(p = 0.0346/p=0.1775). DISCUSSION: VSI over time provides novel information regarding the vascular heterogeneity within tumors and correlates with tumor grade and glioma subtype.

NIMG-57. BOLD fMRI REFLECTS THE LOCAL PRESENCE OF GLIOBLASTOMA

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Glioblastoma (GBM)-induced breakdown of the blood brain barrier is revealed by contrast enhancement (CE) on MRI and corresponds to the presence of bulk tumor tissue. However, vascular function in the CE area and the surrounding, non-enhancing (NE) area of infiltrating glioma cells is less defined. Resting-state BOLD (Blood Oxygen Level Dependent) fMRI has been shown to be sensitive to alterations in neurovascular coupling both within and outside the region of CE in GBM. However, the mechanism by which the tumor disrupts vascular control in these areas is not known. We hypothesize that the alterations in neurovascular coupling seen in GBM are due to the local effects of infiltrating glioma cells. To test this hypothesis, we took 25 radiographically-localized biopsies from CE (n=16) and NE (n=9) regions during open surgical resection of primary GBM in patients with preoperative resting-state BOLD fMRI. The BOLD scan was co-registered to the volumetric T1-weighted + gadolinium scan used for intraoperative stereotactic guidance and the BOLD signal intensity was calculated from a spherical region of interest (radius=2 mm) at each biopsy site. Cellularity of each sample was calculated by averaging cell counts from three high powered fields of highest cellularity on H&E stained sections. Linear robust regression was used to evaluate the relationship between mean signal intensity and cellularity. The BOLD signal intensity was positively correlated to tissue cellularity (correlation coefficient = 0.42, $p<0.01$), indicating that the neurovascular coupling mechanism is disrupted by local effects of glioma cells. Moreover, this result suggests that BOLD fMRI could serve as a clinically useful biomarker for glioma infiltration into non-contrast-enhancing brain regions.

NIMG-58. AUTOMATED APPROACH TO PREDICTING MALIGNANT TRANSFORMATIONS IN RECURRENT LOW-GRADE GLIOMAS USING EX VIVO SPECTROSCOPIC DATA

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OBJECTIVE: To automatically classify recurrent low-grade gliomas (LGGs) that remain grade II versus those that have transformation to a higher grade (grade III or IV) by applying machine learning algorithms on ex vivo nuclear magnetic resonance (NMR) data, acquired from biopsy samples of LGG patients. Multivariate statistical models were used to identify regions in the spectra that were characteristic for each group and to obtain the metabolic signatures of both types of LGGs. METHODS: Due to the high-dimensionality of spectroscopic data, we utilized orthogonal partial least squares discriminant analysis (OPLS-DA) to build the predictive model. This is a supervised learning algorithm well suited for the analysis of data where the number of observations is much smaller than the number of variables. The data comprised high-resolution magic angle spectroscopy (HRMAS) spectra of 112 image-guided tissue samples from 56 patients with recurrent LGG. Part of each sample was examined by a board-certified pathologist to evaluate histological grade and the remaining portion was analyzed using HRMAS. RESULTS: 43 samples (22 patients) originated from gliomas that remained grade II, 52 samples from 26 patients transforming to grade III and 19 samples from 8 patients transforming to grade IV. An OPLS-DA model (R2x=88%, R2y=94%, Q2=61% and root mean squared error of estimation RMSEE = 0.1) was trained and validated using leave-one-out cross-validation, resulting in mean specificity of 0.84 and sensitivity of 0.88. The peak regions containing the highest amount of discriminatory information for distinguishing between LGGs that transformed to a higher grade and those remaining grade II corresponded to glucose, myo-inositol, hypotaurine, choline, glycerophosphocholine, glutathione, 2-hydroxyglutarate, alanine, lactate and lipid. CONCLUSION: Metabolite signatures of tissue samples from lesions that remained grade II versus those that transformed to a higher grade included several features that can be measured non-invasively using in vivo H1 magnetic resonance spectroscopy.

