-suppressed axial sequence (TR = 485, TE = 10, Matrix 350 × 350, FOV = 320×320 mm, NEX = 1, FA = 10.0, Thickness 3.00). Images were taken before contrast administration and five times after contrast injection with 80s intervals. Contrast agent is injected with a dose of 0.1 mmol kg<sup>-1</sup>. Diffusion-weighted images [TR/TE = 1000/83, NEX = 2 and Thickness = 2 mm, FOV = 320 mm, Matrix 180×238] were obtained before contrast and ADC maps were attained.



**Figure 1: (A) Fat saturated T1-weighted, (B) Subtraction, (C) Diffusion weighted images and (D) ADC map of lobulated homogeneous mass. This lesion was a biopsy proven fibroadenoma. Homogeneous texture of the lesion makes ADC quantifications easier. Three ROI placements are shown here.**

All MRIs were evaluated by a radiologist with over eight years of experience in breast MRI interpretation. While placing the ROI,

T1, T2 and contrast enhanced T1 imagings were evaluated as reference. ADC mapping was evaluated at the site, which showed highest diffusion restriction, at the site of whole tumor size, and contralateral normal breast tissue. Region of interest (ROI) volume was freely selected rather than using a specific volume. However, the smallest size of ROI placement was carefully selected while placing the ROI to the darkest point on ADC map. Maximum attention was given not to include either the cystic, necrotic, hemorrhagic parts of the tumor or normal breast parenchyma. ADC values were measured by two different methods by placing ROI in the area covering the entire lesion and then in the most restricted area of the lesion on ADC map (Figures 1 and 2). For lesions with homogeneous signal intensity on DWI and ADC map, ROI was placed to the most enhanced part in post contrast T1-weighted images. Three ROI placements were done for each quantification and ROI with the lowest ADC value was selected from multiple ROIs within the targeted area. This ADC value was considered as the minimum ADC. Then, three ROIs were placed in the contralateral breast area without lesions, and ADC measurement in the normal breast was made and the average was taken. Subsequently, two ADC values and two ADC ratios were obtained by different methods: 1) from the whole tumor; 2) from the most diffusion restricted part on ADC map; 3) ratio of whole tumor ADC value to the contralateral normal breast tissue ADC value; and 4) ratio of the most diffusion restricted part on ADC map to contralateral normal breast tissue ADC value. ADC values were measured from localising a ROI to two dimension ADC maps. The diagnostic accuracies of these four techniques were compared. To interpret DWI, b0 and b1000 sn/mm<sup>2</sup> were used. DWIs were obtained before contrast administration to prevent the possible effect of the contrast agent on DWI of the tumor and to prevent T2 shortening secondary to contrast.



**Figure 2: (A) Fat saturated T1-weighted, (B) Subtraction, (C) Diffusion weighted images and (D) ADC map of heterogeneous mass. This lesion was biopsy proven invasive ductal carcinoma. Three ROI placements are shown here. Maximum attention was given to place the ROI to the most restricted (darkest) part of the tumor on ADC map.**

SPSS version 15.0 for Windows programme is used for statistical analysis. Descriptive statistics; number and percentage for categorical variables, mean, standard deviation, median and interquartile range for numerical variables (25th and 75th percentile). When comparisons of numerical variables between two independent groups did not provide normal distribution,

**Table I: Comparison of ADC values and ratios achieved by four different ADC quantification methods.**

	ROI	Mean	SD	25th percentile	75th percentile	Median	p-value
Maximum tumor diameter	Malignant	30.4	23.9	18	33	25	<0,001
	Benign	22.9	20.4	12	26.75	15.5	
Whole lesion ADC x10 <sup>-3</sup> mm <sup>2</sup> /sn	Malignant	0.96	0.19	0.85	1.06	0.95	<0,001
	Benign	1.32	0.22	1.17	1.46	1.29	
Darkest point ADC x10 <sup>-3</sup> mm <sup>2</sup> /sn	Malignant	0.79	0.17	0.68	0.86	0.77	<0,001
	Benign	1.21	0.23	1.05	1.37	1.21	
Whole lesion/contralateral breast ADC x10 <sup>-3</sup> mm <sup>2</sup> /sn	Malignant	0.74	0.15	0.64	0.83	0.72	<0,001
	Benign	1.02	0.20	0.91	1.09	0.98	
Darkest point/contralateral breast ADCx10 <sup>-3</sup> mm <sup>2</sup> /sn	Malignant	0.60	0.14	0.52	0.68	0.60	<0,001
	Benign	0.94	0.20	0.80	1.01	0.93	

