Title

SURG-03. SUBCORTICAL STIMULATION MAPPING OF DESCENDING MOTOR PATHWAYS FOR PERIROLANDIC GLIOMAS: ASSESSMENT OF MORBIDITY AND FUNCTIONAL OUTCOME IN OVER 700 PATIENTS

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Glioblastoma (GBM) is a highly aggressive and most common form of malignant primary brain tumor in adults (WHO grade IV). Despite surgical and adjuvant therapeutic interventions, including chemotherapy with the alkylating agent TMZ and cranial irradiation, GBM relapse is inevitable with a median survival of <15 months. Extensive intratumoral heterogeneity (ITH) in GBM is believed to be the leading cause of therapy resistance and disease relapse, suggesting that therapy acts as a selection pressure or bottleneck for tumor evolution from minority cell populations present at time of initial diagnosis. Recently, the advent of CRISPR-Cas9 technology has led to the development of genome-wide libraries of sgRNAs capable of introducing insertion-deletion (indels) within exons, leading to a frameshift mutation two-thirds of the time. Here, we present the first genome-wide CRISPR-Cas9 knockout screen in patient-derived GBM BTICs aimed to discover synthetic lethal sensitizers of conventional chemoradiotherapy. Briefly, we performed genome-wide CRISPR-Cas9 screens in treatment-naïve GBM BTICs subjected to *in vitro* chemotherapy with TMZ and irradiation. By comparing sgRNA dynamics at each doubling period, we were able to identify potent sensitizer genes exclusive to combined chemoradiotherapy, and not TMZ or irradiation alone. Candidate sensitizer genes were validated in an arrayed format to evaluate impact on GBM BTIC self renewal, proliferation, and sensitivity to TMZ and radiation. We aim to further validate these sensitizers of conventional chemoradiotherapy by performing a focused CRISPR-Cas9 genetic screen in our patient-derived xenograft model of treatment-refractory GBM. Ultimately, adjuvants targeting sensitizer genes could greatly enhance the impact of conventional chemoradiotherapy in GBM patients, leading to an increase in patient survival.

STEM-43. GSK3β PROMOTES THE BMX-MEDIATED STAT3 ACTIVATION TO MAINTAIN GLIOBLASTOMA STEM CELLS

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Glioblastoma (GBM) is the most lethal brain cancer containing highly tumorigenic glioma stem cells (GSCs). As GSCs contribute to malignant behaviors including tumor angiogenesis, cancer invasion, therapeutic resistance and tumor recurrence, targeting GSCs may significantly improve GBM treatment. Here we demonstrate that the glycogen synthase kinase 3β (GSK3β) promotes the BMX-mediated STAT3 signaling to maintain GSCs and thus targeting GSK3β impairs GBM tumor growth. GSK3β is preferentially activated in GSCs relative to matched non-stem tumor cells (NSTCs) and neural progenitor cells (NPCs). Functional inhibition of GSK3β by its inhibitors or shRNA reduced activating phosphorylation of BMX kinase and STAT3 in GSCs but not in NPCs that express little BMX. Disrupting GSK3β inhibited GSC tumorsphere formation and induced cell death in GSCs but showed little effect on NPCs. Importantly, disruption of GSK3β potently suppressed GSC-driven tumor growth in vivo. Ectopic expression of a constitutively active STAT3 (STAT3-C) rescued the effects caused by GSK3β disruption, supporting that GSK3β mediates through STAT3 activation to maintain the GSC phenotype. Collectively, these data indicate that GSK3β is a potential therapeutic target of GSCs. Thus, pharmacological inhibition of GSK3β may potently disrupt GSCs to overcome therapeutic resistance and improve GBM treatment.