NIMG-59. MAGNETIC RESONANCE IMAGING SEQUENCE ARTERIAL SPIN LABELING (ASL) IN THE MONITORING OF PATIENTS WITH GLIOMA: AN AID IN DETERMINING PROGRESSION VS. TREATMENT CHANGE

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INTRODUCTION: The evaluation and follow-up of patients with high grade glioma undergoing treatment continues to be a challenge. Glioblastoma is a highly vascular tumor and there is a need to assess angiogenesis in the course of treatment as response is monitored. ASL is a noninvasive perfusion imaging method which uses blood water as an infusible endogenous tracer. Serial MRI with ASL of 13 patients with treated glioma followed longitudinally over time were reviewed. METHODS: There were 7 cases of glioblastoma, 2 anaplastic astrocytomas, 1 optic glioma, 2 low grade oligodendrogliomas, and 1 low grade astrocytoma. All patients were followed by serial brain MRI, including ASL using 3D pCASL (pseudo-continuous ASL) obtained prior to gadolinium contrast administration. CBF maps (in ml/100gm/min.) were created from ASL data, and maximum CBF measurements were recorded and correlated to enhancing and non-enhancing regions of treated glioma. RESULTS: Elevated CBF values correlated with tumor progression and at times ante-dated changes seen on contrast-enhanced MRI or FLAIR. These regions of increased CBF were typically surrounded by a halo of relatively decreased CBF, probably background of treated tumor. Bland regions of relatively low CBF correlated with treatment effect when contrast-enhanced images suggested tumor progression. Increased CBF from a seizure focus in peri-ictal state can be misinterpreted as tumor progression. CONCLUSIONS: ASL is an emerging MRI technique that provides quantitative CBF measurements without contrast administration, ideal for following patients diagnosed with high grade glioma undergoing treatment. It may be helpful in the setting of a patient with suspicious progression on contrast MRI and fluid attenuated inversion recovery (FLAIR) sequences and no neurological progression, for whom treatment decisions need to be made.

NIMG-60. DIFFUSION IMAGING INTERPRETATION FOR GRADE 2 AND 3 GLIOMAS DEPENDS UPON NEW VS RECURRENT STATUS AND ENHANCING VS NON-ENHANCING STATUS

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The Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) are diffusion imaging parameters that are associated with degree of abnormal tissue microstructure in grade 2 and 3 gliomas. In the current study, we investigated whether the relationship between diffusion imaging and tumor histopathology score, tumor grade, and molecular characteristics is dependent on non-enhancing (NE) vs contrast-enhancing (CE) and newly-diagnosed (ND) vs recurrent (REC) disease status. We examined the median nADC and nFA values for the T2-FLAIR hyperintensity region and at the location of tissue samples in 110 ND-NE, 24 ND-CE, 60 REC-NE, and 40 REC-CE grade 2 and 3 glioma patients. We determined whether the effects of grade, histological diagnosis, and IDH and 1p19q status varied according to enhancement and recurrence status. Patients underwent a pre-surgical 3T MRI (T1-weighted IRSPGR, T2-weighted 3D FSE and/or XETA T2 FLAIR, and 6 directional axial Diffusion Weighted Imaging with b=1000s/mm2). In ND-NE patients, higher nADC and lower nFA were significantly associated with worse tumor score, higher grade, astrocytoma-like diagnosis, intact 1p19, and IDH mutation. However, in REC-NE patients, lower nADC was significantly associated with worse tumor score, intact 1p19q, and IDH wild-type. In CE patients, lower nADC and higher nFA were significantly associated with worse tumor score, and higher grade, and did not differ by recurrence status, diagnostic group or molecular characteristics. In ND-NE patients, higher nADC and lower nFA in may be driven by increased disruption of normal tissue architecture, whereas in CE patients and REC-NE patients, increased tumor cell density may drive lower nADC. These results suggest that when considering nADC and nFA values in tissue sample targeting and in evaluations of tumor severity and treatment response in grade 2 and 3 gliomas, the interpretation of these values depends upon the patient's enhancement and newly-diagnosed vs. recurrent status.

