



Correlation of Peri-Tumoral Edema Determined in T2 Weighted Imaging with Apparent Diffusion Coefficient of Peritumoral Area in Patients with Breast Carcinoma

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Abstract

Background: Breast cancer may result in remodeling of adjacent normal appearing breast tissues. Magnetic resonance imaging (MRI) is increasingly used in the diagnosis and follow-up of breast cancer by means of diffusion weighted imaging, which is based on thermal motion of water molecules in the extracellular fluid.

Objectives: We investigated the correlation of visual assessment of peri-tumoral edema with peri-tumoral and tumoral apparent diffusion coefficient (ADC) values.

Patients and Methods: In this cross-sectional study, from 2016 to 2018, 78 patients with 89 malignant breast lesions (mean age, 47 years) were examined by 1.5-T breast MRI. The lesions were categorized based on the visual assessment of peri-tumoral edema on T2 weighted imaging (T2WI) into two groups: (A) with edema (36 lesions) and (B) without edema (53 lesions). Measuring ADC values in the contralateral normal breast tissue, peri-tumoral tissue and peri-tumoral-normal tissue ADC ratio were compared between the two groups for all lesions.

Results: The number of in situ lesions was higher in group B (7.5% vs 2.7%) with the p value of 0.01. The mean of ADC values in the normal breast tissue was $1.76 \times 10^{-3} \text{ mm}^2/\text{s}$. Tumor ADCs were significantly lower in group A compared to group B ($0.95 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. $1.11 \times 10^{-3} \text{ mm}^2/\text{s}$) with the P value of 0.003. However, peri-tumoral ADCs were significantly higher in group A ($1.82 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. $1.53 \times 10^{-3} \text{ mm}^2/\text{s}$) with the p value of 0.005. The peri-tumoral-normal tissue ADC ratio was 0.87 in group B and about 1 in group A. However, the difference between normal tissue ADCs and peri-tumoral ADCs was only significant (P value of 0.005) in group B. The cut-off point value for differentiating normal tissue ADCs and peri-tumoral ADCs was $1.61 \times 10^{-3} \text{ mm}^2/\text{s}$ with the sensitivity of 65% and specificity of 70%.

Conclusion: Breast cancer with peri-tumoral edema has lower tumoral ADC values, higher peri-tumoral ADC values and lower prevalence of in situ lesions. Visual assessment of peri-tumoral edema on T2WI could predict the tumoral characteristic on diffusion-weighted imaging.

Keywords: Breast Cancer, Magnetic Resonance Imaging, Diffusion Magnetic Resonance Imaging, Apparent Diffusion Coefficient, Peri-Tumoral Tissue

1. Background

Breast cancer may result in remodeling of adjacent normal appearing breast tissues that facilitate local invasion or metastasis (1, 2). Tissues outside the primary tumor may play a critical role in tumorigenesis (3, 4). This earliest stage is characterized by increased angiogenesis, immune cell infiltrates, physiologic changes in PH and oxygen pressure, increased collagen deposition, and tissue stiffness (2).

For characterization of this progressive stiffening, several imaging techniques have been proposed (1, 2). Moreover, achieving tumor-free margins and reducing the risk of local relapse are critical in conservative surgery (5, 6). Currently, histopathologic evaluation on resected tissue specimens plays this role (7). Therefore, providing more information about changes of peri-tumoral tissues and surgical scope using a non-invasive preoperative technique is

highly important.

These days, magnetic resonance imaging (MRI) is increasingly used in the diagnosis and follow-up of breast cancer with a high sensitivity and a moderate specificity (8). Diffusion-weighted imaging (DWI), which is based on thermal motion of water molecules in the extracellular fluid, provides microstructural information and can detect molecular and structural changes of tissues (9). DWI provides quantitative measures as the apparent diffusion coefficient (ADC), which increases the specificity of the diagnostic technique (10). ADC changes inversely with tissue cellularity and stiffness, and a decrease in the ADC value relative to normal tissues appears to be due to malignant changes (11-14). There are only few studies about the ADC characteristic of peri-tumoral tissues, and it has been mentioned that peri-tumoral ADCs are different from normal tissues and are more intense in higher grade cancers with lymphovascular invasion, higher nuclear grade, negative ER, positive HER2, positive Ki67, and lymph node metastasis (2, 5, 15-17). The presence or absence of a prepectoral edema in T2 weighted imaging (T2WI) of breast cancer is significantly associated with prognostic factors including tumoral size, higher nuclear grade, axillary lymph node positivity, and presence of lymphovascular invasion (18).

