Pediatric Brain Tumors

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Central nervous system (CNS) neoplasms are the second most common tumor of childhood and the third leading cause of death in children under 16 years of age. Brain and spinal cord tumors have now surpassed leukemia and lymphoma in mortality from pediatric cancer (Figure 1). The incidence of pediatric brain tumors appears to be on the rise; however, this may be secondary to advancements made in neuroimaging techniques that have enabled CNS tumors to be diagnosed earlier. The exact cause of pediatric brain tumors remains unknown. Primary CNS tumors have been associated with certain hereditary syndromes, which include neurofibromatosis type I (optic pathway-hypothalamic glioma, meningioma, neurofibroma), neurofibromatosis type II (schwannoma and ependymoma), tuberous sclerosis (subependymal giant-cell astrocytoma), and von Hippel-Lindau disease (cerebellar and spinal cord hemangioblastoma). Other syndromes such as Li-Fraumeni, Gardner, and Turcot have also been associated with brain tumors. Variation in cancer rates in different regions have suggested that environmental hazards such as electromagnetic radiation, pesticides, and nitrosamine exposure may be involved, but these concerns appear unsubstantiated. The combination of molecular biologic techniques, together with cytogenetic investigation, has provided insight into the changes that may explain some aspects of the genesis and progression of childhood brain tumors.

In general, pediatric brain tumors carry a better prognosis than adult brain tumors. There is suggestive evidence that the outcome of children treated for central nervous system cancer is correlated with the nature of the treatment facility. Children treated by
an experienced multidisciplinary team had better outcomes than children treated with identical protocols in facilities with less experience. Furthermore, advances in diagnostic capabilities, surgical techniques, and combined radiation and chemotherapy have increased long-term survival rates. However, whether the treatment includes surgery, chemotherapy, radiation, or a combination thereof, the therapeutic index is small. The margin between eradication of the tumor and possible damage to normal brain tissue is narrow. In no other form of childhood cancer does the quality of survival present a greater challenge. This article focuses on the epidemiology, classification, presentation, diagnostic evaluation, complications, and treatment of pediatric brain tumors.

EPIDEMIOLOGY

Twenty percent of all childhood cancers occur in the central nervous system. In the United States, the incidence has risen from approximately 2.4 to 3.3 new cases per 100,000 children per year. Fifteen hundred new pediatric brain tumors are diagnosed annually in the United States. Table 1 demonstrates the estimated number of new cancer cases and deaths in children under 15 years of age in the United States. One can see from the Table that brain tumors occur almost as often as leukemia and lymphoma and are just as likely to cause death. Over the past two decades, the mortality rate from pediatric brain cancer has declined from 2 per 100,000 to less than 0.9 per 100,000 per year, and an increasing proportion of children are surviving into adulthood.

Factors responsible for the improvement in survival parallel advances made in other childhood cancers. More children are cared for in pediatric centers and universities now than a decade ago. Recent developments in neuro-oncology make it more likely that these children will continue to be cared for in such facilities. A multidisciplinary team of medical professionals, including pediatricians, pediatric neurosurgeons, neuro-oncologists, intensivists, respiratory therapists, nutritionists, psychologists, physiotherapists, and many others, see to it that the many needs of these children are met while they undergo their intensive treatment.

CLASSIFICATION

Brain tumors can be classified according to histology and anatomic location. A simple classification of pediatric brain tumors is presented in Table 2. The common anatomic location of these tumors along with their frequency of occurrence is demonstrated in Figure 2. The location of these CNS tumors can be pictured by dividing the brain into two parts separated by a fibrous sheet called the tentorium. Masses arising below the tentorium are described as infratentorial, those above are supratentorial, including the so-called midline tumors. The posterior fossa is located below the tentorium and contains the brain stem and cerebellum. Approximately 50% of childhood brain neoplasms arise in this area. The supratentorial region contains the cerebral hemispheres, and midline structures such as the pituitary gland, hypothalamus, basal ganglia, and pineal region.

