

# Breast Cancer Detection and Diagnosis based on Diffusion Tensor Imaging

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## Introduction:

Our knowledge of the architecture of the mammary gland is based on several detailed anatomical studies of breast autopsies and mastectomy specimens (1) but none of the available imaging methods employed today has succeeded in tracking the full ductal tree. Since mammary malignancies originate from the ductal epithelial cells, and initially spread within the ducts, the ability to monitor and track *in vivo* non-invasively changes in microstructure of the mammary gland tissue and to identify malignant growth is highly significant. We have previously suggested that mapping the anisotropic water diffusion properties of the ducts can help meet this challenge (2), and demonstrated utilization of this approach to detect breast cancer without the injection of a contrast agent (3). In this study we further show that this method indeed enables tracking the ductal trees *in vivo* and identifying the distinct tensor parameters for delineating and diagnosing breast malignant growth.

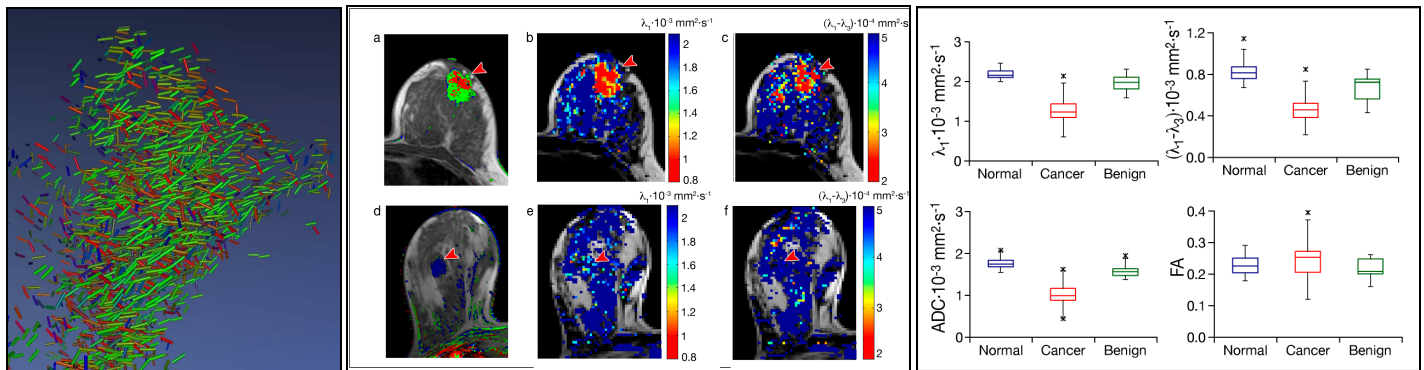
## Methods:

**Subjects:** The study included 21 healthy female volunteers with no current indications of breast pathological findings in mammography and ultrasound, 26 patients with 33 biopsy confirmed breast cancer lesions (21 IDC, 6 ILC and 6 DCIS), and 14 patients with 20 benign lesions (11 fibroadenomas, and 9 other benign). All protocols were approved by the Internal Review Board of Meir Medical Center (Kfar Sabah, Israel) and a signed informed consent was obtained from all subjects.

**Magnetic Resonance Imaging:** Images were acquired on a 3 Tesla Trio scanner (Siemens). The MRI protocol included transversal T2 weighted images with and without fat saturation, axial multi directional diffusion weighted (MDDW) images with fat saturation, acquired with the twice refocused echo planar imaging sequence (4), and a DCE-MRI protocol that was applied only to patients with confirmed cancers or benign lesions. The field of view ranged from 360 to 390 mm, 60 slices were acquired with slice thickness of 2-2.5 mm, covering the whole breasts. 2D DWI datasets were acquired using diffusion sensitizing gradient in 30 or 64 directions at two b values, 0 and 700 mm<sup>2</sup>s<sup>-1</sup>; echo-time/repetition time of 120ms/10400 ms and spatial resolution of 1.9x1.9x2.5mm<sup>3</sup>, or 1.9x1.9x2.5mm<sup>3</sup>.

