

## PEDIATRIC BRAIN TUMORS

**Co-Chairs: Roger Packer, M.D., and Ian Pollack, M.D.**

<b>Participants:</b>	C. David James	Sarah Nelson	Dennis C. Shrieve
Francis Ali-Osman	David Kaplan	Judith J. Ochs	Malcolm Smith
David Ashley	Kenneth A. Krohn	Scott Pomeroy	Evan Snyder
Jaclyn A. Biegel	Larry Kun	Sam D. Rabkin	Diane Traynor
James Boyette	Frederick F. Lang	Richard Ransohoff	Richard Vallee
Greta Bunin	Marla B. Luskin	Lucy B. Rorke	Jeanne Young
Tom Curran	Lorraine Marin	Bruce Rosen	Susan L. Weiner
Henry Friedman	Robert H. Miller	David H. Rowitch	Daphne A. Haas-Kogen
James Goldman	Sherie Morrison	James Rutka	
Alison Hannah	Raymond Mulhern	Gail Segal	
Mark A. Israel			

### STATEMENT OF THE PROBLEM

Childhood brain tumors are the second most frequent malignancy of childhood and the most common form of solid tumor. Tumors of the central nervous system (CNS) comprise 22% of all malignancies occurring among children up to 14 years of age and 10% of tumors occurring among 15-19-year-olds. Although rapid progress has been made in the treatment of some forms of childhood cancer, such as acute lymphatic leukemia, the outcome for children with primary CNS tumors has remained poor and for most tumors has not changed over the past decade. Brain tumors are now the leading cause of death from childhood cancer, accounting for 24% of cancer-related deaths in 1997 among persons up to 19 years of age. In addition, due to either the effects of the tumor or the treatment required to control it, survivors of childhood brain tumors often have severe neurologic, neurocognitive, and psychosocial sequelae.

Tumors in childhood differ significantly from adult lesions in their sites of origin, histological features, clinical presentations, and proclivity to disseminate throughout the nervous system early in the course of illness. Whereas 90% of adult tumors arise in the cerebral cortex, 50% of childhood brain tumors originate infratentorially, in the cerebellum, brain stem, or fourth ventricular region. A large proportion of brain tumors in adults are the result of metastatic lesions from nonprimary brain sites, and the primary tumors are for the most part glial tumors and meningiomas. In contrast, childhood brain tumors mainly represent primary CNS lesions and, although gliomas make up the majority of childhood neoplasms, other tumor types such as medulloblastomas, primitive neuroectodermal tumors, pineoblastomas, atypical teratoid tumors, and other embryonal neoplasms, contribute a significant proportion.

The biological behavior and management of childhood tumors depends on not only the histological character of the tumor but also its location within the nervous system. For example, childhood low-grade cerebellar gliomas may be curable in over 90% of patients with surgery alone, whereas brain stem gliomas (even if "low-grade") carry the dismal prognosis of death for most child patients within 18 months of diagnosis. The aspects of tumor dissemination are extremely important for childhood brain tumors. Control of local disease remains problematic for many forms of childhood brain tumors; however, specific types of tumors, especially embryonal tumors, have a high proclivity for early dissemination within the nervous system and treatment approaches must take into account this tendency for early tumor spread. The neurobiological underpinnings of these differences are largely unknown: the importance of the relationship between tumor type and location is poorly studied; the reasons why tumors primarily arise at certain ages and have proclivity to specific areas of brain are unclear; and the ways to utilize these differences to alter management and improve outcome require further investigation.

The histological heterogeneity of childhood brain tumors makes it necessary to develop separate lines of investigation into the molecular mechanisms of each type of tumor, the effect of the surrounding milieu on the tumor, and the development of effective treatment approaches. A variety of different classification systems have been utilized for childhood brain tumors, and controversy still exists concerning the most appropriate nomenclature for some tumors. The classification systems in use are still based on relatively subjective criteria, making comparison across different studies difficult. Although some subtypes of childhood brain

tumors are relatively rare, such as primitive neuroectodermal tumors (excluding medulloblastoma), atypical teratoid tumors, medulloepitheliomas, dysembryoplastic neuroepithelial tumors, desmoplastic infantile gangliogliomas, and superficial cerebral astrocytomas of infancy, together they constitute a significant percentage of childhood brain tumors and a major cause of morbidity and mortality. Studies focusing on the more frequent adult and pediatric CNS tumors often do not include such rare tumors, which results in missed opportunities to understand these tumors' biology and create more effective treatment regimens.

