Assessment of Therapy-induced Tumour Necrosis with Magnetic Resonance Elastography

Jin Li1, Yann Jamin1, Craig Cummings1, Jessica K.R. Boul1, John C. Waterton2, Jose Ulloa2, Ralph Sinkus3, Jeffery C. Bamber1, and Simon P. Robinson1
1Division of Radiotherapy & Imaging, The Institute of Cancer Research and Royal Marsden NHS Trust, Sutton, United Kingdom, 2Personalised Healthcare and Biomarkers, AstraZeneca, Alderley Park, Macclesfield, Cheshire, United Kingdom, 3Centre de Recherche Biomédicale Bichat Beaugrenoble, Clichy, France

Introduction:
Assessing drug efficacy at an early stage is important in both oncology drug development and cancer treatment. The current criteria for solid tumour therapy response evaluation based on tumour volume measurements (RECIST) are however limited [1]. One fundamental aim of cancer therapeutics is to induce tumour cell necrosis, which morphologically results in total cell lysis [2]. Our hypothesis is that large-scale changes in tissue morphology induced by necrosis are associated with significant alterations in tissue macroscopic viscoelastic properties. Therefore, measuring changes in viscoelastic properties of tumours with magnetic resonance elastography (MRE) may provide novel imaging biomarkers of treatment response. MRE provides a quantitative non-invasive approach to image the viscoelastic properties of tissue in vivo. The evaluation of MRE/histological correlates, and whether changes in the imaging biomarkers reflect predicted changes in the underlying pathology, is important [3].

Purpose:
To investigate and validate the potential of MR elastography measured viscoelasticity for the provision of imaging biomarkers of therapy-induced tumour necrosis.

Methods:
All experiments were performed in accordance with the UK Animals (Scientific Procedures) Act 1986. SW620 colorectal cancer cells (5x10^6) were injected subcutaneously in the flanks of female NCr nude mice. MRE data were acquired from anaesthetised mice bearing size-matched SW620 xenografts prior to, and 24 hours after, treatment with either 200mg/kg of the vascular disrupting agent ZD6126 (n=4), a dose regime known to induce massive central haemorrhagic necrosis [4], or vehicle alone (n=6). 3D MRE data were acquired with a 7 Tesla Microimaging horizontal MRI system (Bruker Instruments, Ettlingen, Germany), using a spin-echo sequence (TE/TR = 27/1001ms, FOV=15.8mmx15.8mm) modified with sinusoidal motion-sensitizing gradients, synchronized with a continuous 1 kHz sinusoidal wave generated by an electromagnetic shaker (Brüel & Kjaer, Nærum, Denmark), applied directly through a carbon fibre rod to a square piston positioned onto the tumour. Care was taken in positioning the animal so as to acquire MRE data from the same location in the tumour prior to and post-treatment. Maps of the absolute value of the complex shear modulus (|G*|), elasticity G0 and viscosity Gt were reconstructed with an isotropic pixel size of 300μm, and the mean [G*], G0 and Gt determined from a region of interest covering the whole tumour. Diffusion-weighted images were also acquired for determination of tumour ADC [5]. Following the post-treatment scan, tumours were excised, formalin fixed, and paraffin-embedded sections cut and stained with haematoxylin and eosin (H&E) for the histological assessment of necrosis.

Results:
Pre-treatment MRE data revealed a heterogeneous distribution of [G*], G0 and Gt in each SW620 xenograft, in agreement with the tumour heterogeneity and local necrosis shown by the H&E staining. Whilst there was no apparent change in viscoelasticity in the vehicle treated cohort, treatment with ZD6126 resulted in a homogenous reduction in [G*], G0 and Gt across the whole tumour. This was associated with massive central haemorrhagic necrosis (Fig.1). Mean values of tumour volume, [G*], G0 and Gt from the vehicle and ZD6126 treated cohorts are reported in Table 1. There was no significant difference in tumour volume following treatment with either vehicle or ZD6126. Mean [G*], G0 and Gt were significantly reduced in the ZD6126 treated cohort, whilst there was no significant change in any parameters in the vehicle cohort. A non-significant increase in ADC was apparent in both the vehicle and ZD6126 cohorts (Fig. 2).

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<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>ZD6126</th>
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<tbody>
<tr>
<td>Volume (mm^3)</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>408±78</td>
<td>450±77</td>
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<tr>
<td>[G*] (kPa)</td>
<td>5.24±0.27</td>
<td>5.25±0.31</td>
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<tr>
<td>G0 (kPa)</td>
<td>4.30±0.17</td>
<td>4.35±0.19</td>
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<tr>
<td>Gt (kPa)</td>
<td>2.40±0.24</td>
<td>2.38±0.25</td>
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Table 1. Tumour volume, [G*], G0 and Gt (mean ± 1 s.e.m.), prior to and 24 hours after treatment with vehicle or ZD6126 (*p<0.05, **p<0.01, Student’s 2-tailed paired t-test on the pre- and post- values).

Discussion:
All the viscoelastic properties [G*], G0 and Gt showed good reproducibility over 24h in the vehicle cohort. Whilst ZD6126 did not cause a significant difference in tumour volume in vivo, the central necrosis induced caused a significant reduction of absolute value of the complex shear modulus, [G*], i.e. tumour stiffness. A similar response has been previously shown following treatment with another vascular disrupting agent CA4P [6]. The reduction in tumour [G*] preceded any apparent change in ADC.

Conclusion:
Tissue viscoelastic properties, as measured by MRE, provide robust and early imaging biomarkers for the detection of therapy-induced tumour necrosis.

References:

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