Evolving imaging in breast cancer: diffusion-weighted magnetic resonance imaging as a predictor of tumor aggressiveness

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Purpose

Breast MRI has been shown to be useful in predicting local disease extension and in detecting foci of disease occult at conventional imaging. The main disadvantage of MRI in the preoperative setting is that it lacks specificity for characterizing these additional findings. MRI false positives may result in extended surgery, additional cost and delay of therapy in women with newly diagnosed breast cancer [1,2].

MRI performances in this setting may be improved by Diffusion-Weighted Imaging (DWI), a method that allows the detection of the random motion of water molecules due to thermal energy. DWI provides a quantitative parameter, Apparent Diffusion Coefficient (ADC), that reflects biological tumor characteristics such as cellularity and water content, two important indexes of tumor aggressiveness. Furthermore, it has been proved that the mean Apparent Diffusion Coefficient (ADC) value of malignant lesions is significantly lower than that of benign findings [3]. Therefore, even if the DWI role in pre-operative breast MRI studies is still debated, we can hypothesize that the ADC values measured by DWI might vary according to the histopathological features of lesions [4]. The aim of our study was to assess whether or not ADC can be used as a prognostic factor in the pre-operative setting, by evaluating the relationship between the ADC values provided by DWI and the histopathological features of MRI detected lesions.

Methods and Materials

A retrospective study was conducted on all patients identified in a prospectively collected database as having performed a bilateral breast MRI at our Institute for loco-regional staging from September 2010 to May 2011.

We included only the women later undergoing breast surgery at our Institution. Exclusion criteria were primary chemotherapy, un-enhancing lesions and lesions < 5mm.

After written informed consent was obtained, each patient performed a bilateral contrast-enhanced breast MRI at our Institute on a 1.5 T magnet equipped with magnetic field gradients of 30 mT/m and a dedicated phased-array coil. Examinations were acquired in the prone position, on the 7th to 14th day of menstrual cycle in premenopausal women or for women receiving hormone replacement therapy (HRT) after a 3 months HRT withdrawal.

The MRI Imaging protocol consisted of:

- Axial T2-weighted Turbo Spin Echo (TSE) (TR 4,000, TE 120, 436 x 323 matrix, 2,2-mm slice thickness, GAP 0,5, time of acquisition=2'50")
• Axial Echo Planar diffusion-weighted spin-echo sequence (TR/TE 10,000/66 ms, FA 90°, matrix 224, field of view (FOV) 310x310, slice thickness 3 mm, acquisition time 70 s, b-value 0 and 900 s/mm²)

• Contrast-enhanced dynamic three-dimensional T1-weighted gradient echo sequence (TR: 499, TE: 4.6, 375 x 321x162 matrix, 2.5-mm slice thickness, FA 90°, GAP=0, time of acquisition=8' 30") performed after intravenous injection of 0.1 mmol/kg of Gadobutrol at a rate of 2 ml/s, followed by 20 ml of saline and 10 s after the contrast medium injection the T1 weighted fat suppressed sequence was repeated 5 times with the same parameters.

Image analysis was performed using a dedicated software and included subtracted images and time-intensity curves of a region of interest (ROI) of 3 x 3 pixels placed in the most enhancing region of the suspicious lesion. The post-processing for DWI included both a qualitative and quantitative analysis of diffusion properties. We evaluated the difference of signal intensity between the b=900 and b=0 images of the lesion previously depicted on the dynamic study. If possible, a ROI was placed on the lesion in the b=900 image and then transferred to the ADC map to calculate the mean ADC of the lesion, sparing the necrotic and cystic components. In case of lesions larger than 1 cm or inhomogeneous, the ADC value was calculated as the mean of 3 measurements.

Our pathologist analysed the surgical specimen of the MRI detected lesions and evaluated classical histopathological and immunohistochemical tumor features:

• size
• histological type
• grade
• estrogen and progesteron receptors (ER, PR)
• Ki-67 expression
• HER2 status

We divided tumors in 4 subtypes according to other studies [5,6]:

LUMINAL A: ER +, PR+, HER2-, Ki67<14%. This subtype includes low-proliferating tumours and carries usually a good prognosis.

LUMINAL B: ER +, PR+; HER2+ or Ki67>14%. Although worse than that of Luminal A, the prognosis for patients with Luminal B tumours tends to be generally better than that of pure HER2-enriched and triple-negative subtype.

HER2- Enriched: ER -, PR-, HER2+.

Triple Negative: ER -, PR-, HER2-. This subtype represents the most biologically aggressive variety of breast cancer.
Correlation between ADC values and histopathological/immunohistochemical features was analyzed using Mann - Whitney U (two-group comparisons) and Kruskal -Wallis H tests (multiple-group comparisons).

**Results**

One hundred and two patients with breast cancer underwent preoperative breast MRI. MRI detected 157 lesions, confirmed by histological analysis: 106 invasive ductal carcinomas (IDC), 25 invasive lobular carcinomas (ILC), 9 tubular carcinomas, 1 mucinous carcinoma, 15 insitu ductal carcinomas (DCIS), 1 insitu lobular carcinoma (LCIS).

The mean ADC value for in situ tumors ($1.14 \times 10^{-3}$ mm$^2$/s) was significantly higher ($p<0.001$) than that for invasive cancers ($0.95 \times 10^{-3}$ mm$^2$/s).

There was a statistically significant difference in mean ADC values among the various histotypes (106 invasive ductal, 25 invasive lobular, 9 tubular and 1 mucinous carcinomas, $p=0.02$). Mucinous cancer showed a very high ADC value due to his content in mucin.

The histological grade could be identified in 110 invasive cancers (20 G1, 74 G2, 16 G3). The ADC for the less aggressive tumors (IS-G1) was significantly higher than the more aggressive ones (G2-G3) ($p<0.001$). (Figure 1)

The histological subtypes were assessed for 107 lesions (41LumA, 59LumB, 6HER2, 1TN). A significant difference in mean ADC was found among the immunohistochemical subtypes, with LumA and LumB showing a higher ADC ($p=0.003$). (Figure 2)

See figure 3,4,5 for clinical cases.

**Images for this section:**
Fig. 1: The ADC for the less aggressive tumors was significantly higher than the more aggressive ones.
Fig. 2: ADC of the different immunohistochemical subtypes.
Fig. 3: Clinical case 1

C.E. 50 yrs
Mucinous carcinoma Luminal A (ER 90%, Pr 90%, HER2-, Ki67 11%)
ADC 1.4 x 10^{-3} \text{ mm}^2/\text{s}
Fig. 4: Clinical case 2

M.M., 67 yrs
DCIS grade 2
ADC 1.1 x 10^{-3} \text{ mm}^2/\text{s}
**Clinical case 3**

**Fig. 5:** Clinical case 3

R.B. 39 yrs
IDC Triple Negative (ER-, PR-, HER2-, Ki-67 >50), grade 3
ADC $0.8 \times 10^{-3}$ mm$^2$/s
Conclusion

Our study demonstrated that, despite some overlap of ADC values among different cancer subtypes, ADC could be a promising prognostic quantitative parameter inversely associated with histopathological factors. Due to the small number of patients and the inhomogeneous distribution of histotypes (most cancers were IDC), our results need to be confirmed by prospective multicenter studies on larger cohorts of patients, to further investigate the potential role of quantitative DWI in this setting.

References