# Diffusion Magnetic Resonance Imaging of the Breast

Fernanda Philadelpho Arantes Pereira, MD[a,b,*],
Gabriela Martins, MD[a,c],
Raquel de Vasconcellos Carvalhaes de Oliveira, MSc[d]

Magnetic resonance (MR) imaging has been increasingly used for accurate diagnosis of both primary and recurrent breast cancers, particularly in cases in which mammography and breast sonography are inconclusive or yield discrepancies. In addition, MR imaging may improve the analysis of the local extent of breast cancer by revealing multifocal and multicenter tumor growth in patients scheduled for conservative breast surgery. Although the high sensitivity of breast MR imaging has proved to be advantageous for preoperative patients, the limited specificity of this imaging method continues to be a significant problem, particularly in patients referred for further clarification and delineation of inconclusive findings obtained using conventional breast imaging techniques.[1]

MR imaging has high sensitivity (89%–100%), but lacks specificity for characterization of breast tumors.[2–6] An overlap between MR imaging findings for benign and malignant lesions persists, resulting in variable specificity (50%–90%).[4,7–9] This phenomenon can be caused by false-positive results related to the menstrual cycle, hormonal therapy, proliferative alterations, fibroadenomas, and papillomas. As a result of this confounding overlap, in some cases it is not possible to make a differential diagnosis between benign and malignant lesions from conventional MR imaging features.[10,11] In addition to morphologic and kinetic analyses, molecular characterization has been expected to be useful for the diagnosis of breast disease. Hence, several studies have investigated the role of advanced MR imaging techniques, such as diffusion-weighted imaging (DWI), in improvement of the specificity of MR imaging for the evaluation of breast lesions.[10,12–18]

DWI has been used in neurologic imaging for some time, but has only recently been applied to breast imaging.[8,12–14,19,20] However, recent developments in MR imaging technology have enabled the clinical application of DWI to the entire body, which has shown great promise for the detection and characterization of most tumor types. Through imaging of alterations in the microscopic motion of water molecules, DWI can yield novel quantitative

and qualitative information reflecting cellular changes that can provide unique insights into tumor cellularity.[21] With respect to breast DWI, a potential role for the apparent diffusion coefficient (ADC), a quantitative measure that is directly proportional to the diffusion of water and inversely proportional to the tumor cellular density,[22] has been reported to be useful for characterizing breast tumors and distinguishing malignant tissues from benign tissues.[13,17,18,23]

## CLINICAL APPLICATIONS OF DIFFUSION IMAGING

Despite improvements in the detection of breast cancer as a result of the widespread application of mammography and ultrasound, breast lesions remain difficult to diagnose and characterize. The primary advantage of MR imaging of the breast is improvement of the detection and characterization of multiple and/or small lesions, even in dense fibroglandular breast tissue. However, the low specificity of MR imaging remains a significant problem.[24]

DWI has been increasingly recognized as a promising quantitative method for use in differential diagnosis of enhancing lesions in breast MR imaging.[25] Based on the principles of DWI, visualization and quantification of the random motions of molecules, this technique can be used to analyze tissue microstructure in vivo. Compared with contrast-enhanced techniques, which can reveal the vasculature and perfusion, this new approach to assess tissue characteristics can provide additional diagnostic information to improve differential diagnosis. In general, the DWI technique is faster than dynamic contrast-enhanced MR imaging. Consequently, this imaging method can easily be added to a standard breast MR imaging protocol.

### DWI of Normal Breast Tissue

In diffusion-weighted images, the normal breast gland has a high signal in images acquired with low b-values and low signal in images acquired with high b-values. Ideally, the background signal for the breast gland should be suppressed to emphasize the tumor signal and to avoid the T2 shine-through effect.[26]

A trend toward a decreased ADC has been observed during the second week of the menstrual cycle, and an increased ADC during the final week before menstruation.[27] Variations in the ADC occur in the breast as a result of normal hormonal fluctuations associated with the menstrual cycle. The reduced ADC in the second week is correlated with reduced water content in the breast, and the increased ADC during the week before menstruation has been attributed to increases in secretion activity, stromal edema, and water volume in the extracellular matrix. Normal breast ADC values seem to vary by only 5.5% across the different menstrual phases.[27] However, no statistically significant influence of the menstrual cycle on the ADC values for the breast has been reported. Because contrast-enhanced breast MR imaging is recommended to be performed in the second week of the menstrual cycle,[28] a similar recommendation may be optimal for DWI. In women with less dense breasts, the ADC values for breast tissue may be artificially reduced as a result of partial volume effects of fat tissue.[20] The mean ADC values in normal breast tissue vary from $1.51 \times 10^{-3}$ to $2.37 \times 10^{-3}$ mm$^2$/s for sequences acquired with b-values ranging from 0 to 1074 s/mm$^2$.[14,16,23,29–32]

### Diffusion of Water in Malignant and Benign Tissues

In biologic tissues, microscopic water molecular motion is induced by both intravascular water movement (flow) and an extravascular component (diffusion).[33] With respect to the extravascular component, the state of the extracellular space is the most important factor that regulates diffusion. If a tissue is made up of tightly packed cells, as occurs in a malignant tumor, the extracellular space is reduced, and diffusion of water is decreased. This phenomenon results in a higher DWI signal intensity, restricted signal intensity on the ADC map, and a lower ADC value (Fig. 1). In contrast, in benign lesions in which the cells are more separated, the extracellular space is larger, diffusion of water is less restricted, and the ADC value is higher.[20,34] Tumor cellularity is inversely correlated with the ADC value, and malignant breast tumors exhibit higher cellularity and lower ADC values than benign breast tumors.

### Specificity and Sensitivity of DWI

There seems to be a consensus in the literature regarding the ability of DWI of the breast to differentiate between malignant and benign breast lesions. Many studies have shown that lower ADC values are associated with breast cancer tissues compared with normal breast tissues or benign tumors.[7,10,12,13,15,16,19,25,29,31,34,35] A meta-analysis of 12 articles reported that the ADC values for benign breast tumors ranged from $1.41 \times 10^{-3}$ to $2.01 \times 10^{-3}$ mm$^2$/s, and those of malignant breast tumors ranged from $0.9 \times 10^{-3}$ to $1.61 \times 10^{-3}$ mm$^2$/s. Variations in ADC values may be present across different studies as a result of technical differences. For example, studies analyzed in the
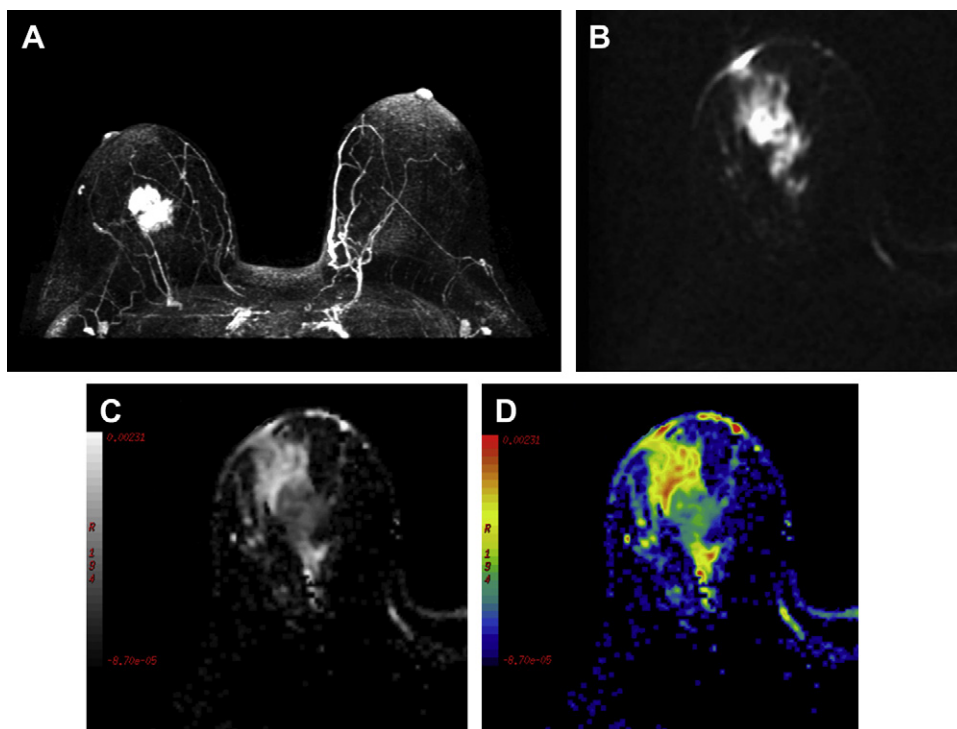
**Fig. 1.** 49-year-old woman with IDC of the right breast. (*A*) Axial maximum intensity projection of a contrast-enhanced T1-weighted three-dimensional spoiled gradient-echo image, first phase, subjected to subtraction technique. (*B*) Axial diffusion-weighted image. (*C*) Axial black-and-white and (*D*) colored ADC maps obtained using b-values of 0 and 750 s/mm$^2$ show enhancement of a highly suspicious mass, evident as increased loss of signal on the ADC black-and-white map and blue on the ADC colored map, which indicate restricted diffusion.

