Diffusional kurtosis as a biomarker of breast tumors

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**Purpose**

1. Diffusional kurtosis imaging (DKI) is a model developed by Jensen and Helpern [1] which derives from Diffusion Weighted Imaging (DWI). This model considers the deviation of water diffusion profile from Gaussian probability distribution due to natural barriers and compartments of biological tissues (cell membranes, intracellular substructures, intra and extracellular space, etc) [1-4].

2. In DKI the Mean Kurtosis (MK) parameter is the measure of this deviation, and the mean diffusivity (MD) corresponds to apparent diffusion coefficient (ADC) calculated using the conventional Gaussian model [1,5-7].

3. Some studies, using the DKI model, have recently been performed in the brain. Results suggested the model to be more complete in characterizing water diffusion in this biologic tissue [2,3,5-7].

4. The goal of this study was to apply DKI in breast tissue, and from here evaluate the capability of MK to distinguish between benign and malignant breast lesions, and also to distinguish between different histological types of breast lesions.

**Methods and Materials**

- **Sample**

  The study enrolled 20 female patients with a mean age±standard deviation of 58.8±12.3 years (range 40-83 years), while some of them presented more than one lesion. In total 23 breast tumors were studied: 3 benign (Fibroadenomas) and 20 malignant lesions (16 Invasive Ductal Carcinomas, IDC; 2 Ductal Carcinoma In Situ, DCIS; 2 Invasive Lobular Carcinoma, ILC) (Fig. 1 on page 4 and Fig. 2 on page 4). Informed consent was obtained from all participants.

  The following inclusion and exclusion criteria were used:

  1. Existing histopathologic diagnosis before or after the MRI examination;
  2. The MRI examination was done at least 7 days after breast biopsy, to avoid edema or hemorrhage;
  3. Women had no previous hormonal replacement therapy, chemotherapy or radiotherapy treatments, as these treatments change tissue signal intensity;
  4. Women had no previous breast surgery, which could change tissue architecture.

- **Image acquisition**
Patients underwent breast MRI in a 1.5T scanner with a bilateral dedicated 4 channel breast coil. Additionally to the normal imaging protocol (T2-weighted sequence, DWI sequence with 2 b-values and ADC map calculation, and dynamic contrast-enhanced T1-weighted sequence, all of them in axial plane) the patients were submitted to a diffusion weighted image acquisition, 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. The duration of this sequence acquisition was approximately 4 minutes (Fig. 3 on page 5, Fig. 4 on page 5, Fig. 5 on page 6 and Fig. 6 on page 6).

• Image analysis and data processing

The 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 $S(b)$ were read. MD and MK parameters were calculated by fitting the DKI model equation using the Levenberg-Marquardt algorithm (Fig. 7 on page 7).

The following equation was used:

$$S(b) = \{\#^2 + [S(0) - \frac{b}{6} \cdot MD + \frac{1}{2} \cdot b^2 \cdot MD^2 \cdot MK]^2\}^{1/2}$$

$S(b)$ - signal intensity corresponding to a b value (arbitrary units),

$S(0)$ - signal intensity when the b value is zero (arbitrary units),

$\#$ - mean signal intensity of the image background noise, obtained by placing the ROIs in "air" (arbitrary units),

$b$ - b value (s/mm$^2$),

MD - mean diffusivity (mm$^2$/s),

MK - mean kurtosis (dimensionless measure).

Mean values of MK and MD were calculated, evaluated and compared between benign and malignant lesions, but also between different histological types. Non-parametric statistics was used (significance $\#=0.05$).
Images for this section:

**Fig. 1:** Number of lesions considered in this study distributed by histological types.
Fig. 2: Histological lesion specimen H & E stained.

Fig. 3: (A, B, C, D, E, F, G) - Benign lesion identified as a Fibroadenoma (FA) on the upper outer quadrant of the right breast. A - T2-weighted image (axial plane). B - T1-weighted weighted with lesion enhancement with gadolinium-based contrast agent (axial plane). C - Contrast-enhanced T1-weighted subtraction image (axial plane). D - Contrast-enhanced T1-weighted subtraction image (sagittal plane reconstruction). E - Perfusion map of the breast tissue (highly perfused regions appear in red). F - Diffusion-weighted image, b=1000 s/mm² (axial plane). G - ADC Map.
Fig. 4: (A, B, C, D, E, F, G) - Malignant lesion identified as an Invasive Ductal Carcinoma (IDC) on the upper outer quadrant of the left breast. A - T2-weighted image (axial plane). B - T1-weighted weighted with lesion enhancement with gadolinum-based contrast agent (axial plane). C - Contrast-enhanced T1-weighted subtraction image (axial plane). D - Contrast-enhanced T1-weighted subtraction image (sagittal plane reconstruction). E - Perfusion map of the breast tissue (highly perfused regions appear in red). F - Diffusion-weighted image, $b=1000$ s/mm² (axial plane). G - ADC Map.

