EPEN-50. THE MANAGEMENT AND TREATMENT OF PEDIATRIC SPINAL CORD EPENDYMOMA: RESULTS FROM A COLLABORATIVE INTERNATIONAL MULTI-INSTITUTIONAL REVIEW

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PURPOSE: Pediatric Spinal cord ependymoma (SCE) is rare, and the management is often heterogeneous across centers. We evaluated the impact of clinical, pathologic, and treatment-related factors on outcomes in a multi-institutional, international cohort. METHODS: SCE patients age <21 years were reviewed across 5 institutions. We utilized nonparametric descriptive statistics, survival, and recursive partitioning analysis (RPA) to examine patient, tumor, histopathologic and treatment characteristics, failure pattern, and cause of death. RESULTS: 125 patients were identified, 18 (14.4%) with metastases. Initial surgery was GTR, and STR in 44, 56% of patients respectively. Histology was grade 1, 2, and 3 in 55, 17.7 and 23.2% respectively. 55 patients with initial GTR were observed (52.7%) or irradiated (43.6%); 60 patients had STR and were observed (40%) or irradiated (60%). The 7-year event-free (EFS) and overall survival (OS) was 60% (95% CI 51.5–71.4) and 79% (95% CI 71.1–87.8) respectively. STR and metastasis increased the hazard for death [HR 1.87, 95% CI 1.02–3.57, p=0.05 (vs. GTR)] and [HR 2.28, 95% CI 1.1–5.2, p=0.048 (vs. localized)] respectively. Across 43 failures, local failure predominated (48.8%). Distant and combined failure occurred in 30.2 and 13.9% respectively. Adjuvant RT offered a 20% absolute improvement (vs. observation) in EFS at 5 years regardless of extent of resection. RPA identified thoracic (vs. non-thoracic), grade (1 & 3 vs. 2), STR (vs. GTR) and metastases as determinants of inferior EFS. CONCLUSIONS: Tumor and treatment-related factors are predictive of EFS. OS is favorable despite diverse schema and frequent distant failures.

EPEN-51. CHILDHOOD INTRACRANIAL EPENDYMOMA: A MULTI-CENTER RETROSPECTIVE ANALYSIS

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Ependymoma is a heterogeneous disease which is resistant to improvement. Current challenges are the unreliability of histologic classification, the uncertain role of adjuvant chemotherapy, and a lack of clinical trials integrating molecular and clinical diagnostics into risk-guided therapy. Ependymoma can show surprising latency, reoccurring many years after the original diagnosis. In this study, we performed a retrospective analysis of ependymoma cases treated at six centers over a period of 12 years. A total of 73 cases were submitted from six sites; 68 cases were retained for review. Median age at diagnosis was 4.1 years and gender was reported as male (50%) and female (50%). Histologic grade was reported as Grade II (49%) and Grade III (50%)(not reported: 1). Anatomic location reported as supratentorial (27%) and infratentorial (73%). Metastatic disease was reported in 9% of patients. At diagnosis, gross total resection was achieved in 59% of cases. Twenty-eight percent of patients have died, 59% of patients are alive (with and without disease), and 13% of patients are lost to follow-up. Maximal safe surgical resection is currently the best predictor of long-term survival but was achieved in only 60% of cases. Biology-based therapy will be the next step towards improving the prognosis of pediatric ependymoma.

EPEN-52. METABOLIC REGULATION OF THE EPIGENOME DRIVES LETHAL INFANTILE EPENDYMOMA

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PFA ependymomas are a lethal glial malignancy of the hindbrain found in infants and toddlers. Lacking any highly recurrent somatic mutations, PFAs have been proposed to be a largely epigenetically driven entity, defined by hypomethylation at the histone 3 lysine 27 residue. Unfortunately, an almost complete lack of model systems has limited the discovery of novel PFA therapies. In this study, we have identified that the PFA hypoxic microenvironment controls the availability of specific metabolites, resulting in diminished H3K27 trimethylation and increased H3K27 acetylation *in vitro* and *in vivo*. Unique to PFA cells, transient exposure to ambient oxygen results in irreversible cellular toxicity. Furthermore, perturbation of key metabolic pathways is sufficient to inhibit growth of PFA primary cultures *in vitro*. Although PFA tumors exhibit a low basal level of H3K27me3, inhibition of H3K27 methylation paradoxically demonstrates significant and specific activity against PFA. Thus, we propose a "Goldilocks Model" of metabolic-epigenetic regulation in PFA ependymoma, whereby increased or decreased H3K27 trimethylation results in cell death. Mapping of PFA ependymoma tumours suggests a cell of origin arising in the first trimester of human development where there is a known hypoxic microenvironment. Therefore, targeting metabolism and/or the epigenome presents a unique opportunity for rational therapy for infants with PFA ependymoma.