meta-analysis used different b-values, varying from 0 to 1074 s/mm$^2$, yet a significant difference in the ADC values was identified between malignant and benign lesions, with a pooled sensitivity of 89.1% (range, 85%–91%) and a pooled specificity of 77% (range, 69%–84%) for an ADC cutoff of 1.1 to 1.6 × 10$^{-3}$ mm$^2$/s.[34]

The literature also shows that increased positive predictive value (PPV) can be achieved by incorporating an ADC threshold into breast MR imaging assessment. In a study by Partridge and colleagues,[18] in which DWI was acquired using b-values of 0 and 600 s/mm$^2$, application of an ADC threshold of 1.8 × 10$^{-3}$ mm$^2$/s for 100% sensitivity produced a PPV of 47%, compared with 37% for MR imaging alone. This methodology would have avoided biopsy for 33% of benign lesions without missing any cancers.

### Correlation of the ADC with Tumor Histology

Several investigators have described an inverse correlation between tumor cellularity and ADC values, and have suggested that further associations with the proliferation rate and tumor aggressiveness may be assumed.[12,25,32,35] ADC

values for the noninvasive malignant lesion, ductal carcinoma in situ (DCIS), were found to be significantly higher than those of invasive cancer, but lower than those of benign lesions, consistent with the less aggressive, but malignant, nature of these lesions.[25] In another study, high-grade DCIS was shown to be associated with a significantly lower ADC value than low-grade DCIS.[23] These and other results suggest that there is a significant correlation between tumor ADC values and tumor histology.[12,14,35–37] Conversely, others investigators have found that no correlation exists between the ADC and breast cancer histology and that no statistically significant difference is present between the ADC values associated with invasive ductal carcinoma (IDC) and DCIS.[32,38] Therefore, further studies are needed to critically evaluate the clinical usefulness of the mean ADC for tumor grading.

### False-positive and False-negative Results of DWI

Several benign lesion subgroups exhibit a remarkable overlap with malignant lesions. According to previous reports,[12,21,39] the diffusion of water

molecules is not only restricted in environments containing high cellularity but also in cases of intra-cellular and extracellular edema, high viscosity regions in abscesses and hematomas, coagulated blood or proteinaceous debris within ducts and cysts, and areas with a high degree of fibrosis. Similar to decreases in extracellular space, these conditions can impede the movement of water molecules. Inflammatory changes also favor high cellularity, granulomatous inflammatory elements, fibrous components, and hemosiderin capabil-ities.[38] These benign conditions can also lead to low diffusion of water and low ADC values.

Fibroadenomas would be expected to have high rates of diffusion and ADC values as a result of stromal myxoid changes and consequently increased mobility of water.[16,38] However, fibroa-denomas with a predominant fibrous component have lower ADC values. In addition, fibrocystic disease, which is characterized by varying degrees of fibrosis and proliferation, can be asso-ciated with ADC values in the range of malignant lesions.[25,35,39]

With respect to false-negative results, the mucinous colloid carcinoma, which is character-ized by the presence of extracellular mucus in the absence of increased cellularity, has been re-ported to have high ADC values.[17,25,35,39] For this reason, further information, such as irregular margins, is required for reliable diagnosis.

Occasionally, DCIS and malignant phyllodes tumor with bleeding present with high ADC values as a result of the strong effects of magnetic suscep-tibility.[31,36] Malignant phyllodes tumor can have high ADC values as a result of cystic areas inside the tumor.[17] Similarly, scirrhous carcinomas may be associated with high ADC values and may, conse-quently, be misdiagnosed as benign in nature.

Papillary cancer has a mean ADC value similar to that of papilloma, a reflection of the similarity between benign and malignant papillary lesions, and it is speculated that hemorrhage is the differen-tiating factor between malignant and benign intra-ductal papillomas.[31,36] Papillomas can also have low ADC values as a result of high cellularity.[17,25,36]

## Technical Issues Associated with DWI

Initial results from studies characterizing DWI seem promising, but the considerable heteroge-neity between studies and the lack of a complete understanding of the factors that influence this heterogeneity represent significant obstacles in the use of this diagnostic tool. For example, varia-tions between studies could be caused by the use of different protocols. Therefore, standardization of DWI parameters and postprocessing methods is necessary to achieve uniform results and to make interstudy comparisons on the diagnostic accuracy of DWI for breast cancer possible.

### Effects of the magnetic strength on DWI

MR imaging scanners operating at 3 T are widely used in the clinic and provide higher signal-to-noise ratio (SNR) and greater spatial resolution than 1.5-T scanners. Small cancers are more clearly visible by DWI at 3 T compared with 1.5 T. However, higher magnetic strengths are also accompanied by an increase in susceptibility arti-facts and nonuniformity of the magnetic field, which can cause image distortions. With the application of parallel imaging techniques, these artifacts can be reduced, and the image quality is markedly improved.[37,40,41]

### Diffusion-weighted techniques

No consensus exists among different research groups regarding the optimal diffusion-weighted technique for the breast. Most groups perform DWI by an echo-planar imaging (EPI) ap-proach.[10,12–14,29,35,39,40,42,43] However, other groups apply fast spin-echo technique. Although EPI is fast and has a high SNR, results using this technique can be distorted by susceptibility and chemical shift artifacts, as well as by breathing and other motion artifacts.[11,36,37] Distortion can be decreased by improving the homogeneity of the magnetic field using manual shimming or parallel imaging. However, EPI remains limited by noise, and thicker slices are generally used compared with contrast-enhanced T1 imaging.

### Determination of the optimum b-value

For clinical MR imaging scanners, the diffusion sensitivity can easily be altered by changing the parameter known as the b-value. Diffusion images are produced using at least 2 different b-values, and the loss of signal between these images is proportional to the amount of diffusion. Images acquired with low b-values are less diffusion-weighted because they use less of a gradient. The diffusion sensitivity is also more affected by microperfusion when low b-values are used, which leads to higher ADC values.[23] On the other hand, high b-value images are strongly diffusion-weighted, highlighting signals from malignant tumors and eliminating signals from normal tissues, but have a lower SNR and, consequently, more image distortion.[26]

The presence of the T2 shine-through effect, in which molecules with long T2 relaxation times produce high signal intensities on diffusion-weighted images, and the high signal intensity of the surrounding normal breast parenchyma can limit lesion visibility on images obtained using lower

b-values. For a given level of a basic T2-dependent signal, a lesion with a lower ADC value requires a higher b-value than a lesion with a higher ADC value to compensate for the T2-dependent signal and avoid T2 shine-through.[26]

DWI is typically performed using at least 2 b-values to enable meaningful interpretation of the results. In theory, the inherent error of ADC calculations can be reduced by the use of more b-values. However, the more b-values used, the longer time the DWI sequence requires.[17] Moreover, no consensus exists as to how many and which b-values should be used for breast DWI.

Pereira and colleagues[17] found no statistically significant difference between the ADC values obtained using different b-value combinations for differentiation of benign and malignant lesions. However, the ADC values calculated using b-values of 0 and 750 s/mm$^2$ were slightly better than the other combinations analyzed. These findings suggest that higher b-values are useful for distinguishing benign from malignant lesions, and that the use of multiple b-values in the DWI sequence is unnecessary, saving examination time. Consistent with these results, a study by Bogner and colleagues[23] found that a combined b-value protocol of 50 and 850 s/mm$^2$ resulted in optimum ADC determination and DWI quality at 3.0 T. ADC calculations performed using multiple b-values were not significantly more precise than those performed with only two.

### Effect of the contrast medium

DWI is generally performed before contrast administration, but it has been reported that it can also be performed after contrast. When DWI is performed after contrast, a reduction in the ADC value is usually expected. Yuen and colleagues[33] reported a mean ADC value reduction of 23% for performance after contrast, and this reduction was generally higher in tumors with relatively high ADC values ($>1.3 \times 10^{-3}$ mm$^2$/s).[44] Investigators have postulated that the contrast causes suppression of the microperfusion effect, leading to a reduction in the ADC value.

