

MAJOR PAPER

Triexponential Diffusion Analysis of Diffusion-weighted Imaging for Breast Ductal Carcinoma *in Situ* and Invasive Ductal Carcinoma

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Purpose: To obtain detailed information in breast ductal carcinoma *in situ* (DCIS) and invasive ductal carcinoma (IDC) using triexponential diffusion analysis.

Methods: Diffusion-weighted images (DWI) of the breast were obtained using single-shot diffusion echo-planar imaging with 15 b-values. Mean signal intensities at each b-value were measured in the DCIS and IDC lesions and fitted with the triexponential function based on a two-step approach: slow-restricted diffusion coefficient (D_s) was initially determined using a monoexponential function with b-values > 800 s/mm². The diffusion coefficient of free water at 37°C was assigned to the fast-free diffusion coefficient (D_f). Finally, the perfusion-related diffusion coefficient (D_p) was derived using all the b-values. Furthermore, biexponential analysis was performed to obtain the perfusion-related diffusion coefficient (D^*) and the perfusion-independent diffusion coefficient (D). Monoexponential analysis was performed to obtain the apparent diffusion coefficient (ADC). The sensitivity and specificity of the aforementioned diffusion coefficients for distinguishing between DCIS and IDC were evaluated using the pathological results.

Results: The D_s , D , and ADC of DCIS were significantly higher than those of IDC ($P < 0.01$ for all). There was no significant correlation between D_p and D_s , but there was a weak correlation between D^* and D . The combination of D_p and D_s showed higher sensitivity and specificity (85.9% and 71.4%, respectively), compared to the combination of D^* and D (81.5% and 33.3%, respectively).

Conclusion: Triexponential analysis can provide detailed diffusion information for breast tumors that can be used to differentiate between DCIS and IDC.

Keywords: breast tumor, diffusion-weighted imaging, intravoxel incoherent motion, triexponential diffusion analysis

Introduction

MRI is an important diagnostic tool for the detection and characterization of breast lesions. The primary purposes of the

breast MRI are to a) detect breast tumors and b) evaluate the extent of the tumor.^{1–3} Differentiation among various malignant breast tumor types, such as ductal carcinoma *in situ* (DCIS) and invasive ductal carcinoma (IDC), is essential for patient treatment and management.^{4,5} Breast tumors can be classified by evaluating signal intensity changes in T₁-weighted dynamic contrast-enhanced MRI (DCE-MRI).⁶ However, there are several cases in which differentiating among various tumor types using DCE-MRI alone may be difficult given the overlapping features that lead to false-positive findings.^{7–9} Despite its variable specificity (75%–98%), DCE-MRI has shown high sensitivity for the diagnosis of breast lesions.¹⁰

Diffusion-weighted imaging (DWI) has been extensively applied to the various body organs and to the central nervous system. DWI of the breast has potential clinical applicability considering evidence showing that specificity can be improved by evaluating the apparent diffusion coefficient (ADC) calculated from DWI as an adjunct technique to DCE-MRI.^{11–13} Many

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studies have reported differences in the *ADC* between benign and malignant breast tumors.^{14–20} Although these observations may be explained by the highly restricted diffusion of water molecules in the malignant tumors owing to the higher cellularity compared with normal tissue and benign tumors, the exact mechanisms have not been fully clarified yet. A previous study showed that *ADC* decreases with increasing b-values in normal mammary glands and malignant breast tumors,²¹ suggesting that the *ADC*, assuming monoexponential signal decay on DWI, depends on the b-values used and includes multiple biological data from the tissues, such as perfusion and cellularity.

