RA-01. ELEVATED CITRATE IN PEDIATRIC ASTROCYTOMAS WITH MALIGNANT PROGRESSION
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In vivo MR spectroscopy (MRS) provides information about metabolite concentrations in tissue. Recently, citrate (Cit) was detected by MRS in subgroups of pediatric brain tumors. Citrate is an intermediate in the tricarboxylic acid (TCA) cycle and accumulated fluorescence when the glycolytic rate exceeds the TCA cycle activity, a feature of malignant tumors. Currently, no practical indicators allow clinicians to predict risk for malignant progression of pediatric astrocytomas (WHO grade II). Medical records and citrate concentrations measured with in vivo MRS of pediatric astrocytomas were reviewed. This included six astrocytomas (WHO grade II) with stable disease (indolent-LGA) for more than 2 years and 7 aggressive grade II astrocytomas (aggressive-LGA), 13 anaplastic astrocytomas (WHO grade III), and 3 glioblastomas (WHO grade IV) with disease progression within 2 years. Citrate was observed in all aggressive-LGA, and in 2 grade II astrocytomas destined for aggressive behavior. Citrate concentration was significantly higher in this group than in indolent-LGA (4.1 ± 1.1 vs 0.6 ± 0.8 mmol/kg; P = 0.0001). There was no consistent pattern for citrate in anaplastic astrocytoma and glioblastoma, with citrate prominent in some lesions while undetectable in others. It is unclear whether citrate accumulation occurred due to fundamental defects of citrate regulation, such as isocitrate dehydrogenase mutations, or secondary to altered physiological conditions. Nonetheless, prominent citrate identified a subgroup of pediatric grade II astrocytomas destined for aggressive behavior. Citrate was not specific for poor outcome as it was not detectable in all high-grade astrocytomas. Among high-grade astrocytomas, tumors with prominent citrate may constitute a metabolic subclass.

RA-02. 11C-METHIONINE UPTAKE AND INTRAOPERATIVE 5-AMINOLEVULINIC ACID-INDUCED FLUORESCENCE ARE SEPARATE INDEX MARKERS OF CELL DENSITY IN GLIOMAS: A SATELLITE IMAGE-HISTOLOGICAL ANALYSIS
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OBJECTIVE: Current standard treatment for glioma is surgical resection followed by radiochemotherapy. The extent of tumor resection is acknowledged as one of the prognostic factors for glioma. 5-aminolevulinic acid (5-ALA)-induced fluorescence guidance and neuronavigation integrated with 11C-methionine positron emission tomography (PET) are widely utilized with the expectation of improving the extent of resection. These 2 novel approaches are beneficial for glioma resections, and the combination of these approaches in glioma surgery appears rational. However, biological characteristics between 5-ALA-induced fluorescence and 11C-methionine uptake have not been clearly elucidated, and studies about the relationship between 5-ALA-induced fluorescence and 11C-methionine uptake have been limited. METHOD: Thirty samples from 11 patients with astrocytic tumors were stereotactically obtained from the relative periphery showing an excellent correlation with the tumor cell density (R2 = 0.9). This correlation was better than the correlation between 11C-methionine uptake and tumor cell density (R2 = 0.8). Moreover, a cut-off value of 2 in the decoupling score was sensitive enough to detect 1,000 tumor cells/mm2, which was not possible by 11C-methionine PET alone. The presented semi-automatic, user-independent analysis of 2 major tracers (or deviation from the expected correlation of 5-ALA-induced fluorescence and 11C-methionine PET imaging) was not specific for poor outcome as it was not detectable in all high-grade astrocytomas. Among high-grade astrocytomas, tumors with prominent citrate may constitute a metabolic subclass.
bevacizumab treatment, but further investigation is necessary to prospectively test this correlation and understand the underlying physiology.

RA-05. ANALYTIC LOCALIZATION OF O6-METHYLGUANINE DNA METHYLTRANSFERASE (MGMT) PROMOTER METHYLATED AND UNMETHYLATED TUMORS: AN ADIFFI STATISTICAL MAPPING STUDY IN 384 DE NOVO GLOBLASTOMA PATIENTS

Benjamin M. Ellingson, Timothy F. Cloughesy, Whitney B. Pope, Taryar Zaw, Heidi Phillips, Shadi Lalezari, Phioanh L. Nghiemphu, Hassana Ibrahim, Korosh Motevallibashinaeini, and Albert Lai; 1University of California Los Angeles, Los Angeles, CA; 2Genetech, San Francisco, CA

Promoter methylation of O6-methylguanine-DNA methyltransferase (MGMT) is associated with a favorable prognosis in glioblastoma multiforme (GBM) and has been hypothesized to occur early in tumor transformation of glial cells. Thus, a possible link exists between the site of malignant transformation and MGMT promoter methylation status. Using the Analysis of Differential Involvement (ADIFFI) statistical mapping technique in a total of 384 patients with GBM, we demonstrate that human de novo GBMs occur in a high frequency contiguous with the posterior subventricular zone (SVZ). MGMT promoter methylated GBMs are lateralized to the left hemisphere, while MGMT unmethylated GBMs are lateralized to the right hemisphere; and tumors near the left superior temporal gyrus to the temporal-parietal junction have a significantly longer overall survival compared with tumor occurring elsewhere, independent of treatment or MGMT methylation status (Cox proportional hazard analysis; KPS, P = 0.0001; MGMT methylation status, P < 0.0001; confluent with ADIFFI “cluster,” P = 0.0072).

RA-06. FUNCTIONAL DIFFUSION MAPS IN FLAIR ABNORMAL REGIONS PREDICT SURVIVAL IN BOTH NEWLY DIAGNOSED GLOBLASTOMA TREATED WITH RADIOCHEMOTHERAPY AND RECURRENT GLOBLASTOMA TREATED WITH BEVACIZUMAB

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Functional diffusion mapping (fDM), a technique that uses voxel-wise changes in apparent diffusion coefficient (ADC) calculated from diffusion MRI, has shown great promise as both an early predictor of response to therapy and as a clinical monitoring tool for patients with malignant gliomas. Despite promising initial findings in conventional cytotoxic therapy and anti-angiogenic therapies, fDMs have only been evaluated in a relatively small cohort of glioma patients. Furthermore, glioblastoma patients were not evaluated exclusively, suggesting these early results may have been sensitive to tumor grade and not solely on response, as these factors were not originally accounted for in initial studies. In the current study, we evaluated the prognostic ability of early fDMs calculated in FLAIR abnormal regions before and after radiochemotherapy in 94 patients with de novo glioblastoma as well as before and after bevacizumab treatment in 77 patients with recurrent glioblastoma. Results suggest newly diagnosed patients having a volume of tissue exhibiting a significant decrease in ADC (eg, hypercellular tissue) greater than 13 cc had a significantly shorter progression-free survival (log-rank, P = 0.003). Additionally, recurrent glioblastoma patients treated with bevacizumab having a volume of tissue exhibiting a significant decrease in ADC greater than 13 cc had a significantly shorter overall survival (log-rank, P = 0.003). Results support the hypothesis that fDMs are predictive biomarkers in patients with glioblastoma, independent of treatment paradigm.

