Characterization of Angiogenic Subtypes of Oligodendroglioma by MR-Perfusion Imaging

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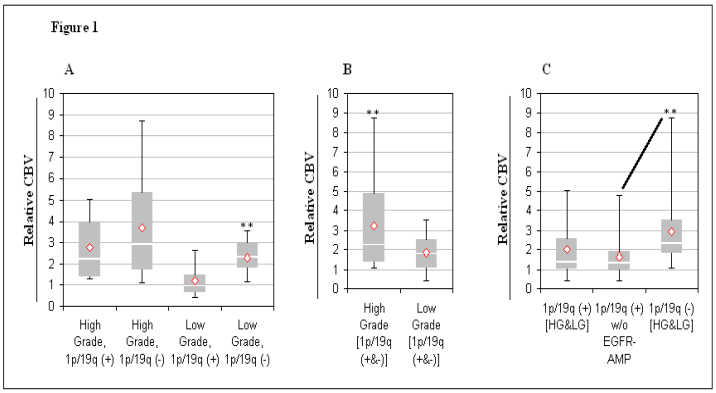
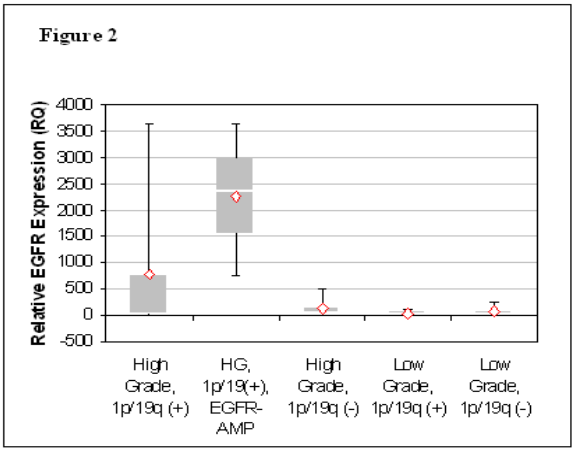
Introduction: Oligodendrogliomas are rare brain neoplasms that often show good response to chemotherapy, with 50-60% of patients responding to temozolomide.Loss of heterozygosity (LOH) of chromosome 1p predicts oligodendroglioma chemosensitivity and LOH of 1p and 19q in high-grade neoplasms predicts radio- and chemo-sensitivity and longer survival (1.2). Therefore, appropriate selection of therapy has been facilitated by molecular classification of oligodendroglial cytogenetic subtypes. Magnetic resonance (MR) perfusion-weighted imaging allows noninvasive determination of relative cerebral blood flow (rCBV), which may reflect the degree of neoplastic angiogenesis and metabolism. We have recently shown that Perfusion-weighted imaging may be useful in predicting the histopathological grade or cytogenetic type of oligodendroglial neoplasms (3). The present study was aimed to correlate rCBV to the markers of angiogenesis and EGFR gene amplification in the oligodendroglial tumors with different cytogentic profiles.

Methods and Materials: We conducted prospective analyses on 39 patients with different grades of oligodendroglial neoplasms resected at the Hospital of the University of Pennsylvania. The resected tumors were subjected to histopathologic and cytogenetic analyses. 31/39 patients were reviewed for pre-operative MR perfusion-weighted analysis**.** Oligodendroglial tumors were stratified into two cytogenetic groups: 1p or 1p/19q loss of heterozygosity (LOH) (group 1), and 19q LOH or intact alleles (group 2). Extracted RNAs from all the tumors were subjected to Real-time RT-PCR using Taqman probe-based protocol to quantify the expression of EGFR, VEGF, CD31 (PECAM) and CD105 (Endoglin). Data was analyzed using Student's t-test (one-tailed). The p-value less than 0.05 was considered significant.

Results: In WHO grade II neoplasms, group 1 showed significantly greater rCBV when compared to group 2 (p=0.013), supporting our previous observations (3). However, in grade III neoplasms, the differences between group 1 and group 2 were not significant (p=0.2) (Fig.1A). Probe-based Real-time RT-PCR analyses showed that 3/20 (15%) group 2 tumor cases exhibited dramatic EGFR amplification, suggesting an existence of a distinct subtype of high-grade oligodendrogliomas with 1p19q intact but with EGFR overexpression (Fig.2). Grade III neoplasms with or without EGFR amplification showed significantly higher rCBV than grade II neoplasms (Normal EGFR, p=0.042; Normal + Amplified EGFR, p=0.017) (Fig1B). Group 1 tumors showed increasing trends in rCBV values over group 2 tumors, irrespective of tumor grade (Fig.1C). The level of significance was high when group 1 tumors were compared to group 2 tumors, independently of the EGFR-amplified subtype (p=0.02), suggesting that EGFR amplification, and other unknown alterations, may play important role in upregulating tumor blood flow in oligodendroglial neoplasms and that EGFR amplification and 1p19q LOH are mutually exclusive markers in these tumors (5) (Fig.1C). Probe-based Real-time RT-PCR analyses of known angiogenic markers showed increased expression of VEGF, PECAM (CD31) and endoglin (CD105) in group 2 tumors including the EGFR-amplified subtype, suggesting that increased expression of VEGF, CD31 and CD105 may play a role in rCBV in 1p19q intact tumors. On the contrary, group 1 tumors showed significantly higher expression of CD31 and CD105 than group 2 (CD31, p=0.006; CD105, p=0.046), if the analysis was done by excluding highly EGFR-amplified tumors, suggesting that genes on 1p19q loci may be inversely correlated to CD31 and CD105 expression in the regulation of tumor blood flow.





Discussion: 1p/19q deletions are associated with elevated rCBV in low-grade oligodendrogliomas. High expression of EGFR in distinct a subpopulation of high-grade non-deleted tumors may contribute in part to increased tumor blood flow and angiogenesis. Differential expression of VEGF, CD31 and CD105 in different grades of oligodendroglial neoplasms with distinct cytogenetic profiles may also contribute to changes in tumor blood flow. Further investigation is warranted to determine the association between changes in tumor blood flow and different biomarkers, which may facilitate further molecular subtyping and better management of different grades of oligodendroglial neoplasms.

Conclusions: Collectively, our data demonstrate that advancements in MR imaging may facilitate molecular subtyping and define distinct angiogenic profiles in cytogenetic subsets of oligodendroglial tumors.

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