tiple lines of therapy. To identify clinical and biologic factors associated with tumor progression, we retrospectively identified 72 unresectable non-NF1-associated hypothalamic/optic pathway PA. Tumors were classified as high-risk (50%) if they progressed after three or more lines of chemotherapy/targeted therapy, progressed after radiation, developed metastatic disease, or died of disease. DNA methylation profiling and transcriptome analysis (RNA sequencing) were performed on treatment-naïve tumors with available tissue (n=40), and the findings were validated by immunohistochemistry (IHC) on additional tumor tissue. The median follow-up of the entire cohort was 12.3 years. High-risk tumors were associated with male sex (M:F = 2.6:1), younger age at diagnosis (median 3.2 years vs. 6.7 years, P = 0.005), and high incidence of KIAA1549-BRAF fusion (81.5% vs. 38.5%, P = 0.0032). High-risk tumors demonstrated decreased CpG methylation and increased RNA expression in many mitochondrial genes and genes downstream of E2F and NKX2.3 transcription factors. Transcriptome analysis identified transcription factor TBX3 and proto-oncogene serine/threonine protein kinase PIM1 as common downstream targets of both E2F and NKX2.3 and potential drivers of tumor progression. IHC confirmed increased expression of TBX3 and PIM1 in high-risk tumors. PIM1 is known to increase the stability and transcriptional activity of MYC, and gene enrichment analysis identified enrichment of MYC targets. Signaling pathways known to be implicated in PA, such as MAPK and PI3K/AKT/mTOR, were also enriched, in addition to pathways related to mitochondrial biogenesis and oxidative phosphorylation. Our results support the model in which the p53-PIM1-MYC axis and TBX3 act alongside MAPK and PI3K/AKT/mTOR pathways to promote tumor progression, highlighting potential new targets for combination therapy and refining disease prognosis.

LGG-14. LOGGIC (LOW GRADE GLIOMA IN CHILDREN) CORE BIOCLINICAL DATA BANK: ESTABLISHMENT AND ADDED CLINICAL VALUE OF AN INTERNATIONAL MOLECULAR DIAGNOSTIC REGISTRY FOR PEDIATRIC LOW-GRADE GLIOMA PATIENTS

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BACKGROUND: The international, multicenter registry LOGGIC Core BioClinical Data Bank aims to enhance the understanding of tumor biology in pediatric low-grade glioma (pLGG) and provide clinical and molecular data. In addition to routine histopathological and molecular analyses, LOGGIC Core determines the driver alteration as precisely as possible to support treatment decisions and participation in interventional trials. Hence, the question arises whether comprehensive implementation of RNA sequencing using Fresh Frozen (FF) tumor tissue to identify underlying gene fusions improves diagnostic accuracy and provides a clinical benefit. METHODS: Establishment of an international molecular and clinical registry including the logistical and analytical pipeline. First analysis of all patients age 0 to 18, which were included in Germany as part of the German HIT-LOGGIC-program between April 2019 and February 2021, and for whom FF tissue was available. This included histopathological evaluation, immunohistochemistry, 850k methylation analysis, gene panel sequencing, RNA sequencing using FF tissue. RESULTS: FF tissue was available in 178/379 included cases. RNA sequencing was performed on 125 samples. In this prospective, population based cohort, we confirmed KIAA1549:BRAF-fusion (57%), BRAFV600E-mutation (9%) and FGFR1-changes (10%) as most frequent alterations. 12% of cases presented rare gene fusions (e.g. TPM3:NTRK1, EWSR1:VGLL1, GOPC:ROS1, SH3PXD2A:HTRA1, PDGFB:LRP1). In 19% of cases, RNA sequencing detected an actionable target not identified by conventional methods. CONCLUSION: The addition of RNA sequencing reveals clinically relevant alterations including rare gene fusions. By demonstrating improvement of diagnostic accuracy and making precision oncology studies (MEKi/RAFi/ERKi/NTRKi/FGFRi/ROSi) more accessible, the added value for pLGG patients becomes apparent. LOGGIC Core is currently being rolled out internationally and aims to define the new state of the art standard molecular diagnostics. We propose to include RNA sequencing as part of routine diagnostic procedures for all pLGG patients, especially in tumors where no common MAPK alteration was identified.

LGG-15. LATE MORTALITY AND MORBIDITY OF ADULT SURVIVORS OF CHILDHOOD GLIOMA TREATED ACROSS THREE DECADES: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY

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PURPOSE: Pediatric low-grade glioma therapy has evolved to delay or eliminate radiation. The impact of therapy changes on long-term outcomes remains unknown. METHODS: Cumulative incidence of late mortality (death >5 years from diagnosis), subsequent neoplasms (SNs), and chronic health conditions (CHCs, CTCAE grading criteria) were evaluated in the Childhood Cancer Survivor Study among 5-year survivors of glioma diagnosed 1970-1999. Outcomes were evaluated by diagnosis decade and by treatment exposures received ≤5 years following diagnosis (surgery-only, chemotherapy ± surgery, and cranial radiation ± surgery or chemotherapy). Relative risk (RRs) with 95%CIs estimated long-term outcomes using multivariable piecewise exponential models. RESULTS: Among 2,684 eligible survivors (age at diagnosis (median [range]), 7 years [0-20 years]; time from diagnosis, 24 years [5-48 years]), exposure to cranial radiation decreased [51% (1970s), 45% (1980s), 25% (1990s)] along with late tumor recurrence (>5 & ≤15 years from diagnosis) [9.8% (1970s), 8.8% (1980s), 5.0% (1990s)]. The 15-year cumulative incidence of late mortality was 10.3% (1970s), 6.5% (1980s), and 6.0% (1990s) (p<0.001, comparison of cumulative incidence curves). The 15-year cumulative incidence of grade 3-5 CHCs was 19.7% (1970s), 17.8% (1980s), and 14.2% (1990s) (p<0.0001). A reduction in SN incidence was not observed. In multivariable analyses excluding treatment exposure, later diagnosis (1990s vs. 1970s) was associated with lower risk of late mortality, grade 3-5 CHCs and SNs. Inclusion of treatment exposure in the model attenuated the effect of diagnosis decade. Radiation or chemotherapy exposure increased risk compared to surgery alone for late mortality (radiation RR 4.95, 95%CI 3.79-6.47; chemotherapy RR 2.88, 95%CI 1.85-4.48), CHCs (radiation RR 4.02, 95%CI 3.28-4.94; chemotherapy RR 1.66, 95%CI 1.13-2.45), and SNs (radiation RR 4.02, 95%CI 3.06-6.13, chemotherapy RR 2.08, 95%CI 1.03-4.23)). CONCLUSION: Late mortality and CHCs decreased in childhood glioma survivors diagnosed from 1970-1999 largely due to therapy changes, particularly avoidance of cranial radiation, without increased late recurrence.