Posterior fossa tumors include medulloblastoma (cerebellar primitive neuro-ectodermal tumor—PNET), brainstem glioma, ependymoma, and cerebellar astrocytoma. Tumors arising in the midline are deep-seated and include pineal region tumors (germ cell tumors, PNET, and pineocytomas), optic pathway/hypothalamic tumors (gliomas), craniopharyngiomas, and suprasellar region germ cell tumors. Approximately 15% of all pediatric brain tumors

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**Table 1**

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>7235</td>
<td>1585</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2470</td>
<td>625</td>
</tr>
<tr>
<td>Brain and spinal cord</td>
<td>1445</td>
<td>405</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>780</td>
<td>219</td>
</tr>
<tr>
<td>Sympathetic nervous system</td>
<td>525</td>
<td>190</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>420</td>
<td>55</td>
</tr>
<tr>
<td>Kidney</td>
<td>410</td>
<td>50</td>
</tr>
<tr>
<td>Bone</td>
<td>320</td>
<td>15</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>200</td>
<td>5</td>
</tr>
<tr>
<td>Other sites</td>
<td>665</td>
<td>65</td>
</tr>
</tbody>
</table>

## Pediatric Brain Tumors

<table>
<thead>
<tr>
<th>Tumor Type (%) of Incidences</th>
<th>Tumor</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial (30 to 50)</td>
<td>Low-grade astrocytoma</td>
<td>Seizures, visual changes, incidental findings, hemiparesis</td>
<td>&gt;90% surgical removal; observation</td>
</tr>
<tr>
<td></td>
<td>High-grade astrocytoma</td>
<td>Seizures, increased ICP, mental status change, hemiparesis</td>
<td>&lt;90% surgical removal; observation of radiation* or chemotherapy</td>
</tr>
<tr>
<td>Midline (10-15)</td>
<td>Optic-nerve chiasmal gliomas</td>
<td>Seizures, endocrinopathies, increased ICP, visual changes</td>
<td>Observation, surgical debulking, radiation* and/or chemotherapy</td>
</tr>
<tr>
<td>Craniopharyngiomas</td>
<td>Seizures, visual changes, increased ICP, endocrinopathies</td>
<td>&gt;95% surgical removal; observation of radiation* or chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Pineal region</td>
<td>Increased ICP, no upward gaze, headache</td>
<td>Low-grade, surgery alone; high-grade, surgery and radiation* and chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Infratentorial/posterior fossa (50 to 60)</td>
<td>Medulloblastoma</td>
<td>Increased ICP, headache, morning vomiting, cranial nerve deficits, ataxia</td>
<td>Maximal surgical resection*; cranial/spinal radiation* and chemotherapy</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Neck pain, torticollis, increased ICP, cranial nerve deficits</td>
<td>Maximal surgical resection ± radiation* (chemotherapy in children)</td>
<td></td>
</tr>
<tr>
<td>Brain stem glioma</td>
<td>Cranial nerve deficits, hemiparesis, usually short history</td>
<td>Malignant tumors, diagnosis by MRI, radiation* ± chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long history/minimal symptoms/focal lesion on MRI usually in midbrain or medulla</td>
<td>Low-grade tumor, surgical debulking and observation or radiation* ± chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>


arise here. Supratentorial hemispheric tumors are usually gliomas, principally astrocytomas, but ependymomas and PNET can also arise here.

Approximately 80% of pediatric brain tumor cases occur in the first decade of life. The anatomic location of brain tumors varies during childhood. This is partly due to the different histologic types of tumors that are found at various ages, in some cases implying a congenital origin. In children younger than 1 year of age, supratentorial tumors predominate. These are often gliomas, teratomas, PNET, and choroid plexus tumors. From ages 1 through 11 years, medulloblastomas and other posterior fossa tumors occur more commonly. The incidence of supratentorial and infratentorial tumors is about the same during late childhood and adolescence. Histologic classification of brain tumors is a topic of constant update and some controversy. Basically, brain
common childhood illnesses. Other findings may be so localized that the anatomic site of the tumor can be predicted prior to diagnostic imaging. Persistent headache and vomiting, especially in the morning, should always arouse suspicion of a brain tumor.

