Advances in Biology and Treatment of Childhood Brain Tumors

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Childhood brain tumors are collectively the most common solid neoplasm and the leading cause of cancer-related death in children. They are a diverse group of diseases and outcome is extremely variable. Current treatment is dependent on histology, location, and in some instances, patient age. Advances in treatment have led to improved survival for some patients, but for many the outcome remains dismal despite aggressive treatment. A growing body of work is aimed at improving the outcome for children with brain tumors not only through clinical trials, but also by focusing on the biologic underpinning of these diseases that have been poorly understood.

Introduction

Childhood brain tumors represent a significant pediatric health problem. They are the most common solid neoplasm and the leading cause of cancer-related death in children less than 15 years of age [1]. Although improvements over the past few decades in surgical care, radiation techniques, and the expanded use of chemotherapy have improved survival rates for many pediatric brain tumor patients, for some subsets of patients the prognosis remains dismal. Patients who successfully survive their disease often have sequelae from their disease or treatment that can significantly effect activities of daily living and cognition.

Childhood brain tumors are a heterogeneous group of several diseases. There are at least 13 major histologic subsets of tumors [2]. They are often further divided by grade and anatomic location. Some subtypes are much more common than others, and even with collaborative group studies, advances in treatment have been slow. Traditional treatment approaches with varying combinations of surgery, radiation, and chemotherapy have led to prolonged survival for the majority of patients with low-grade glioma, medulloblastoma, ependymoma, and central nervous system (CNS) germinoma. For patients with high-grade glioma, brainstem glioma, and disseminated or recurrent tumors of any type, traditional treatment usually only provides a brief interval of disease control.

Improvements in treatment may also come with a better understanding of the biologic underpinnings of brain tumors. Basic research in this area is beginning to shed light on tumor oncogenesis. This article presents the latest information on the diagnosis, treatment, and biology of the more common subsets of pediatric brain tumors.

Medulloblastoma and Supratentorial Neuroectodermal Tumors

Medulloblastoma is the most common malignant brain tumor of childhood. Supratentorial neuroectodermal tumors (SPNET) are much less common, but both are members of the primitive neuroectodermal tumor family of CNS neoplasms and considered a Grade IV lesion by the World Health Organization (WHO). The histologic hallmark of primitive neuroectodermal tumors is the presence of abundant, small, poorly differentiated blue cells.

Medulloblastoma typically arises in the vermis of the cerebellum, causing ataxia and symptoms of hydrocephalus in those it affects. Children with medulloblastoma have been separated into two major risk groups: 1) average-risk patients, who have localized disease at the time of diagnosis and have undergone total or near-total resection; and 2) high-risk patients, who have disseminated disease or tumors that are only partially resected. Medulloblastoma was once considered a fatal disease. But dramatic improvements in treatment over the past few decades have led to increased survival rates. The traditional management of these patients had included surgical resection followed by craniospinal radiation (CSI) to a dose of 36 Gy and a boosted dose to the tumor bed to a total of 54 Gy. With this treatment, patients with average-risk disease have approximately a 60% chance of 5-year progression-free survival. In previous studies, the addition of chemotherapy to the management of patients with medulloblastoma has shown improvement in outcome over radiation alone [3]. The Children's Cancer Group phase III study [4•], comparing eight-drugs-in-1-day chemotherapy before and after external beam radiotherapy (XRT) with vincristine, lomustine, and prednisone after XRT, showed improved outcome for patients treated with the latter therapy. This study

included patients with both average- and high-risk disease and used standard doses of radiation in all patients over 3 years of age. A reduced dose of CSI was used in children between 18 and 36 months of age. This study also supported the finding of previous ones in that patients with average-risk disease had superior outcomes, with 5-year progression-free survival of 78% versus 54% for those with high-risk disease.

Cure of the disease is not always synonymous with good outcome. Many children who survive treatment that includes standard-dose radiation have serious neurocognitive and endrocrinologic dysfunction. A recent study compared neuropsychologic outcome for 31 patients who were treated with either CSI to 25 Gy or CSI to 36 Gy focused radiation to the posterior fossa only [5]. Their findings were similar to past studies, with a significant drop in IQ scores with higher doses of radiation.

