Detection of the differences in the apparent diffusion coefficient values in different histopathological types of malignant breast lesions and comparison of cellular region/stroma ratio and histopathological results

NEVİN KÖREMEZLİ KESKİN
PINAR BALCI
IŞIL BAŞARA AKIN
ESRA YAVUZ GÜRkan
ALİ İBRAHİM SEVİNÇ

See next page for additional authors

Follow this and additional works at: https://journals.tubitak.gov.tr/medical

Part of the Medical Sciences Commons

Recommended Citation
KESKİN, NEVİN KÖREMEZLİ; BALCI, PINAR; AKIN, IŞIL BAŞARA; GÜRkan, ESRA YAVUZ; SEVİNÇ, ALİ İBRAHİM; DURAK, MERİH GÜRAY; and DANYELİ, AYÇA ERŞEN (2018) "Detection of the differences in the apparent diffusion coefficient values in different histopathological types of malignant breast lesions and comparison of cellular region/stroma ratio and histopathological results," Turkish Journal of Medical Sciences: Vol. 48: No. 4, Article 17. https://doi.org/10.3906/sag-1801-89
Available at: https://journals.tubitak.gov.tr/medical/vol48/iss4/17

This Article is brought to you for free and open access by TÜBİTAK Academic Journals. It has been accepted for inclusion in Turkish Journal of Medical Sciences by an authorized editor of TÜBİTAK Academic Journals. For more information, please contact academic.publications@tubitak.gov.tr.
Detection of the differences in the apparent diffusion coefficient values in different histopathological types of malignant breast lesions and comparison of cellular region/stroma ratio and histopathological results

Authors
NEVİN KÖREMEZLİ KESKİN, PINAR BALCI, İŞİL BAŞARA AKIN, ESRA YAVUZ GÜRKA, ALİ İBRAHİM SEVİNÇ, MERİH GÜR DURAK, and AYÇA ERŞEN DANYELİ
Detection of the differences in the apparent diffusion coefficient values in different histopathological types of malignant breast lesions and comparison of cellular region/stroma ratio and histopathological results

Nevin KÖREMEZLİ KESKİN1,*, Pınar BALCI2, İşıl BAŞARA AKIN2, Esra YAVUZ GÜRKA3, Ali İbrahim SEVİNÇ4, Merih Güray DURAK5, Ayça ERŞEN DANYELİ5

1. Department of Radiology, Karabük University Training and Research Hospital, Karabük, Turkey
2. Department of Radiology, School of Medicine, Dokuz Eylül University, İzmir, Turkey
3. Radiology Section, Toyotasa Emergency Hospital, Sakarya, Turkey
4. Department of General Surgery, School of Medicine, Dokuz Eylül University, İzmir, Turkey
5. Department of Pathology, School of Medicine, Dokuz Eylül University, İzmir, Turkey

* Correspondence: nevinkoremezli@hotmail.com

1. Introduction

Magnetic resonance imaging (MRI) is a radiological method that has started to be used increasing frequently in the evaluation of breast lesions (1,2). MRI has high contrast resolution. Thanks to technical developments, rapid sequences and functional examinations can be performed. Diffusion weighted imaging (DWI) is one of these rapid MRI sequences (3). Diffusion occurs as a result of the movements driven by the intrinsic molecular kinetic energy. The magnitude of the gradient applied in diffusion measurement is represented with the “b” value, a parameter that indicates the strength and timing of the gradient in s/mm². The apparent diffusion coefficient (ADC) within tissue can only be measured when there are a minimum of two different “b” values. The most commonly used sequence in diffusion MRI is the single-shot echo planar imaging (EPI) sequence (3,4). Many clinical studies have shown that DWI has high sensitivity in the evaluation of breast lesions and differentiation of the malignant and the benign. Ei Khouli et al. pointed out an increase in the diagnostic accuracy by combining DWI and the conventional MRI (3.0 T) (5). ADC values obtained from any lesion show parallelism with the tumor tissue cellularity (6). Thanks to this property, it contributes to characterization of the malignant lesions in the preoperative phase and diagnosis of the recurrent tumors in the postoperative phase. Malignant breast tumors show areas of high cellularity and low ADC values (7,8).

