Low grade gliomas

LG-001. OPTIC PATHWAY GLIOMAS; FROM CHILDHOOD TO ADULTHOOD
Ben Shofty1, Felix Bokstein2, Zvi Ram3, Liat Ben-Sira2, Sigal Freedman3, Anat Koler2, and Shlomi Constantini1; 1Pediatric Neurosurgery, Tel-Aviv Medical Center, Tel-Aviv, Israel; 2The Gilbert Israeli Neurofibromatosis Center, Tel-Aviv Medical Center, Tel-Aviv, Israel; 3Devision of Neurosurgery, Tel-Aviv Medical Center, Tel-Aviv, Israel

BACKGROUND: Optic pathway gliomas (OPG) are considered relatively benign pediatric tumors. Adult OPG can be divided into two groups; adult patients with tumors diagnosed in childhood, and adult patients diagnosed during adulthood. In this study we have characterized the clinical course of patients belonging to these two groups. METHODS: We retrospectively collected clinical and imaging data for all adult OPG patients who have been monitored in our medical-center between 1990 and 2012. RESULTS: Twenty-two adult patients were included. Age distribution at diagnosis varied widely (6m–66y), as did age at last follow-up (18y–74y). Ten patients were diagnosed at adulthood, 12 in childhood. Of the patients that were diagnosed at adulthood, 6 had radiological progression during adulthood, and 3 of those suffered visual impairment. From this group of 6 patients, 1 had further radiological progression during adulthood accompanied by additional visual decline, 2 patients had additional visual decline during adulthood despite no signs of radiological progression. Of the 6 patients whose tumors were stable during childhood, all 6 remained stable during adulthood. Out of 10 patients diagnosed at adulthood, 6 patients suffered visual deterioration; in 5 of them a concomitant radiological progression was noted. Two patients were diagnosed with high-grade gliomas; both died of their disease. CONCLUSION: OPGs may be active during childhood and adulthood. In this group of patients whose tumors were diagnosed at adulthood, 6 patients had progressive radiological and visual signs during adulthood. Of the 6 patients whose tumors were stable during childhood, 3 had radiological progression during adulthood.

LG-002. THE EFFECT OF CHEMOTHERAPY ON OPTIC PATHWAY GLIOMAS AND THEIR SUB-COMPONENTS; A VOLUMETRIC MR ANALYSIS
Ben Shofty1, Michal Maada-Havukku1, Dafna Ben-Bashat1, Rina Dvir1, Li-Tal Pratt1, Lior Weizman1, Leo Jozkowicz1, Michal Tal1, Lior Ravid1, Li-Ben Stras1, and Shlomi Constantini1; 1The Gilbert Israeli Neurofibromatosis Center, Tel-Aviv Medical Center, Tel-Aviv, Israel; 2Pediatric Neurosurgery, Tel-Aviv Medical Center, Tel-Aviv, Israel; 3Hebrew University, Jerusalem, Israel

Optic pathway gliomas (OPG) represent 5% of pediatric brain tumors. Introduction of novel volumetric imaging methods enable accurate assessment of the tumoral changes under chemotherapy. In this study we examined the effect of first line chemotherapy treatment with vincristine and carboplatin on the gross total solid volume (GTSV) of the tumor as well as its various sub-components. The tumors of 12 patients (7 boys, 5 NFI, mean age at treatment initiation was 7 years (+ 6y) with OPG were measured using our novel, previously described method [1, 2]. Two MR studies per patient were included in this study. One MRI performed before initiation of treatment, and one after a period of at least 6 months on the protocol. Volumetrics of the gross total solid volume, solid-non-enhancing, solid-enhancing, and cystic components were calculated. The relative percentile change of each of the component following treatment was calculated. During the treatment period with vincristine and carboplatin an average reduction of 8% (+ 27%) in the GTSV was noted. Solid-non-enhancing components were reduced by an average of 12% (+ 41%), solid-enhancing were reduced by 17% (+ 78%) and the cystic component grew under therapy by an average of 25% (+ 86%). Two patients had delayed appearance of a cystic component. Treatment with vincristine and carboplatin seems to have an effect mostly on the solid components. The cystic component seems to be unaffected by chemotherapy and contributes to the subsequent growth of the gross total volume, but not of the GTSV.

LG-003. SINGLE AGENT CARBOPLATIN SHOWS COMPARABLE EFFICACY WITH OTHER CHEMOTHERAPEUTIC REGIMENS IN THE TREATMENT OF PAEDIATRIC LOW GRADE GLIOMA
Andrew Dodgshun, Wirginia Maixner, Michael Sullivan, and Jordan Hansford; Royal Children’s Hospital, Melbourne, VIC, Australia

BACKGROUND AND AIMS: Treatment for low grade glioma in childhood is surgical, with radiation reserved. For permissions, please e-mail: journals.permissions@oup.com.

INTRODUCTION: Pediatric supertentorial intraventricular tumors often occur in the deep location of brain and effect most important functions such as consciousness, subtle memory, emotion and temperament. They are with predisposition to the children younger than three years old. They are more frequently benign neoplasm, but malignant tumors can sometimes occur. MATERIALS AND METHODS: We reviewed our experience of surgical treatment for intraventricular neoplasm under three years old in pediatric neurosurgery of Xinhua hospital during 2007-2012. The pathological characteristics of neoplasm, resection of operation, auxiliary treatment, mortality, morbidity and survivorship are considered. Our experience of pediatric neurosurgery is based on a retrospective analysis which enrolled 41 younger children. RESULTS: In our center, infantile supertentorial intraventricular tumors account for 10% of pediatric brain tumors and 64% pediatric intraventricular tumors. In this series, the mean month-age is 15.5, the mean followup time is 5 years and 5 year progression-free survival was 29%. CONCLUSION: Microsurgical resection and pathological characteristics play the most important role in the prognosis of infantile supertentorial intraventricular tumors. Techniques of microsurgical procedure for protecting the relevant anatomy affect the outcome and avoid most complications.

LG-004. THE MANAGEMENT, OUTCOME OF SUPERVENTRICULAR INTRAVENTRICULAR TUMORS IN CHILDREN (YOUNGER THAN THREE YEARS OLD)
Jie Ma and Baosheng Wang; Shanghai Jiaotong University, Shanghai, China

INTRODUCTION: Pediatric supertentorial intraventricular tumors often occur in the deep location of brain and effect most important functions such as consciousness, subtle memory, emotion and temperament. They are with predisposition to the children younger than three years old. They are more frequently benign neoplasm, but malignant tumors can sometimes occur. MATERIALS AND METHODS: We reviewed our experience of surgical treatment for intraventricular neoplasm under three years old in pediatric neurosurgery of Xinhua hospital during 2007-2012. The pathological characteristics of neoplasm, resection of operation, auxiliary treatment, mortality, morbidity and survivorship are considered. Our experience of pediatric neurosurgery is based on a retrospective analysis which enrolled 41 younger children. RESULTS: In our center, infantile supertentorial intraventricular tumors account for 10% of pediatric brain tumors and 64% pediatric intraventricular tumors. In this series, the mean month-age is 15.5, the mean followup time is 5 years and 5 year progression-free survival was 29%. CONCLUSION: Microsurgical resection and pathological characteristics play the most important role in the prognosis of infantile supertentorial intraventricular tumors. Techniques of microsurgical procedure for protecting the relevant anatomy affect the outcome and avoid most complications.

LG-005. ACQUIRED NYSTAGMUS AS THE INITIAL PRESENTING SIGN OF A CHIASMAL GLIOMA IN YOUNG CHILDREN
Helen Toledano1, Orkun Muhunoglu2, Judith Luckmann2, Shalom Michowiz2, and Nitza Goldenberg-Cohen1; 1Schneider Children’s Medical Center, Petach Tikva, Israel; 2Rabin Medical Center, Petach Tikva, Israel; 3Krieger Eye Research Laboratory, Felsenstein Medical Research Center, Petach Tikva, Israel; 4Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

We retrospectively investigated the incidence of nystagmus at presentation of chiasmatic-hypothalamic glioma (CHG) in children. All patients of 41 patients with CHG followed-up in our Center from 2001-2013 were reviewed. 14 patients with NFI were excluded since the CHG was diagnosed by routine MRI screening. Four others had incomplete records and one had only mild pre-chiasmatic thickening on MRI review. The remaining 22 children, with
measurable CHG, were included; 9 boys, 13 girls, age 3.5 ± 4.4 years old mean follow-up 8.3 ± 5.4 years. Thirteen underwent partial resection/ biopsy. 19 were treated by chemotherapy, 2 of whom also received adjuvant radiotherapy. Of the 19 patients with CHG, 15 were less than 2 years old at diagnosis (range 4-21 months, mean 1 ± 0.42 year). The other 7 were 3.8-17 years at diagnosis (mean 9.6 ± 4.1 years). Nine of the 15 young children had monocellular nystagmus at diagnosis, and an additional two had bilateral wandering or end gaze nystagmus (total nystagmus in young children 11/15, 73%). The 4 ≤2yrs without nystagmus had good vision (2), moderate (1) and severe (1) monocellular visual loss. No child older than 2 years at diagnosis presented with nystagmus. At the end of the follow-up, visual acuity in the 11 children with nystagmus: 6 monocellular visual loss, 2 bilateral visual loss and homonymous field defect, 1 bilateral preserved vision with homonymous hemianopia and 2 too young for VA measurement. We conclude that monocellular nystagmus is a more common presenting sign of CHG in children under 2 years of age than previously estimated. This is a subtle clinical sign but has a very narrow differential diagnosis in this age group. The presence of monocellular nystagmus in a young child should raise early suspicion of a chiasmatic tumor and prompt rapid referral for imaging studies. Visual prognosis in this age group is moderate to poor.

