Background: Ependymomas are the third most common CNS tumor in the pediatric population, accounting for 10% of all CNS tumors. Co-occurring extraneural and extracranial metastasis of ependymomas are extremely rare, with only 1 reported adult case in current literature. Case Description: We describe the case of a patient with multiple recurrences of anaplastic ependymoma. Initial imaging showed a 5 x 8 x 8 cm complex cystic mass with nodular enhancing components within the left occipital lobe. The 4th ventricle was intact and imaging was negative for metastasis. Pathology following resection demonstrated perivascular pseudorosettes, areas of calcification, and increased mitotic activity. Biopsy revealed GFAP, EMA, neurofilament, INI-1, and was negative for CAM5.2, confirming anaplastic ependymoma. Methylxanthine studies for PFA or PFB subgroup differentiation were not available. The patient had recurrences at 4-, 5-, and 6-years after his initial diagnosis. Seven years from his initial diagnosis, the patient underwent resection of four nodular lesions from the occipital lobe and surrounding soft tissue. Pathological lesions and the lymph node/soft tissue confirmed anaplastic ependymoma. A PET scan showed increase uptake in the supraclavicular lymph nodes and had multiple bilateral pulmonary nodules. Scans at 3 months post-surgery were negative for extracranial metastases. The patient had further long-term involvement with progression of pulmonary disease. Conclusion: Co-occurring extraneural and extracranial metastasis of ependymoma is a rare occurrence across all populations. To our knowledge, this would be the first published pediatric case of anaplastic ependymoma with lymph node involvement and pulmonary involvement. Treatment of ependymoma typically local and the utility of chemotherapy remains unclear. Treatment options for extraneal metastasis are very limited, illustrating the need for new therapies and further studies directed at understanding the biology of these tumors and the factors that could influence their ability to metastasize to extraneural and extracranial sites.

GERM CELL TUMORS

GERM-01. RECURRENCE PATTERN AND SURVIVAL FOR RELAPSED INTRACRANIAL NON-GERMINOMATOUS GERM CELL TUMORS: A SINGLE-INSTITUTION EXPERIENCE
Lei Wen
Guangdong Sanjiu Brain Hospital, Guangzhou, China

Purpose: Intracranial non-germinomatous germ cell tumors (NGGCTs) have lower overall survival than germinoma because relatively higher recurrence usually occurs after first line therapy. Methods: Between January 2003 and December 2018, 111 consecutive patients diagnosed with NGGCTs receiving first line therapy were reviewed from our single-institutional retrospective study. Data of first line treatment, salvage treatment, clinico-pathological features and survival were collected and analyzed. Results: Totally, thirty patients (30/111, 27.0%) relapsed in our cohort, including 19 patients with accurate relapse information detail, and 11 patients who died of disease progression during follow up but without exact time and site of relapse. The median OS from diagnosis of the disease was 49.2 months (95% CI: 14.1 to 84.3 months) and 3-year OS was 54.3%. Patients who received both CSI and chemotherapy relapsed less than those who received reduced volume of radiotherapy or only CSI or only chemotherapy (22.5% vs. 45.5%, p=0.034). Of 19 patients who had detailed information of recurrence time and site, the median time from diagnosis of disease to relapse was 9.5 months (2.2 to 72.1 months). Regarding to recurrence site, most patients relapsed in primary site (10/19, 52.6%) or distant intracranial (6/19, 31.6%). The recurrence site of other 3 patients were spinal (n=1), ventricular (n=1) and peritoneal (n=1). Conclusion: Protracted follow-up is recommended because late recurrences are not uncommon. Primary tumor site and disease intracranial are the most prevalent relapsed location. Patients who relapsed could benefited from both CSI and salvage chemotherapy.

