Characterization of micro-structural changes in the ultra-early phase of antiangiogenic treatment using non-Gaussian diffusion models

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Introduction: Non-Gaussian diffusion model characterizes the non-Gaussian diffusion in tissuse and could provide additional values in the diagnosis of tumor and therapy assessment [1,2]. This study aims to evaluate the antiangiogenic effects of Sorafenib therapy in ultra-early phase using non-Gaussian methods - diffusional kurtosis imaging (DKI) and stretched exponential in mouse tumor model.

Methods: This study was approved by the local institutional review board for animal care and use. Experiments were performed in 12 female BALB/c-nu nude mice (32-40 days old) , each weighing 14-17 g. MHCC-97 Hepatocellular carcinoma cells were planted subcutaneously in each nude mouse. After implantation of tumor, nude mice were maintained for three weeks. Prior to treatment, all nude mice were scanned on a GE 1.5 T whole body scanner equipped with a phased array wrist coil. For each mouse, 10 axial slices covering whole tumor were scanned using spin-echo diffusion-weighted echo-planar imaging with 7 b-values (0, 500, 1000, 1500, 2000, 2500 and 3000 s/mm^2). Other imaging parameters were: FOV=10 mm, slice thickness=2.5 mm, no interslice gap, acquisition matrix=128 × 128, TR/TE=4000/113.8 ms. The same MRI scan was repeated on all nude mice at 1 hour, 3 hours, 6 hours, 12 hours after the administration of Sorafenib at a dose of 15 mg/kg. One randomly selected mouse was sacrificed for histologic H&E staining at each time point. At each time point, all DWIs were coregistered to the b_0 image and then fitted to the DKI equation $\log(S/S_0) = -b\cdot D + b^2\cdot D^2\cdot K/6$ and the stretched exponential model $S/S0 = \exp(-(b\cdot D)^{\alpha})$. The diffusivity **D**, diffusional kurtosis **K**, distributed diffusion coefficient (DDC) and α were computed from DKI and stretched exponential fitting, respectively [1,2]. The edge of tumor was manually delineated on b_0 image and transferred to the functional maps for measurement. Paired *t* test was used to compare the mean value of metrics between every two consecutive time points using SPSS (Chicago, IL, USA). P-values of 0.05 were considered to be significant.

Results and discussion: Figure 1 showed the change of DKI-derived D and K over time after Sorafenib administration. At 1 hour after treatment, diffusional kurtosis dramatically increased from 0.617 to 1.067 with $p < 0.05$ while D decreased slightly. Figure 2 demonstrated significant decrease of DDC ($p < 0.05$) at 1 hour after treatment. There is no signifiant change of α. The rapid increase of diffusional kurtosis may reflect the increased tissue complexity due to the initiation of cellular edema and central necrosis in the ultra early phase [1]. The decreased DDC may also suggest the appearance of cellular edema. These microstructral changes were confirmed by H&E staining.

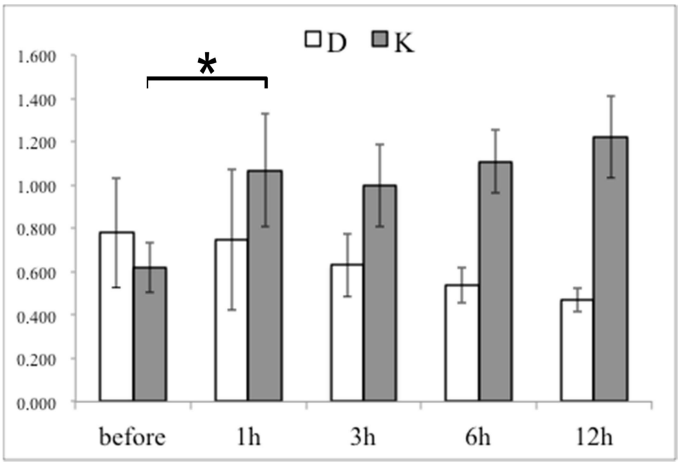

Figure 1. Change of DKI-derived metrics over time.

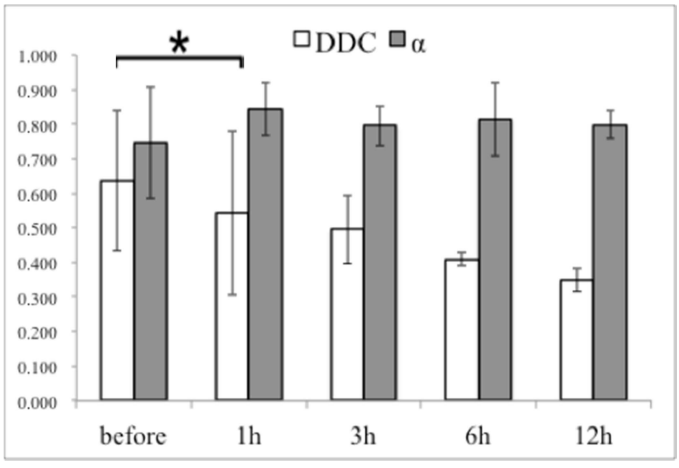

Figure 2. Change of Streched Exponential-derived metrics over time.

Conclusion: Non-Gaussian DKI and stretched exponential-derived diffusional kurtosis and DDC may be able to detect the microstrutral changes in the ultra-early phase of antiangiogenesis treatment.

References: [1] Jens H. Jensen et. al., NMR in Biomedicine 2010. [2] Thomas C. Kwee et. al., NMR in Biomedicine, 2009.