Pathologic studies have revealed that microvessel counts are higher for malignant tumors compared with benign tumors,[33] representing a factor that could potentially increase the ADC values of malignant breast tumors.[23] This phenomenon is referred to as the microperfusion effect. Considering the suppressive effect of contrast on microperfusion, postcontrast ADC values may purely reflect tumor cellularity in these cases. Thus, postcontrast ADC may be a more reliable indicator than precontrast ADC for reflection of the malignant potential of tumors. On the other

hand, Rubesova and colleagues[13] and Baltzer and colleagues[25] did not find a significant difference in ADC values obtained before and after contrast injection.

### Postprocessing

The placement of the region of interest (ROI) is crucial for proper analysis of DWI results.[10,13] First, it is important to localize the lesion on diffusion-weighted images and on the ADC map and to determine the location at which the lesion is best visualized. In most previous studies, the ROI was placed directly on the ADC map. The subtracted images of the dynamic contrast-enhanced sequence can also be referenced to the ROI placement. The ROI should cover the tumor, avoiding areas of hemorrhage or necrosis. In previous studies, ROIs of variable areas have been used, ranging from 8 mm$^2$ to more than 100 mm$^2$.[19,29,35,44] The optimal number and type of ROIs remain to be determined. Further studies are needed to characterize the optimal ROI parameters for measurement of ADC values that best reflect the characteristics of tumors.

### DWI Limitations

#### Movement artifacts

Application of DWI to the breast has previously been limited by movement artifacts. Patient movement during the acquisition of the diffusion-weighted sequences can lead to inaccurate ADC values.[10] In addition, longer acquisition times caused by the use of a greater number of b-values can lead to patient motion. Therefore, improvement of patient comfort to reduce motion, respiratory gating, and the use of alternative pulse sequences or postprocessing techniques to reduce eddy current-based distortions may help to improve the quality of clinical breast DWI data.[18,45]

#### Lesion visibility and size

Even under optimal circumstances, DWI can fail to categorize breast lesions because of the limited spatial resolution and capability of recognizing some lesions on ADC maps, particularly lesions smaller than 1 cm.[7] When lesions cannot be visualized on diffusion-weighted images, the precise localization of the ROI on the ADC map cannot be determined. Studies focused on lesion visibility in DWI compared with contrast-enhanced breast MR imaging detected 89% to 100% of all lesions,[10,12,25,29,42] and good visibility was obtained for 89% to 95.3% of lesions.[10,25,42] However, less visible lesions were reported being either small or benign. Another recent study compared the lesion visibility in DWI results with those of subtracted contrast-enhanced images.[42] Approximately 68.9% of lesions showed the same level of visibility

on DWI as on subtraction images, 20.3% of lesions showed good, but inferior, visibility, and 10.8% of lesions showed poor visibility. All lesions were depicted on diffusion-weighted images.

The critical problem is that breast lesions must be detected as a prerequisite for differential diagnosis. However, current studies have reported a lower to equal lesion detection rate for DWI compared with dynamic contrast-enhanced MR imaging.[10,12,25,29,42] These findings may be at least partially a result of the DWI technique used, because the distortion of EPI remains a major problem for accurate measurement of the ADC, particularly for small lesions.[11,34,36,37]

### Nonmasslike enhancement
Another factor that can affect ADC values is the architecture of tumors. According to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) lexicon, pathologic growth conditions in the breast can be described as mass or nonmasslike enhancement.[46] Guo and colleagues[12] and Sinha and colleagues[16] found that the mean ADC value is inversely proportional to the cell density. Therefore, as nonmasslike enhancement lesions can form large and noncompact lesions, with normal parenchyma in the center of the tumor, a lesser restriction of the diffusion processes may occur in these tumors compared with mass lesions (Fig. 2). This phenomenon has been reported for several pathologic and normal states, including noninvasive ductal carcinomas, lobular carcinoma in situ, atypical ductal hyperplasia, papillomas, hormonal changes, and fibrocystic disease.[47]

These results indicate that ADC measurements have a limited ability to differentiate between benign and malignant nonmasslike enhancement lesions. ADC values for malignant lesions may be in the range of benign lesions in these cases.[25] Therefore, a higher ADC value cutoff may be required for nonmasslike enhancement lesions compared with mass lesions. Yabuuchi and colleagues[47] suggested that an ADC value of less than $1.3 \times 10^{-3}$ mm$^2$/s was a significant factor for indication of malignancy for nonmasslike enhancement lesions. In contrast, Baltzer and colleagues[42] found that ADC measurements failed to be of diagnostic value for these lesions. Further investigation is needed to analyze the precise diagnostic potential of DWI for diagnosis of nonmasslike enhancement lesions.

## ANALYSIS OF DWI AT OUR INSTITUTION

A preliminary study in our institution[17] confirmed the usefulness of DWI for the differential diagnosis of benign and malignant breast lesions. In addition, this study revealed no significant statistical difference between ADC values obtained using different b-value combinations, although b-values of 0 and 750 s/mm$^2$ performed slightly better at differentiating between benign and malignant breast lesions than the other combinations analyzed. However, a further study using a larger population was needed to improve the statistical power and to fortify the previous results.

### Study Population

From August 2007 to March 2010, 156 women with 178 breast mass-type lesions were prospectively enrolled in the study. The study was approved by our institutional review board, and all patients provided informed consent. Exclusion criteria included benign cysts, patient movement, sequences with susceptibility and chemical shift artifacts, lesions not visible on the DWI sequence, and neoadjuvant treatment before MR imaging. From these criteria, 40 lesions from 34 patients were excluded. As a result, the study included 122 patients (age range, 22–86 years; mean age, 46.9 years) with 138 breast lesions.

On histopathologic examination, 81 malignant lesions were identified, including IDC (n = 64), invasive lobular carcinoma (ILC; n = 6), DCIS (n = 4), tubular carcinoma (n = 2), mucinous colloid carcinoma (n = 2), medullary carcinoma (n = 1), adenoid cystic carcinoma (n = 1), and malignant phyllodes tumor (n = 1). The median size of the malignant lesions was 2.1 cm (range, 0.8–11.2 cm).

A total of 57 benign lesions were identified, 19 of which showed histopathologic results, which included fibroadenoma (n = 14), papilloma (n = 2), epidermoid cyst (n = 1), nodular adenosis (n = 1), and ductal ectasia with stroma fibrosis (n = 1). The authors also included 38 lesions classified as BI-RADS [46] category 2 by MR imaging to increase the number of samples of benign lesions for use in identification of more reliable and representative ADC values. The diagnoses were defined by the consensus of 2 experienced breast radiologists with 12 and 9 years of experience, respectively. Benign lesions were followed up for at least 1 year by mammography, sonography, or MR imaging, with no significant modifications in the imaging patterns. The median size of benign lesions was 1.2 cm (range, 0.6–11.4 cm).

