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A Review of Diffusion Magnetic Resonance Imaging in Characterization of Breast Cancers

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Abstract

Diffusion Magnetic Resonance Imaging (dMRI) has widely been used as a part of breast MRI protocols throughout the world, providing valuable information about breast tissue structures. This method has the potential to improve the characterization of benign and malignant breast lesions thereby guiding treatment decisions. DMRI as a non-contrast approach has certain benefits in comparison with the Dynamic Contrast Enhanced (DCE) method. Particularly, dMRI does not need intravenous contrast, which makes the imaging process faster and easier. Although there are still concerns about dMRI images quality, advances in the acquisition methods seem to be promising. More advanced dMRI strategies, such as Diffusion Tensor Imaging (DTI) and Intravoxel Incoherent Motion (IVIM), not only improve diagnosis accuracy, but also present new information about tissue perfusion. This review will present an overview of dMRI in the characterization of breast cancers.

Keywords: Breast Cancer; Diffusion Weighted Imaging; Magnetic Resonance Imaging.

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1. Introduction

For decades, Magnetic Resonance Imaging (MRI) has emerged as an efficient method for the diagnosis of breast lesions [1]. The potential role of MRI in clinical applications including pre-surgical diagnosis and treatment response evaluation has enticed medical societies to consider it as a practical approach since mid-1980s [2]. Although previously the efficiency of MRI was limited due to complicated image acquisition procedure compared to mammography [3], nowadays it is largely used as an adjunct screening tool with mammography, thanks to technological advances. MRI is sought in different clinical applications related to breast, including screening for high-risk women with a greater than 20% lifetime risk of breast cancer, investigating the efficacy of neoadjuvant chemotherapy, and evaluation of patients with axillary lymph node or distant metastasis of unknown origin [4]. Furthermore, MRI is an important tool in pre-operative management and staging of breast cancer [5].

MRI detects tumors that mammograms or ultrasound miss; however, the fact that this modality is prone to high false-positive detection and consequently low specificity, makes it unsuitable for patients with low to moderate risk of breast cancer [6]. The effectiveness of MRI is subject to the way that MRI protocols generate contrast between normal and abnormal breast lesions.

MRI using contrast agents is a sensitive method for characterization of breast lesions. Accordingly, clinical validation of MRI results without contrast agents, such as Gadolinium, has always been controversial. Tumorigenesis leads to an uplift of vascularity and permeability of the vessels; thus, the tumorous tissue absorbs more contrast agent and higher contrast on T1-weighted images would be perceptible [7]. However, contrast agents may impose complications for some patients with impaired kidney function or allergies to contrast agents.

Diffusion-Weighted Imaging (DWI) is a non-contrast procedure that allows mapping of tissue diffusivity by evaluation of the random movement of water molecules [8]. Tissue diffusivity can be quantified by Apparent Diffusion Coefficient (ADC). ADC values have a perceptible correlation with the cellularity of breast lesions, as the tumorous tissue with high cellular density limits diffusivity [9,10]. Therefore, DWI has the ability of showing the image that provides a representation of cellularity and microstructure which is useful to distinguish between benign and malignant breast lesions. DWI may present an unenhanced method to diagnose breast cancer without safety concerns associated with injection of gadolinium-based contrast agent in Dynamic Contrast Enhanced (DCE) MRI. The higher specificity of DWI compared with contrast-enhanced methods in discrimination of breast lesions suggests its potential as a biomarker to reduce false-positives and also makes it a compelling adjunct to contrast-enhancing approaches [9-11]. Although DWI has low image quality, high sensitivity to artifacts in comparison with conventional MRI, and contains poor anatomical information [12], generally malignant breast lesions exhibit different diffusion characteristics compared to normal fibroglandular tissue.

This paper aims to review the role of diffusion imaging in the diagnosis of breast cancers, discuss imaging features of benign and malignant breast tumors, and analyze the potential of dMRI as a breast cancer biomarker.

2. Breast Cancers

Breast tumors appear with several types, developing within different areas of the breast. Most of them begin in cells inside the breast milk ducts or lobules, which lead to ductal cancers or lobular cancers, respectively. However, there is a more general classification for breast cancers based on how invasive they are, which divides them into two major types of non-invasive and invasive breast cancers. Non-invasive breast cancer cells stay within the milk ducts or lobules; so, they do not spread to other tissues of the breast. Two subgroups for non-invasive breast cancer include Ductal Carcinoma In Situ (DCIS) and Lobular Carcinoma In Situ (LCIS), ductal carcinoma is a common case of non-invasive breast tumors. On the other hand, invasive breast cancer cells begin inside the milk ducts or lobules and then grow to the surrounding breast tissue, even in some cases, can invade the lymph nodes and other parts of the body are divided into two subgroups too, Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC).

However, these classifications are insufficient in clinical applications, where molecular biomarkers are likely to be more effective in guiding therapeutic decisions in the individual patient. Accordingly, breast cancers are usually classified by gene expression profiling and the expression of hormonal receptors such as Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal growth factor Receptor 2 (HER2). Based on these expressions, breast cancer has four distinct molecular subtypes: luminal

A with ER- or PR-positive and HER2-negative; luminal B with ER- or PR-positive and HER2-positive; HER2-enriched with ER- and PR-negative and HER2-positive and Triple Negative (TN) or basal-like with ER-, PR-, and HER2-negative.

