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BACKGROUND: Primary central nervous system(CNS) choriocarcinoma(CC) is very rare and has the poorest prognosis among germ cell tumor (GCT). CC usually has extremely high level (HL) of serum beta-human chorionic gonadotropin (bhCG) over than 1,000 mIU/ml. Some studies assign HL bhCG cases to poor prognosis group even without biopsy. The purpose of this study was to find out if there was a good prognosis subset in the HL bh group. MATERIALS AND METHODS: We analyzed 103 cases diagnosed with GCT from 1998 to 2019 in Hokkaido University Hospital and reviewed the literature of CNS CC and bhCG. Survival was assessed using Kaplan-Meier method and log-rank statistics between the group with CC component and that with no CC component but HL bhCG. RESULTS: One out of 103 our cases was diagnosed as a mixed GCT with CC component and did not respond to treatment and died 9 months later. Two cases were treated as CC because of HL bhCG (1,226 and 2,739 mIU/ml) despite that the biopsy showed only germinomas and survived(105 and 37 months), that is, no CC component. Combining our cases with 69 cases in the literature, all 7 cases with no CC component but HL bhCG survived but the median survival of the other 65 cases with CC component was 38.2 months (P=0.02). CONCLUSION: This study has a limitation of selection bias, however, it suggests that patients with no CC component but HL bhCG may have a better prognosis.

GCT-12. INTRACRANIAL GROWING TERATOMA SYNDROME: CLINICAL IMPLICATION FROM SINGLE UNIVERSITY EXPERIENCES

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In general, intracranial germ cell tumors (GCT) are sensitive to chemotherapy, radiation therapy, and have favorable outcomes. However, a rare chemotherapeutic retro conversion phenomenon, known as intracranial growing teratoma syndrome (iGTS), shown a poorer prognosis. We analyze the diagnostic characteristics and the result of treatment response for the patients with iGTS treated in our institutes (SNUH and SNUBH, from 1997 to 2019). The electronic medical records and PACS were used for reviewing the clinical information, follow-up MRI images, tumor markers (alpha-fetoprotein, human chorionic gonadotropin, in serum or cerebrospinal fluids), and pathological findings. Out of 328 intracranial GCT patients, seventeen were finally identified as iGTS. Sixteen out of 17 patients were non-germinomatous GCTs, and 1 were germinomas. Initial pathology was common in order of immature teratoma (26.7%), other than immature teratoma (11.5%), and germinoma (0.5%). All of the tumors showed typical 'honeycomb appearance' in their follow-up MRI images. Sixteen out of 17 tumors were surgically resected as 2nd look surgery. Among them, 13 tumors were gross totally resected. Twelve were alive without evidence of recurrences during follow-up periods, and the other was dead from the progression of the disease. Among the other than the gross total resection group (n=4), two patients were dead, one recurred the tumor, and the other is following up with stable disease after adjuvant radiation therapy. Early detection and total resection of the tumor as possible might be meaningful for favor prognosis, especially in non-germinomatous GCTs patients.

GCT-13. THE TREATMENT OUTCOMES OF INTRACRANIAL GERM CELL TUMORS WITH KSPNO PROTOCOL: SINGLE CENTER RETROSPECTIVE ANALYSIS

