TUMORS OF THE NERVOUS SYSTEM

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INTRODUCTION

Tumors of the brain and spine are the most common solid tumors in children and have the highest mortality of all childhood cancers. Evaluation and monitoring of neurological signs and symptoms are critical to their diagnosis and management. Clinical manifestations are key to localization and narrowing of the differential diagnosis, and advanced neuroimaging allows detailed characterization of identified lesions. Ultimately, histopathology and, more recently, molecular subtyping of tumor tissue are the basis of an integrated diagnosis to inform treatment, which may include observation, surgery, chemotherapy, radiation, immunotherapy, and/or molecularly targeted therapies. There are a wide range of outcomes for tumors of the nervous system depending on the type of tumor, and similarly a large number of potential long-term neurological complications from cancer and cancer treatment.

EPIDEMIOLOGY OF PEDIATRIC CENTRAL NERVOUS SYSTEM TUMORS

The incidence of primary central nervous system (CNS) tumors in children and adolescents is five to six per 100,000 persons.¹ Up to 4,500 new cases of primary brain and other CNS tumors in children ages 0 to 19 years are diagnosed each year. In this age range, CNS tumors represent the largest cause of years of potential life lost due to cancer. Whereas survival rates in some tumor types have improved over the last decade, for others survival rates have plateaued and remain poor.

In younger children (less than 14 years), the most common location for a primary CNS tumor is the

cerebellum, followed by other parts of the brain and brainstem (Figure 9.1). The most frequent tumor types in this age group include pilocytic astrocytoma, high-grade glioma (HGG), and embryonal tumors (Figure 9.2). In adolescents (ages 15–19 years), the most commonly diagnosed tumors are those of the sellar region, followed by the lobes of the cortex (temporal, frontal, parietal, occipital). Spinal cord tumors account for a small percentage of CNS tumors, with ependymal tumors and nerve sheath tumors being the most common.

While many environmental and behavioral factors have been evaluated as potentially increasing the risk of CNS tumors, only exposure to ionizing radiation has been well validated.² In addition to established familial cancer syndromes, there may be increased risk for a child if an immediate family member has a history of a brain tumor.

CLINICAL MANIFESTATIONS

The signs and symptoms of a tumor in the nervous system are dependent on the location of the tumor and may result from local tumor-derived brain injury, focal mass effect, generalized increased intracranial pressure, or disruption of the tumor microenvironment. Clinical presentation, coupled with neuroimaging findings, can be used to delineate the likelihood of a given tumor (as summarized in Table 9.1 for the most common childhood infratentorial tumors).

Headache

Headaches are common and most headaches are not due to brain tumors. However, 30% to 60% of children with brain tumors will present with headaches, often accompanied by neurological deficits.^{3–6} An abnormal neurological examination or seizures are clinical factors more likely to be associated with a CNS tumor.⁷ Headaches can be related to increased intracranial pressure due to

FIGURE 9.1 Distribution of primary brain and other CNS tumors by site in (A) children (age 0–14) compared with (B) adolescents (age 15–19), CBTRUS Statistical Report: US Cancer Statistics – NPCR and SEER, 2012–2016.

CBTRUS, Central Brain Tumor Registry of the United States; CNS, central nervous system; NPCR, National Program of Cancer Registries; SEER, surveillance, epidemiology, and end results.

Source: From Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. *Neuro-Oncol.* 2019;21(suppl 5):v1–v100. doi:10.1093/neuonc/noz150

mass effect from the tumor, local compression or traction on pain-sensitive structures (e.g., dura, large arteries or venous sinuses, cranial nerves), and possibly neurogenic inflammation and central sensitization.⁸

Seizures

Seizures are documented in 20% to 30% of patients presenting with a CNS tumor. Seizures are more commonly associated with supratentorial than with infratentorial

tumors, and they result more often with slow-growing low-grade lesions than with fast-growing malignancies. Of all children presenting with new-onset seizures, about 1% to 3% are found to have a brain tumor.⁹ Seizure onset at initial presentation tends to be related to location (temporal lobe more common than frontal and parietal) as well as histology (low-grade astrocytoma most common).¹⁰ Prophylactic antiseizure medications are not generally recommended in patients with brain tumors who have not had seizures.

FIGURE 9.2 Distribution of primary brain and other CNS tumors by histology in (A) children (age 0–14 years) compared with (B) adolescents (age 15–19 years), CBTRUS Statistical Report: US Cancer Statistics – NPCR and SEER, 2012–2016.

ATRT, atypical teratoid/rhabdoid tumor; CBTRUS, Central Brain Tumor Registry of the United States; CNS, central nervous system; NOS, not otherwise specified; NPCR, National Program of Cancer Registries; PNET, primitive neuro-ectodermal tumor; SEER, surveillance, epidemiology, and end results.

