Computer-aided IVIM/Kurtosis Diffusion MRI for breast lesions: comparison with BI-RADS MRI categories

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Aims and objectives

IVIM (IntraVoxel Incoherent Motion) MRI, which can provide separate information on tissue perfusion and water diffusion (a marker of tissue microstructure) [1], has recently undergone a striking revival especially for body organ studies, including breast cancer [2-5]. A key feature of IVIM MRI is that it does not involve contrast agents, an alternative for perfusion MRI in patients exposed to the risk of nephrogenic systemic fibrosis (NSF). Diffusion MRI has proven useful to differentiate benign and malignant breast lesions, to evaluate tumor extension [6-8], and to predict the response to neoadjuvant chemotherapy in breast cancer patients [9].

The purpose of our study was to evaluate the diagnostic performance of a newly developed computer-aided diagnostic tool based on IVIM and non-Gaussian diffusion MRI using a Kurtosis model [10; 11], and to compare its diagnostic performance with BIRADS category for breast lesions.

Methods and materials

Principles

IVIM model - In the presence of the magnetic field gradient pulses of a diffusion MRI sequence, the MRI signal gets attenuated due to separate and additional diffusion and perfusion effects (Fig.1).

The signal attenuation, S, can be written as [1]:

\[ S = S_{0\text{PERF}} F_{\text{perf}} + S_{0\text{DIFF}} F_{\text{diff}} \] [1]

Where \( S_{0\text{PERF}} \) and \( S_{0\text{DIFF}} \) are the fractions of the perfusion and diffusion components, respectively, to the overall signal, \( S_0 \), when \( b=0 \). One has \( S_{0\text{PERF}} = S_0 f_{\text{IVIM}} \) and \( S_{0\text{DIFF}} = S_0 (1- f_{\text{IVIM}}) \) where \( f_{\text{IVIM}} \) is the (T1,T2-weighted) volume fraction of incoherently flowing blood in the tissue. \( F_{\text{diff}} \) is the signal attenuation from diffusion in the tissue and \( F_{\text{perf}} \) the signal attenuation from the IVIM effect.

In a simple model one has [1] (Fig.2):

\[ F_{\text{perf}} = \exp [-b(D^*)] \] [2]

where \( b \) is the degree of diffusion-sensitization of the MRI sequence, \( D^* \) the pseudo-diffusion coefficient associated to the IVIM effect (including the diffusion coefficient of water in blood).
With the notable exception of the work by Lu et al. [12], in the IVIM MRI context $F_{\text{diff}}$ has always been treated as a simple monoexponential [3; 13; 14] (and the overall IVIM signal in Eq.[1] as a biexponential):

$$F_{\text{diff}} = \exp(-b.ADC) \ [3]$$

where ADC is the Apparent Diffusion Coefficient.

Although the ADC concept has been (and still is) extremely useful [15], it has been well established that the signal decay, $F_{\text{diff}}$, in biological tissues exhibits a curvature at high b values (Fig.1) not predicted by Eq.[3] and that more comprehensive modeling might be required to take into account the non-Gaussian nature of diffusion in tissues. Several phenomenological models have been proposed to describe this curvature, notably two: the bi-exponential model [16; 17] and the cumulant (polynomial) expansion (sometimes referred to as the "kurtosis") model [10; 11]. In this study we have chosen the Kurtosis model, as it appears more robust when using medium-range b values (lower than 3000s/mm²) [17]. With the kurtosis model one has:

$$F_{\text{diff}} \approx \exp [-bADCo+(b.ADCo)^2K/6] \ [4]$$

ADCo is the virtual ADC which would be obtained when b approaches 0. The dimensionless coefficient K (Kurtosis) characterizes the degree of deviation of the signal behavior from a mono-exponential decay (K = 0 when the diffusion driven molecular displacements obey a Gaussian law), a marker of the heterogeneity of the diffusion environment (Fig.3).

**Noise effects** - Another source of systematic error when processing diffusion MRI data results from the non-Gaussian nature of the noise in magnitude reconstructed images, resulting in a systematic shift from a noise-free signal [18]. This source of error is particularly prominent at high b values or with high ADCs for which the signal:noise ratio (SNR) becomes low. The main effect of such noise is that it may mimic another curvature in the diffusion signal attenuation plot (Fig.1): At high b values, when SNR becomes low, the signal reaches a "noise floor" and does not get to 0. The signal attenuation appears curved, and fitting signals with diffusion models will give erroneous values. As the diffusion component of the signal will not be estimated properly, the perfusion component, which is very sensitive to such errors, will, in turn, be affected, with an underestimation of $f_{\text{IVIM}}$ which can even become "negative". It is thus particularly important to correct for this noise bias all IVIM MRI data, especially when using high b values. Unfortunately, the retrieval of true signal values from noise corrupted data is far from trivial, both theoretically and practically. In this study, we have used a new procedure where a Noise Correction Factor is experimentally obtained through a alcane phantom calibration process relying on the diffusion MRI signal property itself [19].
Patient population

This prospective study was approved by an institutional review board of Kyoto University Hospital, and informed consent was obtained from the patients. Between June and December of 2013, 124 consecutive patients suspected of breast lesions were enrolled in this study. Exclusion criteria and the number of excluded patients are shown in Figure 4. Finally 83 patients (20-88 years; mean 53.0 years) with 88 lesions were included in the analysis (Table 1).