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Dho et al. (BTRT, 2017) reported that 1.1% (127/11,827) of primary brain tumors are intracranial germ cell tumors (iGCT) in Korea. We analyzed the epidemiology and treatment results of germ cell tumors in our institution. From 2004 to 2019, among 6494 patients with intracranial neoplasms the 61 (0.9%) patients with iGCTs were enrolled: histologically diagnosed in 50 patients and clinically in 11 respectively. Pediatric patients underwent treatment according to the KSPNO protocol, and adult patients were treated with bleomycin, etoposide, and cisplatin regimens. The median age was 20 years (range: 1–42) and the follow-up period was 7.7 months (range: 10.0–203.4 months), respectively. The tumors arise most frequently in the pineal area (n=30, 49.2%). There were no significant differences in outcomes between protocols, but in KSPNO protocol group showed lower tumor recurrence rate (11.5% vs. 20%, p=0.494) and mortality (0% vs. 5.2%, p=0.503). According to the pathological subtype, the outcomes showed statistically significant differences between germinoma and non-germinomatous germ cell tumor (NGGCT) groups. The 10-year progression-free survival was 93.2% and 67.1% in the germinoma and the NGGCT group, respectively (p=0.009). The NGGCT pathological type (p=0.021) was a significant recurrence associated factor in multivariate analysis. Significant adverse events (CTCAE version 5.0 grade≥3) were showed in 14 patients (7 patients in both KSPNO and other treatment protocol groups). Pure germinoma has a higher survival rate and a lower recurrence rate than NGGCT. And KSPNO protocol might be safe and effective. For appropriate treatment for iGTCs, a multidisciplinary approach might be needed.

GCT-14. SECOND-LOOK SURGERY FOR INTRACRANIAL GERM CELL TUMORS

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OBJECTIVE: The authors present their experiences of second-look surgery in patients with intracranial GCTs who showed less than complete response despite normalizing or decreasing tumor markers after chemotherapy. METHODS: Retrospective review of 14 patients who underwent second-look surgery for an intracranial GCT was performed. RESULTS: Of 40 consecutive patients with newly diagnosed intracranial GCTs treated between August 2003 and 2019, 14 patients (35%) underwent second-look surgery. The mean age was 9.2 years. The initial diagnoses were mixed germ cell tumor in 6, immature teratoma in 4, yolk sac tumor in 2, and germinoma 2. Second-look surgery was performed after 1–3 courses of chemotherapy. Magnetic resonance imaging (MRI) at the surgery demonstrated increasing residual tumor in 8 and stable residual tumor in 6. Tumor markers were normalized in 10 and nearly-normalized in 4. Gross total resection was achieved in 12 patients and near-total resection in 2. Histopatholgy at second-look surgery revealed mature teratoma in 6, immature teratoma in 3, fibrosis with atypical cells in 2, and fibrosis in 3. Eleven patients subsequently underwent additional chemo-radiation therapy according to the initial diagnosis. All patients are alive with no evidence of recurrence with a mean follow-up of 69 months. CONCLUSIONS: Second-look surgery plays an important role in the treatment of intracranial GCTs. Surgery may be encouraged at a relatively early phase after chemotherapy when the residual tumor increases or does not change the size despite normalized or nearly-normalized tumor markers in order to achieve complete resection and improve the outcome.

GCT-15. INTEGRATED CLINICAL, HISTOPATHOLOGICAL, AND MOLECULAR DATA ANALYSIS OF 190 CENTRAL NERVOUS SYSTEM GERM CELL TUMORS FROM THE IGCT CONSORTIUM

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BACKGROUND: We integrated clinical, histopathological, and molecular data of central nervous system germ cell tumors to provide insights into their management. METHODS: Data from the Intracranial Germ Cell Tumor Genome Analysis Consortium were reviewed. A total of 190 cases were classified as primary GCTs based on central pathological reviews. RESULTS: All but one of the cases that were bifocal (neurohypophysis and pineal glands) and cases with multiple lesions including neurohypophysis or pineal gland were germinomas (34 of 35). Age was significantly higher in patients with germinoma than other histologies. Comparison between tumor marker and histopathological diagnoses showed that 18.2% of histopathologically diagnosed germinomas were marker-positive and 6.1% of non-germinomatous GCTs were marker-negative, suggesting a limitation in the utility of markers or histopathology alone using small specimens for diagnosis. Comparison between local and central histopathological diagnoses revealed a discordance of 12.7%. Discordance was significantly less frequent in biopsy cases, implying difficulty in detecting all histopathological components of heterogeneous GCTs. Germinomas at the typical sites (neurohypophysis or pineal gland) showed a better PFS than those at atyp-

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