(EMT) is important for invasion and metastasis in many cancers. This study aimed to evaluate and compare treatment outcomes with the expression of EMT-related transcription factors in pediatric ependymomas. MATERIAL AND METHODS: Medical and radio-imaging data of 22 (11 boys, 11 girls) patients aged <15 years with intracranial ependymomas were reviewed from January 1983 to December 2018. Six cases were subdivided into clinicopathological-molecular subgroups and immunohistochemically analyzed for Slug and ZEB. RESULTS: The median age at the start of treatment was 5 years (range 8 months–15 years) (9 cases were aged <3 years). The median progression-free survival (PFS) was 25.6 (range, 0.8–383.5) months; the median overall survival (OS) was 81.9 (range, 2.9–383.5) months. Extent of resection and malignant histology were significant prognostic factors for OS and PFS in multivariate analysis. There were 6 cases (2 cases of PFA, 2 of PFB, 1 of ST and 1 case of ST-RELA). Nuclear expression of ZEB1 was found in all tumors; however, that of Slug increased only in PFA and PFB tumors, which were associated with a poor prognosis. CONCLUSION: Expression of EMT-related transcription factors was increased in pediatric ependymomas. These data suggest that EMT is a novel therapeutic target for treating pediatric intracranial ependymomas.

EPEN-03. LONG-TERM FOLLOW-UP OF AIEOP 2ND SERIES OF CHILDREN AND ADOLESCENT WITH PRIMARY INTRACRANIAL (ST:SUPRATENTORIAL; PF: POSTERIOR FOSSA) EPENDYMOMA AND METHYLATION GROUPS RE-ANALYSES

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BACKGROUND: This 2002–2014 Italian prospective study stratified 160 patients by surgical resection (complete=NED/incomplete=ED) and centrally-reviewed grade. Grade2/NED patients received focal radiotherapy (RT) up to 59.4Gy, Grade3/NED received 4 courses of VEC(vincristine,etoposide,cyclophosphamide) after RT.ED patients received 1–4 VEC courses, second-look surgery, 59.4 Gy+8Gy boost on measurable residue. METHODS: We re-analyzed data at 115 months follow-up including methylation profile on available samples. RESULTS: Global PFS/OS at 5/10 years were 66/59% and 80/74%, respectively. Of the 64 relapsers at median 20 months, 53 died at median 37/18 months after diagnosis/relapse, respectively.10/64 relapsed after 5 years (66–126 months); 4 died, relapse was local in 8/10, metastatic 1, combined 1;5/10 patients were below age 3, 5 females, 8 PF tumors. Their survival post-relapse was not longer than earlier relapsers'. At univariable analysis, age over 3 years, female sex, complete surgery, grade 2, no shunt confirmed better PFS/OS. 66/95 analyzed tumors received a score >0.80 through the DNA methylation-based central nervous system tumor classifier: 41/8 as PFA/PFB, respectively,14/17 ST as RELA-positive (3 scored for other molecular entities i.e. anaplastic PXA, LGG MYB, HGNET). Prognostic factors were equally distributed among PFA/PFB groups,1 only group B patient relapsed locally at 96 months. CONCLUSIONS: Already published prognostic factors remained at long-term follow-up;6.2% patients had late relapses. OS after relapse was not better in late relapsers. Group B confirmed better prognosis but all patients had received «at least» adjuvant RT. Modern ependymoma trials need long follow-up to draw firm conclusions.

EPEN-04. ONCOGENIC 3D TUMOR GENOME ORGANIZATION IDENTIFIES NEW THERAPEUTIC TARGETS IN EPENDYMOMA

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By profiling enhancers in primary ependymoma tumors, we have recently identified putative oncogenes, molecular targets, and functional pathways. Inhibition of selected targets diminished the proliferation of patient-derived neurospheres and increased survival in mouse models of ependymoma. While enhancers frequently regulate the nearest gene, identification of enhancer target genes remains to be a challenge in the absence of chromosome conformation information. Consequently, we have now used HiC to map the 3-dimensional organization of tumor chromatin in the two most common and aggressive ependymoma subgroups: posterior fossa group A (PF-EPN-A) and supratentorial ependymomas with gene fusions involving the NF-κB subunit gene RELA (ST-EPN-RELA). By an integrative analysis of enhancer and gene expression in the context of the newly derived HiC data, we find that a large number of the predicted enhancer target genes are enriched for strong physical interactions. Importantly, we also identify many new putative tumor-dependency genes activated by long-range promoter-enhancer interactions and complex tumor-specific chromatin clusters of regulatory elements. Complementary to the analysis of gene-enhancer interactions, we have also leveraged the HiC data for resolving structural rearrangements underlying copy number alterations. Copy number gains of the 1q arm of chromosome 1 are especially associated with poor survival. Our preliminary results in PFA relapse samples show complex structural variants underlying 1q gain that lead to inter-chromosomal rearrangements and affect several genes that potentially contribute to poor survival. In ongoing work we are testing the relevance of the novel candidate genes for tumor cell growth and proliferation in-patient derived ependymoma models.

EPEN-05. CLINICAL AND GENETIC EVOLUTION OF EPENDYMOMA EXPOSED FROM A MULTI-RECURRENCE GIRL CASE

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Ependymomas are glial brain tumors accounting for approximately 2~3% of all primary tumors of the central nervous system (CNS), and 12% of all pediatric intracranial tumors. To better understand the evolution process of ependymomas, we studied the clinical, pathological and genetic development of a rare girl case with repeatedly recurrent ependymoma. This girl was diagnosed as ependymoma at age of 9 years old, and experienced 7 times tumor relapse and received 9 times surgeries but finally ceased at 19 years old with multiregional recurrences. The pathological characteristics, radiographic images and therapeutic strategies of the patient were all retrieved. Molecular markers confirmed the diagnosis of anaplastic ependymoma based on the updated WHO guideline for CNS tumors. Whole-genome sequencing (WGS) was performed to elucidate the landscape of mutation signatures and to identify potential driver mutations along the tumor progression. The seven tumor specimens showed a highly branched evolutionary pattern. There were six gene mutations found in 5 of the 7 specimens (PCDHA4, PCDHA8, SEC14L6, SETD2, RIOK2, and SLCO2A1) and three