Since breast cancer is a genetic disease, common features such as tumor size and grade cannot predict prognosis and response to treatment adequately. Indeed, tumors even with the same anatomy and patients with the same risk factor respond to similar treatments differently, depending on the genes the cancer expresses, which indicates the tumor molecular subtype. This shows the importance of upfront characterization of breast lesion molecular subtype to aid in regulating the treatment approach. Early detection and treatment can decrease the risk of breast cancer recurrence, which implies accurate assessment approaches be developed to distinguish these subtypes.

3. Diffusion MRI: Techniques and Considerations

Generally, movement of water molecules occurs due to two different reasons: (1) normal processes in the body, such as circulation of blood, (2) random motion of water molecules caused by the collision of molecules with each other, which is referred to as Brownian motion. This random movement of molecules, especially water molecules, is known as diffusion that provides meaningful information about tissue micro-structure. As diffusion is restricted by cell membrane, diffusion is restricted in tumor regions with high cellular density and therefore, providing valuable information for the characterization of breast lesions [13]. In this regard, diffusion coefficient (mm^2/s) is a factor that reflects the degree of diffusion restriction and represents the flux of molecules through a surface in one second.

The sensitivity of the MR signal to tissue diffusivity can be determined by regulating the diffusion gradients. This sensitivity is adjustable via changing the strength of the gradients and the time between the two gradients, integrated into a single parameter, named b-value, that represents the effect of applied diffusion gradients on MR signal [14]. Higher b-value results in a darker image due to signal loss in the normal tissue with mobile molecules, whereas restricted regions, such as tumor, appear brighter and therefore, more distinguishable on the dMR image.

The magnitude of the diffusion of water molecules within the tissue, assuming an isotropic diffusion, can be provided by DWI, formulated with the following relationship between b-value and signal intensity (Equation 1):

$$S_{DWI} = S_0 . e^{-b.D} \quad (1)$$

Where S_0 is the signal intensity before application of diffusion gradients, and D is the mass diffusivity of tissue [15] .

In practice, DWI scans are not purely diffusion-weighted, and it could be T1-weighted or T2-weighted in case of using pulse sequences with short Repetition Time (TR) or long Time to Echo (TE), respectively. However, as the prime purpose of diffusion imaging is to only capture the diffusivity of the tissue DWI image, long TR and short TE must be used. DWI is an integration of diffusion-weighted and T2-weighted images, hence bright regions on the image could mean either restricted diffusion or just a presence of normal tissue with free water having a long T2 relaxation time, which is referred to as T2 shine-through [16] . Bright DWI pixels may be a result of fat molecules not tending to move much, which makes fat suppression methods inevitable for the accurate detection of tumors.

In practice, pure diffusion coefficients in each voxel, as an average of all voxel molecules' diffusivity, can be calculated using 2-3 DWI images with different b-values. In fact, in $S_{DWI} = S_0 . e^{-b.D}$, the parameter S_0 represents a T2-weighted signal that would be excluded by the acquisition of S_{DWI} based on several b-values. Consequently, D, i.e. the average mass diffusivity of each voxel presents a pure representation of ADC, which is apparent as the diffusivity in the voxels is averaged and is independent of T2 relaxation times [17]. Naturally, restricted diffusion areas with a bright appearance on DWI images are dark on ADC maps, while the regions with freely moving molecules seem brighter.

3.1. Diffusion Tensor Imaging (DTI)

In addition to conventional DWI, there are other approaches based on the diffusion concept for extracting valuable information from tissue microstructures. For most media like liquids, the diffusion is almost the same along different directions, so, measuring diffusion in only one direction using DWI could be sufficient. This is not true for anisotropic materials with complicated or in some cases, inhomogeneous structures like biological tissues, where there are obstacles restricting diffusion in specific directions. Therefore, ADC quantities, which are acquired via a single direction gradient, would not represent all

diffusivity-related information about the tissue. A 3x3 array named diffusion tensor fulfills this representation (Equation 2):

$$\begin{bmatrix} D_x & D_{xy} & D_{xz} \\ D_{xy} & D_y & D_{yz} \\ D_{xz} & D_{yz} & D_z \end{bmatrix} \quad (2)$$

Where, the three diagonal terms reflect the diffusivity along each conventional direction and the other six ones reflect a correlation between these directions. Calculation of this matrix for each voxel makes another method of diffusion representation by MRI, called Diffusion Tensor Imaging (DTI). Naturally, in case of isotropy, off-diagonal elements are equal to zero and the DT matrix is diagonal. However, in body tissues, isotropy cannot be assumed and therefore, the diffusion tensor matrix is not diagonal. In such cases, the eigenvalues of the tensor matrix (λ1, λ2, λ3) are used instead. This approach provides measurements of DTI-related parameters, such as Mean Diffusivity (MD), which is obtained by averaging the eigenvalues, and is technically equal to ADC. Fractional Anisotropy (FA) is another single scalar parameter, which is a function of λ1, λ2, and λ3, and describes to what extent the diffusion is anisotropic [18]. FA takes values from 0 (isotropic with λ1 = λ2 = λ3) to 1 (diffusion in only one direction with λ1 >> λ2 ≥ λ3) [19].

The anisotropy of diffusion in a tissue depends on the structure of that tissue. Particularly, in breast parenchyma with a network of branching ducts, water molecules are more likely to diffuse along the walls of the ducts, rather than in directions perpendicular to that [20]. However, tumors block the ducts, thereby restricting the path of diffusion of the molecules and changing DTI parameters, such as FA. As breast cancer is a heterogeneous disease, DTI could provide more information about breast tumors in comparison with conventional DWI and improve the ability to distinguish between benign and malignant lesions [21]. As an illustration, some studies have shown that higher FA associates with breast tumor malignancy [22]. This may be due to the fact that malignancy leads to an increase in the diffusion of water molecules in one direction and a decrease in the others, making tensor matrix eigenvectors more asynchronous resulting in higher FA [23].

