retrieved from the archives of the Brain Tumor Reference Center, Institute of Neuropathology, University of Bonn. DNA and RNA were extracted from FFPE tumor samples. Gene fusions were identified by FISH using break-apart probes for *ALK, NTRK1, -2, -3, ROS1* and *MET*, Molecular Inversion Probe (MIP) methodology, and targeted RNA sequencing. RESULTS: 37 supratentorial GBM occurred in the first year of life, 13 GBM between one and four years. 18 cases showed fusions of *ALK* to different fusion partners; all occurred in the first year of life (18/37 cases, 48.6%). Fusions of *ROS1* were found in 5, *MET* in 3, *NTRK1*, -2, -3 in 10 cases. 12 cases showed no and two novel fusions. The different methods led to comparable results; targeted RNA sequencing was not successful in a fraction of cases. Break-apart FISH led to reliable results on the next day, MIP technology represented the most sensitive method for analysis of FFPE samples. CONCLUSIONS: Gene fusions involving the tyrosine kinase genes *ALK, MET, ROS1* and *NTRK1, -2, -3* occurred in 72% of glioblastomas of children younger than four years; the most frequent were *ALK* fusions occurring in infant GBM. DNA based MIP technology represented the most robust and sensitive assay.

HGG-35. PEDIATRIC PLEOMORPHIC XANTHOASTROCYTOMA WITH ANAPLASIA TREATED WITH SURGERY AND ADJUVANT CHEMOTHERAPY: A CASE SERIES OF 3 LONG-TERM SURVIVORS

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OBJECTIVE: Pleomorphic xanthoastrocytoma (PXA) with anaplasia is a rare histological subtype of central nervous system astrocytoma and generally treated as high grade gliomas. The optimal extent of therapy required is unknown. Here we report on 3 pediatric cases of PXA with anaplasia. We also describe molecular features and methylation profile of PXA with anaplasia compared to age-matched PXA without anaplasia. METHODS: Our institutional database was queried for cases of PXA since 1998 and 3 cases with anaplasia were identified and records reviewed. RESULTS: 2/3 patients were male and all were aged 12 at diagnosis. All underwent a gross total resection (GTR), where the diagnosis of PXA with anaplasia was made. Immunohistochemistry demonstrated that two cases were BRAF V600E positive and two were CD34 positive. Methylation profiling revealed unique pattern of CpG methylation/unmethylation. All patients underwent 5400cGy radiation to the surgical bed. 2/3 patients received concurrent temozolamide with radiation followed by maintenance chemotherapy with temozolamide and lomustine for 6 cycles as per the Children's Oncology Group Protocol ACNS0423. These two patients had a continued complete response. The third patient received temozolamide following radiation and subsequently had recurrent disease at the end of treatment and went on to have a re-resection GTR and achieved complete response after 6 cycles of lomustine, vincristine and procarbazine. All are alive with no evidence of disease at more than 2 years post treatment completion (OS=100%,EFS=67%). CONCLUSIONS: This rare pediatric tumor is not well understood. The genetic landscape may be informative for optimizing treatment and prognosis.

HGG-36. HIF-2: A NEW DRUG TARGET IN PEDIATRIC HIGH-GRADE GLIOMA WITH PROMISING PRECLINICAL RESULTS

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Pediatric high-grade gliomas (pHGGs) have a very dismal prognosis and need new innovative strategy for treatment. Despite the past discovery of histone H3 driver mutations, we are not able for instance to stop this induced epigenetic remodulation. Therefore, proactive translational studies wish to go further discovering new targetable proteins in pHGG. In our past clinical work, we were able to link significantly HIF-2alpha to a worse pHGG outcome and to their treatment resistance. We designed this new work to determine in several patient-derived cell lines (6 PDCLs) with or without H3.3 mutation the variation of HIF-2alpha, its role, its induction in normoxic and hypoxic microenvironment and its transcriptional targets using RNAseq, metabolomics and ChipSeq analyses. Complementary functional analyses were performed using siRNA strategy during cultures and migration assays. Finally, preclinical drug testing involving commercialized and non-commercialized HIF-2alpha specific inhibitors in the same PDCLs were evaluating their antiproliferative and pro-apoptotic effect. Our results confirmed the central role of HIF-2alpha in cell resistance to treatment, in pHGG stemness features and its direct link with metabolism adaptation and histone interaction. After the confirmation of its frequent presence in multiple PDCLs initiated from thalamic pHGGs and DIPG, we were using inhibitors in a single and combinatorial strategy targeting HIF-2alpha plus another hypoxia biomarker (mTor). This preclinical targeting was highly effective to favor cell arrest, apoptosis and to stop cell migration. In conclusion, HIF-2alpha seem to be a major biomarker in pHGGs that might be targeted giving a useful new opportunity for pHGG treatments.