**Data processing:** The diffusion weighted images were analyzed by a propriety software that provided a fast analysis and tracking. The diffusion tensor was calculated, pixel by pixel, by non linear fitting of the diffusion dataset to Stejskal-Tanner equation, as previously described (2,3) yielding 3 eigenvectors ( $v_1$ ,  $v_2$ ,  $v_3$ ) and their corresponding eigen-values  $\lambda_1$ ,  $\lambda_2$  and  $\lambda_3$ . Results were presented in 3D vector maps of  $v_1$  (Fig. 1), and in parametric maps of the eigen-values in color coded maps, overlaid on the corresponding T2 weighted images (Fig. 2). An absolute anisotropy factor was defined as  $\lambda_1/\lambda_3$ . Apparent diffusion coefficient (ADC), and fractional anisotropy (FA) values were also calculated. The dynamic contrast enhanced dataset was obtained and analyzed using the 3TP method (5,6).

**Statistical Analysis:** Percentile values of the diffusion parameters were calculated for the entire fibro-glandular tissue of the breasts in the healthy volunteers and within the ROI of the cancers and benign lesions delineated manually based on correlation with the enhancement in DCE-MRI images and the histopathological findings. Unpaired, two tailed t-test was applied for evaluating statistical differences between the diffusion parameters of the fibroglandular tissue, cancers and benign lesions. The median values of the diffusion parameters served as predictors in ROC analysis aimed to evaluate the diagnostic ability of DTI.



**Fig. 1 (left).** A 3D vector map of  $v_1$  in the left breast of a healthy volunteer. A sagittal view is presented. Note the dominant direction of  $v_1$  towards the nipple (in green)

**Fig. 2 (middle)** Parametric diffusion maps of breast lesions. The arrow heads point to the lesions: **a-c** an IDC lesion, **d-f** a fibroadenoma lesion. **a&d:** color coded parametric maps of DCE-MRI (3TP analysis), **b&e:**  $\lambda_1$  maps, **c&f:**  $\lambda_1/\lambda_3$  maps.

**Fig. 3 (right)** Statistical analysis of the diffusion parameters in normal breast fibroglandular tissue, cancers and benign lesions.

## Results:

The diffusion coefficients in three orthogonal directions ( $\lambda_1$ ,  $\lambda_2$ ,  $\lambda_3$ ) were high in the normal fibroglandular tissue, with the largest eigen-value  $\lambda_1$  of  $(2.1 \pm 0.2) \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ . The direction of  $\lambda_1$  and the presence of fractional anisotropy  $>0.15$  enabled tracking the ductal trees and separating them from fibrous tissue. Statistical analysis of the diffusion parameters in normal breast fibroglandular tissue, cancers and benign lesions revealed that  $\lambda_1$ , ADC and  $\lambda_1/\lambda_3$  values of cancers were significantly lower than in normal tissue ( $p < 0.001$ ) and in benign lesions ( $p < 0.0001$ ,  $p < 0.0001$ ,  $p < 0.004$ , respectively), while FA of cancers was not significantly different from that of normal tissue ( $p < 0.27$ ) and benign ( $p < 0.29$ ), due to the normalization to ADC (Fig. 3). ROC curve analysis, using the median value of  $\lambda_1$  as a predictor yielded an area under the curve (AUC) of 0.98 with 96% sensitivity/ 96% specificity for differentiating cancers from normal tissue and an AUC of 0.97 with 92% sensitivity/92% specificity for differentiating malignancy from benignancy. ADC provided a similar performance as  $\lambda_1$  but with a slightly lower specificity for differentiating cancers from normal tissue. Cancers also exhibited significantly lower values of  $\lambda_1/\lambda_3$  than normal tissue with a 91% sensitivity /72% specificity.

## Conclusions:

Breast DTI is a completely non invasive fast method that demonstrates a high potential for cancer detection and diagnosis as a stand alone method or in conjunction with DCE-MRI. Further studies to characterize the diffusion properties of benign breast diseases and assess the DTI specificity for distinguishing cancer from benign lesions are now underway.

**References:** 1. Going, J. J. Breast Cancer Res, 8: 107, 2006. 2. Eyal E. *et al*, prog 508, ISMRM, 2008. 3. Eyal E. *et al*, prog 362, ISMRM, 2010. 4. Reese, TG *et al*. MRM, 49:177-182, 2003. 5. Degani *et al* Nature Medicine 3(7):780-782, 1997. 6. Kelcz F *et al*. Am. J. Roentgenol 179:1485-1492, 2002.