Abstracts for the
Second International Symposium
on Central Nervous System
Germ Cell Tumors

November 18–21, 2005

Los Angeles, California
The purpose of this study is to further characterize the immunohistochemical profile of CNS germinomas and correlate it with the expression of CD117 (c-kit) in relation to possible mutations of the c-kit gene. Biopsy material from 20 CNS germinoma cases was studied immunohistochemically. In 10 cases, archived frozen tumor tissue was available for c-kit proto-oncogene mutation analysis. DNA extracted from regions with >80% tumor density underwent whole genome amplification prior to mutation analysis. In one additional case, mutation analysis was performed on paraffin-embedded tissue. Results: Sequence analysis and reverse sequencing were performed on c-kit’s exons 9, 11, 13, and 17. The neuroanatomical distribution of tumors is as follows: 10 pineal, six suprasellar, two thalamic, one basal ganglia, and one in the posterior third ventricle. There were 15 males and five females, with an average age of 13.25 years and an age range of 7 to 17 years. The immunohistochemical profile revealed strong positive staining for PLAP and CD117 in all 100% of cases. The latter was always diffuse and stronger than PLAP. This difference was more accentuated in tissue frozen for intraoperative consultation and subsequently fixed in formalin and processed similarly. H&E showed a weak diffuse cytoplasmic staining with few scattered strongly stained cells. AFP, CEA, and CD30 were consistently negative. Staining for vimentin and keratin reveal few scattered cells showing focal cytoplasmic staining. Molecular analysis for c-kit mutations showed 1/11 tumors with exon 17 (N822Y) mutation. This mutation represents gain-of-function mutation. We conclude that CD117 is a reliable immunohistochemical marker for germinomas. No relation between immunophenotype and mutations analysis was identified. The 9% c-kit mutation rate in our study is consistent with previous reports of low frequency of c-kit mutations in germinomas.

**B2. GENE THERAPY STRATEGIES FOR CENTRAL NERVOUS SYSTEM GERM CELL TUMORS: FROM BENCH TO BEDSIDE**

Maria G. Castro, Gwenyalyn D. King, James F. Curtin, Marianela Candolfi, Chunyuan Liu, Kurt Kroeger, Mariana Puntel, Weidong Xiong, and Pedro R. Lowenstein; Gene Therapeutics Research Institute, Cedars Sinai Medical Center, Departments of Medicine and Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California, USA

Intracranial germ cell tumors (CNSGCTs) constitute a group of neoplastic lesions which include teratoma, malignant germinoma, embryonal carcinoma, yolk sac tumors, and chorionicarcinoma. The current treatment for CNSGCTs includes a combination of tumor resection, irradiation of the tumor cavity to prevent tumor spread, and craniospinal irradiation to control spread of the tumor to the leptomeninges. Chemotherapy is also used to prevent leptomeningeal and systemic tumor dissemination. Combination therapy, using cisplatin-based chemotherapy with radiation therapy, yielded promising results, achieving survival rates of 30% to 60%. Patients with progressive disease could benefit from resection of the primary tumor. In these patients, a more aggressive treatment regime would be justified, including high doses of chemotherapy with stem cell treatment. Since some patients do not develop metastatic disease, this highlights the importance of local tumor control using a combination of surgery, chemotherapy, and radiotherapy. In spite of the advances in patient’s survival and improved treatment modalities, taking into account the side effects of both chemotherapy and radiotherapy, and also to improve outcomes in patients with disease. Forward and reverse sequence, it is critical to develop new treatment strategies, such as stem or gene therapies. Gene therapy utilizes gene transfer vectors, such as viruses or plasmid DNA, to transfer therapeutic genes to target tissues or tumors. One of the most powerful viral vectors for gene transfer into the CNS is recombinant adenoviruses (RAds), which are currently being used in clinical trials for treating GBMs with very promising results (Trask et al., Mol. Ther. 1:195, 2000). RAds have also been used successfully in preclinical models of intracranial brain tumors (Dewey et al., Nat. Med. 5:1236, 1999; Ali et al., Mol. Ther. 10:1071, 2004). New generation RAds, deleted of all viral genes, can sustain long-term and stable therapeutic gene expression, even in the presence of a systemic antiviral immune response. As could be encountered in human patients (Thomas et al., PNAS 97:7482, 2000). We have recently shown that using a combination of suicide/conditional cytotoxic (HSV1-TK plus ganciclovir) gene therapy together with the expression of the cytokine, soluble human fms-like tyrosine kinase (Flt3L), which generates a very powerful systemic immune response against the tumor, we can achieve cure in 80% of animals bearing large intracranial tumors. Importantly, the combined gene therapy elicited immunological memory protecting the animals from a new tumor challenge. We propose that combining HSV1-TK with Flt3L adenosial gene therapy may provide an effective adjuvant treatment modality for CNSGCTs in patients that present with disseminated disease. This work was funded by NIH/ NINDS 1RO1 NS44556.01, 1RO3 TW006273.01, 1RO1 NS42893.01, US5 NS045309.01, and 1R21 NS47298.01, the Linda Tallen and Paul Kane Foundation, and the BOG at CSMC.

