Published in final edited form as:
J Child Neurol. 2008 October ; 23(10): 1122–1127. doi:10.1177/0883073808320758.

Childhood Brain Tumors: Accomplishments and Ongoing Challenges

Roger J. Packer, MD[1]
Executive Director, Neuroscience and Behavioral Medicine

Director, Brain Tumor Institute

Director, Daniel and Jennifer Gilbert Neurofibromatosis Institute Children's National Medical Center

Professor of Neurology and Pediatrics The George Washington University

Professor in Neurosurgery University of Virginia Charlottesville, VA

Professor of Neurology (Clinical) Georgetown University Washington, DC

[1]Center of Excellence for Neuroscience and Behavioral Medicine, Division of Child Neurology, Children's National Medical Center, Washington, DC

Abstract

The management of childhood brain tumors, which consist of many different histological subtypes, continues to be a challenge. Outcome, measured not only by survival rates but also by the effects of disease and therapy on quality of life, has improved over the past two decades for some tumor types, most notably medulloblastomas. For others, however, there has been little progress, and quality of life for long-term survivors remains suboptimal. Because of advances in our understanding of the biology underlying childhood brain tumors, treatments may change dramatically in the years ahead. Accordingly, survival rates may improve and long-term sequelae lessen.

Introduction

The symposium “Neurobiology of Disease in Children: Tumors of the Central Nervous System,” held at the 36th annual meeting of the Child Neurology Society, focused on the status of our understanding of the biology of childhood brain tumors and how recent changes in treatment have affected outcome. To address these issues, crucial questions must be considered. The first is whether our understanding of the neurobiology, genetics, or cause of childhood brain tumors has increased significantly. This is a difficult issue to address globally given the many histological subtypes of brain tumors that occur in children. More than 50% of all childhood brain tumors are gliomas. In contrast to those that occur in adults, most gliomas that occur in children are classified as low-grade and little is known about their biology. Furthermore, increasing evidence suggests childhood high-grade gliomas differ biologically from those occurring in adulthood.[2] Embryonal tumors, composed of multiple subtypes, are the most common form of malignant childhood brain tumors, and the biology of these tumors varies depending on histological type, with the most known about medulloblastoma. The next question that must be addressed is whether these new insights

Contact Information: Roger Packer, MD Children's National Medical Center 111 Michigan Avenue, NW Washington DC 20010 Phone : 202-476-5973 Fax: 202-476-2864 rpacker@cnmc.org.

have led to different or better management. More simply, have alterations in therapy improved survival, and, as an important corollary, improved quality of life? In this paper, we briefly review the major categories of childhood brain tumors, with a focus on how greater knowledge of tumor biology can potentially translate into more effective and safer therapies.

Medulloblastoma

Medulloblastoma, the most common childhood brain tumor, is often used as an example of how “modern” therapy has resulted in improved survival.[3] Recent multicenter, often prospective, randomized clinical trials have demonstrated a stepwise improvement in the reported 5-year event-free survival rate. In the 1960s through the mid-1980s, reported 5-year event-free survival rates for children with medulloblastoma were in the 50% to 60% range. Children with nondisseminated medulloblastoma who underwent total or near-total surgical resection followed by 3600 cGy of craniospinal radiation and a total dose of 5400 cGy to 5580 cGy of primary site irradiation had an approximately 60% to 65% likelihood of survival at 5 years. The outcome of children with disseminated tumors was less favorable, with survival rates of 35% to 40% after similar therapy.

One of the earliest factors associated with improved survival was the extent of surgical resection.[3,4] Studies demonstrated that children with nondisseminated tumors who had undergone a total or near-total resection had a higher likelihood of disease control. Total surgical resection, therefore, has been recommended for all children with nondisseminated medulloblastomas whenever possible. Although this likely remains the correct approach with respect to disease control, there is increasing concern that more aggressive surgery for medulloblastoma has led to a higher incidence of posterior fossa mutism syndrome.[5] This syndrome, once considered rare, is characterized by the delayed onset of mutism (usually 6 hours to 24 hours after surgery) associated with severe hypotonia, other manifestations of cerebellar dysfunction, emotional lability, supranuclear palsies, and, possibly, a higher incidence of long-term intellectual sequelae. In two prospective North American studies performed by the Children's Oncology Group in the 1990s and early 2000s, a nearly 25% incidence of the syndrome was identified, with probable permanent sequelae seen in as many as 50% of children with this complication. This syndrome is associated with surgically related vermian damage, and it is unclear whether alterations in surgical techniques during the past two decades have led to an increased incidence of the syndrome or whether there is just increased recognition of the entity. The former seems more likely.

