

# Can Diffusion-Weighted Imaging Detect Antihormonal Resistance in Patients with Prostate Cancer Bone Metastases?

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## Target Audience

MR physicists, radiologists and oncologists interested in oncologic imaging, in particular monitoring of treatment response to antihormonal treatment.

## Purpose

Previous work has shown that diffusion-weighted imaging (DWI) allows monitoring treatment response to androgen deprivation in prostate cancer bone metastases<sup>1</sup>. Thereby, it was observed that significantly decreased prostate specific antigen (PSA) values in responders at 1 month after treatment onset correlate with increased mean apparent diffusion coefficients (ADCs) across the lesions as well as high tumor volume fractions with significantly increased ADCs on functional diffusion maps (fDMs). The aim of the present work is to determine whether this approach also permits detecting onset of antihormonal resistance after long duration of antihormonal therapy.

## Methods

**Study Population:** The study was approved by the institutional review board and informed written consent was obtained from all patients. Eight men (mean age, 73 years; range, 66 – 86 years) with pathologically proven prostate cancer and a total of 18 metastases were included. All bone metastases were confirmed by diagnostic skeletal scintigraphy. No patient had undergone antihormonal treatment or other therapies before enrolment in the study.

**Data Acquisition:** MRI was performed within two days before start of androgen deprivation and repeated at 1, 2, and 3 months after treatment begin. Thereafter, MRI was completed every 4 months until antihormonal resistance was detected or over a maximum period of 31 months. Antihormonal resistance was considered to be present when the PSA value increased by more than 50% relative to the value at 1 month and/or new metastases were detected. Axial anatomical imaging was performed on a 1.5 T MR scanner (Achieva, Philips Healthcare, Best, the Netherlands) together with DWI, using 5 b-values ranging from 0 to 800 s/mm<sup>2</sup>.

**Data Analysis:** Data analysis was implemented in Matlab (The Mathworks, Natick, MA, USA). Eddy current-induced image warping was corrected<sup>2</sup> and ADC maps computed. Regions of interest across all metastases of each patient were defined on the pretreatment ADC maps and mean ADCs at each time point calculated. Thereby, diagnostic information of the skeletal scintigrams and the conventional MR images was taken into account. For fDM analysis each posttreatment ADC map was coregistered to the corresponding pretreatment ADC map<sup>3</sup>. Assuming unchanged ADCs under therapy, the significance thresholds for the fDMs were determined for each patient in pelvic gluteal muscle tissue using one-way analysis of variance (ANOVA) over all time points<sup>1</sup>. Furthermore, a cluster size threshold was set<sup>1</sup>. In doing so, the percentage of voxels that showed a significant increase (red voxels), a significant decrease (blue voxels) or no change (green voxels) in their ADCs at each posttreatment time point relative to the pretreatment values was computed for every lesion (see Figure 1). For statistical analysis, mean ADCs and the percentages of red and blue voxels were then calculated on a per-patient basis for each time point as the weighted mean according to the size of each metastasis in the patient.

**Statistical Analysis:** Statistical analysis was performed using SPSS (IBM Corporation, Armonk, NY, USA). Starting at 1 month after treatment onset, timecourses of the mean ADCs and of the percentages of red and blue voxels were analyzed using repeated measures ANOVA. Occurrence of antihormonal resistance was entered as between-subjects factor. The last time point in the analysis corresponded either to the time point of detection of antihormonal resistance or 31 months, in patients resistant and non-resistant to antihormonal therapy, respectively.