**B3. REPLICATION COMPETENT RETROVIRUSES: A NEW TECHNIQUE FOR TREATING GERMINOMAS**

T.C. Chen, W. Wang, S. He, and N. Kasahara; Department of Neurosurgery, University of Southern California, Los Angeles, California, USA

Germinomas are rapidly proliferating tumors which disseminate widely within the central nervous system and are very radiation sensitive. For the past five years, we have been working on a replication competent retrovirus (RCR) containing a variety of suicide genes including cytosine deaminase (CD), thymidine kinase (TK), purine nucleoside phosphorylase (PNP), and Egr-TNF (tumor necrosis factor). We have demonstrated that RCR is capable of selectively transducing glioma cells at a high frequency both in vitro and in vivo (Wang et al., Humane GNC Ther. 14:117, 2005). In vivo, RCR-CD has been used in intracranial glioma models (both immune deficient and immune competent) and has been shown to prolong survival by greater than 300% compared to nontreated animals (Tai et al., Mol. Ther., accepted, 2005). RCR does not transduce normal brain cells and has been found capable of selectively tracking glioma cells that have invaded the normal brain. RCR could be an ideal gene therapy agent for treatment of germinomas because of its ability to selectively transduce dividing cells and track tumor cells throughout the central nervous system. Moreover, RCR-Egr-TNF could potentially be used in conjunction with radiation therapy, using radiation to activate the EgR promotor, leading to intratumoral secretion of TNF, and inducing a hemorrhagic radiation necrosis of the tumor. Because of the strong bystander effect, neighboring teratoma cells may also be killed at the same time. This new gene therapy technology may be applied to germinoma treatment in the near future.

**B4. GENOMIC PROFILING OF INTRACRANIAL GERM CELL TUMORS**

C.C. Lau; Texas Children’s Cancer Center, Baylor College of Medicine, Houston, Texas, USA

Intracranial germ cell tumors (GCTs) are relatively rare and heterogeneous brain tumors affecting primarily children and adolescents. Although pure germinomas in general have favorable prognosis, other malignant GCTs such as embryonal carcinoma, yolk sac tumor, and chorionicarcinoma have much poorer outcome. The goal of future developments in the management of intracranial GCT is to reduce treatment-related morbidity in germinoma patients and improve survival in those with nongerminomatous GCT. Such therapeutic advancements will depend on our improved understanding of the biology of these tumors. Since the phenotype and clinical behavior of every tumor is determined by the underlying genetic alterations, we hypothesize that the use of comprehensive genomic profiling to identify these genetic alterations is a systematic and unbiased approach to charac-
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 lack of an appropriate tissue source. We have recently mini-

izing a number of genomic technologies to carry out whole-genome scan-

ning using minute quantities of formalin-fixed, paraffin-embedded brain tumor tissues. These technologies include (1) laser capture microdissection (LCM) to obtain a homogeneous population of cells from a paraffin-embedded biopsy tissue sample that are contaminated 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 material, which is equivalent to approximately 20,000 cells per cell; and (3) microarray-based comparative genomic hybridization (aCGH) and high-throughput whole-genome allelotype 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 these phenotypic and genotypic alterations that are clinically relevant to intracra-
nial GCT. This presentation describes the results and implications of aCGH profiles and genome-wide allelotype profiles of CNS germ cell tumors from patients with various ethnic backgrounds.

*B5. MOLECULAR ANALYSIS OF CHILDHOOD INTRACRANIAL AND EXTRACRANIAL MALIGNANT GERM CELL TUMOURS R.D. Palmer, 1,2 N.A. Foster, 1 I. Roberts, 1 K. D’Areuca, 3 K. Nathanson, 3 J.C. Nicholson, 4 and N. Coleman, 1 on behalf of the United Kingdom Children’s Cancer Study Group (UKCCSG); 1MRC Cancer Cell Unit, 3Department of Pediatric Oncology, Addenbrooke’s Hospital, Cambridge, UK; 2Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

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. Unsus-

pervised clustering divides the tumors by histology, producing “cancer sig-
natures,” 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 chromosomes 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 with any of the parameters. These findings indicate that both gonadal and nongonadal GCTs originate from PGCs that have erased their methylation imprint. Furthermore, this study indi-
cates 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.

*B6. GENETIC ANALYSIS OF CENTRAL NERVOUS SYSTEM GERM CELL TUMORS (CNS-GCT) D.T. Schneider, 1 S. Zahn, 1 K. Alemazkour, 2 S. Zahn, 1 L. Looijenga, 3 G. Calaminus, U. Göbel, and D.T. Schneider; 1Clinic of Pediatric Oncology, Hematology and Immunology, Heinrich-Heine-University, Duesseldorf, Germany

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 hybridiza-
tion. Among these, there were six germinomas, seven malignant nongeri-
nomatous 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 package. Appropriate BACs were optimized in a database of novel probes. 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 chromo-
some 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), 5p (n = 4), and the X chromosome (n = 4). In two cases, gain or loss was confined in an amplicon at 12p11.2, which is the commonly amplified region on 12p. Notably, we observed no difference in the genetic profiles of germinomatous and nongerminomatous CNS-GCTs. At the current state of this ongoing study, we have found no significant differences with specific genetic signatures. Our overall objective is to fully characterize these phenotypic and genotypic alterations that are clinically relevant to intracra-
nial GCT. This presentation describes the results and implications of aCGH profiles and genome-wide allelotype profiles of CNS germ cell tumors from patients with various ethnic backgrounds.