Adjuvant therapy for children with medulloblastoma has been based primarily on postoperative staging, and for the past quarter century patients have been stratified into average-risk (totally or near-totally resected and nondisseminated) or high-risk (disseminated and/or partially resected) groups. Although this schema has been in place for many years, assigning patients to these risk groups remains subjective. This is of major importance, as therapy is now increasingly based on risk assignment. In a recent prospective study of more than 400 children completed by the Children's Oncology Group, central review of neuroradiographic features found that submitted images were either inadequate for interpretation or were misinterpreted in nearly 20% of the cohort.[6] For patients in whom metastatic disease was missed and who were assigned to less aggressive therapy, overall survival was significantly poorer. A host of neurobiologic parameters associated with outcome for children with medulloblastoma have been identified. To date, studies of these parameters have been retrospective in nature and have not been incorporated into prospective studies to modify risk stratification.

Although a definitive randomized trial comparing treatment with radiation alone to treatment with radiation and chemotherapy has not been performed for children with

medulloblastoma, evidence increasingly suggests that the addition of chemotherapy during and after radiation therapy has improved survival for those between 3 years and 21 years of age.[6,7] In essentially every study to date, the best 5-year survival rates for children with nondisseminated medulloblastoma after treatment with radiation therapy alone ranges from 60% to 65%.With the addition of chemotherapy before and after radiotherapy using various regimens, 5-year progression-free survival rates of 80% to 85% are now being reported.[6,8,9] This has allowed the conventional dose of craniospinal radiation therapy to be reduced from 3600 cGy to 2400 cGy, with probable improvement in neurocognitive outcome. These encouraging results in patients with nondisseminated, totally or near-totally resected tumors have led to studies that are now evaluating further reductions in craniospinal radiation doses (down to 1800 cGy) for patients with average-risk disease.

Survival rates for patients with high-risk disease also are improving. Aggressive chemotherapy during and after radiation therapy has resulted in survival rates ranging from 60% to 70%, compared with 30% to 40% with radiotherapy alone.[8] These improvements have been accomplished with more aggressive surgery, detailed radiotherapy planning, and the routine use of chemotherapy. Interestingly, and somewhat surprisingly, chemotherapy used before radiation, which by design delays the initiation of radiotherapy, has not been as successful in controlling disease as using chemotherapy during and after radiotherapy. Most studies are now focusing on the use of chemotherapy primarily during and after radiotherapy.[6,7,9]

The incorporation of biology not only into stratification but also into therapy has been frustratingly slow. Increasingly, evidence shows that medulloblastomas arise from one of the cerebellum's two germinal zones – either the ventricular zone or the external granular layer.[10] Because the potential precursor cells in these two zones differ biologically, it has been postulated that medulloblastomas also differ biologically depending on the germinal region from which they arise. The external granular layer is thought to possess more restrictive neuronal precursors and is more likely to give rise to desmoplastic medulloblastomas.[11] Sonic hedgehog signaling has been implicated as integral to the development of desmoplastic medulloblastomas and possibly other types as well. In contrast, more classical midline medulloblastomas are believed to arise from cells of the ventricular zone, possibly from less-restricted neural stem cells. Disseminated medulloblastomas have been shown to differ in their molecular genetic makeup relative to tumors that are not metastatic, and the overexpression of certain genes has led to the postulation of a metastatic pathway that can be targeted for treatment.[12] At present, inhibitors of the Sonic hedgehog pathway, as well as those of growth receptors and components of aberrant signaling pathways (believed active in “classical” medulloblastomas), are in early clinical trials. However, with the exception of retinoic acid, a pro-apoptotic agent, biologic therapies have not yet been incorporated into prospective clinical studies.

Developing new therapies for medulloblastoma is crucial, as survivors presently face multiple sequalae, including abnormal cognition, hormonal deficits, neurologic deficits, obesity, and the possibility of developing secondary tumors.[13–17] Some of these long-term sequelae are related to the tumor and are possibly associated with other prediagnostic factors, such as concomitant hydrocephalus. However, many of the sequelae have been predominantly related to the therapy the children have received, including surgical complications, cranial irradiation-induced long-term brain injury, and the additive side effects of chemotherapy, such as cisplatin-induced ototoxicity.