### MR Imaging Acquisition, Analysis and Data Collection

All MR imaging examinations, including DWI, were performed on a 1.5-T MR System with a bilateral
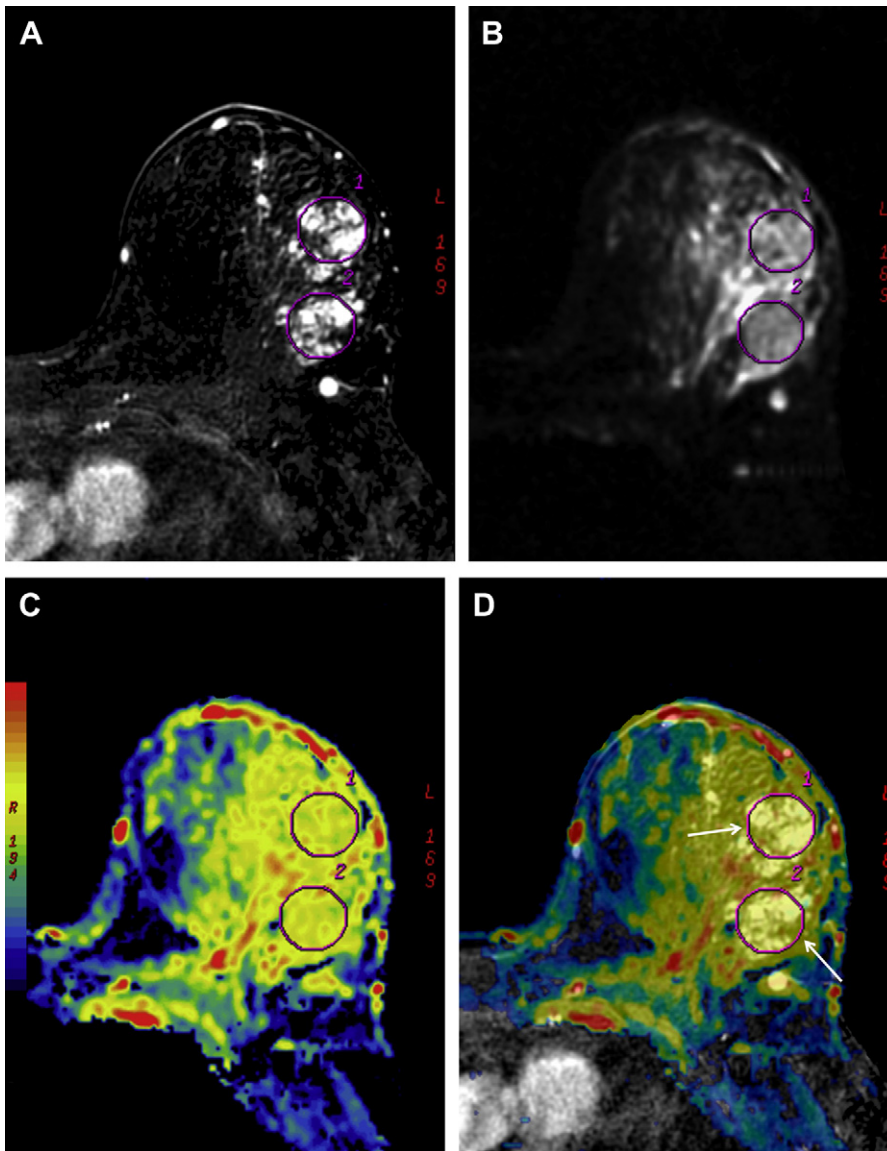
**Fig. 2.** 62-year-old woman with nonmasslike enhancement of the left breast. (*A*) Axial contrast-enhanced T1-weighted three-dimensional spoiled gradient-echo image, first phase, subjected to subtraction technique. (*B*) Axial diffusion-weighted image. (*C*) Axial colored ADC map obtained using b-values of 0 and 750 s/mm$^2$. (*D*) Fusion axial contrast-enhanced T1-weighted subjected to subtraction technique and axial colored ADC map reveal a nonmasslike enhancement lesion classified as highly suspicious by conventional MR imaging. Because nonmasslike enhancement lesions form large but noncompact lesions, a lesser restriction of the diffusion processes may occur, evident as yellow, and not blue, on the ADC colored map. Note that even using the subtracted image as reference to the ROI placement, there are still no enhancing areas, which may not represent tumor inside the ROIs (*white arrows*).

8-channel breast coil. DWI was performed using an axial single-shot EPI sequence centered on the lesion (**Table 1**). Standard sequences, including pre- and postcontrast sequences, were acquired before DWI.

All images were transferred to a workstation, and the DWI sequence was postprocessed using commercial software to obtain black-and-white and color ADC maps. Color maps used a color scheme, ranging from blue (diffusion restriction) to red (no diffusion restriction). The ADC maps of each lesion were calculated using 5 b-values (0, 250, 500, 750, and 1000 s/mm$^2$) and also using the b 0 s/mm$^2$ value in combination with the other b-values (0 and 250 s/mm$^2$, 0 and 500 s/mm$^2$, 0 and 750 s/mm$^2$, 0 and 1000 s/mm$^2$).

**Table 1**
**Protocol used for the DWI study at our institution**

| Parameter | Value |
|---|---|
| Sequence | DWI single-shot EPI |
| TR/TE | 1800 ms/93.8 ms (minimum TE) |
| FOV | 360 mm |
| Matrix | 160 × 192 |
| Slice thickness/interval | 5 mm/0 mm |
| NEX | 16 |
| rBW | 25 kHz |
| b-values | 0, 250, 500, 750, 1000 s/mm$^2$ |
| Scan time | 224 s |
| Scan time for b-value | 56 s |

*Abbreviations:* FOV, field of view; NEX, number of excitations; rBW, receive band width; TE, echo time; TR, repetition time.

DWI and ADC maps are typically noisy and were therefore viewed in conjunction with contrast-enhanced images. To achieve standardized conditions for analysis and to avoid contamination of the data by adjacent structures, 2 similar circular ROIs with a median area of 49 mm$^2$ (range, 16–536 mm$^2$) were individually placed within the target lesion in the same location for the 5 ADC maps described earlier, and the average ADC was acquired for each b-value combination. Apparent necrotic or cystic components were avoided by referring to conventional MR images.

The median ADC values were correlated with imaging findings and histopathologic diagnoses. The cutoff ADC value and the sensitivity and specificity of DWI to differentiate between benign and malignant lesions were calculated for all b-value combinations. Comparisons between the median ADC values for noninvasive ductal carcinoma and different grades of IDC were also performed for all b-value combinations. *P*-values less than .05 were considered statistically significant.

### Results

The median ADC values obtained using 5 b-values and b 0 s/mm$^2$ value in combination with the other b-values were significantly lower for malignant breast lesions (median, 0.82–1.19; interquartile range [IQR] 0.72–1.4 × 10$^{-3}$ mm$^2$/s) than for benign lesions (median, 1.38–1.71; IQR 1.22–1.93 × 10$^{-3}$ mm$^2$/s) (*P*<.001, **Table 2**).

All of the b-value combinations used to calculate the ADC resulted in high sensitivity and specificity for the differentiation of benign and malignant lesions (**Table 3**). The only significant difference that occurred between the different b-value combinations was for the combination of b 0 and 250 s/mm$^2$, which exhibited a significantly lower area under the curve (AUC) compared with the other combinations (*P* = .019). No significant differences were observed between the other b-value combinations (*P*>.05). Consistent with previous findings, the ADC values calculated using b-values of 0 and 750 s/mm$^2$ were still slightly better than the other b-value combinations. Based on a cutoff value of 1.24 × 10$^{-3}$ mm$^2$/s for ADCs calculated using b-values of 0 and 750 s/mm$^2$, 4 of 57 benign lesions (two fibroadenomas, one papilloma, and one nodular adenosis) and 7 of 81 malignant lesions (3 IDC, one ILC, 2 mucinous colloid carcinomas, and one malignant phyllodes tumor) were misdiagnosed, resulting in a sensitivity of 91.4% and a specificity of 93%. The ADC values calculated using b-values of 0 and 250 s/mm$^2$ yielded the poorest differentiation between benign and malignant lesions, resulting in a sensitivity of 81.5% and a specificity of 87.7%, based on a cutoff value of 1.47 × 10$^{-3}$ mm$^2$/s.

With respect to the different benign histologic types, for the b-value combination of 0 and 750 s/mm$^2$, the median ADC values for fibroadenoma, papilloma, epidermoid cyst, nodular adenosis, and ductal ectasia with stroma fibrosis were 1.46 × 10$^{-3}$ mm$^2$/s, 1.22 × 10$^{-3}$ mm$^2$/s, 1.32 × 10$^{-3}$ mm$^2$/s, 0.99 × 10$^{-3}$ mm$^2$/s, and 1.99 × 10$^{-3}$ mm$^2$/s, respectively. With respect to the different malignant histologic types, for the b-value combination of 0 and 750 s/mm$^2$, the median ADC values for IDC, ILC, DCIS, tubular carcinoma, mucinous colloid carcinoma, medullary carcinoma, adenoid cystic carcinoma, and malignant phyllodes tumor were 0.91 × 10$^{-3}$ mm$^2$/s, 0.94 × 10$^{-3}$ mm$^2$/s, 0.91 × 10$^{-3}$ mm$^2$/s, 0.84 × 10$^{-3}$ mm$^2$/s, 1.59 × 10$^{-3}$

**Table 2**
**ADC values by b-value combination for benign and malignant lesions**

| b-Value Combinations (s/mm$^2$) | ADC values ($\times 10^{-3}$ mm$^2$/s) | | | | | |
| | Benign Lesions (n = 57) | | Malignant Lesions (n = 81) | | | |
| | Median | IQR | Median | IQR | P-value |
|---|---|---|---|---|---|
| 0, 250, 500, 750, and 1000 | 1.45 | 1.30−1.58 | 0.907 | 0.76−1.01 | <0.001 |
| 0 and 250 | 1.71 | 1.56−1.93 | 1.190 | 1.04−1.40 | <0.001 |
| 0 and 500 | 1.59 | 1.44−1.77 | 1.010 | 0.90−1.19 | <0.001 |
| 0 and 750 | 1.51 | 1.34−1.64 | 0.931 | 0.83−1.03 | <0.001 |
| 0 and 1000 | 1.38 | 1.22−1.55 | 0.820 | 0.72−0.94 | <0.001 |

mm$^2$/s, $0.86 \times 10^{-3}$ mm$^2$/s, $0.93 \times 10^{-3}$ mm$^2$/s, and $1.84 \times 10^{-3}$ mm$^2$/s, respectively.