Even within the tumor types commonly found in both children and adults, studies focusing on tumors occurring in adults may not result in new insights for pediatric tumors. The molecular aspects of glial neoplasia in children, for example, appear to differ substantially from those in adults. Most childhood low-grade gliomas are pilocytic astrocytomas, whereas this tumor type is relatively infrequent in adults. Pilocytic astrocytomas have a different biology than fibrillary or other grade 2 lesions. For example, one major difference is that pilocytic astrocytomas rarely mutate into higher-grade lesions, whereas fibrillary astrocytomas often do so. Furthermore, even fibrillary low-grade gliomas in childhood rarely mutate into higher-grade tumors in the childhood years, despite this common occurrence in adults. For progress to be made in this subset of tumors, research must be focused directly on pediatric low-grade gliomas.

The differences between the neurobiological features of glial neoplasia in children and those of the disease in adults are not limited to low-grade tumors. Approximately 40% of grade IV gliomas in adults exhibit amplification of epidermal growth factor receptor, whereas this change is less commonly detected in childhood glioblastomas. In addition, P53 mutations, which are observed in 50% of grade III and grade IV gliomas in adults, are rarely seen in high-grade gliomas in children. These differences may at least partly account for the somewhat better prognosis for childhood high-grade gliomas; a subset of children with high-grade glial tumors, including glioblastoma multiforme (as high as 20% in some studies), survive after treatment. In addition, evidence from randomized prospective studies shows that long-term survival for childhood glioblastoma multiforme is improved by the addition of chemotherapy to radiotherapy; such data are lacking in adults.

A focused effort to define relevant molecular markers for prognosis in childhood glial tumors may facilitate improved diagnostic and therapeutic stratification of patients and more appropriate treatment. Treatment strategies may also need to differ for childhood and adult high-grade gliomas. Also needed are innovative classification systems that integrate molecular, neurobiological, and neuroimaging aspects with histological diagnosis to develop more clinically relevant nomenclatures for these tumors; this will guide epidemiological research, biological studies, and treatment approaches.

The molecular pathways involved in the development of primitive neuroectodermal tumors are just being unraveled. Research focused on the glial tumors that predominate in adults may not lead to a better understanding of these primitive embryonal tumors. Although such tumors are not unique to childhood, they are substantially more common in children than in adults. There has been significant controversy over the most appropriate classification of childhood primitive neuroectodermal tumors, primarily whether all such tumors should be grouped into one category or better subdivided based purely on tumor location. Recent studies have suggested, although not proven, that although these tumors share histological similarities, molecular features of the lesions occurring outside the posterior fossa are distinct from those arising in the posterior fossa. In addition, studies have recently shown that other molecular features, such as TrkC expression, correlate with outcome in medulloblastoma and may lead to better stratification systems. Other neurobiological abnormalities have been noted in these primitive neuroectodermal tumors, and research into the molecular pathways involved in tumor development and growth is needed.

Infants and very young children with primary CNS tumors often harbor lesions that are apparently unique to the early childhood years. Some of these tumors, such as atypical teratoid tumors and medulloepithelioma, although rare, are a significant problem in the pediatric age range. More global investigations into brain tumors, especially research focusing on more common adult tumors, will fail to address these important lesions. Many of these embryonal tumors are apparently true congenital tumors, and studies of the mechanism of their development may also lead to important insights into general brain development. Similarly, studies of brain development may lead to insights into the neurobiological aspects of these and other embryonal tumors.

Also related to age are the effects of therapy on the developing nervous system. As stated previously, some childhood brain tumors are true congenital lesions, whereas others, such as medulloblastoma and ependymoma, peak in incidence before age 5 years. Given the proclivity of primitive tumors to disseminate within the nervous system early in the course of disease, treatment approaches must focus on controlling not only local disease but also disease in all sites of the nervous system. This often requires treatment to be aimed at the entire nervous system in the young child and heightens the likelihood of treatment-related brain injury.