HGG-37. PAEDIATRIC GLIOBLASTOMA CELLS SHOW CRITICAL DEPENDENCIES ON EPIGENOMIC AND EPITRANSCRIPTOMIC CONTROL OF GENE EXPRESSION BY H3.3G34R/V MUTATIONS

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H3.3G34R/V mutations are restricted to glioblastomas of the cerebral hemispheres, and occur predominantly in adolescents and young adults. We had previously shown these mutations to result in a global re-organisation of the activating mark H3K36me3 to drive transcription of key developmental transcription factors and oncogenes such as MYCN, however the precise mechanism was unclear. Using multiple H3G34R/V samples and ChIP-seq with antibodies specific to both wild-type and mutant histone H3.3, we show a high degree of incorporation of mutant histone into nucleosomes, with only a minority (<15%) remaining wild-type only. Heterogenous G34-mutant nucleosomes displayed significantly elevated H3K36me3 binding, the majority apparently in *trans* to the mutation on the wild-type H3.3, and expression signatures associated with chromatin modification, cell cycle progression, DNA repair and gene transcription. Super-enhancer analysis by H3K27ac ChIP-Seq highlighted lineage-dependent transcription factors and previously identified targets MYCN and NOTCH1 (both stabilised by FBXW7, down-regulated by loss of chromosome 4q), as well as specific H3K36 lysine demethylases and splicing factors. Whole-genome CRISPR-Cas9 screening of patient-derived H3.3G34R/V cells identified critical dependencies on these latter targets, in addition to a general essentiality for genes involved in RNA processing. Assessment of RNA methylation by MeRIP-seq revealed a strong concordance of m6A-modified RNA and H3K36me3 binding, with differentially modified transcripts in mutant cellsassociated with the 3'-UTR but also the promoter and gene bodies. These data highlight the critical nature of the epitranscriptome in H3.3G34R/V-mutant paediatric glioblastoma, and highlight novel targets for therapeutic intervention.

HGG-38. A COMPARATIVE PROTEOMIC-ANALYSIS OF THE CELL MEMBRANE FRACTIONS OF HISTONE 3 MUTATED BRAIN TUMOURS TO IDENTIFY NOVEL THERAPEUTICS

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Improvements in the treatments for childhood and adolescent brain tumours, High-Grade Glioma (pHGG) and Diffuse Intrinsic Pontine Glioblastoma (DIPG), have not advanced much and they continue to carry a very poor prognosis. These brain tumours are now defined by mutations affecting histone 3 proteins, indeed 80% of DIPGs harbour histone H3.1 and H3.3 K27M somatic mutations whilst 30% of pHGGs exhibit H3.3 G34R or G34V mutations. We hypothesized that the histone 3 mutant tumours will have distinct mutation specific surfactome. We therefore analysed the cell surface proteomics of pHGG and DIPG, in order to identify novel targets for therapy. We have at first isolated the cell membrane fractions from a range of patient cells carrying different histone 3 mutations (G34R, G34V, K27M), relative to wild type histone 3. A comparative quantitative mass-spectrometry analyses of these cell surface membrane fractions is then performed to identify specific targetable factors, which can be then be used for tumour specific precision-therapy. Results of these experiments will be presented.