LG-006. METASTATIC GLIOFIBROMA (GF) IN AN INFANT WITH BRAF: KIAA1549 GENE RearRangement AND RESPONSE TO WEEKLY VINBLASTINE (VBL) CHEMOTHERAPY Matthew Schniederjan1, Laura Hayes2, Barun Brahma2, and Thomas Cummings1, Oren Becher1, and Sri Gururangan1; 1Duke University Medical Center, Durham, NC, USA; 2Phoenix Children’s Hospital, Phoenix, AZ, USA; 3Lucile Packard Children’s Hospital, Stanford, CA, USA

BACKGROUND: Gliofibroma is a rare astrocytic tumor with mixed glial and mesenchymal elements, varied clinical presentation and behavior, and unclear histogeny. We report the case of an infant who presented with an extensive GF of the brain stem and spinal cord that responded to metronomic VBL chemotherapy. Her tumor was also positive for BRAF duplication that has not been previously reported with GF. CASE REPORT: A 3 month-old female presented with upper extremity weakness. MRI identified heterogeneous intramedullary mass extending from lower brain stem to the upper thoracic spine. Tumor biopsy yielded limited tissue that was consistent with a low-grade tumor of uncertain origin. She was treated with weekly carboplatin + vincristine for 3 months with stable disease (SD). Chemotherapy was then discontinued due to malnutrition and poor wound healing. Tumor progression with leptomeningeal disease occurred 8 months later. She then underwent a partial resection of tumor in the cervical cord. Pathology review now confirmed diagnosis of GF based on a biphasic lesion composed of islands of GFAP positive glial tissue intermingled with a fibroblastic stroma consisting of cytologically bland spindle cells with ovoid nuclei and pale cytoplasm. These latter cells were positive for reticulin and vimentin but negative for S-100 protein, GFAP, and actin. There was no evidence of a BRAF: KIAA1549 gene rearrangement in >20% of tumor cells. Weekly Carboplatin alone was reintitated with temporary disease stabilization but progressive disease occurred 7 months later. Treatment was changed to weekly VBL chemotherapy after 8 weeks and currently SD at 8 months. CONCLUSION: This is the first report of a GF positive for BRAF duplication, a molecular marker typically associated with pilocytic astrocytomas. Metronomic vinblastine therapy might be a useful modality of treatment for patients with GF.

LG-007. RECURRENT GANGLIOGLIOMA WITH BRAF V600E MUTATION RESPONSE TO VEMURAFENIB: CASE REPORT Dolly Aguilar1, Claire Mazewski1, Anna Janss1, Robert Craig Castellino1, Matthew Schmedes2, Laura Hayes1, Talia Slaight2, and Toby MacDonald3; 1Children’s Health Care of Atlanta, Emory University School of Medicine, Atlanta, GA, USA; 2Children’s Health Care of Atlanta, Atlanta, GA, USA

Gangliogliomas historically have had poor response to chemotherapy and radiation. Over 50% brainstem gangliogliomas harbor BRAF V600E mutation. We report a marked tumor response to the BRAF inhibitor vemurafenib in a 18 MO male with a progressive refractory brainstem ganglioglioma (WHO grade I). Initial presentation included upper airway obstruction, vocal cord paresis, swallowing dysfunction and impaired ambulation. He underwent a subtotal resection followed by involved-field proton radiation. Pathology revealed a phasic lesion composed of islands of GFAP positive glial tissue intermingled with a fibroblastic stroma consisting of cytologically bland spindle cells with ovoid nuclei and pale cytoplasm. These latter cells were positive for reticulin and vimentin but negative for S-100 protein, GFAP, and actin. There was no evidence of a BRAF: KIAA1549 gene rearrangement in >20% of tumor cells. Weekly Carboplatin alone was reintitated with temporary disease stabilization but progressive disease occurred 7 months later. Treatment was changed to weekly VBL chemotherapy after 8 weeks and currently SD at 8 months. CONCLUSION: This is the first report of a GF positive for BRAF duplication, a molecular marker typically associated with pilocytic astrocytomas. Metronomic vinblastine therapy might be a useful modality of treatment for patients with GF.

LG-008. A RETROSPECTIVE MULTICENTER ANALYSIS OF CHILDREN WITH LOW GRADE GLIOMAS - RESULTS OF THE JAPANESE PEDIATRIC BRAIN TUMOR CONSORTIUM Kazuo Ogata1, Chiharu Kiyokamo2, Hideyuki Sakamoto3, Hikoaki Yamagawa4, Miyako Kano5, Sachio Kamiyama6, Yoshiyuki Kosaka7, Junko Hirado8, Tetsuya Takimoto9, Atsuko Nakazawa10, and Junichi Hara11; 1Department of Pediatrics, National Hospital Organization, Osaka National Hospital, Osaka, Japan; 2Department of Pediatric Oncology, Osaka City General Hospital, Osaka, Japan; 3Department of Neuro-Oncology, Saitama Medical International Medical Center, Saitama, Japan; 4Department of Pediatrics, Yamagata University Hospital, Yamagata, Japan; 5Department of Pediatrics, University of Miyazaki Hospital, Miyazaki, Japan; 6Department of Hematology/Oncology, Hiroyo Children’s Hospital, Hiroyo, Japan; 7Division of Data Analysis, Child Cancer Center, National Center for Child Health and Development, Tokyo, Japan; 8Department of Pathology, Child Cancer Center, National Center for Child Health and Development, Tokyo, Japan; 9Department of Pathology, Osaka City General Hospital, Osaka, Japan

We retrospectively investigated long-term history of children with low-grade gliomas (LGGs) diagnosed at 27 centers in Japan from 1998 to 2013. PATIENTS: 219 children (mean age 5.9 years (range: one month-15 years), tumor location: cerebrum 46, cerebellum 57, optic pathway/thalamus 87, midbrain 4, others 25) were assessed. In 67 patients tumors were totally removed. Histologic WHO grading was grade II in 12 patients, LG (A128), grade II in 51(diffuse A 20, pilomixoid A 11) and LGG, NOS in 18. In six patients histological examinations were not done. RESULTS: Initially, 99 received chemotherapies and 24 received radiotherapy. The patients were followed for median of 35 months (one-year 190 +) months from diagnosis. At present 93 patients have been in complete remission and 117 in stable disease, but recurrence have been observed in 83 among them. Seven patients died of diseases. In one of them, malignant transformation of the disease was observed 9 years after diagnosis. For all LGG 15-year OS and PFS were 94.5 ± 2.6% and 43.0 ± 5.2%. 10-year OS and PFS of PA, DA, and LGG, NOS were 95.1 ± 3.3% and 38.2 ± 6.4%, 70.6 ± 20.8% and 50.7 ± 12.9%, 100% and 72.7 ± 17.7%, respectively. Among PA, 10-year PFS of optic pathway was inferior to that of cerebellum (18.4 ± 7.0% vs.60.3 ± 9.0%). In patients with residual tumor after surgery, 10 year PFS was 33.7 ± 6.2%, which was worse than that in patients whose tumors were totally removed (66.1 ± 8.8%). There were no patients suffering recurrence 7.9 years after diagnosis. As the sequelae, epilepsy, hydrocephalus and lost vision were seen. 31 have some endocrinal problems (26 need therapy) and 28 need some support for living. One had second malignancy. CONCLUSIONS: LGGs especially PA have clinically benign appearance and the incidence of malignant transformation was low. Pathologic diagnosis, tumor location and resection extent influence the outcome of the disease. We also need to follow the late effect sequel.
LG-009. A MULTI-INSTITUTIONAL PHASE II STUDY OF VINORELBINE IN CHILDREN WITH RECURRENT OR PROGRESSIVE LOW-GRADE GLIOMA
Eva D. Huang1, Donna Mun1, Linda Bidmon1, Susan Chi1, Jeffrey Knipstein1, Michal Oren1, Rina Divr1, Kristina Hardy1, Brian Rood1, and Roger Packer1; 1Children's National Medical Center, Washington, DC, USA; 2Dana Farber Cancer Institute, Boston, MA, USA; 3NOVA Fairfax, Falls Church, VA; 4Petech Medical Center, Tel Hashomer, Israel; 5Children's Hospital of Tel Aviv, Israel

BACKGROUND: Unacceptable pediatric low-grade gliomas (PLGGs) can be life-threatening, cause significant morbidity, and are likely to recur. Vinorelbine is a vinca alkaloid with significantly less neurotoxicity than vincristine and some preliminary evidence of efficacy, primarily in newly-diagnosed patients. In this prospective, international multi-institutional trial, vinorelbine was investigated in children with recurrent/progressive PLGG. METHODS: Children less than 18 years-old with progressive PLGG who had failed at least one non-surgical therapy were eligible. Vinorelbine was administered at the COG-defined maximum tolerated dose. 30mg/m2 weekly for six consecutive weeks followed by a two-week rest. Treatment was continued for one year in the absence of progression or unacceptable toxicity. RESULTS: Thirteen patients at five centers were enrolled at a median age of four years (range, 3-10yr), 2 with NF1, 7 male. Histologies were: pilocytic astrocytoma (4), diffuse glioma (7), brainstem LGG (2), and optic pathway glioma (1). Most had metastatic disease (n = 8, 61%), and had a median of two previous non-surgical therapies (range, 1-6). Two partial response (1 BSG, 1 PA) and one minor response (fibrillary) were noted; no patient with response has progressed at a median of 23 months from therapy initiation. Median progression free survival was 14 months (range, 2-27). The majority of patients (12) experienced at least one episode of grade 3-4 neutropenia or thrombocytopenia. There were no progressive non-hematologic toxicities. CONCLUSIONS: Despite these high-risk, heavily pretreated patients, almost a quarter demonstrated an objective response with prolonged stabilization of disease. Therapy was well-tolerated with no neurotoxicity but frequent transient suppression. Vinorelbine may be an effective agent for use in the context of recurrent PLGG but should be tested both as a single agent and in combination in greater numbers of patients.

