(EMT) is important for invasion and metastasis in many cancers. This study aimed to evaluate and compare treatment outcomes with the expression of EMT-related transcription factors in pediatric ependymomas. MATERIAL AND METHODS: Medical and radio-imaging data of 22 (11 boys, 11 girls) patients aged <15 years with intracranial ependymomas were reviewed from January 1983 to December 2018. Six cases were subdivided into clinicopathological-molecular subgroups and immunohistochemically analyzed for Slug and ZEB. RESULTS: The median age at the start of treatment was 5 years (range 8 months–15 years) (9 cases were aged <3 years). The median progression-free survival (PFS) was 25.6 (range, 0.8–383.5) months; the median overall survival (OS) was 81.9 (range, 2.9–383.5) months. Extent of resection and malignant histology were significant prognostic factors for OS and PFS in multivariate analysis. There were 6 cases (2 cases of PFA, 2 of PFB, 1 of ST and 1 case of ST-RELA). Nuclear expression of ZEB1 was found in all tumors; however, that of Slug increased only in PFA and PFB tumors, which were associated with a poor prognosis. CONCLUSION: Expression of EMT-related transcription factors was increased in pediatric ependymomas. These data suggest that EMT is a novel therapeutic target for treating pediatric intracranial ependymomas.

EPEN-03. LONG-TERM FOLLOW-UP OF AIEOP 2ND SERIES OF CHILDREN AND ADOLESCENT WITH PRIMARY INTRACRANIAL (ST:SUPRATENTORIAL; PF: POSTERIOR FOSSA) EPENDYMOMA AND METHYLATION GROUPS RE-ANALYSES

Maura Massimino[1], Francesca Romana Buttarelli[2], Hendrik Witt[3,4], Pascal Johann[3,4], Simone Minasi[2], Stefan M. Pfister[3,4], Kristian W. Pajtler[3,4], Manila Antonelli[5], Francesco Barretta[6], Piergiorgio Modena[7], Lorenza Gandola[8], Maria Luisa Garrè[9], Daniele Bertin[10], Angela Mastronuzzi[11], Maurizio Mascarin[12], Lucia Quaglietta[13], Elisabetta Viscardi[14], Iacopo Sardi[15], Antonio Ruggiero[16], Bianca Pollo[17], Annamaria Buccoliero[18], Luna Boschetti[1], Veronica Biassoni[1], Elisabetta Schiavello[1], Luisa Chiapparini[19], Alessandra Erbetta[19], and Felice Giangaspero[5,20]; [1]Fondazione IRCCS Istituto Nazionale dei Tumori, Pediatrics, Milano, Italy, [2]Università La Sapienza, Human Neurosciences, Roma, Italy, [3]Hopp-Children's Cancer Center Heidelberg KiTZ, Heidelberg, Germany, [4]German Cancer Research Center DKFZ, German Cancer Consortium DKTK, Heidelberg, Germany, [5]Università La Sapienza, Radiological-Oncological and Anatomo-Pathological Sciences, Roma, Italy, [6]Fondazione IRCCS Istituto Nazionale dei Tumori, Clinical Epidemiology and Trial Organization, Milano, Italy, [7]A,S,S,T, Lariana - Ospedale Sant' Anna di Como, Genetic Laborator, Como, Italy, [8]Fondazione IRCCS Istituto Nazionale dei Tumori, Pediatric Radiotherapy, Milano, Italy, [9]IRCCS Giannina Gaslini, Neuro-oncology, Genova, Italy, [10]A,O,U, Città della Salute e della Scienza, Pediatric Oncology, Torino, Italy, [11]IRCCS Ospedale Pediatrico Bambino Gesù, Pediatric Hematology and Oncology, Roma, Italy, [12]Centro di Riferimento Oncologico CRO, Radiotherapy, Aviano, Italy, [13]Ospedale Santobono-Pausilipon, Pediatric Oncology, Napoli, Italy, [14]Padova University, Pediatric Oncology, Padova, Italy, [15]Ospedale Pediatrico Meyer, Pediatric Oncology, Firenze, Italy, [16]Fondazione Policlinico Universitario Agostino Gemelli, Pediatric Oncology, Roma, Italy, [17]Fondazione IRCCS Istituto Neurologico Carlo Besta, Pathology, Milano, Italy, [18]Ospedale Pediatrico Meyer, Pathology, Firenze, Italy, [19]Fondazione IRCCS Istituto Neurologico Carlo Besta,nr, Milano, Italy, [20]IRCCS Neuromed, Pathology, Pozzilli, Italy

