

# Medulloblastoma

by

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Medulloblastoma is the most common primary malignant central nervous system tumor arising in childhood. Survival rates for children with medulloblastomas have nearly doubled and so has the recognition that many survivors are impaired and new forms of treatment are needed. Its understanding and management represents both the progress and challenges involved in the treatment of children with brain tumors over the past quarter century. Medulloblastomas arise in the fourth ventricle, between the brain stem and cerebellum in a region termed the posterior-fossa. Symptoms may be caused by direct compression of the tumor of structures in this region of brain or due to blockage of cerebrospinal fluid at the outlets of the third or fourth ventricles and secondary hydrocephalus. Common symptoms include headaches and vomiting due to hydrocephalus and progressive unsteadiness. Diagnosis is usually made within one to three months of onset of symptoms, as medulloblastoma is a fast growing tumor. Occasionally due to bleeding within the tumor, a patient will be in a coma or have severe acute neurologic compromise at the time of diagnosis.

Histologically, medulloblastomas have a very characteristic appearance and are composed of primitive cells. There has been much controversy, in the past, over the origin of these cells, as there is no such thing as a medulloblast in the central nervous system. Some have believed that microscopically similar tumors arising in the pineal region (pineoblastomas) or cortex (supratentorial PNETs) were biologically identical, but

recent molecular studies demonstrate that these are different tumors. It is now believed that medulloblastomas represent a group of different tumor types which arise in the posterior-fossa and have similar microscopic appearances. Medulloblastomas emanate from at least two different types of primitive, possible stem cells, in the nervous system – one arising from the midline of the cerebellum and another arising from a more laterally placed portion of the cerebellum, composed of possibly more restricted stem cells. These different origins may explain, in part, the difference in prognosis between children with similar microscopically appearing medulloblastomas. Multiple different molecular pathways (cellular signaling pathways which underlie tumor development and propagation) have been noted in patients with medulloblastoma. The different molecular signals that these tumors may possess also suggest that medulloblastoma is not just one disease and gives added insight into potential targets for treatment.

## Surgery

The first step in management of medulloblastoma is almost always surgery. Because of associated hydrocephalus in over 80% of patients at the time of diagnosis, a decision needs to be made how best to relieve intracranial pressure and divert cerebrospinal fluid prior to surgery. In most centers, these measures include the use of high-dose steroids to relieve pressure and a temporary lateral ventricular drain (a ventriculostomy) placed prior to surgery. With the placement of such a drain and subsequent surgery to remove the tumor, permanent ventriculoperitoneal shunting can now be avoided in well over 50% of children with medulloblastoma. Another approach, which is increasingly used, is third ventriculostomy, where a small hole is made in the ventricular system at the time of definitive surgery, allowing cerebrospinal fluid to drain; also negating the need for a permanent ventriculoperitoneal shunt.

It has been shown in multiple studies that in children with medulloblastomas localized to the primary site at the time of diagnosis, the degree of resection is of importance in determining the likelihood of survival. Patients whose tumors are totally, or near totally, removed fare better than those whose tumors are only partially resected or biopsied. Although it has been conventionally stated that patients with greater than

1.5 cm<sup>2</sup> of residual disease after surgery have a poorer prognosis, this has not been conclusively shown. Surgery is not without its risks and removal of the medulloblastoma may result in a direct damage to the brainstem or cerebellum. Such damage can be seen on the post-operative MRI. In addition to direct postoperative damage, it has also been increasingly reported that surgery may result in a complication which has been termed the “posterior-fossa mutism syndrome”. Children with this impairment seem to awaken relatively well from surgery and may say a few words. However, within 24 to 48 hours, it becomes obvious that the child is mute and has associated deficits including hypotonia (low tone), dysmetria (difficulty reaching for objects), swallowing difficulties, marked irritability, and often emotional lability. The exact cause of the syndrome is unclear, but there is increasing evidence that this is due to a surgically-induced disruption of critical pathways connecting the brainstem to the cortex. The immediate postoperative MRI scan may not show this damage, but years later atrophy is often seen in the cerebellum and, at times, in the brainstem. This syndrome has been reported in as high as 25% of patients after surgery and may result in permanent difficulties in up to one-half of those afflicted.