No statistically significant difference was evident between the median ADC values for noninvasive ductal carcinoma and the different grades of IDC using any of the b-value combinations. For the b-value combination of 0 and 750 s/mm$^2$, the median ADC value for DCIS was $0.91 \times 10^{-3}$ mm$^2$/s, and the median ADC values for IDC grades I, II, and III were $0.92 \times 10^{-3}$ mm$^2$/s, $0.88 \times 10^{-3}$ mm$^2$/s, and $1.02 \times 10^{-3}$ mm$^2$/s, respectively (P = .426).

### Comments

The present results confirmed the findings of our previous study.[17] Both studies showed that the median ADC value for benign lesions was significantly lower than that of malignant lesions for all b-value combinations analyzed. Moreover, no statistically significant difference was observed between ADC values calculated using most of the b-value combinations analyzed, although the ADC calculated using b-values of 0 and 750 s/mm$^2$

was slightly better than the others. These findings suggest that higher b-values can be useful for distinguishing benign from malignant lesions and that use of multiple b-values in DWI sequences is unnecessary.

Based on the diagnostic criteria used in this study, only two fibroadenomas (14.2%) and 4 invasive carcinomas (5.7%) were not appropriately classified using the ADC. These results indicate that DWI can effectively discriminate between fibroadenomas and invasive carcinomas (**Figs. 3** and **4**). This capability could likely prove to be useful for lesion characterization, because fibroadenomas have characteristics that overlap with malignant lesions in both sonography and dynamic contrast-enhanced MR imaging studies.[16,48,49] In our series, 5 fibroadenomas were misdiagnosed as suspect by MR imaging, but 3 of these lesions were correctly diagnosed as benign by DWI.

The primary limitations of our study were similar to those reported in the literature, including poor quality data as a result of patient movement and

**Table 3**
**Sensitivity and specificity of the ADC in differentiation of benign from malignant lesions for each b-value combination**

| b-Value Combinations (s/mm$^2$) | Cutoff ($\times 10^{-3}$ mm$^2$/s)[a] | Sensitivity (%) | 95% CI[b] | Specificity (%) | 95% CI[b] | AUC[c] |
|---|---|---|---|---|---|---|
| 0, 250, 500, 750, and 1000 | 1.17 | 90.1 (73/81) | 81.4−95.6 | 94.7 (54/57) | 85.4−98.9 | 0.929 |
| 0 and 250 | 1.47 | 81.5 (66/81) | 73.0−90.0 | 87.7 (50/57) | 79.2−96.2 | 0.891 |
| 0 and 500 | 1.34 | 91.4 (74/81) | 85.3−97.5 | 91.2 (52/57) | 83.8−98.6 | 0.928 |
| 0 and 750 | 1.24 | 91.4 (74/81) | 85.3−97.5 | 93.0 (53/57) | 86.4−99.6 | 0.941 |
| 0 and 1000 | 1.12 | 91.4 (74/81) | 85.3−97.5 | 91.2 (52/57) | 83.8−98.6 | 0.943 |

Numbers in parentheses indicate number of lesions.
  [a] ADC cutoff value.
  [b] Confidence interval.
  [c] Area under the curve, represents the probability that the ADC value accurately characterizes a breast lesion as malignant or benign according to the cutoff value.
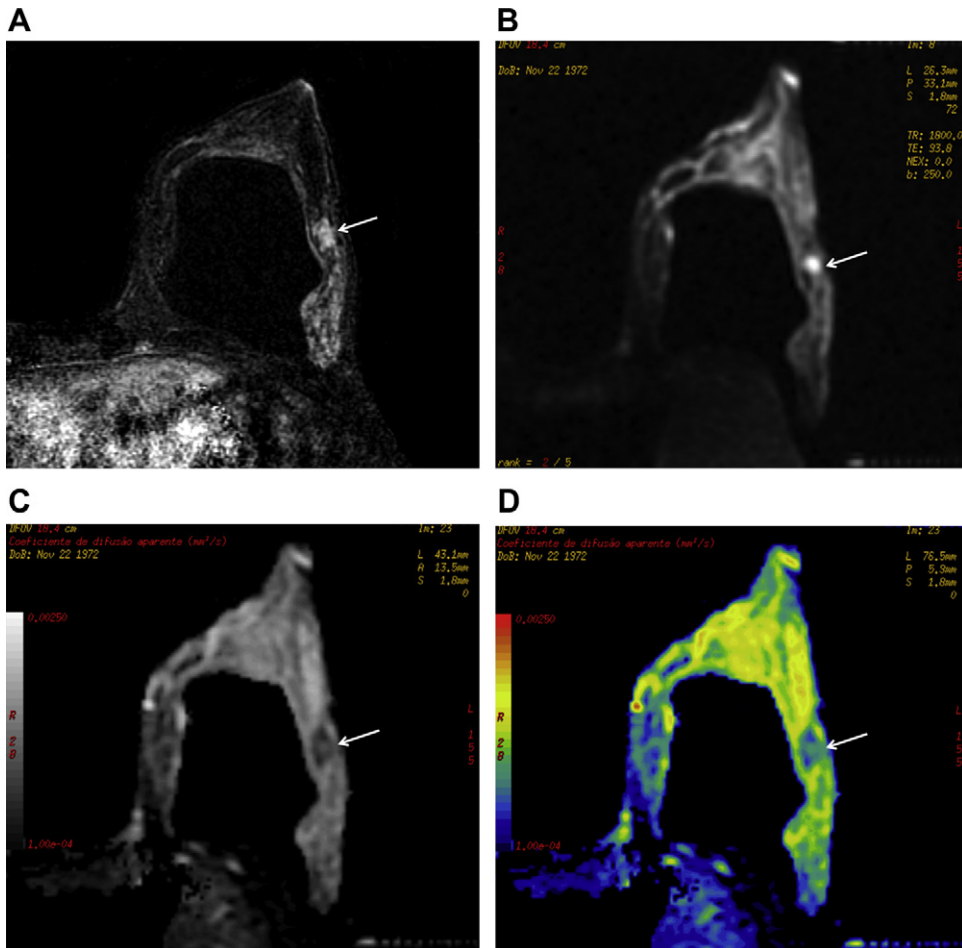
Fig. 3. 35-year-old woman with IDC of the left breast. (*A*) Axial contrast-enhanced T1-weighted three-dimensional spoiled gradient-echo image, in late phase. (*B*) Axial diffusion-weighted image. (*C*) Axial black-and-white and (*D*) colored ADC maps obtained using b-values of 0 and 750 s/mm$^2$ reveal a 1.1-cm mass (*white arrows*) classified as probably benign by conventional MR imaging. Note the low signal on the ADC black-and-white map and the blue on the ADC colored map, which indicates a malignant lesion.

difficulty visualizing some lesions on DWI, particularly small lesions. Limited ADC value measurements resulting from motion artifacts (10.1%) or from lack of visibility of the lesion on DWI, even after correlation with contrast-enhanced images (7.9%), resulted in exclusion of these cases. However, generally, good lesion visibility (92.1%) was obtained in the present study, and 8 of the 14 nonvisible lesions (57.1%) were smaller than 1 cm.

Despite these limitations, our results and the results of others suggest that DWI of the breast can provide additional information for the characterization of mass breast lesions in a rapid and straightforward manner. Furthermore, combination of ADC measurements with dynamic studies that interpret enhancement patterns, which exhibit good sensitivity but variable specificity for characterizing lesions, can increase the overall accuracy of MR imaging, reducing the number of unnecessary invasive procedures. In our study, the overall specificity of MR imaging increased from 82.4% to 93% with the use of DWI.