BACKGROUND: This 2002–2014 Italian prospective study stratified 160 patients by surgical resection (complete=NED/incomplete=ED) and centrally-reviewed grade. Grade2/NED patients received focal radiotherapy (RT) up to 59.4Gy, Grade3/NED received 4 courses of VEC(vincristine,etoposide,cyclophosphamide) after RT.ED patients received 1–4 VEC courses, second-look surgery, 59.4 Gy+8Gy boost on measurable residue. METHODS: We re-analyzed data at 115 months follow-up including methylation profile on available samples. RESULTS: Global PFS/OS at 5/10 years were 66/59% and 80/74%, respectively. Of the 64 relapsers at median 20 months, 53 died at median 37/18 months after diagnosis/relapse, respectively.10/64 relapsed after 5 years (66–126 months); 4 died, relapse was local in 8/10, metastatic 1, combined 1;5/10 patients were below age 3, 5 females, 8 PF tumors. Their survival post-relapse was not longer than earlier relapsers'. At univariable analysis, age over 3 years, female sex, complete surgery, grade 2, no shunt confirmed better PFS/OS. 66/95 analyzed tumors received a score >0.80 through the DNA methylation-based central nervous system tumor classifier: 41/8 as PFA/PFB, respectively,14/17 ST as RELA-positive (3 scored for other molecular entities i.e. anaplastic PXA, LGG MYB, HGNET). Prognostic factors were equally distributed among PFA/PFB groups,1 only group B patient relapsed locally at 96 months. CONCLUSIONS: Already published prognostic factors remained at long-term follow-up;6.2% patients had late relapses. OS after relapse was not better in late relapsers. Group B confirmed better prognosis but all patients had received «at least» adjuvant RT. Modern ependymoma trials need long follow-up to draw firm conclusions.

EPEN-04. ONCOGENIC 3D TUMOR GENOME ORGANIZATION IDENTIFIES NEW THERAPEUTIC TARGETS IN EPENDYMOMA

Konstantin Okonechnikov[1,2], Jens-Martin Hübner[1,2], Owen Chapman[3], Abhijit Chakraborty[4], Meghana Pagadala[3], Rosalind Bump[5], Sahaana Chandran[5], Katerina Kraft[6], Rocio Acuna Hidalgo[7], Stefan Mundlos[7], Robert Wechsler-Reya[8], Edwin F. Juarez[3], Nicole Coufal[9], Michael Levy[10], John Crawford[9,11], Kristian Pajtler[1,2], Derek Reid[12], Anthony Schmitt[12], Hannah Carter[3], Ferhat Ay[4], Jesse Dixon[5], Jill Mesirov[3], Stefan M Pfister[1,2], Marcel Kool[1,2], and Lukas Chavez[3]; [1]Hopp Children's Cancer Center at the NCT Heidelberg (KiTZ), Heidelberg, Germany, [2]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [3]Department of Medicine, University of California San Diego (UCSD), San Diego, CA, USA, [4]Division of Vaccine Discovery, La Jolla Institute for Allergy and Immunology, San Diego, CA, USA, [5]Salk Institute for Biological Studies, San Diego, CA, USA, [6]Center for Personal Dynamic Regulomes, Stanford University, Stanford, CA, USA, [7]Max Planck Institute for Molecular Genetics, Berlin, Germany, [8]Tumor Initiation and Maintenance Program, NCI-Designated Cancer Center, Sanford Burnham Prebys Medical Research Discovery Institute, San Diego, USA, [9]Department of Pediatrics, University of California, San Diego, San Diego, CA, USA, [10]Department of Neurosurgery, University of California San Diego – Rady Children's Hospital, San Diego, CA, USA, [11]Department of Neurosciences, University of California San Diego – Rady Children's Hospital, San Diego, CA, USA, [12]Arima Genomics, Inc, San Diego, CA, USA

