

# Childhood Brain Tumors

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## 1. Introduction

Central nervous system (CNS) cancers are the second most frequent malignancy in childhood and the most common solid tumor in this age group. In recent years, significant advances in surgery, radiotherapy, and chemotherapy have favorably impacted survival for children with these tumors. However, a significant proportion of patients with CNS tumors suffer progress disease despite such treatment. Advances in the understanding the nature of the blood-brain/tumor barrier, chemotherapy resistance, tumor biology, and the role of angiogenesis and other signaling pathways in tumor progression and metastases have led to the advent of newer therapeutic strategies that circumvent these obstacles or target specific receptors that control signal transduction and/or angiogenesis in tumor cells. Ongoing clinical trials will determine if these novel modalities of treatment will improve the outcome of children with brain tumors.

### 1.1 Epidemiology of pediatric brain tumors

An estimated 2400 children between the ages of 0-19 years are diagnosed with invasive primary central nervous system (CNS) tumors in the United States each year. (Bleyer 1999; Gurney, Smith et al. 1999) The incidence of CNS tumor in children < 20 years is 4.58 per 100,000 person years (CBTRUS report, 2009). Brain tumors are second only in frequency to acute lymphoblastic leukemia (ALL) in children. Pilocytic astrocytomas ((0.79 per 100,000 person-years) malignant glioma (0.51 per 100,000 person-years), and medulloblastoma (0.49 per 100, 000 person-years) are the commonest tumors (Figure 1) (Gurney, Smith et al. 1999). The incidence of low-grade astrocytomas, PNET, and ependymoma is inversely proportional to age while that of malignant glioma is relatively constant between birth to < 20 years (Bleyer 1999). The incidence of CNS tumors in children was found to have increased by 35% between the years 1975-84 (Smith, Freidlin et al. 1998). This increase has been mainly attributed to the introduction of magnetic resonance imaging (MRI) in the 1980s that improved detection of low grade tumors previously unidentifiable by other less optimal imaging modalities (Smith, Freidlin et al. 1998). Brain growth occurs rapidly during early gestation and peaks around 4 months after birth but continues until 2-3 years thereafter (Baldwin and Preston-Martin 2004). Hence, it is more vulnerable to genotoxic damage and neoplastic transformation than any other organ in the body due to its relatively longer course of development both in utero

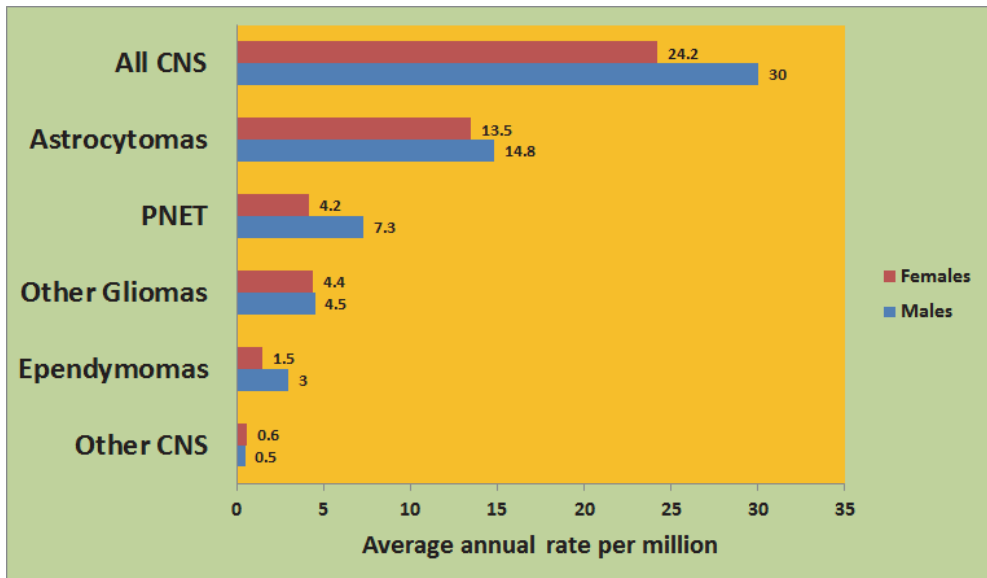
and post-natal life during which the rapidly dividing cells become susceptible to exposure to potential environment toxins and DNA damage (Baldwin and Preston-Martin 2004).

In addition, it appears that fetal brain is less able to efficiently repair DNA alkylation induced by various mutagenic agents. The blood-brain barrier (discussed further below) is also not complete in the fetal brain and facilitates free transfer of carcinogens into the vulnerable neural tissue (Baldwin and Preston-Martin 2004). While hereditary genetic syndromes do cause a proportion of pediatric brain tumors, it is distinctly rare. Only about 5% of CNS malignancies are the direct consequence of a specific gene defect (Table 1). However, in the majority of sporadic brain tumors, the factors that incite neoplastic transformation are largely unknown but are likely to be multi-factorial due to an interplay of both genes and the environment. One known environmental cause of brain tumors is ionizing radiation and can induce both benign and malignant gliomas or occasionally primitive neuro-ectodermal tumors (PNET) (Ron, Modan et al. 1988) (Hader, Drovini-Zis et al. 2003). Ron et al., reported a 33.1 relative risk (RR) of developing nerve sheath tumors of the head and neck in children who had received up to 600 cGy of irradiation for *tinea capitis* infection in the 1950s (Ron, Modan et al. 1988). There was a lower but excess incidence of both meningiomas (RR 9.5) and malignant gliomas (RR 2.6) as well in this cohort. In recent years, radiation exposure is solely due to therapeutic irradiation of the brain for CNS leukemia or brain tumors and has been associated with a 22-fold risk of developing secondary brain tumors (mostly glioblastoma multiforme) especially in children less than 5 years at diagnosis (Neglia, Meadows et al. 1991). The role of other environmental toxins is relatively unclear (Gurney, Smith et al. 1999).

## 2. Factors that contribute to treatment failure in children with brain tumors

Although the annual mortality rate for pediatric cancers has steadily decreased over the last two decades, the proportion of deaths from CNS tumors in the same population has increased from 18% to 30% (Bleyer 1999). These figures clearly highlight the suboptimal outcomes in children with CNS malignancies compared to other pediatric tumors.

Surgery, chemotherapy, and radiotherapy have long been established as treatment modalities for patients with brain tumors. It has also become obvious that a significant proportion of brain tumor patients suffer progressive disease during or following cytotoxic therapy. The causes for such therapeutic failure have been attributed to the presence of the blood-tumor barrier and drug or radio-resistance. (Groothuis 2000; Bredel 2001) The refractoriness of brain tumors to cytotoxic therapy stems from a multitude of factors that can be broadly classified as apparent or inherent cellular resistance (Bredel 2001; Scotto and Bertino 2001). Apparent resistance to a cytotoxic agent is usually due to the presence of the blood-brain barrier (BBB) (Groothuis 2000), the cell kinetics of a large tumor that has a smaller growth fraction (larger number of cells in the  $G_0$  fraction of the cell cycle), and hypoxic areas that limits the effect of cytotoxic therapy (Scotto and Bertino 2001). Inherent resistance can be either *de novo* or acquired. The various mechanisms of resistance to cytotoxic agents that are typically used in brain tumors are listed in Table 2.



\*incidence rates by histologic group and sexage <20, all races, SEER1990-95

Fig. 1. Malignant CNS tumor age-adjusted

| SYNDROME                  | GENE                        | CHROMOSOME     | TUMORS   |
|---------------------------|-----------------------------|----------------|--|
| Neurofibromatosis Type I  | <i>NF-1</i>                 | 17q11          | Optic Gliomas<br>Astrocytomas<br>Neurofibromas                             |
| Neurofibromatosis Type II | <i>NF-2</i>                 | 22q12          | Vestibular schwannomas<br>Meningiomas<br>Spinal cord ependymomas           |
| Von Hippel Lindau         | <i>VHL</i>                  | 3p25           | Cerebellar hemangioblastomas   |
| Tuberous Sclerosis        | <i>TSC1 and TSC2</i>        | 9q34 and 16p13 | Subependymal Giant Cell Astrocytoma  |
| Turcot                    | <i>APC</i>                  | 5q21           | Medulloblastoma<br>Colorectal polyps                                       |
|                           | <i>MLH1</i><br><i>PMS-2</i> | 3p21<br>7p22   | Glioblastoma multiforme<br>Colorectal polyps                               |
| Gorlin                    | <i>PTCH</i>                 | 9q31           | Medulloblastoma<br>Basal Cell Carcinoma<br>Ovarian Fibromas                |
| Li- Fraumeni              | <i>P53</i>                  | 17p13          | Astrocytoma<br>PNET<br>Soft tissue sarcoma<br>Breast Carcinoma<br>Leukemia |

Table 1. Common Genetic Syndromes and associated tumors

| Mechanism of resistance                       | Drug   | Cellular Enzyme/protein involved in resistance  |
|---|--|---|
| Decreased entry into cell<br>Increased efflux | Vinca alkaloids<br>Etoposide<br>Anthracyclines<br>Trimetrexate         | ↑ p-glycoprotein expression   |
| Increased inactivation                        | Cyclophosphamide<br>Cisplatin<br>Camptothecins                         | ↑ aldehyde dehydrogenase<br>↑ glutathione and metallothioneins<br>↑ Cytochrome P-450 (e.g., CYP3A4) |
| Increased DNA repair following DNA damage     | Nitrosoureas<br>Temozolomide<br>Cyclophosphamide<br>Platinum compounds | ↑ alkyl guanine alkyltransferase<br>↑ poly-ADP ribonucleotide polymerase (PARP)                     |
| Decreased topoisomerase binding               | Etoposide<br>Anthracyclines<br>Camptothecins                           | Topoisomerase I and II  |
| Mismatch repair deficiency                    | Temozolomide<br>Platinum compounds<br>Busulfan                         | MSH-2, 3, and 6; MLH1   |

Table 2. Mechanisms of cellular drug resistance in brain tumors.

| Distribution   | No. of patients (%) (of n = 713)* |
|--|-----------------------------------|
| <b>Tumor location</b>                                |                                   |
| <i>Cerebellar hemisphere</i>                         | 225 (32%)                         |
| <i>Cerebral hemisphere</i>                           | 197 (28%)                         |
| <i>Midline (basal ganglia, thalamus, brain stem)</i> | 135 (19%)                         |
| <i>Cerebellar vermis</i>                             | 128 (18%)                         |
| <i>Chiasmatic-hypothalamic</i>                       | 28 (4%)                           |
| <b>Tumor histology</b>                               |                                   |
| <i>Juvenile pilocytic astrocytoma</i>                | 396 (76%)                         |
| <i>Fibrillary astrocytoma</i>                        | 43 (8%)                           |
| <i>Ganglioglioma</i>                                 | 32 (6%)                           |
| <i>Oligodendroglioma</i>                             | 28 (5%)                           |
| <i>Pleomorphic xanthoastrocytoma</i>                 | 8 (1.5%)                          |
| <i>Other gliomas</i>                                 | 7 (1.3%)                          |
| <i>Mixed gliomas</i>                                 | 6 (1.2%)                          |

\* Tumor location and histology in 713 children enrolled on CCG 9891/ POG 9130 low grade glioma study (adapted from Wisoff, J. H., J. M. Boyett, et al. (1998)

Table 3. Distribution of low-grade gliomas in children based on location and histology

## 2.1 The blood-brain barrier

The BBB is composed of endothelium that covers almost the entire capillary network supplying the brain. The endothelium in the BBB is non-fenestrated with high-resistance tight junctions. Other components of the BBB include the astroglial processes, basement membrane, and pericytes (Gururangan and Friedman 2002) (Gururangan and Friedman 2004). The foot processes of the astrocytes cover the entire capillary endothelium and are essentially interposed between the endothelium and the neurons (Gururangan and Friedman 2004). There is minimal pinocytotic activity across the endothelial cells. Hence, in a physiologic state, the BBB functions as a diffusion barrier preventing hydrophilic molecules less than 180 kilo Daltons from passively entering the brain, and is intended to keep noxious substances from damaging the neuronal cells (Englehard and Groothuis 1999). The BBB serves to transport nutrients and water soluble substances between the blood and the CNS (Engelhard 2000). It also serves as a conduit for carrier mediated, energy-dependent specialized transport systems that enable specific molecules in the blood to cross the endothelium into the neurons (e.g., the glucose transporter, GLUT-1) or from the cell back to blood (e.g., p-glycoprotein efflux pump) (Englehard and Groothuis 1999). The endothelium is fenestrated and permits free exchange of large molecules in some areas of the brain including pituitary and pineal glands, the median eminence, area postrema, subfornical organ, and the lamina terminalis. The absence of the BBB is reflected by the appearance of normal contrast enhancement in these areas in neuroimaging studies.

### **2.1.1 Brain tumors cause disruption of the blood-brain barrier**

The proliferation and invasion of tumor cells in the brain generally results in the disruption of the brain microvasculature, breach of the BBB, and development of vasogenic edema even in small tumors (Gururangan and Friedman 2002). The BBB is histologically abnormal in the presence of a tumor with thickened basement membrane, increased pinocytotic activity within the endothelial cells, and diminished interaction between the pericytes and astrocytic foot processes causing increased fenestrations between endothelial cells and exudation of plasma into the tumor. This interstitial edema can in turn influence cerebral blood flow, brain metabolism, and intracranial pressure. Tumor cells also secrete pro-angiogenic factors including basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF) resulting in the influx of new blood vessels into the tumor, a process called tumor angiogenesis (Folkman 2007). These tumor capillaries are different from the capillaries of the normal brain in that they are hyperplastic, have frequent fenestrations, lax intercellular junctions, and less well developed glial processes abutting on the abluminal surface of the endothelium (Groothuis 2000). Thus the continuing proliferation of the tumor cells in the brain actually results in disruption of the BBB (Stewart 1994). However, it is possible that such disruption can be variable between tumors and even within a given tumor. Also, it is likely that small tumors (for e.g., the infiltrative edge of a malignant glioma) might have a relatively intact BBB that might lead to chemotherapy failure (Stewart 1994).

### **2.1.2 Blood-brain barrier and efficacy of brain tumor chemotherapy**

In the ongoing search for more effective chemotherapeutic agents for patients with brain tumors, there is a general bias towards choosing lipophilic agents with a high octanol-water partition coefficient (a measure of the lipid solubility of the drug) to enable rapid transfer of these drugs from the blood to the tumor cells despite an intact BBB (Englehard and Groothuis 1999). However, as indicated in the previous section, it appears that the BBB might be disrupted even in small tumors allowing drug entry. Also, studies have shown that the average concentration of chemotherapeutic agents in brain tumors does not significantly differ from their extra cranial counterparts, although the homogeneity of drug distribution varies both within and between brain tumor deposits (Stewart 1994; Gururangan and Friedman 2002). Also, it must be remembered that while lipophilic drugs do penetrate the blood-brain barrier better, it does not necessarily translate into equal efficacy in all patients with brain tumors (Stewart 1994). There are clearly other reasons for chemotherapy failure in such patients besides the BBB (Groothuis 2000; Gururangan and Friedman 2002). Nevertheless, it is possible that disruption of the BBB may not be uniform in brain tumors and areas of the brain surrounding the main tumor may have a relatively intact BBB. This notion has led to an increasing trend towards devising methods that further disrupt the blood-tumor barrier to facilitate entry of chemotherapy into brain tumors. Such increased disruption could potentially increase drug concentration in areas where the barrier has not been completely disrupted by the tumor (Stewart 1994) and help chemotherapy reach areas of adjacent tumor infiltration wherein the barrier may be relatively intact (Stewart 1994; Englehard and Groothuis 1999). Alternatively, the BBB can be by-passed using strategies like intra-arterial or intra-theal delivery of chemotherapeutic agents; convection-enhanced delivery of large molecules like toxins directly into the tumor;

or intracavitary administration of chemotherapy wafers (e.g., Gliadel™ wafers, Eisai Pharmaceuticals, Woodcliff Lake, NJ) (Gururangan and Friedman 2002).