NIMG-61. PATTERNS OF GLIOBLASTOMA RECURRENCE IN LOW FIELD INTENSITY REGIONS DURING TTFIELDS TREATMENT

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INTRODUCTION: Glioblastoma (GBM) is an aggressive neoplasm that invariably recurs despite recent advances in therapy. Here, we describe a series of patients treated with Tumor Treating Fields (TTFields) who developed brain stem recurrence post TTFields therapy. TTFields is an FDA-approved therapeutic option for recurrent supratentorial GBM, as a monotherapy after surgical and radiation options have been exhausted, and recently in combination with maintenance temozolomide (TMZ) for treatment of newly diagnosed adult GBM patients. TTFields is a non-invasive, regional antimitotic treatment modality, alternating electric fields to tumors, through transducer arrays placed on the scalp of GBM patients. TTFields disrupts normal cell division processes, selectively targeting proliferating cancer cells. Some mechanisms of escape have been described (eg, out of field recurrence). It is known that the brainstem dose not receive high intensity TTFields due to anatomic limitations of the treatment delivery. METHODS: Six cases were obtained by retrospective chart review from multiple providers that have experience with prescribing and planning treatment with TTFields. Clinical and radiographic reviews were performed after de-identification of patient records. Cases were compared according to demographics, tumor location and molecular genetics. RESULTS: Patients were a median age of 60 years old (range 52-69), who underwent standard therapy including surgery radiation, adjuvant TMZ, and subsequently received TTFields. There were various tumor locations at baseline presentation. Median duration of TTFields prior to development of brainstem recurrence was 3.5 months, range 2-5 months. Most patients discontinued treatment on TTFields after recurrence. CONCLUSIONS: Treatment options for patients with GBM are limited, however TTFields have been shown to improve OS when added to TMZ. TTFields can only be delivered in therapeutic intensities to the supratentorial brain. These out-of-field recurrences are of concern, given the stable primary supratentorial tumor. Further investigation is warranted to improve treatment of the entire nervous system with TTFields.

NIMG-62. GENERALIZED Q-SPACE MRI (GQI) REVEALED GLIOBLASTOMA ARCHITECTURE THAT REFLECT THE DEGREE OF TUMOR NECROSIS: A POTENTIAL PROGNOSTIC IMAGING BIOMARKER

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INTRODUCTION: Glioblastoma is characterized by significant histologic heterogeneity, with varying degrees of tumor necrosis. METHODS: We utilized the generalized Q-space Imaging (GQI) algorithm to analyze MRI derived from rodent glioblastoma models and clinical images derived from glioblastoma patients. Correlative analysis was performed between GQI findings, the degree of tumor necrosis, and overall survival. RESULTS: In rodent glioblastoma models, GQI showed that glioblastomas possess a central region (termed "core") characterized by disorganized diffusion and a highly coherent periphery (termed "shell") characterized by highly organized diffusion tracts. Histologic analysis revealed that the core region was associated with a high degree of necrosis while the shell regions harbored anaplastic cells and elevated mitotic index. When GQI was applied to MRIs available through The Cancer Imaging Atlas (TCGA), we found that the core/shell (c/s ratio) varied significantly between patients. Moreover, the c/s ratio of glioblastomas linearly correlated with the degrees of necrosis observed on histologic sections ($p<0.01$). The degree of necrosis, in turn, inversely associated with patient survival. These findings were validated in an independent cohort of glioblastoma patients (n=24). CONCLUSION: GQI demonstrates regional differences in diffusion properties in glioblastomas. These differences reflect the extent of tumor necrosis and were prognostic of overall survival. These results suggest that GQI represent a non-invasive tool for assessing the anatomical organization glioblastoma and may offer prognostic value in the clinical setting.

NIMG-63. OPTIMAL PATIENT AND FAMILY EDUCATION IS KEY TO IMPROVING THE EFFICACY OF TUMOR TREATING FIELDS PLUS CHEMOTHERAPY IN TREATMENT OF GBM

