LGG-50. HUMAN INDUCED PLURIPOTENT STEM CELL ENGINEERING ESTABLISHES A HUMANIZED MOUSE PLATFORM FOR PEDIATRIC LOW-GRADE GLIOMA MODELING

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A major obstacle to identifying improved treatments for pediatric low-grade brain tumors (gliomas) is the inability to reproducibly generate human xenografts. To surmount this barrier, we leveraged human induced pluripotent stem cell (hiPSC) engineering to generate low-grade glioma (LGG) lesions representing the two most common pediatric pilocytic astrocytoma-associated molecular alterations, *NF1* loss and *KIAA1549:BRAF* fusion. Using hiPSCs, we identified the susceptible cells of origin for these tumors, and demonstrated that the resulting tumors retain LGG histologic features for at least 6 months in vivo. Finally, this platform enabled the successful long-term growth of patient-derived pLGGs *in vivo*. Taken together, these avatars establish tractable experimental humanized platforms to elucidate the pathogenesis of childhood brain tumors.

LGG-51. RESECTION EXTENT AND BRAF V600E MUTATION STATUS DETERMINE POSTOPERATIVE GROWTH VELOCITY IN PEDIATRIC LOW-GRADE GLIOMA: RESULTS FROM A SINGLE-CENTER COHORT ANALYSIS

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Despite the favourable outcome and excellent long-term overall survival rates, pediatric LGG show vast variety of clinical behavior and limited predictability regarding progress or senescence. We comparatively analyzed the tumor growth velocity (TGV) of PLGG post subtotal resection (STR) to investigate the impact of surgery, histological subtype, tumor location and the most frequent BRAF aberrations (BRAF V600E mutation vs KIAA1549-BRAF fusion) on tumor growth rates, aiming to identify potential variables to prognosticate further progress or senescence. A total of 53 patients vs 94 patients in the pre- and postoperative cohort, respectively, could be observed over a mean follow-up time of 40.2 vs 60.1 months. Distribution of histopathological diagnosis and tumor sites showed similarity to previously published cohort studies. Comparative analysis of pre- and postoperative TGV showed a significant difference as mean preoperative TGV accounted for 0.264 cm^3/mo, while postoperative TGV after 1st, 2nd and 3rd STR showed reduction to 0.085 cm^3/mo, 0.024 cm^3/mo and -0.016 cm^3/mo, respectively ($p < 0.001$). Results remained significant after excluding patients who had obtained (neo)adjuvant treatment. Resection extent showed remarkable correlation with postoperative reduction of TGV ($R = 0.97$, $P < 0.001$). Comparison of postoperative TGV of BRAF V600E mutant LGG and BRAF wild-type LGG showed significant difference of means (0.123 cm^3/mo and 0.016 cm^3/mo, $p = 0.47$), consistent to previous analyses, suggesting BRAF V600E positive LGG as a high-risk subgroup. Histological type, tumor location and BRAF-KIAA1549 fusion showed no significant impact on postoperative TGV. The results suggest that surgery, beyond cytoreductive purpose, impacts PLGG kinetics post STR by inducing a significant deceleration of tumor growth. As postoperative growth velocity showed clear correlation to resection extent and residual tumor burden, surgery, as radical as possible while preserving neurological function, appears to remain the mainstay of therapy besides advancing therapeutic approaches.

LGG-52. VOLUMETRY-BASED RESPONSE CHARACTERIZATION OF RECURRENT PEDIATRIC LOW-GRADE GLIOMAS IN PNOC CLINICAL NEURO-ONCOLOGY TRIALS

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BACKGROUND: Endpoints in clinical trials using novel treatments are evaluated by RANO criteria, which provide an estimate of tumor size from two-dimensional measurements along the most prominent axial slice. However, pediatric low-grade gliomas (pLGG) commonly have variegated shapes with solid and cystic components, potentially resulting in misevaluation of true tumor volume and thus, ultimately, trial outcome. OBJECTIVES: We aim to characterize treatment response through volumetric assessment of progressive/recurrent pLGGs treated with single-agent everolimus on PNOC001 clinical trial. We seek to identify clinically relevant criteria that provide added value to response assessment beyond 2D measurements. METHODS: In a cohort of 44 patients we performed 3D-segmentation of solid, cystic and whole tumor within our PACS-framework and compared results to previously carried-out central imaging review by RANO criteria which had yielded 15 PD, 27 SD, 2 PR and 0 CR. RESULTS: 8 tumors were solid only and 36 had a mixed solid-cystic appearance. When evaluating the entire tumor (i.e. solid and cystic components combined) and using the same RANO cutoff criteria, one case changed from PR to SD, one changed from SD to PR, 3 changed from SD to PD, and 7 changed from PD to SD, resulting in an overall discordance of 27% of cases. CONCLUSION: We propose that incorporation of volumetrics into response assessment provides additional and potentially more accurate information beyond RANO-based measurements. It is crucial to note that the above-reported changes represent numerical discrepancies as opposed to true-to-reality changes in clinical outcome. Determining representative thresholds for the deployment of volumetric measures in clinical trials will be critical. Future work will include data from the PNOC002 clinical trial and evaluate inter-reader agreement and reader discordance. With the availability of PACS-based 3D-tools in neuroradiology practice, well-defined volumetric criteria could be incorporated prospectively into treatment response analysis in clinical trials.

LGG-53. EVALUATION OF KIAA-BRAF1549 FUSIONS IN PILOCYTIC ASTROCYTOMA WITH CLINICOPATHOLOGICAL CORRELATION

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BACKGROUND: Pilocytic astrocytomas (PAs) are the primary tumors most frequently found in children and adolescents, accounting for 5.4% of all gliomas. The overall prognosis of PAs is good, yet a substantial no of cases have a poor outcome, with recurrence, and ultimately death. The KIAA1549-BRAF fusion is a useful putative diagnostic marker for PAs and BRAF also is an important therapeutic marker. AIM AND OBJECTIVES: To study the frequency of KIAA1549-BRAF fusion (16-9, 15-9 and 16-11) in different locations of PAs using qRT-PCR technique in FFPE samples. METHODOLOGY: Three different exon rearrangements of KIAA1549-BRAF (16-9, 15-9 and 16-11) fusions were assessed in 50 cases of PAs by using qRT-PCR (gold standard). FISH assay was also performed in all the cases. RESULTS: Out of 50 PAs, 32 were localised in midline structures such as the cerebellum, optic pathway, hypothalamus, and brain stem while 18 in non-midline regions like the cerebral hemispheres. Majority of the cases (35/50); 70% were positive for KIAA1549-BRAF fusion by RT-PCR. Of these, (16/35); 45.7% harboured 15-9 fusion, (15/35); 42.8% harboured 16-9 fusion, and only (4/35); 11.4% had 16-11 fusion. Only (24/30); 48% KIAA1549-BRAF showed fusion by FISH assay. There was 54.2% concordance between FISH and RT-PCR results. KIAA1549-BRAF fusion was observed in 78% of midline and 55.5% of non-midline cases. The frequency of KIAA1549-BRAF fusion decreased with increasing age, 77% in the age group <20, 54% in the age group 20-40 and 30% in the age group >40. CONCLUSION: 15-9 and 16-9 KIAA1549-BRAF were the most frequently occurring fusions dominantly seen in the midline. The presence of fusion is inversely proportional to the age of patients. qRT-PCR is the gold standard technique and FISH assay has moderate concordance with qRT-PCR platform.