Source: From Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. *Neuro-Oncol.* 2019;21(Suppl 5):v1–v100. doi:10.1093/neuonc/noz150

TABLE 9.1 POSTERIOR FOSSA TUMORS OF CHILDHOOD

TUMOR TYPE (%)	AGE AT DIAGNOSIS	SYMPTOMS	SIGNS	TEMPO (TIME TO DIAGNOSIS)	IMAGING FEATURES
Medulloblastoma (40%)	Peak 1–9	Headaches; vomiting; balance difficulties	Truncal hypotonia/unsteadiness; abducens palsy; papilledema	Relatively rapid; 2–4 months	Mass with hypercellular characteristics; possible hemorrhage, calcification; enhancement, obstructive hydrocephalus >80%
Cerebellar (pilocytic) astrocytoma (40%)	Peak 5–15	Balance difficulties; headaches; vomiting later	Appendicular → Truncal hypotonia	3–6 months	Mass with hypocellular characteristics; cysts common; enhancement; obstructive hydrocephalus relatively common
Diffuse intrinsic brainstem glioma (10%–20%)	Peak 5–15	Diplopia; facial weakness; unsteadiness; crossed hemiparesis; swallowing difficulties	Cranial neuropathy; cerebellar deficits; hemiparesis; hemisensory loss	Erratic; 1–6 months	Expansile pontine mass; hypocellular; variable, usually only focal enhancement; hydrocephalus <20%
Ependymoma (10%–20%)	Throughout childhood; often <4	Double vision; hearing loss; unsteadiness	Sixth, seventh, eighth nerve paresis; cerebellar deficits	2–6 months	Fourth ventricular/cerebello-pontine angle mass; extension to upper cervical canal; heterogeneous calcifications common; variable hydrocephalus
Atypical teratoid/rhabdoid tumors (less than 5%; 10%–20% infants)	Infancy; often less than 3 years	Vomiting; head tilt; unsteadiness; lethargy	Cerebellar deficits; sixth and seventh palsies	1–3 months	Large midline or lateral mass; hemorrhagic; necrosis; hydrocephalus

Mental Status Changes

Acute changes in mental status are less common because CNS tumors tend to grow gradually; however, alterations can occur in association with rapid tumor growth and edema, intratumoral hemorrhage, seizures, metabolic derangement, or other acute complications. Behavioral changes, irritability, or somnolence can all be part of the initial presentation and can provide information about tumor localization and potential complications such as hydrocephalus. Cerebrospinal fluid (CSF) obstruction and herniation can lead to acute changes in consciousness and are neurological emergencies. Developmental regression or plateauing of developmental milestones can be an early clue in large tumors, especially in infants and young children with cortical tumors. Falling school performance and/or new-onset learning issues may be early signs of frontal lobe or large sellar/suprasellar tumors. Irritability or even euphoria can be part of the “diencephalic syndrome,” associated with failure to thrive in infants with infiltrating diencephalic tumors.

Focal Neurological Deficits

Focal neurological deficits can be important findings in the diagnosis of a new brain tumor. Papilledema and abducens nerve palsies can occur in children with increased intracranial pressure independent of the tumor location. Classically, bitemporal hemianopia occurs with sellar lesions, but infiltrating gliomas in this area often lead to more complex visual field loss. Pineal tumors may present with dorsal midbrain (Parinaud) syndrome with paralysis of upgaze, convergence retraction nystagmus, light-near dissociation, and bilateral eyelid retraction. Cranial nerve findings are localizing in tumors that infiltrate the brainstem, associated with cerebellar deficits and long-tract signs. Crossed hemiparesis with ipsilateral facial paresis and contralateral hemiparesis can occur with brainstem lesions. Ataxia and gait changes suggest posterior fossa lesions, particularly of the cerebellum or the cerebellar peduncles.

Focal motor deficits are common with tumors involving the cortex or the motor tracts. Brain tumors may result in focal or generalized seizures. Spinal cord involvement,

particularly cord compression, is an important consideration in the differential diagnosis of motor or sensory deficits, especially if associated with bowel and bladder dysfunction. Any of these findings may be seen in isolation or in combination with other neurological signs and symptoms.

Endocrinopathies

Some tumors present with an endocrinopathy instead of a neurological deficit, sometimes delaying the diagnosis of the tumor. The most common tumors that present with an endocrinopathy are pituitary and pineal tumors, craniopharyngioma, germ cell tumors, and hypothalamic lesions. Tumors of the suprasellar region may lead to over-secretion of the involved hormone, such as growth hormone, prolactin, corticotropin, or thyrotropin because of compression of the pituitary gland or stalk.¹¹ Compression of the hypothalamic–pituitary axis by a tumor may lead to growth failure, diabetes insipidus, or precocious puberty.