RA-07. RESTING-STATE NETWORK PROPERTIES AND SEIZURE OUTCOME AFTER BRAIN TUMOR RESECTION

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Brain tumors are accompanied by a range of symptoms, including cognitive deficits and epilepsy. Resection is often performed, but the outcome of neurosurgery unexplainably varies across individual patients. A new method of investigating the functional status of the brain is by applying “network theory” to neurophysiological measurements. By calculating functional connectivity between different brain areas, a network of the brain can be constructed. The brain network tends to be a “small world,” combining both local specialization and overall global integration. It is clear that brain networks are suboptimal (and thus less small world) in brain tumor patients. The aim of this study was assessing the effects of brain tumor resection on functional connectivity and network properties and correlating them with epilepsy outcome, in order to investigate whether brain tumor resection leads to improved network organization. Resting-state magnetoencephalography recordings of 15 brain tumor patients before and after tumor resection were studied. Two measures of functional connectivity were calculated in 5 frequency bands ranging from delta to beta. Weighted networks were constructed and several properties (path length for global integration, clustering coefficient for local specialization, overall small-world-ness) were calculated. Total SIL scores increased in the beta band after surgical intervention, while a decrease in interhemispheric theta band phase lag index has been reported previously. After resection, SIL-based clustering coefficient and small-world index increased in the low alpha band, indicating more optimal network architecture after surgery. Moreover, patients who were seizure-free after surgery showed an increase in small-world index, while those still suffering from seizures did not show a significant change in small-world topology after tumor resection. The changes in functional connectivity and network properties observed after tumor resection seem to indicate normalization of these characteristics, which is correlated with postoperative seizure outcome.

RA-08. TRYPTOPHAN KINETICS MEASURED BY AMT-PET IN LOW-PERFUSION AND HIGH-PERFUSION BRAIN TUMORS

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INTRODUCTION: Dynamic [11C]methyl-L-tryptophan positron emission tomography (AMT-PET) studies have suggested that increased tryptophan transport rates (characterized by AMT volume of distribution [VD]) correlate with increased tumor proliferation, while increased unidirectional AMT uptake ratios (K-ratios) are caused by tryptophan transport rates (VD-ratios) and also have a higher tumor histologic grade. Increased unidirectional AMT uptake ratios (K-ratios) are unrelated to tumor perfusion (P = 0.4). CONCLUSIONS: Brain tumors of various grades demonstrate high AMT SUVs regardless of perfusion status. High-perfusion lesions show higher tryptophan transport rates (VD-ratios) and also have a higher tumor histologic grade. Increased unidirectional AMT uptake rates (K-ratios) are unrelated to tumor perfusion and may be caused by kynurenine pathway activation, which is thought to be a mechanism of tumor immune resistance.

RA-09. INTENSITY NORMALIZATION TECHNIQUES FOR MULTICENTER CLINICAL TRIAL EVALUATION OF DYNAMIC SUSCEPTIBILITY CONTRAST (DSC)-MRI ESTIMATES OF CEREBRAL BLOOD VOLUME (CBV) IN HUMAN GLIOMAS

Benjamin M. Ellingson, Timothy F. Cloughesy, Taryar M. Zaw, Shadi Lalezari, Phioanh L. Nghiemphu, Korosh Motevallibashinaeini, Albert Lai, Jonathan Golden, and Whitney B. Pope; University of California Los Angeles, Los Angeles, CA

Dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) is a well-established biomarker for cerebral blood volume (CBV) evaluation in gliomas; however, DSC-MRI estimates of CBV are subject to
and relative. The use of image intensity transformation algorithms provides a mechanism for obtaining quantitatively similar CBV maps in the same intensity scale. In the current study, we compare “standardization,” “Gaussian normalization,” and “Z-score normalization” CBV transformation techniques. To accomplish this, the coefficient of variance (CV) in normal appearing white matter and contrast-to-noise ratio (CNR) was compared between the 3 CBV transformations across 3 different MR scanners in 96 patients with gliomas. Results: Standard normalization of 18F-FDOPA PET maps provided the lowest CV in normal white matter (19% vs 22%-31% for other techniques), and was statistically better than the other techniques when different MR scanners were used at follow-up. Additionally, Gaussian normalization provided the highest tumor contrast-to-noise for all tumor grades (approximately 25% higher compared to other techniques). In summary, results suggest Gaussian normalization of leakage-corrected CBV maps may be the best choice for image intensity correction for use in large scale, multicenter clinical trials where MR scanners and protocols vary widely.

RA-10. 3,4-DIHYDROXY-6-18F-FLUORO-L-PHENYLALANINE POSITRON EMISSION TOMOGRAPHY PARAMETRIC RESPONSE MAPS (18F-FDOPA PET PRMS) PREDICT SURVIVAL IN RECURRENT GLOBLASTOMA TREATED WITH BEVACIZUMAB. Benjamin M. Ellingson, Timothy F. Cloughesy, Robert Harris, Whitney B. Pope, Phoebah L. Ngheimhut, Albert Lai, Tatyar Zaw, and Wei Chen; University of California Los Angeles, Los Angeles, CA

Amino acid and amino acid analog positron emission tomography (PET) tracers are a unique class of brain tumor imaging agents that have demonstrated high specificity for detecting brain tumor recurrence because of high tumor accumulation and low uptake in normal brain. In the current study, we examined the diagnostic ability of voxel-wise changes in 3,4-dihydroxy-6-18F-fluoro-l-phenylalanine (18F-FDOPA) PET uptake, or 18F-FDOPA PET parametric response maps (PRMs), to predict survival in 17 recurrent glioblastoma patients evaluated before and after treatment with bevacizumab. Results suggest the percentage of pre-treatment contrast-enhancing tumor that showed a significant decrease in 18F-FDOPA PET uptake was linearly correlated with overall survival (Pearson correlation coefficient, R2 = 0.2832, P = 0.0279). Patients exhibiting a decrease in 18F-FDOPA PET after bevacizumab in more than 25% of pre-treatment contrast-enhancing tumor regions had more than a 6-month median survival advantage (log-rank, P = 0.0098).

RA-11. A NEW METHOD FOR DETECTING CANCER USING F-18 FDG DUAL-POINT SUBTRACTION CO-REGISTERED TO MR. Mark A. Ahlman and Pierre Giglio; Medical University of South Carolina, Charleston, SC

Cancer continues to retain F-18 fluorodeoxyglucose (FDG) at delayed imaging time points, whereas inflammatory or normal tissue releases tracer sooner. Using this mechanism, early evidence has shown that dual-point or delayed imaging of cancer with FDG can help differentiate inflammatory or normal tissue from neoplastic disease. We describe 2 cases where our novel protocol of Dual-Point PET Subtraction Co-registered to MR (DPPSCOM) with FDG appears to show excellent qualitative and quantitative spatial resolution for recurrent disease. Patient 1 has a left parietal metastasis from breast cancer previously treated with chemotherapy and radiation. MR spectroscopy was suggestive of recurrence of disease along the lateral border of the lesion. Ten-minute early and delayed PET images of the brain were taken at ~60 and 240 minutes uptake time, respectively. Standard uptake value measurements and visual analysis did not disclose any significant abnormalities or differences in metabolism between the time points. DPPSCOM clearly showed “positive” areas that directly corresponded with the positive MR spectroscopy region of interest. Patient 2 has a GBM treated with chemotherapy and radiation. Regional cerebral blood volume (CBV) by MR was suggestive of recurrence. Using a similar technique as with patient 1, DPPSCOM showed excellent correlation with CBV but also showed a gradient of information that appears to demonstrate the heterogeneous activity of cancer with useful quantitative information. Early experimentation with DPPSCOM demonstrates exciting results and employs a technique that utilizes the same radiotracer, equipment, and staff available to most tertiary nuclear medicine departments. DPPSCOM may be useful for higher yield and accurate 3D biopsy and surgical planning, radiation treatment planning, and increased sensitivity for identifying recurrent tumor in PET positive cancer, particularly early for the CNS. Further study is ongoing to technically validate the procedure and idealize the protocol for easy processing, accurate interpretation, and integration into intervention planning software.