2. Objectives

The goal of this study was to evaluate the subjective presence of peri-tumoral edema in T2WI and its relationship with tumoral ADCs, peri-tumoral ADCs, peri-tumoral-normal tissue ADC ratios, and tumor characteristics.

3. Patients and Methods

3.1. Study Population

In this cross-sectional study, 78 female patients with 89 breast cancer lesions (invasive and in situ) with the mean age of 47 ± 7.7 years were investigated between 2016 and 2018 by preoperative 1.5-T breast MRI. Our institutional ethics committee approved this study, and informed consent was obtained from all participants.

All breast cancers were confirmed by histopathologic evaluations of specimens collected from lumpectomy or mastectomy. The exclusion criteria were as follows: diagnostic intervention or chemotherapy before MRI examination, small size for visibility in ADC images, incomplete fat suppression and suboptimal DWI, lack of breast parenchyma surrounding tumors (we excluded three similar cases), and artifacts due to patient motion. We asked the patients about a positive family history of breast cancer.

3.2. Breast MRI Protocol

Examinations were performed by a 1.5 T Signa system (General Electric Medical Systems, USA) using a phased-array four channel breast coil for both breasts in a standard prone position.

The parameters of the applied MRI sequences were as follows: the axial T1-weighted sequences: repetition time (TR)/echo time (TE): 400ms/10ms; bandwidth (BW): 31.25 Hz/pixel; field of view (FOV): usually 32 mm; slice thickness: 5.0 mm; matrix size: 384×256 ; number of excitations (NEX): 1; axial short tau inversion recovery (STIR): TR/TE: 4500 ms/63 ms; bandwidth: 62.50; FOV: usually 32; slice thickness: 5.0 mm; matrix size: 320×256 ; NEX: 1; dynamic MRI using a three-dimensional fat suppressed T1-weighted spoiled gradient-echo sequence: TR/TE: 9 ms/4 ms; BW: 31.25; FOV: 32; slice thickness: 4.0 mm with no intersection gap; matrix size: 352×288 ; NEX: 1; flip angle (FA): 300 (after bolus injection of 0.2 mmol/kg of Dotarem, followed by 15 mL normal saline flush); DWI echo planer image: TR/TE: 7700 ms/89 ms; FOV: 38; flip angle: 90; NEX: 4; matrix: 192×192 pixels; and slice thickness: 5 mm with spatial fat suppression and with two respective b factors (0 and 800 s/mm²). The ADC maps were automatically calculated using the MRI system software. DWI was the last sequence after 10 min of Dotarem injection.

3.3. Image Analysis

A radiologist blinded to the clinical and histopathological information with more than ten years of experience reviewed all MR images. The size of the breast lesion was measured on its largest diameter on the dynamic contrast-enhanced (DCE) MRI images.

First, in the slice with the largest tumor cross section on the ADC map, one freehand region of interest (ROI) was drawn to cover the whole lesion. Cystic or necrotic, fatty regions and hematoma inside the lesion were attempted to be avoided. Then, three small ROIs about 10 mm² were placed in the peri-tumor fibroglandular tissue adjacent to the tumor contour on the ADC map, and their mean was recorded as a peri-tumoral ADC value (Figure 1). Furthermore, we measured the ADC value of the normal breast tissue. Two large ROIs were placed on the contralateral healthy fibroglandular breast tissue, and their mean was designated as a mean ADC value of normal tissues. Afterwards, the peri-tumoral-normal tissue ADC ratio was calculated.