Multi-exponential signal decay in DWI has been reported to be caused by various physiological processes and factors, such as perfusion, intra- and extracellular diffusions, and the permeability of blood vessels and cell membranes.^{14,19,22,23} Le Bihan et al. reported that biexponential signal attenuation, including the effects from perfusion and diffusion, was observed in tissues when DWI was performed with the b-value range used in clinical settings.²⁴ The same authors first introduced intravoxel incoherent motion (IVIM) analysis with a biexponential function to provide both perfusion and diffusion information. The usefulness of IVIM analysis has been reported in various organs, such as the brain, liver, kidney, breast, and prostate.^{25–35} Other studies have demonstrated that fast and slow diffusion components exist in the brain and result in a biexponential decay on DWI acquired over an extended range of b-values.^{22,29,36} Hayashi et al.³⁷ evaluated the diffusion coefficients of three components, i.e., perfusion-related diffusion, fast-free diffusion, and slow-restricted diffusion (respectively, denoted by D_p , D_f , and D_s), using triexponential analysis of DWI data with multiple b-values in normal and liver cirrhosis cases. They successfully demonstrated the usefulness of triexponential analysis for the diagnosis of liver cirrhosis. Nakagawa et al.³⁸ first performed triexponential analysis of breast images in IDC and fibroadenoma (FA), and showed that a) the D_p in IDC was significantly higher than in FA, and b) the D_s was significantly lower than FA. These results are mainly attributed to the abundant perfusion and high cellularity in malignant tumors, and suggest that it is possible to differentiate between benign and malignant breast tumors with triexponential analysis. We, therefore, hypothesized that a more accurate differentiation of DCIS from IDC using triexponential analysis may be possible because it can provide more detailed information on perfusion and diffusion compared with bi- and monoexponential analyses. However, no prior report has compared the triexponential diffusion coefficients of DCIS with those of IDC.

Therefore, the current study evaluated three diffusion coefficients in DCIS and IDC using triexponential analysis and compared the results with bi- and monoexponential analyses.

Materials and Methods

Subjects

The institutional review board approved this retrospective study. Written informed consent requirement was waived

considering the retrospective study. A total of 108 female patients with malignant breast lesions were included in the present study. All patients (age range, 31–82 years; mean, 56.7 years) underwent preoperative breast MRI at our institution, including DWI, from November 2012 to July 2014. None of the cases received neoadjuvant chemotherapy or hormonal therapy prior to MRI, and the tumors were surgically resected and pathologically evaluated. Consequently, the following pathological diagnoses were obtained: IDC (n = 66, age range = 31–82 years, mean = 56.1 years) and DCIS (n = 18, age range = 41–78 years, mean = 59.2 years). Mixed pathology cases (IDC and DCIS, n = 24) were excluded from the study. In our hospital, breast MRI was conducted without considering the menstrual cycle, even among premenopausal females.

Imaging conditions

All patients were examined on a 3.0 T MRI system (Signa HDxt; GE Healthcare, Milwaukee, WI, USA) equipped with an eight-channel breast phased array coil. For triexponential analysis, 2D single-shot spin echo diffusion echo-planar imaging with fat suppression was performed with the b-values of 0, 20, 40, 80, 120, 200, 400, 600, 800, 1000, 1200, 1500, 2000, 2500, and 3000 s/mm². The transverse DWI of the breast was obtained with the following parameters: TR, 5025 ms; TE, 89.2 ms; FOV, 360 × 360 mm; parallel imaging the array spatial sensitivity encoding technique (ASSET) factor, 2; acquisition matrix, 128 × 128; slice thickness, 6.0 mm; slice gap, 1.5 mm; number of slices, 17; number of excitations, 2; separate diffusion measures in three orthogonal directions; and acquisition time of 7 min and 14s. The diffusion time was held constant in all b-value scans. DWI covered the whole mammary glandular tissue.

Diffusion analysis

The diffusion-weighted images of the breast were analyzed retrospectively using the software Image J (version 1.40g; National Institutes of Health, Bethesda, MD, USA). Signal intensities were measured in ROIs on all the b-values images (Fig. 1). The ROIs were manually drawn in all lesions (one per patient) on the DWIs. They were chosen to be slightly smaller than the actual lesions to avoid partial volume effects attributed to the surrounding normal tissues. Care was taken to exclude necrotic or cystic areas in the tumor. This was achieved by choosing the ROIs with reference to the early phase of contrast-enhanced T₁-weighted and T₂-weighted images. The mean ROI size was 67.2 mm² (range, 7.9–462.8 mm²) and 36.7 mm² (range, 7.9–106.8 mm²) on IDC and DCIS, respectively.