The clinical manifestation of pediatric CNS tumors depends on several factors, including the growth rate of the tumor, its location, and the age of the patient. In general, more aggressively growing tumors are malignant and present acutely. Benign tumors are more often slow growing and insidious in onset. Tumors involving the cerebellum usually present with findings related to an elevation in intracranial pressure (ICP) due to obstruction of the fourth ventricle outlets and ataxia. Signs of increased ICP include headache, nausea, vomiting, and diplopia. Brain stem involvement leads to cranial nerve deficits, which may present with double vision, slurred speech, and swallowing disorders. Occasionally, brain stem tumors may also lead to hydrocephalus by compression of the aqueduct of Sylvius. In contrast, supratentorial masses present with more localizing findings such as hemiparesis and seizures. Children with tumors of the midline, such as optic/hypothalamic gliomas or craniopharyngiomas, usually present with endocrinopathies (diabetes insipidus, growth disorders), decreased vision, visual field defects, and signs of ICP, but rarely with hydrocephalus. Pineal region tumors usually present with increased ICP due to hydrocephalus and difficulties with upward gaze. A summary of pediatric brain tumors and their associated clinical signs is summarized in Table 2. In general, infants with brain neoplasms usually have nonspecific symptoms, which include irritability, vomiting, lethargy, and failure to thrive. An excessive growth of head circumference detected in regular pediatric visits should also raise a suspicion of either hydrocephalus or a brain tumor.

INCREASED INTRACRANIAL PRESSURE
Tumor growth in the CNS may be associated with an elevated intracranial pressure (ICP) either due to a space-occupying lesion or due to hydrocephalus. The most common signs are headaches and vomiting, but a decrease in degree of alertness and even posturing (decortication or decerebration) may be seen in more advanced cases. Tumors such as medulloblastoma, ependymoma, and cerebellar astrocytoma often lead to obstructive hydrocephalus by compressing the fourth ventricle and prevent the egress of cerebrospinal fluid and lead to an elevation of ICP. (See the article by Madikians and Conway on pp 613-620 for a detailed description of CSF dynamics.)

Children with increased ICP should be monitored closely in an inpatient setting. Those who are alert and neurologically intact are given dexamethasone, which usually decreases tumor swelling and possibly CSF production within the first day of treatment.

Patients with progressive neurologic dysfunction such as increasing somnolence, downward eye deviation, and posturing require emergent placement of a ventricular drain to allow the outflow of CSF if tumor resection cannot be performed acutely.\(^6\)\(^7\) Approximately one third of patients with posterior fossa tumors will require permanent ventriculoperitoneal shunts following surgical debulking.

**DIAGNOSTIC EVALUATION**

If the neurologic examination reveals signs of intracranial hypertension, an immediate diagnostic evaluation should be done, following stabilization of the patient. The role of neuroimaging in the evaluation of pediatric brain tumors is threefold: (1) identification of the neoplasm at the earliest possible stage following onset of symptoms, (2) accurate localization of the tumor so that biopsy or surgical excision may be undertaken and other forms of therapy may be considered, and (3) depiction of the size and nature of the neoplasm before, during, and after the various forms of therapy so that tumor response, residual or recurrent disease, or spread of tumor can be detected and quantified.\(^8\)

Magnetic resonance imaging (MRI) has surpassed computed tomography (CT) as the preferred diagnostic study for pediatric brain tumors.\(^9\) The MRI uses magnetic fields to create a "lifelike" picture of the brain. Advantages of MRI include superior resolution, easy manipulation of the image plane, and avoidance of ionizing radiation. MRI is also sensitive to acute, subacute, and chronic presence of blood products within tissue. Imaging of tissue is further improved with the use of contrast agents such as gadolinium-pentetic acid, which crosses the blood-brain barrier and enhances the signal abnormalities. One disadvantage of MRI is the length of time required for the study. Patients must remain motionless in a dark, noisy, tunnel-like atmosphere for up to 1 hour. Most young children will require sedation or anesthesia to complete the study. CT, on the other hand, is a quicker and less expensive test that can be used in an emergency situation such as with a sudden change in neurologic status, especially when intracranial bleeding or hydrocephalus is suspected.