GERM-02. MANAGEMENT STRATEGY FOR CHEMO-REFRACTORY, PROGRESSIVE PEDIATRIC IMMATURE TERATOMA
Sarah MeNutt1, Nidhi Shah1, and Elias Rizk1
1Penn State School of Medicine, Hershey, PA, USA; 2Penn State Health, Hershey, PA, USA

Background: Localized NGGCT, a heterogeneous entity, treated with chemo-radiotherapy harbors an overall survival of around 93% based. Failure of a child whose progressed on chemotherapy, while tumor markers remain within normal range. Salvage therapy for progressive immature teratoma is variable, and can include sur-

GERM-03. CLINICAL FEATURES AND OUTCOME OF CHILDREN WITH INTRACRANIAL NON-GERMINOMATOUS GERM CELL TUMORS: A POPULATION STUDY IN HONG KONG
Anthony P.Y. Liu1,2, Dennis T.L. Ku1, Eric Fui1, Chung-Wing Luk1, Jeffrey P.W. Yau1, Siu-Cheung Ling1, Godfrey C.F. Chan1,2, and Matthew M.K. Shung3
1Department of Paediatrics and Adolescent Medicine, Hong Kong Children's Hospital, Hong Kong, Hong Kong, 2Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong, 3Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong, Hong Kong

The incidence of central nervous system non-germinomatous germ cell tumor (NGGCT) is four times higher in Chinese children than in the Western population. Reports on the outcome of Asian patients are nonetheless limited. Here we aim to summarize the experience of treating pediatric NGGCT in Hong Kong. Leveraging a population-wide pediatric oncology database, Chinese children with NGGCT diagnosed from 2002–2020 (n=43) were retrospectively studied. The diagnoses of NGGCT were made either with elevation in tumor markers (AFP/βhCG; n=19), or by histology with/without concomitant rise in tumor markers (n=24). Most patients were treated with a combination of chemotherapy (cisplatin/etoposide/bleomycin, carboplatin/etoposide or carboplatin/etoposide/ifosfamide) and radiation (craniospinal or boost, whole ventricular boost, or focal). The male:female ratio was 37:6, and the median age of diagnosis was 11.2 years. Primary tumor locations were pineal in 18, sellar/suprasellar in 12, basal ganglia in 9, supratentorial in 3 and posterior fossa in 1. Three had metastases assessed by histological findings: 1 with mixed NGGCT, 8 had malignant/immature teratoma, 3 had embryonal carcinoma, and 1 had yolk sac tumor. With a median follow-up of 8 years, 8 patients progressed (local=7, distant=1), and 9 patients died (progression=5, palliative treatment=1, sepsis=1, procedural complications=1). The respective 5-year PFS and OS were 74.9±6.9% and 82.2±6.1%. In multivariate analysis, high serum βhCG level and no radiation use were significantly associated with inferior PFS. Outcome did not differ according to chemotherapeutic reagents used or radiation fields. Four patients had growing teratoma syndrome. Long-term neuroendocrine sequelae were common. In conclusion, children with NGGCT had reasonable outcome after multi-modal therapy in Hong Kong. Effort should be made to minimize tumor and treatment-related toxicities. The role of tumor markers for risk-stratification within NGGCT needs to be further interrogated.

GERM-04. PRIMARY INTRACRANIAL GERM CELL TUMORS ARE MORE PREVALENT AMONG PEDIATRIC PATIENTS OF ASIAN/PACIFIC ISLANDER RACE/ETHNICITY IN THE UNITED STATES
Nayan Lamba1 and Bryan Jorgulescu1
1Massachusetts General Hospital, Boston, MA, USA; 2 Dana-Farber Cancer Institute, Boston, MA, USA

