Published in final edited form as:

Magn Reson Imaging Clin N Am. 2013 August ; 21(3): 601–624. doi:10.1016/j.mric.2013.04.007.

Diffusion weighted MRI of the breast: Protocol optimization, guidelines for interpretation, and potential clinical applications

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Synopsis

There has been increasing interest in the use of diffusion weighted MRI (DWI) for breast imaging. This technique has shown promise for improving the positive predictive value of breast MRI for detection of breast cancer, evaluating tumor response to neoadjuvant chemotherapy, and as a non-contrast MRI alternative for breast cancer screening. However, there is currently no standardized approach to DWI of the breast and data quality varies widely. Prior to implementing DWI into clinical practice, it is important to understand the pertinent technical considerations and current evidence of clinical applications of DWI of the breast. This article provides an overview of basic principles of DWI, optimization of breast DWI protocols, imaging features of benign and malignant breast lesions, promising clinical applications, and potential future directions.

Keywords

diffusion weighted imaging; breast MRI; screening MRI; oncologic imaging; MRI; Breast cancer diffusion; b-value; Apparent Diffusion Coefficient (ADC); neoadjuvant chemotherapy

Introduction

Diffusion-weighted imaging (DWI) is an MRI technique that characterizes the three-dimensional mobility of water in vivo and enables indirect assessment of tissue microstructure. DWI is an established diagnostic tool in neuroimaging, initially used for detecting acute stroke, but application to other areas of the body has been challenging due to technical limitations. More recent advances in MR technology including echo-planar imaging (EPI), high amplitude gradients, multichannel coils, and parallel imaging have been instrumental in extending the use of DWI outside of the brain¹⁻⁵. DWI was first applied for breast imaging in 1997 by Englander and colleagues⁶, and there have been numerous studies exploring the clinical utility of the technique since then.

DWI has shown promise for the detection and characterization of breast cancer. As a result, a growing number of imaging centers are incorporating DWI into the clinical breast MR examination. However, DWI techniques are not standardized and there is no uniform

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method of interpretation, which limits widespread use. Apparent diffusion coefficient (ADC) values allow quantification of diffusion signal and can facilitate in differentiating benign and malignant breast tumors⁷⁻¹⁹ as well as identifying early response in tumors undergoing preoperative treatment²⁰⁻²⁷.

The purpose of this review is to cover the basic principles of diffusion, discuss protocol optimization, review malignant versus benign diffusion imaging features, and discuss potential clinical applications of this promising technology.

Basic Principles of DWI

Above the temperature of 0 K, gas and liquid molecules move through thermal agitation, a process known as molecular diffusion. In pure water, this movement called Brownian motion is random, as first formally described by Einstein in 1905²⁸. In vivo, the motion of water molecules is restricted by intra and extracellular compartments as well as tissue cellularity²⁹. The degree of water diffusion in biologic tissue is inversely correlated to the tissue cellularity and the integrity of cell membranes. In the case of breast tumors, which typically have high cellular density and intact cell membranes, the motion of water molecules is more restricted than in the normal parenchyma. By contrast, in areas of low cellularity or where the cellular membrane has been breached, the motion of water molecules is less restricted (Fig 1).

DWI is a type of MRI scan performed using motion sensitizing gradients to measure the Brownian motion of water. While contrast-enhanced MRI demonstrates tissue vascularity, DWI reflects the microscopic cellular environment and is sensitive to characteristics such as cell density, membrane integrity, viscosity, and microstructure.

MR Acquisition

DWI involves short acquisition times, approximately 2-5 minutes, and can easily be incorporated into standard clinical breast MRI exams. It is typically performed using a T2-weighted spin-echo prepared EPI sequence with an additional pair of motion-sensitizing gradient pulses (Fig 2), based on methods originally proposed by Stejskal and Tanner³⁰. Diffusion gradients should be applied in at least three orthogonal directions to obtain rotationally invariant measures. EPI is used because image acquisition is very fast, which minimizes effects of subject motion. Multiple factors determine the sensitivity of the diffusion sequence to water motion, the primary of which is the degree of diffusion-weighting, described by the b-value (unit sec/mm²), given by:

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3) \quad (1)$$

where γ is the proton gyromagnetic ratio, G is the gradient strength, δ is the gradient duration, and Δ is the time delay between the leading edges of the two diffusion-sensitizing gradients³¹, as indicated in Fig 2. Water protons moving between the timing of the gradients will not be properly phased at the time of readout. As a result, the resulting MRI signal is reduced in intensity proportional to the water mobility, and is described by equation:

$$S_D = S_0 e^{-b \cdot ADC} \quad (2)$$

where S_0 is the signal intensity without diffusion-weighting, S_D is the signal intensity with diffusion-weighting, b is the applied diffusion sensitization (sec/mm²), and ADC is the apparent diffusion coefficient, defined as the average area a water molecule occupies per unit time (mm²/second)³¹. In vivo, diffusion is quantified by the ADC, accepting that the diffusion process in tissues is not free and is modulated by a composite of mechanisms

(microstructural hindrances, microcirculation) that all contribute to the signal attenuation. In general, ADC can be calculated directly from two acquisitions with different b-values using:

$$\text{ADC} = \ln(S_1/S_2) / (b_2 - b_1) \quad (3)$$

where b_1 is the minimum b-value (e.g. 0 sec/mm²) and b_2 is the maximum b-value (e.g. 800 sec/mm²), S_1 is the signal intensity at $b=b_1$, S_2 is the signal intensity at $b=b_2$ and repetition time (TR) and echo time (TE) remain constant²⁹.

The standard diffusion sequence generates two sets of images (Fig 3): T2 weighted reference images obtained without diffusion gradients (S_0), and diffusion-weighted images obtained with diffusion gradients (S_D) that reflect water mobility. Since the diffusion-weighted images are T2-weighted images that have been sensitized to diffusion, diagnostic information can be masked by extraneous long T2 signal, an artifact known as 'T2 shine through'. The parametric ADC map is created to enable diffusion quantification without T2 shine through effects. An area of restricted diffusion such as a breast tumor (arrow) is bright on the diffusion weighted image and dark on the greyscale ADC map (Fig 3).

Protocol optimization

DWI protocol optimization includes appropriate b-value selection, sufficient signal to noise ratio (SNR), adequate fat suppression, and artifact reduction via shimming and parallel imaging. Furthermore, DWI post-processing analysis requires standard noise filtering, image registration, and consistent methods for region of interest (ROI) measurement for ADC calculation. Consistency in DWI acquisition timing pre- or post-contrast is also recommended.