BASIC COMPONENTS OF DIAGNOSIS

Imaging

Both CT and MRI are quite sensitive in diagnosis of childhood brain tumors, although MRI is superior in detection of small cortical infiltrating lesions isodense to normal brain.¹² MRI also demonstrates the character and extent of lesions far better than CT. Other imaging techniques, such as MR spectroscopy, MR angiography, MR tractography, and positron emission tomography, can be helpful in delineating the type of lesion present, its metabolic properties, and its relation to other regions/tracts of the brain, but are infrequently needed for diagnosis. Given the propensity of childhood brain tumors to disseminate within the nervous system at diagnosis or early in the course of illness, MRI of the entire neuroaxis is often indicated at diagnosis, pref-

erably prior to surgery to avoid confounding postsurgical artifacts, to determine the extent of disease.¹³

Pathological and Molecular Diagnosis

For decades, the classification of brain tumors was based primarily on light microscopy findings. Electron microscopy and later immunohistochemical staining were often useful adjuncts in characterizing brain tumors. Various classification schemas have been used, and the “World Health Organization (WHO) Tumors of the Central Nervous System” is an accepted international classification¹⁴ (see Table 9A.1 in the online appendix for this chapter, accessible on Springer Publishing Connect: connect.springerpub.com/content/book/978-0-8261-4399-0/chapter/ch09). Molecular features have been increasingly incorporated into brain tumor classifications. In the most recent WHO Classification, a two-tiered approach is used for medulloblastoma, classifying the tumor on the basis of its histological/immunohistochemical features and molecular genetic properties (Table 9.2). For other tumors, such as midline infiltrating gliomas and some other embryonal tumors, molecular findings have also been incorporated.

Various RNA- and DNA-based platforms have been used to molecularly characterize childhood brain tumors, including RNA analysis, DNA copy number, whole exome and genome sequencing, and methylation profiling.^{15–18} Histologically agnostic classification schemas using methylation profiling and clustering have also been developed and are useful in not only subclassifying tumors within broader tumor types, but also identifying distinct molecular subgroups of rare tumors.¹⁹

Exceptions to the need for tissue for diagnosis exist, including secreting germ cell tumors, primarily of the pineal or suprasellar region, as CSF protein markers can be used to confirm diagnosis; diffuse infiltrating lesions of the brainstem radiographically consistent with diffuse intrinsic gliomas; presumed low-grade gliomas (LGGs)

TABLE 9.2 EMBRYONAL TUMORS (MODIFIED, WORLD HEALTH ORGANIZATION)

MEDULLOBLASTOMA	OTHER EMBRYONAL	ATYPICAL TERATOID/RHABDOID TUMOR
<ul style="list-style-type: none">Medulloblastoma, genetically defined (WNT-activated; SHH-activated; non-WNT/non-SHH)Medulloblastoma, histologically defined (classic, desmoplastic/nodular; extensive nodularity; anaplastic)	<ul style="list-style-type: none">Embryonal with multilayered rosettes (C19MC-altered; NOS)MedulloepitheliomaCNS neuroblastomaCNS ganglioneuroblastomaCNS tumor, NOS	<ul style="list-style-type: none">CNS embryonal tumor with rhabdoid features (inactivation of <i>SMARCB1</i> or inactivation of <i>SMARCA4</i>)CNS embryonal tumor with rhabdoid features (without <i>SMARCB1</i>/<i>SMARCA4</i> status known; or with expression of both)
Pineoblastoma (listed in WHO with pineal region tumors)		

CNS, central nervous system; NOS, not otherwise specified; SHH, sonic hedgehog; WNT, wingless.

of the visual pathway in children neurofibromatosis type 1; and subependymal giant cell astrocytomas in individuals with tuberous sclerosis complex. Even in these situations, histological confirmation is often obtained to molecularly characterize the tumor.

Cancer Predisposition Syndromes

Identification of cancer predisposition syndromes is an increasingly important component of diagnosis. Historically, cancer predisposition syndromes were thought to underlie less than 1% of all primary childhood brain tumors other than those associated with specific genetic conditions (e.g., NF1 and low-grade gliomas, tuberous sclerosis complex and subependymal giant cell astrocytomas, von Hippel-Lindau and cerebellar and spinal hemangio-blastomas).^{20,21} Recent retrospective and prospective studies suggest that the incidence is considerably higher.^{20–22}

Germline mutations have been identified in at least 6% of medulloblastomas, with the highest prevalence in the SHH- and WNT-associated subgroups.²³ Germline mutations in *SUFU* and *PTCH1* are the most common in SHH-associated medulloblastomas arising in infancy. Some of these young children with medulloblastoma have frank manifestations of Gorlin syndrome, also known as the nevoid basal cell carcinoma syndrome, usually secondary to *PTCH1* mutation. Gorlin syndrome is characterized by skeletal and dermatologic features including macrocephaly, calcification of the falx cerebri, odontogenic keratocyst of the jaw, and rib fusions; multiple basal cell carcinomas develop later in life, especially in the radiation field.²⁴ In children with WNT-associated medulloblastomas, *APC* mutations may be present, including some as part of Turcot syndrome. Other medulloblastoma-associated germline mutations such as *PALB2* and *BRCA2* have been observed. Rare genetic conditions such as Rubinstein–Taybi and Fanconi syndromes have also been associated with an increased incidence of predominantly embryonal tumors.²⁰

