# EVALUATION OF DIFFUSION-WEIGHTED IMAGING AS A PROGNOSTIC BIOMARKER IN CASTRATION RESISTANT PROSTATE CANCER WITH BONE METASTASES

Raquel Perez-Lopez[1,2], Matthew D. Blacklegde[1], David Lorente[1,2], Ulrike Naumann[1], Joaquin Mateo[1,2], Thian Yiliang[2], Zaki Ahmad[2], David J. Collins[1], Martin O. Leach[1], Gerhardt Attard[1,2], Johann S. de Bono[1,2], Dow-Mu Koh[1,2], and Nina Tunariu[1,2]

[1]*The Institute of Cancer Research, Sutton, Surrey, United Kingdom,* [2]*The Royal Marsden NHS Trust, Sutton, Surrey, United Kingdom*

**AUDIENCE:** This study would be of interest to radiologists and clinicians involved in diagnosis and response assessment of advanced prostate cancer.

**BACKGROUND:** Prostate cancer is the second most common cancer in men in the Western World. Due to the high incidence of bone involvement in metastatic castration-resistant prostate cancer (mCRPC) patients, which is poorly characterized by standard imaging techniques currently available, response assessment to anticancer therapies for these patients remains an unmet medical need. Previous studies have demonstrated high sensitivity for diffusion-weighted imaging (DWI) in the diagnosis of bone metastases in patients with prostate carcinoma[1]. Limited data are available regarding the role of DWI as a response biomarker for metastatic bone disease [2-4]. This study aimed to determine if quantitative variables derived from DWI could serve as prognostic biomarkers in CRPC.

**HYPOTHESIS:** We hypothesized that volume of bony disease, quantified by DWI assessment, is a prognostic biomarker of overall survival with mCRPC.

**METHODS:** This is an observational, retrospective study conducted under institutional research ethics committee approval. We included mCRPC patients from a single institution with whole body DW-MRI performed between June 2010-October 2012 (with at least one year of follow-up). MRI was performed on a 1.5-T Siemens Avanto (Siemens). Single-shot twice-refocused diffusion-weighted echo planar images in a transverse plane and 4 stations were acquired covering from vertex to mid thighs with the following parameters: 14000/68/180ms TR/TE/TI; 380-420mm FOV, 5mm slice thickness, three orthogonal diffusion directions and b-values of 50 and 900 s/mm$^2$ with Inversion Recovery fat saturation with 4 averages. Mono-exponential ADC maps were generated using Siemens system software. Images were processed and analyzed with open-access imaging assistant software (Osirix v5.6). Regions of interest (ROIs) including all the areas of signal abnormality in keeping with bone metastatic disease observed between C2 and mid thighs were drawn. Histograms representing ADC values of the ROI for each patient were generated using Microsoft Excel 2010. Data obtained from the MRI assessments, as well as clinical and demographic characteristics were collected onto an anonymized database. Overall survival, defined as time from performing the MRI to death by any cause, was correlated with key MRI parameters including: overall volume of disease (calculated multiplying the number of pixels by the pixel volume in each case accounting for differences in the size of the field of view), ADC values (median, mean, distribution) and volume of disease according to pre-specified bins of ADC values to differentiate active disease[5]. Kaplan-Meier estimates were used to assess each pre-specified bin survival. Cox regression was used to investigate the prognostic value of the different variables in univariate and multivariate analyses. SPSS software was used for statistical analyses.