3.2. IVIM

As previously mentioned, DWI measures the diffusion of water molecules assuming that it is constant within a voxel and can be presented by a mono-exponential model ($S = S_0.e^{-b.D}$). Based on this formula, ADC or D can be obtained by calculating the slope of the curve describing $\ln(S/S_0)$ vs. different b-values. However, the DWI signal attenuates because of microscopic perfusion due to microcirculation of blood in the capillary network [15]. This signal loss for weaker gradients (fewer b-values) is so compelling that the mono-exponential model does not present DWI signal as a function of mass diffusivity (D) properly anymore, thereby complicating ADC calculation. In fact, the curve describing $ln(S/S_0)$ vs. b-value is not linear anymore, so it is not possible to find a single slope corresponding to the curve. This phenomenon has been called Intravoxel Incoherent Motion (IVIM) that suggests a new model separating tissue diffusivity and perfusion by a bi-exponential formula, as the following Equation [24]:

$$S = S_0\left[(1-f)e^{-b.D} + fe^{-b.(D+D^*)}\right] \quad (3)$$

Where f is the perfusion fraction (dimensionless quantity between 0 and 1) reflecting the fraction of the voxel occupied by capillaries, and D^* is the pseudo-diffusion coefficient representing the signal loss due to blood perfusion. Accordingly, the IVIM imaging method implies two diffusion coefficients D and D^*, which are perfusion-independent and perfusion-related, respectively. Moreover, as a new parameter acquired via diffusion imaging, can be used to produce a perfusion map of the tissue.

4. MR Imaging of Breast Cancers

Breast cancer subtypes can be predicted by MRI, which especially performs more effectively in some breast lesions. For example, although calcified DCIS clearly appears as white spots on a mammogram, non-calcified DCIS can easily be missed due to incomplete breast lesion calcification [25], where MRI with detection ability of both calcified and non-calcified DCIS can improve breast cancer diagnosis. However, DCIS is not generally detectable using T2-weighted or unenhanced T1-weighted MR images. As DCIS has T1 and T2 relaxation times near to normal breast parenchyma, it seems isointense or on rare occasions, relatively hypointense [26]. The differential enhancement of DCIS tumors can also be measured using the DCE method, which includes assessing the growth rate of the abnormal vessels that support DCIS lesions [27].

Discrimination of Medullary Breast Carcinoma (MBC: very rare type of IDC) may be more complicated, as

these tumors have high-grade histologic features but less aggressive behavior [28]. These malignant tumors have more convenient prognosis in comparison with other breast carcinomas, however in the terms of radiological detection, they can be mistaken for benign fibroadenoma tumors [29]. In fact, they usually appear as non-calcified masses with indistinct borders at mammography and ultrasonography, which make them undetectable from other benign lesions and even other malignant tumors [30]. On the other hand, MRI findings of medullary carcinoma have shown that they have an oval or lobular shape with smooth borders, which makes them distinguishable from benign masses [31]. Nonetheless, the ability of conventional or dynamic MRI to differentiate MBC from other types of breast malignancies has not been truly proven yet. Also, there are fewer common subtypes of carcinomas, for which even the contrast-enhanced approaches are incapable of accurately helping in their differentiation. Particularly, for mucinous carcinoma (a very rare type of IDC) using either conventional MRI that presents mucin as lobular shapes with high signal on T2-weighted images or even dynamic MRI, it is not easy to differentiate pure and mixed mucinous carcinoma [32].

In addition to breast cancer types, many efforts have been made to find correlations between MRI extracted features and the molecular studies by different studies [33, 34]. For example, in a study, a correlation was found between DCE MRI perfusion parameters and prognostic factors or immunohistochemical subtypes of breast cancers [35]. Also, similar studies found a significant correlation between DCE features and the luminal A and B subtypes of breast cancer [36]. Particularly, a recent study showed that luminal A and B tumors had the lowest enhancement values, while the highest enhancement values were associated with the HER2 tumors [37]. This study attributed this result to increased neoangiogenesis of the HER2 subtype, which is more aggressive than luminal A and B subtypes.

4.1. Role of DWI

Different breast cancer types may show slightly different behavior in terms of diffusion. Diffusion imaging provides better contrast in the diagnosis of DCIS tumors, as these lesions have higher cellularity than normal breast tissue, and lower cellularity in comparison with invasive tumors (IDC, ILC), so it exhibits lower ADC values than normal breast parenchyma and higher than invasive cases [38]. This characterization can be more challenging for smaller tumors like tubular carcinomas (a subtype of IDC), which are in most cases even less than 1cm in diameter. These lesions are usually presented with similar morphologic patterns and high signal intensity on T2-weighted images [39]. As hyperintensity on T2 images occurs for benign breast lesions as well, diffusion imaging representing lower ADC values for tubular carcinoma may be used as a useful method for differentiating benign tumors from tubular carcinomas. Similarly, diffusion imaging usually represents low ADC values for medullary invasive cancers as well as other subtypes of IDC lesions [40], so evaluation of DWI efficiency for differentiation of malignant tumors needs further investigation.

