EPEN-17. RECURRENT INFRATENTORIAL EPENDYMOMAS IN CHILDREN: A META-ANALYSIS ON MOLECULAR-BASED OUTCOMES

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The overall prognosis of infratentorial ependymoma differs based on molecular signature, however the impact of recurrence on prognosis remains poorly defined in the pediatric population. PubMed, Scopus, Embase, and Ovid were searched for publications on recurrent infratentorial ependymomas in patients under 25 years of age. Exclusion criteria were case series of less than 5 patients and studies that did not provide individualized patient data. Our search yielded 472 unique articles, of which 17 were included in the analysis. There was a total of 460 recurrent ependymomas reported, with 52.8% WHO grade II tumors and 47.2% grade III. The overall mortality for recurrent infratentorial ependymoma was 49.1% (226/460). The pooled median survival was 32.39 months after recurrence (95% CI: 23.45-41.33). Gross total resection was achieved in 237 (53.1%) patients at initial presentation. Raw mean survival post-recurrence was 32.9 months (SD: 11.2 months) for those who received GTR for their primary tumor versus 23.7 months (SD: 10.8 months) for those who received subtotal resection (STR) ($p < 0.001$). There was no difference in survival between those that received GTR (49.3 months, 95% CI: 32.3-66.3) versus STR (41.4 months, 95% CI: 11.6-71.2) of their recurrent tumor (p=0.610). In the studies that provided molecular classification, there were 169 PFA tumors (83.3%) and 34 PFB (16.6%), with 28 that demonstrated 1q gain. PFA-A tumors demonstrated worse post-progression survival (24.7 months, 95% CI: 15.3-34.0) compared to PF-B (48.0 months, 95% CI: 32.8-63.2) (p=0.0073). The average post-recurrence survival for tumors with 1q gain was 5.93 months (SD: 9.15). The overall mortality rate for recurrent infrantentorial ependymomas was found to be 49.8%, with a pooled median survival of 32.39 months. Almost 90% of recurrent infratentorial ependymomas were of the PFA molecular subtype, and those tumors that demonstrated 1q gain had a worse survival than those that did not.

EPEN-18. ONCOGENIC 3D GENOME CONFORMATIONS IDENTIFY NOVEL THERAPEUTIC TARGETS IN EPENDYMOMA

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Ependymoma (EPN) is an aggressive pediatric tumor that occurs throughout the central nervous system. The two most aggressive molecular subgroups of EPN are the supratentorial ZFTA-fusion associated group (ST-EPN-ZFTA) and the posterior fossa group A (PF-EPN-A). Although the molecular characteristics underlying the tumorigenesis of these subgroups have been extensively studied, these tumors remain difficult to treat. Hence, innovative therapeutic approaches are urgently needed. Here, we used genome-wide chromosome conformation capture (Hi-C), complemented with CTCF (insulators) and H3K27ac (active enhancers) ChIP-seq, as well as gene expression and whole-genome DNA methylation profiling in primary and relapsed EPN tumors and cell lines, to identify chromosomal rearrangements and regulatory mechanisms underlying aberrant expression of genes that are essential for EPN tumorigenesis. By integrating these heterogenous data types, we have observed the formation of new topologically associated domains ('neo-TADs') caused by intra- and inter-chromosomal structural variants in both tumors. In addition, we observed 3D chromatin complexes of regulatory elements, and the replacement of CTCF insulators by DNA hyper-methylation in PF-EPN-A tumors. These tumor-specific 3D genome conformations can be associated with the transcriptional upregulation of nearby genes. Through inhibition experiments we validated that these newly identified genes, including RCOR2, ITGA6, LAMC1, and ARL4C, are highly essential for the survival of patient-derived EPN cell lines in a disease subgroup-specific manner. Thus, our study identifies novel potential therapeutic vulnerabilities in EPN and extends our ability to reveal tumor-dependency genes and pathways by oncogenic 3D genome conformations even in tumors that lack known genetic alterations.

EPEN-19. IMPACT OF MOLECULAR CLASSIFICATION ON PROGNOSIS IN CHILDREN AND ADOLESCENTS WITH SPINAL EPENDYMOMA: RESULTS FROM THE HIT-MED DATABASE

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PURPOSE: Ependymomas of the spinal cord are rare among children, and individual risks of disease progression are difficult to predict. This study aims at evaluating the prognostic impact of DNA methylation-based classification in children with spinal ependymoma. METHODS: Eighty-two patients with spinal ependymoma <22 years registered in the HIT-MED database between 1992 and 2021 were included. Clinical, radiological, and histopathological data were collected retrospectively. DNA methylation profiles of 46 tumors were classified according to the Heidelberg Brain Tumor Classifier. RESULTS: Spinal myxopapillary ependymoma (SP-MPE, n=27) was the most common methylation group followed by spinal ependymoma (SP-EPN, n=15). Two cases belonged to *MYCN*-amplified subgroup, one had no match, and one was re-classified as anaplastic pilocytic astrocytoma (the latter excluded from final analysis). WHO grade I and III ependymomas (according to the WHO 2016 classification) classified predominantly as SP-MPE, whereas grade II ependymomas clustered into SP-MPE and SP-EPN. 6/15 patients with SP-EPN (40%) suffered from *Neurofibromatosis type 2*. Among patients with SP-MPE, 23 underwent gross-total and four a subtotal resection (GTR/STR). Relapses of SP-MPE were more common following STR (5-year progression-free survival (5y-PFS) [STR] 25.0% [95% confidence interval: 0.0-68.4], [GTR] 75.0% [53.4-96.6], p=0.003). In the SP-EPN group, 2/8 patients relapsed after STR (5y-PFS 64.3% [22,3-100]) and 0/7 after GTR (n.s.). WHO I° ependymoma had significantly inferior PFS than II° and III° ependymoma (5y-PFS [I°] 39.0% [5.8-62.2], [II°] 82.4% [67.8-97.0], [III°] 50.5% [18.9-82.1], p=0.009). However, PFS did not significantly differ between SP-MPE and SP-EPN (5y-PFS 65.9% [44.9-86.9], 76.9% [46.3-100], respectively). CONCLUSION: Spinal ependymomas of WHO grade I go along with relatively poor PFS in our cohort, while DNA methylation profiling does not segregate patients into distinct risk groups. Still, larger cohorts and further investigations of methylation class heterogeneity in pediatric spinal ependymomas are needed to complete the basis for future clinical decision-making.