

**Abstracts for the
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terizing these tumors. Because of the current trend in limiting the surgical intervention of intracranial GCT to only obtaining biopsy for diagnosis, comprehensive genetic profiling of these tumors has not been done because of the scarcity of tissues. We have recently overcome this obstacle by optimizing a number of genomic technologies to carry out whole-genome scanning using minute quantities of formalin-fixed, paraffin-embedded brain tumor tissues. These technologies include (1) laser capture microdissection (LCM) to harvest homogeneous populations of cells from a paraffin section with mixed cell types, which is very typical of the majority of intracranial GCT; (2) whole-genome amplification of DNA extracted from LCM-harvested cells using as little as 1 ng of DNA as starting materials, which is equivalent to approximately 200 captured cells; and (3) microarray-based comparative genomic hybridization (aCGH) and high-throughput whole-genome allelotyping using amplified DNA. We have optimized each of these technologies and have validated this integrated approach for the study of pediatric brain tumors. Our overall objective is to fully characterize the phenotypic and genotypic alterations that are clinically relevant to intracranial GCT. This presentation describes the results and implications of aCGH profiles and genome-wide allelotyping profiles of CNS germ cell tumors from patients with various ethnic backgrounds.

***B5. MOLECULAR ANALYSIS OF CHILDHOOD INTRACRANIAL AND EXTRACRANIAL MALIGNANT GERM CELL TUMORS**

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We studied the gene expression characteristics and genomic abnormalities of frozen MGCTs banked with the UKCCSG to determine whether these heterogeneous tumors share fundamental genetic abnormalities and whether distinct profiles associate with particular clinical and/or pathological features. In this study, 38 MGCTs underwent histological confirmation followed by nucleic acid separation using TRIzol. RNA quality and integrity were determined by spectrophotometry and microelectrophoresis. Standard Affymetrix protocols were followed for the U133A genechip and analyzed by using GeneSpring. Extracted and DOP-PCR-amplified DNA, once labeled, underwent both metaphase and array CGH analysis (at 1-MB intervals) across the entire genome. Of 38 MGCTs analyzed, there were 14 germinomas (3 intracranial), 23 yolk sac tumors (9 within teratomas), and 1 embryonal carcinoma. All yielded suitable DNA, and 32 produced high-quality RNA. Expression analysis demonstrates substantial homology between tumors, and supervised clustering against mature and immature gonad controls reveals "new cancer biomarkers" in this tumor group. Unsupervised clustering divides the tumors by histology, producing "cancer signatures," with as few as 133 genes discriminating between germinomatous and nongerminomatous tumors. Regarding CGH, recurrent gains of 1q, 12p, and 19 were observed in greater than half of the cases, with frequent gains on chromosome 2, 11q, 17, 20, and 21. Loss of 1p, 4, 6q, and 13 was present in a third or more of cases. When compared to the clinical parameters and outcome information from the UKCCSG GC II Protocol, there was no correlation between any particular genetic abnormality and histology, age at presentation, primary site, tumor stage, or survival. Array CGH analysis confirmed these gains and losses, but also consistent and novel areas of genomic imbalance, with areas which discriminate between histologies. We conclude that while broadly similar (irrespective of whether intracranial or extracranial), the gene expression profiles of pediatric MGCTs differ significantly from controls and cluster independently by histology. A limited number of genes account for these differences and are currently under further investigation. The genomic imbalances present confirm previous gains and losses on chromosomes 1, 4, 6, 12, 13, and 20, but with chromosomes 17 and 19 in particular meriting further investigation.

***B6. GENETIC ANALYSIS OF CENTRAL NERVOUS SYSTEM GERM CELL TUMORS (CNS-GCT)**

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The objective of our study was to characterize genetic profiles in CNS-GCT in children and adolescents. After histologic review, fresh-frozen or archival tumor samples from 17 patients (12 male, 5 female, median age of 11 [neonate–25 years]) were analyzed with comparative genomic hybridization. Among these, there were six germinomas, seven malignant nongerminomatous CNS-GCTs, and four pure teratomas. Tumor DNA and normal male control DNA were differentially fluorescence-labeled and co-hybridized against normal metaphases. The tumor-to-control ratio of fluorescence was analyzed with a designed software package (Applied Imaging Inc.). All germinomatous and nongerminomatous CNS-GCT and two of four pure teratomas showed multiple chromosomal imbalances. Chromosomal gains (median, 5; range, 1–9) were observed more frequently than losses (median, 1; range, 0–4). Among the chromosomal losses, parts of chromosome 11 (n = 5), 18 (n = 3), and Y (n = 2) were deleted most frequently. Chromosomal gains were most commonly found at 12p (n = 10), 1q (n = 7), 8 (n = 8), 3p (n = 4), and the X chromosome (n = 4). In two cases, gain of 12p was sharply confined to an amplicon at 12p11, thus delimiting the commonly amplified region on 12p. Notably, we observed no difference in the genetic profiles of germinomatous and nongerminomatous CNS-GCT. At the current state of this ongoing study, we have found no significant correlation of specific genetic imbalances with clinical outcome. We conclude that malignant germinomatous and nongerminomatous CNS-GCTs show similar patterns of chromosomal imbalances. Their genetic profiles correlate with those found in mediastinal and gonadal GCTs in children and adolescents, which are characterized by gain of 12p in malignant GCT of adults. This observation and accompanying epigenetic studies reflect the common histogenesis of gonadal and nongonadal GCT. This study was supported by a Max-Eder grant of the Deutsche Krebshilfe.

Previous studies demonstrating biallelic expression of the imprinted genes H19 and IGF2 and loss of DNA methylation of the SNRPN gene have indicated a common precursor cell of GCTs, being the primordial germ cell (PGC). We applied the novel MS-SNuPE technique for the analysis of the IGF2/H19 imprinting control region (ICR) in 55 GCTs (22 children, 7 adolescents, 26 adults) from representative clinical and histologic subgroups. Most GCTs showed low levels of methylation at the IGF2/H19 ICR. All eight ovarian GCTs, 9 of 10 testicular seminomas, 7 of 10 testicular nonseminomas (all adolescents/adults), 6 of 9 testicular yolk sac tumors (YSTs), and 12 of 14 nongonadal GCTs (all infants/children) showed hypomethylation. The highest methylation levels were observed in three childhood YSTs and 2 of 4 spermatocytic seminomas, which are derived from advanced stages of spermatogenesis. We conclude that the predominantly low methylation status of most of the other GCTs correlates with studies demonstrating erasure of the methylation imprint of the IGF2/H19 ICR during embryonal PGC migration and early spermatogenesis. These findings indicate that both gonadal and nongonadal GCTs originate from PGCs that have erased their methylation imprint. Furthermore, this study indicates that imprinting control mechanisms other than the proposed CTCF boundary model are regulating IGF2 expression during this stage of germ cell development and derived GCTs. This study was supported by a Max-Eder grant of the Deutsche Krebshilfe.

***B7. ANALYSIS OF THE H19/IGF-2 IMPRINTING STATUS WITH THE METHYLATION-SENSITIVE SINGLE NUCLEOTIDE PRIMER EXTENSION (MS-SNUPE) METHOD IN HUMAN GERM CELL TUMORS (GCTS) REFLECTS THEIR ORIGIN FROM DIFFERENT STAGES OF PRIMORDIAL GERM CELL DEVELOPMENT**

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Previous studies demonstrating biallelic expression of the imprinted genes H19 and IGF2 and loss of DNA methylation of the SNRPN gene have indicated a common precursor cell of GCTs, being the primordial germ cell (PGC). We applied the novel MS-SNuPE technique for the analysis of the IGF2/H19 imprinting control region (ICR) in 55 GCTs (22 children, 7 adolescents, 26 adults) from representative clinical and histologic subgroups. Most GCTs showed low levels of methylation at the IGF2/H19 ICR. All eight ovarian GCTs, 9 of 10 testicular seminomas, 7 of 10 testicular nonseminomas (all adolescents/adults), 6 of 9 testicular yolk sac tumors (YSTs), and 12 of 14 nongonadal GCTs (all infants/children) showed hypomethylation. The highest methylation levels were observed in three childhood YSTs and 2 of 4 spermatocytic seminomas, which are derived from advanced stages of spermatogenesis. We conclude that the predominantly low methylation status of most of the other GCTs correlates with studies demonstrating erasure of the methylation imprint of the IGF2/H19 ICR during embryonal PGC migration and early spermatogenesis. These findings indicate that both gonadal and nongonadal GCTs originate from PGCs that have erased their methylation imprint. Furthermore, this study indicates that imprinting control mechanisms other than the proposed CTCF boundary model are regulating IGF2 expression during this stage of germ cell development and derived GCTs. This study was supported by a Max-Eder grant of the Deutsche Krebshilfe.

***B8. GENOME-WIDE HIGH-RESOLUTION IDENTIFICATION OF NOVEL GENOMIC ALTERATIONS IN BRAIN TUMORS**

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Malignant brain tumors are the most devastating cancers. However, the molecular pathogenesis remains poorly understood. A comprehensive molecular profiling of the tumors will allow increased accuracy of disease risk stratification for patients with brain tumors and will lead to the identification of novel therapeutic targets. Recently, through a combination of novel genetic approaches and biochemical methods, we have identified and characterized several new genetic alterations contributing to the pathogenesis of brain tumors. Whereas comprehensive screens for activating or inactivating mutations would require sequencing and functional studies of tens of thousands of genes, measurements of the genomic DNA copy-number, or gene dosage, within chromosomal segments can be far more amenable for analysis. Complete sequencing of the human genome has made possible the development of novel techniques that narrow the resolving power of genome-wide screens to regions covering one or a small handful of genes (≤ 1 Mb). Through a genome-wide high-resolution screening, we identified multiple genetic alterations of medulloblastomas by digital karyotyping.

OTX2 (human orthodenticle homolog 2) is one of the identified oncogenes of anaplastic medulloblastomas. We found that *OTX2* was amplified more than 10-fold in several medulloblastoma cell lines. Normally, *OTX2* is expressed during the brain development and turned off in adult brain tissues. Gene expression analyses showed that *OTX2* transcripts were present at high levels in 14 of 15 (93%) medulloblastomas with anaplastic histopathologic features. Knock-down of *OTX2* expression by siRNAs inhibited medulloblastoma cell growth in vitro, whereas pharmacologic doses of all-trans-retinoic acid repressed *OTX2* expression and induced apoptosis only in medulloblastoma cell lines that expressed *OTX2*. These observations suggest that *OTX2* is essential for the pathogenesis of anaplastic medulloblastomas and that these tumors may be amenable to therapy with all-trans-retinoic acid. Recently, we also detected the expression of *OTX2* in pineoblastomas.

*B9. HUMAN GERM CELL TUMORS: IDENTIFICATION OF RELEVANT SUBGROUPS

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On the basis of various characteristics, including age of the patient at clinical presentation, histology, chromosomal constitution, status of genomic imprinting, and chromosomal constitution, different entities of human germ cell tumors (GCT) can be recognized (Oosterhuis and Looijenga, *Nat. Rev. Cancer*, 2005). These are found at specific anatomical locations, including hypothalamus/pineal gland regions. The clinical behavior is dependent on a number of parameters, including sex of the patient, age at clinical presentation, and histology of the tumor. Within the brain, two groups of GCT can be distinguished, (1) yolk sac tumors and teratomas and (2) seminomatous tumors (classified as germinoma) and nonseminomas. These entities of GCT have specific genomic aberrations, which support existence of different pathogenetic pathways and genes involved. One of the most recent steps forward in the diagnosis of seminomatous-GCT and embryonal carcinoma, being the undifferentiated component of nonseminomas, is identification of OCT3/4 (POU5F1) as a immunohistochemical marker (Looijenga et al., *Cancer Res.*, 2003). Its value has been demonstrated in multiple independent studies, and it is now generally considered as most informative. This presentation includes an update on the actual status of OCT3/4-POU5F1.

*EP1. EPIDEMIOLOGY AND OUTCOME OF CNS GERM CELL TUMORS IN THE UNITED STATES, SEER, 1975–2000, A DISEASE OF ADOLESCENTS AND YOUNG ADULTS (AYA)

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Data from the NCI Surveillance, Epidemiology and End-Results (SEER) Program were analyzed to determine the incidence and outcome of CNS germ cell tumors in the United States. The SEER incidence and SEER 5-year survival of CNS germ cell tumors were determined for each 5-year age group and 15-year age group from 0 to 44 years of age between the years 1975 to 2000. CNS germ cell tumors were seen almost exclusively in individuals between the ages of 0 and 34, with a peak incidence of 0.2 per 100,000 person-years at ages 15 to 19. Thirty-four percent of CNS germ cell tumor occurred between ages 0 and 14, 57% between 15 and 29, and 9% between 30 and 44. The incidence of CNS germ cell tumors in males, all ages combined, was 3.7 times that seen in females, but in the adolescent and young adult group, the incidence in males was more than 12 times that seen in females. A marked male predominance was seen for pineal region germ cell tumors (male:female of 18:1), but there was no gender predilection for pituitary location. Pineal region tumors outnumbered suprasellar tumors by a ratio of 5.4:1. The 5-year survival rates, in the recent era, for all subtypes of CNS germ cell tumors combined were 81% for ages 0 to 14 and 94% for ages 15 to 29. These survival statistics mainly represent the outcome for germinomas, which comprised 58% of the 0–14-year age group and 82% of the 15–29-year group. A steady improvement in survival for CNS germ cell tumors has been seen over the last two decades in individuals 0–14 years of age and 15–29 years of age. CNS germ cell tumors are predominantly an AYA neoplasm, and thus they are the model tumor type for future international collaborative AYA trials. We propose a multicontinent, combined age approach to the treatment of CNS germ cell tumors, which will allow for randomized trials and further advancement in knowledge of these rare tumors.

*EP2. EPIDEMIOLOGY OF INTRACRANIAL GERM CELL TUMOURS (ICGCT)

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Epidemiological data on ICGCT are available in cancer registries and clinical case series. Significant discrepancies between registry data and clinical series and clinical series raise the question of the quality and reliability of the information available. We reviewed data from IARC on nine countries (Japan, Singapore, Germany, UK, Denmark, US, Israel, Colombia, Canada), the Brain Tumor Registry of Japan (BTRJ), information collected from 25 series of patients with ICGCT (1132 patients), and publications on teratoma in infants (n = 232). Data were collected on age, gender, histology, tumor site, tumor markers, and outcome. Data from registries confirm significant variation in the incidence of ICGCT, with a higher incidence in Asian countries. ICGCTs account for 0.4% (SEER-US) to 2.4% (Japan-Osaka) of all CNS tumors and 8.1% (Israel) to 41% (Denmark) of all germ cell tumors. During the period 1984 to 1996, the BTRJ recorded 1463 ICGCTs (vs. 591 medulloblastomas), which represent 2.8% of all CNS tumor and 15.3% of all pediatric CNS tumors. SEER data for 1975 to 1995 suggest a steep increase in the incidence of ICGCT (0.5 cases/million in 1975–1979 to 1.9/million in 1990–1995). Differences are reported in the male/female ratio ranging from 1.0 (SEER-US) to 3.47 (BTRJ). The M/F ratio is significantly higher in published series (n = 3.6). Information on tumor site, histology, and tumor markers is available only from published series and the BTRJ. Forty-eight percent of ICGCTs arise in the pineal area and 30% in the suprasellar region. Some risk factors for ICGCT have been identified, including Klinefelter's syndrome and Down syndrome. The high prevalence in the Asian population seems to persist in transplanted populations. In infants, teratomas account for 5.4% of brain tumors, with large variations between series and no evidence of ethnic specificity. We conclude that available data on epidemiology of ICGCT are limited. Significant benefit would be achieved in considering national and international registries that systematically collect relevant information on these tumors.

*EP3. INTRACRANIAL GCTS IN THE FIRST YEAR OF LIFE: REPORT ON 10 CASES OBSERVED BY THE INFANTS CNS STUDY IN ITALY

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CNS GCTs in the first year of life seem to represent distinct clinicopathological entities, but more studies are necessary in order to better clarify their biological, genetic, and clinical peculiarities. All cases with diagnosis of GCTs and age ≤ 1 year, registered by the Italian study for infant CNS tumors, were eligible for the present study. Ten cases were registered, three males and seven females, whose ages ranged from 0 to 1 year (median, 5 months). Tumor types were as follows: mature teratoma (MT), three; immature teratoma (IT), five; gonadoblastoma, one; and yolk sac tumor (YST), one. Sites of involvement were as follows: posterior fossa, two; suprasellar, one; pineal, one; cerebral hemisphere, three; temporal fossa + skull base, one; sphenoidal bone with intracranial extension, one; and spinal, one. All patients presented with negative markers. The three cases with MT are alive at 11, 12 and 14 years from diagnosis; two of them underwent complete surgical removal. Residual tumor after surgery was present in one case; no irradiation was delivered in all three cases; in the case with residual tumor, no progression was observed at last follow-up (14 years after operation).

In the five cases of IT, three showed only foci of IT in a prevalent mature component; all of them are long-term survivors (mean follow-up of 9 years) without any adjuvant treatment after surgery. Two patients had pure IT containing mainly neuroepithelial tissue; both required chemotherapy (one because no tumor removal was possible; the second because of regrowth after complete removal and a "wait and see" approach). The first case had severe complications during chemotherapy, preventing its completion; this patient died of tumor progression. The patient with gonadoblastoma died soon after diagnosis, as no treatment was feasible (congenital huge tumor); the patient with YST is a long-term survivor (7 years from diagnosis), having been treated with systemic chemotherapy for one year (carboplatin, cyclophosphamide, vincristine, bleomycin and etoposide). We conclude that CNS GCTs in the first year of life are mainly teratomas; a consistent proportion of them present with immature components that, when limited to foci within a mature pattern and completely removed, do not require adjuvant treatment.

***EP4. CNS GERM CELL TUMORS IN CANADA**

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The Canadian Pediatric Brain Tumor Consortium, a network of all pediatric neuro-oncology programs in Canada, conducted a national survey to determine frequency and characteristics of CNS germ cell tumors in Canada. A national retrospective hospital chart review was done. Inclusion criteria for patients were to be under the age of 18 years with a diagnosis as having a CNS germ cell tumor between 1990 and 2004. Chart review included age and year of diagnosis, pathological diagnosis, ethnic origin, location of tumor, and biological markers. A total of 112 cases were ascertained, which revealed a mean yearly incidence of 0.09 cases per 100,000 person-years. Though incidence of case ascertainment varied from year to year, clear trends were not seen. Incidence of germinomas (N = 72) was 0.67 per 100,000 person-years with a 2.4:1 male prevalence. Mean age of onset was 12 years. Tumor locations were pineal (41.7%), suprasellar (31.9%), bifocal (15.3%), basal ganglia (5.6%), and hemispheric (5.6%). Twenty-five percent had evidence of disseminated disease at diagnosis. The incidence of nongerminoma GCT (N = 40) was 0.37 cases per 100,000 person-years, with a 7:1 male predominance. Mean age was 10.5 years. Tumor locations were pineal (70%), suprasellar (25%), bifocal (2.5%), and basal ganglia (2.5%). Furthermore, 22.5% had evidence of disseminated disease at time of onset.

