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Original Article

Breast Imaging with Diffusion-Weighted Magnetic Resonance Imaging: Evaluating Apparent Diffusion Coefficient Values and Biomarker Expression in Benign and Malignant Lesions

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ABSTRACT

Objective: In the literature, apparent diffusion coefficient values are known to be able to discriminate between benign and malignant breast lesions. We aim to evaluate the most efficient *b*-value to discriminate between benign and malignant lesions and also to reveal the potential relationships between diffusion-weighted imaging and apparent diffusion coefficient values and biomarker expression.

Methods: We retrospectively evaluated the magnetic resonance imaging and pathological data of 60 breast lesions, categorized as BI-RADS 4, 5, and 6. Signal intensity values obtained from diffusion-weighted imaging at B0, B1000 and apparent diffusion coefficient values were recorded. A possible correlation between apparent diffusion coefficient values and tumor grade, receptor expression (that of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2), and Ki-67 score was investigated.

Results: Twenty-two (36.6%) lesions were malignant, and 38 (63.4%) lesions were benign. Mean apparent diffusion coefficient values of malignant lesions were significantly lower than that of benign lesions ($187 \pm 215 \times 10^{-6}$ and $625 \pm 118 \times 10^{-6}$ mm^2/s, respectively). We detected lower apparent diffusion coefficient values in estrogen receptor- and progesterone receptor-negative tumors, also lower apparent diffusion coefficient values were correlated with higher Ki-67 index ($P < .05$). We cannot find any significant relationship between apparent diffusion coefficient values and human epidermal growth factor receptor 2 expression ($P > .05$). We showed that signal intensity values obtained at B1000 were more efficient than those obtained at B0 in differentiating benign and malignant lesions. Apparent diffusion coefficient values obtained from ipsilateral, pathologically proven metastatic lymph nodes were significantly lower from contralateral lymph nodes.

Conclusion: Apparent diffusion coefficient values can be used effectively to predict breast malignancy, estrogen receptor/progesterone receptor negativity, and Ki-67 index. Diffusion-weighted imaging obtained at B1000 is more effective in predicting malignancy compared to B0.

Keywords: ADC, biomarkers, breast cancer, DWI

INTRODUCTION

Breast cancer is a relatively common and potentially life-threatening disease that affects millions of women worldwide.[1] Early detection and accurate diagnosis are crucial in improving patient outcomes and reducing mortality rates. Over the years, imaging techniques have played a pivotal role in the diagnosis and management of breast cancer, enabling health-care professionals to detect lesions earlier, assess their characteristics, and guide treatment decisions.

Conventional imaging techniques, such as mammography (MG) and ultrasound (US), have long been the mainstay for breast cancer screening and evaluation. Mammography is widely used due to its ability to detect microcalcifications and architectural distortions associated with early-stage breast cancer. However, it has certain limitations, particularly in women with dense breast tissue, where the sensitivity of mammography may be reduced.[2] Ultrasound, on the other hand, is valuable for differentiating solid masses from cysts and guiding targeted biopsies. Despite their effectiveness, these techniques may not provide sufficient information for precise characterization of breast lesions, especially when it comes to distinguishing between benign and malignant cases[3].

In recent years, diffusion-weighted imaging (DWI) has emerged as a promising modality for breast imaging. Diffusion-weighted imaging utilizes the random motion of water molecules within tissues to generate contrast and provide insights into tissue microstructure. It is based on the measurement of the apparent diffusion coefficient (ADC), which reflects the degree of water molecule diffusion within the tissue. By measuring

ADC values, DWI can offer valuable information about tissue cellularity, organization, and vascularity, which are essential in differentiating benign and malignant lesions.[4]

Diffusion-weighted imaging is a noninvasive technique, requires no ionizing radiation exposure, and does not require the administration of contrast medium. The short examination time, especially when using parallel imaging, is an additional advantage, as is the ability to assess the tumor completely. Furthermore, both conventional morphologic and physiologic assessments can be made during the same examination.[5]

