Intravoxel Incoherent Motion (IVIM) analysis of breast cancer lesions

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Purpose

Breast tumor lesions often affect local diffusion of water molecules and microcirculation [1]. In particular, malignant tumors are often more vascularized than normal gland tissue or benign tumors [1]. Therefore, the goal of this study was to assess whether Intravoxel Incoherent Motion (IVIM) parameters could be used to differentiate between benign and malignant lesions, and also between histological sub-types and lesion grade.
Methods and Materials

- Sample

This study enrolled 34 women with a mean age±standard deviation of 57±12 years (age range of 30 to 83 years). 37 breast lesions were considered since some women had multiple lesions. From these 37 lesions: 4 were benign lesions, namely Fibroadenomas (FA), and 33 were malignant lesions, including 27 Invasive Ductal Carcinomas (IDC) and 6 Ductal Carcinoma In Situ (DCIS) (Fig. 1 on page 5, Fig. 2 on page 5 and Fig. 3 on page 5). Regarding the 27 IDC lesions: 5 IDC lesions were classified as on G1 grade, 14 IDC lesions on G2 and the other 8 IDC lesions on G3, where G1 corresponds to more differentiated lesions and G3 to less differentiated lesions. Informed consent was obtained for all patients.

Inclusion/exclusion criteria

1. Lesions with edema or hemorrhage were excluded;
2. MRI examination was done before breast biopsy or at least 7 days after biopsy, to avoid edema and hemorrhage;
3. Women who had undergone chemotherapy and/or radiotherapy treatments and previous breast surgery were excluded, as treatments can change signal intensity and tissue organization.

- Image acquisition

Data was acquired on a 1.5T MRI scanner with a bilateral 4-channel breast coil. Each patient was submitted to normal breast MRI examination protocol (T2-weighted sequence, DWI sequence with 2 b-values (0 and 1000 s/mm$^2$) with Apparent Diffusion Coefficient (ADC) map calculation, and dynamic contrast-enhanced T1-weighted sequence (axial plane and post-processing image subtraction and reconstructions in axial and sagittal planes).

An additional diffusion-weighted image acquisition was done before contrast administration, which consisted of a single-shot echo-planar imaging sequence (SS-EPI) with 6 b-values (0, 50, 250, 500, 750, 1000 s/mm$^2$) in 3 diffusion-sensitizing directions. The technical parameters were as follows: TR/TE=12931/85 ms; FOV=340x340 mm$^2$; Matrix=228x226; number of slices=50; thickness=3 mm; gap between slices=0.6 mm; bandwidth=1686.5 Hz; NEX=1. Scan time was approximately 4 minutes.

- Image analysis and data processing
Lesions were identified in 2 different slices, where they were best visualized, and regions-of-interest (ROIs) were placed on each b-value image. Lesion's signal intensity values were read for each b.

The apparent diffusion coefficient (ADC), which combines both diffusion and perfusion effects, was calculated by fitting the full data (b=0 to 1000 s/mm²) to the mono-exponential model [1-3]:

\[ S_b = S_0 \exp(-b \text{ADC}) \]

where \( S_b \) is the lesion's signal intensity for a particular b-value, and \( S_0 \) is the signal at \( b=0 \) s/mm², derived from the fit.

IVIM model: true diffusion (D), pseudo-diffusion (D*) and perfusion fraction (PF) were calculated according to the method presented by Patel et al. [2]. Initially, data for high b-values (b=250 to 1000 s/mm²) was fitted to a mono-exponential model:

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

with \( S_b \) given as above and \( S_{\text{int}} \), the signal at \( b=0 \) s/mm² resulting from the fit [2]. D was also derived from the fit. PF was calculated from \( \text{PF} = (S_0 - S_{\text{int}})/S_0 \) with \( S_0 \) being the signal at \( b=0 \) s/mm², as given above. Then D and PF values were used in the bi-exponential model with the full data (b=0 to 1000 s/mm²):

\[ S_b/S_0 = (1-\text{PF}) \exp(-bD) + \text{PF} \exp(-bD*) \]

to derive the D* coefficient [1-4].

Mean values of these parameters were calculated and compared between benign and malignant lesions, and also between FA, IDC and DCIS lesion groups. Parameters were also compared among different grades of IDC lesions. In order to evaluate if there were significant differences between these groups of lesions, non-parametric tests were applied (significance #=0.05).
**Fig. 1:** MRI images showing a FA lesion in the left breast (axial plane). A - T2 sequence. B - T1 contrast enhanced images showing tumor enhancement. C - Subtracted image. D - Perfusion map (highly perfused regions appear in red). E - Different b-values diffusion-weighted images.