D_p , D_f , D_s , and their corresponding fractions (denoted as F_p , F_f , and F_s , respectively) were calculated from the following triexponential fitting using the Levenberg–Marquardt algorithmml:

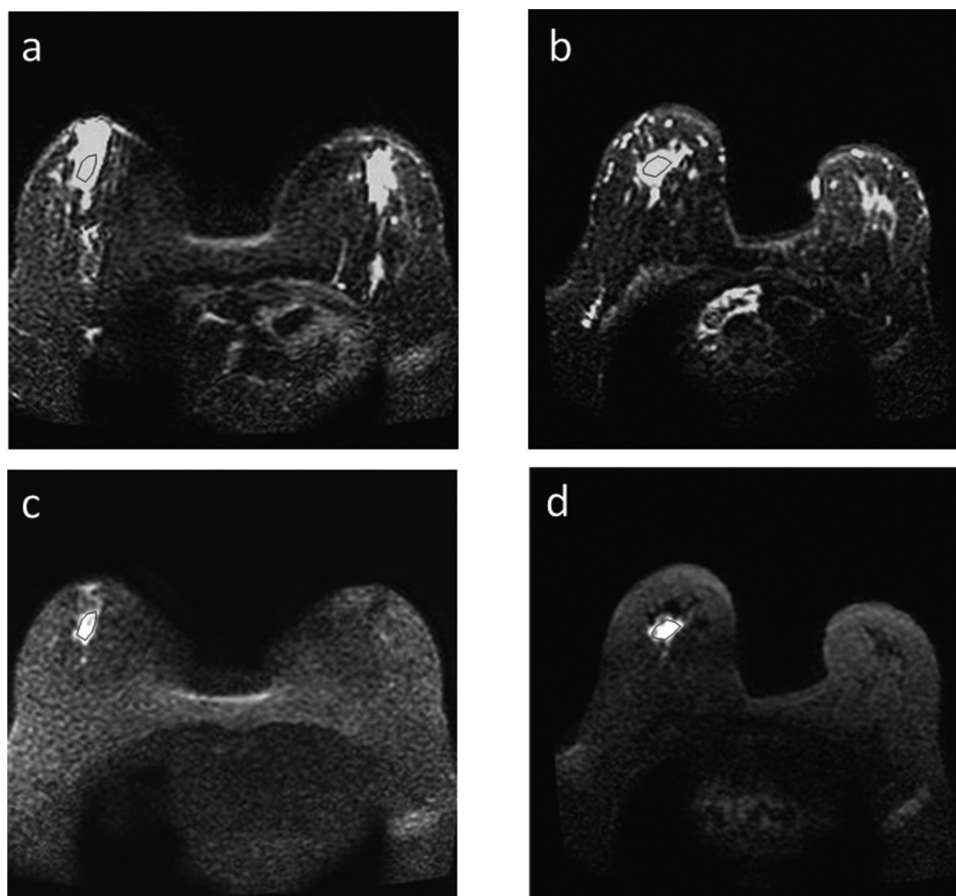


Fig. 1 Examples of region of interest setting on breast diffusion-weighted images with a b-value of (a, b) 0 and (c, d) 1500 s/mm² in (a, c) ductal carcinoma *in situ* and (b, d) invasive ductal carcinoma.