By profiling enhancers in primary ependymoma tumors, we have recently identified putative oncogenes, molecular targets, and functional pathways. Inhibition of selected targets diminished the proliferation of patient-derived neurospheres and increased survival in mouse models of ependymoma. While enhancers frequently regulate the nearest gene, identification of enhancer target genes remains to be a challenge in the absence of chromosome conformation information. Consequently, we have now used HiC to map the 3-dimensional organization of tumor chromatin in the two most common and aggressive ependymoma subgroups: posterior fossa group A (PF-EPN-A) and supratentorial ependymomas with gene fusions involving the NF-κB subunit gene RELA (ST-EPN-RELA). By an integrative analysis of enhancer and gene expression in the context of the newly derived HiC data, we find that a large number of the predicted enhancer target genes are enriched for strong physical interactions. Importantly, we also identify many new putative tumor-dependency genes activated by long-range promoter-enhancer interactions and complex tumor-specific chromatin clusters of regulatory elements. Complementary to the analysis of gene-enhancer interactions, we have also leveraged the HiC data for resolving structural rearrangements underlying copy number alterations. Copy number gains of the 1q arm of chromosome 1 are especially associated with poor survival. Our preliminary results in PFA relapse samples show complex structural variants underlying 1q gain that lead to inter-chromosomal rearrangements and affect several genes that potentially contribute to poor survival. In ongoing work we are testing the relevance of the novel candidate genes for tumor cell growth and proliferation in-patient derived ependymoma models.

EPEN-05. CLINICAL AND GENETIC EVOLUTION OF EPENDYMOMA EXPOSED FROM A MULTI-RECURRENCE GIRL CASE

Zhong-ping Chen[1], Jing Wang[1], Shao-yan Xi[1], Qi Zhao[1], Yun-fei Xia[1], Cheng-cheng Guo[1], Qun-ying Yang[1], Zhao-jie Li[2], Zhi Li[2], Fu Han[3], Fang Wang[4], Ke Sai[1], Hai-ping Cai[1], Xiang-heng Zhang[1], Chao Ke[1], and Jian Wang[1]; [1]Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China, [2]Guangdong Provincial Hospital, Guangzhou, Guangdong, China, [3]Chinese Traditional Medicine Hospital of Guangdong Province, Guangzhou, Guangdong, China, [4]Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Ependymomas are glial brain tumors accounting for approximately 2~3% of all primary tumors of the central nervous system (CNS), and 12% of all pediatric intracranial tumors. To better understand the evolution process of ependymomas, we studied the clinical, pathological and genetic development of a rare girl case with repeatedly recurrent ependymoma. This girl was diagnosed as ependymoma at age of 9 years old, and experienced 7 times tumor relapse and received 9 times surgeries but finally ceased at 19 years old with multiregional recurrences. The pathological characteristics, radiographic images and therapeutic strategies of the patient were all retrieved. Molecular markers confirmed the diagnosis of anaplastic ependymoma based on the updated WHO guideline for CNS tumors. Whole-genome sequencing (WGS) was performed to elucidate the landscape of mutation signatures and to identify potential driver mutations along the tumor progression. The seven tumor specimens showed a highly branched evolutionary pattern. There were six gene mutations found in 5 of the 7 specimens (PCDHA4, PCDHA8, SEC14L6, SETD2, RIOK2, and SLCO2A1) and three

in 6 of 7 the samples (RYR1, SNX25, DSC2). Strikingly, there was one gene, ADGRL3, which was found to be consistently mutated in the entire disease progression process. Our findings therefore suggest that ADGRL3 might play roles in the disease progression of ependymoma patient.

EPEN-06. CHEMOTHERAPY OF RECURRENT EPENDYMOMA: LONG-TERM RESPONSE ONLY IN FEW CASES

Jonas Adolph[1], Stephan Tippelt[1], Ruth Mikasch[1], Stefan Pfister[2,3], Kristian Pajtler[4,3], Hendrik Witt[4,3], Olaf Witt[4,3], Brigitte Bison[5], Monika Warmuth-Metz[5], Rolf-Dieter Kortmann[6], Stefan Dietzsch[6], Torsten Pietsch[7], Beate Timmermann[8], and Gudrun Fleischhack[1]; [1]University Hospital of Essen, Pediatrics III, Pediatric Hematology and Oncology, Essen, Germany, [2]University Hospital Heidelberg & German Cancer Research Center (DKFZ), Heidelberg, Germany, [3]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, [4]University Hospital Heidelberg & German Cancer Research Center (DKFZ), Heidelberg, Germany, [5]University Hospital of Wuerzburg, Institute for Diagnostik and Interventional Neuroradiology, Wuerzburg, Germany, [6]University of Leipzig, Radiooncology, Leipzig, Germany, [7]University Hospital of Bonn, Institute of Neuropathology, Bonn, Germany, [8]Department of Particle Therapy, University Hospital Essen, West German Proton Therapy Centre Essen (WPE), West German Cancer Center (WTZ), German Cancer Consortium (DKTK), Essen, Germany

