ical sites (p=0.03). A molecular-clinical association study revealed frequent MAPK pathway mutations in males (51.4 vs 14.3 %, p=0.007), and PI3K/mTOR pathway mutations in basal ganglia cases (p=0.004). Basal ganglia cases also had frequent chromosomal losses. Some chromosomal aberrations (2q, 8q gain, 5q, 9p/q, 13q, 15q loss) showed potential prognostic significance. CONCLUSIONS: These in-depth findings of this study regarding the clinical and molecular heterogeneity will increase our understanding of the pathogenesis of this enigmatic tumor.

GCT-16. LONG-TERM CLINICAL OUTCOMES OF GERM CELL TUMORS

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BACKGROUND: Intracranial germ cell tumors (GCT) are mainly arising in adolescent term and treated with chemotherapy concomitant with radiation therapy. There is accumulating evidence that the progress of treatment. Besides, long-term outcome and adverse effects are major problem in treatment. So, we must grasp the influence of these outcomes on daily and social life. Then we investigated in clinical outcome in cases of GCT treated in our institution. METHOD: We reviewed the clinical features and outcomes of 52 cases of intracranial GCT in 1975 to 2019. Ages on diagnosis are 5–35 years old (median 14 years old), consisted with 44 male cases. The pathological distributions are these: pure germinoma: 40 cases, non-germinomatous germ cell tumor (NGGCT): 10 cases (mature teratoma: 4, mixed germ cell tumors: 3, and one cases of choriocarcinoma, embryonal carcinoma, yolk sac tumor), unidentified pathology: 2 cases. Almost all cases have biopsied and treated by chemotherapy and radiation therapy. RESULTS: Chemotherapy with ICE regimen (ifosphamide, cisplatin, etoposide) or CARE regimen (carboplatin, etoposide) concomitant with radiation therapy (mainly, extended local irradiation) have done in almost cases by the era. Clinical outcomes are relatively well in our cases, but 10 cases experienced recurrence. 3 cases have dead. Some cases with suprasellar involvement have need hormone replacement in long term. There are 10 cases at work. CONCLUSION: Almost cases have gained better outcome and ADL. But there is slightly lower rate in work or marriage. Serial evaluation in outcome, and higher brain functions should be performed in follow up.

GCT-17. WHAT IS THE CLINICAL OUTCOME OF PROTON BEAM THERAPY FOR PATIENTS WITH INTRACRANIAL GERM CELL TUMOR IN KOREA?

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PURPOSE: To evaluate the clinical outcome of patients with intracranial germ cell tumor treated with proton beam therapy (PBT). MATERIALS AND METHODS: Fifty-seven patients with intracranial germ cell tumor treated with PBT between 2009 and 2016 were retrospectively analyzed. RESULTS: Median follow-up duration was 63.7 months (range, 5.6–204.5). Thirty-seven patients (64.9%) were pure germinoma and 20 patients (35.1%) were non-germinomatous germ cell tumor (NGGCT). All patients except 2 patients received chemotherapy before PBT. Twenty-one patients (36.8%) of localized germinoma were treated with whole ventricle irradiation (WVI), while 36 (63.2%) patients who were diagnosed as disseminated germinoma or NGGCT received cranio-spinal irradiation (CSI). Two patients with pure germinoma in basal ganglia showed disease relapse at 3.0 and 6.9 years after PBT at the primary site and pituitary gland, respectively. There was one patient with NGGCT who died of chemotherapy-related mortality at 4.7 years after PBT while her disease was complete remission. The 7-year progression-free survival and overall survival were 70.8% and 100% for focal germinoma, 100% and 100% for disseminated germinoma, 100% and 100% for focal NGGCTs, and 100% and 80.0% for disseminated NGGCTs, respectively. CONCLUSIONS: PBT of pure germinoma resulted in comparable clinical outcomes to that with photon radiotherapy. Our result for NGGCT is also excellent compared to other reports. Failure patterns of germ cell tumors originating in basal ganglia needs to be assessed in large pooled data.

GCT-18. CLINICAL FEATURES OF GERM CELL TUMORS IN CHILDREN

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INTRODUCTION: Here, we discuss the presentation, histology, therapy, and outcome of germ cell tumors in children. METHODS: Treatment outcome and management was assessed for children diagnosed with germ cell tumors from 2007 to 2017 at Kagoshima University. RESULTS: Twenty-six patients (20 boys, 6 girls) with a mean age of 11.5 ± 4.9 years were included in this study. Patient tumor types included: germinoma (n = 19); immature teratoma (n = 3); yolk sac tumor (n = 3); choriocarcinoma (n = 1); embryonal carcinoma (n = 1). The most common patient clinical features were headache and vomiting associated with hydrocephalus. The median follow-up period was 96.5 months. Tumor location was pineal (n=9), bifocal (n=6), suprasellar (n = 5), basal ganglia (n=2), frontal lobe (n=2), and cerebellum (n=2). Surgical procedures included stereotactic biopsy (n=13), endoscopic third ventriculostomy and biopsy (n=8), and tumor decompression (n=5). All patients with germ cell tumors underwent adjuvant chemotherapy and radiation therapy; patients with germinoma or immature teratoma were still alive, while patients with embryonal carcinoma, yolk sac tumor, or choriocarcinoma had poor prognosis with a median survival of 16 months. CONCLUSIONS: Patients with germinoma had a relatively good prognosis, while patients with embryonal carcinoma, yolk sac tumor, or choriocarcinoma had a poor prognosis. A multidisciplinary approach including surgical strategy based on location, appropriate radiation planning, and chemotherapy is needed for effective treatment and improved outcomes.

