plunging, M0 diagnosed specimens containing >50% lytic cells and/or less than 10 nucleated cells showed a decreased 5y-PS (61%). Further investigation of cytological parameters revealed a poor outcome for cases harboring >3 tumor cell clusters and individual tumor cells (5y-PS 33%) vs. cases with >2 individual tumor cells but no clusters (5y-PS 61%). In bi-variable Cox regression, ≥ 2 vs. 0 or 1 tumor cells were associated with a Hazard Ratio (HR) of 0.52 (95% Confidence Interval [CI]: 0.12, 2.30; p=0.39), whereas >3 vs no tumor cell clusters were associated with a HR of 0.894 (95%-CI: 1.66, 48.22; p=0.01). CONCLUSIONS: CSF staging in medulloblastoma should comprise lumbar specimens with <50% lytic cells and a minimum of 10 nucleated cells. The predictive value of CSF cytology in M1 cases may predominantly depend on tumor cell clusters. The latter finding needs to be confirmed in prospective trials.

PATH-08. THE IMPORTANCE OF RE-DIAGNOSIS OF TUMORS PREVIOUSLY CLASSIFIED AS CENTRAL NERVOUS SYSTEM PRIMITIVE NEUROECTODERMAL TUMORS

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BACKGROUND: The recent molecular analyses have revealed that central nervous system primitive neuroectodermal tumors (CNS PNETs) those having clusters of small round tumor cells are genetically different tumors. However, the concepts of CNS PNET are complicated, and it is difficult to diagnose them appropriately in clinical field. To overcome this difficulty, we reviewed previous studies associated with CNS PNETs, and carried out several approaches, those are relatively easy access to use in clinics, for our 8 samples of small round cell tumors diagnosed initially. METHODS: We used in combination with immunohistochemistry (IHC), Sanger sequence, Pyrosequence, polymerase chain reaction (PCR), real time PCR and copy number analysis referring recent reports. RESULTS: In 91.3%, the diagnosis obtained a different result with discordance were identified. The most frequent disagreement was between neuropathologists in the designation of LCA. In LCA, pathologists used either Hematoxylin and Eosin or immunohistochemical staining, but there were not always correlated. The pathologists preferred using immunohistochemical staining using antibodies against EMA, CD99, and the proliferation marker Ki-67. CONCLUSIONS: The re-diagnosis of these cases can improve the prognosis of the patients with CNS PNET. The LCA needs to be reclassified in the WHO 2016 classification and used immunohistochemistry in routine practice.

PATH-09. SJMB12 CLINICAL TRIAL: DISCREPANCY BETWEEN LOCAL AND CENTRAL PATHOLOGY IN ASSESSING ANAPLASTIC MEDULLOBLASTOMA – REPORT FROM A SINGLE SITE EXPERIENCE

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INTRODUCTION: SJMB12 is a phase 2 clinical trial led by the Sr. Jude Children’s Research Hospital (Sr. Jude) that enrols patients with medulloblastoma. 32% of patients tested on their biological subgroup. The largest group anaplastic (LCA) histologic variant was identified in an important independent risk factor associated with poor outcome. However, the histologic criteria for LCA is subjective, making the distinction between anaplastic and non-anaplastic medulloblastoma difficult in some cases. METHODS: Pathological central review was performed at Sr. Jude. For all patients enrolled in the study to date, concordance was assessed between the initial and central review diagnosis and histologic variant calls made at the Royal Children’s Hospital Melbourne (RCH) and at Sr. Jude, respectively. RESULTS: Since the SJMB12 clinical trial opened locally in 2014, 34 patients were enrolled, and 31 were eligible for this retrospective study. A total of 12 (39%) cases with discordance were identified. The most frequent disagreement was between the designation of LCA (10 cases, 32%). In five cases the tumor was not designated as LCA variant locally. In five cases the initial designation of LCA was refuted centrally. Overall, this led to a change of treatment stratum for four patients (13%). CONCLUSION: A high discordance rate exists between neuropathologists in the designation of LCA variant. Differences in the interpretation of the subjective histologic criteria and inconsistencies in the material submitted for central review contributed to the discordance. Incorporation of more objective histologic criteria and implementation of unbiased diagnostic tools may improve the generalisability of future risk stratification.

