Investigating the utility of diffusion-weighted imaging (DWI) for monitoring treatment efficacy during MR guided High Intensity Focused Ultrasound (MRgHIFU) therapy in bone applications

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Target Audience: Researchers with interest in MR guided High Intensity Focused Ultrasound (MRgHIFU) in bone applications.

Purpose: MRgHIFU offers a safe and effective treatment option for pain palliation in bone metastases by thermal ablation at the periosteum (1). Thermal monitoring in soft tissue proximal to the focus is achieved using the proton resonance frequency shift (PRFS) method, but visualisation of any induced lesions relies on contrast enhanced T1-W imaging (2). However, Gadolinium-based contrast agents are not recommended during treatment due to potential breakdown of the Gadolinium chelate by HIFU (3); other strategies are therefore needed to monitor intra-interventional lesion formation to estimate treatment efficacy (4). In other studies of response, diffusion-weighted imaging (DWI) has proved useful for assessing tissue damage during therapy (5). This study investigates DWI for monitoring treatment efficacy during MRg-HIFU therapy in bone applications by (i) evaluating repeatability of apparent diffusion coefficient (ADC) measurement, (ii) investigating ADC change after sonication and correlating changes with visualised post-sonication lesions on tissue dissection.

Methods: Ex-vivo studies were conducted using fresh lamb leg samples from a local butcher (n=7) on a 3T Achieva MR / Sonalleve HIFU clinical system (Philips Healthcare, Vantaa, Finland). Each lamb leg was warmed to room temperature and placed in good acoustic contact with a dampened Aquaflex gel-pad (Parker Laboratories Inc, USA) placed over the HIFU window coil, and secured in place using the HIFU pelvis coil. 3D T1-W imaging was acquired and imported into the Sonalleve console for treatment planning. A single shot EPI DW sequence with SPAIR and gradient reversal off-resonance fat suppression was acquired twice consecutively on separate samples using 3 b-values of 0, 100 and 700 s/mm^2 (Δ 32.9ms, δ 6.1ms, TR 6000ms, TE 67ms, TI 116ms, 20 slices, 5 mm slice thickness, no gap, voxel size 3.5x3.55x5 mm, recon 1.48 mm, phase R-L, 2NSA, scan time 2:06 minutes). A series of HIFU treatment cells (4, 8 and 12mm in diameter), with the focus centred on the outer layer of the bone cortex were planned, and PRFS thermometry acquired during sonication. DWI was performed repeatedly up to 120 minutes post sonication. This process was repeated for HIFU cell sizes ranging from 4-12 mm in diameter and at powers ranging from 20-190 W, ensuring that treatment cells were far enough apart to avoid heating of neighbouring cells. T1-W images were also acquired on completion of all sonications in each lamb leg. Images analysed using in-house software had ADC maps calculated by applying a Levenberg-Marquardt (LM) least squares fit to the b=100 & 700 s/mm^2 data. ROIs were drawn on ADC maps at slice positions matched to coincide with heated regions seen on PRFS thermometry (*Figure 1*). Coefficients of variation were calculated. ADC measurements for each cell size at a range of sonication powers were plotted as a time intensity series. A series of 4 and 8mm cells, doubly sonicated at 160W for maximal lesion formation and imaged using DWI and a wide variety of T1- and T2-W sequences acted as a control set for lesion visibility. Lamb legs were dissected on completion of experiments to visualise any tissue damage.

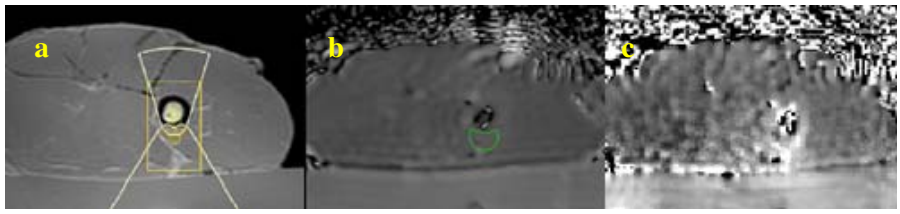


Figure 1: Thermal dose contours applied to a T1W image (a) determined the ROI position on each ADC map (b). Change in ADC after sonication is shown as high signal in the % ADC difference image (c)

