cember 2009, 11 recurrent/refractory patients (10 MMGCT, 1 germinoma; 10 males; mean age 16.5 years, range 7–46 years) have been treated with up to four cycles of gemcitabine (800mg/M2), paclitaxel (170mg/M2) and oxaliplatin (100mg/M2) administered on one day at 14 days intervals. RESULTS: All 11 patients were enrolled on a prospective multicenter trial, which was closed in October 2019. Three patients achieved complete remissions (tumor marker and/or imaging studies), five achieved partial remissions, two developed disease progression (PD), and one was withdrawn after one cycle for severe paclitaxel neurotoxicity followed by rapid tumor progression and death. One patient with PD after one cycle had pathologically-confirmed metastatic transformation to pure embryonal rhabdomyosarcoma, and rapidly expired. A second patient, with pure pineal choriocarcinoma, progressed after the second GemPOx cycle, ultimately died of tumor progression. Eight of the 11 responsive patients subsequently underwent HDCx+AuHPCR; five of these received some form of radiotherapy. Seven patients (six MMGCT, one germinoma) are alive and disease-free without recurrence for a mean of 94 months (range 74–118 months) since completion of therapy. CONCLUSION: GemPOx is an effective re-induction regimen for patient with recurrent CNS germ cell tumors, with acceptable toxicities; when followed by marrow-ablative chemotherapy and subsequent irradiation/re-irradiation, the regimen produces encouraging long-term disease-free survival.

GCT-67. CENTRAL NERVOUS SYSTEM GERMINOMA IN TWO CAUCASIAN AMERICAN SIBLINGS WITH AUTISM SPECTRUM DISORDER

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BACKGROUND: Central nervous system germ cell tumors (CNS-GCT) account for approximately 5% of all pediatric brain tumors. These tumors are pathologically heterogeneous, but have recurrent somatic mutations in KIT and rare germline variants in a Japanese cohort. Chromosomal abnormalities, specifically Klinefelter Syndrome, are associated with increased tumor development and familial cases have been reported, but no germline tumor syndromes are known. We describe a pair of siblings, both with autism spectrum disorder (ASD) that developed CNS-GCT, which previously has not been described outside of Japan. CASES: We report two siblings with ASD who developed CNS germinomas within two months of each other. The older brother, with basal ganglia and hypothalamic tumors, underwent surgical resection followed by treatment per ACNS0232 with chemotherapy and whole-ventricular irradiation (WVI). The younger sibling, with a midbrain tumor, also received ACNS0232, but due to poor response required additional chemotherapy and WVI. Both siblings are without evidence of disease 7 years after end of therapy. Genetic testing, including chromosomal microarray, karyotyping, and whole genome sequencing did not elucidate any variant identified as causative at that time. CONCLUSIONS: CNS-GCT are rare tumors, diverse in both histopathologic diagnosis and clinical outcomes. Currently there are known somatic alterations and germline chromosomal disorders associated with increased tumor development, but no known inheritable causes. Despite this, familial CNS-GCT have been reported in patients of Japanese descent. The description of two Caucasian American siblings with ASD and CNS-GCT is novel, refuting that familial CNS-GCT are limited to the Japanese population.

GCT-69. VOLUMETRIC CHANGE BEFORE CHEMORADIOTHERAPY AND INFLUENCE OF DIAGNOSTIC RADIATION EXPOSURE IN INTRACRANIAL GERMINOMAS