GCT-19. MODELING GERM CELL TUMORS WITH KIT MUTANT HIPSCS

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Central Nervous System Germ Cell Tumor (CNS GCT) is the second most common pediatric brain tumor in Japan, and within CNS GCT, germinoma is the most common subtype, accounting for 62.3%. Recent reports of transcriptome and methylome analysis suggested that germinoma highly resemble the state of gonocytes, the germ cells at around 5th to 7th week of human embryo development. It is also identified that 60% of germinoma harbored somatic mutations in *KIT/RAS* pathway. As the protocol to derive gonocytes from human iPSCs have been reported, we aimed to recapitulate tumorigenesis by generating human iPSCs bearing common genetic mutations and derive gonocytes from them. We first introduced the most common mutation *KITD816V* to human iPSCs using CRISPR/Cas9, and confirmed in iPSCs that mutated KIT was phosphorylated in the absence of ligand stimulation, and also found that KIT activation contribute to the phosphorylation of AKT but not of ERK. Upon differentiation towards primordial germ cell -like cells (PGCLCs), KIT mutant lines were efficiently induced into PGCLCs, however, by comparing conditions with or without KIT ligand (SCF), mutant lines exhibited less dependency to SCF compared to wildtype cells. Mutant cells were further differentiated to gonocytes following published protocol and the cells were collected for transcriptome analysis. By comparing with the transcriptome of germinoma, we confirmed that germinoma samples express germ cell genes similar to gonocytes. We are attempting to identify the molecular mechanism of tumorigenesis in relation to KIT activation using this system.

GCT-20. EVALUATION OF NEURORADIOLOGICAL RESPONSE TO INDUCTION CHEMOTHERAPY FOR PATIENTS WITH LOCALISED GERMINOMA IN THE SIOP CNS GCT II TRIAL

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INTRODUCTION: The SIOP-CNS-GCT-96 trial demonstrated excellent survival for patients with germinoma. Localised patients received either craniospinal irradiation (CSI) 24Gy plus tumour-bed-boost 16 Gy or 2xcarboPEI chemotherapy (carboplatin/etoposide alternating with etoposide/ifosfamide) and focal-radiotherapy 40 Gy. Following trial closure, whole-ventricular-irradiation (WVI) was delivered with focal-radiotherapy to avoid ventricular relapse. Accordingly, current research priorities focus on reducing treatment burden and long-term neurocognitive sequelae. METHODS: SIOP-CNS-GCT-II employed national central radiological review to assess whether dropping the 16Gy boost was safe for localized germinoma in complete-remission (CR) following 2xcarboPEI: i.e. no disease on clinical/marker/radiological assessment. Any abnormal

thickening/enhancement after chemotherapy was to be classified as partial-remission (PR). Patients with less than CR after chemotherapy received a boost. RESULTS: Shortly before trial closure (2018), it was noted that national CR rates were discrepant across the largest recruiting countries. For German patients, CR rates were ~80%, compared with ~30–40% for UK and France. A formal neuroradiology review was therefore convened. A total of 59 cases were randomly selected (UK, n=32; France, n=14 and Germany, n=13), including those deemed to be in CR and PR. Cases included those with disease at pituitary, pineal and bifocal sites. Both diagnostic scan and scan after induction chemotherapy were used for assessment. Detailed analysis is ongoing and will be presented. CONCLUSION: Residual changes at both pituitary and pineal sites of uncertain significance may remain after chemotherapy. This process should facilitate consensus to define the best response criteria allowing treatment reduction for CNS germinoma for future clinical trials.

GCT-21. CENTRAL NERVOUS SYSTEM GERMINOMA - PONDERING THE NEXT STEPS

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Central nervous system germinoma (CNS) represents one successful example where the introduction of chemotherapy into the treatment allowed significant and meaningful reductions in the volume and dose of radiation therapy while maintaining excellent outcomes. However, the long-term toxicities and morbidities of the current therapies, in addition to their substantial negative impact on the social wellbeing of germinoma patients, should clearly indicate that the current achievements are not enough. While stepwise cutback of the radiation therapy needs to be commended, real progress must be achieved in the exploration and investigation of biological and molecular markers. Furthermore, the differences that still exist between the several working groups around the globe in determining the tumor marker cut-offs that help diagnose these tumors illustrate their shortcomings, and therefore the need for newer and more reliable methods. Additionally, efforts should focus on the inclusion of metastatic and basal ganglia/thalamic germinomas in future prospective clinical trials given the lack of evidence on the best treatment strategy for these patients. A comprehensive review of all major CNS germinoma clinical trials will be presented aiming to lay a foundation for researchers and clinicians alike who are currently working on designing innovative approaches for this group of patients. This review also details the current issues of debate, and provides suggestions which may assist in the design of future prospective clinical trials for children with CNS germinomas.