## POTENTIAL APPLICATIONS OF DIFFUSION IMAGING

Our results indicate that DWI can serve as a powerful tool for differentiating benign from malignant breast lesions. In addition to this use, DWI also shows potential for use in several additional diagnostic and therapeutic applications, including monitoring of neoadjuvant chemotherapy (NAC), evaluation of peritumor tissues, and assessment of axillary lymph nodes. These promising novel applications of DWI are discussed in the following sections.
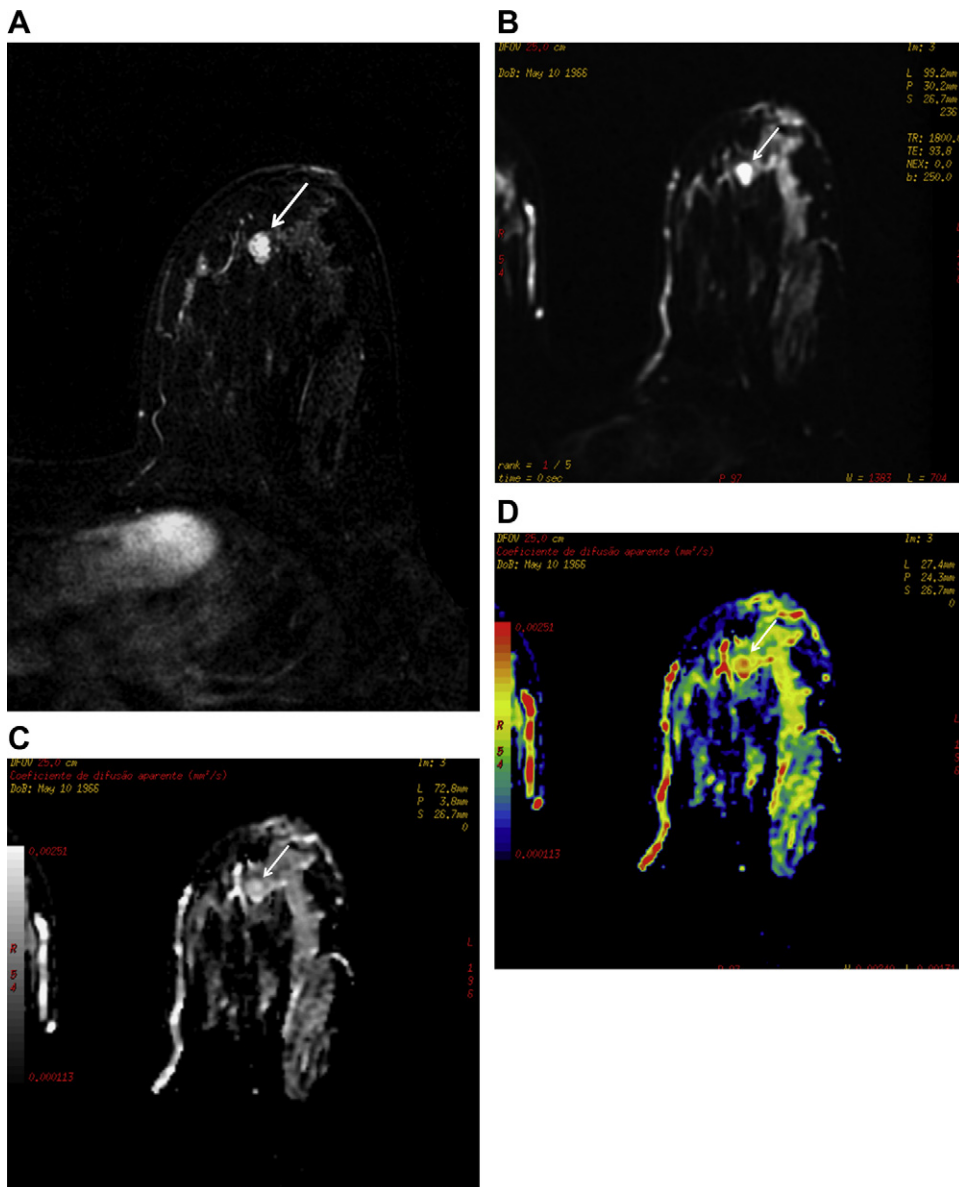
**Fig. 4.** 43-year-old woman with fibroadenoma of the left breast. (*A*) Axial contrast-enhanced T1-weighted three-dimensional spoiled gradient-echo image, first phase, subjected to subtraction technique. (*B*) Axial diffusion-weighted image. (*C*) Axial black-and-white and (*D*) colored ADC maps obtained using b-values of 0 and 750 s/mm^{2} reveal a 1.3-cm mass (*white arrows*) classified as suspicious by conventional MR imaging. Note the high signal on the ADC black-and-white map and the red on the ADC colored map, which suggest that the lesion is benign.

## Application of DWI to Monitoring of NAC

NAC is used to achieve tumor shrinkage, allowing breast conservation surgery for a proportion of patients with locally advanced breast cancer. Large clinical trials assume that the degree of response of the primary tumor to NAC is correlated with patient survival.[50] However, 20% to 25% of all patients with breast cancer do not respond to chemotherapy. Identification of surrogate biomarkers able to predict therapeutic outcomes earlier or more accurately than the current methods would be valuable for individualized tailoring of treatment and would allow for more cost-effective use of resources.[51]

Imaging modalities can be used to track tumor changes in response to a particular chemotherapy

regimen. Several imaging modalities have been used to assess the extent of response to primary breast cancer treatment. MR imaging is considered to be the best available choice for evaluating the tumor and its response to the administered treatment as a result of the higher accuracy of this technique compared with the traditional methods of physical examination and mammography.[52]

A role for DWI in monitoring and predicting early breast tumor responses to NAC has previously been described.[21,30,51,53] Chemotherapy treatment results in cell lysis and loss of cell membrane integrity, which results in an increase in extracellular space and a concomitant increase in diffusion of water. Based on these effects, interest is growing in the measurement of changes in diffusion to detect tumor responses. Therefore, DWI may prove to be valuable for monitoring the effectiveness of treatment and for assessing changes caused by cell swelling and apoptosis rather than the application of conventional radiologic response indicators.

Pickles and colleagues[53] reported that a significant increase in the ADC occurred before a decrease in tumor size measured by MR imaging in a cohort of patients with invasive breast cancer examined before and after the first and second NAC cycles. The increase in the ADC value at the first cycle time point was significant, but the decrease in the longest diameter at the second cycle time point was only of borderline significance. Sharma and colleagues[30] found a statistically significantly larger increase in the ADC after the first chemotherapy cycle in responders compared with nonresponders, indicating the potential of this method for assessment of early responses. At this time point, no change in tumor size was evident for either group. These results underscore the potential usefulness of DWI for assessing treatment responses at early time points, before changes in tumor size.

A comparison between the ability of MR imaging and DWI to detect residual tumors revealed accuracy rates of 89% and 96%, respectively, which were not found to be statistically significant.[54] DWI exhibited, at minimum, equivalent accuracy levels to contrast-enhanced MR imaging for monitoring NAC. Therefore, use of DWI to visualize residual breast cancer without the need for contrast medium could be advantageous.

## Application of DWI to Evaluation of Peritumor Tissues

Conservative surgery has become a well-established alternative to mastectomy for treatment of breast cancer. However, for conservative surgery to be successful, it is necessary to remove an adequate volume of breast tissue to achieve tumor-free margins and to reduce the risk of local recurrence without compromising the cosmetic outcome. Therefore, accurate determination of the transition boundary between the tumor and normal tissue is critical for deciding the surgical scope.

A previous study was designed to analyze changes in ADC values in peritumor tissues using DWI.[55] This study was based on the hypothesis that genetic and molecular alterations precede phenotypic changes in peritumor tissues. Therefore, DWI may be able to detect alterations earlier than conventional MR imaging. These investigators revealed that the ADC value of malignant lesions was statistically lower than that of peritumor tissues. They also found that the ADC values increased gradually from the innermost to the outermost layers of peritumor tissues. These results suggest that DWI can be used to predict the involvement of peritumor tissues, which could be highly beneficial for surgery preparation.

## Application of DWI to Assessment of Axillary Lymph Nodes

Preliminary studies have shown that diffusion can be used to detect lymph nodes affected by malignant cells after the nodes have undergone changes and increases in cellularity that lead to diffusion restriction and low ADC values.[21] In a retrospective feasibility study, DWI was evaluated as a potential tool for characterization of pelvic lymph nodes in patients with prostate cancer.[56] The results from this study showed that there was a highly significant difference between the mean ADC values of malignant versus benign lymph nodes. Use of a cutoff of $1.30 \times 10^{-3}$ mm$^2$/s resulted in good accuracy (85.6%), sensitivity (86.0%), and specificity (85.3%) for differentiation between malignant and benign lymph nodes using ADC values. These findings indicate that DWI is an accurate technique for the analysis of pelvic lymph nodes.