***EP5. CHILDHOOD CANCER REGISTRY IN ARGENTINA: CNS GERM CELL TUMORS, 2000–2003; REGISTRO ONCOPEDIATRICO HOSPITALARIO ARGENTINO, ROHA FUNDACION KALEIDOS**

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ROHA is a not-for-profit institution committed (Fundacion Kaleidos) since 2000 to gathering and disseminating epidemiologic data on childhood cancer, working as a registration net all over the country. The main activity of this net is to establish a childhood cancer registry at almost all the institutions where children with cancer are treated in Argentina. The total Argentine population is 36,260,130 (Census 2001), of which 28% are aged under 15. The Registry collected data from 67 sources, eight population-based cancer registries, and two cooperative medical groups. This report includes a total of 4435 cancers, among which are 34 CNS germ cell tumors (0.8%) diagnosed between 2000 and 2003 in persons younger than 15 years of age. Primary tumor sites were coded by using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) and grouped by histologic type according to the International Classification of Childhood Cancer (ICCC, 1996). After an intensive and exhaustive effort, we have registered about 90% of the estimated cases of leukemia and 80% of the remaining tumors; additionally, we have documented the migration patterns of these patients. We present our CNS germinal tumor experience, number of cases, the distribution of cases by age and sex, location, treatment and overall survival.

***EP6. DESCRIPTIVE EPIDEMIOLOGY OF PRIMARY GERM CELL TUMORS OF THE BRAIN AND CENTRAL NERVOUS SYSTEM IN THE UNITED STATES**

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The objective of this study was to estimate the incidence, describe temporal trends in incidence, and estimate survival rates for all primary germ cell tumors of the brain/CNS (GCTs) and for the following subgroups of GCT: malignant GCT, nonmalignant GCT, and malignant pineal GCT. CBTRUS compiled data on all primary GCT diagnosed between 1997 and 2001 from 15 state cancer registries. Age-adjusted rates were standardized to the Year 2000 U.S. standard population. CBTRUS compiled data from six state cancer registries for all primary GCT diagnosed from 1985 to 1999. Multiplicative Poisson regression was used to calculate the average annual percent change (AAPC [95% CI]) in incidence rates over the time period while controlling for age, sex, race, and microscopic confirmation, and to statistically compare trends over time. Joinpoint regression analysis was utilized to identify sharp changes in incidence over time. Relative sur-

vival rates for primary malignant GCT for cases diagnosed between 1973 and 2001 in nine SEER areas were also estimated. The overall incidence rate for GCT was 0.08/100,000 person-years (py) (CBTRUS; N = 361). The rate was highest in children 0 to 19 years and young adults 20 to 34 years (0.18 and 0.10/100,000 py, respectively). Rates were higher in males than in females (0.11 vs. 0.05/100,000 py), and in whites than in blacks (0.09 vs. 0.04/100,000 py). Overall the incidence of primary GCT (N = 140) did not significantly increase over the time period 1985 to 1999 (AAPC = 3.0% [-0.9%, 6.9%]). However, incidence rate trends varied by sex, with females experiencing a significant increase over the time period (AAPC = 10.7% [2.5%, 19.6%]) compared to no significant change in males (AAPC = 0.8% [-3.6%, 5.2%]). Among children (ages 0–19), there was a significant positive time trend (AAPC = 5.1% [0.5%, 9.9%]), while among young adults (ages 20–34), there was no significant change in incidence over time (AAPC = -0.4% [-8.6%, 7.7%]). The one-, five-, and 10-year survival rates following diagnosis of a primary malignant GCT were 88%, 75%, and 70%, respectively (SEER; N = 363). Additional rates by GCT subgroup, age, sex, and race are presented. This analysis adds to the scant literature on trends in incidence of nonmalignant and malignant GCT of the brain/CNS and may facilitate, along with other descriptive epidemiologic studies, the identification and elucidation of risk factors for these tumors.

***G1. LONG-TERM FOLLOW-UP OF INTRACRANIAL GERMINOMA TREATED WITH PRIMARY CHEMOTHERAPY FOLLOWED BY FOCAL RADIATION TREATMENT: THE SFOP-90 EXPERIENCE**

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Intracranial germinoma is highly radiosensitive and associated with excellent long-term survival after craniospinal irradiation. Recent studies aim at optimizing the therapeutic ratio and have examined whether primary chemotherapy allows for reducing volume and/or dose of irradiation. We report long-term results of the SFOP-90 prospective study that delivered combined approach with focal radiotherapy (RT). From 1990 to 1999, 60 nondisseminated, uni-bifocal germinomas, histologically proven (49, three with mature teratoma component) or presumed (11), all with HCG <50 IU/l- α FP <12 ng/ml, received four alternating courses of etoposide-carboplatin, etoposide-ifosfamide, followed by 40 Gy to the tumor bed. Five- and eight-year OS and EFS were analyzed according to Kaplan-Meier; pattern of relapse was reviewed with respect to radiation fields. Special efforts were made to conduct an evaluation of neuropsychological profile and academic achievement. Seventeen girls and 43 boys, ages 5 to 24 (median 13), were registered: pineal, 48%; suprasellar/hypophysitis, 36%; and bifocal, 11%. Major response to chemotherapy was obtained in all but four patients (removal of residue showed teratoma in three, necrosis in one). At median follow-up, 76 m (range, 7–136), results were as follows: Five- and eight-year OS, 98% \pm 3.6; EFS, 83% \pm 3.1; relapse rate, 16.4%; median time, 36.5 m (range, 10–122). Ventricular dissemination was the predominant pattern of relapse (8/10), at margins or out of radiation field. One patient died of a second relapse. Twenty percent of the children/adolescents had a neuropsychological outcome evaluation that showed good preservation. Quality of staging/management constantly improved over years. Updated results and analysis of predictive factors of ventricular dissemination are presented. We conclude that localized germinoma patients treated by the combined approach using focal irradiation achieve good survival rates and neuropsychological outcome. Pattern of relapse shows the ventricular system as the area at risk of dissemination and suggests enlargement of radiation field at prophylactic dose to include the ventricles. Identification of predictive factors of ventricular spread is necessary if focal radiotherapy is considered.

***G2. REVIEW OF CONTEMPORARY NORTH AMERICAN CLINICAL TRIALS IN PRIMARY CNS GERMINOMA**

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Large volume, full-dose radiotherapy (RT) currently used in the curative management of localized CNS germinoma may cause long-term neurocognitive, endocrine, and hearing impairments. Exploratory studies in the United States, Europe, and Japan have used combined chemotherapy (CHT) and RT or CHT alone to decrease RT morbidity. The Beth Israel Germinoma Consortium (BIGC) accrued 38 patients from 1998 to 2004 using a protocol combining CHT with carboplatin, etoposide, cisplatin, and cyclophosphamide followed by reduced dose \pm volume RT in complete responders (CRs). The overall CR rate to CHT was 89% (34/38), and 87% (26/30) of the M0 patients (those with localized disease) received reduced volume (involved field rather than whole ventricular) and reduced dose (30 rather

than 45 Gy) RT. After a median follow-up of 45 months, all 38 patients are alive, and the PFS is 89%. COG has very recently launched a phase 3 germinoma trial (ACNS0232) comparing standard radiotherapy (Reg A) to CHT followed by the response-based, reduced radiotherapy (Reg B) similar to the BIGC pilot for patients 25 years and under with histologically confirmed, newly diagnosed primary CNS germinoma (serum and CSF AFP are normal and serum and CSF HCG are both <50 mIU/ml). The goals of this study include comparing OS and PFS as well as cognitive function and quality of life. Patients will be assigned to localized (M0) or disseminated disease (M+) categories, and all M+ patients will receive CSRT. All M0 patients in Reg A will receive whole ventricular RT (24 Gy) with a boost (21 Gy) to the primary tumor, and all M+ patients will receive CSRT (24 Gy) with a boost (21 Gy) to measurable disease. M0 patients in Reg B who have a CR to CHT will receive only involved field RT (30 Gy), and M+ patients in CR will receive CSRT (21 Gy) with a boost (9 Gy) to measurable disease. The inclusion criteria for M+ are as follows: patients with multiple intracranial lesions, leptomeningeal brain or spinal disease, + CSF cytology, endoscopic observation of intraventricular seeding, intraparenchymal primary tumor; patients with pineal region primaries who present with DI; and M0 patients who have a dramatic reduction in the "uninvolved" pineal or infundibulum after chemotherapy. The BIGC pilot will be reported in detail. ACNS0232 plans to accrue 225 patients over five years. The ACNS0232 trial should be able to resolve whether a reduction in dose and volume of RT, facilitated by neoadjuvant CHT, will improve the cognitive performance and quality of life in long-term survivors of CNS germinoma without compromising overall survival.

G3. RESPONSE TO CARBOPLATIN AND ETOPOSIDE WITH RADIATION IN PRIMARY CNS GERMINOMA

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Treatment for CNS germinoma aims to reduce toxicity and maintain effectiveness. We report on a series of patients treated with combined chemotherapy and radiation. Ten patients with germinoma underwent four cycles of carboplatin and etoposide, followed by radiation treatment. Six patients received involved field irradiation only, two whole ventricle, and two craniospinal axis irradiation. Medical records were reviewed to collect data regarding acute hematopoietic toxicity, treatment response, and survival. Patient characteristics were as follows: Age ranged from 8 to 22 years, with a median of 12.8; seven patients had biopsy-positive germinoma, two had mixed germinoma and mature teratoma, one was diagnosed on the basis of radiographic appearance and presence of CSF beta HCG; two patients had gross total tumor resection. Chemotherapy toxicity was as follows: Grade III/IV neutropenia and thrombocytopenia was seen in 70% of evaluable courses and grade III/IV anemia in 25%; 70% of patients required platelet transfusion, and 40% required packed red blood cell transfusion. The average time to recovery from chemotherapy was 23 days. Chemotherapy response was as follows: Of six patients evaluable for chemotherapy response, four had complete or near complete responses, and two had partial responses. One patient who underwent a gross total resection of tumor developed recurrent disease on chemotherapy. Survival is as follows: Nine of 10 patients are alive without disease, with median follow-up of 16 months. We conclude that acute hematopoietic toxicities are frequent but transient on this regimen. Our report supports the use of preirradiation chemotherapy, showing a high response rate allowing for reduction in volume and dose of radiation therapy in a subset of patients while maintaining good survival over a short follow-up time.

*G4. UPDATE OF PROTOCOL PATIENTS WITH CNS GERMINOMA TREATED ACCORDING TO SIOP CNS GCT 96

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The SIOP CNS GCT 96 offers for germinoma two treatment options, either combined treatment with four cycles Carbo-PEI followed by focal RT (40 Gy) (option B) or craniospinal RT, 24 Gy, with a tumor boost of 16 Gy (option A) (also to metastatic sites). In case of metastatic disease, combined-therapy patients also receive craniospinal RT. The comparison of the two therapy arms aims to clarify if both treatment options are equivalent in terms of event-free survival (EFS) rate and toxicity. All registered protocol patients with diagnosis until 01/01/2004 regardless of age and dissemination are evaluated. Protocol patients are all patients who receive the complete and correct therapy according to dissemination. In SIOP 96, 170 protocol patients with CNS germinoma are registered: 127 boys and 43 girls, with a median age of 13. Main localization is as follows: pineal region (49%), suprasellar/hypophysis region (28%), bifocal disease (22%),

and other (1%). A total of 113 patients receive option A treatment, of whom 13 are metastatic; 57 patients are treated according to option B, of whom 13 are disseminated. Diagnosis is obtained by stereotactic biopsy in 69 patients, open biopsy in 35 patients, and subtotal or total resection in 42 children; one patient is diagnosed through cytology, and for three patients, no information is available. EFS for option A is 0.93 ± 0.03 (follow-up, 2–116 months, median 35 months) and 0.90 ± 0.04 for option B (follow-up, 4–83 months, median 26 months). Eleven events occurred. Under option A, two patients died of complications that are not directly related to therapy, four patients relapsed locally, and three have a different diagnosis at relapse (2 × YST, 1 × im. teratoma). Under option B, there were one local relapse (germinoma [G]), three ventricular (2 × G, 1 × choriocarcinoma), and one spinal (G). We conclude that the outcome of patients with germinoma, with either combined treatment or craniospinal RT only, is excellent. Relapses reveal the importance of complete staging and of control of subclinical disease (ventricular). Registered acute or long-term toxicity of both therapy options is under evaluation. In the forthcoming germinoma protocol, all patients with localized germinoma and a complete workup (CSF, serum, imaging) are treated with a combined approach, including ventricular RT. All metastatic patients will receive craniospinal RT. This study is supported in part by Deutsche Krebshilfe.

*G5. HCG-PRODUCING GERMINOMA: ANALYSIS OF JAPANESE PEDIATRIC BRAIN TUMOR STUDY GROUP RESULTS

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Germinoma with syncytiotrophoblastic giant cells (STGCs) are considered to behave more aggressively than usual germinoma, but there is a controversy. The clinical behavior of germinoma, which produce human chorionic gonadotropin (HCG), is not well understood yet. To clarify the clinical significance of germinoma with STGC and HCG-producing germinoma, the tumor marker values and their correlation to the clinical course or response to the treatment were analyzed. Patients with germ cell tumor who were registered for the multi-institutional Japanese Pediatric Brain Tumor Study Group were analyzed. There were 131 germinoma and 39 germinoma with STGC or HCG-producing germinomas (here designated as HCG germinoma). The patients were treated according to the study group protocol (Matsutani 1998); briefly, chemotherapy (ICE regimen [ifos, CDDP, etoposide]) or CARE regimen (CBDCA, etoposide) was given initially followed by extended local radiotherapy. The number of courses of the chemotherapy and the radiation dose were determined according to the classification of germ cell tumors of the study group. The range of HCG value was 2 to 200 mIU/ml, and the beta-HCG value was 0 to 233 in HCG germinoma (except one extreme case). These values were lower than those of choriocarcinoma (up to 8,492 for HCG and 20,048 for beta HCG, only one of HCG or beta-HCG was elevated in some patients). After induction therapy, the total tumor-free rate for germinoma was 90.1%, whereas it was 84.6% for HCG germinoma. The recurrence rate was 12.4% and 12.8%, respectively. The five-year-survival rate was 98.3% and 100%, respectively. Since there was no significant difference between two groups in terms of clinical course, the intensity of treatment was compared. The mean radiation dose was higher in HCG germinoma (27.8 Gy vs. 36.9 Gy, $P < 0.01$), and the number of chemotherapeutic courses was also greater in HCG germinoma (3.1 times vs. 5.3 times, $P < 0.01$). However, the mean number of chemotherapeutic courses until tumor disappearance was somewhat smaller in HCG germinoma (1.9 vs. 1.7). Thus HCG germinomas did not show a worse clinical course compared to germinoma with this intensified treatment protocol. Since the number of chemotherapeutic courses until the good tumor response was not different, we are planning to treat with same regimen for germinoma and HCG germinoma in the coming new study protocol.

*G6. UPDATE ON PROTOCOL PATIENTS WITH LOCALIZED GERMINOMA TREATED ACCORDING TO SIOP CNS GCT 96 (OPTION B: CARBOPEI + FOCAL RT)

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The concept of combined treatment with chemotherapy and focal irradiation in localized intracranial germinoma was part of the SFOP TGM TC90 protocol. Based on this experience, this treatment option was therefore incorporated in the SIOP CNS GCT 96 trial. All registered germinoma patients (diagnosis until 31/12/03) regardless of age, with histologically

proven (resection or biopsy), tumor marker negative (AFP < 25 ng/ml and HCG < 50 IU/l), uni- or bifocal (only if pineal and suprasellar) nonmetastatic (no tumor cells in CSF and negative spinal MRI) intracranial tumors and protocol therapy were included. The five-year EFS and survival according to Kaplan-Meier are analyzed. In SIOP 96, 31 boys (ages 6–25, median 13) and 13 girls (ages 5–15, median 10) were registered. Main localization was the pineal region (48%), followed by suprasellar/hypophysial region (30%) and bifocal disease (20%), and other (2%). Within five years of follow-up time, events occurred only in five of 44 patients (8, 9, 10, 18, and 22 months after diagnosis). With a median follow-up of 26 months (4–83 months), EFS was 0.87 ± 0.06 , and OS was 0.91 ± 0.06 . Out of five event patients, two had a local relapse, and two had a ventricular and one a spinal relapse. Relapse diagnoses were obtained clinically (imaging + markers). In one patient with local relapse, histology after relapse treatment showed an additional teratoma component. One patient with ventricular spread showed choriocarcinoma (clinical) (no CSF-diagnostics at primary diagnosis). He died after several relapses. The second patient with ventricular relapse died of complication. The other three relapse patients are in second remission. We conclude that with a combined therapy approach, patients with localized germinoma achieve excellent survival rates. The ventricular area can be defined as the area of risk. Over 50% of relapse patients achieve second long-term remission. This study was supported in part by Deutsche Krebshilfe.

G7. BIFOCAL INTRACRANIAL GERMINOMA: ARE THEY METASTATIC LESIONS?

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Simultaneous involvement of the pineal and the neurohypophysial regions by a germinoma, also called bifocal germinoma, is variously described in the literature, and its incidence ranges from 6% to 26%. The pathophysiology of these bifocal germinoma is unknown, and as a consequence, it is unclear whether these lesions should be treated as metastatic or nonmetastatic tumors. Few series have focused on this particular subgroup. The objective of this study was to review the incidence, the clinical and radiological characteristics, the therapeutic management, and the outcome for patients with bifocal germinoma. We conducted a retrospective chart and radiology review. Our inclusion criteria were as follows: radiological diagnosis of bifocal lesion involving the pineal and the neurohypophysial region (CT and/or MRI), negative spinal MRI and CSF, negative tumor markers (serum and CSF). Among the 17 CNS patients with germinoma diagnosed and initially treated at our institution between 1990 and 2004, six patients (5 M and 1 F) fulfilled the inclusion criteria. Median age at diagnosis was 12.8 years (range, 9–15 years). Three patients had an Asian background. Median time for presenting symptom to diagnosis was four months (range, 1–48 months). All patients presented with diabetes insipidus. Four had panhypopituitarism. Five of six patients had sign of increased ICP, three of six had Parinaud's syndrome. All had negative serum tumor marker (β HCG, α FP), two had elevated HCG in the CSF. On CT and/or MRI, four patients had a pineal mass associated with a suprasellar mass, and two had a pineal mass with abnormal enhancement of neurohypophysial area. Four patients had hydrocephalus. Three patients were treated without biopsy, one based on a neurosurgeon's decision, and the two others had elevated CSF β HCG (14 and 3 UI/l). Three patients underwent an endoscopic biopsy of the pineal mass. In one patient, the endoscopic procedure confirmed the neurohypophysial involvement suspected on imaging. All patient received chemotherapy (3 to 4 cycles of VP16/carboplatin/ifosfamide or VP16/cisplatin) followed by focal radiation. Complete remission was achieved after two cycles in four patients and after four cycles in two patients. Focal field of radiation involved the whole ventricular system (2400 cGy), with a boost to the primary sites (1600 cGy) in four patients. Two other patients received only focal radiation to the primary sites (2500 cGy, 3500 cGy). At a median follow-up time of 48.1 months (range, 6–73.4 months), all patients are alive in first complete remission. This experience suggests that bifocal germinoma can be considered as a locoregional disease rather than metastatic entity and that focal radiotherapy in addition to chemotherapy may be sufficient to provide an excellent outcome. Refinement of the staging of CNS germinoma with new diagnostic tools will likely increase the awareness of these bifocal lesions.