HGG-39. CLINICAL CHARACTERISTICS AND OUTCOME OF PATIENTS WITH RADIATION-INDUCED GLIOMA

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The development of gliomas subsequent to therapeutic cranial irradiation is a rare but serious complication. The purpose of this study is to understand the clinical characteristics and outcome of patients with radiation-induced glioma (RIG). Between 2001 and 2018, we identified 10 patients with RIG, which satisfied the Cahan's criteria in our data base. There was no sex predominance (M: 5, F: 5), and the median age of the primary diseased was 13.5 years (range: 1–39). The primary diseases included 2 germinoma, 2 acute lymphoblastic lymphoma, 2 medulloblastoma, 1 diffuse astrocytoma, 1 pilocytic astrocytoma, 1 pituitary adenoma and 1 metastatic tumor from

lung cancer. All the patients received cranial radiation (range: 12–60 Gy). The median latency time between primary disease and RIG was 16 years (range: 9–30 years), which was not correlated with age at the time of primary disease (r^2= 0.014, p=0.74). Radiation-induced gliomas included 8 glioblastoma and 2 grade III glioma based on histological diagnosis. After surgical removal or biopsy of the RIG, 4 patients underwent chemotherapy alone (nimustine, temozolomide (TMZ), carboplatin and etoposide), and 6 received chemotherapy (nimustine, TMZ, bevacizumab) combined with radiotherapy (range: 40-66Gy). The median progression free survival and survival time from RIG were 10.1 and 27.5 months, respectively. In summary, RIG may occur many years after successful initial treatment using radiotherapy, and the outcome of our patients with RIG supports the use of radiotherapy and/or chemotherapy after surgical resection.

HGG-40. EXCEPTIONAL SYNCHRONOUS OCCURENCE OF A BRAF V600E MUTANT GLIOBLASTOMA AND A H3.3K27M MUTANT DIFFUSE INTRINSIC PONTINE GLIOMA: A CASE REPORT

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We report herein the case of a 17-year-old female who presented with intracranial hypertension and diplopia. Magnetic resonance imaging showed a large left cystic and solid temporoparietal lesion, associated with an infiltrating lesion of the brainstem, hypointense in T1 and hyperintense in FLAIR sequences, without enhancement after injection of gadolinium. Complete resection of the parietal mass and biopsy of the brainstem lesion were performed. Histopathological analysis of the parietal mass showed glioblastoma (WHO grade IV) with no IDH1/2 or H3.3/H3.1 gene mutation detected by Sanger sequencing. Immunohistochemistry found the expression of the proteins of mismatch repair system. Whole exome and RNA sequencing identified a BRAF-V600E mutation. The brainstem lesion was a diffuse midline glioma, H3K27M-mutant (grade IV) according to the 2016 WHO classification. Pan-genomic SNP arrays of the 2 tumors showed distinct genetic alterations. The parietal glioblastoma displayed complex genomic alterations whereas the brainstem glioma harbored chromosome 7q gain, chromosome 9p and 10 losses, and RB, TP53 and CDKN2A homozygous deletions. The patient was treated by concomitant radiochemotherapy (according to Stupp protocol). After 12 cycles of temozolomide, there was complete remission persistant in the parietal lobe. The brainstem tumor was stable but progressed after 3 months of temozolomide discontinuation. Treatment with mTOR inhibitors was initiated. At 21-month follow-up, the patient remains with few symptoms. No predisposition syndrome was identified in the patient or her family. Concurrent glioblastomas with distinct driver gene mutations are exceptional.

HGG-41. STRUCTURAL VARIANT DRIVERS IN PEDIATRIC HIGH-GRADE GLIOMA

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BACKGROUND: Driver single nucleotide variants (SNV) and somatic copy number aberrations (SCNA) of pediatric high-grade glioma (pHGGs), including Diffuse Midline Gliomas (DMGs) are characterized. However, structural variants (SVs) in pHGGs and the mechanisms through which they contribute to glioma formation have not been systematically analyzed genome-wide. METHODS: Using SvABA for SVs as well as the latest pipelines for SCNAs and SNVs we analyzed whole-genome sequencing from 174 patients. This includes 60 previously unpublished samples, 43 of which are DMGs. Signature analysis allowed us to define pHGG groups with shared SV characteristics. Significantly recurring SV breakpoints and juxtapositions were identified with algorithms we recently developed and the findings were correlated with RNAseq and H3K27ac ChIPseq. RESULTS: The SV characteristics in pHGG showed three groups defined by either complex, intermediate or simple signature activities. These associated with distinct combinations of known driver oncogenes. Our statistical analysis revealed recurring SVs in the topologically associating domains of MYCN, MYC, EGFR, PDGFRA & MET. These correlated with increased mRNA expression and amplification of H3K27ac peaks. Complex recurring amplifications showed characteristics of extrachromosomal amplicons and were enriched in coding SVs splitting protein regulatory from effector domains. Integrative analysis of all SCNAs, SNVs & SVs revealed patterns of characteristic combinations between potential drivers and signatures. This included two distinct groups of H3K27M DMGs with either complex or simple signatures and different combinations of associated variants. CONCLUSION: Recurrent SVs associate with signatures shaped by an underlying process, which can lead to distinct mechanisms to activate the same oncogene.