In summary, the management of children with medulloblastomas who are older than 3 years of age has resulted in improved reported survival rates. Some of the more recent reported

improvements may be more apparent than real, however, as reclassification has resulted in a more pristine favorable average-risk group and possibly a less-aggressive high-risk subset of patients. As neuroimaging becomes more refined and consistent across centers (or rapid centralized radiographic review is instituted) and biologic parameters are incorporated into the stratification systems, more patients will likely be considered to have higher-risk disease, and comparison of outcome to that reported in the past will be even more difficult.[18–25] Although biologic advances have been impressive, they have not yet changed stratification in real time. Furthermore, although new therapeutic targets have been identified, they have yet to be fully validated or exploited. Improvements in reported survival rates for children with medulloblastoma have not been associated with a dramatic improvement in quality of life. The reduction of craniospinal radiation therapy has been beneficial, but significant late sequelae remain common, and in some situations, as is the case of posterior fossa mutism syndrome, may even be occurring at an increased rate.

Infantile Embryonal Tumors

Infantile malignant tumors are extremely difficult to treat, and many questions remain regarding their management. For example, there is no consistent definition of which patient is too young for radiation treatment, especially focal radiation. The identification of the atypical teratoid/rhabdoid tumor in the mid-1980s and separation of this tumor from other infantile embryonal tumors was a significant diagnostic advance.[26,27] However, this has not led to effective therapy for this tumor type, as the likelihood of survival of children with teratoid/rhabdoid tumors remains extremely low, with 3-year survival being reported in no more than 10% to 20% of infants with this disease.

The therapy of nondesmoplastic infantile medulloblastomas also remains suboptimal, although there is some suggestion that intensification of chemotherapy may have improved the likelihood of long-term control. It is unclear whether the reintroduction of focal radiation therapy following chemotherapy for these children will improve survival. For the 30% of infants with disseminated medulloblastomas, there has been little in the way of improvement. The incorporation of new biologic approaches is desperately needed for infants with all embryonal brain malignancies.

For infants with nondisseminated medulloblastomas, there is some evidence that intensification of therapy, be it with higher-dose chemotherapy supported by peripheral stem cell rescue or the introduction of additional drugs to multiagent chemotherapeutic regimens, such as methotrexate, has led to improved survival.[28–30] However, significant questions remain whether the major reasons for this reported higher survival rate are due to other factors, such as the removal of patients with teratoid/rhabdoid tumors from the medulloblastoma subgroup, as patients with teratoid/rhabdoid tumors have an exceedingly dismal prognosis, and/or the inclusion of more favorable-risk patients on clinical trials, rather than to a direct effect of therapy. It has been recently found that the desmoplastic variant of medulloblastoma, which comprises between 30% and 60% of infantile medulloblastomas, has a significantly better prognosis than the so-called classical medulloblastoma.[29] In a relatively small study of 23 children with classical and 20 children with disseminated medulloblastomas treated with chemotherapy, which included intrathecal and intravenous methotrexate, 85% of children with desmoplastic tumors survived, compared with 34% for children with classical tumors. Thus, if more infants with desmoplastic tumors were inadvertently enrolled in a small clinical trial, it would significantly skew results.

Low-Grade Gliomas

Low-grade gliomas comprise the majority of childhood brain tumors. In contrast to those occurring in adults, pediatric low-grade gliomas are predominantly pilocytic tumors.[1,31,32] Results of a prospective trial performed by the Children's Oncology Group disclosed that degree of resection was the most important predictor of outcome for children with low-grade tumors, essentially independent of histological subtype, and in the 334 children in that study who underwent gross total resection, 10-year progression-free survival was over 95%. Patients with subtotal and near-total resected tumors fared less well. Patients with pilocytic tumors and gangliogliomas had the best survival rates.

