Diffusion-weighted MRI detects early treatment response after antivascular therapy of prostate tumors

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Purpose: Prostate cancer is the commonest malignancy in the aging male population. Currently change in tumor size is used to assess tumor response to chemotherapy. This, however, is a late tumor response assessment and valuable time may be lost before switching to alternate therapies. There are various protocols to treat the non-operable prostate tumor patient. One such treatment is to target tumor vasculature. The purpose of our study is to image early tumor response to antivascular therapy, using diffusion weighted MR imaging. Changes in diffusion precede changes in tumor size. Therefore its assessment could save valuable time in patient management.

Methods: DU-145 prostate tumor cells were inoculated subcutaneously in the flank of SCID male mice (n=17). 10^6 tumor cells were inoculated in 0.05 ml of inoculum. After 6 weeks post inoculation, volume matched tumors ranging from 0.5 to 1.2 cm in diameter were imaged pre treatment and 24h, 48h and 72h post i.v. treatment with 200mg/kg of the antivascular agent ZD6126 (AstraZeneca, UK). For diffusion measurements, a diffusion weighted spin echo sequence was applied (TE 40ms, TR 1500ms, NEX 1, slice thickness 1mm, 7-10 slices, FOV 1.2 x 1.2 to 1.6 x 1.6 cm with 5 b values ranging from 0, 200, 400, 500 to 800 sec/mm^2). All measurements were performed on a Bruker 11.7T Avance system with a 150 G/cm triple axis gradient set. ADC maps were calculated for each slice of the tumor using ImageJ (NIH, Bethesda, MD). The tumor histograms were analyzed using thresholding. An ADC value $\geq 0.9\ 10^{-3}$ mm^2/sec was used to indicate the threshold value for areas of increased water diffusion in necrotic areas from solid viable tumor tissue. The diffusion data were compared to histology at various time points. All tumors were excised at the end of the study and stained with hematoxylin and eosin. Percent necrosis in the histology sections was evaluated using the Chalkley method (1).

Results: Post i.v. antivascular treatment, histological analyses showed significantly increased necrosis in the treated group (58% ±7.5 SE, n=10) compared to the control group (23.9% ± 9.0 SE, n=7, p=0.01). Representative diffusion images of a responding tumor together with the corresponding hematoxylin and eosin stained section from this tumor are shown in Figures 1a-c. Two of the treated tumors showed more than 50% necrosis pre-treatment in MR diffusion images and were excluded from the treatment response calculations but were included in the imaging versus histology correlation. Three tumors did not respond to antivascular therapy as detected by MR imaging which was confirmed by histology. Therefore these three tumors were also excluded from the treatment response calculations. 24h post treatment, there was a trend toward restricted diffusion (decreasing % of ADC value $\geq 0.9\ 10^{-3}$ mm^2/sec) compared to the pretreatment diffusion values. By 48h and 72h post treatment, there was a significant increase in the percentage of ADC values $\geq 0.9\ 10^{-3}$ mm^2/sec compared to the pretreatment measurements (p=0.02 48h and p=0.02 72h, Figures 1 and 3, n=7 control, n= 5 treated). A significant linear correlation was observed between the percentage of ADC values $\geq 0.9\ 10^{-3}$ mm^2/sec with the amount of necrosis in the histological sections at 48h and 72h post treatment, as evaluated by the Chalkley method (r=0.91, p<0.001, Fig. 2).

Conclusion: These results are consistent with previous studies on dynamic contrast MR imaging demonstrating significant increases of tumor necrosis following treatment with ZD6126 (2). Here we have shown that diffusion weighted MR imaging is useful in monitoring early response to treatment with ZD6126 in our prostate cancer animal model and may be a valuable method to monitor patients with prostate cancer or other tumors post antivascular therapy.

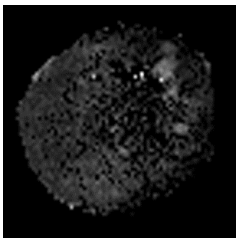

Figure 1a : ADC map of a Du-145 tumor (92 mm^3) pre ZD6126.

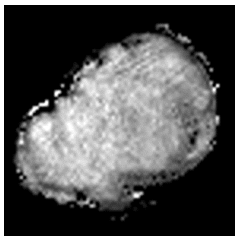

Figure 1b: ADC map of the tumor (89 mm^3) in Fig.1a 48 h after drug treatment.

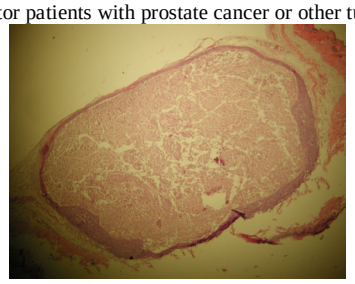

Figure 1c: H&E stained section obtained from the treated tumor in Fig.1b showing extensive necrosis, consistent with the significant increase of ADC in this tumor.

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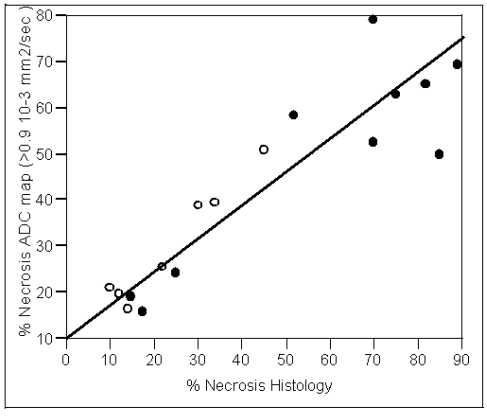

Figure 2: Correlation between %Necrosis ADC versus % necrosis with histology for (O)control tumors, and (●) tumors treated with ZD6126

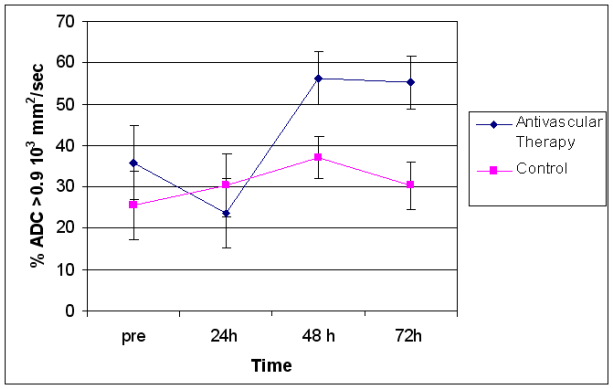

Figure 3: Changes in ADC following treatment with ZD 6126.

References:

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