idation cohort (n=71). RESULTS: Patients with desmoplastic medulloblastoma (DMB) or medulloblastoma with extensive nodularity (MBEN) (n=42) had 93% 5-year PFS, 100% 5-year OS and 93% 5-year CSI-free survival. Patients with CMB/LCA (n=45) had 37% 5y-PFS, 62% 5y-OS and 39% 5y-CSI-free survival. Local radiotherapy did not improve survival in CMB/LCA patients. All DMB/MBEN assessed by DNA methylation profiling belonged to the SHH_INF subgroup. Group 3 patients (5y-PFS 36% [n=14]) relapsed more frequently than SHH_INF (5y-PFS 93% [n=28]) or Group 4 patients (5y-PFS 83% [n=6], p<0.001). SHH_INF split into iSHH-I and iSHH-II subtypes in HIT-2000-BIS4 and the validation cohort, without prognostic impact (5y-PFS: iSHH-I 73% vs. iSHH-II 83%, p=0.25, n=99). Mean IQ was 90 (radiotherapy-free survivors) vs. 74 (patients that received CSI) [p=0.012]. CONCLUSION: Systemic chemotherapy and intraventricular methotrexate led to favorable survival in both iSHH-subtypes of SHH-activated DMB/MBEN with acceptable neurotoxicity. Survival in non-WNT/non-SHH CMB/LCA patients was not improved by local radiotherapy. Survival was more favorable in patients with Group 4 than in patients with Group 3 medulloblastoma.

MBCL-08. INTEGRATIVE MOLECULAR ANALYSIS OF PATIENT-MATCHED DIAGNOSTIC AND RELAPSED MEDULLOBLASTOMAS

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INTRODUCTION: The next generation of clinical trials for relapsed medulloblastoma demands a thorough understanding of the clinical behavior of relapsed tumors as well as the molecular relationship to their diagnostic counterparts. METHODS: A multi-institutional molecular cohort of patient-matched (n=126 patients) diagnostic MBs and relapses/subsequent malignancies was profiled by DNA methylation array. Entity, subgroup classification, and genome-wide copy-number aberrations were assigned while parallel next-generation (whole-exome or targeted panel) sequencing on the majority of the cohort facilitated inference of somatic driver mutations. RESULTS: Comprised of WNT (2%), SHH (41%), Group 3 (18%), Group 4 (39%), primary tumors retained subgroup affiliation at relapse with the notable exception of 10% of cases. The majority (8/13) of discrepant classifications were determined to be secondary glioblastomas. Additionally, rare (n=3) subgroup-switching events of Group 4 primary tumors to Group 3 relapses were identified coincident with MYC/MYCN pathway alterations. Amongst truly relapsing MBs, copy-number analyses suggest somatic clonal divergence between primary MBs and their respective relapses with Group 3 (55% of alterations shared) and Group 4 tumors (63% alterations shared) sharing a larger proportion of cytogenetic alterations compared to SHH tumors (42% alterations shared; Chi-square p-value < 0.001). Subgroup- and gene-specific patterns of conservation and divergence amongst putative driver genes were also observed. CONCLUSION: Integrated molecular analysis of relapsed MB discloses potential mechanisms underlying treatment failure and disease recurrence while motivating rational implementation of relapse-specific therapies. The degree of genetic divergence between primary and relapsed MBs varied by subgroup but suggested considerably higher conservation than prior estimates.

MBCL-09. ISOLATED M1 METASTASES IN PEDIATRIC MEDULLOBLASTOMA: IS POSTOPERATIVE RADIOTHERAPY FOLLOWED BY MAINTENANCE CHEMOTHERAPY SUPERIOR TO POSTOPERATIVE SANDWICH-CHEMOTHERAPY AND RADIOTHERAPY?