This study aimed to identify the abnormal signal alterations detected using DWI in different histopathological types of malignant breast lesions, to detect the differences in the ADC values, and to compare cellular region/stroma ratio and histopathological results.

Background/aim: This study aimed to compare the apparent diffusion coefficient (ADC) values of malignant breast lesions with different histopathological types on diffusion-weighted imaging (DWI) and the cellular region/stroma (CR/S) ratio and histopathological results.

Materials and methods: Breast diffusion-weighted magnetic resonance findings of 59 patients were retrospectively analyzed for malignant breast lesions. The CR/S ratio was calculated using breast wide-excisional biopsy or mastectomy specimens.

Results: Receiver operating characteristic analysis was performed for malignant lesions and subtypes. An ADC threshold of 1.260 × 10⁻³ mm²/s was set to detect invasive ductal carcinoma with 80.8% sensitivity and 81.4% specificity. An ADC threshold of 1.391 × 10⁻³ mm²/s was set to detect invasive lobular carcinoma lesions with 88.2% sensitivity and 79.5% specificity. The ADC value for lesions with low CR/S ratio (n = 21) was 1.135 ± 0.429 × 10⁻³ mm²/s and it was 1.155 ± 0.429 × 10⁻³ mm²/s in the high CR/S ratio group (n = 18).

Conclusion: ADC value calculation does not seem to be used as an alternative for histopathological detection, which is the gold standard for the differentiation of subtypes of malignant breast cancer. In addition, since there is a positive correlation between CR/S ratio and ADC values, it may be a strong marker to evaluate the stromal component of lesions.

Key words: Diffusion-weighted imaging, cellular region/stroma ratio, magnetic resonance imaging
these values with the cellular region/stroma (CR/S) ratio and histopathological results.

2. Materials and methods

Before the present study, permission was obtained from the ethics committee of the faculty. Informed patient consent was obtained before inclusion in the study and the study was conducted in accordance with the principles of the Declaration of Helsinki.

2.1. Study population

Images of 59 patients (age range: 25–76 years) who underwent routine breast MRI examination including diffusion weighted sequences in August 2011–November 2013 were analyzed retrospectively. Study inclusion criteria were to have mass size of ≥1.5 × 1.5 cm and to have Breast Imaging Reporting and Data Systems (BI-RADS) Category 4, 5, or 6 lesions detected in the breast imaging. Measurements were also made on the contralateral normal breast tissues of the patients. MRI scans of premenopausal patients were performed in the 2nd week of their menstrual cycle. Patients with cardiac pacemakers that contraindicate MRI and with surgical clips or prostheses that are incompatible with MRI were excluded from the study. In addition, patients who had lesion diameter of <1.5 cm, who underwent excisional or incisional biopsy before MRI, who received chemotherapy or radiation therapy before MRI, and those with artifacts with MRI were also excluded from the study.

2.2. MRI and DWI evaluation

All patients underwent MRI using a 1.5 T MRI device (Gyroscan Achieva, Philips, ACS-NT). Fat-suppressed TSE T1 and T2 weighted axial, gradient echo T1 weighted axial, contrast gradient echo T1 weighted dynamic, and late-phase axial sequences were performed as the routine breast sequences by using a standard breast coil in the prone position with a 40 cm field of view (FOV). Images with a slice thickness of 3 mm and slice spacing of 0.3 mm (TR: 515 m/s, TE: 8 m/s, matrix: 512 × 512) were obtained for the precontrast TSE T1 SPIR-weighted images. Before entry into the MRI device, a catheter was inserted into an antecubital vein of each patient for injection of the contrast agent. For dynamic examination, 8 images were produced for each section in the axial plane at 30-s intervals using T1-weighted FFE sequences with TR: 15 m/s, TE: 5 m/s, lying angle: 20°, matrix: 256 × 256, slice thickness: 4 mm, and slice spacing: 0.4 mm. Gadolinium-based contrast agent (a dose of 0.1–0.2 mmol/kg) was manually intravenously administered in 20 s.