Single-shot or multishot echo-planar imaging (EPI) is regarded as baseline techniques for DWI acquisition. On high *b*-values, cancers are typically hyperintense given adequate baseline T2 signal. As the basic DWI sequence is T2-weighted, lesions with higher water content will show a high signal on low *b*-value images and may retain a (relatively) high signal on high *b*-value images. Consequently, a high signal on high b-values images may be due to a very high T2 signal or true diffusion restriction with little signal decrease of a moderately high T2 signal.[6]

The ability of DWI to discriminate between benign and malignant breast lesions has been investigated extensively, and DWI has shown promising results. Malignant breast lesions generally exhibit lower ADC values due to their higher cellularity and restricted water diffusion.[7] On the other hand, benign lesions, such as fibroadenomas or cysts, tend to have higher ADC values due to their lower cellularity and increased water diffusion.[8]

However, the role of DWI signal intensity (SI) values and the optimal selection of *b*-values in DWI for breast imaging remain as the areas of ongoing research. *B*-values represent the strength and timing of diffusion-sensitizing gradients used in DWI magnetic resonance imaging (DW-MRI). Different *b*-values can influence the sensitivity and specificity of DWI-MRI in detecting and characterizing breast lesions. Therefore, determining the most efficient *b*-value for discriminating between benign and malignant lesions is essential for improving the accuracy and diagnostic performance of DWI.[9]

Furthermore, beyond the discrimination between benign and malignant lesions, DWI has the potential to provide valuable insights into the molecular characteristics of breast tumors.[10] The correlation between ADC values and biomarker expression, such as that of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and the proliferation marker Ki-67, has been of great interest.[11] Understanding these relationships can aid in predicting tumor aggressiveness, assessing treatment response, and personalizing therapeutic strategies.

In this study, we aimed to evaluate the most efficient *b*-value in discriminating between benign and malignant breast lesions using DWI. Additionally, we aimed to investigate the potential relationships between DWI and ADC values and biomarker expression, including that of ER, PR, HER-2, and Ki-67. The findings from this research will contribute to the growing body of knowledge regarding the utility of DWI.

MAIN POINTS

- ADC values can be used effectively to predict breast malignancy, ER/PR receptor negativity and Ki-67 index. DWI obtained in B1000 is more effective in predicting malignancy compared to B0.
- DWI has been shown to have the ability to distinguish between benign and malignant breast lesions. Malignant breast lesions usually exhibit lower ADC values due to their higher cellularity and restricted water diffusion. On the other hand, benign lesions tend to have higher ADC values due to their lower cellularity and increased water diffusion.
- Of the 60 lesions, 22 (36.6%) were malignant and 38 (63.4%) were benign. The mean ADC values of malignant lesions were significantly lower than those of benign lesions ($187 \pm 215 \times 10^{-6}$ and $625 \pm 118 \times 10^{-6}$ mm^2/s ,respectively).
- Lower ADC values were observed in ER and PR negative tumors, and there was a positive correlation between lower ADC values and higher Ki-67 index.
- DWI with optimal b-values and ADC value analysis holds great promise as a valuable imaging technique in the evaluation of breast lesions. By providing non-invasive information about tumor characteristics, including malignancy, receptor expression, and proliferative activity, DWI can aid in clinical decision-making and contribute to improved patient management in breast cancer.

METHODS

Our study was a retrospective study and included patients who applied to our clinic between January 2022 and June 2022. Our study was approved by the Erzincan Binali Yıldırım University Ethics Committee (Ethics committee approval number: EBYU-KAEK-2023-4/21 E-1845473.11. ED.28465). A retrospective analysis was performed on MRI images and pathological data from 60 breast lesions classified as BI-RADS 4, 5, and 6. Patients reported as BI-RADS 4, 5, and 6 in the breast MRI report were included in the study. Inappropriate image quality was chosen as an exclusion criterion. Five patients were excluded from the study and 60 patients were included in the study.

