Evaluation of the Efficiency of DTI Anisotropy Indices to Detect Breast Cancer

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Introduction: DTI tracks the water diffusion in different directions and thereby allows characterizing microstructures with restricted diffusion such as brain fibers [1,2] or breast ductal /glandular trees [3,4]. Tissue microstructure organization is demonstrated in vector and parametric maps of anisotropy indices that are derived from the eigenvectors and eigenvalues of the diffusion tensor respectively, where the most commonly used measures of anisotropy are fractional anisotropy (FA), relative anisotropy (RA) and volume ratio (VR). In breast DTI, FA is the most common anisotropy index that was applied for both characterization of the normal fibroglandular tissue [5-8] and for cancer diagnosis [9-12]. In these studies malignant lesions exhibit low ADC values as compared to normal tissue and benign lesions. However, FA values exhibited conflicting results in cancers as compared to normal tissue, inhibiting the use of this parameter for diagnostic purposes. We have previously reported 3T-DTI results that presented at pixel resolution maps of the three symmetric tensor eigenvalues ($\lambda1$, $\lambda2$ and $\lambda3$) corresponding to the eigenvectors in the breast tissue frame, vector maps of the prime eigenvector and parametric maps of two anisotropy indices FA and a maximal anisotropy [3,4]. These studies revealed that $\lambda1$values and the maximal anisotropy ($\lambda1$-$\lambda3$) are the most sensitive independent parameters for the detection and diagnosis of breast cancer lesions whereas FA values span a range which was not significantly different from those of normal breast tissue and exhibited a significantly lower CNR compared to the maximal anisotropy index. Here we describe further studies focusing on evaluating the various anisotropy indices and examining their ability to differentiate cancer from normal breast tissue.

Methods: The study was approved by the IRB of Meir Medical Center and included patients with biopsy confirmed breast cancer lesions. Images were acquired on a 3T scanner (Trio, Siemens). The MRI protocol included axial bilateral T_2-weighted images; DTI with fat suppression ,with diffusion gradients applied at 30 or 64 directions, TE of 120 msec , two b values 0 and 700 sec/mm^2, and a DCE-MRI protocol. For all sequences 60 slices were acquired with slice thickness of 2-2.5 mm, and in-plain spatial resolution of the DTI was 1.9x1.9 mm^2. The DTI datasets were analyzed using propriety software, yielding 3 eigenvectors and their corresponding eigenvalues [4]. Results were presented as 2D parametric maps at pixel resolution, overlaid on the corresponding T_2-weighted images, in 2D vector maps and in 3D ellipsoids' maps constructed from the diffusion tensor parameters (Fig. 1). The anisotropic indices, FA, RA and 1- VR, were calculated according to the definitions reported previously [1,2], and the maximal anisotropy index was calculated as $\lambda1$-$\lambda3$. Tumors' ROI were delineated on $\lambda1$ maps of the central tumor slice, using a threshold of $\lambda1<0.0017$ mm^2/sec, in correlation with the enhancement in DCE-MRI images. A comparable size ROI of normal fibroglandular tissue was delineated in the contralateral breast. Statistical analysis included calculations of the medians of the various anisotropy indices in the ROIs of the each cancer and the corresponding normal tissue, calculation of the contrast to noise ratio [4], and two tailed paired t-test for evaluating whether the differences of each index between cancer and normal tissue are significant.

Results and Discussion: DTI datasets of 13 patients (median age: 46, range: 38-58) with biopsy confirmed breast cancer (9 IDC with 7 including also DCIS foci, 4 ILC, Median diameter of the lesions: 24 mm, range: 12-50 mm) were analyzed with a propriety software. Figure 1 demonstrates analysis of DTI parameters in a typical example of IDC. The cancer region can be clearly identified by its low value of $\lambda1$ compared to the surrounding tissue with $\lambda1\geq1.7$x10-3 mm^2/s. The corresponding 3D ellipsoids' map clearly shows the diminution of the ellipsoids size in the cancer region as compared to the normal tissue and their approximately round shape. We also demonstrate in this figure parametric maps of two anisotropic indices as well as the T_2-w and DCE/3TP map that confirm the location of the cancer. It can be clearly seen that the maximal anisotropy rather than FA is a more efficient parameter for characterizing anisotropy and differentiating cancer from normal tissue. This conclusion is further proven by the statistical analysis demonstrated in Table 1. The values of FA, RA and 1-VR in cancers are not significantly different from those in normal breast tissue, however the maximal anisotropy shows a high significance ($p<0.0002$). Furthermore the CNR of the maximal anisotropy is significantly higher ($p<0.006$) than the CNR of the other indices (Table 2).