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**Fig. 2:** MRI images showing an IDC lesion in the left breast (axial plane). A - T2 sequence. B - T1 contrast enhanced image. C - Perfusion map (highly perfused regions appear in red). D - Different b-values diffusion-weighted images.

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Fig. 3: MRI images showing a DCIS lesion in the left breast (axial plane). A - T2 sequence. B - T1 contrast enhanced image showing tumor enhancement. C - Perfusion map (highly perfused regions appear in red). E - Different b-values diffusion-weighted images.

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Results

• Benign vs. Malignant breast lesions

Benign lesions showed higher ADC, D and D* mean values than malignant lesions. On the other hand, PF mean values were observed to be higher in malignant tissues than in benign tissues (Table 1 on page 8 and Fig. 4 on page 8). Significant differences were observed in ADC and D (p=0.007 and 0.005, respectively) between benign and malignant lesions. No other significant differences were observed.

• Histological lesion types - FA vs. IDC vs. DCIS

FA lesions showed higher ADC, D and D* mean values than IDC or DCIS lesions, while they showed intermediate PF mean values. IDC lesions showed higher D* and PF mean values than DCIS lesions, and IDC showed lower values than DCIS lesions regarding ADC and D parameter (Table 2 on page 8 and Fig. 5 on page 9). Significant differences in ADC and D were found between FA and IDC lesions (p=0.007 and 0.005, respectively) and also between FA and DCIS lesions (p=0.033 and 0.032, respectively). Significant differences were also found in PF between IDC and DCIS lesions (p=0.041).

• IDC lesions - G1 vs. G2 vs. G3

It was observed that G3 IDC lesions showed higher ADC and D values than lesions in other grades. G1 lesions showed higher D* values and G3 showed the lowest D* values. PF values were higher for G2 and lower for G1 lesions. (Table 3 on page 9 and Fig. 6 on page 10). No significant differences were found between lesion grades.
Table 1: Mean ± standard deviations of ADC, D, D* and PF parameters for benign and malignant lesions.

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**Table 1:** Mean ± standard deviations of ADC, D, D* and PF parameters for benign and malignant lesions.

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>ADC (x10^-3 mm^2/s)</th>
<th>D (x10^-3 mm^2/s)</th>
<th>D* (x10^-3 mm^2/s)</th>
<th>PF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign (n=4)</td>
<td>1.52±0.30</td>
<td>1.34±0.33</td>
<td>13.07±2.65</td>
<td>12.50±0.13</td>
</tr>
<tr>
<td>Malignant (n=33)</td>
<td>1.04±0.20</td>
<td>0.85±0.16</td>
<td>11.40±1.31</td>
<td>13.18±0.03</td>
</tr>
</tbody>
</table>

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**Fig. 4:** Distribution of Benign versus Malignant Breast Lesions - ADC, D and D* [x10^-3 mm^2/s].

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Table 2: Mean ± standard deviations of ADC, D, D* and PF parameters for different histological lesion types.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>ADC (x10^-3 mm²/s)</th>
<th>D (x10^-3 mm²/s)</th>
<th>D* (x10^-3 mm²/s)</th>
<th>PF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA (n=4)</td>
<td>1.52±0.30</td>
<td>1.34±0.33</td>
<td>13.07±2.65</td>
<td>12.50±0.03</td>
</tr>
<tr>
<td>IDC (n=27)</td>
<td>1.03±0.19</td>
<td>0.84±0.16</td>
<td>11.61±1.17</td>
<td>13.89±0.05</td>
</tr>
<tr>
<td>CDIS (n=6)</td>
<td>1.07±0.25</td>
<td>0.93±0.19</td>
<td>10.48±1.62</td>
<td>10.00±0.04</td>
</tr>
</tbody>
</table>

Fig. 5: Distribution of Different histological lesion types - ADC, D and D* [x10^-3 mm²/(2)/s].

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Table 3: Mean ± standard deviations of ADC, D, D* and PF parameters for IDC lesion grades.

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<table>
<thead>
<tr>
<th>IDC grading</th>
<th>ADC (x10^(-3) mm^2/s)</th>
<th>D (x10^(-3) mm^2/s)</th>
<th>D* (x10^(-3) mm^2/s)</th>
<th>PF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (n=5)</td>
<td>1.01±0.21</td>
<td>0.85±0.21</td>
<td>12.12±0.98</td>
<td>12.20±0.02</td>
</tr>
<tr>
<td>G2 (n=14)</td>
<td>1.02±0.20</td>
<td>0.82±0.14</td>
<td>11.64±1.32</td>
<td>15.07±0.07</td>
</tr>
<tr>
<td>G3 (n=8)</td>
<td>1.05±0.21</td>
<td>0.88±0.18</td>
<td>11.22±0.99</td>
<td>12.88±0.03</td>
</tr>
</tbody>
</table>

Fig. 6: Distribution of IDC Lesions Grading - ADC, D and D* [x10^(-3) mm^2/s].