In addition, the visual assessment of surrounding breast parenchyma of the tumor on T2WI was carried out and based on the presence of peri-tumoral edema, the lesions were categorized into two groups: (A) with peri-tumoral edema (36 lesions) (Figure 2) and (B) without peri-tumoral edema (53 lesions) (Figure 3). Finally, peri-tumoral

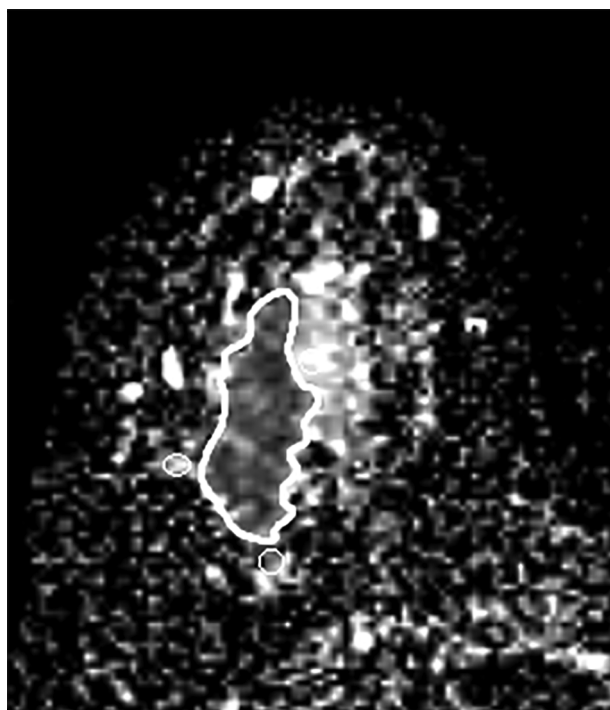


Figure 1. In the slice with the largest tumor cross section on the apparent diffusion coefficient (ADC) map one freehand region of interest (ROI) was drawn to cover the whole lesion. Then three small ROIs about 10 mm^2 were just placed in the adjacent peri-tumor fibroglandular tissue.

tissue ADCs and the peri-tumoral-normal tissue ADC ratio were compared between the two groups.

3.4. Statistical Analysis

Statistical analysis was performed using SPSS for Windows software (SPSS Inc. Released 2009. PASW Statistics for Windows, version 18.0. Chicago: SPSS Inc). The variables including age, tumor size, tumoral ADCs, peri-tumoral ADCs, and peri-tumoral ADC/normal tissue ADC were compared in the two groups with and without peri-tumoral edema in T2WI using independent sample *t*-test. Moreover, the relationship was evaluated between tumoral and peri-tumoral ADCs in invasive and in situ breast cancers using analysis of variance (ANOVA). Tumor state was evaluated in the two groups with and without peri-tumoral edema using Fisher's exact and chi-square tests. A *P* value of lower than 0.05 was considered statistically significant. The receiver operating characteristic (ROC) analysis was used to evaluate the potentiality of the ADC value in differentiation of the normal breast tissue and peri-tumoral ADCs. Finally, diagnostic indices of selected cut-off point of ADC (including sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV] and accuracy) were determined.

4. Results

In this study, 78 patients with 89 breast cancers (invasive and in situ) with the average age of 47 ± 7.7 years were investigated. The participants were divided into two groups of 36 (40%) patients with peri-tumoral edema (group A) and 53 (60%) patients without peri-tumoral edema (group B). About 19% of our cases had a positive family history of breast cancer. The mean age was 47.08 ± 7.84 years in group A and 47.06 ± 7.51 years in the other group. There was no significant difference between the two groups considering age ($P > 0.05$). The percentage of positive family history was 22.2% in group A and 30.1% in group B, but there was no significant difference between the two groups ($P > 0.05$). Moreover, the mean tumor size was $31.41 \pm 21.50 \text{ mm}$ and $27.71 \pm 19.71 \text{ mm}$ in groups A and B, respectively, but there was no significant difference between them ($P > 0.05$) (Table 1).

Tumor ADCs were significantly lower in group A compared to group B ($0.95 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. $1.11 \times 10^{-3} \text{ mm}^2/\text{s}$). However, peri-tumoral ADCs were significantly higher in group A ($1.82 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. $1.53 \times 10^{-3} \text{ mm}^2/\text{s}$) compared to the other group.

In our study, the mean of ADC values was $1.76 \times 10^{-3} \text{ mm}^2/\text{s}$ in the normal breast tissue; whereas, the mean of the peri-tumoral tissue was $1.65 \times 10^{-3} \text{ mm}^2/\text{s}$ in the two groups, with the difference being significant ($P = 0.01$). Peri-tumoral tissue ADCs were $1.82 \times 10^{-3} \text{ mm}^2/\text{s}$ in group A and $1.53 \times 10^{-3} \text{ mm}^2/\text{s}$ in the other group.