B-value

As defined above in Eq. 1, the b-value is proportional to the diffusion time interval multiplied by the square of the gradient strength³². It describes the degree of diffusion-weighting and is inversely proportional to SNR. The choice of b-values depends on the imaging application. For example, the optimal b-values for breast imaging are lower than the optimal b-values for neuroimaging because normal tissue ADCs are much higher in the breast. In vivo, ADC measures of malignant and benign tumors and noncancerous breast tissue are strongly dependent on the maximum b-value applied^{33,34}, Fig 4. To reproduce reported ADC thresholds for lesion characterization, similar b-values must be utilized

Multiple DWI studies have been performed comparing breast tumor conspicuity and diagnostic accuracy at varying b-values. For lesion conspicuity and detection purposes, a high b-value (800-1500 sec/mm²) may be preferred to optimize lesion contrast to adjacent tissues^{33,35,36}, Fig 5. For differentiation between benign and malignant lesions, choice of b-value may be less critical. One study comparing four b-values from 250-1000 sec/mm² found no significant difference in the ability to discriminate breast lesions, although they reported that 750 sec/mm² offered the best combination of sensitivity (92.3%) and specificity (96.2%) with an ADC threshold for malignancy of 1.24×10^{-3} mm²/sec³⁷.

DWI acquisition using multiple b-values (more than two) provides a more accurate sampling of signal decay for calculation of ADC. However, studies of multiple b-value acquisitions in the breast found no improvement in the ability to discriminate benign and malignant lesions over standard two b-value acquisitions^{37,38}. Thus, ADC calculation using two b-values remains the standard at this time^{39,40}.

While most diffusion-weighted protocols use $b=0 \text{ sec/mm}^2$ as the reference for calculating ADC, a non-zero minimum b -value ($b \geq 50 \text{ sec/mm}^2$) may be preferable in vivo to obtain ADC measures free from perfusion and flow contamination. However, studies investigating this approach for breast imaging have not clearly demonstrated a diagnostic advantage³⁸. Determination of optimal b -values for breast imaging and lesion characterization remain areas of active research.

Signal to noise ratio (SNR)

DWI is inherently associated with limited SNR, which depends on a number of factors. Adequate SNR is necessary for lesion conspicuity and for accurate ADC measurement. A higher SNR can also be used to increase the spatial resolution of DWI. Performing DWI at higher field strength can provide valuable increase in signal. Additional methods to improve SNR for DWI include increasing voxel size (increasing slice thickness and/or reducing in-plane spatial resolution), increasing the number of averages, and reducing TE. Short TE also reduces susceptibility artifacts that can occur with higher b -values³⁶. Choice of b -value also affects SNR. It has been shown that the b -value that provides the highest SNR for a spin-echo diffusion-weighted sequence is $b = 1.1/\text{ADC}$ ⁴¹. For breast imaging, with typical reported ADC values of $1.6\text{--}2.0 \times 10^{-3} \text{ mm}^2/\text{sec}$ for normal tissue, this corresponds to an optimal diffusion-weighting of approximately $b = 600 \text{ sec/mm}^2$. Alternatively, a higher b -value improves contrast resolution (as discussed in the previous section) at the cost of SNR.

It is important to note that breasts with low mammographic density, corresponding to a low volume of fibroglandular tissue, will typically yield visually low SNR on diffusion weighted images if fat suppression is properly performed (Fig 6)

Fat Suppression

Reproducible consistent fat suppression is essential for high quality DWI in the breast. Fat suppression is critical to minimize EPI-related image artifacts such as ghosting and chemical shift. Furthermore, ADCs will be underestimated without adequate fat suppression, affecting normal tissue more than tumor⁴². The ADC difference between normal tissue and tumor may not be as significant without adequate fat suppression, resulting in decreased tumor conspicuity. This effect is greater in patients with lower breast density, likely due to increased intravoxel partial-volume averaging of fat and tissue⁴².

The optimal fat suppression technique will vary across platforms. However, in general spectral fat suppression is preferred. In a prospective study of 165 consecutive patients, spectral fat suppression was significantly better than inversion recovery for lesion delineation due to increased SNR and led to less variability in ADC measurements¹³. Baron and colleagues compared four fat suppression techniques for breast DWI at 1.5T: inversion recovery, spectral selection attenuated inversion recovery (SPAIR), fat saturation, and water excitation. While water excitation had the highest SNR, this was not significantly different from fat saturation and SPAIR⁴³.

Fat suppression quality is most readily assessed on the $b=0 \text{ sec/mm}^2$ images. An example of high quality DWI with good, uniform fat suppression is shown in Fig 7. It is important to note that even though fat suppression is essential, it is imperfect. Even in high quality DWI scans, fat signal that is not fully suppressed may appear to gain relative signal strength at high b -value DWI since the non-fat tissues are losing signal as diffusion-weighting increases whereas residual fat signal is relatively unaffected by diffusion-weighting (Fig 7c).

Common Breast DWI Artifacts

Echo-planar imaging (EPI) is recommended for DWI because it provides fast, motion-freezing imaging with high SNR^{13,44,45}. However, magnetic susceptibility effects and chemical shift artifacts are magnified with this sequence. To reduce EPI-related artifacts in the breast, good shimming and fat suppression are therefore essential. Shimming is used to decrease magnetic field inhomogeneities. In the breast, spatial distortion of EPI images occurs due to magnetic susceptibility changes at tissue-air interfaces such as the breast/skin surface and chest wall/lung⁴⁶, which are amplified in the case of inadequate shimming. Most fat suppression techniques (ChemSat, FatSat; SPIR; SPAIR) also rely on good shim quality over the imaged breast volume.

EPI uses a single excitation and alternating readout trajectory to acquire all lines in k-space that form an image. As a result, before Fourier transform of k-space data, every alternate line must be reversed. This can introduce phase mismatch from deviation in the linear gradient course, eddy currents, or inadequate shimming. When phase mismatch occurs, it can cause a mirror image which is slightly shifted and of reduced intensity, called a 'ghost artifact'. Incorporating a parallel imaging technique has been shown to minimize EPI-related susceptibility artifacts in DWI and improve image quality and subsequent image interpretation⁴⁷, particularly for DWI at 3T⁴⁸. Several common breast DWI artifacts are illustrated in Fig 8.