*G8. TREATMENT FOR INTRACRANIAL GERMINOMA: FINAL RESULTS OF JAPANESE STUDY GROUP

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After histological verification by surgery, two kinds of chemotherapy (3 courses) were delivered prior to irradiation. A total of 228 patients were evaluated. The median follow-up period was 6.3 years. Results were as follows. (1) A total of 123 patients with germinoma were treated by CARE (carboplatin 450 mg/m² on day 1, etoposide 150 mg/m² on days 1–3), followed by local irradiation (24 Gy). Whole-brain irradiation was applied for widely disseminated tumor in the brain. For large tumors or multiple tumors, an ifosfamide, cisplatin, and etoposide combination, or ICE therapy, was delivered. The total tumor-free rate was 89% after the treatment. Sixteen patients recurred and two patients died. The five-year overall survival rate was 98%. The recurrence rate significantly differed according to radiation volume: 0% by whole-brain irradiation, 28% by limited local field irradiation with less than 2-cm margin, and 6% by extended local field irradiation. (2) A total of 38 patients with HCG-secreting germinomas were treated in the same strategy as the intermediate prognosis group because of their high recurrent rate. In spite of five recurrences, the five-year OSR is 100%. There was no statistical difference in serum HCG or HCG-beta titers between recurrent and nonrecurrent patients. It is concluded that the combination of CARE and 24 Gy of whole ventricular irradiation would be an optimal treatment for pure germinoma.

G9. THERAPY AND LONG-TERM SURVIVAL IN PATIENTS WITH CNS GERMINOMA: THE ST. JUDE CHILDREN'S RESEARCH HOSPITAL (SJCRRH) EXPERIENCE (1987–2004)

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The purpose of this study was to describe the therapy and evaluate the long-term survival in patients treated for CNS germinoma at a single institution. Between 1987 and 2004, 22 patients (16 male) were diagnosed with pathology-proven CNS germinoma. Location of the primary tumor included the suprasellar region (10 patients) and pineal region (12 patients). The median age at diagnosis was 12.9 years (range, 8–16 years), and the last clinical follow-up averaged 6.7 years (range, 1.5–16 years) from initial diagnosis. Primary therapy included craniospinal irradiation (CSI) (n = 22 patients); median neuraxis dose was 2767 cGy (range, 2100–3600 cGy). Eighteen patients had additional radiation therapy boost (CSI/B) to the primary tumor site to a median dose of 4863 cGy (range, 3600–5400 cGy). Six patients received chemotherapy (C) prior to radiation. Initial response to treatment was as follows: one patient with CSI had stable disease (SD), one patient with CSI/B had partial response (PR), six patients with CSI/B had SD, eight patients with CSI/B had no evidence of disease (NED), three patients with CSI + C had NED, two patients with CSI/B + C had SD, one patient with CSI/B + C had NED. At last follow-up, 17 patients had NED, and three had SD. Two patients with NED after initial treatment (CSI/boost) subsequently died: One patient developed a secondary brain tumor (glioblastoma multiforme) 7.3 years after initial treatment, and the other patient died with cardiac failure of unknown etiology 16 years after initial treatment. The overall survival rate (OS) at five and 10 years was 100% and 86%, respectively. The progression-free survival rate (PFS) at five and 10 years was 96% and 85%, respectively. Death occurred in two patients at a median of 145 months from initial diagnosis (range, 99–192 months). All male patients have survived. The OS of pineal region germinoma at five and 10 years was 100% versus a five- and 10-year OS of 100% and 75%, respectively, in patients with suprasellar region germinoma. Our data confirm that CNS germinomas have an excellent prognosis. In our single-institution series, factors that favorably influence the OS are male gender and pineal location of tumor.

G10. THE EARLY APPEARANCE OF GERMINOMA IN THE BASAL GANGLIA

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Most intracranial germinomas occur in the midline areas such as pineal or suprasellar regions, but sometimes arise in the basal ganglia or thalamus. We report a case of an 11-year-old left-handed boy with a germinoma in the basal ganglia who presented with slowly progressive hemiparesis and mixed aphasia. CT scans demonstrated a subtle high-density area over the basal ganglia and anterior horn of lateral ventricle on the right side

and ipsilateral hemiatrophy in the basal ganglia and cerebral cortex. The MR images also showed hemiatrophy of the right basal ganglia and cerebral cortex. The lesion was not enhanced by contrast medium. FDG-PET disclosed glucose hypometabolism in the right hemisphere. Follow-up MR images 11 months later demonstrated heterogeneously enhanced tumor with multiple cysts in the basal ganglia. The diagnosis of germinoma was established by open biopsy. Combination therapy with carboplatin, etoposide and radiation therapy were carried out, but the patient's neurological deficits remained unchanged. It is suggested that germinoma in the basal ganglia should be included in the differential diagnosis of a lesion that is associated with cerebral hemiatrophy. In the early stages, the diagnosis of germinoma in the basal ganglia and thalamus is difficult because of its rarity and nonspecific findings. Since this tumor is highly sensitive to radiotherapy and chemotherapy and is potentially curable, early detection and prompt treatment, before the full-blown neurological deficits emerge, are desirable.

***G11. TREATMENT OF PRIMARY CNS GERMINOMAS: THE CHILDRENS HOSPITAL LOS ANGELES EXPERIENCE, 1985-2005**

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In the 20-year period since the availability of MR imaging, 35 patients with newly diagnosed, pathologically and tumor-marker confirmed pure germinomas ($n = 31$) or germinomas with mature/immature teratomas ($n = 4$) were treated at our institution. Mean age at diagnosis was 13 (range, 7 to 25). Sex ratio was M:F = 26:9. Sites of tumor were as follows: suprasellar (11), pineal (16), basal ganglia (1), and thalamus (2). Five patients had metastasis at diagnosis, all of which were intracranial metastasis. Two patients had malignant CSF cytology at diagnosis. Elevated beta-HCG levels ($<350 \mu\text{g/dl}$) were documented in the serum (4/30) and CSF (11/33) at diagnosis. Fifteen patients underwent third ventriculostomies and seven patients, ventriculo-peritoneal shunts. Gross total resections were confirmed at diagnosis in eight patients (25%), partial resections in five patients, and biopsies only in 18. Six patients were treated with irradiation only, one craniospinal and five ventricular field + boost to pre-chemo tumor volume. Four of 35 received chemotherapy only, and 25/35, chemotherapy and irradiation. Nineteen of these patients with combined treatment received low-dose irradiation, and six received full-dose irradiation. Six patients have developed recurrent tumor, between 12 months and 51 months following initial diagnosis. Five of the relapsing patients had been treated with combined chemotherapy and irradiation, all receiving local field irradiation plus chemotherapy. One relapsing patient received irradiation only and died from progressive disease. Two additional patients died, one of renal failure during a chemotherapy-only treatment regimen, and one died of disseminated varicella several years off treatment, also following a chemotherapy-only treatment regimen. The overall survival at a mean of four years from diagnosis is 91%. Of patients treated with RT only initially, five of six survive. Of patients treated with chemotherapy only initially, two of four (50%) survive. Of patients treated with combined irradiation and chemotherapy, 25 of 25 (100%) survive. A combination of reduced-dose ventricular field irradiation and boost plus chemotherapy in patients with pathologically confirmed germinoma and tumor markers documented that $<350 \mu\text{g/dl}$ produces outstanding survival. Long-term follow-up studies are in progress to assess the impact of treatment upon neuropsychological functioning and quality of life and will be presented.

G12. CLINICAL CHARACTERISTICS OF GERMINOMA IN THE BASAL GANGLIA

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Germinoma in the basal ganglia (BG) accounts for 10% of intracranial germinoma. Development of MRI has been projecting new images of the disease. Case reports have shown their association of atrophy of BG with Wallerian degeneration of cerebral peduncle. Here we report detailed clinical characteristics of five cases of germinoma in the BG since 1998. All cases were male, and the median age was 11 years. Initial symptoms were hemiparesis in all five cases and precocious puberty in three. MRI findings were irregular and mixed-intensity BG lesions with minimal Gd enhancement in T1WI and ill-defined, high-intensity lesion in T2WI with prominent atrophy down to cerebral peduncle, as has been reported. The four cases in which HCG-beta was measured showed high values. In three cases, serum HCG-beta values were less than 1 ng/ml, but were 400-12,800 pg/ml measured by an ultrasensitive EIA technique ($<30 \text{ pg/ml}$ in normal control).

After chemotherapy using CBDCA and VP16 following 50 Gy of irradiation, the high-intensity lesions in T2WI did not disappear but stabilized for 22 to 80 months. Hemiparesis did not improve in any cases. One case recurred after 31 months as a choriocarcinoma. Degeneration of cerebral tissue with minimal Gd enhancement in MRI and secretion of HCG-beta in pg/ml levels would be the characteristic, and maybe early features of germinoma in the BG.

G13. SPONTANEOUS REGRESSION IN INTRACRANIAL GERMINOMA

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We have treated 35 patients with intracranial germinoma since 1997 and experienced four cases that showed spontaneous regression before surgery. Case 1 is a 24-year-old man who had a one-year history of polyuria, polydipsia, and visual disturbance. MRI demonstrated two tumors measuring 2.5 and 2.0 cm in diameter, in the pineal and neurohypophyseal regions, respectively. His visual function drastically recovered after cerebral angiography (CAG). MRI showed that both tumors decreased in size to half that before surgery. Case 2 is an 18-year-old man who presented with headache and diplopia. His tumors were located in the lateral ventricle, neurohypophysis, and pineal region. First, we made a plan to remove the pineal tumor. Our strategy, however, was changed to remove the lateral ventricle tumor since the pineal tumor significantly regressed after CAG. In Case 3, two tumors in the pineal region and neurohypophysis were detected in a 20-year-old man. MRI showed significant regression of tumors immediately before surgery. In Case 4, a 22-year-old man presented with headache. MRI disclosed tumors in the subcallosal area and pineal region, accompanied with hydrocephalus. Both tumors shrank markedly, and hydrocephalus improved before surgery. It is well known that germinoma has chemosensitive and radiosensitive features. We speculate that the preoperative small dose of radiation, such as CT or CAG, is associated with tumor regression in our series. Thus, to make a final strategy of surgery, MRI immediately before surgery is strongly recommended for the tumor evaluation.

***G14. PHASE II PRE-IRRADIATION CHEMOTHERAPY FOR CENTRAL NERVOUS SYSTEM GERM CELL MALIGNANCIES**

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Central nervous system germ cell tumors (CNS GCTs) are rare primary CNS tumors that are sensitive to radiation (RT) and to chemotherapy (CT). Primary therapy with cranial and craniospinal axis RT is associated with neurologic and endocrine toxicities. Since these tumors are sensitive to CT, we sought to investigate if the use of neoadjuvant CT in conjunction with lower dose RT would allow for optimal tumor-related outcomes with fewer toxicities. Patients >3 years of age with newly diagnosed CNS GCTs were eligible. Pathology was centrally reviewed. Serum and cerebrospinal fluid tumor markers (alpha-feto protein [AFP] and beta-human chorionic gonadotropin [HCG]) were measured in all but two patients. Patients with germinoma (G) who had elevated AFP were classified as nongerminomas (NG). Therapy was with intravenous cisplatin (20 mg/m^2) and VP16 (100 mg/m^2) on days 1 to 5, delivered every 28 days for four cycles. Patients were then treated with RT: Patients with G who had a complete response (CR) were treated with 30 Gy, and those with $<$ CR received 54 Gy. All NG patients with a CR received a dose of 54 Gy, and those with $<$ CR received 59 Gy. All patients who had disseminated disease at entry received craniospinal axis RT, with a dose ranging from 19 to 36 Gy (depending on the pathology and response to CT). Patients who had residual tumor after RT were evaluated for surgery. Neurocognitive and endocrine status was evaluated during follow-up. Thirty-four patients (20 G and 14 NG) were enrolled between 1991 and 2004. The median age was 14 years; median duration of follow-up was 7.3 years and 5.7 years for G and NG, respectively. Among the G patients, CT resulted in CR in 11 (55%), partial response (PR) in three (15%), stable disease (SD) in four (20%), and regression (REGR; decrease in size not meeting criteria for PR) in two (10%). Likewise, in NG patients, five (36%) had CR, seven had (50%) PR, and one (7%) each had SD and REGR. After RT, all G patients achieved a CR, and 12 (86%) of the NG patients had CR, with one each having an unknown response and SD. The latter patient underwent surgery after RT. To date, six (2 G and 4 NG) patients have progressed (median time to progression is 6.5 years for G and 4.1 years for NG). Twenty-nine patients were evaluable for toxicity. Only 10 toxicity events that were of grade 4 severity occurred (mainly hematological and gastrointestinal), with no grade 5 events. All but one patient (who died

of metastatic disease) are alive. We conclude that the use of neoadjuvant CT with RT results in a very high rate of response in CNS GCTs. This strategy appears to permit the use of decreased doses of RT with acceptable toxicity and excellent, long-term, tumor-related outcomes. Further evaluation and follow-up will be needed to assess the impact of therapy on cognition and endocrine status.

***HP. PRIMARY CNS GERM CELL TUMORS: A HISTORICAL PERSPECTIVE**

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Fifty years ago tumors in the suprasellar and pineal regions were diagnosed on the basis of symptoms and imaging which consisted of skull views and air studies. Tumor resection was uncommon, especially in the pineal region, so that tumor histology was usually unknown. Despite these limitations, a five-year survival rate of 80% could be achieved in children and young adults (≤ 25 years) with high-dose radiation treatment (RT) alone. The relative value of craniospinal RT (CSRT) and local RT was controversial. In older patients the same treatments gave much poorer survival rates, about 35%. Autopsy data and the increasing frequency of a histological diagnosis and analogy with gonadal germ cell tumors (GCT) indicated that the high cure rate in the young was due to the higher frequency of CNS germinomas at this age. Over the last 40 years the development of CT and MRI imaging has allowed for the precise anatomical definition of the primary tumor and any metastases. Simultaneously, neurosurgical advances dropped operative mortality to 1% and permitted resection of the primary tumor. A tissue diagnosis became available in most patients. Curative chemotherapy for gonadal GCT was progressively developed over these years and was shown to be effective in CNS GCT. Over the last 15+ years the relapse-free survival rate for germinomas treated with RT \pm resection alone became 90% to 100%, and this proved to be superior to results with chemotherapy alone. Thus for nonmetastatic germinomas the challenge became the achievement of this result with minimum morbidity by the combination of effective chemotherapy and local low-dose RT. The salvage of relapsed germinoma became practical and allowed the search for minimum treatment to be aggressively pursued. In contrast, the overall cure rate for nongerminomatous (NG) GCT was, in the era of RT alone, about 25%. The spectrum of specific tumors within NG GCT has compounded the search for successful treatment. It remains unclear whether there is a need to modify treatment protocols for specific tumor histologies. Clearly, chemotherapy has markedly improved overall results with five-year survival rates of about 70% and initial complete response rates of $>70\%$ reported. Local control remains the main challenge. Pilot studies which incorporate initial chemotherapy, high-dose local RT and aggressive resection of residual tumor have shown the most promise. The price for these impressive achievements has been high. With current modalities there can be, at best, only moderate room for further increase in cure rates. Decreased treatment morbidity will be an important end point in new studies. Since CNS GCTs are rare, treatment progress will be slow and will require effective international clinical trials. There remains a need for small innovative pilot studies.

***IM1. ADVANCED IMAGING OF INTRACRANIAL GERM CELL TUMORS.**

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In this presentation a brief review of past imaging techniques of germ cell tumors will be made followed by the modern approach to the imaging workup of patients with suspected germ cell tumors. The various imaging characteristics of the different types of germ cell tumors will be discussed with particular reference to advanced imaging techniques. Emphasis will be placed on quantitative methods such as multivoxel proton and phosphorus MR spectroscopy, diffusion and perfusion imaging, diffusion tensor imaging, and FDG-PET imaging. The strengths and weaknesses of the various techniques will be discussed. The current imaging protocols for diagnosis and surveillance imaging will be presented.

***IM2. PREOPERATIVE MR CHARACTERIZATION OF PINEAL GERMINOMAS: COMBINED DIFFUSION-WEIGHTED, DIFFUSION TENSOR AND MR SPECTROSCOPIC IMAGING**

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Being able to preoperatively distinguish between different types of pineal germ cell tumors by advanced imaging techniques may have implications for combined surgical and oncologic management. *Our overall hypothesis is that pineal germ cell tumors may be distinguished by advanced MR imaging techniques preoperatively according to their metabolic profiles and cellular composition.* The purpose of this paper was to characterize the MR spectroscopic and diffusion imaging properties of pure pineal germinoma. The quantitative MR spectral appearance of pineal germinoma with correlation to apparent diffusion coefficient (ADC) and fractional anisotropy (FA) measurements has not been published previously. We characterize pediatric pineal germinomas using in vivo short-echo time (TE) single voxel 1H-MR spectroscopy with absolute quantitation and both diffusion-weighted and diffusion tensor imaging with quantitative ADC and FA measurement to identify characteristic metabolic and cytological features. Multiplanar brain MR imaging, including diffusion-weighted imaging with ADC map, diffusion tensor imaging (25 direction, b value = 1000) with both ADC and fractional anisotropic mapping and short TE proton MR spectra (1.5 T) in six pediatric patients with pathology-proven intracranial pineal germinoma, was reviewed retrospectively. Short TE spectra acquisition permits detection of N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr), as well as fast-decaying components (glutamate, glutamine, myo-inositol (mI), taurine (Tau), and lipids/macromolecules). Voxels were sized to include as much lesion as possible while minimizing inclusion of adjacent brain. Water signal was used as an internal reference, and peak intensities were corrected for the fraction of necrotic/cystic tissue included in the region of interest (ROI) since most metabolites are intracellular (exception, lactate). Automated quantitative analysis was performed by using commercially available software (LC model) to generate absolute metabolite concentrations that were compared with other pediatric tumors studied in this institute. ADC values were computed from ROIs placed over solid tumor regions within the voxel location used for MRS. Scatter plots were derived comparing ADC to specific metabolite concentrations. Diffusion tensor imaging was performed in a subset of patients and analyzed on separate workstation with both ADC and FA maps computed. The MRS pattern of six germinoma patients was similar in many ways to observations in other brain tumors: (1) absent NAA peak and (2) NAA/Cr reduction and Cho/Cr elevation. However, several unexpected features were noted. Creatine concentrations were not different from the concentration observed in other tumors, whereas absolute choline was reduced. Prominent lipids/macromolecular peaks were consistently observed in all germinomas, whereas in other tumors classes a more heterogenous pattern was observed. Taurine, a metabolite so far only identified in medulloblastoma, was identified in all six tumors. Relatively low homogenous ADC values reflected the primitive cellular nature of germinoma. No correlation between ADC values and individual metabolite concentrations was detected. The degree of FA change was also homogenous, as demonstrated in a subset of cases. Pineal germinomas demonstrate consistent metabolic profiles with respect to both diffusion-weighted imaging and MRS. Pineal germinomas are characterized by elevated choline, lipid/macromolecular, and taurine peaks with reduced or absent NAA peak. The diffusion-weighted and tensor-imaging properties of pure pineal germinomas are homogenous and reflect the hypercellular nature of the tumor. The significance of these observations needs to be evaluated by comparison with the MRS and diffusion patterns of other nongerminoma germ cell traditionally included in the differential of pineal lesions, which is an ongoing project.

***IN1. THE THIRD INTERNATIONAL CNS GERM CELL TUMOR STUDY GROUP PROTOCOL: PRELIMINARY RESULTS**

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The overall intent of this protocol was to treat patients with newly diagnosed primary intracranial germ cell tumors with one of two risk-tailored therapeutic regimens, administering two cycles of chemotherapy beyond the point of achievement of complete radiographic resolution and tumor marker normalization, and to avoid the use of irradiation in such patients.

