

T2 FLAIR sequences. LQ less than 0.3 was considered RN. Result: Twenty-two patients were followed for a median 320 days. Sixteen patients developed radionecrosis in 21 of 62 lesions (33%), four of which were symptomatic (20%). Eleven of these lesions received 3 fractions and ten received one fraction. RN risk increased with increasing tumor volume (log odds ratio=1.12,  $p=0.04$ ). There was no difference in incidence of RN in patients who received whole brain radiotherapy (WBRT) ( $p=0.11$ ), hypo-fractionation ( $p=0.98$ ) or had a higher maximum dose ( $p=0.71$ ). Radiographic RN, however, did not clear in any patients who developed it. Eight patients developed a local recurrence (12%), six of which occurred in the single fraction group. Conclusion: Radionecrosis was significantly related to tumor volume but not fractionation, WBRT, or maximum dose. Overall, our results indicate patients receiving SRS for multiple brain metastasis have a higher rate of radionecrosis than the literature and poorer survival despite having equivalent local control.

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#### Extent of resection in glioblastoma: Incorporating clinical and molecular data

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Background: The benefits of increasing extent of resection (EOR) for both overall survival and progression-free survival (PFS) in glioblastoma has been well documented. However, models predicting surgical outcomes have failed to incorporate a patient's IDH status, a known prognostic factor. We isolate the impact of IDH on surgical outcomes. We determine the effect modification of increasing EOR and decreasing residual tumor volume (RTV) on IDH status. Methods: We performed a retrospective cohort study of 98 patients with glioblastoma who had undergone either biopsy or surgical resection. Tumor volumes were determined by volumetric analysis. Univariable and multivariable Cox PH Regression models were built using overall survival and PFS as endpoints. Results: Increasing EOR and decreasing RTV were both associated with prolonged overall survival and PFS. When IDH status was added to multivariable models, the model utilizing RTV provided a slightly better fit compared to EOR. An interaction term between RTV and IDH status was characterized, such that at low RTVs the prognosis of an IDH mutant is significantly better than that of an IDH wild-type, an effect that is less important as RTV increases. The significance of this term was confirmed by improved fit upon insertion into multivariable models. Conclusion: Minimizing RTV and increasing EOR are important prognostic factors for both IDH wild-type and IDH mutant glioblastoma. The protective benefit of the IDH mutation at lower RTVs suggests these patients are the best candidates for aggressive surgical resection.

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#### The impact of repeated surgery on survival for patients with recurrent glioblastoma

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Background: Recurrent glioblastoma portends a poor prognosis and the role of repeat surgery in improving survival remains uncertain. Therefore, we undertook a systematic review and meta-analysis in order to determine if repeat surgical resection provides a meaningful survival benefit for patients with recurrent glioblastoma. Methods: Two independent reviewers searched for articles that reported on overall-survival of patients with recurrent glioblastoma using MEDLINE, Embase, Google Scholar, and Cochrane from January 2000 to 2018. Studies that compared overall survival of patients treated with single surgery compared to repeat surgery in the temozolomide era were included for analysis. Primary outcomes were odds ratio for survival at 6, 12, and 24 months from date of initial diagnosis. Secondary outcomes were ratio odds ratio for survival at 6, 12, and 24 months from date of repeat surgery. The proportions of patients who had the outcomes of interest were pooled using random-effects model. Quality assessment was performed using the Newcastle Ottawa Scale. Heterogeneity across trials was quantified by the I<sup>2</sup> statistic. Publication bias was evaluated visually using funnel plots and quantified by the Egger regression. Results: Fourteen articles reporting on 3048 patients were included for analysis. The majority of articles were deemed to be of high quality with Newcastle Ottawa scale greater than 7 points. Pooled analysis showed improved overall survival following repeat surgery at 6- (OR 1.73, 95% CI 1.23-2.45,  $p < 0.05$ ), 12- (OR 1.71, 95% CI 1.20-2.45,  $p < 0.05$ ), and 24-months (OR 2.24, 95% CI 1.01-4.95,  $p < 0.05$ ) and from date of initial diagnosis at 6- (OR 8.22, 95% CI 5.23-12.93,  $p < 0.01$ ), 12- (OR 4.16, 95% CI 3.25-5.36,  $p < 0.01$ ), and 24- (2.35, 95% CI 1.77-3.11,  $p < 0.05$ ) months. Conclusions: Repeat surgery for recurrent glioblastoma is associated with a significant survival advantage independent of other salvage therapies that include chemotherapy, radiation, and other antineoplastic regimens.

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#### Untangling the NFI-Calpain signaling axis in malignant glioma

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Malignant gliomas (MG) are highly infiltrative tumours with a poor prognosis. Nuclear factor I (NFI) is a family of 4 transcription factors (NFIA, B, C and X) implicated in the regulation of genes involved in MG cell migration and infiltration, particularly the neural stem cell marker, brain fatty acid binding protein (B-FABP). NFI activity is regulated by its phosphorylation status, with hypophosphorylated NFI being the active form. Our results indicate that the phosphatase calcineurin is able to dephosphorylate NFI. In turn, calcineurin is cleaved and activated by calpain proteases. We have identified CAST, a gene that encodes calpain inhibitor, calpastatin, as a putative target of NFI based on chromatin immunoprecipitation. Putative NFI binding elements are located in intron 3 of the CAST gene. To determine whether there is a bona fide alternative promoter within intron 3 of CAST, we carried out gel shifts as well as luciferase reporter gene assays using both the canonical and alternative promoters of CAST. These assays confirmed CAST alternative promoter usage in MG cells. Knockdown of individual NFIs revealed a role for NFIC and NFIX in the repression of CAST gene expression, specifically in cells expressing the hypophosphorylated (active) form of NFI. NFI depletion also altered the subcellular localization of both calpain and calcineurin protein. Our results suggest a feedback loop for the

NFI –calcineurin – calpain – calpastatin pathway in MG cells which may regulate cell migration.