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BACKGROUND: Spontaneous regression in intracranial germ cell tumors has been reported in some literatures, but the mechanism has not been well known. We retrospectively measured the tumor volume before chemoradiotherapy and analyzed factors that influence reduction of tumor volume. PATIENTS AND METHODS: Plural MRI scans were done before the first course of chemotherapy regimen in 27 patients with primary intracranial germinomas. Their age ranged from 8 to 31 years. 35 lesions from them were enrolled and included 13 pineal, 4 neurohypophyseal, 4 basal ganglia, 4 bifocal type, and 2 multiple lesions. All regions were verified as pure germinoma or HCG-producing germinoma by histopathological examination. Tumor volume of 35 lesions was analyzed by volumetric assessment based on MRI. Ratio of volumetric change between the first MRI and the scan immediately before chemotherapy was defined as shrinking rate (%). Period between disease onset and the first chemotherapy was 20 to 47 days. Diagnostic radiation dose was calculated in each case. RESULTS: Initial tumor volume ranged from 0.962 to 72.356 cubic centimeters (mean: 8.27). Diagnostic radiation dose: 40.5 to 910.1 mGy. Shrinking rate ranged from -57.8 to 85.4% (mean: 30.8). In 10 regions, shrinking rate was within 30%. Shrinking rate was significant positively influenced by diagnostic radiation dose ($p<0.05$) and negatively influenced by initial volume ($p<0.05$). But, other factors such as age, sex, histopathological parameters did not influence tumor shrinkage. CONCLUSION: This study shows that the volume of intracranial germ cell tumors is changing dynamically before chemoradiotherapy in many cases. Diagnostic exposure to low-dose radiation influences tumor shrinkage of intracranial germinomas.

GCT-70. INTRACRANIAL GROWING TERATOMA SYNDROME IN CHILDREN

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Germ cell tumors account for less than 5% of all intracranial malignancies in children. Intracranial growing teratoma syndrome (GTS) is a rare pathophysiologic process characterized by growth of mature teratoma elements of a non-germinomatous germ cell tumor (NGGCT) during or following treatment with chemotherapy, in addition to normalization of or declining AFP/βHCG of the cerebral spinal fluid (CSF)/serum. A 13-year-old male presented with headache, emesis, and diplopia. MRI of the brain/spine revealed a localized 3.1 x 3.1 x 3.2 cm pineal tumor. Biopsy confirmed NGGCT (germinoma, immature and mature teratoma). Serum AFP (227ng/ul) and βHCG (12 IU/L) and CSF AFP (21ng/ul) and βHCG (31 IU/L) were elevated. Prior to cycle two of chemotherapy, he developed unstable gait and moderate hearing loss. Repeat MRI brain demonstrated tumor enlargement (4.4 x 5.2 x 5.1 cm) and obstructive hydrocephalus, although serum AFP/βHCG had normalized. Gross total resection of tumor confirmed GTS, without residual immature/malignant elements. Following six cycles of multiagent chemotherapy (carboplatin, etoposide, ifosfamide) and proton beam craniospinal irradiation (36 Gy with 18 Gy boost), he remains free of disease at eleven months since diagnosis. The pathogenesis of GTS remains unclear. Care must be taken to avoid misdiagnosing GTS as progressive NGGCT, as treatment and prognosis differ significantly. Second-look surgery, with a goal of complete resection, should be considered in cases of NGGCT when residual tumor grows during or following therapy, as this may represent GTS. Although histologically benign, GTS can be fatal. In patients with GTS, complete resection is usually curative.

GCT-71. SIOP STRATEGY TREATMENT FOR CENTRAL NERVOUS SYSTEM GERM CELL TUMORS IN A MIDDLE INCOME COUNTRY

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BACKGROUND/OBJECTIVES: Central nervous system (CNS) germ cell tumors (GCTs) represent 3% of primary paediatric brain tumours in occident. They can be divided into major groups including germinomas and nongerminomatous GCTs (NGGCTs). The aim is to describe demographic characteristics, Event Free Survival (EFS) and Overall Survival (OS) in patients with GCTs treated at Oncology Unit of Garrahan Hospital (HG). DESIGN/METHODS: Retrospective analysis of patients with GCTs admitted between September 1st,2000 to September 1st,2019. Variables analysed: age, localization, treatment, relapse and death. Patients were treated per SIOP-CNSGCTs protocol. For statically analysis SPSS (IBM), for EFS/OS Kaplan-Meyer, Long-rank for significance. RESULTS: Fifty-seven patients were included, comprising 38 Germinomas and 19 NGGCTS. Median age was 146 months (range 11–228). Primary site in localized Germinomas were pineal (16p), suprasellar (7p) and bifocal (7p). Five-year EFS and OS of 100% and 88.5%, respectively. Four patients presented metastatic disease, with an EFS and OS of 60.9% and 66.6%. Tumor site in localized NGGCT were pineal(8p) and suprasellar(5p). Five-year EFS was 81.8% and OS was 80.2%. No patients presented metastatic disease. All patients with high-risk tumor markers at diagnosis relapsed. No significative differences were found in OS neither EFS between groups (Germinomas OS5y 90% vs NGGCTs 74.6%p=0.19[CI95%0.0786–1.689]), (Germinomas EFS5y 78.9% vs NGGCTs5y 81.8%p=0.85[CI95%0.3046–4.230). Global OS and EFS5y was 83% and 72.9%. CONCLUSION: OS of our cohort is lower than what has been shown in current literature. This result may be related to the lack of resources and lower social economic status in our population.