Angiography is used infrequently and has been progressively replaced by magnetic resonance angiography (MRA), which uses MRI to noninvasively visualize these pathways. Occasionally, brain vascular malformations may be mistaken for tumors, and these tests may be helpful in elucidating the issue.

Children who are diagnosed with brain tumors, especially those of the posterior fossa such as medulloblastoma and ependymoma, may also require visualization of the spinal canal. MRI scans of the spine are performed in search of evidence of metastatic spread. When possible, these tests should be performed prior to surgery in order to avoid confusion caused by the presence of blood products following surgery.

Lumbar puncture, bone marrow aspirate, and bone scan are other diagnostic studies that may be performed after surgery as part of the evaluation of children diagnosed with malignant brain tumors, such as medulloblastomas and ependymomas, to look for tumor dissemination.

**TREATMENT**

**Surgery**

The primary treatment modality of pediatric brain tumors is surgery. However, surgery alone is curative in only approximately 20% of cases and further therapy, such as chemotherapy and radiation, may be required. Neurosurgical goals include establishment of tissue diagnosis, and reduction in overall tumor mass with the relief of elevated ICP and other neurologic dysfunction produced by the tumor mass. Gross total resection of both malignant and benign tumors has been correlated with prolonged survival rates.\(^10\) Some tumors (ie, diffuse brain stem gliomas) are not amenable to surgery because their location makes the risk of neurologic deficits too great.

Advanced neurosurgical methods such as ultrasonic surgical aspiration, carbon dioxide laser therapy, neuroendoscopy, and intraoperative guidance systems, electrocorticography and evoked potential monitoring have increased procedure efficacy and diminished perioperative complication rates.

**Radiation Therapy**

Radiation therapy affects the ability of cells to continue dividing by damaging DNA strands. Many pediatric brain tumors are radiosensitive. However, because of the toxicity to the developing brain, radiation methods have been modified to allow a more precise targeting of radiation through three-dimensional planning systems and, when possible, a decrease in the overall volume irradiated. Volume and dosage of radiation vary according to different histologic diagnoses. For instance, children with medulloblastomas receive radiation to the entire brain and spine, with a boost dose to the original tumor area; whereas children with brain stem gliomas receive involved field radiation (localized to the tumor area only). In young children and infants, there is a major thrust for deferral of radiation because of unacceptable long-term effects such as substantial cognitive impairment. Therefore, chemotherapy has been increasingly utilized in this patient population in an attempt treat these children until their age permits use of radiation therapy. The older the child, the lesser the side effects of radiation therapy, but long-term effects are described even in the adult population.\(^11\)

**Chemotherapy**

Chemotherapy has been increasingly utilized in the treatment of both malignant and benign tumors,
especially in infants, where it has replaced radiation therapy in the postoperative treatment. Its use sometimes allows a deferment of radiation treatment for several years, giving the young brain time to develop. Median survival rates for high-risk medulloblastoma and high-grade astrocytoma have increased due to the addition of chemotherapy. A silent revolution in the management of brain tumors has been the use of low-intensity chemotherapy for low-grade gliomas (e.g., optic/hypothalamic gliomas), producing shrinkage or stabilization in up to 70% of patients. Recent advances in chemotherapy include primarily supportive care measures such as the use of hematopoietic growth factors and autologous stem cell harvesting and reinfusion. Hematopoietic growth factors, such as G-CSF (granulocyte colony-stimulating factor) reduce the duration of myelosuppression, thereby allowing for the administration of higher and more frequent doses of chemotherapy. Stem cells, which more recently have been obtained through bone cell separation (leukopheresis) equipment, are utilized after very high doses of chemotherapy in order to replenish the depleted bone marrow. It is hoped that this will allow for chemotherapy dose escalations with improved cure rates of certain malignant tumors such as malignant astrocytomas and disseminated medulloblastomas.