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Conclusion

Le Bihan et al. described for the first time the IVIM model and argued that it could distinguish molecular diffusion of water from the microcirculation of blood (perfusion) in brain tissue [2,4-6].

In this study ADC and D parameters were shown to be more robust in discriminating between lesion types and subtypes than D* and PF, which reflect microcirculation.

- Benign lesions showed higher ADC and D mean values than malignant lesions. This can be explained by the fact that malignant lesions have higher cellularity which restricts water movement. In both lesions types, ADC values are consistently higher than D values because ADC, besides measuring water diffusion, it is also sensitive to perfusion effects, while D represents intrinsic tissue diffusion [5,6]. In addition, it was observed that in general, differences in mean values and significances are higher when considering D rather than ADC. This suggests that intrinsic tissue diffusion could be a better parameter for lesion characterization.

- IDC lesions showed lower mean values of D than DCIS lesions (although, in this study, not significantly different). A possible explanation is that DCIS lesions are confined to mammary ducts and surrounding tissue architecture is more preserved, translating into higher D values.

- D* values in benign lesions were shown to be higher than in malignant lesions. This is contrary to what was expected since D* is considered to be a perfusion marker within each voxel and it is believed that malignant lesions are more perfused than benign lesions [4]. Patel et al. study in cirrhotic and non-cirrhotic liver, alerted for the fitting uncertainty in IVIM studies for D*, due to fitting errors [2]. These results should, therefore, be compared to dynamic contrast enhanced perfusion results for better understanding of benign lesions behavior.

- While D* may have some limitations in perfusion quantification, PF may have more success showing if there is any microperfusion effect for low b-values. This is because it is easier and more robust to determine if signal intensity at low b-values is higher than expected, based on diffusion alone (Fig. 7 on page 13, Fig. 8 on page 13 and Fig. 9 on page 14) [5, 6]. In fact, in this study, benign lesions showed lower PF values than malignant lesions because the latter are more perfused at the capillary level. Significantly higher PF mean values were observed for IDC in comparison
to DCIS lesions. This could translate higher perfusion of the invasive lesion, as it is possible to observe on Fig. 3 on page 15 (C) where DCIS lesion shows a low perfusion grade. Relatively to IDC lesions grading, it was observed that PF values in G2 and G3 stages are lower than in G1 which could suggest that fast growing tumors perhaps have an inefficient blood supply.

In the future, the imaging protocol will include a larger number of b-values lower than 200 s/mm$^2$, because this b-value range is where pseudo-diffusion has more influence on signal decay. This could probably improve the accuracy of the determination of IVIM parameters [2].

This study, like the study done by Thakur et al., shows that diffusion-weighted imaging quantitative parameters are still more reliable than IVIM parameters, namely in distinguishing between different breast lesion types [1]. Nevertheless, it was also observed that PF could distinguish between IDC and DCIS lesion subtypes, and as such IVIM parameters could have a role in more comprehensive lesion characterization. Finally, since the study sample is small and as many questions remain unanswered, more investigation on this topic is necessary.
**Fig. 7:** IVIM diffusion decay curves. This is a patient with a FA lesion. MRI signal drops on lower b-values. These 3 curves represent mono-exponential fit for all b-values (red), mono-exponential fit for high b-values (green), and bi-exponential fit which is the curve that better represents MRI signal obtained (blue).

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Fig. 8: IVIM diffusion decay curves. This is a patient with an IDC lesion. MRI signal drops on lower b-values. This curve drop is higher on FA than in IDC lesions. These 3 curves represent mono-exponential fit for all b-values (red), mono-exponential fit for high b-values (green), and bi-exponential fit which is the curve that better represents MRI signal obtained (blue). Note: a.u. =arbitrary units.

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**Fig. 9:** IVIM diffusion decay curves. This is a patient with a DCIS lesion. MRI signal drops on lower b-values. These 3 curves represent mono-exponential fit for all b-values (red), mono-exponential fit for high b-values (green), and bi-exponential fit which is the curve that better represents MRI signal obtained (blue).

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**Fig. 3:** MRI images showing a DCIS lesion in the left breast (axial plane). A - T2 sequence. B - T1 contrast enhanced image showing tumor enhancement. C - Perfusion map (highly perfused regions appear in red). E - Different b-values diffusion-weighted images.

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References


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