Furthermore, misregistration within the DWI sequence between the $b=0$ and different diffusion gradient images can cause inaccuracies in breast ADC calculation^{12,13}. These misalignments may be due to patient motion during the acquisition or eddy-current based distortions in the direction of the different diffusion gradients (Fig 9)⁴⁵. Image registration algorithms may help improve alignment prior to calculating ADC. In one study, 10% of breast lesions had misregistration between the DW images that could not be rectified with a post-processing spatial registration algorithm¹⁶. There are many additional artifacts associated with DWI which are outside the scope of this article⁴⁵.

Pre- and post-contrast imaging

Many practices place DWI after the DCE-MRI scan, which is considered to be the most critical part of the examination, in case patients are not able to tolerate the entire examination. The influence of contrast administration on DWI is controversial with some studies demonstrating little effect^{11,49-51} and others suggesting that the effect may be tissue specific and dependent on image timing after contrast administration⁵²⁻⁵⁶. Our own data shows that ADCs increase significantly after DCE-MRI in both malignant and normal tissue at 3T, but this effect can be neutralized by using normalized ADCs (see below)⁵⁷. The reason for the observed ADC change requires further investigation. Regardless of where DWI is placed in the routine breast MRI protocol (before or after contrast), consistency in timing across exams is recommended for optimal ADC interpretation.

Example DWI protocol

An example of a standard protocol for DWI that is currently used as part of a multi-center clinical trial through the American College of Radiology Imaging Network is presented in Table 1. Of note, the multi-b-value acquisition used in this study is for research purposes and two b-values (e.g. 0, 800 sec/mm²) are acceptable for clinical purposes.

Diffusion weighted imaging interpretation

DWI assessment includes both qualitative interpretation of diffusion-weighted images for lesion detection and quantitative measures of ADC for lesion characterization. Qualitatively,

areas of restricted diffusion will be higher signal intensity on diffusion weighted images and lower signal intensity on ADC map images.

ADC quantitation

For quantitative interpretation at our institution, a commercially-available image registration software tool (Diffusion Registration tool, Philips Healthcare, Best, The Netherlands) is first used to spatially align the diffusion weighted images, using the $b=0$ sec/mm² images as reference. Noise-level thresholding is applied to mask the $b=0$ sec/mm² images before creating diffusion maps. ADC maps are next created using either scanner software or offline processing by applying Eq. 3 on a voxel-by-voxel basis at each slice location.

For lesion measurements: After identification on a DCE-MRI image, a region of interest (ROI) is manually defined at the corresponding location (typically hyperintense) on the $b = 800$ sec/mm² DW images to encompass as much of the abnormality as possible while staying within the border of the hyperintense region (Fig 10A-C). Susceptibility-based EPI distortions commonly causing pixel shifts on DWI (Fig 8C,D) currently limits the ability to propagate ROIs directly from DCE-MRI¹³. Care is taken to avoid areas of hemorrhage or necrosis by comparing with conventional T1- and T2-weighted images. For measurement of normal fibroglandular tissue: An ROI is drawn in a region of normal appearing fibroglandular tissue identified on the $b=0$ sec/mm² image, with care taken to avoid including adipose tissue (Fig 10D). The mean DWI signal intensity and ADC are calculated for the lesion and normal breast parenchyma.

ADC normalization

ADC normalization may reduce variation from individual breast characteristics and technical factors such as whether DWI is performed pre- or post-contrast⁵⁷. Normalized ADC is calculated as:

$$nADC = ADC_{\text{lesion}} / ADC_{\text{normal}} \quad (4)$$

where ADC_{lesion} and ADC_{normal} are the mean ADC of the lesion and normal breast parenchyma tissue, respectively. El Khouli et al reported that the degree of ADC overlap between benign and malignant lesions is reduced with ADC normalization and consequently, the diagnostic performance of DWI is increased⁵⁸. They reported an optimal normalized ADC cutoff of 0.7, which provided 83.3% sensitivity and 92% specificity. However, use of this parameter requires further investigation and is hindered in cases of extensive disease, very fatty breasts or other factors where normal tissue is difficult to assess.

Imaging features of normal breast parenchyma

The development of standardized interpretation criteria requires an understanding of the appearance and normative range of ADCs in the breast parenchyma on diffusion imaging. Breast ADC can vary widely between individuals and different baseline ADCs may affect the conspicuity of malignancy. A number of studies have attempted to establish a normative range of breast ADC. The reported mean ADCs of normal breast tissue varies widely from 1.51×10^{-3} to 2.09×10^{-3} mm²/sec (with max b-values ranging from 600 to 1000 sec/mm²)^{14,15,17,33,59}. Hormonal fluctuations may moderately influence breast ADC values, although comparisons with menstrual phase have been variable⁶⁰⁻⁶². Our own work has shown that increased mammographic breast density is associated with higher baseline ADC when compared to decreased mammographic breast density, $1.71 \pm 0.28 \times 10^{-3}$ mm²/sec vs. $1.41 \pm 0.29 \times 10^{-3}$ mm²/sec (at $b=800$ sec/mm²), $p < 0.0001$ ⁶³. Increased intravoxel partial-volume averaging with fat may lead to lower ADC measures in women with less dense

breasts, such as the example in Fig 6. These findings are in agreement with those showing significantly lower ADC in postmenopausal compared to premenopausal women⁶¹, as lower breast density is associated with increased age and postmenopausal status. Suppression of the signal from normal breast fibroglandular tissue with higher b-values may help increase tumor conspicuity and avoid T2 shine through artifact⁴⁰, as illustrated in Fig 5.

Imaging features of Malignancy

The essential concept behind detecting malignancy with quantitative diffusion imaging is that breast cancer has significantly lower ADCs than benign breast lesions or normal tissue^{7,9-13,15-19,64,65}. This is due to the relatively increased tumor cellularity which restricts diffusion, manifested by bright signal on diffusion weighted images and dark signal on a corresponding ADC map^{7,8,14,66,67} (Fig 11, Fig 12). A meta-analysis of 13 studies evaluating the diagnostic performance of quantitative breast DWI in 964 lesions (615 malignant and 349 benign) demonstrated pooled sensitivity of 84% (95% CI: 0.82, 0.87) and specificity of 79% (95% CI: 0.75, 0.82)⁶⁸. Malignant lesion mean ADC ranged from $0.87\text{--}1.36 \times 10^{-3} \text{ mm}^2/\text{s}$. Recommended threshold ADC cutoffs varied from 0.90 to $1.76 \times 10^{-3} \text{ mm}^2/\text{s}$. All except three studies used a maximum b-value of 1000 sec/mm². Another meta-analysis of 12 articles performed between 2000-2008 recommended a threshold for malignancy of $1.23 \times 10^{-3} \text{ mm}^2/\text{sec}$ at b=1000 sec/mm²³⁴.