## Results

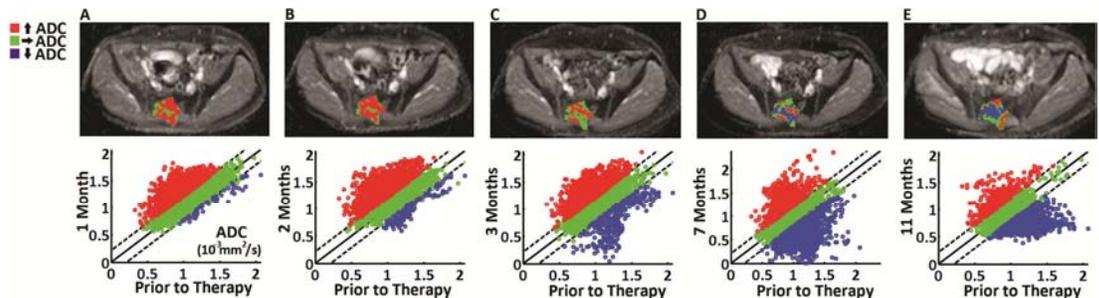
Starting at 1 month after treatment begin, repeated measures ANOVA showed a significant decrease of the mean ADCs ( $p = 0.016$ ) over time (see Figure 2a). Analysis of the fDM timecourses showed that the percentage of red voxels decreased ( $p = 0.004$ ) while the percentage of blue voxels increased ( $p = 0.014$ ) simultaneously (see Figure 2b). No significant differences between resistant and non-resistant patients were observed. However, Figure 2b illustrates that the percentage of red voxels was lower ( $p = 0.151$ ) in resistant than in non-resistant patients. Moreover, the percentage of blue voxels in resistant patients increased more rapidly ( $p = 0.087$ ) over time.

## Discussion and Conclusion

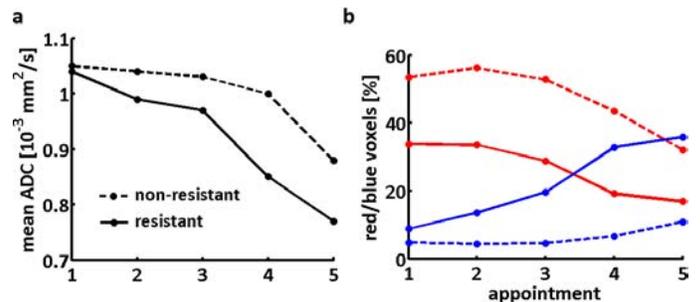
The present study indicates that mean ADCs and fDMs permit detecting onset of antihormonal resistance in patients suffering from prostate cancer bone metastases. Starting at 1 month after begin of androgen deprivation, the results show that decreasing ADCs are observed. Probably due to the small number of patients, statistical significant differences between resistant and non-resistant patients were not reached. However, the results indicate that a rapid increase of the percentage of blue voxels might precede onset of antihormonal resistance (see Figure 2). This preliminary work needs to be validated in future studies including larger patient cohorts.

## References

<sup>1</sup>Reischauer C, Froehlich JM, Koh DM, et al. Bone metastases from prostate cancer: assessing treatment response by using diffusion-weighted imaging and functional diffusion maps-initial observations. *Radiology*. 2010;257(2):523-531. <sup>2</sup>Netsch T, van Muiswinkel A. Quantitative evaluation of image-based distortion correction in diffusion tensor imaging. *IEEE Trans Med Imaging*. 2004;23(7):789-798. <sup>3</sup>Nestares O, Heeger DJ. Robust multiresolution alignment of MRI brain volumes. *Magn Reson Med*. 2000;43(5):705-715.



**Figure 1:** Example of fDMs defined at a single level through one lesion superimposed onto the corresponding ADC map (first row) and scatterplots of pretreatment versus posttreatment voxel ADCs over the entire tumor (second row) at **A:** 1 month, **B:** 2 months, **C:** 3 months, **D:** 7 months, and **E:** detection of antihormonal resistance (11 months) after commencement of therapy. The percentage of red voxels decreased while the percentage of blue voxels increased over time.



**Figure 2:** Timecourses of **a:** the mean ADCs and **b:** the percentages of red and blue voxels averaged over the resistant patients (solid lines) and the non-resistant patients (dashed lines). The percentage of red voxels was lower and the percentage of blue voxels increased more rapidly over time in resistant than in non-resistant patients.