Results: ADC changes were observed in soft tissues adjacent to the bone but not in the bone cortex, where lack of signal precludes analysis. The coefficient of variation for repeat baseline ADC measurements was 1.0% (*Figure 2*). ADC time intensity series for 12, 8 and 4 mm cells at a range of powers up to the maximum possible for that cell size are shown in *Figure 3*. After 20mins ADC changes were stable up to 2 hours post sonication. The doubly sonicated control cells resulted in ADC increases of approximately 20%, which were sustained 30 minutes after sonication and always produced visible lesions in dissected soft tissues *(Table1, Figure 4)*. At a power of 80W there was a peak change in ADC of 20% with 12mm cells, 15% with 8mm cells and 7% with 4mm cells. At a power of 60W, however, changes in ADC were 10-12% regardless of cell size. Similarly, at 20W, ADC changes were 5% regardless of cell size. In no instance were any lesions visible on T1- or T2-W sequences. For single sonications, dissections showed that lesions were consistently induced at powers of ≥120 W, were occasionally seen at 80W and were not seen at ≤ 60W.

Figure 2: Bland-Altman plot showing repeatability of the ADC measurement

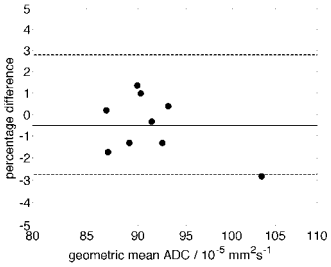
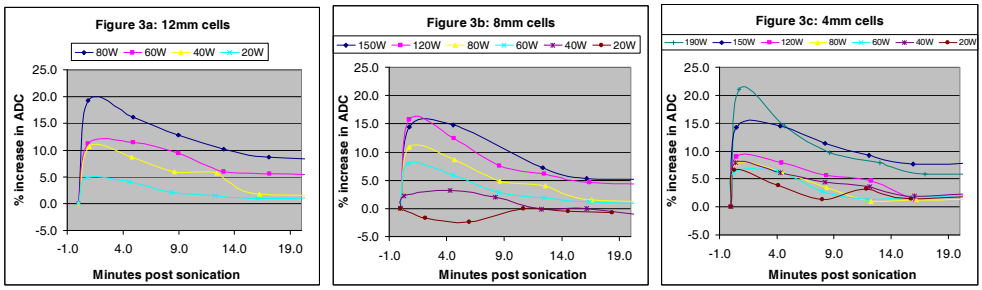


Figure 3: Percentage increase in ADC over time for (a) 12mm, (b) 8mm, (c) 4mm cells at a range of powers from 20-190W

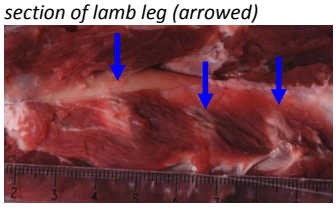


Discussion and Conclusions: ADC measurements were highly repeatable. For all cell sizes, the percentage of ADC change increased with increasing power, peaking 2 mins after sonication and reducing by half by 20mins, after which changes were stable. The initial large increases in ADC can probably be explained by the temperature dependence of ADC (6), but the sustained increase 20 minutes after sonication suggests that tissue changes have occurred, which standard T1- and T2-W imaging was not able to detect. A sustained 20% increase in ADC produced visible tissue damage, but difficulties in dissecting the lamb legs accurately led to uncertainty regarding the cut-off ADC change at which lesions were seen. The short duration of the DW sequence means that it can be acquired between sonications without impacting total HIFU treatment time, but further in-vivo studies are required to establish thresholds for predicting onset of damage more accurately.

Cell	Time after sonication (mins)	% increase in baseline ADC
1	8.8	20.1
2	13.1	20.6
3	27.4	21.5
4	30.6	18.9

Table 1 showing sustained increase in ADC 30 minutes after double sonication at 160W (control cells).

Figure 4 showing 3 lesions on this section of lamb leg (arrowed)



References: (1) Hurwitz et al, 2014, JNCI, 106(5); (2) Jenne et al, 2012, Z. Med. Phys 22:311-322; (3) Ikink et al, 2014, Eur Radiol 24(9):2118-27; (4) Trumm et al, 2013, Radiologe 53(11):1001-8; (5) Chen et al, 2008, MRM 59:1365-72; (6) Le Bihan et al, 1989, Radiology 171:853-7

Acknowledgements: CRUK and EPSRC support to the Cancer Imaging Centre at ICR and RMH in association with MRC & Dept of Health C1060/A10334, C1060/A16464 and NHS funding to the NIHR Biomedicine Research Centre and the Clinical Research Facility in Imaging. We would also like to acknowledge support from the Focused Ultrasound Foundation (FUSF) and Philips Healthcare through the FUSF Centres of Excellence programme.