**Table II: Predictive values, diagnostic accuracy rates and cut-off values of used four ADC quantification methods.**

	AUC	95% CI	Cut-off value	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy	Kappa value	p-value
Whole lesion ADC	0.896	0.855-0.936	≥1,100	87.0%	81.4%	76.3%	90.1%	83.7%	0.669	0.038
Most restricted part ADC	0.932	0.899-0.965	≥0,936	90.0%	87.7%	83.3%	92.8%	88.7%	0.767	0.185
Whole lesion/contralateral breast ADC	0.901	0.863-0.938	≥0,851	86.0%	81.4%	76.1%	89.4%	83.3%	0.660	0.060
Most restricted part / contralateral breast ADC	0.941	0.914-0.969	≥0,709	92.0%	82.9%	78.6%	93.8%	86.7%	0.729	0.005

Mann-Whitney U-test was used. ROC curve analysis was performed for cut-off values. The consistency of the results was examined with the kappa Value. The rates in dependent groups were compared with the McNemar test. Statistical significance level of alpha was accepted as  $p < 0.05$ .

## RESULTS

A total of 246 MRI scans of 246 (100 benign, 146 malignant) breast tumors were finally studied. The mean age of patients was  $49.3 \pm 8.7$  years ranging between 21-79 years. According to the pathology results, most common benign lesion was fibroadenoma ( $n=68$ , 27.64%) and most common malignant lesion was invasive ductal carcinoma ( $n=104$ , 42.28 %). Core biopsy was performed in 68 fibroadenoma cases, There were eight cases of mastitis and three cases of abscess, on which biopsy was performed due to complex mass-like appearance on ultrasound. Solid parts were carefully biopsied. Mean area of the masses in two dimensions was  $3.15 \pm 0.21$  cm<sup>2</sup> with maximal diameters between 0.6 and 31.6 cm. The mean tumor size of benign and malignant lesions was measured  $22.9 \pm 20.4$  mm and  $30.4 \pm 23.9$  mm, respectively.

Mean ADC values and ratios of benign and malignant lesions were statistically significant in all of four used measurement methods to quantify ADC ( $p < 0.001$ ) with mean ADC values of the malignant lesions were significantly lower than benign ones (Table I). Cut-off values of ADC values and ratios were determined with ROC analysis (Table II). Highest positive

and negative predictive value and diagnostic accuracy rate were achieved when the most restricted part ADC value was calculated.

Additionally, diagnostic accuracy of ADC improved when the tumor size in two dimensions was higher than the mean tumor size; as there was a dramatic decrease in positive predictive value and diagnostic accuracy rate of ADC values when the tumor size is under mean tumor size (Table III).

## DISCUSSION

Breast MRI is a widely used diagnostic modality to evaluate the breast with high sensitivity that is reported as 89-100%.<sup>1-13</sup> MRI has superiority to ultrasonography and mammography as it helps detection of breast lesions in dense breast tissue, identifies the accompanying invasive components. Additionally, breast MRI is the chosen method for screening high risk patients and also assessment of treatment response.<sup>4,8,9,11</sup> However; the specificity of conventional contrast enhanced MRI is not as high as its sensitivity. Zhang *et al.* found the sensitivity and specificity of dynamic contrast-enhanced magnetic resonance imaging in determining lesion morphology and kinetics as 93% and 71%, respectively. At this point, advanced MRI applications have been introduced to identify benign and malignant lesions more accurately.