SURGICAL THERAPY

SURG-01. COMPLETE RESECTION IS NOT ASSOCIATED WITH IMPROVED SURVIVAL IN MGMT NON-METHYLATED GLIOBLASTOMA: RESULTS FROM THE GLARIUS TRIAL

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BACKGROUND: Although it is known that upfront complete surgical resection is associated with improved survival in glioblastoma, studies are lacking to confirm whether this holds true for the unfavorable patient population of O-6-methylguanine-DNA methyltransferase (MGMT) non-methylated glioblastoma. Here, we investigated the association of survival with the extent of resection in the GLARIUS study, a randomized phase II trial of bevacizumab/irinotecan (BEV/IRI) versus standard temozolomide (TMZ) in MGMT non-methylated glioblastoma. **METHODS:** Patients included in the modified intention-to-treat (ITT, n=170) population were stratified by extent of resection (partial vs. complete) as determined by early (>72h) postoperative contrast-enhanced MRI. In a Kaplan-Meier analysis, we compared overall survival (OS) between the groups in each treatment arm. A Cox regression analysis was used to detect whether complete resection was of prognostic value and independent of canonical prognostic markers, including age and Karnofsky performance score (KPS). **RESULTS:** In the BEV/IRI arm, 58 patients (50%) each underwent partial (PR) and complete resection (CR). In the TMZ arm, 29 patients (55%) underwent partial and 24 (45%) complete resection. Prognostic factors, including age and KPS, were balanced between patients with PR and CR. Neither in the BEV/IRI arm (CR, median OS [mOS], 17.3 [95% CI, 15.5-21.4] versus PR, mOS, 16.5 [95% CI, 14.9-17.9]; Hazard Ratio [HR], 0.79 [95% CI, 0.53-1.20]; p=0.28) nor in the TMZ arm (CR, mOS, 18.0 [95% CI, 17.1-21.3] versus PR, mOS, 15.3 [95% CI, 10.6-21.1]; HR, 0.77 [95% CI, 0.43-1.40]; p=0.40) patients with CR derived a significant OS benefit compared to those with PR. In a multivariable Cox regression analysis, this effect did not change after accounting for canonical prognostic markers. **CONCLUSIONS:** In the GLARIUS trial, patients with complete resection derived no relevant survival benefit as compared with partially resected patients. However, the small sample size, in the TMZ arm in particular, limits our analysis.

SURG-02. EFFECTS OF HIGH DOSE 5-ALA IN THE RESECTION OF GLIOBLASTOMA

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INTRODUCTION: Prior studies have found more extensive resection of high grade glioma with the use of 5-aminolevulinic acid (5-ALA) fluorescence-guided surgery (FGS) compared to conventional resection alone leading to longer progression free and overall survival.1, 2 Currently the standard dose of 5-ALA is 20mg/kg of patient body weight. The objective of the current study is to investigate how higher doses of 5-ALA affect residual tumor volume (RTV) and overall survival in patients with glioblastoma. **METHODS:** As part of a previous phase I and II clinical trial (NCT01128218), 5-ALA was administered at doses of 10, 20, 30, 40 and 50 mg/kg to patients with suspected high grade glioma. A total of 22 patients were found to have newly diagnosed glioblastoma on histology. Patients receiving low doses of 5-ALA (10-30 mg/kg) (n = 6) were compared to those receiving high dose (40-50 mg/kg) (n = 16). Pre- and post-operative contrast enhanced T1W MRI were evaluated with volumetric analysis for RTV and for complete resection of the enhancing tumor (CRET) (volume < 0.0175cm3). **RESULTS:** Less median RTV was found in the high dose 5-ALA group (0.181 cm3) compared to the low dose group (0.884 cm3) though this was not statistically significant (p = 0.149). Eight of the 16 patients (50%) receiving high dose 5-ALA achieved a CRET compared to zero of the low dose patients (p=0.03). There was no significant difference found in survival between the high dose and low dose Group (p = 0.2849). **CONCLUSIONS:** This study found that high doses of 5-ALA FGS are associated with less RTV and greater probability of CRET. Due to the limited number of patients included, we could not adequately draw any conclusions about dose and its relationship to survival. Further studies with a larger patient population are warranted.