MRI acquisitions

Breast MRI was performed at 3T (Trio B17, Siemens Medical Solutions) using a dedicated 16-channel breast array coil. The following images were obtained after localizers were acquired: 1/ Bilateral fat-suppressed T2-weighted images; 2/ Trace-weighted diffusion images (single shot EPI) with spectral attenuated inversion recovery (SPAIR) for fat suppression with the following parameters: b values [0, 5, 10, 20, 30, 50, 70, 100, 200, 400, 600, 800, 1000, 1500, 2000, 2500 sec/mm²]; repetition time/echo time 4,600/86 ms, flip angle 90°, field of view 160×300 mm², matrix 80×166, slice thickness 3.0 mm, Bandwidth 1585, acquisition time 3 min 55 sec; GRAPPA with acceleration factor of 2; 3/ Dynamic contrast (DCE) images: T1-weighted images obtained using a 3-dimensional fat-suppressed gradient-echo sequence (repetition time/echo time 3.7/1.36 ms, flip angle 15°, field of view 330×330 mm², matrix 346×384, slice thickness 1 mm, acquisition time 60 sec). The T1-weighted contrast-enhanced images were acquired before and 0-1, 1-2 and 5-6 min after injection of a gadolinium-based contrast agent (ProHance®, Eisai, Tokyo, Japan).

Data processing

IVIM MRI images were processed in two steps, first estimating the diffusion parameters from the kurtosis diffusion model, then estimating the perfusion parameters from the residual signal (please refer to Fig.1). This two-step process was motivated to increase robustness (as there are fewer parameters to estimate for each step) and justified because IVIM perfusion effects are not expected to contribute to the signal for b values above a cutoff value. The cutoff value for the IVIM effects was determined as 200 sec/mm² after examination of several cases: After the removal of the diffusion component the residual signal was found not to differ significantly from noise for b values above 200 sec/mm² (data not shown).

The signal, S_{200-2500}, acquired with b values larger than the cutoff value was first fitted with the kurtosis model equation, leading to estimates of ADC₀ and K:

\[ S_{200-2500} = \left\{ [S_{0 \text{DIFF}} \exp (-bADC₀+(b.ADC₀)^2K/6)]^2 + NCF \right\}^{1/2} \] [5]
where \( b \) is the degree of diffusion-sensitization of the MRI sequence, \( S_{0\text{DIFF}} \) is the virtual signal what would be obtained at \( b = 0 \) (estimated in the fitting process), NCF is the noise correction factor determined from an alkane phantom [19]. The starting values were \( \text{ADC}_0 = 3 \times 10^{-3} \text{ mm}^2/\text{sec} \) and \( K = 0 \).

Estimates of perfusion parameters, flowing blood fraction, \( f_{\text{IVIM}} \), and pseudo-diffusion coefficient, \( D^* \), were then obtained by fitting the total signal, \( S(b) \), acquired with \( b \) values smaller than the cutoff value and corrected for noise effects, with the IVIM model, after the diffusion component estimated in the first step has been removed from the signal:

\[
[S(b) - \text{NCF}^2]^{1/2} - S_{0\text{DIFF}} \exp[-b\text{ADC}_0 + (b\cdot\text{ADC}_0)^2K/6] = S_{0\text{PERF}} \exp(-bD^*) [6]
\]

where \( S_{0\text{PERF}} \) is the estimated signal what would be obtained at \( b = 0 \) if only perfusion effects were present. Fitting was performed using the values for \( S_{0\text{DIFF}}, \text{ADC}_0 \) and \( K \) estimated in the first step. The starting value for \( D^* \) was \( 2 \times 10^{-2} \text{ mm}^2/\text{sec} \).

Finally, \( f_{\text{IVIM}} \) was estimated as:

\[
f_{\text{IVIM}} = \frac{S_{0\text{PERF}}}{(S_{0\text{PERF}} + S_{0\text{DIFF}})} [7]
\]

Overall, this 2-step process differs from the biexponential diffusion/perfusion model which has often been found in the literature [3; 13; 14], taking into account both perfusion, non-Gaussian diffusion and noise effects.