*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 S. Severs, K. Alemazkour, S. Zahn, L. Looijenga, G. Calaminus, U. Göbel, and D.T. Schneider; 1Clinic of Pediatric Oncology, Hematology and Immunology, Heinrich-Heine-University, Duesseldorf, Germany

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 nonsertoli seminomas (all adolescents/adults), 6 of 9 testicular yolk sac tumors (YSTs), and 12 of 14 nongonal GCTs (all infants/children) showed hypo-
methylation. The highest methylation levels were observed in three child-
hood 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 indi-
cates 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 H. Yan; Brain Tumor Center, Department of Pathology, Duke University Medical Center, Pediatric Brain Tumor Foundation Institute, Durham, North Carolina, USA

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 iden-
tification 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 pathogen-
esis of brain tumors. Whereas comprehensive screens for activating or inac-
tivating 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 will enable 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.
Abstracts for the Second International Symposium on Central Nervous System Germ Cell Tumors


A. Bendel, J. Watterson, L. Ries, and A. Bleyer; Children's Hospitals and Clinics, Minneapolis, Minnesota, Minnesota; National Cancer Institute, Bethesda, Maryland; St. Charles Medical Center, Bend, Oregon; Children's Oncology Group, Arcadia, California; USA

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 3-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 tumors 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 5:1. 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 38% of the 0–14-year age group and 82% of the 15–29-year group. A steady improvement in survival for suprasellar cell growth in vitro, whereas pharmacological 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 medulloblastoma, 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**

L.H.J., Loojenga; Pathology/Laboratory for Experimental Patho-Oncology, Erasmus University Medical Center Rotterdam/Daniel den Hoed Cancer Center, Josaphine Nelkens Institute, DR, Rotterdam, The Netherlands

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 Loojenga, Nat. Rev. Cancer, 2005). These are found at specific anatomical locations, including hypothalamic 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 main types 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 more recent steps forward in the diagnosis of seminomatous-GCT and embryonal carcinoma, being the undifferentiated component of nonsemionomas, is identification of OCT3/4 (POUSF1) as a immunohistochemical marker (Loojenga 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-POUSF1.

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

E. Boufert and M. Matsutani; Department of Neurosurgery, Hospital for Sick Children, Toronto, Canada; 2Saitama Medical School, Saitama, Japan

Epidemiological data on ICGCT are available in cancer registries and clinical series. Significantly different pharmacology between these 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 463 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 1980–1995). 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 clinical case series. Differences in histology 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**


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, one; sphenoidal bone with intracranial extension, one; and spinal, one. All patients were treated with aggressive multimodal therapy 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 the 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
D. Keene,1 E. Bouffet,2 J. Brossard,3 A. Carret,4 B. Crooks,5 Eisenstat,4 C. Fryer,6 C. Mpofu,7 A. Moghrabi,8 I. Odame,9 D. Strouther,10 S. Zell,11 and R. Silver7 on behalf of the Canadian Pediatric Brain Tumor Consortium; 1Ottawa, 2Toronto, Sherbrooke, Montréal, Halifax, 3Winnipeg, 4Vancouver, 5Saskatoon, Montreal, 6Hamilton, 7Calgary, 8London, and 9Kingston; Canada

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 risk factors. Among children under 19 years, there was a significant positive annual percent change (AAPC [95% CI]) in incidence over the time period 1993 to 1999 (AAPC = 3.0% [0.8–6.9%]). However, incidence trend rates 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% [0.0%, 3.6%]; P < 0.05). Among children aged 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 NS may facilitate, along with other descriptive epidemiologic studies, the identification and elucidation of risk factors for these tumors.

F. Moreno,2 E. Schwartzman,1 M. Scopinaro,1 D. Alderete,1 P. Reichel,1 V. Welsh,1 M. Matus,1 B. Diaz,1 ROHA - C.A. Buenos Aires, 2Hospital de Niños Eva Perón, Santiago del Estero; 3Hospital de la Madre y el Niño, Formosa; and 4Hospital Provincial del Centenario, Santa Fe; Argentina

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 5 to 24 (median 13). Among children under 15 years of age, 15.5% have a CNS GCT. After an intensive and exhaustive effort, 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 MALIGNANT CNS GERM CELL TUMORS OF THE BRAIN AND CENTRAL NERVOUS SYSTEM IN THE UNITED STATES
J.M. Propp,3 N. Li,4 S. Hoffmann,1 and B.J. McCarthy2,1 University of Illinois at Chicago, and 2Central Brain Tumor Registry of the United States (CBTRUS), Chicago, Illinois, USA

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 registry data on all primary GCTs diagnosed between 1997 and 2001 from 15 state cancer registries were included. 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. Multivariate 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. Jointpoint regression analysis was utilized to identify sharp changes in incidence over time. Relative survival 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 = 363). The rate was highest in children 0–9 years and young adults 20–24 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 = 0.8% [-0.9%, 6.9%]). However, incidence trend rates 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% [0.0%, 3.6%]; P < 0.05). Among children aged 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 NS may facilitate, along with other descriptive epidemiologic studies, the identification and elucidation of risk factors for these tumors.
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 germi- nome trial (ACNS0232) comparing standard radiotherapy (Reg A) to CHT followed by focal radiation. The response-based, reduced radiation therapy (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 confirming COG and PFS as well as assessing cognitive function and quality of life. Patients will be assigned to localized (M0) or disseminated disease (M+), and all M+ patients will receive CSRT. All M0 patients in Reg A who have resection of tumor developed recurrent disease on chemotherapy. SURVIVAL of 16 months. We conclude that acute hematopoietic toxicities are frequent but transient on this regimen. Our report supports the use of 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**

T.B. Kaprelian, D.A. Haas-Kogan, M. Prados, and A. Banerjee; University of California San Francisco, San Francisco, California, USA

Treatment for CNS germinoma aims to reduce toxicity and maintain effectiveness. We report on a series of patients treated with combined chemother- apy and radiation. The 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 germini- oma, two had mixed germinoma and mature teratoma, one was diag- nosed 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: None 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. This 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**

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

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 equival- ent 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 were 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/hypothysis 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 of patients, open biopsy in 35 patients, and subtotal resection (Reg B) in 2 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, 4–154 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 × em. 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 dis- ease (ventricular). Registered patients with multiple metastases or long-term survivors. The concept of combined treatment with chemotherapy and focal irra- diation in localized intracranial germinoma was part of the SIOP TGM TC90 protocol. Based on this experience, this treatment option was there- fore incorporated in the SIOP CNS GCT 96 trial. All registered germinoma patients (diagnosis until 31/12/03) regardless of age, with histologically...
G7. BILOCAL INTRACRANIAL GERMINOMA: ARE THEY METASTATIC LESIONS?