ADC value has an inverse correlation with the ratio of non-mucinous to mucinous parts and higher cellularity of tumor cells, which restrict the mobility of water molecules [41]. Consequently, pure mucinous carcinomas with more mucinous component (more than 90%) enable water molecules to move more freely in comparison with mixed ones and therefore provides higher ADC values. Although this difference in diffusivity facilitates better differentiation of malignant subtypes of breast cancers, the purely mucinous tumor with high ADC value causes an overlap between this malignant subtype and benign lesions and even in some cases healthy breast tissue. For example, fibroadenoma and benign phyllodes tumors with high ADC values (more than usual benign lesions) due to the presence of myxomatous or edematous stroma may overlap with pure mucinous carcinoma [41] .

On the other hand, many studies have aimed at the discrimination of different molecular subtypes using DWI [42]. Particularly, multiple studies found ADC values to be significantly lower in ER-positive in comparison with ER-negative breast tumors [43, 44]. Similarly, there are investigations suggesting that PR-positive tumors present lower ADC values in contrast to the negative group [44, 45]. This happens on the grounds that tumors with positive ER or PR tend to have lower neovascularity, thereby showing lower ADC values [46, 47]. These results are compatible with the fact that the expression ER and PR are likely to be corresponded with slower growing and so lower grade cancers, which mean higher cellularity and lower diffusivity. On the other hand, ADC values for HER2-positive have been reported to be higher in comparison with HER2-negative tumors in a number of studies [43, 46]. In fact, tumors with positive HER2 tend to have a higher degree of neovascularity, thereby including more permeability that leads to more ADC

value by overcoming cellularity [46]. Similarly, in the case of TN tumors, neovascularity leads to higher ADC values in comparison with non-TN tumors, in spite of high cellularity [48]. Nevertheless, there are studies asserting that there is no such a significant correlation between ADC value and molecular subtypes [42]. After all, achieving a more compelling result implies more studies with a larger number of patients and in multiple centers.

5. Diffusion MRI as a Biomarker of Breast Lesions

Depending on the histological type of breast abnormality, from in-situ carcinomas to invasive cancers, different treatment strategies including surgery or chemotherapy must be adopted. Decision making about the course of treatment for patients depends on core biopsies, which are invasive, prone to sampling errors [49]. In this regard, upfront prediction of the histological subtype of breast lesions based on biomarkers derived from MRI scans can aid in more personalized treatment planning for the patient.

However, any biomarker needs to be validated to indicate its association with the biological characteristics of the lesions. In order to assess the potential of a biomarker, it is necessary to examine its performance in smaller population of patients before it is used clinically. Naturally, DWI with the capability of characterizing cellular density, structural architecture, perfusion, etc. is not an exception. In addition, the fact that breast ADC values are prone to a small dynamic range in different body tissues [50] implies further accuracy and more concordant results related to optimum ADC discriminator level. To fulfill this accurate differentiation, multiple studies attempt to propose their thresholds based on the hypothesis that aggressive breast tumors have lower ADC value in comparison with in-situ tumors [51]. For instance, one study suggested the cutoff of $1.02 \times 10^{-3}\ mm^2/sec$ for minimum ADC to discriminate invasive breast cancer from DCIS by applying b-values 0 and 600 sec/mm^2. This threshold was found to be $1.01 \times 10^{-3}\ mm^2/sec$ in another study with 50 and 850 sec/mm^2 as b-values [51]. Similarly, there are studies showing that those in-situ tumors have lower ADC value than benign breast lesions. For instance, in a study, it was shown that ADC, acquired using b-values of 0 and 600 sec/mm^2, with a threshold of $1.81 \times 10^{-3}\ mm^2/sec$ results in the detection rate of 91% [9, 38]. However, the existence of any correlation between ADC value and tumor grade or ki67 proliferation index, which is a percentage describing how aggressive a tumor is, has not been proven yet. In fact, although there are studies finding this association [52], other studies have doubted that there exists such a correlation between ADC value and tumor grade [53].

As malignant tumors have higher cellularity and lower diffusivity compared to the benign lesions and healthy breast tissues, adoption of an optimal ADC threshold would characterize malignancy from non-malignancy [54, 55]. Nevertheless, choosing the appropriate ADC threshold to obtain adequate sensitivity and specificity is a challenge. Indeed, this threshold varies depending on the maximum b-value. DWI can be used as an adjunct method for increasing the specificity of DCE-MRI or another screening approach. Naturally, the threshold for ADC value must be lower for the former case and higher in the latter. A recent meta-analysis based on 13847 lesions suggests that an ADC threshold of $1.00 \times 10^{-3}\ mm^2/sec$ can be used for distinguishing breast cancers from benign lesions [55]. Furthermore, benign lesions with diffusivity as high as malignant tumors, such as proteinaceous debris in ducts and fibrosis, hematoma, or abscess, make characterization more complicated, and therefore, additional methods like T2-weighted imaging that show benign lesions with higher signal intensities can be helpful [56]. (Table 1)

5.1. Diffusion MRI as a Supplementary Method

Generally, DWI using single-shot Echo-Planar Imaging (EPI) sequence on 1.5T scanners has been widely used in many investigations for discrimination of

Table 1. The correlation between maximum b-value and Apparent Diffusion Coefficient (ADC) threshold in breast tumors

Study	b-values $(sec/(mm^2))$	ADC threshold (mm^2/sec)
Zhao, Suhong, *et al.* [52]	0-600	1.02×10^{-3}
H, Bickel, *et al.* [51]	50-850	1.01×10^{-3}
SC, Partridge, *et al.* [9]	0-600	1.81×10^{-3}
A, Surov, *et al.* [56]	Multi range (meta-analysis)	1.00×10^{-3}

breast lesions [57-59]. This imaging technique usually leads to poor spatial resolution and requires T2-weighted images for gaining anatomical information. Accordingly, DWI is often used as an adjunct method to DCE-MRI in order to compensate for the inherent false-positive detection of breast lesions using MRI scans and to increase the specificity of diagnosis. However, nowadays, due to increasing technological developments, including new MR scanners and imaging sequences, DWI can be considered as a supplemental method for breast imaging.