One could predict that metastasis to lymph nodes present in the axilla should result in similar effects on the ADC, specifically restricted diffusion and corresponding low ADC values. However, further studies are necessary to investigate the usefulness of DWI for characterization of malignant axillary lymph nodes. In addition, characterization of the necessary lymph nodal invasion level required to restrict diffusion and reduce the ADC value is needed for clinical applications. It also remains unclear whether DWI can accurately diagnose small metastases.

## Use of DWI for Cancer Screening in Clinical Practice

The usefulness of DWI in clinical practice remains to be determined. DWI is often used as a supportive

tool when results from conventional MR imaging are unclear. Applications using DWI for assessment of the response to NAC are also under development. Therefore, DWI has primarily been used for diagnostic purposes. However, the power of DWI for evaluation of high-risk patients who undergo screening MR imaging remains unknown.

The objectives of cancer screening are to improve the prognosis of patients with cancer and to reduce mortality. The accurate and timely detection of cancer is crucial to decreasing cancer-related mortality. High-risk groups are likely to be given priority for screening. Insufficient objective data are available to evaluate the effectiveness of DWI for cancer screening, and future studies in this area are needed. DWI can be predicted to be a useful screening tool because of its short scan time, cost-effectiveness, and high sensitivity.[36,37]

### Use of DWI as a Stand-alone Technique

Because DWI does not require the injection of any contrast agent, it could possibly be of value as a stand-alone technique in severely ill patients, who cannot tolerate extended examinations. Furthermore, in patients with impaired renal function, the risk of nephrogenic systemic fibrosis is avoided using this technique.[25]

An initial investigation focused exclusively on malignant lesions showed a high rate of sensitivity for a contrast-free diagnostic approach combining DWI and short T1 inversion recovery imaging.[25,43] However, before such an approach could be introduced into the clinical routine, a possible incremental increase in value of contrast-free breast MR imaging over conventional methods must be validated. Knowledge regarding the diagnostic usefulness of ADC values compared with standard morphologic and dynamic descriptors remains limited. In a recent investigation, quantitative diffusivity measurements resulted in high, but nonetheless clearly inferior, diagnostic parameters compared with routine breast MR imaging.[25,42] Therefore, further studies are needed to quantitatively compare the accuracy of contrast-free and contrast-enhanced MR imaging of the breast.

### Diffusion Tensor Imaging: An Extension of DWI

Diffusion tensor imaging (DTI) extends standard DWI, characterizing diffusion in at least 6 directions, to measure the full diffusion tensor and to characterize the motion of water in greater detail. In addition to the ADC value, DTI enables calculation of the degree of diffusion anisotropy (or directionality).[57] Therefore, information obtained by DTI for normal and altered breast tissue may also be useful for detecting disease and assessing local invasion.

In the brain, diffusion anisotropy measures have been useful for elucidating organization and development of white matter and for identifying abnormalities.[57] With recent advancements in MR imaging technology, DTI has also enabled unique microstructural characterization of normal and abnormal tissues in other areas of the body. The general assumption in previous studies has been that water diffusion in breast tissue is isotropic, with equal mobility in all directions. However, in more organized breast tissues, such as the parenchyma, which has a network of branching ducts and associated periductal fibrous stroma that extends radially and posteriorly from the nipple, it is possible that water molecules tend to follow a less restricted path and diffuse preferentially along or parallel to the ducts.[57] This phenomenon may result in anisotropic diffusion in normal breast tissue that can be detected by DTI.

Partridge and colleagues[57] found low to moderate diffusion anisotropy in normal fibroglandular tissue. Fractional anisotropy (FA) measurements differed between breast regions and were generally higher in the outer posterior region. This observation may reflect microstructural differences in the fibroglandular tissue. A higher concentration of smaller tapering ducts and terminal ductolobular units in the peripheral breast could influence diffusion directionality and increase posterior FA measurements in this region. Characterization of these influences on DTI measurements may be important for clinical interpretation of DTI results and standardization of techniques. Future studies are necessary to assess the clinical usefulness of DTI for breast imaging by comparing diffusion anisotropy in breast tumors and normal tissue. DTI may be able to detect disruptions in the normal anisotropy of water diffusion in the breast caused by cancer growth and may lead to new indices for identification of breast cancer.

### SUMMARY

Diffusion sequences can be used for characterization and differentiation of malignant and benign breast lesions. Use of DWI as a diagnostic tool can increase the specificity of breast MR imaging and can reduce the number of false-positive results and associated unnecessary biopsies. In addition, DWI can be performed without significantly increasing examination time and can easily be introduced into the standard breast MR imaging protocol. Furthermore, novel applications for DWI are under development, including monitoring of

the response to NAC, evaluation of peritumor tissues, assessment of axillary lymph nodes, and characterization of the advanced DTI technique. Although DWI is not currently recommended as a stand-alone diagnostic tool, future studies without injection of contrast agents may support the use of DWI in this capacity.

The performance of DWI under different conditions and at different field strengths must be better characterized to define a universal protocol. In addition, determination of the diagnostic criteria is also important, such as the threshold ADC value for quantitative diagnosis and the signal intensity for qualitative diagnosis. Potential pitfalls related to the diagnosis of nonmass-type enhancement lesions and small mass-type lesions, as well as movement artifacts, should be taken into consideration.

## REFERENCES

1. Kuhl CK. Current status of breast MR imaging. Part II. Clinical applications. Radiology 2007;244(3): 672—91.
2. Kuhl CK. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. Radiology 2007;244(2):356—78.
3. Schnall MD, Blume J, Bluemke DA, et al. Diagnostic architectural and dynamic features at breast MR imaging: multicenter study. Radiology 2006;238(1): 42—53.
4. Macura KJ, Ouwerkerk R, Jacobs MA, et al. Patterns of enhancement on breast MR images: interpretation and imaging pitfalls. Radiographics 2006;26(6): 1719—34.
5. Wierner JI, Schilling KJ, Adami C, et al. Assessment of suspected breast cancer by MRI: a prospective clinical trial using a combined kinetic and morphologic analysis. AJR Am J Roentgenol 2005;184(3): 878—86.
6. Bedrosian I, Mick R, Orel SG, et al. Changes in the surgical management of patients with breast carcinoma based on preoperative magnetic resonance imaging. Cancer 2003;98(3):468—73.
7. Marini C, Iacconi C, Giannelli M, et al. Quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesion. Eur Radiol 2007;17(10): 2646—55.
8. Kuhl CK, Mielcareck P, Klaschik S, et al. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? Radiology 1999;211(1):101—10.
9. Fischer U, Kopka L, Grabbe E. Breast carcinoma: effect of preoperative contrast-enhanced MR imaging on the therapeutic approach. Radiology 1999;213(3):881—8.
10. Wenkel E, Geppert C, Schulz-Wendtland R, et al. Diffusion weighted imaging in breast MRI: comparison of two different pulse sequences. Acad Radiol 2007;14(9):1077—83.
11. Sinha S, Sinha U. Functional magnetic resonance of human breast tumors: diffusion and perfusion imaging. Ann N Y Acad Sci 2002;980:95—115.
12. Guo Y, Cai YQ, Cai ZL, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. J Magn Reson Imaging 2002;16(2):172—8.
13. Rubesova E, Grell AS, De Maertelaer V, et al. Quantitative diffusion imaging in breast cancer: a clinical prospective study. J Magn Reson Imaging 2006; 24(2):319—24.
14. Woodhams R, Matsunaga K, Iwabuchi K, et al. Diffusion-weighted imaging of malignant breast tumors: the usefulness of apparent diffusion coefficient (ADC) value and ADC map for the detection of malignant breast tumors and evaluation of cancer extension. J Comput Assist Tomogr 2005;29(5): 644—9.
15. Kuroki Y, Nasu K, Kuroki S, et al. Diffusion-weighted imaging of breast cancer with the sensitivity encoding technique: analysis of the apparent diffusion coefficient value. Magn Reson Med Sci 2004;3(2): 79—85.
16. Sinha S, Lucas-Quesada FA, Sinha U, et al. In vivo diffusion-weighted MRI of the breast: potential for lesion characterization. J Magn Reson Imaging 2002;15(6):693—704.
17. Pereira FPA, Martins G, Figueiredo E, et al. Assessment of breast lesions with diffusion-weighted MRI: comparing the use of different b values. AJR Am J Roentgenol 2009;193(4):1030—5.
18. Partridge SC, De Martini WB, Kurland BF, et al. Quantitative diffusion-weighted imaging as an adjunct to conventional breast MRI for improved positive predictive value. AJR Am J Roentgenol 2009;193(6):1716—22.
19. Yabuuchi H, Matsuo Y, Okafuji T, et al. Enhanced mass on contrast-enhanced breast MR imaging: lesion characterization using combination of dynamic contrast-enhanced and diffusion-weighted MR images. J Magn Reson Imaging 2008;28(5): 1157—65.
20. Kelcz F. Diffusion weighted imaging of breast — promises and problems. Eur Radiol 2009;19(Suppl 4): S856—8.
21. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol 2007;188(6):1622—35.
22. Paran Y, Bendel P, Margalit R, et al. Water diffusion in the different microenvironments of breast cancer. NMR Biomed 2004;17(4):170—80.
23. Bogner W, Gruber S, Pinker K, et al. Diffusion-weighted MR for differentiation of breast lesions at