Germline mutations of the *TP53* gene, underlying Li–Fraumeni syndrome, are associated with an increased incidence of various childhood brain tumors including medulloblastoma and HGGs.²⁰ Biallelic germline mutations of the mismatch repair family of genes predispose to childhood brain tumors, primarily gliomas. Affected children with mismatch gene germline mutations may show a neurofibromatosis-like phenotype, including café au lait spots and axillary freckling.^{20,21} The rhabdoid predisposition syndrome due to *SMARCB1* germline mutation underlies 40% or more of children with atypical teratoid/rhabdoid tumors.^{20,21} Germline mutations of *PTEN* (Cowden syndrome) predispose to cerebellar

gangliocytoma. *DICER1* germline mutations have been noted in pineoblastomas.^{20,21}

BASIC MANAGEMENT APPROACHES

Surgery

Surgery is indicated to confirm diagnosis for almost all presumed childhood brain tumors and usually can be performed safely with minimal to no mortality and an “acceptable” degree of transient, and, less frequently, permanent morbidity.^{25–27} The diagnostic goals of surgery are to obtain enough tissue not only for definitive diagnosis, but also increasingly for molecular analysis. For low-grade lesions, especially grade 1 (pilocytic) astrocytomas and mixed low-grade glioneuronal tumors, complete surgical resection results in avoidance of the need for adjuvant therapy and, for the majority, long-term disease control. For other “malignant” childhood brain tumors, including medulloblastomas, other embryonal tumors, pineoblastomas, ependymomas (both benign and anaplastic), and possibly HGGs, aggressive surgical resections are critical components of management because patients undergoing total or near-total removals have a higher likelihood of long-term disease control and/or the need for less aggressive therapies.

Preoperative stereotactic localization, intraoperative motor and sensory monitoring, and intraoperative MRI allow more extensive resections and decrease morbidity.^{27,28} Functional MRI and MR tractography prior to surgery to map expressive and receptive language areas and critical motor and sensory regions may reduce the likelihood of surgically associated sequelae.^{27,28} Monitoring of evoked responses is frequently employed during surgery for posterior fossa tumors, especially those of the cerebellopontine angle, to mitigate cranial nerve damage, and for spinal cord tumors, to decrease the likelihood of paralysis.^{27,28}

For deep-seated lesions such as diffuse intrinsic brainstem and thalamic gliomas and infiltrating visual pathway gliomas, the role of surgery is less well defined. Extensive resections are often impossible in these situations, but tissue obtained at the time of surgery, increasingly via stereotactic biopsies, can be critical for treatment planning. High-frequency focused ultrasound and laser-guided tissue heating are other techniques used to treat deep-seated lesions.²⁹

Although the morbidity and mortality associated with brain tumor surgery has decreased with improvement in surgical techniques and intraoperative monitoring, sequelae do occur.^{30–32} Transient worsening of focal neurological deficits after surgery occur in up to 10% of patients. Posterior fossa surgery can be associated with

the delayed (i.e., 24–72 hours after surgery) onset of mutism, severe irritability, and other neurological deficits. This “posterior fossa in mutism syndrome” occurs in 5% to 40% of children undergoing medulloblastoma surgery, and half of these children experience permanent neurological or intellectual dysfunction.^{30–32} This complication likely results from disruption of the dentate nuclei or the dentato-rubro-thalamo-cortical pathways.

Staging and Disease Stratification

Following surgery, and in selected situations even occurring before surgery, staging procedures are performed to better identify the extent of disease and guide therapy.³³ For most aggressive childhood brain tumors including all embryonal tumors, ependymomas, and possibly HGGs, MRI of the entire neuroaxis is recommended prior to initiation of treatment. For tumors with a propensity to disseminate in the CNS with resultant leptomeningeal disease spread, CSF cytological examination for free-floating tumor cells or clusters of cells is complementary to MRI.³⁴

Following surgery, in addition to evaluation for leptomeningeal tumor spread, quantification of the amount of residual disease at the primary tumor site is often integrated into staging. Evaluation for metastatic spread outside the CNS is usually not indicated, except for the possible exception of infants or very young children with embryonal tumors and widely metastatic CNS disease. Based on these findings, patients with medulloblastoma are conventionally separated into “average” and “high” or “poor-risk” groupings to guide therapy.³³ More recently, this information has been integrated with molecular findings to further refine subgroups.³⁵ Staging has some utility for other embryonal tumors and possibly ependymomas, but it has not been extensively used to alter treatment for other pediatric brain tumors, such as HGGs and LGGs.