Although early investigations have shown that many breast cancers detected by DCE-MRI are visible on DWI as well [60], there are concerns about whether DWI has the sufficient potential to be used clinically as a supplementary method for breast cancer detection [59]. Several studies have attempted to assess this potential and have reported different results in terms of sensitivity and specificity [57-59]. Some studies claimed that DWI detects fewer cancers than DCE and also its sensitivity decreases for smaller lesions due to poor spatial resolution in comparison with DCE. A meta-analysis on 14 studies between 2008 and 2014 has shown that the pooled sensitivity and specificity of DWI-MRI were 86.0% and 75.6%, respectively, whereas the pooled sensitivity and specificity of DCE-MRI were 93.2% and 71.1% [54]. Although this study asserted that the combination of DWI and DCE method provides better results (sensitivity 91.6% and specificity 85.5%) in comparison with using them individually, it can be perceived that DWI presents comparable results to DCE [61].

5.2. Reporting and Application of Diffusion MRI in Clinic

Using diffusion imaging in clinic has faced two challenges: 1- the wide range of threshold, sensitivity, specificity, and accuracy of derived factors of diffusion imaging for differentiation of benign and malignant lesions, 2- the different signal to noise ratio of diffusion images due to the different MR vendor's specifications such as equipment and imaging sequences/protocol and 3- not enough existing validated threshold for decision making. With all these pitfalls diffusion imaging has not been incorporated into the Breast Imaging and Reporting Data system yet [62, 63]. In spite of all problems and due to the valuable information, which can be acquired from diffusion imaging, DWI can be aided on the sequences of breast MRI. ADC map as a single exponential model has been used widely in the clinic due to the short scanning time and simple post-processing; also previous studies have shown promising results of using ADC map for differentiating benign and malignant lesions [64]. In the study of Baltzer *et al.* [65], they evaluated ADC ranges for differentiating benign and malignant breast lesions based on a meta-analysis of previous studies. Based on diffusion level, breast lesions were categorized into 5 groups with, 1- very low, 2- low, 3- intermediate, 4- high, and 5- very high diffusion. Figure 1 shows the clinical examples of different diffusion levels in different breast lesions.

In Figure 2, the range of ADC value for benign, malignant, and normal tissue of breast is shown; as it is depicted, there are crossovers between the subgroups which means still DWI cannot be used in practice and it can be used in conjunction with other imaging sequences of breast MRI.

5.3. Image Analysis and Machine Learning

Image analysis approaches, including image registration and segmentation, can directly influence ADC measures of the tissue properties. As ADC maps are obtained from different b-values, the impact of patient motion and therefore, spatial misalignment or pixel shifts, is inevitable. Moreover, ADC maps lack anatomical details, thus, it is necessary to analyze them in combination with other images, such as T2-weighted images. Nonetheless, co-registration of DWI and anatomical images is challenging, as DWI acquisition is prone to affine and non-linear image distortion due to patient motion and magnetic field inhomogeneities, respectively. To correct these distortions, the most common approach is to correct DWI distortions before registration of DWI to the anatomical images. This includes affine registration of each of the DWI images to a reference image (usually $b = 0$ s⁄mm^2).

Another critical issue in the discrimination of lesions using ADC is the placement of Region Of Interest (ROI). The fact that ADC maps inherently have poor anatomic details, implies that ROIs should be drawn on DCE or T2-weighted images. However, some studies have used DWI to guide ROI selection and have shown the efficiency of DWI for the characterization of the lesion. Moreover, there are different strategies for ROI selection based on whether to choose the whole lesion or only the most restricted or hypointense area on the ADC map. Several studies have shown that choosing ROIs over the restricted regions or the solid portions of the tumor generally perform better

than the methods considering the whole-lesion for discrimination of lesions. Nonetheless, the reported findings of these studies may have been affected by measurement of the average of ADC values within the solid portion or the whole lesion, resulting in more reliable mean ADC-value measurements for differentiation of the benign from malignant lesions based on the ROIs over the solid portion compared to the ROIs over the whole lesion. As mentioned before, breast cancers are heterogeneous, and measurements of mean values over the whole lesion area could average out the interrelationships of the voxels in the cancerous tissue. Accordingly, quantification of heterogeneous regions can be more reliably carried out using radiomics methods.

