Diffusion Weighted MRI for Early Detection and Progression Monitoring of Prostate Cancer in a Transgenic Mouse Model

Deborah K. Hill[1,2], Eugene Kim[1,2], Jose R. Teruel[1,2], Siver A. Moestue[1,2], and Tone F. Bathen[1]

[1]*Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Sør Trøndelag, Norway,* [2]*St. Olavs University Hospital, Trondheim, Sør Trøndelag, Norway*

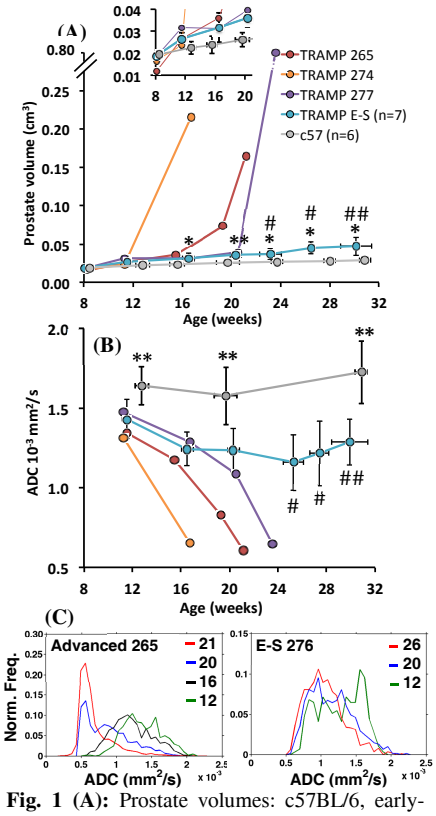

Fig. 1 (A): Prostate volumes: c57BL/6, early-stage (E-S), advanced (individual mice). Insert at top shows detail of prostate volume 8-20wks. **(B)** Whole prostate ADCs calculated using all b-values. Owing to E-S mice termination: # n=6, ## n=5. *p<0.05, **p<0.005, E-S TRAMP and c57 prostate. (**C**) ADC histograms from advanced and E-S TRAMP prostates; legend is mouse age (weeks).

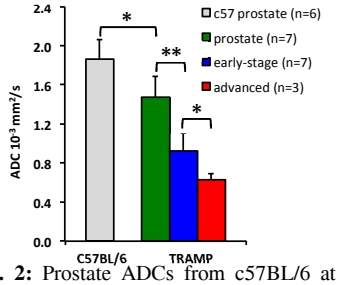

Fig. 2: Prostate ADCs from c57BL/6 at 30 weeks old, and TRAMP mice at termination. *p<0.05, **p<0.005.

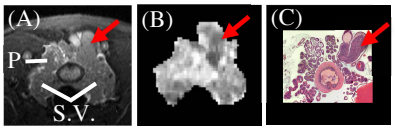

Fig. 3: (A) T2W image of a TRAMP prostate at 26 weeks. Prostatic tissue (P), and seminal vesicle (S.V.) are indicated. The ADC map (**B**) clearly contains a region of low ADC, suspected to be onset of PCa, which was validated with histology (**C**).

Target Audience: Preclinical and clinical researchers in the field of prostate cancer.

Introduction: Prostate cancer (PCa) is the most common malignancy among men in the USA and Europe, and constitutes a substantial healthcare problem. Effective PCa management would identify and treat patients with aggressive disease, but avoid over-treating less aggressive cases [1]. Early detection of PCa gives the opportunity for disease development to be monitored and helps to determine the best course of treatment. The Apparent Diffusion Coefficient (ADC) of tumour and tissue water, derived from diffusion-weighted (DW) MRI, has been shown to correlate with Gleason score, a histological measure of PCa aggressiveness, and indicates risk in patients [2].

In this study the effectiveness of DW-MRI for both detecting early onset of PCa and for characterising disease progression was investigated for the transgenic adenocarcinoma of the mouse prostate (TRAMP) model. The TRAMP model is widely used in chemoprevention and therapy response studies, yet disease progression is frequently assessed with inadequate methods (palpation or genitourinary (GU) weight). The MRI protocol described in this study will greatly aid longitudinal research projects in TRAMP mice.