Current investigation is exploring refinements in treatment in an attempt to reduce potential morbidity without sacrificing disease control. In an attempt to improve long-term outcome for survivors, the Children's Cancer Group also recently evaluated the outcome for children with average-risk disease treated with reduced- dose CSI followed by chemotherapy [6••]. This cohort included 65 children between the ages of 36 and 120 months of age who were considered as having average-risk medulloblastoma. All patients were treated with postoperative radiation to a dose of 23.4 Gy to the craniospinal axis and 55.8 Gy to the tumor field. Adjuvant vincristine chemotherapy was administered concurrently with radiation, and lomustine, vincristine, and cisplatin were administered after radiation. The progression-free survival at 3 and 5 years was 86% and 79%, respectively. The main side effect from chemotherapy was high-frequency hearing loss. These results are encouraging and suggest that it is feasible to treat average-risk medulloblastoma with reduced-dose radiation and chemotherapy.

The outcome for children with SPNET is generally felt to be poor and worse than outcome for those with medulloblastoma. The treatment of SPNET has been extrapolated from the data on medulloblastoma because it is much less common and the tumors are histologically similar. The outcome for patients with SPNET treated with identical therapy as patients with high-risk medulloblastoma at two large institutions was recently reported [7•]. The 22 patients in this study had tumors that arose in the pineal region, cortex, thalamus, or suprasellar region. The progression-free survival was 47% at 3 years and 37% at 5 years. There was a significant difference in progression-free survival between patients with localized disease versus disseminated disease. There was no statistical association between tumor location and survival. Although not statistically significant, there was a trend toward better survival in patients with complete or near-complete resections as compared with those with partial resection or biopsy. This suggests that there may be biologic differences between medulloblastoma and SPNET.

Treatment advances have been made despite a poor understanding of the biologic underpinnings of medulloblastoma. Current laboratory investigation is shedding light on medulloblastoma oncogenesis. Neurotrophins, which have an important role in the developing and mature nervous system, also appear to be involved in medulloblastoma. Tumors that express the neurotrophin receptor trkC appear to be more responsive to treatment [8]. It has been shown that trkC activation leads to apoptosis of medulloblastoma tumor cells [9••]. Activation of trkA by nerve growth factor (NGF) has also been shown to lead to apoptosis of medulloblastoma cells [10]. It has further been demonstrated that a *ras* or *raf* signaling pathway [11•] may mediate this apoptosis.

The human neurotropic Jamestown Canyon (JC) virus has also been implicated in medulloblastoma tumorigenesis. In a recent study, half of the tumors contained DNA sequences of the JC virus genome [12•]. Immunohistochemical evaluation of these tumor samples revealed expression of the JC viral oncogenic protein, T antigen, in tumor cells. These are only some of the exciting basic science developments in medulloblastoma that may not only enhance our understanding of the disease, but also lead to more effective therapies.

Ependymoma

Ependymomas account for 6% to 12% of all intracranial tumors in childhood, and most commonly develop in the posterior fossa, followed by the lateral ventricle and the spinal cord [2]. Although many patients have prolonged disease-free survival after surgery and adjuvant radiation or chemotherapy, a large percentage of patients will eventually have recurrence and ultimately do not survive their disease. Five-year overall-survival rates from 40% to 70% have been reported [13–16]. Because ependymoma is a relatively rare tumor, these series include patients treated over the past four decades.

Advances in neuroimaging have allowed for better quantitative assessment of disease status. Extent of resection appears to have a significant bearing on outcome. Patients who have had complete resections on postoperative magnetic resonance imaging (MRI) have a 5-year progression-free survival rate of 68% compared with only 8.9% for patients with incompletely resected tumors [14]. A recent study from Germany that included 55 children with ependymoma also concluded that extent of resection was the only significant prognostic indicator of outcome [17]. This group reported a 3-year progression-free survival of 83.3% after complete resection compared with 38.5% for incomplete resection. Therefore, there is good rationale for neurosurgeons to achieve a complete resection when possible.