Radiation Therapy

Radiation therapy is a primary form of adjuvant therapy for many pediatric brain tumors that cannot be controlled with surgery alone.^{36–38} Photon radiotherapy has been the primary modality used, and step-wise refinements, such as stereotactic fractionated radiotherapy and intensity-modulated radiotherapy, have made treatment more exacting, limiting the amount of scattered radiation to uninvolved portions of the brain and other organs.³⁸

The most significant change in practice has been the wider use of proton-beam irradiation. Protons, which are heavier particles than photons, limit the

amount of radiation scatter to the surrounding brain and other organs.^{36,38} Craniospinal radiotherapy dosimetry demonstrates that proton-beam radiotherapy clearly can spare scatter radiation to organs such as the heart, lungs, and ovaries. Disease control has been shown to be similar with proton-beam radiation compared with photon-based radiation therapy, and early results show possibly better neurocognitive and endocrinologic outcomes. This experience has to be tempered by reports of focal brain injury, especially to the brainstem in young children, associated with proton-beam treatment.³⁹

In selected cases, highly focused radiation therapy (gamma knife, cyberknife, etc.), either given externally, stereotactically in a single or a limited number of fractions, or via implantation of radioactive seeds (brachytherapy), has been used to control focal lesions.³⁸ Overall such approaches and the use of different dose-fractions and schedules, such as hypo- and hyperfractionated radiation, have not played a major role in the management of childhood brain tumors.^{40,41}

For the majority of patients with HGGs and LGGs, ependymomas, craniopharyngiomas, and other nonembryonal childhood brain tumors who require postsurgical adjuvant radiation therapy, focal radiation therapy to the tumor bed with a margin (dependent in part on the type of tumor to be treated) is used, with daily doses ranging between 150 cGy and 180 cGy to a total dose of 5,500 cGy to 5,960 cGy.³⁸ Local swelling due to tumor necrosis and associated cytokine release may occur during (acute) and soon after radiation (subacute—arbitrarily up to 3 months after completion of radiation), resulting in usually transient neurological complications. Acute symptoms are most frequently headaches, fatigue, and possibly worsening of focal, preexisting deficits. Tumor or treatment-related edema can usually be controlled by the judicious use of steroids; in more severe cases, bevacizumab, a monoclonal antibody that inhibits VEGF-mediated angiogenesis, can be used to decrease tumor/treatment-related edema.

For embryonal tumors, especially medulloblastomas outside the age of infancy and early childhood, standard treatment also includes the use of craniospinal radiation (radiation delivered to the whole brain and spine including cauda equina) to at times treat frank leptomeningeal disease, but most commonly, prophylactically, to prevent leptomeningeal disease relapse. Dependent on the results of staging studies and possibly the age of the patient, doses of craniospinal radiation usually have ranged between 2,340 cGy and 3,600 cGy, and such treatment is usually fairly well tolerated in the acute and subacute time

frames. Between 2 to 6 weeks following completion of craniospinal radiotherapy, patients may develop electroshocks down their spine, termed “Lhermitte phenomena” or the somnolence syndrome.⁴² The latter is manifested by extreme fatigue, headaches, loss of appetite, increased need for sleep, and possibly exacerbation of preexisting neurological symptoms. Somnolence syndrome is usually transient, possibly secondary to demyelination, does not require treatment, and resolves, usually spontaneously, 7 to 14 days from onset. The major risks of the whole brain component of craniospinal therapy are long-term sequelae, including stroke, neurocognitive damage, endocrinologic dysfunction, and radiation-associated secondary tumors. Because of these potential sequelae, there have been multiple studies performed attempting to reduce the needed total dose of craniospinal radiation by adding chemotherapy; in infants and very young children, strategies have been employed to delay or omit radiation therapy entirely.

Chemotherapy

Chemotherapy is an integral component of the management of most high-grade childhood brain tumors. In most situations, chemotherapy is given in an adjuvant fashion after surgery,³⁷ usually with or after radiotherapy, in multiagent regimens. High-dose chemotherapy regimens supported by peripheral stem cell rescue are frequently used for infants with embryonal tumors prior to radiotherapy and, in selected cases, as sole adjuvant postsurgical treatment. For children with LGGs, who require postsurgical treatment, chemotherapy is commonly used as an alternative to radiotherapy in an attempt to at least delay, if not obviate, the need for radiotherapy.

Chemotherapy, especially when coupled with radiation therapy, can be neurotoxic (see Table 9A.2 in the online appendix for this chapter, accessible on Springer Publishing Connect: connect.springerpub.com/content/book/978-0-8261-4399-0/chapter/ch09). Methotrexate, primarily given at high doses as part of multiagent chemotherapy regimens for infants and young children with embryonal tumors, and, in some studies intrathecally, as part of induction or maintenance chemotherapy for medulloblastoma, can result in leukoencephalopathy.⁴³ An antiseizure drug may be started in the setting of seizures and then rapidly discontinued, but if there are recurrent seizures the drug is usually continued longterm at least until completion of chemotherapy treatment. Reduction or cessation of methotrexate may not result in major improvement in imaging findings, and residual deficits, including those of cognition, may persist.

Cisplatin, a component of most embryonal tumor regimens, can cumulatively result in cochlear damage and permanent hearing loss.^{43,44} Vincristine, a common component of medulloblastoma and other tumor therapies, can result in small-fiber axonal neuropathy with resultant permanent gait difficulty and troubling sensory neuropathy.^{43,44} PEG-asparaginase, which is often used in induction chemotherapy for children with acute lymphoblastic leukemia, can cause clotting, specifically cerebral sinus venous thrombosis, presenting as headache sometimes with vision impairment.