Methods: TRAMP (n=10) and control (n=6) mice from the same genetic background (c57BL/6) were monitored by MRI every 4 weeks from 8 weeks of age. TRAMP mice were screened for cancer onset using high-resolution T_2-weighted (HR T2W) images and ADC maps obtained from DW-MRI; once cancer onset was suspected, scanning was performed every 1-2 weeks, and mice were terminated when tumour formation was detected (early-stage group) or when there was a large tumour present (advanced group). c57BL/6 controls were terminated at 30 weeks of age. Upon sacrifice, the GU tract (prostate, seminal vesicles, bladder) was dissected, weighed, and formalin-fixed for histological analysis (hematoxylin, eosin and saffron staining). MRI was performed on a 7T Bruker Biospec magnet with an 86mm diameter volume resonator for RF transmission and a quadrature mouse heart surface coil for reception. **DWI** was performed using a multi-shot EPI sequence: TE=28.5ms, TR=3000ms, averages=4, matrix size=128x128, slice thickness=0.99mm, in plane resolution 0.2x0.2mm^2, and b-values=0, 100, 200, 400, 800 s/mm^2 along three orthogonal gradient orientations. **HR T2W** images were acquired using a RARE spin echo sequence: TE=36ms, TR=5500ms, rare factor=4, averages=10, matrix size=256x192, slice thickness=0.33mm, in plane resolution 0.1x0.1mm^2. **Prostate volumes** were assessed by manually drawn ROIs from T2W images using OsiriX. **Diffusion analysis:** ADC histograms and median values were calculated for the entire prostate using all b-values. ROIs of suspicious regions in TRAMP prostates were drawn based on b800 images and ADC maps; for the early-stage group, ADC was also calculated for an area of prostate with normal appearance in the same slice. **Statistics:** Data reported are mean±S and statistical significance between groups was calculated using the Wilcoxson rank sum test.

Results & Discussion: Cancer onset and growth characteristics vary in the TRAMP mice; the average termination age was 28.3±3.6 weeks (early-stage group, n=7) and 20.5±3.5 weeks (advanced group, n=3). **Fig. 1A** shows that TRAMP prostates begin to grow more rapidly than c57BL/6 controls from 8 weeks of age, with the difference approaching statistical significance by 12 weeks (p=0.07), and reaching significance by 16 weeks (p=0.02). ADC values of whole TRAMP prostates were significantly lower than c57BL/6 controls from 12 weeks of age (p=0.001, **Fig. 1B**). Reduced ADC has been linked with increased cellularity [3]; the significant difference between TRAMP and c57BL/6 whole prostate ADCs observed at 12 weeks is likely to be a result of increased cellularity in TRAMP prostates, owing to the formation of prostate intraepithelial neoplasia (PIN) [4], which could later develop to PCa. ADC histograms of the entire prostate display a shift in the distribution towards lower ADC values as cancer progresses (**Fig. 1C**). Histograms appear to be sensitive to distinguishing cancer from prostate tissue, where a bimodal distribution in **Fig. 1C**, 20 weeks, is clearly visible. **Fig. 2** shows that, at termination, median ADC values of c57BL/6 prostate were significantly higher than 'normal' TRAMP prostate (p=0.02); early-stage cancer region ADCs were significantly lower (p=0.0006) than the 'normal' TRAMP prostate tissue regions, and advanced cancer regions had a significantly lower ADC value than early-stage regions (p=0.02). ADC maps provided clearer visualisation of cancer onset than HR T2W images (**Fig. 3**).

Conclusion: DW-MRI facilitated early detection of cancer onset in TRAMP prostates before lesions were seen on HR T2W images, with ADCs of the whole prostate distinguishing TRAMP from c57BL/6 prostates before a significant difference in volume was observed in T2W images. Median ADC values of prostate regions were consistent with literature values for different stages of PCa progression [5], thus providing a non-invasive means to assess cancer aggressiveness. Differences observed between ADC values of whole TRAMP and c57BL/6 prostates at 12 weeks indicate that ADC is sensitive to detection of PIN in TRAMP mice. ADC histograms allowed differentiation between cancer and prostate tissue in TRAMP mice. Our study therefore suggests that DW-MRI represents a valuable tool for detecting and monitoring cancer progression in TRAMP mice.

References: [1] R. Nagarajan *et al. Advances in Urology* (2012), [2] P. C. Albertsen *et al. Journal of the American Medical Association* (1998), [3] D. A. Hamstra *et al. Journal of Clinical Oncology* (2007), [4] V. Jeet *et al. Cancer and Metastasis Review* (2010), [5] R. Sriram *et al. Int. Soc. Mag. Reson. Med.* 4115 (2014).