Introduction: Primary intracranial germ cell tumors (GCTs) appear to be more prevalent among pediatric patients in eastern Asia than in the U.S. However, it is unclear whether data to evaluate whether this difference remains true after race/ethnicity among U.S. pediatric patients. Methods: Pediatric patients (age<14) presenting between 2004–2017 with a primary intracranial GCT were identified by ICD-O-3 histological and topographical classification from the National Cancer Database (comprising >200,000 cancers newly diagnosed in children in the U.S.), and categorized by race/ethnicity for age stages. Results: Patients’ age, sex, race/ethnicity, and overall survival, and tumor location...
and size were evaluated. Results: 889 pediatric patients with primary intracranial GCTs were identified, which were overwhelmingly male (64.8%) and pure germinomas (64.0%). Non-germinomatous (24.5%) and mixed (11.1%) GCTs were also present. Our dataset comprised 4.9% of intracranial tumors in pediatric males and 2.9% of intracranial tumors in pediatric females. Asian/Pacific Islander pediatric patients in the U.S. had a notably higher prevalence of GCTs: among Asian/Pacific Islander patients, the prevalence of all brain tumors was 11.6%, which was comprised of 4.5% in White non-Hispanic patients, 2.8% in Black non-Hispanic patients, and 6.0% in Hispanic patients. Despite the much lower prevalence of GCTs among female patients overall, this predominance also persisted for Asian/Pacific Islander females, among whom 7.5% of brain tumors were compared to only 2.5% in White non-Hispanic patients, 2.4% in Black non-Hispanic patients, and 4.1% in Hispanic patients. Overall, 9.4% of pediatric primary intracranial GCTs occurred in patients of Asian/Pacific Islander race/ethnicity, in contrast to 4.0% of diffuse astrocytosis/oligodendroglial tumors, 2.8% of other astrocytic tumors, and 4.6% of embryonal tumors. Conclusions: Primary intracranial GCTs affect a substantially larger proportion of both male and female pediatric patients of Asian/Pacific Islander race/ethnicity in the United States.

HIGH GRADE GLIOMAS

HGG-01. 3D GENOME STRUCTURE IMPACTS GENE EXPRESSION IN PEDIATRIC HIGH-GRADE GLIOMA
Tina Huang, David Scheiber, Ye Hou, Anna Piantu, Elizabeth Bartoun, Ali Shilatifard, Feng Yue, and Amanda Saratsis \(^{1,2,3}\); Northwestern University, Chicago, IL, USA, \(^{2} \) Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA

Introduction: Pediatric high-grade gliomas (pHGGs), including glioblastoma multiforme (GBM) and diffuse intrinsic pontine glioma (DIPG), are highly morbid brain tumors. Up to 80% of DIPGs harbor a somatic missense mutation in genes encoding Histone H3. To investigate whether the H3K27M mutant protein is associated with distinct chromatin structure affecting transcription regulation, we generated the first high-resolution Hi-C and ATAC-Seq maps of pHGG cell lines, and integrated these with tissue and cell genomic data. We generated sequencing data from patient-derived cell lines (DIPG n=6, GBM n=3, normal n=2) and frozen tissue specimens (DIPG n=1, normal brainstem n=1). Analyses included cell line RNA-Seq, ChIP-Seq (H3K27ac, H3K27me3, H3K27M) and genome-wide chromatin conformation capture (Hi-C), as well as tissue ATAC-Seq. Publicly available pediatric glioma tissue ChIP-Seq data was integrated with cell data. Results: We identified tissue-specific enhancers and regulatory networks for known oncogenes in DIPG and GBM. In DIPG, FOX, SOX, STAT and SMAD families were among top H3K27Ac enriched motifs. Significant differences in Topologically Associated Domains (TADs) and DNA looping were observed at OLIG2 and MYCN in H3K27M mutant DIPG, relative to wild-type GBM and normal cells. Pharmacologic treatment targeting H3K27ac (BET and Bromodomain inhibition) altered the TAD structure. Functional analysis of differential en- riched enhancers in DIPG implicated SOX2, SUZ12, and TRIM24 as top- activated upstream regulators. Distinct genomic structural variations leading to enhancer hijacking and gene co-amplification were identified at AZM, JAG2, and FLRT1. Conclusion: We show genomic structural variations enhance promoter interactions that impact gene expression in pHGG in the presence and absence of the H3K27M mutation. Our results imply that tridimensional genome alterations may play a critical role in the pHGG epigenetic landscape and thereby contribute to pediatric gliomagenesis. Further studies examining the impact of the alterations, including CRISPR knock-down of target enhancer regions, is therefore underway.

