Evaluation of different mathematical models for diffusion weighted imaging of prostate cancer xenografts in mice

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Purpose

To evaluated prostate cancer (PCa) model tumor progression using different mathematical models and their fitting quality for diffusion weighted imaging (DWI) signal decay using b-values up to 2000 s/mm^2.

Methods

10^6 androgen independent human PCa cells expressing red fluorescence protein (PC3-RFP, Anticancer Inc., USA) were implanted in right hind limbs of 10 nude mice. The anesthetized mice were imaged once a week using a 7T animal MR scanner (7T Pharmascan, Bruker GmbH) with 72 mm volume transmitter and 10 mm surface receiver coil. Multislice T_2-weighted images were obtained (TR/TE 2500/33 ms, field of view (FOV) = 30 × 30 mm2, matrix size 256 × 256, 15 slices) to localize a slice with maximum tumor diameter for DWI measurements. Diffusion weighted single shot spin echo echo planar imaging was applied with the parameters: TR/TE 3750/25.3 ms (low b-value set) 3000/30 ms (high b-value set), FOV 3×1.5 cm^2, matrix 128×64, slice thickness 1 mm, three orthogonal diffusion directions, and two different sets of b-values: low b-set (15 b values in total): 0, 2, 4, 6, 9, 12, 14, 18, 23, 25, 28, 50, 100, 300, 500 s/mm^2, and high b-set (12 bvalues in total): 0, 100, 300, 500, 700, 900, 1100, 1300, 1500, 1700, 1900, 2000 s/mm^2. For further analysis, the mean value of the signal from three directions was calculated. The tumor area was manually delineated based on T_2 weighted anatomical image. Signal intensity of all voxels within the ROIs were fitted using the following 4 models separately for low and high b-value sets:

1. Monoexponential: $S(b) = S(0)e^{-bADC_m}$

2. Stretched exponential: $S(b) = S(0)e^{-(bADC_s)^{\alpha}}$

3. Kurtosis $S(b) = S(0)e^{(-bADC_k+\frac{1}{6}b^2ADC_k^2K)}$

4a. Biexponential: low b-set $S(b) = S(0)(1-f_p)e^{-bD_f} + f_p e^{-bD_p}$

4b. Biexponential: high b-set: $S(b) = S(0)(1-f_f)e^{-bD_s} + f_f e^{-bD_f}$

To determine the best regression, corrected Akaike information criteria difference (ΔAICc) and F-test (F) with 1% level of significance were used.

The difference (d) in median values per ROI between two repeated scans performed 4 weeks after the initial scan was calculated for a subset of mice (six mice for low b-values and seven for high b-values) in order to evaluate short term repeatability. Root mean squared difference (rmsd) and coefficient of repeatability (r) were calculated as follows:

$$rmsd = \sqrt{\sum_{i=1}^{n} d^2 \times (n-1)^{-1}} \quad r = 1.96 \times rmsd$$

Results

The differences of the fitted values between the weeks are shown in Figure 1(high b-valeus). DWI data obtained using low b-values were fitted better by the stretched exponential model as compared with mono-exponential, kurtosis and bi-exponential models based (ΔAICc) and F-test. The kurtosis model was preferred over the stretched exponential model in average in ~75% of voxels based on ΔAICc for high b-set. The bi-exponential models still provided significantly better fit to data than the stretched exponential and kurtosis models based on F-test. No major changes in model preference were present between different time points. f_p median value at 1st, 2nd, 3rd, 4th week were 4.6%, 3.5%, 4.5%, 2.6%, respectively.

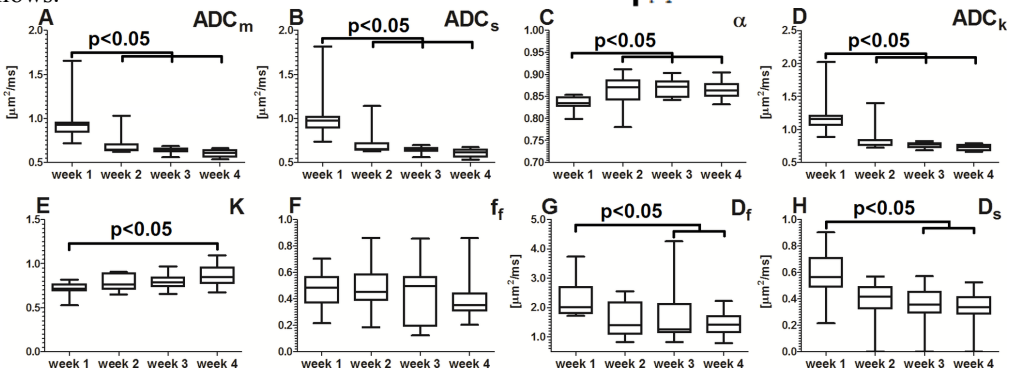

Figure 1 Median values of the parameters data obtained using high b-values

Table 1 Coefficient of repeatability, r(%),as percentage of the averaged median.

	ADC$_m$	ADC$_s$	α	ADC$_k$	K	f$_p$	f$_f$	D$_p$	D$_f$	D$_s$
r(%)- low b-set	19.9	28.8	11.9	22.6	59.7	491.8	NA	399.1	163.2	NA
r(%)- high b-set	28.6	31.4	10.4	27.6	42.7	NA	197.4	NA	164.5	254.8

Conclusions The tumor growth was successfully followed for 4 weeks. Due to low repeatability of the biexponential model parameters derived from low and high b-values DWI data using independent least square fitting on a voxel level, a degree of caution should be applied if these parameters are used for cancer characterization and therapy response monitoring in this tumor model.

References 1. Akaike H. In: Petrov BN, Csaki F, editors. Budapest: Akademiai Kaido; 1973. p 267–281.