INTRODUCTION: The efficacy of chemotherapy in recurrent ependymoma is unclear. We present results from the German HIT-REZ-studies. METHODS: 137 patients were analyzed regarding the treatment with chemotherapy at first recurrence, the time from first relapse to progression (PFS) and to either time-point of death or last follow-up (OS). Tumor response evaluation was based on MRI and clinically; molecular data was available in 80. RESULTS: In our cohort, 96 patients (20 supratentorial, 73 infratentorial, 3 spinal) received chemotherapy during first recurrence: 49 (51.0%) temozolomide (TMZ) monotherapy, 12 (12.5%) HIT-SKK regime, 9 (9.4%) carboplatin/etoposide (CE) and 26 (27.1%) other combinations. In 19.8% (26.5% in TMZ), chemotherapy was administered prior to surgery (neoadjuvant), which resulted in tumor progression in 78% (85% in TMZ). Gross-total resection was achieved in 86% without neoadjuvant chemotherapy and in 74% (69% in TMZ) with neoadjuvant treatment. Switching to trofosfamide/etoposide (TE) after surgery and unresponsiveness to TMZ showed further progression in all cases of tumor-residuum after surgery. Regarding 1-year-PFS, treatment with HIT-SKK (50.0%±14.4%) or CE (55.6%±16.6%) was advantageous over TMZ (30.2%±6.7%). However, 5-y-OS was lower in CE (19.0% ±16.8%) than in TMZ (39.8%±7.7%) and HIT-SKK (42.9%±8.7%). Long-term control was seen in individual cases of TMZ, HIT-SKK and CE, with TMZ providing longest response of 72 months. CONCLUSION: Neoadjuvant TMZ has no significant advantage regarding PFS. However, in few cases chemotherapy prevented progression after incomplete resection. Difficulties in response evaluation and variability in therapies hinder conclusions. Supported by the German Children's Cancer Foundation

EPEN-07. PATTERNS OF EXTRANEURAL METASTASES IN PEDIATRIC SUPRATENTORIAL EPENDYMOMA: CASE SERIES AND REVIEW OF THE LITERATURE

Priya P. Chan[1], Nicholas S. Whipple[1], Arie Perry[2], David A. Solomon[2], Holly Zhou[3], Luke L. Linscott[4], John R. W. Kestle[5], and Carol Bruggers[1]; [1]Division of Pediatric Hematology-Oncology, Department of Pediatrics, University of Utah, Salt Lake City, UT, USA, [2]Department of Pathology, University of California, San Francisco, San Francisco, CA, USA, [3]Department of Pathology, University of Utah, Salt Lake City, UT, USA, [4]Department of Radiology, Primary Children's Hospital, Salt Lake City, UT, USA, [5]Department of Neurosurgery, University of Utah, Salt Lake City, CA, USA

BACKGROUND: Ependymomas account for 10% of all malignant pediatric intracranial tumors. Standard therapy includes maximal safe surgical resection followed by involved-field radiation. Up to 50% of localized pediatric ependymomas recur. Extraneural metastases at time of recurrence are rarely reported. OBJECTIVE: To describe extraneural metastases of pediatric ependymomas. METHODS: Retrospective review of patients' medical records and literature review. RESULTS: Three patients with history of locally recurrent, supratentorial ependymoma developed extraneural metastases: one in a cervical lymph node, one with a scalp nodule, and one with a dural lesion. Each extraneural recurrence had similar histologic and molecular features as the initial diagnosis. The cervical lymph node recurrence was treated with multimodal therapy; she is without disease four years later. The isolated scalp nodule occurred at the exit site of a subgaleal drain placed during prior resection. Following nodule resection, he developed additional scalp and lymph node disease and is receiving palliative care. The isolated dural recurrence occurred at the exit site of a ventriculoperitoneal shunt placed following a previous resection. She died of progressive disease 18 months after dural lesion resection. Reports of lymph node, scalp, and dural metastases of ependymomas are exceedingly rare, and outcomes are poor. CONCLUSIONS: Extraneural manifestations of ependymoma are rare. Regional seeding from prior surgical procedures may play a role in metastatic spread. Extraneural metastases should be considered in children previously treated for ependymoma who develop local findings even in the absence of CNS relapse. Salvage therapy with curative intent should be considered using a multimodal approach.