Commonly used chemotherapeutic agents include the alkylators, such as cyclophosphamide, ifosfamide, and nitrosoureas (CCNU); mitotic inhibitors, such as vincristine, epipodophyllotoxins (VP-16), and platinum compounds (cisplatin and carboplatin); and occasionally anti-folate agents, such as methotrexate. All of these agents act by disrupting some aspect of cell growth or division. The alkylators cause cross-linkage of DNA strands and interfere with cell replication. Acute side effects of these compounds include severe nausea and vomiting, hemorrhagic cystitis (cyclophosphamide and ifosfamide), and possible renal and liver damage. In addition, all of the alkylators produce bone marrow toxicity, leading to neutropenia, thrombocytopenia, and anemia. The vinca alkaloids or mitotic inhibitors (vincristine and vinblastine) inhibit microtubule formation, which is required spindle formation during mitosis. Common acute side effects include jaw pain, abdominal discomfort, and fever. Chronic side effects relate to damage to peripheral nerves leading to weakness, sensory changes (pins and needles, cramps), and constipation. The platinum compounds damage the DNA strands. Renal failure is a known toxic side effect, and patients require vigorous hydration. Nausea and vomiting are also prominent. Chronic side effects include ototoxicity and chronic renal failure with a Fanconi-like syndrome. During infusion, VP-16 can cause blood pressure changes, nausea, and vomiting. It also produces substantial bone marrow toxicity. Hair loss is a common complication after most chemotherapeutic agents.

The management of nausea and vomiting has improved dramatically after the introduction of serotonin antagonist agents such as ondansetron and granisetron. Older agents such as metoclopramide, antihistamines, chlorpromazine, and benzodiazepines are also effective as adjunctive medications.

The pediatrician following these patients should be aware of the following. Bone marrow suppression due to chemotherapy leads to a decrease in white blood cells including neutrophils, which are the largest group of leukocytes. They are the body's first line of defense against infection and neutropenia (<1000 granulocytes/mm³) usually occurs 8 to 12 days following the administration of these drugs. In the neutropenic patient who becomes febrile, there is a 60% or greater likelihood of a documented infection being present.

During neutropenia, fever is defined as a temperature greater than 38.5°C at one recording or two recordings of 38.0°C 2 hours apart. The decrease in polymorphonuclear cells leads to a muted immune response and signs of infection such as erythema, edema, and purulent discharge may not be present. Microbiologic confirmation of infection occurs in only 25% to 30% of cases and is clinically documented in another 30% to 40%. Patients with fever and neutropenia should be evaluated and empiric antibiotic coverage instituted because fever may be the only sign of infection. Common pathogens include gram-negative bacilli (arising from the gastrointestinal tract) such as Escherichia coli, Klebsiella, and Pseudomonas aeruginosa, and gram-positive organisms (skin) such as Staphylococcus epidermidis, Staphylococcus aureus, and beta-hemolytic streptococcus. The risk of infection by gram-positive organisms is greater in patients who have indwelling venous catheters. The combination of an antipseudomonal penicillin (ticarcillin clavulanate, carbenicillin, or piperacillin) or a cephalosporin with antipseudomonal activity (cefazidime or cefoperazone) and an aminoglycoside (gentamicin, tobramycin, or amikacin) is a well-established regimen.

Controversy exists concerning the addition of vancomycin. If no organism is identified within 72 hours of treatment and the patient defervesces, the standard approach is to continue therapy until the granulocytopenia resolves (count > to 1000 cells/mm³ or >500 cells/mm³ with evidence of recovery of platelets and red blood cells). Adjustment of the initial regimen should be considered when the fever persists for over 3 days or there is evidence of infection progression. The best ways to prevent or minimize infection include handwashing, avoiding people with colds, and immediate evaluation of fever. However, the majority of organisms isolated are of endogenous origin. Children under treatment with febrile neutropenia do not benefit from isolation or the use of masks.
Patients may also require the administration of blood products following their chemotherapy. Platelet counts below 50,000 are associated with an increased risk of bleeding; below 20,000, there is an increased risk of spontaneous bleeding; and below 10,000, spontaneous bleeding into the CNS and gastrointestinal tract may occur. Red blood cells should be considered in patients with a falling hemoglobin count and signs of fatigue, shortness of breath, and tachycardia. Usual parameters for transfusion of packed red blood cells are hemoglobin of less than 8 g/dL. Blood transfusion must be used with caution due not only to the risk of infection (1/50,000 for hepatitis and 1/1,000,000 for HIV), but also due to risk of graft versus host disease. Immunosuppressed patients are susceptible to engraftment of foreign white blood cells. Thus, these must be depleted from blood products before transfusion by irradiation and special filters for leukocytes.

