Neuro-Oncology 16:i30–i39, 2014.
doi:10.1093/neuonc/nou070

NEURO-ONCOLOGY

Abstracts

GERM CELL TUMOURS

GC-001. TREATMENT OUTCOME FOR GERM CELL TUMOR (GCT) BRAIN: EXPERIENCE FROM A SINGLE CENTRE

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BACKGROUND: Radiation treatment of GCT brain, in particular germinomas which are highly radio-sensitive,over the years has evolved from the cranio-spinal irradiation(CSI) to more conformal treatment like whole ventricle radiation followed by tumor bed boost (WV + TB), without compromising the results. We report our experience of treatment outcome of patients treated consecutively over a period of more than ten years with both the methods. METHOD: Twelve consecutive patients registered and treated in radiotherapy department between 2000 and 2013 after surgery (biopsy/decompression) and chemotherapy, were analysed in December 2013. Total Number (Histo-pathology) 12 (Germinoma- 9, Non-Germinoma-2, No histology-1); Median age (Years) 13 (Range 5-24 years); Gender-M/F (%) 10:2(83:17); Co-morbidities None; Pre-Surgery KPS >90 (92%); Surgery (n) Biopsy/Decompression ± VP shunt (11), No Surgery (1); Sub-site Pineal- 7(58%), Supra-sellar-5(42%). TREATMENT: Ten patients received 3D-CRT, while two received IMRT. Three received CSI while nine received WV + TB. CSI dose ranged from 23.4 Gy - 36 Gy in 13-20 fractions. For WV the intended dose was 36Gy/20 fractions followed by 9Gy/5 fractions to TB. Pre-radiation all received combination chemotherapy, cisplatin or carboplatin ± etoposide ± irinotecan. RESULTS: All the patients tolerated and completed treatment with no serious adverse effects. Follow-up was done with serial tumor markers, hormonal, visual, auditory assessment and MRI. Two patients,both non-germinomas treated with CSI progressed and died with-in one year of treatment. Ten patients (9-germinomas, 1-no histology) till date are doing fine,without any loco-regional or distant failures. Ten year overall survival is around 80%.Two patients have developed hormonal imbalance and are on treatment,while one of them developed progressive bilateral optic atrophy which was present prior to radiotherapy. CONCLUSION:Our results are comparable with the reported literature.The overall survival in Germinomas is 100%,Treatment related effects are minimal as a result of reduced dose and limited treatment volume,-contributing possibly to better outcome along with various other reasons.

GC-002. ATYPICAL LOCATION AND CLINICAL BEHAVIOR OF A SUBSET OF INTRACRANIAL GERM CELL TUMORS IN CHILDREN YOUNGER THAN 3 YEARS OF AGE

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BACKGROUND: Intracranial germ cell tumor (ICGCT) represents 3-15% of pediatric brain tumors. According to the current WHO classification, ICGCTs are classified as germinomas and non-germinomatous germ cell tumors. Germinomas are exquisitely radiosensitive, and chemo-radiotherapy is equally effective. Non-germinomatous germ cell tumors, though more aggressive than germinomas, can be treated effectively with intensive chemo-radiotherapy. ICGCTs in infants and very young children are typically mature teratomas which have excellent outcome after gross total resection. ICGCTs excluding mature teratomas, in this young age group, are extremely rare. There is also no published series or reported incidence of ICGCTs which excludes mature teratomas in children younger than 3 years of age. METHODS AND MATERIALS: We describe a series of 15 ICGCTs excluding mature teratomas in children younger than 3 years of age from 3 international institutions over 20 years and PubMed Search. RESULTS: These tumors, with possible in-utero origins, often occur in atypical locations. The clinical behavior differed significantly from their counterparts in older children. In this young age group, germinoma is highly aggressive while non-germinomatous germ cell tumors may be cured without radiotherapy. Ongoing genomic studies with whole exome sequencing reveal insights to our understanding of its tumor biology. We have also successfully created an orthotopic mouse xenograft model of metastatic germinoma from one of the patients in reported this series. CONCLUSIONS: New treatment strategies are needed to improve outcome for ICGCT in this age group, particularly for germinoma. The creation of the pediatric metastatic germinoma mouse model on the patient in our series will facilitate preclinical drug testing in our search for effective chemotherapeutic and biologic agents against this aggressive subset of tumors.

GC-003. WHOLE EXOME SEQUENCING IDENTIFIED GENES INVOLVED IN THE MAPK AND PI3K PATHWAYS AS THE MAIN TARGETS FOR MUTATIONS IN INTRACRANIAL GERM CELL TUMORS

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Intracranial germ cell tumors (iGCTs) are one of the most common brain tumors in East Asia, particularly in Japan. Unlike many other pediatric brain tumors, the biology of iGCTs is largely unknown. We performed whole exome sequencing in a large series of iGCTs to elucidate their molecular pathogenesis. A total of 133 iGCTs (69 pure germinomas, 56 NGGCTs and 8 metastatic tumors) were collected from 13 centers participating in the Intracranial Germ Cell Tumor Consortium in Japan. Somatic mutations in all coding exons were investigated by whole exome sequencing (WES) in 41 tumors and the matched normal DNAs. Based on the WES data, 41 candidate genes were selected according to the frequency and/or significance of the mutations found, and sequenced using the IonTorrent system in a further 89 iGCTs. On average, 15.4 non-synonymous somatic mutations were observed in each tumor, ranging from 1 to 140 by WES in 41 iGCTs. The combined WES and IonTorrent screenings showed that KIT was the most frequently mutated gene (27%), followed by RAS (KRAS/ HRAS/ NRAS, 13%). Altogether, genes involved in the MAPK pathway were mutated in 46% of tumors. MTOR (7%) was the second most frequently mutated single gene. Collectively, the genes involved in the PI3K/MTOR pathway (e.g., MTOR, PTEN) were mutated in 13% of iGCTs. Mutations were generally mutually exclusive to each other within each pathway. These alterations were significantly more common among pure germinomas than NGGCTs. The mutated MTOR protein was shown to have increased kinase activity, which was suppressed by specific MTOR inhibitors. Thus, a comprehensive analysis of iGCTs revealed that alterations of the MAPK and PI3K pathways play a critical role in the development of iGCTs. Our findings will hopefully help developing a targeted therapy for therapy-resistant iGCTs.

GC-004. β SUBUNIT OF HUMAN CHORIONIC GONADOTROPIN IS EXPRESSED IN ALL HISTOPATHOLOGICAL SUBTYPES OF GERM CELL TUMORS

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β subunit of human chorionic gonadotropin (hCGβ) has been deemed as a characteristic marker for germinomas with syncytiotrophoblastic giant cells (STGC) and choriocarcinoma. Germinomas which secrete hCGβ have been suggested to have worse prognosis than those without and categorized in the intermediate or poor prognosis group. We quantified hCGβ mRNA levels by

qPCR in 76 intracranial germ cell tumors (iGCTs) (37 pure germinomas, 7 mature teratomas, 6 immature teratomas, 17 mixed germinomas, 4 yolk sac tumors, 1 mixed non-germinomatous GCT (NGGCT), 1 choriocarcinoma, 1 embryonal carcinoma and 2 metastases). The primers were designed to target the common sequences shared by all subtypes of the hCGβ gene. Most GCTs expressed hCGβ mRNA in higher levels than the normal brain tissue (relative ratio: $0.46\text{-}2.2\times10^{6}$). The expression was the highest in choriocarcinoma followed by germinomas with STGC ($72.6\text{-}2.1\times10^{5}$) and mixed germinomas with a choriocarcinoma component ($8.5\times10^{2}\text{-}6.8\times10^{4}$). Expression levels among pure germinomas were highly variable ($0.46\text{-}1.4\times10^{3}$). NGGCTs also showed a wide range of expression. The mRNA expression was positively correlated to the hCGβ concentration in CSF, but not in blood, especially in pure germinomas ($R^2 = 0.47$). Among the pure germinoma cases who were followed up for over 5 years ($n = 15$), hCGβ expression was slightly higher in cases that recurred ($n = 3$) than those didn't (5.7 vs 3.5, $p = 0.20$). The mRNA expression in tumors that arose in basal ganglia was higher than those in other locations (126.0 vs 29.2, $p = 0.05$). Our results indicated that any GCTs are potentially capable of expressing hCGβ irrespective of the histology. In pure germinomas, the hCGβ mRNA levels were highly variable but did not show a bimodal distribution. Our findings thus do not support to subclassify germinomas into hCG-producing and non-producing tumors and suggest a limitation of adopting CSF or blood hCGβ concentration to aid clinical decision-making of GCTs apart from choriocarcinomas.