$$S_b/S_0 = F_p e^{-bD_p} + F_f \exp(-bD_f) + F_s \exp(-bD_s) \quad [1]$$

where S_b and S_0 are signal intensities for a given b-value and for a b-value of 0 s/mm², respectively. To improve the fitting accuracy and robustness of the analysis, the fitting procedure was performed with a two-step approach.³⁹ The contribution of perfusion and free diffusion on the signal intensity can be negligible for b-values > 800 s/mm². Thus, D_s was first calculated for b-values > 800 s/mm² using the following equation (monoexponential function),

$$S_b/S_{int} = \exp(-bD_s) \quad [2]$$

where S_{int} is the zero intercept at a b-value of 0 s/mm² in the first fitting procedure for b-values over 800 s/mm². Subsequently, D_s was applied to the triexponential function (Eq. [1]). In addition, the published value⁴⁰ of the diffusion coefficient of free water at 37°C (3.0×10^{-3} mm²/s) was assigned to D_f . Using fixed D_s and D_f values, the D_p and F_p , F_f , and F_s , were determined for all b-values.

Moreover, bi- and monoexponential analyses were performed and compared with the triexponential analysis. We used a segmented approach for biexponential

analysis. First, the perfusion-independent diffusion coefficient was calculated using the monoexponential function for b-values > 200 s/mm² because the contribution of perfusion on the signal intensity is quite small for b-values > 200 s/mm²,^{31,41}

$$S_b/S_{int} = \exp(-bD) \quad [3]$$

where D is the perfusion-independent diffusion coefficient. Subsequently, D was applied to the following equation (biexponential function). By fixing the value of D , perfusion-related diffusion coefficient (D^*) and the fraction (F) were determined using all the b-values,

$$S_b/S_0 = F \exp(-bD^*) + (1 - F) \exp(-bD) \quad [4]$$

Monoexponential analysis was performed using the following equation (monoexponential function) with all b-values,

$$S_b/S_0 = \exp(-b \cdot ADC) \quad [5]$$

where ADC is the apparent diffusion coefficient.

All fitting procedures were implemented and executed in MATLAB (version 2014a; MathWorks, Natick, MA, USA).

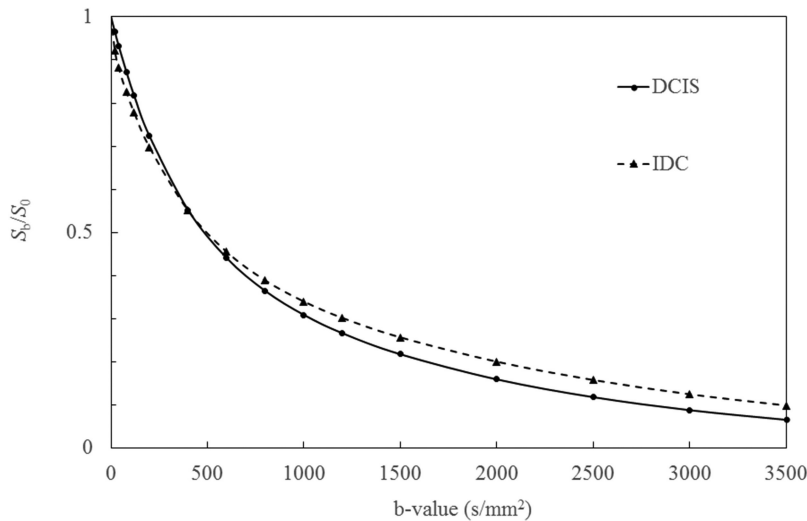


Fig. 2 Examples of triexponential signal intensity curves of diffusion-weighted images at each b-value in DCIS and IDC. DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma.

Moreover, SNR measurement at the highest b-value ($b = 3000 \text{ s/mm}^2$) was conducted to ensure that the SNR was high enough for accurate diffusion analysis. The SNR was calculated as a quotient of the mean signal intensity in the ROI inside the breast lesion and the standard deviation of the background noise near the lesion ROI.

statistical analyses

Statistical analyses were performed using SPSS for Windows (version 19.0; IBM, Armonk, NY, USA). Mann–Whitney U-test was used to compare the diffusion coefficients derived from tri-, bi-, and monoexponential analyses between DCIS and IDC. The relations between diffusion coefficients were evaluated using Spearman’s correlation coefficient. A P value < 0.05 was considered statistically significant.