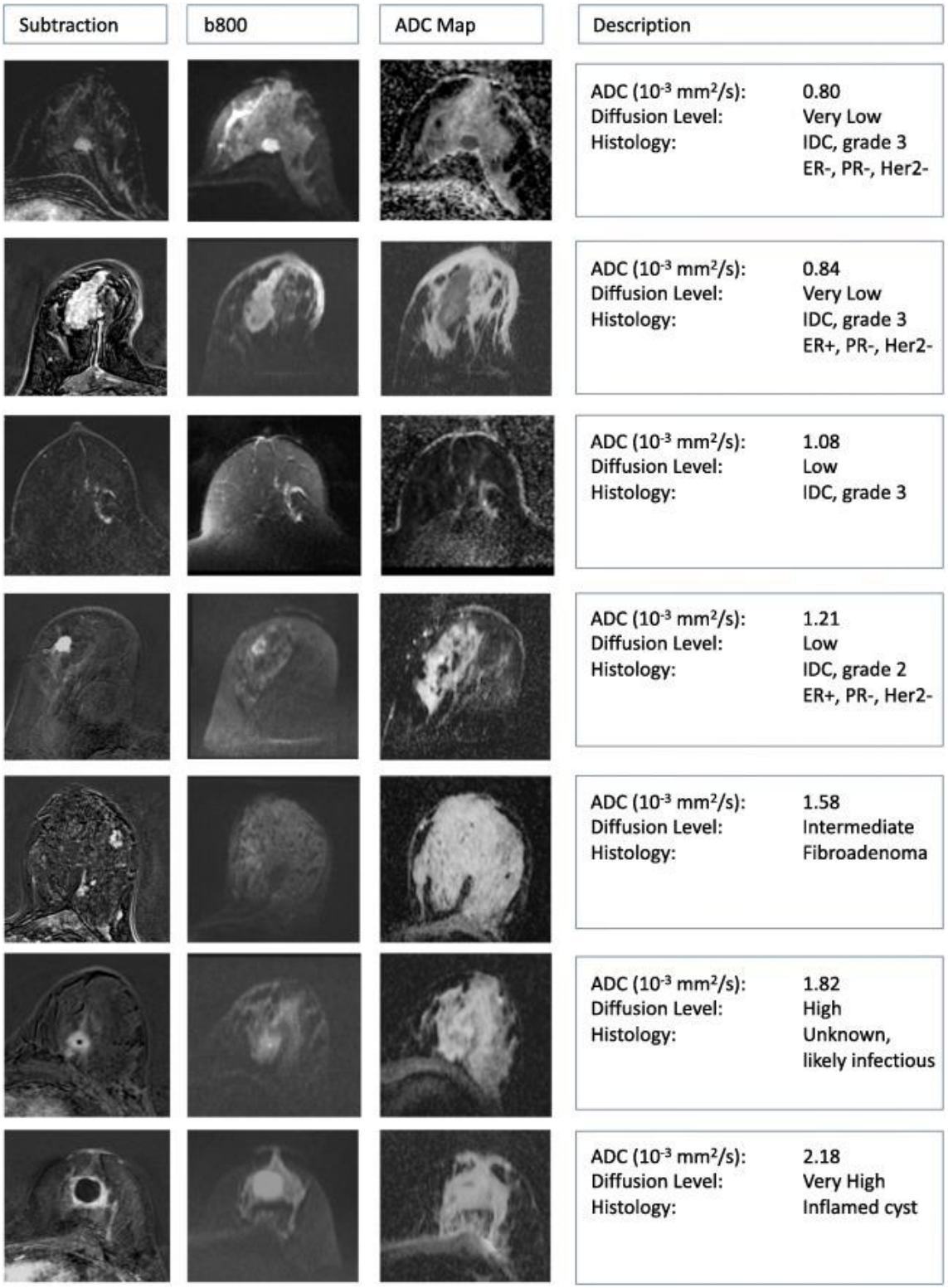

Figure 1. Clinical examples illustrating the diffusion levels, with curtesy of Baltzer *et al* [65]

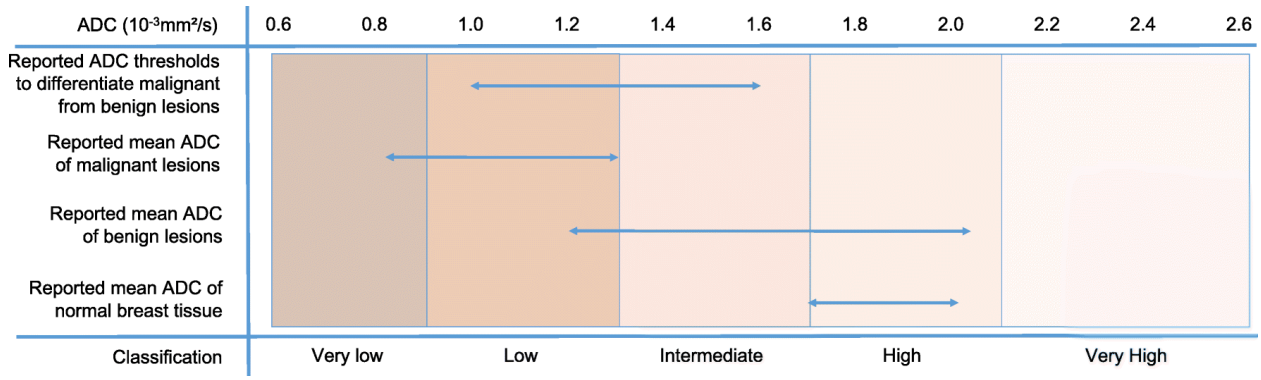

Figure 2. Apparent Diffusion Coefficient (ADC) thresholds and value ranges for malignant, benign, and normal tissue. In this graph, the lower horizontal arrows show the range of reported mean ADC values for normal breast tissue, benign, and malignant lesions. The top arrow shows the range of suggested thresholds to differentiate between benign and malignant lesions. Note that this graph simply lists ranges as taken from the original tables and no data pooling was performed. The color bars correspond to the diffusion levels that were defined and agreed upon by the working group in order to standardize the description of the diffusion values, with curtesy of Baltzer *et al* [65]