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**Lysosome disruptor's siramesine and the kinase inhibitor lapatinib induce synergistic cell death through ferroptosis in glioma cells**

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Glioblastoma is inherently resistant to radiation and drug treatments. This is mediated by the most common forms of cell death are often actively inhibited. Identifying and exploiting alternative cell death pathways are essential to overcoming or bypassing drug resistance. Ferroptosis, a newly described, morphologically and biochemically distinct, cell death mechanism is characterized by iron-dependent cellular accumulation of reactive oxygen species. The combination of siramesine, a lysosome disruptor, and lapatinib, a dual tyrosine kinase inhibitor (TKI), synergistically induced death in glioma cancer cells. This cell death had characteristics of ferroptosis: it was blocked by the ferroptosis inhibitor ferrostatin-1 and the iron chelator deferoxamine. In addition, the amount of ROS and lipid peroxidation were increased in glioma cells. Iron transport protein remained unchanged but reactive iron levels increased. One target for kinase inhibitors is protein disulfide isomerase (PDI). Knockdown of PDI in combination with siramesine increased cell death that was blocked by ferrostatin-1. Taken together, drug combinations that alter reactive iron and ROS levels might induce ferroptosis and overcome drug resistance in glioma cells.

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**Prognostic significance of PD-L1 expression in meningioma for tumor recurrence; associated with hypoxia and NFKB2 activation**

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Estimation of tumor recurrence in meningioma patients is one of the important clinical challenges. The prognostic impact of immune modulatory molecule PD-L1 in several malignancies has been demonstrated. We studied the association of PD-L1 expression in meningioma with tumor recurrence and the underlying mechanism of its activation. Immunohistochemical staining (IHC) was performed for detection of PD-L1 and NFKB2 on whole sections of meningiomas diagnosed between 1998-2016 at Toronto Western Hospital. The biologic role of hypoxia in activation of PD-L1 in meningioma was investigated using gene set enrichment analysis (GSEA)-based on RNAseq data in validation cohorts. We analyzed a total of 93 meningioma cases: F/M ratio 58/35; WHO grade I(41), II(43), III(9), 42(47%) cases with tumor recurrence and median follow up was 6.97 yrs. PD-L1 expression on tumor cells (PD-L1TC) in 33(35%) cases was identified with distinctive patchy distribution. Univariate analysis

indicated expression of PD-L1TC as a prognostic factor for tumor recurrence ( $p < 0.0001$ ). Multivariate analysis showed that PD-L1TC expression is an independent prognostic factor for tumor recurrence after adjusting for extent of resection (EOR), WHO grade and maximum tumor diameter ( $p < 0.0001$ ). Analysis of RNAseq data of two GEOMeningioma studies demonstrated prominent expression of NFKB activation associated with PD-L1 expression. IHC analysis confirmed increased expression of NFKB2 protein in 26(30%) cases, which correlated with PD-L1TC expression ( $p = 0.02$ ). Furthermore, GSEA on a RNAseq data of 88 sporadic meningiomas using Hypoxia gene signature of HUVEC cells we found that the hypoxic sporadic meningiomas have significantly elevated PD-L1 expression ( $p < 0.001$ ). Our data strongly suggest that PD-L1TC expression serves as a significant prognostic marker for tumor recurrence and . We found that hypoxia and NFKB2 activation are potential underlying mechanisms. These results also provide a rationale for potential adjuvant therapeutic role for PD-L1 inhibitors in meningioma.

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**Does exercise improve progression free survival (PFS) and quality of life (QOL) in patients with glioblastoma? A trial in progress**

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Background: Glioblastoma is the most common adult malignant glioma, with poor prognosis and adverse neurological sequelae. Physical activity improves outcomes in patients with other cancers, but has not been evaluated in GBM. This prospective, single-arm intervention trial examines feasibility and preliminary efficacy of exercise on PFS, cognition and QOL in newly diagnosed GBM patients. Method: Participants are English-speaking GBM patients scheduled for concurrent chemoradiation at PMH, 18-65 years old, ECOG  $\leq 2$ . The 3-month home-based exercise program includes aerobic and resistance training, tailored to prior fitness level, current physical status, and individual interests. Assessments of physical and neurocognitive functions, mood, fatigue, sleep, and QOL, occur within 2 weeks of starting chemoradiation, and approximately 3, 6, 12, and 18 months later, or until tumor progression. Feasibility will be assessed by accrual, retention, and adherence rates. Outcomes include PFS (RANO criteria), change in cognition (reliable change index method), physical activity and sleep (actigraphy, self-report questionnaires). Time-to-event outcomes will be estimated (Kaplan-Meier), and mixed modelling will explore individual and disease variables that contribute to outcomes. Results: During the first five months of recruitment, 13 of 19 eligible patients consented. Nine completed the exercise program. One patient died after the intervention and none of the others progressed. No exercise-related serious adverse events occurred. Preliminary results will be presented at the meeting. Discussion: Exercise appears feasible for GBM patients. Effects on survival, performance status, cognition, sleep, mood, and QOL are ongoing. Results may guide physical activity recommendations in GBM and generate avenues for translational research.