Receiver operating characteristic (ROC) analysis was conducted to evaluate the sensitivity and specificity of each diffusion coefficient for differentiating between DCIS and IDC. The optimal cutoff values were chosen using the maximum Youden index (i.e., sensitivity + specificity – 1). Additionally, logistic regression analysis was performed to derive models that distinguish between DCIS and IDC using the combination of diffusion coefficients (i.e., D_p and D_s or D^* and D).

Results

Examples of signal intensity curves for DCIS and IDC fitted by triexponential function are shown in Fig. 2. DCIS had a smaller signal intensity attenuation than IDC, especially at the lower b-values. By contrast, at the higher b-values, DCIS had greater signal attenuation than IDC.

The diffusion coefficients derived by tri-, bi-, and monoexponential analyses in DCIS and IDC are shown in Fig. 3 showing the corresponding box plots. D_s , D , and ADC of

DCIS were significantly higher than those of IDC ($P < 0.01$ for all). No statistical difference in D_p and D^* was observed between DCIS and IDC ($P > 0.05$ for all). ROC analysis showed that the best cutoff values for D_p , D_s , D^* , D , and ADC to differentiate between DCIS and IDC were $3.02 \times 10^{-3} \text{ mm}^2/\text{s}$ (71.4% sensitivity and 40.4% specificity), $0.56 \times 10^{-3} \text{ mm}^2/\text{s}$ (64.3% sensitivity and 82.5% specificity), $4.89 \times 10^{-3} \text{ mm}^2/\text{s}$ (92.9% sensitivity and 40.4% specificity), $0.78 \times 10^{-3} \text{ mm}^2/\text{s}$ (71.4% sensitivity and 82.5% specificity), and $0.81 \times 10^{-3} \text{ mm}^2/\text{s}$ (92.9% sensitivity and 57.9% specificity), respectively. Logistic regression analysis showed a sensitivity and specificity of 85.9% and 71.4% for the combination of D_p and D_s and 81.5% and 33.3% for the combination of D^* and D , respectively.

Table 1 shows the relationships among all diffusion coefficients with tri-, bi-, and monoexponential analyses. There was no significant correlation between D_p and D_s , but there were weak positive correlations between D^* and D .

The mean SNRs at $b = 3000 \text{ s/mm}^2$ were 12.37 ± 7.12 and 38.8 ± 31.7 for DCIS and IDC, respectively.

Discussion

In this study, we performed diffusion analyses of breast tumor DWI using tri-, bi-, and monoexponential functions, and compared the diffusion coefficients between DCIS and IDC.

The D_s estimated based on triexponential analysis was significantly higher in DCIS than in IDC. Sigmund et al. reported that the diffusion coefficient of the slow diffusion component obtained with biexponential analysis was dependent on tissue cellularity and was lower in malignant breast lesions than in normal fibroglandular tissue.⁴² Therefore, we speculated that the D_s of the restricted diffusion component obtained with triexponential analysis also reflected the cellularity. A previous