Between 2001 and December 2003, 25 patients aged 4 months to 24.5 years (median, 13.3 years) were enrolled on this study. Patients were stratified between two risk-tailored treatment plans. Regimen A: Low-risk pure germinoma (G-LR) localized nonmetastatic, normal CSF and serum tumor markers. Regimen B: Intermediate risk germinoma (G-IR), with either β -HCG positive syncytiotrophoblastic giant cells and/or CSF elevation of β -HCG less than 50 mIU/ml, and high-risk (NG-HR) biopsy-proven nongerminomatous germ cell tumor or elevated serum and/or CSF alpha-fetoprotein, elevated serum β -HCG, elevated CSF β -HCG greater than 50 mIU/ml, or any type with disseminated disease as determined by MRI and/or CSF cytology. Regimen A patients received in cycles 1, 3, and 5 carboplatin/etoposide and in cycles 2, 4, and 6 cyclophosphamide/etoposide. Regimen B patients received in cycles 1–6 carboplatin/cyclophosphamide/etoposide. Patients who achieved complete response (CR) after two cycles and four cycles received two more cycles and finished the treatment. Those without CR after four cycles were to undergo second look and/or irradiation and/or autologous bone marrow transplantation (only for HR) in order to obtain complete radiological response and tumor marker normalization. Results were as follows: 24% of the patients had G-LR, 36% G-IR, and 36% HR. Seventeen of the 25 patients achieved CR after two courses of treatment (CR2m = 68.0%; 95% CI, 49.7%–86.3%); 18 of the 25 patients achieved CR after four courses of treatment (CR4m = 72.0%; 95% CI, 54.4%–89.6%). Only one patient received irradiation as part of initial therapy, and four patients (16%) received irradiation therapy at time of relapse. With a median follow-up time of 28.6 months (range, 12.5–51.5 months), 22 patients are alive without disease, and 20 patients have not relapsed during their follow-up period. The two-year overall survival and event-free survival rates are 87.7% \pm 6.7% and 70.1% \pm 9.5%, respectively. The preliminary results obtained in this selected group of patients have showed feasibility and effectiveness with this strategy. Longer follow-up is required to determine eventual durable survival.

***IN2. HIGH-DOSE CHEMOTHERAPY (HDC) WITH AUTOLOGOUS STEM CELL RESCUE (ASCR) IN PATIENTS WITH RECURRENT CNS GERM CELL TUMORS (GCT)**

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Multidrug chemotherapy and irradiation are used alone or in combination for most patients newly diagnosed with CNS GCT. Treatment options are more limited for patients with recurrent CNS GCT. Over the past several years, we have used HDC with ASCR in patients with recurrent CNS GCT. We published our initial results (Modak et al., *J. Clin. Oncol.* 22:1934, 2004) and now present an update with additional patients. Patients with recurrent germinomatous and nongerminomatous CNS GCT were treated on one of four thiotepa-based regimens. The regimens included (1) thiotepa, 300 mg/m²/day (d) and etoposide, 250 mg/m²/d for three days; (2) carboplatin dosed by using the Calvert formula with an AUC = 7 (maximum 500 mg/m²/d) for three days followed by thiotepa 300 mg/m²/d and etoposide 250 mg/m²/d for three days; (3) temozolomide 150 to 350 mg/m²/d for five days followed by thiotepa 300 mg/m²/day and carboplatin dosed by using the Calvert formula with an AUC = 7 (maximum 500 mg/m²/d) for three days; (4) two courses of thiotepa, 200 mg/m²/d for three days, given four to six weeks apart. The single HDC regimen used was based upon the year of transplant. The sequential high-dose thiotepa regimen was given to patients who had more than minimal residual disease at the time of HDC. Twenty-seven patients with recurrent CNS GCT (germinomas, n = 13; nongerminomatous germ cell tumors, n = 14) were treated between 1986 and 2005. Twenty patients received a single course of high-dose chemotherapy; seven patients received the tandem high-dose thiotepa. Ten patients received adjuvant irradiation following the HDC (craniospinal, n = 8; cranial, n = 1; focal, n = 1). Toxicity primarily consisted of pancytopenia and mucositis. There were no toxic deaths. Ten of 13 patients (77%) with recurrent germinomas are alive without disease at a median of 41 months following HDC. Six of 14 (43%) patients with recurrent nongerminomatous germ cell tumors are alive without disease at a median of 27 months following HDC. We conclude that HDC can be administered safely to patients with recurrent CNS GCT and results in long-term survivors, especially those with recurrent germinoma.

***IN3. CASE REVIEW OF LONG-TERM SURVIVORS OF MALIGNANT PINEAL TUMORS TREATED WITH BLOOD-BRAIN-BARRIER DISRUPTION ENHANCED DELIVERY OF PLATINUM-BASED CHEMOTHERAPY**

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A recent case of a malignant HCG secreting pineal tumor brought us to look at our long-term survivors who had malignant pineal tumors. Pineoblastoma in adults, as in children, has a poor prognosis and often disseminates to the CSF analogous to malignant pineal germ cell tumors. We also have reviewed our use of STS in the prevention of ototoxicity. A case series of five long-term survivors of pineoblastoma treated with intrathecal (i.a.) carboplatin (200 mg/m²/day), cyclophosphamide i.v. (330 mg/m²/day), and etoposide or etoposide phosphate i.v. (200 mg/m²/day) with osmotic opening of the blood-brain barrier (BBB) on two consecutive days was reviewed. The treatment course was repeated every four weeks for a total of 12 courses. One of the five had received prior radiation therapy, and none had received prior chemotherapy. All five received subsequent radiation therapy within three to seven months after completion of the chemotherapy. Three had focal therapy, and two received radiotherapy to the whole brain and spine. Four of the five had radiographic evaluable disease prior to therapy. Three cases had complete response and one had partial response. The nonevaluable case has remained without any evidence of disease. Median survival is 10.8 years (range, 4.2–15.5 years). Four of the five remain without evidence of tumor recurrence after the chemotherapy and follow-up radiation therapy. One case disseminated to the lumbar spine after initial treatment with radiation therapy (case 1). Prior radiation therapy had been to brain and cervical and thoracic spine, and the tumor recurrence in the lumbar spine and was confirmed by a biopsy. Enhanced chemotherapy with blood-brain-barrier disruption (BBBD) was started after the development of lumbar metastases. Five months after the completion of a year of chemotherapy with BBBD, lumbar spine metastases were again noted, and radiation therapy was delivered to the lumbar spine. Follow-up spine MRI continued to show enhancing lesions, so another year of BBBD with enhanced chemotherapy was completed without further recurrence. All of the five currently are alive and well without evidence of disease. Adverse events that occurred during therapy included neutropenia, infection, hearing loss, mild anemia requiring PRBC transfusion (1 episode), and one episode of cardiac dysrhythmia. Ototoxicity for the most part can be avoided by administering sodium thiosulfate. It is concluded that carboplatin-based chemotherapy with enhanced delivery with BBBD is a very effective and durable front line treatment for pineoblastoma. Adverse events are minimal, and ototoxicity has been minimal since the addition of sodium thiosulfate following BBBD. Current results with sodium thiosulfate as an otoprotectant are also discussed.

IN4. SALVAGE TREATMENT FOR REPEATEDLY RECURRENT GERMINOMAS

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Although germinomas are very radiosensitive/chemosensitive and highly curable, about 10% of patients recur. We studied recurrence cases in our 25 years of experience and tried high-dose chemotherapy for repeatedly recurrent cases. Between 1978 and 2004, we treated 41 cases of germinomas (a median follow-up of 77 months). Seven cases had recurrence. Three of them had been treated with conventional chemotherapy alone, and four other cases received extended local irradiation (24 Gy) plus tumor boost irradiation (21 Gy) with platinum-based chemotherapy. As salvage treatment to recurrent tumors, extended local irradiation was done in the former three cases, which showed complete remission for the long term. The other four cases were treated with second-line chemotherapy (ifosfamide/ carboplatin/etoposide) alone. However, although tentative complete remission was achieved, three of the cases showed repeated recurrence for a short time. Finally, high-dose chemotherapy (high-dose carboplatin and etoposide and melphalan) with peripheral blood stem cell rescue was performed in these three cases. They had no lethal toxicity, and complete remission was continued in all three cases. The significant prognostic factors for germinoma recurrence were conventional chemotherapy alone and limited radiation field. High-dose chemotherapy is recommended as salvage treatment for recurrent tumors.

***L1. CURRENT APPROACHES IN THE MANAGEMENT OF LEPTOMENINGEAL DISEASES: POTENTIAL APPLICATIONS TO CNS GERM CELL TUMORS**

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The leptomeninges are a common site of recurrence of CNS germ cell tumors, in part because the blood:CSF barrier limits the penetration of drugs to this site. Potential treatment approaches for leptomeningeal tumor spread include the direct instillation of drugs into the cerebrospinal fluid (CSF). Intrathecal (IT) administration of drugs, such as methotrexate (MTX), is a form of regional drug delivery that has been successfully used in the treatment and prevention of the meningeal spread of leukemia and lymphoma. Because of the small volume of CSF, MTX concentrations exceeding 100 μM can be achieved with a dose of 12 mg, resulting in a substantial pharmacokinetic advantage for this route of administration. Although IT MTX will induce a remission in 80% to 90% of children with acute lymphoblastic leukemia (ALL) that has relapsed in the leptomeninges, few of these patients are cured with IT therapy alone, and remission induction rates are substantially lower for leptomeningeal spread in solid tumors. However, as adjuvant or preventive therapy in children with newly diagnosed ALL, IT MTX alone or in combination with IT cytarabine or cranial radiation significantly reduces the meningeal relapse rate. A major limitation of IT drug administration is nonuniform distribution of drug throughout the subarachnoid space. After intralumbar injection of 6.25 or 12.5 mg/m², peak ventricular CSF MTX concentrations ranged from 0.6 to 22 μM , which is substantially lower than the >100- μM peak concentration achieved after an intraventricular dose of 6.25 mg/m². MTX concentration within the CSF after IT administration is dependent on the site and mode of administration, bulk CSF movement and absorption, choroidal drug uptake and clearance, and diffusion or transport of drug across the CSF-brain interface. Surgically implanted ventricular access devices, such as the Ommaya reservoir, were developed to provide a convenient and reliable route of delivering drugs directly into the ventricular CSF. Although there are no large, prospective comparative trials testing the efficacy of this route of administration, retrospective studies suggest that the use of these devices is more efficacious and less toxic than the traditional intralumbar route. In addition, intraventricular MTX injection achieves higher and less variable drug concentrations in the ventricular CSF and better distribution of drug throughout the subarachnoid space. The limited number of agents that can be safely administered IT also limits the effectiveness of this treatment approach in solid tumors. The clinical development of new IT agents is a slow process. The new agents currently under development, such as mafosfamide, busulfan, and gemcitabine, have greater clinical activity in solid tumors than MTX and cytarabine, and it is hoped that they will improve the efficacy of IT drug delivery for the treatment and prevention of leptomeningeal recurrences.

***L2. INTRATHECAL CHEMOTHERAPY FOR NEOPLASTIC MENINGITIS: EXPERIENCE WITH MAFOSFAMIDE, ETOPOSIDE AND DEPOT CYTARABINE IN 38 CHILDREN WITH DISSEMINATED MALIGNANT INTRACRANIAL TUMORS.**

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Treatment options for leptomeningeal disseminated brain tumors are limited by the lack of effective drugs for intrathecal therapy of non-hematologic malignancies. We report on our experience with intrathecal mafosfamide, a preactivated cyclophosphamide derivative, etoposide, and depot cytarabine. Between May 1994 and April 2005, 38 patients aged 2 to 19 years with various poor-prognosis intracranial tumors received intrathecal mafosfamide (n = 32), etoposide (n = 12), and depot cytarabine (n = 7). Mafosfamide was administered at a dose of 20 mg once or twice weekly until remission was achieved and every two to six weeks thereafter as maintenance therapy for a total of 928 administrations (2–63/patient, maximal cumulative dose 1225 mg). Etoposide was given at a dose of 0.5 mg \times 5 d every to 3 to 6 weeks for a total of 127 courses (1–31/patient, maximal cumulative dose 71.5 mg). Depot cytarabine was given at a dose of 50 mg in patients older than 9 years and at a dose of 25 mg in a 22-month-old boy once every two to three weeks until remission was achieved, for a total of 21 applications (1–6/patient, maximal cumulative dose 300 mg). Immediate toxicities such as transient headaches, nausea and vomiting, neck pain, and fatigue occurred with mafosfamide but were manageable with premedication. Etoposide rarely caused any discomfort. Transiently decreased vision and bladder control, fever, fatigue, seizure, and headache were also observed with depot cytarabine. No systemic toxicities and so far no long-term adverse effects attributable to intrathecal therapy as evidenced by MRI or neurologic evaluation were observed with either mafosfamide, etoposide, or depot cytarabine. Intrathecal therapy appears to be best suited to treat tumor cells floating in the CSF. Early treatment, appropriate dose,

and scheduling of administration are probably crucial. Further research should show whether intrathecal therapy when given at initial treatment may help to reduce the dose of preventive radiotherapy.

***LE1. ENDOCRINE DISTURBANCES AND DIABETES INSIPIDUS (DI) IN PATIENTS WITH MALIGNANT CNS GERM CELL TUMORS: CLINICAL APPEARANCE AND DEVELOPMENT UNDER TREATMENT IN SIOP CNS GCT 96**

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Endocrine disturbances are frequent in patients with CNS GCT. The interval between the appearance of endocrine symptoms and diagnosis varies extensively. This evaluation aims to describe frequency, time of appearance before diagnosis, and further presentation of endocrine impairment under chemotherapy in germinoma and nongerminoma registered in SIOP CNS GCT 96. All malignant CNS GCTs registered in SIOP CNS GCT 96 until diagnosis 01/01/2004 were analyzed according to kind and frequency of endocrinological disturbances at diagnosis, time point of first appearance, and management problems under chemotherapy. In SIOP 96, 349 males (ages 0–42, median 13) and 128 females (ages 0–22, median 11) with a malignant CNS GCT have been registered (germinoma n = 289, nongerminoma n = 188). Tumor locations are pineal (50%), suprasellar/hypophysial (30%), pineal + suprasellar (14%), and other (6%). Because of tumor location, 83% of patients with suprasellar involvement and 16% of patients with pineal or other tumor origin presented with one (disturbance of sexual hormones n = 9, growth disturbance n = 8, DI n = 90) or more endocrinological failures (n = 109) at diagnosis. Most patients with only one endocrine symptom at diagnosis develop partial or complete panhypopituitarism during follow-up. Retrospectively, for 96% of patients with endocrine disturbances at diagnosis, this was the first symptom of the tumor and was detectable between 9 days and 10 years (median, 6 months) before diagnosis. A total of 188 patients (87%) presented DI postoperatively. These patients underwent craniospinal irradiation (RT) (germinoma n = 66), two courses of CarboPEI + RT (germinoma n = 35), four courses of PEI + RT (nongerminoma n = 62). Among patients treated with CarboPEI, 15 cases (43%) with problems of water balance or handling of DI are described: two slight (grade 1), six moderate (grade 2), and seven severe (grade 3). For CisPEI (n = 26, 42%), six show slight (grade 1), eight moderate (grade 2), nine severe (grade 3), and three untreatable water imbalance. In the germinoma group with RT alone, four cases, all severe, are described (three at the beginning and one case six months after RT). Endocrine impairment is a major issue in CNS GCTs. Exact diagnosis, along with adapted substitution during lifelong therapy with endocrine follow-up under expert supervision, is mandatory. This study was supported in part by Deutsche Krebshilfe.

LE2. GERM CELL CANCER: AN ONCOLOGIST'S PERSONAL PERSPECTIVE

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The objectives of this study were to document the consequences of survivorship and to describe the impact upon quality of life of recurrent, disseminated germ cell cancer on a pediatric oncologist/neuro-oncologist. At 26 years of age, while undertaking my pediatric residency in Birmingham, England, I was diagnosed with testicular seminoma, after a period of six months in which both I and my physicians procrastinated as to possible causes for the slowly enlarging, seemingly paratesticular mass. I underwent an orchiectomy followed by "prophylactic" abdominal irradiation (an enlarged node on lymphangiography was "overlooked" at diagnosis). I was "assured" that my cure rate was greater than 90% and that I didn't need to worry about fertility. Nine months later, after experiencing significant gastro-esophageal discomfort, a barium swallow and chest radiograph demonstrated mediastinal nodal and pulmonary metastases. Serum tumor markers were negative. Lymphangiography was negative below the diaphragm. I underwent mediastinal irradiation, achieving a complete response. However, my physicians at that point were talking only in terms of anecdotal cures. One month following completion of my irradiation, one year to the day after my initial orchiectomy, I underwent surgery for a second tumor (found to be a pure germinoma), which I had palpated on the opposite testicle one week previously. Repeat lymphangiography, tumor markers, and chest radiography were normal. A radiation oncologist recommended oral chlorambucil five days per month for one year and levamisole ("the thinking physician's laetrile") three days per week for two weeks each month following the chlorambucil. After a first year following treatment in which imminent recurrence was anticipated, experiencing transient decline in lung function and a transient episode of irradiation-associated hepatitis, no further recurrences or "major" events developed over the ensuing

28 years. "Minor" events included the "unexpected" finding of primary hypothyroidism 12 years after the mediastinal irradiation, documentation of pulmonary function at the lower limits of normal, and, after 28 years, documentation of coronary artery disease. Infertility has been countered by adoption of a daughter, now 19 years old; impotency has been avoided through monthly intramuscular injections of testosterone. Colonoscopy every three years for the last 15 years has been unremarkable. Annual chest radiographs are obtained, required for tuberculin positivity rather than for surveillance for recurrence, and show no abnormalities. Having survived disseminated, recurrent cancer, it has been a defining experience in my life, contributing to a pervasive sense of optimism yet realism toward my own life and that of my family and my patients. I have found a degree of empathy with patients that I do not believe would have been possible without my own experience. I have learned how patients often ease the path for their physicians to communicate honestly with them. I have also learned that, sadly, despite such life-defining experiences, it is also all too easy to "let slip" such lessons with the passage of time. Infrequent dreams are experienced, in which my cancer returns and I must face the possibility of death once again—not bad dreams, but "reawakening" experiences. Every head or back ache is still considered as a late recurrence (such things are not unknown with germ cell cancer) in need of prompt medical evaluation and exclusion. Despite infertility, hormonal medication dependency, mild pulmonary dysfunction, and coronary artery disease, my life in general and my professional life in particular have been all the richer and productive for this experience. The role of optimism yet realism and open, honest dialogue in confronting metastatic, recurrent germ cell cancer, cannot be underestimated.

