

Threshold of Apparent Diffusion Coefficient in the Differentiation between Benign and Malignant Breast Lesions on MR Mammography

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Abstract

Objective: The aim of this study was to determine whether the suggested threshold ADC measurements can be used to characterize benign and malignant breast lesions.

Materials and Methods: Sixty two female patients between the ages of 15-64 years (mean age, 44 years) with 49 benign and 25 malignant histopathologically verified breast masses were included in this study. The patients were examined with a 1.5 Tesla system (Optima MR 450W, GE Healthcare, South Carolina, USA) using a bilateral phased-array breast coil. The images were obtained with b values of 0 and 600 mm²/s. The ADC values were calculated for breast masses and for normal fibro glandular tissue.

Results: The threshold ADC value to differentiate benign and malignant lesions used was 1.03×10^3 mm²/s. For ADC ratio between the lesions and normal fibroglandular tissue, the threshold used was 0.8. The mean ADC value of benign lesions was $2.03 \pm 0.07 \times 10^3$ mm²/s, while that of malignant lesions was $0.86 \pm 0.15 \times 10^3$ mm²/s. The mean ADC ratio values were 0.7 ± 0.09 and 1.3 ± 0.13 for malignant and benign lesions, respectively. The differences between the ADC and ADC ratio values of the benign and malignant lesions were statistically significant.

Conclusion: In conclusion, DW-MRI using the suggested threshold ADC measurements can be used as an adjunct to dynamic contrast enhanced MR mammography to increase the confidence in discrimination of benign and malignant breast lesions.

Keywords: Breast masses; DWI; MR Mammography; ADC; ADC ratio

Introduction

Over the past two decades, magnetic resonance imaging (MRI) has proven to be a valuable diagnostic tool in oncology [1-4]. Rapid improvements in MRI techniques have resulted in MR images with excellent spatial resolution and soft tissue contrast, which contribute to the differentiation of suspected tumors. However, using conventional MRI sequences, difficulty in differentiating benign from malignant lesions may arise when malignant and benign lesions share certain morphologic and contrast-enhancement characteristics. In these cases, diffusion-weighted MR imaging (DWI) might be of value in tumor assessment, as it has the ability to provide tissue contrast based on molecular diffusion [5]. Initially, DWI in other than intracranial sites did not yield sufficient image quality due to susceptibility artefacts and motion artefacts. More recently, technical advances in MRI have enabled the performance of DWI both intra- and extracranially. Diffusion-weighted images can be assessed in two ways, qualitatively, by visual assessment of signal intensity, and quantitatively, by measurement of the apparent diffusion coefficient (ADC). The ADC value quantifies water proton motion, which in biological tissues is a combination of true water diffusion and capillary perfusion. The ADC value can theoretically be used to characterize tissues, as the degree of diffusion is correlated to cellular density and extracellular space volume [6,7]. Malignant tumors are reported to

have a high cellular density and low extracellular space volume, which is associated with impeded water proton diffusion and low ADC values. In contrast, various benign lesions are characterized by an increased amount of extracellular matrix with minimal increase of cellular density, which may result in higher ADCs [8,9].

Recent studies have shown a high accuracy rate in the differentiation between malignant and benign breast lesions using DW-MRI and ADC measurements. The measured ADC values were significantly lower in malignant lesions compared to benign lesions [10-12]. Breast lesions could be distinguished from each other using a threshold ADC value of 1.03×10^3 mm²/s and a threshold ADC ratio value of 0.8 [13].

The aim of this study was to determine whether the suggested threshold ADC measurements can be used to discriminate benign and malignant lesions.

Materials and Methods

Patient selection

In the period from January 2013, till January, 2015, sixty two female patients with indeterminate lesions on mammography or ultrasound (US) were included in the study. Breast MRI, including diffusion weighted imaging (DWI), and ultrasound-guided core-needle biopsy were done for them. The biopsies were performed within one month of the MRI. The lesions included in the study were those one cm or

more. DWI results were compared with histopathological data, which were considered the gold standard.

The patients' ages varied between 15 and 64 years (mean age, 44 years). Informed written consents were obtained from each patient prior to MRI and biopsy.