EPEN-53. C11ORF95-RELA REPROGRAMS 3D EPIGENOME IN SUPRATENTORIAL EPENDYMOMA

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Ependymoma is the third most common malignant brain tumor in children. However, there is no effective chemotherapy identified and treatment is limited to surgery with or without adjuvant radiation therapy currently. Thus, to develop targeted therapy based on the underlying biology is an urgent need. Since 2014, *C11orf95-RELA* fusion was found to be the most recurrent structural variation in approximately 70% of supratentorial ependymomas (ST-EPN), but the molecular mechanisms of oncogenesis are unclear. Here we utilized HEK293T transgene models and a ST-EPN cell line to investigate the epigenomic changes and transcriptional regulations by C11orf95-RELA fusion. By applying ChIP-seq and HiChIP approaches, we found C11orf95-RELA is a novel transcription factor that recognizes a specific DNA motif dictated by the C11orf95 component while the RELA component is required for driving the expression of ependymoma-associated genes such as *CCND1* and *L1CAM*. Moreover, C11orf95-RELA modulates chromatin states and mediates chromatin interactions, leading to transcriptional reprogramming in ST-EPN cells. Multiple signaling pathways such as Notch signaling and G-protein signaling are identified to be involved in ST-EPN development. Our findings provide important characterization of the molecular underpinning of *C11orf95-RELA* fusion and shed light on potential therapeutic targets for *C11orf95-RELA* subtype ependymoma.

EPEN-54. ACNS0831, PHASE III RANDOMIZED TRIAL OF POST-RADIATION CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED EPENDYMOMA AGES 1 TO 21 YEARS

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PURPOSE: The primary objective of this study is to determine the EFS and OS of children with gross total and near totally resected ependymoma (EPN) treated with post-operative focal radiation therapy (RT) followed by randomization to either RT alone or RT + 4 cycles of maintenance chemotherapy with vincristine, cisplatin, cyclophosphamide and etoposide. Secondary objectives include estimating the EFS and OS of children not randomized, evaluation of neurobehavioral and quality of life (QoL) endpoints, and EPN biomarkers. RESULTS: 479 patients enrolled, 451 were eligible. Of 325 eligible randomized patients, 161 were randomized to RT alone and 164 to RT + maintenance chemotherapy. Age range (1–21 years, median 4.9 years). The planned primary analysis was based on intent-to-treat, irrespective of actual treatment received. Based on the data available as of 12/31/2019, estimated 3-year EFS in the RT + maintenance chemotherapy

vs. RT arms were 78% vs. 72%, respectively, which did not meet statistical criteria to establish the benefit of maintenance chemotherapy post RT (1-sided log-rank p-value=0.074). Due to significant noncompliance (30.5% in the RT + maintenance vs 4.3% in the RT arm), a planned secondary "as treated" analysis was performed. With median follow-up of 42.6 months among patients without events, the 3 year EFS estimates for patients who received any chemotherapy (n=114) vs. those who received RT only (n=196) were 80% vs. 71%, respectively (1-sided p-value = 0.0121). CONCLUSION: Early results in this randomized trial suggest that there may be some EPN patients who benefit from maintenance chemotherapy. Genomic analyses are ongoing.

EPIDEMIOLOGY

EPID-01. TRENDS OF INCIDENCE IN PEDIATRIC BRAIN TUMORS IN KUMAMOTO PREFECTURE, JAPAN

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BACKGROUND/PURPOSE: One of the most problematic issues Japan has is a declining birthrate resulting in an aging society. There are some reports on the trends of incidence in brain tumors in the elderly, whereas few reports on those in the children. The aim of this study is to investigate the trends of incidence in childhood primary brain tumors. METHODS: The population of children aged <15 years was available from Kumamoto Prefecture's annual census between 1990 and 2017. During the period 301 childhood primary brain tumors (124 gliomas, including astrocytic tumors and ependymomas, 35 embryonal tumors, 34 germ cell tumors, 22 craniopharyngioma, and 86 others) were registered with the Kumamoto Brain Tumor Data Bank, and investigated. RESULTS: The average of the annual incidence rate per 100,000 child populations was 3.90 for total brain tumors, 1.63 for gliomas, 0.44 for embryonal tumors, 0.42 for germ cell tumors, 0.26 for craniopharyngioma, and 1.15 for others. Divided into the first half from 1990 to 2003 and the second half from 2004 to 2017, there was no significant difference in the incidence of brain tumors aged <15 years between the two periods. However, the average of the annual incidence rate/100,000 child populations was 3.02 in the first half, while significantly increased in the second half of 4.78 (p=0.00075, t-test). DISCUSSION & CONCLUSIONS: The average number of children aged <15 years in Kumamoto Prefecture was 31,2737.9 from 1990 to 2003, while decreased remarkably to 251460.2 from 2004 to 2017. A decrease in the number of children may affect increasing the incidence rate of pediatric brain tumors.

