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

Ka-Loh Li[1], Sha Zhao[2], Amy Watkins[1], Xiaoping Zhu[1], and Alan Jackson[1]

[1]*Wolfson Molecular Imaging Centre, University of Manchester, Manchester, United Kingdom,* [2]*Imaging, 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 (v_e) measured using DCE-MRI modeling techniques. However, previous studies showed there was no such correlation demonstrated between ADC and v_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/mm^2). 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.

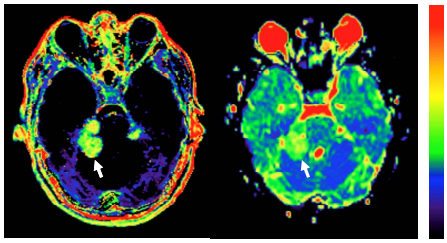

Fig. 1. Comparison of the v_e (left) and ADC (right) heterogeneity in a vestibular schwannoma (arrows).

Figure 2 demonstrates the scatterplot of median ADC versus median v_e of the tumors pre- and post-treatment. Correlation analyses showed a weak correlation between the 2 parameters (Pearson's r = 0.56, P = 0.02).

On the other hand, pre-treatment median ADC and v_e showed a strong correlation (r = 0.97, P = 0.007) between the 2 parameters. This is displayed in Figure 3 with the associated linear regression line and best-fit parameters. However, this well correlated relationship was lost over the course of Avastin therapy. The post-treatment median v_e values showed lower than those seen from the pre-treatment regression line at the corresponding post-treatment ADC.

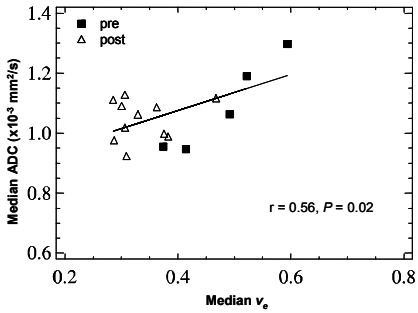

Fig. 2. Median ADC vs. median v_e for the 5 benign brain tumors pre- and post-therapy.

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).

CONCLUSIONS

In a small cohort of patients with benign tumors, vestibular schwannomas (4) and melingioma (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 post-treatment median v_e values showed significantly lower than expected from the pre-treatment regression line. This study may provide useful information for better understanding of v_e and ADC as imaging biomarkers for cancer treatment response in vestibular schwannomas over the course of bevacizumab treatment.

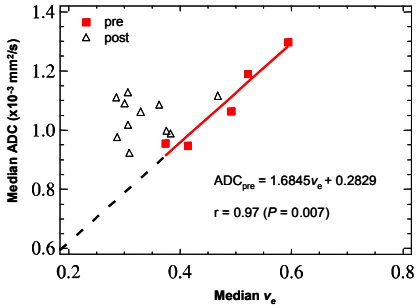

Fig. 3. Correlation and linear regression analysis performed on the pre-treatment median ADC and median v_e values.

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

tumors	pre-therapy		3 months post-therapy			
	v_e[b]	ADC[b]	v_e[b]	ADC[b]	$v_{e,\,exp}$[c]	v_e - $v_{e,\,exp}$
1	0.59	1.297	0.30	1.091	0.48	-0.18
2	0.52	1.190	0.29	1.111	0.49	-0.20
3	0.49	1.063	0.47	1.116	0.49	-0.02
4	0.37	0.954	0.38	0.988	0.42	-0.04
5[a]	0.41	0.947	0.38	0.998	0.42	-0.04

[a]Tumor 5 is a meningioma; Tumors 1 - 4 are vestibular schwannomas.
[b]measured v_e and ADC (x 10^{-3}mm^2/s) values
[c] v_e values estimated using pre-treatment regression line

REFERENCES

1. Anderson et al. MRI 2000; 18:689-695.
2. Mills et al. AJNR Am J Neuroradiol 2010; 31: 549 –53.
3. Arlinghaus et al. MRI 2011; 29: 630–638.
4. Gultekin et al. ISMRM annual meeting 2011;p3047.
5. Langer et al. Radiology 2010;255:485-494.
6. Yankeelov et al. MRI 2007; 25: 1-13.
7. Padhani and Khan. Targ Oncol 2010; 5:39–52.
8. Li et al. MRM, in press.