MRI Technique

All MRIs were obtained using a 1.5 Tesla MRI (Optima MR 450W, GE Healthcare, South Carolina, USA) using a bilateral phased-array breast coil. Conventional sequences of routine breast MRI were performed for all patients. The sequences used for the conventional MRI studies were axial STIR and sagittal fat-suppressed T2-weighted (TR/TE, 3850/67.4 ms and 4664/99.8 ms, respectively; slice thickness, 5 mm; matrix, 512 × 512), sagittal T1-weighted (TR/TE, 542/13 ms; slice thickness, 5 mm; matrix, 512 × 512), DWIs and contrast-enhanced three-dimensional dynamic Water VIBRANT-Flex sequences (TR/TE, 7.1/3.3 ms; flip angle, 12°; slice thickness, 1.5 mm; matrix, 512 × 512). One precontrast sequence was followed by six postcontrast sequences for dynamic contrast-enhanced images. Gadopentetate Dimeglumine (Magnevist; Schering, Berlin, Germany) was used as a contrast medium. The contrast medium was given intravenously over 20 s by an automatic MR-compatible injector. The dose was 0.1 mmol/kg.

The DWI sequences were performed with a two-dimensional echo-planar imaging (EPI) sequence (TR/TE, 8700/63.2 ms; slice thickness, 5.5 mm; matrix, 256 × 256) in the axial plane. The images were obtained with b values of 0 and 600 mm²/s. The ADC map images were created automatically by the system.

MRI Interpretation

On DWI, the region of interest (ROI) was placed on the solid portion of each lesion, avoiding any cystic components. The ADC values of the contralateral normal breast tissue were measured, to obtain the ADC ratio of the lesions to the normal breast tissue. A standard 5 mm diameter circular ROI was used. Three different measurements were obtained for each lesion. The lowest ADC values obtained were considered the final values, rather than the mean of the three measurements.

Histopathological Analysis

Core-needle biopsy was done under ultrasound guidance for all patients. Evaluation was performed using slices stained with hematoxylin-eosin.

Statistical Analysis

The mean ADCs for benign and malignant lesions were compared using Student's t test. The diagnostic performance of DWI was evaluated by comparison of the area under curve (AUC). P<0.05 was considered statistically significant.

Results

This study included 74 solid breast lesions detected in 62 patients. Forty-nine lesions were diagnosed as benign and 25 lesions as malignant. Eleven patients had multiple lesions (two lesions in ten patients and three lesions in one patient). The histopathological types of the lesions (after ultrasound-guided core-needle biopsy) are shown

in Table 1. The lesion sizes ranged from 1 to 4 cm. The mean lesion size was 2.3 cm.

For differentiation of benign and malignant lesions, a threshold ADC value of 1.03×10^3 mm²/s and a threshold ADC ratio value of 0.8 were used [13].

Diagnosis	Number of Lesions
Malignant Lesions	
Invasive ductal carcinoma	21
Invasive lobular carcinoma	1
Ductal carcinoma in situ	2
Malignant cystosarcoma phyllodes	1
Benign Lesions	
Fibroadenoma	30
Atypical ductal hyperplasia	1
Postoperative changes	2
Focal fibroadenosis	16

Table 1: Distribution of Benign and Malignant Lesions in the Study.