***LE3. RISK OF SECOND TUMORS IN INTRACRANIAL GERMINOMA PATIENTS TREATED WITH RADIATION THERAPY**

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Long-term sequelae of radiotherapy (RT) in germinoma survivors include neurocognitive and neuroendocrine effects and second tumor (ST). The risk of second malignant neoplasm (SMN) is 5%–12%. In this review, we examine the risk of developing ST in intracranial germinoma patients followed or treated at our institution. Between 1977 and 2002, 27 patients were diagnosed with intracranial germinoma by either radiographic findings and documented treatment response (n = 3) or by biopsy (n = 24). All of the patients were treated with RT, and eight received chemotherapy. Median dose to the primary tumors was 4580 cGy (range, 1440–5040 cGy). The cumulative incidence of ST was calculated from the date of diagnosis to the date of ST, last follow-up, or death by using the Kaplan-Meier method. Patients who did not develop ST were censored at the time of death or date of last follow-up. The median age at diagnosis was 16 (range, 8–35). Median follow-up time was 4.5 years (range, 0.3–22.8 years). Five patients (18%) developed an ST, of which four (15%) were SMNs (testicular tumor, glioblastoma multiforme [GBM], thoracic mesothelioma with known asbestos exposure, and calvarial osteosarcoma). One patient developed a falx meningioma. The median time to the development of an ST was 12.5 years (range, 2.0–14.3 years). The cumulative incidence of SMN was 10% at 11 years (95% CI, 0%–25%). There was no significant association of age at diagnosis, gender, radiation dose, or chemotherapy with the development of ST. There were seven total deaths, of which three were related to SMNs (mesothelioma, osteosarcoma, and GBM). Two of the three SMNs were in the radiation portals, as was the meningioma. The patient whose death was related to a mesothelioma had prior asbestos exposure. One death was due to respiratory failure and immunocompromised status due to noncompliance with replacement hormone therapy. One patient died with tumor progression. The cause of the two remaining deaths could not be determined. The relative contributions of RT and inherent patient susceptibility to ST in this population cannot be determined and emphasize the need for long-term surveillance. Current trials of chemotherapy and reduced RT dose and volume offer the prospect of a lower ST risk.

***LE4. CENTRAL NERVOUS SYSTEM GERM CELL TUMORS: LATE EFFECTS ARISING FROM TREATMENT**

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Primary CNS germinoma is readily curable with relatively large-volume/high-dose radiotherapy, but the late effects may alter ultimate neurocognitive functioning and quality of life. Prior studies of other brain tumors have associated radiation therapy with deficits in the domains of intelligence, attention, memory, and psychomotor processing speed, with risk factors

including young age at irradiation and increased irradiation volume and dosage level. Furthermore, cranial irradiation may also lead to diminished height, neuroendocrine dysfunction, and hearing loss. Unfortunately, few germ cell tumor follow-up studies have adequately examined late effects of therapy, and most are notably limited by single assessments of IQ on a small subset of survivors. Consequently, further inquiry is warranted that includes baseline and biannual psychological assessments that extend beyond a singular measure of intelligence and provide data on a range of domains such as attention-concentration, memory, and executive functioning, as well as quality of life, social-emotional, and behavioral functioning. However, obtaining baseline assessments of pediatric brain tumor patients, as well as follow-up testing of survivors, has proven difficult in previous studies for a variety of reasons, ranging from a lack of insurance reimbursement, insufficient testing personnel, inconsistent referrals, and variable interest on the part of oncologists, parents, and patients. Compliance therefore continues to be a major concern negatively impacting the viability of late effects studies, which directly limits our scientific knowledge and thus the ability to design new treatment protocols that attempt to improve overall and event-free survival, as well as long-term patient functioning. Obtaining test data following two to three months after radiation therapy will maximize the number of baseline assessments received, allowing for a significantly larger window of time to capture data on a patient who has completed treatment. Moreover, providing assessments at the conclusion of treatment will yield a timely evaluation in terms of preparation for school reentry and appropriate accommodations when warranted. Additionally, it is important to obtain biannual assessments because neuropsychological changes arise over time, whereby survivors who received cranial irradiation continue to learn but at a lesser rate than that expected for the normal population. Consequently, collaboration between the medical oncology and psychology disciplines is required to ensure maximum compliance to obtain follow-up data on the late effects of treatment on this population to clarify the impact of age at diagnosis, duration of follow-up, gender, location, and radiotherapy parameters upon the late effects arising from the treatment of this readily curable form of brain cancer.

***LE5. ENDOCRINE EFFECTS OF PRIMARY CNS GERM CELL TUMORS AND THEIR TREATMENT**

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Tumors of germ cell lineage comprise 1% to 2% of intracranial tumors in adults and up to 4% in children. The peak incidence is from the end of the first decade to the end of the second decade of life. Suprasellar germ cell tumors represent less than one third of intracranial germ cell tumors, the most common site being the pineal region. Diabetes insipidus (DI) is almost universal at the time of diagnosis and implies involvement of the floor of the third ventricle in the region of the infundibulum. Compression of the visual pathway with signs of optic atrophy or restriction of the visual fields is also common at presentation. Somewhat less common presenting signs include anterior, pituitary hormone deficiencies, short stature in the prepubertal population, and hypogonadism in the older individual. Nongerminomatous germ cell tumors (NGGCT) may secrete hCG in sufficient amounts to induce pseudo-precocious puberty in boys but not girls. If reviewed from the perspective of the commonest endocrine deficiency, then of 79 patients presenting to an Endocrine Unit with DI, only 8% were found to have a germinoma over an average follow-up period of 7.6 years, and 52% were considered to have idiopathic DI. Thickening of the pituitary stalk or enlargement of the pituitary gland increased the likelihood that the underlying pathology was a germinoma. Treatment with craniospinal irradiation may profoundly affect growth by inducing growth hormone deficiency (GHD) and impaired spinal growth. The risk of GHD is related to the dose of irradiation delivered to the hypothalamic-pituitary region; if the dose is sufficient, then panhypopituitarism may ensue, and it is important to remember that pseudo-precocious puberty of any duration may itself precipitate true central precocious puberty.

***LE6. FERTILITY AFTER TREATMENT FOR A CENTRAL NERVOUS SYSTEM GERM CELL TUMOR**

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For individuals who are survivors of CNS GCT, fertility can be affected by both the tumor itself as well as the therapies used to treat the tumor. Impaired fertility can occur following damage to the pituitary gland, damage to the ovaries/testicles or damage to both. If the pituitary gland is damaged, which can be caused by the tumor and/or therapies to treat the tumor (e.g., surgery, brain radiation), fertility can be restored with specialized hormonal treatments so long as the ovaries/testicles are relatively normal. Damage to the ovaries/testicles can occur following certain types of treatments, including radiation therapy to the whole spine and, especially, after

treatment with certain chemotherapy drugs. The chemotherapy drugs most commonly associated with reduced fertility are the class of drugs known as alkylating agents, which include cyclophosphamide, ifosfamide, thiotepa, and melphalan. Problems with fertility are more common in males and following the use of higher doses of these drugs. Those at greatest risk for infertility are individuals who have undergone autologous stem cell rescue following treatment with high-dose chemotherapy. Some women who remain fertile following completion of therapy may be at risk of entering menopause at an early age. Spinal radiation in females may predispose to preterm births and miscarriages. Tests for fertility include (1) for females, menstrual history and blood tests and (2) for males, blood tests and a sperm analysis. Treatment options are more limited if the fertility problem is due to direct injury to the ovaries/testicles. Nonetheless, newer assisted reproductive technologies (e.g., intratesticular sperm retrieval followed by in vitro fertilization) offer the possibility of parenthood for some survivors who would have been considered infertile in the past.

LE7. VOLUME-REDUCED RADIATION FOLLOWED BY PLATINUM-BASED CHEMOTHERAPY IMPROVES ANTERIOR PITUITARY FUNCTION OF THE POST-PUBERTAL PATIENTS WITH NEUROHYPOPHYSEAL GERMINOMA

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The aim of this prospective study is to assess how 24-Gy, extended local radiotherapy followed by three cycles of platinum-based chemotherapy improves anterior pituitary functions of the postpubertal patients with neurohypophyseal germinoma. Nine patients (6 males; median 18.2 years of age) were enrolled who received this therapy after biopsy. All achieved a CR during chemotherapy. They were evaluated with dynamic hormonal examination enhanced by hypoglycemia with insulin, LH-RH, and TRH, respectively, before biopsy and one year after this treatment. Serum titers of cortisol, GH, LH, FSH, TSH, and PRL were measured at 0, 30, 60, and 90 min after stimulations. The hormonal impairment was judged according to peak values of cortisol (18<, GH(10<, JH(5<, FSH(5<, base and peak values of PRL(20>, 20<), and delayed peak or prolonged plateau of TSH. Median follow-up time was 55 months. All patients have been in full performance status without recurrence. The numbers of normalized patients were two before and two after this treatment (2/2) in ACTH, 2/2 in GH, 1/6 in LH, 2/6 in FSH, 4/8 in PRL, and 2/4 in TSH. The numbers of the patients with post-therapeutic progressive function were only two in TSH and one in ACTH. Clinically, a male recovered from ED, and two females from amenorrhea. We conclude that anterior pituitary functions of the postpubertal patients with neurohypophyseal germinoma can be always preserved and occasionally improved after this treatment.

***LE8. QUALITY OF SURVIVAL (QOS) IN CNS GERMINOMA (CNS-G) VS. CNS NONGERMINOMA (CNS-NGGCTS) TREATED ACCORDING TO MAKEI 86/89**

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In the past, treatment of malignant CNS germ cell tumors included craniospinal radiotherapy (RT) alone. For CNS-G this was standard treatment. CNS-NGGCTS were treated with a combination of chemotherapy (CT) and RT, which was mainly craniospinal with a higher dosage. Although both diseases are highly malignant tumors, the survival rate for CNS-G is excellent (~90%), whereas the prognosis for CNS-NGGCTS needed to be improved. This study highlights the question of whether the higher treatment burden of the patients with CNS-NGGCTS is reflected in a more negative QoS. Eighty-five patients (61 CNS-G and 24 CNS-NGGCTS) out of 111 patients in the database of the German MAKEI 86/89 studies participated in the inquiry (at least 5 years after treatment). For this, questionnaires concerning psychosocial reintegration (e.g., education, partner, activity), possible disabilities, and quality of life (QoL) (i.e., PEDQOL, Flechtner) were sent to the hospital in charge of the patients. Patients are distributed according their diagnosis. QoS is investigated by using self-reported disabilities, status of reintegration, and QoL as indicators. Characteristics for patients with CNS-G are as follows: 48 boys and 13 girls; age at diagnosis, 7–31 (mean, 14.1); mean age at inquiry, 19.2. Characteristics of patients with CNS-NGGCTS are as follows: 19 boys and 5 girls; age at diagnosis, <1–20 (mean, 13.8); mean age at inquiry, 18.5. Resection (subtotal/total) was performed in 50% of all patients. RT was administered in 100% CNS-G (mean, 20 Gy) and in all but one patient with CNS-NGGCT (mean, 43 Gy). In comparing CNS-G and CNS-NGGCTS, CT was given as 23%/88%. The most prevalent disabilities are impaired vision (44%/25%) and gross motor disabilities (30%/54%). Hormone substitution is still nec-

essary in 49%/46% of the patients. Of these patients, 49%/62% have finished school education already, and 25%/8% have completed professional training. Only 11%/0% patients have permanent partners, but reported a good social integration (e.g., number of friends, sport club membership). QoL questionnaires reveal a significant difference with regard to physical and cognitive functioning, to the disadvantage of patients with CNS-NGGCTS ($P < 0.05$). We conclude that survivors of CNS-NGGCTS show a more negative QoS than those of CNS-G. To some extent, this may be due to the self-perception of physical and cognitive impairment. This reflects the severity of the disease and the more intensive treatment. This study was supported in part by Deutsche Krebshilfe.

***LE9. GARDEN OF EDEN MEETS THE INTERNET: UNDERSTANDING NEW MODES OF COMMUNICATION FOR PATIENTS WITH BRAIN TUMORS IN CHANGING HEALTH CARE SYSTEMS**

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The dramatic change in health care delivery from private-practitioner based to health maintenance organizations (HMOs) in the United States has created a vacuum of responsibility for self care which the patient has needed to fill. The patient's mode of response to this challenge could be affected by mythical interpretations of good and evil from biblical Genesis. How patients ask for and receive health and medical information has followed a doctor-centric model since prehistory to the 1970s. In 1993 Al Gore opened national health resource information to the world through the Internet. More than 50% of adults and children have become Web surfers. The Internet has changed the professional relationship in unanticipated ways. With the democratization of knowledge, a shift has occurred in the balance of power. But patients are not physicians. Though they can become experts in their own disease, patients often do not understand the context of the information they have gathered. As a practical resolution, the lay cancer community has created a sophisticated model for offering and disseminating updated information for the Web-savvy information seeker (www.virtualtrials.com receives 110,000 hits per month), including funding and directed research funds. In toto this has accelerated a fundamental change in the patient-doctor relationship which could not have been anticipated 10 years ago. This presentation explores the development of these events and provides practical solutions for overcoming challenges that have left physicians unable to satisfy their patient's needs and the patient feeling that his or her needs are not being met. The principles apply not just to brain tumors, but to any catastrophic illness.

***MET1. BRAIN METASTASES FROM GYNECOLOGICAL CANCERS: INTRA-ARTERIAL CHEMOTHERAPY WITH OR WITHOUT BLOOD-BRAIN BARRIER OPENING**

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Infusion of chemotherapy into the carotid and/or vertebral arteries is an effective treatment for different brain malignancies. Presented is a series of five cases of brain metastases (BM) arising from gynecological malignancies treated with multimodal therapy consisting of focal radiation; intra-arterial, platinum-based chemotherapy; and infusion into a carotid and/or vertebral artery with or without blood-brain-barrier (BBB) opening; also, intravenous etoposide phosphate and cyclophosphamide was given. The files of five patients with gynecological cancers (one endometrial and four ovarian) with BM were retrospectively reviewed with approval of the Institutional Review Board. The functional performance during the course of treatment and survival period is presented. These patients were treated in a multimodal fashion using intra-arterial chemotherapy with or without BBB opening as the first therapy, continued by focal radiation to residual lesions. Five patients with BM from gynecological cancers were treated with intracarotid and/or intravertebral chemotherapy; three had BBB opening and two did not. Carboplatin was infused intra-arterially into a cerebral vessel; simultaneously, intravenous chemotherapy was administered. Residual lesions were then treated with stereotactic radiation. Two years after starting treatment, the three patients with the highest KPS remained fully functional. The two patients with the lowest KPS died within six months after the diagnosis of BM. The median survival starting from the moment when the primary tumor was diagnosed was 46 months. The median time between the primary diagnosis and the diagnosis of BM was 22 months. The median survival from the diagnosis of BM was 32 months. The complications seen were related to chemotherapy toxicity (hematological). Ototoxicity can be avoided for the most part by delayed administration of sodium thiosulfate. Combined platinum-based regimens are the standard chemotherapy for disseminated gynecological malignancies. This treatment is also effective for BM from these organs when administered into the carotid and/

or vertebral arteries; it can be complemented with stereotactic radiation to focal residual lesions. The survival rates achieved with this multimodal approach are comparable to other treatment options with the advantage of preserving good neurological function. This multimodal treatment to BM should be considered as an adjunct to surgery.

***MET2. BRAIN METASTASES FROM SYSTEMIC GERM CELL TUMORS**

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Central nervous system metastases represent a not uncommon but difficult management issue in patients with extracranial germ cell tumors. Their presentation varies from being an incidental finding on imaging studies at diagnosis or during the course of treatment to the catastrophic clinical consequences of acute raised intracranial pressure and/or cerebral hemorrhage. CNS metastases are an adverse prognostic and predictive factor in patients with germ cell tumors of both testicular and extragonadal origin. Despite this, early aggressive surgical and radiation therapy management of these metastases in combination with systemic chemotherapy can facilitate cure in 30% to 80% of patients. This presentation delineates the demographics, presentation, clinical outcome, and therapeutic management of patients with brain metastases from extracranial germ cell tumors.

***NG1. UPDATE OF PROTOCOL PATIENTS WITH CNS NONGERMINOMA TREATED ACCORDING TO SIOP CNS GCT 96**

G. Calaminus,¹ C. Alapetite,² D. Frappaz,³ M.L. Garré,⁴ S. Koch,¹ R.D. Kortmann,⁵ J. Nicholson,⁶ U. Ricardi,⁷ and F. Saran⁸; University Hospitals of ¹Düsseldorf and ²Leipzig, Germany; ³Paris and ³Lyon, France; ⁴Genova and ⁷Turin, Italy; ⁶Cambridge and ⁸Sutton, UK

In SIOP CNS GCT 96 for CNS nongerminoma, treatment is guided by dissemination. Patients with localized disease (including bifocal disease) receive after four courses PEI focal RT with 54 Gy, whereas patients with dissemination (CSF positive, mets on imaging) are treated with craniospinal RT (54 Gy). All registered protocol patients with diagnosis until 01/01/2004 regardless of age and dissemination are evaluated. Protocol patients are all patients who receive the complete and correct treatment according to dissemination. In SIOP 96, 122 protocol patients with CNS nongerminoma are registered: 98 boys (ages 4–28; median, 12) and 24 girls (ages 7–20; median, 11). Main localizations are pineal region (55%), suprasellar/hypophysis region (30%), bifocal disease (8%), and other (7%). Diagnosis is obtained by markers + imaging (43%), with biopsy (28%), and with resection (26%). Ninety-six patients without dissemination receive chemo + focal RT, and 26 patients with metastases are treated with craniospinal RT. EFS for nonmetastatic disease is 0.68 ± 0.06 (follow-up time, 2–100 months; median, 25 months) and 0.72 ± 0.10 for metastatic disease (follow-up time, 1–94 months; median, 33 months). Thirty-one events occurred, 25 in patients with focal RT (10 local, 7 [local +] ventricular, 1 spinal, 5 combined, 1 DOD, 1 DOC) and six in patients with craniospinal RT (2 local, 1 [local +] ventricular, 1 [cranial +] spinal, 1 abdominal, 1 DOC). OS is, respectively, 0.77 ± 0.06 (focal RT) and 0.68 ± 0.11 (craniospinal RT). In CNS nongerminoma, chemo + focal RT (≥ 50 Gy) is able to control subclinical disease. Metastatic patients achieve comparable survival rates with chemo + craniospinal RT (equivalent RT-dosage to tumor). Survival is less favorable than in germinoma patients. Relapses are curable only in 20%. In the forthcoming protocol, treatment will be guided additionally by AFP level at diagnosis and residual disease after chemo (which are reported separately) to further decrease relapse risk. This study was supported in part by Deutsche Krebshilfe.

***NG2. MARKERS IN SERUM/CEREBROSPINAL FLUID (CSF) IN NONGERMINOMATOUS CNS GERM CELL TUMORS (GCT): IMPLICATION OF SITE AND DISSEMINATION**

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Markers (AFP/HCG) are important for a clinical diagnosis in GCT. In SIOP CNS GCT 96, elevation of AFP > 25 ng/ml and β -HCG > 50 IU/liter in serum/CSF, together with a typical imaging, suggests a clinical diagnosis. The implications of differences in AFP/ β -HCG levels between serum and

CSF and the impact of site/dissemination on marker elevation are unclear. In 109 of 196 patients enrolled in SIOP CNS GCT 96, both markers have been measured in serum and CSF. All other patients were excluded. AFP elevation was detected in 61 patients, and the only marker in 33, and β -HCG elevation was seen in 71 patients, as the only marker in 43 cases. Of the 61 patients with AFP elevation in serum/CSF, eight patients showed higher AFP levels in CSF than in serum. Eight had disseminated disease but no higher CSF than serum values. Of 71 patients, 17 with β -HCG in serum/CSF presented with metastases. Fifty patients showed higher CSF than serum values, and 12 were metastatic. Interestingly, 24/50 had only an increase of HCG in CSF according to the defined limit of 50 IU/liter, but 8/24 showed no elevation (>5 IU/liter) in serum. In pineal cases, 42 patients presented with raised AFP, seven with higher CSF levels. Thirty-three patients had raised HCG, 23 with higher CSF levels. In suprasellar cases, 13 patients showed AFP elevation, higher in CSF in one. Twenty-four patients present with raised HCG, higher in CSF in 16 (chi-squared test not significant). AFP-secreting tumors occur predominantly in the pineal region. Measurement of markers in CSF and serum is mandatory to detect patients with marker elevation in CSF alone. There is no correlation between level of tumor markers in serum or CSF and dissemination or tumor site. This study was supported in part by Deutsche Krebshilfe.