GC-005. NEUROPSYCHOLOGICAL OUTCOMES OF STANDARD RADIOTHERAPY ALONE VS CHEMOTHERAPY FOLLOWED BY RESPONSE-DEPENDENT REDUCED RADIOTHERAPY FOR PRIMARY CNS GERMINOMA (COG ANCS0232)

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PURPOSE: CNS germinomas are highly curable tumors following high dose and large volume CNS irradiation (RT); however, patients may experience long-term morbidities. The Children's Oncology Group (COG) composed a phase III study (ACNS0232) to reduce such morbidities by comparing standard RT alone (Regimen A) to experimental therapy of pre-RT chemotherapy followed by response-dependent, reduced RT (Regimen B). METHODS: 21 patients (17 males, 4 females) were randomized to either Regimen A (whole ventricular RT-24GY with involved field boost-45Gy; $N = 10$) or Regimen B (chemotherapy followed by involved field RT only-30Gy; $N = 11$). Standardized measures of intelligence, memory, executive functioning, academic achievement, quality of life, and social-emotional functioning were administered at 9 months (T1) and 30 months (T2) after diagnosis. RESULTS: At T1, 19/21 (91%) of patients (age range = 9.25-20.75 years) were evaluated [Regimen A = 9; Regimen B = 10]. T2 testing was completed for 13/19 (68%) of patients (mean follow up = 37 months; SD = 10) [Regimen A = 5; Regimen B = 8]. Independent samples t-tests indicated no significant differences between treatment groups on any outcome measures at T1 or T2, and general linear models demonstrated no significant group differences in outcome measures over time. Full Scale, Verbal and Performance IQ remained within the average range for T1 and T2. Immediate and delayed verbal and visual memory, attention/concentration, executive functioning, social-emotional functioning, and quality of life remained stable and within normal limits for both treatment groups. CONCLUSIONS: Although there was no significant difference in the 2 treatment groups, the small sample size does not permit the detection of more subtle differences. These results warrant larger studies over a longer follow-up of children with CNS germinoma treated with induction chemotherapy followed by whole ventricular radiotherapy plus boost to accurately confirm the presence or absence of long-term morbidities from risk factors such as dose and volume of radiotherapy, age at diagnosis and length of follow-up.

GC-006. HCG-β SECRETION IS NOT A RISK FACTOR IN THE TREATMENT OF GERMINOMAS

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OBJECTIVE & METHOD: In order to propose to treat pure germinomas (pGER) and HCG secreting germinomas (hGER) with a same strategy as a single entity of "germinoma", we selected 37 patients with pGER and 19 with hGER from data-base of the 1st mult-institutional clinical study for intracranial germ cell tumors (1995 - 2003) in Japan. Their tumors grew in and around the third ventricle, and were treated by the planned RT volume to the extended local field. RESULTS: (1) As some patients in hGER refused to receive higher dose of RT and adjuvant CMT because of dramatic disappearance of their tumors during the initial treatment, 7 patients were finally treated by RT with less than 30 Gy and 12 with more than 40Gy, and 11 patients were treated by CMT with less than 4 cycles and 8 with more than 5 cycles. However, there was no significant difference in PFS between lower RT dose group and higher one, and between less CMT cycles group and more one. (2) Thirty-seven patients with pGER were treated by planned regimen with 24 Gy RT and 3 cycles of CMT. (3) The 10 and 15 year PFS were both 97.6% in pGER ($n = 37$), and 94.1% and 80.7% in hGER (19), that did not show any statistical difference. CONCLUSION: The results showed that all germinomas with or without HCG-βsecretion would be successfully treated by 24Gy RT with 3 cycles of carboplatin-etoposide combinations. This proposal will be supported by the facts of detectable HCG-β in CSF in most germinoma patients, and expression of higher degrees of HCG-β mRNA as compared with the normal brain tissue in most germinoma tissues.

GC-007. THE TREATMENT OUTCOME OF INTRACRANIAL GERMINOMA IN A SINGLE INSTITUTION

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BACKGROUND AND OBJECTIVE: The treatments for intracranial germinoma have been improved and result in better outcome. However, there is currently no consensus on the best treatment for this tumor. The aim of this study was to evaluate the long-term outcome of intracranial germinoma which treated at Kyoto University Hospital from 1979 to 2012. PATIENTS AND METHODS: Sixty patients were diagnosed as intracranial germinoma and treated with radiotherapy and/or chemotherapy at our institution from 1979 to 2012. Kaplan-Meier and Cox proportional hazards models were used to estimate survival and identify factors predictive of recurrence and survival. RESULTS: All patients received radiotherapy and their irradiation methods were various such as whole-brain irradiation, craniospinal irradiation, whole-ventricle irradiation, Intensity-Modulated Radiation Therapy (IMRT) and local field irradiation. In chemotherapy, Cisplatine, cyclophosphamide and etoposide were used in early cases, etoposide and carboplatin regimen was in the recent cases. ICE regimen was selected in recurrent germinomas. The median follow-up time was 101 months. 5-year and 10-year progression free survival rate were 87.2% and 86.4%, respectively. 5-year and 10-year overall survival rate were 100% and 95.5%, respectively. Three patients had died and one of them was related with traffic accident. Eight patients were received the second line chemotherapy for recurrent tumor. CONCLUSIONS: The treatment strategy has been shifted to reduce the dose and field of irradiation by combination of chemotherapy. IMRT improves target dose delivery and spares organs at risk, but it is necessary to make a plan delivering adequate dose for basal ganglia.

GC-008. DYNAMICAL VOLUMETRIC CHANGES OF PRIMARY INTRACRANIAL GERMINOMAS BEFORE CHEMORADIOTHERAPY

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BACKGROUND: Spontaneous regressions in intracranial germinomas have been reported in some cases, but the natural history of them has not been well known. To answer a part of that question, we retrospectively measured the tumor volume before and after chemo-radiotherapy and analyzed volumetric changes and the correlation with other clinical parameters. PATIENTS AND METHODS: Twenty-nine cases with primary intracranial germinomas and HCG-producing germinomas were treated in our hospital from 1994 to 2013. In eight of them, plural MRI scans were done before

the first course of chemotherapy regimen. Their age ranged from 16 to 26 years. Endoscopic or open biopsies were performed in all. Two were bifocal type. Tumor volume of ten lesions was analyzed by volumetric assessment based on MRI. Ratio of volumetric change between the first MRI on admission and the scan immediately before chemotherapy was defined as shrinking rate (%). Ratio of volumetric change influenced by the first course of chemotherapy was defined as response rate (%). Period between disease onset and the first chemotherapy was 22 to 47 days. RESULTS: Initial tumor volume ranged from 0.962 to 24.15 cubic centimeter (mean: 6.39). Diagnostic radiation dose was estimated to be from 52.2 to 910.1 mSv. Shrinking rate ranged from -57.8 to 85.3% (mean: 29.1). Only in 3 cases, shrinking rate was within $\pm$30%. There is no significant relationship between diagnostic radiation dose and shrinking rate. Shrinking rate had no correlation with age, sex and response rate. Shrinking rate was negatively influenced by initial volume ($p = 0.049$). CONCLUSION: This study shows the possibility that the volume of intracranial germinomas are changing dynamically for a short time before chemoradiotherapy in most cases and spontaneous regression is a part of volumetric changes. More information about large-scale study is needed to give light on the biological nature of them.

GC-009. ESTABLISHING AREAS OF CONSENSUS FOR THE MANAGEMENT OF INTRACRANIAL GERM CELL TUMOURS (ICGCTS) USING A MULTI-DISCIPLINARY DELPHI METHOD

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BACKGROUND: ICGCTs are a relatively rare and heterogeneous group of tumours that may occur at a number of anatomical sites, including the pineal, neurohypophyseal (suprasellar) and basal ganglia regions. Following International CNS GCT Symposia in Kyoto in 2003 and Los Angeles in 2005, the Third Symposium was held in Cambridge, UK in April 2013 and discussions were held regarding potential areas for consensus. A method of identifying and defining areas of consensus in the management of ICGCTs would be a foundation for improving our understanding of this disease, to facilitate improved patient outcomes [1]. METHOD: Following the meeting, consensus statements were initially prepared by the authors, before distribution for voting amongst selected Third Symposium delegates, reflecting Far East & Australasian, European and American practice and representing all disciplines. As per the Delphi method [2], to achieve consensus, statements required 70% agreement from delegates, with a 60% response rate. CONCLUSION: Our Delphi approach will define key areas of consensus and identify areas of different practice where future consensus will improve ICGCT understanding. In addition, we expect that it will improve outcomes both by guiding current practice and by facilitation of future multinational clinical trials. [1] Murray MJ, Horan G, Lowis S, Nicholson JC. Highlights from the Third International Central Nervous System Germ Cell Tumour Symposium; laying the foundations for future consensus. E-Cancer Medical Science 2013;7:333. [2] Murphy MK et al, Consensus development methods, and their use in clinical guideline development: a review. Health Technology Assessment 1998;2:No.3.