Usually, the mean value of the ADC values within the ROI is used to distinguish different grades of tumors. In fact, just the mean value as a single feature of the lesion may not reflect all valuable information about the ROI. As breast cancer is a heterogeneous disease, it seems necessary to calculate some additional information about the spatial distribution of diffusion-derived parameters within the ROI. Thus, extracting spatial features, representing the heterogeneity within a lesion can prompt an improved discrimination between benign and malignant breast tumors [66, 67].Thus, extracting spatial features, representing the heterogeneity within a lesion can prompt improved discrimination between benign and malignant breast tumors. Also, using radiomics, which is the extraction of mathematical patterns that are hidden within medical images, may potentially predict disease genotypes and enable monitoring of the entire tumor. In fact, different molecular breast cancer subtypes lead to different spatial heterogeneity of tissue diffusivity, which could be quantified by radiomic analysis. In other words, DWI radiomic features enable the separation between breast cancers of different receptor statuses and molecular subtypes. In the multiple studies, different approaches to investigate DWI radiomic signatures were used which have shown mixed results [68]. Therefore, deep learning neural networks could be a suitable option with very large heterogeneous datasets in which the classifier has sufficient training data to learn.

Many radiomic breast MRI analyses require extraction of imaging features over the whole-breast region, including volumetric percentage breast density or background parenchyma contrast enhancement. Accordingly, the whole breast is necessary to be segmented in order to have deep learning models focus on effective breast regions. As manual segmentation seems impractical, automated whole-breast segmentation can be a considerable option. Several studies have developed computational methods for automated whole-breast segmentation in breast DCE MRI [69]. Similarly, another study provides a practical approach for automatic whole-breast segmentation, which sheds light on applying a deep learning-based method on whole-breast segmentation for DWI MRI scans across different MRI protocols and scanners [70].

Accordingly, it is common to adopt a machine learning approach with the capability to generate predictive models for making decisions about tumor grade [71]. This strategy facilitates the application of higher-order features from the ROI, which may lead to better sensitivity and specificity of diagnosis. Many studies have evaluated the potential of machine learning methods based on breast MR images [72, 73]. Although these investigations usually concentrate on DCE-MRI scans or multi-parametric MRI, including DCE and DWI, there are few studies that have focused on the potential of machine learning for the prediction of breast lesions based on only DWI images [66, 67, 74, 75]. As an example, one study demonstrated that the features of the ADC map do not necessarily reflect all available information from DWI images [74]. Nonetheless, they suggested that using multiple features from a combination of diffusion models, such as ADC and IVIM, improves prediction accuracy for the characterization of benign and malignant breast lesions. For this purpose, the authors used Support Vector Machine (SVM) as the learning approach with the highest prediction accuracy

among other machine learning methods, which has also been used in many studies for the classification of breast lesions [66, 67, 75].

5.4. Multi-Component Analysis of Diffusion MRI (IVIM)

Although ADC map can easily be calculated from DWI images only based on two b-values in a mono-exponential model, this calculation is more complicated in case of biexponential model using multiple b-values. As mentioned earlier, IVIM presents additional information about net tissue diffusivity, including D, the diffusion coefficient, D*, the pseudo-diffusion coefficient, and f, the perfusion fraction. D map has a better image quality or SNR in comparison with the other two IVIM-derived components [76,77]. However, the estimation of D and f maps simultaneously could help to capture both diffusion and perfusion information of the tissue in a shorter time [78]. Nonetheless, measuring the D* map needs high SNR data and so it is specifically time-consuming [79].

To evaluate different IVIM model parameters, it is important to consider that normal breast tissue is not highly vascular [80]. It has been shown that normal breast tissue and particularly cysts show high ADC and D values and in contrast, they are likely to have a low f value [76]. Moreover, it suggested that there is no difference between ADC and D values in cysts and they show very low f value as they are full of fluids without capillaries. So, they can simply be represented by mono-exponential model. Several studies have rejected the presence of perfusion effects in fibroglandular breast tissue [81], but few others asserted that due to non-negligible perfusion values in fibroglandular tissue, it can be represented by a biexponential model [76].

The biexponential model should be assumed for other benign and malignant breast tumors. Not surprisingly, similar to ADC value, the D value can be used for discrimination of benign and malignant lesions and it is likely to be lower in malignant lesions in comparison with benign lesions [77, 82]. Nonetheless, due to the varying tumor vascularity among different masses, the D* value is prone to lack of repeatability in different studies and so it is not effective in the differentiation of benign from malignant lesions. As an illustration, although some authors have suggested that the value of D* in benign breast masses is higher than malignant masses [83], another study showed that the D* value of the malignant tumor is insignificantly higher than benign lesions [77]. On the other hand, this characterization can be performed with higher diagnosis sensitivity using f value. Multiple studies have maintained that the f value of benign lesions is significantly lower than malignant lesions, which denotes that the malignant tumors have a higher blood volume of microcirculation perfusion [77, 82, 83].

It can be concluded that lower D and higher f values are suggestive of the possibility of malignancy. Therefore, combining ADC and IVIM values can facilitate an improvement in diagnostic sensitivity of breast tumors and this combination can effectively complement existing traditional DCE-MRI and DWI to distinguish between malignant breast tumors and cysts, particularly for high-risk women (Table 2).

5.5. Limitations and Challenges

5.5.1. Mixed Data and Optimization of B-Values

There is considerable overlap between ADC values reported for benign and malignant lesions, and in particular benign lesions with low ADC values, which overlap with malignancies. This may lead to challenges for implementing a diagnostic ADC threshold. These are due to technical challenges in breast DWI acquisition related to field inhomogeneity and specifically the range of b-values, which are adopted to obtain ADC map.