***NG3. A PHASE II STUDY TO ASSESS THE ABILITY OF NEOADJUVANT CHEMOTHERAPY \pm SECOND-LOOK SURGERY TO ELIMINATE ALL MEASURABLE DISEASE PRIOR TO RADIOTHERAPY FOR NGGCT, CHILDREN'S ONCOLOGY GROUP STUDY ACNS0122**

S. Goldman, E. Bouffet, P. Chuba, T. Zhou, and I. Pollack; The Children's Oncology Group, Children's Memorial Hospital, Chicago, Illinois; and Children's Oncology Group, Arcadia, California; USA

This protocol is aimed at improving progression-free survival and overall survival of intracranial NGGCT, initially by achieving an increased CR/PR rate to a three-drug neoadjuvant chemotherapy regimen (carboplatin, VP-16, alternating with ifosfamide, VP-16) followed by CSI with involved-field boost radiation. For those patients not obtaining CR/PR after neoadjuvant chemotherapy (defined by neuroimaging and tumor marker response), second-look surgery will be performed. For those patients with persistent positive markers, residual malignant elements as assessed histologically, or residual unresectable disease, an attempt to increase survival will be made by using myeloablative chemotherapy (thiotepa/VP-16) with PBSC, prior to CSI. The objectives of this study are (1) to observe response rate following three cycles of neoadjuvant chemotherapy (carbo/VP-16 alternating with ifosfamide/VP-16), (2) to evaluate progression-free survival (PFS) and overall survival (OS) following this regimen, (3) to monitor serum and CSF tumor markers (alpha-fetoprotein, beta-HCG) after each cycle of this regimen, and to correlate marker response with radiographic and clinical measures of response, as well as findings at second-look surgery in patients with radiological evidence of residual disease, and (4) to determine whether additional complete responses can be achieved following high-dose chemotherapy (thiotepa and VP-16) with peripheral stem cell rescue in patients with persistently positive markers, histological evidence of residual malignant elements, or unresectable residual tumors following initial neoadjuvant chemotherapy. As of May 1, 2005, 26 patients have been enrolled, and no unexpected GR IV toxicities have been noted. We plan to enroll 80 to 100 children over a projected 42-month period. Accrual is on target.

***NG4. OVERVIEW AND CRITIQUE OF CLINICAL TRIALS IN CNS NONGERMINOMATOUS GERM CELL TUMORS: BALANCING SURVIVAL AGAINST ACUTE TOXICITIES AND LATE EFFECTS OF TREATMENT**

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This paper explores the difficulties in defining and refining optimal treatment approaches for children and teenagers with germ cell tumors (GCTs) of the central nervous system. Primary GCTs of the CNS are rare, comprising less than 2% of intracranial malignancies before the age of 20. CNS GCTs comprise germinomas and nongerminomatous (secreting) germ cell tumors (NGGCTs). Included in this latter group are endodermal sinus tumor, embryonal carcinoma (yolk sac tumor), choriocarcinoma, mature or immature teratomas with malignant elements, or "mixed" tumors, which comprise both germinomas and elements of both NGGCTs in varying proportions. Patients with GCTs, particularly tumors arising in the suprasellar area, are more likely to have neuroendocrine disorders such as diabetes insipidus, hypothyroidism, growth failure, or hypogonadism. In addition, these patients appear to be at increased risk of neuropsychological deficits. Pediatric experience with neuraxis irradiation indicates a variable but commonly significant degree of intellectual dysfunction in long-term survivors.

Thus, the treatment of these midline tumors poses a serious dilemma for children because of the risk of potentially serious long-term sequelae in survivors. The first study of the International CNS Germ Cell Tumor Study Group treated patients with carboplatin, etoposide, and bleomycin with or without additional cyclophosphamide. The goal of the study was to assess outcomes in patients treated without radiation therapy. Fifty percent of all patients were treated successfully with chemotherapy only (Balmaceda et al., *J. Clin. Oncol.* 14:2908, 1996). The second international study intensified therapy using cisplatin and cyclophosphamide in all patients; with a median follow-up of 6.3 years, 14 of 20 patients with secreting nongerminomatous GCTs were alive without disease, including eight without relapse or progression (Kellie et al., *J. Clin. Oncol.* 22:846, 2004). The five-year overall survival and event-free survival were 0.75 and 0.45, respectively. The Children's Oncology Group initiated a Phase II study in January 2004 to assess the ability of neoadjuvant chemotherapy \pm second-look surgery to eliminate measurable disease prior to radiation using carboplatin, etoposide, and ifosfamide. All patients will receive craniospinal irradiation and also a boost to the involved field. Large, cooperative clinical trials are necessary to define the optimal therapy for patients with nongerminomatous GCTs. Gains in overall survival must be measured against quality of life and neuropsychologic and neuroendocrine outcomes. The prospective identification of biologic or molecular markers may aid the identification of patients for whom less intensive or more intensive therapy is required. It is likely these challenges will take another decade or longer to resolve.

***NG5. CENTRAL NERVOUS SYSTEM SECRETING GERM CELL TUMORS (CNS-SGCT): A SINGLE INSTITUTIONAL EXPERIENCE WITH LONG FOLLOW-UP**

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In this report of a chemoradiotherapy strategy, definition of CNS-SGCT followed SIOP guidelines. From June 1988 to June 2004, 16 patients were accrued to a treatment that consisted of PEB (4 pre-/2 post-RT courses) + CSI (24 Gy/30 Gy if CR/PR after PEB) + tumor boost, that is, focal RT until 1994, thereafter whole-ventricle RT (45 Gy). The M/F ratio was 6.5, and the median age was 13. Eleven of the 16 patients presented with endocrine symptoms lasting two months to six years, 10 of 11 had diabetes insipidus; nine of 15 had hydrocephalus; four presented with metastatic deposits, three with positive CSF, one pulmonary; nine had multiple intracranial locations. Eleven patients underwent surgery, for hydrocephalus shunt in seven (2 + tumor biopsy, 1 + subtotal, 1 + total removal), two had total/subtotal removal, and two had biopsy. Alpha-fetoprotein (AFP) was pathologic in serum/CSF in 10, β HCG in 14. AFP highest values were <100 in four, <500 in four, and >1000 in two. β HCG highest values were <100 in three, <500 in six, <1000 in three, and >1000 in two. Seventy-five percent of patients responded to PEB (CR + PR); the patient with lung involvement rapidly progressed and died. One, who had marker normalization after two cycles of PEB, was submitted to residual teratoma excision. One with CSF seeding received CSI + 4 PEB courses, and one girl received focal radiotherapy only. Fifteen of 16 patients had marker decrease after PEB: 11/15 normalization; all CR after RT. Two patients relapsed at 7 and 11 months with dissemination; the girl locally irradiated relapsed at 92 months (ventricular); one died of pneumonia elsewhere before RT. Three of four patients who progressed/relapsed had markers over 1000. A fourth with AFP > 1000 UI/liter in serum and CSF therefore received intensification pre-RT and two myeloablative courses after RT obtaining CCR at 24 months. At a median follow-up of 93 months, 5-year EFS/OS was 75%, 10-year EFS and OS were 62.5% and 75%, respectively. Of the 12 survivors, six have a professional activity, three are students, and three are unemployed. This treatment strategy was efficacious with a good outcome quality. High-risk patients according to markers, more than according to stage, need treatment intensification.

***NG6. TREATMENT FOR INTRACRANIAL NONGERMINOMA: FINAL RESULTS OF JAPANESE STUDY GROUP**

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Nongerminomas were divided into two groups, the intermediate prognosis group (malignant teratoma and mixed tumors mainly composed of germinoma or teratoma) and the poor prognosis group (choriocarcinoma, yolk sac tumor, embryonal carcinoma, and their mixed tumors). Patients in the intermediate prognosis group were treated by CARE (carboplatin 450 mg/m² on day 1, etoposide 150 mg/m² on days 1–3) followed by local irradiation (50 Gy). They received additional chemotherapy five times. Patients

in the poor prognosis group were treated by ICE (IFOS 900 mg/m², cisplatin 20 mg/m², and etoposide 60 mg/m² on days 1–5) followed by whole neuroaxis irradiation. They received additional chemotherapy five times. Results were as follows. (1) The total tumor-free rate after the initial treatment in 40 patients in the intermediate prognosis group was 52%. Eight patients recurred and four of them died. The five-year overall survival rate was 97%. The recurrence rate was significantly different between disease-free patients and those with residual tumors after the initial treatment. (2) In 27 patients in the poor prognosis group, six patients recurred and died. The three-year overall survival rate was 56%, and patients without recurrence are living, with a median follow-up period of 5.4 years. Throughout the whole study, we have not encountered any serious complications.

***NG7. UPDATE ON PROTOCOL PATIENTS WITH MALIGNANT NONGERMINOMATOUS CNS GERM CELL TUMORS (NGGCT) TREATED ACCORDING TO SIOP CNS GCT 96: IMPACT OF AFP LEVEL AND RESIDUAL TUMOR ON OUTCOME**

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The interim analysis of 126 patients with NGGCTs registered on SIOP CNS GCT 96 between 1996 and 01/01/2002 identified AFP > 1000 ng/ml at diagnosis and residual disease after the end of therapy as adverse prognostic indicators. We therefore studied all protocol patients registered since this analysis (up to 01/01/2004) to see if these findings were upheld. All patients diagnosed and registered between 01/01/2002 and 01/01/2004, regardless of age and stage, were analyzed according to initial AFP level and the presence of residual disease and its surgical management after chemotherapy (CT) and at the end of treatment (following radiotherapy, RT). In SIOP 96, 21 boys (ages 7–21; median, 12) and 13 girls (ages 1–17; median, 9) were included in this cohort. The primary site was the pineal in 47%, suprasellar/hypophyseal region in 26%, bifocal in 15%, and other sites in 12%. Six of 34 had metastatic disease and were treated with craniospinal RT after CT. The remainder had focal RT. AFP was <1000 ng/ml in 29 patients (3 relapses) and >1000 ng/ml in five (2 relapses) (Fisher's exact $P = 0.08$). Complete response after treatment was achieved in 19 cases, and of these, seven underwent resection for residual after CT (no relapses). Residual disease was found in nine patients after RT, none of whom had further surgery (5 relapses) (Fisher's exact $P < 0.01$). In six patients, no response data were available. Of 23 patients with AFP <1000 ng/ml at diagnosis and response data, six had residual disease after treatment (3 relapses), compared to three with AFP >1000 ng/ml (2 relapses). Two patients who relapsed died of disease, and three are still on treatment. The risk of relapse for patients with AFP >1000 ng/ml is about 40%, for all those with residual disease around 50%, and in the presence of both risk factors, more than 60%. These results suggest the need for treatment intensification in patients with these risk factors in order to improve their chances of survival. This study was supported in part by Deutsche Krebshilfe.

***NG8. REVIEW OF THE SFOP TGM-TC 90 AND 92 PROTOCOLS FOR PATIENTS WITH INTRACRANIAL SECRETING GERM CELL TUMORS (SGCT)**

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In the first SFOP TC-90 protocol (1990–1992), based on 12 alternating courses of carboplatin-VP16 and ifosfamide-VP16 during one year, and focal radiotherapy (RTX) only in case of residue, four of four patients who received RTX are in first CR, compared to only one of 13 patients treated with chemotherapy (CT) only, although six of 13 were cured after relapse. In the TC-92 protocol (1992–1999), 38 patients (median age, 12.5 years) were treated with six to eight courses of the same CT, resection of a residue and focal 50–55 Gy RT (craniospinal for metastatic patients [M +]). Tumors were pineal in 23 patients, suprasellar in 11, bifocal in two, and in other sites in two, and five were M +; 19 secreted α FP; 12, HCG; six, both. One embryonal carcinoma was not secreting. One patient who had postsurgical complications died early. One M + patient never achieved CR. The other patients achieved biological CR, two of them with additional cis-platinum, but two had marker reevaluation at the beginning of RT. Fourteen patients had a surgical removal of a residue. RT deviations were as follows: 40 Gy in one patient and focal RT in two M +. Eleven patients relapsed: the three patients irradiated with elevated markers, the two M + patients irradiated focally, one with late CR, and five others, eight to 73

months after diagnosis; five patients were salvaged. Two nonrelapsed patients developed AML at seven and 31 months, and one died, and another patient died in CR late after treatment in bad neurological condition. With a median follow-up longer than five years, five-year survival is 73% (range, 57%–85%) and EFS 60% (range, 43%–74%). Among the four patients with AFP >1000 ng/ml, one M + and one with marker elevation before RTX died; two are alive in CR1. A higher survival rate was achieved with the combined approach, as compared to the previous series treated with CT only. RT should be performed only in patients in biological remission. Relapses could be salvaged.

***NG9. MULTIMODALITY THERAPY FOR CNS NONGERMINOMA GERM CELL TUMORS (NGGCT): RESULTS OF A PHASE II CONSORTIUM**

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CNS nongerminoma germ cell tumors (NGGCT) are more refractory to therapy than their germinoma counterparts, but treatment with both radiation therapy and chemotherapy has produced a better outcome than either modality alone. From our earlier pilot study, patients who achieved disease-free status prior to RT, either by surgery or chemotherapy, had the most favorable prognosis. A sequel study was conducted, with the goal of further improving outcome by increasing the CR rate prior to RT by intensifying CHT and second-look surgery, where feasible. Following surgical or tumor marker diagnosis of NGGCT and complete neuroaxis staging, patients were initially treated with four cycles of multiagent CHT¹. In patients not achieving CR, a second-look surgery was encouraged, followed by tandem cycles of submyeloablative high-dose CHT² with PBSC support. Eligible patients had a CNS NGGCT confirmed histologically, or by elevated serum/CSF markers for AFP or β -HCG (>100 IU/dl). Patients received neoadjuvant CHT¹: cisplatin (20 mg/m²/day 5), etoposide (75 mg/m²/day \times 5), ifosfamide (1.2 g/m²/day \times 5) \times 4 cycles. Patients who achieved less than CR underwent second-look surgery and/or received two additional cycles of DI-CHT²: carboplatin (400 mg/m²/day \times 3), cyclophosphamide (2 g/m²/day \times 2), with PBSC support. All patients received 36 Gy CSRT except for patients with localized disease with a CR after surgery or CHT who received 36 Gy WV RT + primary site(s) boost. Between October 1998 and March 2003, 27 patients were enrolled with the following characteristics: M/F, 20/7; ages, 1.5–26 years; 10 suprasellar, 13 pineal, 3 pineal/suprasellar, 1 posterior fossa; 20 M0, 7 M+. Responses after CHT¹: 12 CR - 9/27 (2 confirmed CR at second-look surgery and 3 probable CR with min residual, unconfirmed surgically); CR rendered by initial surgery, 4/27; partial response (PR) to CHT¹, 10/27; progressive disease (PD), 1/27. Of the 10 patients with PR to initial CHT, four underwent second-look surgery, of whom two were rendered surgically CR, and five patients received CHT², converting three to a CR. In total, 21/27 patients were rendered CR prior to receiving RT (12 with CHT¹, 3 with CHT², and 6 with surgery). There was a trend toward better three-year PFS in the 15 patients who achieved CR before RT (71%) as compared with the six patients who did not (50%). At a median follow-up of 59 months, 18/27 patients (66%) are without disease progression (17 NED and 1 toxic death without progression), and 20/27 patients (74%) remain alive. Nine of 27 patients experienced a relapse, which was outside the RT field in three of six patients who had disease progression after RT. The median TTP was 9 months (4–54 months). This pilot study achieved a higher CR rate prior to RT than our earlier study (78% vs. 61%), with an encouraging 66% five-year PFS. The attainment of a CR prior to RT may have contributed to improved progression-free survival. The pattern of relapse outside the radiation field in three of six patients who progressed after RT emphasizes the need for craniospinal RT volume in these patients.

***NG10. INTRACRANIAL TERATOMA: EXPERIENCE WITH REGISTERED FOLLOW-UP PATIENTS IN SIOP CNS GCT 96**

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Intracranial teratoma (TER) is a specific entity of CNS GCTs defined as "benign" disease. Complete resection is the treatment of choice but not always feasible because of the tumor volume at diagnosis and its involvement with critical structures. No standardized treatment exists in incompletely resected or recurrent TERs. We analyzed the outcome of an unselected group of teratoma patients registered on the SIOP CNS GCT 96 study.

All registered patients with the diagnosis of a primary CNS TER until 31/12/2003 were analyzed, along with outcome in relation to age, tumor size, grade of immaturity, surgical intervention, and additional treatments. Twenty-one boys (ages 0–19; median, 6) and five girls (ages 0–8; median 0) with TER were identified. The primary tumor localization was pineal in 54%, suprasellar/hypophysal in 19%, and other (mainly newborns) in 27% of cases. Median tumor size was 5 cm (range, 1.2–8 cm). In two cases, no surgery was performed because of tumor size. Median follow-up is 29 months (range, 2–108). One newborn received palliative care only and died, and a second (age 3 years) failed to respond to one cycle of carboPEI and died. In six patients a biopsy/partial resection, in three patients a subtotal resection, and in 15 patients a total resection was achieved at the first surgical intervention. Histology confirmed an immaturity grade 0 (mature) in 11 patients, grade 1 in three patients, grade 2 in five patients, and grade 3 in four patients. In addition, one patient with a mixed TER grade 1 contained elements of a rhabdomyosarcoma. Only one patient in the group of grade 0/1 TERs (n = 14) received postoperative additional therapy (24 Gy craniospinal radiotherapy). In this group, five events occurred (all alive). Seven of 10 patients with grade 2/3 TERs received adjuvant chemotherapy and additional irradiation (n = 4). In this group, three events occurred (all dead). Only one patient of the whole cohort recurred with a mixed malignant tumor and died subsequently. Event-free survival of the whole group (n = 26) was 53% \pm 13%, and overall survival was 79% \pm 9% at five years. We conclude that tumor size in infants tends to be larger and less operable than that in older patients. Adjuvant treatment was usually offered only to patients with immature TER. The impact of resection and/or adjuvant treatment for outcome remains unclear. A standardized treatment recommendation is needed to define optimal treatment strategies in the future. This study was supported in part by Deutsche Krebshilfe.

NG11. OUR EXPERIENCE WITH CNS IMMATURE TERATOMA

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We reviewed our experience with CNS teratoma retrospectively to evaluate the role of surgery for these tumors. Between 1980 and 2004, five patients with CNS immature teratoma and two patients with immature teratoma mixed with germinoma were treated at Kyoto University Hospital. They were all histologically verified. Serum titers of AFP and/or HCG were elevated in all cases. Five patients underwent total removal of the tumor followed by radiation therapy with or without chemotherapy, and all of them were almost fully active in their daily life. In another case with pineal immature teratoma, the patient suffered severe morbidity because of intratumoral hemorrhage from partially resected tumor. The other was the most recent case in which suprasellar residual immature teratoma showed malignant transformation with sarcomatous component after a four-year stable period. In our cases with CNS immature teratoma, a high extent of removal of the tumor followed by adequate adjuvant therapy generally conferred a favorable outcome. In the management of the residual tumor occurring after initial therapy, our experience supports the importance of the second-look surgery; otherwise, it is necessary to observe the residual tumor cautiously because of its malignant potential.