Although there have been anecdotal reports of long-term survival after surgery only, most series suggest that radiotherapy is indicated postoperatively. If there is no evidence of tumor dissemination on MRI or cerebral spinal

fluid (CSF) cytology, local radiation to the tumor bed at standard doses ranging from 5000 to 6000 cGy are usually given. Patients treated with CSI do not appear to have better long-term survival, and there are well-documented long-term side effects from this treatment. Because recurrence is almost always at the primary site, there is little rationale to use CSI unless there is evidence for tumor dissemination. Even with CSI, most patients with disseminated disease do poorly.

The role of chemotherapy in the treatment of ependymoma is unclear. Most studies suggest that it does not alter time to progression. In the German HIT 88/89 and HIT 91 trials [17], two different regimens were given. One was postsurgical chemotherapy consisting of ifosfamide, etoposide, cisplatin, and methotrexate followed by radiation therapy, and the other was postoperative radiation followed by methotrexate, cisplatin, and vincristine. There was no significant difference in outcome between these two regimens, and no clear improvement in outcome compared with patients treated with radiation alone in other studies.

When chemotherapy was used in children less than 3 years of age as a means to defer radiation, many patients showed a good initial response to treatment, suggesting activity of chemotherapy. In a large study, however, this group of patients had a 2-year progression-free survival of only 42% [18]. There is some evidence that very young children do less well than older children regardless of treatment regimen, and that ependymoma may be more aggressive when it presents early in life.

Chemotherapy has also demonstrated activity in patients with recurrent ependymoma [19,20]. A recent study retrospectively analyzed the treatment given to patients with recurrent ependymoma at a single institution over a 19-year period [21]. There were 16 patients included in the study and they were treated with a variety of regimens. There did appear to be a fairly high initial-response rate (67%) in patients treated with platinum-based regimens, although median time to progression was short at 6 months.

Stereotactic radiosurgery has also been evaluated in the treatment of recurrent ependymoma [22••]. Twelve patients with recurrent ependymoma, 11 of whom had previously been treated with XRT, underwent stereotactic radiosurgery. The 3-year local control rate was 68%. There were two in-field failures, one marginal failure, and two distant failures. These results suggest that stereotactic radiosurgery can prolong survival in patients with recurrent ependymoma. It may also enhance disease-free survival when used as part of the initial management, especially in those patients with residual disease after surgery. One drawback of this therapy is that tumor volumes must be relatively small, typically no bigger than 3 cm in any dimension.

As with medulloblastoma, the tumor biology of ependymoma is poorly understood. In a cytogenetic study of 33 ependymomas, several genetic aberrations were found, but the most frequent chromosomal abnormality observed was complete or partial monosomy 22 [23]. Abnormalities were also found on chromosomes 7, 2, and 6. It has been postulated that there may be a putative ependymal tumor suppressor gene on chromosome 22, and the search for this gene is underway.

A group in the Netherlands performed segregation analysis with chromosome 22 markers in a family in which four cousins developed ependymoma [24•]. Their analysis revealed that the tumor suppressor gene might be present in region 22pter-22q11.2. Further work in this area may lead to a better understanding of ependymoma tumorigenesis.

High-grade Glioma and Brainstem Glioma

Anaplastic astrocytoma and glioblastoma multiforme are among the most difficult tumors to treat in children. Despite aggressive treatment with surgery, radiation, and chemotherapy, most series have reported 5-year survival rates of less than 20%. The patients who have prolonged survival tend to have tumors that can be completely resected. These tumors may be inherently less aggressive than most high-grade gliomas that often infiltrate critical areas of the brain, precluding safe resection. Radiation therapy is felt to typically prolong survival. There is some evidence that the combination of radiation and chemotherapy leads to improved survival over radiation alone [25]. There are, however, no standard regimens that have consistently been shown to produce long-term survival in patients with high-grade gliomas.

The prognosis for children with intrinsic brainstem glioma is equally as dismal. These tumors are readily identified on MRI, which shows an enlarged, swollen, and hypointense pons with little or no contrast enhancement. These tumors cannot be helped with surgery because they infiltrate vital and eloquent structures. Most patients will respond to involved field radiation treatment, but recurrence in 6 to 12 months is generally the rule. Hyperfractionated radiation to a dose of 78 Gy has not altered outcome [26]. The role of chemotherapy remains unclear. Although various agents have been reported to have some response, chemotherapy has not been shown to alter long-term survival.