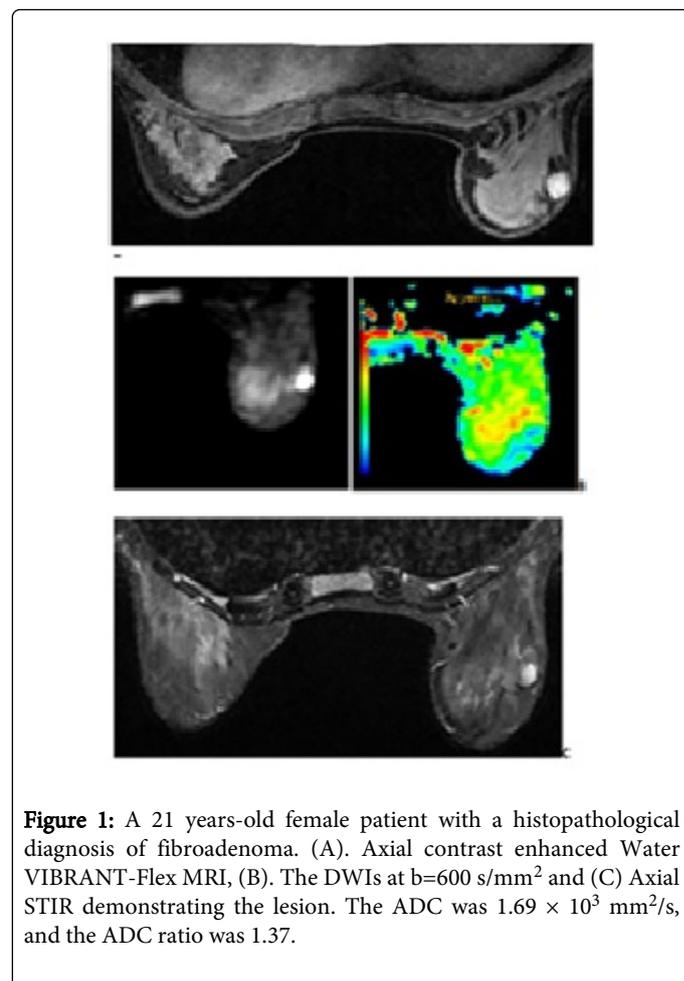


Figure 1: A 21 years-old female patient with a histopathological diagnosis of fibroadenoma. (A). Axial contrast enhanced Water VIBRANT-Flex MRI, (B). The DWIs at b=600 s/mm² and (C) Axial STIR demonstrating the lesion. The ADC was 1.69×10^3 mm²/s, and the ADC ratio was 1.37.

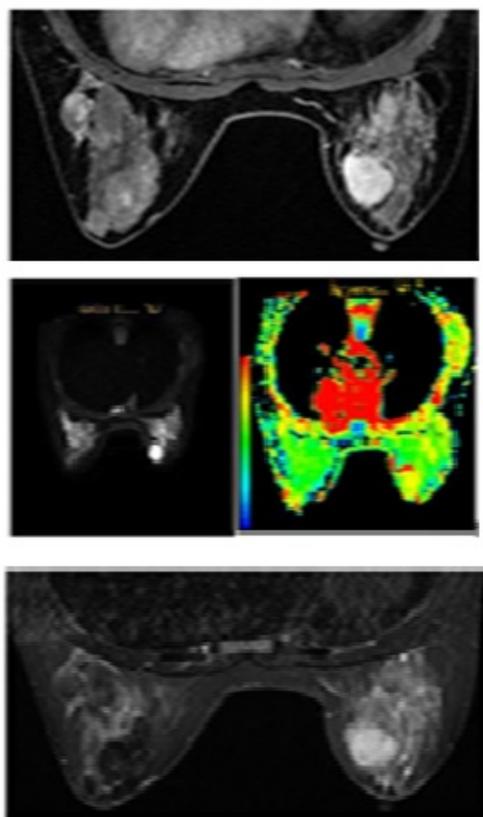


Figure 2: A 25 years-old female patient with a histopathological diagnosis of malignant cystosarcoma phyllodes. (A). Axial contrast enhanced Water VIBRANT-Flex MRI, (B). The DWIs at $b=600$ s/mm^2 and (C). Axial STIR demonstrating the lesion. The ADC was 1.18×10^3 mm^2/s , and the ADC ratio was 0.91. NB: The right breast demonstrated fibrocystic changes not included in the study.

The mean ADC value of benign lesions was $2.03 \pm 0.07 \times 10^3$ mm^2/s , while that of malignant lesions was $0.86 \pm 0.15 \times 10^3$ mm^2/s . The mean ADC ratio values were 0.7 ± 0.09 and 1.3 ± 0.13 for malignant and benign lesions, respectively. The differences between the ADC and ADC ratio values of the benign and malignant lesions were statistically significant (Figures 1 and 2).

The ADC values ranged from 0.65 to 1.18×10^3 mm^2/s in malignant lesions. The lowest ADC value of all malignant lesions (0.65×10^3 mm^2/s) was found in invasive ductal carcinoma. The highest ADC value (1.18×10^3 mm^2/s) was in malignant cystosarcoma phyllodes.

The ADC values ranged from 1.26 to 2.67×10^3 mm^2/s in benign lesions. The highest ADC value (2.67×10^3 mm^2/s) was in postoperative changes. Of all benign lesions, fibroadenoma had the lowest ADC value (1.26×10^3 mm^2/s).

The lowest ADC ratio (0.5) was found in invasive ductal carcinoma, and the highest ratio (2.1) was found in focal fibroadenosis.

There were no benign lesions that had ADC or ADC ratio values under the threshold values of 1.03×10^3 mm^2/s and 0.8, respectively. For one lesion, from a total of 25 malignant lesions, higher ADC and ADC ratio values than the threshold (1.18×10^3 mm^2/s and 0.81,

respectively) were obtained. The histopathological finding of this lesion was malignant cystosarcoma phyllodes.

The ADC and ADC ratio values of the breast lesions showed using the fore mentioned threshold ADC and ADC ratio values, 98.6% sensitivity, and 100% PPV.

