

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

Rahul Kumar<sup>1</sup>, Maximilian Deng<sup>2</sup>, Kyle Smith<sup>1</sup>, Anthony Liu<sup>1</sup>, Girish Dhall<sup>3</sup>, Laura Kleese<sup>4</sup>, Daniel Bowers<sup>4</sup>, Murali Chintagumpala<sup>5</sup>, Sarah Leary<sup>6</sup>, Javad Nazarian<sup>7</sup>, Brent Orr<sup>1</sup>, Arzu Onar-Thomas<sup>1</sup>, Stefan Pfister<sup>2</sup>, Andrey Korshunov<sup>2</sup>, Giles Robinson<sup>1</sup>, Amar Gajjar<sup>1</sup>, David Jones<sup>2</sup>, Vijay Ramaswamy<sup>8</sup>, and Paul Northcott<sup>1</sup>; <sup>1</sup>St. Jude Children's Research Hospital, Memphis, TN, USA, <sup>2</sup>German Cancer Research Center (DKFZ), Heidelberg, Germany, <sup>3</sup>Children's Hospital of Los Angeles, Los Angeles, CA, USA, <sup>4</sup>University of Texas Southwestern Medical Center, Dallas, TX, USA, <sup>5</sup>Texas Children's Hospital, Houston, TX, USA, <sup>6</sup>Seattle Children's Hospital, Seattle, WA, USA, <sup>7</sup>Children's National Hospital, Washington, DC, USA, <sup>8</sup>Hospital for Sick Children, Toronto, ON, Canada

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?

Denise Obrecht<sup>1</sup>, Martin Mynarek<sup>1</sup>, Christian Hagel<sup>2</sup>, Robert Kwicien<sup>3</sup>, Michael Spohn<sup>2,4</sup>, Michael L. Bockmayr<sup>1,4</sup>, Brigitte Bison<sup>5</sup>, Monika Warmuth-Metz<sup>5</sup>, Stefan M. Pfister<sup>6,7</sup>, David T.W. Jones<sup>6,8</sup>, Dominik Sturm<sup>6,7</sup>, Andreas von Deimling<sup>9</sup>, Felix Sahm<sup>9,6</sup>, Katja von Hoff<sup>10</sup>, B.-Ole Juhnke<sup>1</sup>, Martin Benesch<sup>11</sup>, Nicolas U. Gerber<sup>12</sup>, André O. von Bueren<sup>13</sup>, Carsten Friedrich<sup>14</sup>, Rolf-Dieter Kortmann<sup>15</sup>, Rudolf Schwarz<sup>16</sup>, Torsten Pietsch<sup>17</sup>, and Stefan Rutkowski<sup>1</sup>; <sup>1</sup>Pediatric Hematology and Oncology, University Hospital Hamburg-Eppendorf, Hamburg, Germany, <sup>2</sup>Department of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, <sup>3</sup>Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany, <sup>4</sup>Research Institute Kinderkrebs-Zentrum Hamburg, Hamburg, Germany, <sup>5</sup>Institute of Diagnostic and Interventional Neuroradiology, University Hospital Würzburg, Würzburg, Germany, <sup>6</sup>Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, <sup>7</sup>Division of

Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany, <sup>8</sup>Pediatric Glioma Research Group, German Cancer Research Center (DKFZ), Heidelberg, Germany, <sup>9</sup>Clinical Cooperation Unit Neuropathology, German Consortium for Translational Cancer Research (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany, <sup>10</sup>Charité – University Medical Center Berlin, Berlin, Germany, <sup>11</sup>Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria, <sup>12</sup>Department of Oncology, University Children's Hospital, Zürich, Switzerland, <sup>13</sup>Department of Pediatrics, Obstetrics and Gynecology, Division of Pediatric Hematology and Oncology, University Hospital of Geneva, Geneva, Switzerland, <sup>14</sup>Division of Pediatric Oncology and Hematology, University Children's Hospital Rostock, Rostock, Germany, <sup>15</sup>Department for Radiation Therapy, University Medical Center Leipzig, Leipzig, Germany, <sup>16</sup>Department for Radiotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, <sup>17</sup>Institute of Neuropathology, Brain Tumor Reference Center of the German Society for Neuropathology and Neuroanatomy (DGNN), University of Bonn, DZNE German Center for Neurodegenerative Diseases, Bonn, Germany

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  $\geq 4$  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( $\pm 6.0$ ) and 60.0( $\pm 6.5$ )%, while OS was 79.1( $\pm 5.2$ ) and 72.9( $\pm 5.9$ )%. 10y-OS was 54.4( $\pm 7.5$ ). 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<sub>PFS</sub>=0.176, p<sub>OS</sub>=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)

Warissara Rongthong, Teeradon Treechairusame, Nan Suntonpong, and Kullathorn Thephamongkhon; Faculty of Medicine Siriraj Hospital, Bangkok, Thailand

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

Stefan Dietzsch<sup>1</sup>, Felix Placzek<sup>1</sup>, Klaus Pietschmann<sup>2,1</sup>, André O. von Bueren<sup>3</sup>, Christiane Matuschek<sup>4</sup>, Albrecht Glück<sup>5</sup>,