Molecular-Targeted Therapy

Molecular-targeted therapy (MTT) uses drugs or other substances to target specific molecules involved in the growth and spread of cancer cells.⁴⁵ Small-molecule tyrosine kinase inhibitors, effective in other forms of cancer, have not yet been shown to be effective in childhood brain tumors.⁴⁵ Reasons for this may include utilization of the agent in non-molecularly enriched patient populations whose tumors did not harbor the molecular target in sufficient quantities; lack of specificity of the agent chosen; alternative growth pathways or escape mechanisms; and inability of the agent to reach the target, primarily due to a relatively intact blood-brain barrier. Monoclonal antibodies, engineered to target specific cell surface antigens and proteins, have been somewhat more effective, and the vascular endothelial growth factor inhibitor bevacizumab has shown to be of benefit in NF2-associated acoustic neuromas and to improve visual function and control disease in children with recurrent LGGs.^{45–48} Rapamycin and other mTOR inhibitors have demonstrated efficacy in tuberous sclerosis-associated subependymal giant astrocytomas and, to some extent, in recurrent LGGs.⁴⁵ Both BRAF inhibitors and MEK inhibitors have shown high response rates in children with progressive LGGs and are being compared to standard chemotherapy for children with newly diagnosed disease.^{45,49,50} Drugs targeting the epigenetic aberrations of childhood brain tumors, especially for diffuse intrinsic HGGs, of which over 80% harbor epigenetic abnormalities, are also under active study.⁴⁵

By and large, MTTs have different side effects than do standard chemotherapy and cause less bone marrow suppression.^{45,49,50} However, the specific side effects are highly dependent on the molecular agent chosen, for example, the MEK-inhibitors frequently cause dermatologic toxicity, which can be dose-limiting, and bevacizumab may result in hypertension, proteinuria, and growth plate

damage. The long-term effects of targeting cellular pathways critical in development are unknown.^{45,49,50}

Immunotherapy

Innovative therapies designed to harness a patient's own immune system and amplify the antitumor response have been a recent focus in cancer treatment strategies. These approaches have moved to the pediatric sector and include vaccines, oncolytic viruses, immune checkpoint inhibitors, and adoptive T-cell therapy.

Therapeutic cancer vaccines may include peptides from known tumor-associated antigens, dendritic cells with antigen priming, or personalized neoantigens from patient-specific tumor tissue.^{51–53} Similarly, genetically modified viruses (including adenovirus, herpes simplex virus, measles virus, and many others) are used to stimulate an immune response by inducing apoptosis, tumor cell lysis, and T-cell activation as well as directly attack the tumor cells.^{54,55} Immune checkpoint inhibition is a novel therapeutic mechanism in which monoclonal antibodies are infused to prevent the tumor-driven downregulation of the immune response when T-cell receptors (e.g., PD1) bind to specific tumor cell ligands (e.g., PDL1).⁵⁶ Certain patient populations, such as those with biallelic mismatch repair deficiency and high mutational tumor burden, have shown response to this type of treatment.⁵⁷ Adoptive cellular therapy techniques are continuing to evolve and use a patient's own immune cells (T cells, natural killer cells), which are extracted, modified, and expanded to induce immune responses when infused back into the patient.^{58–61} One specific type of adoptive cellular therapy is chimeric antigen receptor T-cell (CAR-T cell) therapy. This treatment has been used for refractory leukemia in children and is being evaluated in children with refractory brain tumors. Neurological adverse effects after CAR-T cell therapy associated with high levels of cytokines in the blood and CSF include headache, confusion, delirium, language disturbance, seizures, and rarely acute cerebral edema as part of a syndrome called immune effector cell-associated neurotoxicity syndrome (I-CANS).^{62–64} Pseudoprogression, a local inflammatory response related to the immunotherapy rather than true tumor progression, is a known complicating factor of these therapies and can lead to significant neurological signs and symptoms. New guidelines for assessment of the significance of neuroimaging findings related to this phenomenon, attempting to better separate tumor progression from treatment-related imaging changes, have been established.⁶⁵

SPECIFIC TUMOR TYPES

Neuroglial Tumors

Neuroglial tumors are neuroepithelial tumors that arise, at least partially, from glial cells and include astrocytomas, oligodendrogliomas, and mixed glioneuronal tumors (named by their cell of origin), as well as diffuse midline gliomas, HGGs, and ependymomas.

LOW-GRADE GLIOMA

Glial tumors histopathologically classified as WHO grade I or II are considered LGGs. Comprising nearly one-third of all CNS tumors in children 19 years of age or younger, LGGs are the most common pediatric brain tumor (see Table 9A.3 in the online appendix for this chapter, accessible on Springer Publishing Connect: connect.springerpub.com/content/book/978-0-8261-4399-0/chapter/ch09).⁶⁶ These are a heterogeneous group of tumors that include most frequently pilocytic astrocytoma (previously named juvenile pilocytic astrocytoma), which is WHO grade I, often located in the cerebellum and the optic pathways and identified by a biphasic pattern and Rosenthal fibers on histology. Other relatively common low-grade astrocytic tumors include diffuse astrocytoma (WHO grade II); subependymal giant cell astrocytoma (SEGA; WHO grade I) as seen in tuberous sclerosis complex; pleomorphic xanthoastrocytoma (PXA; WHO grade II); and pilomyxoid astrocytoma (WHO grade II). Oligodendrogliomas (WHO grade II), which may occur in childhood, are much more frequent in adults.

LGGs often present with seizures, headache, behavioral changes, or focal sensorimotor deficits. While symptom onset is typically gradual, obstructive hydrocephalus secondary to mass effect can occur and cause acute signs and symptoms of increased intracranial pressure. LGGs, and much less frequently other infiltrating CNS tumors, involving the hypothalamus can present in infancy with failure to thrive, emaciation, and little in the way of focal neurological deficits (the “diencephalic syndrome”). Such children are said to be euphoric, but they are often irritable; subtle neurological deficits, such as nystagmus or visual field loss, may be seen.

Imaging characteristics of LGGs are variable depending on the subtype. Pilocytic astrocytomas (Figure 9.3) are typically well-defined, enhancing lesions that often have cystic components (a large cyst and enhancing mural nodule is typical), sometimes with calcifications. Their solid components are hypodense on CT and T2 hyperintense on MRI and show facilitated diffusion, reflective of their hypocellularity. Diffuse astrocytomas

FIGURE 9.3 Pilocytic astrocytoma. Axial T2-weighted image (A) and coronal contrast-enhanced T1 image (B) reveal a mixed solid-cystic left cerebellar tumor. The solid component is hyperintense on the T2 images and typically enhances after contrast administration (long arrows, A and B); the more lateral cystic component has a thin, incomplete rim of enhancement (short arrows, B). Obstructive hydrocephalus is evident due to the compression of the fourth ventricle (dilated lateral ventricles, B).

are less well-defined lesions often confined to white matter and cause expansion of the adjacent cortex, typically with limited enhancement. Others, such as oligodendrogliomas and PXAs, are cortically based.

Molecular characterization of LGGs has brought significant advancement in understanding the biology of these tumors, as well as expanding treatment options. Aberrant mitogen-activated protein kinase (MAPK) pathway signaling is known to play an important role in the development of LGG, which has led to the development of molecularly targeted therapies to prevent constitutive activation along the pathway and slow tumor growth.⁶⁷ Early data came from studying patients with neurofibromatosis type 1 (NF1), about 10% to 15% of whom develop an LGG.⁶⁸ NF1 is caused by a germline mutation in *NF1* tumor-suppressor gene, which produces a GTPase-activating protein that typically functions as a negative regulator of RAS, and without this gene there is downstream upregulation of RAS/MAPK leading to dysregulated cell growth. Other somatic driver mutations in the same pathway are common in LGGs, including *BRAF* point mutations (specifically V600E) and fusions (most frequently *KIAA1549:BRAF*); less commonly, *FGFR1* and *MYB* mutations occur.⁶⁹ In childhood pilocytic astrocytomas, *BRAF* fusions are by far the most common mutation seen. Molecular data are increasingly being used to classify tumors, with the most recent WHO classification of CNS tumors in

2016 including diffuse astrocytoma *IDH*-mutant versus *IDH*-wildtype as discrete entities; but *BRAF* mutational status is not yet a component of WHO classification. In addition, oligodendroglioma is now characterized by 1p/19q co-deletion, but this is infrequently seen in pediatrics.

Management of LGG is dependent on the location and degree of resection. Surgery is typically first line with the goal of gross total resection when possible, followed by observation with interval neuroimaging and clinical monitoring. For tumors that are subtotaly resected or would cause significant morbidity to remove, such as hypothalamic/optic pathway tumors, additional treatment may be undertaken after pathological confirmation. Optic pathway tumors and other diencephalic masses in children with NF1 are usually treated as pilocytic astrocytomas without pathological confirmation unless the lesion is considered “atypical” clinically or radiographically. Outpatient chemotherapy with agents such as carboplatin and vincristine, or vinblastine, have been used to stop the growth of the childhood LGGs, and result in tumor control in 80% or more of those treated; after treatment with carboplatin and vincristine, over 40% demonstrate objective tumor shrinkage. Functional improvement in vision and neurological function is much less frequent. Disease control is maintained in 30% to 40% of those with non-NF1-associated lesions and approximately 70% of NF1-associated lesions 3 to 5 years from treatment. More recently, MEK-inhibitors have been used as second-line agents to treat LGG, and in ongoing clinical trials are being compared with chemotherapy to assess their efficacy as first-line therapy. *BRAF* V600E inhibitors are being used in those with *BRAF* V600E mutations. Radiation therapy can be considered, but its association with long-term neurocognitive and endocrine toxicities has led to its avoidance in younger children and those at higher risk for secondary tumors such as patients with NF1. It is usually used as frontline treatment in older patients or in those with recalcitrant disease after chemotherapy or MTT.