RA-12. IMPROVED OUTCOME IN RECURRENT GLOBLASTOMA (RGBM) PATIENTS TREATED WITH BEVACIZUMAB (BEV) AND SORAFENIB (SOR) IS PREDICTED BY A GREATER DROP IN APPARENT DIFFUSION COEFFICIENT (ADC) ON MRI IMAGING. Timothy J. Kaufmann1, S. Keith Anderson2, Kurt A. Jaeckle3, Joon H. Uh1, Donald W. Northfelt4, Patrick J. Flynn4, Jann C. Buckner4, and Eva Galanis5; Mayo Clinic Rochester, MN; 2Mayo Clinic Jacksonville, FL; 3Mayo Clinic Scottsdale, AZ; 4Minneapolis Oncology, Minneapolis, MN

INTRODUCTION: Antiangiogenic therapy is associated with sometimes dramatic drops in the apparent diffusion coefficient (ADC). Low ADC in tumors is often a poor prognostic sign, as it in part reflects tumor cellularity. However, antiangiogenic therapy has an edema-decreasing effect that also lowers ADC, and the significance of large drops in ADC while on such therapy is unknown. METHODS: MRI scans of 19 patients enrolled in the North Central Cancer Treatment Group phase II trial of bevacizumab (BEV)/sorafenib (SOR) in the treatment of recurrent glioblastoma were evaluated at baseline (n = 19), at day 3 (n = 8), and at 4 weeks (n = 19), blinded to clinical outcomes. Regions of interest were drawn around enhancing tumor on each scan, and ADC statistics were calculated for baseline ADC and change in ADC, including the use of 2-mixture generalized lambda distributions to model the ADC histogram data. Linear models along with Kaplan-Meier and Cox proportional hazards models were used to correlate ADC metrics with progression-free survival (PFS) and overall survival (OS).

RESULTS: The change in ADC from baseline to 4 weeks following initiation of BEV/SOR correlated with survival statistics. Specifically, the Kaplan-Meier survival curves were less favorable for those with less than a 25% decrease in mean ADC (HR = 3.9, P = 0.018 for OS, and hazard ratio = 4.8, P = 0.012 for PFS). Changes in ADC by day 3 were not associated with survival. PFS tended to increase as the mean ADC of the lower distribution of ADC for baseline scans increased (slope = 0.334, P = 0.071). CONCLUSION: A decrease of more than approximately 25% in mean ADC following the initiation of antiangiogenic therapy represents a favorable prognostic factor. This is in contradistinction to prior initiation of antiangiogenic therapy, when a lower ADC has been previously shown to be a negative prognostic sign.

RA-13. NOVEL USE OF MR SPECTROSCOPY TO DETECT CREBROSPINAL FLUID LACTATE AND DIAGNOSE NEOPLASTIC MENINGITIS. Omar Zalatim1, Cody Weston1, Dana Allison2, Daniela Bot2, Santosh Kunwar3, Michael Glantz2, Jonas Sheehan1, and Robert E. Harbaugh4; 1Penn State Hershey Medical Center, Hershey, PA; 2University of Utah School of Medicine, Salt Lake City, UT

INTRODUCTION: Neoplastic meningitis (NM) affects at least 5% of all cancer patients. If diagnosed early, intrathecal chemotherapy can ameliorate neurologic symptoms and prolong survival in this patient population. Currently, the gold standard in diagnosis is by cerebrospinal fluid (CSF) cytology, which has a poor sensitivity of 40-65%. The level of lactate acid in CSF is reliably elevated in NM, and is an effective method to characterize the concentration of clinically relevant metabolites. The aim of this study was to determine the diagnostic utility of ventricular MRI spectroscopy (MRS) in patients with suspected NM. METHODS: We performed a retrospective chart and imaging review of 21 patients with known cancer and progressive neurologic symptoms suspicious for NM. Data collected on each of the patients included demographic information and CSF cytology. Ventricular MRS was reviewed by an independent blinded radiologist. RESULTS: Of the 21 patients, 15 (71%) were male. The sensitivity and specificity for MRS was 95% and 71%, respectively, with a positive likelihood ratio of 3.3 and diagnostic odds ratio of 32.5. Previous studies have shown that 19% of patients with known cancer and neurologic findings have NM. Using these data with our results, the chance of a cancer patient with neurologic symptoms having NM is 83%, and if the MRS is negative, the chance becomes 23%. CONCLUSIONS: Ventricular MRS is a reliable non-invasive diagnostic tool with a high sensitivity and specificity that can be used in diagnosis of NM. Further studies are needed to confirm its utility in prognostication and effect on survival.

RA-14. VOXEL-WISE FUNCTIONAL 11C-METHIONINE POSITRON EMISSION TOMOGRAPHY ANALYSIS BUT NOT CONVENTIONAL MRI CORRESPONDS TO TREATMENT RESPONSE OF WT1 IMMUNOTHERAPY FOR RECURRENT HIGH-GRADE GLIOMA. Yasuyoshi Chiba, Manabu Kinoshita, Naoki Kagawa, Yasunori Fujimoto, Akhiro Tsubo, Jun Hatahara, Haruo Sugiyma, Naoya Hashimoto, and Toshibi Yoshimine; Osaka University Graduate School of Medicine, Suita, Japan
OBJECTIVE: The purpose of this study was to evaluate early changes in volumes and apparent diffusion coefficient (ADC) in the contrast-enhancing high-grade glioma (CEL) and non-enhancing lesion (NEL) of post-surgical newly diagnosed grade IV glioma patients being treated with radiotherapy (RT) and 3 different treatment regimens. METHODS: Ninety-nine patients were evaluated: 31 with temozolomide (TMZ) alone, 41 with TMZ and an anti-vascular endothelial growth factor (VEGF) agent, and 27 with TMZ and an anti-protein kinase C (PKC) agent. RESULTS: From pre- to post-RT, patients receiving RT + TMZ alone demonstrated no significant change in CEL or NEL volumes. The median nADC in the CEL and NEL significantly increased (P < 0.0004 and P < 0.0014), respectively. Patients receiving the anti-PKC agent demonstrated a significant decrease in CEL volume (P < 0.0015) but no change in NEL volume. The median nADC increased significantly in the CE and NEL (P = 0.0001 and P = 0.0033). Patients receiving the anti-VEGF agent reduced edema more effectively than the anti-PKC agent and reduced the magnitude of the RT effect more than either the anti-PKC agent or TMZ alone. While it is too early to evaluate the relationship of these early changes to survival, this will be achieved as soon as the data become available.