Due to the specific breast architectural features diffusion in the ductal/glandular system is relatively fast and anisotropic. On the other hand, diffusion in the connective fibrous tissue surrounding the ducts is fast and isotropic as a result of the high water content and low cell density in this tissue. Overall the differences in the ADC of these two tissue components is small. However, in the presence of malignancy, blockage of the ducts and lobules by cancer cells increases the tortuosity and restriction of the water movement, causing a reduction in the diffusion coefficients in all directions in approximately an isotropic manner. Since FA, RA, and 1-VR are normalized to a combination of the three diffusion coefficients, when the diffusion coefficients change markedly these indices fail to serve as independent anisotropy indicators. For example a reduction in ADC will artificially increase the three normalized indices for the same absolute difference in the coefficients. On the other hand, the maximal anisotropy is not normalized and the difference between the two diffusion coefficient will reflect the maximum possible difference in the anisotropic movement irrespective of ADC. Thus, our results explain the conflicting reports of the efficiency of FA to detect cancer and confirms the ability of the maximal anisotropy to serve as an independent marker for detecting cancer. It should be pointed that the maximal anisotropy is highly sensitive but not specific since the fibrous/connective breast tissue is also close to isotropic [4].

However , using the parametric maps of both $\lambda1$ and $\lambda1$- $\lambda3$ provide a high efficiency for detecting cancer.

Conclusion: The simultaneous reduction in the diffusion coefficients and in the un-normalized maximal anisotropy index can be efficiently used for detecting breast cancer, while the normalized anisotropy indices fail to differentiate cancer from normal tissue.

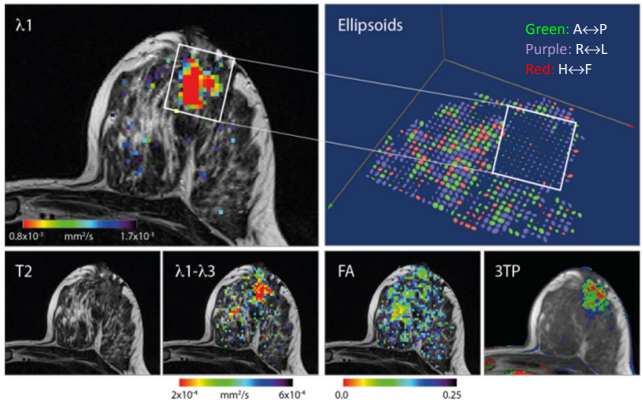

Figure 1. Parametric DTI maps of IDC and the corresponding 3D ellipsoids' map of the cancer and the surrounding tissue. The white boxes indicate the cancer locus. All values above the thresholds indicated in the scales were not colored.

Table 1. Mean ±SD values of the median anisotropy indices in the ROIs.

FA		RA		1-VR		λ1-λ3, mm2/s	
Cancer	Normal	Cancer	Normal	Cancer	Normal	Cancer	Normal
0.25±0.06	0.26±0.07	0.21±0.05	0.21±0.05	0.07±0.03	0.09±0.07	(4.9±1.4)x10^{-4}	(8.4±2.1)x10^{-4}
p< 0.6		p<0.6		p<0.2		p<0.0002	

Table 2. CNR±SD of the anisotropy indices

FA	1-VR	RA	(λ1-λ3)
0.25±0.22	0.25±0.23	0.24±0.22	0.76±0.35

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