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The Warburg effect, characterized by elevated glucose uptake and flux to lactate, is a metabolic hallmark of cancer. Recent studies have identified deuterium ^{2}H-magnetic resonance spectroscopy (MRS) using 6,6'-^{2}H-glucose as a novel method of imaging the Warburg effect in high-grade primary glioblastomas (GBMs). However, its utility for imaging low-grade gliomas has not been tested. The goal of this study was to determine whether 6,6'-^{2}H-glucose can be used for imaging tumor burden and treatment response in mutant isocitrate dehydrogenase (IDHmut) low-grade gliomas *in vivo*. We examined mice bearing orthotopic tumors of the patient-derived BT257 astrocytoma model. ^{1}H-MRS, providing a readout of steady-state metabolite levels, confirmed the presence of 2-hydroxyglutarate, the product of IDHmut, in BT257 tumor tissue but not normal brain. Previous studies comparing IDHmut gliomas with GBMs suggest that IDHmut gliomas undergo lactate dehydrogenase silencing, potentially leading to a non-glycolytic phenotype. Nevertheless, our results indicated that, compared to normal brain, glucose uptake and concomitant flux to lactate were significantly higher in BT257 tumor tissue. Importantly, 6,6'-^{2}H-glucose metabolism to lactate was observed in BT257 tumor-bearing mice, but not tumor-free mice. Furthermore, imaging studies confirmed spatial localization of lactate production to the tumor vs. contralateral normal brain. We then examined the ability of 6,6'-^{2}H-glucose to assess treatment response. Poly-(adenosine 5′-diphosphate-ribose) polymerase inhibitors (PARPi) inhibit IDHmut glioma growth and are in clinical trials for IDHmut glioma patients. Treatment with the PARPi niraparib reduced 6,6'-^{2}H-glucose flux to lactate in BT257 tumor-bearing mice. Importantly, this reduction was observed at early time-points when no difference in tumor volume could be detected using anatomical imaging, pointing to the ability of 6,6'-^{2}H-glucose to assess pseudoprogression. Collectively, our results suggest that IDHmut gliomas display a glycolytic phenotype amenable to non-invasive ^{2}H-MRS-based imaging of tumor burden and treatment response.

BIMG-06. RESPONSE ASSESSMENT OF BEVACIZUMAB THERAPY FOR GLIOBLASTOMA BY USING MULTIPLE PET TRACERS

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OBJECTIVE: Use of the positron emission tomography (PET), such as 18F-fluorodeoxyglucose (FDG), 11C-Methionine (MET), 18F-Fluorothymidine (FLT), and 18F-Fluoromisonidazole (FMISO), is expected to lead the way for novel applications aimed at achieving efficient malignancy grading and treatment of gliomas. The aim of this study was to assess FDG, MET, FLT, and FMISO PET studies to evaluate the biological effects induced by bevacizumab (BEV) therapy in glioblastoma patients. **METHODS:** Seventy-one patients with glioblastoma were treated biweekly with BEV from July 2013 to November 2020. FDG, MET, FLT, and FMISO PET scans were obtained at baseline and at follow-up (4 weeks after treatment onset). Measures of FDG, MET, FLT, and FMISO avidity were recorded; the measures were SUVmax, metabolic tumor volume (MTV; volume of tumor with SUV>42% of SUVmax), SUVmean (within the MTV), tumor-to-normal ratio (TNR), tumor-to blood ratio (TBR), and total lesion avidity (TLA; calculated as MTV x SUVmean). The prognostic analysis was performed in relation to the response assessment by multiple PET tracers using progression-free survival (PFS) and overall survival (OS). **RESULTS:** Under the assessment of the Cox proportional hazard model, increased changes of FDG SUVmax, MET TLA at follow-up, FLT TLA at follow up, increased changes of FLT TLA, increased changes of FMISO TBR and FMISO MTV were significant prognostic factor of PFS. Increase changes of FDG TLA and FLT TLA and increased changes of FMISO TBR were significant prognostic factor of OS. **CONCLUSION:** Increased changes in FLT TLA and FMISO-PET after BEV therapy may be a useful biomarker for predicting PFS and OS in glioblastoma.