Discussion

The growth of diffusion-weighted breast imaging as a research tool implies that this modality has potential as an adjunct in the radiologic diagnosis of breast cancer [14].

Breast lesions could be distinguished from each other using a threshold ADC value of 1.03×10^3 mm^2/s and a threshold ADC ratio value of 0.8. We think that new studies should validate ADC measurements using a larger group of patients [13]. In our study, we followed the authors' threshold values to detect if they could be used to differentiate benign from malignant breast lesions in a different group of patients. We also wanted to use them in the future as a standard for characterization of breast lesions by MRI.

The Echo planar imaging sequence (EPI) is very sensitive in breast imaging because of the large surrounding fat tissue. However, Echo planar DWI can result in image distortion due to eddy currents, signal loss, and image-blurring artifacts caused by magnetic field in homogeneities [11-12,15]. These artifacts could impair ADC measurements [11,16]. In this study, EPI was used and caused no significant problems due to image artifacts.

If the selected b value is less than 400 mm^2/s , the image is affected by the microcirculation and the flow of blood in the capillaries. There is a marked increase in the number of capillaries in malignant tumors. Therefore, if a low b value is selected, pseudo diffusion will occur in malignant lesions, where the ADC values are high due to capillary perfusion [11,17]. It has been reported that the DWI with high b values are more reliable in differentiating between lesions, though signal loss is more severe [11-12,17]. Bogner et al. [18] reported that using variable b values does not provide an advantage, and they reported the ideal b value as 850 mm^2/s . Partridge et al. [19] used b value of 600 mm^2/s in their research. In our study, we couldn't use the optimal highest b-value as the available on our machine was a b value of 600 mm^2/s , as per vendor.

Kinoshita et al. [20] mentioned that lesions <10 mm in diameter cannot be detected using DWI. However, Partridge et al. [19] mentioned that diffusion-weighted MRI of the breast was not affected by lesion size. We preferred including lesions equal to or greater than one cm in diameter to ensure they were detected by DWI. The range of lesion size in our study was 1-4 cm. No lesions were missed by DWI.

During ADC measurement, we have taken into account the lowest ADC value obtained from each lesion. Studies have shown that a minimum ADC value has a higher sensitivity and specificity compared to a mean ADC value, especially in heterogeneous lesions [8-22].

Park et al. [16], Gimi et al. [23] and El Khauli et al. [10] reported that ADC ratio values improved the diagnostic performance of MRI because the ADC value is variable with the gradient factor b. For every lesion in our study, both ADC and ADC ratio values were obtained. However, in the only false negative case, both the ADC and ADC ratio of the lesion gave false negative readings. In their study [13], medullary and invasive ductal carcinomas showed false negative findings on DWI, and central necrosis was the reason for the obtained

higher ADC and ADC ratio values. The false negative case in our study was diagnosed histopathologically as malignant cystosarcoma phyllodes, and though we didn't include the cystic areas of the lesion in our measurements, the high readings might have been due to microscopic necrotic portions of the lesion.

Lobular carcinoma in situ, atypical ductal hyperplasia, papillomas, and fibrocystic disease can cause incorrect ADC measurements [24]. The cases of atypical ductal hyperplasia and focal fibroadenosis, in our study, were correctly diagnosed on DWI.

Breast lesions could be distinguished from each other using a threshold ADC value of $1.03 \times 10^3 \text{ mm}^2/\text{s}$ with 88.5% sensitivity, and 100% PPV and a threshold ADC ratio value of 0.8 with 91.4% sensitivity, and 100% PPV [13]. Less sensitivity was obtained in other studies [8,21,22], likely because they used mean, rather than the lowest ADC values. The ADC and ADC ratio values of breast lesions in our study, showed a statistically significant difference between malignant and benign lesions, using the fore mentioned threshold ADC and ADC ratio values, with 98.6% sensitivity, and 100% PPV.

The main limitations of the study were the small population and the large size of the lesions. Further investigation of the role of DWI in the detection and differential diagnosis of lesions less than one cms and lesions with non-mass-like enhancement on MRI is needed. In addition, we did not plan the MRI procedure according to the menstrual cycle of patients. However, according to Partridge et al. [19], the ADC values of normal fibroglandular breast tissue demonstrated changes during menstruation; which were not statistically significant.

In conclusion, DW-MRI using the suggested threshold ADC measurements can be used as an adjunct to dynamic contrast enhanced MR mammography to increase the confidence in discrimination of benign and malignant breast lesions.

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