RA-15. INITIAL CLINICAL TRIALS OF CARBON-11-Labeled 4DST For MALIGNANT BRAIN TUMORS AS A PET MOLECULAR IMAGING PROBE TO MEASURE DNA SYNTHESIS RATE
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INTRODUCTION: As uncontrolled cell proliferation is an integral part of malignant tumor, measurement of the DNA synthesis rate of tumor tissues in vivo is an important goal of tumor diagnosis. Recently, we developed [methyl-11C]4-thiothymidine ([11C]4DST) as a novel DNA synthesis marker usable as a positron emission tomography (PET) molecular imaging probe. This is the first clinical PET probe ever reported: its incorporation into the DNA fraction of tumors was biochemically confirmed (Toyohara et al. J Nucl Med. 2006; 47:1717). In our first clinical trials of using this probe for patients with malignant brain tumor, we aimed to examine this molecular imaging technique to provide useful information that cannot be obtained by other present imaging methods. METHODS: Nine patients with malignant brain tumors (6 malignant glioma, 2 metastatic tumor, and 1 malignant lymphoma) and 3 normal controls underwent [11C]4DST PET scans. [11C]methionine ([11C]MET) PET scans were also performed in the same day. RESULTS: There were no adverse events throughout the study period. [11C]4DST showed little uptake in the normal brain, resulting in low background for imaging of brain tumors. [11C]4DST PET demonstrated rapid tumor uptake and retention of radioactive in patients with aggressive tumor masses. Patlak plots showed a linear increase, indicating irreversible trapping of [11C]4DST in tumor tissues. The distribution pattern of [11C]4DST in tumor regions was not always identical to that of [11C]MET. Large discrepancies were noted in tumors that showed effective treatment with temozolomide or gamma knife radiosurgery and those that did not.

RA-17. PREDICTION OF HIGH-GRADE MENINGIOMA BASED ON THE ASSESSMENT OF PREOPERATIVE MRI
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High-grade (atypical or anaplastic) meningiomas grow aggressively and recur frequently, resulting in poor prognosis. As the utility of noninvasive treatments for brain tumors increases, it is becoming important to assess the likelihood that a tumor is not benign before treatment initiation. We attempted to find the characteristics to determine risk factor for high-grade meningioma on MR imaging before operation. We reviewed 65 meningiomas (benign, 39 cases; high-grade, 26 cases) and assessed 4 characteristics: 1) tumor-brain interface (TBI) on T1-weighted imaging; 2) capular enhancement: the layer of the brain-tumor interface on T1-weighted gadolinium-enhanced imaging (T1Gd); 3) heterogeneity on T1Gd; and 4) tumor 1 (WT1) gene product in patients with recurrent high-grade gliomas (HGG). The WT1 is a member of the Kruppel-like factors, which have been identified as being overexpressed in glioblastoma multiforme (GBM) (Frischer et al. Cancer Res. 2000; 64:4023-33). We assessed the correlation between the expression of WT1 and the risk factors for high-grade meningiomas. The expression of WT1 was evaluated by the image analysis software. RESULTS: The significant difference was found between high-grade and benign meningiomas in TBI (P < 0.001) and heterogeneity (P < 0.001). The median expression of WT1 was significantly increased in high-grade meningiomas (P < 0.001) compared with benign meningiomas. CONCLUSION: The expression of WT1 was significantly increased in high-grade meningiomas. TBI and heterogeneity were useful characteristics to determine high-grade meningioma. Our results suggest that conventional MR imaging is still useful to detect malignant meningioma, even though some advanced MR imaging techniques have shown potential for differentiating benign and high-grade meningiomas.
at baseline and on follow-up MRI. RESULTS: For the 13 patients, 7 required treatment (surgery and/or chemotherapy) for symptomatic tumor progression (5 sporadic OPGs and 2 cases of NF-1). The median follow-up interval was 15 years (range, 7 months to 10.5 years). There was no difference in ADC values between sporadic and NF-1-associated OPG. OPG that required therapy had significantly higher baseline mean ADC (1389 x 10^(-3) mm²/s; SD, 0.22), whereas OPG with low mean ADC (1235 x 10^(-3) mm²/s; SD, 0.18) remained clinically asymptomatic and stable (Stratified Mann-Whitney test, P = 0.0002). An increase in mean ADC of 100 x 10^(-3) mm²/s doubled the odds the patient will require treatment (odds ratio = 2.16; 95% confidence interval, 1.35-3.10; P < 0.0001). Enhancing tumor patterns did not produce a visible change in tumor status (Fisher’s exact test, P = 0.192). CONCLUSION: Significantly higher mean ADC was seen in OPG that required therapy for tumor progression. MRI may be a useful prognostic tool in further defining a subset clinically significant sporadic or NF-1-associated OPG.

RA-19. COMPARISON OF VOLUME CHANGES IN ELEVATED RCBV AND ANATOMIC LESIONS IN PATIENTS WITH NEWLY DIAGNOSED GBM BEING TREATED WITH RT AND EITHER TMZ ALONE, TMZ + ANTI-VEGF OR TMZ + ANTI-PKC THERAPIES
INTRODUCTION: Standard measures for assessing therapy response for patients with glioblastoma multiforme (GBM) depend on volume changes in the anatomic lesion in MR images. Because anti-angiogenic therapies induce vascular remodeling that may alter the apparent contrast enhancement lesion (CEL) and T2 lesion (T2L), there is a need for alternative response assessment metrics. Dynamic Susceptibility Contrast (DSC) imaging is a promising method for this application because it provides a measure of elevated relative cerebral blood volume (rCBV), a marker of increased perfusion and malignant tumor. METHODS: 103 patients newly diagnosed with GBM were imaged on a 3-T MR scanner. This study population included all patients thought to have glioblastoma. Patients were followed up with volume FLAIR sequences that gave high tumor-to-brain contrast. A semi-automated assessment of tumor volume was efficiently estimated via the MIM software. This study confirmed that quantitative tumor volume assessments can be performed in a clinical setting, which informs management decisions.

RA-20. SEMI-AUTOMATED VOLUMETRIC ANALYSIS OF LOW-GRADE GLIOMAS
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INTRODUCTION: Accurate volume measurement is important in predicting outcome and defining management plans in patients with low-grade gliomas (LGGs). Volume assessments are potentially more accurate than linear measurements. This work aims to study the initial impact of semi-automated volumetric analysis in the clinical setting. METHODS: LA vs. 3D LA were followed up with volume FLAIR sequences that gave high tumor-to-brain contrast. A semi-automated assessment of tumor volume (MIM software, www.mimsoftware.com) was based on a thresholding and region-growing technique. Longitudinal studies over time were spatially coregistered and difference images allowed a visual assessment of areas of apparent tumor growth. A total of 137 studies have been processed in 85 patients (44 men, 41 women; mean age, 44.13 years). Histology was available in 22 patients (6 WHO grade II gliomas, 7 WHO grade III gliomas, 1 WHO grade II oligodendroglioma, 6 WHO grade III anaplastic, and 2 WHO IV). Seventeen of the remaining 63 patients were presumed LGGs undergoing radiological follow-up only. Patients had between 1 and 6 studies over up to 3 years of follow-up. RESULTS: Calculated tumor volumes were 0.03-160.67 mL. In patients receiving chemotherapy, the average rate of tumor volume change was 0.05% per month. These results suggested that semi-automated volumetric analysis provided accurate volumetric measurements in a busy neuro- oncologic practice. The purpose of this retrospective study was to evaluate the role of non-model-based semi-quantitative indices obtained from DCET1 MR perfusion (DCET1MRP) in differentiating pseudo-progression from true progression. Forty-eight (30%) of 162 patients were diagnosed with diffuse intrinsic pontine gliomas, and are frequently treated without biopsy. We present a case of a 22-month-old female who presented with a wide-based, unsteady gate, facial asymmetry, and disconjugate gaze that developed over a period of weeks. MRI showed a non-enhancing, lobulated expandable pontine mass, with satellite lesions. Because of the atypical imaging characteristics, biopsy was performed. The unexpected diagnosis of pilomyxoid astrocytoma, a tumor type not previously described in this location, was made. This case should serve to expand the radiographic differential diagnosis of atypical pontine tumors, and we recommend consideration of biopsy to confirm pathologic diagnosis.