L. Lafay-Cousin,1 B.A. Millar,1 C. Gneid,2 J. Drake,2 U. Bartels,2 A. Huang,1 and E. Bouffet1
1Pediatric Brain Tumor Program and Department of Pediatric Neurosurgery, Hospital for Sick Children, Toronto; 2Radiation Therapy Department, Princess Margaret Hospital, Toronto; Canada

Simultaneous involvement of the pineal and the neurohypophyseal 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 germinomas 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 objectives of this study were 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 neurohypophyseal region (CT and/or MRI), negative spinal MR 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 male and 1 female) 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 4 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 basilar artery compression). All had negative serum tumor markers (βHCG, αFP), 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 suprasellar mass without a pineal tumor. Four patients had hydrocephalus. Three patients were treated without biopsy, one based on a neurosurgeon’s decision, and the other two had elevated CSF (βHCG [14 and 3 U/l]). Three patients underwent an endoscopic biopsy of the pineal mass. In one patient, the endoscopic procedure confirmed the neurohypophyseal involvement suspected on imaging. All patient received chemotherapy 3 to 4 cycles of VP16/carboplatin (intrathecal or VP16/cisplatin) followed by focal irradiation. 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

M. Matsutani; Japanese Pediatric Brain Tumor Study Group, Japan

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 followed: (1) A total of 123 patients (54%) had primary tumor with normal spinal fluid (CSF) and negative serum tumor marker (βHCG, αFP). Two patients with meningitis died at the beginning of chemotherapy. Of these patients, 93% achieved complete remission. With a follow-up period of over 5 years, the overall survival rate (OS) was 100%, and the event-free survival rate (EFS) was 100% (95% CI: 0.95–1.00). (2) A total of 33 patients (15%) had meningitis and achieved complete remission, but had local tumor recurrence. Of these patients, 93% achieved local control with a median follow-up of 4 years. (3) A total of 60 patients (26%) had local relapse, and 94% achieved local control. (4) A total of 4 patients (2%) had spinal relapse, and all achieved complete remission. (5) A total of 6 patients (3%) had local and spinal relapse, and all achieved complete remission. In conclusion, chemotherapy plus local craniospinal irradiation can achieve the cure of patients with intracranial germinoma with a low rate of relapse.}


B. Morris, T. Merchant, M. Kocak, A. Broniscer, M. Fouladi, M. Krasin, L. Kun, and A. Gajjar; Division of Neuro-Oncology, Department of Hematology-Oncology, Division of Radiation Oncology, Department of Biological Sciences, and Department of Biostatistics, St. Jude Children’s Research Hospital, Memphis, Tennessee, USA

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 neurexia dose was 2767 Gy (range, 2100–3600 Gy). Eighteen patients had additional radiation therapy boost (CSI/B) to the primary tumor site to a median dose of 4863 Gy (range, 3600–5400 Gy). 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/B had SD, two patients with CSI/B had SD, one patient with CSI/B 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 of cardiac failure. At median follow-up of 8.9 years (range, 3.4–14.8 years), the overall survival rate (OS) at five and 10 years was 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

T. Nagasaka, K. Katoh, T. Naito, S. Hayashi, T. Okamoto, H. Ikeeda, and S. Inao; Department of Neurosurgery, Nagaoya First Red Cross Hospital, Nagaoya, Japan

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 hematohypophysis in the basalganglia and cerebral cortex. The MR images also showed hematohypophysis of the right basalganglia and cerebral cortex. The lesion was not enhanced by contrast medium. FDG-PET disclosed high hypometabolism in the right hemispheres. Follow-up MR images 11 months later demonstrated heterogeneous enhanced tumor with multiple cysts in the basalganglia. The diagnosis of germinoma was established by open biopsy. Combination therapy with carboplatin, etoposide and irradiation therapy was carried out, but the general and 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 hematohypophysis. In the early stages, the diagnosis of germinoma in the basalganglia 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.

A. Nasta, M. Krieger, I. Gonzalez, J. Villablanca, R. Jubran, C. Anderson, S. Zacharoulis, B. Britt, J. Derrickson, F. Gilles, G. McCombe, M.D. Nelson, A. Panigraphy, A. Oeha, R. Lavey, and J. Finlay; Children’s Hospital Los Angeles, Los Angeles, California, USA

In the 20-year period since the availability of MR imaging, 35 patients with newly diagnosed, pathologically and tumor-marker confirmed pure germinoma (n = 31) or germinomas with mature/immature teratoma (n = 4) were treated at our institution. Mean age at diagnosis was 15 (range, 7 to 25). Sex ratio was M:F = 26:9. Sites of tumor were as follows: suprasellar (11), pineal (16), basalganglia (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 μg/dl) were documented in the serum (4/30) and CSF (11/33) at diagnosis. Fifteen patients underwent third ventriculostomy and seven patients, ventriculo-peritoneal shunts. Gross total resections were achieved in eight patients (25%), partial resections in five patients, and biopsies only in 18. Six patients were treated with irradiation only, one cranial and one 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 after treatment, also following a chemotherapy-only treatment regimen. The overall survival at a mean of four years from diagnosis is 91%. Of 31 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, 2.5 of 25 (100%) survive. A combination of reduced-dose ventriculo-peritoneal fluid irradiation and boost platinotherapy in patients with pathologically confirmed germinoma and tumor markers documented that <350 μg/dl produces outstanding survival. Long-term follow-up studies are in progress to assess impact of treatment upon neuropsychological functioning and quality of life and will be presented.