Englander *et al.* first utilised DWI in breast tissue in 1997.<sup>4</sup> In the past two decades; many studies have been published

regarding the use of ADC values in further work-up of the breast lesions.<sup>1-16</sup> No need to contrast administration is one of the advantages of DWI. In this regard, DWI may be an alternative for patients in whom contrast agents cannot be administered (patients with severe renal dysfunction and at risk of nephrogenic systemic fibrosis or patients who developed anaphylaxis or severe allergic reaction to gadolinium-based contrast agents.<sup>17</sup> Additionally, giving quantitative results and short acquisition times (typically 2-4 minutes) are superiorities of DWI and makes it an acceptable imaging method candidate.<sup>18</sup>

Discrepancy in mean ADC values of benign and malignant breast lesions were found in the literature; Guo *et al.* reporting  $1.57 \pm 0.23 \times 10^{-3} \text{ mm}^2/\text{s}$ ,  $0.97 \pm 0.20 \times 10^{-3} \text{ mm}^2/\text{s}$ ; Orguc *et al.* stating  $2.00 \pm 0.55 \times 10^{-3} \text{ mm}^2/\text{s}$ ,  $1.04 \pm 0.29 \times 10^{-3} \text{ mm}^2/\text{s}$ , and Altay *et al.* describing  $1.47 \pm 0.25 \times 10^{-3} \text{ mm}^2/\text{s}$ ,  $0.96 \pm 0.25 \times 10^{-3} \text{ mm}^2/\text{s}$ .<sup>1,14,16</sup> The present authors believe that different measures are the result of various size and localisation of ROI placement and quantification methods as there is no standardisation in ADC measurement.<sup>4,8,9,11,19</sup> Differences in ADC values demonstrate that radiologists need the results of various quantitative techniques before utilising general cut-off values in clinical practice. For this reason, we aimed to investigate the role of DWI in breast cancer diagnosis by comparing ADC values and ratios that were obtained by three different ROI placements.

In this study, the mean ADC values and ratios quantified by four different measurements were significantly lower in malignant masses; which was concordant with the literature.<sup>1-12</sup>

Many different techniques for ROI placement have been used. Gity *et al.* placed the ROI to whole lesion and to the most prominent diffusion restricted point of the lesion in DWI.<sup>7</sup> Aydın *et al.* placed the ROI to the darkest point of the lesion on ADC map.<sup>12</sup> Bickel *et al.* used the minimum, average and maximum ADC values quantified by 2D and 3D ROIs.<sup>19</sup> This study revealed that placing the ROI has an essential role in the performance of DWI and ADC values. ROI placed to the darkest point on ADC map performs better in terms of sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy rate with a cut-off value of  $0.936 \times 10^{-3} \text{ mm}^2/\text{s}$  (CI=0.899-0.965), when compared with ROI placed to the whole lesion on ADC map. However, highest sensitivity rate (92.0%) and negative predictive value (93.8%) were achieved by calculating the ratio of darkest point ADC to contralateral breast tissue. On the other hand, ratio of the darkest point ADC to contralateral breast ADC has higher sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy rate with a cut-off value of  $0.709 \times 10^{-3} \text{ mm}^2/\text{s}$ ; when compared to the ratio of whole lesion ADC to contralateral breast ADC (Table II). The obtained ADC values of benign and malignant breast lesions are exceedingly connected to ROI placement and the size of

the ROI. Internal signal heterogeneity of the breast lesions leads to different calculated ADC values and it depends on whether only small areas with relatively homogeneous ADC, larger areas with less homogeneous ADC, or even the whole lesion (especially when necrosis or hemorrhage are present within the lesion) that ROI is placed into.