3.0 T: how does selection of diffusion protocols affect diagnosis? Radiology 2009;253(2):341—51.

24. Kuhl CK. Concepts for differential diagnosis in breast MR imaging. Magn Reson Imaging Clin N Am 2006;14(3):305—28.

25. Baltzer PAT, Dietzal M, Vag T, et al. Diffusion weighted imaging — useful in all kinds of lesions? A systematic review. Eur Radiol 2009;19(Suppl 4): S765—9.

26. Geijer B, Sundgren PC, Lindgren A, et al. The value of b required to avoid T2 shine-through from old lacunar infarcts in diffusion-weighted imaging. Neuroradiology 2001;43(7):511—7.

27. Partridge SC, McKinnon GC, Henry RG, et al. Menstrual cycle variation of apparent diffusion coefficients measured in the normal breast using MRI. J Magn Reson Imaging 2001;14(4):433—8.

28. Kuhl CK, Bieling HB, Gieseke J, et al. Healthy premenopausal breast parenchyma in dynamic contrast-enhanced MR imaging of the breast: normal contrast medium enhancement and cyclical-phase dependency. Radiology 1997; 203(1):137—44.

29. Park MJ, Cha ES, Kang BJ, et al. The role of diffusion-weighted imaging and the apparent diffusion coefficient (ADC) values for breast tumors. Korean J Radiol 2007;8(5):390—6.

30. Sharma U, Danishad KK, Seenu V, et al. Longitudinal study of the assessment by MRI and diffusion-weighted imaging of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. NMR Biomed 2009; 22(1):104—13.

31. Woodhams R, Matsunaga K, Kan S, et al. ADC mapping of benign and malignant breast tumors. Magn Reson Med Sci 2005;4(1):35—42.

32. Yoshikawa MI, Ohsumi O, Sugata S, et al. Comparison of breast cancer detection by diffusion-weighted magnetic resonance imaging and mammography. Radiat Med 2007;25(5): 218—23.

33. Yuen S, Yamada K, Goto M, et al. Microperfusion-induced elevation of ADC is suppressed after contrast in breast carcinoma. J Magn Reson Imaging 2009;29(5):1080—4.

34. Tsushima Y, Takahashi-Taketomi A, Endo K. Magnetic resonance (MR) differential diagnosis of breast tumors using apparent diffusion coefficient (ADC) on 1.5-T. J Magn Reson Imaging 2009; 30(2):249—55.

35. Hatakenaka M, Soeda H, Yabuuchi H, et al. Apparent diffusion coefficients of breast tumors: clinical application. Magn Reson Med Sci 2008;7: 23—9.

36. Razek AA, Gaballa G, Denewer A, et al. Diffusion-weighted MR imaging of the breast. Acad Radiol 2010;17(3):382—6.

37. Kuroki Y, Nasu K. Advances in breast MRI: diffusion-weighted imaging of the breast. Breast Cancer 2008;15(3):212—7.

38. Belli P, Constantini M, Bufi E, et al. Diffusion-weighted imaging in breast lesion evaluation. Radiol Med 2010;115(1):51—69.

39. Woodhams R, Kakita S, Hata H, et al. Diffusion-weighted imaging of mucinous carcinoma of the breast: evaluation of apparent diffusion coefficient and signal intensity in correlation with histologic findings. AJR Am J Roentgenol 2009;193(1):260—6.

40. Matsuoka A, Minato M, Harada M, et al. Comparison of 3.0 and 1.5-tesla diffusion-weighted imaging in the visibility of breast cancer. Radiat Med 2008; 26(1):15—20.

41. Lo GG, Ai V, Chan JK, et al. Diffusion-weighted magnetic resonance imaging of breast lesions: first experiences at 3.0T. J Comput Assist Tomogr 2009;33(1):63—9.

42. Baltzer PA, Renz DM, Herrmann KH, et al. Diffusion-weighted imaging (DWI), in MR mammography (MRM): clinical comparison of echo planar imaging (EPI) and half-Fourier single-shot turbo spin echo (HASTE) diffusion techniques. Eur Radiol 2009; 19(7):1612—20.

43. Kuroki-Suzuki S, Kuroki Y, Nasu K, et al. Detecting breast cancer with non-contrast MR-imaging: combining diffusion-weighted and STIR imaging. Magn Reson Med Sci 2007;6(1):21—7.

44. Kim SH, Cha ES, Kim HS, et al. Diffusion-weighted imaging of breast cancer: correlation of the apparent diffusion coefficient value with prognostic factors. J Magn Reson Imaging 2009;30(3):615—20.

45. Le Bihan D, Poupon C, Amadon A, et al. Artifacts and pitfalls in diffusion MRI. J Magn Reson Imaging 2006;24(3):478—88.

46. American College of Radiology (ACR). ACR BIRADS: magnetic resonance imaging. In: Ikeda DM, Hylton NM, editors. ACR breast imaging reporting and data system, breast imaging atlas. Reston (VA): American College of Radiology; 2003. p. 111—4.

47. Yabuuchi H, Matsuo Y, Kamitani T, et al. Non-mass-like enhancement on contrast-enhanced breast MR imaging: lesion characterization using combination of dynamic contrast-enhanced and diffusion-weighted MR images. Eur J Radiol 2010;75(1): 126—32.

48. Stomper PC, Winston JS, Herman S, et al. Angiogenesis and dynamic MR imaging gadolinium enhancement of malignant and benign breast lesions. Breast Cancer Res Treat 1997;45(1): 39—46.

49. Hochman MG, Orel SG, Powell CM, et al. Fibroadenomas: MR imaging appearances with radiologic—histopathologic correlation. Radiology 1997;204(1): 123—9.

50. Ma B, Meyer CR, Pickles MD, et al. Voxel-by-voxel functional diffusion mapping for early evaluation of breast cancer treatment. Inf Process Med Imaging 2009;21:276—87.

51. Turnbull LW, Ma B, Meyer CR, et al. Diffusion changes in chemotherapy of breast cancer: the earliest sign? Eur Radiol 2009;19(Suppl 4): S948—9.

52. Iacconi C, Giannelli M, Marini C, et al. The role of mean diffusivity (MD) as a predictive index of the response to chemotherapy in locally advanced breast cancer: a preliminary study. Eur Radiol 2010;20(2):303—8.

53. Pickles MD, Gibbs P, Lowry M, et al. Diffusion changes precede size reduction in neoadjuvant treatment of breast cancer. Magn Reson Imaging 2006;24(7):843—7.

54. Woodhams R, Kakita S, Hata H, et al. Identification of residual breast carcinoma following neoadjuvant chemotherapy: diffusion-weighted imaging—comparison with contrast-enhanced MR imaging and pathologic findings. Radiology 2010; 254(2):357—66.

55. Yili Z, Xiaoyan H, Hongwen D, et al. The value of diffusion-weighted imaging in assessing the ADC changes of tissues adjacent to breast carcinoma. BMC Cancer 2009;9:18.

56. Eiber M, Beer AJ, Holzapfel K, et al. Preliminary results for characterization of pelvic lymph nodes in patients with prostate cancer by diffusion-weighted MR-imaging. Invest Radiol 2010;45(1):15—23.

57. Partridge SC, Murthy RS, Ziadloo A, et al. Diffusion tensor magnetic resonance imaging of the breast. Magn Reson Imaging 2010;28(3):320—8.