GC-010. TREATMENT OF PATIENTS WITH INTRACRANIAL GERMINOMA, SINGLE CENTER EXPERIENCE

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BACKGROUND: The purpose of the study was to evaluate outcome and patterns of failure in patients with intracranial germinomas treated at the Department of Pediatric Hematology and Oncology in Prague between 1998-2012. METHODS: 17 consecutive patients (4 girls, 13 boys) with histologicaly proven CNS germinoma were treated. Median patient age at diagnosis was 14,6 years (range 5.4 -18.6). Eleven patients had localised, 6 metastatic germinoma. The primary tumors were localised in pineal region in 11, suprasellar in 4, two were bifocal. Initial tumor markers for human chorionic gonadotropin (HCG) and alfa-fetoprotein were evaluated in serum and cerebrospinal fluid in all patients except one. In two patients HCG was elevated ($>$ 50 IU/l) in CSF. Endoscopic biopsies were performed in four, partial resections in 10 and gross total resections in 3 patients. The primary treatment involved platinum based chemotherapy, followed by definitive radiotherapy (focal, whole ventricular or craniospinal) in 16 patients, one girl with metastatic germinoma was treated with craniospinal radiotherapy only. RESULTS: The estimated 5-year event- free survival (EFS) for the entire group is 74,5%, 5-year overal survival (OS) is 80.2%. Five patients experienced relapse, all relapses occurred in CNS, one was combined with massive abdominal involvement and elevation of AFP and HCG 1.1 year post diagnosis. Treatment failures in patients with localised germinoma occurred 2.2, 4.2 and 6.5 years post diagnosis in patients treated with focal radiotherapy, all relapses were outside the radiation field. All patients with relapse of CNS germinoma have died. One patient developed meningeoma 8 years post treatment and is disease free after complete resection. CONCLUSION: Based on the patterns of failure and risks of late reccurence, our results support the use of whole ventricular field versus local field in patients with localised CNS germinoma. Supported by the "Project for Conceptual Development of Research Organization 00064203"

GC-011. ELEVATED BODY TEMPERATURE AFTER RESECTION OF AN INTRACRANIAL GERM CELL TUMOUR IN THE PINEAL GLAND REGION

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INTRODUCTION: Intracranial germinoma arise typically in the pineal gland region. The pineal gland hormone Melatonin is involved in many regulatory processes like the circadian rhythm and it also plays a role in body temperature regulation. We describe the case of a boy with an intracranial germ cell tumour that developed circadian rhythm disturbances and elevated temperatures without an infectious focus after chemotherapy and operation in the pineal gland region. MATERIAL AND METHODS: A 15 year old boy was diagnosed with an intracranial non germinomateous germ cell tumour. He was first treated with 3 cycles of chemotherapy (Cisplatinum, Etoposid and Iphosphamid) followed by radical resection of the tumour which necessitated complete pinealectomy. The histology revealed only residual benign teratoma. Postoperatively the boy received one last cycle of chemotherapy. In the first four weeks following the operation and the chemotherapy the boy presented with daily elevated body temperature swinging between 38.5-39.4°C. He was treated with several courses of antibiotics and infectious serum parameters and hematological leucopenia resolved rapidly. With repetitive MRI scans infection of the central nervous system could be excluded. Despite of this, the high temperatures remained unchanged. The boy had also developed in the same time period an abnorm sleep pattern with night time insomnia and short daytime sleeping periods. We began melatonine replacement therapy and the circadian rhythm and the body temperature normalized rapidly. CONCLUSION: After pinealectomy for germ cell tumours, patients can develop non infection related elevated body temperature. Melatonine replacement therapy might be used for treatment.

GC-012. IDENTIFICATION AND TREATMENT STRATEGY OF CHEMO-RESISTANT GERMINOMAS

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Intracranial germinomas are highly sensitive to radio-chemo-therapy, resulting in complete remission of the tumors and good prognosis of the patients. However, some germinomas show a resistance to the standard therapy for germinomas. In the present study, we identified clinical features and treatment strategy of chemo-resistant germinomas by analyzing the patients with germinomas that were histologically verified. METHODS: 23 patients with pure germinoma (18) and mixed germinoma (5) were studied. The mean age was 15.3 years. Male were 18 and female were 5. Tumor locations were pineal region (7), suprasellar region (6), pineal and suprasellar regions (6), basal ganglia (3), and ventricle (1). All tumor samples obtained by biopsy or resection were histologically examined. All cases were first treated by chemotherapy (carboplatin and etoposide: CE x 3 courses) followed by 24 Gy radiation at whole ventricular zones. RESULTS: 20 patients showed complete response (CR) after chemotherapy alone. Three patients were treated by additional chemotherapy and further radiation to 50 Gy. Among these, two did not still respond the treatment.

One patient with pure germinoma showed rapid growth of the tumor and died one year later. The histology of the growing tumor was germ cell tumor associated with sarcoma. Another patient with mixed germinoma is now observed for the residual tumor. All three patients presented with slightly high values of both serum AFP and HCG-b in CSF. CONCLUSION: Germinomas showing non-CR to the standard chemotherapy may have different components that require radical resection in the early stage. Particularly, germinomas presenting atypical imaging and positive tumor markers should be carefully treated.

GC-013. USEFULNESS OF NEUROENDOSCOPIC SURGERY IN PEDIATRIC GERM CELL TUMORS

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OBJECTIVE: The purpose of this report is to discuss the diagnostic efficacy and safety of neuroendoscopic surgery in the management of germ cell tumor. METHODS: From 2004 to 2013, 16 pediatric patients with central nervous system germ cell tumors were treated at Ehime University. Serum and CSF were collected and analyzed for tumor markers AFP and HCG-beta. When preoperative MR imaging and tumor markers implied germinoma or mixed germ cell tumor with a germinoma component, we performed neuroendoscopic surgery to obtain tumor tissues for histological diagnosis followed by endoscopic third ventriculostomy (ETV) in the patients who are complicated with hydrocephalus. RESULTS: Endoscopic tumor biopsy was performed in 10 patients whose tumors were located in the pineal, suprasellar and thalamic region. Simultaneous ETV was performed in 5 patients with obstructive hydrocephalus. 3 patients with suprasellar and pineal tumors were performed the endoscopic biopsy and VP shunt operation. Histological examination disclosed one was immature teratoma, two were mixed tumor of germinoma and teratoma, and eights were germinoma. Serum AFP was elevated in 2 patients (13-24ng/ml) and CSF HCG-beta was detected in 6 patients (0.11-4.7ng/ml). In one of 2 patients with teratoma and positive AFP, MRI obtained 12 days after endoscopic biopsy disclosed marked enlargement of immature teratoma. In another case, at 16 months after adjuvant therapy, recurrence of the tumor whose histology were changed to choriocarcinoma was observed. Postoperative complication was found in one patient. Intracranial hemorrhage was observed, but there was no permanent morbidity. CONCLUSIONS: Endoscopic biopsy with concomitant third ventriculostomy is an effective and safe in the management of germinoma. However, the surgical specimens obtained by neuroendoscopic surgery are very small and not enough to rule out other compornent of tumor except germinoma. Therefore if mixed germ cell tumor is suspected, we must determine carefully the indication of endscopic surgery as means for histological diagnosis.

GC-014. LONG TERM OUTCOMES AND LATE EFFECTS FOR CHILDHOOD INTRACRANIAL GERMINOMAS

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BACKGROUND: Pediatric central nervous system (CNS) germinomas have favorable cure rates. However, given the rarity of this tumor, long term follow-up data for these patients are limited. The purpose of this study is to assess the long term overall survival (OS) and causes of late mortality in these patients. METHODS: Using the Surveillance, Epidemiology and End Results (SEER) database, we evaluated the long term OS and causes of mortality in 5-year survivors of childhood CNS germinoma. Children less than 20 years old with a diagnosis of CNS germinoma who survived at least 5 years were included in the analysis. Standardized mortality ratios (SMRs) using US population data were calculated to compare observed versus expected all-cause death and death from stroke in the study population. The cumulative incidences of second malignant neoplasms (SMNs) and death due cancer were calculated using a competing risks model. RESULTS: A total of 301 patients were eligible for analysis. Median age at diagnosis was 14 years. Median follow up time was 9.8 years (range = 5.0 - 37.8 years). The male to female gender ratio was 2.9 : 1. Overall survival at 20 and 30 years was 86.4% and 58.7%, respectively. Five year survivors experienced a nearly 13-fold increase in mortality risk compared their peers (SMR 12.45 [95% Confidence Interval (CI): 8.6-17.5]) and a 100-fold increase in risk of death from stroke (SMR 100 [95% CI: 20-292.2]). Cumulative incidence of SMN at 25 years was 7.2% [95% CI: 2.2 - 16.3] and cumulative incidence of death due to cancer, either recurrence or SMN, at 25 years was 19.7% [95% CI: 10.2-31.7]. CONCLUSION: Although many CNS germinoma patients survive 5 years, these patients have a significantly increased risk of mortality compared to their peers. SMNs, recurrent disease and cerebrovascular disease are largely responsible for this increased risk.

GC-015. RE-IRRADIATION BY PROTON BEAM THERAPY WITH CHEMOTHERAPY FOR A PATIENT WITH RECURRENT GERM CELL TUMOR

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INTRODUCTION: Standard treatment for recurrent intracranial germ cell tumor has not been established. We report a patient with recurrent germ cell tumor who underwent chemotherapy and re-irradiation by proton beam therapy (PBT). CASE PRESENTATION: A 18-year-old boy presented with headache and vomiting. CT images showed hydrocephalus due to pineal and suprasellar mass with calcification. He underwent ventriculo-peritoneal shunt. In our institution, he underwent whole-ventricle irradiation 23.4GyE/13Fr by PBT followed with chemotherapy (ifosfamide, cisplatin and etoposide). His serum βhCG elevated without evidence of recurrence in MRI and cerebrospinal fluid 22 months after completing the initial treatment. Two months later, repeated MRI images showed dorsal cerebellar mass. He underwent chemotherapy with high-dose cyclophosphamide, carboplatin and vincristine combined with peripheral blood stem cell transplantation and cranio-spinal irradiation 30.6GyE/17Fr by PBT. His serum βhCG and MRI image have showed no findings of recurrence for 11 months. He currently enjoys his active life at a university with hormone replacement therapy. CONCLUSION: A patient with a recurrent germ cell tumor safely underwent re-irradiarion by PBT outside the previously irradiated field. Proton beam therapy may preserve the normal brain tissue from high-dose radiation. Our strategy rescued this patient without neurocognitive deficits. We need to investigate late adverse effects in this patient and to compile data about re-irradiation by PBT.

