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