PATH-10. PROGNOSTIC RELEVANT IMMUNOPHENOTYPES OF PEDIATRIC HIGH-GRADE NON-BRAINSTEM GLIOMAS

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Pediatric diffuse astrocytomas comprise a wide range of malignancies with variable prognosis. The 4th grading system used now not always clearly characterizes the biological behavior of these tumors. We collected 24 pediatric supratentorial non-brainstem high grade glioma cases. Patient age ranged from 1 to 18 years old (median 11y). Main tumor locations were as follows: parietal lobe 8 cases; temporal lobe 3 cases; occipital lobe 3 cases. Eight of them were totally removed. All patients were treated with standard CT and RT. The main objective was to assess the prognostic impact of histopathological and molecular criteria on progression-free (PFS) and overall survival (OS) of high grade glioma. The following criteria were analyzed: IDH1 R132H, BRAF V600E expression, ALT-phenotype, CDKN2A deletion, and PFS and neuronal markers expression. RESULTS: IDH1 R132H mutation was identified in 3 cases. 4 cases carried BRAF V600E mutation with CDKN2A deletion and expressed PAX5 phenotype. 3 showed undifferentiated glioma morphology and ALT-phenotype. Also there was a group of tumors without any of the above mentioned genetic changes. Interestingly 3 of them were post radiation tumors. Statistical analysis showed that low OS correlated with ALT-phenotype and neuronal markers expression (p<0.015), differences in the presence of molecular changes (p<0.03). Mutation of IDH1R132H was a favorable prognostic factor as in the adult population. PFS was affected only by the presence of neuronal expression (p<0.015). Employing immunohistochemical analyses with surrogate molecular markers in complex with FISH can provide additional prognostic information in case of pediatric high grade gliomas.

PATH-11. PROSPECTIVE (EPI-)GENETIC CLASSIFICATION OF > 1,000 PEDIATRIC CNS TUMORS—THE MNP 2.0 STUDY

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The large variety of CNS tumor entities affecting children and adolescents, some of which are exceedingly rare, results in very diverging patient outcomes and renders accurate diagnosis challenging. To assess the diagnostic and prognostic utility of routine DNA methylation analysis, we conducted a large-scale retrospective and prospective multi-center study of >1,000 pediatric CNS tumors. (Epi-)genetic classification and gene panel sequencing, the Molecular Neuropathology 2.0 study prospectively integrated these (epi-)genetic analyses with reference neuropathological diagnostics as an international trial for newly-diagnosed pediatric patients. In a four-year period, 1,215 patients with sufficient tumor tissue were enrolled from 65 centers, receiving a reference neuropathological diagnosis according to the WHO classification in >97%. Using 10 FFPE sections as input, DNA methylation analysis was successfully performed in 95% of cases, of which 78% with sufficient tumor cell content were assigned to a distinct epigenetic tumor class. The remaining 22% did not match any of 82 represented classes, indicating novel rare tumor entities. Targeted gene panel sequencing of >130 genes performed for 96% of patients with matched blood samples detected diagnostically, prognostically, or therapeutically relevant somatic alterations in 48%. Germline DNA sequencing data indicated potential predisposition syndromes in >10% of patients. Discrepant results by neuropathological and epigenetic classification (29%) were enriched in high-grade gliomas and implicated clinical relevance in 5% of all cases. Clinical follow-up suggests improved survival for some patients with high-grade glioma histology and lower-grade molecular profiles. Routine (epi-)genetic profiling at the time of primary diagnosis adds a valuable layer of information to neuropathological diagnostics and will improve clinical management of CNS tumors.

PATH-13. PLEOMORPHIC XANTHOASTROCYTOMA INTEGRATED GENOMIC CHARACTERIZATION - WHAT HAVE WE LEARNED?

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Recent genetic studies have identified complex genomic signatures of pleomorphic xanthoastrocytoma (PXA) and recognized it as a distinct clinicopathologic entity. Genetic alterations include mutations in CBL, EGFR, KRAS, PIK3CA, and alterations in 1q21-q23, 2q24, 9p24, 10q11, and 13q31-q32. However, the relevance of these genetic changes for clinical outcomes, survival, and patient management remains largely unknown, and a further genomic characterization of this tumor entity is warranted. Here, we present the largest multi-center case series to date of PXA and integrate the molecular profiles into a detailed biological classification. Using comprehensive genomic analyses including whole-exome sequencing and clinical follow-up, we address the clinical relevance of identified genetic alterations.

Abstracts
PATH-14. GENETIC SUSCEPTIBILITY AND OUTCOMES OF PRIMARY INTRACRANIAL ASTROCYTOMA WITH THE ADULT ID-MUTANT SUBTYPE
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INTRODUCTION: Previously thought to be rare, recent case series have shown that IDH mutations in young patients are more common than previously described. In this study, we analyzed IDH-mutant tumors to determine clinical significance of these mutations in children, adolescents and young adults. METHODS: Through this multi-institution study (10 institutions), we collected 64 IDH1/2-mutant infiltrating astrocytoma specimens from 58 patients aged 4–26.6 (M=4, 0;6). Specimens included 46 low-grade (LGG) and 18 high-grade (HGG) astrocytomas. Tumor sequencing data (n=45), germline sequencing data (n=37) and outcome data (n=40) were analyzed. RESULTS: Similar to adults, most sequenced tumors had a co-mutation in the TP53 gene, while ATRX mutations were less common. Loss of heterozygosity (LOH) was primarily seen in HGGs. Approximately 20% (n=21) of patients with germline data available had a mutation in a cancer predisposition gene. Mismatch repair (MMR) mutations were most common (n=12; MSH6 n=9), followed by TP53 mutations (n=7). All patients with MMR gene mutations had HGGs and poor progression-free survival (PFS: 10.1 months and 2 years, mean PFS:9 months) and overall (OS <30% at 2 years) survival. Despite an OS of 90% at 5 years, many LGG patients had tumor progression/recurrence requiring additional treatment (PFS: 80% at 2 yrs, 40% at 5 yrs, 8% at 10 yrs). Four LGG tumors (12%) with TP53 loss (TP53-1q11 deletion) underwent malignant transformation. CONCLUSION: IDH-mutant tumors in pediatric patients are strongly associated with cancer predisposition and increased risk for progression/recurrence or malignant transformation. Routine screening for IDH1/2 mutations in children will greatly impact patient management.

