activity when cells are exposed to autophagy inhibitors such as chloroquine [5]. To this date it remains elusive whether increased autophagy phenotype is the result of IDH1 mutation or if it either represents a secondary co-existing condition in the setting of the IDH1 mutation. Autophagy is also a mechanism of detoxification induced by chronic heavy metal exposure in both normal and cancer cells. Thus, we hypothesized that autophagy activity in IDH1 mt glioma is partially induced by chronic heavy metal exposure, leading to increased cell survival and abnormal DNA repair. Our approach included characterization and quantification of metal content on IDH1 mt glioma cell lines and tissues, in addition to correlation analyses of the celullar metallome with autophagy markers, ROS and DNA repair of IDH1 mt glioma cells allowed us to explore targets responsible for cell survival and DNA repair response. Furthermore, we evaluated the potential therapeutic value of Chloroquine (CQ) and bafylomicin for IDH1 mutant gliomas targeting autophagy pathway in combination with TMZ and radiation. We demonstrated that 2-HG induces autophagy activity via LC3B activation, and autophagy inhibiton by beclin gene silencing results in a reduction of 2-HG leading to cell starvation and apoptosis. Remarkably, we observed a positive correlation on at least six different metals with autophagy induced LC3B and beclin1 expression that significantly differed between the mutant and the wt genotype in glioma cell lines. ROS and DNA repair were also positively associated with at least 6 different metals and only seen in the IDH1 mt cell lines, then suggesting a possible explanation for the increase on autophagy, analysis of both LC3B and beclin 1 expression demonstrated a positive correlation with Mo98, Fe54, and Zn 66 on IDH1 mt cell lines and a positively correlation with Mo98 and V concentrations in relation to H2AX expression. Co, SeO Mo, V and Mg were positively correlated to ROS expression. TMZ and CQ induced autophagy pathway activation as measured by LC3B, Beclin, Atg expression. Silencing beclin in IDH1 mutant glioma cell lines induced apoptosis and reduction on 2-HG production after treatment with TMZ and radiation. Overall the results contained in this study 1) identify cellular metal content in relationship to mechanisms leading to increased autophagy on IDH1 mt glioma cells. 2) evaluate the combination of CQ and TMZ to potentially target and inhibit autophagy as a mechanism downstream the 2-HG production in IDH1 mt glioma cells.

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Disparities in survival for patients with glioblastoma multiforme

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Background: Glioblastoma multiforme (GBM) is the most common malignant primary brain cancer in adults. Recent efforts have elucidated genetic features of tumor cells and thus enhanced our knowledge of GBM pathophysiology. The most recent clinical trials report median overall survival between 14 and 20 months. However, real-world outcomes are quite variable and there is a paucity of data within the literature. Methods: Three hundred seventy two GBM patients were diagnosed in the province of British Columbia between January 2013 and January 2015. We have performed a retrospective review on the survival outcomes of the 278 patients who underwent surgical resection as part of the initial treatment. Results: Our results indicate a median age of 61.8y at time of diagnosis with a slight preponderance of males. The median overall survival was 10 months for patients who underwent surgery. As expected, patients over the age of 65 and those with worse initial Karnofsy Performance Status (KPS) scores had a poorer prognosis. Moreover, we have found extent of resection (EOR), treatment strategies and treatment location affect overall survival. Conclusion: The present study highlights factors which affect patient survival after surgery in British Columbia. Our outcomes are slightly worse than survival reported in the US. Variability in pathologic classification and in treatment strategy likely contribute to this difference. Further efforts should ensure access to the gold-standard of care.

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Inhibiting PARP-1 to restore temozolomide sensitivity and prevent resistance in glioblastoma

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Adult Glioblastomas (GBMs) remain one of the least curable brain cancers despite the discovery and use of DNA alkylating agent Temozolomide (TMZ). TMZ provides a moderate survival benefit to sensitive patients whose O6-methylguanine-methyltransferase (MGMT) gene is silenced by promoter methylation. Unfortunately, TMZ potential is stunted because of the rapid onset of tumour recurrence and acquired resistance believed to result from the upregulation of DNA damage repair by the base excision repair (BER), mismatch repair (MMR), or homologous recombination (HR) systems. Our laboratory previously demonstrated that cell lines obtained from recurrent, TMZ-resistant GBMs could be re-sensitized to TMZ when treated with an inhibitor of poly (ADP-ribose) polymerase-1 (PARP-1) – a protein instrumental in the recruitment of BER machinery. From this preliminary research, we postulate that PARP-1 inhibition may not only be used to overcome established resistance in GBM but may also be used to prevent its emergence altogether. To test this hypothesis, we utilized the MGMT-methylated GBM cell line U251N and developed an in vitro model of inducible TMZ resistance. We verified that prolonged treatment of U251N cells with TMZ resulted in the emergence of resistant colonies that resembled recurrent GBM clinically observed in TMZ-treated patients. However, when the parental U251N line was co-treated with TMZ and PARP-1 inhibitor ABT-888, resistant colonies failed to appear. Therefore, PARP-1 inhibition may possess the potential to maintain tumour sensitivity to TMZ as well as evade the otherwise inevitable development of resistance in GBM.

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Long-term survivors of brain metastases

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Purpose: We identified key clinicopathologic features of brain metastasis (BM) patients who are long-term survivors (LTS).