A multicenter trial evaluated the feasibility of treating patients with newly diagnosed high-grade gliomas using concurrent dose-intensive chemotherapy and radiation treatment [27•]. Twelve patients with either cortical high-grade glioma or intrinsic pontine glioma were treated with procarbazine, lomustine (CCNU), and vincristine followed by stem cell rescue while receiving standard radiation treatment. This regimen appeared to result in unacceptable neurotoxicity, and median overall survival was only 11 months.

Other brainstem glioma trials have combined radiation with a variety of agents, including busulfan and thiotepa, followed by bone marrow transplant and high-dose tamoxifen [28,29]. The addition of these high-dose regimens did not alter outcome. These frustrating results were similar to previous studies, and in a large meta-analysis of 27 clinical trials and 576 pediatric patients with high-grade

gliomas and brainstem gliomas, impact of chemotherapy could not be demonstrated [30•].

As with adult patients, children with high-grade gliomas and brainstem gliomas typically succumb to their disease, and even aggressive treatment usually only provides a short interval of disease control. This is one area where new and innovative treatment approaches are greatly needed.

Low-grade Glioma

Low-grade gliomas are collectively the most common type of pediatric central nervous system tumor. They account for approximately one third of childhood brain tumors and can arise in any part of the nervous system. The most common form is the juvenile pilocytic astrocytoma (JPA), a WHO Grade I tumor, that is usually well circumscribed and has only narrow areas of infiltration. The other common form is the fibrillary astrocytoma, graded as a WHO II tumor because of its tendency to be more infiltrative. Other low-grade gliomas, such as ganglioglioma and oligodendroglioma, can occur in children.

The treatment of low-grade glioma is highly dependent on tumor location. If the tumor can be completely or near-completely resected, then surgery alone can provide prolonged, disease-free survival. After complete resection, for example, patients with a cerebellar pilocytic astrocytoma have 10- to 20-year survival rates of 90% to 100%. Low-grade gliomas that arise in other areas, such as the diencephalon, optic pathways, back of the brainstem, and basal ganglia/thalamus, are often not amenable to surgical resection because of proximity or invasion of vital structures. Although surgery provides diagnosis and at times good disease control, most low-grade tumors will slowly grow if significant amounts of the tumor are not resected. There is evidence that both radiation and chemotherapy have activity in low-grade gliomas, and patients with evidence of progressive disease or large tumors not amenable to surgery should be considered for adjuvant treatment.

The role of adjuvant therapy for residual or progressive disease is currently being defined. Radiation therapy typically results in objective tumor shrinkage in patients with low-grade gliomas, and may improve the duration of disease-free survival in children with partially resected lesions [31]. The survival rate in children with cerebral or diencephalic low-grade gliomas is 40% to 70% at 5 years with radiation therapy, but declines to 11% to 50% at 10 years [32,33]. Even though radiation therapy may provide disease control, there has been reluctance to use it in very young children because of the known deleterious side effects on the developing nervous system. In a population where relative long-term survival is expected, the cognitive, endocrine, and vascular sequelae of radiation make it a less appealing option for young patients. Also of concern is the potential for secondary neoplasms in patients treated with radiation who are long-term survivors.

Refinements in radiation therapy seek to reduce the risk of potential side effects. Proton beam therapy delivers high, homogeneous doses of proton radiation to target volumes. Steep-dose gradients are used to spare normal neighboring tissues. A series of seven patients with progressive optic pathway gliomas treated with proton beam therapy has been reported [34•]. All patients in this small series were considered stable by MRI and vision examination at a median follow up of 37 months. It is not clear, however, that proton beam therapy differs from the latest three-dimensional conformal radiation techniques in terms of disease control and long-term side effects. More focused forms of radiation, such as Gamma Knife (Leskell, Sweden), for either small areas of clearly defined residual disease or localized progressive disease in children with low-grade gliomas, may also eventually prove to have a useful role in treating this disease.

Over the past two decades, there have been multiple reports on the efficacy of chemotherapy in children with newly diagnosed and recurrent low-grade gliomas. The majority of these studies report responses or disease stabilization for most patients. A series of 78 patients treated with carboplatin and vincristine for progressive low-grade gliomas reported a 3-year progression-free survival of 68% and radiographic responses in 56% of patients [35]. A combination of 6-thioguanine, procarbazine, dibromodulcitol, CCNU, and vincristine (TPDCV) has been evaluated in a series of 42 patients [36]. Median time to progression was 132 weeks, with a 5-year survival rate of 78%. The Children's Cancer Group is currently conducting a phase III trial randomizing patients to treatment with carboplatin and vincristine or thioguanine, procarbazine, CCNU, and vincristine. The long-term side effects of treatments will need to be weighed against efficacy. Newer agents, such as temozolamide, which appear to have minimal toxicity, may also be effective. The optimal treatment for low-grade glioma remains a work in progress and will likely be altered as adjuvant treatments become more targeted.

Germ Cell Tumors

Intracranial germ cell tumors account for approximately 5% of pediatric brain tumors. They are a histologically diverse group, much like their gonadal counterparts, with six subtypes recognized by the WHO. Germ cell tumors are broadly divided into two groups: 1) pure germinoma (GCT); and 2) nongerminous germ cell tumor (NG-GCT), which contains more primitive elements and is generally felt to be more malignant. Like other extragonadal germ cell tumors, most CNS tumors originate in the midline structures, particularly the pineal and suprasellar regions. Patients often present with hypothalamic-pituitary dysfunction, especially diabetes insipidus, in addition to headache, hydrocephalus, and focal neurologic deficits.

Germ cell tumors are relatively unique among brain tumors because their diagnostic evaluation includes not only neuroimaging, but also assessment of protein markers α-fetoprotein (AFP) and human chorionic gonadotropin (HCG) in both blood and CSF. Tissue diagnosis may be limited by small sampling size, and elevated tumor markers may indicate the presence of NG-GCT when it is not apparent histologically. Because patients with NG-GCT tend to have a poorer prognosis, this has bearing on current treatment strategies.

Surgical intervention is indicated for patients with germ cell tumor for tissue diagnosis and relief of hydrocephalus. Because of tumor location and lack of evidence for improved outcome with radical resection, aggressive surgery is currently not felt to be indicated. Germinomas are highly radiosensitive, and treatment with whole brain radiation alone produces excellent long-term survival rates approaching 90% [37,38]. A recent study not only looked at disease outcome, but also long-term endocrine and cognitive outcome for patients treated with low-dose craniospinal irradiation (median 25.6 Gy) and a boost to the primary site of disease (median 50.4 Gy) [39•]. All 12 patients in the study were free of disease at a median follow-up of 69 months, and there were no significant drops in IQ or growth failure that could be attributed to the radiation. These favorable results were supported by another study that assessed quality of life through questionnaires in 22 adult survivors of germinomas treated with craniospinal radiation [40]. The reported quality of life was good, with the majority of patients completing higher education and having normal proportioned height and weight.

There is a unique precedent for treating CNS germ cell tumors with chemotherapy because of the histologic similarities of germ cell tumors throughout the body that are known to respond to cisplatin-based chemotherapy regimens. Most studies have used platinum-based chemotherapy with radiation treatment and report long-term survival rates in the 90% range. A small study that compared standard-dose radiation alone with a combination of reduced-dose radiation and chemotherapy found no difference in survival [41]. Patients treated with chemotherapy alone, however, appear to have higher rates of failure. Although these patients can be salvaged with radiation therapy at the time of recurrence [42], there seems to be little rationale to treat patients with chemotherapy alone except in very young children where radiation effects are typically more significant. Larger studies are needed to determine the dose and field of radiation needed to control disease, and if the addition of chemotherapy improves outcome. As with other brain tumors, treatment outcome must balance potential sequelae.

Patients with NG-GCT tend to do poorly compared with patients with pure germinoma, with 5-year survival rates of less than 50% when treated with radiation alone [43]. The use of combination chemotherapy seems justified for this group of patients. Six patients treated with radiation and high-dose chemotherapy followed by autologous stem cell rescue were reported to be alive with good performance status and free of disease 1 to 7 years after diagnosis [44•]. Larger studies in this area are warranted.

The Children's Cancer Group is currently evaluating the role of combination chemotherapy and radiation in all patients with germ cell tumors. Patients with pure germinoma are treated with chemotherapy followed by involved field radiation for localized disease and craniospinal radiation for patients with dissemination. Patients with NG-GCT are treated with higher-dose chemotherapy and craniospinal radiation.