HGG-02. NEUROPHYSIOLOGICAL SMALL MOLECULE SCREEN TO TARGET NEURON-GLIOMA INTERACTIONS IN PEDIATRIC HIGH GRADE GLIOMAS
David Rogowski, Sara Mulaywhe, Craig Thomas, and Michelle Monje; Stanford University, Palo Alto, CA, USA

Neurons stimulate glioma growth via synaptic and paracrine signaling mechanisms. We recently demonstrated that neurons form AMPA receptor-dependent synapses with glioma cells, and that neuronal activity also induces potassium-evoked currents that are amplified by gap junctions coupling glioma cells. However, our understanding of the neurotransmitters, receptors, and ion channels participating in neuron-glioma signaling remains incomplete. Recent studies have described a co-culture strategy to screen small molecules for agents that may disrupt neuron-glia signaling. Glioma cell proliferation is increased tenfold when cultured together with neurons; this robust biological effect can be probed in a targeted screen of compounds influencing neurotransmitter receptors and ion channels. The neurophysiological small molecular library tested was adapted to include approved anti-epileptics, neuroleptics, and antidepressants, as well as a variety of other compounds acting on different neurotransmitter types and ion channels. Hits from the primary screen were run through a secondary screen, chosen by end points alone without co-culture, comprised 4.9% of intracranial tumors in pediatric males and 2.9% of intracranial tumors in pediatric females. Asian/Pacific Islander pediatric patients in the U.S. had a notably higher prevalence of GCTs: among Asian/Pacific Islander patients, the prevalence of all brain tumors was 11.6%, which was comprised of 4.5% in White non-Hispanic patients, 2.8% in Black non-Hispanic patients, and 6.0% in Hispanic patients. Despite the much lower prevalence of GCTs among female patients overall, this predominance also persisted for Asian/Pacific Islander females, among whom 7.5% of brain tumors were compared to only 2.5% in White non-Hispanic patients, 2.4% in Black non-Hispanic patients, and 4.1% in Hispanic patients. Overall, 9.4% of pediatric primary intracranial GCTs occurred in patients of Asian/Pacific Islander race/ethnicity, in contrast to 4.0% of diffuse astrocytosis/oligodendroglial tumors, 2.8% of other astrocytic tumors, and 4.6% of embryonal tumors. Conclusions: Primary intracranial GCTs affect a substantially larger proportion of both male and female pediatric patients of Asian/Pacific Islander race/ethnicity in the United States.

HGG-03. THE GLYCOSPHINGOLIPIDS METABOLISM IS A NOVEL TARGET IN H3K27M-MUTANT DIFFUSE MIDDLE GLIOMA
Claudia Paret, Roger Sandhoff, Khalifa El Malki, Katrin BM Frauenknecht, Arthur Wingertzer, Nadine Lehmann, Nadine Wewinger, and Jorge Faber; University Medical Center of the Johannes Gutenberg-University, Mainz, Germany, \(^{2} \) German Cancer Research Center, Heidelberg, Germany, \(^{3} \) Institute of Neuropathology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

