experience relapses, with no established standard of care. Their rarity limits knowledge of their outcomes and associations with location, metastatic status, impact of surgery, serum, and cerebrospinal fluid (CSF) biomarkers, to only a few smaller trials and case series.This international multi-institutional retrospective study for relapsed/refractory germinomas and NGGCTs, will evaluate the association between different treatment modalities and 5-year OS and EFS; patterns of relapse, including along biopsy tracts; and potentially identify predictors of recurrence. De-identified patient data at primary and relapse time points will be collected focusing on treatment approaches such as surgery, conventional/high dose chemotherapy, photon/proton radiation therapy; timing and site of relapse; imaging characteristics and serum/CSF biomarkers (BHCG/AFP). Our collaborators include multiple sites across North America, Australia, Europe, Africa, South America, the Middle east, India, Singapore, and Malaysia. 6 recurrent intracranial germinomas on the CBTN (Children's Brain Tumor Consortium) database were assessed, demonstrating a male gender preponderance (4) and recurring in the suprasellar region (3), frontal lobe (2) and spinal cord (1). 2 underwent gross total resection while 1 had biopsy only. Conventional or high-dose chemotherapy was administered in 5, while 2 received craniospinal and 1 proton radiation. 4 patients are alive. Median OS was 738 days and EFS 1093 days. However, biomarker (AFP/BHCG) data was unavailable. Updated results will be presented at the conference. With global partnership and contribution, we anticipate this study to help bridge existing gaps in our knowledge of this rare patient cohort and establish a consensus standard of care, through prospective clinical trials in the future. We acknowledge the CBTN for kindly providing data access.

GCT-21. LONG-TERM OUTCOME AND FOLLOW UP OF INTRACRANIAL GERM CELL TUMORS: REDUCED-DOSE RADIOTHERAPY AND INTENSIFIED CHEMOTHERAPY IMPROVES CLINICAL OUTCOME AND QUALITY OF LIFE FOR LONG-TERM SURVIVORS

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BACKGROUND: Intracranial germ cell tumors (iGCT) are heterogeneous tumors with several histopathology. Chemoradiotherapy is effective and required for treatment against them, but optimal treatment intensity should be selected from the viewpoint of both improvement of clinical outcome and avoidance of late complications. We introduced a protocol with reduced-dose radiotherapy and intensified chemotherapy for iGCT. OBJECTIVE: We retrospectively analysed the clinical outcome, especially for non-germinomatous germ cell tumors and long-term clinical outcome of late complications, enrollment and employment, as indicators of quality of life (QOL). MATERIALS AND METHODS: Thirty-eight children and young adults (28 men and 10 women) with iGCTs treated in our institution from 1997 to 2013 were enrolled in this study. They consisted of 26 germinomas including HCG-producing cases and 12 non-germinomatous GCTs (NGGCT). Local irradiation was selected for all patients, and the dose of irradiation was 23.4-54 Gy. The whole-brain irradiation was made in patients who had intracranial dissemination, but any prophylactic irradiation to the whole brain and spinal cord was not performed. For NGGCT, high-dose chemotherapy and peripheral blood stem cell transplantation (PBSCT) were introduced. Second-look surgeries were performed for cases with residual tumors after induction chemotherapies. RESULTS: In germinoma group and NGGCT group, 10-year progression-free survival was 86% and 84%, 10-year overall survival was 93% and 91%, respectively. About late complications, endocrinological replacement (39%), cerebrovascular disease such as cavernous hemangioma and arterial stenosis (18%), secondary neoplasm (2.6%) were observed. Regarding QOL, enrollment and return to school rate was 92% and employment and the return rate was 89%, which were influenced by hemipararesis associated with basal ganglia lesion, intractable epilepsy and whole-brain irradiation. CONCLUSION: Reduced-dose radiotherapy and intensified chemotherapy for iGCT, especially NGGCT, improved the clinical outcome and QOL of long-term survivors, suppressing late complications. Further comprehensive follow-up and analysis are needed.