By using the standard subtraction program integrated into the Philips MRI console, the precontrast dynamic images were extracted from the corresponding postcontrast dynamic images in pixels to obtain the subtract series, which contributed to the revealing of the contrasting profile. Initial dynamic serial images were transferred to the workstation (EasyVision-M, Philips, ACS-NT, USA) in a digital environment to draw the time-signal intensity curves of the lesions. In addition, after the patients were asked to hold their breath before the injection of the contrast agent, DWI was performed in the axial plane using the single-shot echo planar spin-echo sequence with the following parameters: TR/TR: 5250/90 m/s, matrix: 128 × 128, FOV: 35 cm, slice thickness: 3 mm, and slice spacing: 1.5 mm. Both breasts were examined in approximately 200 slices. For each slice, three different “b” values of “b = 100 s/mm²”, “b = 500 s/mm²”, and “b = 1000 s/mm²” were used. Diffusion gradients were applied simultaneously in three perpendicular directions (x, y, z). Each DWI sequence was acquired in approximately 4 min. A diffusion group consisting of five images for each slice obtained was created using anisotropic and isotropic (trace) diffusion slices along the respective directions of b = 0, x, y, z. ADC values were automatically calculated using a specific program of the MRI console to create ADC maps and all images were transferred to the digital archiving system (PACS: Picture Archiving and Communication System).

2.3. Data assessment

All conventional sequences and DWI scans were assessed by two radiologists with 4 and 5 years of experience, respectively. These assessments were based on the presence and prevalence of the breast lesions with abnormally contrast enhancement, presence/absence of restricted diffusion detected via high signaling regions in the DWI scans of the breast tissues accounting for the lesions (b = 1000 s/mm²), and the values measured in the ADC map. ADC values of the contralateral normal breast tissues were considered for the control group. Necrotic and cystic components of the lesions and, for the normal breast, adipose tissue measurement area were excluded during the ADC measurements. ADC values were measured three times each from the nonnecrotic and noncystic parts of the lesions to calculate the arithmetic mean. The ADC value was calculated via the standard region of interest with the standard deviation as a measure of variation. Measurements made in this scope were then compared with the pathological result of the lesion. Histopathological results were accepted as the “gold standard”.

2.4. Histopathological evaluation

To compare the ADC and CR/S ratio, hematoxylin and eosin-stained tumor sections of the breast wide excision or mastectomy materials were reexamined and a total of five images were obtained: two from the most cellular region, one from the most peripheral and one from the least cellular region, and one from the transition region between these two regions (midcellular region), all under 20× magnification (Olympus DP70, Olympus Optical Co. Ltd., Japan).
In this study, all histopathology images were segmented manually by pathologists using a software tool (Arachne by Netform Engineering, İzmir, Turkey, http://www.netformvision.com/arachne.asp) (accessed 16.08.2013). The Arachne software tool was developed in C++ programming language for the Windows operating system. Arachne allows pathologists to label each grid square as various types (tumor, stroma, lumen, etc.) by mouse clicks and calculates the requested label ratios of any kind and other digital features using the input label grid information. Following manual intervention, digital features are automatically calculated by Arachne using the provided data. In the scope of this study, the cellular and extracellular regions were marked and boxed in different colors with the help of this program. The diameter of each box was defined as 80 µm² in the design phase of the study so as to ensure that it could cover at least one cell. A third color was used to mark the artificial spaces of the tissue, which were then excluded from the calculations. The ratio of the selected regions (the cellular and extracellular regions) to each other was automatically calculated using the Arachne software. The procedure was repeated for each image. The arithmetic mean of the five images of the same individual case was calculated to obtain the final values. The procedure took approximately 20 min for each case. The cases with Tru-Cut biopsy specimens were excluded from the study since they did not have a tumor site large enough to obtain five images under 20× magnification.

