Title

NIMG-46. LONGITUDINAL RESTING-STATE FUNCTIONAL CONNECTIVITY CONFIRMS MARIZOMIB (MRZ) CROSSES THE BLOOD BRAIN BARRIER (BBB) AND CORRELATES WITH HALLUCINATION SEVERITY IN RECURRENT GBM PATIENTS

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NIMG-44. QUANTITATIVE MULTI-PARAMETRIC IMAGE PROFILING REVEALS REMARKABLE HETEROGENEITY WITHIN IDH-WILDTYPE GLIOBLASTOMA, OFFERING PROGNOSTIC STRATIFICATION BEYOND CURRENT WHO CLASSIFICATIONS

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PURPOSE: The current WHO classifies astrocytomas by IDH mutational status given the significantly poorer prognosis of IDH-wildtype tumors, representing ~95% of de novo glioblastoma. Our previous studies revealed remarkable heterogeneity of these tumors, dividing them in three distinct radiographic subtypes (Rad-S). In this study, we hypothesize that this heterogeneity expands in Rad-S within IDH-wildtype glioblastoma, subdividing them further according to prognosis. METHODS: We analyzed pre-operative multi-parametric magnetic resonance imaging (mpMRI) data (T1,T1-Gd,T2,T2-FLAIR,DTI,DSC) of a retrospective cohort of pathology-proven de novo IDH-wildtype glioblastoma (n=76). Comprehensive quantitative imaging phenomic (QIP) features were extracted from distinct cancerous sub-regions (enhancing, non-enhancing, edematous), using the Cancer Imaging Phenomics Toolkit (CaPTk-www.cbica.upenn.edu/captk). QIP features comprised intensity histogram, volumetric, morphological, statistical, and textural descriptors. Unsupervised clustering of these features alone revealed tumor Rad-S, based on unambiguous clustering assignments across 1000 permutations, that were evaluated through survival and molecular characteristics. RESULTS: Three Rad-S were identified within IDH-wildtype glioblastoma, with statistically significant survival differences (long-:intermediate-:short-survival, median(months)=19.4:12.3:7.0, distribution=19.7%:34.2%:46.1%) measured by Kaplan-Meier analysis (P<0.001,log-rank) and Cox-Model (hazard-ratio=3.21,95%CI:2.51–4.61). Rad-S correlate with survival independent of age, resection-status, post-surgical therapy, additional genetic alterations, and MGMT promoter methylation status. Importantly, long-survival Rad-S, compared to others, showed statistically significant (P<0.001,Kruskal-Wallis) central hypo-intense non-enhancing region surrounded by hyper-intense rim (T1-Gd), lower angiogenesis/neovascularization (DSC) and cell-density (DTI), and higher water concentration (T2). CONCLUSIONS: Quantitative analysis of mpMRI yields three distinct Rad-S within IDH-wildtype glioblastoma offering complementary stratification beyond current WHO classification, which is independent of any factor known to affect prognosis. These Rad-S provide an additional prognostic indicator as a component of precision diagnostics that may impact choice/timing of surgery, chemotherapy, bevacizumab and radiation, allowing personalized treatment. Further, our current understanding in clinical setting is insufficient to explain prognostic differences among the Rad-S. These results provide guidance for ongoing investigation to elucidate pathologic mechanism and consequently targeted therapeutic strategies.

NIMG-45. MULTIVARIATE PATTERN ANALYSIS OF DE NOVO GLIOBLASTOMA PATIENTS OFFERS IN VIVO EVALUATION OF O^6-METHYLGUANINE-DNA-METHYLTRANSFERASE (MGMT) PROMOTER METHYLATION STATUS, COMPENSATING FOR INSUFFICIENT SPECIMEN AND ASSAY FAILURES