RA-21. PILOMYXOID ASTROCYTOMA OF THE PONS
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Aggressive appearing pontine neoplasms, which manifest on MRI as infiltrative, expansile, and occasionally enhancing, are not uncommon to represent diffuse intrinsic pontine gliomas, and are frequently treated without biopsy. We present a case of a 22-month-old female who presented with a wide-based, unsteady gate, facial asymmetry, and disconjugate gaze that developed over a period of weeks. MRI showed a non-enhancing, lobulated expansile pontine mass, with satellite lesions. Because of the atypical imaging characteristics, biopsy was performed. The unexpected diagnosis of pilomyxoid astrocytoma, a tumor type not previously described in this location, was made. This case should serve to expand the radiographic differential diagnosis of atypical pontine tumors, and we recommend consideration of biopsy to confirm pathologic diagnosis.

RA-22. ROLE OF NON-MODEL-BASED SEMI-QUANTITATIVE INDICES OBTAINED FROM DCET1 MR PERFUSION IN DIFFERENTIATING PSEUDO-PROGRESSION FROM TRUE-PROGRESSION
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Increasing use of various combinations of aggressive chemotherapy and radiation therapy for gliomas has led to complex post-treatment morphologic and imaging appearance, and “pseudo-progression” is not uncommon in a busy neuro-oncologic practice. The purpose of this retrospective study was to evaluate the role of non-model-based semi-quantitative indices obtained from DCET1 MR perfusion (DCET1MRP) in differentiating pseudo-progression from true progression. Forty-eight (30%) of 162 patients were diagnosed with diffuse intrinsic pontine gliomas, and are frequently treated without biopsy. We present a case of a 22-month-old female who presented with a wide-based, unsteady gate, facial asymmetry, and disconjugate gaze that developed over a period of weeks. MRI showed a non-enhancing, lobulated expansile pontine mass, with satellite lesions. Because of the atypical imaging characteristics, biopsy was performed. The unexpected diagnosis of pilomyxoid astrocytoma, a tumor type not previously described in this location, was made. This case should serve to expand the radiographic differential diagnosis of atypical pontine tumors, and we recommend consideration of biopsy to confirm pathologic diagnosis.

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David Jellinek, Paul D. Griffiths, David Jellinek, Paul D. Griffiths, David Jellinek, Paul D. Griffiths

The purpose of this study was to evaluate the role of tumor blood volume measured using DSC T2* MR perfusion in survival prediction compared to the molecular sub-classes of glioblastoma multiforme (GBM). Fifty-seven patients with treatment-naive GBM underwent DSC T2* MR perfusion studies at 2 different institutes. Of these, 30 patients had gene expression data available from TCGA. Relative cerebral blood volume (rCBV) maps were generated using NordicICE (Nordic Neuro Lab) software using leakage correction. rCBVmax and rCBVmean of the contrast-enhancing part of the lesion (CER) as well as rCBV_NEL of the non-enhancing part of the lesion (NEL) were measured. All the patients were sub-classified into classical, mesenchymal, neuronal, and proneural based on Verhaak classification, and also into mesenchymal, proneural, and proliferative based on the Phillips classification system. We correlated the perfusion parameters with the molecular sub-classes as well as with patient survival. Cox regression was used to test the association of the perfusion parameters with survival accounting for potential confounders. Additionally, we included each of the Verhaak and Phillips classification groups as predictors. P-values were derived from Wald chi-square tests of the hazard ratio. No statistically significant differences were noted for rCBVmax and rCBVmean as well as rCBV_NEL between the 4 classes using Verhaak or 3 classes using Phillips classification system.

INTRODUCTION: Glioblastoma multiforme is a tumor that occurs in patients with acute myeloid leukemia (AML) and rarely involves the central nervous system. Here we report the first case of a ring-enhancing, intracranial granulocytic sarcoma and its management.

RA-25. ATYPICAL IMAGING APPEARANCE OF INTRACRANIAL GRANULOCYTIC SARCOMA
Nandini Guha-Thakurta and J.M. Debnath; The University of Texas MD Anderson Cancer Center, Houston, TX

INTRODUCTION: Granulocytic sarcoma is a tumor that occurs in patients with acute myeloid leukemia (AML) and rarely involves the central nervous system. Here we report the first case of a ring-enhancing, intracranial granulocytic sarcoma and its management. CASE REPORT: A 26-year-old man with AML relapsed on chemotherapy. On presentation to the ER with fever and dizziness, imaging of the brain revealed no evidence of an intracranial abnormality. Due to absence of neurologic deficits and presence of positive blood cultures, broad-spectrum antimicrobials and anti-toxoplasmosis drugs were started. A repeat MRI scan following development of a headache revealed a ring-enhancing mass in the left cerebral hemisphere. After a 10-day interval, a minimal increase in the size of the mass was noted on follow-up MRI, while diffusion-weighted imaging (DWI) did not reveal any restricted signal, excluding a pyogenic abscess. Following a non-diagnostic biopsy, the mass was surgically resected, and histological examination led to the diagnosis of granulocytic sarcoma. The patient received radiotherapy and stem cell transplant after surgery and is currently disease-free. CONCLUSIONS: Intracranial granulocytic sarcomas are predominantly described as homogeneously enhancing extra-axial tumors and rarely as intra-axial lesions. Since their appearance as a ring-enhancing mass has not been reported before, DWI can aid in differentiating such a manifestation from a pyogenic abscess. This is especially relevant in the context of an underlying systemic infection. Adequate and timely therapy can result in complete response without neurologic deficits.