2.5. Statistical analysis
Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The Mann–Whitney U test was used for group comparisons of the measurable variables and two-tailed variant analysis for the repeated measurements of the ADC values. The Spearman correlation test and kappa consistency test were used to compare the counted variables. The receiver operating characteristic (ROC) curve was drawn to analyze the validity and reliability of the mean ADC values of ductal and lobular breast lesions due to their high incidence. The t-test was used to estimate the statistical significance level of the mean ADC values in distinguishing both lesions. ADC measurement values of both observers were analyzed via correlation analysis. Statistical significance was set at P < 0.05.

3. Results
The measurements of the malignant breast lesions and normal breast tissues (b = 1000 s/mm²) produced mean ADC values of 1.725 ± 0.508 × 10⁻³ mm²/s for normal breast tissues and 1.98 ± 0.410 × 10⁻³ mm²/s for malignant breast lesions. The mean ADC value was calculated to be 1.078 ± 0.340 × 10⁻³ mm²/s for the invasive ductal carcinoma (IDC) lesions (n = 26), 1.151 ± 0.340 × 10⁻³ mm²/s for the invasive lobular carcinoma (ILC) lesions (n = 22), 0.783 ± 0.188 × 10⁻³ mm²/s for the ID + ILC lesions (n = 7), 1.241 ± 3.32 for the IDC + invasive cribriform carcinoma (ICC) lesion (n = 1), 1.075 ± 0.154 × 10⁻³ mm²/s for the ITC lesion (n = 1), 0.845 × 10⁻³ mm²/s for the medullary carcinoma lesion (n = 1), 2.568 ± 0.165 × 10⁻³ mm²/s for the mucinous carcinoma lesions (n = 7), 1.241 × 10⁻³ mm²/s for the IDC + invasive lobular carcinoma (ILC) lesions (n = 1), 0.927 × 10⁻³ mm²/s for the tubular carcinoma (ITC) lesion (n = 1), 0.754 × 10⁻³ mm²/s for the Langerhans-cell histiocytosis (LCH) lesion (n = 1), and 0.650 × 10⁻³ mm²/s for the lymphoma lesion (n = 1). Separate ROC analyses were performed for the malignant lesions, IDC lesions, and ILC lesions. Accordingly, the threshold ADC value to differentiate the malignant tissue from the normal breast tissue was set at 1.260 × 10⁻³ mm²/s, with 79.7% sensitivity and 81.4% specificity (area under curve [AUC] = 85.7%). Similarly, the threshold ADC value for the detection of IDC lesions was set at 1.260 × 10⁻³ mm²/s, with 80.8% sensitivity and 81.4% specificity and the threshold ADC value for the detection of ILC lesions was set at 1.391 × 10⁻³ mm²/s, with 88.2% sensitivity and 79.5% specificity (AUC = 87.2% and 84.3%, respectively) (Table 1; Figure 1). Since the AUC and the sensitivity and specificity values were high, the threshold ADC value had high discriminatory power. The results of the t-test conducted to compare the IDC and ILC values produced no statistically significant difference in the mean ADC values of the two groups (P = 0.45). Correlation between the two observers in the measurements of the ADC maps at b = 100, 500, and 1000 s/mm² of the lesion (the localization and size of which was detected in MRI on the T1-weighted sequences) was tested by the correlation test and found to be consistent with P < 0.001.