Breast MRI examinations were performed with a 1.5-T whole-body imaging system (MAGNETOM Aera, Siemens, Erlangen, Germany). The patients were scanned in the prone position with the breast suspended in a 16-channel breast coil. Precontrast transverse acquisitions were performed using a T1-weighted fast spin echo sequence and transverse T2 -weighted fast spin echo short-tau inversion recovery (STIR) imaging, while precontrast sagittal acquisitions were performed using a T2-weighted fast spin echo sequence imaging with fat suppression. Diffusion-weighted images were acquired with fat saturation using axial echo planar imaging (EPI) sequences at b-1000 s/mm^2 before contrast administration. Sagittal pre- and postcontrast dynamic imaging was performed using a 3D multiphase fast gradient echo pulse sequence. Additionally, transverse postcontrast T1-weighted images were acquired using the fast spoiled gradient-recalled echo sequence in the same manner as it was used to acquire the precontrast images, without a change in the patient's position. Subtraction images were created. The patients were given a bolus intravenous injection of gadolinium contrast (0.2 mmol/kg). Both morphological features and kinetic characteristics of the lesions were examined. Region of interest (ROI) values were made using circular ROI.

Then a possible correlation between ADC values and tumor grade, receptor expression (that of ER, PR, and HER-2), and Ki-67 score was investigated. ADC values from histologically diagnosed axillary lymph nodes were also analyzed.

All assessments were made by a single radiologist with 5 years of experience.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences Statistics for Windows, version 20.0, software (IBM SPSS Corp., Armonk, NY,, USA). Normal distribution of the data was evaluated with the Kolmogorov–Smirnov test. Numerical variables with normal distribution were shown as mean ± standard deviation values. Student's *t*-test was used to analyze the difference between mean ADC values of the groups. Spearman's and Pearson's correlation analyses were applied to define possible correlations between the ADC values and pathological parameters. Logistic regression analysis was applied to define the diagnostic efficacy of the DWI SI values.

RESULTS

Of the 60 lesions, 22 (36.6%) were malignant and 38 (63.4%) were benign. The malignant group consisted of 6 cases (27.2%) of ductal carcinoma in situ, 10 cases (45.4%) of invasive ductal carcinoma, 5 cases (22.7%) of invasive lobular carcinoma, and 1 case (4.5%) of B-cell lymphoma. The benign group consisted of 22 cases (57.8%) of fibroadenoma, 7 cases (18.4%) of sclerosing adenosis, 5 cases (13.1%) of benign phyllode tumor, and 4 cases (10.5%) of usual ductal hyperplasia. The mean ADC values of malignant lesions were significantly lower than those of benign lesions ($187 \pm 215 \times 10^{-6}$ and $625 \pm 118 \times 10^{-6}$ mm^2/s, respectively). The results are shown in Table 1.

There were 3 ER-negative and 7 PR-negative tumors, and ADC values of these receptor-negative tumors were lower ($187 \pm 215 \times 10^{-6}$ mm^2/s) . The level of the Ki-67 proliferation index was available for 23 patients. The mean value was 12.36 ± 21.68%. A Ki-67 value of 25% was used as the threshold for discriminating between tumors with low Ki-67 expression (<25%) and high Ki-67 expression (≥25%). And these tumors had a high Ki-67 expression (≥25%). Ki-67 proliferation index was evaluated in 23 lesions; 12/23 had high and 11/23 had low index. Tumors with low expression of Ki-67 had higher ADC values than tumors with high expression of Ki-67 ($187 \pm 215 \times 10^{-6}$ and $625 \pm 118 \times 10^{-6}$ mm^2/s, respectively; $P < .005$). It was observed that there was a positive correlation between them.

Lower ADC values were observed in ER- and PR-negative tumors, and there was a positive correlation between lower ADC values and higher Ki-67 index ($P < .05$). However, no significant relationship between ADC values and HER-2 expression was found. Diffusion-weighted imaging SI values obtained at $b=1000$ demonstrated higher efficiency in differentiating between benign and malignant lesions compared to $b=0$ ($P < .05$).

Furthermore, ADC values obtained from ipsilateral metastatic lymph nodes were significantly lower than (ADC values $187 \pm 215 \times 10^{-6}$) those from contralateral lymph nodes ($P < .05$).