RA-26. USE OF MR SPECTROSCOPY AND DIFFUSION TO DIFFERENTIATE GBM FROM SOLITARY CEREBRAL METASTASES
Christina Kotsaris, Iain D. Wilkinson, David Jellinek, Paul D. Griffiths, Nader Khandanpour, and Nigel Hoggard; Sheffield, United Kingdom; Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, United Kingdom

INTRODUCTION: Differential diagnosis between glioblastomas and metastatic lesions is often impossible based on conventional MRI. Yet, they have a vastly different therapeutic approach. The aim of the study was to evaluate the ability of 3-T physiological MRI in the discrimination of these common tumor types. METHODS: Thirty-seven patients with glioblastomas and 15 patients with metastatic lesions were examined prior to treatment with conventional MRI followed by MR spectroscopy, diffusion-weighted imaging, and perfusion-weighted imaging. The diagnostic accuracy of these parameters was estimated based on receiver operator characteristic curves. RESULTS: Significant differences were found in NAA/Cr area ratios (P = 0.013), Cho/Cr area ratio (P = 0.014), and height (P = 0.023) ratios between glioblastomas and metastatic tumors. The most prominent difference was found in Cr/Cr2 area ratio (P = 0.006) and height (P = 0.001) ratios as well as apparent diffusion coefficient (ADC) (P = 0.002) and ADC ratios (P = 0.017). The diagnostic accuracy of Cr/Cr2 height ratio and ADC was 0.92 and 0.86, respectively. When ADC was added to the Cr/Cr2 height ratio, 96% of glioblastomas and 90% of metastatic tumors were correctly classified (94.3% of the cases). CONCLUSION: MR imaging seems to be able to differentiate between glioblastomas and metastatic lesions. Differences in Cr/Cr2 ratio probably reflect diverse metabolic energy pathways in this new biomarker whose significance needs further investigation. Diffusion imaging seems to have a complimentary role while perfusion measurements do not.

RA-27. CHO/CR RATIO APPEARS TO BE AN INDEPENDENT IMAGING BIOMARKER OF SURVIVAL FOR PATIENTS NOT SUITABLE FOR OPEN RESECTION OF GliOBLASTOMA
Christina Kotsaris, Iain D. Wilkinson, David Jellinek, Paul D. Griffiths, Paul Bambrough, and Nigel Hoggard; University of Sheffield, Sheffield, United Kingdom; Sheffield Teaching Hospital NHS Foundation Trust, Sheffield, United Kingdom

INTRODUCTION: Patients not suitable for open glioblastoma resection comprise a rather neglected category characterized by unawareness and uncertainty concerning the appropriate treatment and overall prognosis. The aim of this study is to identify physiological MR imaging biomarkers that can be measured non-invasively and help predict the outcome in patients with newly diagnosed, non-operative tumors. METHODS: Twenty-four patients with gliomas were identified who were deemed inoperable due to poor performance status and/or position of the tumor.

RA-24. THE APPLICATION OF MRI FOR DISTINCTION BETWEEN GBM PROGRESSION AND PSEUDOPROGRESSION IN PATIENTS TREATED WITH STANDARD CHEMORADIO THERAPY – PRELIMINARY DATA
Leor Zach, David Guez, David Last, Dianne Daniels, Chen Hoffman, and Yael Mardor; Sheba Medical Center, Ramat-Gan, Israel

Previous studies suggest that a significant number of glioblastoma multiforme (GBM) patients with radiological deterioration after chemoradiation do not suffer from tumor recurrence but from pseudoprogression induced by the treatment. Reliable distinction between these conditions is essential for appropriate patient management. We have recently demonstrated the advantages of a delayed contrast extravasation MRI methodology for depiction of subtle blood-brain barrier (BBB) disruption with high spatial resolution and high sensitivity to BBB abnormalities in ischemic stroke. Disruption patterns are clearly visualized on BBB function maps depicting the distribution of 3 permeability populations: fast, slow, and no permeability. In the current study, newly diagnosed GBM patients treated with the standard Stupp protocol underwent MRI 3 weeks after chemoradiation and every 2 months thereafter. BBB function data are acquired at 15-90 min post-Gd, enabling high sensitivity to slow permeability components. Preliminary results of 4 patients reaching 4.5 months follow-up are presented. In 2 patients suspected for progression/pseudoprogression, similar enhancing regions on T1-Gd, present entirely different permeability patterns. Moreover, a third patient with stable disease shows no fast component while the other 3 patients present 30-60% fast component. Regions of interest were defined on T1-Gd and the correlation between slow permeability in the first MRI and the change in tumor volume at 4.5 months was studied. Using the 15-90 min maps, a trend suggesting that a larger slow component correlates with later decrease in lesion volume (R² = 0.47, P < 0.08) was determined. The 90-min data provided significant correlation (R² = 0.64, P < 0.03). Combining both time points resulted in a stronger correlation (R² = 0.8, P < 0.007), confirming the additional value of the additional information obtained at 90 min. These preliminary results suggest that the unique vessel permeability characterization obtained here provides new valuable information that may be applied for prediction/determination of treatment effects. The correlation between permeability characteristics, their change in time, and patient outcome is yet to be seen.
standard diagnostic MR imaging with diffusion-weighted imaging, perfusion-weighted imaging, and single-voxel PRESS spectroscopy. RESULTS: Using Kaplan-Meier curves to identify possible physiological imaging biomarkers, we identified 146 pediatric brain tumor patients (age, 0.17-17; median, 8.4 years) with untreated brain tumors who were scheduled for radiotherapy in combination with concomitant and 6 cycles of adjuvant TMZ for newly diagnosed GBM. MRIs were obtained at regular intervals: postoperatively (ie, prior to the concomitant phase; time point 1 [TP1]), prior to the adjuvant phase [TP2], and after 3 TMZ courses [TP3]. Conventional MR tumor size was defined as the product of the 2 largest perpendicular transverse T1-weighted enhancing tumor diameters. Perfusion MR imaging was used to assess quantitative relative cerebral blood volume (rCBV) measurements of the contrast-enhanced areas of maximal perfusion. Overall survival (OS) was used as the outcome variable. The value of conventional and perfusion MR parameters in predicting OS was examined using Cox regression analyses, in which the effects of both absolute and relative changes in tumor measurements during treatment on OS were estimated. RESULTS: Thirty-seven patients were included, in whom 101 conventional and 91 perfusion MRIs were performed. Absolute tumor measurements both on conventional and perfusion MR images were used to predict overall survival (OS) in the analyses. The most upregulated mRNAs of interest (ROIs) over solid portions of the tumor and avoiding areas of necrosis, cyst, or hemorrhages. Pathology was obtained in all tumors. RESULTS: Of the 22 tumors, 7 were high-grade (WHO grade III/IV), including diffuse intrinsic pontine glioma (1), diffuse intrinsic pontine glioma (1), diffuse intrinsic pontine glioma (1), melanoma (1), and ependymoma grade III (1); and 15 were low-grade (WHO grade I/II), including ganglioglioma (2), grade I pilocytic astrocytoma (7), grade II astrocytoma (7), ependymoma grade II (1), and medulloblastoma (1). There were significant differences in rCBF between high-grade and low-grade tumors: mean ASL CBF (ml/g/min) in high-grade tumors was 25.4, low-grade, 37.5 [P = 0.001]; the maximum ASL CBF (ml/g/min) in high-grade tumors was 79.4, low-grade, 52.3 [P = 0.005]. CONCLUSION: Mean and maximum ASL CBF values were significantly higher in high-grade than in low-grade pediatric brain tumors. ASL CBF is not invasive and valuable in children, may provide additional insight into tumor physiology and predict grade in pediatric brain tumors.