Evaluations of the pathological grading of the lesions produced mean ADC values of 1.462 ± 0.699 × 10⁻³ mm²/s for the grade 1 lesions (n = 8), 1.014 ± 0.280 × 10⁻³ mm²/s for the grade 2 lesions (n = 27), and 1.104 ± 0.362 × 10⁻³ mm²/s for the grade 3 lesions (n = 22). Pathological grading of two lesions, one diagnosed as LCH and the other as lymphoma, was not reported. The Kruskal–Wallis test was used to test any histopathological grading-based statistically significant difference between the mean ADC measurements, which revealed no statistically significant difference between the grade 1, 2, and 3 lesions (P = 0.263). The highest CR/S ratio was found to be 13.79, the minimum to be 0.11 (mean: 1.46), and the median to be 0.46. CR/S ratios were classified into the two groups of high CR/S (above the median value) and low CR/S (below the median value). The CR/S ratio was recorded to be 2.11 ± 3.32 for the IDC (n = 19), 0.55 ± 0.76 for the ILC (n = 10), 1.53 ± 1.62 for the IDC + ILC (n = 4), 0.15 for IDC + ICC (n = 1), 0.30 for the ICC (n = 2), 3.56 for the medullary carcinoma (n = 1), 0.44 for the ITC (n = 1), and 0.38 for the
Due to the disproportional numeric distribution and prevalence, the chi-square test revealed no statistically significant relationship of the CR/S ratios of the histological subtypes of IDC, ILC, and others in distinguishing between the subtypes \( (P = 0.48) \) (Table 2).

However, the nonparametric Spearman correlation test revealed a positive correlation between the variables regarding the relationship between histopathological grading and the CR/S ratio \( (P < 0.0001; r = 0.583) \). In other words, the CR/S ratio increased in parallel with the increase in the histopathological grade. The Pearson correlation test was used to analyze the correlation between the mean ADC values and CR/S ratio. Mean ADC value was calculated to be \( 1.135 \pm 0.429 \times 10^{-3} \text{ mm}^2/\text{s} \) in those with low CR/S ratio \( (n = 21) \) and \( 1.155 \pm 0.429 \times 10^{-3} \text{ mm}^2/\text{s} \) in those with high CR/S ratio \( (n = 18) \). A positive correlation was observed between mean ADC values and CR/S ratio, though not at a statistically significantly level \( (P = 0.62; r = 0.08) \) (Table 3).

### Table 1. Specificity and sensitivity of threshold ADC value in malignant tissues and subtypes.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>ADC 1000</th>
<th>Threshold ADC value, ( \times 10^{-3} \text{ mm}^2/\text{s} )</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant lesions</td>
<td>1.260</td>
<td>1.260</td>
<td>79.7</td>
<td>81.4</td>
<td>85.7</td>
</tr>
<tr>
<td>IDC</td>
<td>1.260</td>
<td>1.260</td>
<td>80.8</td>
<td>81.4</td>
<td>87.2</td>
</tr>
<tr>
<td>ILC</td>
<td>1.391</td>
<td>1.391</td>
<td>88.2</td>
<td>79.5</td>
<td>84.3</td>
</tr>
</tbody>
</table>


Figure 1. ROC curves showing high sensitivity for the threshold ADC value in malignant lesions, IDCs, and ILCs.

4. Discussion

The only imaging method that, under current conditions, visualizes cellularity is DWI \( (9, 10) \). Breast imaging is generally performed at 1.5 T and high b values, and the measurement accuracy of the mean ADC values is observed to increase at 3 T and b values of >850 mm/s \( (11, 12) \). Lesions with lower ADC values are observed to have better contrast in studies conducted on brain tumors by assigning high b values. This finding indicates that MRI and DWI are much better in young and high-density breasts with increased prevalence of ductal carcinoma in situ (DCIS) \( (13) \). In a study where they used b values of 0 and 700 s/mm², Kinoshita et al. reported the mean ADC value of \( 1.22 \pm 0.19 \times 10^{-3} \text{ mm}^2/\text{s} \) of IDC-diagnosed masses in the DWI scans acquired with single-shot turbo spin echo (HASTE) sequences \( (8) \). In another study where Reiko et al. \( (14) \) evaluated the mean ADC values in the discrimination of IDC and non-IDC cases, the ADC value for IDC was found to be statistically significantly lower than that for non-IDC. In the study conducted by...
Sinha et al. (15), in EPI sequences with b values of 0 and 400 mm²/s, the mean ADC value of the malignant breast lesions was found to be 1.60 ± 0.36 × 10⁻³ mm²/s. When considered together with the results of many other studies, the study by Sonmez et al. (16) is observed to produce lower mean ADC values in malignant breast tumors. In the model study where Rahbar et al. (17) compared contrast-enhanced dynamic MRI and DWI in DCIS grading by using b values of 0 and 600 mm²/s, better contrast-to-noise ratio was observed to be produced at high b values.