Table 1. Lesion Characterization

	Total	Percent
Malignant group	32	36.6
Ductal carcinoma in situ	6	27.2
Invasive ductal carcinoma	10	45.4
Invasive lobular carcinoma	5	22.7
B-cell lymphoma	1	4.5
Benign group	38	64.4
Fibroadenoma	22	57.8
Sclerosing adenosis	7	18.4
Benign phyllode tumor	5	13.1
Usual ductal hyperplasia	4	10.5

Table 2. Estrogen Receptor (ER), Progesterone Receptor (PR), and c-erbB2 Amplification Characteristics of the Lesions

	ER		PR		c-erbB2	
Pathological Diagnosis	+	–	+	–	+	–
Ductal carcinoma in situ	6	0	5	1	4	2
Invasive ductal carcinoma	8	2	6	4	5	5
Invasive lobular carcinoma	4	1	3	2	2	3
B-cell lymphoma	1	0	1	0	0	1
Total	19	3	15	7	11	1

Twenty-one of 60 (35.5%) patients had histopathologically proven metastatic axillary lymph nodes on MR images; 39/60 (65%) patients did not have any pathological axillary lymph node.

Estrogen receptor (ER), progesterone receptor (PR), and c-erbB2 amplification characteristics of lesions are shown in Table 2.

Case examples can be seen in Figures 1-3.

DISCUSSION

Our findings demonstrated that ADC values obtained from DWI can serve as an effective tool in predicting breast malignancy, as evidenced by the significantly lower mean ADC values observed in malignant lesions compared to benign lesions. These results are consistent with previous studies like Razek et al's study that have reported lower ADC values in malignant breast tumors due to their higher cellularity and restricted water diffusion.[5] Therefore, ADC values derived from DWI can provide valuable information for differentiating between benign and malignant breast lesions.

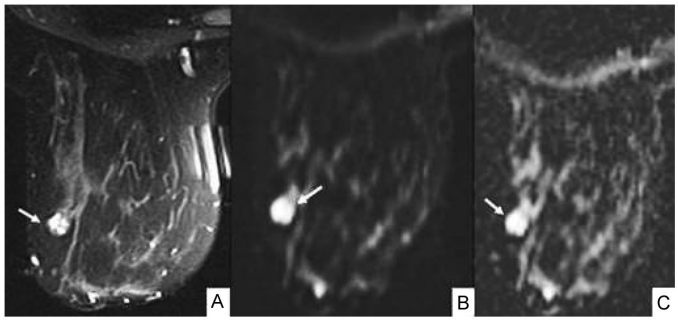

Figure 1. Contrast enhanced axial image (a), DWI (b), and ADC map (c) of a benign lesion (fibradenoma).

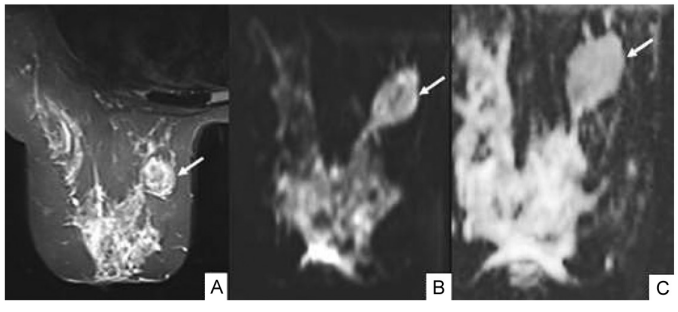

Figure 2. Contrast-enhanced axial image (A), DWI (B), and ADC map (C) of a malignant lesion (DIS). Apparent diffusion coefficient value of the lesion at B1000 is 143×10^{-6}. ADC, apparent diffusion coefficient; DIS, I added wrong figures, I need to delete and the rights. dissemination in space; DWI, diffusion-weighted imaging.

