Non-Gaussian Diffusion NMR discriminates between low- and high-risk prostate cancer.

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Prostate cancer (Pca) is the second most common malignancy and the fifth leading cause of death in men worldwide. Current diagnostic methods, based on PSA measurement and biopsy, are limited by low specificity (36%) and invasive procedures; moreover, 30% of tumor-grade were under-estimated[1]. High-grade PCa is treated with more aggressive therapy, including surgery or radiations, than low-grade PCa; discriminating correctly different tumor grade is mandatory to plan patient treatment. Prostate tissue has a glandular structure, composed by several compartments: acini, formed by secretory cells and connected to ducts; the glandular structure is supported by the connective tissue of stroma.
PCa development is characterized by microstructural modifications, due to the growth of undifferentiated cells and alteration of cell membranes, that change each compartment volume fraction[2].
The Diffusion-weighted NMR (DW-NMR) imaging is sensible to the tumor modifications, since this technique exploits the diffusion of biological water molecules as an endogenous contrast agent.
Diffusion is the stochastic thermally-induced displacement of molecules, that colliding with the structures and barriers they encounter during motion, probe the tissue and reveal its histoarchitecture at microscopic scale, non-invasively. By using a couple of pulsed magnetic-field gradients, the NMR acquired signal, named DW signal, is proportional to the Fourier Transform of molecules motion propagator; if the displacements probability distribution (dpd) is Gaussian-shaped, as it happens in homogeneous media, the signal mono-exponentially decays. Nevertheless, prostate, as any biological systems, is a complex and inhomogeneous media, which exhibits a non-Gaussian diffusion. In order to obtain additional information on tissue microstructures, inaccessible to Gaussian-diffusion NMR technique, we estimate the Kurtosis, i.e. the fourth-order term of the cumulant expansion, that quantifies the deviation of dpd from a Gaussian distribution, providing a measure of tissue heterogeneity[3].
In this work, we compare two NMR technique, Diffusion Tensor Imaging (DTI) and Kurtosis Imaging (DKI), based respectively on Gaussian and non-Gaussian diffusion, to test their diagnostic potential in PCa identification and stadiation.
31 patients with different tumor grades (TG) PCa were enrolled to be examined by a 3T scanner, after two months from the first biopsy. Diffusion-weighted images were acquired with 5 different diffusion weights, i.e. b-values up to 2500s/mm^2. Parametric maps of Mean Diffusivity (MD) and apparent Kurtosis (K) were obtained by using an in-house algorithm developed in Matlab.
One-way ANOVA was performed to test statistical significance of differences in MD and K values calculated in benign prostate and in PCa among different TG. The linear correlation between diffusion parameters and the tumor grade was estimated by the Pearson's test.

Malignant tissue shows a significantly higher K and lower MD values compared to the healthy tissue ($p<10^{-4}$).
K-values of PCa were positively correlated with TG ($r=0.37;p<0.004$), while MD-values were negatively correlated with TG ($r=-0.31;p=0.02$). Both K and MD can significantly discriminate between low- and high-grade PCa; however K showed the highest significance ($p_K=0.005;p_{MD}=0.015$).
These results may be explained considering that, in healthy prostate, water diffusion is almost free in acini and ducts, restricted in stroma and highly restricted in secretory cell layer. The histopathological evidences show that tumor progression causes prostate glands to change in size and shape and malignant cells to infiltrate compartments. The overall effect of these modification lead to a decrease of diffusivity and an increase of heterogeneity.
Our results demonstrate that non-Gaussian diffusion parameter K is more sensitive to tumor-induced microstructural changes, suggesting that DKI could provide a reliable, non-damaging and less expensive diagnostic exam. Since DKI is a non-invasive technique, it also could be employed to follow-up patients, evaluating therapy response.

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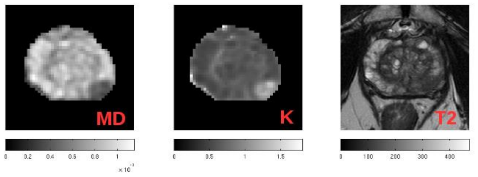

Figure 1. Diffusion parametric maps of Mean Diffusivity (MD, left) and Kurtosis (K, center). In addition, a high-resolution T2-weighted image (T2, right) is showed as anatomical reference.

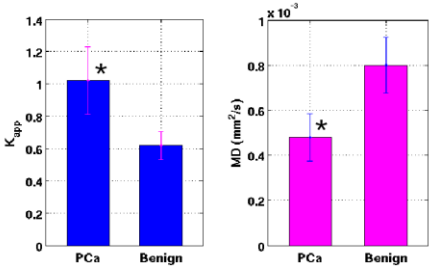

Figure 2. Bar-graphs represent mean value and standard deviation measured in PCa and benign tissue of Kurtosis (left image) and Mean Diffusivity (right image) Statistical significance ($*p<10^{-4}$).

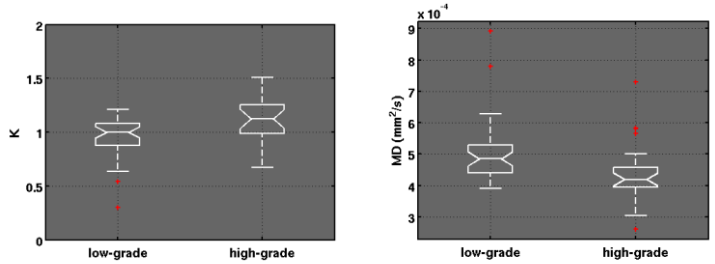

Figure 3. Box-plots represent mean values measured in low- and high-grade PCa of Kurtosis (left image) and Mean Diffusivity (right image).