GC-016. TREATMENT OF PRIMARY INTRACRANIAL GERM CELL TUMORS: SINGLE-CENTER EXPERIENCE WITH 42 CLINICALLY DIAGNOSED CASES

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BACKGROUND AND OBJECTIVE: Primary intracranial germ cell tumors (GCTs) are a class of heterogeneous tumors. Surgery can quickly relieve tumor compression and provide histological diagnosis. It is very difficult to treat some patients who are unable to be pathologically diagnosed. This study retrospectively analyzed the clinical data and outcomes of patients with clinically diagnosed primary intracranial GCTs in the single-center. METHODS: Patients who were clinically diagnosed as primary intracranial GCTs based on clinical symptoms, signs, neuroimaging characteristics and tumor markers but not histologically diagnosed by surgical resection or biopsy were included in this study. Patients were analyzed for clinical characteristics, treatment patterns, outcomes and adverse reactions. RESULTS: From May 2002 to July 2012, 42 patients were included. The median age was 16.5 years old (4-30). Most tumors were found in male, teenagers and located in the pineal and suprasellar regions. Patients were assigned to diagnostic chemotherapy group (25 cases), diagnostic radiotherapy group (5 cases) and gamma knife radiosurgery group (12 cases) based on their initial anti-tumor therapy. The 4-year survival rates were 84.3%, 75.0% and 70.1%, respectively (P = 0.44). The 4-year survival rates were 77.8% and 80.0% (P = 0.98) in patients with secretory tumors (30 cases) and non-secretory tumors(12 cases) . The major adverse reactions were grade III - IV bone marrow suppression (35.2%) and grade II - III nausea/vomiting(45.8%). CONCLUSION: Surgical removal of tumor or biopsy is the most accurate method to determine the pathological property of tumor. But for some patients who can not be pathologically diagnosed, they can receive comprehensive treatments such as chemotherapy combined with radiotherapy once they are clinically diagnosed as having primary intracranial GCTs, and some of them can still have good responses. Key Words:Primary Intracranial Germ Cell Tumor; Clinical Diagnosis; Diagnostic Radiotherapy; Diagnostic Chemotherapy

GC-017. WHOLE VENTRICULAR IRRADIATION WITH FOCAL BOOST AFTER CHEMOTHERAPY IN LOCALIZED GERMINOMAS: ANALYSIS OF AN INTERIM COHORT

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The SFOP TGM-90 and SIOP GCT 96 protocols showed that ventricular relapses occurred where only focal radiation was delivered after chemotherapy in localized germinomas. The SIOP GCT96 was amended accordingly and the current SIOP GCTII trial was designed to expand radiation field to the ventricular system. Between the administrative closure of GCT 96 and opening of GCT II, interim patients were treated with additional ventricular radiotherapy and their outcome was retrospectively assessed. RESULTS: 40 patients were treated between 09/2002 and 09/2012: 31 males and 9 females. Medium age was 14 years (8 to 40). Primary was located in pineal (16), suprasellar (13) or bifocal (13). All received 4 cycles of chemotherapy alternating VP carboplatin-etoposide with Ifosfamide-etoposide followed by 24 Gy to whole ventricle and a 16 Gy local boost by photons (32) or protons (8) while they were in CR (16), VGPR (12), PR (4) or SD (2). One patient treated with 3DCRT while in VGPR post chemo relapsed locally and in the spine 13 month post diagnosis and was salvaged by further chemo and radiation. All patients are currently alive in CR. The overall and disease free survival at ten year is respectively 100 and 97%. CONCLUSION: The strategy currently used in SIOP GCT II provides excellent outcome. Further follow up is warranted to assess efficacy and toxicity of this strategy.

GC-018. CHARACTERISTICS OF EXTRACRANIAL GERM CELL TUMOURS IN CHILDREN AT NATIONAL HOSPITAL OF PEDIATRICS, HANOI, VIETNAM

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BACKGROUND: The aim of this study was to evaluate characteristics of extracranial GCT in children at NHP. METHOD: A retrospective review of 168 children with extracranial GCT had been treated at NHP between 2008 and 2013. Pathology, age, sex, primary tumour, metastases and disease stage were analyzed. RESULTS: There was 78.6% of children under 5 years old in this study. Boy/girl = 1.2/1. Clinical signs could include big testis (41.7%), abdominal distension (30.6%), touching abdominal tumour (25%) or sacrococcygeal (11.1%), defecation and urination difficulty (8.3%). Gonadal GCT hold 55,9%. Almost tumour at extragonadal were sacrococcygeal tumour (16.1%). Most of mature teratoma were found in ovary (50%), sacrococcygeal (55.6%) and mediastinum (61.5%). Tumour in testis almost were yolk sac tumour (56.5%). Children under 5 years old usually had tumour at testis (44.7%) or sacrococcygeal (18.9%). Children over 5 years old usually had tumour in ovary (55.6%) or mediastinum (19.4%). All tumours had imaging of sound mix, heterogeneous. AFP were normal in all patients with mature teratoma. AFP increased in 1/3 of immature teratoma, almost of yolk sac tumour and mixed malignant GCT. Teratoma were found most frequently (mature: 69, immature: 34), followed by Yolk sac tumour (n = 51), Mixed malignant GCT (n = 10), Dysgerminoma (n = 2) and Embryonal carcinoma (n = 2). The GCT were located in sites: testis (n = 62), ovary (n = 32), sacrococcygeal (n = 27), mediastinum (n = 13), retroperitoneum (n = 14), abdominal cavity (n = 13), neck (n = 3), shin (n = 1) and miscellaneous (n = 10). Most patients (81) were Stage I, 64 patients were Stage II, 13 patients were Stage III, 6 patients were Stage IV and 4 patients operated in other hospitals could not classified. CONCLUSION:Extracranial GCT in children had variable pathology and primary location. Most of patients admitted in early stage.

GC-019. A SINGLE CENTRE EXPERIENCE OF OCCULT MALIGNANT OR INFLAMMATORY DISEASE IN 64 CHILDREN WITH THICKENED PITUITARY STALK (TPS) AND/OR IDIOPATHIC CENTRAL DIABETES INSIPIDUS (ICDI)

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INTRODUCTION: Children with TPS and/or ICDI present to different (endocrine, oncology, ophthalmology) specialists. Their rarity, absence of agreed radiological criteria or consensus guidance, make their management (to exclude an occult malignancy) problematic. Biopsy is too dangerous and cases may remain undiagnosed or evolve over decades. AIMS: 1) to longitudinally characterize a large childhood cohort presenting with TPS and/or ICDI 2) to assess radiological, clinical, visual and endocrine correlates over time. METHODS: We searched the terms "thickened pituitary stalk" or "idiopathic diabetes insipidus" in electronic radiology and clinical document libraries at our split-site centre (UCLH/GOSH) over the last 30 years. 64 retrospective longitudinal data sets in patients presenting with TPS (12), ICDI (20) or both (32) were collected and MRI scans reviewed. RESULTS: Patients without ICDI were older (TPS: 9.6 $\pm$ 1.4 years) at presentation than those with ICDI (5.2 $\pm$ 0.9) and TPS + ICDI (5.6 $\pm$ 0.7 years) ($p < 0.02$), but of similar age at last review (12.3 $\pm$ 1.5 vs 11.4 $\pm$ 1.8 vs 12.5 $\pm$ 1.1 years). TPS + ICDI patients were more likely (62.5%) than either ICDI (15%) or TPS (16.7%) to have histiocytosis. Tumours were identified in 22% TPS + ICDI and 25% ICDI 1.0 $\pm$ 0.5 and 2.5 $\pm$ 1.4 years later respectively, but not in TPS. 58% TPS cases remained unexplained (vs 55% ICDI and 12.5% TPS + ICDI) at a shorter follow-up (2.9 vs 5.5 and 6.6 years) and just 8% had DI at last review. Multiple anterior pituitary deficits evolved with time across groups (GHd, 40-60%, TSHd 8-35%, ACTHd 0-30%) but visual deficits, present in 8-20% at presentation, increased only in TPS + ICDI (6.2-28.2%). CONCLUSIONS: Longitudinal endocrine and visual assessment of all patients with TPS and ICDI is important. ICDI is a negative prognostic factor for malignant disease, whilst the combination with TPS is more often associated with histiocytosis. TPS alone is unlikely to lead to malignancy but should be prioritized for endocrine follow-up.