GCT-72. ANALYSIS OF MICRORNA EXPRESSION PROFILE OF INTRACRANIAL GERM CELL TUMORS: A PROMISING TOOL FOR DIFFERENTIAL DIAGNOSIS

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INTRODUCTION: One of the major limitations of pathological diagnosis for intracranial germ cell tumors (iGCTs) is tumor heterogeneity, which cannot be evaluated using limited amount of tumor tissues. In this study, we performed comprehensive analysis of microRNA (miRNA) of iGCTs to identify miRNAs profile to help determine tumor diagnosis. METHODS: RNA was extracted from frozen samples of 16 germinoma and 14 NGGCTs. Five non-iGCT pediatric brain tumor tissues were used as control. miRNA expression analysis was performed using a 3D-Gene Human miRNA Oligo Chip ver.22 (Toray Industries, Inc) which was designed to detect 2565 miRNAs. The miRNA expression profile was analyzed using t-SNE dimensionality reduction and weighted average difference method (WAD). RESULTS: Different histological subtypes of the iGCTs and control samples were clustered into distinct classes. Furthermore, we found that the germinoma, NGGCTs and control samples may be readily distinguished by expression patterns of miR-200 and miR-371a-3p: a high expression of miR-200 was observed in the NGGCTs, whereas a high expression of miR-371a-3p was observed in all cases of germinoma and some of NGGCTs. Neither of miR-200 nor miR371-3p was highly expressed in control samples. CONCLUSION: Our data indicated that germ cell tumor and other pediatric brain tumors, and also germinoma and NGGCT can be distinguished by expression patterns of 2 micro RNA, miR-200 and miR-371a-3p. These 2 microRNA may serve as a useful tool for supporting the pathological diagnosis of iGCTs.

GCT-73. EXPRESSION PROFILING OF INTRACRANIAL GERM CELL TUMORS REVEALS UPREGULATION OF RAS THROUGH MRNA-MICRORNA SIGNALING PATHWAY

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Intracranial germ cell tumors (IGCTs) account for 3% of CNS tumors in children in the U.S. and 11% in Japan and East Asian countries. IGCTs are separated into two distinct subtypes based on histology: germinomas and non-germinomatous germ cell tumors (NGGCTs). The deep central location of IGCTs makes surgical resection and therefore molecular subtype classification difficult, and previous gene expression studies are limited. We performed mRNA expression profiling (Human Genome U133 Plus 2.0) and microRNA expression profiling (ABI TaqMan) with 36 and 49 IGCTs, respectively. Sample stratification using non-negative matrix factorization clustering of gene expression revealed two distinct subgroups that delineated germinomas from NGGCTs. Employing stepwise model building in each data set separately, we were able to separate these groups using only mRNA probes for the LIN28B and L1TD1 genes, and two microRNA, microRNA-26a and microRNA-373. MicroRNA26a suppresses the LIN28B gene and is down-regulated in germinoma. LIN28B directly binds and suppresses the let-7 microRNA family, which suppress the KRAS oncogene, previously found to be mutated in ~19% of IGCTs. L1TD1 is required for human stem cell renewal and directly interacts with LIN28B for its RNA binding function. LIN28B and L1TD1 are both known to be upregulated in other systemic germ cell tumors, but this has not yet been documented in IGCTs. In conclusion, these results show that intracranial germinomas have similar gene expression compared to systemic seminoma, and suggest a mechanism by which activation of LIN28B and L1TD1 downregulates the let-7 microRNA and subsequently upregulates KRAS.