LG-010. GANGLIOGLIOMA IN CHILDREN AND ADOLESCENTS - NATURAL COURSE AND RESPONSE TO TREATMENT IN 193 PATIENTS OF THE LOW GRADE GLIOMA (LGG) STUDIES OF THE GERMAN SOCIETY OF PEDIATRIC ONCOLOGY/HEMATOLOGY
Daniela Kandels1, René Schmidb1, Marina Geh1, Sabine Breitmüller-Grem1, and Astrid K. Gnekow1; 1Children's Hospital, Klinikum Augsburg, Augsburg, Germany; 2Institute of Biostatistics and Clinical Research, University of Muenster, Muenster, Germany

OBJECTIVE: Ganglioglioma is rare among LGG of childhood and adolescence showing a variable course. We analyzed the role of surgical and non-surgical therapy with respect to the risk of progression/recurrence in large prospective registered pediatric cohort. METHOD AND RESULTS: Among 2675 LGG patients of the HIT-LGG-1996- and German SIOP-LGG-2004-cohort 193 patients with ganglioglioma WHO grade I were included (7.2%): median age at diagnosis 10.6 years (range 0.2-17.5), none NF1, 60.1% male. Localization: hemispheric 122 (73%), supratentorial midline 19 (visual pathways 4), cerebellum 25, caudal brainstem 21, spinal 6; disseminated 5. Main symptom: seizures in 97/122 hemispheric tumors (in 64/78 temporal lobe tumors), increased ICP in 24/71 non-hemispheric tumors, focal neurological symptoms (hemiparesis, cranial nerve paresis, ataxia) in 48/71 non-hemispheric tumors. First surgical intervention achieved complete resection in 66.4% hemispheric tumors, but only in 14.1% of others. Relapse followed complete resection in 9.9% (9/91), while progression developed in 43.1% (44/102) after incomplete resection/biopsy. Further surgery was performed in 37/53 progressive/relapsed patients, 12 needed one or more non-surgical treatments, additionally. Twenty-seven patients with unselectable, progressive (17) or symptomatic (10) behavior underwent non-surgical treatment (17 radiotherapy, 10 chemotherapy). Nine needed at least one additional treatment for further progression over a period of up to 22 years (median 6.4) from diagnosis. After 5.8 years median follow-up (range 0.6-22.0) 5-years-OS is 96.9%, while 5-years-DFS from first surgery to relapse/progression/first treatment/death declines to 67.9% (88.5% complete vs.49.8% incomplete resection, p < 0.001; 77.9% hemispheric vs. 50.7% non-hemispheric tumors, p < 0.001). CONCLUSION: Prognosis for pediatric ganglioglioma is excellent after complete resection of hemispheric tumors. Successful management for progressive tumors relies on second surgery, yet a third requires additional non-surgical therapies. New trials have to investigate into the role of the molecular-genetic signature, since V600E-BRAF-mutation in ganglioglioma seems to predict shorter recurrence-free survival.

LG-011. GENE EXPRESSION ANALYSIS OF 151 PEDIATRIC LOW-GRADE GLIOMAS REVEALS UNDERLYING MOLECULAR HETEROGENEITY
Guillaume Bergthold1, Pratit Randopadhayay2, Benjamin Rich1, Jennifer Chen1, Santino Sanult5, Gunjan Kumar3, Lori Ramakrishnan3, Todd Golub1, Barbara Tabak5, Ruben Furrer-Luna3, Patrick Y Weng3, Charles Stiles5, Jacques Grill3, Mark W Kieran1, Keith L Ligon4, and Rameen Beroukhim1; 1Dana-Farber Cancer Institute, Boston, MA, USA; 2Brigham And Women’s Hospital, Boston, MA, USA; 3Broad Institute of MIT and Harvard, Cambridge, MA, USA; 4Institut Gustave Roussy & Universite Paris Sud, Villejuif, France

BACKGROUND: Low-grade gliomas (LGGs) represent the most frequent pediatric brain tumor. They are clinically constituted by a broad and heterogeneous group of diseases. Recent genomic analyses performed on different cohorts of PLGGs (pediatric low-grade gliomas) suggest that these tumors are mostly driven by MAPK pathway alterations. However, little is known about the molecular characteristics inherent to their clinical and histological heterogeneity. METHODS: We performed gene expression profiling on 151 paraffin-embedded PLGGs from different locations, ages and histological subtypes, across 6100 selected genes known to be dysregulated in cancer. Using unsupervised and supervised analysis, we compared molecular features associated with age, location, histologic subtype, and BRAF genomic status of the tumors. We further compared the differences in ages with a cohort of expression data from normal brain samples (BrainSpan database). RESULTS: Non-mutative gene expression distinguished three molecular groups mostly according to their location in the brain, and some by histological subtypes. We found that supratentorial pilocytic astrocytomas (PAs) were significantly enriched with genes of IL-12 activation pathway, compared to infratentorial PAs (p < 0.001, Gene Set Enrichment Analysis). We did not observe statistically significant differences between BRAF duplicated and BRAF V600E mutated tumors, suggesting that they seem to be all driven by similar molecular patterns. Finally, after controlling for location and histology, we found that a majority of genes upregulated in the adolescent PAs, compared to childhood tumors are similarly over expressed in matched normal brains (p < 0.001). CONCLUSION: Through a large cohort of expression profiles of pediatric LGGs we identified molecular differences associated with age, location, histological subtypes. Some molecular differences between childhood and adolescent LGGs are reflected similarly in normal brain.

LG-012. OPTIC NERVE TORTUOSITY IN NEUROFIBROMATOSIS TYPE 1 AND RISK OF OPTIC PATHWAY GLIOMA DEVELOPMENT
Michael J. Fisher1, Marc H. Levin2, Gregory T. Armstrong3, Julian H. Broad4, Robert Zimmerman5, Larissa T. Bilaniuk1, Tamara Feygin5, and Grant T. Liu2; 1Children’s Hospital of Philadelphia, Philadelphia, PA, USA; 2University of California San Francisco, San Francisco, CA, USA; 3St. Jude Children’s Research Hospital, Memphis TN, USA

BACKGROUND: Optic nerve tortuosity (ONT) and thickening of optic nerve and sheath are MRI abnormalities seen in patients with neurofibromatosis type-1 (NF1). It is unknown whether they are precursors to the development of optic pathway gliomas (OPG). METHODS: Children with NF1 and ≥1 year of subsequent visual acuity (VA) data after initial MRI were identified retrospectively. Three neuroradiologists independently reviewed the earliest available MRI to provide a consensus assessment. Subjects with OPG on baseline MRI were excluded. ONT was identified using validated criteria. In parallel, presence of nerve tortuosity or thickening was established by clinical MRI and reported. Optic nerve and sheath thicknesses (cross-sectional diameter) were measured. VA at last follow-up was recorded; data was censored at time of treatment. RESULTS: 133 evaluable subjects were identified. Median age at earliest MRI was 3.6 years (range 1.0-18.5). Twenty subjects (15%) ultimately developed OPG. Clinical reports noted tortuosity in 21 subjects (16%), who developed OPG with significantly greater frequency than those without tortuosity (33% vs. 12%, p = 0.02). Use of the validated scale established only 7 subjects (5%) with ONT; however, incidence of subsequent OPG was even greater (57% vs. 13%, P = 0.0001). In subjects who developed OPG, tumor-related vision loss (VA < 0.2 logMAR below age-normal acuity) was not significantly different between those with and without baseline ONT (14% vs. 4%, p = 0.32). There was no difference between mean optic nerve (2.3 vs. 2.2mm, p = 0.86) or nerve sheath thicknesses (5.2 vs. 5.4mm, p = 0.74) between subjects who did and did not develop OPG. CONCLUSIONS: In NF1, ONT is associated with increased risk for OPG development. Closer surveillance of those subjects with tortuosity may be indicated.
with ONT may be warranted, although ONT does not appear to predispose to OPG-related vision loss.

LG-013. THE EVOLUTION OF NEUROENDOCRINE MORBIDITY AFTER PAEDIATRIC OPTIC PATHWAY GLIOMAS: A MULTIVARIATE SURVIVAL ANALYSIS OF PATIENT-, TUMOUR- AND TREATMENT-RELATED FACTORS IN 166 PAVES WITH NEUROENDOCRINE MORBIDITY OVER 30 YEARS Hoong-Wei Gan1, Kim Phipps2, and Helen A. Spoudeas3; 1University College London Institute of Child Health, London, UK; 2Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

BACKGROUND: Up to 50% of paediatric low-grade gliomas affect the optic pathway or suprasellar midline (OPGs), where they can cause significant long-term hypothalamic-pituitary morbidity, the aetiology of which is unclear.

METHODS: We analysed tumour- and treatment-related predictors of neuroendocrine morbidity by retrospective case note review of 166 consecutive OPG patients at a large quaternary centre between 1980-2010 using multivariate Cox, linear and logistic regression. RESULTS: Patients were of median (range) age 4.9 (0.2-15.4) years at diagnosis and followed for 8.3 (0.04-26.8) years. Despite high 20-year overall survival (OS, 81.0%), progression-free (PFS) and endocrine event-free (EEF) survival were only 47.2% and 20.8% respectively. EEFs declined up to 15 years post-diagnosis, being worse in recent treatment eras (p = 0.02) without improvement in OS or PFS. Hypothalamic tumour involvement (p = 0.0003) predicted earlier endocrine failure more than radiotherapy (p = 0.008), though radiotherapy increased the density of endocrinopathies (endocrine morbidity score, p < 0.00001) more than hypothalamic involvement (p = 0.006). GH deficiency was most prevalent (40.3%), followed by central precocious puberty (26.0%), gonadotrophin deficiency (20.4%), ACTH deficiency (13.3%) and TSH deficiency (13.3%). Posterior pituitary dysfunction (PPD) was unusual (7.2%) but was associated with 6/13 deaths, and only occurred at tumour diagnosis or after surgical intervention (50% after shunt or biopsy procedures alone). 32.5% of patients became obese (BMI z SD > 2SDS). In subcohort analyses, radiotherapy was only associated with GH deficiency, obesity and insulin resistance. Tumour extent largely predicted neuro-ophthalmological morbidity. Female sex was a new, independent protective factor against endocrine and cognitive morbidity. CONCLUSIONS: The evolution of hypothalamic-pituitary dysfunction is caused by both OPG tumour location, which predicts its speed of onset, and radiotherapy, which predicts its severity. Our data suggests more recent chemotherapy-based strategies are associated with greater endocrine morbidity without benefitting survival. PPD can be life-threatening, occurring even after minor biopsies and is present in a significant proportion of OPG-related deaths.