This 2-step process was performed on a voxel-by-voxel basis, providing parametric maps of \( f_{\text{IVIM}}, D^*, \text{ADC}_0 \) and \( K \), as well as on a ROI basis using the nonlinear subspace trust region fitting algorithm built into Matlab (Mathworks, Natick, MA, USA).

**ROIs**

Two readers (with 6 years and 10 years of experience in breast MRI, respectively, blinded to the final pathological results), manually drew regions of interests (ROIs) in consensus on the slice with the largest tumor area using the diffusion-weighted images, avoiding T2-shine through areas usually found in necrotic or cystic parts under guidance of the DCE and T2-weighted images. ROIs were defined as slightly smaller than the actual lesions in order to reduce partial volume effects. ROIs were also drawn in the normal homogeneous breast parenchyma as controls, avoiding contamination by fatty tissue.

**Computer-aided diagnostic method**

Diagnostic maps were generated assigning for each voxel a 4 level color scale based on the number (0, 1, 2 or 3) of the above IVIM/Diffusion parameters falling above/below previously defined thresholds (\( f_{\text{IVIM}} \# 2.07 \%, K < 0.80 \) and \( \text{ADC}_0 \# 1.40 \times 10^{-3} \text{ mm}^2/\text{sec} \))
The diagnosis was established according to the highest level score present within the lesion. Those levels were hypothesized as equivalent to BIRADS category 2 to 5 (Fig.6).

**Statistical analysis**

Analysis was performed per individual lesion (n=88). The kappa-statistic was used to assess agreement between imaging modalities of the diagnostic performance according to the categories, along with the 95% confidence intervals. Kappa values were interpreted using the following agreement scale: 0.81-1, excellent; 0.61-0.8, good; 0.41-0.6, moderate; 0.21-0.4, poor. Sensitivity and specificity, positive predictive value and negative predictive value were calculated by assigning as follows; category 4 and 5 as malignant and category 2 and 3 as benign for BI-RADS category, category 3 and 2 as malignant and category 1 and 0 as benign for diagnostic map category. All statistical analyses were conducted by using statistical software Medcalc (version 11.3.2.0, Mariakerke, Belgium).

**Images for this section:**

![Diagram](image_url)

**Fig. 1**: Components of the diffusion-weighted MRI signal: Perfusion (IVIM), Diffusion (average diffusion, ADCo, and Kurtosis), noise floor. A « standard » ADC calculation from b=200 and b=1000 (orange broken line), as often found in the literature, would lead to an underestimation of ADCo and an overestimation of fIVIM.
Fig. 2: The IVIM effect: perfusion seen as pseudo-diffusion.

Fig. 3: Explanation of the Kurtosis model which can quantify the deviation from Gaussianity (free diffusion) occurring in biological tissues.
Fig. 4: Studies patient population according to the inclusion and exclusion criteria.
<table>
<thead>
<tr>
<th></th>
<th>Lesions (n = 88)</th>
<th>Patients (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>ILC</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>DCIS</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Benign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraepithelial papilloma</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Fibrocystic change</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Cyst</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 1:** Number of evaluated lesions according to histopathological findings. IDC; Invasive ductal carcinoma, ILC; Invasive lobular carcinoma, DCIS; Ductal carcinoma in situ. *one patient with IDC on both sides, one patient with IDC on left side and cyst on right side, one patient with fibroadenoma on both sides, one patient with fibroadenoma on left side and cyst on right side, and one patient with cysts on both sides.*
**Fig. 5:** Principle of the computer-assisted diagnostic tool (case of an invasive ductal carcinoma in a 64 year old woman).

**Fig. 6:** BI-RADS MRI classification and corresponding diagnostic map category based on probability of malignancy. All of the lesions with category 6 were re-categorized to category 5 on MR findings.
Results

Diagnostic maps provided valuable information on tumor features. Examples of parametric diffusion and perfusion maps obtained in an invasive ductal carcinoma and a fibroadenoma cases are shown in Figure 7 and Figure 8.

In Figure 7, the high $f_{\text{IVIM}}$ fraction area at the periphery of the tumor in $f_{\text{IVIM}}$ map matches the enhancing lesion very well in CE images. Central necrosis is suspected in the parametric maps (white arrows; high ADC₀, low K and $f_{\text{IVIM}}$) as well as conventional images. The peripheral area presenting a low ADC₀/high K/high $f_{\text{IVIM}}$ combination in the parametric maps (yellow arrows) are potentially the most viable parts, as clearly shown as red and orange pixels (malignancy likely) in the diagnostic map, where biopsy should be made.