### 3. Angiogenesis and brain tumors

In 1971, Dr. Judah Folkman proposed that continued tumor growth after the initial tumor take (up to a 2 mm<sup>3</sup> size) is dependent on growth of new blood vessels into the tumor (Folkman 2007). This influx of new capillaries was termed 'tumor angiogenesis'. This initial hypothesis has since been confirmed in several studies and has led to the discovery of several pro angiogenesis and anti-angiogenesis factors (Folkman 2007). The principal pro-angiogenesis mediators are  $\alpha$  and  $\beta$  fibroblast growth factors (b-FGF), vascular endothelial growth factor (VEGF), angiogenin, and other factors (Folkman 2007). The principal negative regulators of new capillary growth are endostatin, thrombospondin-1 and 2, and angiostatin (Folkman 2007). While tumor dormancy is generally dependent on a balance between positive and negative regulators of angiogenesis, an excess of stimulators results in the "angiogenic switch" and exponential tumor growth (Hanahan and Folkman 1996). These pro-angiogenic factors can be produced by the tumor cells, mobilized from the extracellular matrix through matrix metalloproteases (MMP), or released by macrophages or neutrophils attracted to the tumor through elaboration of VEGF (Folkman 2007). The angiogenic process also leads to tumor invasion and ultimately metastasis to other body sites (Folkman 2007). This induction of angiogenesis is the reason why neovascularization is present in most brain tumors (Li, Folkherth et al. 1994). Immunohistochemical studies have demonstrated the presence of angiogenic factors including b-FGF in high concentrations in brain tumors (Li, Folkherth et al. 1994). This peptide stimulates vascular endothelial cell proliferation and such cells either produce or possess receptors for b-FGF. Li et al. have detected b-FGF in the cerebrospinal fluid (CSF) in 62% of children with brain tumors but none in controls (Li, Folkherth et al. 1994). The CSF specimens with elevated b-FGF increased the DNA synthesis of capillary endothelial cells *in vitro* and such activity was blocked by neutralizing antibody to b-FGF. The concentration of b-FGF in CSF was also correlated with increased micro vessel density (MVD) in histologic sections of the brain tumors and negatively correlated with prognosis. While b-FGF was the only proangiogenic factor studied in this report, it is possible that other angiogenic peptides could mediate growth of brain tumors including VEGF, integrins ( $\alpha_v\beta_3$ ,  $\alpha_v\beta_5$ ,  $\alpha_3\beta_1$ ), Platelet derived growth factor (PDGF), plasminogen activator, cyclooxygenases, and copper. VEGF is highly expressed in several types of primary brain tumors (Leung, Chan et al. 1997; Huang, Held-Feindt et al. 2005) and is an important growth factor that sustains endothelial proliferation, survival, and motility (Kerbel 2008). There are four cognate VEGF receptors including VEGFR-1 (flt-1), VEGFR-2 (KDR), VEGFR-3, and VEGFR-4. However, VEGFR-2 is the most important receptor that mediates the effects of VEGF on the endothelial cells (Kerbel 2008). The level of VEGF expression has also been correlated with outcome in patients with glioblastoma multiforme (Kim, Li et al. 1993).

The demonstration of the role of angiogenesis in sustaining tumor growth has led to the exploration of inhibitors of angiogenesis as a means of curtailing tumor progression. Elegant pre-clinical studies in mouse tumor xenograft models have shown dramatic tumor regression and cure of animals bearing tumors (Boehm, Folkman et al. 1997). There are at least 40 such inhibitors in various stages of clinical development in a wide variety of tumors

in centers in the U.S and Europe, and should help our understanding of the toxicity, dose schedules, and possibly the usefulness of these agents in these malignancies.(Folkman 2007). Three of these agents have received FDA approval, including Bevacizumab (Avastin™, Genentech Corporation, San Francisco, USA) (for colorectal cancer, lung cancer, glioblastoma multiforme), Sorafenib (Nexavar™, Bayer Pharmaceuticals, Berlin, Germany)(for renal carcinoma), and Sunitinib (Sutent™, Pfizer Corporation, USA) (for renal carcinoma) (Folkman 2007). In particular, Bevacizumab (a humanized antibody against VEGF), AZD2171 (Cediranib, Astra Zeneca, U.K.) (VEGF-R2 inhibitor), and Cilengitide (an integrin  $\alpha_v\beta_3$ ,  $\alpha_v\beta_5$  inhibitor) (EMD121974; Merck KGaA, Darmstadt, Germany) have undergone extensive evaluation in adults with malignant glioma and are currently being tested in phase III trials against standard therapy (Reardon, Desjardins et al. 2008).

## 4. Advances in the treatment of pediatric brain tumors

### 4.1 Low-grade gliomas

Pediatric low-grade gliomas (LGG) are a heterogeneous group of tumors and constitute the most frequent CNS neoplasia encountered in children (30-40% of all CNS tumors diagnosed in the United States) (Watson, Kadota et al. 2001). They can be classified based on histology or location (Table 3). Pilocytic astrocytoma is the commonest LGG in children with an incidence of 0.79 per 100,000 person-years. The commonest neurocutaneous syndrome associated with LGG is Neurofibromatosis Type I (NF-1). The genetic mutation is NF-1 is located on chromosome 17q and results in loss of the GTP-ase activating protein (GAP), Neurofibromin. Lack of Neurofibromin activity results in increased activity of the RAS- MAPK, cyclic AMP, and mTOR signaling pathways, and cellular proliferation (Rubin and Gutmann 2005). About 15% of patients with NF-1 develop LGG (typically pilocytic astrocytoma, WHO grade I) and less commonly, other gliomas (Reed and Gutmann 2001). NF-1 patients with LGG have a more favorable prognosis than those with sporadic tumors (Gururangan, Cavazos et al. 2002). The risk factors for development of non-NF-1 LGG is largely unknown although one case-control study identified an increased risk of developing low grade brain stem gliomas in the offspring of mothers who ingested an excessive amount of cured meats during pregnancy (Preston-Martin, Pogoda et al. 1996).

The pathology of pilocytic astrocytoma is one of low cellularity and a biphasic pattern of solid sheets of bipolar cells and Rosenthal fibers along with areas of micro and macro cysts (Burger, Scheithauer et al. 2000). The tumor nuclei typically lack anaplasia. The tumor demonstrates hyalinized glomerular blood vessels that are quite leaky and hence cause intense contrast enhancement on neuroimaging studies. The pilomyxoid astrocytoma is a closely related tumor type that occurs predominantly in the hypothalamic/chiasmatic region and is characterized by the presence of a myxoid matrix and angiocentric arrangement of monomorphous bipolar cells, and has a high predilection for leptomeningeal spread (Louis, Ohgaki et al. 2007).

### 4.2 Treatment

Since these tumors only rarely metastasize through the neuraxis, local control using surgery and/or radiotherapy have been the traditional components of therapy for patients with LGG. Due to a direct positive correlation between extent of resection and progression-free and



overall survival (PFS and OS), aggressive surgery of tumor should be attempted in tumor locations where feasible (Watson, Kadota et al. 2001). The cystic cerebellar astrocytoma is an example of a LGG that can be resected completely without causing neurologic deficits and results in cure rates of over 90% (Figure 2) (Watson, Kadota et al. 2001). Similarly, exophytic tumors of the brain stem including the cervico-medullary region are typically pilocytic astrocytomas, amenable to complete surgical removal, and have an excellent prognosis (Watson, Kadota et al. 2001). Tectal plate gliomas usually present with hydrocephalus due to early compression of the cerebral aqueduct. Patients with these tumors are observed without any treatment after controlling hydrocephalus with a third ventriculostomy. The operating microscope and ultrasonic surgical aspirator allows the surgeon to perform an adequate tumor resection without compromising adjacent normal brain. Pre-operative imaging can be correlated with intra-operative observation using frame-based or frameless stereotactic system that also help in guiding the surgeon with trajectories to deep-seated lesions. Functional magnetic resonance imaging, positron emission tomography, and electrode grids for mapping areas of the cerebral cortex have helped the surgeon to accurately delineate tumor margins and improve post-surgical morbidity in these patients. However, tumors in certain areas of the brain (about 30% of all LGG) are still unsafe for surgical resection and include the optic pathway, diencephalon (hypothalamus and thalamus), and intrinsic portion of the brain stem. For tumors in such locations and those that recur after initial surgical resection and/or cause functional impairment, chemotherapy and/or radiotherapy (RT) can be used for disease control. There are no reported prospective randomized trials assessing the benefits of adjuvant radiotherapy in children with LGG (Watson, Kadota et al. 2001). Extrapolating data from adult phase III trials, it seems appropriate to use focal radiotherapy in doses of 45-54 Gy in 1.8 to 2.0 Gy fractions. Three-D conformal RT, intensity modulated RT, and proton-beam therapy are new radiation delivery techniques that are designed to minimize damage to normal brain but await validation in larger studies (Watson, Kadota et al. 2001). A preliminary report from St. Jude Children's Hospital explored the usefulness of 3-D conformal RT in patients with localized LGG (Merchant, Happersett et al. 1999). Thirty eight patients (median age 8.7 years, range 2.2-18.7) with LGG (JPA, 25) were enrolled on this phase II trial. With a median follow-up of 17 months (range, 3-44), four patients have suffered local failures, 3 within the clinical target volume (CTV) and one just outside the CTV. While data from this study is encouraging for limited field radiotherapy, long-term follow up is required to assess the impact of field reduction on long-term complications and outcome. In view of the deleterious effect of radiotherapy on the growing brain in young children, chemotherapy agents including vincristine, actinomycin-D, cyclophosphamide, carboplatin, lomustine, and etoposide have been employed individually or in combination in patients with progressive LGG to delay or avoid irradiation (Gururangan, Cavazos et al. 2002). Following preliminary clinical evidence of activity, carboplatin, a second-generation cisplatin analog, either alone or in combination with vincristine, has been used as a frontline therapy for children with low-grade glioma, particularly for those with optic pathway tumors (Friedman, Krischer et al. 1992; Packer, Ater et al. 1997; Gururangan, Cavazos et al. 2002). Objective responses and disease stabilization have been observed in 25-58% and 80-90% of patients respectively in these studies. The three-year PFS in patients with recurrent low-grade glioma following this chemotherapy regimen has been reported to be 64-68% (Packer, Ater et al. 1997; Gururangan, Cavazos et al. 2002). Myelosuppression is the main toxicity related to carboplatin followed by allergic reactions in

about 10-30% of patients (Gururangan, Cavazos et al. 2002). An alternative nitrosourea – based chemotherapy regimen [6-Thioguanine, Procarbazine, Lomustine (CCNU), Vincristine, and Dibromodulcitol] was reported by Prados et al., and was shown to produce prolonged disease stabilization in children with progressive LGG (Prados, Edwards et al. 1997). This treatment combination without Dibromodulcitol (TPCV regimen) was evaluated in comparison with the carboplatin + vincristine combination in a Children's Oncology Group phase III trial in 401 eligible children with progressive or symptomatic LGG (Ater, Holmes et al. 2008). The results of this study, available in abstract form, showed that both regimens were efficacious in prolonging disease-free survival (median time to progression of 3.2 and 4.9 years for carboplatin + vincristine and TPCV regimens respectively) and enabled delaying radiotherapy. The overall survival was 86% for non- NF-1 children and 98% for those with NF-1 ( $p= 0.0017$ ), again demonstrating that NF-1 patients with recurrent LGG have a better prognosis than those without NF-1. Recently, we and others have also reported on the efficacy of Temozolomide (an oral methylating imadazole tetrazinone compound) in both adults and children with LGG (Kuo, Weiner et al. 2003; Quinn, Reardon et al. 2003; Gururangan, Fisher et al. 2007). In a phase II trial of 26 children with progressive/recurrent optic pathway or juvenile pilocytic astrocytoma, the disease stabilization rate was over 50% for a median interval of 34 months (Gururangan, Fisher et al. 2007).

### 4.3 Molecular alterations in pediatric LGG and novel therapies

While *Nf-1* loss is clearly related to the genesis of tumors in patients with NF-1, the molecular events in sporadic LGG had not been well characterized until recently. Several groups have now identified tandem duplication of 7q34 that contains the *BRAF* gene in about 60-80% of sporadic pilocytic astrocytomas resulting in a fusion product between *KIAA1549* and *BRAF* that includes the *BRAF* kinase domain without the auto-inhibitory N-terminus (Pfister, Janzarik et al. 2008; Yu, Deshmukh et al. 2009). This is an activating mutation that is also present in 50% of fibrillary astrocytomas. On the other hand, an activating point mutation in Exon 15 position 600 of the *BRAF* gene (*BRAF* V600E) is found in over 40% of gangliogliomas but only rarely in pilocytic astrocytomas (Dougherty, Santi et al. 2010). *BRAF* is a member of the RAF family of serine-threonine protein kinases and is a key intermediary in the RAS-RAF-MEK-ERK- MAP kinase pathway (Yu, Deshmukh et al. 2009). Activation of *BRAF* would signal downstream via MEK-ERK and finally MAP-kinase resulting in cellular proliferation. In fact, tumors with activating mutations of *BRAF* were found to have overexpression of MAP-K (Kolb, Gorlick et al. 2010).

In contrast to sporadic tumors, *BRAF* mutations are not found in NF-1 associated pilocytic astrocytomas (Yu, Deshmukh et al. 2009). It is therefore possible that this mutation is an initiating event only in non- NF-1 tumors. Interestingly, this activating mutation seems to be preferentially expressed in posterior fossa tumors (Yu, Deshmukh et al. 2009). In addition to *BRAF* mutations, *HIPK2* (Homeo-box interfering protein kinase 2) amplifications have been identified in a proportion of sporadic pilocytic astrocytomas that also harbor *BRAF* rearrangements (Yu, Deshmukh et al. 2009). The significance of this molecular event is unknown. In addition, VEGF overexpression has also been observed in pilocytic astrocytomas and might explain the intense vascular proliferation seen in these tumors (Leung, Chan et al. 1997).