The optimal ADC threshold will depend on the purpose of the DWI and may be set higher if DWI is used for screening and lower if DWI is used to increase the specificity of DCE-MRI. Our previously recommended ADC threshold of $1.81 \times 10^{-3} \text{ mm}^2/\text{sec}$ (b= 600 sec/mm²) is designed to allow maximum sensitivity¹⁶. We and other investigators have also suggested a lower threshold of $1.6 \times 10^{-3} \text{ mm}^2/\text{sec}$ (b₂=600 sec/mm² or 750 sec/mm²) to optimize both sensitivity and specificity, allowing for more false-negative lesions^{14,17,58}.

Non-invasive malignancy can be more challenging to detect, especially at higher b-values. We found that pure DCIS lesions (Fig 13) demonstrate both higher signal on DWI (mean contrast-to-noise ratio (CNR) = 1.83 ± 2.7) and lower mean ADC ($1.50 \pm 0.28 \times 10^{-3} \text{ mm}^2/\text{s}$) than normal tissue ($2.01 \pm 0.37 \times 10^{-3} \text{ mm}^2/\text{s}$, p < 0.0001). Applying an ADC threshold of $<1.81 \times 10^{-3} \text{ mm}^2/\text{sec}$ (b= 600 sec/mm²) detected 91% of DCIS⁶⁹. A separate analysis comparing high and low nuclear grade DCIS demonstrated that maximum lesion size and mean CNR most significantly discriminated high from low grade lesions⁷⁰. While we did not observe DCIS grade to significantly impact ADC, others have shown a significant negative trend between mean ADC and lesion grade⁷¹.

Non-mass enhancement (NME) on DCE-MRI can potentially represent malignancy that is less compact than mass lesions, such as the example in Fig 10C. As ADC is inversely correlated with cellular density^{7,12}, NME lesions could exhibit higher ADC due to more interspersed normal fibroglandular tissue. Indeed, several recent studies comparing NME and mass lesions confirmed higher mean ADC for malignant NME versus mass lesions, and determined that the optimal ADC cutoff for differentiating benign from malignant lesions was also higher for NME^{18,65,72,73}. However, success at characterizing NME with DWI are varied and some have not been able to distinguish malignant NME from benign lesions based on ADC⁷⁴.

Rare malignant lesions, such as mucinous carcinoma (1-7% of breast malignancies), have relatively high water content and low cellular density. Thus, they can represent a diagnostic challenge as they not only have ADCs above the diagnostic threshold (mean $1.8 \pm 0.4 \times 10^{-3} \text{ mm}^2/\text{s}$, b=1500 sec/mm²) but they have more typically benign features on DCE-MRI such as circumscribed margins and T2 hyperintensity⁷⁵. Higher b-values can also help with the specific diagnosis of mucinous carcinoma due to decreased DWI signal intensity.

Imaging features of Benign Lesions

In general, benign lesions exhibit higher mean ADC than malignant lesions (Fig 14), but there is significant overlap. An analysis of 19 studies performed between 2002 and 2010 found ADCs of benign lesions to range from $1.19\text{--}1.92 \times 10^{-3} \text{ mm}^2/\text{sec}$ (with all of the studies except one using maximum b-values ranging from 600–1500 sec/mm^2)³⁶. There have been few studies characterizing the ADCs of specific benign breast lesion subtypes^{14,16,76,77}. Our work has demonstrated that DWI can help discriminate between false-positive lesions identified at DCE-MRI. In a study of 175 false-positive benign breast lesions, 46% had ADCs higher than a previously determined diagnostic threshold ($1.81 \times 10^{-3} \text{ mm}^2/\text{sec}$ where $b=600 \text{ sec}/\text{mm}^2$)⁷⁷, (Fig 15). Fibroadenomas were the most common false positive DCE-MRI finding, in agreement with other investigators¹⁸, and demonstrated high mean ADC of $1.94 \pm 0.38 \times 10^{-3} \text{ mm}^2/\text{sec}$ (Fig 16). The most common benign lesions with mean ADC below the diagnostic threshold were high risk lesions ($1.46 \pm 0.39 \times 10^{-3} \text{ mm}^2/\text{sec}$) such as atypical ductal hyperplasia (Fig 17). We further found that most papillomas exhibited low ADC and lymph nodes (which could not be identified by other imaging features such as high T2 signal or fatty hila) had the lowest mean ADC of all false-positive lesions ($1.28 \pm 0.23 \times 10^{-3} \text{ mm}^2/\text{sec}$).

Some benign lesions may be difficult to correctly characterize using DWI. As opposed to simple cysts that typically demonstrate high ADC, proteinaceous cysts can have both restricted diffusion and rim enhancement, mimicking a necrotic or cystic carcinoma (Fig 18). These may have high DWI signal intensity, even at the higher b-values. The presence of a T2 bright lesion without enhancement in the same location on a prior exam can be helpful for appropriate characterization. Additional benign lesions that can cause low ADCs include hematoma, abscess, proteinaceous debris in ducts and fibrosis⁴⁰. These can often be distinguished by additional imaging or clinical features. A hematoma or debris within dilated ducts may have increased non-contrast T1 signal and infection often presents with clinical signs and symptoms. A hematoma will have varied signal intensity on DWI and ADC depending on age (Fig 19).

Potential Clinical Applications

Tumor Characterization

Dynamic contrast enhanced MRI of the breast has high sensitivity for detecting breast cancer. Overlap in the appearance of benign and malignant breast lesions on DCE-MRI can produce many false positives. A meta-analysis of 44 studies evaluating the diagnostic performance of DCE-MRI demonstrated a sensitivity of 90% and specificity of 72%⁷⁸. Diffusion weighted imaging holds strong potential as an adjunct MRI technique to reduce unnecessary biopsies. This has been the most explored application of DWI for breast imaging, and it has consistently improved accuracy for lesion characterization on DCE-MRI^{7,16-18,58,79,80}. Two meta-analyses evaluating the diagnostic performance of quantitative breast DWI demonstrated overall better specificity than DCE-MRI^{34,68}. Multiple studies have evaluated optimal ADC thresholds for reduction of false positive findings at DCE-MRI, as discussed above^{14,16,17,58}.