Furthermore, the peri-tumoral-normal tissue ADC ratio was 0.87 in group B and approximately 1 in group A. However, the difference between normal tissue ADCs and peri-tumoral ADCs was significant only in group B (*P* value < 0.05) (Table 2). The cut-off point value for differentiating normal tissue ADCs and peri-tumoral ADCs was $1.61 \times 10^{-3} \text{ mm}^2/\text{s}$ with a sensitivity of 65%, specificity of 70%, accuracy of 68%, PPV of 45% and NPV of 85%.

Only one (2.7%) lesion in group A and four (7.5%) lesions in group B were in situ cancers, but the difference was not significant ($P > 0.05$) (Table 1). The in situ cancer in group A had a large non-mass enhancement pattern on dynamic MRI and also had some microinvasive foci in histopathology. The mean ADC value was significantly lower in invasive cancers than in situ tumors ($1 \times 10^{-3} \text{ mm}^2/\text{s}$ vs. $1.49 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively). Furthermore, the mean of peri-tumoral tissue ADCs was $1.65 \times 10^{-3} \text{ mm}^2/\text{s}$ in invasive cancers (regardless of the presence of edema) and $1.74 \times 10^{-3} \text{ mm}^2/\text{s}$ in in situ tumors. However, the difference between normal tissue ADCs and peri-tumoral tissue ADCs was significant only in invasive cancers (*P* value < 0.05) (Table 3).