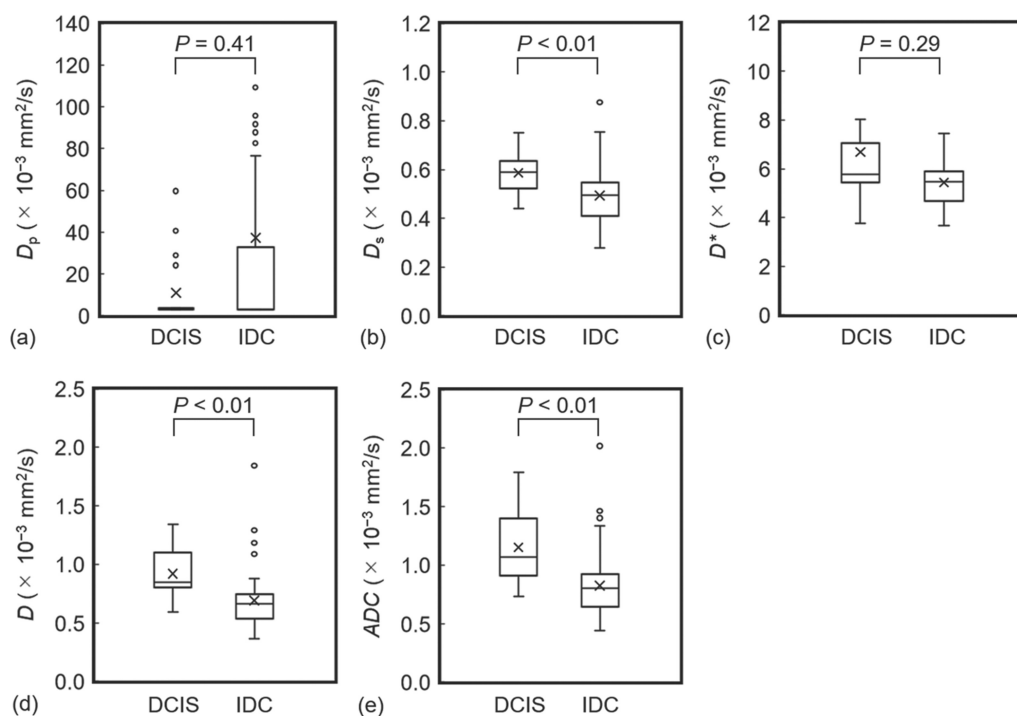


Fig. 3 Box plots of (a) D_p , (b) D_s , (c) D^* , (d) D , and (e) ADC in DCIS and IDC. For each group, the box plot illustrates the median (horizontal line inside box), mean (cross), and outlier (circle) values, interquartile range (box), and minimal and maximal values (lines extending above and below box). ADC , apparent diffusion coefficient; D , perfusion-independent diffusion coefficient; D^* , perfusion-related diffusion coefficient; DCIS, ductal carcinoma in situ; D_p , perfusionrelated diffusion coefficient; D_s , slow-restricted diffusion coefficient; IDC, invasive ductal carcinoma.

Table 1 Correlation coefficient (R) and P values between diffusion coefficients with tri-, bi-, and monoexponential analyses.

	D_p		D_s		D^*		D		ADC	
	R	P	R	P	R	P	R	P	R	P
D_p	NA	NA	0.088	0.467	0.795	0.001	0.095	0.430	0.212	0.076
D_s			NA	NA	0.278	0.019	0.910	0.001	0.85	0.001
D^*					NA	NA	0.252	0.034	0.347	0.003
D							NA	NA	0.98	0.001
ADC									NA	NA

ADC , apparent diffusion coefficient; D , perfusion-independent diffusion coefficient; D^* , perfusion-related diffusion coefficient; DCIS, ductal carcinoma in situ; D_p , perfusionrelated diffusion coefficient; D_s , slow-restricted diffusion coefficient; NA, not applicable.

study demonstrated lower cellularity in DCIS compared with high-grade IDC.⁴³ This explains our finding that DCIS had a higher D_s than IDC. Moreover, DCIS had a significantly larger D obtained with biexponential analysis and ADC obtained with monoexponential analysis than IDC. These results can be also explained by the difference in cellularity between DCIS and IDC.

The D_p obtained with triexponential analysis tended to be lower in DCIS than in IDC, although no significant difference was observed between both. Previous studies with

triexponential analysis have demonstrated that D_p reflects perfusion in tissues.^{37,39} In addition, Jensen et al.¹ reported that the signal enhancement in T₁-weighted images after contrast media administration was larger in mass lesions, including IDC, compared with non-mass lesions, including DCIS. Thus, the lower D_p in DCIS may be associated with the lower neovascularization compared with IDC.^{44,45} However, the values exhibited large variabilities in both DCIS and IDC. This is likely responsible for the lack of a significant difference in D_p between DCIS and IDC, and can

be attributed to the physiological noise observed in lower b-values.⁴⁶ D_p variability should be mitigated by further optimization of imaging parameters and more robust fitting approaches, which need to be validated in future studies.