The most dramatic change in approach to therapy for childhood low-grade tumors over the past 20 years has been the recognition that despite their histologically benign characteristics, progressive, non-fully resectable tumors are responsive to chemotherapy. Various chemotherapeutic approaches have been used and the widest experience has been with the combination of carboplatin and vincristine.[33] This regimen stabilizes disease in nearly 90% of patients and measurably shrinks tumors in 50% to 60% of children less than 5 years of age who have progressive low-grade gliomas. In children with neurofibromatosis type 1 and progressive low-grade gliomas, nearly 75% of patients maintained their response 3 years to 5 years after treatment, but only 30% to 40% of those children without neurofibromatosis type 1 were progression-free 3 years to 4 years after initiating therapy. The efficacy of other drugs to improve this progression-free survival rate and delay the need for radiotherapy remains under study, as is the assessment of the short- and long-term safety of alternative regimens.

A better understanding of the biology of childhood low-grade tumors is needed. Biologic-based therapies may be quite effective, as prolonged disease stabilization to avoid the need for radiotherapy is often the over-riding goal. The long-term outcome of patients with low-grade tumors, especially after treatment with radiotherapy, is another area that needs to be explored. As radiotherapy techniques become more refined, there may be a need to revisit how early radiotherapy can be “safely” incorporated into treatment.

High-Grade and Brainstem Gliomas

Progress in the management of high-grade gliomas, including brainstem gliomas, has been minimal over the past two decades.[34–36] Other than the recognition that some brainstem gliomas (eg, tectal tumors and exophytic cervicomedullary lesions) are more likely to be low-grade pilocytic lesions and should be treated differently than diffuse intrinsic brainstem gliomas, approaches to therapy have changed little.[37,38] Treatment approaches for diffuse intrinsic brainstem tumors, including those involving preradiation chemotherapy and postradiation chemotherapy or those that have increased the total dose of radiotherapy by means of different radiation fractionation schedules (primarily hyperfractionated radiation therapy), have not resulted in improved survival and often have caused increased morbidity. At present, a host of biologic agents are under study and are primarily being used concomitant with radiotherapy, to act as both radiosensitizers and antineoplastic agents.

A major limitation in discovering new directions for the therapy of brainstem gliomas is the lack of tissue available for biologic study. In most cases, tissue confirmation is not needed for diagnosis. Although there is some evidence that newer surgical techniques may cause less morbidity, there is still a significant inherent risk in biopsy and it is unclear whether biopsy can be ethically performed unless the information obtained from biopsy of diffuse intrinsic lesions will be used to alter therapy for the patient being operated upon. At the same time, without more biologically driven interventions, it is going to be difficult to make progress in the management of this tumor.

Similarly, there has been little progress over the past quarter century in the management of high-grade gliomas.[37–39] Data increasingly suggest that pediatric high-grade gliomas differ biologically from those arising in adults.[2] However, the clinical significance of these differences is unclear, as is how these differences can be exploited to direct therapy.

Ependymomas

Increasing survival rates have been recently reported for childhood ependymomas. Surgery remains an extremely important component of management and the best survival rates have been reported in patients whose tumors have been grossly totally resected.[40,41] With present means of radiotherapy, over 75% of patients with infratentorial tumors after gross total resection and focal, primarily conformal, radiotherapy can be expected to survive without evidence of recurrent disease 5 years from diagnosis.[41] Preliminary data also suggest a lack of significant neurocognitive deficits secondary to the radiotherapy used.

Various factors have been variably associated with outcome for children with ependymomas.[42] These include tumor location, patient age, and degree of histological anaplasia. There is increasing interest in once again using chemotherapy, either prior to or after radiotherapy, in patients with subtotally resected tumors. The role of second-look surgery after chemotherapy, prior to radiotherapy, is under study. However, an extremely important issue in these types of studies is the surgically related morbidity of reoperation.

Most of the progress in the treatment of childhood ependymomas has been to the result of more aggressive surgery and earlier use of conformal radiotherapy. Whether treatment-related sequelae will increase, with a resulting decrease in quality of life of long-term survivors, is a major issue that should be carefully evaluated. To date, new approaches for childhood ependymomas have not been biologically based, although there is new information concerning the cellular origin of these tumors.

Summary

In summary, progress has been made in the management of childhood brain tumors. Much of this progress has been slow, but real, and has been documented in painstaking multicenter prospective studies performed over many years. There are improvements in progression-free survival, and probably in overall survival, for children with medulloblastoma and possibly some subsets of patients with ependymomas and infants with malignant gliomas. Alterations (? reductions in intensity) of therapy may have also resulted in improved quality of life for children with medulloblastomas and low-grade gliomas, although this is far from completely proven.