Fig. 5: (A, B, C, D, E, F, G) - Malignant lesion identified as a Ductal Carcinoma In Situ (CDIS) on the upper outer quadrant of the right breast. A - T2-weighted image (axial plane). B - T1-weighted weighted with lesion enhancement with gadolinum-based contrast agent (axial plane). C - Contrast-enhanced T1-weighted subtraction image (axial plane). D - Contrast-enhanced T1-weighted subtraction image (sagittal plane reconstruction). E - Perfusion map of the breast tissue (highly perfused regions appear in red). F - Diffusion-weighted image, $b=1000$ s/mm² (axial plane). G - ADC Map.
Fig. 6: (A, B, C, D, E, F, G) - Malignant lesion identified as a Invasive Lobular Carcinoma (ILC) on the upper inner quadrant of the left breast. A - T2-weighted image (axial plane). B - T1-weighted weighted with lesion enhancement with gadolinum-based contrast agent (axial plane). C - Contrast-enhanced T1-weighted subtraction image (axial plane). D - Diffusion-weighted image, b=1000 s/mm2 (axial plane). E - ADC Map.
**Fig. 7:** Diffusion weighted images with different b values, where the ROIs were placed. b-values in s/mm².
Results

Inevitable DKI?

In order to assess the necessity of considering the DKI model instead of just studying conventional DWI, an evaluation of lesions which had zero value in MK was made. The results showed that only one lesion (FA) had a zero MK value and an ILC lesion had MK = 0.11. All the other lesions had MK values superior to 0.55 (Fig. 8 on page 10).

Benign and Malignant

It was observed that benign lesions (\((1.70\pm0.27) \times 10^{-3} \text{ mm}^2/\text{s}\)) had higher mean values of MD relatively to malignant lesions (\((1.33\pm0.35) \times 10^{-3} \text{ mm}^2/\text{s}\)) (Table 1 on page 11 and Fig. 9 on page 11). On the other hand, MK presents higher mean values in malignant lesions (1.18±0.43) than in benign ones (0.50±0.44) (Table 1 on page 11 and Fig. 10 on page 12).

Non-parametric statistical tests (Mann-Whitney) revealed significant statistical differences between benign and malignant lesions for the MK parameter (\(p=0.036\)), however those differences weren't significant using the MD parameter (\(p=0.055\)).

Different histological types

Regarding the MD parameter, it was found that CDIS lesions (\((1.80\pm0.28) \times 10^{-3} \text{ mm}^2/\text{s}\)) had mean values very close to FA (\((1.70\pm0.27) \times 10^{-3} \text{ mm}^2/\text{s}\)). On the other hand, the ILC lesions (\((1.25\pm0.11) \times 10^{-3} \text{ mm}^2/\text{s}\)) had mean values closer to IDC (\((1.28\pm0.34) \times 10^{-3} \text{ mm}^2/\text{s}\)) (Table 2 on page 13 and Fig. 11 on page 13).

Statistical tests (non-parametrical Mann-Whitney test) showed significant differences between FA and IDC (\(p=0.038\)) and also between IDC and CDIS (\(p=0.049\)). No statistical significant differences were found between ILC and other lesion groups (\(p>0.05\)).

Regarding the MK parameter, it can be clearly seen that IDC lesions (1.28±0.36) had the highest mean value of all lesions. Contrary to this, the FA lesions (0.50±0.44) presented the smallest mean values. Finally, CDIS lesions (0.85±0.28) had a slightly higher mean values than ILC (0.75±0.90) (Table 2 on page 13 and Fig. 12 on page 14).
Statistical tests (non-parametrical Mann-Whitney test) showed significant differences between FA and IDC (p=0.019). There were no significant differences between IDC and CDIS, CDIS and FA, nor between ILC and other groups of lesions (p>0.05).

**Correlation between MD and MK**

It is difficult to establish threshold value because the FA, CDIS and ILC lesions samples are very limited in number. FA lesions have MK values smaller than 1 and MD values larger than $1.47 \times 10^{-3}$ mm$^2$/s. CDIS lesions have MK values ranging between 0.65 and 1.04, and MD values larger than $1.60 \times 10^{-3}$ mm$^2$/s. ILC lesions have a wide range of values of MK parameter but a small range considering the MD values (Table 3 on page 15 and Fig. 13 on page 15).