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BACKGROUND: Impact of isolated spread into the cerebrospinal fluid (CSF) is still not investigated comprehensively for childhood medulloblastoma and the best therapeutic strategy is currently unclear. MATERIAL AND METHODS: Sixty-six patients with isolated M1-MB registered to the HIT-MED-database from 2000–2018 were identified. CSF and MRI were centrally reviewed for all patients. Patients were stratified by age and either treated with upfront craniospinal irradiation (CSI) followed by maintenance chemotherapy (CT) or with postoperative CT and delayed CSI. RESULTS: Forty-nine patients were non-infants ≥4 years and seventeen were infants <4 years. Median age was 7.3y (1.1–18.0). 83.3% were histologically classified as CMB, 12.1% as LCA-MB and 4.6% as DMB. Molecular subgroup was Gr.3 in 25.8%, Gr.4 in 28.8%, SHH in 4.5%, WNT in 1.5% and not evaluated for 39.4%. Lumbar puncture was performed on median postoperative day 19 (range: 14–77). Median follow-up for survivors was 7.6y (range: 1.2–15.9). The whole cohort showed a 3y- and 5y-PFS of 68.0(±6.0) and 60.0(±6.5)%, while OS was 79.1(±5.2) and 72.9(± 5.9)%. 10y-OS was 54.4(±7.5). Patients with upfront CSI had more favourable outcomes (5y-PFS 66.1 vs. 55.8% [p=0.119]; 5y-OS 90.6 vs. 64.5% [p=0.035]). The trend towards improved survival in patients with postoperative CSI was retained when only non-infants were considered (p_{PFS}=0.176, p_{OS}=0.055). M1-persistence occurred exclusively in patients with postoperative CT. CONCLUSION: Isolated M1-MB is rare. Patients without contraindication for CSI appear to benefit from treatment by upfront CSI followed by maintenance CT, while cumulative CT-doses would be reduced compared to sandwich strategies.

MBCL-10. LOCAL RECURRENCE AND SURVIVAL OUTCOMES OF MEDULLOBLASTOMA (MB) IN ADOLESCENT AND YOUNG ADULT PATIENTS (AYA)

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OBJECTIVE: The aim of this study is to evaluate the local recurrence-free survival (LRFS) and overall survival (OS) of MB in AYA patients at our institute. METHOD: Patients 15–39 years old with MB who was sent for post-operative radiation therapy (RT) in 2007 - 2017 at our institute were included. Kaplan-Meier statistics were used to estimate the LRFS and OS. RESULTS: Seven patients were included. The median age at RT was 18.3 years (16.7–28.6 years). Male was more common than female, 5 males vs. 2 females. NTR or GTR was achieved in 71.4% (5 in 7 patients). Only one patient had metastatic disease (M1) and received combined chemotherapy-RT. The rest 6 patients were received RT alone, all were M0. The median craniospinal irradiation (CSI) dose and total RT dose were 36Gy (23.4-46Gy) and 54Gy (54-56Gy), respectively. Five patients had available follow-up MRI brain. Local recurrence (LR) was found in one patient at 4.3 years after finished RT. Her initial treatment was subtotal resection (STR) followed by RT alone; CSI 36 Gy and posterior fossa boost to 55.8Gy. The 2-years and 5-years LRFS were 100% and 66.7%, respectively. Both 2-years and 5-years OS were 100%. The median follow-up time was 7.6 years (0.4–11.5 years). CONCLUSION: Our study shows high 2-years LRFS and OS of post-operative RT alone in AYA MB. Combined chemotherapy-RT should be considered in STR or M1. More number of patients and molecular histopathology subtype reports are still needed to confirm this report.

MBCL-11. TIME TO RADIOTHERAPY IMPACTS SURVIVAL IN PEDIATRIC AND ADOLESCENT NON-METASTATIC MEDULLOBLASTOMA TREATED BY UPFRONT RADIOTHERAPY – A REPORT FROM THE HIT 2000 TRIAL

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PURPOSE: To evaluate prognostic factors and impact of participation in a randomized trial in non-metastatic medulloblastoma. METHODS AND PATIENTS: 382 patients with non-metastatic medulloblastoma aged 4–21 years with primary neurosurgical resections between 2001 and 2011 were enrolled into the HIT 2000 trial and centrally reviewed. Between 2001 and 2006, 176 of these patients participated in the randomized trial HIT-SIOP PNET 4. Three different radiotherapy protocols were applied. Molecular subgroup was available for 157 patients. RESULTS: Median follow-up was 6.35 [0.09–13.86] years. The 5-year progression-free (PFS) and overall survival (OS) rates were 80.3 % ± 2.1 % and 86.5 % ± 1.8 %, respectively. On univariate analysis, there was no difference in PFS and OS according to radiotherapy protocols or in patients who participated in the HIT-SIOP PNET 4 trial or not, while histology, molecular subgroup and postoperative residual tumor influenced PFS significantly. Time interval between surgery and irradiation (≤48 days vs. ≥49 days) failed the significance level (p=0.052). On multivariate analyses, molecular subgroup (WNT activated vs. Group3 HR 5.49; p=0.014) and time interval between surgery and irradiation (HR 2.2; p=0.018) were confirmed as independent risk factors. CONCLUSION: Using a centralized review system, multiprofessional and multiinstitutional collaboration as established for pediatric brain tumor patients in Germany, and risk-stratified therapy, outcome for non-metastatic medulloblastoma treated within HIT-SIOP PNET4 could be maintained outside the randomized trial. Prolonged time to radiotherapy negatively influenced survival.