GC-020. CLINICAL PATTERNS AND TREATMENT OUTCOMES IN GERMINOMA PATIENTS TREATED WITH CISPLATIN-BASED CHEMOTHERAPY AND LOCAL IRRADIATION: THE EXPERIENCE FROM JAPANESE PEDIATRIC BRAIN TUMOR CONSORTIUM

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BACKGROUND: Although prognosis of pure germinoma and βhCG-producing germinoma are relatively good, complications of radiotherapy are inevitable. To explore the possibility of reducing dose of radiation with combined optimal chemotherapy, we retrospectively analyzed patients registered in Japanese Pediatric Brain Tumor Consortium (JPBTC). PATIEENTS and TREATMENT: 23 patients with pure gemionoma and 11 patients with βhCG-producing germinoma were registered from multi-institutions in Japan from 1999 to 2006. Our recommended regimens were as follows. Patients with pure germinoma received three courses of CDDP/ETP and followed by local irradiation (24Gy). Patients with residual tumor after three courses of chemotherapy received additional two courses of CDDP/ETP and local irradiation (30Gy). Patients with βhCG-producing germinoma receive five courses of CDDP/ETP/CPM/VCR with intrathecal MTX (IT-MTX), followed by local irradiation (50Gy). RESULTS:Tumors recurred in 9 of 23 patients with pure germimona, and 5-year EFS and OS was 78.3% and 100%, respectively. In 11 patients with βhCG-producing germinoma, both 5-year EFS and OS were 100%, although 6 patients received only CDDP/ETP without CYM or VCR. Tumors recurred 2-9 years after diagnosis, in some patients, sites of recurrence were common sites of the germinoma and recurred tumors showed good response to the second treatment. CONCLUSIONS:The results demonstrated that more intensive approach is required for patients with pure germinoma and that intensity of treatment can be reduced for patients with βhCG-producing germinoma. In our current JPBTC phase 2 study, since 2007, patients with pure germinoma receive additional one course of CDDP/ETP and IT-MTX, and patients with βhCG-producing germinoma receive five courses of CDDP/ETP/lower-dose CYM and reduced local irradiation of 24 Gy. In some patients recurred tumors seemed to be de novo, this pattern of relapse, namely, occurring in time and space might suggest that disseminated dormant progenitor cells acquire tumorigenic change intermittently.

GC-022. IMPACT ON OUTCOME OF HCG ELEVATION ALONE IN SIOP CNS GCT 96 PATIENTS TREATED AS NONGERMINOMATOUS/SECRETING GERM CELL TUMOURS (NGGCT)

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BACKGROUND/AIMS: NGGCT were diagnosed in SIOPCNSGCT96 by raised serum and/or csf markers, (AFP > 25 ng/ml and/or HCG >50 IU/l), with or without histology, and treated with 'PEI' chemotherapy (4 courses) followed by radiotherapy according to dissemination. This subanalysis aimed to establish if patients with HCG elevation alone behaved differently to the group as a whole. METHODS: 177 NGGCT patients, registered upto Sept 2010, had follow-up data. Of these, 57 were diagnosed based on raised HCG with normal AFP and no yolk sac tumour (YST) or embryonal carcinoma (EC) histologically. Age was 4-22 years (median 13); 41 boys, 36 localised (13 pineal, 15 suprasellar, 4 bifocal, 4 other) and 21 metastatic. HCG was 51-200 IU/l in 19, 201-1000 in 21 and >1000 in 17. The distribution of age, site and dissemination were similar between the subgroups. They were analysed with respect to surgery performed, histological diagnoses made and survival. RESULTS: 11/19 patients with HCG 51-200, 15/21 with HCG 201-1000 and 11/17 with HCG >1000 were diagnosed by markers alone, whilst 9 and 11 respectively had biopsy and/or resection; of those with diagnostic histology, 16 contained germinoma ± teratoma components. 5-year event-free (EFS) and overall (OS) survival of patients with HCG 51-200(n = 19) were 0.94 and 1.0 respectively. For the 21 with HCG 201-1000, 5-year EFS was 75% and OS 81%, and for the 17 with HCG > 1000, EFS 65% and OS 94%. When patients with HCG over 200 were combined (n = 38), 5-year EFS was 0.70 (p = 0.05) and OS 0.87 (p = 0.12). CONCLUSION: Patients with raised HCG <200 IU/l have the most favourable outcomes. Subdivision of HCG values above 200 IU/l, carries no prognostic value in this group. These findings raise the question of whether we are over-treating germinoma that have raised HCG and warrant further discussion regarding thresholds for marker diagnosis of NGGCT.

GC-023. PAEDIATRIC INTRACRANIAL GERM CELL TUMOURS -EXPERIENCE FROM A TERTIARY PAEDIATRIC INSTITUTION IN MALAYSIA

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INTRODUCTION: Intracranial germ cell tumour (GCT) is a rare malignant tumour, constituting 2-8 % of all primary intracranial tumours in children. It is radio and chemosensitive and is potentially curable without surgery. METHODS: A retrospective analysis was conducted on consecutive patients with intracranial GCT admitted at Institut Pediatrik Hospital Kuala Lumpur (IPHKL), a major paediatric referral hospital in Malaysia. All patients admitted from 2006- 2012 were included. The aim was to assess demographic factors, clinical features and treatment outcome. RESULTS: Twenty six patients were identified. Seventeen (65%) were diagnosed with pure germinoma and 9(35 %) with non-geminomatous germ cell tumours (NGGCT) or mixed type. There were 17 males and 9 females, age range between 7 to 16 yrs (mean 11.2 yrs) and duration of symptoms prior to presentation ranged between 4 days to 3 years (mean 5.8 months).The tumour location includes pineal gland (13), suprasellar (8), pineal/suprasellar (1), basal ganglia (3) and thalamic (2). Six had disseminated CNS disease at the time of diagnosis. The most frequent presenting symptoms were headache and vomiting (62%). Twelve patients had features of endocrine dysfunction at presentation, panhypopituitarism (9), isolated diabetes insipidus (1), precocious puberty(2). Ophthalmologic findings of decreased acuity, double vision, bitemporal hemianopia, strabismus and btotal lindness were present in 12 patients. All the diagnoses were confirmed by histopathology: tumour biopsies (18) and tumour resections (8). Twelve patients had hydrocephalus and 5 required VP shunts. All patients received chemotherapy followed by radiotherapy except 1 patient who refused chemotherapy. Overall survival was 84%. Four patients died: NGGCT(3) and germinoma(1). Morbidity was mainly due to endocrine insufficiency (11), neurological sequelae (8) and visual impairment (3). CONCLUSION: Intracranial GCT carries a good prognosis. The majority of survivors have residual morbidity.

GC-024. LONG TERM OUTCOMES IN CHILDREN WITH INTRACRANIAL GERMINOMA: A SINGLE INSTITUTION EXPERIENCE FROM 2000-2013

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BACKGROUND: Intracranial germinomas are the most common central nervous system (CNS) germ cell tumour and have an excellent prognosis of >90% overall survival with radiation therapy alone. However, in children, volume and dose of CNS irradiation will influence endocrine, growth, and neurocognitive outcomes. Hence, cooperative groups have modified therapy by giving chemotherapy followed by reduced CNS irradiation to minimize morbidity. METHODS: This retrospective cohort study analyzed the outcome of intracranial germinoma patients diagnosed and treated at SickKids in Toronto, Canada, from 2000-2013. RESULTS: Twenty-five children (14 male, 11 female; median age 12.92 years; range 6-17 years) were identified. The median follow up was 61 months (1 month to 12 years). Median duration of symptoms prior to diagnosis was 5 months (range 1-36 months). Tumour location was suprasellar (n = 9), bifocal (8), pineal (6), and within basal ganglia (2). Three children had ventricular and one child had craniospinal dissemination. 16/25 presented with diabetes insipidus. 3/25 had only elevated serum human chorionic gonadotropin (HCG, mean 19 IU/L), 4/25 only elevated CSF HCG (mean 21.3 IU/L), and 2/25 had both elevated serum and CSF HCG (mean 23 and 104.5 IU/L respectively). 24/25 children received carboplatin-based chemotherapy followed by either ventricular irradiation (23.4-24 Gy) ± boost (16 Gy) (n = 15), whole brain (23.4 Gy) (n = 3), focal (40 Gy) (n = 4) or craniospinal irradiation (n = 2). One child was treated with craniospinal irradiation only. Five-year progression free survival was 96%. Overall survival was 100%. Information on education status was available for 11 of 16 survivors now >18 years of age. Of those, 1 did not complete high school, 3 completed high school, and 7 are attending college/university. CONCLUSION: Our data suggests excellent survival with combined treatment modality and also great potential for academic success.

GC-025. CLINICAL CHARACTERISTICS AND NEUROIMAGINGS OF INTRACRANIAL NON-PINEAL GERM CELL TUMORS

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PURPOSE: We retrospectively analyzed clinical characteristics and neuroradiological findings of the non-pineal intracranial germ cell tumors (GCTs). METHODS AND RESULTS: From 1994 to 2013, there were 14 neurophophyseal GCTs (11 germninomas, one germinoma with STGC, one choriocarcinoma and one mixed germ cell tumor, 8 boys and 6 girls) and 5basal ganglia GCTs (2 germinomas and 2 mixed germ cell tumors and one germinoma with STGC, 4 boys and one girl). Age was ranged from 6 to 18 years old. All GCTs except for 2 (choriocarcinoma and mixed germ cell tumor) were histologically verified. All neurohypophyseal GCTs initially manifested diadetes inspidus (DI), followed by anterior pituitary dysfunction. Period from onset to diagnosis was from 4 months to 56 months with mean of 22 months. Two basal ganglia germinomas initially showed hemiparesis and involuntary movement, followed by mental retardation within 6 to 8 months after onset. Initial MRI showed a small lesion at the pituitary stalk in the neurohypohyseal GCTs and an infiltrative lesion without mass effect in basal ganglia germinoma. Two mixed GCTs in the basal ganglia developed hemiparesis and disturbed consciousness and showed a large mass on MRI. All patients except for one mixed GCT were treated by chemotherapy and local radiation. 13 out of 14 patients with neurohypohyseal GCTs were tumor free survival, but none of them showed any improvement of hormone deficiency. Two with basal ganglia germinomas had persistent hemiparesis with mental retardation. Two with mixed GCTs were expired within 1 year after diagnosis; one was Down syndrome and one was died from adrenal insufficiency due to high dose chemotherapy. CONCLUSION: To improve the quality of life, we have to properly diagnose as germinoma at least while the symptoms remain DI in the neurohypohyseal germinoma and hemiparesis in the basal gangalia germinoma.