GCT-74. RETROSPECTIVE LITERATURE REVIEW OF CENTRAL NERVOUS SYSTEM (CNS) GERM CELL TUMORS (GCTS) IN PATIENTS WITH DOWN SYNDROME (DS)

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BACKGROUND: A standard-of-care has not been established for the management of DS patients who develop primary CNS GCTs – the most common CNS neoplasm in DS – despite being more susceptible to treatment-related adverse events. METHODS: A review of the English-language medical literature between 1960 and 2020 was conducted. RESULTS: Thirty-one cases of CNS GCTs in DS patients (median nine-years-old; 21 males) were reported; the majority (23/31) originated from East Asia. Twelve had germinomas (39%), 12 had non-germinomatous germ cell tumors (NGGCTs) (39%), and seven had teratomas (22%). Four patients (13%) died from tumor progression (one germinoma *versus* three teratoma). Seven patients (23%) died from treatment-related complications (four germinoma *versus* three NGGCT). Of the germinoma patients, two died from chemotherapy-related sepsis, one from post-surgery cardiopulmonary failure, and one from Moyamoya following radiation-therapy (RT) only. Of the NGGCT patients, one died from chemotherapy-related sepsis, one from post-surgical infection, and one from pneumonia following surgery/chemotherapy/RT. Three-year overall survival (OS) was 58.1% for all patients, 52.5% for germinoma, 64.8% for NGGCT, and 60% for teratoma. Three-year OS for patients who received RT or chemotherapy was 63.6% and 59.6% respectively. Twenty patients (65%) remain alive (seven germinoma *versus* nine NGCCT *versus* four teratoma). Ten patients (32%) experienced serious treatment-related complications (five germinoma *versus* five NGGCT). CONCLUSIONS: Patients with DS and CNS GCTs are at an increased risk of treatment-related complications. Therefore, a different therapeutic approach may need to be considered for this patient population in order to mitigate the treatment-related complications and long-term neurocognitive sequelae.

GCT-75. ISOLATED PITUITARY STALK THICKENING

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OBJECTIVES: Only few studies have examined the predictive factors and outcome of isolated pituitary stalk thickening (PST) in children. We aim to describe our institutional cohort to determine predictors of future malignancy. METHODS: A search of the radiology, endocrinology and neuro-oncology databases was performed to identify patients with isolated PST diagnosed between January 2000 and June 2019. Clinical data was collected. A detailed radiology review of baseline and follow up magnetic resonance imaging (MRI) was undertaken in a blinded fashion by two examiners. RESULTS: Forty-four patients were identified, with 37 meeting criteria for isolated PST and adequate imaging. Median age of baseline MRI was 9.9 years (range 0.9–17.5). Twenty-three were female (62%). Median follow up time was 5 (0.31–18.6) years. Indication for MRI was symptoms of diabetes insipidus (DI) in 28 patients with the remainder having other concerns for endocrine disturbance (7), headache (1) or visual impairment (1). Thirty-five subjects had pituitary dysfunction (95%), including 30 with diabetes insipidus (81%). Nine patients developed a malignancy (24%), with germinoma (5), Langerhans cell histiocytosis (3) and lymphoma (1) at a median of 0.36 years, 0.63 years and 1.1 years respectively. Elevated white blood cell count (>5 x 10^6/L) in initial cerebrospinal fluid analysis was predictive of future diagnosis of germinoma or lymphoma (p=0.027). CONCLUSION: In this cohort 24% of children with PST were eventually diagnosed with a neoplasia after a median of 0.63 years. Pleocytosis in initial CSF samples was predictive for future development of germinoma or lymphoma.

GCT-76. 24GY WHOLE VENTRICULAR RADIOTHERAPY ALONE IS SUFFICIENT FOR DISEASE CONTROL IN LOCALISED GERMINOMA IN CR AFTER INITIAL CHEMOTHERAPY – EARLY RESULTS OF THE SIOP CNS GCT II STUDY

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