### Disease Stratification

Following surgery, children with medulloblastoma have conventionally been separated, based on age, the degree of tumor resection or residual disease, and the extent of disease at the time of diagnosis, into risk groups. For determination of extent of disease at diagnosis, neuroimaging of the entire neuroaxis for evidence of tumor dissemination, preferably to be done prior to surgery or, if not, after surgery, and cerebrospinal fluid analysis (by a spinal tap) for free-floating tumor cells must be performed. Children less than 3 years of age have been arbitrarily separated from those greater than 3 years because of concerns over the neurotoxic effects of treatment used for older patients, which cannot be tolerated in younger patients. This has resulted in patients being separated into so-called average- and high-risk groupings. However, it has become increasingly clear over the past decade that such clinically-based separation or stratification of patients can likely be improved with the incorporation of new molecular

findings from an individual child's medulloblastoma tissue. The exact biologic parameter or best combination of biological parameters to be used to separate patients into risk groups is under active study. However, it does seem clear that the average- and high-risk groupings will be modified in the near future.

### Management of Children Three Years of Age or Greater

Children greater than 3 years of age with average-risk disease are those with no evidence of tumor dissemination and total or near-total tumor removal, and those with poor-risk disease are those with disseminated disease and/or partial tumor removal. Recently, children with histologically anaplastic medulloblastomas have also been placed in the poor-risk group. For these older children, increasing evidence suggests that those children who have abnormalities in a specific signaling pathway, the WNT pathway (who will also often have chromosomal abnormalities - a monosomy of the 6<sup>th</sup> chromosome), carry an extremely favorable prognosis. In contradistinction, even average-risk patients who have worrisome molecular findings, including elevation of an oncogene called 'myc' or possibly other unfavorable biologic parameters such as over-activation of the ras-map kinase pathway or over-expression of ERBB2, may fare less well. These biologic parameters, however, have not been proven to be of utility, yet, by prospective trials.

For children 3 years of age or older with average-risk disease, treatment now conventionally employs both radiation and chemotherapy. Unfortunately, children with medulloblastoma cannot only be treated with radiotherapy to the primary tumor site, but also require radiation to the entire neuroaxis (brain and spine) to prevent tumor relapse. This is craniospinal radiotherapy. Craniospinal radiotherapy may cause significant long-term sequelae including progressive intellectual loss and endocrinologic dysfunction. For this reason, the amount of radiation that has been utilized for children with average-risk disease has been decreased over the past decade. Studies have demonstrated that the dose of craniospinal radiotherapy can be decreased from 3600 cGy to 2400 cGy (a one-third reduction) without an increased rate of tumor relapse. Studies are ongoing attempting to try to decrease the dose of craniospinal radiation down to as low

as 1800 cGy in younger patients (between ages 3 and 7 years) with nondisseminated tumors. Patients in these exploratory studies have to be extremely carefully chosen because if there is spread of disease which is missed at the time of diagnosis, these reduced doses of radiation therapy will likely result in tumor relapse and death.

Chemotherapy has been shown to be of benefit for children with medulloblastoma, as long as the chemotherapy is given during and after radiotherapy. Pre-radiation chemotherapy has not been shown to improve survival. Some studies, especially those coupling chemotherapy with reduced-dose craniospinal radiation therapy, have resulted in overall poorer survival rates than treatment with radiotherapy alone. A variety of different chemotherapeutic regimens have been shown to be of benefit, including the use of vincristine during radiotherapy and the combination of vincristine, cisplatin, and CCNU, or vincristine, cisplatin, and cyclophosphamide, following radiotherapy, for up to one year. Other approaches which have been successfully used include the use of higher-dose chemotherapy with vincristine, cisplatin, cyclophosphamide, and etoposide supported by peripheral stem cell rescue following standard doses of radiotherapy. All of these studies have resulted in five-year disease control rates of 80% or more in patients with nondisseminated disease.