HGG-42. CLINICAL FEATURES AND TREATMENT OUTCOME OF MALIGNANT GLIOMAS IN CHILDREN AND ADOLESCENTS

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INTRODUCTION: Malignant gliomas in children and adolescents are rare. They are difficult to treat and are associated with an extremely poor prognosis. SUBJECTS AND METHODS: The treatment and outcomes of WHO grade IV -gliomas and diffuse intrinsic pontine gliomas (DIPG) in children and adolescents (Age 4–39, median 28) treated at our institute since 2001 were retrospectively reviewed. Thirty-five cases were included in this study. Nine cases were located in their brain stem and 2 of them were diagnosed as DIPG clinically without biopsy. Three (brain stem -2, thalamus-1) cases were diffuse midline glioma H3 K27 M mutant. Remaining 30 cases were diagnosed histologically as glioblastoma. Expect for 2 cases, all were irradiated. Twenty-four cases were treated with temozolomide (TMZ). Bevacizumab (BEV) was administrated as an initial therapy in 10 cases (concomitant with TMZ in 9 cases) and was administrated at the time of relapse in 9 cases. In summary, 19 cases were treated with BEV. RESULTS: Median survival time (MST) of all cases was 16.8 (4.4 -152.3) months. In total, BEV did not prolonged overall survival (OS), MST 16.02 vs 14.44, (p=0.498). Among adolescents (age 15–39), patients treated with BEV had a trend of longer OS but did not reached statistical significance, MST 19.64 vs 10.76 (p=0.167). An extent of resection and KPS =>70 at discharge from hospital were beneficial factors associated with prolonged OS. CONCLUSION: As well as in elderly cases, multidisciplinary treatment including resection, radiation and chemotherapy including BEV improves outcomes.

HGG-43. CONGENITAL GLIOBLASTOMA MULTIFORME: A CASE REPORT OF A RARE PEDIATRIC BRAIN TUMOR, MOLECULAR ANALYSIS, AND REVIEW OF THE LITERATURE

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Congenital brain tumors are rare, accounting for less than 4% of all pediatric brain tumors. Congenital glioblastoma multiforme (GBM) is rarer still, accounting for 3–15% of congenital brain tumors. There is literature to suggest that these tumors differ from pediatric and adult GBM clinically and molecularly, and as such should be treated as their own distinct entity. Our case is a 4 week old male who initially presented to his pediatrician for enlarging head circumference and upward gaze palsy. An MRI was obtained revealing a right parietal mass. He underwent gross total resection the following day with pathology revealing glioblastoma, WHO grade IV. Further analysis revealed ATRX retained, p53 immunoreactivity in 15–20% of nuclei, IDH1 and IDH2 wildtype, MGMT promoter not methylated, H3K27M wildtype, no 1p and/or 19q deletion/codeletion. Interestingly, RNA analysis of his tumor detected the PPP1CB-ALK fusion transcript as well as amplification of the ALK gene. Co-occurrence of these mutations has been reported in a small number of pediatric glioblastoma patients and PPP1CB-ALK fusions are one of the most common receptor tyrosine kinase fusions in infantile gliomas. ALK rearrangements and amplifications suggest a potential therapeutic target with tyrosine kinase inhibitors in glioblastoma. This patient serves as an example of a rare congenital glioblastoma with unique molecular features that may suggest novel treatment opportunities. We present his clinical course along with a pertinent review of the literature.

HGG-44. DEFECTS OF MISMATCH REPAIR PROTEINS IN PEDIATRIC HIGH GRADE GLIOMAS

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