Investigating the relationship between the apparent diffusion coefficient and extravascular extracellular volume fraction in patients with vestibular schwannomas undergoing bevacizumab treatment

Ka-Loh Li¹, Sha Zhao¹, Amy Watkins¹, Xiaoping Zhu¹, and Alan Jackson¹

¹Wolfson Molecular Imaging Centre, University of Manchester, Manchester, United Kingdom, ²Imaging, Genomics and Proteomics, University of Manchester, Manchester, United Kingdom

INTRODUCTION

Apparent diffusion coefficient (ADC) measurements have been shown (in well-controlled situations) to have an inverse relationship with tumor cell density [1] and would be expected to correlate with the extravascular extracellular volume fraction (e) measured using DCE-MRI modeling techniques. However, previous studies showed there was no such correlation demonstrated between ADC and e in glioblastoma multiforme [2], breast cancer [3], and primary liver cancers [4]. This indicates that the extravascular extracellular space into which the contrast agent distributes (v_e) is not the only factor affecting the ADC measurements. There are numerous factors that may affect the ADC other than cell density [3,5]. Moreover, many studies have shown that successful treatment is reflected by increases in tumor ADC values, and decreases in tumor v_e values [6]. These changes are also affected by many factors, such as tumor type, the type of treatment administered, and the timing of imaging with respect to the treatment [7]. Investigating these changes will lead to better understanding the two parameters as imaging biomarkers for cancer treatment response. In this contribution, we compare and correlate the two parameters for patients with vestibular schwannomas over the course of bevacizumab treatment.

MATERIALS AND METHODS

DCE-MRI data were acquired from three patients with neurofibromatosis type 2 (NF2) related vestibular schwannomas using a 1.5-T Philips scanner. The patients received four scans: baseline, 2 days, 3 and 6 months post treatment with the anti-vascular endothelial growth factor antibody bevacizumab (Avastin; Genentech). The diffusion weighted echo planar images were acquired with three b values (0, 400, and 800 s/mm²). A newly developed Dual Injection DCE-MRI technique that provides high spatial resolution 3D pharmacokinetic maps (voxel size 1.0 x 1.0 x 2.0 mm) with whole brain coverage and improved parameter accuracy [8] was employed to obtain the v_e (and other kinetic parameter), and scaled fitting error (SFE) maps. Spatial co-registration was performed between the v_e and ADC volume maps, and the ADC maps were then re-sampled to match the resolution of the high spatial resolution DCE-MRI acquisitions. The tumor region of interest (ROI) on each slice was segmented on the 10 minutes post-contrast images using a Bayesian segmentation algorithm. In addition, voxels with SFE higher than 0.5 and/or zero v_e were excluded from the statistical analysis. The changes in the tumor median ADC and median v_e values over the course of bevacizumab treatment were compared. Scatterplots of median ADC and v_e of tumors were generated. A linear regression analysis was performed to investigate correlation between the tumor median ADC and median v_e values before treatment. The deviations of the post-treatment median v_e values from the pre-treatment regression line were calculated.

RESULTS

Five tumors (4 vestibular schwannomas, 1 meningioma) from the three patients were analysed. Vestibular schwannomas typically exhibit increased ADC values compared to the surrounding unaffected tissue. Figure 1 shows the typical co-registered v_e and ADC maps from a patient with bilateral vestibular schwannomas before treatment. The intratumoral heterogeneity pattern in ADC appears different from that in v_e.

CONCLUSIONS

In a small cohort of patients with benign tumors, vestibular schwannomas (4) and meningioma (1), pre-treatment median ADC and median v_e values were well correlated, despite of the difference between their heterogeneous patterns. This well correlated relationship was lost after Avastin treatment. The pre-treatment median v_e values showed significantly lower than those seen from the pre-treatment regression line at the corresponding post-treatment ADC.

Table 1 compares changes in v_e and ADC values 3 months post-treatment. In addition, ‘expected’ v_e values (v_e,exp) corresponding to each of the post-treatment ADC, were estimated using the pre-treatment regression line (v_e = (ADC - 0.2829)/1.6845). Note that, the measured v_e were significantly lower than v_e,exp (one-sided paired t-test, P = 0.03).

Table 1. v_e and ADC values pre- and 3 months post-treatment

<table>
<thead>
<tr>
<th>Tumors</th>
<th>pre-treatment</th>
<th>3 months post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>v_e</td>
<td>ADC</td>
<td>v_e</td>
</tr>
<tr>
<td>1</td>
<td>0.59; 1.297</td>
<td>0.30</td>
</tr>
<tr>
<td>2</td>
<td>0.52; 1.190</td>
<td>0.29</td>
</tr>
<tr>
<td>3</td>
<td>0.49; 1.063</td>
<td>0.47</td>
</tr>
<tr>
<td>4</td>
<td>0.37; 0.954</td>
<td>0.38</td>
</tr>
<tr>
<td>5</td>
<td>0.41; 0.947</td>
<td>0.38</td>
</tr>
</tbody>
</table>

v_e and ADC values estimated using pre-treatment regression line

REFERENCES

4. Gultekin et al. ISMRM annual meeting 2011;p3047.
8. Li et al. MRM, in press.

Fig. 1. Comparison of the v_e (left) and ADC (right) heterogeneity in a vestibular schwannoma (arrows).

Fig. 2. Median ADC vs. median v_e for the 5 benign brain tumors pre- and post-therapy.

Fig. 3. Correlation and linear regression analysis performed on the pre-treatment median ADC and median v_e values.