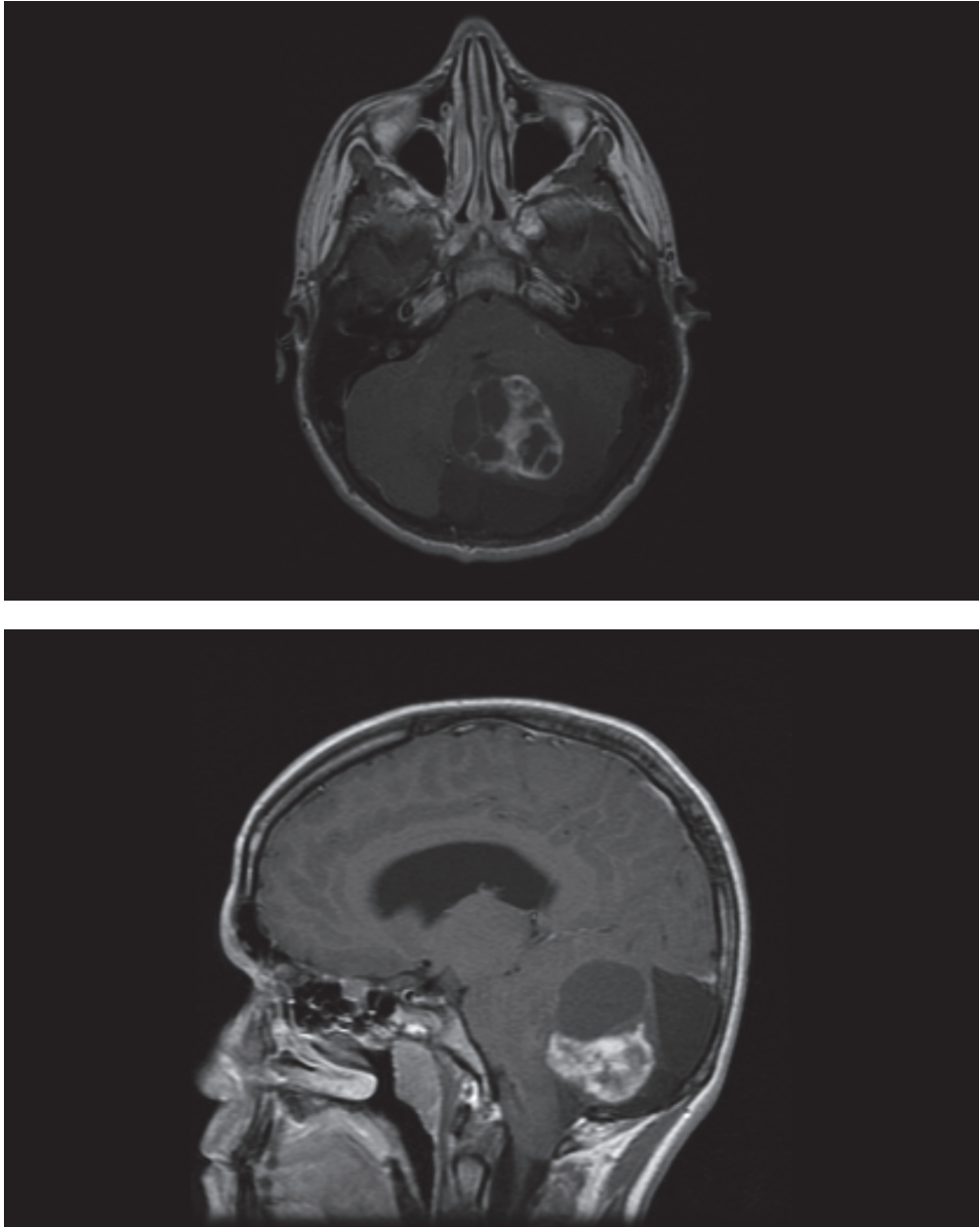


Fig. 2. T-1 weighted axial and sagittal gadolinium enhanced images of the brain in a 4-year old male demonstrating an enhancing cystic lesion in the cerebellum that is compressing the IV ventricle and causing hydrocephalus. Histology of this mass was a pilocytic astrocytoma.

Biologic therapies are being increasingly used in children with recurrent LGG using information on expression of specific targets in these tumors. The intense vascularity of pilocytic astrocytoma implies that these tumors might be susceptible to anti-angiogenic therapies. Using the principle of metronomic chemotherapy that preferentially kills tumor endothelial cells rather than tumor (Kerbel, Vioria-Petit et al. 2000), Bouffet et al., conducted a phase II study of intravenous vinblastine 6 mg/m<sup>2</sup>/week administered for up to 52 weeks in 51 patients with recurrent LGG (Bouffet, Jakacki et al. 2008). Disease stabilization was obtained in 42% of patients at a median follow up of 31 months from starting treatment. In a recent phase I study of Lenalidomide (an immune modulating drug and angiogenesis inhibitor) in children with recurrent brain tumors, Warren et al., reported objective responses in 2 patients with an optic pathway glioma and pilocytic astrocytoma respectively (Warren, Goldman et al. 2011). Similarly, Packer et al., have observed sustained objective responses or disease stabilization and improvement in neurologic deficits in 7 of 9 children with multiply recurrent LGG treated with Bevacizumab plus irinotecan (Camptosar™, Pfizer corporation, USA) (Packer, Jakacki et al. 2009). A multi-institutional phase II trial of the same combination in children with recurrent LGG has just been completed and results of this study should be available soon.

Since about 70% of sporadic pilocytic astrocytomas express activating BRAF mutations, there has been an interest in using targeted inhibitors of the BRAF pathway. In the pediatric pre-clinical testing program (PPTP), AZD6244, a potent and selective inhibitor of MEK1/2 kinases, demonstrated significant activity in one of two JPA xenografts that carried the activating V600E mutation (Kolb, Gorlick et al. 2010). There is an ongoing multi-institutional phase I trial in the United States through the National Cancer Institute sponsored Pediatric Brain Tumor Consortium (PBTC) using AZD6244 in older children with recurrent low-grade gliomas testing the toxicity, pharmacokinetics, and preliminary assessment of efficacy of this agent in this population (Larry Kun M.D., Memphis, TN; personal communication 2011).

## **5. Primitive neuroectodermal tumors**

Primitive neuroectodermal tumors (PNET) of the central nervous system (CNS) are a group of aggressive embryonal neoplasia that occurs both in adults and children. Under this broad rubric, three tumors are mainly recognized based on their location - medulloblastoma, which occurs exclusively in the cerebellum, pineoblastoma in the pineal gland, and supratentorial PNET in the cerebral hemispheres or suprasellar region. Although histologically similar with a propensity for aggressive neuraxis dissemination, these tumors markedly differ in terms of genetic makeup and prognosis. In recent years, much controversy has been generated in the histologic classification of PNET (Rorke 1983). Simultaneously, considerable progress has been made in identifying the molecular characteristics of these tumors, particularly medulloblastoma (Pomeroy, Tamayo et al. 2002 ; Gilbertson 2004). Also, significant strides have been made in the treatment of patients with these malignancies.

### **5.1 Medulloblastoma**

Medulloblastoma is the most common malignant brain tumor in children. About 400 children are diagnosed with this tumor each year in the United States (Gurney, Smith et al. 1999). The peak age of onset is between 5-9 years of age. Over 90% of medulloblastoma

typically arise from the superior medullary velum, grows and fills the cavity of the fourth ventricle (Figure 3a) (Mclendon, Enterline et al. 1998). The tumor mass can encroach on to

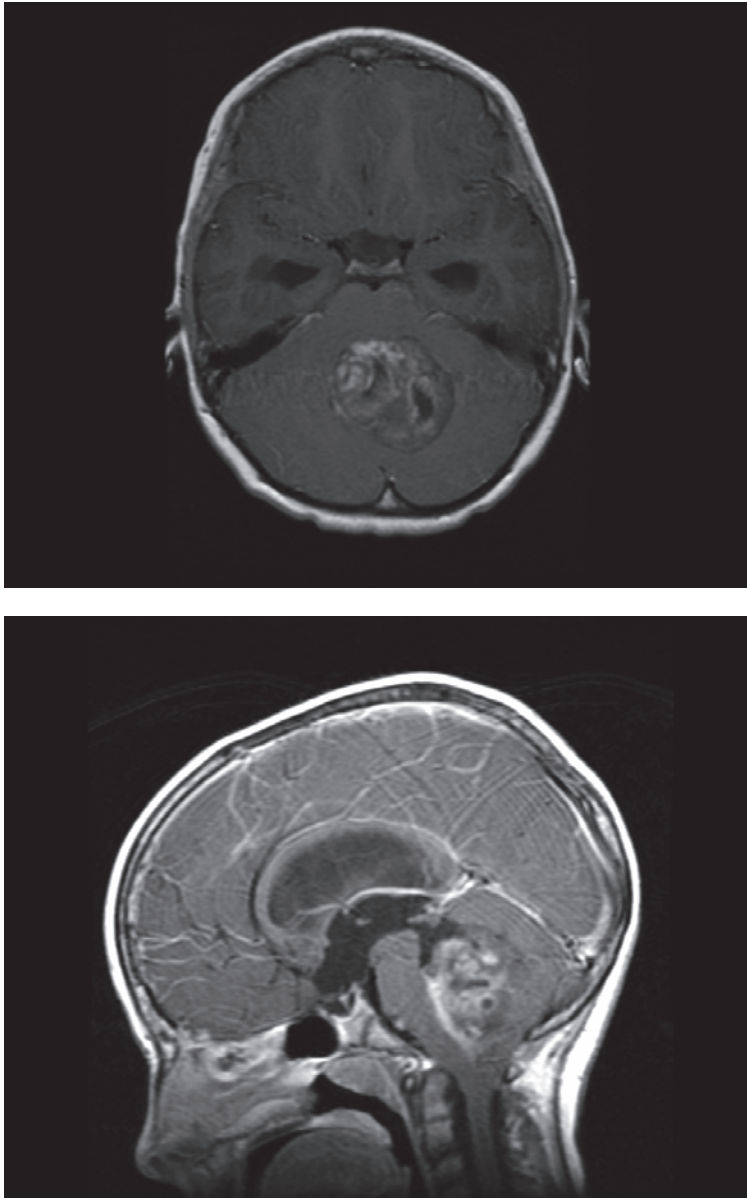


Fig. 3. a: Figure: T-1 weighted axial and sagittal gadolinium enhanced images of the brain in a 16-year old black female that demonstrates a heterogeneously enhancing mass filling the IV ventricle and causing obstructive hydrocephalus

the cisterna magna and sometimes infiltrates the floor of the fourth ventricle or brain stem. A minority of tumors, particularly in patients over 16 years of age, arises more laterally in the cerebellar hemispheres (McLendon, Enterline et al. 1998). Macroscopically, these tumors are soft, friable, and moderately demarcated from the cerebellar tissue. Areas of central necrosis may be present. The microscopic structure of medulloblastoma is characterized by densely packed cells with round to oval carrot-shaped highly hyperchromatic nuclei surrounded by scanty cytoplasm. Neuroblastic rosettes are a typical but not constant feature. The main pathologic subtypes of medulloblastoma recognized in the 2000 World Health Organization (WHO) classification of brain tumors include classic, desmoplastic, extensive nodularity with advanced neuronal differentiation, and the large cell/anaplastic varieties (Giangaspero, Perilongo et al. 1999; Giangaspero, Bigner et al. 2000; Leonard, Cai et al. 2001; Louis, Ohgaki et al. 2007). The predominant presenting symptoms in patients with this tumor are those of raised intracranial pressure including irritability, headache, lethargy, vomiting, and poor school performance (Packer, Cogen et al. 1999). Additional symptoms due to invasion of other local structures include truncal ataxia, nystagmus, neck stiffness, and cranial nerve palsies. Dissemination of tumor to the leptomeninges (Figure 3b) occurs in about 10-30% of cases, with infants suffering this complication more frequently than older children. In less than 10% of cases, the tumor can spread outside of the neuraxis (Packer, Cogen et al. 1999). Patients with certain genetic disorders including Gorlin's (nevroid-basal cell carcinoma syndrome), p-53 germline mutation, and Turcot's syndromes have a higher risk of developing medulloblastoma (Packer, Cogen et al. 1999).



Fig. 3. b: T-1 weighted sagittal gadolinium enhanced image of the spine in a 2-year old black female with posterior fossa medulloblastoma demonstrating multiple nodular metastatic lesions along the spinal cord

## 5.2 Treatment

Patients with medulloblastoma are classified as average or high-risk to enable assignment of appropriate treatment based on the extent of tumor following surgery. Those with average risk disease are over  $> 3$  years of age and have  $\leq 1.5$  cm<sup>2</sup> of tumor in the primary site and no brain stem involvement or metastatic disease (Packer, Cogen et al. 1999). Patients with high-risk medulloblastoma include children  $< 3$  years at the time of diagnosis, and those who have gross residual disease post-surgery or metastatic disease (Packer, Cogen et al. 1999). Conventional therapy for patients with low-risk medulloblastoma is complete surgical resection followed by craniospinal irradiation (24-36 Gy) and a focal boost to the primary site (54 - 56 Gy) with a 5-year event-free survival rate of approximately 60% (Packer, Cogen et al. 1999; Freeman, Taylor et al. 2002). The addition of chemotherapy (vincristine, cisplatin, and lomustine or cyclophosphamide) appears to benefit patients with high-risk features and might help to decrease the dose of neuraxis irradiation in patients with average risk disease (Packer, Cogen et al. 1999; Freeman, Taylor et al. 2002). Infants with medulloblastoma fare poorly with standard chemotherapy and irradiation and have a higher incidence of neuro-cognitive deficits following radiotherapy (Duffner, Horowitz et al. 1993; Walter, Mulhern et al. 1999). There is evidence that some infants can be successfully treated with high-dose chemotherapy alone without neuraxis irradiation (Mason, Grovas et al. 1998). 3-D conformal radiotherapy is currently being utilized in children with medulloblastoma in an attempt to delivery radiation boost to the tumor bed and residual tumor and decrease radiation scatter to the cochlea, supratentorial brain, and hypothalamus. Preliminary results from single- institution studies appear promising with no increased failures documented in the posterior fossa (Merchant, Happersett et al. 1999; Wolden, Dunkel et al. 2003) and lesser risk of oto-toxicity and neuro-cognitive deficits. The validity of these results will be further tested in a randomized fashion in the ongoing Children's Oncology Group (COG) phase III trial (ACNS 0331) for average- risk medulloblastoma in children.

Patients with recurrent tumors fare very poorly despite conventional retrieval therapy with few or no long-term survivors. The use of high-dose chemotherapy (HDC) with stem cell rescue has been useful in prolonging PFS in a proportion of patients with tumors that are localized and sensitive to standard chemotherapy, relapse following chemotherapy only, and hence can also receive standard doses of radiotherapy in addition to HDC (Dunkel, Boyett et al. 1998; Gururangan, Dunkel et al. 1998; Gururangan, Krauser et al. 2008). In contrast, studies at Duke University Medical Center and others have shown that this strategy does not seem to be efficacious in those patients who relapse after receiving standard chemotherapy and radiotherapy (Gururangan, Krauser et al. 2008). Recurrent medulloblastoma is invariably associated with leptomeningeal dissemination (LMD) at some point in its disease course. Treatment for LMD with currently available options is suboptimal. Intrathecal chemotherapy with thiotepa, mafosfamide, or busulfan has been tested in phase I/II clinical trials in patients with LMD (Gururangan and Friedman 2002). However, benefits are transient since the delivered chemotherapy is unable to penetrate beyond a few millimeters into the tumor tissue from CSF due to the high interstitial pressure within the tumor. More innovative therapies are needed to improve outcome for patients with recurrent medulloblastoma through a better understanding of the biology of the tumor.