Some preliminary studies have suggested that ADC may correlate with prognostic pathologic markers such as cancer grade or biomarkers including hormone and growth receptor status⁸¹⁻⁸⁵. However, the results have been variable. The association between ADC and invasive tumor grade is not clear with some investigators demonstrating a significant inverse relationship^{81,84} and others demonstrating no significant association^{82,86,87}. For in situ disease, DWI has shown potential for distinguishing high versus low grade DCIS^{70,71}. Similarly mixed results have been reported in comparison with other histopathological and

immunohistochemical breast tumor features, and more studies are clearly needed to assess the association between ADC and tumor biomarkers

Non-contrast MRI Screening

While DCE MRI is highly sensitive for the identification of breast cancers, most women do not have access to this exam due to high cost. In addition, gadolinium-based contrast agents used for breast DCE MRI can sometimes cause life-threatening complications^{88,89}. Minimum DCE MRI examination times are approximately 30 minutes; however, adding time before the exam to insert a peripheral catheter to deliver the contrast and after the exam to monitor for possible contrast related reactions, can extend total examination time to over an hour. Identifying a non-contrast screening tool that complements mammography and is faster, less expensive, and potentially safer than DCE-MRI could have important clinical impact.

DWI may offer a viable non-contrast method of breast MR screening without the costs and toxicity associated with DCE-MRI^{15,59,90}. Many mammographically and clinically-occult breast cancers detected by DCE MRI are also visible on DWI, such as those in Figs 11-13, and can be differentiated from benign breast lesions based on ADC¹⁷ (Fig 18). Additionally, in a study of asymptomatic women, non-contrast DWI provided higher accuracy for detection of breast malignancies than screening mammography⁹¹. Another study investigating women with suspicious breast masses reported comparable sensitivity and specificity between standard breast MRI and unenhanced MRI (T2-weighted and DWI) for differentiation of breast cancer from benign lesions based on specific diagnostic criteria⁹². Higher b-values to increase diffusion-weighting could be considered in the screening population to increase lesion detection and decrease false positive exams. The potential of DWI as a non-contrast alternative for breast MRI screening has only been explored in a handful of studies and requires further investigation.

Treatment Response

Another potential application for DWI is treatment monitoring. Neoadjuvant chemotherapy is increasingly used to monitor treatment response and enable more breast conserving surgeries. Accurate methods to monitor response in the tumor and predict outcome early in the course of treatment would improve ability to individualize therapies. Tumor response is typically measured by change in size. However, morphologic changes may not reflect early treatment response and there is widespread interest in imaging alternative markers such as tumor cellularity, vascularity or rate of cell proliferation.

DWI reflects changes in interstitial water diffusion rates due to cytotoxic effects of neoadjuvant chemotherapy. The central hypothesis is that successful treatment of a tumor with cytotoxic agents results in significant damage and/or killing of malignant cells, thus altering cell membrane integrity and the degree of cellularity. The fractional volume of interstitial space is thereby increased due to cell loss, resulting in an increase in water mobility within the damaged tumor tissue. It is hypothesized that increased ADC on DWI is proportional to the chemotherapeutic treatment effect²².

Multiple studies have reported that increases in tumor ADC in response to treatment (Fig 20) are detectable earlier than changes in size or vascularity as measured by DCE-MRI and may provide valuable early indication of treatment efficacy^{21,22,26,27}. Some studies have found ADC measures to be predictive of breast cancer treatment outcome. In separate studies, baseline ADC was lower in clinical responders versus non-responders²³⁻²⁵, and change in ADC with treatment was significantly greater in responders^{20,23,25} even after the first cycle of chemotherapy^{21,24}. In prediction of pathologic response, Fangberget et al

further showed mid-treatment ADC was higher in patients who ultimately achieved a pCR compared to those with residual disease²⁰.

However, not all studies demonstrate that ADC is predictive of clinical response to chemotherapy⁹³⁻⁹⁵. These disparate findings may be attributable to a number of study design factors including differences in DWI acquisition and analysis, chemotherapy cycle and image timing, treatment regimens, and/or patient populations. Further larger studies using standardized approaches are needed to validate whether ADC can be used as a predictive biomarker for breast cancer therapy.

Lymph nodes

Preliminary studies have shown promise for the use of DWI to detect metastatic disease in lymph nodes^{96,97}. To date there is only one published study evaluating its ability to evaluate axillary lymph nodes in patients with newly diagnosed breast cancer, which reported ADC values were significantly lower in metastatic versus benign axillary nodes⁹⁸. However, our own work investigating ADC for discriminating nodes deemed suspicious on conventional breast MRI has not reproduced these findings⁹⁹. The typical appearance of a level I axillary lymph node metastasis on DWI is shown in Fig 21.

Current Limitations

Prior to widespread adoption of DWI for breast tumor assessment, multi-center trials are required to validate the promising single center findings and define recommendations. Towards these goals, the American College of Radiology Imaging Network is currently conducting a large multi-center trial to evaluate the utility of DWI for measuring breast tumor response to neoadjuvant treatment (ACRIN 6698), and is initiating another study to evaluate DWI as an adjunct to DCE-MRI for improving diagnosis of breast cancer (ACRIN 6702). There are a number of challenges in performing DWI in multi-center clinical trials, including lack of standardization in image acquisition, analysis and interpretation, leading to variability in image quality and diagnostic ADC criteria. Thus standardized cross-platform protocols and rigorous quality control measures are essential to ensure reliable data across sites and generalizable results.

The detection of smaller lesions (< 1cm) remains challenging with DWI due to limited spatial resolution. With current hardware limitations of most clinical MRI scanners, EPI in-plane spatial resolution is typically limited to 2 mm for axial bilateral breast imaging due to the imaging field of view (FOV) and the number of phase and frequency encoding steps that can be acquired before the signal decays⁴⁶. Both higher magnetic field strength (Fig 22) and alternative acquisition strategies including reduced field of view techniques⁴⁶ (Fig 23) are being investigated to achieve higher spatial resolution. Small cancers may also be easier to detect if measures are taken to reduce magnetic susceptibility artifacts and inhomogeneity of the magnetic field.

Hand drawn ROI based techniques have limitations including ROI reproducibility, ROI accuracy, and the time required to draw ROIs. Semi-automated methods for performing a voxelwise analysis have shown promise for overcoming these challenges^{100,101}. However, it remains difficult to propagate ROIs directly from DCE-MRI, where lesions are best visualized, due to common distortions of the EPI image resulting in shifts in position.