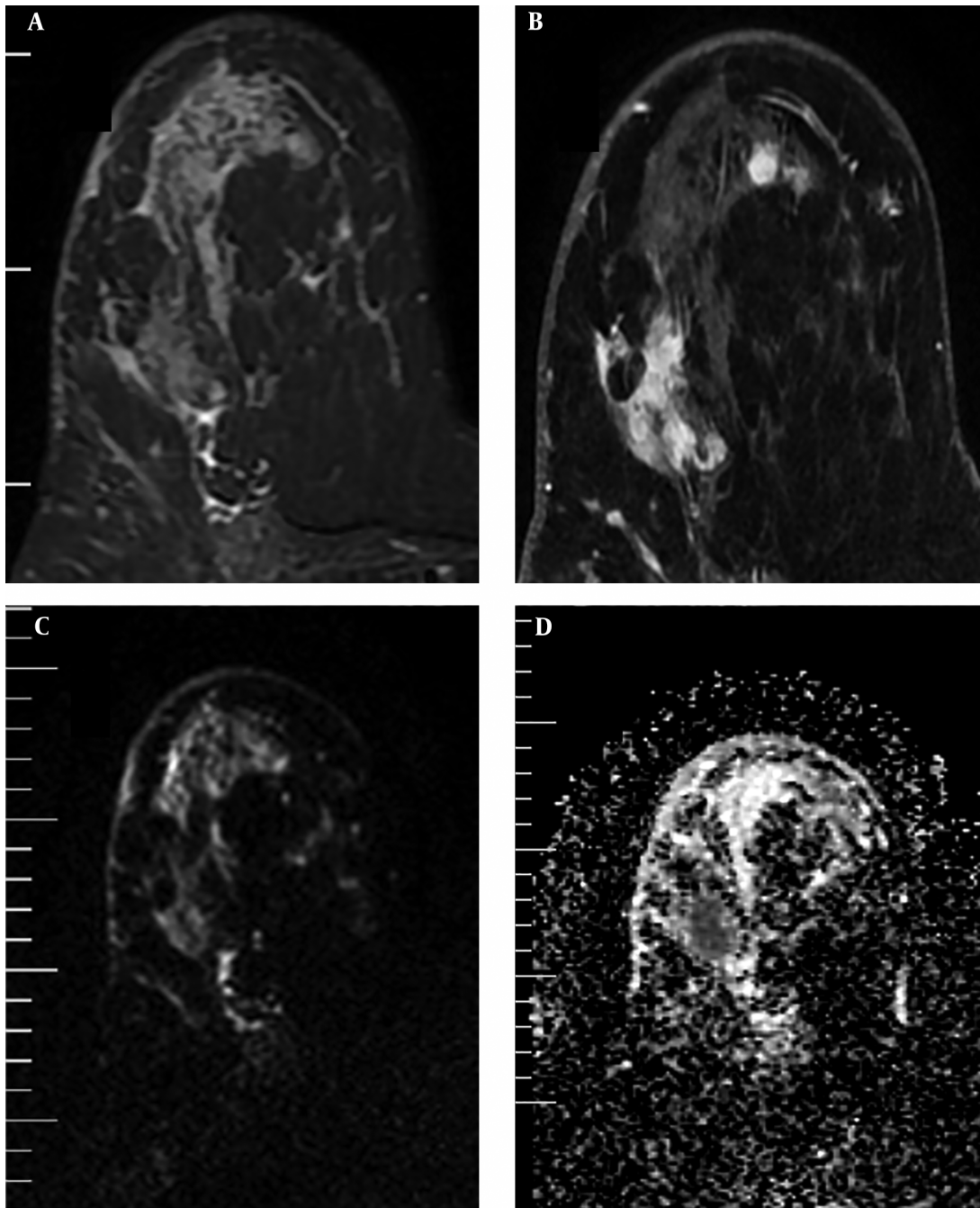


Figure 2. A case of invasive ductal carcinoma in a 36-year old lady with peri-tumoral edema. A, T2 Weighted Imaging (T2WI); B, Post contrast image (early phase); C, Diffusion-weighted imaging (DWI), D: Apparent diffusion coefficient (ADC).

5. Discussion

Despite the widespread application of different modalities in the detection and characterization of breast cancer in many literatures, only few studies have investigated

the role of imaging in the evaluation of changes in peri-tumoral tissues (2, 5, 15-17).

In recent years, DWI and ADC values have been extensively used in differentiation of malignant and benign breast lesions. Relatively high cellular density in malig-