### 5.3 Molecular characteristics and biologic therapy

There has been a profusion of studies describing the molecular characteristics of medulloblastoma including the Sonic-Hedgehog and WNT signaling pathways, Trk-C expression, c-Myc amplification, OTX-2 amplification, presence of isochromosome 17q, erBB-2 and 4 over-expression, and PDGFR  $\alpha$  and RAS/MAP-kinase activation, that can predict the biologic behavior and outcome independent of clinical characteristics (Packer, Cogen et al. 1999; MacDonald, Brown et al. 2001; Gilbertson 2004; Di, Liao et al. 2005). At least one clinical trial has prospectively validated the usefulness of some of these molecular markers and, in future, could potentially help to decrease therapy for those patients with favorable biologic features (Gajjar, Chintagumpala et al. 2006). Whereas patients with WNT pathway activation identified by beta-catenin point mutations on residue S33 and S37 have a 100% survival with standard risk adapted therapy, those with either SHH or non-SHH/non-WNT tumors have an inferior survival (Gajjar, Chintagumpala et al. 2006; Schwalbe, Lindsey et al. 2011). More recently, gene expression profiling of medulloblastoma has revealed that tumors cluster within four distinct molecular groups; WNT, SHH, Group C, and D (Northcott, Korshunov et al. 2010). Interestingly, each group could be identified by immunohistochemistry or mRNA based expression potentially allowing for easy categorization of prospective patients at diagnosis (Northcott, Korshunov et al. 2010; Schwalbe, Lindsey et al. 2011). Such classification has potential advantages of allowing for stratification of intensity of standard therapy based on the known prognosis of each group and possibly using specific small molecule kinase inhibitors specific for that group. An activating mutation of the Smoothed gene is present in about 10% of sporadic medulloblastoma and tumors harboring this mutation would be responsive to Smoothed inhibitors. GDC 0449 (Genentech Corporation, San Francisco, USA) is one such inhibitor that has shown excellent activity in transgenic PATCH mouse models of medulloblastoma (Romer, Kimura et al. 2004) and in one patient with metastatic medulloblastoma (Rudin, Hann et al. 2009). Recently, retinoids including All Trans Retinoic Acid (ATRA) and 13-cis retinoic acid have been found to mediate apoptosis in medulloblastoma cells and decrease tumor growth in xenograft mouse models, especially those bearing anaplastic medulloblastoma with OTX-2 amplification (Hallahan, Pritchard et al. 2003) (Di, Liao et al. 2005). On this basis, an ongoing COG trial will test the efficacy of 13 cis-retinoic acid in a randomized fashion along with maintenance chemotherapy in children with high-risk medulloblastoma. A recent pre-clinical study demonstrated that while 9-cis retinoic acid reduced growth of an OTX-2 overexpressing D425 medulloblastoma xenograft implanted in the flanks of athymic mice but failed to do so in intracranial implants of the same tumor (Bai, Siu et al. 2010). Fibroblast growth factor (FGF) expression was implicated in the failure of retinoic acid therapy in the intracranial tumor model and resistance can be abrogated by combining 9- cis retinoic acid with a specific FGF inhibitor (Bai, Siu et al. 2010).

### 5.4 Pineoblastoma and other supratentorial PNET

The incidence of pineoblastoma is approximately 3-10% of all primary malignant brain tumors in all age groups (Jakacki 1999) They constitute approximately 45% of all pineal parenchymal tumors. They usually occur in the first 2 decades of life with most cases occurring in the within 10 years. A familial tendency for occurrence of PNET in pineal or suprasellar region has been observed in patients with familial retinoblastoma, also called the trilateral retinoblastoma syndrome (Paulino 1999; Singh, Shields et al. 1999). Other supratentorial PNETs including cerebral neuroblastoma, ependymoblastoma, and



medullopithelioma constitute 1-2% of all CNS tumors and about 6% of all CNS PNETs. These tumors occur commonly in the cerebral hemispheres, periventricular region, thalamus, hypothalamus, basal ganglia, and rarely as diffuse leptomeningeal disease without a evidence of a primary tumor (Jennings, Slatkin et al. 1993; Dai, Backstrom et al. 2003). These tumors mostly occur in young children with a median age at diagnosis of 5.5 years (range, 4 weeks to 10 years) and a male predominance (Jakacki 1999). Supratentorial PNETs have been known to occur following cranial irradiation as a second malignancy (Hader, Drovini-Zis et al. 2003). No specific genetic associations have been noted in patients with these tumors. The histologic features of these tumors are similar to that of medulloblastoma.

The clinical features of pineoblastoma include those due to hydrocephalus due early compression of the aqueduct and pressure on the tectum of the mid-brain which produces the Parinaud's syndrome. Cerebral PNETs typically cause headache, vomiting, and seizures depending upon the location of the tumor (Berger, Edwards et al. 1983; Dai, Backstrom et al. 2003).

#### **5.4.1 Treatment**

The treatment of these tumors includes surgical resection, chemotherapy, and radiotherapy (Jakacki 1999; Gururangan, McLaughlin et al. 2003). However, survival for patients with these tumors is far inferior compared to those with medulloblastoma. Infants with supratentorial PNET have a dismal prognosis with standard chemotherapy and irradiation (Duffner, Horowitz et al. 1993; Jakacki 1999). In contrast, a PFS of over 60% has been observed in older children with pineoblastoma treated with lomustine (CCNU), vincristine, and prednisone or the "8 in 1" drug regimen following neuraxis irradiation and a focal boost to the pineal region (Jakacki 1999). The use of HDC with stem cell rescue plus radiotherapy has also resulted in improved survival in some children with these tumors especially for those with metastatic disease (Mason, Grovas et al. 1998; Gururangan, McLaughlin et al. 2003; Gururangan, Driscoll et al. 2008; Chintagumpala, Hassall et al. 2009). The efficacy of HDC in infants with pineoblastoma has been encouraging even without the need for radiotherapy (Gururangan, McLaughlin et al. 2003). Optimal management of children with pineoblastoma and other supra-tentorial PNETs continues to be a challenge and further therapeutic refinements are needed especially for those with recurrent disease.

#### **5.4.2 Molecular characteristics**

Although supratentorial PNETs resemble medulloblastoma histologically, the inferior survival seen in this group despite using intensive therapies as used for metastatic medulloblastoma suggest that there are intrinsic biologic differences between these two tumors. The most common non-random chromosomal abnormality is 4q loss occurring in 50% of cases (Li, Bouffet et al. 2005). In contrast to medulloblastoma, none of the supratentorial PNETs expresses isochromosome 17q. Other molecular characteristics include high NOTCH2 expression, and p53 dysfunction (as indicated by p53 immunopositivity) (Li, Bouffet et al. 2005). In addition, heritable loss of the mismatch repair gene PMS2 (homozygous missense mutation in exon 14) results in learning difficulties, café-au-lait spots, and early onset of supratentorial PNETs has been described in two siblings of a heavily consanguineous family (De Vos, Hayward et al. 2006). It appears that supratentorial PNETs might arise due to impaired DNA repair mechanisms as evidenced by the presence

of high p53 immunopositivity, occurrence following exposure to radiotherapy, and in the context of mismatch repair mutations (Li, Bouffet et al. 2005).

## 6. High-grade glioma

High-grade glioma (HGG) including anaplastic astrocytoma (AA, WHO grade III) and glioblastoma multiforme (GBM, WHO Grade IV) constitutes about 14% of CNS tumors in children. These tumors can occur anywhere in the brain. In a recent Children's Cancer Group study report of 131 evaluable children with HGG, over 90% of tumors occurred in a supratentorial location (63% in the superficial cerebral hemisphere (Figure 4a and 4b) and 38% in the deep or midline cerebrum and only 8% occurred in the posterior fossa (including brain stem and cerebellum) (Wisoff, Boyett et al. 1998). The principal histologic features of AA are increased cellularity, nuclear atypia, and marked mitotic activity. The neoplastic cells are consistently positive for glial fibrillary acidic protein and have a proliferative index of around 5-10%. GBM on the other hand is made up of pleomorphic astrocytic cells with brisk mitotic activity, nuclear atypia, vascular proliferation, and areas of necrosis.

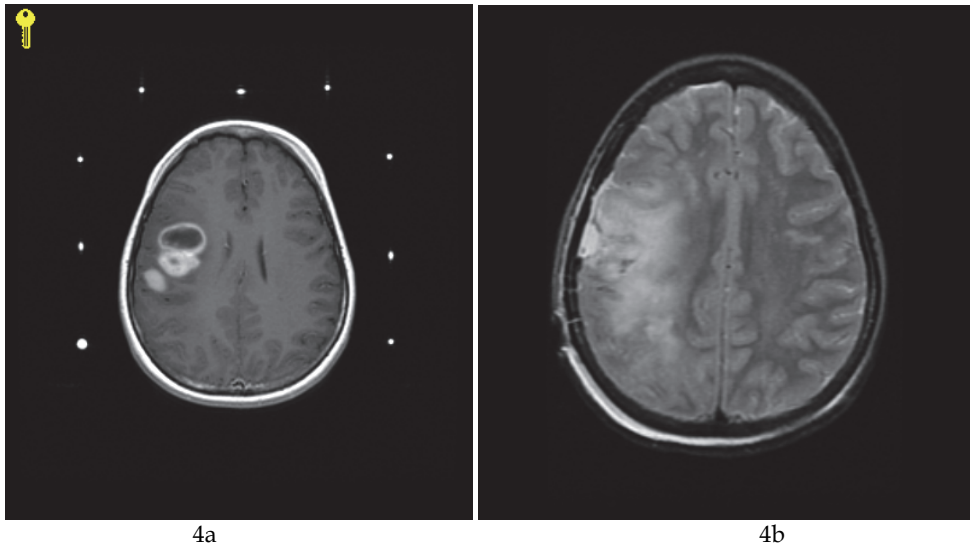


Fig. 4. a and b: Axial T-1 weighted gadolinium enhanced and T-2 weighted images of the brain in a 13-year old boy who presented with seizures. Biopsy of the enhancing lesion revealed an anaplastic astrocytoma. Note the satellite lesion posterior to the main tumor mass and the extensive T-2 signal abnormality that extends beyond the enhancing lesion and indicates peritumoral edema and potentially non-enhancing tumor

### 6.1 Treatment

Treatment of HGG in any site includes adequate surgical resection, radiotherapy, and chemotherapy. The efficacy of this combined modality approach was recently demonstrated in a Children's Cancer Group phase III randomized study (CCG-945) in which children with HGG received surgical resection followed by either vincristine, lomustine (CCNU), and

prednisone (control arm) or the "8 in 1" chemotherapy regimen (experimental arm) (Finlay, Boyett et al. 1995; Wisoff, Boyett et al. 1998). While there was no difference in 5-year PFS between the two arms of the study, the extent of surgical resection ( $> 90\%$  vs.  $\leq 90\%$  resection) as assessed by post-operative imaging, was highly predictive of outcome with patients who had complete resection ( $> 90\%$ ) having a significantly better 5-year PFS as compared to those with less extensive resection ( $\leq 90\%$ ) [AA + GBM, 35% vs. 17%,  $p = 0.006$ ; AA, 44% vs. 22% and GBM, 29% vs. 4%]. Based on the favorable outcome and FDA approval of using Temozolomide (Temodar™, Schering Plough Corporation, Kenilworth, New Jersey) concurrently with radiotherapy in adults with newly diagnosed glioblastoma multiforme especially those with methylation of the MGMT promoter (Cohen, Johnson et al. 2005), a pediatric phase II study was done in children with newly diagnosed malignant glioma in conjunction with radiotherapy followed by maintenance treatment for one year (Cohen, Pollack et al. 2011). The outcome for children with either Grade III or IV astrocytoma was no different compared to those who were treated on CCG-945 but over expression of MGMT was associated with poorer survival (Cohen, Pollack et al. 2011). Temozolomide does not provide the same benefit in children as it does for adults with HGG either at diagnosis or relapse (Gilbert, Friedman et al. 2002; Lashford, Thiesse et al. 2002). Other chemotherapeutic agents including irinotecan (CPT-11) have been utilized in children with HGG with only modest benefit (Turner, Gururangan et al. 2002). The combination of BCNU or Temozolomide with topoisomerase I inhibitors like CPT-11 has demonstrated synergism in pre-clinical studies (Gururangan and Friedman 2002). These combinations have been tested in adult clinical trials at our institution but with only modest benefits (Reardon, Quinn et al. 2004; Quinn, Jiang et al. 2009). Although mismatch repair defects in the tumor is a putative mechanism for resistance in tumors that do not respond to methylating agents like Temozolomide despite low AGAT expression, very few such tumors have been noted to harbor MMR deficiency (Pollack, Hamilton et al. 2010). Alternatively, excessive base excision repair (BER) could be operative in the face of overexpression of the enzyme poly (ADP-Ribose) polymerase (PARP) in these tumors. Inhibition of PARP prior to treatment with Temozolomide would prevent BER and make the tumor sensitive to the drug again. ABT-888 (Olaparib™, Abbot Laboratories, USA) is an effective PARP inhibitor that has been shown to effectively deplete PARP in tumors and is undergoing clinical testing both as a single agent and in combination with chemotherapy and other cytotoxics. Temozolomide + ABT-888 is currently being evaluated both in adults with malignant glioma and children with recurrent brain tumors.

Children with midline HGG including those in the thalamus and diffuse intrinsic lesions within the brain stem (e.g., diffuse pontine glioma) are unresectable based on location and have a grave prognosis (Reardon, Gajjar et al. 1998; Mandell, Kadota et al. 1999). While patients with thalamic tumors undergo biopsy to confirm histology of HGG, it is no longer deemed necessary in patients with MRI findings of a diffuse intrinsic brain stem glioma. The use of radiotherapy and chemotherapy has had little impact on the dismal outcome of these patients in recent years (Mandell, Kadota et al. 1999; Cohen, Heideman et al. 2011).

Since drug resistance and the blood-brain barrier are considered to be the most important impediments to effective chemotherapy in brain tumors, strategies have been devised to circumvent these barriers (Gururangan and Friedman 2002). For locally invasive tumors like HGG, therapies that circumvent the BBB include intra-cavitary implantation of BCNU wafers (Gliadel™ wafers, Aventis Corporation, USA), use of agents that disrupt the BBB,

intra-arterial chemotherapy with or without BBB disruption, and convection-enhanced delivery (CED) (Gururangan and Friedman 2002). A modest but significant efficacy was noted with the use of polymers impregnated with BCNU (Gliadel™ wafers, Aventis Corporation, USA) in a phase III randomized double-blind trial in adults with malignant glioma (Brem, Piantadosi et al. 1995; Westphal, Hilt et al. 2003). Intra-arterial chemotherapy using agents like carmustine, cisplatin, and etoposide, despite some theoretical advantages, has not proven to be useful but has some prohibitive neuro-toxicities (Gururangan and Friedman 2002). Transient disruption of the BBB can be achieved with chemical agents including mannitol, prostaglandin, histamine, and bradykinin that then facilitate chemotherapy entry into the brain tumor (Gururangan and Friedman 2002). Recently, Labridimil (Cereport™), a bradykinin analogue, has been used as a BBB disrupting agent prior to carboplatin chemotherapy (Warren, Patel et al. 2001). However, preliminary trials using this combination have had disappointing results.

