Towards clinical qualification of whole-body diffusion-weighted MRI in patients with metastatic castration resistant prostate carcinoma with bone metastases.

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Purpose

To clinically qualify whole-body diffusion-weighted imaging (DWI) for assessment of prostate cancer bone metastases.

Preliminary data

1. Multiparametric MRI with DWI correlates with bone biopsies histological parameters. Methods: we reviewed 43 consecutive bone biopsies from 33 CRPC patients and DWI within 12-weeks before bone biopsy. Also included 10 patients with DWI and no bone metastases. Differences in DWI between bone biopsy positive/negative for tumor cells were assessed using Mann-Whitney tests. Correlations between DWI and cellularity were assessed using Spearman's correlation (*r*). Results: mADC in bone metastases and non-metastatic bone was $993x10^{-6}mm^2/s$ vs $601.8x10^{-6}mm^2/s$, median normalized (n) nDWI signal was 4 AU vs 1.6 AU; $p<0.001$. There was a significant inverse correlation of ADC and positive correlation of nDWI signal with tumor cellularity; $p<0.001$.
2. Volume of bone metastases by whole-body DWI is a prognostic biomarker in patients with CRPC. Methods: we reviewed 43 consecutive patients with whole-body DWI at baseline. Total volume of bone metastases by DWI (tDV) was correlated with established prognostic factors for CRPC using *r*. Survival was assessed with Kaplan-Meier analysis. Results: tDV correlated with all prognostic factors for mCRPC (hemoglobin: $r=20.521$; $p<0.001$; prostate-specific antigen: $r=0.556$; $p<0.001$; lactate dehydrogenase: $r=0.534$; $p<0.001$; alkaline phosphate: $r=0.572$; $p<0.001$) and CTC count ($r=0.613$; $p=0.004$). tDV was associated with overall survival (hazard ratio: 1.74; 95% CI: 1.02, 2.96; $p=0.035$).
3. Changes in whole-body DWI are indicators of response in prostate cancer bone metastases. Methods: 21 patients within the TOPARP trial in CRPC patients underwent whole-body DWI at baseline and after 12-weeks. Association between tDV and median apparent diffusion coefficient (mADC) changes and binary response to treatment was assessed using logistic-regression. Results: change in tDV and mADC at 12-weeks associated with response to therapy ($p<0.01$, $p=0.04$ respectively).

On-going research

A phase II multicenter clinical study of whole-body DWI in CRPC patients with bone metastases aiming 1) to identify and validate ADC percentage change as response biomarker to abiraterone/enzalutamide; 2) to explore early ADC changes (after 4 weeks of treatment) and radiomics signatures as biomarkers of response and resistance to abiraterone/enzalutamide; 3) to use DWI for guiding tumor bone biopsies in order to identify subclonal resistance to abiraterone/enzalutamide and study tumor evolution.

Stage 1 of the study will investigate the optimal cut-off point for percentage ADC change (ΔμADC) as an indicator of response. In the Stage 2 we aim to validate the ΔμADC. A sample size of 69 patients to be treated with abiraterone or enzalutamide is required in Stage 1. The sample size for Stage 2 will be calculated based on emerging data from Stage 1.

First site of the study activated, Vall d'Hebron University Hospital, September 2018.

Conflicts of Interest: The authors have no conflicts of interest to disclose.

Acknowledgements: Supported by BRC (BRC A38), Stand Up to Cancer (SU2C- AACR-DT0712), ECMC funding from Cancer Research UK and Dept of Health (CRM064X), Cancer Research UK (C12540/A12829, C12540/A13230, C1491/A15955, C1491/A9895), CRUK and EPSRC in association with MRC and Dept of Health (C1060/A10334, C1060/A16464), Prostate Cancer UK (PG14-016-TR2), Prostate Cancer Foundation (20131017). R.P.L., J.M., D.O. and E.C. supported by PCF Young Investigator Awards.