More work is also needed to assess the sensitivity and specificity of DWI as a stand-alone tool without the benefit of DCE-MRI images. There is little data on the false positive rates associated with qualitative breast DWI interpretation, which may be reduced using higher b-value acquisitions. Quantitative methods further facilitate the discrimination of benign and malignant lesions and can help to reduce DWI false positives.

Future applications

Future work should investigate technical improvements to improve DWI as a screening tool, including improving spatial resolution, using higher b-values and further development of computer-assisted evaluation tools and diagnostic DWI maps to highlight suspicious features on DWI. This will provide valuable preliminary data on the potential of non-contrast MRI for screening and positive results and will support implementation of larger scale prospective trials. Further investigation continues into semi-automated analysis, which may allow for more consistent and reproducible results. Diffusion tensor imaging, an extension of DWI to characterize diffusion directionality is also being explored to provide additional useful information on tissue microstructural alterations caused by malignancy¹⁰²⁻¹⁰⁴.

Summary

Diffusion weighted MRI is safe, highly sensitive, and can be done at a fraction of the time of DCE-MRI. DWI used in conjunction with DCE-MRI increases the specificity for cancer detection and used alone holds promise of being useful for widespread cancer screening. Before this promise is realized, more work must be done to standardize breast DWI acquisition and interpretation approaches to facilitate multi-center trials that will evaluate and optimize sensitivity and specificity for cancer detection.

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Key points

1. DWI has shown potential to improve accuracy for lesion characterization on DCE-MRI in multiple studies.
2. DWI may be a non-contrast method of breast MR screening that could be used as an adjunct to mammography.
3. Increases in tumor ADC in response to chemotherapy may provide valuable early indication of treatment efficacy.
4. Malignant lesions demonstrate restricted diffusion manifested by high signal intensity on DWI and low ADC values.
5. Reproducible uniform fat suppression and techniques to reduce artifacts are essential for high quality DWI in the breast.
6. To reproduce reported ADC thresholds for lesion characterization, similar b-values must be utilized.
7. ADC normalization may reduce variation from individual breast characteristics and technical factors.

Figure 1.

Schematic comparing water diffusion in tissues with differing cellularity. The net distance (indicated by red dashed arrows) traveled by protons in the extracellular fluid during a specific time is much greater in regions of low cellularity (right) where random motion is not impeded by the presence of cellular membranes. In this way, the degree of water diffusion in biologic tissue is inversely correlated to the tissue cellularity and the integrity of cell membranes.

Figure 2.

Pulse sequence diagram of a diffusion-weighted spin echo sequence based on a Stejskal-Tanner encoding scheme. Two precisely matched diffusion-sensitizing gradients are inserted before and after a 180° RF refocusing pulse. Important factors defining the degree of diffusion-sensitization are the gradient amplitude (G), duration (δ), and the time between the two sensitizing gradients (Δ).

Figure 3.

Example images obtained with DWI scan. Shown are corresponding slices from A. S_0 with $b=0$ s/mm² (primarily T2-weighted). B. S_D with $b=800$ s/mm². C. ADC map. An invasive tumor (arrow) exhibits reduced diffusivity on DWI, appearing hyperintense on S_D ($b=800$ s/mm²) images (B) and hypointense on the ADC map (C).

Figure 4.

Influence of diffusion weighting (b-value) on breast ADC measures. Data acquired in a single normal volunteer over a range of b-values. Data points represent the mean of bilateral ADC fibroglandular tissue measures at each b value. ADC generally decreases with increasing b value. Adapted from Magn Reson Imaging. 2010 Apr;28(3):320-8.

Figure 5.

Effect of b-value on lesion conspicuity. The chosen b-value can greatly affect the resulting image contrast, as well as ADC. In this example, a malignant lesion (arrow) is best visualized at higher b-values. Low b-values may allow too much signal from normal tissue. At higher b-values, the SNR is decreased, but lesion contrast may be increased.

Figure 6.

Example of a patient with low mammographic parenchymal breast density. A 60 year old female with a family history of breast cancer underwent breast MRI for high risk screening.

A. MLO view mammogram demonstrating scattered fibroglandular densities in a normal breast. Axial MR images are shown at the level of the nipple.

B. Post-contrast T1 weighted image shows sparse fibroglandular tissue.

C. DWI $b=0$ s/mm^2 image where signal comes primarily from vessels and fibroglandular tissue.

D. ADC map (mean $\text{ADC} = 1.04 \times 10^{-3} \text{mm}^2/\text{sec}$ for normal fibroglandular tissue).

Figure 7.

Example of a high quality DWI study in a patient with a breast lesion. A. Enhancing lesion and regions of normal appearing fibroglandular and adipose tissue are readily distinguished on the post-contrast T1 weighted image. B. DWI $b=0$ s/mm² image demonstrates uniform, effective fat suppression with good SNR in fibroglandular tissue and no apparent artifacts or distortions. C. The lesion retains high signal on the $b=800$ s/mm² diffusion-weighted image due to restricted diffusion. Fat signal appears relatively brighter on the $b=800$ s/mm² image due to signal decrease of the fibroglandular tissue.

Figure 8. Common technical challenges of breast DWI. Illustrated in separate subjects are examples of A. Poor shimming causing poor fat suppression and detrimental chemical shift artifacts on DWI. B. Low SNR of $b=0$ s/mm² image due to long TE (100ms). C. Magnetic susceptibility artifact (arrows) causing distortion at air/tissue skin surface on DWI (right) in comparison with undistorted T1-weighted image (left). D. Another example of distortion at air/tissue skin surface (arrow) due to magnetic susceptibility differences (right) in comparison with undistorted T1-weighted image (left).

Figure 9.

Spatial misregistration between images within a DWI sequence due to motion or eddy-current artifacts causes ADC inaccuracies. In this example, the lesion appears shifted in the DWI $b=600 \text{ s/mm}^2$ image (obtained with diffusion gradients applied in the x direction) with respect to the $b=0 \text{ s/mm}^2$ image and other $b=600 \text{ s/mm}^2$ images (obtained with gradients in the y and z directions) due to eddy current effects. This misalignment causes an artifactual increase in ADC (arrow).

Figure 10.