Convection-enhanced delivery is a recently described method of delivering large molecules via a micro infusion pump directly into the tumor using strategically placed catheters (Kunwar 2003; Sampson, Akabani et al. 2003). Using a pressure gradient, the solution containing the large molecules (typically a tumor toxin) penetrates directly through the tumor by convection and reaches several centimeters beyond the tumor (Gururangan and Friedman 2002). Toxins used have been fusion proteins made up of pseudomonas exotoxin and either Transforming growth factor or interleukin -13 (IL-13 PE38QQR) (Kunwar, Prados et al. 2007). The latter molecules are designed to target the cognate receptors expressed selectively on glioma cells and spare normal brain tissue. Once the glioma cells are targeted, the exotoxin is internalized and causes cytotoxicity (Kunwar, Prados et al. 2007) This strategy has undergone extensive testing in the clinic and has been proven to be reasonably safe (Kunwar, Prados et al. 2007). However, a recent phase III trial (PRECISE) comparing outcome of adults with recurrent GBM who received CED of IL-13PE38QQR with those who were treated with BCNU wafers showed no difference in outcome (Kunwar, Chang et al. 2010). The reasons for lack of better benefit from this promising strategy could be due to poor catheter placement, inadequate expression of target receptors in the tumor, or other unknown factors.

The problem of drug resistance to alkylating agents has been extensively addressed at Duke University Medical Center and is predominantly due to overexpression of alkyl guanine alkyltransferase (AGAT) in tumor cells. The cellular enzyme, O<sup>6</sup> guanine DNA alkyl transferase (AGAT), is responsible for removing the alkyl groups from the O<sup>6</sup> -position of deoxyguanosine and prevents cross-linking of DNA (Dolan and Pegg 1997). Increased expression of this DNA repair protein is the major mechanism of resistance to nitrosoureas and other alkylating agents (Dolan and Pegg 1997). O<sup>6</sup>-Benzylguanine (O<sup>6</sup>-BG) is a modulating agent that demonstrates high affinity for AGAT and effectively enhances nitrosourea activity *in vitro* and *in vivo* (Dolan and Pegg 1997). Friedman et al. at Duke University Medical Center conducted a phase I trial of O<sup>6</sup>-BG in patients with malignant glioma and determined the optimum biologic dose that depletes tumor tissue of AGAT to be 100 mg/m<sup>2</sup> (Friedman, McLendon et al. 1998). This dose of O<sup>6</sup>-BG has been subsequently used in combination with BCNU in a phase I trial in adults with recurrent HGG (Friedman, Pluda et al. 2000). The MTD of BCNU when used in this combination was 40 mg/m<sup>2</sup> given every 6 weeks. However, a phase II trial of this combination in adults with recurrent malignant glioma did not demonstrate any objective response, suggesting that elevation of

AGAT is not the only mechanism for treatment failure in these patients (Quinn, Dolan et al. 2001). Treatment failure in this setting could also be related to limitations of achieving adequate intratumor drug concentrations due to the lower dose of BCNU. For similar reasons, the combination of oral Temozolomide plus O<sup>6</sup>BG in the clinic has met with limited success in both adults and children with recurrent malignant glioma (Warren, Aikin et al. 2005; Quinn, Jiang et al. 2009). Since high concentration of a chemotherapeutic agent like BCNU can be achieved in tumor through intracavitary application with minimal systemic exposure, a recent phase II study at Duke University Medical center explored the use of O<sup>6</sup>BG prior to implantation of Gliadel™ wafers with some improvement in survival (Quinn, Jiang et al. 2009). Although defective mismatch repair (MMR) is a putative mechanism for resistance to methylating agents like Temozolomide, very few human tumors exhibit MMR deficiency (Pollack, Hamilton et al. 2010). Alternatively, excessive base excision repair (BER) mediated by overexpression of the enzyme Poly (ADP- Ribose) Polymerase (PARP) is another resistance mechanism than can cause failure of Temozolomide therapy irrespective of AGAT expression (Palma, Wang et al. 2009). ABT-888 (Olgaparib™, Abbott Laboratories, Abbott Park, Illinois, USA) is a potent PARP inhibitor that has shown effective PARP depletion in tumors and restores sensitivity to Temozolomide (Palma, Rodriguez et al. 2008; Palma, Wang et al. 2009). It is currently undergoing evaluation in combination with Temozolomide in adults with malignant glioma and children with recurrent brain tumors.

## 6.2 Molecular characteristics and specific biologic therapies

The molecular characteristics of pediatric HGG is quite different from its adult counterpart. Isocitrate dehydrogenase (IDH) 1 and 2 mutations that characterize secondary GBM in adults are almost unknown in pediatric tumors (Yan, Parsons et al. 2009; Paugh, Qu et al. 2010). Focal PDGFR amplification is a common event as is chromosome 1q gain (Paugh, Qu et al. 2010). However, EGFR amplification, EGFR vIII mutation, and PTEN loss are less common (Bax, Gaspar et al. 2009; Paugh, Qu et al. 2010). Some of these molecular markers of disease have been chosen as targets for inhibition using small molecule protein kinase inhibitors including ZD1839 (Iressa™, Astra Zeneca Pharmaceuticals, New Jersey, USA) targeting EGFR and STI571 (Gleevec™, Novartis Pharmaceuticals, USA) the PDGF receptor (Pollack, Jakacki et al. 2007). It is likely that these small molecule inhibitors might have some indirect negative effect on tumor angiogenesis by affecting downstream targets that are involved in new blood vessel formation (Folkman 2007). Phase I trials of these two drugs have been completed in children with newly diagnosed and recurrent HGG (including diffuse pontine glioma) through the PBTC but no specific efficacy was observed with either drug (Pollack, Jakacki et al. 2007). Bevacizumab, a humanized monoclonal antibody against VEGF, recently gained approval by the FDA for treatment of GBM in adults on the basis of impressive responses and improvement in overall survival noted in adults with recurrent GBM treated with Bevacizumab alone or Bevacizumab plus CPT-11 (Cohen, Shen et al. 2009; Friedman, Prados et al. 2009). A PBTC phase II trial of this combination in children with recurrent malignant glioma and diffuse pontine glioma however failed to show efficacy in either tumor type (Gururangan, Chi et al. 2010). The reasons for the lack of efficacy of Bevacizumab in pediatric malignant gliomas are unknown. It is possible that VEGF is not the prime mediator of angiogenesis in these tumors. It is also likely that angiogenesis inhibition might be better if it is used in newly diagnosed patients and in the setting of minimal disease following initial surgical resection. The Children's Oncology Group is currently doing a phase III study

exploring the efficacy of Bevacizumab, vorinostat (Zolinza™, Merck Pharmaceuticals, USA), a histone deacetylase inhibitor, or Temozolomide concurrently with radiotherapy followed by Bevacizumab plus Temozolomide for 6 months in children newly diagnosed malignant glioma (Fouladi M., Cincinnati, OH; 2011; personal communication). Since it is unlikely that these drugs will be efficacious as single agents, future studies will address whether small molecule protein kinase inhibitors can work additively or synergistically with cytotoxics, other kinase inhibitors, and anti-angiogenic agents.

## 7. Ependymoma

Ependymomas are the third most common CNS neoplasm and occur in about 10% of all children with brain tumors. The tumor typically arises from the neuroepithelial cells lining the ventricles. The incidence of ependymomas is inversely related to age, with the peak incidence occurring in children less than 6 years of age (Allen, Siffert et al. 1998). Over 90% of all childhood ependymomas are intracranial in location and less than 10% occur in the spinal cord. Of the intracranial tumors, 66% are infratentorial (Figure 5) and 34% supratentorial in location. No specific risk factors are associated with ependymomas except for the increased frequency of spinal cord ependymomas in patients with neurofibromatosis type II. Ependymomas are soft and friable and grayish-red in appearance. Microscopically, they are extremely cellular with the tumor cells forming pseudo-rosettes around blood vessels. Specific histologic variants include the clear-cell, papillary, myxopapillary, and anaplastic (WHO grade III). About 20% of patients with ependymomas have metastatic spread of disease either at the time of diagnosis or relapse.

### 7.1 Treatment

The current standard of care for patients with non-metastatic ependymoma includes adequate surgical resection followed by focal radiotherapy to the tumor site. Patients who present with metastatic disease would require neuraxis irradiation as well. Complete surgical resection alone could cure a proportion of patients with grade II ependymoma arising in the cerebral hemispheres (Awaad, Allen et al. 1996). Extent of surgical resection is directly correlated with outcome and hence a complete resection should be attempted either at diagnosis or following initial cytotoxic therapy. Young children with disease confined to the infratentorial compartment especially in the cerebello-pontine angle are at high risk for post-surgical complications as the tumor encompasses blood vessels and cranial nerves in this region (Morris, Li et al. 2009). Aggressive surgery in inexperienced hands can result in severe dysphagia, vocal cord paralysis, and ataxia but is usually associated with neurologic recovery over a period of several months (Morris, Li et al. 2009). Focal radiotherapy is usually directed at the tumor bed (gross tumor volume, GTV) plus a 1-cm margin (clinical target volume, CTV) with additional corrections for day to day variations in patient positioning (planned target volume, PTV) (Merchant, Li et al. 2009). The dose of radiotherapy should be between 45-60 Gy with conventional fractionation and administered over 6 weeks (Merchant, Li et al. 2009). Proton, intensity-modulated, or 3-D conformal radiotherapy is being increasingly used to avoid injury to normal structures including hearing and cognition. Since the majority of recurrences are local, there is no specific advantage to using craniospinal radiotherapy in patients with non-metastatic disease including those with anaplastic histology (Taylor 2004). The use of

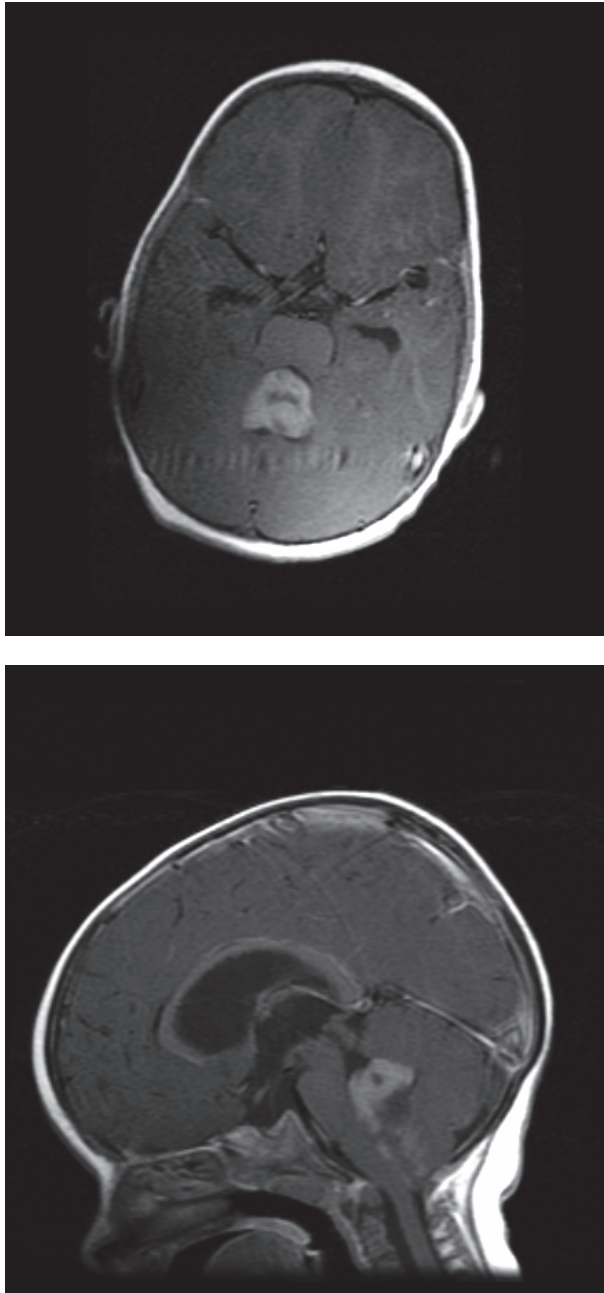


Fig. 5. T-1 weighted axial and sagittal images of the brain following gadolinium administration in a 15 month old boy showing a uniformly enhancing lesion within the fourth ventricle that on histology was found to be a well-differentiated ependymoma.

chemotherapy has been found to be ineffective in patients with ependymomas and might be explained partly by the over-expression of p-glycoprotein in over 80% of these tumors (Chou, Barquin et al. 1996; Bouffet and Foreman 1999). Currently, this modality is used mainly in infants (children < 4 years of age) in whom even focal radiotherapy to areas of the brain can have devastating consequences on neuro- cognitive function (Duffner, Horowitz et al. 1993). Platinum compounds (cisplatin or carboplatin) and cyclophosphamide are the most commonly used agents against ependymoma (Duffner, Horowitz et al. 1993; Bouffet and Foreman 1999). Although objective responses have been observed in some studies, outcome for those who receive chemotherapy plus irradiation is similar to those following radiotherapy alone. It is possible that chemotherapy can be used upfront in some children to allow for more radical second look surgery following tumor shrinkage. Survival for children with ependymoma is between 40-77% at 5 years post-treatment. Outcome for children with recurrent tumors remains poor despite salvage chemotherapy (Bouffet, Capra et al. 2009).

The most important prognostic factor in children with ependymoma is the extent of surgical resection. Patients who have inadequate tumor resection experience a worse outcome. Other poor prognostic factors include young age, infratentorial location of tumor, and avoidance of radiotherapy (Kilday, Rahman et al. 2009). Anaplastic tumors have been found to confer an independently worse prognosis in a recent meta-analysis of over 2000 patients (Rodriguez, Scheithauer et al. 2008) but not in other studies (Messahel, Ashley et al. 2009). It is possible that the impact of histopathology on prognosis might be dependent on the inter-observer differences in assessment of anaplasia amongst neuropathologists (Puget, Grill et al. 2009).

## 7.2 Molecular characteristics

It is also worth noting that about 50% of patients relapse after focal radiotherapy for localized grade II ependymoma following a gross total resection (Kilday, Rahman et al. 2009). It is clear that tumor biology plays an important part in determining prognosis in such apparently low-risk patients. Recent studies have noted that over-expression of ERBB-2/4 and nucleolin, gain of chromosome 1q, and homozygous deletion of the CDKN2A gene are associated with a worse prognosis independent of clinical factors (Gilbertson, Bentley et al. 2002; Kilday, Rahman et al. 2009; Puget, Grill et al. 2009). On the other hand, gains of chromosomes 9, 15q, and 18, and loss of chromosome 6 were associated with excellent survival. Such molecular alterations need to be validated in larger studies and might serve as targets for future novel biologic therapies and also facilitate identification of a group of patients who have a good prognosis who could be successfully managed with conservative treatment

## 8. Germ cell tumors

CNS germ cell tumors in children are rare and constitute about 2-5% of all pediatric brain tumors. Intracranial germ cell tumors are typically classified as either germinomas or non-germinomatous germ cell tumors (NGGCT). The former includes pure germinomas and germinomas with syncytiotrophoblastic cells and the latter yolk-sac tumors (secreting alpha-fetoprotein, AFP), choriocarcinomas (secreting beta subunit of human chorionic gonadotropins,  $\beta$ -HCG), embryonal carcinoma (secreting carcinoembryonic antigen, CEA), teratomas (mature and immature), and mixed germ cell tumors (including varying



components of germinoma and NGGCT) (Rosenblum, Matsutani et al. 2000). The incidence of these tumors is higher in the Asian population (15-18% of all childhood brain tumors) compared to western countries (Rosenblum, Matsutani et al. 2000). The peak age of onset is 10-12 years of age and occasionally in the second to third decade of life (Rosenblum, Matsutani et al. 2000). There is a sex predilection for tumor site and histologic type with female predominance for tumors that originate in the suprasellar region and NGGCT. CNS germ cell tumors occur commonly in the pineal region (45%), suprasellar region (35%), both (10%), and other sites including intraventricular, basal ganglia, thalamus, medulla oblongata, and cerebral hemispheres (10%) (Rosenblum, Matsutani et al. 2000). Presentation of bifocal tumors is not uncommon and represents development of tumors in two independent sites and not metastasis (Figure 6). Presenting symptoms in patients with germ cell tumors depend on the location of tumor. Suprasellar germ cell tumors can present with isolated diabetes insipidus caused by pituitary stalk thickening, hydrocephalus, visual disturbances, delayed growth, or precocious puberty (Diez, Balmaceda et al. 1999; Rosenblum, Matsutani et al. 2000). Pineal tumors can cause hydrocephalus due to early compression of the aqueduct and paralysis of upward gaze and convergence due to pressure on the tectum of the mid-brain (Parinaud's syndrome). Leptomeningeal seeding occurs in about 10-15% of patients and can cause symptoms of spinal cord compression due to block disease (Diez, Balmaceda et al. 1999). It is important to remember that patients with germinoma can have isolated cerebrospinal fluid positivity for malignant cells without any evidence of spinal cord dissemination on neuroimaging.