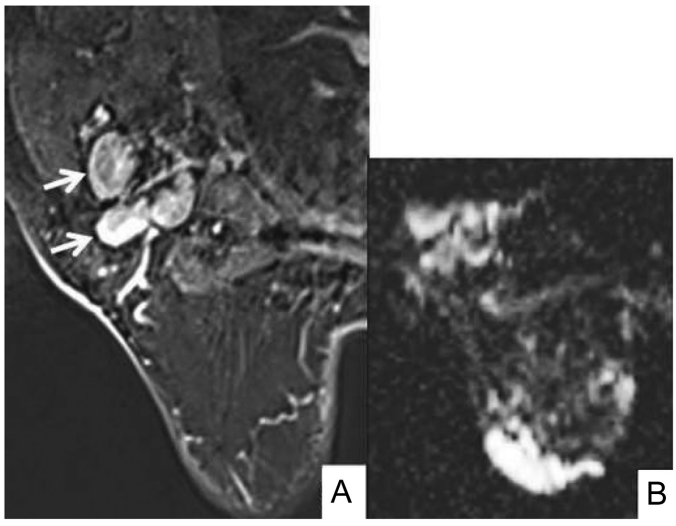

Figure 3. Contrast-enhanced axial image (A), and ADC map (B) of a histologically proven malignant axillary lymph node (invasive ductal carcinoma metastasis). Apparent diffusion coefficient value at B1000 is 810 × 10^{-6}. ADC, apparent diffusion coefficient.

Furthermore, Kim et al's study shows similar results to our study; our study revealed important associations between ADC values and biomarker expression. Lower ADC values were observed in ER- and PR-negative tumors, suggesting a potential link between decreased water diffusion and nonexistence of hormone receptor.[12]

Additionally, Surov et al's study shows similar results to our study; we found that lower ADC values correlated with a higher Ki-67 index, indicating a potential relationship between limited water diffusion and increased tumor proliferation. These findings highlight the potential of DWI and of ADC values as noninvasive biomarkers for predicting tumor grade and assessing the aggressiveness of breast cancer.[13]

Regarding the selection of *b*-values, our study demonstrated that SI values obtained at b1000 were more efficient than those obtained at B0 in differentiating benign and malignant lesions. This suggests that higher *b*-values may provide more accurate information to detect and characterize breast lesions, similar to the results of the Kuroki et al's study.[14.]

Our study revealed that ADC values in axillary lymph nodes ipsilateral, pathologically proven metastatic lymph nodes were significantly lower than in contralateral normal lymph nodes, as in the study of Fornasa et al.[15.]

Guo et al's study shows similar results to our study that the ADC is useful in differentiating benign from malignant breast lesions.[16]

Breast cancer is now a significant cause of worldwide morbidity and mortality. Further, the increasing rate of breast cancer continues to be a major area of concern for both clinicians and researchers. Increased awareness in the affected population leads to more frequent physical examinations and diagnostic imaging procedures; thus, it can be expected to result in an earlier diagnosis and hence improved prognosis.[13]

The results of this study indicate that ADC values can effectively predict breast malignancy, ER and PR negativity, and Ki-67 index. Diffusion-weighted images obtained at $b=1000$ provides higher efficiency in predicting malignancy compared to $b=0$. Axillary metastatic lymph nodes exhibit lower ADC values compared to contralateral normal lymph nodes. Lower ADC values were observed in ER- and PR-negative tumors, suggesting a potential link between decreased water diffusion and nonexistence of hormone receptor. Additionally, lower ADC values were correlated with a higher Ki-67 index, indicating a potential association between restricted water diffusion and increased tumor proliferation. Optimizing the selection of *b*-values in DWI protocols can improve the diagnostic performance and reliability of this imaging modality for breast cancer evaluation.

These findings and the findings in the literature highlight the potential of DWI and ADC values in improving the characterization and assessment of breast lesions, aiding in treatment planning and patient management.

Study Limitations

The main limitations of our study were the retrospective design and the relatively small sample size. Further large-scale prospective studies are warranted to validate our findings and explore additional correlations between DWI-MRI, biomarker expression, and clinical outcomes. Also, the fact that MR measurements were made by the same radiologist is a limitation.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erzincan Binali Yıldırım University (Date: April 21, 2023 No.: E-1845473.11. ED.28465.

Informed Consent: Due to the retrospective design of the study, informed consent was not obtained.

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Declaration of Interests: The authors declare that they have no competing interest.

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