G12. CLINICAL CHARACTERISTICS OF GERMINOMA IN THE BASAL GANGLIA
R. Nishikawa and M. Matsutani; Department of Neurosurgery, Saitama Medical School, Saitama, Japan

Germinoma in the basalganglia (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 proven by open biopsy, 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 gad enhancement in T1WI and ill-defined, high-intensity lesion in T2WI with prominent atrophy of 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 pg/ml in normal control).

After chemotherapy using CBDA and VP16 following 50 Gy of irradiation, the high-intensity lesions in T2WI did not disappear but stabilized for 2 to 80 months. Hemiparesis did not improve in any cases. One case recurred after platinum therapy. 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.

G11. SPONTANEOUS REGRESSION IN INTRACRANIAL GERMINOMA
N. Uemiya, J-L. Adachi, K. Mishima, R. Nishikawa, and M. Matsutani; Department of Neurosurgery, Saitama Medical School, Saitama, Japan

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 following RT. 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
R. D. Rao,1 K. Ballman,2 P. Schomberg,3 W. A. Smithsonian,4 P. Kelly,5 B. Scheithauer,5 J. C. Buckner1; Departments of Oncology,1 Biostatistics,2 Pediatric Oncology,3 Neurosurgery,4 and Pathology,5 Mayo Clinic, Rochester, MN 55905, USA

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 complications. 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 chorionadotropin [HCG]) were measured in all but two patients. Patients with germoma (G) who had elevated AFP were classified as nongerminomas (NG). Therapy was with intravenous cisplatin (20 mg/m2) and VP16 (100 mg/m2) 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 RT only initially, two of three (66%) with a 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 pathologic 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. Since patient underreatment 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 hematomatous 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.

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

D. Jenkins; The Hospital for Sick Children, Toronto, Canada

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 craniopinal 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 ± 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.

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

A. Panigrathy, K. Mrieger, K. Moore, M.D. Nelson, F. Gilles, L. Gonzalez, J. Finlay, G. McCombe, and S. Bluml; Departments/Divisions of Radiology, Neurological Surgery, Neuro-Oncology, Neurology and Neuroradiology, USC Keck School of Medicine, Childrens Hospital Los Angeles, Los Angeles, California, USA

Being able to preoperatively distinguish between different types of pineal germ cell tumors by advanced imaging techniques may have important 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 is to report 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. Multimodal brain MR imaging, including diffusion-weighted imaging with ADC map, diffusion tensor imaging (23 direction, b value = 1000) with ADC and fractional anisotropy 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 acquisitions permits detection of N-acetyl aspartate (NAA), choline (Cho), and other metabolite peaks (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/Cho 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 heterogeneous 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 germinomas. No correlation between ADC 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 tumors traditionally included in the differential of pineal lesions, which is an ongoing project.

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

D. Jenkin; The Hospital for Sick Children, Toronto, Canada

The overall intent of this protocol was to treat patients with newly diagnosed 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, localized nonseminomatous germ cell tumors with defined 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-IR, 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% ± 6.7% and 70.1% ± 9.5%, respectively. The primary 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 CENTRAL NERVOUS SYSTEM GERM CELL TUMORS (GCTs)**

S. Gardner, S. Modak, J. Allen, and J. Finlay; New York University, New York, New York; Memorial Sloan-Kettering Cancer Center, New York, New York; Children's Hospital Los Angeles, Los Angeles, California; USA

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 for three days; (2) carboplatin dosed by using the Calvert formula with an AUC > 7 (maximum 500 mg/m²), 200 mg/m² in three days followed by thiotepa 300 mg/m²/day for three days; (3) temozolomide 150 to 350 mg/m²/day 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/day) for three days; (4) two courses of thiotepa, 200 mg/m²/day 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 therapy. 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**

E.A. Newelt; Departments of Neurology and Neurosurgery, Oregon Health and Science University, Portland, Oregon, USA

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 SIS in the prevention of ototoxicity. A case series of five long-term survivors of pineoblastoma treated with intraarterial (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, 4.2–15.3 years). Four of the five remain without evidence of tumor recurrence after the chemotherapy and follow-up period. 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 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 an 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**

J.A. Takahashi, M. Shirahtaa, Y. Kawabata, and N. Hashimoto; Department of Neurosurgery, University Hospital, Kyoto, Japan

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 chemotherapry 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 irradiation field. High-dose chemotherapy is recommended as salvage treatment for recurrent tumors.
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, fewer 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 irradiation 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 to 12.5 mg/m², peak ventricular CSF MTX concentrations ranged from 0.6 to 2.25 μM, which is substantially lower than the ~100-μM peak concentration achieved in the intraventricular dose of IT MTX administra-
tion 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 barrier. Surgically implanted ventricular access devices, such as the Ommaya reservoir, were developed to provide a convenient and reli-
able 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 have demonstrated that IT MTX achieves higher and less variable drug concentrations in the ventricular CSF and better distribu-
tion 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 activ-
ity 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.