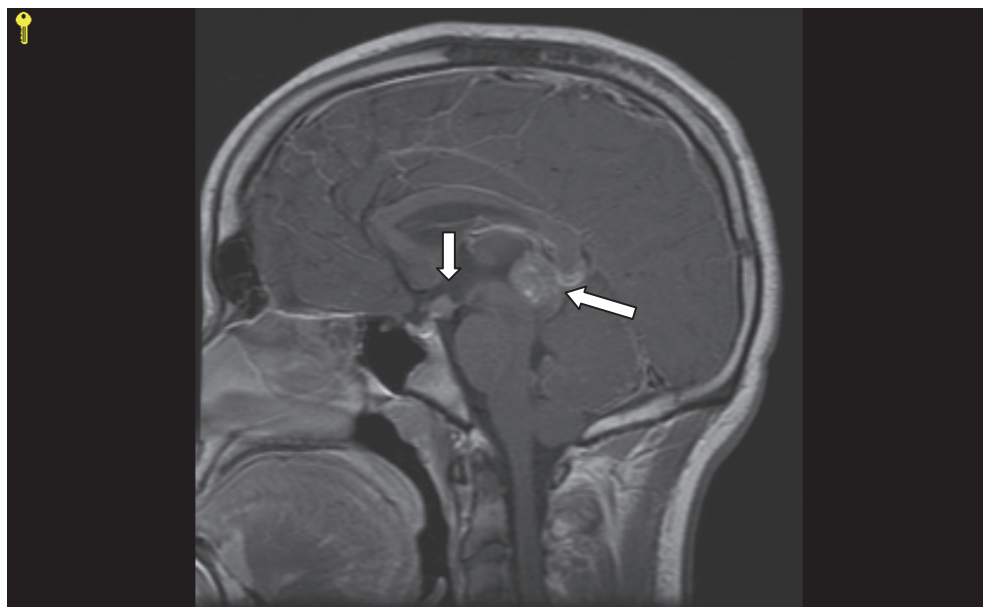


Fig. 6. T-1 weighted sagittal image of the brain following gadolinium in an 18-year old black male showing enhancing lesions in the suprasellar and pineal region (white arrows) that was found to be a pure germinoma on biopsy of the pineal mass

Histologically, germinoma consists of a uniform sheet of cells that have vesicular nuclei, prominent nucleoli, and a glycogen-rich cytoplasm. Additional features include lymphocytic infiltration, and scattered syncytiotrophoblastic cells (Rosenblum, Matsutani et al. 2000). Teratomas recapitulate somatic development from the three embryonic germ layers with mature forms demonstrating adult tissue including cartilage, bone, and teeth and the immature variety composed of primitive neuro-epithelial cells arranged in an abortive formation of neural tubes (Rosenblum, Matsutani et al. 2000). Yolk-sac tumors are composed of primitive appearing epithelial cells in a loose myxoid matrix and eosinophilic hyaline globules immunoreactive for AFP (Rosenblum, Matsutani et al. 2000). The histologic diagnosis of a choriocarcinoma requires the identification of cytotrophoblastic and syncytiotrophoblastic giant cells that are positive for beta-HCG and human placental lactogen (Rosenblum, Matsutani et al. 2000). Embryonal carcinoma consists of large cells that proliferate in nests and sheets, forming abortive papillae and embryoid bodies with germinal discs and miniature amniotic cavities, large nucleoli, and high mitotic index. The cells are positive for cytokeratin and human placental alkaline phosphatase (Rosenblum, Matsutani et al. 2000).

In addition to neuro-imaging studies and biopsy confirmation, patients with intracranial germ cell tumors usually have serum and CSF estimated for protein markers including AFP and beta-HCG, for diagnosis and assessment of tumor response (Gregory and Finlay 1999). If the markers are elevated in CSF samples, diagnosis can be made and treatment initiated without the need for a biopsy (Gregory and Finlay 1999).

### 8.1 Treatment

The standard treatment for patients with pure germinoma is radiotherapy (Diez, Balmaceda et al. 1999). This tumor is exquisitely sensitive to irradiation and excellent survival has been obtained with this modality alone. Germinomas typically spread via the ventricular wall and it is extremely important to include the whole ventricular volume (radiotherapy dose up to 24 Gy) in addition to the primary site (up to 45 Gy) in the radiation field for patients with localized disease and the craniospinal axis (up to 24 Gy) in those with metastatic disease (Diez, Balmaceda et al. 1999). The use of 3-D conformal radiotherapy technique can minimize long-term side effects of irradiation (Diez, Balmaceda et al. 1999). Using this strategy, cure can be achieved in over 90% of these patients (Diez, Balmaceda et al. 1999). Germinoma is very responsive to chemotherapy as well with excellent objective responses (>90%) reported with single agent cyclophosphamide or carboplatin (Diez, Balmaceda et al. 1999). In recent years there have been several clinical trials in the United States, Japan, and Europe that have attempted to use chemotherapy combinations (carboplatin + etoposide, carboplatin + etoposide + bleomycin  $\pm$  cyclophosphamide, or ifosfamide + carboplatin + etoposide) with the aim of avoiding or reducing the dose and extent of radiotherapy and its associated neuro-psychologic sequelae on the brain. This strategy has been reasonably successful although the progression-free survival with chemotherapy alone is only 50-60% (Diez, Balmaceda et al. 1999). However, most of the patients who fail chemotherapy can be salvaged with radiotherapy underscoring the importance of the latter modality in the cure of patients with germinoma. While some series have indicated that patients with germinoma with beta-HCG elevation up to 50 I.U have an inferior outcome, recent reports have demonstrated that with adequate doses of radiotherapy these patients do just as well as those with pure germinoma (Shibamoto, Takahashi et al. 1997). It must be emphasized that the use of chemotherapy alone in patients with germinoma is effective in only a proportion

of patients and is not the standard of care (Diez, Balmaceda et al. 1999). Only large randomized trials of standard radiotherapy alone *vs.* chemotherapy plus reduced dose irradiation will clearly establish the efficacy of chemotherapy in safely allowing dose and field reductions in radiotherapy and whether patients who receive the chemotherapy plus reduced dose irradiation will have fewer neuro-cognitive deficits.

Patients with NGGCT do very poorly with radiotherapy alone with only 20-60% surviving progression-free with this modality alone (Diez, Balmaceda et al. 1999). The addition of chemotherapy as used for patients with germinoma has improved the survival to around 45 - 80% (Diez, Balmaceda et al. 1999). Patients with recurrent germ cell tumors have a poor prognosis. A proportion of patients with chemo sensitive disease have been salvaged with high-dose chemotherapy and autologous stem cell rescue (Modak, Gardner et al. 1997; Tada, Takizawa et al. 1999).

## 9. Choroid plexus tumors

Choroid plexus tumors are rare in children and comprise 2-4% of brain tumors in this population (Greenberg 1999) Choroid plexus tumors can either be a choroid plexus papilloma (60% - 80%) or carcinoma (20% -40%).(Greenberg 1999). The predominant location of these tumors is in the lateral ventricles and less commonly in the III and IV ventricles. Choroid plexus tumors that occur in the lateral ventricles are invariably found in infants or young children with a median age of diagnosis of 24 months (Greenberg 1999). These tumors typically arise from the choroid plexus epithelium and are extremely vascular. The histologic findings in a choroid plexus papilloma include a papillomatous component lined by single layer of columnar or cuboidal epithelium and a central core of vascular stromal tissue and the absence of mitosis and normal tissue invasion. In contrast, choroid plexus carcinoma consists of sheets of cells without papillary formation, nuclear atypia and pleomorphism, frequent mitoses, and invasion of sub ependymal brain tissue. Children with choroid plexus tumors frequently present with hydrocephalus due to mechanical obstruction and/or CSF overproduction (Figure 7) (Greenberg 1999). Up to 30% of children present with metastatic disease at diagnosis.

### 9.1 Treatment

Surgical resection of choroid plexus papilloma frequently results in long-term cure (Greenberg 1999). The management of choroid plexus carcinoma is more complex. While adequate surgical resection is the most important determinant of long-term disease control, tumors can be extremely large and vascular at diagnosis precluding adequate resection without causing excessive blood loss or neurologic damage (Greenberg 1999). In these situations, it might be more beneficial to confirm the diagnosis on a limited stereotactic biopsy and treat patients with chemotherapy prior to definitive surgical resection (Greenberg 1999). The standard chemotherapy regimen used in infants and young includes vincristine, cisplatin/carboplatin, cyclophosphamide, and etoposide and can be used in a neoadjuvant or adjuvant setting (Greenberg 1999).

The efficacy of post-operative radiotherapy in patients with choroid plexus carcinoma is unclear (Greenberg 1999; Fitzpatrick, Aronson et al. 2002). The need for craniospinal irradiation for this disease with a high predilection for neuraxis dissemination argues against the use of this modality in young children due to the risk of neuro-cognitive deficits

and endocrine sequelae. In general, it appears that the degree of surgical resection seems to determine the outcome of patients with choroid plexus carcinoma irrespective of the adjuvant chemo/radiotherapy received post-surgery (Fitzpatrick, Aronson et al. 2002)

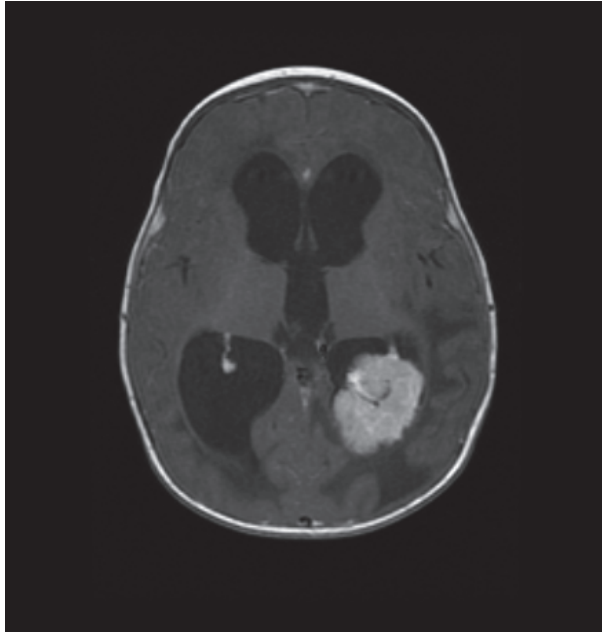


Fig. 7. T-1 weighted axial image of the brain following gadolinium in a 4-month old male showing a large uniformly enhancing lesion in the left occipital horn that on biopsy was found to be a choroid plexus papilloma with some features of anaplasia

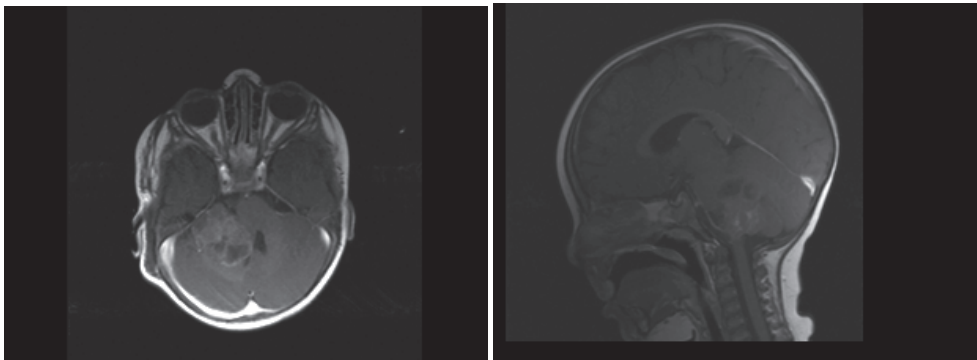


Fig. 8. T-1 weighted axial and sagittal images following gadolinium contrast in a 4 month old white male showing a heterogeneously enhancing cystic solid mass in the region of the right foramen of Lushka and cerebello-pontine angle causing mass effect on the brain stem and IV ventricle. Tumor resection revealed an atypical teratoid rhabdoid tumor

## 10. Atypical teratoid rhabdoid tumors

Atypical Teratoid Rhabdoid tumor (ATRT) of the CNS is a rare embryonal tumor that occurs predominantly in children less than 5 years of age (Rorke, Packer et al. 1996; Oka and Scheithauer 1999). Originally described in 1987, this tumor, in the past, had been mistaken for and treated as a PNET of the nervous system (Packer, Biegel et al. 2002). In recent years, there has been an explosion in knowledge regarding criteria for histologic diagnosis and molecular characteristics of the tumor (Packer, Biegel et al. 2002). ATRT constitutes 1-2% of CNS malignancies in children with a reported incidence of 1.38 per 100,000 children/year (Woehrer, Slavic et al. 2010). The tumors can occasionally be familial due to a rhabdoid tumor predisposition syndrome (Janson, Nedzi et al. 2006). The median age at diagnosis is 2.1 years and 90% of patients are less than 5 years at diagnosis (Oka and Scheithauer 1999). Less than 10% of patients are in older children up to the ages of 10-15 years (Oka and Scheithauer 1999) (figure 8). The commonest location is in the posterior fossa in over 60% of cases; other sites include the cerebral hemispheres, suprasellar region, third ventricle, pineal region, and spinal cord (Rorke, Packer et al. 1996; Oka and Scheithauer 1999). There is a high predilection for CSF dissemination in about 30% of cases (Oka and Scheithauer 1999). Histologically the tumor consists of sheets of rhabdoid cells, areas that resemble classic PNET along with mesenchymal and epithelial differentiation (Rorke, Packer et al. 1996). The rhabdoid cell has an eccentric round nucleus, prominent nucleolus, and a plump cell body. Immunohistochemical staining is positive for vimentin, cytokeratin, and epithelial membrane antigen. Staining for INI-1 gene product can be done using the BAF-47 antibody and absence of INI-1 expression in the nucleus is confirmatory for the presence of ATRT.