GCT-22. OUTCOMES OF CHILDREN WITH LOCALIZED AND METASTATIC GERMINOMA TREATED WITH CHEMOTHERAPY FOLLOWED BY RADIATION THERAPY WITHOUT PRIMARY TUMOR BOOST

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BACKGROUND: Response-based radiation therapy has been the approach for germinoma after chemotherapy. However, the presence of residual lesions at the end of chemotherapy did not demonstrate a negative impact on progression-free survival (PFS). Similarly, resection of residual tumors after chemotherapy did not show a survival benefit. AIM: Our study objective was to determine long-term outcomes of a cohort who received chemotherapy and radiation therapy without primary tumor boost even in the absence of complete response to chemotherapy. METHOD: This retrospective study analyzed the outcome of germinoma patients diagnosed and treated at a tertiary care center from January 2006 to December 2021. RESULTS: Twenty-nine children (14 male; median age 12.8 years) were identified. Median follow-up was 63 months (range 9-187 months). Twenty children had localized disease and tumor location was suprasellar (n= 9), pineal (n= 10), and bifocal (n= 1) while 9 children had metastatic disease at presentation. All patients completed multi-agent chemotherapy followed by either whole ventricular (WVI) (23.4 Gy) (n = 23), whole brain (WBI) (23.4 Gy) (n = 5) or craniospinal radiation (CSI) (23.4 Gy) (n= 1). Two children, who had localized disease at presentation and received WVI after chemotherapy, relapsed 9 months and 32 months after completion of treatment respectively. None of them had local relapses. Location of relapse was distant, outside (n= 1) and inside (n= 1) the radiation field. Five-year PFS was 93% and overall survival (OS) was 100%. CONCLUSION: In this limited experience, excellent 5-year PFS and OS rates were achieved with chemotherapy followed by radiation therapy delivered without primary tumor boost. This study also demonstrated the absence of local relapse despite omitting primary tumor boost in patients with localized and metastatic germinoma.

HIGH GRADE GLIOMA

HGG-01. A NOVEL GENETICALLY ENGINEERED H3.3G34R MODEL REVEALS COOPERATION WITH ATRX LOSS IN UPREGULATION OF PRC2 TARGET GENES AND PROMOTION OF THE NOTCH PATHWAY

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BACKGROUND: Pediatric high-grade gliomas (pHGGs) are an aggressive CNS tumor which are often characterized by mutations in *H3F3A*, the gene that encodes Histone H3.3 (H3.3). A substitution of the Glycine at position 34 of H3.3 with either Arginine or Valine (H3.3G34R/V), was recently described in a large cohort of pHGG samples and has been characterized as occurring in anywhere between 5-20% of pHGGs. Attempts to study the mechanisms of H3.3G34R have proven difficult due to the developmental nature of the disease and the requirement of co-occurring mutations for model development. METHODS: We utilized the RCAS system to develop a genetically engineered mouse model (GEMM) that incorporates PDGF-A activation, TP53 loss and the H3.3G34R mutation both in the context of ATRX loss and ATRX presence in nestin expressing progenitors. RESULTS: We show that in H3.3G34R expressing mice, ATRX loss significantly increased tumor latency from 90 days to 143 days ($p < 0.01$, Log rank test) and decreased tumor incidence from 81% to 57% ($p < 0.01$, Fisher's exact test). By contrast, H3.3G34R did not significantly impact tumor latency in either our ATRX loss (163 days to 143 days, $p = 0.178$, Log-rank test) or our ATRX expressing (95 days to 90 days, $p = 0.415$, Log-rank test) models. Transcriptomic analysis revealed that ATRX loss in the context of H3.3G34R upregulates the PRC2 associated genes *Hoxa2*, *Hoxa3*, *Hoxa5*, and *Hoxa7* ($p < 0.05$, unpaired t-test). GSEA analysis and RT-qPCR data suggest that ATRX loss works synergistically with H3.3G34R to promote NOTCH pathway activation through upregulation of the NOTCH ligand *Dll3* ($p < 0.01$, unpaired t-test). CONCLUSIONS: Our study proposes a model in which ATRX loss is the major contributor to transcriptomic changes in the majority of H3.3G34R pHGGs. Broadly, our work highlights the importance of studying mechanisms of co-occurring genetic events separately and in combination.

HGG-02. EPIGENETIC TRANSCRIPTION REGULATION AND 3D GENOME STRUCTURE IN PEDIATRIC HIGH-GRADE GLIOMA

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INTRODUCTION: Pediatric high-grade gliomas (pHGGs), including glioblastoma multiforme (GBM) and diffuse intrinsic pontine glioma (DIPG), are highly morbid brain tumors. Up to 80% of DIPGs harbor a somatic missense mutation in genes encoding Histone H3. To investigate whether the H3K27M mutant protein is associated with distinct chromatin structure affecting transcription regulation, we generated the first high-resolution Hi-C and ATAC-Seq maps of pHGG cell lines, and integrated these with tissue and cell genomic data. METHODS: We generated sequencing data from patient-derived cell lines (DIPG n=6, GBM n=3, normal n=2) and frozen tissue specimens (DIPG n=1, normal brainstem n=1). Analyses included cell line