H3K27M-mutant diffuse middle glioma (H3K27M-mutant DMG) is a rare malignant brain tumor entity in children and adults with a median overall survival of around 12 months. Genomic and proteomic analysis may help to identify new target structures, however not all relevant targets are covered by these analyses. Glycosphingolipids and particularly gangliosides play a major role in brain development and have been involved in the pathology of brain tumors. The expression of cerebroside sulfate ganglioside via glycosylceramide synthase (GCS) is one of the first steps in the synthesis of glycosphingolipids. Therefore, targeting GCS may inhibit their synthesis. Here we analysed the glycosphingolipids composition and tested GCS inhibitors in an in vitro model of H3K27M-mutant DMG. Methods: H3K27M-mutant DMG primary cells were established from needle biopsies of two paediatric patients and characterised by immunohistochemistry. Glycosphingolipids were analysed by thin layer chromatography, liquid chromatography, mass spectrometry and flow cytometry. The effect of the GCS inhibitor eliglustat on the cell proliferation was examined. Results: The primary cells maintained the features of the tumour of origin, including the H3K27M mutation. Neutral glycosphingolipids with a 1 to 1 mass ratio of monosaccharides and the ganglioside GD2 were expressed at high concentration. Eliglustat completely abrogated the proliferation of the H3K27M-mutant DMG primary cells. Conclusions. The glycosphingolipids oncometabolism represents a novel target in H3K27M-mutant DMG. The GCS inhibitors eliglustat and miglustat are already used to treat paediatric patients with the lysosomal storage disorders Niemann Pick’s B and Gaucher’s disease and miglustat can cross the blood-brain barrier. Thus, our finding may accelerate the access of H3K27M-mutant DMG patients to novel innovative clinical studies based on the inhibition of the glycosphingolipids metabolism.

HGG-04. TARGETING GABAERGIC NEURON-GLIOMA SYNAPSES IN DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) THROUGH ANTI-EPILEPTIC DRUG REPURPOSING
Tara Barron, Vilina Mehta, Pamelyn Woo, and Michelle Monje; Stanford University, Palo Alto, CA, USA

Pediatric high-grade gliomas, including diffuse intrinsic pontine glioma (DIPG), are the leading cause of brain cancer-related death in children. While enormous progress has been made in recent years for many forms of cancer, high-grade gliomas remain seemingly intractable, indicating that fundamental aspects of glioma growth are not yet sufficiently understood. Neuronal activity drives glioma growth both through paracrine signaling and through direct neuron-to-glioma synapses. Recently glutamatergic, AMPA receptor-dependent synapses were discovered between microenvironmental neurons and malignant glioma cells. The depolarizing current that results from synaptic and other forms of electrical neuron-glia signaling promotes pediatric high-grade glioma proliferation and regulates growth. Neuron-glia cell synapses mediated by other neurotransmitters remain largely unexplored, though glioma cells express genes encoding neurotransmitter receptors such as GABA \(_{A}\) receptors. GABAergic input has a depolarizing effect on glioma cells, but the magnitude of depolarization is heterogeneous between high-grade glioma subtypes and between patient-derived DIPG xenograft models. We have identified functional GABAergic neuron-to-glioma synapses mediated by GABA \(_{A}\) receptors in patient-derived DIPG xenograft models, lorazepam, a benzodiazepine that increases GABA \(_{A}\)-mediated currents, increases glioma growth. Conversely, levetiracetam, an anti-epileptic drug that reduces synaptic transmission including at GABAergic neuron-glioma synapses, reduces glioma growth. Conversely, levetiracetam, an anti-epileptic drug that reduces synaptic transmission including at GABAergic neuron-glioma synapses, increases glioma growth. However, levetiracetam, an anti-epileptic drug that reduces synaptic transmission including at GABAergic neuron-glioma synapses, is often given to pediatric glioma patients to treat nausea, seizures or anxiety. In patient-derived DIPG xenograft models, lorazepam, a benzodiazepine that increases GABA \(_{A}\)-mediated currents, increases glioma growth. Conversely, levetiracetam, an anti-epileptic drug that reduces synaptic transmission including at GABAergic neuron-glioma synapses, increases glioma growth. Conversely, levetiracetam, an anti-epileptic drug that reduces synaptic transmission including at GABAergic neuron-glioma synapses, increases glioma growth.