TREATMENT AND PROGNOSIS

Low-Grade Gliomas

A complete surgical resection is the operative goal for cerebral and cerebellar low-grade gliomas. Among those who undergo total resection, 10-year survival rates exceed 80% for cerebral lesions and 90% for cerebellar lesions. Radiation is used for an incompletely resected low-grade glioma only when there is evidence of disease progression, resulting in a 10-year survival rate of over 80%. Low-grade gliomas of the optic pathways and hypothalamus are rarely amenable to radical surgical resection and require treatment at the time of progression. Younger children have benefited from low-intensity chemotherapy and deferral of radiation. Long-term survival rates approach 70% to 80%; endocrine and visual morbidities due to tumor or treatment are frequent.

High-Grade Glioma

Maximal resection followed by involved field radiation is the usual treatment for many of these tumors. Chemotherapy has been shown to prolong survival in several clinical trials.

Primitive Neuro-ectodermal Tumor and Medulloblastoma

Maximal surgical resection is also advisable, except when there is evidence of dissemination at diagnosis. A combination of chemotherapy and craniospinal radiation therapy is the standard of care. Currently, there are several protocols exploring various regimens. Doses of radiation and chemotherapy are set according to risk categories. Young age (younger than 3 years), evidence of tumor dissemination, and large postoperative residual tumor bulk are considered factors of high risk. Very young children (under age 3 years) are usually offered intensive chemotherapy followed by high-dose chemotherapy (myeloablative) and bone marrow rescue with stem cells in an attempt to avoid or defer radiation. Standard risk patients have 5-year median survival rates of up to 80%, whereas children with high-risk disease have 30% to 40% 5-year median survival rates.

Ependymoma

After complete resection, 60% to 80% 5-year survival rates are possible. However, complete resection is not always possible because of infiltration of vital structures. Ependymomas may seed the spinal column in 3% to 15% of cases. Patients with residual or recurrent disease are treated with radiotherapy. Chemotherapy, although of questionable effectiveness, has been tried in several clinical trials for both newly diagnosed and recurrent disease.

Cranioopharyngioma

These tumors present a formidable surgical challenge because of their proximity to the optic nerves, the hypothalamus, and vessels in the circle of Willis. Most pediatric neurosurgeons favor complete microsurgical resection as the treatment of choice for newly diagnosed cranioopharyngioma. Seventy percent to 90% of tumors are amenable to total resection. Following radiographically confirmed total resection, no adjuvant therapy is necessary. Recurrences range from 0% to 20%. The overall outcome is variable and endocrine problems, including pan-hypopituitarism, visual field deficits, and even cognitive deficits, are not uncommon. Radiation is usually reserved for residual or recurrent tumors.

Brain Stem Gliomas

Gliomas of the brain stem are described as diffuse, focal, cystic, and exophytic. Brain stem gliomas, which appear as diffuse, infiltrative, intrinsic tumors of the pons on MRI scans, usually behave very aggressively irrespective of tissue diagnosis. Therefore, surgical resection or biopsy is discouraged. The standard treatment is involved field radiotherapy despite the prognosis being extremely poor. Less than 20% of children survive 2 years after diagnosis. Focal brain stem lesions of the medulla and cervicomедullary junction, as well as dorsally exophytic tumors, are generally low grade and may be amenable to debulking. Adjuvant therapy is only required when there is postoperative progression of disease. Surgical morbidity may be high if an aggressive approach is utilized, and children may require ventilatory support and a feeding tube. Tumors of the midbrain usually cause obstructive hydrocephalus, and the only treatment consists of shunting or third ventriculostomy (piercing a hole through an area called lamina terminalis). In general, no oncologic therapy is required unless there is marked tumor growth. These children have a high survival rate, and chronic problems are primarily related to the location and surgery.
OUTCOME