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Current treatment for glioblastoma (GBM) include tumor treating fields (TTFields) in combination with adjuvant temozolomide (TMZ). TTFields are FDA-approval for recurrent and newly diagnosed GBM. TTFields are delivered though a portable, noninvasive device (Optune®, Novocure, Inc, USA) that provides localized treatment. The Optune device captures compliance data through reports that show usage over 28 days of treatment delivered throughout the day. Single-use transducer arrays connected to an electric field generator are applied to the scalp to deliver TTFields. Patient compliance is critical to optimize the overall (OS) survival advantage demonstrated by treated patients. In EF-11, which compared TTFields and provider's choice chemotherapy in recurrent GBM, patients who received daily treatment for >18 hours daily showed higher OS than <18 hours/daily. Cognitive and emotional functioning measured by the EORTC QLQ-C30 improved from baseline in the TTFields arm. In EF-14, comparing TTFields plus TMZ versus TMZ alone in newly-diagnosed GBM, cognitive functioning, emotional functioning, physical functioning, role functioning, and social functioning did not significantly decline with TTFields plus TMZ. It is imperative that patients and their family be educated on complying with 18 hour/daily treatment duration. Discussions on short, daily treatment breaks, daily exercise regimen if feasible, and other resources ('loosely woven' cranial prosthesis, wigs, sun-protecting hats) can help educate and facilitate compliance with 18 hour/daily treatment duration. The noninvasive aspect of TTFields precludes typical systemic side effects associated with chemotherapy. Adverse events associated with TTFields are mild to moderate (grade 1-2) skin irritation, which are easily managed, reversible, and didn't result in treatment discontinuation. The correlation of patient compliance with improved survival and reduced toxicities underscores importance of providing comprehensive patient/family education on use of TTFields in GBM by the treatment team. Data analyses on patient and family education provided by an interdisciplinary treatment team is ongoing and will be presented.

NIMG-64. NOVEL METHODS FOR GENOTYPE-PHENOTYPE CORRELATION IN SCHWANNOMATOSIS

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Schwannomatosis has been linked to mutations in both the *SMARCB1* and *LZTR1* genes, though the majority of cases have no known genetic association. We used a novel gene capturing technique with next-generation sequencing (NGS) and whole body MRI (WBMRI) to search for genotype-phenotype correlation within a cohort of patients with schwannomatosis. WBMRI and three-dimensional computerized volumetry were used to determine the number and volume of internal nerve sheath tumors. Custom biotinylated cRNA baits were used to capture the entire gene regions of *SMARCB1*, *LZTR1*, and *NF2* genes from patient blood samples, and next generation sequencing was performed. Genotype-phenotype correlation was evaluated using Wilcoxon and Spearman testing in SAS 9.4. Thirty-three patients with clinically diagnosed schwannomatosis were included in the study. Gene capture was excellent (approximately 72% efficient), and NGS median coverage was 938-fold. A predicted disease-causing mutation was identified in *LZTR1* in 5 patients (median age 42, 0 familial), *SMARCB1* mutation in 9 patients (median age 43, 3 familial), and neither gene in 17 patients (median age 42, 2 familial). No pathogenic *NF2* mutations were identified. Average tumor number was 2.2 in the *LZTR1* group (median total body tumor volume 20.3cc) and 5.8 in the *SMARCB1* group (median volume 130.6cc), ($p=0.4569$ for tumor number and $p=0.2775$ for volume). Median pain score was 3.6 in the *LZTR1* group and 1.6 in the *SMARCB1* group ($p=0.0392$). In conclusion, we used a highly efficient method for deep, targeted germline sequencing in patients with schwannomatosis. While numbers were small, pain was significantly higher in *LZTR1*-mutant patients than *SMARCB1*-mutant patients, which should be considered for development of disease models and targeted therapies. The anatomic limitations of WBMRI will be addressed in future studies by the addition of dedicated neuraxis imaging. Larger studies of schwannomatosis patients are needed to refine these preliminary observations.

NIMG-65. IN VIVO DETECTION OF 2-HYDROXYGLUTARATE IN LOW-GRADE IDH-MUTANT GLIOMAS WITH STABLE DISEASE

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The accumulation of 2-hydroxyglutarte (2HG) that is associated with isocitrate dehydrogenase (IDH) mutations can be non-invasively detected using MRS, with sequences such as asymmetric and 2HG-edited PRESS. Nine patients with grade 2 IDH-mutant glioma (5 oligodendroglioma and 4 astrocytoma) were studied 2-38 months after surgery and were clinically