***NP1. GENE EXPRESSION AND PRODUCTION BY CNS PURE GERMINOMAS OF HUMAN CHORIONIC GONADOTROPIN BETA (HCG-BETA) SUBUNIT AS ASSESSED BY REAL-TIME PCR AND AN ULTRA SENSITIVE EIA**

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CNS pure germinomas (PGs) produce and secrete minimum tumor markers. Although recent advances in sensitive immunohistochemistry have suggested possible production by PG of HCG-beta, lack of sensitivity of current IRMAs has so far failed to consistently detect HCG-beta in the peripheral blood (PB) or cerebrospinal fluid (CSF) of most patients with PG. In previous studies, we developed a novel and ultrasensitive EIA (immune complex transfer-EIA, ICT-EIA) for HCG-beta, which was 1000 times more sensitive (LD, 0.03 pg/ml) than conventional IRMAs (LDV, 100.0 pg/ml) with high specificity (cross-reactivity with LH < 0.02%). All samples obtained from patients with germinomas as well as healthy controls showed detectable levels of HCG-beta (>2.0 pg/ml). High levels of HCG-beta in the CSF of PG, with an increased CSF/PB ratio (>2.0), suggested possible production of HCG-beta by tumors; those were immunohistologically negative for HCG-beta. In the present study, we examined gene expression (real-time PCR, ABI 7000) and production of HCG-beta (ICT-EIA) in histologically

verified specimens from PG (n = 4), meningioma (n = 5), teratoma (n = 3), and germinoma with STGC (n = 1). Both gene expression and tissue content were high in PG, whereas meningiomas and teratomas showed minimum HCG-beta gene expression and content. Samples from germinoma with STGC and placenta showed highest gene expression and tissue contents of HCG-beta. HCG-beta levels in both PB and CSF of patients with CNS degenerative diseases or non-germ cell tumors of young adults were 5 to 30 pg/ml, with a CSF/PB ratio of less than 1.5, whereas untreated PG showed high levels of 47.5 to 173.0 pg/ml, with a CSF/PB ratio of 2.0 to 10.0. When patients were successfully treated, both the size of the tumor and HCG-beta levels in CSF and PB fell to <30 pg/ml, with decreased CSF/PB ratios (around 1.0). These results suggest (1) that PGs produce and secrete HCG-beta into the CSF and (2) that HCG-beta in the CSF as assessed by the ICT-EIA could be a useful tumor marker in patients with PG.

*NP2. PATHOLOGY OF PRIMARY CNS GERM CELL TUMORS: PROGRESS AND PITFALLS

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Germ cell tumors (GCTs) presenting as primary CNS tumors include the full gamut of germ cell neoplasms seen as primary gonadal tumors. The majority occur either in the suprasellar region, affecting the optic nerves, chiasm, and tracts together with the hypothalamic-pituitary axis and adjacent structures, or in the pineal region, impinging on the quadrigeminal plate, the posterior third ventricle, and the posterior thalamus, although less commonly they present in other sites, notably the basal ganglia. Germ cell tumors of all types have a propensity for dissemination in the neuraxis via cerebrospinal fluid pathways, which has historically mandated neuraxial therapies including craniospinal radiation and, more recently, systemic chemotherapy. The most common histopathologic type by far is the "pure" germinoma, a tumor composed of large primitive germ cells accompanied by abundant reactive small lymphocytes. Less common types include choriocarcinoma, yolk sac tumor/endodermal sinus tumor, and embryonal carcinoma, or combinations of any of these four histological types, often termed "teratocarcinoma" or malignant mixed GCT. Whereas in the gonads these are now all highly treatable tumors, the survival of patients with primary CNS nongerminomatous GCT remains far worse than that of patients with primary CNS germinoma. In addition to these types of tumors, there are also teratomas, which range from fully mature benign tumors ("dermoid cysts") through various grades of immature teratoma including highly malignant examples. The heterogeneity of mixed GCTs is a source for diagnostic error due to sampling. Whereas diagnosis has traditionally been dependent solely on histomorphology, the last two decades have seen the development of a wide array of immunostains for specific markers of GCT types; thus trophoblastic cells of choriocarcinomatous components are readily demonstrated with stains for human chorionic gonadotropin (HCG), and endodermal sinus tumor elements with stains for alpha-fetoprotein (AFP), whereas most germinoma cells are negative for these markers but are positive in stains for placental alkaline phosphatase (PLAP) or human placental lactogen (HPL). These stains provide powerful adjunctive techniques to help document the various cell types in any given example of GCT, particularly in small samples such as stereotactic biopsies, in which diagnostic histologic patterns may be obscure or absent. More recently, these immunostains have been applied to cytopathological diagnosis of cerebrospinal fluid specimens, adding additional sensitivity and specificity to CSF cytological diagnosis. On the horizon with the molecular revolution sweeping all of medicine including pathology is the capacity for use of *in situ* hybridization to identify particular interphase chromosomal abnormalities, assess expression of various receptors and other markers, and thus predict response to particular therapies.

*NP3. MODERN APPROACHES TO THE DIAGNOSIS OF PRIMARY CNS GERM CELL TUMORS

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CNS germ cell tumors represent morphological homologues of germinal neoplasms arising in the gonads or other extragonadal sites. Independent of their location, the accurate histopathological diagnosis is a main predictor for treatment response and outcome and therefore is used as a tool for patient stratification. A main difficulty in pathology is the fact that besides unalloyed forms of germinomas, embryonal carcinomas, choriocarcinoma, yolk sac tumors and teratomas, intracranial germinal neoplasms are often of mixed histologic composition. If only small biopsies are taken, the representativity of the tissue submitted for pathological review is always a point of discussion. The identification of protein markers for most cell types (for example OCT4, OD30, AFP, PLAP) has clearly increased the diagnostic histological accuracy. However, although serum markers are available for yolk sac and choriocarcinomatous differentiation, these are

still lacking for germinomas and embryonal carcinomas. The identification of such markers will be one of the important aims of expression profiling studies of germinomas and other GCT of the CNS. Such studies as well as genetic analysis have made quick advances after laser microdissection methods have been widely introduced in molecular pathology laboratories. Important biological pathways possibly serving as therapeutic targets have also not been identified in most entities. However, in germinomas the SCF/C-kit pathway may be crucial for tumor growth, similar to the dependency of the normal cellular counterpart of germinomas, primordial germ cells, on the pathway. In contrast to extracerebral GCTs, molecular genetic analyses are still sparse on GCT of the brain. Few data by CGH and other techniques have uncovered similarities but also differences of genetic alterations of the structural and epigenetic level. For example, by CGH and array-based technologies, genetic markers will be identified capable to enrich the diagnostic toolbox for GCTs in the future. Further biological analyses will also help to pinpoint the cells of origin of the different pure and mixed GCTs.

*NP4. COEXPRESSION OF C-KIT AND SCF IN CNS GERM CELL TUMORS

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We have previously reported the expression of protooncogene c-kit in CNS germ cell tumors and suggested that the concentration of soluble form of c-kit (s-kit) in cerebrospinal fluid may represent a specific clinical marker for germinoma-containing tumors. Here we investigated the expression of stem cell factor (SCF), a specific ligand of c-kit, in CNS germ cell tumor samples from 16 patients, using immunohistochemical methods to determine the expression of c-kit and SCF. The immunostaining patterns of c-kit and SCF were almost identical. In all germinoma-containing tumors, c-kit and SCF were diffusely expressed on the cell surface of germinoma cells; lymphocytes and interstitial cells were negatively stained. In immature teratomas, only mature components were immunoreactive for both c-kit and SCF. Syncytiotrophoblastic giant cells (STGCs) were negative for both SCF and c-kit. The CSF concentration of SCF was measured by sandwich ELISA to determine the possibility of tumor marker. The level of SCF also increased in germinoma, even in patients with low s-kit level. However, the specificity of SCF seems lower than that of s-kit, since the level of SCF increased in other histological types of brain tumor, such as medulloblastoma. Therefore, a combination of s-kit and SCF may be useful for the diagnosis of germinoma.

*NS1. PROS AND CONS OF PREOPERATIVE NEOADJUVANT OR ADJUVANT CHEMOTHERAPY IN PATIENTS WITH NONGERMINOMATOUS GCTS (NGGCTS): ANALYSIS OF DATA GENERATED IN MAKEI 89 AND P-SIOP

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CNS NGGCTs are heterogeneous with high proliferation, infiltrative growth, and secretion of markers (yolk sac and choriocarcinoma elements). They are mainly located in the pineal or suprasellar area and developing in areas of subtle structures like chiasma opticum or the neurohypophysis. Therefore, it is still under discussion if a clinical diagnosis with markers (AFP/HCG) ± biopsy is appropriate before starting chemotherapy or if a surgical resection should be obtained as a first step. We evaluated protocol patients with CNS NGGCTs who are treated in MAKEI 89 (n = 28) and in P-SIOP (n = 22). Patients are evaluated for site, severe neurological symptoms at diagnosis (e.g., nerve palsies, visual impairment, and motoric dysfunction), markers, and type of surgical intervention at the beginning (clinical diagnosis ± biopsy, subtotal resection, total resection). All patients are treated with comparable chemotherapy (MAKEI 89: 2 × BEP/2 × VIP, P-SIOP: 4 × PEI) and irradiation (MAKEI 89: 50 Gy to tumor, P-SIOP: 54 Gy to tumor). In MAKEI 89, 16 patients had tumors of the pineal region, seven are located in the suprasellar region, and five are in other sites. In P-SIOP, 12 cases are pineal, five are suprasellar, and five are elsewhere. Severe neurological symptoms are seen in 18 of 28 patients in MAKEI 89 and in 13 of 22 patients in P-SIOP. In MAKEI 89, markers are elevated in serum/CSF at diagnosis in 24 patients, whereas in P-SIOP, 20 patients have increased marker at diagnosis. Diagnosis is done clinically (± biopsy) in five MAKEI 89 patients and 13 P-SIOP patients. A subtotal resection is reported in eight MAKEI 89 patients and two P-SIOP patients. A total resection is described in 13 patients from MAKEI 89 and in seven from SIOP 96. The EFS is 0.57 in MAKEI 89 (median follow-up of survivors, 120 months) and 0.68 in P-SIOP (median follow-up, 75 months). In MAKEI 89 four patients and in P-SIOP one patient died perioperatively. We conclude that although surgical techniques for diagnosis and treatment of brain tumors have been

improved within the last 20 years, more patients are diagnosed clinically in P-SIOP as compared to MAKEI 89, which leads to a similar event-free survival. Patients with impaired neurological condition at diagnosis especially may benefit from preoperative chemotherapy and delayed surgery. This study was supported in part by Deutsche Krebshilfe.

***NS2. ROLE OF HISTOLOGICAL DIAGNOSIS OF GERM CELL TUMOR IN THE PINEAL REGION**

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The aim of this study was to investigate the significance of histological diagnosis of germ cell tumor (GCT) arising in the pineal region before chemotherapy and/or radiotherapy. A total of 70 consecutive patients with pineal region tumor who were hospitalized in our department between April 1989 and March 2005 were retrospectively reviewed. Of 70 cases, 62 cases (89%) were diagnosed as GCT with clinical findings, including the clinical backgrounds, MRI findings, and tumor markers. Of 62 cases, 33 patients (53%) underwent endoscopic biopsy (14 cases) or resection (19 cases) of the tumor for treatment and histological diagnosis. As a result, 32 cases (97%) except one case with pineoblastoma were confirmed as pineal GCT. With regard to the eight cases diagnosed as non-GCT lesions, clinical diagnoses were in agreement with histological diagnoses. We adopted the classification that Matsutani et al. proposed, in which the GCTs were classified into three therapeutic groups, with good prognosis, intermediate prognosis, and poor prognosis, based on histological diagnosis or tumor marker in the cases without histological information. Thirty-two cases with histologically verified pineal GCT and 29 cases with clinical pineal GCT without histological confirmation underwent chemotherapy and/or radiation therapy, which was assigned by the above-described classification. Although we obtained excellent response to initial treatment in most cases, eight of 61 cases with pineal GCT had remaining or recurrent tumor which was to be resected. Among them, five resected tumors were mature or immature teratomas. With the exception of the case of pineoblastoma, most of the pineal GCTs could be diagnosed with clinical findings alone. Furthermore, the clinically diagnosed and classified GCTs could be treated effectively by corresponding chemotherapy and radiation therapy. The radical resection, however, should be performed in cases with teratoma at initial presentation or any kind of refractory lesions to chemotherapy and radiation therapy.

***NS3. THE IMPACT OF SURGICAL RESECTION ON THE OUTCOME OF CNS GERMINOMAS: THE RESULTS OF THE INTERNATIONAL CNS GERM CELL TUMOR STUDY GROUP**

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The management of pure CNS germinomas has focused on biopsy, followed by some combination of chemotherapy and/or radiation therapy. However, the benefits of surgical resection prior to adjuvant therapy have not been well documented. To determine if aggressive surgical resection affects the outcome in this patient group, we retrospectively analyzed the data from the First International CNS Germ Cell Tumor Study. Forty-six patients were found to have marker negative, histologically pure germinomas in this study. The average age at diagnosis was 14, and the average length of follow-up was six years. All patients had tissue diagnosis, followed by protocol-based chemotherapy and radiation therapy. Overall, 29 patients had disease recurrence, and eight died of their disease. When patients with suprasellar disease or multifocal disease were excluded, patients who had less than 1.5 cm³ of disease prior to therapy did better, with a 33% recurrence rate and no deaths, compared with a 63% recurrence rate and 25% death rate for those with greater residual disease. Additionally, fewer of the patients with >1.5 cm³ of residual required a second surgery. We thus conclude that there is a possible benefit for surgical resection prior to the initiation of chemotherapy and radiation therapy. This data will be augmented by quality of life data.

***NS4. DISSEMINATION OF INTRAVENTRICULAR TUMORS FOLLOWING ENDOSCOPIC MANIPULATION AND THIRD VENTRICULOSTOMY**

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Endoscopic biopsy with concomitant third ventriculostomy (ETV) is a well-established diagnostic and therapeutic maneuver for hydrocephalus resulting from a tumor of the posterior third ventricle. An iatrogenic fenestration of the floor of the third ventricle in theory could provide a conduit for subarachnoid dissemination of an intraventricular tumor. This series represents the experience at our institution of ETV for hydrocephalus caused by an intraventricular tumor, presented with the goal of identifying a risk for metastasis following this procedure. A review was conducted of all patients for whom an ETV and simultaneous endoscopic biopsy or resection of tumor was performed between 1995 and 2005 at New York-Presbyterian Hospital/Cornell and Memorial Sloan-Kettering Cancer Center. Patients were subsequently stratified as to the known metastatic potential, based upon tumor type, into high potential (Group A) or low potential (Group B) categories. Evaluation for subarachnoid metastases was performed by a review of all available clinical and radiographic data, MR imaging of the brain and spinal cord, and CSF sampling. Eighteen patients (11 male; mean age, 24; range, 2–59) underwent ETV and simultaneous endoscopic biopsy or resection of a posterior third ventricular tumor. Of these patients, 10 were assigned to Group A (5 germinomas, 1 yolk sac tumor, 3 primitive neuroectodermal tumors (PNET), 1 ependymoma), and eight were assigned to Group B (4 astrocytomas, 1 glioblastoma, 1 mixed glioneuronal tumor, 1 central neurocytoma, 1 pineal parenchymal tumor). Of 10 patients assigned to Group A, nine underwent endoscopic biopsy and one had an endoscopic tumor removal. At a mean follow-up of 23.9 months, only one patient was found to develop further CNS metastasis. This patient suffered from progression and diffuse intracranial and spinal leptomeningeal metastasis of a yolk sac tumor and died 11 months postoperatively. One patient with pineoblastoma presented with subarachnoid disease before surgery and was therefore excluded from final analyses. Of eight Group B patients, seven had endoscopic biopsy or partial resection and one underwent complete endoscopic resection. None of these patients experienced subarachnoid extension of their disease (mean follow-up, 9.0 months). Metastatic potential is thus summarized as 5.9% overall, 11.1% in Group A patients and 0% in Group B patients. The rate of tumor dissemination in this series of patients does not differ significantly from published rates for childhood brain tumors with a high potential for spread, including germ cell tumors, PNET, or ependymoma. Larger series of comparative data are required to draw a firm conclusion, but given the known benefit of combined tumor biopsy and ETV for patients with pineal region tumors, our data would support such a surgical approach.

***NS5. FLUORESCENCE DETECTION OF CNS GERM CELL TUMORS WITH 5-AMINOLEVULINIC ACID**

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5-Aminolevulinic acid (5-ALA) induces the specific accumulation of photosensitizing porphyrins in malignant gliomas and has been explored for guiding resection of these tumors. However, the usefulness of fluorescence-guided resections of the CNS germ cell tumors has not been studied. Here, we examined the sensitivity and value of ALA-induced fluorescence for detecting germ cell tumors. Twelve patients underwent ALA-induced protoporphyrin fluorescence detection. Three hours before the induction of anesthesia, 1 g of 5-ALA was administered orally. Intraoperatively, red porphyrin fluorescence was observed with a 455-nm long-pass filter after excitation with violet-blue (405-nm) light. Fluorescing and nonfluorescing samples taken from the tumor tissues were examined histologically. In three cases, fluorescence-guided endoscopic tumor biopsy for pineal and/or suprasellar region tumors was performed. Biopsy specimens were taken on the basis of fluorescence intensity by spectrometric measurement during endoscopic procedures. Bright red fluorescing tumor tissues were observed in 75% (9 of 12) of germ cell tumors. Sensitivity was impaired by two cases of germinoma that contained fibrous tissues with low-density infiltration of germinoma cells. One case of immature teratoma was fluorescence negative. Histological diagnosis of germinoma was successfully established in all three patients who underwent fluorescence-guided endoscopic tumor biopsy. The evidence of tumor dissemination undetectable on neuroimaging was detected in two cases by endoscope. PPIX spectrum with peak at 635 nm was detected in areas of tumor dissemination. The observations in this study indicate the usefulness of ALA-induced tumor fluorescence for guiding germ cell tumor resection. Measurement of 5-ALA-induced PPIX fluorescence intensity with spectrometer may be useful for identifying areas of tumor and for targeting of biopsies under endoscope.

***NS6. THE ROLE OF DELAYED SURGICAL RESECTION OF PRIMARY CNS GERM CELL TUMORS**

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Germ cell tumors (GCTs) of the CNS are a rare, biologically diverse, and therapeutically controversial group of neoplasms. The unique characteristic features of these tumors, including their frequent localization to the pineal region and sensitivity to radiation therapy (RT) and chemotherapy, render them a unique model system in which to test the utility of both novel neurosurgical approaches and creative therapeutic interventions. Surgery plays an important role in the overall management of these lesions. First, endoscopic techniques have been essential in treating associated hydrocephalus, obtaining CSF for analysis, and attempting tissue diagnosis. Second, radical resection is believed to be an important initial step in the management of many pineal region lesions. However, it has become increasingly clear that resection is not recommended in the case of pure germinoma, in which no benefit is conferred by excision, and marker-positive nongerminomatous germ cell tumor (NGGCT), which is responsive to initial chemotherapy and radiation. Experience in systemic GCTs previously revealed that residual radiographic abnormalities after initial chemotherapy often implied fibrosis or teratoma, which could be treated with delayed, second-look surgery. We (Diez et al., *Childs Nerv. Syst.* 15:578, 1999; Weiner and Finlay, *Childs Nerv. Syst.* 15:770, 1999; Sands et al., *Neuro-Oncology* 3:174, 2001; Weiner et al., *Neurosurgery* 50:727, 2002) and others reported that it is becoming acceptable to perform delayed surgery to complete the tumor response that was initiated by aggressive chemotherapy. When chemotherapy is not sufficient to eradicate these tumors completely, a second-look operation should be considered. This approach has been incorporated into international treatment protocols. The challenge lies in recognizing pure germinoma and in determining the exact timing of delayed surgery. We found that this should be avoided in patients in whom tumor markers have not normalized completely. Moreover, in the presence of an asymptomatic mass that is not expanding, and where tumor markers are normal or decreasing, the likely diagnosis is necrosis and/or scar, and avoiding additional surgery may be possible in the risk/benefit analysis.