LE2. GERM CELL CANCER: AN ONCOLOGIST’S PERSONAL PERSPECTIVE
J.L. Finlay; Children’s Center for Cancer and Blood Diseases, Childrens Hospital Los Angeles, Los Angeles, California, USA

The objectives of this study were to document the consequences of sur-
vivance and to describe the impact upon quality of life of recurrent, dis-
seminated 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 courses of treatment. At the time, I underwent craniospinal irradiation (RT) (cranial RT 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 were described: two slight (grade 1), six moderate (grade 2), and seven severe (grade 3). For CsPEI (n = 26, 42%), six show slight (grade 1), eight moderate (grade 2), nine severe (grade 3), and three untreatable water imbalance. In the germi-
oma 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.
Abstracts for the Second International Symposium on Central Nervous System Germ Cell Tumors

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. Inertility has been counteracted 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 continued, required for tuberculosis 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 if one includes such life-defining experiences, it is also possible 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
S.K. Jabbour,1 Z. Zhang,2 and M.D. Wharam3; 1Department of Radiation Oncology and Molecular Radiation Sciences and 2Department of Oncology, Division of Biostatistics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

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 diagnosis or date of last follow-up. The median age at diagnosis was 16 (range, 8–35). Median follow-up time was 4.3 years (range, 0.3–22.8 years). Five patients (18%) developed an ST, of which four (15%) were SMNs (testicular tumor, glioblastoma multiforme [GBM], thoric mesothelioma with known asbestos exposure, and calvarial osteosarcoma). One patient developed a faline meningioma. The median time to the development of an ST was 12.9 years (range, 1.3–33 years). The cumulative incidence of ST 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 explained 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 attributed 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.

*LE4. CENTRAL NERVOUS SYSTEM GERM CELL TUMORS: LATE EFFECTS ARISING FROM TREATMENT
S.A. Sands; Columbia University Medical Center, New York, New York, USA

Primary CNS germoma 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 pediatric germ cell tumor follow-up studies have adequately examined the long-term 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 annual psychological assessments that extend beyond 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.

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
S.M. Shalet; Christie Hospital NHS Trust, Manchester, UK

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 prepuberal 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 subsequently found to have a germinoma or 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 occur. 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
C. Sklar; Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

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, thiota, and melphalan. Problems with fertility are more common in men 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 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., intratubularic 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 NEUROHYPOPHYSIAL GERMINOMA**

K. Sugiyama, K. Arita, Y. Kajiwara, T. Saitoh, T. Nishimoto, and K. Kurisu; Department of Neurosurgery, Hiroshima University Hospital, Hiroshima, Japan

The aim of this prospective study is to assess how 24-Gy, extended low-dose fractionated craniospinal radiotherapy (RT) alone. In the past, treatment of malignant CNS germ cell tumors included extended low-dose fractionated craniospinal radiotherapy (RT) alone, followed by three cycles of chemotherapy. This study followed a similar course of treatment.

**PUBERTAL PATIENTS WITH NEUROHYPOPHYSIAL GERMINOMA**

J.A. Wiener, G. Calaminus, C. Teske, S. Weinspach, and U. Göbel; University Hospital, Düsseldorf, Germany

In the past, treatment of malignant CNS germ cell tumors included craniospinal radiotherapy (RT) alone. For CNS-G this was standard treatment. CNS-GGCTs were treated with a combination of chemotherapy (CT) and RT, which was mainly craniospinal with a higher dose. Although both diseases are highly malignant tumors, the survival rate for CNS-G is excellent (~90%), whereas the prognosis for CNS-GGCTs needed to be improved. This study highlights the question of whether the higher treatment burden of the patients with CNS-GGCTs is reflected in a more negative QoL. Eighty-five patients (61 CNS-G and 24 CNS-GGCTs) 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 to their diagnosis. QoL is investigated by using self-reported questionnaires: status of reintegration, and QoL as indicators. Characteristics of 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-GGCTs are as follows: 19 boys and 5 girls; age at diagnosis, <1–20 (mean, 13.8); mean age at inquiry, 18.5. Resection (subtotal) 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-GGCT (mean, 43 Gy). In comparing CNS-G and CNS-GGCTs, CT was given as 23%/88%. The most prevalent disabilities are impairments vision (44%/55%) and gross motor disabilities (30%/54%). Hormone substitution is still necessary in 49%/46% of the patients. Of these patients, 49%/62% have finished school education already, and 25%/38% have completed professional training. Only 11%/58% 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-GGCTs (p < 0.05). We conclude that survivors of CNS-GGCTs show a significantly more negative QoL than those with CNS-G. To some extent this is 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**

P.M. Zeltzer; Shilysa Inc., Los Angeles, California, USA

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. Hence, patients ask for and require health and medical information. Patient-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**

E.A. Neuwelt and T.P. Murillo; Departments of Neurology and Neurosurgery, Oregon Health and Science University, Portland, Oregon, USA

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; intraarterial, 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, followed by focal radiation to residual lesions. Five patients with BM from gynecological cancers were treated with multimodal therapy consisting of intracavitary 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 following 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). Osteonecrosis 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

D.J. Quinn, 1 O. Hamid, O.E. Streeter Jr., and T.C. Chen; Norris Comprehensive Cancer Center, Keck School of Medicine, and Departments of Medicine, Radiation Oncology, and Neurosurgery, University of Southern California, Los Angeles, California, USA

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, 2 M.L. Garre, 2 S. Koch, 2 R.D. Kortmann, 1 J. Nicholson, 1 U. Ricardi, 1 F. Saran, 2 and G. Calaminus 4; University Hospitals of Dusseldorf and Leipzig, Germany; 2 Paris and 4 Lyon, France; 4 Genova and Turin, Italy; 2 Cambridge and Sutton, 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, met 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, 126 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 ± 0.06 (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

M.L. Garre, 1 C. Alapetite, 1 D. Frappaz, 2 M.L. Garre, 2 S. Koch, 2 R.D. Kortmann, 1 J. Nicholson, 1 U. Ricardi, 1 F. Saran, 2 and G. Calaminus 4; University hospitals of Genova, Italy; 2 Paris and Lyon, France; 2 Dusseldorf and Leipzig, Germany; 4 Cambridge, UK; Turin, Italy; and Sutton, UK

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 multimodal treatment to BM should be considered as an adjunct to surgery.

