Characterising the Transition Zone from Tumor to Normal Brain in Glioblastomas using Multimodal MRI

Sarah A Leir[1], Timothy J Larkin[1,2], Natalie R Boonzaier[2,3], Victoria Lupson[2], Laila A Mohsen[4], Adam Young[1], and Stephen J Price[1,3]

[1]Division of Neurosurgery, Addenbrooke's Hospital, Cambridge, Cambridgeshire, United Kingdom, [2]Wolfson Brain Imaging Centre, Addenbrooke's Hospital, Cambridge, Cambridgeshire, United Kingdom, [3]Department of Clinical Neurosciences, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom, [4]University Department of Radiology, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom

Introduction:

Glioblastomas are the commonest cause of cancer deaths in children, women under 35 years of age and men under 45 years of age. Despite modest improvements in survival with better surgery and combined chemotherapy and radiotherapy, the tumor will still progress in the treated area and virtually all patients will die from progressive disease. Identification of the invasive margin is a key limitation to treating these tumors. Conventional T1-weighted and T2-weighted imaging methods are still used to assess the extent of tumor for resection. However, it has been shown in histological specimens that malignant cells extend for several centimeters beyond the contrast enhancing regions and that the margin from gross tumor into normal brain involves a gradual decrease in tumor cellularity and a change from a malignant metabolic phenotype to normal brain. This transition between tumor edge, peritumoral edema and normal brain remains ambiguous. An improvement in the understanding of the tumor margin would allow individualized tailoring of treatment in particular with planning radiotherapy, more extensive surgical resections and the use of intra-operative oncological therapies. Diffusion-based MR has been shown to be a promising new imaging technique to study tumor invasion. Larger peritumoral abnormalities in gliomas have been demonstrated by diffusion-tensor imaging (DTI) when compared to conventional MR imaging. These DTI abnormalities have been confirmed to identify invasive tumor by image-guided biopsies. A recent review article by Sternberg *et al* (2014) has proposed a model of this transition area and how different imaging modalities can potentially discriminate between them. The objectives of this study are to investigate this concept and to identify biomarkers of invasion which, in turn, would allow better delineation of tumor margins.

Methods:

Eighty patients with presumed glioblastomas were imaged pre-operatively at 3T with anatomical sequences, DTI (12 directions, 5 b values - to measure ADC, *p* and *q*), dynamic susceptibility contrast imaging (to measure rCBV) and short-echo (TE=35ms) 2d chemical shift imaging (to measure the metabolic profile). This data was co-registered to the same imaging space. Regions of interest (ROIs) were selected in a circumferential consecutive pattern with an increasing 10 mm radial distance from the edge of the T1 weighted enhancing region to normal appearing brain of the ipsilateral hemisphere. These were labelled as (1) within T1 enhancing region, (2) first circumference, (3) second circumference and (4) third circumference (Figure 1). The parameters were calculated on a voxel-by-voxel basis and normalized to ROIs from a similar anatomical location in the contralateral hemisphere and expressed as a ratio to normal brain. Results are quoted as mean ± SEM.

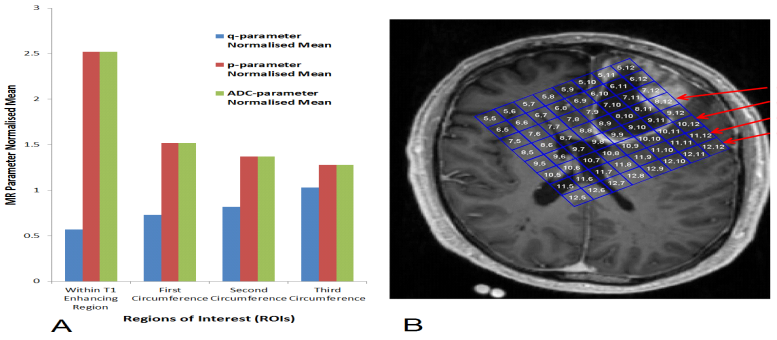

Figure 1: *67 year old male patient with a glioblastoma. (A) Results of DTI parameters (p, q and ADC). (B) Methodology used to select ROIs (1) from within the T1 enhancing region, (2) from the 1st, (3) the 2nd, and (4) the 3rd circumferences for the specified patient.*

Results:

In regions of gross tumor there was a marked decrease in *q,* the anisotropic component of the diffusion tensor, (0.48 ± 0.01) (Figure 2A). The *q*-parameter remained ≥ 23% lower than the contralateral hemisphere at 30 mm from the edge of the T1 enhancing region. There was a marked increase in the *p,* the isotropic component of the diffusion tensor, in the region of gross tumor, (1.97 ± 0.04) which remained raised in comparison to the contralateral hemisphere at a 30 mm distance beyond the edge of the enhancing region (1.42 ± 0.02, $p < 0.000$ at 10 mm; 1.36 ± 0.02, $p < 0.000$ at 20 mm; 1.18 ± 0.02, $p < 0.000$ at 30 mm) (Figure 2B). A similar statistically significant pattern was seen with the ADC-parameter. Perfusion (rCBV) was persistently elevated within each consecutive expanding circumference (1.42 ± 0.07 within T1 enhancing region, 1.39 ± 0.04 at 10 mm, 1.38 ± 0.04 at 20 mm, and 1.56 ± 0.06 at 30 mm). From previous work, an rCBV threshold of 1.26 differentiates between tumor-invaded and non-invaded brain. The spectroscopic measurements demonstrated a marked increase in Cho/Cr within the TI enhancing region (2.55± 0.09) which remained raised in comparison to the contralateral hemisphere at 20 mm beyond the edge of the T1 enhancing region (1.28± 0.02 at 10 mm, 1.14± 0.04 at 20 mm, 1.00± 0.02 at 30 mm). A similar pattern was seen with Gln+Glu/Cr+PCr, Glu/Cr+PCr, Ins/Cr+PCr and GSH/Cr+PCr.

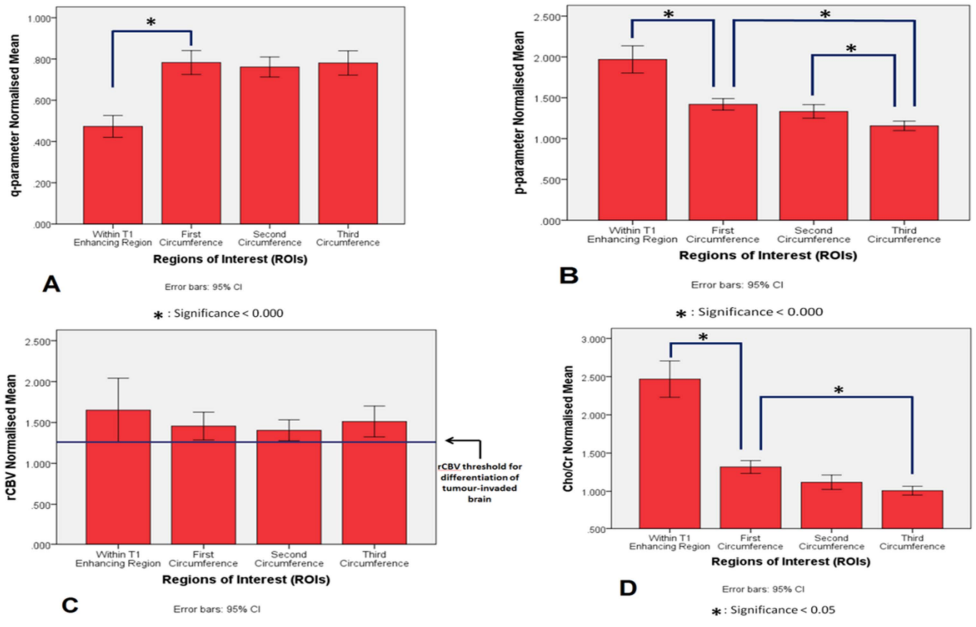

Figure 2: *(A) q-parameter, (B) p-parameter, (C) rCBV and (D) Cho/Cr spectroscopy results from the cohort of patients with glioblastomas.*

Conclusions:

Glioblastomas have an infiltrative pattern of growth that has been shown from histological analysis to extend microscopically for several centimeters beyond the conventional radiographically determined margin of disease. However, to date there has been minimal supportive evidence of this using MR imaging techniques. This is the first study to provide radiological evidence of such extensive infiltration using multimodal MR imaging. This research has demonstrated that MRI biomarkers (DTI, rCBV and spectroscopy) of tumor cell presence extend up to 3 centimeters beyond the conventionally determined tumor margins. This suggests that there continues to be disruption of white matter tracts and tumor cellularity at such a distance beyond the conventionally determined and subsequently treated tumor margin. Incorporating multimodal MRI data into treatment planning will allow more precise surgical resection and enable a more individualized planning of radiotherapy.