INTRODUCTION: To study the value of perfusion and MR imaging in the prediction of survival in patients treated with temozolomide (TMZ) chemo-irradiation for newly diagnosed glioblastoma multiforme (GBM). METHODS: In this prospective cohort study, we included patients who were scheduled for radiotherapy in combination with concomitant and 6 cycles of adjuvant TMZ for newly diagnosed GBM. MRIs were obtained at regular intervals: postoperatively (ie, prior to the concomitant phase; time point 1 [TP1]), prior to the adjuvant phase [TP2], and after 3 TMZ courses [TP3]. Conventional MR tumor size was defined as the product of the 2 largest perpendicular transverse T1-weighted enhancing tumor diameters. Perfusion MR imaging was used to assess quantitative relative cerebral blood volume (rCBV) measurements of the contrast-enhanced areas of maximal perfusion. Overall survival (OS) was used as the outcome variable. The value of conventional and perfusion MR parameters in predicting OS was examined using Cox regression analyses, in which the effects of both absolute and relative changes in tumor measurements during treatment on OS were estimated. RESULTS: Thirty-seven patients were included, in whom 101 conventional and 91 perfusion MRIs were performed. Absolute tumor measurements both on conventional and perfusion MR images were used to predict overall survival (OS) in the analyses. The most upregulated mRNAs of interest (ROIs) over solid portions of the tumor and avoiding areas of necrosis, cyst, or hemorrhages. Pathology was obtained in all tumors. RESULTS: Of the 22 tumors, 7 were high-grade (WHO grade III/IV), including diffuse intrinsic pontine glioma (1), diffuse intrinsic pontine glioma (1), diffuse intrinsic pontine glioma (1), melanoma (1), and ependymoma grade III (1); and 15 were low-grade (WHO grade I/II), including ganglioglioma (2), grade I pilocytic astrocytoma (7), grade II astrocytoma (7), ependymoma grade II (1), and medulloblastoma (1). There were significant differences in rCBF between high-grade and low-grade tumors: mean ASL CBF (ml/g/min) in high-grade tumors was 25.4, low-grade, 37.5 [P = 0.001]; the maximum ASL CBF (ml/g/min) in high-grade tumors was 79.4, low-grade, 52.3 [P = 0.005]. CONCLUSION: Mean and maximum ASL CBF values were significantly higher in high-grade than in low-grade pediatric brain tumors. ASL CBF is not invasive and valuable in children, may provide additional insight into tumor physiology and predict grade in pediatric brain tumors.
ingenuity pathway analysis (IPA). RESULTS: IPA identified gene and microRNA networks, as well as canonical and functional pathways highly associated with cancer, inflammatory response and disease, cell-to-cell signaling, and cell death, as well as functional networks for RNA damage and repair, cell migration, cell morphology, cellular assembly, and organization. CONCLUSION: The edema radiophenotype identified genes and miRNAs, corresponding molecular networks, and canonical genes that were highly associated with cell signaling and inflammatory disease, as well as cell migration and morphology. We were able to identify possible key genes and miRNAs for edema-genesis, cell migration, as well as increased inflammatory response. These represent possible new targets for edema reduction and therapeutic augmentation in GBM.

Radiotherapy (RT) is an integral component in managing patients with glioma, but the damage it may cause to healthy brain tissue and quality of life is of concern. Susceptibility-weighted imaging (SWI) has recently revealed the presence of hemosiderin-containing microbleeds years after receiving radiotherapy (RT). This study’s goals were (1) to use SWI to characterize the evolution of microbleeds in normal-appearing brain tissue that result from RT and (2) to determine whether the administration of an anti-angiogenic agent altered this process. Serial high-resolution, T2*-weighted SWI was acquired on 17 patients with high-grade gliomas over the course of 8 months to 4.5 years post-treatment (65 total scans). All patients received xRT with adjuvant chemotheraphy. Nine newly diagnosed GBM patients were also treated with a PKC-inhibitor anti-angiogenic (AA) therapy. Microbleeds were identified as discrete foci of susceptibility not corresponding to vessels, tumor, or surgical infarct on consecutive slices. Microbleeds were counted in normal-appearing brain, excluding contrast-enhancing tumor and acute hemorrhage. The number of microbleeds increased with time in all patients, with initial onset occurring between 8 and 22 months. No microbleeds disappeared once formed. The average rate of microbleed formation significantly increased (∼3.5-fold) after 2 years post-RT compared to before (P < 0.001). Patients with AA Tx exhibited fewer microbleeds overall (P < 0.05) and a significant reduction in initial rate of microbleed appearance (P = 0.01), supporting the hypothesis that AA drugs have a radioprotective effect on microvasculature. No trends between microbleed size and onset were observed. Microbleed morphology was classified as: (1) stable in size, (2) enlarging in size over time, or (3) initially appearing then remaining large. Some microbleeds appeared in locations without prior visible vasculature, while others stemmed from deteriorating neighboring veins. Current work focuses on quantifying the size and spatial distribution of microbleeds over time, correlating the number and location of microbleeds with radiation dose, and evaluating the effect of other AA therapies.

RA-33. RECURRENT Glioblastoma multiforme: IMPLICATION OF NONENHANCING LESIONS ON BEvacizumab TREATMENT
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Glioblastoma multiforme (GBM) is the most common primary brain tumor, accounting for 15-20% of all intracranial tumors. It is a very aggressive neoplasm with a median survival from diagnosis of 6 to 18 months. Despite aggressive resection and chemoradiation, the tumor always recurs. MRI imaging is an essential tool for diagnosis, treatment planning, and follow-up response to treatment. However, the imaging features of recurrent GBM may be challenging, particularly in patients undertaking novel antiangiogenic therapy. We present such a case treated with repeated surgeries, combined chemoradiation, and bevacizumab. A 51-year-old man underwent gross total resection of left temporal lobe GBM. The tumor recurred 1 year later, requiring a second resection followed by a full course of radiotherapy and temozolomide. Three months after the completion of his treatment, the tumor recurred again. The patient was started on bevacizumab and intrathecal methotrexate due to this regimen with the survivval, with clinical stability. However, his neurologic status then went on to suddenly worsen and he died within weeks. Follow-up MRI obtained every 2 months initially showed no progression of the focal tumor on antiangiogenic therapy. However, the last MRI showed multiple, non-contiguous new areas on various imaging sequences, including new discrete FLAIR signal foci, focal contrast-enhancing lesions, diffuse reticular enhancement, and periventricular non-enhancing signal changes. Since the MRI changes were protean and suggestive of multiple etiologies, including radiation necrosis, tumor recurrence, and progressive tumor, a decision was made for multiple biopsies. As such, multiple lesions with different imaging characteristics were biopsied. All the sampled lesions were reported by pathology as recurrent GBM. In patients treated with bev- acizumab, hyperintensities signify tumor infiltration rather than radiation change or even peritumoral edema. FLAIR sequences should always be used to evaluate progression in this particular clinical setting since this sequence provides early evidence of recurrence.

