Introduction: Malignant gliomas are currently evaluated by subjective assessment of T2- and contrast-enhanced T1-weighted imaging. Glioblastoma multiforme (GBM) is largely considered a single clinical entity for the purposes of treatment rationalisation, although genetic biomarkers which predict response to treatment in glioma from biopsy samples have been discovered. Non-invasive imaging biomarkers which predict glioma behaviour are currently being sought. A glioma edge characteristic, the tumour border sharpness coefficient (TBSC) as described on anatomical MR imaging, has been shown to correlate with 1p/19q status – and therefore with chemosensitivity – in oligodendroglial tumours[1, 2]. Diffusion-weighted imaging exploits the movement of free water molecules and has been described as an indirect proxy of tumour cellular density, tumour infiltration and of tumour extracellular matrix properties[3, 4]. Areas of low diffusion-weighted signal intensity have a high apparent diffusion coefficient (ADC) and vice versa. ADC has been used to differentiate tumour from peri-tumoural oedema and normal brain, and to differentially diagnose enhancing intracranial lesions[5]. In peri-enhancing regions of glioma with abnormal MR signal, ADC has also been found to be high in oedema, low in tumour, and intermediate in mixed tumour/oedema[6]. The TBSC approach has recently been combined with diffusion-weighted imaging to determine the ADC Transition Coefficient (ATC) which is the rate of change of ADC per unit length across the tumour boundary[7]. The work presented here aimed to compare the ATC with survival data in glioblastoma multiforme (GBM) treated by standard postoperative temozolomide (TMZ) chemoradiotherapy. Since ADC may correlate inversely with cellular density and directly with infiltration, it was hypothesised that tumours exhibiting broader zones of ADC transition between tissues would have more diffuse boundaries, which may represent more infiltrative phenotypes with potentially shorter overall survival. In addition to the ATC at the oedema boundary described previously by Jenkinson et al.[referred to here as ATCO], we proposed the ATC at the tumour boundary (ATCT) to additionally reflect invasiveness and cellularity of the advancing solid tumour front.

H$_{0}$: Neither ATCT nor ATCO correlate with survival in GBM patients treated with postoperative TMZ chemoradiotherapy.

Methods: 27 volunteers (16 male, 11 female, aged 18-76 years, mean 58.7) from Salford Royal Foundation Trust Hospital (Salford, UK) with histologically-proven GBM underwent prospective baseline diffusion-weighted imaging in addition to routine clinical imaging. ADC maps were generated on a 3T Philips Achieva with an 8 channel SENSE Head Coil (Philips Medical Systems BV, Best, Netherlands) using DWEPI, TE=68ms TR=2312ms, b=0 and 1000 seconds/mm$^2$, FOV 230mmx230mm, thickness=4mm, interval=5mm, and matrix 128x128. Survival data were available for 23 volunteers. All patients had been treated with TMZ chemoradiotherapy. The post-processing method was modified from Jenkinson et al. and Agahi et al.[7, 8] The axial slices with the largest cross sectional area of solid tumour and oedema were chosen to measure the ATC across the tumour-oedema interface and the oedema-white matter interface respectively. Two adjacent voxels were included in a ROI parallel to the tissue boundary. The mean ADC value in the ROI was measured, and the ROI was moved one voxel towards the tumour centre until four measurements were obtained. Serial measurements were taken at each free edge (i.e. not adjacent to cortex, bone, or CSF) and the ADC slope was derived by linear regression. The ATC was calculated as the mean of these slopes. Two metrics were generated for each tumour: the ATCO into oedema (ATCO) and the ATCT into enhancing tumour (ATCT). The ATC’s for each tumour were compared to participant survival length in days. Correlation was assessed using Kendall’s rank correlation coefficient ($\tau$), and Cox regression analysis to determine the hazards ratio (HR) assuming a proportional hazards model.

Results: Examples of ATC measurements and corresponding anatomical imaging are shown in figure 1 (A to C). Figure 1D shows scatter plots of survival against ATCT and ATCO showing ordinary least squares linear regression fit line.

Discussion: In these patients, no significant correlation was found between length of survival and the transition of ADC values from white matter into peri-tumoural oedema (ATCO). The significant correlation found between the magnitude of ATCT and survival may be related to the distance over which solid tumour transitions into oedema. A narrow transition (i.e. a potentially large negative ATCT) may reflect a lesser degree of infiltration beyond the solid, enhancing component, and a less invasive phenotype. This may explain why such patients are likely to survive longer than those with a broader transitional boundary and potentially more invasive tumour phenotype. By comparing these findings with data collected from additional sources, such as perfusion imaging and image-guided biopsy (which have been contemporaneously acquired in this cohort) the link between survival and imaging biomarkers of the tumour boundary biology can be further explored.

References: