CPT-SIOP-2000 Study: Interim results
January 2009

Wrede Brigitte1, Peters Ove1, Peter Thall2, Hasselblatt Martin1, Pietsch Torsten1, Kortmann Rolf-D4, Warmuth-Metz Monika4, Mahajan Anita1, Lucia Leskova3, Xuemei Wang2, Wolff Johannes EA9,2

1Pediatric Oncology, St. Hedwig Children’s Hospital, University of Regensburg, Germany, 2Biostatistics, MD Anderson Cancer Center, Houston, USA (MDACC), 3Neuropathology, University of Muenster, Germany, 4Department of Neuropathology, University of Bonn, Germany, 5Department of Radiotherapy, University of Leipzig, Germany, 6Department of Radiology, University of Würzburg, Germany, 7Department of Radiation Oncology, MD Anderson Cancer Center, Houston, USA (MDACC), 8Dept. of Hematology and Oncology, University Hospital Motol, Prague, Czech Republic, 9Pediatrics, MD Anderson Cancer Center, Houston, USA (MDACC)

Introduction: Choroid plexus tumors (CPT) are rare, and information about pathogenesis and best treatment is still limited. The ongoing CPT-SIOP-2000 study was designed to elucidate the biology of these tumors and to determine the effectiveness of a carboplatinum versus cyclophosphamide chemotherapy in CPT. The current interim analysis was performed to identify risk factors for all histological CPT groups including the atypical choroid plexus papilloma (APP) newly defined by the WHO in 2007.

Methods: The CPT-SIOP-2000 study protocol consists of a registry for all patients with CPT and a randomized trial for patients requiring postoperative treatment. Patients with choroid plexus papilloma (CPP) and APP, when previously completely resected, were observed, whereas all patients with choroid plexus carcinoma (CPC), with metastasized tumors and incompletely resected APP were treated with a total of 6 courses of chemotherapy (VP16 100 mg/m² d1-5, vincristine 1.5 mg/m² d1 and either carboplatinum 350 mg/m² d1+2 or cyclophosphamide 1000 mg/m² d1+2). Additional irradiation was applied after the second course for those patients older than 3 years of age. Only patients with central pathological review were included.

Results: Until January 2009, 155 patients from 23 nations were registered. Of those, 130 patients were pathologically reference reviewed (46 CPC, 36 APP and 37 CPP, 11 other histology). In general, the accordance between the reference pathology review and the local diagnosis was 67%. Patients with APP were significantly younger (median age 0.6 years) than patients with CPP (2.5 years) and CPC (1.5 years). The rate of metastases in APP was 14%, 19% in CPC and 6% in CPP. 101 out of 119 patients with CPT have been treated or observed according to the protocol. In subgroups defined by histology the event-free survival in APP was 14%, 19% in CPC and 6% in CPP. 101 out of 119 patients with CPT have been treated or observed according to the protocol. In subgroups defined by histology the event-free survival in APP was almost comparable to CPP (the 5-year event free survival (YEFS) was 82% ± 9 SD for APP (n=27) and 92% ± 7 SD for CPP (n=43)) and significantly better than in CPC (5 YEFS 43% ± 14 SD for CPC (n=31, p<0.001). After two cycles of chemotherapy the response rate for all patients treated was 72%. In APP, 2/9 patients had a complete response, 4/9 a partial response and 3/9 patient a stable disease. In CPC, Irradiation was linked to better survival (2YEFS 76% ± 12 SD versus 39% ± 14SD; p<0.03). The event free survival in CPC was significantly better after incomplete tumor resection compared to complete resection (2 YEFS 79% ± 13 SD
versus 44% (116 SD, p<0.03). 16 patients had a relapse (2/43 CPP; 3/27 APP; 11/43 CPC). Distant metastases were present in 58% and local relapse in 75%.

Conclusion: The study design has been proved to recognize those CPT risk patients, who require treatment. Treatment with radiotherapy and chemotherapy showed a good response in CPC as well as in APP patients, which might be more important than complete tumor resection. Survival of APP patients is comparable to CPP under intensified treatment, but close follow up is necessary even in those patients not requiring further treatment. The overall survival of CPC patients, especially for younger patients, and the local tumor control is still not satisfying, and intensified treatment may be necessary.

---

**Choroid plexus carcinoma sensitive to etoposide**

**Su G. Berrak**, Brigitte Wrede, Johannes E. A. Wolff

1Dept of Pediatric Hematology-Oncology, Marmara University Medical Center, Istanbul, Turkey, 2Pediatric Oncology, St. Hedwig Hospital, University of Regensburg, Germany, 3Pediatrics, MD Anderson Cancer Center, USA (MDACC), 4Department of Biostatistics and Applied Mathematics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

**Abstract**

Choroid plexus carcinomas (CPCs) are rare tumors with dismal outcome. Although role of surgery and chemotherapy improving survival in CPCs with residual tumor has been verified, the best chemotherapeutic agent still needs to be established.

This study is based upon a database registering all cases of choroid plexus tumors (CPTs) recorded in the National Library of Medicine (PubMed) until end of 2004. A new PubMed search by using the search terms “choroid plexus tumor” and limiting the search to years 2005-2008 and only to “humans” resulted in 76 titles. Of those 30 contained information about 49 patients that could be added to the database, resulting in a total of 906 CPT patients.

The analysis comparing different drugs was restricted to patients with CPC and residual tumor after surgery (n=141/361 patients). In order to find the best chemotherapeutic drug, patients that had the drug for certain, and those that did not have the drug for certain are compared using Kaplan Meier curves and log rank test. Response to chemotherapy was documented in 34/65 patients (52.3%). According to the documented results there was 19/34 (55.9%) partial + complete responses with 15/34 (44.1%) stable disease + progressive disease responses. The top ranked drug, among drugs that have been used 5 times or more –cyclophosphamide- was found to be used mostly in combination with vincristine (n=18), etoposide (n=17), cisplatin (n=17), carboplatin (n=10) and procarbazine (n=8). Besides, cyclophosphamide, etoposide, cisplatin and carboplatin among different chemotherapeutic agents were found to have a significant effect on survival with univariate Kaplan Meier curves and log rank tests (p<0.05). While these drugs are rarely given as single agent, a Cox regression analysis was performed, with result of etoposide as the only agent that has a significant effect on survival (p<0.05). With a further Cox regression analysis, we have demonstrated that etoposide has a positive effect of on CPCs with residual tumor, regardless of other prognostic factors namely, the patients’ age, sex, location of the tumor or if the patients were given or not given radiation therapy.

In conclusion, chemotherapy should be given to CPCs with residual tumor, in combination with radiotherapy if the patient’s age is appropriate. In terms of chemotherapeutic agent in CPCs, etoposide should definitely be used as part of future treatment protocols, and novel elements should be studied in prospective multi-center studies.

---

**Innovations in radiation for young children**

A. Mahajan, J. Wolff, M. Chintagumpala, J. Weinberg, L. Keetonen, B. DeGracia, H. Porter, S. Woo

1Radiation Oncology, MD Anderson Cancer Center, 2Pediatrics, MD Anderson Cancer Center, 3Oncology, Texas Children’s Hospital, 4Neurosurgery, MD Anderson Cancer Center, 5Diagnostic Imaging, MD Anderson Cancer Center, Houston, Texas

Choroid plexus tumors are uncommon childhood tumors that are being studied through an international collaboration. It is becoming apparent that radiotherapy has an important role in definitive management for these young patients. There are valid concerns regarding radiation therapy in children. These risks are even more significant in very young children and the potential late morbidities that they are at risk for should be considered carefully.
Advances in imaging technology have the potential to facilitate more accurate tumor volumes and to identify susceptible normal tissues. Incorporation of these modalities into treatment planning is an area of active interest in an attempt to improve tumor control and minimize acute and late toxicities.

Radiotherapy techniques have improved markedly over the last 10 years. There is ability to design and deliver a highly conformal plan with the use of three dimensional conformal radiotherapy. There are several different strategies with the most commonly used being intensity modulated radiotherapy (IMRT). This technology requires fast computing capacity, high output linear accelerators with multileaf collimation.

Proton radiotherapy is available at a limited number of centers, but has great potential to optimize treatment outcomes in these young patients even further. With proton radiotherapy there is a reduction in the volume of normal tissue that is exposed to low doses of radiotherapy which may lead to a reduction in secondary malignancies. We have treated 124 patients with central nervous system tumors with proton radiotherapy and our early experience will be reviewed here.

Through these efforts, we hope to improve the therapeutic ratio and increase the tumor control with an acceptable toxicity profile.

Intrathecal treatment for choroid plexus tumors: Literature review and update of a discussion

Michael Rytting1,2,3, Somebody from IRB4, Gudrun Fleischhack4, Irene Slave5, Brigitte Wrede6, Su Berrak7, Johannes E Wolff8

1Pediatrics, MD Anderson Cancer Center, Houston-USA, 2Dept of leukemia, MD Anderson Cancer Center, Houston-USA, 3: Institutional Review Board, MD Anderson Cancer Center, Houston-USA, 4Pediatrics Bonn-Germany, 5Pediatric Oncology Vienna-Austria, 6Pediatric Oncology Regensburg-Germany, 7Pediatric Oncology, Istanbul-Turkey

Choroid plexus tumors have a capacity to metastasize through the cerebrospinal pathway. This is more frequent in the more malignant version of the tumor (choroid plexus carcinoma) but was also reported in the lower grade tumors, even in choroid plexus papilloma. Intrathecal chemotherapy has been discussed in various levels, as summarized in this contribution.

Two sets of data confirm the need for intrathecal chemotherapy for some choroid plexus patients: The retrospective CPT literature database until 2007 had 361 patients with choroid plexus tumors, 36 of which were metastatic. The prospective CPT-SIOP-2000 study had by Jan 2008 106 patients registered and histologically confirmed. Among those 16 had recurrent: 6 local only, 4 distant only, and 6 both local and distant. There are no data available to describe efficacy of certain intrathecal drugs for choroid plexus tumors. Licensed drug that have some evidence of efficacy in other malignancies, when given intrathecally include methotrexate, cytarabine, etoposide, and topotecan. Among those, the evidence of efficacy in choroid plexus tumors was largest for etoposide. This drug, used in the prospective CPT-SIOP-2000 study, shows anti-tumor activity, and in the literature analysis it is the drug with largest survival differences between CPC-patients with residual tumors that received it when compared to those that did not. Based upon those data, the SIOP CPT committee in 2008 changed the recommendation for the next protocol from cytarabine to etoposide. For this drug, there are also toxicity data available from a European phase I study, as well as unpublished data from a protocol in the children’s hospital of Vienna. The question remains whether intrathecal etoposide in the context of an international multicenter study would be allowed in the USA for regulatory reasons. An expert opinion was requested, and the opinion is that either an IND application would be needed at MD Anderson or there would need to be an FDA waiver of such an application.

Writing a protocol to treat choroid plexus tumors

Johannes E Wolff1,2, Brigitte Wrede1, Ove Peters1, Anita Mahajan4, Rolf-Dieter Kortmann3, Su Berrak4, Leiko Wooten5, Leena Ketonen7, Michael Rytting1, Andree Peyrl4, Irene Slave5, Gudrun Fleischhack2, Jeff Weinberg8, Werner Paulus11, J Sterba12, Kiss Csongor14, Natasha Konoplya14, Udo Kordes15, Stephen Fletcher16, John Slopis17, Jonathan Finlay18, Rejin Kebudi1, Adela Canete9, Blanca Diez20, Margaret Nagel1, Martin Hasselblatt11, Xuemui Wang2, Peter Thall2
Writing an international protocol for a rare disease is long continuous process of finding a compromise that is clinically acceptable and scientifically sound. As a result of 2 year discussions, by February 2009 the choroid plexus tumor groups has produced a 280 page document as start point for the next round of discussion. This is the summary:

**Tumors of the choroid plexus epithelium** are rare and account for only 0.5% of all tumors in adults and children. The tumors occur mostly in infants, but have been reported in adults, too. Metastases are mostly within the central nervous system. On histology, the WHO classification 2007 recognizes choroid plexus papilloma (CPP) as the relatively benign (Grade I), and choroid plexus carcinoma (CPC) as the malignant version (Grade III) and atypical choroid plexus papilloma (APP) as an intermediate form (grade II). Tumors have been described, which progressed from lower to higher grade lesions and even the lowest grade can present as metastatic disease. P53 and SV40 can play a role in the molecular genesis of these tumors, in clinical and experimental tumors, PDGF-receptors in the growth of established tumors. The treatment of choroid plexus tumors should start with maximal reasonable achievable tumor resection of all sites. Radiation improves the prognosis, but most children are critically young for radiation. The previous study CPT-SIOP-2000 has established these tumors to be chemotherapy responsive to combinations of etoposide, vincristine and either carboplatin or cyclophosphamide, but which agent was superior could not be determined.

**This study** will address the question, which of four different chemotherapy protocols is superior. The protocols are: a) standard: cyclophosphamide, carboplatin, vincristine, etoposide, b) doxorubicin, actinomycin D, Cisplatin, c) high dose methotrexate and d) temozolomide, irinotecan. In addition, radiation and intrathecal cytarabine is given to all treatment arms following a risk adapted algorithm uniform in all treatment arms. Concerning the statistical method, the study design uses a Bayesian weed out. **Inclusion Criteria** include all histological proven choroid plexus tumor all of which can be enrolled in the registration. **Exclusion criteria** only apply to the treatment protocol and the randomization and include choroid plexus papilloma without metastases and without documentation of growth, completely resected atypical choroid plexus papilloma, previous radiation or chemotherapy, and the typical contraindications for chemotherapy.

**Details of the additional treatment are:**

a) **Standard arm:** Alternating chemotherapy cycles with VP16 100 mg/m² over 1 hour on days 1-5, carboplatin 350 mg/m² over 2 hours on day 2 and 3, vincristine 1.5 mg/m² on day 5 alternating with: VP16 100 mg/m² over 1 hour on days 1-5, cyclophosphamide 1 g/m² over 1 hour on day 2 and 3, vincristine 1.5 mg/m² on day 5. Six blocks are given in 4 week intervals (day1 to day1). Radiation is given between the second and the third cycle only to a small subgroup of patients defined by age histology staging and response to the first to cycles of chemotherapy.

b) **Doxorubicin/cisplatin arm:** Doxorubicin 25 mg/m²/ day over 12 hrs on days 1-3, Dactinomycin 45 µg/kg/day (max. 2 mg), i.v. on day 1, and Cisplatin 70 mg/m²/d over 6 hrs on day 4, and Vincristine 1.5 mg/m²/day (max. 2 mg), i.v. on days 8, 15. An identical second cycle is started on day 28 if the side effects allow it. The further treatment is identical to the standard arm with four more cycles of chemotherapy following radiation in some of the patients in all treatment arms.

c) **Methotrexate arm:** 5g/m² over 24 hours with leucovorin rescue at hour 42 given tree times on days 1,15 and 29. The further treatment is identical in all four treatment arms.

d) **Temozolomide Irinotecan arm:** Temozolomide is given at 150 mg/m²/day x 5 days orally and combined with irinotecan 50 mg/m²/day x 5 days as one hour infusions. Two of these cycles are followed by the common radiation – four cycle chemotherapy protocol.

**Irradiation:** The majority of patients will not receive irradiation. A few subgroups of patients will receive radiation after the second cycle of chemotherapy. The indication for radiation, the field and the dose will be specified based upon the patient’s age, tumor histology, staging and res-
response to the two first cycles of chemotherapy. Maximal radiation will be given to patients over 3 years of age with metastatic CPC non responsive to the first two cycles. These patients receive craniospinal irradiation with 35 Gy and local boost up to a total of 54 Gy.

We expect the proposal to change in the meeting and then next version to be presented to the Children’s Oncology Group. One challenge will be to shorten it until then.

---

**Choroid plexus carcinomas**

R Kebudi¹, Cengiz Canpolat², I Ayan¹, S Berrak², M Imer³, M Özek⁴

¹Istanbul University, Oncology Institute & Cerrahpaşa Medical Faculty, ²Marmara University Medical School, Division of Pediatric Hematology-Oncology, ³Istanbul Medical Faculty, Department of Neurosurgery, ⁴Marmara University Medical School, Department of Neurosurgery, Istanbul-Turkey

**Aim:** Choroid plexus carcinomas (CPC) are rare brain tumors with a dismal prognosis. Although the role of surgery has been well established, the question of whether and which chemotherapy improves the prognosis is still under discussion. We present two children with CPCs and the results of the treatments.

**Cases**

**Case 1.** A 13 year-old girl was admitted with headache, nausea and vomiting for about a month. Cranial CT and MRI revealed a 6.5x4x3 cm lobulated mass with solid and cystic components on the left temporal area, in the left lateral ventricle. She underwent a macroscopic total resection on 27.1.2008, with no residual tumor in her postoperative MR scans. The pathologic diagnosis was atypical choroid plexus papilloma, grade 2. She had no CNS metastases. She was given no further therapy. On routine follow-up MR scans, she was found to have a local relapse. She was operated on 19.03.2008. Pathology was consistent with choroid plexus carcinoma this time. She received the CPT-SIOP 2000 chemotherapy protocol (CycEV-cyclophosphamide, etoposide, vincristine- regimen) during April 2008 – November 2008. At the end of the second course of chemotherapy she had craniospinal radiotherapy. The major acute side effect during chemotherapy was grade3-4 neutropenia, with 6 episodes of febrile neutropenia. She is under regular follow-up with no evidence of disease 3 months after termination of treatment.

**Case 2.** A 9 months old boy was admitted to the emergency for an atonic convulsion and unconsciousness. He had complained of frequent vomiting for the last month. On CT a 3 x 4 x 4 cm heterogeneous hyperdense mass with peritumoral edema in the right temporo-parietal within the lateral ventricle, extending to the 3rd and 4th ventricle, and causing a midline shift was seen. Hemorrhage within the tumor was suspected. The patient underwent immediate surgery; the intraluminal hematoma was discharged by right parietal craniotomy. The tumor was partially resected. Postoperatively he had residual tumor on CT and had status epilepticus and had to be intubated. After having a stable condition he was reoperated after 7 days and a gross total tumor removal was attained. There was no residual tumor, but dilated ventricles on CT. A ventriculoperitoneal shunt was inserted two days later. Pathology was consistent with choroid plexus carcinoma (confirmed by CPT-SIOP 2000 protocol pathology review). There was no seeding on the spinal axis MRI and no atypical cells on the CSF cytology. Due to young age, radiotherapy was not given. Institutional chemotherapy consisting of vincristine, cyclophosphamide, CCNU and procarbazin was initiated. Intrathecal treatment consisting of methotrexate 6 mg was given in the first course only. A total of 5 courses were given. After the fifth course, an elevation in the liver function tests (SGOT 390 U/l, SGPT 290 U/l) occurred, on evaluation HBs Ag was + despite HBV vaccination before chemotherapy. There was no tumor in cranial and spinal axis MRI. Due to socio-economic conditions, the family refused further therapy. At 18 months of age, the child could walk with assistance, could talk. After 2 years, the patient was still in remission, then he was lost to follow up.

**In conclusion,** ACPP can recur as CRC, or CPC may be misdiagnosed as ACPP, necessitating an experienced pathology review. Total resection is known to be very important, the addition of chemotherapy and radiotherapy, or even chemotherapy alone in young children seems to improve prognosis.
Choroid plexus tumors and the Familial Cancer Syndrome: The Children’s Hospital of Los Angeles (CHLA) experience 1991-2006

Children’s Hospital Los Angeles, University of Southern California, Keck School of Medicine

Background:
Choroid plexus tumors (CPT) are rare neoplasms, predominantly of early childhood. An association with the Li-Fraumeni syndrome (LFS) has been reported, but remains poorly defined.

Objective:
Children with CPT were evaluated for P53 mutation and family histories consistent with LFS and its spectrum

Methods:
Chart review of all patients with CPT at CHLA over 15 years (1991-2006) was performed. Charts were also evaluated for associations with multiple primary tumors and family history consistent with the spectrum of LFS.

Results
40 patients with histological diagnosed CPT were identified. Five patients were identified with phenotypic characteristics consistent with the LFS spectrum.

- 10-month male presented with left occipital horn choroid plexus carcinoma (CPC), father had undergone allogeneic transplantation for severe aplastic anemia (AA) a decade earlier, and patient was tested positive for P53 mutation.
- 4-year-old sister of the previous patient harbors the same mutation. Elective MRI revealed small CPC in the left occipital horn and right temporal low-grade glioma.
- 12-month male diagnosed with CPC was also evaluated and tested positive for P53 mutation in view of his father’s death at 39 years of age with esophageal cancer. Paternal grandfather and the great grandfather died of lung cancer.
- 5-year-old male diagnosed with CPC died three years later due to nonlymphatic leukemia. Mother had developed breast cancer at a younger age. P53 mutation analysis is pending.
- 5-year male presented simultaneously with a right lateral ventricular choroid plexus papilloma (CPP) and a posterior fossa anaplastic ependymoma. Multiple family members were diagnosed with cancers at a young age including brain tumors. P53 mutation analysis is pending.

Conclusion
5 of the 40 patients (12.5%) with CPT demonstrated phenotypic characteristics of the LFS and its spectrum. Molecular analysis of all the patients is ongoing. These results indicate that a high index of suspicion for LFS and its spectrum should be maintained in children with CP tumors. Screening of index patient for P53 mutation should be conducted, especially when a family history of pertinent malignancies are also present. A previously unrecognized association of AA with the LFS merits further consideration and study.

Long term survival in disseminated choroid plexus carcinoma without irradiation
Soumen Khatua, MD\textsuperscript{1}, Alan Lavian\textsuperscript{1}, Girish Dhall, MD\textsuperscript{1}, Judith Villablanca, MD\textsuperscript{2}, Alexa Gozali\textsuperscript{1}, and Jonathan Finlay, MD\textsuperscript{1},

\textsuperscript{1}Neural Tumors Program, Center for Cancer and Blood Disorders, Children’s Hospital Los Angeles, Los Angeles, CA, \textsuperscript{2}Department of Pediatrics, University of Southern California, Keck School of Medicine, Children’s Hospital Los Angeles, Los Angeles, CA

Background
Choroid plexus carcinoma (CPC) is a highly aggressive tumor in very young children that frequently metastasizes. Complete surgical resection and radiation therapy provide the best chance of survival in localized CPC. However, long term survival in disseminated CPC is extremely poor and reportedly very rare.

Objective
We evaluated outcome of three patients with primary metastatic CPC, treated at or in consultation with the Children’s Hospital of Los Angeles since January 1993 all of whom are long-term survivors.
Methods

Case 1: 5 ½ year old male was diagnosed with disseminated CPC at one year of age. He underwent subtotal resection of the primary tumor, followed by chemotherapy using 3 cycles of induction chemotherapy with vincristine, cyclophosphamide, cisplatin and etoposide followed by three cycles of myeloablative chemotherapy using carboplatin and thiopeta with autologous hematopoietic cell rescue.

Case 2: 8 year old female diagnosed with disseminated CPC at sixteen month of age treated with partial resection followed by chemotherapy with carboplatin, cyclophosphamide and etoposide for 10 months. Due to persistent disease, she underwent single transplant with carboplatin and thiopeta with autologous hematopoietic cell rescue. She has received no further therapy.

Case 3: 16 year female was diagnosed at 10 month of age with disseminated CPC. She underwent subtotal resection followed by chemotherapy with cisplatin, vincristine, cytoxan and etoposide for 7 months. Due to persistent spinal disease, she then received Fazarabine for 11 months. Chemotherapy was then stopped, as there was no evidence of residual tumor. She has received no further treatment.

Results

These three cases remain free of disease for 3 ½, 6 and 14 years since completion of therapy without recurrences

Conclusions

In this first small series of disseminated CPC, we report long-term survival without irradiation, using high dose chemotherapy with autologous hematopoietic cell rescue in two cases and standard dose chemotherapy in one case. Such irradiation avoiding strategy should be further explored to improve survival and avoid neurocognitive impairment in these aggressive CPC in very young children.

Genetic and genomic analysis determines the role of the P53 pathway in the management of choroid plexus carcinomas

Uri Tabori1, Adam Shlien1,3, Sarah Levitt1, Berivan Baskin2, Peter Ray2, Noa Alon1, Cynthia Hawkins2, Eric Bouffet1, Lucie Laffay-Cousin1, Alexa Gozali, Lisa Shane, Ignacio Gonzalez, Jonathan Finlay, David Malkin1,3

Choroid plexus carcinomas (CPC) are rare pediatric brain neoplasms with unpredictable outcome. Currently, no biological factor exists for better risk stratification and tailoring treatment for these patients. CPC are frequently observed in Li-Fraumeni-syndrome (LFS) families in which germline mutations in the TP53 gene are associated with early onset cancers. In an attempt to determine the role of TP53 pathway dysfunction and genomic instability in choroids plexus tumors, we used genetic analysis of known polymorphisms in the pathway combined with high throughput microarray platforms to examine complex molecular alterations.

TP53 mutation and MDM2 SNP309 polymorphism analysis, was performed on both tumors (n=51) and paired germline (blood, n=25) samples. SNP array was applied to blood and available frozen samples using the Affymetrix 6.0 GeneChip Array to explore genome-wide alterations. Immunostain for P53 was performed on a tissue array. For outcome analysis, we collected data on all patients treated in 2 large neurooncology centres in North America.

TP53 mutations were found in 50% of CPC. All patients with germline TP53 mutations fulfilled the criteria for LFS either by family history of cancer or multiple LFS tumors in the affected individual while all CPC patients without LFS criteria had a WT genotype (p<0.0001). The combination of the aggressive codon-72 and MDM2 SNP309 was observed in the majority (82%) of WT CPCs but not in either normal individuals, non TP53 associated tumors such as medulloblastoma or in already mutated CPC (p=0.01) suggesting an alternative mechanism of p53 dysfunction in non mutated tumors. SNP array analysis revealed extremely high copy number variation (CNV) in LFS related tumors compared to wild type tumors and CPP (p=0.02). Strikingly, germline SNP analysis revealed the same pattern of very high CNV in CPC patients compared to controls. Five years overall survival for P53 immuno-positive and negative CPC were 0% and 82 +/- 9% respectively (p=0.0006). Furthermore, 14/16 patients with WT CPC are alive without radiation therapy.

In summary, our results revealed that germline TP53 mutations in CPC occur strictly in the context of LFS. Mul-
Multiple mechanisms of p53 dysfunction contribute to CPC tumorigenesis. P53 dysfunction leads to higher genomic instability in the germline and tumors and is associated with poor survival. Our findings highlight the role of the P53 pathway in CPC and have implications on the management of these patients.

**Pathology of the SV11 transgenic mouse model of choroid plexus neoplasms**

**Douglas C Miller, MD, PhD**

University of Missouri School of Medicine

There is a long history dating to at least 1962 associating SV40 virus and neoplasms of the choroid plexus in experimental animals. Plexus tumors were among the first produced in transgenic animals, using the SV40 T-antigen as an oncogenic transgene. In collaboration with several individuals in the laboratory of Arnold Levine, then at Princeton University, I examined a series of animals from the SV11 transgenic model to analyze the development of choroid plexus tumors over time. No animals through 28 days post-natal life had any detectable histopathologic alteration of the choroid plexus epithelium despite detectable expression of SV40 T-Ag. The earliest change, seen in animal starting at day 36, was the appearance of small nodules of about 20 cells in tight clusters within the plexus. These multifocal tumorlets were composed of cells smaller than normal plexus epithelial cells with more hyperchromatic nuclei. Examples of such Stage I tumors were seen in all four ventricles. Beginning at day 42 larger tumors was encountered. These Stage II tumors had mostly solid architecture and were mitotically active, but did not have necrosis and did not invade the brain. Beginning at day 56 still larger tumors, which filled or nearly filled the ventricle in which they occurred were found. These Stage III tumors still lacked necrosis and did not invade the brain. They either encompassed or suppressed smaller tumors presumably previously developed in the same plexi, based on the Stage I and Stage II observations. Finally at day 56 and beyond Stage IV tumors, which filled ventricles, invaded through the ependyma into the brain, and had necrosis, were also encountered. SV40 T-Ag was expressed in tumor cells but not other brain cells or non-neoplastic plexus cells after day 28. There was co-localization with over expressed p53 protein. In two animals metastatic spread occurred, one by CSF pathways and one hematogenously into the basal ganglia; no other organs were found to harbor any metastatic tumors in complete autopsies. SV11 mice provide a reproducible animal model of choroid plexus carcinomas arising de novo, without pre-existing benign papillomas. The model may be useful for translational studies of chemotherapy for such tumors.

**Comparative Neuro-Oncology: Choroid plexus tumors in dogs**

**John M. Slopis¹, Stephen A. Fletcher², Jon Levine¹, George Stoica³, Donna F. Kusewitt⁴, Johannes Wolff⁶**

¹Department of Neuro-Oncology, ²Pediatric Neurosurgery, The University of Texas Medical School at Houston, ³Neurology/Neurosurgery, Texas A&M University College of Veterinary Medicine, ⁴Neuropathology, Texas A&M University College of Veterinary Medicine, ⁵Science Park Research Division, MD Anderson Cancer Center, ⁶Pediatrics MD Anderson Cancer Center

The brain anatomy of the dog is far closer to the human brain than most laboratory animals. In a systematic analysis comparing various experimental models with human high grade glioma Candolfi and colleagues came recently to the conclusion that spontaneous dog brain tumors are closest and therefore the best model for the development of drugs to be used in humans. (Candolfi 2007), and Kimmelman proposed spontaneous tumors developing in dogs as the best model for human tumors (Kimmelman 2007). In dogs, brain tumors are frequent with crude estimates suggesting an incidence of 20 per 100,000 (Dobson 2002, Snyder 2006. The histological diversity of brain tumors in dogs matches that seen in humans (Snyder 2006) but the spectrum differs. After meningioma and glioma, choroid plexus tumors rank third in dogs (Katayama 2001). Choroid plexus tumors comprise approximately 10% of all primary brain tumors in dogs (Westworth 2008). Over the past decades diagnostic neuroimaging has developed technologically, supporting clinical etiopathogenesis and also challenging the role of histology in making a tumor type diagnosis. In the past 10 years multi-planar advanced imaging has been rapidly adopted by veterinarians and MRI including MRI-spectroscopy (Barker 1993) has been advocated to guide neurosurgical interventions (Kent 2001, Whelan 1987 and 1988, Gallegos 2008, Hasegava 2008, Peterson 2008, Tamura 2007, Mercier 2007
Polizopoulou 2004) but many of the new neurosurgical techniques used in human have not found their way into standard veterinary practice (Bordelon 2007, Gallegos 2008, Cavanaugh 2008). Many of the radiation reports in dogs, sadly, lack histological diagnosis and thus results have been questioned. Radiotherapy generally requires anesthesia to immobilize the dog. Experience with chemotherapy for brain tumors in dogs is limited. Prednisone and lomustine (60 mg/m² po q6 weeks) resulted in clinical improvement in a maltese dog with brain stem meningioma (Jung 2006) and a miniature schnauzer (Jung 2006b). Hydroxyurea has resulted in response in a meningioma (Tamura 2007). However there has not been any systematic chemotherapy treatment study published in dogs with spontaneous brain tumors done with the intent to cure the animal, and resulting in a statistically significant finding. We have established a collaboration to treat spontaneous occurring brain tumors in pet-dogs using modern neurosurgical techniques and systematic prospective clinical trials, simultaneously following the aims to give the dog the best treatment, learn as much as possible how to treat future dogs, and also how to improve treatment protocols in humans. We expect also choroid plexus tumor data to generate from this program.


---

**A new phase II/III design based on toxicity and treatment failure time: Selecting and testing treatments for choroid plexus tumors**

**Peter F. Thall, Leiko H. Wooten and Johannes Wolff**

The problem of screening several experimental treatments compared to a standard treatment is very common in medical research. In such settings, conventional statistical designs may require impractically large sample sizes to obtain confirmatory results. The common practice of conducting separate single-arm phase II trials for screening prior to phase III is well-known to be highly inefficient and subject to severe selection bias, which in turn may greatly increase the risk of a false positive decision in a subsequent phase III trial. This problem has been solved, for the cases of binary outcomes (1) and time-to-event outcomes (2), by the use of two-stage “select-and-test” designs that first select one or more promising experimen-