GCT-22. PROTEIN DEUBIQUITINATION PATHWAY IS A NOVEL THERAPEUTIC TARGET AGAINST MALIGNANT NON-GERMINOMATOUS CNS GERM CELL TUMORS

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Central nervous system germ cell tumors (CNSGCTs) are rare intracranial neoplasm usually developed in adolescents and young adults. However, in East Asia including Japan, incidence of CNSGCTs is considerably higher compare with other regions of the world. Whereas germinomas generally respond to chemo-radiotherapy well, malignant subtypes of non-germinomatous germ cell tumors (NGGCT) are refractory, and development of novel therapy against NGGCTs is urgently needed. To develop a new therapeutic strategy against aggressive NGGCTs, we have investigated novel molecular targets for NGGCT treatment. We screened a total of 120 CNSGCT tumor tissues (including 55 NGGCT), which were registered to the Intracranial Germ Cell Tumor Consortium (iGCT), and discovered multiple mutations of a molecule that regulates protein ubiquitination and degradation specifically in NGGCT cases (5 of 55 cases; 1 immature teratoma, 3 mixed gem cell tumors, and 1 embryonal carcinoma). An in vitro ubiquitination assay revealed the mutations of this molecule discovered in NGGCT cases were loss of function mutations. Reduced expression of this molecule by knockdown in an established human seminoma cell line Tcam2 or a human yolk sac tumor cell line YST1, which was recently established in our institute, resulted in enhanced proliferation as well as upregulation of MEK-ERK activation. Importantly, treatment of these two GCT cell lines with reduced expression of this molecule by MEK inhibitor trametinib suppressed augmented proliferation of these cells. Taken together, these results suggest that protein ubiquitination-related pathways as well as MEK-ERK cascade may serve as a novel therapeutic target against NGGCTs.

GCT-23. MULTI-INSTITUTIONAL ANALYSIS OF TREATMENT MODALITIES IN BASAL GANGLIA AND THALAMIC GERMINOMA

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BACKGROUND: Central nervous system (CNS) germinomas are radiotherapy (RT)-sensitive tumors with excellent survival. Current treatment strategies combine chemotherapy with RT to reduce the field and dose of RT. There is no standard treatment for germinomas originating in the basal ganglia/thalami (BGTG) given their rarity and poorly-defined imaging characteristics. Craniospinal (CSI), whole brain (WBI), whole ventricle (WVI), and focal RT have been previously utilized; however, the optimal strategy remains unclear. METHODS: Retrospective multi-institutional analysis was conducted across 18 institutions in four countries. RESULTS: For 46 cases with non-metastatic BGTG, the event-free survival (EFS) was 86.9% at both 5 and 10 years, while overall survival (OS) was 100%, and 95.7% respectively at 5 and 10 years. Median RT dose and range for the various treatment volumes were as follows: CSI (n=10): 2340 cGy (1980–3060 cGy), WBI (n=8): 2340 (1800–3000 cGy), WVI (n=14): 2340 cGy (1800–2550 cGy), focal (n=9): 3600 cGy (3060–5400 cGy). There was no statistically significant difference in the EFS based on RT modality (p=0.57), but EFS for subjects with CSI and WBI were both 100%. The three subjects who received chemotherapy alone had significantly lower EFS than those who received chemotherapy and RT (p=0.001), but were salvageable with RT. CONCLUSION: In the largest study to date for BGTG, there were no significant differences in outcomes between patients who received CSI, WBI, WVI or focal RT. This group of patients should be included in future prospective clinical trials, and a more limited RT field may be considered.

GCT-24. RELAPSE PATTERN AND QUALITY OF LIFE IN PATIENTS WITH LOCALIZED GERMINOMA ORIGINATING FROM BASAL GANGLIA REGION

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BACKGROUND: The optimal radiation field in localized basal ganglia (BG) germinoma was not well defined, mostly due to unknown relapse patterns. In our institute, both focal radiotherapy (FR) and craniospinal irradiation (CSI) plus boost were considered in this population until whole-brain radiotherapy (WBRT) plus boost became an option in 2008. Thus, a retrospective study was conducted to address the issue. Furthermore, the health-related quality of life (HRQOL) was also evaluated. METHODS: Patients who were diagnosed as localized BG germinoma between 2000 and 2017 were studied. HRQOL was evaluated by PedsQL 4.0 (≤15 years) and SF-36 (>15 years) questionnaires based on the age at last follow-up. RESULTS: Among 161 patients included, 35 patients received FR, 109 patients