In the study of Guo et al. (6), which used EPI sequences and b values (100, 500, and 1000 s/mm²) similar to the present study, the authors reported the mean ADC value of 0.97 ± 0.20 × 10⁻³ mm²/s in the malignant breast lesions and the threshold ADC value of 1.30 × 10⁻³ mm²/s, with 93% sensitivity and 88% specificity. In the study by Luo et al. (18), the mean ADC value was defined to be 0.87 ± 0.23 × 10⁻³ mm²/s in malignant lesions and the threshold ADC value was 1.22 × 10⁻³ mm²/s, with 88.9% sensitivity and 87.9% specificity. However, in the present study, although the mean ADC value of the malignant lesions (b = 1000) was found to be lower for the IDC lesions than the ILC lesions, no statistically significant difference was found between the mean ADC values in the discrimination of subtypes (P = 0.45). The high mean ADC value of mucinous tumor lesions can be attributed to the brightness of the mucin content in the T2-weighted MRI. Although both the present study and that of Lou et al. as well as some other literature studies produced similar threshold ADC values for the b value of 1000 s/mm² for malignant breast lesions, there are numerical differences in the threshold ADC values when compared with some other studies (18).

Table 2 presents the differences between the data produced by the present study and the previous literature data. These differences can be attributed to the brand of the devices used and the differences in Tesla power and, particularly, b values.

As the grade of malignant tumor lesions increases, the mean ADC value is expected to decrease (18). In the study by Mami et al. (19) on low-grade DCIS patients, those with low grades were observed to produce higher ADC values than those with moderate- and high-grade DCIS. The study by Razek et al. (1) showed a statistically significant decrease in mean ADC values with the increase in the lesion grading of the IDC cases. In a study on brain tumors, mean ADC value of the low-grade gliomas was observed to be higher than that of the high-grade gliomas. Unlike in the literature, the present study produced no histopathological grade-based statistically significant relationship between the mean ADC values of the grade 1, 2, and 3 lesions (P = 0.263). This result is estimated to have resulted from the lesions consisting of heterogeneous and different subtypes and it is thought that the results

### Table 2. CR/S ratio and mean ADC values of malignant subtypes.

<table>
<thead>
<tr>
<th>Histology</th>
<th>CR/S</th>
<th>Mean ADC, × 10⁻³ mm²/s</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC</td>
<td>2.11 ± 3.32</td>
<td>1.123 ± 0.309</td>
<td>19</td>
</tr>
<tr>
<td>ILC</td>
<td>0.55 ± 0.76</td>
<td>1.073 ± 0.184</td>
<td>10</td>
</tr>
<tr>
<td>IDC + ILC</td>
<td>1.53 ± 1.62</td>
<td>0.862 ± 0.219</td>
<td>4</td>
</tr>
<tr>
<td>IDC + ICC</td>
<td>0.15</td>
<td>1.241</td>
<td>1</td>
</tr>
<tr>
<td>ICC</td>
<td>0.30</td>
<td>0.966</td>
<td>1</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>3.56</td>
<td>0.845</td>
<td>1</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>0.38</td>
<td>2.568 ± 0.165</td>
<td>2</td>
</tr>
<tr>
<td>ITC</td>
<td>0.44</td>
<td>0.927</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3.56</td>
<td>39</td>
</tr>
</tbody>
</table>


