GENOMIC MAPPING AND SURVIVAL PREDICTION IN GLIOBLASTOMA: ROLE OF TUMOR BLOOD VOLUME VERSUS MOLECULAR SUB-CLASSIFICATION - A TCGA GLIOMA PHENOTYPE RESEARCH GROUP PROJECT

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Background and Purpose: Molecular sub-classification of glioblastoma (GBM) has led to a better understanding of tumor cell origin and biology; however, it has not shown any significant difference in survival in this sub-group of very aggressive neoplasms. The purpose of this study was to evaluate the role of tumor blood volume estimated using DSC T2* MR perfusion in survival prediction compared to the molecular sub-classes of GBM.

Materials and Methods: 57 patients with treatment naïve GBM underwent DSC T2* MR perfusion studies at 2 different institutes. Of these, 50 patients had gene expression data available from TCGA (1, 2). rCBV maps were generated using NordicICE (Nordic Neuro Lab) software using leakage correction. $rCBV_{max}$, $rCBV_{mean}$ of the contrast enhancing part of the lesion (CEL) as well as $rCBV_{NEL}$ of the non-enhancing part of the lesion (NEL) were measured. All the patients were sub-classified into Classical, Mesenchymal, Neural and Proneural based on Verhaak classification (3) and also into Mesenchymal, Proneural and Proliferative based on Phillips classification system (4). We correlated the perfusion parameters with the molecular sub-classes as well as with patient survival. Cox regression was used to model the association of overall survival with perfusion parameters accounting for potential confounders. Additionally we included each of the Verhaak and Phillips classification groups as predictors. P-values were derived from Wald chi-square tests of the hazard ratio.

Results: ***rCBV analysis using molecular sub-classification:*** No statistically significant differences were noted for $rCBV_{max}$, $rCBV_{mean}$ of CEL as well as $rCBV_{NEL}$ between the 4 classes using Verhaak or 3 classes using Phillips classification system. ***Survival analysis using molecular sub-classification:*** In the present study, the median overall survival was 1.14 years (IQR: 0.49, 2.11). When the Verhaak classification scheme was applied to these samples, the classical sub-class had the best survival, with median of 2.13 years (IQR: 1.53, 2.59) and the proneural sub-class had the worst survival with median 0.41 years (IQR: 0.65, 1.19); (Fig 1a). The difference in survival by Verhaak sub-classification was significant between groups with the difference being more prominent earlier during follow-up (Wilcoxon p=0.0445, log-rank p=0.0696). There was no evidence that the Phillips classification was associated with survival in our sample (log-rank p=0.6432, Wilcoxon p=0.4548). Specifically we see that the best median survival is attributed to the mesenchymal sub-class with 1.28 years (IQR: 0.61, 2.22), followed closely by the proneural subclass with 1.12 years (IQR: 0.33, 1.86). The proliferative sub-class had the worst median survival at only 0.54 years (IQR: 0.34, 3.96) but this class was only represented by six patients (five deaths), one of whom was still surviving at 3.96 years (Fig 1b). ***Survival analysis using only rCBV measures:*** When we looked at rCBV as the sole predictor of survival we observed that each measure appears to infer greater risk as it increases. The hazard ratios are 1.25 (p=0.1918) for $rCBV_{mean}$, 1.24 (p=0.0131) for $rCBV_{max}$, and 2.45 (p=0.0555) for $rCBV_{NEL}$(Table 1 Model 1). Adjusting for patient age at diagnosis and MR scanner type used, showed no effect and were dropped from subsequent models for the sake of parsimony. ***Survival analysis using rCBV and molecular sub-classification:*** When the Verhaak classification was considered in conjunction with rCBV measures, we observed that $rCBV_{mean}$ becomes significant (HR: 1.46, p=0.0212), $rCBV_{max}$ remains significant (HR: 1.24, p=0.0062) and $rCBV_{NEL}$ remains marginally significant (HR: 2.56, p=0.0704). Verhaak classification is significant in the models with $rCBV_{mean}$ (p=0.0250) or $rCBV_{max}$ (p=0.0476) and marginally so for $rCBV_{NEL}$ (p=0.0917 (Table 1 Model 2). The Phillips classification had no effect on the survival model with respect to the estimated hazard ratios of the rCBV measures ($rCBV_{mean}$ HR: 1.27, p=0.1670; $rCBV_{max}$ HR: 1.24, p=0.0152; $rCBV_{NEL}$ HR: 2.51, p=0.0566). Likewise, it does not provide any independent prediction of survival (2-df Chi-square, p=0.5892, p=0.6888, and p=0.6533, respectively) (Table 1 Model 3).

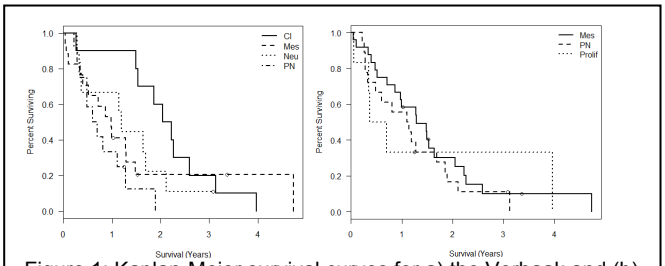

Figure 1: Kaplan-Meier survival curves for a) the Verhaak and (b) the Phillips sub-classes for the present study.

	Parameters	$rCBV_{Mean}$	$rCBV_{Max}$	$rCBV_{NEL}$
Model 1:	**rCBV**	1.25 (0.1918)	1.24 (0.0131)	2.45 (0.0555)
Model 2:	**rCBV +**	1.46 (0.0212)	1.24 (0.0062)	2.56 (0.0704)
	Verhaak	(0.0250)	(0.0476)	(0.0917)
	Classical	0.21	0.26	0.30
	Mesenchymal	0.43	0.48	0.48
	Neural	0.44	0.41	0.55
	Proneural	1.00	1.00	1.00
Model 3:	**rCBV +**	1.27 (0.1670)	1.24 (0.0152)	2.51 (0.0566)
	Phillips	(0.5892)	(0.6888)	(0.6533)
	Mesenchymal	0.72	0.79	0.74
	Proliferative	0.98	1.02	0.87
	Proneural	1.00	1.00	1.00

Table 1: Survival models (N=48, 43 deaths) for each of the rCBV measures alone (model 1), with the Verhaak classification (model 2), and with the Phillips classification (model 3). Hazard ratios (p-values) are given with the classification HRs relative to the proneural sub-type in models 2 and 3.

Conclusion: Increasing rCBV measures appear to relate to poor survival in GBM. Interestingly, the Verhaak classifier appears to have a confounding effect on the hazard ratio for $rCBV_{mean}$ (p=0.0299) and potentially to a lesser degree for $rCBV_{NEL}$ (p=0.0974); though not with $rCBV_{max}$. It is additionally interesting that the Phillips subclasses neither associate with patient survival nor affect the association of rCBV measures with survival. In the future, molecular sub-classification of gliomas could potentially lead to individualized therapy regimens targeting specific biologic pathways. However in the present study, the hemodynamic imaging biomarkers i.e. rCBV measures did not show any difference between different sub-classes of glioblastomas using Verhaak or Phillips classification system based on genomic/molecular mapping. rCBV measures predicted patient overall survival better than the molecular sub-classes, suggesting an important role non-invasive imaging biomarkers could play in patients prognosis and survival.

References:

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