LG-014. OUTCOMES OF CHILDREN AND YOUNG ADULTS WITH RECURRENT PILOCYTIC ASTROCYTOMA TREATED WITH MULTIPLE SURGICAL RESECTIONS Mira Kohutzer, Deepthi Warad, Gesina Kearing, Stephanie Childs, Caterina Giannini, Nicholas Weijen, and Amulya Nageswara Rao; Mayo Clinic, Rochester, MN, USA

Pilocytic astrocytomas (PAs) are low grade gliomas (WHO grade I) with 10-year overall survival (OS) of more than 95% with gross total resection (GTR). There is no clear consensus on most appropriate therapy with recurrent PAs. Treatment considerations include repeat surgical resections, chemotherapy and/or radiation. The study objective was to review the outcomes of children and young adults with recurrent PA who undergo multiple surgical resections. Of 145 patients diagnosed with PA from 1997 to 2012, 28 patients (19.3%) experienced recurrence/progression. Five patients with disseminated disease were excluded. Median age at diagnosis was 10.5 years (n = 23); rane age 3-17.8 years. Tumor site included deep/midline (52%), cerebellum (39%), and cerebrum (9%). Median follow-up time was 8 years (range: 0.34-15.3 years). Median time to first recurrence was 1.2 years (range: 0.2-9.5 years). Eight year OS was 93%. Fourteen patients underwent only repeat surgeries, while the remaining 9 underwent further surgery, chemotherapy and/or radiation. Of the 14 patients, all except one had a GTR or near total resection at second surgery. One patient with a subtotal resection recurred at 10.7 months, underwent a GTR, and has been recurrence free for 86.6 months. Local complications occurred in 21.4% (3/14) and 28.6% (4/14) of patients following first and second resection, respectively. Overall, postoperative neurologic complications occurred in 10/14 patients. Neurologic complications occurred following first and repeat surgeries in 56% and 50%, respectively. Tumor location was not significantly associated with neurologic complications. Bloom score was 2 (mild disability) in 38% and 3 (moderate disability) in 32% of patients at one year after the last surgery. Though GTR offers the best chance for cure, multiple and aggressive surgical resections are often associated with substantial neurologic morbidity. Risk of neurologic deficits and functional decline should be an important consideration in treatment decisions given the excellent long-term survival.

LG-015. TREATMENT RESULTS OF CHILDHOOD INTRACRANIAL PILOCYTIC ASTROCYTOMAS: LONG TERM FOLLOW-UP IN A SINGLE INSTITUTE Hideo Nakamura, Keishi Makino, Takushiro Hide, Jun-ichiro Kuroda, Naoko Kouno, Shigeyuki Yano, and Jun-ichi Kurasaw; Dept of Neurosurgery, Kumamoto University, Kumamoto, Japan

PURPOSE: Pilocytic astrocytoma is a common pediatric glioma that is generally characterized as a benign tumor. The prognosis of almost all children with pilocytic astrocytoma is favorable, however, there are some patients experiencing unfavorable events. The purpose of this study was to review the long-term outcome of such patients. PATIENTS AND METHOD: The medical charts, imaging findings, operative notes, histo-pathological reports, progression-free survival (PFS) and OS were collected and quality of life (QOL) of 46 patients (cerebellar hemisphere: 15, vermis: 11, brain stem: 4, cerebellar hemisphere: 4, hypothalamus: 3, basal ganglia: 6) with pilocytic astrocytoma were reviewed. RESULTS: As initial treatment all patients received surgery (Total removal: 19, Partial removal: 18, Biopsy: 9). 8 patients received chemotherapy (nitrosourea: 3, platinum based: 5) and 11 patients received radiotherapy. Follow-up duration ranged from 1.3 to 43.1 years (median: 15.08). Tumor recurrence was observed in 7 patients and 3 patients (cerebellar vermis, hypothalamus: 1, basal ganglia: 1) were dead. Spinal dissemination was observed in one patient. No malignant change was found at the time of recurrence. Two patients received operation again, 2 patients received chemotherapy and 3 patients received radiotherapy at the time of recurrence. All patients with pilocytic astrocytoma at cerebral and cerebellar hemisphere had experienced uneventful and normal life, however, some patients with hypothalamic or basal ganglia tumor had mentally or intellectually handicaps. CONCLUSION: Almost patients who received complete removal of the tumor had a favorable prognosis and almost recurrent tumors were curable in the patients with pilocytic astrocytoma. Aggressive surgery for the tumor at hypothalamic or basal ganglia region associated with a complication is not recommended.

LG-016. MUTATIONS IN PTPN11 GENE MAY PREDISPOSE TO DEVELOPMENT OF MIDLINE LOW GRADE GLIOMAS Sarah Rush1, Jennifer Madden2, Molly Hemenway3, and Nicholas Foreman4; 1 Akron Children's Hospital, Akron, OH, USA; 2 University of Colorado Denver, Aurora, CO, USA

Mutations in the RAS pathway have become increasingly recognized as tumour necrosis. Noonan syndrome and other RASopathies are known to be associated with a variety of tumors. There are few reports of CNS tumors with PTPN11 mutations. We present three cases of patients with Noonan syndrome with low grade astrocytomas. All patients presented with primary tumors originating in the midline involving the suprasellar and thalamic regions. One patient had disseminated disease at diagnosis. All patients were known to have midline defects which are characteristic of Noonan syndrome although only one patient was known to have pulmonic stenosis which is the hallmark cardiac defect. The two male patients were known to have undescended testicles. Interestingly, both one male and one female patient were known to have congenital deafness which is also not commonly reported in patients with Noonans. All patients had mutations in the PTPN11 gene which are known to be associated with Noonan syndrome. Midline low grade gliomas appear to be more common in patients with features of Noonan Syndrome and mutation of the PTPN11 gene than was previously noted. As more molecular information about low grade gliomas becomes available there is a clear predilection for mutations in the RAS pathway. Identification of the somatic mutation in the PTPN11 gene is in keeping with this mechanism. This case series demonstrates that these tumors should be considered part of the spectrum of this disease.

LG-017. GROWTH-FACTOR-DRIVEN RESCUE TO RECEPTOR TYROSINE KINASE INHIBITORS IN PEDIATRIC LOW GRADE ASTROCYTOMA AND EPENDYMOMA Marraka Sue, Wilfred F.A. den Dunnen, Harm Jan Lourens, Tim J.J. Meulenweg-de Boer, Frank J.G. Overeem, Kim K. Kampen, Elco W. Hoving, and Eveline S.J.M. de Bont; University Medical Center Groningen, Groningen, The Netherlands

INTRODUCTION: Low grade astrocytomas are the most frequent brain tumors in children. Despite a 5-year survival of 80-90%, morbidity can be
serious. The 5-year survival of ependymoma is merely 57%. Therefore, a search for new targeted therapies has started, including receptor tyrosine kinase (RTK) inhibitors. However, single targeted kinase inhibition failed possibly due to tumor resistance mechanisms. The present study will extend our previous observations that vascular endothelial growth receptor (VEGFR) 2, platelet derived growth factor receptor (PDGFR) β, Src, the epidermal growth factor receptor (Erbb) family, and hepatocyte growth factor receptor (HGFR/cMet) are potential druggable targets in pediatric low grade astrocytoma and ependymoma with investigations concerning growth-factor-driven rescue. MATERIAL AND METHODS: RTK expression in pediatric low grade astrocytoma (Res-186, Res-259, UW-467) and ependymomas (197) were determined using flow cytometry analyses. Growth-factor-driven rescue during RTK inhibition (sorafenib, dasatinib, canertinib, crizotinib) was analyzed with WST-1 cell viability assays and on phosphorylation level of the crucial downstream PI3K/Akt and MAPK/Erk survival signaling pathways using western blotting. RESULTS: VEGF-R 1, fibroblast growth factor receptor (FGFR) 1, ErbB-1, HGFR and RON were highly expressed (respectively ≥27.7%, 34-51%, 63-90%, 83-98%, 63-95%) and their respective inhibitors showed induced decrease of tumor cell viability. EGFR, HGF and FGFR, environmentally expressed in brain tumors, showed to be effective rescue inducing growth factors resulting in increased cell viability especially during dasatinib or sorafenib treatment (complete and partial rescue respectively). Growth-factor-driven rescue was less prominent during canertinib or crizotinib treatment. Rescue was underestimated by activin A down-regulating Akt and/or Erk phosphorylation. Combination treatment showed to could overcome growth-factor-driven rescue. CONCLUSIONS: Our study highlights the extensive importance of environmentally present growth factors in developing resistance mechanisms towards RTK inhibitors of great interest to anticipate upon these results in future therapeutic trials with pediatric low grade astrocytoma and ependymoma.


Astrid K. Gnekow1, Daniela Kandels1, David A. Walker2, Giorgio Perilongo3, Jacques Griff3, Tore Stokland4, Astrid Marie Sehested5, Antonie Y. N. van Schouten6, Angela de Paoli7, Gianna Lucad de Salvo8, and for the SIOP Low Grade Glioma Working Group and the participating centers1; 1Children’s Hospital, Augsburg, Germany; 2University of Nottingham, Nottingham, UK; 3University of Padua, Padua, Italy; 4Institute Gustave Roussy, Paris, France; 5University of Tromso, Tromso, Norway; 6University of Copenhagen, Copenhagen, Denmark; 7University of Amsterdam, Amsterdam, The Netherlands; 8Clinical Trials and Biostatistics Unit, Istituto Oncologico Veneto – IRCCS, Padua, Italy

OBJECTIVE: The comprehensive treatment strategy SIOP-LGG 2004 for pediatric LGG included a randomized chemotherapy-arm for non-NF1-patients with progressive/symptomatic, unresectable tumors to investigate into the role of induction intensity. “Standard” Vincristine/Carboplatin (VC) and “intensified” VC plus Etoposide (VE) regimens were compared for the distribution of response at 24 weeks and progression free survival (PFS) to delay the need for radiotherapy. METHODS AND RESULTS: From 2004-12, 497 patients with severe visual/neurologic impairment including diencephalic syndrome (DNS) at diagnosis (60%), or following clinical or radiologic progression (40%) were randomized to VC (249) versus VCE (248), Stratification considered age (≤1 year 14%, 1-8 years 66%, >8 years 19%) and tumor location (chiasmatic 8%, chiasmatic-hypothalamic/other supratentorial-midline 42%, others 50%). Histology: pilocytic astrocytoma 58%, diffuse glioma 9%, others/not biopsied 33%; primary dispensation 13.9%. Central radiologic and pathologic review was mandatory. Treatment realization and toxicity were comparable in both arms. At 24 weeks post randomization comparing VC and VCE, radiologic disease control comprised volume-reduction in 47.5% vs. 42.1%, stable disease in 45.0% vs. 50.3%, progression 7.5% vs. 7.6%. After median follow-up of 3.8 years, 5-year-overall survival (OS) is 0.90 (0.897 vs. 0.902) and PFS is 0.46 (0.47 vs. 0.48) with no differences between treatment-arms and location. PFS and OS in both arms were impaired for children <1 year or with DNS, as well as PFS for patients with dissemination at diagnosis. CONCLUSION: Both treatment arms achieved high OS and PFS with a median time to progression of 4.1 months. VC-induction in LGG did not impact upon response or PFS and showed no advantage in the presence of clinical risk factors. Although Vincristin/Carboplatin is considered as standard-chemotherapy, further trials should search for new effective agents and strategies, especially for the infant group, and focus upon improving visual and neurological outcome, as well.
CONCLUSIONS: HER2 may be a novel oncogene in PA, though its exact role in tumorigenesis, prognostic implications, or potential benefit from ad-