The long-term effects of the tumor and its treatment on outcome are extremely important issues in both children and adults with brain tumors, but because of the above-mentioned reasons, they take on even more significance in childhood. It has been well documented that young children with brain tumors, independent of the form of treatment they receive, have significant neurological and cognitive sequelae. Furthermore, for older children and adolescents, treatment may result in permanent long-term sequelae, especially neurocognitive difficulties. Other common sequelae include endocrinological dysfunction, focal neurological deficits, and psychosocial sequelae.

In a recent retrospective questionnaire review of 1,845 children with brain tumors who survived for at least 5 years, it was noted that seizures, convulsions, or blackouts occurred in 28% of survivors; headaches, including migraines, were a problem in 37% of patients; and motor disabilities, such as balance problems, weakness of the arms or legs, or tremors, were noted in over 50% of children. A sizeable minority of patients had blindness in one or both eyes, double vision, hearing loss, or persistent tinnitus. Over 50% of those surviving for 5 years from the date of diagnosis of their childhood brain tumors required special education or learning-disabled classroom settings, including 70% of those less than 3 years of age and 62% of those between 3 and 9 years of age. The incidence of secondary brain tumors in long-term survivors of childhood brain tumors is rising, and second malignancies are almost always fatal for this patient population. These sobering numbers highlight the problems faced by survivors of childhood

brain tumors and the need for further research into means to reduce long-term sequelae and remediate such problems when they arise.

## **CHALLENGES AND QUESTIONS**

On the largest scale, the overriding challenge for research into pediatric brain tumors is to improve outcome for children with a host of different types of brain tumors. The predominant barriers are the relative infrequency of any individual tumor type, the presence of embryonal/primitive tumors that often disseminate to the leptomeninges, and the lack of interest in, focus on, and funding for research on these primitive tumors. Specific challenges associated with improving outcomes for children with pediatric brain tumors and barriers to meeting these challenges are grouped below into four categories: Tumor Biology, Epidemiology, Treatment, and Long-Term Sequelae.

### **Tumor Biology**

#### **Challenges**

- Improved understanding of the genetic and environmental factors involved in the development of childhood CNS tumors
- Increased understanding of the cellular origin of different types of pediatric brain tumors
- Greater insight into the relationship between normal brain development and the neurogenetic/biologic underpinnings of childhood nervous system tumors
- Determination of factors responsible for the proclivity of some childhood brain tumors to disseminate within the nervous system early in the course of illness
- Clarification of the relationship between age, development, and outcome of childhood brain tumors
- Enhanced understanding of the biologic differences between childhood and adult gliomas and the development of treatment approaches that take advantage of such differences
- Better understanding of the neurobiology of childhood primitive neuroectodermal tumors (including medulloblastoma) and other less common embryonal tumors
- Development of better animal models that mimic human pediatric brain tumors, including those primarily occurring in children, such as PNETs and other rarer pediatric tumors (e.g., atypical teratoid tumors)
- Definition of relevant molecular markers for the prognosis of the diverse forms of childhood brain tumors

#### **Barriers**

- Insufficient appreciation of the important distinction between research required for childhood brain tumors and research required for adult tumors
- Lack of emphasis placed on the defining biologic differences between histologically identical tumors occurring in children and adults, especially the low- and high-grade gliomas
- Paucity of investigations focused on the molecular, genetic, and biologic aspects of embryonal childhood brain tumors, including primitive neuroectodermal tumors
- Lack of understanding of the relationship between normal brain development and aberrations of such development in the etiology of childhood brain tumors
- Lack of understanding of the uniqueness of the rarer childhood brain tumors; their overall importance, in total; and the need to study these types of neoplasms individually
- Lack of usable surrogate markers to determine the prognosis of childhood brain tumors and to evaluate the potential efficacy of agents used to treat such tumors

### **Epidemiology**

## **Challenges**

- Creation of a biologically-based classification of childhood brain tumors that integrates molecular aspects, neurobiological parameters and other neurodiagnostic findings
- Determination of the incidence of individual types of childhood brain tumors, including low grade neoplasms, congenital tumors, and embryonal neoplasms

## **Barriers**

- Variability in the classification of rare childhood brain tumors, especially congenital and embryonal lesions
- Lack of methods to study individual tumor types that occur less commonly
- New coding of low-grade gliomas as "benign" tumors, which could increase the likelihood that children with these diagnoses will not be included in cancer registries
- Lack of funding for epidemiological research, especially for the less common, but critically important, childhood brain tumor subtypes