Progress in brain tumor treatment creates a challenge: as more and more children survive longer, the quality of life posttreatment becomes an important issue. Children undergo intensive therapies in order to increase their survival time. What is the quality of life for these survivors? The late effects of brain tumor therapy include neurologic and neuropsychologic problems, endocrinopathies, and, rarely, secondary neoplasms. These create a lasting medical, emotional, and financial burden that has a significant impact on the patient, their family, and society.

Recent studies have demonstrated neuropsychologic disturbances in children who survive brain tumors. These include a high incidence of intellectual impairment as well as emotional and behavioral disturbances. The causes for these deficits are likely a combination of prolonged hydrocephalus and direct tumor damage, surgical morbidity, and whole brain irradiation. The younger the child, the more affected he or she tends to be. The more affected children often require special education and supportive services such as physical and occupational therapy, speech therapy, and psychologic counseling. Furthermore, children who receive cisplatin and radiation may have substantial hearing loss requiring hearing devices.

Endocrine dysfunction may be seen following resection of midline tumors or after craniospinal irradiation. Diabetes insipidus is commonly seen after the resection of a craniopharyngioma, a germ cell tumor, or even a hypothalamic glioma. CNS radiation is associated with hypothalamic failure, which translates into panhypopituitarism. Thus, children may require cortisol, thyroid hormone, and growth hormone replacement. In addition, radiation to the spine can cause a dysfunction of the thyroid gland directly as well as cause damage to the vertebral growth plate. Both growth hormone deficiency and spinal growth dysfunction will lead to short stature. Lastly, several chemotherapeutic agents (e.g., cyclophosphamide) may cause gonadal dysfunction and subsequent sterility.

Radiation therapy and chemotherapeutic agents may be associated with oncogenesis. Meningioma is the most common secondary neoplasm seen following CNS radiation, but sarcomas and high-grade gliomas have also been reported. The risk of secondary tumors seems to be cumulative over the years, reaching up to 10% after 20 years post-radiation therapy.

Secondary leukemia and lymphomas have developed in children receiving chemotherapy for brain tumors, especially after high doses of VP-16; however, they are quite uncommon.

FUTURE DEVELOPMENTS

The goals of the future are to provide an improvement in cure rates and a reduction of long-term side effects of therapeutic interventions. Technical advancements in surgical procedures will allow for safer tumor resections. New targeting techniques will allow safer irradiation of the brain tumor. The combination of immunology and cytogenetics, including antitumor gene therapy, and the use of monoclonal antibodies are promising alternative forms of oncologic therapy. Increased delivery of chemotherapeutic agents by disruption of the blood-brain barrier is also on the horizon. However, the future of oncologic therapy will likely reside in a better understanding of basic mechanisms of oncogenesis, therefore allowing for more specific and less toxic medications.

The past two decades have seen dramatic improvement in the survival rates for some forms of pediatric brain tumors. The general pediatrician must be involved at the very beginning and institute a rapid work-up once the diagnosis is suspected, and refer the patient to a pediatric neurologist and/or neurosurgeon who is associated with a center of excellence. In the current healthcare environment, it is mandatory that the general pediatrician become a vital member of the multidisciplinary team that is needed to treat these children. An aggressive approach to supportive care has been instrumental in decreasing the perioperative morbidity and mortality seen in these children. The initial assessment, perioperative care, appropriate management of infection, nutrition, and overall health maintenance are essential components of care. Therefore, the pediatrician is in an excellent position to become an indispensable member in the multidisciplinary team responsible for managing these children, not only in the acute phases of treatment, but also during long-term follow up and care.

REFERENCES

17. Spataro R, Elliott R, Jenkins R, et al. The effectiveness of chemotherapy for treat-