LG-024. TARGETING BRAF MUTANTS FOR PEDIATRIC LOW-GRADE ASTROCYTOMAS
Yu Ma, Sara Buhrle, Catherine Pilarz, John Albertia, Charles Stiles, and Nathanael Gray; Dana-Farber Cancer Institute, Boston, MA, USA

Activating mutations in BRAF drive disease in most pediatric low-grade astrocytomas (PGLCs). The BRAF V600E point mutation is prevalent in Grade II or higher PGLAs. However, KIAA1549:BRF fusion mutations dominate pilocytic astrocytomas, the most common form of PGLA. In principle, these PLAG driver mutations represent attractive therapeutic targets for a wide range of RAF inhibitors currently under development for adult solid tumors. In practice pediatric PLAGs present two significant barriers to a positive therapeutic response to these drugs: 1) the blood/brain barrier and 2) the inability of the current generation of type 1 RAF inhibitors (vemurafenib or dabrafenib) to block signaling of the RAF dimers that are formed by BRAFKIAA1541:BRF fusion mutants. We performed preclinical character-
ilication of 17 RAF pathway inhibitors with the goal of identifying drugs that accommodate the special challenges of RAF pathway inhibitors for pediatric PLGAs. Our studies identified compounds efficacious in vivo that exhibit a strong growth inhibitory effect with con-
firmed pCH17 (average gene copy number of 17q12 and centromere 17). We also screened over 1700 compounds from corporate libraries in a panel of 17 BRAF mutant cell lines and confirmed 23% of tumor cells, with a HER2 to centromere 17 ratio of 2.4 (amplification present if ratio >2.2). Immunohistochemistry staining for HER2 protein expression was negative in both cases. Patient (A) is now 8 years from resection with no disease recurrence. Patient (B) had an early tumor recurrence but was successfully treated with alternating cycles of carboplatin vincristine and oral temozolomide for 12 months. He is now 9 months off therapy with no radiologic evidence of disease. CONCLUSIONS: HER2 may be a novel oncogene in PA, though its exact role in tumorigenesis, prognostic implications, or potential benefit from ad-
vanced HER2-targeted therapies remains unknown.

LG-025. OVERALL SURVIVAL OF 435 CHILDREN DIAGNOSED WITH BRAINSTEM LOW-GRADE GLIOMAS: AN ANALYSIS OF THE SURVEILLANCE EPIDEMIOLOGY AND END RESULTS (SEER) DATABASE
Gary Mason, Roger Facker, and Eugene Hwang; Children’s National Medical Center, Washington, DC, USA

BACKGROUND: Pediatric low-grade gliomas (PLGAs) generally have very good overall survival rates; however, PLGAs in the brainstem have inferior outcomes and are reported less frequently. This analysis was undertaken to better describe the factors affecting overall survival in this population. METHODS: The authors identified children diagnosed with brainstem LGs (WHO Grade I & II glioma, astrocytoma, fibrillary astrocy-
toma) and pilocytic astrocytomas between 1973 and 2008 through the Surveillance Epidemiology and End Results (SEER) database. Cox propor-
tional hazards regression was performed utilizing both univariate and multi-

LG-021. HER2 AMPLIFICATION OR POLYSOMY CHROMOSOME 17 (PCH17) IN BRAINSTEM Pilocytic Astrocytoma (PA)
Michael Dell1, Roger M. Lendon1, Oren Bencher2, Matthias Karajannis2, Jeffery Wisotzki1, Carrie Mah1, Kristin Schroeder1, and Sri Gururangan1; 1Duke University Medical Center, Durham, NC, USA; 2New York University Langone Medical Center, New York, NY, USA

BACKGROUND: HER2 amplification and pCH17 have been described in adult solid tumors including breast and ovarian carcinomas. This molecular alteration is probably an early event in oncogenesis and is associated with a worse prognosis. While BRAFKIAA1549 gene fusion is the characteristic molecular alteration in PA, the occurrence of HER2 amplification or pCH17 have not been previously reported in this tumor. We present two cases of brain stem PA with HER2 amplification and pCH17, respectively.

CASE REPORTS: The two patients: (A) a 16-year-old male with a tectal mass and (B) an 11-year male with a dural pontine mass, both underwent gross total resection at diagnosis. Pathology was consistent with PA in both cases. Patient (A) was positive for BRAFKIAA1549 gene fusion and demonstrated pCH17 (average gene copy number of 17q12 and centromere 17 were both >2.5), without HER2 amplification. Patient (B) was negative for BRAFKIAA1549 gene fusion, CDK2NA loss, and IDH1/2 mutations. HER2 was amplified in 23% of tumor cells, with a HER2 to centromere 17 ratio of 2.4 (amplification present if ratio >2.2). Immunohistochemistry staining for HER2 protein expression was negative in both cases. Patient (A) is now 8 years from resection with no disease recurrence. Patient (B) had an early tumor recurrence but was successfully treated with alternating cycles of carboplatin vincristine and oral temozolomide for 12 months. He is now 9 months off therapy with no radiologic evidence of disease. CONCLUSIONS: HER2 may be a novel oncogene in PA, though its exact role in tumorigenesis, prognostic implications, or potential benefit from ad-
vanced HER2-targeted therapies remains unknown.

LG-023. PRESENTATION AND OUTCOME OF METASTATIC LOW GRADE ASTROCYTOMA
Maja Anderson1 and Sarah Leary1; 1Seattle Children’s Hospital, University of Washington, and Fred Hutchinson Cancer Research Center, Seattle, WA, USA

In rare cases, low grade astrocytoma (LGA) present with widespread lepto-

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Activating mutations in BRAF drive disease in most pediatric low-grade astrocytomas (PGLCs). The BRAF V600E point mutation is prevalent in Grade II or higher PGLAs. However, KIAA1549:BRF fusion mutations dominate pilocytic astrocytomas, the most common form of PGLA. In principle, these PLAG driver mutations represent attractive therapeutic targets for a wide range of RAF inhibitors currently under development for adult solid tumors. In practice pediatric PLAGs present two significant barriers to a positive therapeutic response to these drugs: 1) the blood/brain barrier and 2) the inability of the current generation of type 1 RAF inhibitors (vemurafenib or dabrafenib) to block signaling of the RAF dimers that are formed by the KIAA1541:BRF fusion mutants. We performed preclinical character-
ilication of 17 RAF pathway inhibitors with the goal of identifying drugs that accommodate the special challenges of RAF pathway inhibitors for PLAG. All compounds were evaluated for ability to inhibit the growth and survival of neural stem cell-derived cell lines dependent on either the BRAF(V600E) point mutation or KIAA15491549 truncation fusion muta-
tion for growth and survival; potent compounds were confirmed to inhibit RAF pathway signaling, assessed by inhibition of ERK phosphorylation. Additionally the compounds were evaluated for ability to cross the blood/brain barrier and access tumor sites using a combination of traditional phar-
camokinetik experiments and novel mass spectrometry imaging technology. Based on these data compounds were selected for evaluation in murine models of PLAG. Our studies have led to the identification of compounds that act in vivo against murine models of PLAG and ex vivo against primary human pilocytic astrocytomas. A surprising and potentially useful finding is that subsets of type 2 BRAF inhibitors exhibit a strong growth inhibitory effect with con-
comitant inhibition of pERK on cells expressing the truncation fusion mutation.

LG-025. OVERALL SURVIVAL OF 435 CHILDREN DIAGNOSED WITH BRAINSTEM LOW-GRADE GLIOMAS: AN ANALYSIS OF THE SURVEILLANCE EPIDEMIOLOGY AND END RESULTS (SEER) DATABASE
Gary Mason, Roger Facker, and Eugene Hwang; Children’s National Medical Center, Washington, DC, USA

BACKGROUND: Pediatric low-grade gliomas (PLGAs) generally have very good overall survival rates; however, PLGAs in the brainstem have inferior outcomes and are reported less frequently. This analysis was undertaken to better describe the factors affecting overall survival in this population. METHODS: The authors identified children diagnosed with brainstem LGs (WHO Grade I & II glioma, astrocytoma, fibrillary astrocy-
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patients under the age of twenty with a low-grade glioma in the brainstem were identified, 47.8% male, median age 7 (range, 0-19). The 5- and 13-year OS for all patients were 80.6% ± 2.0% and 74.8% ± 2.6%, respectively. Analysis of age at diagnosis showed that OS at less than 1-year: 75% ± 21.6%; between 1-5 years old: 88.8% ± 2.9%, and between 5-20 years old: 69.3% ± 3.3%. The 15-year OS for grade I lesions was 86.2% ± 2.6% and for grade II lesions was 53.8% ± 4.6%. The 15-year OS for patients who did not or did receive radiotherapy was 89.9% ± 3.3% and 53.2% ± 4.0%, respectively. Age groups, grade, and resection for irradiation had significantly higher risks in a multivariate analysis (hazard ratios = 1.9, 2.2, and 5.6, respectively). CONCLUSIONS: Most of the deaths in children with brainstem LGGs happen within the first year after diagnosis. Higher grade and younger (<1 year) or older (>5 year) age at diagnosis were associated with lower overall survival, as was utilization of irradiation, potentially due to the lack of response for some tumors. However, long-term outcomes remain reasonable, although inferior to the overall survival of incompletely resected non-brainstem LGG.