Example of basic region of interest (ROI) approach for quantitation of ADC values. Lesions are typically first identified on contrast-enhanced DCE-MRI and then ROIs are defined on DWI images at the corresponding location (outlined in yellow). The ROI is propagated to the ADC map to calculate the mean pixel value. Examples given illustrate

- A. Large 37mm spiculated mass (with clip artifact) determined to be invasive ductal carcinoma.
- B. Small 9mm clumped nonmass enhancement determined to be DCIS.
- C. Large 67mm segmental, heterogeneous nonmass enhancement determined to be LCIS.
- D. Region of normal appearing fibroglandular breast tissue.

Figure 11.

Malignant breast lesion. A 44 year old female with a family history of breast cancer presents for a high risk screening MRI. Mammogram 6 months earlier was negative. Axial 3T MR images are shown. An 11 mm irregular mass (arrow) with spiculated margins and heterogeneous internal enhancement is present in the central right breast, posterior depth. The mass demonstrates restricted diffusion. The diffusion characteristics and DCE-MRI images are suspicious. This mass was biopsied and was invasive ductal carcinoma.

A. Post-contrast T1W subtraction MIP.

B. Post-contrast T1W image.

C. DWI $b = 800 \text{ s/mm}^2$ image demonstrates a high signal intensity mass (arrow).

D. ADC map demonstrates corresponding low values in the mass (mean $\text{ADC} = 0.88 \times 10^{-3} \text{ mm}^2/\text{sec}$) (arrow).

Figure 12.

Malignant breast lesion. A 42 year old female with history of invasive lobular cancer on the right, status post-mastectomy presents for high risk screening MRI. Mammogram performed the same day was negative. Axial 3T MR images are shown. An 11 mm lobular mass (arrow) with irregular margins and heterogeneous internal enhancement is present in the central left breast, mid depth. The mass demonstrates restricted diffusion. The diffusion characteristics and DCE-MRI images are suspicious. This mass was biopsied and was invasive lobular carcinoma.

A. Post-contrast T1W subtraction MIP.

B. Post-contrast T1W image.

C. DWI $b = 800 \text{ s/mm}^2$ image demonstrates a high signal intensity mass (arrow).

D. ADC map demonstrates corresponding low values in the mass (mean $\text{ADC} = 1.12 \times 10^{-3} \text{ mm}^2/\text{sec}$) (arrow)..

Figure 13.

Noninvasive malignancy. A 58 year old female with a family history of breast cancer presents for a high risk screening MRI. Mammogram performed the same week was negative. Axial 3T MR images are shown. A 9 mm focal area of clumped non-mass enhancement (arrow) is present in the central left breast, anterior depth. The non-mass enhancement demonstrates restricted diffusion. The diffusion characteristics and DCE-MRI images are suspicious. The area was biopsied and was high grade DCIS.

A. Post-contrast T1W subtraction MIP.

B. Post-contrast T1W image.

C. DWI $b = 800 \text{ s/mm}^2$ image demonstrates an area of high signal intensity (arrow).

D. ADC map demonstrates corresponding low values in the lesion (mean $\text{ADC} = 1.12 \times 10^{-3} \text{ mm}^2/\text{sec}$) (arrow).

Figure 14.

Benign lesion. A 53 year old female BRCA1 carrier presented for a high risk screening MRI. Axial 3T MR images are shown. A 7 mm oval mass (arrow) with smooth margins and homogeneous enhancement is present in the central right breast, mid depth. The mass does not demonstrate restricted diffusion and has high T2 signal (not shown). Based on conventional MR imaging characteristics, the mass was assigned a benign (BI-RADS 2) assessment code instead of recommending an image guided biopsy.

A. Post-contrast T1W subtraction MIP.

B. Post-contrast T1W image.

C. DWI $b = 800 \text{ s/mm}^2$ image demonstrates a high signal intensity mass (arrow).

D. ADC map demonstrates corresponding high values (mean $\text{ADC} = 1.84 \times 10^{-3} \text{ mm}^2/\text{sec}$) (arrow).

Figure 15.

Study of 175 false positive lesions (recommended for biopsy based on DCE-MRI and determined to be benign). A. Box plots show median and range of ADCs for each subtype in the order of frequency. *AD* = adenosis, *AM* = apocrine metaplasia, *DHU* = usual ductal

hyperplasia, *FA* = fibroadenoma, *FC* = fibrocystic change, *FF* = focal fibrosis, *FM* = fibromatosis, *HE* = hemangioma, *IF* = inflammation, *LN* = lymph node, *LoN* = lobular neoplasia (ALH, LCIS), *NBT* = normal breast tissue, *PA* = papilloma, *PSH* = pseudoangiomatous stromal hyperplasia. Dashed horizontal line indicates previously determined ADC diagnostic threshold of $1.81 \times 10^{-3} \text{ mm}^2/\text{s}$. High risk lesions (ADH, LoN), indicated by hashed pattern, were the most common non-malignant subtypes with ADC below threshold, overlapping with malignancies. B. Benign (non-high-risk) lesions ($n = 147$) showed significantly higher ADCs than high-risk lesions ($n = 28$) and malignant lesions ($n = 31$, from an earlier study). * = Significant difference from benign lesions, $p < .0001$. However, there were no differences in ADC between the high-risk and malignant lesion types ($p = .1$). Reprinted with permission Radiology 2012 Dec;265(3):696-706.

Figure 16.

Benign lesion. A 51-year-old woman with a personal history of cancer in the right breast underwent breast MRI for high-risk screening. Axial MR images are shown, with insets indicating ROI for DWI quantitation. A 19-mm lobular mass (arrow) with smooth borders and heterogeneous enhancement is present in the left breast 27 mm from the nipple at middle depth and assigned a BI-RADS category 5. The lesion is a biopsy proven fibroadenoma.

A. Post-contrast T1W subtraction image.

B. Post-contrast T1W image: the lesion (arrow) shows 100% persistent delayed kinetics (blue).

C. Axial T2W MR image. The lesion is hyperintense.

D. DWI image demonstrates a high signal intensity mass.

E. ADC map demonstrates corresponding high values (mean $ADC = 2.11 \times 10^{-3} \text{mm}^2/\text{sec}$).

F. Histologic examination. Hematoxylin-eosin stain; original magnification, $\times 20$. Reprinted with permission Radiology 2012 Dec;265(3):696-706.

Figure 17.

High risk lesion. A 61-year-old woman with personal history of right-breast DCIS underwent breast MRI for high-risk screening. Axial MR images are shown, with insets indicating ROI for DWI quantitation. A 13 mm lobular heterogeneously enhancing mass (arrow) with a smooth margin is present in the subareolar region of the left breast and is classified as BI-RADS category 4. The lesion is biopsy proven atypical ductal hyperplasia with intraductal papilloma.