### 10.1 Treatment

Treatment of ATRT has traditionally been surgical resection followed by intensive chemotherapy and irradiation. However, most infants with ATRT have been reported to succumb to the disease with progression-free survival of < 20% despite treatment. However, a recent study from Dana Farber Cancer Institute in Boston, MA, has reported a more favorable outcome of 53% 2-year PFS with intensive chemotherapy plus irradiation in young children with ATRT (Chi, Zimmerman et al. 2009). Older patients with ATRT seem to do better than infants with the same intensive multimodality treatment (Tekautz, Fuller et al. 2005).

### 10.2 Molecular characteristics and biologic therapies

The molecular characteristic of this tumor has been well delineated in recent years. The tumor typically demonstrates monosomy of chromosome 22 that results in deletion of the tumor suppressor gene HSN5-*INI1* located on chromosome 22q11.2 (Biegel, Kalpana et al. 2002). Robust pre-clinical models have clearly demonstrated that deletion of the HSN5-*INI1* gene is directly responsible for tumor development and restoration of the gene in the tumor cells can cause tumor regression. *INI1* mediates tumor suppression by recruiting HDAC to the cyclin D-1 promoter and preventing cyclin D1 expression (Tsikitis, Zhang et al. 2005). Cyclin D-1 overexpression is commonly seen in CNS ATRTs and the combination of Fenretinide plus Tamoxifen has been shown to synergistically down regulate cyclin D-1 expression and cause tumor regression in animals bearing ATRT xenografts (Alarcon-Vargas, Zhang et al. 2006). It remains to be seen if this strategy would work in children with CNS ATRT.

## 11. References

- Alarcon-Vargas, D., Z. Zhang, et al. (2006). "Targeting cyclin D1, a downstream effector of INI1/hSNF5, in rhabdoid tumors." *Oncogene* 25(5): 722-734.
- Allen, J. C., J. Siffert, et al. (1998). "Clinical manifestations of childhood ependymoma: a multitude of syndromes." *Pediatr Neurosurg* 28(1): 49-55.
- Ater, J., E. Holmes, et al. (2008). "Results of COG Protocol A9952: A Randomized Phase 3 study of two chemotherapy regimens for incompletely resected low-grade glioma in young children (LGG 18)." *Neuro-oncology*: 451.
- Awaad, Y. M., J. C. Allen, et al. (1996). "Deferring adjuvant therapy for totally resected intracranial ependymoma." *Pediatric neurology* 14(3): 216-219.
- Bai, R., I. M. Siu, et al. (2010). "Evaluation of retinoic acid therapy for OTX2-positive medulloblastomas." *Neuro-oncology*.
- Baldwin, R. T. and S. Preston-Martin (2004). "Epidemiology of brain tumors in childhood--a review." *Toxicology and applied pharmacology* 199(2): 118-131.
- Bax, D. A., N. Gaspar, et al. (2009). "EGFRvIII deletion mutations in pediatric high-grade glioma and response to targeted therapy in pediatric glioma cell lines." *Clinical cancer research : an official journal of the American Association for Cancer Research* 15(18): 5753-5761.
- Berger, M. S., M. S. Edwards, et al. (1983). "Primary cerebral neuroblastoma. Long-term follow-up review and therapeutic guidelines." *Journal of neurosurgery* 59(3): 418-423.
- Biegel, J. A., G. Kalpana, et al. (2002). "The role of INI1 and the SWI/SNF complex in the development of rhabdoid tumors: meeting summary from the workshop on childhood atypical teratoid/rhabdoid tumors." *Cancer research* 62(1): 323-328.
- Bleyer, W. A. (1999). "Epidemiologic impact of children with brain tumors." *Childs Nerv Syst* 15(11-12): 758-763.
- Boehm, T., J. Folkman, et al. (1997). "Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance." *Nature* 390(6658): 404-407.
- Bouffet, E., M. Capra, et al. (2009). "Salvage chemotherapy for metastatic and recurrent ependymoma of childhood." *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery* 25(10): 1293-1301.
- Bouffet, E. and N. Foreman (1999). "Chemotherapy for intracranial ependymomas." *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery* 15(10): 563-570.
- Bouffet, E., R. Jakacki, et al. (2008). "Phase II study of weekly vinblastine in recurrent/refractory pediatric low-grade gliomas (abstr# LGG13)." *Neuro-Oncology*: 450.
- Bredel, M. (2001). "Anticancer drug resistance in primary human brain tumors." *Brain Res Brain Res Rev* 35(2): 161-204.
- Brem, H., S. Piantadosi, et al. (1995). "Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group." *Lancet* 345(8956): 1008-1012.
- Burger, P. C., B. W. Scheithauer, et al. (2000). *Pilocytic Astrocytoma. Pathology & Genetics: Tumors of the Nervous System*. P. Kleihues and W. K. Cavenee. Lyon, IARC Press: 45-51.

- CBTRUS. (2009). "CBTRUS (2009). CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004-2005. Source: Central Brain Tumor Registry of the United States, Hinsdale, IL." from [www.cbtrus.org](http://www.cbtrus.org).
- Chi, S. N., M. A. Zimmerman, et al. (2009). "Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 27(3): 385-389.
- Chintagumpala, M., T. Hassall, et al. (2009). "A pilot study of risk-adapted radiotherapy and chemotherapy in patients with supratentorial PNET." *Neuro-oncology* 11(1): 33-40.
- Chou, P. M., N. Barquin, et al. (1996). "Ependymomas in children express the multidrug resistance gene: immunohistochemical and molecular biologic study." *Pediatr Pathol Lab Med* 16(4): 551-561.
- Cohen, K. J., R. L. Heideman, et al. (2011). "Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group." *Neuro-oncology* 13(4): 410-416.
- Cohen, K. J., I. F. Pollack, et al. (2011). "Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group." *Neuro-oncology* 13(3): 317-323.
- Cohen, M. H., J. R. Johnson, et al. (2005). "Food and Drug Administration Drug approval summary: temozolomide plus radiation therapy for the treatment of newly diagnosed glioblastoma multiforme." *Clinical cancer research : an official journal of the American Association for Cancer Research* 11(19 Pt 1): 6767-6771.
- Cohen, M. H., Y. L. Shen, et al. (2009). "FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme." *The oncologist* 14(11): 1131-1138.
- Dai, A. I., J. W. Backstrom, et al. (2003). "Supratentorial primitive neuroectodermal tumors of infancy: clinical and radiologic findings." *Pediatric neurology* 29(5): 430-434.
- De Vos, M., B. E. Hayward, et al. (2006). "PMS2 mutations in childhood cancer." *Journal of the National Cancer Institute* 98(5): 358-361.
- Di, C., S. Liao, et al. (2005). "Identification of OTX2 as a medulloblastoma oncogene whose product can be targeted by all-trans retinoic acid." *Cancer research* 65(3): 919-924.
- Diez, B., C. Balmaceda, et al. (1999). "Germ cell tumors of the CNS in children: recent advances in therapy." *Childs Nerv Syst* 15(10): 578-585.
- Dolan, M. E. and A. E. Pegg (1997). "O6-benzylguanine and its role in chemotherapy." *Clin Cancer Res* 3(6): 837-847.
- Dougherty, M. J., M. Santi, et al. (2010). "Activating mutations in BRAF characterize a spectrum of pediatric low-grade gliomas." *Neuro-oncology*.
- Duffner, P. K., M. E. Horowitz, et al. (1993). "Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors." *N Engl J Med* 328(24): 1725-1731.
- Dunkel, I. J., J. M. Boyett, et al. (1998). "High-dose carboplatin, thiotepa, and etoposide with autologous stem- cell rescue for patients with recurrent medulloblastoma. Children's Cancer Group." *J Clin Oncol* 16(1): 222-228.
- Engelhard, H. H. (2000). *Brain Tumors and the blood brain barrier. Neuro-Oncology, The essentials.* M. S. Berger and M. Bernstein. New York, NY, Thieme Publishers.

- Englehard, H. H. and D. G. Groothuis (1999). The Blood-Brain barrier: Structure, Function, and response to neoplasia. The Gliomas. M. S. Berger and C. B. Wilson. Philadelphia, PA, W.B. Saunders Company: 115-120.
- Finlay, J. L., J. M. Boyett, et al. (1995). "Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs- in-1-day regimen. Childrens Cancer Group." *J Clin Oncol* 13(1): 112-123.
- Fitzpatrick, L. K., L. J. Aronson, et al. (2002). "Is there a requirement for adjuvant therapy for choroid plexus carcinoma that has been completely resected?" *J Neurooncol* 57(2): 123-126.
- Folkman, J. (2007). "Angiogenesis: an organizing principle for drug discovery?" *Nature reviews. Drug discovery* 6(4): 273-286.
- Freeman, C. R., R. E. Taylor, et al. (2002). "Radiotherapy for medulloblastoma in children: a perspective on current international clinical research efforts." *Med Pediatr Oncol* 39(2): 99-108.
- Friedman, H. S., J. P. Krischer, et al. (1992). "Treatment of children with progressive or recurrent brain tumors with carboplatin or iproplatin: a Pediatric Oncology Group randomized phase II study." *J Clin Oncol* 10(2): 249-256.
- Friedman, H. S., R. E. McLendon, et al. (1998). "DNA mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma." *J Clin Oncol* 16(12): 3851-3857.
- Friedman, H. S., J. Pluda, et al. (2000). "Phase I trial of carmustine plus O6-benzylguanine for patients with recurrent or progressive malignant glioma." *J Clin Oncol* 18(20): 3522-3528.
- Friedman, H. S., M. D. Prados, et al. (2009). "Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 27(28): 4733-4740.
- Gajjar, A., M. Chintagumpala, et al. (2006). "Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial." *Lancet Oncol* 7(10): 813-820.
- Giangaspero, F., S. H. Bigner, et al. (2000). Medulloblastoma. Pathology & Genetics Tumors of the Nervous System. P. Kleihues and W. K. Cavenee. Lyon, IARC Press: 129-137.
- Giangaspero, F., G. Perilongo, et al. (1999). "Medulloblastoma with extensive nodularity: a variant with favorable prognosis." *J Neurosurg* 91(6): 971-977.
- Gilbert, M. R., H. S. Friedman, et al. (2002). "A phase II study of temozolomide in patients with newly diagnosed supratentorial malignant glioma before radiation therapy." *Neuro-oncol* 4(4): 261-267.
- Gilbertson, R. J. (2004). "Medulloblastoma: signalling a change in treatment." *Lancet Oncol* 5(4): 209-218.
- Gilbertson, R. J., L. Bentley, et al. (2002). "ERBB receptor signaling promotes ependymoma cell proliferation and represents a potential novel therapeutic target for this disease." *Clin Cancer Res* 8(10): 3054-3064.
- Greenberg, M. L. (1999). "Chemotherapy of choroid plexus carcinoma." *Childs Nerv Syst* 15(10): 571-577.
- Gregory, J. J., Jr. and J. L. Finlay (1999). "Alpha-fetoprotein and beta-human chorionic gonadotropin: their clinical significance as tumour markers." *Drugs* 57(4): 463-467.



- Groothuis, D. R. (2000). "The blood-brain and blood-tumor barriers: a review of strategies for increasing drug delivery." *Neuro-oncol* 2(1): 45-59.
- Gurney, J. G., M. A. Smith, et al. (1999). *CNS and miscellaneous intracranial and intraspinal neoplasms*. Bethesda, MD, National Cancer Institute.
- Guruangan, S., I. J. Dunkel, et al. (1998). "Myeloablative chemotherapy with autologous bone marrow rescue in young children with recurrent malignant brain tumors." *J Clin Oncol* 16(7): 2486-2493.
- Gururangan, S., C. M. Cavazos, et al. (2002). "Phase II study of carboplatin in children with progressive low-grade gliomas." *J Clin Oncol* 20(13): 2951-2958.
- Gururangan, S., S. N. Chi, et al. (2010). "Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 28(18): 3069-3075.
- Gururangan, S., T. Driscoll, et al. (2008). "A Retrospective Study of High-dose Chemotherapy (HDC) With Autologous Stem Cell Rescue (ASCR) in Children and Adults with Supratentorial Primitive Neuroectodermal Tumors (S-PNET): The Duke Experience 1991-2004 (Abstr# PNET-MED 3)." *Neuro-oncology*: 476.
- Gururangan, S., M. J. Fisher, et al. (2007). "Temozolomide in children with progressive low-grade glioma." *Neuro-oncology* 9(2): 161-168.
- Gururangan, S. and H. S. Friedman (2002). "Innovations in design and delivery of chemotherapy for brain tumors." *Neuroimaging Clin N Am* 12(4): 583-597.
- Gururangan, S. and H. S. Friedman (2004). "Recent advances in the treatment of pediatric brain tumors." *Oncology* 18(13): 1649-1661; discussion 1662, 1665-1646, 1668.
- Gururangan, S., J. Krauser, et al. (2008). "Efficacy of high-dose chemotherapy or standard salvage therapy in patients with recurrent medulloblastoma." *Neuro Oncol* 10(5): 745-751.
- Gururangan, S., C. McLaughlin, et al. (2003). "High-dose chemotherapy with autologous stem-cell rescue in children and adults with newly diagnosed pineoblastomas." *J Clin Oncol* 21(11): 2187-2191.
- Hader, W. J., K. Drovini-Zis, et al. (2003). "Primitive neuroectodermal tumors in the central nervous system following cranial irradiation: a report of four cases." *Cancer* 97(4): 1072-1076.
- Hallahan, A. R., J. I. Pritchard, et al. (2003). "BMP-2 mediates retinoid-induced apoptosis in medulloblastoma cells through a paracrine effect." *Nat Med* 9(8): 1033-1038.
- Hanahan, D. and J. Folkman (1996). "Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis." *Cell* 86(3): 353-364.
- Huang, H., J. Held-Feindt, et al. (2005). "Expression of VEGF and its receptors in different brain tumors." *Neurological research* 27(4): 371-377.
- Jakacki, R. I. (1999). "Pineal and nonpineal supratentorial primitive neuroectodermal tumors." *Childs Nerv Syst* 15(10): 586-591.
- Janson, K., L. A. Nedzi, et al. (2006). "Predisposition to atypical teratoid/rhabdoid tumor due to an inherited INI1 mutation." *Pediatric blood & cancer* 47(3): 279-284.
- Jennings, M. T., N. Slatkin, et al. (1993). "Neoplastic meningitis as the presentation of occult primitive neuroectodermal tumors." *Journal of child neurology* 8(4): 306-312.
- Kerbel, R. S. (2008). "Tumor angiogenesis." *The New England journal of medicine* 358(19): 2039-2049.