LG-026. SECOND-LINE TREATMENT FOR PROGRESSIVE LOW-GRADE GLIOMAS (LGG): A MONOINSTITUTIONAL EXPERIENCE

Veronica Biaissoni, Elisabetta Schiavello, Luca Bergamaschi, Stefano Chiaravalli, Filippo Spreafico, and Maura Massimino; Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

BACKGROUND: Frequently LGG relapse after chemotherapy requiring second-line treatment. METHOD: From 1996 to 2013, patients relapsing after cisplatin/etoposide (JCO 2002, J Neuro-oncology 2010) received regimens containing etoposide 500mg/m2 day 0, vinorelbine 140mg/m2 day 0/14 and B (actinomycin-D 1.5mg/m2 day 0, vincristine 1.4mg/m2 day 0/14). A + B were repeated 6 times over 44 weeks. MRI was performed every 3 months during treatment, neurologist/clinical examination was performed before each course. 11 patients (7 males, mean 5.6yrs) were treated at a median time of 25 months from the first-line. RESULTS: 5/11 had a clinical-radiological diagnosis. 6/11 were histologically confirmed (5 pilocytic astrocytoma, 1 ganglioglioma). 2/11 had dienesthetic syndrome, 2 NF1 and 1 had drug-resistant epilepsy. Sites of progression/relapse were: hypothalamic-optochiasmatic in 5, cervico-bulbar in 2, mesencephalic in 1, metastatic from first diagnosis in 3 (1 fronto-basal + leptomeningeal, 1 dorsal spine + leptomeningeal, 1 hypothalamic-optochiasmatic + spine). 3 patients received also surgery at relapse. Median observation time from diagnosis was 102 months; EFS/PFS from the beginning of the 2nd-line and OS from diagnosis being respectively 51, 60 and 74%. 10/11 patients were evaluable for response: 6 had SD, 3 PR and 1 patient with cervico-bulbar pilocytic astrocytoma had PD requiring radiotherapy, 2/11 died for PD and 1 for acute myeloid leukaeemia 5 months after completing 2nd-line. No severe treatment-related toxicity and no ototoxicity/renal failure related to actual and previous platinum exposure were observed. No child had a WBC nadir <2,000/mm3. 2 treatment modifications were required: vincristine 75% in 1 patient due to neuromuscular toxicity, VCR omission and blood transfusional support in 1 patient with resistant-epilepsy requiring multiple antiepileptics. CONCLUSION: Even if preliminary, these data suggest that this treatment regimen proves effective in childhood LGG already treated with platinum-based chemotherapy, with satisfying PFS and OS and omission/delay of radiotherapy.

LG-027. THE IMPACT OF PUBERTY ON TUMOR INCIDENCE AND PROGRESSION IN CHILDHOOD LOW GRADE GLIOMA

Rahul Krishnatry1, Tatiana Kroupnik2, Nataliya Zhukova2, Matthew Mistry3, Veronica Biassoni, Elisabetta Schiavello, Luca Bergamaschi, Allen Kaplan; Phoenix Children’s Hospital, Phoenix, AZ, USA

OBJECTIVES/BACKGROUND: The term Pilomyxoid Astrocytoma (PMA) was introduced by Tihan in 1999 and added to the World Health Organization (WHO) Classification of Tumours of the CNS as a new variant of pilocytic astrocytoma (PA) in 2007. Due to an increased incidence of local recurrence, malignant transformation, and leptomeningeal dissemination, PMAs are considered to be grade II tumors. These tumors typically occur in the hypothalamus/chiasmatic area, but can be found in multiple areas, including brainstem, cerebral hemispheres or cerebellar cord. Recent reviews suggest a spectrum of PAs with coexistent features of PMA and PA representing an intermediate form of tumor. We attempted to determine if Positron Emission Tomography (PET) with both [18F]fluorodeoxyglucose (FDG) and [11C] l-methionine (CMET), and...
Proliferative Index (PI) help better define PMAs. METHODS: We reviewed our database for patients with a diagnosis of PMA. We report patients’ clinical and neuroradiographic findings (including MRI and PET), pathology (PI), location and outcome. RESULTS: We found 59 patients with a diagnosis of PMA ages 3.6 months to 8 years. Locations were hypothalamic/ suprasellar (n = 3), cervical spine (n = 1), and cerebral medul lary (n = 1). Positron Emission Tomography scans were performed on 6 of 5 patients. Three patients showed FDG hypermetabolism and one showed MET hypermetabolism. The PI was abnormally elevated in all 3 cases. The one patient with progressive disease had both FDG hypermetabolism and an elevated PI. CONCLUSION: Although our cohort is small, our data suggests that in comparison to PAs, PMAs are more metabolically active on PET, have elevated PI as compared to PAs, and are more aggressive neoplasms. Given the current awareness and correct pathologic diagnosis is essential for appropriate therapy. Further molecular and genetic studies will better define this spectrum of astrotomas.

LG-030. GLIAL TUMOURS IN THE POSTERIOR FOSSA Nicole Siew1, Rebecca Hoi1, Ah Moy Tan2, Mei Yoke Chan2, and Shui Yen Soh2,1 Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; 2Haematology/Oncology Service, KK Women’s and Children’s Hospital, Singapore, Singapore

INTRODUCTION: Gliomas are the most common group of primary central nervous system (CNS) tumours of childhood. Around half of these are infratentorial, mostly arising from the cerebellum or brain stem. We perform a retrospective review of posterior fossa gliomas in paediatric patients from KK Women’s and Children’s Hospital (KKH). METHODS: Data were obtained from the Singapore Childhood Cancer Registry (SCCR) and hospital chart records. We included all patients aged 0–19 years with posterior fossa glial tumours diagnosed and treated in KKH between July 1997 and June 2012 (15 years). Information on patient demographics, clinical presentation, treatment and outcome were collected. RESULTS: We identified 49 patients with posterior fossa gliomas. There were 26 (53%) boys. The ethnicity distribution were Chinese (35, 71.4%), Malay (9, 18.4%), and Indian (5, 10.2%). Age at diagnosis ranged from 0.5 to 12.2 years (median 5.8 years). The most common presentations were vomiting (50.0%), headache (48.1%), unsteady gait (48.1%), and cranial nerve palsies (33.3%). All of the 29 cerebellar tumours underwent resection - the histological diagnoses were ependymoma (11/49, 22%), cerebellar pilocytic astrocytoma (17/49, 35%) and cerebellar giant cell glioblastoma (1/49, 2%). There were 17 brainstem gliomas (35%), most of which were not biopsied. All except one of the brainstem gliomas arose from the pons. Histological diagnoses were available for 4 patients with brainstem gliomas - 2 were of WHO grade III/IV; the other 2 were low grade. Another 3 patients (6%) had diffuse or multifocal disease. The 5-year overall survival for patients with brainstem gliomas, posterior fossa ependymoma and cerebellar astrocytoma were 18%, 18% and 89% respectively. CONCLUSIONS: Posterior fossa gliomas are a heterogeneous group of tumours with outcomes dependent on their location and histology. The survival outcome is poor for brainstem gliomas and posterior fossa ependymomas.

LG-031. TUMOR MYOINOSITOL LEVELS PREDICT PROGRESSION FREE SURVIVAL IN PEDIATRIC LOW GRADE GLIOMAS
Eleni Orphanidou-Vlachou1, Rebecca Hoe1, Ah Moy Tan2, Mei Yoke Chan2, and Shui Yen Soh2,1 Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; 2Haematology/Oncology Service, KK Women’s and Children’s Hospital, Singapore, Singapore

BACKGROUND: The majority of brain tumours in children are low grade but they are a source of significant morbidity and mortality. The difficulty of predicting and monitoring response to treatment hampers management and new non-invasive techniques to improve this are required. Metabolites measured by magnetic resonance spectroscopy are markers of survival for children’s brain tumours. Myoinositol is associated with low grade in adult neuroepithelial tumours (DNET), 4 pilomyxoid astrocytomas. High myoinositol (>4.1mmol/l) at diagnosis was associated with better progression free survival at 5 years (95% vs 45%; p = 0.005) with a relative risk of 12. None of the other major metabolites were significantly associated with progression free survival. Overall survival was 90% at 5 years. CONCLUSION: Tumour myoinositol levels at diagnosis are associated with a better progression free survival in children with low grade brain tumours. This metabolite can be readily measured non-invasively using magnetic resonance spectroscopy and should be incorporated into prospective studies to determine its role in managing these patients.

LG-032. PEDIATRIC PATIENTS WITH DIFFUSE ASTROCYTOMAS HAVE A DISTINCT CLINICAL COURSE TO THOSE DIAGNOSED AS ADULTS, WITH EXCELLENT VERY LONG TERM SURVIVAL
Pratiti Randopadhyay, Guillaume Berghold, Nadine Sauer, Adam Green, Hayley Malken, Gabriel Dabscheck, Karen Marcus, Nicole Ullrich, Liliana Goumnerova, Susan Chu, Rameen Beroukhim, Mark Kieran, and Peter Manley; Dana-Farber Cancer Institute, Boston Children’s Hospital and Harvard Medical School, Boston, MA, USA

BACKGROUND: While children with pediatric low-grade glioma have been shown to have excellent overall survival, the long-term outcomes of those with diffuse astrocytoma(DA) has not been thoroughly documented. In particular, it has been unclear as to whether pediatric DAs undergo malignant transformation. We interrogated the outcome data from the SEER database to determine very long-term outcomes of patients diagnosed with DAs.

METHODS: 1,356 patients with a histological diagnosis of diffuse astrocytoma were identified. Of these, 173 patients died of non-tumor related causes. 260 patients were pediatric patients aged less than 19 years of age at diagnosis. Cox proportional hazards regression was performed. Kaplan-Meier curves for overall cancer specific survival were generated. RESULTS: The 30-year cancer specific OS was 26% ± 2%. Pediatric patients had a 30 year overall survival of 76% ± 3% while adult patients had an inferior 30 year overall survival of 13% ± 3 (p value <0.0001). Cox proportional hazards regression analysis revealed that age at diagnosis (p <0.0001), decade of diagnosis (p <0.0001), admistration of radiation (p <0.001) and extent of surgical resection (p <0.0005) were prognostic. While adult patients had ongoing rates of death 20–30 years post diagnosis, likely a reflection of malignant transformation, the rate of death appeared to plateau in the pediatric patients, with a reduction of overall survival of only 7% between 5 and 30 years post diagnosis. CONCLUSIONS: We show that DAs are associated with an excellent overall survival in pediatric patients, in contrast to those patients diagnosed in their adult years. Our data suggests a very low rate of malignant transformation in adult survivors of pediatric DAs. Therapeutic and management strategies for pediatric tumors should therefore aim for disease control during childhood and adolescence with an emphasis on minimizing long-term toxicities.