GC-026. PROTONTHERAPY FOR WHOLE VENTRICULAR IRRADIATION IN LOCALIZED INTRACRANIAL GERMINOMA: WHICH BENEFIT. THE FRENCH EXPERIENCE

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AIM: A characteristic ventricular pattern of relapse in localized Germinoma(G) after combined approach with chemotherapy and Tumour-Bed irradiation, was evidenced in the French-SFOP-TGM90 and the SIOP-CNS-GCT-96 studies. This led to an amendment recommending target volume enlargement to include the ventricular system. Orsay Proton Centre offered from 2011 using proton beams, to potentially optimise the radio-therapeutic index for this large and complex volume. We report dosimetric and early clinical results. METHODS: Between [2003-2013], 28 newly diagnosed, localized germinoma patients, median age 16[6-29], primary site pineal(14), suprasellar(9), bifocal(5) were referred to Institut-Curie and received 3DC-RT in 3, IMRT in 10, and from May 2011, conformal proton therapy in 15 patients using passive-scattering delivery. All patients received 24CGE to whole-ventricles followed by a 16CGE involved-field boost to the primary site, 1.6CGE/fraction. RESULTS: Large ventricular PTV (median 273cc) required gantry room with collimator size 140-180mm. Patients dosimetric comparison of protontherapy (15) versus IMRT (10) to the ventricular-system, showed similar conformity (median 1.6 vs 1.5) and homogeneity (median 1.05 vs 1.09) index. Comparison of volume of isodoses 18, 15 and 10 CGE showed improved normal tissue protection using proton beams with an IMRT/Proton ratio respectively of 1.28, 1.46, and 1.36. Dosimetric benefit was showed for both supratentorial and infratentorial parenchyma, and cochlea. Compliance to treatment and early tolerance was excellent. At short-term follow-up: median 14mths[8-22], overall survival is 100%, no relapse was observed. CONCLUSIONS: Ventricular irradiation with proton beams using double scattering delivery is on the way of optimisation with improved protection of normal tissues and early tolerance. Long-term follow-up is required to evaluate disease control and potential benefit on cognitive and socio-professional outcome, in this rare tumour occurring in adolescents and young adults. Intensity Modulated ProtonTherapy IMPT with fine Pencil Beam Scanning technology is required for further benefit.

GC-027. CLINICAL PICTURES OF INTRACRANIAL GERM CELL TUMORS, AT INITIAL PRESENTATION

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PURPOSE: To clarify the clinical pictures of intracranial germ cell tumors (iGCT) at initial presentation. METHODS: Sixty patients with intracranial germ cell tumors who were treated at the International Medical Center, Saitama Medical University and whose clinical symptoms were well documented on charts were retrospectively analyzed. RESULTS: The age distribution was between 4 years and 48 years (median 15 years). The tumors were located at pineal in 20 patients (male 20, female 0), neorohypophysis 12 (male 5, female 7), bifocal (peneal and neurophypophysis) 12 (male 11, female 1), basal ganglia 7 (male 7, female 1), multiple sites 7 (male 7, female 0) and other location 1 (male 1, female 1). The histological diagnoses were germinoma in 42 patients, immature teratoma 5, mature teratoma 1, choriocarcinoma 2, yolk sac tumor 1 and mixed GCT in 9 patients. The initial symptoms and signs includes increased intracranial pressure in 19 (31.7%, pineal 60%, bifocal 50%), diabetes insipidus 18 (30%, neurophypophyseal 75%, bifocal 50%), eye movement disorder 17 (28.3%, pineal 60%, bifocal 25%), pupil abnormality 12 (20%, pineal 55%, bifocal 8.3%). Other neural and endocrinological symptoms were precocious puberty, hemiparesis or ataxia according to the location or abnormal production of beta-human chorionic gonadotropin (hCG). CONCLUSION: Most germ cell tumors were more in males than females except for neurohypophyseal localization where the numbers were almost equal ($p < 0.01$). Majority of patients who presented with increased intracranial pressure had tumor at pineal lesion ($P < 0/01$).

GC-028. PRIMARY INTRACRANIAL GERMINOMAS ARE CHARACTERIZED BY GLOBAL DNA HYPOMETHYLATION

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OBJECTIVE: To elucidate the pathogenesis of intracranial germ cell tumors (iGCTs), we are currently conducting a comprehensive genomic analysis. In pediatric central nerves system tumors, several large-scale epigenetic analysis have been reported to date, however there are very few studies on the methylation status in iGCTs. iGCTs often arise as a mixture of different histological subtypes in any combination and/or may change subtypes at the time of recurrence, the pathogenesis of which is rather difficult to explain by a single gene mutation alone. In this study, we analyzed a methylation status genome-wide in iGCTs to investigate the role of epigenetic mechanism in their pathogenesis. METHODS: DNA was extracted from frozen samples of 58 GCTs (19 germinomas, 11 teratomas, 16 mixed GCTs, 1 embryonal carcinoma, 5 yolk sac tumors, 3 choriocarcinomas, 3 seminomas). A genome-wide methylation status was analyzed using HumanMethylation450 BeadChip (Illumina®). Clustering analysis was performed using approximately 20,000 probes showing the highest standard deviations across all samples. RESULTS: Germinomas generally showed a prominent hypomethylation pattern in almost all genomic regions, which is a unique epigenomic feature not previously observed in any other cancer types. According to the methylation pattern, GCTs were subclassified into the following 3 categories; global hypomethylation (LM), partial hypomethyltion (PLM) and global hypermethylation (HM). Germinomas and seminomas showed clear tendency to be categorized as LM or PLM, while non-germinomatous GCT and normal control tissues were HM. CONCLUSION: We conclude that intracranial germinomas and seminomas are characterized by a global DNA hypomethylation. Therefore, it is likely that germinoma develop through a unique pathogenesis even among the GCTs, and the methylation status in iGCTs could serve as a useful molecular marker that may predict molecular subtypes.

GC-029. LONG TERM OVERALL SURVIVAL IN STANDARD RISK NON-GERMINOMATOUS GERM CELL TUMOURS (NGGCT) TREATED ACCORDING TO SIOP CNS GCT 96

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OBJECTIVE: In SIOP CNS GCT 96 AFP $>$ 1000 ng/ml and age $<$6yrs has been identified as high risk in intracranial Non-Germinomatous Germ Cell Tumors (NGGCT). This evaluation focuses on standard risk patients. PATIENTS AND TREATMENT: 156 protocol patients with standard risk NGGCT were registered between 01.01.1996 and 24.09.2010; 141 were eligible. Age range was 6-29 years (median 12 years); 111 were boys. 108 were localised (59 pineal, 31 suprasellar, 8 bifocal, 10 other), and 33 metastatic. Patients with localised disease received 4 courses of Cisplatin/Etoposide/Ifosfamide (PEI) followed by focal radiotherapy (RT) of 54 Gy. Patients with metastases received 4xPEI followed by 30 Gy craniospinal RT (CSI) and 24 Gy boosts to tumor and macroscopic metastatic sites of disease. RESULTS: Progression-free survival (PFS) of the 108 patients with chemo + focal radiotherapy was 0.71 ± 0.04 (median follow-up 73 months), and of those with chemo and CSI 0.74 ± 0.08 (median follow-up

73). 8 relapses were observed after CSI (n = 33), including 3 local, 1 distant and 4 combined. 27 relapsed after chemo + focal RT (n = 108) including 19 local, 5 combined and 3 distant. 2 patients died after progression under therapy. Overall survival (OS) was 0.83 ± 0.04 in localised and 0.79 ± 0.10 in metastatic diease. Relapses occurred until 72 months of follow-up.Of the 35 relapse patients 19 died of disease and 16 were salvaged.12 with chemo, which was platin based in all and RT and one with chemo alone, two had teratoma and received surgery only. Time to relapse did not differ compared to those who could not be salvaged. CONCLUSION: Long term is excellent (80%). Relapses can occur late therefore a follow-up for at least 6 years with regular imaging is necessary. A proportion of patients can be salvaged after relapse. Further investigations are necessary to optimise salvage recommendations. Supported in part by Deutsche Krebshilfe.