**RESULTS:** Thirty-nine patients receiving treatment for mCRPC had DW-MRI scans within the defined time period; 33 patients were included in this analysis: 11 patients (33%) with metastatic disease limited to bone and 22 patients (66%) with nodal and/or visceral disease in addition to bone metastases. The remaining 6 cases were not analyzed, as they had no bone involvement. Median overall survival (OS) of the population was 15 months (SD 3,2 months). Median ADC value of the ROIs for each individual was 950 µm$^2$/s (SD 174 µm$^2$/s) with a median volume of bony disease of 832ml (range 56-2242 ml). Histograms of the ADC values for each patient and the whole population are illustrated in **figure 1**. A significant correlation between the volume of bone disease and OS was observed (HR 1.99, p 0.016). The volume of disease quantified by DW-MRI also correlated with variables commonly used in clinical practice including the bone turnover biomarker alkaline phosphatase. Correlation with survival was stronger for volume of disease with ADC values between 750-1450 µm$^2$/s (HR 2.24, p 0.028). Survival was significantly higher for those patients with less than 500ml of bone disease in the 750-1450 µm$^2$/s bin of ADC (**figure 2**). Volume assessment of selected ROIs with ADC values below 750 µm$^2$/s has no prognostic significance.

**DISCUSSION:** The volume of bony metastatic involvement with ADC values 750-1450 µm$^2$/s, which is likely to represent active disease, correlated strongly with overall survival from CRPC and was a stronger prognostic biomarker than overall disease volume measures, which were also prognostic. This is to our knowledge the first time that parameters derived from DWI of bone metastasis have been shown to have prognostic value, supporting further development of this functional imaging technique in the assessment of patients with metastatic prostate cancer. Studies are now ongoing to confirm these results with a validation set.

**CONCLUSION**: Assessment of bone metastases from prostate cancer by DWI provides valuable information on outcome from advanced CRPC patients.

**REFERENCES: 1.** Gutzeit A et al. Skeletal Radiology. April 2010, Vol 39, Issue 4, 333-343. **2.** Reischauer C, et al. Radiology 2010; 257:523–531. **3.** Messiou C, et al. Eur Radiol 2011; 10:2169–217 **4.** Horger M, et al. AJR 2011; 196:1373. **5.** Padhani AR, et al. AJR 2013 Jan;200(1):163-70.

**ACKNOWLEDGEMENTS:** CRUK and EPSRC Cancer Imaging Centre in association with MRC and Department of Health (England; grant C1060/A103334), NIHR funding to the Clinical Research Facility in Imaging and the Biomedical Research Centre.

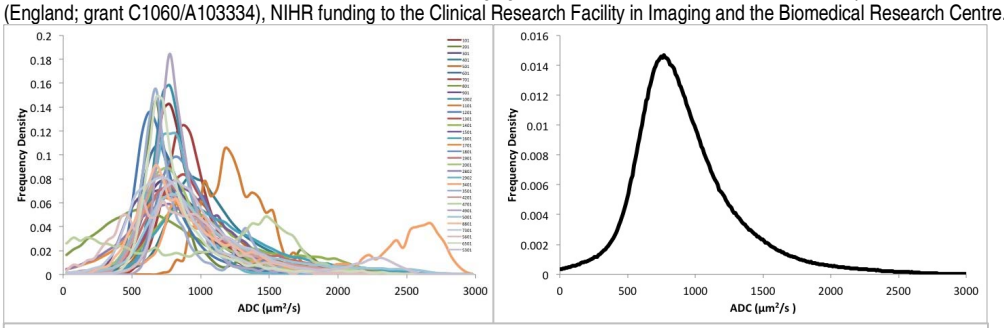


**Figure 1.** Histogram representation of ADC values for selected ROIs in each patients (left) and whole population (right)

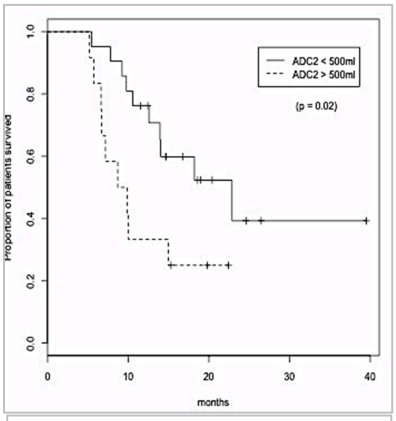


**Figure 2.** Kaplan-Meier curve for volume of disease with ADC 750-1450