However, little progress has been made in the management of high-grade gliomas, brainstem gliomas, disseminated medulloblastomas, and subsets of infants with malignant tumors. A major issue that needs to be addressed is whether biologic data that are just becoming available can be used to change the way childhood brain tumors are treated. There has been an explosion in the understanding of the biology of childhood brain tumors, but these advances have not yet been integrated into treatment. Many biologic targets have been identified, but few have been validated as crucial processes that sustain tumor growth or spread. The major question that must be answered is whether treatments aimed at these targets will result in better disease control in patients, with less morbidity. What is also needed is more focused neurobiologic investigations into rarer childhood brain tumors and study of the differences between histologically similar tumors arising in children and adults. Although translating these molecular findings into biologically based management is a major goal and likely the best hope for future improvements in outcome for most of the tumor types that comprise childhood brain tumors, incorporating these new therapies will

require a critical analysis of the impact of these advances, not only on survival, but also on quality of life.

Acknowledgments

This article was presented at the Neurobiology of Disease in Children: Symposium on Central Nervous System Tumors, in conjunction with the 36th annual meeting of the Child Neurology Society, Quebec City, Quebec, October 10, 2007.

References

1. Central Brain Tumor Registry of the United States. Statistical report: primary brain tumors in the United States, 1995–1999. Published by the Central Brain Tumor Registry of the United States; 2005.
2. Pollack IF, Finkelstein SD, Woods J, et al. Expression of p53 and prognosis in children with malignant gliomas. N Engl J Med. 2002; 346:420–427. [PubMed: 11832530]
3. Packer RJ, Cogen P, Vézina G, Rorke LB. Medulloblastoma: clinical and biologic aspects. Neuro Oncol. 1999; 1:232–250. [PubMed: 11550316]
4. Albright AL, Sposto R, Holmes E, et al. Correlation of neurosurgical subspecialization with outcomes in children with malignant brain tumors. Neurosurgery. 2000; 47:879–887. [PubMed: 11014428]
5. Robertson PL, Muraszko KM, Holmes EJ, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg. 2006; 105(S6 Pediatrics):444–451. [PubMed: 17184075]
6. Packer RJ, Gajjar A, Vézina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol. 2006; 24:4202–4208. [PubMed: 16943538]
7. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. J Clin Oncol. 2003; 21:1582–1591.
8. Gajjar A, Chintagumpala M, Ashley D, et al. 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. 2006; 7:813–820.
9. Kuhl J, Muller HL, Berthold F, et al. Preradiation chemotherapy of children and young adults with malignant brain tumors: results of the German pilot trial HIT'88/'89. Klin Padiatr. 1998; 210:227–233. [PubMed: 9743957]
10. Read TA, Hegedus B, Wechsler-Reya R, Gutmann DH. The neurobiology of neurooncology. Ann Neurol. 2006; 6:3–11. [PubMed: 16802285]
11. Raffel C, Jenkins RB, Frederick L, et al. Sporadic medulloblastomas contain PTCH mutation. Cancer Res. 1997; 57:842–845. [PubMed: 9041183]
12. MacDonald TJ, Brown KM, LaFleur B, et al. Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease. Nat Genet. 2001; 29:143–152. [PubMed: 11544480]
13. Ris MD, Packer R, Goldwein J, et al. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. J Clin Oncol. 2001; 19:3470–3476. [PubMed: 11481352]
14. Mulhern RK, Kepner JL, Thomas PR, et al. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. J Clin Oncol. 1998; 16:1723–1728. [PubMed: 9586884]
15. Gurney JG, Kadan-Lottick NS, Packer RJ, et al. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. Cancer. 2003; 47:663–673. [PubMed: 12548609]

16. Packer RJ, Gurney JG, Punyko JA, et al. Longterm neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: Childhood Cancer Survivor Study. J Clin Oncol. 2003; 21:3255–3261. [PubMed: 12947060]

17. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2006; 98:1528–1537. [PubMed: 17077355]

18. Eberhart CG, Kratz J, Wang Y, et al. Histopathological and molecular prognostic markers in medulloblastoma: c-myc, N-myc, TrkC, and anaplasia. J Neuropathol Exp Neurol. 2004; 63:4441–4449.