LG-033. PEDIATRIC BRAINSTEM GANGLIOGLIOMAS SHOW BRAFV600E MUTATION IN A HIGH PERCENTAGE OF CASES
Andrew Donson1, BK Kleinschmidt-DeMasters2, Dara Assner1, Lynne Bemis1, Diane Brinker1, Jean Mulcahy-Levy1, Amy Smith4, Michael Handler2, Sarah Rush1, and Nicholas Foreman1; 1UC Denver, CO, USA; 2University of Minnesota at Duluth, MN, USA; 3Children’s Hospital Colorado, CO, USA; 4University of Minnesota at Duluth, MN, USA; 5Auckland Children’s Hospital, Auckland, New Zealand

Brainstem gangliogliomas (GGs) often cannot be resected, have a much poorer prognosis than those located in more common supratentorial sites, and may benefit from novel therapeutic approaches. Therapeutically-targetable BRAFv600E ¼ (p. V600E) (BRAFV600E) mutations are harboured in roughly 50% of collective GGs taken from all anatomical sites. Large numbers of pediatric brainstem GGs, however, have not been specifically assessed and anatomic- and age-restricted assessment of genetic and biological factors are becoming increasingly important. Pediatric brainstem GGs, however, have not been specifically assessed and anatomic- and age-restricted assessment of genetic and biological factors are becoming increasingly important. Pediatric brainstem GGs, however, have not been specifically assessed and anatomic- and age-restricted assessment of genetic and biological factors are becoming increasingly important. Pediatric brainstem GGs, however, have not been specifically assessed and anatomic- and age-restricted assessment of genetic and biological factors are becoming increasingly important. Pediatric brainstem GGs, however, have not been specifically assessed and anatomic- and age-restricted assessment of genetic and biological factors are becoming increasingly important. Pediatric brainstem GGs, however, have not been specifically assessed and anatomic- and age-restricted assessment of genetic and biological factors are becoming increasingly important. Pediatric brainstem GGs, however, have not been specifically assessed and anatomic- and age-restricted assessment of genetic and biological factors are becoming increasingly important.

METHODS: We reviewed a single institution database of pediatric brainstem GGs identified between 2002 and 2017. Genetic analyses were performed using Ion Torrent PGM sequencing. The PGM system utilizes an Ion S5 sequencer and Ion Sphere particles that are loaded into an Ion PGM sequencer. Sequencing results were validated using Sanger DNA sequencing.

RESULTS: A total of 12 pediatric brainstem GGs were identified. The median age of presentation was 4.7 years (mean 7.2 year range was 0.5 to 14 years) and 7/12 patients were males (58.3%). All specimens were positive for BRAFV600E mutation, with 2 showing co-mutation of K-RAS. The median follow-up was 5.6 years (range 0.5 to 14 years).

CONCLUSION: BRAFV600E mutations are commonly identified in pediatric brainstem GGs, providing a potential for targeted therapy.
approach, yielding a final BRAFV600E mutation frequency of 54% (7/13) in brainstem GGs. BRAFV600E-targeted therapeutics should be a consideration for the high percentage of pediatric brainstem GGs refractory to conventional therapies.

**LG-034. LOW GRADE GLIOMAS TREATED IN A UNIVERSITY-BASED COMBINED NEURO-ONCOLOGY SERVICE IN SOUTH AFRICA**

Alan Davidson1, Anthony Figari2, Komala Pillay3, Tracy Kilborn4, Llewellyn Padayachy2, Marc Hendricks1, Ann van Eyssen1, and NEUROPSYCHOLOGICAL SEQUELAE, CLINICAL OUTCOMES, ENDOCRINOPATHIES, AND Viable and effective strategy for the management of low grade gliomas in PFS of 33%. CONCLUSION: Multidisciplinary team management is a

Estimated 5-year Progression Free survival (PFS) for the whole group was 92.3% for WHO I tumours and 74.2% for WHO II tumours.

**RESULTS:** There were 60 children, aged 0.41 to 13.75 years (median 5.38). Forty six tumours (77%) were WHO grade I, and 14 were WHO grade II, including 7 fibrillary astrocytomas, 4 pilomyxoid astrocytomas and one pleomorphic xanthoastrocytoma. The commonest sites were cerebellum (30%), hypothalamus (20%), cerebrum (15%) and optic tract (12%). Fourteen patients were managed expectantly at diagnosis, including 5 of the 8 with neurocutaneous syndromes. Thirty two patients underwent definitive surgery in the form of debulking or gross total resection, and 11 patients required surgery for recurrence or progression. Fifteen patients (25%) received radiotherapy; 5 at diagnosis, 4 as second line treatment and 6 after surgery for recurrence. Thirteen patients (median age 2.67) were treated with chemotherapy; 11 of them with vincristine and carboplatin and 6 after surgery for recurrence. Thirteen patients (median age 2.67) were treated with chemotherapy; 11 of them with vincristine and carboplatin and as the first line regimen. Ten of these patients had juvenile pilocytic astrocytomas and 3 had pilomyxoid astrocytomas. One progressed, three showed stable disease and nine responded, reducing in volume by 40-93% (median 68%). Estimated 5-year Overall Survival (OS) was 89.2% for the whole group; 92.3% for WHO I tumours and 74.2% for WHO II tumours. Estimated 5-year Progression Free survival (PFS) for the whole group was 53.5%. The patients treated with chemotherapy had an OS of 100% and a PFS of 33%. CONCLUSION: Multidisciplinary team management is a viable and effective strategy for the management of low grade gliomas in low and middle income settings.

**LG-035. PEDIATRIC TECTAL PLATE GLIOMAS: A REVIEW OF CLINICAL OUTCOMES, ENDOCRINOPATHIES, AND NEUROPSYCHOLOGICAL SEQUELAE**

David Gass, Marko Dewire, Lionel Chow, Susan R. Rose, Sarah Lawson, Charles Stevenson, Blaise Jones, Anna Pui, Mary Sutton, David Pruitt, Maryam Fouland, and Trent Hummel; Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

**INTRODUCTION:** Pediatric tectal plate gliomas are indolent slow-growing gliomas that commonly present with symptoms of increased intracranial pressure or incidentally when evaluating other issues with brain or cranial pressure (72%) versus an incidental finding in 7 (28%). Median follow-up was 41 months (Range: 4-143 months). Five of 25 (20%) experienced progressive disease after diagnosis. Additionally, 5 of 25 (20%) required more than one surgical procedure due to failure of initial endoscopic third ventriculostomy. Four of 25 presented with endocrine dysfunction (premature puberty or short stature), which ultimately resolved after cerebral

spinal fluid diversion. Only one of 19 patients evaluated was noted to have endocrine dysfunction after diagnosis. Of 11 with available neuropsychological testing, six had at least some impairment in their neurocognitive function. CONCLUSIONS: Although historically tectal gliomas have been considered indolent tumors that are rarely progressive, 20% of patients in our cohort experienced disease progression and required further therapy. Neurocognitive deficits may occur, while endocrine deficiency is uncommon. Thus, regular multidisciplinary oncology and imaging follow-up, as well as formal neurocognitive evaluation and management are imperative in order to provide early recognition of disease progression or recurrent hydrocephalus and to improve school functioning in this population.

**LG-036. BRAF-KIAA1549 SIGNATURE GUIDED TREATMENT RECOMMENDATIONS IN A PATIENT WITH A HISTOLOGIC DIAGNOSIS OF A GRADE-3 ASTROCYTOMA**

Oléa Cruz, Carmen de Torres, Mariona Sunol, Andres Morales, Candela Santiago, Mariana Alamar, Monica Rebollo, and Laura Mora; Hospital Sant Joan de Déu. University of Barcelona, Esplugues, Barcelona, Spain

**INTRODUCTION:** We report a patient with the histological diagnosis of a posterior fossa high-grade astrocytoma for whom therapeutic management was planned based upon molecular characterization instead of histologic review. PATIENT AND TREATMENT: A 21-month-old boy consulted because of persistent vomiting and delay in the acquisition of neurologic milestones. Magnetic resonance imaging (MRI) showed a left cerebellar tumor. MRI features suggested the diagnosis of pilocytic astrocytoma. He underwent gross total resection and recovered from surgery without sequelae. Histologic review was conclusive of anaplastic astrocytoma, showing a highly cellular tumor with 25% positivity for Ki-67 and negative immunostaining for p53. Given the high-grade histology compatible with a grade-3 astrocytoma, adjuvant chemotherapy was initially suggested. Surprisingly, the tumor expressed the BRAF-KIAA1549 16-9 fusion transcript, a fusion gene associated with pilocytic astrocytoma, hence associated with a more benign biologic behavior and a favorable outcome. The discrepancy between high-grade histology and favorable molecular findings raised a debate regarding the need for adjuvant therapy. Finally, the decision was made to favor the molecular profile and consequently the patient did not receive any adjuvant treatment. Two years from diagnosis, the patient has had a favorable clinical course with normal developmental skills and no evidence of disease recurrence. COMMENTS: Molecular genetic characterization of pediatric brain tumors is improving our knowledge in these diverse diseases. Gene truncated fusions involving BRAF are known features characteristic of pilocytic astrocytomas. This specificity has diagnostic utility and can guide therapeutic decisions in controversial cases.

**LG-037. BRAF MUTATIONS IDENTIFIED IN DISSEMINATED OLIGODENDROGLIAL-LIKE LEPTOMENINGEAL TUMOR OF CHILDHOOD**

Nadine Sauer1, Andrew Dodgshun2, Hayley Malkin1, Guillaume Berghold1, Peter Manley1, Susan Chi1, Shakti Ramkisson1, Duncan MacGregor2, Rameen Beroukhim1, Mark Kieran1, Michael Sullivan2, Keith Ligon1, John Bandopadhyay1, and Jordan Hansford1; Dana Farber Cancer Institute, Boston, MA, USA; 2Royal Children's Hospital, Melbourne, Australia

**BACKGROUND:** Disseminated oligodendroglial-like leptomeningeal tumor (DOLT) of childhood is a recently described group of lesions, not currently classified by the WHO. Their defining features include diffuse leptomeningeal spread, often with a discrete spinal cord nodule, and oligodendroglioma-like pathologic features. To date there have been few published case examples of the molecular pathology of these tumors. We present a retrospective IRB-approved multi-institutional review of the clinical course and frequency of BRAF mutations in DOLT tumors.