For children with poor-risk medulloblastoma, treatment is not as straightforward. In most cases, higher doses of craniospinal radiation therapy are required (3600 cGy) and there have been attempts to make chemotherapy more effective by increasing the dosage of chemotherapy or utilizing additional agents. One approach, currently under study, is the use of a radiosensitizing chemotherapy (carboplatin) during radiation. Another therapeutic attempt is to use higher dose chemotherapy, once again supported by peripheral stem cell rescue, following radiotherapy. These more aggressive approaches have resulted in somewhat better survival rate, ranging between 60 and 65%, at five years, in children with poor-risk medulloblastoma.

## Newer Therapies

Over the next few years, therapy for older children with medulloblastoma will likely change. For children with average-risk disease, because of the concern over treated-

related sequelae, there will further attempts to both reduce the dose of craniospinal radiation therapy and to decrease the volume of radiotherapy needed for the local tumor boost. Conformal radiotherapy techniques are now widely being employed attempting to spare the hearing apparatus (cochlea) in children with medulloblastoma. In addition, proton beam irradiation is now being utilized, as it has significant theoretic advantages over standard photon radiotherapy, as there is a decrease in the amount of scatter irradiation to sites outside the nervous system, including the cochlea and organs such as the heart, lungs, bowel, and ovaries. Over the next few years a host of biologic agents will also be incorporated in attempts to both increase survival and make treatment safer.

### Medulloblastomas in Infants

For infants with medulloblastoma, there has been significant reluctance to give craniospinal radiation therapy. Such therapy is likely to cause severe neurocognitive damage and likely will result in mental retardation in most survivors. Once again, separation of patients into risk groups may be helpful in guiding therapy. Up to approximately five years ago, all infants with medulloblastoma were treated in a similar fashion. However, there is increasing evidence that a subgroup of infants with medulloblastoma have a relatively more benign form of the disease, namely those children with tumors that have been termed “desmoplastic/nodular” based on microscopic features. It is also believed that desmoplastic tumors are driven by a specific molecular pathway, the sonic hedge-hog pathway, and may be more sensitive to chemotherapy.

For children less than 3 years of age with nondisseminated medulloblastoma, most centers now recommend the initial use of chemotherapy, usually in fairly high dose, in an attempt to delay, if not completely avoid, the need for radiotherapy. In those patients whose tumors are not disseminated and are totally removed at the time of surgery, especially if they have desmoplastic tumors, chemotherapy alone may be all that is needed. There is no clear-cut consensus on which drug regimen is best; however, both high-dose chemotherapy regimens supported with peripheral stem cell

rescue and those including a potentially neurotoxic drug, methotrexate, given both in the cerebrospinal fluid (intrathecally) and at high-dose systemically, have resulted in apparent better control rates. In those children with the so-called “classical”, nondesmoplastic medulloblastoma, there is a question whether after chemotherapy, localized radiotherapy should be given. Survival rates for infants with non-disseminated medulloblastomas treated with chemotherapy alone or with chemotherapy plus local radiotherapy, have ranged between 30 and 50%. In those children with the “nodular/desmoplastic variant”, survival rates of 70% or greater with chemotherapy alone have been demonstrated.

For infants less than 3 years of age with disseminated disease and/or partially resected tumors, especially with unfavorable histological features, treatment with chemotherapy has not been nearly as successful. Although some children can survive after treatment with chemotherapy alone, this occurs in probably 20% or less. Infants with disseminated disease rarely will be successfully treated with chemotherapy alone. For these higher-risk patients, craniospinal radiotherapy may be needed for long-term disease control, but may also result in severe sequelae. It is hoped that the incorporation of new biologic agents will improve the likelihood of long-term survival.

### Long-term Sequelae

A major concern in the treatment of children with medulloblastoma are the sequelae of treatment. Because of the tumor and its associated hydrocephalus, there may already be significant brain damage prior to the initiation of any treatment. Surgical complications have been reported to increase the likelihood of poor neurologic and intellectual outcome, especially if there is posterior-fossa mutism. Radiotherapy, as previously described, can result in significant long-term sequelae, including progressive intellectual compromise. Such progressive damage is most severe in younger children, especially those less than 5 to 7 years of age, and in those receiving higher doses of craniospinal irradiation therapy. After 3600 cGy of craniospinal radiation therapy, progressive intellectual declines, with I.Q.'s falling 20 to 30 points, have been frequently seen in children less than 7 years of age. In older children, there is less measurable

decline, but often significant learning disabilities are evident. The uses of reduced doses of craniospinal radiation therapy likely results in less intellectual compromise, but there continues to be significant IQ falls in the younger age group, ranging between 10 and 20 points within three years.