EPEN-09. IMPACT OF MOLECULAR SUBGROUP ON OUTCOME FOR INFANTS <12 MONTHS WITH INTRACRANIAL EPENDYMOMA - GERMAN EXPERIENCE FROM HIT2000, INTERIM-2000-REGISTRY AND I-HIT-MED REGISTRY

Denise Obrecht[1], Martin Mynarek[1], Katja von Hoff[2], Hendrik Witt[3], Kristian W. Pajtler[4,5], B.-Ole Juhnke[1], Monika Warmuth-Metz[6], Brigitte Bison[6], Rolf-Dieter Kortmann[7], Beate Timmermann[8], Stefan M. Pfister[4,5], Felix Sahm[3,9], Dominik Sturm[9,10], Andreas von Deimling[3], Ulrich Schüller[11,12], Torsten Pietsch[13], Martin Benesch[14], Nicolas U. Gerber[15], and Stefan Rutkowski[1]; [1]Pediatric Hematology and Oncology, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [2]Charite – University Medical Center Berlin, Berlin, Germany, [3]Clinical Cooperation Unit Neuropathology, German Consortium for Translational Cancer Research (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany, [4]Hopp Children's Cancer Center Heidelberg (KiTZ) and Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), Heidelberg, Germany, [5]Department of Pediatric Oncology, Hematology and Immunology, Heidelberg University Hospital, Heidelberg, Germany, [6]Institute of Diagnostic and Interventional Neuroradiology, University Hospital Würzburg, Würzburg, Germany, [7]Department for Radiation Therapy, University Medical Center Leipzig, Leipzig, Germany, [8]Department of Particle Therapy, University Hospital Essen, West German Proton Therapy Centre Essen (WPE), West German Cancer Center (WTZ), Germany, German Cancer Consortium (DKTK), Essen, Germany, [9]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, [10]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Consortium for Translational Cancer Research (DKTK), Heidelberg, Germany, [11]Department of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [12]Research Institute Kinderkrebs-Zentrum Hamburg, Hamburg, Germany, [13]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, [14]Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria, [15]Department of Oncology, University Children's Hospital, Zürich, Switzerland

BACKGROUND: For infant ependymoma (EP), decision for radiotherapy during first-line therapy is a dilemma. We analyzed therapy outcomes of EP patients younger than 12 months at diagnosis according to molecular subgroup. PATIENTS AND METHODS: Between 2001 and 2017, 30 patients with histological diagnosis of intracranial EP <12 months at diagnosis with DNA-methylation profiling available were registered in HIT-MED-studies/-registries. RESULTS: In 3/30, DNA methylation-based CNS tumor classification suggested a diagnosis other than EP or could not be assigned to a reference class. Of the remaining 27 tumors, 16 were classified as PF-A, 8 as *RELA*-fusion positive and 3 as *YAP*-fusion positive. Median age at diagnosis was 0.73 (0.30–0.99) years. After a median follow-up time of 5.36 (0.20–12.90) years, 59.3% experienced progressive disease (PD). 5y-PFS and -OS for the whole cohort were 38.2% and 73.1%. *RELA*- and *YAP*-fusion positive EP had significantly better OS than PF-A (5y-OS for PF-A: 55.9%; *RELA* 100%; *YAP* 100%; p=0.023). PFS was not significantly different. All but one patient with relapsed PF-A died despite multimodal salvage strategies. In contrast, patients with relapsing *RELA*- and *YAP*-fusion positive EP (n=5), survived with a combination of re-surgery and first or second local radiotherapy. CONCLUSION: In this cohort of infants <12 months, patients with PF-A had a significantly inferior OS compared to patients with *RELA*- and *YAP*-fusion positive EP. Salvage therapy was ineffective for patients with PF-A, whereas patients with can *RELA*- and *YAP*-fusion positive EP can be long-term survivors after PD. Therefore, subgroups-specific therapy should be discussed.

EPEN-10. SPINAL MYXOPAPILLARY EPENDYMOMA AND METHYLATION-PROFILING: THE MD ANDERSON CANCER CENTER (MDACC) EXPERIENCE

Sumit Gupta, Xiangjun Tian, Jing Wang, Jason Huse, Laurence Rhines, Wafik Zaky, Claudio Tatsui, and Soumen Khatua; MD Anderson Cancer Center, Houston, TX, USA

INTRODUCTION: Spinal myxopapillary ependymoma (MPE) is a rare histological variant of ependymoma, classified as WHO grade I tumor. Further interrogation of the molecular and clinical profile is warranted,