

## Assessing thermal damage using Dynamic Contrast Enhanced MRI

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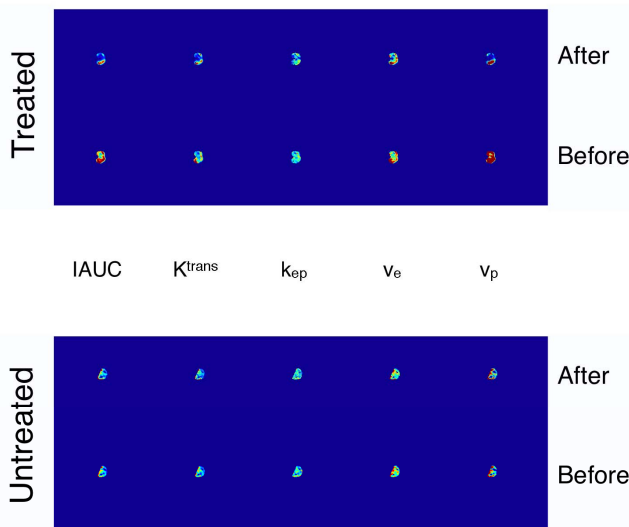
**Introduction:** Dynamic contrast-enhanced MRI (DCE-MRI) is traditionally applied within tumor studies for evaluation of vascular disrupting therapies. In addition to causing direct cancer cell death hyperthermia is known to cause vascular damage as well as being a potent enhancer of radiotherapy even at thermal doses which themselves do not affect tumor growth. MRI-guided focused ultrasound (FUS) facilitates hyperthermic treatment inside the MRI-scanner making it feasible to compare DCE-MRI measurements before and after hyperthermia.

**Aim:** The aim of this study was to evaluate regional tumor perfusion response to FUS-induced hyperthermia using DCE-MRI, and subsequently evaluate the anti-tumor effect of varying heat doses.

**Methods:** A C3H mammary carcinoma was grown subcutaneously in the rear right foot of female CDF1-mice and treated when a volume of 200 mm<sup>3</sup> was reached. Mice were anaesthetized and loosely constrained in specially constructed perspex jigs. Two DCE-MRI measurements separated by 45 min were performed on either hyperthermia-treated or untreated animals. Prior to each DCE-MRI acquisition, a parametric map of the longitudinal relaxation time (T1) was measured using the Look-Locker sequence. DCE-MRI was performed using a similar orientation and image parameters as in the T1 measurement and a temporal resolution of 7 s. Analysis of DCE-MRI data was performed using an ROI of the entire tumor. Parametric T1 maps were employed to convert from signal intensities to contrast agent concentrations. Two sets of parameters were inferred from the data: 1) the integrated area-under-the-curve (IAUC), and 2) parameters obtained from fitting the DCE-MRI data to Tofts kinetic model: the volume transfer constant,  $K^{trans}$ ; the rate constant,  $k_{ep}$ ; blood plasma volume fraction,  $v_p$  and the extracellular volume fraction,  $v_e = K^{trans}/k_{ep}$ . Hyperthermia using an in-house constructed small animal system integrated with a 1.5 T clinical system (Philips Medical Systems, Best, The Netherlands) and was performed as a 60 sec exposure at a acoustic power density of 0.27 W/cm<sup>2</sup> commenced 10 min after the first DCE-MRI measurement. The anti-tumor effect of either 60 sec or 180 sec exposure at the same power density as above was assessed by measuring the time taken to grow from 200 mm<sup>3</sup> to 1000 mm<sup>3</sup> (TGT5).

**Results:** When DCE-MRI parameters were compared between scans for untreated animals no significant change was observed, yielding changes (defined as before value – after value and represented with 95% confidence intervals) of  $\Delta IAUC = 0.86$  mM s [-1.38 : 3.10],  $\Delta K^{trans} = 0.06$  ms<sup>-1</sup> [-0.13 : 0.25],  $\Delta k_{ep} = 0.38$  ms<sup>-1</sup> [-0.86 : 1.62],  $\Delta v_e = 3.66 \times 10^{-3}$  % [-11.95 : 19.27] and  $\Delta v_p = 3.74 \times 10^{-3}$  % [-3.58 : 11.06], confirming that inferred parameters were stable over the course of the study. In treated animals all parameters significantly decreased following hyperthermia with changes of  $\Delta IAUC = 3.31$  mM s [2.35 : 4.26],  $\Delta K^{trans} = 0.23$  ms<sup>-1</sup> [0.15 : 0.30],  $\Delta k_{ep} = 3.27$  ms<sup>-1</sup> [2.11 : 4.43],  $\Delta v_e = 24.65 \times 10^{-3}$  % [2.12 : 47.19] and  $\Delta v_p = 12.94 \times 10^{-3}$  % [7.60 : 18.27]. When change in parameter was compared between treated and untreated the change was significantly greater in the treated group for all parameters apart from  $v_p$  as well. Evaluating the same treatment using a growth time assay showed no significant delay in tumor growth. When a 180 sec exposure was applied a small yet significant increase in tumor growth time was observed.

**Conclusions:** DCE-MRI inferred parameters consistently identified heat and FUS induced damage to the tumor vasculature. The applied heat treatments influenced only marginally on tumor growth time. This method will be useful in quantifying heat induced tumor damage when assessing the effect of mild hyperthermia in combination with radiation as a cancer treatment.



**Caption:** Examples of maps of the DCE-MRI derived parameters before and after treatment. Parameter maps show from left to right in each panel:  $IAUC$ ,  $K^{trans}$ ,  $K_{ep}$ ,  $v_e$  and  $v_p$ . Upper panel shows a treated animal, with the first scan (before treatment) in the bottom part of the panel and the second scan (after treatment) in the upper part. The lower panel shows a treated animal with first (before treatment) and second (after treatment) scans arranged as in the former case.