lationships in pediatric brain tumor patients. METHODS: Forty-nine patients (ages 7-18y.o.) with any brain tumor diagnosis underwent resting state functional Magnetic Resonance Imaging (rsfMRI) during regularly scheduled clinical visits. All patients were tested with the NIH Toolbox Cognition Battery. One-hundred thirty-nine age- and sex-matched typically developing children were used as controls. All data were processed to minimize artifactual sources of variance. Functional brain networks were created for each patient via rsfMRI data from 300 regions of interest that sample the whole brain. Multilinear models were implemented to examine brain-behavior relationships, while accounting for demographic and clinical factors. RESULTS: Functional network organization was significantly altered in patients compared to controls (p<0.001). Network organization was more affected in patients who received whole-brain radiation therapy than those who did not (t=2.52, p<0.015). Patients demonstrated significant impairments in multiple domains of cognitive performance, e.g. attention (p<0.0001). Weak relationships were found between cognitive performance and network organization, none of which survived multiple comparison correction. CONCLUSIONS: Brain network architecture is significantly altered in pediatric brain tumor patients. Whole-brain radiation was related to the largest changes. Most network and cognitive changes were significant with large effect sizes, yet brain-behavior relationships were weak. Our results suggest that systems-level changes in brain organization may provide insight into long-term changes in brain function in pediatric brain tumor patients.

IMG-15. RADIOMIC PROFILING OF PEDIATRIC LOW-GRADE GLIOMA IMPROVES RISK STRATIFICATION BEYOND CLINICAL MEASURES

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PURPOSE: Treatment response is heterogeneous among patients with pediatric low-grade glioma (pLGG), the most frequent childhood brain tumor. Upfront prediction of progression-free survival (PFS) may facilitate more personalized treatment planning and improve outcomes for the pLGG patients. In this work, we explored the additive value of radiomics to clinical measures for prediction of PFS in pLGGs. We further sought associations between the derived risk groups and underlying alterations in key genomic and transcriptomic variables. METHODS: Quantitative radiomic features were extracted from pre-operative multi-parametric MRI scans (T1, T1-post, T2, T2-FLAIR) of 96 patients with newly diagnosed pLGG (median age, 8.59, range, 0.35-18.87 years; median PFS, 25.23, range, 3.03-124.83 months). Multivariate Cox proportional hazard's (Cox-PH) regression models were fitted using 5-fold cross-validation on a training cohort of 68 subjects and tested on 28 patients. Three models were generated using (1) only clinical variables (age, sex, and extent of tumor resection), (2) radiomic features, and (3) clinical and radiomic variables. The dimensionality of radiomic features in Cox-PH models was reduced by applying Elastic Net regularization penalty to identify a subset of variables that are most predictive of PFS. The patients were then stratified into three groups of high, medium, and low-risk based on model predictions. RESULTS: Cox-PH modeling resulted in a concordance index (c-index) of 0.55 for clinical data, 0.65 for radiomics, and 0.73 for a combination of clinical and radiomic variables, highlighting the additive value of radiomics to the readily available clinical information in prediction of PFS. Radiogenomic assessments revealed significant differences in expression of BRAF, NF1, TSC1, ALK (p<0.01), and RB1 (p<0.05) genes in the high-risk group, compared to the medium and low-risk groups. CONCLUSION: Our results demonstrate the value of integrating radiomics with clinical measures to improve risk assessment of patients with pLGG through improved pretreatment prediction of PFS.