EPID-03. COMPARISON OF SURVIVAL IN ADULT AND PEDIATRIC PATIENTS WITH MEDULLOBLASTOMA: A 2018 SEER BASED ANALYSIS

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Medulloblastoma (MB) is the most common high-grade primary brain malignancy in children and accounts for 1% of adult brain tumors. Previous studies have compared survival in pediatric and adult MB from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) database finding no difference. However, diagnostic subgroup analyses are limited. We examined survival in children (age 0–19) and adults (20–79) coded as MB in the 2018 SEER database (2000–2016), using Kaplan Meier analysis, log-rank test and Cox proportional hazard ratios (HR) with 95% confidence intervals (CI).). MB in SEER-18 is defined as ICD-O-3 histology codes 9470–9474 (n=1,728). ICD 9473, supratentorial PNET (sPNET, n=97) is biologically distinct so was analyzed separately. 5-year survival for MB, excluding sPNET, was similar in children (n = 1,091, 75.3%) and adults (n= 488, 79.1%) (HR=0.97, CI: 0.79 – 1.17, p=0.50). Subtype analyses showed no survival difference comparing adults and children with desmoplastic nodular MB (n=222, p=0.09), large cell MB (n=73, p=0.46), or MB NOS (n=1330, p=0.10). In contrast, children with sPNET had improved survival (n=65, 72.3%) compared to adults (n=29, 51.7%) (HR = 2.0, CI: 1.10 – 3.92; p=0.02,). In conclusion, 2018 SEER data for MB continue to show no survival difference between adults and children, suggesting adult patients could appropriately be entered on pediatric MB treatment protocols. Further analyses of the 2018 data are ongoing adjusting for sex, race, and treatment. Comparison of adults and children with MB and sPNET will be re-evaluated using the new 2016 World Health Organization classification.

EPID-04. MORBIDITY IN PAEDIATRIC BRAIN TUMOURS: 17 YEARS' EXPERIENCE IN A TERTIARY NEUROSURGICAL UNIT

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The treatment of paediatric brain tumours has shown significant improvement over the last 2 decades. The aim of our study is to evaluate the prevalence of various effects among this population within our institution. 102 patients diagnosed with a brain tumour at the age of 0–18 years between 2002 and 2018 were identified within a single paediatric institution. Data was collected retrospectively based on electronic medical records. Medulloblastoma (20.6%) was the most common subtype followed by pilocytic astrocytoma (18.6%) and craniopharyngioma (11.8%). Overall, the 5-years survival rate was approximately 77%. Endocrine dysfunction was reported in 36% of the population, mainly due to tumour located in suprasellar region and irradiation causing progressive pituitary dysfunction. Neurological disorders such as epilepsy, weakness, cranial nerves palsy, visual and hearing impairment were present in 46% of the population. Importantly, 20.4% of patients who received chemotherapy had some degree of sensorineural hearing loss. 16% of the population suffered from impaired neurocognition which is likely an underestimation as screening could not be performed on all patients. Other significant complications are infections (12%) and ventriculoperitoneal shunt dysfunction (7%). Most of these effects can be attributed to direct injury to the developing brain caused by the tumour or related to its treatment during surgical excision and the long term side effects of chemotherapy and radiation therapy. Morbidities in various domains can pose significant challenges to survivors of paediatric brain tumours. Active screening and surveillance of these effects can help improve the health outcomes of survivors of paediatric brain tumours.

EPID-05. EVALUATION OF THE INCIDENCE OF CENTRAL NERVOUS SYSTEM TUMORS IN A CHILDHOOD CANCER TREATMENT CENTER AND THE CREATION OF A SPECIFIC GROUP

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Central Nervous System Tumors (CNST) are the main solid neoplasm of childhood, representing 20% diagnosis. Based on this information, a search was carried out at a reference treatment center for childhood cancer in the state of Sao Paulo, belonging to University of Sao Paulo- ITACI/HCFMUSP, and at between 2017 and 2019, 352 new patients, 116 of which were neoplasm of CNS (32.9%). Aiming at an incidence of new cases, in 2019, an institutional group was created, with a team composed of Pediatric Oncologists, Neurosurgeons, Radiologists, Radiotherapists and Pathologists. In this first year, 31,8% of the 132 new patients were diagnosed with CNS tumor. According to WHO 2016, 15 patients were classified as a group that includes Diffuse Astrocytomas, Oligodendrioglial Tumors and Other Astrocytic Tumors. Among the other patients, 14.2% were Medulloblastomas, 4.7% Embryonic Tumors and 2.3% ART / RT. Patients diagnosed with diffuse brainstem glioma accounted for 11.9% of the total. The institution had a diagnosis of Angiocentric Glioma, Craniopharyngioma, Plexiform Neurofibroma and Anaplastic Ependymoma. Neuronal-glial tumors accounted for 9.5% of cases. Choroid plexus tumors represents 5%. Among them, 4.72% had metastatic tumors: Neuroblastoma and Ewing's Sarcoma. Of the total of 42 patients, there were 5 deaths, 4 due to disease progression and one due to clinical complications. With the group, the discussions were carried out, allowing us to analyze that the presence of the Radiotherapy, Neurosurgery and Pathology team from the first moment, optimized the beginning of treatment and increased the patients' survival.

EPID-06. DIAGNOSTIC INTERVAL TIME OF PEDIATRIC CNS TUMORS: A REPORT OF THE CANCER IN YOUNG PEOPLE IN CANADA (CYP-C) DATABASE

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INTRODUCTION: CNS tumors are the second most common neoplasm in children and have historically been associated with longer time to diagnosis. Data on the time-to-diagnosis for Canadian children with CNS tumors