

RADIO-GENOMICS: GENOMIC MAPPING, GLIOMAS AND PERFUSION IMAGING -- A TCGA GLIOMA PHENOTYPE RESEARCH GROUP PROJECT

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Background and Purpose: Recent developments in microarray analysis of cancer genomes have led to an additional interest in correlation of gene expression with imaging features in gliomas to better understand the physiologic basis for the imaging heterogeneity of these aggressive neoplasms. The limited number of publications on this topic has correlated the presence or absence of contrast enhancement with various gene expression pathways affecting tumor cell mitosis, migration, angiogenesis, hypoxia, edema and apoptosis. The purpose of this exhibit is to discuss glioma genomic mapping and its integration/correlation with tumor kinetics, hemodynamic and physiologic parameters with the intent of improving understanding of the molecular basis for commonly used tumor perfusion parameters (such as blood volume and permeability) and show how these imaging biomarkers perform versus various molecular sub-classification systems.

Approach/Methods: We will discuss the role The Cancer Genome Atlas (TCGA)¹ and Repository for Molecular Brain Neoplasia (REMBRANDT), which provide extensive multidimensional datasets, are playing in presenting a unique opportunity to integrate imaging and genomic data which in turn provides a more sophisticated understanding of gliomas. The role perfusion imaging (beyond the morphologic features) can play as far as correlation with immuno-histochemical and molecular basis of gliomas and patient survival will be discussed in detail. We will present our data² regarding correlation of perfusion parameters with genomic expression related to tumor angiogenesis which forms the physiologic basis of these parameters. We will discuss the correlation of perfusion parameters with specific genes, pathways and molecular sub-classifications of gliomas and particularly high-grade gliomas^{3,4,5}. Additionally we will review the prognostic role of CBV (cerebral blood volume) measures versus molecular sub-classification systems³.

Findings/Discussion: Correlation of the perfusion parameters has shown that some of the pro-angiogenic genes (*TNFRSF1A*, *HIF1A*, *KDR*, *TIE1* and *TIE2/TEK*) have a positive correlation and some of the anti-angiogenic genes (*VASH2*) have an inverse correlation with tumor perfusion parameters (CBV and PS), suggesting a molecular basis for these imaging biomarkers¹. In another study of glioblastomas, rCBV measures did not show any difference between different sub-classes of glioblastomas using Verhaak or Phillips classification system based on genomic/molecular mapping³. In fact, rCBV measures predicted patient overall survival better than the molecular sub-classes, suggesting an important role non-invasive imaging biomarkers could play in patient prognosis and survival³. We will also discuss other published data on this subject.

Summary/Conclusion: Integration of imaging and genomic data is critical for a better understanding of gliomas, particularly considering the increasing focus on utilization of imaging biomarkers for patient survival and treatment response. Correlation of glioma perfusion parameters can help provide a better understanding of angiogenesis, specific genes and pathways; and can provide opportunities to target those specific molecular markers/pathways for improving patient response and prognosis.

References: 1) Cancer Genome Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature* 2008;455:1061-8. 2) Jain, R., Poisson, L., Narang, J., Scarpace L., Rosenblum, M., Rempel, S., Mikkelsen, T. Correlation of Perfusion Parameters with Genes Related to Angiogenesis Regulation in Glioblastoma: A Feasibility Study. *Am J Neuroradiology* (in press). 3) Jain, R., Poisson, L., Narang, J., Scarpace, L., Gutman, D., Flanders, A., Daniel, B., Jaffe, C., Mikkelsen, T. Survival prediction using molecular classification of glioblastomas: Role of tumor blood volume estimation using DSC T2* MR perfusion. 16th Annual meeting of Society of Neuro-oncology, Orange County, Nov 17-20, 2011. 4) Phillips HS, Kharbanda S, Chen R, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression and resemble stages in neurogenesis. *Cancer Cell* 2006;9:157-73. 5) Verhaak RG, Hoadley KA, Purdom E, et al. Cancer Genome Research Network integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell* 2010;17:98-110.