A comparative study of MRI diffusion-related parameters for the early detection of radiation-induced tissue changes in a rodent tumour model

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Introduction

The MR diffusion technique allows probing the microstructure of biological tissues. Anisotropic diffusion is commonly studied using diffusion tensor imaging (DTI). Analysis of the MR signal as a bi-exponential decay with definition of a slow compartment and of a fast compartment has also been proposed (1). When restrictions or hindrance of the water molecules movements are present, these models can not lead to accurate descriptions of the diffusion because they assume an inexact Gaussian probability density function (PDF) of the diffusion process. The PDF of the diffusion process can be directly measured using q-space imaging (QSI) (2). Using this technique, a non-Gaussian PDF can be studied in terms of parameters reflecting the shape of the distribution (height, width, kurtosis,…). From a biophysical point of view, the most exact framework should be used to analyze MR data. However from a clinical point of view, the diagnostic accuracy of parameters derived from techniques assuming Gaussian vs non-Gaussian PDF should be empirically assessed. We previously performed a preliminary comparative study (3) assessing early effects of external radiation therapy in a rodent tumour model (rhabdomyosarcoma in rats). The present paper reports a more extended and refined analysis of the data. Parameters obtained from DTI (mono- and bi-exponential analysis) and QSI (tensor analysis) were compared.

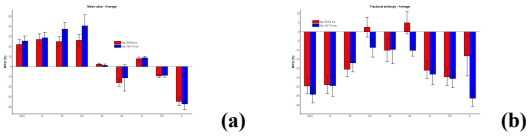
Material and methods

Micro-fragments of a syngenic rhabdomyosarcoma were subcutaneously grafted in both thighs of 10 male WAG/RijHsd rats resulting in 19 analyzable tumors. After reaching a sufficient size for efficient MR imaging (ranging from 1 to 3cm in diameter), rats were anesthetized and embedded within a homemade and individually-tailored alginate mould fitting the inner volume of a 4-channel wrist coil (Sense Wrist Coil, In Vivo Corp, Gainesville, Florida). Acquisitions were performed on a clinical 3T system equipped with 80mT/m gradients (Achieva 3T, Philips Health Care, Best, The Netherlands). The SE-EPI QSI sequence had diffusion weighting for 16 b-values ranging from 0 to 22 000 s/mm^2 (or equivalently: 16 equidistant q-values in the range 0 – 110 mm^{-1}) and for 6 diffusion gradient directions. Five axial slices of 5mm thickness covering the central area of the tumors were obtained. The in plane resolution was 1.5mm. 2 signal averages and a SENSE-factor of 2 were used. The acquisition time was about 10 minutes. Two acquisitions were performed: one with $\delta/\Delta = 35/54\,ms$ (i.e. gradient duration/diffusion time) (TE=110ms) and one with $\delta/\Delta = 16/113\,ms$ (TE=150ms). Immediately after the completion of the MR procedure, external radiation therapy (RT) was delivered to each tumor (14 Gy in a single dose). A similar MR diffusion protocol was repeated 72 h after RT with re-use of the same mould as for the pre-RT session. Rats were thereafter euthanatized and tumors were excised for histological analysis. Data was processed using a homemade software developed with Matlab (The Mathworks Inc). Data for b=1000 s/mm^2 was used to reconstruct standard ADC images. A mono-exponential fit using all 16 b-values yielded a diffusion coefficient D and a bi-exponential fit yielded Df (fast), Ds (slow) and amplitudes Af (fast) and As (slow). Q-space analysis yielded PDFs for all six directions. The PDFs were characterized by three quantities: the height (RTOP: return to origin probability), the width (FWHM: full width at half maximum) and the excess kurtosis (k). A tensor analysis of the different quantities enabled the generation of mean value (trace/3) and fractional anisotropy (FA) maps for each diffusion parameter. To study the effect of RT on the tumours, a texture analysis was performed for the maps corresponding to the central slice through the tumours on pre- and post-RT examinations. The selected region of interest (ROI) was the whole cross-sectional area of the tumour. For these ROIs, the following quantities were calculated for all diffusion-related parameters: average, standard deviation (i.e. contrast), skewness, uniformity and entropy. The relative differences between pre- and post-RT examinations were also calculated for all quantities. A global value for all tumours was expressed in terms of the mean (MRD: mean relative difference) and of the error on the mean. Significance of the differences in MRD was assessed using the Wilcoxon signed rank test for paired data. Significance level was thresholded at 5 %.

Results and discussion

All diffusion maps (mean value) delineated more or less the same contours of radiation-induced necrosis. Delineation was less sharp on slow ADC and kurtosis maps because they were more susceptible to noise. Changes in anisotropy delineated different regions affected by irradiation: they did not correspond to those revealed by mean values. Only but for kurtosis maps, a crude correspondence was observed. The effect of irradiation on the diffusion parameters is shown in Figure 1. The MRDs revealed the expected changes due to irradiation of the tumours: the different diffusion coefficients increased, the amplitude of the fast component increased, and for the PDFs, the FWHM increased and the RTO-probability and kurtosis decreased. These changes were all compatible with the less restricted diffusion resulting from the presence of necrosis and oedema. Because the PDF was normalized, the height and width were inversely related. The comparison of the MRDs revealed that the different diffusion coefficients and the kurtosis were the most sensitive parameters to radiation-induced tissue changes. The use of a sequence with shorter δ and longer Δ leaded to some significant changes in the diffusion parameters themselves (e.g. the width w increased from 20 to 30 μm due to the effects of the finite duration of the diffusion encoding gradients). However, only the MRDs for the classical and fast ADC changed significantly. As a result most parameters did not take advantage (with respect to sensitivity) of a change in δ/Δ . Fractional anisotropy (average) decreased after RT, again consistently with the presence of necrosis/edema. Almost all parameters exhibited high sensitivity. Note that kurtosis benefited from changing δ/Δ (significant differences were found for parameters very sensitive to restriction: the slow component and kurtosis). The contrast of the mean values increased after RT, thereby reflecting the appearance of necrotic tissue which modified the uniformity of the ROIs. For kurtosis, contrast decreased: this can be explained by the transition from a noisy ROI to a ROI with increased homogeneity. Best contrast was obtained for the diffusion coefficients and the width of the PDF. Changing δ/Δ decreased the contrast at first visual evaluation but the differences were not significant. Contrast in fractional anisotropy decreased for parameters obtained from ADC and QSI analysis. The other texture parameters (skewness, uniformity and entropy) did not yield additional information.

In conclusion, our study shows that diffusion coefficients (obtained from 2 b-factors, mono- or bi-exponential fits) were very sensitive to radiation-induced tissue changes in an experimental model. Q-space analysis yielded at least the most sensitive parameter: the excess kurtosis of the PDF. A tensor analysis indicated that the mean value and anisotropy of the tensors allowed the delineation of different sub-areas within irradiated tumors, thereby offering additional tissue information of which clinical relevance requires further investigation in human cohorts of irradiated patients.



(a) **(b)**

Figure 1: Bar diagram for the MRDs of the diffusion related parameters obtained with the two diffusion sequences. Here the texture parameter "average" is displayed. The error bar represents the error on the mean. **(a)** : mean values of the tensor, **(b)** : fractional anisotropies.

References: **(1)** S.E. Maier et al, Magn. Reson. Med., 51(2), 321-330 (2004)**, (2)** Y. Assaf et al, Magn. Reson. Med., 47(1), 115-126 (2002)
(3) D. Rommel et al, Proc. Intl. Soc. Mag. Reson. Med. 17 (2009), 4152