Hormonal deficits are common following higher doses of craniospinal radiation therapy, primarily due to irradiation received by the hypothalamic region. Dependent on dose and volume of radiotherapy, 50% or more of patients will be growth hormone insufficient and a somewhat lower percentage insufficient in thyroid hormone production. Late or abnormal menses, as well as precocious puberty, can also be seen because of hypothalamic involvement. Hormonal sequelae can be partially overcome by replacement therapy including growth hormone replacement. However, because of the effects of radiation therapy on the spine, most patients with medulloblastoma, treated with craniospinal radiotherapy, will suffer some degree of short stature. The long-term psychosocial implications of medulloblastoma and its treatment and its effects on other outcomes such as the ability to live independently in the future, gain employment, and have families, is under increasing scrutiny and medulloblastoma patients are clearly challenged in these and other issues as they age. Another issue that these long-term survivors have to face is the possibility of secondary malignancies, either due to genetic predispositions or secondary to radiation and/or chemotherapy.

## Summary

The management of patients with medulloblastoma has greatly changed over the past 20 to 30 years and continues to evolve rapidly. There is no question that more children with medulloblastoma are now surviving years after treatment, many cured of their disease. These children, as they grow, face many challenges including schooling and gaining independence in the future. It is hoped, as the molecular understanding of this disease improves, as is now rapidly happening, therapy can be modified and personalized so that more children not only survive, but survive with a better quality of life.

**Studies Open or Soon To Be Opened for Children with Medulloblastoma in the Washington, DC Region.**

<p><b>Study</b></p> <p>Participating Institutions</p> <p>Eligibility Comments</p>	<p><b>Treatment of Children with Average-Risk Medulloblastoma with Reduced-Dose Radiation Therapy and One of Two Chemotherapies: A Phase III CCG/POG Study</b></p> <p>Children's National Medical Center, Georgetown University Hospital, Inova Fairfax Hospital Children (greater than 3 years of age) with non-disseminated medulloblastomas</p> <p>This is a randomized study comparing two different chemotherapeutic approaches but utilizing a reduced-dose craniospinal radiation therapy for all patients; the study has accrued nearly 400 patients. <b>The study closed December 2000. In well-staged patients, greater than 80% are alive and free of disease greater than 5 years from diagnosis. Both treatment arms did well.</b></p>
<p><b>Study</b></p> <p>Participating Institutions</p> <p>Eligibility</p> <p>Comments</p>	<p><b>Treatment of Children with Average-Risk Medulloblastoma with Reduced-Dose Radiotherapy and VCR, CCNU and CPPD Chemotherapy</b></p> <p>Children's National Medical Center</p> <p>Children (greater than 3 years of age) with non-disseminated and totally/near totally resected medulloblastoma This is a continuation of a study demonstrating a greater than 80% five-year survival rate in children with medulloblastoma</p>
<p><b>Study</b></p> <p>Participating Institutions</p> <p>Eligibility Comments</p>	<p><b>Multi-agent Chemotherapy and Deferred Radiotherapy for Infants with Malignant Brain Tumors (Children's Oncology Group)</b></p> <p>Children's National Medical Center, Georgetown University Children (less than 3 years of age) with malignant brain tumors, including medulloblastoma</p> <p>This is a nationwide study utilizing high-dose chemotherapy and deferring and obviating radiotherapy in children with medulloblastomas and other malignant brain tumors. This study is now closed. Nationally, preliminary results are encouraging.</p>
<p><b>Study</b></p> <p>Participating Institutions</p> <p>Eligibility Comments</p>	<p><b>High-Dose Chemotherapy and Peripheral Stem Cell Rescue and Metronomic Chemotherapy in Infants with Malignant Brain Tumors (Children's National Medical Center)</b></p> <p>Children's National Medical Center Infants with malignant brain tumors including medulloblastoma</p> <p>This currently open study utilizes high-dose chemotherapy and peripheral stem cell rescue for infants with malignant brain tumors in an attempt to improve survival and delay, if not obviate, the need for radiotherapy. Metronomic therapy is being offered, after completion of radiotherapy.</p>
<p><b>Study</b></p>	<p><b>ACNS0331 – A Study Evaluating Limited Target-boost Irradiation</b></p>