The ADC values are directly affected by b values selected.<sup>5,6</sup> In the literature; with the use of higher b values ( $> 500 \text{ mm}^2/\text{s}$ ) and using at least two values is necessary to acquire more reliable results.<sup>17,19,20</sup> There is no evidence to suggest that choice of minimum b value improves diagnostic performance (*i.e.* 0 or 50 sec/mm<sup>2</sup>).<sup>21</sup> Variable ADC cut-off values found to discriminate benign and malignant breast lesions so far. In this point; ADC normalisation gains importance as it eliminates the effect of chosen b value as it is a ratio and enables radiologists to perform independent and parallel measurements across institutions. Azab *et al.* calculated the ADC value by placing multiple ROI in the lesion and selecting the minimum one. Then they divided minimum ADC to contralateral normal breast tissue ADC to achieve normalised ratio. In their study; they found the cut-off value of 0.9 with high sensitivity (92.2%) and specificity (94.4%) differentiating benign from malignant.<sup>22</sup> In this study, the authors performed the same method and found a cut-off value of 0.941 with high sensitivity (92%) and specificity (82.9%). When compared, the cut-off value used in this study has significant low specificity with nearly the same sensitivity. In another study which consisted of 93 patients with 101 breast lesions; adding normalised ADCs to contrast enhanced breast MRI improved the diagnostic performance with increase in the area under the curve (AUC) from 0.89 to 0.98.<sup>23</sup> They calculated multiple ADC values from the lesion and the breast parenchyma and used the median ADC value to calculate the normalized ratio. The present results are controversial in terms of normalised ADC values that AUC and false negative ratio improved. However, the highest diagnostic accuracy rate (88.7%) was achieved with the most restricted part ADC value. The difference can be the result of different ADC quantifying methods that the authors used.

In 2019, European Society of Breast Radiology (EUSOBI) international breast DWI working group published a paper to issue a consensus statement in image processing, visualisation and interpretation of DWI in breast MRI. While the group had no consensus on the size of ROI to be used, they suggested to select the minimum ADC value within the lesion, which was similar to the literature; as it would provide more accurate discrimination between benign and malignant lesions.<sup>17</sup> These results were consistent with the consensus statement that placing the ROI to the darkest point on ADC map resulted in an increase in sensitivity, specificity, positive predictive value and diagnostic accuracy rate.

In another aspect, the positive predictive value, negative predictive value and diagnostic accuracy rate of calculated



ADC values and ratios were higher when lesions were larger than the mean size (Table III). ROI placement in smaller lesions constitutes a problem. The authors believe that taking the mass size into account would be a logical approach while evaluating ADC values.

Time spent for ROI placement and ADC measurement is highly important that influences the applicability of this imaging method. In this study, placing the ROIs to the large heterogeneous tumors took longer when compared with ROI placement to the smallest restricted area on ADC map. In large tumors, placing ROI to the most restricted part was difficult in tumors with necrotic areas where drawing complex ROIs around the necrotic parts was necessary. In this regard, placing smaller ROIs has the further advantage of shortening the time spent for ADC measurements.

There are several limitations of this study. Firstly, due to its retrospective design, the study results could not be utilised in clinical diagnosis. As a result, this study has a lack of information about different ADC quantification methods on the decision of treatment management. Secondly, patients included in the study were derived from a single clinic. Thirdly, all the ADC calculations were obtained by a single radiologist which resulted in lack of information about inter-observer variability. Lastly, the institutional standard protocol was performed to obtain MR images. The calculated ADC value is affected by the scanning parameters (TR and TE), and b value used for DWI. It was believed that there is a need for a consensus approach in terms of MRI parameters.

## CONCLUSION

ADC ratio achieved by division of the whole lesion or darkest point ADC values divided by contralateral breast tissue did not improve the diagnostic accuracy rate, when compared with the diagnostic accuracy of whole lesion ADC value and darkest point ADC value. Highest diagnostic accuracy rate was obtained from the measurement of darkest point ADC value. In addition, positive and negative predictive values and diagnostic accuracy rates of ADC values and ratios increase as the lesion size increases.

### ETHICAL APPROVAL:

This study was conducted in accordance with the 1964 Helsinki Declaration and approved by the Ethics Committee of the Hospital.

### PATIENTS' CONSENT:

The consents of the patients was waived.

### CONFLICT OF INTEREST:

The authors declared no conflict of interest.

### AUTHORS' CONTRIBUTION:

BD, BAU: Contributed to the study conception and design.  
BD: Data collection and analysis.

BAU: Wrote first draft of manuscript.

All authors read and approved the final manuscript.

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