The choice of b-value depends on the tissue under study. For instance, brain tissue with lower diffusion in comparison with breast requires higher b-values. For breast tissue, the choice of optimal maximum b-value has been controversial. Although ADC is useful in the differentiation of malignant from benign breast

Table 2. Different diffusion parameters, advantages and disadvantages in breast tumors

Parameter	Images acquisition	Malignant tumors
Diffusion coefficient (D)	Better SNR	Low value
Pseudo-diffusion coefficient ($\boldsymbol{D^*}$) perfusion fraction ($\boldsymbol{f}$)	Time consuming	Lack of repeatability High value

tumors, the threshold of ADC value for such discrimination can vary depending on the maximum b-value, which complicates the comparison of results among different studies. This dependence stems from the existence of cell membranes in tissue hindering diffusion from being completely Gaussian. The curve describing $\ln(S/S_0)$ versus different b-values is a straight line just for pure water, not for biological tissues. Accordingly, the slope of this curve, which is ADC, is not similar for different b-values and tends to decrease as the b-value increases [15]. Therefore, using multiple b-values can potentially improve the quantification of ADC, as considering only two points is not adequate for accurate estimation of non-straight curve slope. Nonetheless, some studies have reported little improvement in the diagnosis of breast lesions using multiple b-values, while the cost of time and artifacts increases [84].

As the b-value denotes the diffusion gradient effect, by increasing maximum b-value, better DWI contrast is achieved. However, it leads to lower SNR due to more attenuation of the diffusion signal. Therefore, many studies have attempted to implicate an optimum maximum b-value to fulfill this trade-off in order to obtain the best sensitivity and specificity for the characterization of breast lesions. The International Breast DWI working group suggested 800 s/mm^2 for upper b-value [85]. Another study implied a combined b-value protocol of 50 and 850 s/mm^2 provides a high accuracy for breast lesions identification at 3.0 T [86]. Also, another investigation asserted that the ADC calculated from b-values of 0 and 750 s/mm^2 was slightly better than the other b-value combinations [87]. On the other hand, a meta-analysis on almost 200 studies asserted that although the choice of b-values significantly affects the ADC of breast lesions, sensitivity, and specificity are not much affected by the choice of b-values [88]. Nevertheless, this investigation recommended b-values of 0 and 1000 s/mm^2 for optimal differentiation of benign from malignant lesions. This result also conforms with another meta-analysis that claimed that the b-values of 0 and 1000 s/mm^2 were the most commonly used in 29 different studies [89]. Furthermore, there are studies suggesting that a maximum b-value higher than 1000 s/mm^2 leads to better results, but they are in a minority [90, 91]. After all, one study presented an ADC threshold of $1.00 \times 10^{-3}\, mm^2/sec$ can be for distinguishing breast cancers from benign lesions independent of the choice of b-values [55].

5.5.2. Signal to Noise Ratio (SNR)

The acquired MRI signal is always prone to the presence of background noise. This noise floor affects the ADC value calculated as the slope of the DWI signal versus the b-value curve. As the b-value increases, the DWI signal decays to a non-zero noise level, thus the slope of the obtained curve is less than the real value. Consequently, the background noise causes underestimation of ADC value, thereby leading to a bias towards malignancy in the case of breast lesion conspicuity. This means that in the presence of background noise (poor SNR), lower specificity is obtained which is not desirable, especially in the case of breasts with lower mammographic density or cases with the performance of fat suppression [56].

It seems necessary to consider practical solutions to improve SNR in breast DWI. Naturally, repeating image acquisition and limiting the spatial resolution may not be suitable, because the former leads to long scanning time, and by using the latter, detection of small lesions will be challenging. On the other hand, after a shorter TE, not only has the DWI signal less time to attenuate thereby causing higher SNR, but also this reduces the susceptibility artifacts [92]. However, shorter TE contributes to lower contrast between benign and malignant lesions, making the approach less intriguing. Similarly, using lower b-values to achieve better SNR can lead to a poor contrast resolution. A better solution can be to apply a stronger diffusion gradient pulse in a shorter time provided that the b-value does not change, thus TE reduces, and as a result, SNR improves [93]. Nonetheless, this method merits more investigations to ensure that this approach has adequate potential for the improvement of SNR.

6. Conclusion

DWI has increasingly been used for the diagnosis of breast cancers. The existing convincing evidence on the effectiveness of DWI-derived parameters implies that they can play a role as imaging biomarkers in clinical applications. DWI has the capability of detecting tumors without contrast agents and providing information about biological properties of the tissue, which merits as a possible adjunctive method to DCE. However, although DWI as a cost-effective method facilitates the implementation of multiparametric protocols, the effectiveness of this approach for screening examinations implies more investigations. Indeed, considering the existing pieces

of evidence, breast DWI can be recommended as a part of multiparametric MRI for patients with irresolute result, and also patients whom administration of contrast agents would put them in danger. Furthermore, there is still the issue of lack of standardization of DWI imaging protocols, including the best maximum b-value. This challenge can even be more complicated for the advanced DWI techniques, including DTI and IVIM, wherein additional tissue properties can be provided, but there is not enough evidence justifying the better performance of these techniques in comparison with conventional ADC evaluation in the diagnosis of breast lesions. In order to address this issue, the presentation of a generalizable clinical guideline seems necessary, which implies multicenter investigations to validate single-center studies. By adopting these multicenter approaches and given the advances in artificial intelligence, breast DWI seems to be promising in the discrimination of suspicious breast lesions in near future.

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