RELATIONSHIP OF SUBVENTRICULAR ZONE WITH TUMOR BLOOD VOLUME, TUMOR GENOMICS AND PATIENT SURVIVAL IN PATIENTS WITH GLIOBLASTOMA : A TCGA GLIOMA PHENOTYPE RESEARCH GROUP PROJECT

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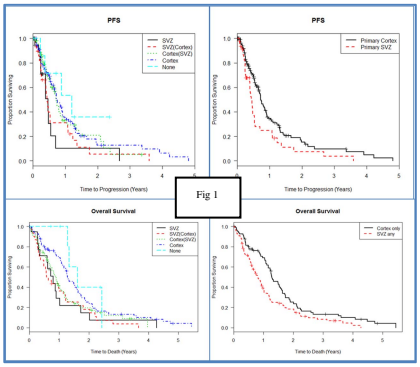
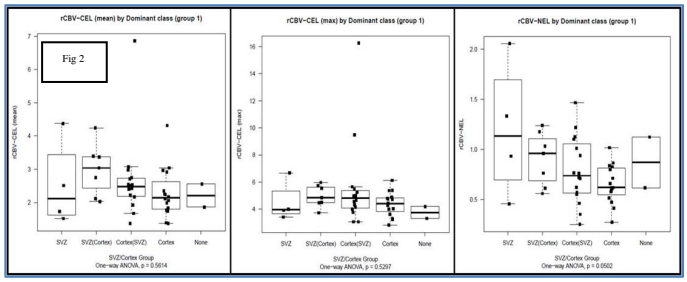
Introduction: Glioblastoma (GBM), the most common primary malignant brain tumor in adults, is an extremely heterogeneous tumor, in its clinical presentation, which is also reflected in its varied histopathology and imaging phenotype [1], likely a reflection of its very varied genomic make up. This heterogeneity not only confounds evaluation of these tumors, particularly from an imaging standpoint, but also likely plays a role in tumor growth, progression and resistance to therapy [2]. It has been suggested that this heterogeneity, in part, may relate to the cells of origin [1]. In particular, in recent years, the cancer stem cell (CSC) model for cancer initiation and evolution has been proposed, which suggests tumors generate from cells with stem cell characteristics (CSCs) [2]. These CSCs then, not only maintain their population within the tumor, but also continue to generate differentiated daughter cells constituting the bulk of the tumor [2]. The purpose of this retrospective study was to evaluate whether location of GBM relative to the subventricular zone (SVZ) is associated with differences in patient overall survival (OS), progression free survival (PFS) and how it is correlated with the genomic/molecular expression as well as imaging phenotype specifically to the vascular phenotype and tumor blood volume measured non-invasively using DSC T2* MR perfusion.

Material and Methods: Patients with primary untreated GBM, molecular information assayed by TCGA (The Cancer Genome Atlas) and pre-surgical imaging collected by TCIA (The Cancer Imaging Archive) were included (n=203). Clincial and molecular data (level 3) were obtained from TCGA. Survival analysis included Kaplan-Meier estimates, log-rank tests, and Cox regression. Molecular analysis, of non-GCMIP tumors, included t-test screening of differential expression and functional analysis by Ingenuity Pathway Analysis. Tumor locations (contrast enhancing lesion, CEL) were classified by consensus into one of four groups according to the classification system previously defined by Lim et al [3]: Group I - Involving cortex and SVZ; Group II - Involving SVZ only; Group III - Involving cortex only; Group IV - Involving neither SVZ nor cortex. The group I tumors were then further subdivided by consensus of two neuroradiologists into tumors with primarily SVZ (group Ia) and primarily cortical involvement (group Ib). SVZ and cortical involvement required CEL touching the ventricle lining or invading cortex, respectively. DSC T2* MR perfusion data was available for 45 patients and rCBV (mean and maximum) of both the contrast enhancing lesion (CEL) and non-enhancing lesion (NEL) was evaluated [4,5].

Results: 92 patients (45.3%) were classified as Group 1, 18 (8.9%) as group 2, 86 (42.4%) as group 3, and 7 (3.4%) as Group 4. Those patients with SVZ involvement have shorter PFS (log-rank p=0.0098) as well as OS (median 0.81 years, 95% CI(0.64, 0.99)) compared to those with only cortex involvement (median 1.28 years, 95% CI (1.16, 1.63), log-rank p=0.0030) (Fig 1). Although age is a significant predictor of OS, it does not affect the influence of SVZ involvement (HR: 1.62 for SVZ vs Cortex only, crude vs HR=1.62 age adjusted). Other clinical factors were not differential. When evaluating rCBV-CEL, there was no statistically significant difference between the tumors in the various groups for either rCBV-CELmean or rCBV-CELmax (ANOVA p=0.5614 and p=0.5297, respectively; Fig 2). When evaluating rCBV-NEL, it was found that there is some evidence of difference in mean rCBV-NEL-max between the five groups (p=0.0502) (Fig 2). From collapsing SVZ levels, we find that SVZ groups show statistically significant higher rCBV-NEL-max on average than cortex-involved groups (SVZ-any (I, II), p=0.0144; SVZ-primary (Ia, II), p=0.03415).





Genes within canonical signaling pathways (e.g., RAC, ERK/MAPK, JAK/STAT) and Immune signaling pathways, especially those including TNF, show increased activity in SVZ originating tumor (Group II) relative to Cortex originating tumors (Group III). Though classic stem cell markers (e.g., CD133) are not differential, networks of overexpressed genes suggest a developmental role with emphasis on histone modification (e.g., HOXB genes and HIST3H3). Deactivation of select miRNA is also proposed as a mechanism for increased expression of genes in SVZ-originating tumors.

Conclusions: GBM patients with tumors involving the SVZ have worse survival compared to those without SVZ involvement. Patients with tumors located in the SVZ have shown increased blood volume in NEL, suggesting that these tumors probably have an aggressive vascular phenotype which accounts for poor survival. Our work also proposes molecular differences between SVZ-originating and cortex-originating GBM tumors which may drive observed survival and imaging phenotype differences. Further work on epigenetic contributions is warranted.

References:

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