SURG-03. SUBCORTICAL STIMULATION MAPPING OF DESCENDING MOTOR PATHWAYS FOR PERIROLANDIC GLIOMAS: ASSESSMENT OF MORBIDITY AND FUNCTIONAL OUTCOME IN OVER 700 PATIENTS

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INTRODUCTION: We report our experience with intraoperative stimulation mapping to locate the descending subcortical motor pathways in patients undergoing surgery for hemispheric gliomas within or adjacent to the rolandic cortex, and describe the morbidity and functional outcomes associated with this technique. **METHODS:** The retrospective analysis included 702 patients undergoing resection of hemispheric perirolandic gliomas within or adjacent to descending motor pathways. Data regarding intraoperative stimulation mapping results and patient postoperative neurological status were collected. **RESULTS:** Of 702 patients, stimulation mapping identified the descending motor pathways in 300 cases (45%). New

or worsened motor deficit was seen postoperatively in 210 cases (30%). Of these 210 cases, there was improvement in the motor function to baseline by 3 months postoperatively in 160 cases (76%), while the deficit remained in 50 cases (24%). Majority (56%) of long-term deficits were mild or moderate (antigravity or better). Patients in whom the subcortical motor pathways were identified during surgery with stimulation mapping were more likely to develop an additional motor deficit postoperatively compared to those in whom the subcortical pathway could not be found (45% vs. 19% respectively, p<0.001). This difference also remained when considering the likelihood of a long-term deficit (i.e. persisting >3 months; 12% vs. 3.2%, p<0.001). A significant region of diffusion restriction around the resection cavity was seen in 20 patients with long-term deficits and was more common in cases when the motor pathways were not identified. Thus, long term deficits that occur in settings where the subcortical motor pathways are not identified seem in large part due to local ischemic injury to descending tracts. **CONCLUSION:** Stimulation mapping allows surgeons to identify the descending motor pathways during resection of tumors in perirolandic regions and to achieve an acceptable rate of morbidity in these high risk cases.

SURG-04. CRANIAL BONE DEFECTS IN PATIENTS TREATED WITH TTFIELDS: A CASE SERIES

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BACKGROUND: Glioblastoma multiforme (GBM) is the most abundant primary brain tumor with a devastating prognosis. Treatment of newly diagnosed GBM is generally based on maximal safe resection and subsequent concomitant chemoradiation followed by adjuvant temozolomide (TMZ). Tumor-treating-fields (TTFields) are a new treatment modality added to the temozolomide maintenance with proven efficacy in a large clinical trial. The therapy is based on anti-mitotic effects of alternating electric fields applied locally through so called transducer arrays being directly attached to the scalp. Patients with cranial bone defects, e.g. missing bone, were excluded from the clinical trial with TTFields and clinical experience regarding safety and feasibility is missing. We here report on cases with cranial defect on TTFields therapy. CASES: We observed four patients with recurrent GBM and missing cranial bone (female=1, male=3) at four different centers in Germany. The median age when starting the therapy was 55 years (range 51 - 69 years). All patients received first-line treatment at best clinical practice and experienced progressive disease. Craniectomy was indicated due to different reasons like inflammation or wound healing deficit. Thereafter, treatment with TTFields started in these patients at first and later recurrence. There were no severe adverse events observed in this population. The median monthly compliance was 83 % and with a range of 78 – 84 % compliance, all patients exceeded 75 % as suggested by study data to enable most efficient therapy. **CONCLUSIONS:** This multicentric and retrospective case series describes patients who were treated with TTFields despite a cranial bone defect. All patients were compliant to the therapy and there were no severe or additional side effects observed. Our observation provides first evidence that this setting is feasible and safe. Additional studies are warranted to increase clinical evidence for the safe use of TTFields in patients with cranial bone defects.

SURG-05. THE IMPACT OF SURGERY IN MOLECULARLY DEFINED LOW-GRADE GLIOMA: AN INTEGRATED CLINICAL, RADIOLOGICAL AND MOLECULAR ANALYSIS

