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

Masako Ohno†, Naoki Ohno†, Tosiaki Miyati*, Hiroko Kawashima2,3, Kazuto Kozaka3, Yukihiro Matsuura1, Toshifumi Gabata4, and Satoshi Kobayashi1,2,3

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/mm$^2$. 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).

Results: The $D_s$, $D_f$, 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 $T_1$-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
studies have reported differences in the ADC between benign and malignant breast tumors. Studies have been conducted to evaluate the diffusion coefficients of three components in malignant tumors. The ADC decreases with increasing b-values in normal mammary glands and malignant breast tumors, 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.

Multieponential signal decay in DWI has been reported to be caused by various physiological processes and factors, such as perfusion, intra- and extracellular diffusion, and the permeability of blood vessels and cell membranes. 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. 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. 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. Hayashi et al. 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. 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 algorithm:

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where \( S_b \) and \( S_0 \) are signal intensities for a given \( b \)-value and for a \( b \)-value of 0 s/mm\(^2\), 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/mm\(^2\). Thus, \( D_s \) was first calculated for \( b \)-values > 800 s/mm\(^2\) using the following equation (monoexponential function),

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

where \( S_{\text{int}} \) is the zero intercept at a \( b \)-value of 0 s/mm\(^2\) in the first fitting procedure for \( b \)-values over 800 s/mm\(^2\). Subsequently, \( D_s \) was applied to the triexponential function (Eq. [1]). In addition, the published value\(^{40} \) of the diffusion coefficient of free water at 37°C (3.0 \( \times \) 10\(^{-3} \) mm\(^2\)/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/mm\(^2\) because the contribution of perfusion on the signal intensity is quite small for \( b \)-values > 200 s/mm\(^2\).\(^{31,41} \)

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

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,

\[
S_b/S_0 = F\exp(-bD') + (1-F)\exp(-bD) \tag{4}
\]

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

\[
S_b/S_0 = \exp(-b \cdot ADC) \tag{5}
\]

where \( ADC \) is the apparent diffusion coefficient.

All fitting procedures were implemented and executed in MATLAB (version 2014a; MathWorks, Natick, MA, USA).
Moreover, SNR measurement at the highest b-value (b = 3000 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 \(\times\) \(10^{-3}\) mm\(^2\)/s (71.4% sensitivity and 40.4% specificity), 0.56 \(\times\) \(10^{-3}\) mm\(^2\)/s (64.3% sensitivity and 82.5% specificity), 4.89 \(\times\) \(10^{-3}\) mm\(^2\)/s (92.9% sensitivity and 40.4% specificity), 0.78 \(\times\) \(10^{-3}\) mm\(^2\)/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 \(D\).

**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...
A previous study demonstrated lower cellularity in DCIS compared with high-grade IDC. This explains our finding that DCIS had a higher $D_s$ than IDC. Moreover, DCIS had a significantly larger $D_p$ 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. In addition, Jensen et al. reported that the signal enhancement in $T_1$-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. 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

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

|            | $D_p$ | $D_s$ | $D^\ast$ | $D$   | ADC  |
|------------|-------|-------|----------|-------|------|
|            | R     | P     | R        | P     | R    | P    |
| $D_p$      | NA    | NA    | 0.088    | 0.467 | 0.795| 0.001|
| $D_s$      | NA    | NA    | 0.278    | 0.019 | 0.910| 0.001|
| $D^\ast$   | NA    | NA    | 0.252    | 0.034 | 0.347| 0.003|
| $D$        | NA    | NA    | NA       | NA    | 0.98 | 0.001|
| ADC        | NA    | NA    | NA       | NA    | NA   | NA   |

$ADC$, apparent diffusion coefficient; $D$, perfusion-independent diffusion coefficient; $D^\ast$, perfusion-related diffusion coefficient; DCIS, ductal carcinoma in situ; $D_p$, perfusion-related diffusion coefficient; $D_s$, slow-restricted diffusion coefficient; NA, not applicable.
be attributed to the physiological noise observed in lower b-values.\textsuperscript{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 \(D_t\) 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 \(D_t\) 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 \(D_t\), 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/mm\(^2\)) in both DCIS and IDC were sufficiently high for accurate estimation of diffusion coefficient (a SNR > 5 is needed).\textsuperscript{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.\textsuperscript{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 \(D_{f\text{r}}\) 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\textsuperscript{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\textsuperscript{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 \(D_t\) especially in DCIS cases. In such cases, the corresponding fractions (\(F_p\) and \(F_t\)) do not make sense and, therefore, do not provide suitable physiological information. Moreover, previous studies have reported that several factors, such as blood volume, \(T_2\) and \(T_1\) differences between blood and tissues, and noise contribution, can strongly affect the diffusion component fraction.\textsuperscript{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 \(D_t\) 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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