ROC and logistic regression analyses were performed to evaluate the diagnostic performance of the diffusion coefficients obtained from different diffusion models. Accordingly, our results found that ADC had the highest sensitivity, but limited specificity. Restricted diffusion and perfusion can affect ADC in opposite directions. Therefore, the confounding effect on ADC may be attributed to the lower specificity. Importantly, in terms of sensitivity and specificity, the combination of D_p and D_s with triexponential analysis outperformed the combination of D^* and D with biexponential analysis. These results suggest that triexponential diffusion analysis may have better diagnostic performance for differentiating between DCIS and IDC than biexponential diffusion analysis.

Although there was no significant correlation between D_p and D_s with triexponential analysis, D^* with biexponential analysis was weakly correlated with D . These findings indicate that the triexponential diffusion coefficients, i.e., D_p and D_s , do not necessarily represent the same type of information. Thus, the triexponential analysis could separate the effects of perfusion and diffusion in a better manner than biexponential analysis. Moreover, given that the same DWI data used for triexponential analysis can also be applicable to bi- and monoexponential analyses, the amount of information never decreases but rather increases.

The SNRs at the highest b-value (3000 s/mm²) in both DCIS and IDC were sufficiently high for accurate estimation of diffusion coefficient (a SNR > 5 is needed).³⁹ However, we note that rigorous SNR measurements could not be used given that the use of parallel imaging introduces spatially varied noise, leading to position dependency of accuracy on SNR measurements.

There are several limitations associated with this study. First, we did not compare directly the D_s value in the tumor with cellularity. To clarify the relationship between them, the comparison between the D_s and the tumor cellularity obtained from the histopathological specimen should be pursued in the future. Second, the small number of DCIS cases resulted in an imbalanced number of subjects, which could potentially affect statistical results. Thus, further studies with a larger cohort are required. Third, the diffusion coefficients in the IDC case differed from those reported by Nakagawa et al.³⁸ The differences can be explained by the different b-values, fitting procedures, SNR, and MRI systems. Note that we used the modified triexponential fitting procedure, in which the D_f value was fixed to the diffusion coefficient of free water at 37°C to improve the accuracy and robustness of the analysis. This was because the original fitting reported in previous papers^{37,38} induced considerable fitting errors, perhaps due to the large number of variables in the model and the

relatively small blood volume in tissues. By contrast, previous reports^{39,47} have shown that the modified fitting successfully demonstrated a strong correlation between D_p and cerebral blood flow derived by arterial spin labeling. We, therefore, considered that triexponential diffusion analysis with the modified fitting procedure would be suitable for extracting breast tumor perfusion information from DWI data. This choice could have presumably contributed to the observed differences in the diffusion coefficients. Further optimization of the fitting procedures and imaging parameters, including the b-values, is recommended to obtain more accurate and robust diffusion coefficients. Fourth, the fraction of diffusion components obtained with tri- and bi-exponential analyses was not evaluated given that the D_p values were approximated to D_f , especially in DCIS cases. In such cases, the corresponding fractions (F_p and F_f) do not make sense and, therefore, do not provide suitable physiological information. Moreover, previous studies have reported that several factors, such as blood volume, T_2 difference between blood and tissues, and noise contribution, can strongly affect the diffusion component fraction.^{48–50} Thus, future studies need to consider more robust estimation and interpretation of the diffusion component fractions.

Conclusion

In conclusion, the D_s value that reflects restricted diffusion was significantly higher in DCIS than IDC. There was no correlation between D_p and D_s with triexponential analysis, while D^* and D with biexponential analysis exhibited a weak positive correlation. Triexponential diffusion analysis can provide more detailed information on perfusion and diffusion in breast tumors, and could thus assist in the differentiation between DCIS and IDC.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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