This protocol is aimed at improving progression-free survival and overall survival of intracranial NCSSG, 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 or 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 radiological 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 support 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.

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 tumors (embryonal carcinoma/sacroid tumor), choriocarcinoma, 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.
*NG5. CENTRAL NERVOUS SYSTEM SECRETING GERM CELL TUMORS (CNS-SGCT): A SINGLE INSTITUTIONAL EXPERIENCE WITH LONG FOLLOW-UP

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 6.3, 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 removal, and two had biopsy. Alpha-fetoprotein (AFP) was pathologic in serum/CSF in 10, betahCG in 14. AFP highest values were <500 ng/ml in six, <1000 ng/ml in five, >1000 ng/ml in one. Seventy-five percent of patients responded to PEB (CR + PR); the patient with lung involvement rapidly died and was censored. 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 after normalization; 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. Four with AFP > 1000 U/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 73%, respectively. Of the 12 survivors, six have a professional activity, three are students, and three are unemployed. The 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
M. Matsutani, Japanese Pediatric Brain Tumor Study Group, Japan

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 tumors, 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. Complete response after first-line 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 survival (DFS) and those with residual disease after the initial treatment. 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 were 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 TUMOURS (NGGCT) TREATED ACCORDING TO SIOP CNS GCT 96: IMPACT OF AFP LEVEL AND RESIDUAL TUMOR ON OUTCOME
J.C. Nicholson, C. Alapeitte, D. Frappaz, M.L. Garré, S. Koch, R.D. Kortmann, U. Ricardi, F. Saran, and G. Calaminus, University hospitals of Cambridge, UK; Paris and Lyon, France; Genova, Italy; Düsseldorf and Leipzig, Germany; Turin, Italy; and Sutton, UK

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 chemotherapeutic (CT) and at the end of therapy (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 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 = 0.01). 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.
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 of 106 months longer than five years, 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
P.L. Robertson,1 J. Siffert,2 R.J. Jakacki,3 L. H sukin,4 L. Velasquez,2 and J.C. Allen2; 1University of Michigan Medical Center, Ann Arbor, Michigan, USA; 2Beth Israel Medical Center, New York, New York, USA; 3Children’s Hospital of Pittsburgh, Pennsylvania, USA; 4Children’s and Women’s Hospital, Vancouver, B.C., Canada

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 1 and second-look surgery, if feasible. Following surgical or tumor marker diagnosis of NGGCT and complete neuroaxis staging, patients were initially treated with four cycles of multianti-CHT. In patients not achieving CR, a second-look surgery was encouraged, followed by tandem cycles of chemotherapy and/or local irradiation. Patients in biological remission (stable disease) after second-look surgery were followed with serial tumor markers (AFP or B-HCG) every 2 months. Two (1.5%) patients progressed after RT and were treated with chemotherapy alone. The median CR duration was 40 months (range, 10–72 months). In summary, this study confirms that, when combined with surgery, chemotherapy produces increased CR rates but at the cost of increased toxicity. Further improvement in outcome may be achieved by utilizing molecular markers as a means of selecting patients for chemotherapy and/or RT.

NG10. INTRACRANIAL TERATOMA: EXPERIENCE WITH REGISTERED FOLLOW-UP PATIENTS IN SIOP CNS GCT 96
F. Saran,1 C. Alapetite,2 D. Frappaz,3 M.L. Garré,4 S. Koch,5 R.D. Kortmann,4 J. Nicholson,4 U. Ricardi,4 and G. Calaminus5; University hospitals of Sutton, UK; Paris and Lyon, France; Genova, Italy; Dusseldorf and Leipzig, Germany; Cambridge, UK; Turin, Italy

Intracranial teratoma (TER) is a specific entity of CNS GCTs defined as “benign” disease. Complete resection is the treatment of choice but not always possible 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/hypophyseal in 19%, and other (mainly newborns) in 27% of cases. Median tumor size was 3 cm (range, 1.2–8 cm). In two cases, intratumoral hemorrhage was performed before surgery. For 8 TER with CT only, RT should be performed only in patients in biological remission. Relapses could be salvaged.