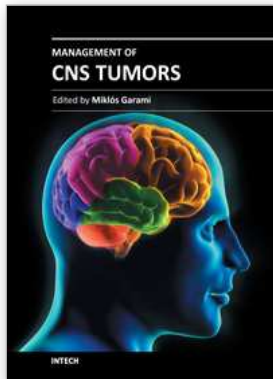
- Kerbel, R. S., A. Vioria-Petit, et al. (2000). "'Accidental' anti-angiogenic drugs. anti-oncogene directed signal transduction inhibitors and conventional chemotherapeutic agents as examples." *Eur J Cancer* 36(10): 1248-1257.
- Kilday, J. P., R. Rahman, et al. (2009). "Pediatric ependymoma: biological perspectives." *Molecular cancer research : MCR* 7(6): 765-786.
- Kim, K. J., B. Li, et al. (1993). "Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo." *Nature* 362(6423): 841-844.
- Kolb, E. A., R. Gorlick, et al. (2010). "Initial testing (stage 1) of AZD6244 (ARRY-142886) by the Pediatric Preclinical Testing Program." *Pediatric blood & cancer* 55(4): 668-677.
- Kunwar, S. (2003). "Convection enhanced delivery of IL13-PE38QQR for treatment of recurrent malignant glioma: presentation of interim findings from ongoing phase 1 studies." *Acta Neurochir Suppl* 88: 105-111.
- Kunwar, S., S. Chang, et al. (2010). "Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma." *Neuro-oncology* 12(8): 871-881.
- Kunwar, S., M. D. Prados, et al. (2007). "Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 25(7): 837-844.
- Kuo, D. J., H. L. Weiner, et al. (2003). "Temozolomide is active in childhood, progressive, unresectable, low-grade gliomas." *J Pediatr Hematol Oncol* 25(5): 372-378.
- Lashford, L. S., P. Thiesse, et al. (2002). "Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study." *J Clin Oncol* 20(24): 4684-4691.
- Leonard, J. R., D. X. Cai, et al. (2001). "Large cell/anaplastic medulloblastomas and medulloblastomas: clinicopathological and genetic features." *J Neurosurg* 95: 82-88.
- Leung, S. Y., A. S. Chan, et al. (1997). "Expression of vascular endothelial growth factor and its receptors in pilocytic astrocytoma." *The American journal of surgical pathology* 21(8): 941-950.
- Li, M. H., E. Bouffet, et al. (2005). "Molecular genetics of supratentorial primitive neuroectodermal tumors and pineoblastoma." *Neurosurgical focus* 19(5): E3.
- Li, V. W., R. D. Folkerth, et al. (1994). "Microvessel count and cerebrospinal fluid basic fibroblast growth factor in children with brain tumours." *Lancet* 344(8915): 82-86.
- Louis, D. N., H. Ohgaki, et al. (2007). "The 2007 WHO classification of tumours of the central nervous system." *Acta neuropathologica* 114(2): 97-109.
- MacDonald, T. J., K. M. Brown, et al. (2001). "Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease." *Nat Genet* 29(2): 143-152.
- Mandell, L. R., R. Kadota, et al. (1999). "There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy." *Int J Radiat Oncol Biol Phys* 43(5): 959-964.

- Mason, W. P., A. Grovas, et al. (1998). "Intensive chemotherapy and bone marrow rescue for young children with newly diagnosed malignant brain tumors." *J Clin Oncol* 16(1): 210-221.
- McLendon, R. E., D. S. Enterline, et al. (1998). Tumors of central neuroepithelial origin. Russell & Rubinstein's Pathology of Tumors of the Nervous System. D. D. Bigner, R. E. McLendon and J. M. Bruner. London, Arnold. I: 308-571.
- Merchant, T. E., L. Happersett, et al. (1999). "Preliminary results of conformal radiation therapy for medulloblastoma." *Neuro-oncol* 1(3): 177-187.
- Merchant, T. E., C. Li, et al. (2009). "Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study." *The lancet oncology* 10(3): 258-266.
- Messahel, B., S. Ashley, et al. (2009). "Relapsed intracranial ependymoma in children in the UK: patterns of relapse, survival and therapeutic outcome." *European journal of cancer* 45(10): 1815-1823.
- Modak, S., S. Gardner, et al. (1997). High dose chemotherapy with autologous stem cell rescue in patients with recurrent central nervous system germ cell tumors. Childhood Cancer into the 21st century: An international conference to mark the 20th anniversary of the UKCCSG,, London, United Kingdom.
- Morris, E. B., C. Li, et al. (2009). "Evolution of neurological impairment in pediatric infratentorial ependymoma patients." *Journal of neuro-oncology* 94(3): 391-398.
- Neglia, J. P., A. T. Meadows, et al. (1991). "Second neoplasms after acute lymphoblastic leukemia in childhood." *The New England journal of medicine* 325(19): 1330-1336.
- Northcott, P. A., A. Korshunov, et al. (2010). "Medulloblastoma Comprises Four Distinct Molecular Variants." *J Clin Oncol*.
- Oka, H. and B. W. Scheithauer (1999). "Clinicopathological characteristics of atypical teratoid/rhabdoid tumor." *Neurologia medico-chirurgica* 39(7): 510-517; discussion 517-518.
- Packer, R. J., J. Ater, et al. (1997). "Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas." *Journal of neurosurgery* 86(5): 747-754.
- Packer, R. J., J. A. Biegel, et al. (2002). "Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop." *Journal of pediatric hematology/oncology : official journal of the American Society of Pediatric Hematology/Oncology* 24(5): 337-342.
- Packer, R. J., P. Cogen, et al. (1999). "Medulloblastoma: clinical and biologic aspects." *Neuro-oncol* 1(3): 232-250.
- Packer, R. J., R. Jakacki, et al. (2009). "Objective response of multiply recurrent low-grade gliomas to bevacizumab and irinotecan." *Pediatric blood & cancer* 52(7): 791-795.
- Palma, J. P., L. E. Rodriguez, et al. (2008). "The PARP inhibitor, ABT-888 potentiates temozolomide: correlation with drug levels and reduction in PARP activity in vivo." *Anticancer Res* 28(5A): 2625-2635.
- Palma, J. P., Y. C. Wang, et al. (2009). "ABT-888 confers broad in vivo activity in combination with temozolomide in diverse tumors." *Clin Cancer Res* 15(23): 7277-7290.
- Paugh, B. S., C. Qu, et al. (2010). "Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 28(18): 3061-3068.

- Paulino, A. C. (1999). "Trilateral retinoblastoma: is the location of the intracranial tumor important?" *Cancer* 86(1): 135-141.
- Pfister, S., W. G. Janzarik, et al. (2008). "BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas." *The Journal of clinical investigation* 118(5): 1739-1749.
- Pollack, I. F., R. L. Hamilton, et al. (2010). "Mismatch repair deficiency is an uncommon mechanism of alkylator resistance in pediatric malignant gliomas: a report from the Children's Oncology Group." *Pediatric blood & cancer* 55(6): 1066-1071.
- Pollack, I. F., R. I. Jakacki, et al. (2007). "Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: a Pediatric Brain Tumor Consortium report." *Neuro-oncology* 9(2): 145-160.
- Pomeroy, S. L., P. Tamayo, et al. (2002). "Prediction of central nervous system embryonal tumour outcome based on gene expression." *Nature* 415(6870): 436-442.
- Prados, M. D., M. S. Edwards, et al. (1997). "Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen." *J Neurooncol* 32(3): 235-241.
- Preston-Martin, S., J. M. Pogoda, et al. (1996). "Maternal consumption of cured meats and vitamins in relation to pediatric brain tumors." *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 5(8): 599-605.
- Puget, S., J. Grill, et al. (2009). "Candidate genes on chromosome 9q33-34 involved in the progression of childhood ependymomas." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 27(11): 1884-1892.
- Quinn, J. A., M. E. Dolan, et al. (2001). "Phase II Trial of BCNU plus O6-benzylguanine for patients with recurrent or progressive malignant glioma (abstr # 251)." *Proc Am Assoc Clin Oncol* 20: 64a.
- Quinn, J. A., S. X. Jiang, et al. (2009). "Phase II trial of Gliadel plus O6-benzylguanine in adults with recurrent glioblastoma multiforme." *Clinical cancer research : an official journal of the American Association for Cancer Research* 15(3): 1064-1068.
- Quinn, J. A., S. X. Jiang, et al. (2009). "Phase II trial of temozolomide (TMZ) plus irinotecan (CPT-11) in adults with newly diagnosed glioblastoma multiforme before radiotherapy." *J Neurooncol* 95(3): 393-400.
- Quinn, J. A., S. X. Jiang, et al. (2009). "Phase I trial of temozolomide plus O6-benzylguanine 5-day regimen with recurrent malignant glioma." *Neuro-oncology* 11(5): 556-561.
- Quinn, J. A., D. A. Reardon, et al. (2003). "Phase II trial of temozolomide in patients with progressive low-grade glioma." *J Clin Oncol* 21(4): 646-651.
- Reardon, D. A., A. Desjardins, et al. (2008). "The emerging role of anti-angiogenic therapy for malignant glioma." *Current treatment options in oncology* 9(1): 1-22.
- Reardon, D. A., A. Gajjar, et al. (1998). "Bithalamic involvement predicts poor outcome among children with thalamic glial tumors." *Pediatr Neurosurg* 29(1): 29-35.
- Reardon, D. A., J. A. Quinn, et al. (2004). "Phase 2 trial of BCNU plus irinotecan in adults with malignant glioma." *Neuro Oncol* 6(2): 134-144.
- Reed, N. and D. H. Gutmann (2001). "Tumorigenesis in neurofibromatosis: new insights and potential therapies." *Trends Mol Med* 7(4): 157-162.
- Rodriguez, F. J., B. W. Scheithauer, et al. (2008). "Ependymoma and intraparenchymal calcifying pseudoneoplasm of the neural axis: incidental collision or unique reactive phenomenon?" *Acta neuropathologica* 115(3): 363-366.

- Romer, J. T., H. Kimura, et al. (2004). "Suppression of the Shh pathway using a small molecule inhibitor eliminates medulloblastoma in Ptc1(+/-)p53(-/-) mice." *Cancer cell* 6(3): 229-240.
- Ron, E., B. Modan, et al. (1988). "Tumors of the brain and nervous system after radiotherapy in childhood." *The New England journal of medicine* 319(16): 1033-1039.
- Rorke, L. B. (1983). "The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumors." *J Neuropathol Exp Neurol* 42(1): 1-15.
- Rorke, L. B., R. J. Packer, et al. (1996). "Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity." *Journal of neurosurgery* 85(1): 56-65.
- Rosenblum, M. K., M. Matsutani, et al. (2000). *CNS Germ cell tumors. Pathology & Genetics Tumors of the central nervous system*. P. Kleihues and W. K. Cavenee. Lyons, France, IARC Press: 208-214.
- Rubin, J. B. and D. H. Gutmann (2005). "Neurofibromatosis type 1 - a model for nervous system tumour formation?" *Nature reviews. Cancer* 5(7): 557-564.
- Rudin, C. M., C. L. Hann, et al. (2009). "Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449." *The New England journal of medicine* 361(12): 1173-1178.
- Sampson, J. H., G. Akabani, et al. (2003). "Progress report of a Phase I study of the intracerebral microinfusion of a recombinant chimeric protein composed of transforming growth factor (TGF)-alpha and a mutated form of the Pseudomonas exotoxin termed PE-38 (TP-38) for the treatment of malignant brain tumors." *J Neurooncol* 65(1): 27-35.
- Schwalbe, E. C., J. C. Lindsey, et al. (2011). "Rapid Diagnosis of Medulloblastoma Molecular Subgroups." *Clin Cancer Res*.
- Scotto, K. W. and J. R. Bertino (2001). *Chemotherapy susceptibility and resistance. The Molecular Basis of Canc.* J. Mendelsohn, P. M. Howley and M. A. Israel. Philadelphia, W.B. Saunders: 387-400.
- Shibamoto, Y., M. Takahashi, et al. (1997). "Prognosis of intracranial germinoma with syncytiotrophoblastic giant cells treated by radiation therapy." *Int J Radiat Oncol Biol Phys* 37(3): 505-510.
- Singh, A. D., C. L. Shields, et al. (1999). "New insights into trilateral retinoblastoma." *Cancer* 86(1): 3-5.
- Smith, M. A., B. Freidlin, et al. (1998). "Trends in reported incidence of primary malignant brain tumors in children in the United States." *J Natl Cancer Inst* 90(17): 1269-1277.
- Stewart, D. J. (1994). "A critique of the role of the blood-brain barrier in the chemotherapy of human brain tumors." *J Neurooncol* 20(2): 121-139.
- Tada, T., T. Takizawa, et al. (1999). "Treatment of intracranial nongerminomatous germ-cell tumor by high-dose chemotherapy and autologous stem-cell rescue." *J Neurooncol* 44(1): 71-76.
- Taylor, R. E. (2004). "Review of radiotherapy dose and volume for intracranial ependymoma." *Pediatric blood & cancer* 42(5): 457-460.
- Tekautz, T. M., C. E. Fuller, et al. (2005). "Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 23(7): 1491-1499.

- Tsikitis, M., Z. Zhang, et al. (2005). "Genetic ablation of Cyclin D1 abrogates genesis of rhabdoid tumors resulting from *Ini1* loss." *Proceedings of the National Academy of Sciences of the United States of America* 102(34): 12129-12134.
- Turner, C. D., S. Gururangan, et al. (2002). "Phase II study of irinotecan (CPT-11) in children with high-risk malignant brain tumors: the Duke experience." *Neuro-oncol* 4(2): 102-108.
- Walter, A. W., R. K. Mulhern, et al. (1999). "Survival and neurodevelopmental outcome of young children with medulloblastoma at St Jude Children's Research Hospital." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 17(12): 3720-3728.
- Warren, K. E., A. A. Aikin, et al. (2005). "Phase I study of O6-benzylguanine and temozolomide administered daily for 5 days to pediatric patients with solid tumors." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 23(30): 7646-7653.
- Warren, K. E., S. Goldman, et al. (2011). "Phase I trial of lenalidomide in pediatric patients with recurrent, refractory, or progressive primary CNS tumors: Pediatric Brain Tumor Consortium study PBTC-018." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 29(3): 324-329.
- Warren, K. E., M. C. Patel, et al. (2001). "Phase I trial of lobradimil (RMP-7) and carboplatin in children with brain tumors." *Cancer Chemother Pharmacol* 48(4): 275-282.
- Watson, G. A., R. P. Kadota, et al. (2001). "Multidisciplinary management of pediatric low-grade gliomas." *Semin Radiat Oncol* 11(2): 152-162.
- Westphal, M., D. C. Hilt, et al. (2003). "A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma." *Neuro-oncology* 5(2): 79-88.
- Wisoff, J. H., J. M. Boyett, et al. (1998). "Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945." *J Neurosurg* 89(1): 52-59.
- Woehrer, A., I. Slavic, et al. (2010). "Incidence of atypical teratoid/rhabdoid tumors in children: a population-based study by the Austrian Brain Tumor Registry, 1996-2006." *Cancer* 116(24): 5725-5732.
- Wolden, S. L., I. J. Dunkel, et al. (2003). "Patterns of failure using a conformal radiation therapy tumor bed boost for medulloblastoma." *J Clin Oncol* 21(16): 3079-3083.
- Yan, H., D. W. Parsons, et al. (2009). "IDH1 and IDH2 mutations in gliomas." *The New England journal of medicine* 360(8): 765-773.
- Yu, J., H. Deshmukh, et al. (2009). "Alterations of BRAF and HIPK2 loci predominate in sporadic pilocytic astrocytoma." *Neurology* 73(19): 1526-1531.



## **Management of CNS Tumors**

Edited by Dr. Miklos Garami

ISBN 978-953-307-646-1

Hard cover, 464 pages

**Publisher** InTech

**Published online** 22, September, 2011

**Published in print edition** September, 2011

Management of CNS Tumors is a selected review of Central Nervous System (CNS) tumors with particular emphasis on pathological classification and complex treatment algorithms for each common tumor type. Additional detailed information is provided on selected CNS tumor associated disorders.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Sri Gururangan (2011). Childhood Brain Tumors, Management of CNS Tumors, Dr. Miklos Garami (Ed.), ISBN: 978-953-307-646-1, InTech, Available from: <http://www.intechopen.com/books/management-of-cns-tumors/childhood-brain-tumors>

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