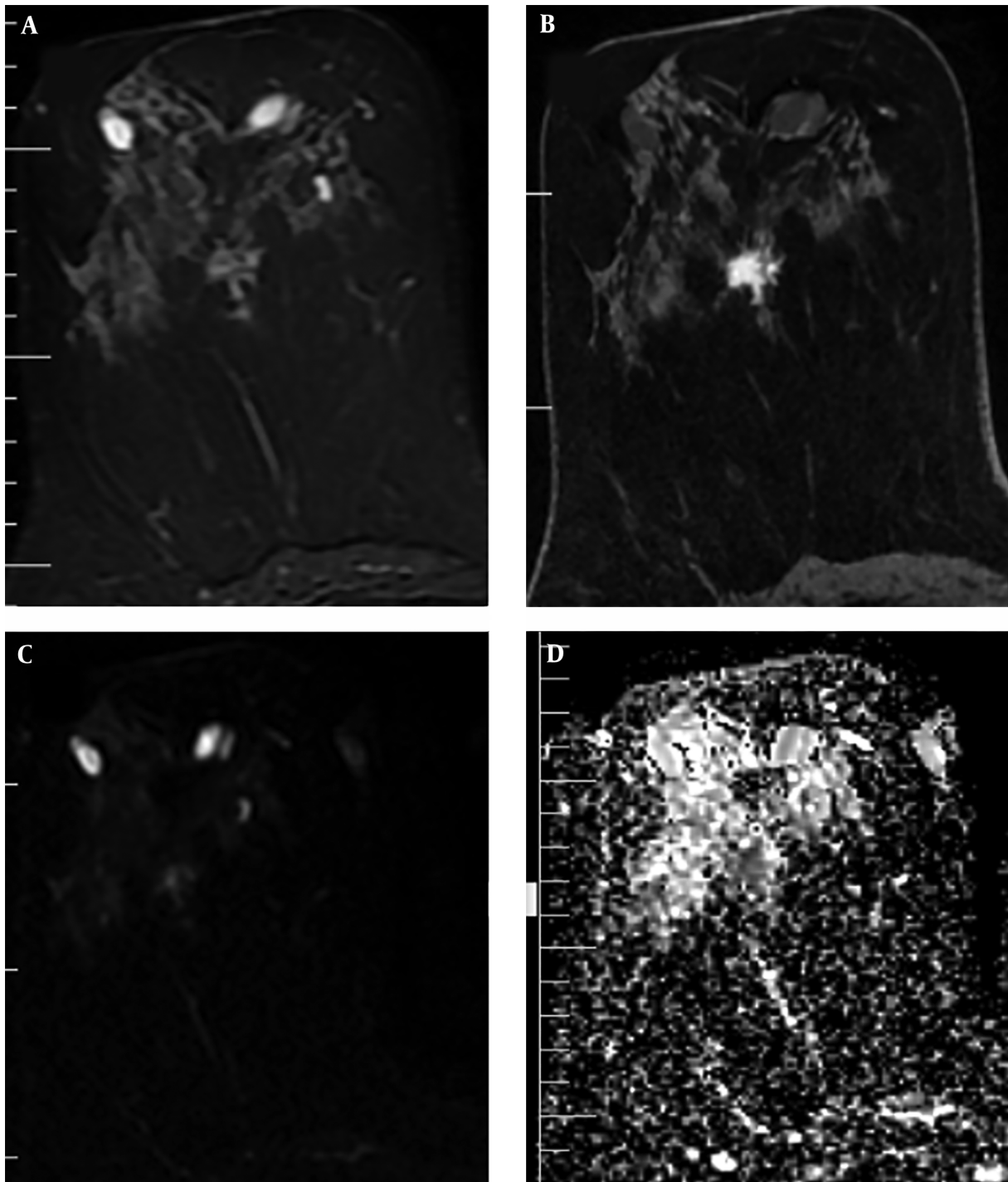


Figure 3. A case of invasive ductal carcinoma in a 42-year old lady without peri-tumoral edema. A, T2 Weighted Imaging (T2WI); B, Post contrast image (early phase); C, Diffusion-weighted imaging (DWI); D: Apparent diffusion coefficient (ADC).

nant lesions produces a low ADC value (13, 19-21).

In the present study, ADC values were significantly

lower in malignant lesions compared to normal tissues ($0.95 \times 10^{-3} \text{mm}^2/\text{s}$ in group A and $1.11 \times 10^{-3} \text{mm}^2/\text{s}$ in group

Table 1. Age, Tumor Size, Positive Family History and Tumor State in the Two Groups with and Without Peri-Tumoral Edema in T2WI^a

	No peri-tumoral edema (n = 53)	Peri-tumoral edema (n = 36)	OR (CIs)	P value
Tumor state			0.35 (0.04 - 3.27)	0.338
Invasive	49 (92.45)	35 (97.22)		
In situ	4 (7.55)	1 (2.78)		
Family history of breast cancer			1.51 (0.57 - 4.04)	0.406
Positive	16 (30.18)	8 (22.22)		
Negative	37 (69.81)	28 (77.77)		
Age	47.06 ± 7.51	47.08 ± 7.84		0.942
Tumor size	27.71 ± 19.71	31.41 ± 21.50		0.326

Abbreviations: CI, confidence interval; OR, odds ratio; T2WI, T2 weighted imaging.

^aValues are expressed as No. (%) or mean ± SD.

Table 2. Tumoral and Peri-Tumoral ADCs and Peri-Tumoral ADC/Normal Tissue ADC in the Two Groups with and Without Peri-Tumoral Edema in T2WI^a

	No peri-tumoral edema (n = 53)	Peri-tumoral edema (n = 36)	P value
Tumor ADC	1.11 ± 0.27	0.95 ± 0.2	0.003
Peritumor ADC	1.53 ± 0.29	1.182 ± 0.25	< 0.01
Peritumor ADC/normal tissue ADC	0.87 ± 0.17	1.03 ± 0.14	< 0.01

Abbreviation: ADC, apparent diffusion coefficient; T2WI, T2 weighted imaging.

^aValues are expressed as mean ± SD.

Table 3. Tumoral and Peri-Tumoral ADCs in Invasive and In Situ Breast Cancers^a

	Tumoral ADCs ($\times 10^3 \text{ mm}^2/\text{s}$)	Peri-tumoral ADCs ($\times 10^3 \text{ mm}^2/\text{s}$)	P value
Invasive (n = 84)	1.03 ± 0.22	1.65 ± 0.32	< 0.01
In situ (n = 5)	1.49 ± 0.51	1.74 ± 0.15	

Abbreviation: ADC, apparent diffusion coefficient.

^aValues are expressed as mean ± SD.

B vs. $1.76 \times 10^3 \text{ mm}^2/\text{s}$ in normal tissues).