A. Post-contrast T1W subtraction image.

B. Post-contrast T1W image: the lesion (arrow) shows mixed kinetics overall, 28% delayed persistent enhancement (blue), 34% delayed plateau (green), and 38% delayed washout (red).

C. Axial T2W MR image. The lesion (arrow) is hypointense.

D. DWI image demonstrates a high signal intensity mass (arrow).

E. ADC map demonstrates corresponding low values (mean $ADC = 1.06 \times 10^{-3} \text{ mm}^2/\text{sec}$) (arrow).

F. Histologic examination. Hematoxylin-eosin stain; original magnification, $\times 200$. Reprinted with permission Radiology 2012 Dec;265(3):696-706.

Figure 18.

Cyst in a 53 year old female BRCA1 carrier who underwent a high risk screening MRI. Axial 3T MR images are shown. A 10 mm round mass (arrow) with smooth margins and rim enhancement is present in the central right breast, mid depth. The mass demonstrates restricted diffusion. If diffusion images were used alone, this mass would be suspicious. Correlation with DCE-MRI images demonstrates thin rim enhancement and high T2 signal, which allowed characterization as a benign proteinaceous cyst (BI-RADS 2).

A. Post-contrast T1W image.

B. Post-contrast T2W image.

C. Post-contrast T1W subtraction image.

D. DWI $b = 800 \text{ s/mm}^2$ image demonstrates a high signal intensity mass (arrow).

E. ADC map demonstrates corresponding low values (mean $\text{ADC} = 0.48 \times 10^{-3} \text{ mm}^2/\text{sec}$) (arrow).

Figure 19.

Hematoma in a 54 year old female who underwent a staging MRI for newly diagnosed cancer in the right breast. The patient had a left breast stereotactic biopsy 21 days ago that was benign and concordant. Axial 3T MR images are shown. A 7 mm round mass (arrow) with smooth margins and no enhancement is present in the central left breast, anterior depth. The mass demonstrates restricted diffusion. If diffusion images were used alone, this mass would be suspicious. Correlation with DCE-MRI images demonstrated no enhancement, high T2 signal, and high pre-contrast T1 signal, which allows characterization as a benign hematoma (BI-RADS 2). Incidentally noted is susceptibility artifact from a biopsy clip in the anterior aspect of the hematoma.

A. Pre-contrast T1W image.

B. Post-contrast T2W image.

C. Post-contrast T1W subtraction image.

D. DWI $b = 800 \text{ s/mm}^2$ image demonstrates a high signal intensity mass (arrow).

E. ADC map demonstrates corresponding low values (mean $\text{ADC} = 0.28 \times 10^{-3} \text{ mm}^2/\text{sec}$) (arrow).

Figure 20.

Example of serial DWI tumor measures in a 48 year old female undergoing chemotherapy (cyclophosphamide/doxorubicin), for invasive ductal carcinoma. A. Pretreatment: the tumor is identified on DCE-MRI (left) and an ROI is drawn at the corresponding location of hyperintensity on the DWI $b=800 \text{ s/mm}^2$ image (middle) and propagated to the ADC map (mean $\text{ADC} = 1.09 \times 10^{-3} \text{ mm}^2/\text{sec}$). B: Post 3 months of treatment: the same tumor region is measured, with the ROI adjusted for any change in size and shape of the lesion (mean $\text{ADC} = 1.99 \times 10^{-3} \text{ mm}^2/\text{sec}$). This subject exhibited a complete pathologic response at the end of neoadjuvant therapy.

Figure 21.

Axillary metastasis. A 30 year old female underwent a staging MRI after newly diagnosed invasive ductal carcinoma in the left breast. Axial 3T MR images are shown. A 23 mm irregular mass (arrow) with smooth margins and homogeneous internal enhancement is present in the left axilla. The mass demonstrates restricted diffusion. The diffusion characteristics and DCE-MRI images are suspicious. This mass was biopsied and was metastatic carcinoma.

A. Post-contrast T1W image.

B. Post-contrast T1W subtraction image.

C. DWI $b = 800 \text{ s/mm}^2$ image demonstrates a high signal intensity mass (arrow).

D. ADC map demonstrates corresponding low values (mean $\text{ADC} = 0.98 \times 10^{-3} \text{ mm}^2/\text{sec}$) (arrow).

Figure 22.

Improved signal enables increased spatial resolution on diffusion weighted MRI at 3T when compared to 1.5T in a patient newly diagnosed with DCIS (arrow). There is improved anatomic detail for both the reference post-contrast T1-weighted image with fat saturation at 3T (B) and the DWI image at 3T (D) when compared to respective images at 1.5T (A, C). *J Magn Reson Imaging*. 2012 May;35(5):1222-6.

Figure 23.

Reduced-field of view (rFOV) imaging can be used to improve spatial resolution and allow air-tissue interfaces to be excluded from the shim volume. This has been shown to reduce susceptibility induced artifacts and image distortion. In the example case, overall image quality was improved on T2 weighted ($b = 0$) and DW images for rFOV DWI compared to standard FOV. Singer L, et al. Acad Rad 2012; 19(5):526–534.

Table 1

Standardized I-SPY 2 and ACRIN 6698 MRI Acquisition Parameters

Parameter	DWI
Sequence Type	DW SE-EPI
2D or 3D sequence	2D
Slice orientation	Axial
Laterality	Bilateral
Frequency direction	A/P
Phase direction	R/L
FOV - frequency	260-360 mm ^(a)
FOV - phase	300-360 mm ^(a)
Matrix - frequency (acquired)	128-192
Matrix - phase (acquired)	128-192
Reconstruction Matrix	256×256
In-plane resolution	1.7 - 2.8 mm
Fat-suppression	Active fat-sat
TR	4,000 ms
TE	Minimum (50-100ms)
Flip Angle	90 degrees
b-values	0, 100, 600, 800 sec/mm ²
Slice thickness (acquired)	4-5 mm
# of slices	Variable; bilateral coverage; adjust to keep w/in single acquisition
Slice Gap	No gap
Parallel imaging factor	2
# of excitations/averages	2
Sequence acquisition time	4-6 minutes (multi-b sequence ~ 5 min)

^(a) Adjust up to 400 mm to accommodate large body habitus if necessary. From ACRIN 6698 Site Imaging Manual, Version 1.0 (<http://www.acrin.org/TabID/825/Default.aspx>)