IMG-16. NON-INVASIVE METABOLIC IMAGING OF RESPONSE TO THERAPY IN DIFFUSE MIDLINE GLIOMAS

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Diffuse midline gliomas (DMGs) are universally lethal pediatric tumors that are defined by the presence of histone H3K27 alterations. The infiltrative nature and anatomical location of these tumors prohibit surgical resection. Radiotherapy, which is standard of care, does not significantly enhance long-term outcome. Novel therapies are sorely needed for DMG patients. Imipridone drugs ONC201 and ONC206 have demonstrated anti-tumor activity in preclinical cancer models, including DMGs and have shown promise in pilot studies in DMG patients. Successful clinical deployment of imipridones requires the identification of companion imaging biomarkers that report on response to therapy. Magnetic resonance spectroscopy (MRS) is a safe, non-radioactive, non-invasive method of imaging metabolism *in vivo*. ^{1}H-MRS assesses steady-state metabolite levels and is used in clinics. ^{2}H-MRS following administration of ^{2}H-labeled substrates is a novel, clinically translatable method of imaging metabolic pathway activity. Our results indicate that treatment of SF7761 DMG cells with ONC206 causes a significant reduction in ^{1}H-MRS-detectable lactate, glutamate, glutathione and phosphocholine, pointing to inhibition of glycolysis, oxidative phosphorylation, redox and phosphatidylcholine biosynthesis respectively. Examination of [6,6'-^{2}H]-glucose metabolism using ^{2}H-MRS indicates that lactate production from [6,6'-^{2}H]-glucose is significantly reduced in ONC206-treated SF7761 cells relative to controls. We then investigated the effect of ONC206 on mice bearing orthotopic SF8628 DMG tumors. At day 7 following the treatment onset, at a timepoint when no change in tumor volume can be observed by anatomical imaging, *in vivo* ^{1}H-MRS-detectable lactate and total choline are reduced relative to day 0. Collectively, our studies indicate that imipridones induce alterations in DMG metabolism that can be leveraged for non-invasive ^{1}H- and ^{2}H-MRS-based imaging of response to therapy. By providing clinicians with an early readout of treatment response prior to anatomical changes, our biomarkers will enable early assessment of treatment response and, thereby, clinical translation of these promising therapeutics.

IMG-17. ADVANCED MRI ON THE CELLULAR AND VASCULAR PHENOTYPE OF MOUSE EPENDYMOMA MODELS AND CHEMO-RADIATION TREATMENT RESPONSE

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Ependymoma (EPN) is an aggressive pediatric brain tumor, for which the benefits of chemotherapy in pediatric patients have not been defined. EPN treated with surgery and radiation recur in 23-66% of patients. Our group has previously established aggressive behaviors of EPN, including high tumor cellularity, cytological anaplasia, high mitotic index, tumor necrosis, and the presence of inflammatory cells such as M2-type myeloid cells. Here we report on an advanced 9.4 Tesla MRI protocol for characterizing the cellular and vascular phenotype and treatment response to chemo-radiation therapy (CRT) in an orthotopic mouse model of patient derived xenografts (PDX) of pediatric EPN . Female severely immune deficient (SCID) mice were used for intracranial inoculation of disaggregated tumors from pediatric EPN patients (n=22). High-resolution T2w-MRI was able to detect cerebellar microlesions as small as 0.2 mm diameter; the median tumor volumes at the baseline were 21±12 mm3. Using diffusion-weighted based cell-size imaging, iron-oxide based vessel-size imaging and quantitative T2-maps, the EPN-specific phenotype was characterized by an increased cell size (S=14 microns), increased vessel density index (Q=0.54), and low ADC values (0.63x10-3). Once the intracranial tumors reached at least 5 mm3, animals were treated with CRT (10 Gy radiation plus 30 mg/kg 5-fluorouracil, n=6). CRT resulted in a tumor shrinkage, tumor necrosis with decreased cell sizes and increased ADC values, and a dramatic vascular-inflammatory response (decreased Q and DT2 values with the injection of iron oxide nanoparticles as macrophage-specific contrast). In summary, orthotopically implanted PDX EPN in mice closely mimic histological features, anatomical location and radiological features of the primary tumors. A significant decrease in vessel size density and an increase in inflammatory cells were seen as soon as 2 days after CRT. The late response (2 weeks post CRT) is characterized by decreased cellularity, cell size, and tumor volumes.

IMMUNOTHERAPY

IMMU-01. COMBINING CD28 AND 4-1BB COSTIMULATION *IN TRANS* ENHANCES THE ANTI-GLIOMA EFFICACY AND PERSISTENCE OF B7-H3 CAR T CELLS IN IMMUNE-COMPETENT BRAIN TUMOR MODELS

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We and others have demonstrated that B7-H3 CAR T-cells have potent antitumor responses in xenograft models for brain tumors; however, these models do not recapitulate the immunosuppressive tumor microenvironment (TME) in patients with high-grade glioma. To evaluate the safety and efficacy of antigen-specific CAR T-cells, we adapted the immune-