MBCL-12. MOLECULAR SIGNATURES AND TUMOR INFILTRATING IMMUNOLOGICAL CELLS ASSOCIATED WITH ASIAN MEDULLOBLASTOMA PATIENT SURVIVAL

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BACKGROUND: Medulloblastoma is an aggressive pediatric brain tumor with surgery and post-resection radiotherapy plus chemotherapy as the major type of treatment currently. METHODS: A cohort of 52 medulloblastoma patients were treated in Taipei Medical University Hospital and Taipei Veterans General Hospital. Among them, 28 (53.85%) are male. The average age at presentation is 7.21 ± 4.15. Genome-wide RNA profiling were performed on fresh-frozen surgical samples. Tumor infiltrating immune cell percentages were inferred by the cibersort immune deconvolution algorithm. RESULTS: A total of 13 leading genes, including DLL1, ASIC2, SLC22A17, TRPM3, RPS2P5 and KCNC3, were found to be significantly associated with overall survival (All P < 0.001). A risk score was constructed, which is indicative of overall survival (Hazard Ratio [HR] = 2.720, 95% confidence interval [CI] = 1.798 ~ 4.112, P < 0.001) and recurrence-free survival (HR = 1.645, CI = 1.337 ~ 2.025, P < 0.001). After adjustment of clinical factors, the score remained significantly associated with overall survival (HR = 2.781, CI = 1.762 ~ 4.390, P < 0.001) and recurrence-free survival (HR = 1.604, CI = 1.292 ~ 1.992, P < 0.001). The percentage of Natural Killer and T follicular helper (Tfh) cells were higher in patients with better overall survival (P = 0.046 and 0.001, respectively). Furthermore, the Tfh percentage is also positively associated with mutation burdens in the expressed exonic regions (P < 0.001). CONCLUSION: Higher mutation burdens are correlated with higher levels of tumor infiltrating Tfh cells, which is indicative of better post-surgery prognosis.

MBCL-13. CORRELATION OF HISTOPATHOLOGY, CHROMOSOMAL MICROARRAY, AND NANOSTRING BASED 22-GENE ASSAY FOR MEDULLOBLASTOMA SUBGROUP ASSIGNMENT ON "HEAD START" 4 CLINICAL TRIAL

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"Head Start" 4 (HS 4) is a prospective randomized clinical trial that tailors treatment based on medulloblastoma molecular subgroups and response to induction chemotherapy to compare efficacy of one versus three (tandem) cycles of myeloablative chemotherapy. Advances in RNA and DNA profiling have identified four molecular subgroups of medulloblastoma with prognostic significance: Sonic Hedgehog (SHH) subtype, WNT subtype, Group 3, and Group 4. In HS 4 trial, we utilize a combination of histopathology and immunohistochemistry (pathology/IHC), as well as chromosomal microarray analysis (CMA) utilizing OncoScan™ (Thermo Fisher) to classify medulloblastoma samples into either SHH, WNT, or non-WNT/non-SHH (Group 3/4) subgroups at the time of diagnosis. NanoString based 22-gene assay is performed retrospectively to test concordance. We have pathology/IHC, CMA, and NanoString data on 26 infants and young children with medulloblastoma enrolled on HS 4. Pathology/IHC was able to assign samples to SHH, WNT, and non-WNT/non-SHH subgroups in all but two cases: one case was classified as Group 3, and the second as SHH by both CMA and NanoString. CMA was indeterminate in six cases, of which, pathology/IHC was able to assign all six samples aforementioned three subgroups. NanoString was indeterminate in two cases: one case was classified as SHH by CMA and pathology/IHC, and the second case was indeterminate by CMA but was assigned as non-WNT/non-SHH on pathology/IHC. There is excellent correlation between NanoString and combination of histopathology and CMA for core medulloblastoma subgrouping on HS 4. Methylation studies are ongoing.

MBCL-14. A STUDY OF LOW-DOSE CRANIOSPINAL RADIATION THERAPY IN PATIENTS WITH NEWLY DIAGNOSED AVERAGE-RISK MEDULLOBLASTOMA

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INTRODUCTION: Medulloblastoma is one of the most common malignant brain tumors in children. To date, the treatment of average-risk (non-metastatic, completely resected) medulloblastoma includes craniospinal radiation therapy and adjuvant chemotherapy. Modern treatment modalities and now risk stratification of subgroups have extended the survival of these patients, exposing the long-term morbidities associated with radiation therapy. METHODS: We performed a single-arm, multi-institution study, seeking to reduce the late effects of treatment in patients with average-risk medulloblastoma prior to advances in molecular subgrouping. To do so, we