***NS7. ADVANCES IN NEUROSURGICAL MANAGEMENT OF PINEAL AND SUPRASellar REGION PRIMARY CNS GERM CELL TUMORS**

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Surgical intervention for primary CNS germ cell tumors (GCTs) is commonly required for both diagnostic and therapeutic purposes. The deep and central location of these tumors imposes inordinate demands when conventional surgical approaches are used for tumor removal and prohibitive limitations with standard tumor biopsy methods. Fortunately, advances in surgical technology have created alternatives to conventional procedures that have truly revolutionized the surgical management of this disease. The evolution of minimally invasive endoscopic neurosurgery, heralded by advances in lens technology and light intensity, has afforded procedures that now allow exposure and tumor manipulation with minimal to no brain retraction. The pineal region, posterior third ventricle, infundibular region, suprasellar cistern, and pituitary fossa, all sites regularly affected by GCT, lend themselves to endoscopic approaches. Additionally, because of the concomitant finding of CSF obstruction in the majority of patients, simultaneous endoscopic procedures aimed at symptomatic relief of hydrocephalus such as endoscopic third ventriculostomy (ETV) further the appeal of an endoscopic approach. During the years of 1995 to 2005, a primary endoscopic approach has been used in the management of 86 patients, 12% (10) of whom had CNS germ cell tumors. From this group of patients, 31 primary endoscopic resections were performed and 55 endoscopic biopsies were done. Thirty-eight patients underwent a simultaneous procedure aimed at treating CSF obstruction: 18 endoscopic third ventriculostomies (ETV), 16 endoscopic septostomies, and four endoscopic tumor cyst decompressions. Endoscopic biopsy yielded a diagnostic sample in 96% (53/55) of cases, and total endoscopic tumor removal was accomplished in 90% (28/31) of cases. There were no patient deaths and four procedure-related morbidities (2 superficial wound infections, 1 aseptic meningitis, and 1 stroke) for a total complication rate of 4.7% and permanent morbidity rate of 1.2%. The use of endoscopic surgery in the management of intraventricular brain tumors results in an excellent diagnostic yield and a high rate of tumor removal with minimal morbidity. The anatomical position of primary CNS GCTs allows minimally invasive endoscopic procedures to be used for diagnostic purposes, tumor resection, and treatment of hydrocephalus. The safe application of these techniques is governed by rigid patient selection, the intended surgical goal, and the experience of the surgeon.

NS8. THE DIAGNOSTIC VALUE OF PREOPERATIVE RADIOLOGIC AND SEROLOGIC TESTING IN PINEAL REGION TUMORS IN CHILDRENM.D. Krieger¹ and J.G. McComb²; ¹Division of Neurosurgery and ²Department of Pediatrics, Childrens Hospital Los Angeles, Los Angeles, California, USA

The management of pineal region tumors is highly contingent upon accurate diagnosis. Pure germinomas, the most common childhood tumors in this location, are effectively treated with chemotherapy and/or radiation. However, the management of nongerminomatous germ cell tumors, pineocytomas, pineal primitive neuroectodermal tumors (PNETs), and astrocytomas is more controversial, although surgical resection clearly plays a role. To ascertain the ability of preoperative diagnostic testing to determine therapy, we retrospectively reviewed the records of 50 consecutive patients with pineal region tumors treated at one institution over 10 years. This series consists of 19 germinomas, 12 nongerminomatous germ cell tumors (teratomas, embryonal carcinomas, choriocarcinomas, or germ cell tumors of mixed histology) 15 PNETs (pineoblastomas), three astrocytomas, and one pinealoma. Patients included 34 boys and 16 girls, with an age range of 6 months to 16 years (mean, 9.5 years). The preoperative MRI report included the correct histological diagnosis in the differential in 46 cases (92%). In six of the cases, the report incorrectly indicated the tumor was "likely germinoma"; however, the correct histology was mixed germ cell tumor in three cases, PNET in two, and astrocytoma in one. Serological markers (BHCG and AFP) were obtained in 44 patients (88%). These tests were normal or mildly elevated in all of the patients with germinoma, PNET, astrocytoma, or pinealoma. However, they were elevated in only five of the 12 (42%) nongerminomatous germ cell tumors. Preoperative serological and radiological evaluation of pineal region tumors is not conclusive in making a histological diagnosis and could lead to inappropriate therapy.

***RT1. DEFINING THE OPTIMAL RADIATION THERAPY FOR SECRETING CNS GERM CELL TUMORS (SGCTS): A CRITICAL REVIEW OF THE LITERATURE**

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The nonsurgical standard of care in intracranial sGCTs is cisplatin-based chemotherapy followed by radiotherapy (RT). The optimal radiotherapeutic management of localized tumors remains controversial. We reviewed the current published literature with respect to the pattern of relapse in relation to dose and volume of radiation therapy used (localized versus craniospinal). We performed a Medline search of the literature published since 1985 in the English language. Three hundred eight patients (from 1962 onward) with a median age of 12.8 years (range, 1.3–37 years) were identified on the basis of histological confirmation and/or significantly raised tumor markers at diagnosis. Median follow-up was 56.9 months (range, 2–96 months). The data were analyzed according to total dose prescribed and type and dose of radiation therapy (focal versus craniospinal). Median dose prescription to the primary tumor was 48 Gy for focal RT (range, 24–60 Gy), and doses of craniospinal RT varied between 21.6 and 35 Gy with a primary tumor boost to a total dose of 50 to 60 Gy. Within the patient group, 67 relapses (21.7%) were identified. The local relapse rate was 15.2%, spinal relapse rate was 5.5%, and systemic metastases rate was 0.65%, with no clear differences between patients treated with localized or extended volume RT. Patients receiving a primary tumor dose of less than 50 Gy had a 24.5% relapse rate compared to 23% in the patients treated with a higher dose. The verifiable outcome reported was better than that suggested by current preliminary data of international prospective clinical trials and is likely biased by the imprecise reporting of patterns of relapse and difficulties of identifying individual patient outcomes in the usually very small series. We were unable to identify a clear irradiation dose-response relationship. For localized intracranial sGCTs, there appeared to be no difference in relapse rates or pattern of relapse when treating with localized radiotherapy alone compared to craniospinal irradiation. Prospective international studies of larger patient groups are necessary to address the role of RT in sGCTs.

***RT2. OUTCOME AFTER REDUCTION OF IRRADIATION DOSAGE IN PATIENTS WITH INTRACRANIAL NONMETASTATIC GERMINOMA: A COMPARISON BETWEEN MAKEI 89 AND SIOP CNS GCT 96**

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Craniospinal irradiation plus tumor boost is still standard treatment for intracranial germinoma and leads to excellent survival rates. In MAKEI 89, 30 Gy CSI + 15 Gy TU (single fraction 1.5 Gy) were given. This was reduced to 24 Gy CSI + 16 Gy TU (single fraction 1.6 Gy) in SIOP 96 to reduce long-term effects. Because there is no special trial for adults, these patients were additionally registered. Predominantly in the adult oncology there are still existing doubts if this reduced dosage is adequate. All registered patients (diagnosis until 31/12/03) regardless of age with histologically proven (resection or biopsy), tumor marker negative (AFP < 25 ng/ml and HCG < 50 IU/liter), nonmetastatic (uni- or bifocal [only pineal and suprasellar] disease without tumor cells in CSF and negative spinal MRI) intracranial germinoma and protocol therapy were included. For the most possible comparability, only five-year EFS and overall survival according to Kaplan-Meier was analyzed. In MAKEI 89, 24 boys (ages 7–32; median, 16) and six girls (ages 7–31; median, 9.5) and in SIOP 96 65 boys (ages 7–42; median, 13) and 24 girls (ages 7–22; median, 12) were registered. Main localization was the pineal region (53%) followed by the suprasellar/hypophysal region (28%), bifocal disease (18%), and other (1%). Within the five-year follow-up time, events occurred only in three of 30 patients (MAKEI 89) and in five of 89 patients (SIOP 96). EFS was 0.90 ± 0.05 in MAKEI 89 and 0.91 ± 0.05 in SIOP 96 (log-rank $P = 0.74$). Only one of the eight event patients had a pure germinoma at relapse. Events in MAKEI 89 were as follows: DOC, one patient; metachronous disease (testis [EC]), one patient; abdominal relapse (VP-shunt; GER + CHC), one patient. Events in SIOP 96 were as follows: DOC (sickle cell anemia), one patient; local relapse, four patients (1 GER, $2 \times$ YST, $1 \times$ TER). In the three patients with high malignant components at relapse, incomplete primary diagnostics (marker and/or cytology) of CSF was performed. Only the two relapsed patients of MAKEI 89 achieved second long-term remission. We conclude that excellent EFS is similarly achievable by reduced craniospinal irradiation + tumor boost. Both applied irradiation dosages are not able to control nongerminomatous tumor elements detected at relapse. Therefore, complete initial diagnostics in serum and CSF (+ imaging) is mandatory for treatment guidance. This study was supported in part by Deutsche Krebshilfe.

***RT3. ADVANCES IN RADIATION THERAPY TECHNIQUES APPLICABLE TO PINEAL AND SUPRASSELLAR REGION TUMORS**

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Radiation therapy (RT) is almost systematically curative in children and adolescents with intracranial germinomas. Although there is rather consistent data regarding dose response at the primary site for irradiation alone, there remains considerable controversy regarding the appropriate target volume (ranging from local to ventricular to full cranial to craniospinal volumes). It has largely been in the context of recent combined chemotherapy (CT) with RT studies that volume definitions have been reconsidered regarding (1) use of margins >1 cm at the primary tumor bed and (2) protocol therapy evolving from wide local to at least full ventricular system coverage. Documented dosimetric studies suggest that three-dimensionally planned ventricular radiation volumes do spare a considerable proportion of the normal brain. Sophisticated photon and proton techniques are also capable of sparing higher-dose exposure of much of the normal brain in the context of treating the primary tumor site, if challenging us to compare intermediate dose level volumes that may actually be increased. Prospective comparisons with detailed dose-volume data are vital in correlating neurocognitive and quality of life parameters key to comparing current therapeutic approaches. Treatment of "malignant" germ cell histiotypes requires CT and RT, with similar questions in defining the appropriate target volumes and dose levels, as well as better determining the appropriate, perhaps response-adapted dose to the primary tumor site(s). Data regarding initial or wider radiation volume and outcome are disparate in this setting. The higher dose levels required demand even more attention to optimizing radiation delivery to adequately encompass the primary site(s) of involvement and the selected ventricular, cranial, or craniospinal volume. The roles of radiosurgical "boost" or delayed resection for residual disease sites also need to be considered. To proceed confidently with maximal dose conformity, idealized neuroimaging must be combined with a better appreciation of the patterns of failure in recent and ongoing studies, enabling us to

identify the appropriate target volume in integrating RT and CT. Response-adjusted radiation dose levels for the "malignant" histiotypes require prospective studies with detailed radiation parameters.

***RT4. SIMULTANEOUS INTEGRATED BOOST RADIOTHERAPY FOR INTRACRANIAL GERMINOMA**

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A conventional radiotherapy technique for intracranial germinomas is to initially treat the whole ventricular system and then boost the tumor bed. The boost portion of the treatment delivers a varying dose to the ventricular volume outside the primary tumor bed that is unaccounted for in the prescription. In order to deliver a predefined dose to the ventricles and hypothalamic-pituitary axis, more intensive dose to the tumor bed, and less intensive dose to the normal brain tissue outside the ventricles in a shortened overall treatment time, we use an intensity-modulated radiation therapy technique incorporating a simultaneous-integrated boost (SIB-IMRT) to treat patients with intracranial pure germinoma at Childrens Hospital Los Angeles. Upon presentation, the patients undergo MRI scanning of the brain and spine, serum, cerebrospinal fluid alpha-fetoprotein and beta-human chorionic gonadotropin level determination, and biopsy to establish the diagnosis of localized intracranial germinoma. They are then treated with four cycles of carboplatin, 300 mg/m²/day on days 0 and 1, and etoposide, 150 mg/m²/day on days 0, 1, and 2, repeated at three-week intervals. An MRI of the brain after the fourth cycle is done to determine the response to chemotherapy. If there has been a complete response, SIB-IMRT is initiated within four weeks of completion of chemotherapy. If a residual mass is noted on the MRI, a biopsy may be performed to determine whether residual nongerminomatous tumor elements are present. The SIB-IMRT delivers 200 cGy per fraction to the prechemotherapy tumor bed plus a 4-mm margin while simultaneously delivering a minimum dose of 170 cGy per fraction to the whole ventricular system plus a 3-mm margin. The radiation therapy course is a total of 15 fractions given once daily over three weeks to deliver a total dose of 30 Gy to the primary tumor bed and a minimum dose of 25.5 Gy to the ventricles. Eight non-coplanar beams are used to minimize the radiation dose to the surrounding normal brain and pituitary gland. Nine patients with intracranial germinoma were treated on this protocol between September 2004 and May 2005. All have had a complete response to chemotherapy and tolerated the radiation and chemotherapy well. There have been no tumor recurrences to date. Neurocognitive testing has been done at baseline and will be repeated annually. The described chemoradiotherapy protocol is well tolerated and has produced complete responses in all patients to date. Long-term tumor control and late effects data are being collected while additional patients are being accrued.

***RT5. WHOLE-VENTRICULAR IRRADIATION (WVRT) IN INTRACRANIAL GERM CELL TUMOURS (CNS GCTS): AN EVALUATION OF CONFORMAL AND INTENSITY MODULATED RADIOTHERAPY (IMRT) PLANNING**

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WVRT to a dose of 24 Gy is an important part of the next generation of prospective national and international collaborative studies for CNS GCTs. We analyzed the impact of different treatment techniques of WVRT in terms of target volume coverage and dose to normal tissues. A planning target volume (PTV) to the total dose of 24 Gy in 15 fractions, encompassing the whole ventricles plus 1-cm margin, as per SIOP CNS GCT 05 protocol, was defined in five cases with primary CNS GCTs by using CT/MRI fusion. Organs at risk outlined were supratentorial brain, infratentorial brain, pituitary gland, eyes, and parotid glands. Conformal treatment plans were produced for lateral opposed fields, three non-coplanar fields, four non-coplanar fields, and seven-field IMRT, reflecting an increasing degree of complexity. All treatment fields used 1-cm-wide multileaf collimation. Normal tissue doses and PTV coverage was evaluated by analyzing dose volume histograms (DVHs). PTV isodose coverage for all techniques complied with ICRU 62 criteria. For infratentorial brain, the percentage volume receiving 5 Gy (V_5) was maximal with IMRT and four non-coplanar fields (97%; range, 93%–100% and 85%–100%, respectively) and minimal with parallel pairs (77.2%; range, 73%–82%); the percentage volume receiving 20 Gy (V_{20}) was maximal with four non-coplanar fields (68%; range, 58%–85%) and minimal with IMRT (26%; range, 22%–30%). For supra-

tentorial brain, V_5 was maximal with four non-coplanar fields (88%; range, 87%–98%) and minimal with parallel pairs (68%; range, 59%–85%); V_{20} was maximal with parallel opposed fields (54%; range, 45%–72%) and minimal with IMRT (31.2%; range, 36%–25%). For parotid glands, no plan exceeded 10 Gy to 15% of the gland. For the pituitary gland, IMRT plans provided a mean dose sparing of 18 Gy (range, 7–26 Gy) when compared with non-IMRT plans. Average conformity index (CI) was 1.5 for IMRT plans, 2.0 for four non-coplanar field plans, 2.2 for three non-coplanar field plans, and 2.8 for parallel pair plans. All techniques provide clinically acceptable PTV coverage. The IMRT solution permits considerable sparing of supratentorial normal tissue volumes for radiation doses >7 Gy, which, as for sparing of the pituitary gland, could impact on late sequelae such as neurocognitive function and endocrine deficits. While IMRT is the technologically best solution for WVRT in the context of localized germinomas, prospective evaluation is required to exclude a potential increase in second malignant tumors due to low-dose irradiation of the meninges.

***RT6 ROLE OF RADIATION THERAPY (RT) IN THE MANAGEMENT OF CNS GERM CELL TUMORS (GCT)**

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Radiation therapy plays an important role in the management of CNS GCTs, including the germinomas and nongerminomatous GCTs. The role of RT has evolved over the last decade based on data from both retrospective studies and randomized trials. Radiation therapy alone results in an excellent outcome for patients with CNS germinoma. For patients with localized disease, treatment includes 20–24 Gy to the tumor plus ventricles, with a 16–30-Gy boost to the tumor, for a total dose of 36–52 Gy (usual doses 21 Gy + 24 Gy = 45 Gy). The minimum acceptable final dose to the tumor is ≥ 40 Gy. The results of so-called involved-field approaches (i.e., tumor + 2-cm margin) are inadequate and are associated with local failure in one-quarter to one-third of patients, compared to $<5\%$ with larger fields (either ventricular or whole-brain radiation). For patients with disseminated disease, craniospinal RT to 22–30 Gy is followed by an 18–30-Gy boost to the tumor (usual doses 24 Gy + 21 Gy = 45 Gy). With these RT-alone approaches, the local control rate is $\sim 95\%$ with five- and 10-year survival times of $\sim 95\%$ and $\sim 90\%$, respectively. Despite these results, the use of large fields and high doses may result in decreased quality of life (QOL) and neurocognitive function, especially children with disseminated disease. Both retrospective and prospective data have shown that chemotherapy plus response-based reduced-dose RT (in the range of 24–35 Gy, typically 30 Gy) results in local control rates and two- to five-year survival times similar to those with RT alone. Longer follow-up is needed to assess whether the 10-year survival data hold up, to see if QOL and neurocognitive function are indeed improved, and to see if there are no late effects of chemotherapy, compared to treatment with RT alone. A randomized trial in CNS germinoma comparing RT alone to chemo-RT is being planned by the Children's Oncology Group. The current schema of this study will be presented. Unlike CNS germinoma, RT alone is inadequate treatment for nongerminomatous GCTs (the only exception being incompletely resected mature teratoma, which may be observed or irradiated). Results of retrospective and prospective studies using chemo-RT appear promising. Several technical innovations in radiation therapy will likely improve outcome (better local tumor control with reduced late effects) in patients with CNS GCTs. Stereotactic radiosurgery with gamma knife or linear accelerator-based techniques has a role to play in recurrent, previously irradiated GCTs and selected patients with newly diagnosed GCTs (mainly residual/recurrent mature teratoma in which radiation is recommended). Intensity-modulated radiation therapy is a promising new method to deliver whole-ventricular RT allowing maximum sparing of surrounding white matter and grey matter (cortex). In this presentation, data supporting the information provided in this abstract are reviewed.

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