Conclusions

Advances in the management of brain tumors have led to significant improvement in survival rates for some children with brain tumors. Most children with medulloblastoma, ependymoma, low-grade glioma, and CNS germinoma will have prolonged disease-free survival with current treatments. At times, however, significant treatment side effects are traded for disease control. Current work in this area is focusing on modifying treatment so that intellect, endocrine function, vision, hearing, and long-term health are improved.

Patients with high-grade glioma, brainstem glioma, NG-GCT, SPNET, and disseminated or recurrent tumor of any type tend to do poorly, and despite aggressive treatment, most will not survive their disease. Because standard treatment modalities do not appear curative, novel approaches, such as gene therapy and anti-angiogenesis factors, are currently being explored. The first pediatric gene therapy trial using a retroviral vector to treat recurrent supratentorial brain tumors demonstrated safety of this potential treatment [45••]. Genetically altered herpes simplex viruses also offer promise as an oncolytic agent, and a phase I study in adults with recurrent malignant glioma demonstrated its safety [46•]. Further viral gene therapy studies are warranted.

The biologic underpinnings of all brain tumors remain poorly understood. Work in this area may not only lead to a better understanding of tumorigenesis, but also lead to more targeted treatment. The recent advances in the understanding and treatment of brain tumors and the promise of continued investigation offer hope to patients who are often faced with devastating diseases.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Russell DS, Rubinstein LJ: *Pathology of Tumors of the Nervous System*, edn 4. Baltimore: Williams and Wilkins; 1977.
2. Kleihues P, Cavenee W. *Pathology and Genetics of Tumors of the Central Nervous System*. Lyon, France: International Agency for Research on Cancer; 1997.

3. Packer RJ, Sutton LN, Elterman R, *et al.*: **Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, and vincristine chemotherapy.** *J Neurosurg* 1994, **81:**690-698.
4. • Zeltzer PM, Boyett JM, Finlay JL, *et al.*: **Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study.** *J Clin Oncol* 1999, **17:**832-845.

This is a large, prospective, clinical trial that demonstrates improved outcome for children with medulloblastoma, based both on extent of disease and treatment protocol.

5. Grill J, Renaux VK, Bulteau C, *et al.*: **Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes.** *Int J Radiat Oncol Biol Physics* 1999, **45:**137-145.
6. • • Packer RJ, Goldwein J, Nicholson HS, *et al.*: **Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group Study.** *J Clin Oncol* 1999, **17:**2127-2136.

This large, prospective, clinical trial demonstrates the ability to reduce the dose of craniospinal radiation in patient's with average-risk medulloblastoma.

7. • Reddy AT, Janss AJ, Phillips PC, *et al.*: **Outcome for children with supratentorial primitive neuroectodermal tumors treated with surgery, radiation, and chemotherapy.** *Cancer* 2000, **88:**2189-2193.

This study suggests that supratentorial neuroectodermal tumor is a more aggressive disease than medulloblastoma.

8. Segal RA, Goumnerova LC, Kwon YK, *et al.*: **Expression of the neurotrophin receptor TrkC is linked to a favorable outcome in medulloblastoma.** *Proc Natl Acad Sci U S A* 1994, **91:**12867-12871.
9. • • Kim JY, Sutton ME, Lu DJ, *et al.*: **Activation of neurotrophin-3 receptor TrkC induces apoptosis in medulloblastomas.** *Cancer Res* 1999, **59:**711-719.

This is a very exciting article that gives a clear demonstration of how TrkC expression induces apoptosis, and may explain why TrkC is associated with improved outcome.

10. Muragaki Y, Chou TT, Kaplan DR, *et al.*: **Nerve growth factor induces apoptosis in human medulloblastoma cell lines that express TrkA receptors.** *J Neurosci* 1997, **17:**530-542.
11. • Chou TT, Trojanowski JQ, Lee VM: **A novel apoptotic pathway induced by nerve growth factor-mediated TrkA activation in medulloblastoma.** *J Biol Chem* 2000, **275:**565-70.

This article suggests a signaling pathway in medulloblastoma apoptosis.