### Table 3. Mean ADC values of low and high ratios of CR/S (P = 0.62) (Pearson correlation analysis, r = 0.08).

<table>
<thead>
<tr>
<th>CR/S ratio</th>
<th>n (%)</th>
<th>Mean ADC, × 10⁻³ mm²/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>21 (51.2)</td>
<td>1.135 ± 0.428</td>
</tr>
<tr>
<td>High</td>
<td>18 (48.8)</td>
<td>1.155 ± 0.428</td>
</tr>
<tr>
<td>Total</td>
<td>39 (100)</td>
<td></td>
</tr>
</tbody>
</table>

CR/S: Cellular region/stroma, ADC: apparent diffusion coefficient.
will comply with the previous literature results when the grades of a single subtype are considered.

One of the major prognostic factors of malignant breast lesions is the histopathological characteristic of the lesions (20). These characteristics are classified as the size and grade of the lesion. According to the American Joint Committee on Cancer (AJCC/UICC) TNM staging system, 7th edition, the Nottingham Histologic Score System (Elston–Ellis modification of Scarff–Bloom–Richardson Grading System) is used (20). This system defines the final grade according to glandular/tubular differentiation, nuclear pleomorphism, and mitotic activity. Different parameters are considered in lesion grading of different organ malignancies.

The stromal tissue that surrounds the tumor cells in malignant breast lesions plays a key role in the development and behavior of the tumor. In a study in which Kruijf et al. (21) investigated the relationship between the CR/S ratio and relapse in triple-negative breast cancer, the life-long relapse risk was found to be 2.92 times higher for tumors with more than 50% stromal content compared to those with a lower stromal content. The literature defines the stromal content amount as one of the prognostic factors of primary tumors of colorectal cancer (21). In a study where Unlu et al. (22) evaluated the prognostic value of the tumor stromal content in laryngeal cancer, the stromal content was observed not to be a prognostic factor but was recorded to be low, as expected, in cases with perinodal invasion. The analyses made in the scope of this present study by using the CR/S ratio calculation program proved a statistically significant relationship between grade and cellularity (P < 0.0001). There was a positive correlation between grade and CR/S ratio: high grades were accompanied by high CR/S ratios. The direct relationship documented by the literature between histopathological grade and prognosis, on one hand, and particularly cellularity, on the other, in neuroectodermal tumors does not apply to most of the tumors with epithelial origin (21,23). Breast lesions are also in the group of tumors with epithelial origin, and particularly the stromal content, as well as cellularity, has a significant impact on tumor behavior. For this reason, in the scope of this study, it may be misleading to establish a one-to-one relationship between the grade and CR/S ratio of malignant subtypes of the limited and heterogeneous study group. Another reason may be consideration by the pathologist of such criteria as the cell number and nuclear pleomorphism-atypia in detection of the grade (21). In conclusion, although the CR/S ratio seems to be quite helpful in the discrimination of lesions with malignancy potential, not effective marker in the differentiation of subtypes of malignant breast lesions currently. In the present study, the mean ADC value was 1.051 × 10⁻³ mm²/s with a CR/S ratio of 3.93 in one case with histopathologically confirmed IDC + ILC (Figures 2a–2d). There are only a limited number of literature studies pointing out the relationship between cellularity and ADC values. In the study by Koray et al. where the authors examined the ADC values and cellularity of pediatric cerebellar tumors by manually counting the cell nuclei in pathology preparations instead of using an automatic program, a negative correlation was shown between cellularity and ADC values (23). However, although cellularity is shown to be the sole marker that identifies the diffusion characteristics of the extracellular region of brain tumors with neuroectodermal origin, other parameters such as the stromal content amount should be considered together with cellularity in breast tumors with epithelial origin (24). Cellularity is directly proportional to the malignity potential of the tumor in central nervous system tumors. However, breast tumors are of epithelial origin, and the cellularity may not always affect the biological behavior adversely. In the present study, a positive correlation was observed between the increased CR/S ratios and the increased ADC values (P = 0.62; r = 0.08). Although these data seem to be the opposite of the relationship of the mean ADC value with cellularity, there