The peri-tumoral tissue generally had lower ADC values compared to the normal breast tissue ($1.65 \times 10^3 \text{ mm}^2/\text{s}$ vs. $1.76 \times 10^3 \text{ mm}^2/\text{s}$, respectively). However, it was nearly similar ($1.82 \times 10^3 \text{ mm}^2/\text{s}$) to normal tissue in group A due to peri-tumoral edema, and the peri-tumor to normal tissue ADC ratio in this group was about 1. Furthermore, the peri-tumoral tissue ADC value in in situ cancers had no difference with the normal breast tissue ($1.74 \times 10^3 \text{ mm}^2/\text{s}$ vs. $1.76 \times 10^3 \text{ mm}^2/\text{s}$, respectively).

The findings showed that invasive cancers (and not in situ ones) could affect adjacent peripheral parenchyma and that DWI had the ability to show these changes. In addition, the presence of peri-tumoral edema in our study had a significantly important effect on the ADCs of the peri-tumoral tissue. We also found that the presence of peri-tumoral edema had association with lower tumoral ADCs. We assume that the presence of peri-tumoral edema on T2WI is related to higher grade tumors. Unfortunately,

we did not evaluate the relation of peri-tumoral edema with pathologic biomarkers and lymphovascular invasion. However, it has been shown by some studies that higher grade tumors with lymphovascular invasion, higher nuclear grade, negative ER (estrogen receptor), positive HER2 (human epidermal growth factor receptor 2), positive Ki67, and lymph node metastasis have lower tumoral ADCs and higher peri-tumoral ADCs (2, 5, 15-17). The findings related to peri-tumoral ADCs in these studies might be related to the presence of peri-tumoral edema. Only one of these studies evaluated the presence of peri-tumoral edema, which found no relationship between the presence of peri-tumoral edema and the presence of lymphovascular invasion (16, 18). Uematsu et al. (18) found that prepectoral edema had low prevalence (9% among breast cancers) but it is a specific finding for breast cancer and had high association with prognostic factors such as larger tumor size, higher histological grade, high lymphovascular invasion, higher rate of axillary lymph node positivity, higher rate

of inflammatory breast cancer, higher rate of neoadjuvant chemotherapy, and presence of chemoresistant breast cancer (18).

Cheon et al. (22) assessed the association of disease recurrence with clinical-pathologic features and peritumoral edema in 353 invasive breast cancers. They found that peri-tumoral edema was an independent factor associated with disease recurrence and higher T & N stage, higher tumor grade, and higher Ki-67 index. Furthermore, they reported that peri-tumoral edema is a well-known and important contributor to morbidity or mortality in brain and meningeal tumors (22). In their study, peri-tumoral edema was present in 22.9% of invasive breast cancers. In our study, the percentage of peri-tumoral edema was 41% among invasive cancers, while it was reported 15% - 32% in other studies (23, 24). Costantini et al. (23) reported a higher frequency of peri-tumoral edema in triple-negative breast cancers.

Our study had some limitations. First, peri-tumoral edema was evaluated subjectively. Second, we included a relatively small number of patients. Finally, we did not assess pathologic biomarkers and lymphovascular invasion.

In conclusion, our results suggest that the presence of peri-tumoral edema identified at T2WI can predict tumoral characteristics on DWI. Moreover, our findings indicate that peri-tumoral edema has correlation with lower tumoral ADCs and higher peri-tumoral ADCs and is usually not observed in in situ cancers. The presence of peri-tumoral edema may be associated with higher grade tumors and provides other prognostic factors in patients with breast cancer. Further prospective studies with larger number of patients and concurrent evaluation of prognostic factors and peri-tumoral edema are needed to confirm our results.

Footnotes

Authors' Contributions: Study concept and design: Behnaz Moradi. Analysis and interpretation of data: Behnaz Moradi and Masoumeh Banihashemian. Drafting of the manuscript: Mohammad Ali Kazemi. Critical revision of the manuscript for important intellectual content: Masoumeh Gity and Ali Arabkheradmand. Statistical analysis: Ghazaleh Arabkheradmand.

Conflict of Interests: We have no conflict of interest.

Ethical Approval: We received ethical approval code 9411282007 by Ethical Committee.

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Informed Consent: We implemented a cross sectional study in which patients had already undergone MR imaging based on their own clinical indications before initia-

tion of the study. No unnecessary imaging or intervention was performed. Patient consent was waived due to the nature of the study.

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