Abstracts for the Second International Symposium on Central Nervous System Germ Cell Tumors

NG11. OUR EXPERIENCE WITH CNS IMMATURE TERATOMA
M. Shirahata, J.A. Takahashi, M. Oda, H. Katsuki, and N. Hashimoto; Department of Neurosurgery, Kyoto University Hospital, Kyoto, Japan

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 due to 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 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 ULTRASENSITIVE EIA
H. Katakami1, S. Hashida1, and M. Matsuuti1; Japanese Pediatric Brain Tumor Study Group; Departments of Medicine, Miyazaki University Medical College, Miyazaki; Institute of Health Science, Tokushima Bunri University, Tokushima; 1Department of Neurosurgery, Saitama Medical College, Saitama; Japan

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 (immuno complex transfer-EIA, ICT-EIA) for HCG-beta, which was 10,000 times more sensitive (LD, 0.03 pg/ml for conventional IRMA, LD of 30–1000 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 immunohistoologically 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

Neuro-Oncology ■ OCTOBER 2005
verified specimens (of P/G = 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% of HCG-beta. HCG-beta levels in both PB and CSF of patients with CNS STGC and placenta showed highest gene expression and tissue contents of HCG-beta gene expression and content. Samples from germinoma with STGC were high in PG, whereas meningiomas and teratomas showed minimum

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

D.C. Miller; New York University School of Medicine, New York, New York, USA

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 tract together with the hypothalamo-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 along the neuraxis via cerebrospinal fluid pathways, which has historically mandated neuraxial therapies including craniospinal irradiation 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. A combination of any of these four histologic 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 CNS NGGCTs (for example OCT4, OD30, AFP, PLAP) has clearly increased 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**

H. Takeshima, H. Uchida, S. Yoneuse, H. Nakamura, and J-L. Kuratsu; Kagoshima University Medical School, Kagoshima; Kumamoto University School of Medicine, Kumamoto; Japan

We have previously reported the expression of proteinocogene 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 c-kit and 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. Synctiotrophoblastic 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, c-kit expression of SCF seems lower than that of s-kit, since 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 NONGERRINOMATOUS GCTS (NGGCTS): ANALYSIS OF DATA GENERATED IN MAKEI 89 AND P-SIOP**

U. Gebel, 1S. Koch, 1M. Rambeck, 1M. Kraligare, 2M. Garre, 2M. Mann, 3G. Calaminus, 4Birmingham, UK; 6Genova, Italy

CNS NGGCTs are heterogeneous with high proliferation, infiltrative growth, and secretion of markers (yolk sac and chorionicarcinoma 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/CHG) is possible 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: 40 Gy to tumor, P-SIOP: 34 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 redefined if in 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 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"
M. Kanamori, T. Kubo, and T. Tomitaka; Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan

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 2003 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 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"
M. Krieger, B. Diez, S. Kellie, J. Villablanca, A.R. Kim, I. Dunkel, and J.L. Finlay, for the International CNS Germ Cell Tumor Study Group; Children's Hospital Los Angeles, Los Angeles, California, USA

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 endoscopic biopsy or partial resection and one underwent complete resection 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.

"NS4. DISSEMINATION OF INTRAVENTRICULAR TUMORS FOLLOWING ENDOSCOPIC MANIPULATION AND THIRD VENTRICULOSTOMY"
N. Luther, J.J. Dunkel, and M.M. Souweidane; 1Department of Neurological Surgery, Weill Cornell Medical College, New York, New York; 2Division of Neurosurgery, and 3Department of Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, New York; USA

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 intraventricular localization of the third ventricle in the third ventricular pouch provides 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 the risk for metastasis following this procedure. A review of the clinical data for patients for whom an ETV and simultaneous endoscopic biopsy or resection of the tumor was performed between 1995 and 2005 at New York-Presbyterian Hospital/Weill 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 glioneural 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 pineal tumor and died 11 months postoperatively. One patient with a 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 GERMINOMA TUMORS WITH 5-AMINOLEVULINIC ACID"
K. Mishima, T. Tachikawa, J. Adachi, S. Ishihara, R. Nishikawa, and M. Matsutani; Department Neurosurgery, Saitama Medical School, Saitama, Japan

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 fluorescence for detecting germ cell tumors. Twelve patients underwent ALA-induced fluorescent biopsies. ALA-induced fluorescence biopsies were performed in three hours before the induction of anesthesia. One 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 tissues were examined histologically. In three cases, fluorescence-guided diagnostic 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 fluorescence for detecting 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.
Germ cell tumors (GCTs) of the CNS are a rare, biologically diverse, and therapeutically controversial group of neoplasms. The unique characteristics 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 diagnostic. 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 (Duez 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. These cooperative 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.

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 and radiological techniques 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 allow exposure and tumor manipulation with minimal morbidity and brain retraction. The pineal region, posterior third ventricle, infundibular region, suprasellar cistern, and pituitary fossa, all sites regularly affected by GCTs, 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 2003, 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 35 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% (33/35) 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 septic 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.
**RT4. SIMULTANEOUS INTEGRATED BOOST RADIOTHERAPY FOR INTRACRANIAL GERMINOMA**

R.S. Lavey and A.J. Olch; Radiation Oncology Program, Childrens Hospital Los Angeles, and Departments of Pediatrics and Radiation Oncology, University of Southern California Keck School of Medicine, Los Angeles, California; USA

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 shorted 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, cerebrospinal fluid alpha-fetoprotein and beta-human chorionic gonadotropic 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 and then-field CT is repeated every three months up to the time of 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 recurred lesion is a nongerminomatous tumor elements or 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 23.5 Gy to the ventricles. Eight non-co planar 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.
tentorial brain, $V_5$ was maximal with four non-coplanar fields (88%; range, 87%–98%) and minimal with parallel pairs (68%; range, 59%–83%); $V_{20}$ was maximal with parallel opposed fields (74%; range, 45%–72%) and minimal with IMRT (31.2%; range, 36%–23%). 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.

*RTs ROLE OF RADIATION THERAPY (RT) IN THE MANAGEMENT OF CNS GERM CELL TUMORS (GCT)
E.G. Shaw; Department of Radiation Oncology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

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 $>$95% with five- and 10-year survival times of $>$95% and $>$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.