GC-030. PROFILE AND OUTCOME OF HIGH RISK INTRACRANIAL NON-GERMINOMATOUS GERM CELL TUMOURS (NGGCT) TREATED IN SIOP CNS GCT 96

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BACKGROUND: In SIOP CNS GCT 96 AFP >1000 ng/ml at diagnosis is associated with a dismal prognosis. METHODS: Until 31.05.2012, 23 patients with NGGCT AFP >1000 ng/ml in serum/CSF were treated according to SIOP CNS GCT 96. Median age was 12 years, 16 were boys. 18 were localised, 5 metastatic. RESULTS: In these 23 patients the range of AFP was 1100-27100 ng/ml. Histological diagnosis was present for 10/23 patients. 13/23 were diagnosed by tumour markers only. 2/10 had a complete resection at diagnosis, both were in CR after therapy but had an event in follow up. 4/10 patients had a biopsy, 1/4 was in CR after therapy, 2/4 had an event in follow up. 4/10 had an incomplete resection at diagnosis and no second look resection, 1/4 was in CR after therapy, 2/4 had an event. 2/13 patients diagnosed through tumour markers had delayed incomplete resection after chemo, 1/2 was in CR after therapy, no events occurred. 11/13 patients had no resection, none of them was in CR after therapy, 7/11 had an event. In summary there were 13 relapses/progressions including 9 local, 3 combined and 1 distant. Relapses occurred between 3 and 38 months. 5 years event-free survival (EFS) was 0.40 + 0.11 (median follow-up 32 months, CR 10/23), OS: 0.43 + 0.12; (median follow-up 50 months, alive 12/23). CONCLUSION: Resection does not improve prognosis,in such high risk patients if treated with standard treatment If first line treatment is not successful, Patients with relapse show no benefit from intensive relapse therapy. Other mechanisms seem to play a role in respect to the biological behaviour of this high risk group which needs further evaluation. Supported in part by Deutsche Krebshilfe

GC-031. THE IMPACT OF SURGERY IN LOCALIZED INTRACRANIAL GERMINOMA: FINAL RESULTS OF SIOP CNS GCT 96

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BACKGROUND: Data from SIOP CNS GCT 96 have demonstrated that long-term remission rates >80% are achieved in histologically proven localized germinomas (G) with a reduction of radiation dose in combination with chemotherapy. With advances in neurosurgical techniques the safety of biopsy by stereotactic or endoscopic techniques as well as of resective surgery has improved. The relative merit of biopsy based histological confirmation only versus debulking procedures has not been formally demonstrated in these reduced radiation dose regimens. METHODS: Until 24.09.2010, 254 patients with G were registered to SIOP CNS GCT 96. Median age was 13 years (range 4-42 yrs), 193 were boys. Localized disease was present in 201 patients, with unifocal presentation in 163 cases, and bifocal disease in 35 cases. Reduced dose craniospinal radiation (CSI) with 24Gy and a 16 Gy focal boost (Option A) was used in 107/163, and chemotherapy followed by focal radiotherapy with 40Gy (Option B) in 51/163 patients. We analyzed the impact of the type of initial surgery in unifocal disease (stereotactic biopsy vs resection) on the outcome and with respect to the treatment. RESULTS: Initial surgery was biopsy in 61/163 and a resective procedure in 102/163 patients. There were 3 relapses after biopsy, with 1/43 patients after treatment option A and 2/16 patients after treatment option B. Six relapses occurred after initial resection, in 2/64 patients after treatment A and 4/35 after treatment B. The type of initial surgery had no significant influence on the relapse rate, independent of treatment (p = .0.458). Two patients had a second resection after chemo prior to focal RTX (option B; G in one patient) and 1 patient after radiotherapy (option A), all are in CR. CONCLUSIONS: The results of SIOP CNS GCT 96 do not support an attempt at upfront tumor debulking in patients with intracranial germinoma.

GC-032. DELAYED DIAGNOSIS MAY ADVERSELY AFFECT THE QUALITY OF SURVIVAL FOR PATIENTS WITH INTRACRANIAL GERM CELL TUMOURS

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BACKGROUND AND AIMS: The diagnosis of an intracranial malignant germ cell tumour (icMGCT) frequently follows a prolonged symptom interval. This retrospective study aimed to review the clinical presentation data in these patients and examine the effect of length of symptom interval (SI). METHODS: Clinical data for all patients diagnosed with an icMGCT between January 2002-December 2011 from 5 centres (3 UK (n = 35), 1 German (n = 11) and 1 Canadian (n = 31)) were reviewed. RESULTS: The study cohort included 77 patients (55 Germinoma, and 25 Non-germinoma (NGGCT)) with pineal (31), suprasellar (21), bifocal (22) and other intracranial site disease (3). Median age at diagnosis was 13.9 years (0.6-22.6) and included 11 metastatic and 51 male patients. The median time to diagnosis from first symptom (SI) was 3 months (0-69), but in 26 patients (34%) this interval was more than double this time (>6 months). A SI > 6months was strongly associated with metastatic disease at diagnosis (p = 0.0007) and older patients (p = 0.009). Patients with SI < 6 months have raised intracranial pressure (RICP) as the most common first symptom (70%). This is significantly different to those with SI > 6months where RICP is infrequent (12%, p < 0.0001) and endocrine symptoms (diabetes insipidus) are prevalent (77%) first symptoms. Overall 36% of patients do not have first symptoms related to RICP or visual disturbances whereas only 12% remain free of these symptoms at diagnosis. CONCLUSION: A third of patients with an icMGCT have symptoms for more than 6 months prior to diagnosis. Delayed diagnosis is associated with metastatic disease and progression of symptoms, including the development of visual disturbances and RICP resulting in an increased risk of developing long term effects. Early recognition of symptoms related to hormonal disturbances, in particular DI, may improve timely diagnosis and late effects in these patients.

GC-033. ESTABLISHMENT OF PATIENT TUMOR-DERIVED ORTHOTOPIC XENOGRAFT MODELS OF METASTATIC PEDIATRIC GERMINOMA

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Despite comprising up to 10% of pediatric CNS tumors, an animal model of intracranial germinoma has not been previously established. The standard of care for germinoma is radiation therapy, with recent evidence that neo-adjuvant chemotherapy may allow reduction of radiation dose; however, concern for neuro-cognitive toxicity persists despite the reduction of radiation. A clinically relevant animal model of germinoma would facilitate investigation and discovery of novel agents which may obviate the need for radiation in the future. To develop xenograft mouse models, we implanted germinoma tumor cells from two children with metastatic disease, one from a surgical specimen of a cervical metastatic tumor and the second from disseminated tumor cells in the CSF, directly into the right cerebral hemispheres of NOD-SCID mice. Both patient tumor samples have undergone whole exome sequencing and were found to have mutations in c-kit. The tumors have been serially passaged in xenografts for 3-5 times, with each passaged tumor maintaining the ability to generate tumors, suggestive of the persistence of viable tumorigenic/tumor stem cells. Data from additional tumor models established by our lab have confirmed

molecular and genetic fidelity between xenograft-initiating human brain tumors and their corresponding murine models. The orthotopic location in the mouse brain of the xenograft model should also reasonably replicate the human germinoma tumor microenvironment. Cultured cells are currently growing from both tumor models in order to establish germinoma cell lines. In summary, our orthotopic xenograft murine models of two metastatic pediatric germinomas are the first to be established for this tumor type. These models will allow much needed pre-clinical drug testing of chemotherapeutics and combination therapies as well as further biologic characterization of pediatric germinomas.

GC-034. AN UNUSUAL CASE OF MEDIASTINAL NONSEMINOMATOUS GERM CELL TUMOR (MNSGCT) WITH LATE, CENTRAL NERVOUS SYSTEM (CNS) MATURE TERATOMA (MT) DISSEMINATION

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INTRODUCTION: Anterior mNSGCTs are the most common extragonadal-GCT and carry a poor prognosis 40-50%-overall survival, with a dismal outcome upon relapse. We present a patient with CNS-disseminated MT after successful treatment for mNSGCT and his response to novel management. CASE REPORT: A 20-year-old male diagnosed in 11/14/09 with a poor-risk, primary mNSGCT. Chest CT showed a 10x12x15cm chest mass extending to the left upper lobe, no evidence of metastasis in the peri-bronchial lymph nodes (LN), abdomen, pelvis; and negative testicular ultrasound and head CT. He had elevated serum markers: LDH 752, AFP 169.7; and negative β-HCG. Pathology revealed yolk sac tumor with necrosis, immunohistochemistry was positive for AFP, c-KIT, PLAP, AE1:AE3 and CK7; negative for D2-40, HCG, CD30. He underwent BEPx4 and resection of the residual tumor with negative surgical margins, LN, and normalized tumor markers. In 1/2011 he presented with ataxia and visual disturbance. Brain and spine MRI on 4/6/11 showed innumerable lesions with normal CSF and serum AFP. Pathology was compatible with MT, +GFAP, low Ki67%. From 7/2011-2/2013 he received PD-0332991, a cyclin-dependent kinase 4/6 (CDK4/6)-inhibitor since mature teratomas express high levels of retinoblastoma protein (pRB), whose cell growth is stimulated by CDK4/6. His pathology demonstrated 2+ staining for nuclear pRB in 90% of tumor cells. Since 4/2013 he's received weekly PEG-interferon given its response to a variety of tumors and minimal toxicity. He remains clinically stable with mildly progressive ataxia and radiographically stable disease. DISCUSSION: This is a rare presentation of CNS-metastatic teratoma, which is a radiation-chemotherapy-resistant, purely surgical disease, which lacks effective therapies. CONCLUSION: To the best of our knowledge this is the first reported case of a patient with primary mNSGCT with late dissemination to the CNS as mature teratoma. We are encouraged by stabilization of disease over a 3-year period with non-surgical therapy.

GC-035. CNS GERMINOMA - WHERE DOES PEDIATRIC NEURO-ONCOLOGY END AND ADULT NEURO-ONCOLOGY START?