In Figure 8, dynamic contrast-enhanced MR image shows weak and slow/persistent kinetics in the lesion, where $f_{\text{IVIM}}$ fraction is also low, with slightly higher values visible at the periphery of the lesion (white arrows). High ADC₀/low K/low $f_{\text{IVIM}}$ throughout the lesion highly suggests the presence of a free-diffusion tissue component. Diagnostic map shows only category 0 and 1, suggesting benign tumor.

The 4 level diagnostic classification determined by this computer-aided diagnostic tool was in good agreement (Kappa value 0.72 (CI: 0.62 - 0.81)) with the BI-RADS MRI category 2 to 5 (Table 2).

Both diagnostic map and BI-RADS MRI category achieved 100 % sensitivity and negative predictive value. Specificity and positive predictive value for diagnostic map category were slightly higher than BI-RADS MRI category (Table 3).

Images for this section:
**Fig. 7:** Comparison of the computer-aided IVIM/Kurtosis maps, the conventional images of invasive ductal carcinoma in a 44-year-old woman.

**Fig. 8:** Comparison of the computer-aided IVIM/Kurtosis maps and the conventional images of fibroadenoma in a 63-year-old woman.
Table 2: The comparison of diagnostic map and BI-RADS MRI category.

<table>
<thead>
<tr>
<th>Diagnostic map Category</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>1</td>
<td>4</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 3: The diagnostic performance of diagnostic map and BI-RADS MRI category.

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic Category</th>
<th>BI-RADS MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100 % (93.7 - 100.0)</td>
<td>100 % (93.7 - 100.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>67.7 % (48.6 - 83.3)</td>
<td>64.5 % (45.4 - 80.8)</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>85.1 % (74.3 - 92.6)</td>
<td>83.8 % (72.9 - 91.6)</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>100 % (83.9 - 100.0)</td>
<td>100 % (83.2 - 100.0)</td>
</tr>
</tbody>
</table>
Conclusion

This study demonstrates that the novel categorization of the breast cancer using diffusion and perfusion parameters obtained from the non-Gaussian diffusion/IVIM model could well differentiate malignant from benign breast tumors with high sensitivity and specificity, comparable to BI-RADS MRI. With state-of-art MRI scanners it is now becoming possible to extract further useful information from IVIM MRI, acquiring data beyond the usual b value of 1000 sec/mm². An important feature of $\text{ADC}_0$ and $K$ is that they do not depend on the b values used for image acquisition [20]. This is not the case for typical DWI protocols where the ADC is calculated from just 2 b-values - making it difficult to compare studies across centers. Furthermore, the use of a simple ADC to describe the diffusion component of the signal will not only give a partial account of tissue features, but may also introduce a significant bias the estimated perfusion parameters: Fitting the curved diffusion signal attenuation with a straight line according to Eq.[3] may result in a pseudo-IVIM effect, as acquired data points at low b values will automatically appear above the fitted diffusion signal decay. The perfusion fraction, $f_{\text{IVIM}}$, will, thus, be overestimated (Fig.1). Conversely, large IVIM effects, if ignored, will make the signal decay more curved than it should, leading to an overestimation of Kurtosis model parameters.

While $\text{ADC}_0$ represents diffusion at low b values, K comes mainly from the curvature of the diffusion signal decay observed at high b values (Fig.1). $\text{ADC}_0$ is considered to reflect more diffusion in the extracellular space, which also reflects the amount of cell filling (shape and size) in tissues and cell proliferation. Large K values point out to enhanced diffusion hindrance effects in malignant tissues, likely related to cell proliferation and membrane interactions with diffusing water.

We have shown that diffusion and perfusion MRI parameters can reliably be obtained in a clinical setting with IVIM MRI. In the context of breast cancer the combination of the diffusion parameters, $\text{ADC}_0$, K and $f_{\text{IVIM}}$ may help improve diagnostic accuracy and guide biopsy location. Although these preliminary results need to be validated at a broader scale, they suggest that images of tissue structure and blood microvasculature can be obtained without contrast agents using IVIM MRI, an interesting alternative for perfusion MRI. With further study, these applications might play an important role in the screening, the diagnosis or the monitoring of the breast cancer, and serve as a potential prognostic biomarker of breast.

In conclusion, this computer-aided tool has a diagnostic performance comparable to BI-RADS MRI, using only 3 parameters estimated from a single IVIM/Diffusion MRI acquisition. It has the potential to evaluate both tissue microvasculature and microstructure without the need of contrast agents.
**Fig. 1:** Components of the diffusion-weighted MRI signal: Perfusion (IVIM), Diffusion (average diffusion, ADCo, and Kurtosis), noise floor. A «standard» ADC calculation from \(b=200\) and \(b=1000\) (orange broken line), as often found in the literature, would lead to an underestimation of ADCo and an overestimation of fIVIM.
References