19. Ellison DW, Onilude OE, Lindsey JC, et al. beta-Catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour committee. J Clin Oncol. 2005; 23:7951–7957. [PubMed: 16258095]

20. Grotzer MA, Hogarty MD, Janss AJ, et al. MYC messenger RNA expression predicts survival outcome in childhood primitive neuroectodermal tumor/medulloblastoma. Clin Cancer Res. 2001; 7:2425–2433. [PubMed: 11489822]

21. Gilbertson S, Wickramasinghe C, Hernan R, et al. Clinical and molecular stratification of disease risk in medulloblastoma. Br J Cancer. 2001; 85:705–712. [PubMed: 11531256]

22. Grotzer MA, Janss AJ, Fung K, et al. TrkC expression predicts good clinical outcome in primitive neuroectodermal brain tumors. J Clin Oncol. 2000; 18:1027–1035. [PubMed: 10694553]

23. Pomeroy S, Tamayo P, Gaasenbeek M, et al. Prediction of central nervous system embryonal tumour outcome based on gene expression. Nature. 2002; 415:436–442. [PubMed: 11807556]

24. Gajjar A, Hernan R, Kocak M, et al. Clinical, histopathologic, and molecular markers of prognosis: toward a new disease risk stratification system for medulloblastoma. J Clin Oncol. 2004; 15(22): 984–993. [PubMed: 14970185]

25. Ray A, Ho M, Ma J, et al. A clinicobiological model predicting survival in medulloblastoma. Clin Cancer Res. 2004; 10:7613–7620. [PubMed: 15569993]

26. Rorke LB, Packer RJ, Biegel JA. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg. 1996; 85:56–65. [PubMed: 8683283]

27. Packer RJ, Biegel JA, Blaney S, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop. J Pediatr Hematol Oncol. 2002; 24:337–342. [PubMed: 12142780]

28. 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. N Engl J Med. 1993; 328:1725–1731. [PubMed: 8388548]

29. Rutkowski S, Bode U, Deinlein F, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med. 2005; 352:978–986. [PubMed: 15758008]

30. Geyer JR, Sposto R, Jennings M, et al. Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. J Clin Oncol. 2005; 23:7621–7631. [PubMed: 16234523]

31. Pollack IF. The role of surgery in pediatric gliomas. J Neurooncol. 1999; 42:271–288. [PubMed: 10433110]

32. Wisoff JH, Boyett JM, Berger MS, et al. 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. 1998; 89:52–59. [PubMed: 9647172]

33. Packer RJ, Ata J, Allen J, et al. Treatment utilizing carboplatin and vincristine for children with newly-diagnosed progressive low-grade gliomas. J Neurosurg. 1997; 56:747–754. [PubMed: 9126887]

34. 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 Neurooncol. 1989; 7:165–177. [PubMed: 2550594]

35. Finlay JL, Boyett JM, Yates AJ, et al. 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. 1995; 13:112–123. [PubMed: 7799011]

36. MacDonald TJ, Arenson E, Sposto R, et al. Phase II study of high dose chemotherapy before radiation in children with newly diagnosed high-grade astrocytoma: final analysis of Children's Cancer Group study 9933. Cancer. 2005; 104:2862–2871. [PubMed: 16315242]

37. Rubin G, Michowitz S, Horev G, et al. Pediatric brain stem gliomas: an update. Childs Nerv Syst. 1998; 14:167–173. [PubMed: 9660117]

38. Mandell LR, Kadota R, Freeman C, et al. 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. 1999; 43:959–964. [PubMed: 10192340]

39. Farmer JP, Montes JL, Freeman CR, et al. Brainstem Gliomas. A 10-year institutional review. Pediatr Neurosurg. 2001; 34:206–214. [PubMed: 11359114]

40. Horn B, Heideman R, Geyer R, et al. A multi-institutional retrospective study of intracranial ependymoma in children: identification of risk factors. J Pediatr Hematol Oncol. 1999; 21:203–211. [PubMed: 10363853]

41. Merchant TE, Jenkins JJ, Burger PC, et al. Influence of tumor grade on time to progression after irradiation for localized ependymoma in children. Int J Radiat Oncol Biol Phys. 2002; 53:52–57. [PubMed: 12007941]

42. Bouffet E, Perilongo G, Canete A, et al. Intracranial ependymomas in children: a critical review of prognostic factors and a plea for cooperation. Med Pediatr Oncol. 1998; 30:319–329. [PubMed: 9589080]