PATH-15. PROTEOMIC SIGNATURES PREDICT GRADE IN PEDIATRIC AND YOUNG ADULT INFILTRATIVE ASTROCYTOMAS
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BACKGROUND: Infiltrative astrocytomas in children and young adults pose a treatment challenge due to the difficulty of achieving gross total resection and tumor resistance to irradiation and chemotherapy. Histopathologic grade is an essential part of determining prognosis and treatment, but is subjective and provides limited understanding of the molecular mechanisms underlying tumor development and progression. METHODS: We performed liquid chromatography/mass spectrometry (LC/MS-MS) on 28 FFPE samples of primary infiltrative astrocytomas (10 grade II, 8 grade III and 10 grade IV – WHO classification) from Nationwide Children’s Hospital (NCH). Initial unsupervised clustering was performed. Lasso regression yielded a protein signature separating low- and high-grade astrocytomas. RESULTS: A similar cohort of pediatric and young adult infiltrative astrocytomas from the Proteome Data Commons (PDC) (n=28) of the National Cancer Institute. RESULTS: Unsupervised clustering of NCH samples essentially recapitulated grade with a lasso regression yield a 10-protein signature that distinguished grade II from grade III/IV tumors. This 10-protein signature when applied to the PDC validation dataset, accurately predicted grade for 89.3% of the tumors (p=0.0014). CONCLUSIONS: We identified a quantitative protein signature that can reliably distinguish between low- and high-grade infiltrative astrocytomas from FFPE tissue. Further validation will enable the development of an objective prognostic protein expression test that complements and may outperform current histopathological strategies. Additionally, proteomic profiling of tumors will clarify the molecular mechanisms contributing to treatment resistance. A high-grade infiltrative astrocytoma that is low-grade at initial presentation represents a treatment challenge.

PATH-16. CORRELATION OF PATHOLOGICAL AND RADIOGRAPHIC DIAGNOSES FOR CHILDREN WITH BRAIN TUMORS AT TWO MAJOR HOSPITAL IN KENYA
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BACKGROUND: Central nervous system (CNS) tumors are the leading solid tumors in the childhood population but vastly underreported in the African population. There’s limited data on childhood brain tumors as well as the histopathological distribution in Kenya. Our study aimed at assessing the spectrum as well as the level of correlation with imaging in diagnosis of brain tumors between two major hospital settings. METHODS: This was a cross-sectional retrospective descriptive study conducted at the two major hospitals in Kenya: Kenyatta National Hospital (KNH) and Moi Teaching and Referral Hospital (MTRH). Children who underwent treatment for brain tumors between 2015 and 2017 and whose tissue biopsies were available at the laboratory archives were included. RESULTS: 87 cases were available for review, and the majority of the affected population were of ages 5–9 years. The most affected site was infratentorial compartment (48.3%) with gliomas and medulloblastomas being equally distributed. Majority of the gliomas were low grade (69%) with pilocytic astrocytoma being the most common subtype (42.9%). The overall sensitivity for the diagnosis of brain tumors through radiology was 69.4%. The level of correlation of histopathological to radiological diagnosis was statistically insignificant with P and kappa values of 0.814 and -0.024 respectively. CONCLUSION: Gliomas and medulloblastomas were the commonest tumors at both centers. Histopathological diagnoses have a high concordance of histopathologists. The level of agreement between histopathological and radiological diagnosis was high. Next steps include standardizing clinical, radiological and pathological details within Kenya.

PATH-17. INTRAGENIC COPY NUMBER BREAKPOINT ANALYSIS OF METHYLATION DATA FROM CNS TUMORS IDENTIFIES NOVEL SUBGROUP-SPECIFIC CANDIDATE FUSION GENE ENRICHMENTS
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Methylation array-based molecular profiling has refined the classification of brain tumors and now forms an important part of their integrated individualized management. The spatial nature of the input data poses significant challenges for data analysis, e.g., spatiotemporal variation, targeting multiple loci, and co-occurring events. In this study, a novel computational approach was developed to identify intragenic copy number breakpoints specific to histological subtypes. The approach was validated using an established panel of pediatric brain tumors. Further, a novel candidate fusion gene was identified within the ZNF666 gene. This work underscores the potential of these approaches to improve our understanding of the genome and improve treatment of childhood brain tumors.