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INTRODUCTION: The WHO classification of gliomas has been revised completely and is now predominantly based on molecular criteria. This requires re-evaluation of the impact of surgery in molecularly defined low-grade glioma subtypes. We performed a retrospective study to assess the interaction between molecular markers and postoperative tumor volume on overall survival in patients with low-grade glioma. **METHODS:** We included 228 adult patients who underwent surgery for a supratentorial low-grade glioma since 2003. Pre-and postoperative tumor volume were assessed with semi-automatic software on T2-weighted images. Targeted next-generation-sequencing was used to classify the samples according to current WHO 2016 classification. The impact of postoperative tumor volume on overall survival, corrected for molecular profile, was assessed using a Cox proportional-hazards model. **RESULTS:** Median follow-up was 5.8 years. In 39 (17.1%) of cases, glioma subtype was revised after molecular analysis. Complete resection was achieved in 35 patients (15.4%). In 54 patients (23.7%) a small tumor residue (0.1-5.0 cm3) remained. In multivariate analyses, postoperative tumor volume was associated with overall survival with a HR of 1.01 (95% CI 1.002-1.02; p=0.016) per 1 cm3 increase in volume. The impact of postoperative volume was particularly strong in IDH mutated astrocytoma patients, where even very small postoperative tumor volumes (0.1-5.0 cm3) already negatively affected overall survival (Log-rank test, p = 0.027). **CONCLUSIONS:** Our data provides the necessary re-evaluation of the impact of surgery for all molecular low-grade glioma subtypes. Importantly, even a small postoperative volume has a negative impact on overall survival in IDH mutated astrocytoma, which argues for a second-look operation in this glioma subtype even when minor residual tumor remains.

SURG-06. LASER ABLATION IN STEREOTACTIC NEUROSURGERY (LAISE): A MULTI-INSTITUTIONAL RETROSPECTIVE ANALYSIS OF LITT FOR BRAIN METASTASIS

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INTRODUCTION: Laser Interstitial Thermotherapy (LITT; sometimes called Stereotactic Laser Ablation or SLA,) is a minimally invasive procedure increasingly used to treat brain tumors. Previous reports have described small numbers of patients from a few centers. Here we describe the treatment and results of 40 patients with 83 brain metastasis treated at 9 centers 2015-2016 and compare this to outcomes in 68 patients with gliomas. **METHODS:** De-identified data on patients undergoing LITT in a retrospective database were analyzed using standard statistical methods. **RESULTS:** The median age of patients treated for metastatic brain tumor was older than in patients with gliomas (59.1 yrs. vs. 53.8 yrs.; p =0.0422). Patients were predominately female (55%) and white (75%). Lesions were mostly recurrent (70%), or residual (5%), though 22.5% were newly diagnosed. The most frequent primaries were lung (52.6%), breast (13.2%), colon (5.3%) and melanoma (5.3%). Tumor locations include supratentorial (90.4%), thalamic 2.4%) and brainstem (7.2%). 32.5% were considered to be inoperable, 10% were unable to tolerate radiotherapy, and 2.5 % were unable to tolerate chemotherapy. Median pre-op KPS was 80 (+/-11.2) and median ECOG Performance status was 1.3(+/- 1.5). Previous treatments included steroids (87.5%) RT (71.1%), radiosurgery (54.2%), craniotomy (26.5%) and WBRT (14.5%). Metastasis treated with LITT were more often recurrent compared to gliomas (70% vs. 51.5%; p = 0.047) but were also smaller (7.9 cc vs 12.9cc; p =0.0083). Median lasing time was 38.6 min. Discharge status was home (79.5%), rehabilitation (10.3%), and SNF (5.1%). Average follow-up was 300.9 days and median survival was 421 days which was shorter than patients with glioma (568 days), but only 4.8% suffered a neurological death. **CONCLUSION:** LITT is safe and effective for the treatment of challenging brain metastasis including recurrent and otherwise inoperable tumors with survival and CNS survival equal or better than alternative treatments.

SURG-07. CIRCUMFERENTIAL RESECTION OF GLIOBLASTOMA: A NOVEL SURGICAL TECHNIQUE FOR MAXIMISING EXTENT OF RESECTION AND PROLONGING SURVIVAL

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INTRODUCTION: Evidence suggests that cytoreduction is associated with improved survival in glioblastoma (GBM) and that maximal, or gross total resection of the tumor offers the best chance for prolonged survival. We developed a novel surgical technique for removal of GBM called Circumferential resection during which we identify the interface between the enhancing rim of GBM and surrounding brain structures enabling more complete resection. We evaluate the impact of this method on extent of resection and