12. • Krynska B, Del Valle L, Croul S, *et al.*: **Detection of human neurotropic JC virus DNA sequence and expression of the viral oncogenic protein in pediatric medulloblastomas.** *Proc Natl Acad Sci U S A* 1999, **96:**11519-11524.

The work suggests that JC virus plays a role in medulloblastoma oncogenesis.

13. Merchant TE, Haida T, Wang MH, *et al.*: **Anaplastic ependymoma: treatment of pediatric patients with or without craniospinal radiation therapy.** *J Neurosurg* 1997, **86:**943-949.
14. Pollack IF, Gerszten PC, Martinez AJ, *et al.*: **Intracranial ependymomas of childhood: long-term outcome and prognostic factors.** *Neurosurgery* 1995, **37:**655-666.
15. Chiu JK, Woo SY, Ater J, *et al.*: **Intracranial ependymoma in children: analysis of prognostic factors.** *J Neuro-Oncol* 1992, **13:**283-290.
16. Kovalic JJ, Flaris N, Grigsby PW, *et al.*: **Intracranial ependymoma long term outcome, patterns of failure.** *J Neuro-Oncol* 1993, **15:**125-131.
17. Timmermann B, Kortmann RD, Kuhl J, *et al.*: **Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91.** *Int J Radiat Oncol Biol Physics* 2000, **46:**287-295.
18. Duffner PK, Horowitz ME, Krischer JP, *et al.*: **Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors [comments].** *N Engl J Med* 1993, **328:**1725-1731.
19. Goldwein JW, Glauser TA, Packer RJ, *et al.*: **Recurrent intracranial ependymomas in children. Survival, patterns of failure, and prognostic factors.** *Cancer* 1990, **66:**557-563.
20. Sexauer CL, Khan A, Burger PC, *et al.*: **Cisplatin in recurrent pediatric brain tumors. A POG Phase II study. A Pediatric Oncology Group Study.** *Cancer* 1985, **56:**1497-1501.
21. Gornet MK, Buckner JC, Marks RS, *et al.*: **Chemotherapy for advanced CNS ependymoma.** *J Neuro-Oncol* 1999, **45:**61-67.
22. • • Stafford SL, Pollock BE, Foote RL, *et al.*: **Stereotactic radiosurgery for recurrent ependymoma.** *Cancer* 2000, **88:**870-875.

This study demonstrates the effectiveness of treating recurrent ependymoma with radiosurgery, and suggests it may have a role in up-front treatment.

23. Vagner-Capodano AM, Zattara-Cannoni H, Gambarelli D, *et al.*: **Cytogenetic study of 33 ependymomas.** *Cancer Genet Cytogenet* 1999, **115:**96-99.
24. • Hulsebos TJ, Oskam NT, Bijleveld EH, *et al.*: **Evidence for an ependymoma tumour suppressor gene in chromosome region 22pter-22q11.2.** *Br J Cancer* 1999, **81:**1150-1154.

This article suggests a possible tumor suppressor gene for ependymoma.

25. Sposto R, Ertel IJ, Jenkin RD, *et al.*: **The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study Group.** *J Neuro-Oncol* 1989, **7:**165-177.
26. Freeman CR, Bourgouin PM, Sanford RA, *et al.*: **Long term survivors of childhood brain stem gliomas treated with hyperfractionated radiotherapy. Clinical characteristics and treatment related toxicities. The Pediatric Oncology Group.** *Cancer* 1996, **77:**555-562.
27. • Jakacki RI, Siffert J, Jamison C, *et al.*: **Dose-intensive, time-compressed procarbazine, CCNU, vincristine (PCV) with peripheral blood stem cell support and concurrent radiation in patients with newly diagnosed high-grade gliomas.** *J Neuro-Oncol* 1999, **44:**77-83.

This study demonstrated extreme toxicity with concurrent high-dose chemotherapy and radiation.

28. Bouffet E, Raquin M, Doz F, *et al.*: **Radiotherapy followed by high dose busulfan and thiotepa: a prospective assessment of high dose chemotherapy in children with diffuse pontine gliomas.** *Cancer* 2000, **88:**685-692.
29. Broniscer A, Leite CC, Lanchote VL, *et al.*: **Radiation therapy and high-dose tamoxifen in the treatment of patients with diffuse brainstem gliomas: results of a Brazilian cooperative study. Brainstem Glioma Cooperative Group.** *J Clin Oncol* 2000, **18:**1246-1253.
30. • Huncharek M, Wheeler L, McGarry R, Geschwind JF: **Chemotherapy response rates in recurrent/progressive pediatric glioma; results of a systematic review.** *Anticancer Res* 1999, **19:**3569-3574.