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BACKGROUND: CNS germ cell tumors occur primarily in children and young adults. Sixty-eight percent of histologically verified cases typically occur in the second decade of life. There is a male predominance (2-2.5:1) and the incidence is higher in Asia when compared to the West. Patients in the late teens and early twenties are often seen in adult neuro-oncology clinics that have limited experience in managing these tumors. CASE STUDIES: Case one: 20-year-old right-handed man presented with several weeks of diplopia. Brain MRI identified a mass in the pineal region with associated hydrocephalus. Stereotactic biopsy of the lesion revealed germinoma. Systemic and CNS staging, including CSF was negative. Case two: 22-year-old man presented with fatigue, decreased libido, frequent urination and excessive thirst. Brain MRI demonstrated 2 enhancing lesions (pineal region and pituitary stalk). Trans-sphenoidal biopsy of the infundibular mass was performed and pathology revealed germinoma. Systemic and CNS staging, including CSF analysis was normal. Both patients received chemotherapy with carboplatin 300 mg/m sq on day 1 and 2, and etoposide 150 mg/m sq on days 1,2 and 3 every 3 weeks for the total of 4 cycles. Both patients achieved complete radiographic response following chemotherapy and were consolidated with irradiation to the whole ventricular system (30.6 Gy in 17 fractions). They both remain in remission; case one - 475 days; case two - 383 days from diagnosis and their neurologic and endocrine symptoms have resolved. DISCUSSION: CNS germinomas are rarely encountered in adult neuro-oncology clinic. Treatment of these patients requires multidisciplinary expertise and involvement of pediatric neuro-oncology as most of the therapeutic approaches were developed for young patients. We chose the approach described above based on the published literature and toxicity profile. Clinical trials in adults developing CNS germ cell tumors are challenging but needed to establish the best approach.

GC-036. ASSOCIATION OF RARE GERMLINE VARIANTS OF JMJD1C WITH INTRACRANIAL GERM CELL TUMORS

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Intracranial germ cell tumors (IGCTs) are rare and biologically diversified tumors affecting mainly male adolescents with the highest incidence in Japan and other Asian countries. Previously we reported that the KIT/RAS and AKT/mTOR signaling pathways are frequently mutated in 62 cases of IGCTs including novel recurrent somatic mutations in KIT (26%), its downstream mediators KRAS (15%), NRAS (5%) and its negative regulator CBL (11%). For the AKT/mTOR pathway, we observed somatic mutations in MTOR (8%), as well as copy number gain and overexpression of AKT1. Moreover, we identified loss-of-function mutations in BCORL1 (10%), a transcriptional corepressor and tumor suppressor. In addition to somatic mutations, we also observed significant enrichment of novel and rare germline variants in JMJD1C in 10 patients including a rare dinucleotide polymorphism (AA to GC, S880P) in 3 genetically unrelated individuals. Among the 10 patients, 9 carriers were from Japan and 1 was from Hong-Kong. JMJD1C germline variants were significantly enriched in the Japanese populations in control cohorts and further enriched (about 5 fold) in Japanese IGCT patients. The odds ratio is 4.8, indicating a strong association between JMJD1C variants and the risk of developing IGCT. The rare variant association tests also revealed significant association of JMJD1C genotype with this disease. JMJD1C is a histone demethylase and coactivator of the androgen receptor. Like BCORL1, there are two conserved LXXLL NR-interacting motifs at the C-terminal, which mediate the interaction with nuclear receptors. Indeed, JMJD1C is known to interact with the thyroid hormone receptor in the thyroid and was reported to interact with the androgen receptor (AR) in human. A recent report showed that it is required in the development and maintenance of germ cells in mice.

GC-037. RESIDUAL GERMINOMA AT SECOND-LOOK SURGERY AFTER INITIAL CHEMOTHERAPY IN A PATIENT WITH CENTRAL NERVOUS SYSTEM MIXED MALIGNANT GERM CELL TUMOR

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Central nervous system (CNS) germ cell tumors (GCT) are classified as either germinomas (65%) or mixed malignant germ cell tumors (MMGCT); a heterogeneous group of tumors comprised of two or multiple GCT elements including germinoma, mature teratoma (MT), immature teratoma (IT), embryonal carcinoma (EC), yolk sac tumor (YST), or choriocarcinoma. Germinomas are exquisitely chemotherapy sensitive and is rare to find germinoma elements on second-look surgery after initial induction chemotherapy. Out of 126 patients enrolled on the first and second international CNS GCT studies, 10 patients underwent second-look surgery after three cycles of chemotherapy for residual radiographic abnormality. Three of 10 patients had MT, two had IT, and five had necrosis/scar tissue pathologically. We report a patient with CNS MMGCT who had pure germinoma on second-look surgery after receiving six cycles of chemotherapy. A 9-year old Hispanic female presented with 1-year history of increased urination/thirst, 4-week history of eye deviation, and a 2-week history of headaches and difficulty chewing. A brain and spine MRI showed a large suprasellar and pineal mass with leptomeningeal dissemination along various cranial nerves and in the spinal cord. Her serum HCGβ was normal, serum AFP was 63.8, CSF AFP was 15.7 and CSF HCGβ was 76. Pathology showed a MMGCT with features of germinoma (>90%), EC

(<5%), and YST (<5%). She received six cycles of chemotherapy with carboplatin/VP-16 alternating with Ifosfamide/VP-16. MRI of the brain and spine after six cycles of chemotherapy showed complete radiographic resolution of all tumor burden, with the exception of suprasellar mass, which grew in size. Tumor markers normalized in the serum and CSF. Growing teratoma syndrome was suspected. She then underwent a second-look surgery, which revealed pure germinoma on histopathology. In conclusion, although rare, Germinoma elements can be present on second-look surgery in patients with < complete response to initial chemotherapy.

GC-038. DOSIMETRIC BENEFITS OF PROTON THERAPY FOR INTRACRANIAL GERMINOMA

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Intracranial germinomas(ICG) are commonly diagnosed and treated at child and adolescent period of life. In this study, we evaluated whether proton beam therapy(PBT) would have dosimetric benefits over the photon beam radiotherapy(XBT) techniques for various types of ICG targets. Three-dimensional conformal radiotherapy(3D-CRT), intensity modulated radiotherapy(IMRT), passively scattered proton therapy(PSPT), and spot scanning proton therapy(SSPT) plans were performed. Targets were defined for 4 different areas, and included whole ventricle(WV), pineal gland(PG), suprasellar(SS), and basal ganglia(BG). For targets, plan quality indexes such as conformity index(CI), homogeneity index(HI), and gradient index(GI) were calculated. Also, minimum, maximum, and mean dose were calculated for normal brain, temporal lobe, hippocampus, and pituitary gland, and were compared. As a result, modified plan quality index for targets, calculated by GI/(CI × HI), were 7.2, 6.4, 4.1 and 3.0 for 3D CRT, IMRT, PSPT and SSPT plans, respectively, suggesting superior plan quality for PSPT and SSPT. For WV, there was low (<20% dose reduction) benefit of PSPT and SSPT in saving hippocampus whereas temporal lobes and pituitary gland showed moderate (20-40% reduction) to high (>40% reduction) degree of benefit in PSPT and SSPT. Also, normal brain volume receiving more than 10Gy/15Gy dose reduced to 74% and 46% of 3D-CRT in PSPT and SSPT, respectively. For targets covering SS tumor area, there was moderate benefit of PSPT and SSPT for temporal lobes and hippocampus, but low for pituitary gland. However, for targets of PG, PSPT and SSPT showed high benefit in saving all 3 organs at risk(OAR). For tumors arising in BG, there was moderate benefit of saving 3 OARs. In conclusion, PBT provides superior tumor conformity and normal tissues savings over XBT in different tumor locations of ICG. It is awaited whether this extent of normal tissue saving could be translated into clinical benefits in children with ICG.

GC-039. NON-GERMINOMATOUS GERM CELL TUMORS WITH SYNCHRONOUS PINEAL AND SUPRASELLAR INVOLVEMENT

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INTRODUCTION: Bifocal presentation of central nervous system (CNS) germinomas, with synchronous pineal and suprasellar involvement, is common, and associated with favorable outcome. The incidence and outcome of bifocal presentation of non-germinomatous germ cell tumors (NGGCT) is less well described. METHODS: Cases with NGGCT and bifocal involvement were identified using an institutional database; individual medical records were reviewed. RESULTS: Of 13 patients with CNS NGGCT diagnosed between Jan 2006 and Dec 2011, 4 (31%) had synchronous suprasellar and pineal involvement at presentation. Mean age was 11.5 years. Cerebrospinal fluid (CSF) alpha-fetoprotein (AFP) was mildly to moderately elevated in all 4 patients. Beta-human chorionic gonadotropic was significantly elevated in 1 patient. Biopsy was performed in 1 patient, and revealed germinoma and yolk sac tumor elements. One patient was lost to follow-up. The other 3 patients are alive with median follow-up of 43 months. One patient who initially refused radiotherapy suffered a relapse in the third ventricle 10 months after diagnosis, and underwent successful salvage therapy with high-dose chemotherapy and craniospinal radiation. The other 2 underwent multi-modality therapy and remain progression-free. CONCLUSION: Our experience suggests that bifocal involvement is a common in patients with CNS NGGCT, and may not be associated with a poorer prognosis. Elevated AFP in all 4 patients suggests an association between bifocal presentation and yolk sac histology.