### Table 4. Mean ADC values of malignant lesions in the literature and the present study.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Mean ADC value</th>
<th>IDC</th>
<th>ILC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sequence</td>
<td>b value</td>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Sönmez et al. (16)</td>
<td>EPI</td>
<td>0–1000</td>
<td>0.82 ± 0.07</td>
<td>-</td>
</tr>
<tr>
<td>Guo et al. (6)</td>
<td>EPI</td>
<td>0–1000</td>
<td>0.97 ± 0.27</td>
<td>-</td>
</tr>
<tr>
<td>Luo et al. (18)</td>
<td>EPI</td>
<td>0–1000</td>
<td>0.87 ± 0.23</td>
<td>-</td>
</tr>
<tr>
<td>Reiko et al. (14)</td>
<td>EPI</td>
<td>0–750</td>
<td>1.12 ± 0.24</td>
<td>1.09 ± 0.23</td>
</tr>
<tr>
<td>Our study</td>
<td>EPI</td>
<td>0–1000</td>
<td>1.098 ± 0.41</td>
<td>1.078 ± 0.294</td>
</tr>
</tbody>
</table>

ADC: Apparent diffusion coefficient, EPI: echoplanar imaging.
Figure 2. T1W image and T2W image with fat suppression; BI-RADS 5 lesion with localized lobular and irregular margins (a, b). The upper outer quadrant of the right breast showing contrast enhancement in the postcontrast series, pharmacokinetic curves showing type 2 curving (c). Limited diffusion with a mean ADC value of $1.051 \times 10^{-3} \text{ mm}^2/\text{s}$ and CR/S ratio of 3.93 (d). Histopathology: IDC + ILC, grade 2.
is no literature study indicating a relationship between the CR/S ratio and the ADC value of malignant breast lesions. In this study, since it is reproducible and reliable, automatic software was used to calculate the CR/S ratio. Although this study suggests for breast carcinomas that increased ADC values may be associated with high cellularity and that high tumor cellularity may be associated with high grade, these results offer no final prediction about the biological behavior of the tumor because none of the aforementioned parameters are independent prognostic factors themselves. Fluid diffusion in the extracellular region was expected to be limited and, in turn, the ADC ratio was expected to decrease as the cellularity increased. However, the stromal content in the extracellular region may play a role in diffusion limitation in breast carcinomas.

There are new techniques available; Perou et al. suggested four intrinsic breast cancer subtypes (luminal-A, luminal-B, HER2-enriched, triple-negative) that could be defined at the gene expression level (25). In pathologic evaluation new techniques and immunohistochemistry allow us to determine new markers such as hormone receptor, human epidermal growth factor receptor-type 2 (HER2), and proliferation index. In the literature there are many indications of subtype differentiation of breast cancer according to MRI characteristics (26,27). In our study we have not evaluated ADC values and cellularity values of breast lesions according to molecular subtypes. This is one of the limitations of this study. Furthermore, the number of patients in this study is small. This is another limitation of our study. By increasing the number of patients and the classification of lesions according to molecular subtypes, the results of ADC values and CR/S ratios would provide us a strong marker in the diagnosis and discrimination of different subtypes of breast malignant lesions.

In conclusion, ADC and DWI combined with conventional breast MRI enable prediction at high sensitivity and specificity to differentiate the histopathological subtypes of malignant lesions from normal breast tissue. However, ADC calculation does not seem to be an alternative of the golden standard of histopathology in the differentiation of the subtypes. In addition, the positive correlation between the ADC values and the CR/S ratio is thought to possibly be used as a strong marker in evaluation of the stromal component of lesions.

Acknowledgment

The authors would like to thank Dr Devrim Önder (PhD) and Prof Dr Sülen Sarıoğlu (MD), the designers of Arachne software, for providing the software for this particular study.

References