This large review article includes results of 27 treatment trials.

31. Shaw EG, Daumas-Duport C, Scheithauer BW, *et al.*: **Radiation therapy in the management of low-grade supratentorial astrocytomas.** *J Neurosurg* 1989, **70:**853-861.
32. North CA, North RB, Epstein JA, *et al.*: **Low-grade cerebral astrocytomas. Survival and quality of life after radiation therapy.** *Cancer* 1990, **66:**6-14.
33. Guthrie BL, Laws ER, Jr: **Supratentorial low-grade gliomas.** *Neurosurg Clin North Am* 1990, **1:**37-48.
34. • Fuss M, Hug EB, Schaefer RA, *et al.*: **Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique.** *Int J Radiat Oncol Biol Physics* 1999, **45:**1117-1126.

This article suggests that proton beam therapy may have a role in treating low-grade gliomas.

35. Packer RJ, Ater J, Allen J, *et al.*: **Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas.** *J Neurosurg* 1997, **86:**747-754.

36. Prados MD, Edwards MS, Rabbitt J, *et al.*: **Treatment of pediatric low-grade gliomas with a nitrosourea-based multiagent chemotherapy regimen.** *J Neuro-Oncol* 1997, **32:**235-241.
37. Matsutani M, Sano K, Takakura K, *et al.*: **Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases.** *J Neurosurg* 1997, **86:**446-455.
38. Hardenbergh PH, Golden J, Billet A, *et al.*: **Intracranial germinoma: the case for lower dose radiation therapy.** *Int J Radiat Oncol Biol Physics* 1997, **39:**419-426.
39.• Merchant TE, Sherwood SH, Mulhern RK, *et al.*: **CNS germinoma: disease control and long-term functional outcome for 12 children treated with craniospinal irradiation.** *Int J Radiat Oncol Biol Physics* 2000, **46:**1171-1176.
This study suggests excellent outcome for patients treated with radiation alone.
40. Sutton LN, Radcliffe J, Goldwein JW, *et al.*: **Quality of life of adult survivors of germinomas treated with craniospinal irradiation.** *Neurosurgery* 1999, **45:**1292-1297.
41. Fouladi M, Grant R, Baruchel S, *et al.*: **Comparison of survival outcomes in patients with intracranial germinomas treated with radiation alone versus reduced-dose radiation and chemotherapy.** *Childs Nervous Syst* 1998, **14:**596-601.
42. Shibamoto Y, Sasai K, Kokubo M, Hiraoka M: **Salvage radiation therapy for intracranial germinoma recurring after primary chemotherapy.** *J Neuro-Oncol* 1999, **44:**181-185.
43. Fuller BG, Kapp DS, Cox R: **Radiation therapy of pineal region tumors: 25 new cases and a review of 208 previously reported cases.** *Int J Radiat Oncol Biol Physics* 1994, **28:**229-245.
44.• Tada T, Takizawa T, Nakazato F, *et al.*: **Treatment of intracranial nongerminomatous germ-cell tumor by high-dose chemotherapy and autologous stem-cell rescue.** *J Neuro-Oncol* 1999, **44:**71-76.
This small study suggests improved survival for patient's with nongerminous germ cell tumor treated with high-dose chemotherapy and radiation.
45.•• Packer RJ, Raffel C, Villablanca JG, *et al.*: **Treatment of progressive or recurrent pediatric malignant supratentorial brain tumors with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration.** *J Neurosurg* 2000, **92:**249-254.
The study demonstrates safety of intracerebral inoculation of viral vector gene therapy in pediatric patients.
46.• Markert JM, Medlock MD, Rabkin SD, *et al.*: **Conditionally replicating herpes simplex virus mutant, G207 for the treatment of malignant glioma: results of a phase I trial.** *Gene Ther* 2000, **7:**687-694.
This study demonstrates safety of genetically altered herpes virus as an oncolytic agent in the treatment of brain tumors.