Methods: We screened a prospective database of 1892 patients (treated 2006-2017), identified 92 (5%) who lived > 3 years following BM diagnosis, and performed per patient analyses. Results: Median age at diagnosis of BM was 57 years (range 19-77), 77% were women. The most common tumors were lung (50%), breast (26%), thyroid (7%) and skin (5%). 42% had tumors with drug-targetable oncoproteins (e.g. EGFR mutant) and 15% expressed hormonal receptors. ECOG was <2 in 70%. 47% had stage IV disease at diagnosis (75% with brain as the first site). 55% had controlled extracranial disease at the time of BM diagnosis. Median BM diameter was 1.5 cm (range 0.2-7) and 62% had a single lesion. Treatment was with surgery, radiosurgery, whole brain radiation (WBRT), or systemic therapy alone in 38%, 62%, 52%, and 4%, respectively. 53% received targeted- or immuno-therapy. Median follow up was 63 months (range 36-113). 61% failed intracranially at a median 24 months (range 1-99). 5 and 10-year survival (from BM diagnosis) was 82%, and 34%, respectively. Neither upfront WBRT nor other variables tested correlated with improved survival. In patients who died, an MRI was available within 3 months from death in 57%; of those 55% had no active intracranial disease, suggesting that the majority of deaths were non-neurologic. Conclusion: In general, LTS of BM had a limited number of BM, inactive extracranial disease, and drug targetable mutations.

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Radiation induced meningioma in adult survivors of childhood leukemia or primary brain tumor treated with cranial radiotherapy: Incidence and screening recommendations

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Purpose: Cranial radiotherapy (CRT) was commonly given for childhood leukemia and brain tumors. Survivors are at risk of late effects including radiation induced meningioma (RIM). Surveillance for RIM is not standardized . We aimed to determine the incidence, latency, and screening patterns for RIM. Materials and Methods: Retrospective chart review of all patients aged <18 years at the time of radiation (RT), treated with CRT for leukemia or a brain tumor in BC between 1981-2006. Patient, tumor, and treatment characteristics were collected. Actuarial statistics were calculated with Kaplan-Meier Curves. Patients were censored at the date of last normal cranial imaging, or development of a RIM. Results: 392 patients were identified. Median age (range) at CRT was 9.6 years. Median CRT dose was 28Gy. The original diagnosis was leukemia in 50%, glioma in 13%, medulloblastoma in 8%, ependymoma in 7%, neuroectodermal tumor in 7%, germ cell tumor in 5%, craniopharyngioma in 4%, and other pathologies in 6%. Median (range) of clinical follow-up (FU) was 13.2 (0-37.5) years. Median (range) of cranial imaging FU was 15.5 (0-21.2) years. There was no documented cranial imaging FU in 144 patients. Forty-eight patients developed a RIM. The median age (range) at RT for patients with RIM was 6.7 years. Only 8 of these cases presented with associated symptoms. The earliest RIM in our cohort occurred 10.2 years after CRT. On actuarial analysis, the median (95% CI) time to development of a meningioma was 29.8 (28.9-30.7) years. Incidence (95% CI) of meningioma at 10 years was 0%, 15 years was 5 (2-9)%, 20 years was 12 (6-18)%, 25 years was 33 (23-43)% and 30 years was 47 (37-68)%. Amongst patients with a RIM, the median dose of CRT was 45 Gy. The lowest dose of RT in a patient who developed RIM was 12 Gy. RT was delivered to the whole brain in 58% and partial brain in 42% of patients with a RIM. Conclusions: After CRT in pediatric patients, there is a significant risk of developing a RIM and a steady increase in this risk with ongoing follow-up. We recommend standardization of surveillance for these patients with screening beginning 10 years after completion of CRT.

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Characterization of the molecular consequences of CIC-knockout and neomorphic IDH1 R132H mutation on transcriptomic and epigenomic landscapes

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CIC, or Capicua, encodes a transcriptional repressor that is itself repressed by RAS/MAPK signalling. CIC is a recurrent target of somatic mutation in type 1 low grade gliomas (LGG), with at least half of the alterations predicted to be deleterious. Type 1 LGGs are a cohort of tumours that are molecularly defined by the loss of heterozygosity of chromosome arms 1p and 19q and the presence of neomorphic IDH1/2 mutations. Despite the high frequency of mutations in CIC within this tumour type, CIC‟s putative tumour suppressive role remains to be elucidated. It is also unclear how CIC may cooperate with neomorphic IDH1/2 to promote gliomagenesis. To comprehensively characterize the molecular consequences of CIC loss, we performed RNA-seq, Whole Genome Bisulfite Sequencing, and ChIP-seq on 6 different histone modifications on isogenic CIC-wildtype (WT) and CIC-knockout (KO) normal human astrocytes. To also investigate the collective effects of CIC deficiency and neomorphic IDH1 on the transcriptome and epigenome, we generated the same dataset in isogenic CIC-WT and CIC-KO astrocytes possessing the IDH1 R132H mutation. Analysis of differentially expressed genes illustrates the enrichment of oncogenic pathways in specifically the CIC-KO, IDH1-R132H cells, supporting a synergistic relationship between CIC loss and IDH1-R132H in driving tumour progression. Integrative analyses are ongoing to unveil the epigenetic mechanisms underpinning the regulatory changes in these isogenic cell line models.

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A systematic review in quality of life of patients with meningiomas: Effort towards developing a disease-specific questionnaire

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BACKGROUND: Meningiomas are the most common primary benign brain tumors in adults. Given the extended life expectancy of most meningiomas, consideration of quality of life (QOL) is important when selecting the optimal management strategy. There