In association with our studies for developing a stem cell (SC)-based therapy for the treatment of glioblastoma (GBM), we compared the patho- toblasts of 2 SC sources, human mesenchymal stem cells (hMSCs) and fetal neural stem cells (fNSCs), toward 2 GBM models: circumscribed U87 and highly infiltrative GBM26. We used conventional and contrast-enhanced MRI at 14.1 Tesla and monitored the location of hMSCs and fNSCs labeled with micron-size iron oxide particles (MPIOs). To assess pathotropism, SCs were injected in the contralateral hemisphere of mice with U87 tumors. MPIO-labeled SCs showed significant signal changes compared to tumor for both SC types. SCs were found to localize first (day 3 to 7) at the tumor rim. At later time points (day 5 to 7), SCs were also found within the tumor mass. To monitor SC biodistribution after intratumor injection, MPIO-labeled hMSCs and fNSCs were injected intra-tumorally in mice with U87 or GBM26 tumors. Both SCs were found to distribute throughout the tumor in both GBM models. Interestingly, in the U87 model, areas of hyposignal co-localized first with the post-Gd-enhancing regions (ie, regions of high vas- cular permeability), consistent with SC tracking by vascular endothelial growth factor. In the GBM26 model, no rim of hyposignal was found, consistent with the diffusely infiltrative nature of GBM26 cells. Prussian blue, endothelial growth factor receptor staining and Dragon Green fluorescence revealed a localization of iron from MPIO-labeled SCs that was consistent with the MR images. Staining for macrophages and tumors showed that MPIOs were absent in both those cell types and suggested that the MPIOs remained within the labeled SCs. In summary, our results indicate that hMSCs and fNSCs showed similar properties as concerns tumor tropsim and intratumoral dissemination, and that MPIO labeling of SCs is a promising approach to pursue for localizing SCs in patients who receive stem cell therapy.

RA-34. LONGITUDINAL EVALUATION OF MPIO-LABELED STEM CELL TROPISM AND BIODISTRIBUTION IN GBM MODELS USING MR IMAGING AND DCE-MRI AT 14.1 TESLA
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In vivo MRI data to ex vivo brain tissue following expiration and brain dissection. METHODS: One 70-year-old male patient with an unoperated brain tumor was evaluated for this study. The patient initially presented with a diffusely infiltrating WHO grade II astrocytoma, as determined by stereotactic biopsy. The patient underwent radiation treatment, with concomitant temozolomide, radiographically progressed, and began treatment with bevacizumab. Following 3 cycles, subtle radiographic progression was noted, and accutane was added, followed by the reintroduction of temozolomide. The patient’s final imaging study was acquired 17 days prior to death. The patient consented to brain donation to our research institution, and his brain was fixed in formalin solution and sliced 2 weeks later using a custom-made rigid designed to allow for slicing in the same axial orientation as the gathered imaging. Histological samples were taken from 72 x 2 cm regions exhibiting suspicious imaging findings and 1 additional region with normal-appearing brain. Samples were processed fixed in paraffin into 5 μm sections. Standard H&E staining was performed, and a final diagnosis of
glioblastoma resulted. H&E slides were photographed in entirety at high resolution under a microscope, spliced together, and segmented into reveal cell nuclei only. Photos were then coregistered and resampled to the MRI resolution for voxel-wise comparison to multiple MR acquisitions using custom developed software. A total of 1,209 voxels were compared to histology. RESULTS: Cellularity was significantly correlated ($P < 0.000001$) to fluid-attenuated inversion recovery, relative cerebral blood volume, and T1 + contrast, and inversely correlated to apparent diffusion coefficient.

RA-36. ADC-FLAIR MISMATCH EXCLUDING ENHANCEMENT (AFMEE), A POTENTIAL BIOMARKER OF TUMOR INFILTRATION
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INTRODUCTION: The detection of brain tumor invasion beyond contrast enhancement continues to remain a challenging radiographic problem. While areas of increased fluid-attenuated inversion recovery (FLAIR) signal represent vasogenic edema, some regions are thought to contain invading brain tumor cells. Decreases in apparent diffusion coefficient (ADC) have been shown to correlate with an increase in tumor cellularity. We hypothesize that regions exhibiting increased FLAIR signal yet decreased ADC, excluding contrast enhancement, contain infiltrating tumor. In this study, we analyze imaging prior to surgery to determine if initial ADC-FLAIR mismatch excluding enhancement (AFMEE) is indicative of infiltrating tumor and subsequently tumor grade. METHODS: Ninety-two patients with brain tumors were evaluated for this study. Of these, 11 had WHO grade I tumors, 21 had WHO grade II, 21 had WHO grade III, and 39 had WHO grade IV. Patients underwent routine clinical imaging prior to surgery, which included contrast-enhanced T1, FLAIR, and diffusion-weighted imaging (DWI). DWI was used to calculate ADC. Each image then went through a series of segmentations. T1 + C images were segmented to determine regions of enhancement. These voxels were then excluded from subsequent analysis under the assumption that known viable tumor exists there. FLAIR images were also segmented to determine regions of heightened signal. ADC maps were then masked with the enhancing FLAIR regions of interest, and then further segmented to determine regions of decreased or normal ADC. The volume of AFMEE was thus determined. These values were then statistically compared across tumor type. Ex vivo histology from 1 additional patient, following expiration, was analyzed for precise histological validation. Four 2 x 2-cm regions were sampled from regions exhibiting AFMEE 17 days prior to expiration. RESULTS: Grade IV lesions showed a significantly greater volume of AFMEE than grade III lesions, and histological validation revealed viable tumor at all 4 regions sampled.

RA-37. CORRELATION OF MRI IMAGING CHARACTERISTICS WITH PATTERNS OF PROGRESSION IN PATIENTS WITH RECURRENT GliOBLASTOMA TREATED WITH BEVACIZUMAB
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In a patient cohort ($n = 124$) with recurrent glioblastoma (GBM) who were treated with bevacizumab (BEV) while participating in the BRaIN study, we evaluated patterns of tumor progression in relation to tumor imaging characteristics and apparent diffusion coefficient (ADC) classifiers from baseline MRI scans. An independent neuroradiologist reviewed MRI scans on baseline and recurrent tumors. Tumor patterns were scored as either local or non-local (including distant, diffuse, and multifocal). Enhancement was scored as either avid or non-avid (including partial and faint). Border was scored as either well-defined or non-well-defined. Necrosis was scored as being present or not. Lower curve ADC mean (ADC-L) and lower curve portion (LCP) were developed from ADC histogram analyses. Pearson correlation analyses showed significant linear relationship between tumor patterns and scores of enhancement and border in both baseline ($P < .0001$) and recurrent tumors ($P < .05$ for enhancement; $P < .001$ for border). ADC-L was correlated with patterns of baseline tumors ($P < .0001$) but not recurrent tumors. In Cox regression model, hazard ratio for progression-free survival (PFS) in patients with avid versus non-avid enhancement was 5.50 ($P < .05$), and in patients with well-defined versus non-well-defined border was 0.09 ($P < .05$). Hazard ratio for overall survival (OS) in patients with well-defined versus non-well-defined border was 0.03 ($P < .05$). In a preliminary decision tree model, factors correlated with PFS < 6 months were non-focal pattern of recurrent tumor, ADC-L < 1.429, and LCP > 0.875; focal pattern of recurrent tumor, 1.429 > ADC-L > 0.964, and LCP < 0.6 months. Non-well-defined tumor border correlated with OS < 6 months. Analyses of MRI imaging characteristics, combined with ADC histogram analyses, constitute a more powerful approach to predict clinical outcomes in BEV-treated patients with GBM.