**PROCEDURE:** Patients were identified through a pathology database search of all cases with disseminated low-grade neoplasms with an oligodendrogial-like component. De-identified clinical information was collected by chart review and all imaging was reviewed. We retrieved the results of genomic analyses for alterations in BRAF. RESULTS: Eight patients (2-11 years age) were identified from the Dana-Farber/Boston Children’s Hospital and the Royal Children's Hospital, Melbourne pathology databases. Seven patients presented with diffuse leptomeningeal involvement while one patient initially had a temporal lesion that later disseminated. Three patients had an identifiable primary lesion, of which two were located in the spinal cord. Clinical information regarding treatment and follow-up was available on seven patients. Six patients received chemotherapy (86%). All seven patients are alive. BRAF testing was performed in five patients. BRAF duplication was identified in two (40%) and BRAF V600E
LG-038. LOW-GRADE TUMORS ASSOCIATED WITH CORTICAL DYSPLASIA AND FOCAL EPILEPSY: A SURGICAL PEDIATRIC CASE SERIES

Raffaella Alessandri, Alessandro De Benedictis, Andrea Caraci, Angela Mastronuzzi, Erika Rebessi, Paola Palma, Emidio Procaccini, and Carlo Ehsio Marras; Department of Neurosciences, Neurosurgery Unit, Bambino Gesù Children Hospital, Rome, Italy

Among the neoplasms causing intractable epilepsy, a minority of glioneuronal tumors (WHO grade I) can be found in association with malformation of cortical development or within cortical dysplasia. The true incidence of this association is underestimated because not all the epileptogenic lesions underwent epilepsy surgery or the sample collection is sometimes not correct. Six pediatric patients (3M-3F; age range 2-15 years) who underwent surgery for low-grade tumors associated with cortical dysplasia were analyzed. All patients underwent a preoperative study including brain MRI, video EEG and neuropsychological assessment. Follow up ranged from 3 to 24 months. Epilepsy onset ranged from 7 months to 13 years (mean 8.05 mo). Seizure frequency varied from several per day to few per month. In 5 of 6 patients the epileptogenic area including the tumor was localized in the temporal lobe. According to the preoperative study, extension of the resection over tumor edges was planned by the epilepsy surgery team. Histological examination documented ganglioglioma in 3 patients and low-grade astrocytoma in 3 patients. Cortical dysplastic areas adjacent to the tumor and dysplasia were reported in the whole series. All patients were seizure free after surgery (Engel Class I). Our experience suggests that resection of epileptogenic areas surrounding brain tumors allows sometimes to define dysplastic areas and to determine a seizure-free outcome with improved quality of life.

LG-039. CLINICAL RESPONSES OF PATIENTS WITH DIFFUSE LTEOMENINGEAL NEUROEPITHELIAL TUMORS TO CHEMOTHERAPY

Dolly Aguilera1, Robert Craig Castellino1, Anna Janss1, Mathew Schniederjan1, Rene McNall2, Sungjin Kim3, Tobey MacDOnald1, and Claire Mazewski1; 1Children's Health Care of Atlanta, Emory University School of Medicine, Atlanta, GA, USA; 2University of Alberta, Faculty of Medicine Undergraduate Program, Edmonton, AB, Canada; 3Paediatric Haematology/Oncology, London Health Sciences Centre, London, ON, Canada; 4Paediatric Haematology/Oncology, Kingston General Hospital, Kingston, ON, Canada; 5Division of Haematology/Oncology, CHEO, CHB0 Research Institute, Ottawa, ON, Canada; 6Pediatric Oncology Group of Ontario, Toronto, ON, Canada

BACKGROUND: Paediatric Low-grade Gliomas (PLGG) are most frequent paediatric CNS malignancy with excellent 5-year overall survival (OS). Existing data is focused on short-term outcomes due to lack of follow up in adulthood. Several groups have recently reported alterations in RAS/MAPK pathway in majority of PLGGs however their effect on oncologic outcome is unclear. METHODS: Ontario population-based study of PLGG patients treated since 1985. Comprehensive demographic, clinical, treatment, pathological and long-term outcome were collected from Pediatric Oncology Group of Ontario (POGO) and CCO (Cancer Care Ontario) databases. Molecular data was obtained on SickKids patients only. RESULTS: In the Ontario cohort (n = 1199), OS at 5 and 15 years was 96.1±1% and 93.1±1% respectively. No statistical significance in long-term OS was observed for different pathology subtypes (p = 0.5). However excess mortality beyond 10 years was observed for plasmacytoid PLGGs. Long-term survival advantage was observed for patients treated with radiation in the whole cohort. However, patients with thalamic tumors exhibited late deaths with 25% drop in survival from 5 to 25 years post-diagnosis (p = 0.0001; 66% of them were irradiated). Major cause of death was tumor transformation (45.3%) and 30% died of causes unrelated to tumor growth. Tumor progression was the cause of death in 11% of patients, occurring exclusively in 5 years post-diagnosis. Average time to death was significantly longer for transforma-
tions, 6.2 years (0.5-22.2 years), secondary malignancies, 15.1 years (9.8-23 years) (p < 0.0001) and death from other causes, 7.7 years (0.2-21.5 years) (p < 0.05). Fifteen years OS for BRAF-fusion positive and negative non-completely resected PLGG (n = 175) was 89.9±4.5% and 63.7±8.02% respectively (p = 0.0048). CONCLUSIONS: Long term outcome for children with PLGG is excellent. Tumor progression is rarely a cause of death and effect of radiation treatment on long-term outcome in PLGG needs further investigation. BRAF-fusion can be a positive predictor of very long-term survival.

LG-040. CLINICAL AND MOLECULAR DETERMINANTS OF LONG-TERM SURVIVAL IN CHILDREN WITH LOW GRADE GLIOMA: A POPULATION BASED STUDY

Natalie A Zhukova1, Jason Pollock2, Matthew Mason1, Iris Fried1, Rahul Krishnathry1, Ana Guerreiro Stucklin1, Ute Bartels1, Anne Huang1, Normand Lapierre2, Peter Dirks2, Shayna Zelcer2, Mariana Sylva10, Donna Johnston11, Katrin Scheinemann1, Jason An12, Cynthia Hawkins1, Paul Nath1, Mark Greenberg1, Eric Boulfet1, David Maller1, Uri Tabori1; 1Div. of Hematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada; 2Div. of Neurosurgery, The Hospital for Sick Children, Toronto, ON, Canada; 3Div. of Pathology, The Hospital for Sick Children, Toronto, ON, Canada; 4Neurosurgery, The Hospital for Sick Children, Toronto, ON, Canada; 5Radiation Medicine Centre, The Hospital for Sick Children, Toronto, ON, Canada; 6Hadasah Medical Centre, Jerusalem, Israel; 7Radiation Medicine Program, Princess Margaret Hospital, Toronto, ON, Canada; 8Division of Haematology/Oncology, McMaster Children’s Hospital, Hamilton, ON, Canada; 9University of Alberta, Faculty of Medicine Undergraduate Program, Edmonton, AB, Canada; 10Paediatric Haematology/Oncology, London Health Sciences Centre, London, ON, Canada; 11Paediatric Haematology/Oncology, Kingston General Hospital, Kingston, ON, Canada; 12Division of Haematology/Oncology, CHEO, CHB0 Research Institute, Ottawa, ON, Canada

INTRODUCTION: Intrinsic tectal gliomas are a distinct subgroup of brainstem gliomas often associated with an indolent disease course and favorable prognosis following treatment for hydrocephalus. However, a m-

ority of these lesions may progress and require treatment. We sought to identify patient and radiographic variables which may impact the rate of growth and progression of these tumors over time. PATIENTS & METHODS: An IRB approved retrospective review identified 24 consecutive children diagnosed with tectal lesions over the past 10 years at CHLA. All underwent routine serial magnetic resonance imaging (MRI). Patient, tumor, and treatment related factors including MRI and MR spectroscopy were reviewed. RESULTS: A total of 24 consecutive children were followed or died for MRI findings of 19 tumors. The average age at diagnosis was 10 years (range 1.8-20 years). There were 14 females and 10 males. Median follow-up was 6.6 years. Four patients had neurofibromatosis and were diagnosed asymptomatic on routine MRI. The remaining 20 patients presented with hydrocephalus and were treated with a shunt (n = 1) or endoscopic third ventriculostomy (n = 19, successful in 14 patients). Twelve tumors exhibited growth over time, including all patients with enhancing tumor (n = 7). Four patients more than doubled
their tumor volume (range 2.5-9.5 years after diagnosis). Of these, two patients had serial MR spectroscopy indicating rising choline peaks which led to treatment with irradiation (60 Gy); following radiation their tumors stabilized and the volume declined. The other two patients had stable MR spectroscopy despite progressive growth and their tumors ultimately stabilized without intervention. CONCLUSIONS: Significant disease progression is rare with tectal gliomas. The addition of MR spectroscopy to routine serial MR imaging may be useful for early identification of tumor progression. Irradiation is a durable and effective treatment for stabilizing tectal tumors that progress.

LG-042. EFFICACY OF BEVACIZUMAB AND IRINOTECAN IN CHILDREN WITH PROGRESSIVE LOW GRADE GLIOMAS
Kanyalakshmi Ayyanar1, Thomas Moriarty2, Karen Moeller2, and Darren Farber1; 1University of Louisville, Louisville, KY, USA; 2Norton Hospital, Louisville, KY, USA

We report a series of 4 children with progressive or refractory Low grade glioma, who were treated with Bevacizumab and Irinotecan. All 4 patients gliomas responded to therapy, and 1 patient is alive 2 years after therapy without tumor progression. 2 patients did not have NF-1 and had hypothalamic/optic pathway tumor. Patient #3, diagnosed at 6 months of age, completed several courses of chemotherapy including Vincristine, carboplatin and Temozolamide, TPCV and eventually was treated with Bevacizumab (10mg/kg) and Irinotecan every 2 weeks for 2 years. She was treated with Bevacizumab every 3 weeks. She is surviving without tumor progression for 2 years now. Patient # 4, diagnosed at 8 years of age, treated with Vincristine, carboplatin and Temozolamide. She developed tumor progression about 1 year later. She was given Bevacizumab (10mg/kg) and Irinotecan every 2 weeks, for about 8 months, then Bevacizumab was given every 3 weeks and her treatment was stopped after 16 months, per parents request with stable tumor on Imaging. Her tumor progressed 4 months later when she received radiation therapy. She then developed radiation necrosis and is receiving Bevacizumab only currently.