In this study, no significant correlation (Spearman test) was observed between MD and MK values for the IDC lesion group (p=0.879). Because of the wide range of MD and MK values, classification of these lesions was done in terms of its stage (G1 well differentiated, G2 moderate and G3 less differentiated). It was observed that the half of the IDC G2 lesions have MD values below $1 \times 10^{-3}$ mm$^2$/s with MK values between 0.79 and 1.78. In addition, other 3 cases of IDC G2 lesions, MK and MD values, respectively, range from 1.48 to 1.62, and from 1.39 to $1.47 \times 10^{-3}$ mm$^2$/s. Concerning IDC G1 lesions it is observed that MK values range from 1.12 to 1.38 and MD values are higher than $1.25 \times 10^{-3}$ mm$^2$/s. The IDC G3 lesions are difficult to analyze because there are only 2 of these cases (Table 3 on page 15 and Fig. 13 on page 15).

**Images for this section:**
**Fig. 8:** Distribution of MK results for all the 23 lesions considered.

<table>
<thead>
<tr>
<th>Diffusion parameters</th>
<th>Lesion types</th>
<th>Benign</th>
<th>Malignant</th>
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<td></td>
<td>(mean values± standard deviation)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.70±0.27</td>
<td>1.33±0.35</td>
</tr>
<tr>
<td>MD (x10⁻³ mm²/s)</td>
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<td>0.50±0.44</td>
<td>1.18±0.43</td>
</tr>
<tr>
<td>MK</td>
<td></td>
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</tbody>
</table>

**Table 1:** MD and MK results for benign and malignant lesions.
**Fig. 9:** Distribution of MD results for benign and malignant lesions. MD values = $10^{-3}$ mm$^2$/s.
**Fig. 10:** Distribution of MK results for benign and malignant lesions.

<table>
<thead>
<tr>
<th>Diffusion parameters (mean ± standard deviation)</th>
<th>Histological lesion types</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>FA</td>
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<tr>
<td>MD ($10^{-3}$ mm$^2$/s)</td>
<td></td>
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<tr>
<td>1.70 ± 0.27</td>
<td></td>
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<tr>
<td>MK</td>
<td>0.50 ± 0.44</td>
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</table>

**Table 2:** MD and MK results for the 4 histological types of lesions.
**Fig. 11:** Distribution of MD results for the 4 histological types of lesions. MD values = $10^{-3}$ mm$^2$/s.
**Fig. 12:** Distribution of MK results for the 4 histological types of lesions.

**Table 3:** Descriptive measurements of all histological types of lesions considered in this study (n=23) using MD and MK parameters.
Fig. 13: MD and MK values of all lesions considered in this study. These 4 histological types of lesions are represented in different colors. The IDC lesions stage is also depicted. MD values = $x10^{-3}$ mm$^2$/s.
Conclusion

1. Regarding the need of using the DKI model, it was observed that only two lesions out of 23 had MK values at or closer to zero, which means that the majority of lesion types may have a non-Gaussian probability distribution of water molecules displacement. This comes in agreement with the fact that biologic tissues tend to have natural barriers that modify the water molecules diffusion movement.

2. MD values were higher for the majority of the benign lesions in comparison to the malignant ones. In addition to this, the corresponding MK values of benign lesions were the smallest. Looking at histological types, it was possible to distinguish between IDC and FA using both MD and MK parameters. The increased cellularity, which correspond to more natural barriers and compartments in the tissues, observed in malignant tumors could explain the decreased MD and increased MK values. Thus, if there are less barriers to water molecules diffusion then the MD values will be higher and the MK values will be lower as the displacement probability distribution is approaching the Gaussian profile, a characteristic of homogeneous media.

3. Significant differences were observed in MD values between IDC and CDIS lesions, although both lesions types are malignant. This could be explained by the fact that in CDIS lesions the cellular proliferation is smaller and restricted to the mammary ducts. On the contrary, IDC expands to surrounding tissues, invading the mammary parenchyma. This same argument can explain why IDC and ILC MD values are similar, as both IDC and ILC are invasive tumors.

4. Comparing CDIS and FA, regarding MD and MK values, it was observed that they are similar. This is probably because both of these lesions tend to more or less preserve the tissue structure on which depends the water diffusion.

5. The combined analysis of MD and MK parameters can reveal differences not only between histological types but also within lesions of the same histological type. Some possible reasons that could explain these differences are the cellular size, membrane permeability and/or cellular volume fraction, and also prognostic factors (HER2, ERRB2, estrogen and progesterone receptors, etc), and the neoplasia stage (G1, G2, and G3). It was observed that IDC G1 lesions have MD values higher than 1.25x10^{-3} \text{mm}^2/\text{s} and MK values around 1.25. On the other hand, the majority of IDC G2 lesions have MD values smaller than 1.25x10^{-3} \text{mm}^2/\text{s} and MK values ranging from 0.5 to 1.75. Results suggest that the tumor degree of differentiation is related to changes in water molecule diffusion properties due to changes in tissue architecture.
Although based on a limited number of cases, the study suggests that MK could be used as a tumor biomarker, potentially distinguishing tumor subtypes.

References


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