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BACKGROUND: The promoter methylation status of the gene encoding for the repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) indicates increased efficacy of current standard of care therapy, which is concomitant adjuvant chemoradiotherapy with temozolomide. The MGMT promoter methylation status (MGMTpms) is typically determined as MGMT-methylated or MGMT-unmethylated by tissue-based polymerase chain reaction assays, which can be limited by inadequate specimen or assay failures. Thus, we investigate the hypothesis that integration of subtle, yet distinctive, quantitative imaging phenomic (QIP) features using machine learning may lead to non-invasive determination of MGMTpms. METHODS: We identified a retrospective cohort of 122 (46 MGMT-methylated) pathology-proven de novo glioblastoma patients with available baseline pre-operative multi-parametric magnetic resonance imaging (mpMRI) data (T1, T1-Gd, T2, T2-FLAIR, DSC, DTI). MGMTpms was obtained through MGMT methylation testing (pyrosequencing across 4 CpG sites in the MGMT promoter). Following delineation of distinct abnormal sub-regions (enhancing, non-enhancing, edematous), comprehensive and diverse QIP features were extracted using the Cancer Imaging Phenomics Toolkit (CaPTk, www.cbica.upenn.edu/captk), capturing intensity, volume, morphology, statistics, and texture of each sub-region. A support vector machine multivariately integrated these features towards a non-invasive marker of MGMTpms. RESULTS: The cross-validated accuracy of our MGMT marker in classifying the mutation status in individual patients was 84.43% (sensitivity=80.43%, specificity=86.84%, area under the curve [AUC]=0.85). Our marker revealed MGMT-methylated tumors with lower neovascularization and cell density, when compared with MGMT-unmethylated tumors, and a distinct spatial distribution pattern between MGMT-methylated and MGMT-unmethylated tumors, with the latter being more lateralized to the right hemisphere. CONCLUSION: Multivariate integrative analysis of QIP features extracted from mpMRI yields an accurate, non-invasive marker of MGMTpms in glioblastoma. The proposed non-invasive MGMT marker may contribute to (i) MGMTpms determination for patients with inadequate tissue/inoperable tumors, (ii) stratification of patients into clinical trials, (iii) patient selection for targeted therapy, and (iv) personalized treatment planning. *equal contribution

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INTRODUCTION: MRZ is a second-generation, irreversible proteasome inhibitor currently in clinical trials for GBM. MRZ has ability to cross the BBB in animal models. CNS side-effects (including hallucinations and cerebellar ataxia) are both common adverse events. Here we report on the regional fMRI-derived functional connectivity changes associated with hallucination severity (graded using CTCAE 4.03) after MRZ treatment, administered at day 1, 8, and 15 every 28 days. METHODS: Longitudinal resting-state fMRI whole-brain volumes (TR 2500ms, TE 20ms, flip angle = 71°, slice thickness = 3mm, gap = 0 mm, FOV 19.2 cm, matrix = 64 x 64, 51 slices, 120 volumes) were acquired on six participants at baseline (day 0) and days 1 and 15 of the treatment cycle. Preprocessing included: linear detrending, band-pass filtering, EPI signal from the white matter and CSF masks1; hand-drawn tumor masks; rigid-body realignment parameters; and motion and artifact scrubbing2 as implemented in the CONN toolbox3. Linear models were used to assess the correlations of hallucination severity and longitudinal functional connectivity changes in regions from the Harvard-Oxford atlas. RESULTS: After one day of treatment, we found hallucination severity was associated with decreased functional connectivity between the left lingual gyrus and both the left cerebellum (T(4)=-12.78, p<0.03 FDR) and left temporal cortex (T(4)=-9.56, p<0.04 FDR). After fifteen days, the association persisted but became more prominent between the bi-lateral temporal-occipital fusiform cortex and the bi-lateral cerebellum (left: T(4)=-20.20, p<0.005 FDR; right: T(4)=-17.75, p<0.008 FDR) along with decreased local efficiency in the left lateral occipital cortex (T(4)=-11.25, p<0.05 FDR). CONCLUSIONS: Our data suggest that MRZ induce changes in functional connectivity in selected brain areas, including the optic pathways and the cerebellum, confirming MRZ ability to cross the BBB in humans. Research to determine the relation between functional connectivity and response to MRZ are ongoing.

NIMG-47. A HISTOGRAM-BASED, BACK-PROJECTION METHOD FOR TREATMENT RESPONSE ASSESSMENT IN GLIOBLASTOMA USING MULTI B-VALUE ADVANCED DIFFUSION MRI

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INTRODUCTION: Early and accurate assessment of therapeutic response in glioblastoma is important for clinical patient management, and as platform for clinical trials of novel therapies. Current response criteria such as RANO (Response Assessment in Neuro-Oncology) rely on semi-quantitative measurements with limited sensitivity and specificity, especially early during treatment. Functional diffusion maps based on voxel-to-voxel comparison of quantitative diffusion measures are confounded by change in tumour size. Towards improving response assessment, we propose a histogram-based, voxel back projection method using advanced quantitative diffusion MRI. METHODS: We used least-square fitting to model four dif-