Participating Institutions	<b>and Reduced Dose Craniospinal Radiation Therapy (1800 cGy) and Chemotherapy in Children with Newly-diagnosed Standard Risk Medulloblastoma: A Phase 3 Double Randomized Trial</b>
Eligibility Comments	<b>Children’s National Medical Center</b> , Georgetown University, and INOVA Regional Outpatient Center.  This is a study evaluating the reduction of radiation therapy, in a randomized fashion, to 1800 cGy in children between 3 and 7 years of age with non-disseminated medulloblastoma. It also randomizes patients between standard local radiotherapy and more restricted conformal radiation therapy.
<b>Study</b>	<b>ACNSO332 – Efficacy of Carboplatin Administered Concomitantly with Radiation and Isoretinoin as a Pro-Apoptotic Agent in Other than Average-risk Medulloblastoma/PNET Patients.</b>
Participating Institutions	<b>Children’s National Medical Center</b> , Georgetown University, and INOVA Regional Outpatient Center.
Eligibility Comments	<b>Children’s National Medical Center</b> , Georgetown University, and INOVA Regional Outpatient Center.  This a randomized trial evaluating the efficacy of radiosensitization with carboplatin given during radiotherapy in children with high-risk medulloblastoma and other primitive neuroectodermal tumors except atypical teratoid/rhabdoid tumors.
<b>Study</b>	<b>PBTC-026 – A Feasibility Study of SAHA combined with Isoretinoin and Chemotherapy in Infants with Embryonal Tumors of the Central Nervous System</b>
Participating Institutions	<b>Children’s National Medical Center.</b>
Eligibility Comments	<b>This is a feasibility study adding a new biologic agent, SAHA, a histone d-acetylase inhibitor, with high-dose chemotherapy in children with embryonal tumors including medulloblastoma.</b>
<b>Study</b>	<b>PBTC-022 – A Phase 2 Study of Bevacizumab (Avastin) plus Irinotecan in Children with Recurrent, Progressive, or Refractory</b>
Participating Institutions	

Eligibility Comments	<p><b>Malignant Tumors including Medulloblastomas.</b></p> <p><b>Children's National Medical Center.</b></p> <p><b>This is an ongoing study evaluating the efficacy of this combination of drugs in children with recurrent medulloblastoma.</b></p>
<p><b>Study</b></p> <p>Participating Institutions</p> <p>Eligibility Comments</p>	<p><b>PBTC-025 and 025B – A Phase 1 Pharmacokinetic and Safety Study in Children with Recurrent or Refractory Medulloblastoma to Identify a Pharmacokinetic-based Dose of GDC-0449.</b></p> <p><b>Children's National Medical Center.</b></p> <p><b>This is an innovative biologic study for children and adults with recurrent medulloblastoma.</b></p>

*In 1989, Dr. Roger J. Packer joined the Children's National Medical Center (CNMC) in Washington, DC as Chairman of Neurology and Director of the Brain Tumor Program. Ten years later, he was appointed Executive Director of their newly created Center for Neuroscience and Behavioral Medicine. In 2009, he was appointed Senior Vice-President of the Center for Neuroscience and Behavioral Medicine, and Director of both the Brain Tumor Institute and the Daniel and Jennifer Gilbert Neurofibromatosis Institute at CNMC. He is Professor of Neurology and Pediatrics at the George Washington University, Professor of Neurology at Georgetown University, Professor in Neurosurgery at the University of Virginia and a consultant to the Pediatric Neuro-Oncology Program at the National Cancer Institute. He also chairs the Medulloblastoma Subcommittee of the Children's Oncology Group and serves as a member of the Pediatric Brain Tumor Consortium Steering Committee, and Brain and CNS Committee Commission on Cancer of the American College of Surgeons. He also continues to find time to serve voluntarily as the Senior Medical Advisor to the Childhood Brain Tumor Foundation, [www.childhoodbraintumor.org](http://www.childhoodbraintumor.org) for the past fifteen years, since its inception in 1994.*

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