## **Treatment**

### **Challenges**

- Development of more effective treatments for childhood low- and high-grade gliomas
- Development of more effective and safer treatment approaches for childhood embryonal and primitive tumors
- Development of immunotherapeutic approaches aimed at improving control of localized and disseminated pediatric brain tumor disease
- Development of new, safer approaches to control CNS disseminated disease
- Development of innovative biologically-based treatments for childhood brain tumors

### **Barriers**

- Reluctance of industry to focus on developing drugs for pediatric brain tumors because of the relative rarity of childhood brain tumors
- Difficulty in performing clinical trials for specific brain tumor subtypes because of the relative infrequency of specific types of childhood brain tumors
- Insufficient development of novel therapeutics designed for childhood brain tumors such as primitive neuroectodermal tumors
- Hesitancy to apply new therapies early in their development, especially biologically-based treatments, to childhood brain tumors
- Paucity of research into the impact of new neurobiological treatments, such as anti-growth factor agents and anti-angiogenesis agents, on the developing nervous system
- Limited scope of research focused on the immunocompetence of children with brain tumors and the potential utility of different immunotherapeutic approaches for children with brain tumors

## **Long-Term Sequelae**

### **Challenges**

- Detection of long-term neurologic, cognitive, endocrinologic, systemic and psychosocial sequelae of childhood brain tumors and their treatments, and determination of the incidence of these sequelae

- Investigation into factors that are involved in the development of neurotoxicity and host neurobiological/genetic characteristics that underlie the variable severity of neurologic compromise in an individual child
- Development of new strategies to prevent, ameliorate and remediate neurocognitive and psychosocial sequelae of childhood brain tumors and their treatment
- Evaluation of the impact of innovative biologically-based therapies on the developing nervous system
- Research into factors involved in the development of secondary tumors in long-term survivors of pediatric brain tumors and more effective means to treat such secondary malignancies.
- Research into the effects of the diagnosis of a brain tumor on the family unit, especially parental relationships and the impact on other children in the family

#### **Barriers**

- Lack of appreciation of the severe long-term sequelae suffered by children who have brain tumors, either due to their tumor or its treatment
- Lack of emphasis on the psychosocial sequelae of these tumors on the child and the family
- Lack of information concerning the development and treatment of second malignancies in childhood brain tumor survivors
- Lack of neuro-investigative techniques which take into account the developing nervous system and the differences required in evaluation between adults and children

#### **RESEARCH AND SCIENTIFIC PRIORITIES**

##### **Priority 1: Understand the signaling systems involved in mitogenesis, survival, and cell death for pediatric tumors.**

- Understand how these signaling systems relate to those in developmental neurobiology
- Use this understanding to identify new targets for pediatric brain tumor therapy.

##### **Priority 2: Fully characterize the phenotypic and genetic alterations that are unique to benign and malignant pediatric brain tumors.**

- Develop novel in vitro and animal models that faithfully recapitulate the biology of these tumors.
- Use these models for the identification and prioritization of targeted therapeutic strategies for pediatric brain tumors.

##### **Priority 3: Investigate in detail the impact of the tumor and its treatment on long-term neurological, cognitive, and psychological functional outcome, and develop new means to prevent, ameliorate, and remediate such dysfunction.**

##### **Priority 4: Conduct pediatric clinical trials of novel therapeutic agents at an appropriately early stage in their development; include in these trials comprehensive and noninvasive assessments (including innovative imaging and biological studies) of the short- and long-term effects of such agents on the child and on the developing nervous system.**

#### **RESOURCES NEEDED**

- Tumor banking of pediatric brain tumor tissues
- DNA microarrays applicable to pediatric brain tumors and nervous system development
- Tissue arrays for pediatric CNS tumors
- Development of in vitro model systems for pediatric brain tumors
- Animal model systems for pediatric brain tumors

- Greater availability of well-characterized and validated clones or lines of stem cells
- Imaging techniques for identifying tumors in situ for animal models of pediatric tumors
- Coordinated effort, on a national basis, of core facilities or coordinated individual laboratories with specific expertise and models (both academic and private industry) to facilitate the development of new drugs, biological agents, or other treatment approaches
- Funding for neuropsychological testing
- Validated, user-friendly, pediatric instrument for measuring quality of life
- Development of neuroimaging techniques that correlate with subclinical and clinical neurotoxicity.

Last updated February 09, 2005