BIMG-07. PHARMACOLOGICAL ASCORBATE ENHANCES RADIATION AND TEMOZOLOMIDE EFFECTIVENESS IN GLIOBLASTOMA BY A MECHANISM MEDIATED BY REDOX ACTIVE IRON

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Pharmacological ascorbate (P-AscH^{-}; high dose intravenous infusions of vitamin C generating milli-molar plasma concentrations) has re-emerged as an anti-cancer therapy. Phase 1 clinical trials combining P-AscH^{-} with chemotherapy and ionizing radiation demonstrate safety and promising clinical outcomes in a variety of malignancies. In a first-in-human trial, subjects with newly diagnosed glioblastoma (GBM) and undetectable *MGMT* promoter methylation were treated with P-AscH^{-}, ionizing radiation, and temozolomide. Results demonstrate median progression-free survival (PFS) of 10 months and median overall survival (OS) of 23 months, comparing favorably to historical GBM patients expressing MGMT. P-AscH^{-}'s anti-cancer mechanism is dependent upon the presence of redox active labile iron. In the presence of redox active iron, the formation of hydrogen peroxide, which causes oxidative stress and eventual cell death, selectively forms in cancer cells. Treatment with P-AscH^{-} increased cancer cells' labile iron pool, further enhancing sensitivity to P-AscH^{-}. We investigated the capability of MR imaging (T_2* relaxation time) to measure the redox active iron and predict response to P-AscH^{-}. T_2* relaxation time is influenced by in-field inhomogeneities, such as redox active paramagnetic iron. The active phase 2 trial evaluating P-AscH^{-}, radiation, and temozolomide for GBM, obtains T_2* imaging prior to (baseline) and immediately after ascorbate infusion (NCT02344355). A preliminary analysis of the baseline scan for the first 15 subjects suggests those with faster GBM T_2* relaxation times (≤ 58 ms) have more redox active labile iron pools as well as an improved median PFS (11.4 months) compared to those with slower T_2* relaxation times (> 58 ms; median PFS of 8.5 months). Pre-clinical studies evaluating the effectiveness of iron nano-particle supplementation in GBM animal models are on-going. (Supported by P01 CA217797, R01 CA169046, U01 CA140206, T32 CA078586, P30 CA086862, as well as the Gateway for Cancer Research grant G-17–1500.)

BIMG-08. DEUTERIUM MAGNETIC RESONANCE SPECTROSCOPY USING ^{2}H-PYRUVATE ALLOWS NON-INVASIVE *IN VIVO* IMAGING OF TERT EXPRESSION IN BRAIN TUMORS

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Telomere shortening constitutes a natural barrier to uncontrolled proliferation and all tumors must find a mechanism of maintaining telomere length. Most human tumors, including high-grade primary glioblastomas (GBMs) and low-grade oligodendrogliomas (LGOGs) achieve telomere maintenance via reactivation of the expression of telomerase reverse transcriptase (TERT), which is silenced in normal somatic cells. TERT expression is, therefore, a driver of tumor proliferation and, due to this essential role, TERT is also a therapeutic target. However, non-invasive methods of imaging TERT are lacking. The goal of this study was to identify magnetic resonance spectroscopy (MRS)-detectable metabolic biomarkers of TERT expression that will enable non-invasive visualization of tumor burden in LGOGs and GBMs. First, we silenced TERT expression by RNA interference in patient-derived LGOG (SF10417, BT88) and GBM (GS2) models. Our results linked TERT silencing to significant reductions in steady-state levels of NADH in all models. NADH is essential for the conversion of pyruvate to lactate, suggesting that measuring pyruvate flux to lactate could be useful for imaging TERT status. Recently, deuterium (^{2}H)-MRS has emerged as a novel, clinically translatable method of monitoring metabolic fluxes *in vivo*. However, to date, studies have solely examined ^{2}H-glucose and the use of [U-^{2}H]pyruvate for non-invasive ^{2}H-MRS has not been tested. Following intravenous injection of a bolus of [U-^{2}H]pyruvate, lactate production was higher in mice bearing orthotopic LGOG (BT88 and SF10417) and GBM (GS2) tumor xenografts relative to tumor-free mice, suggesting that [U-^{2}H] pyruvate has the potential to monitor TERT expression *in vivo*. In summary, our study, for the first time, shows the feasibility and utility of [U-^{2}H]pyruvate for *in vivo* imaging. Importantly, since ^{2}H-MRS can be implemented on clinical scanners, our results provide a novel, non-invasive method of integrating information regarding a fundamental cancer hallmark, i.e. TERT, into glioma patient management.

BIMG-09. GLUTAMINE AND GLYCINE BY MR SPECTROSCOPY IDENTIFY AGGRESSIVE GLIOMAS

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Cancers reprogram their metabolism and the resulting alterations in metabolite abundance can be monitored in patients noninvasively using proton magnetic resonance spectroscopy (MRS). We evaluated glutamine, glycine and 2-hydroxyglutarate (2HG) in 27 adult subjects with gliomas (17 male and 10 female; age 22 - 69, median 39 years) using optimized MRS at 3T (PRESS TE 97ms) and examined their association with post-gadolinium enhancement, cell proliferation rate (MIB-1 labeling index), and overall survival of patients. The tumors included 9 glioblastomas (3 IDH mutated and 6 IDH wildtype), 10 astrocytomas (7 IDH mutated and 3 IDH