Overall prognosis for patients with LGG is good. Most of these tumors do not undergo subsequent malignant transformation, especially those with *BRAF* fusions, and some undergo senescence as patients reach adolescence. Ten-year overall survival is greater than 90%.⁷⁰ Those with *BRAF* V600E mutations are more likely to transform to higher grade gliomas. For tumors that are gross totally resected, recurrence occurs in 10% to 20% of cases without adjuvant therapy, compared with 50% to 80% after less than total resection.⁷¹

MIXED GLIONEURONAL TUMORS

Neuronal and mixed glioneuronal tumors are typically low-grade, slow-growing lesions. They make up about 8% of pediatric brain tumors and occur most often in older children and young adults. These tumors have historically been challenging to classify histologically, with components of both glial and neuronal features, and molecular findings are increasingly used to better characterize such lesions.

Glioneuronal tumors are frequently located in the temporal cortex (Figure 9.4) and often present with seizures. There is a group of these tumors termed “low-grade epilepsy-associated brain tumors,” reflecting the common development of epilepsy in these patients.⁷²

The genetic alterations most often seen in each subtype allow more precise categorization and may help identify novel treatment options. Dysembryoplastic neuroepithelial tumors (DNET) have a high incidence of *FGFR1* alterations; DNET of the septum pellucidum is known to have *PDGFRA* mutations.^{73,74} Gangliogliomas are characterized by MAPK pathway activation, especially *BRAF* alterations including V600E mutations (some with concurrent *CDKN2A* homozygous deletion), as well as *BRAF* and *RAF1* fusions, *KRAS*, *NF1*, and *FGFR1/2* mutations.⁷⁵ Dysplastic cerebellar gangliocytoma (otherwise known as Lhermitte-Duclos) and central neurocytoma are associated with *PTEN* mutations. Desmoplastic tumors including desmoplastic infantile ganglioglioma (DIG) and desmoplastic infantile astrocytoma (DIA) are rare lesions in infants frequently characterized by *BRAF*

FIGURE 9.4 Temporal lobe ganglioglioma. A moderately well-defined lesion infiltrates and enlarges the hippocampus and the parahippocampal gyrus of the left temporal lobe (arrows).

V600E or *BRAF* V600D mutations.^{76–78} Diffuse leptomeningeal disseminated glioneuronal tumors (DLGNT) are characterized by *BRAF:KIAA1549* fusion and chromosome 1p deletion, sometimes also with chromosome 19q loss.^{79,80} Other mixed glioneuronal tumors include extraventricular neurocytoma, cerebellar liponeurocytoma, and paraganglioma.

Similar to LGGs, surgery is first-line therapy. Many tumors are observed, even after incomplete resections and are treated by resection and/or other adjuvant means only if still recalcitrant. Evidence for the efficacy of chemotherapy and, for most tumor types, radiotherapy is scant, and for those with treatable molecular targets, MTT is increasingly used before chemotherapy. Overall survival is similar to LGGs, although these tumors are rare and some entities have been recently defined; thus, there is limited data about their long-term outcomes. Gross total resection of the tumor leads to seizure freedom in nearly three-quarters of patients.

HIGH-GRADE GLIOMA

Glial tumors histopathologically classified as WHO grade III or IV are considered HGGs. These tumors are less common in children compared with adults, making up about 10% of pediatric CNS tumors, with equal distribution between males and females.⁸¹ The median age of diagnosis is 9 years, although they can occur from infancy through young adulthood. Pediatric HGGs can rarely arise from LGGs, but more commonly arise de novo with molecular signatures, which differ from adult primary HGGs. HGGs include anaplastic astrocytoma (WHO grade III), glioblastoma (WHO grade IV), and anaplastic oligodendroglioma (WHO grade III).

Patients typically present with signs and symptoms of increased intracranial pressure including headache, early morning nausea and vomiting, diplopia, and papilledema. Focal neurological deficits can be seen, and less commonly seizures given their relatively rapid growth. Patients with cancer predisposition syndromes (Li-Fraumeni, mismatch repair gene, etc.) and those who have had prior CNS ionizing radiation are at higher risk for developing HGG. Imaging is typically characterized by T2 iso/hyperintense infiltrative lesions with marked mass effect on surrounding structures. More prominent diffusion restriction (indicative of hypercellularity), a greater extent of enhancement, and presence of necrosis suggest a higher grade tumor (Figure 9.5). Distant metastases within the brain or spine can be seen. Histology shows glial features, hypercellularity, nuclear atypia, and high mitotic activity, sometimes with microvascular proliferation or pseudopalisading necrosis.

FIGURE 9.5 Glioblastoma. Axial T2-weighted image (A) and ADC map (B) show a fairly small lesion infiltrating a gyrus of the inferior right parietal lobe (arrows, A). Though the T2 appearance is somewhat “innocuous,” the low signal on the ADC image (arrow, B) is characteristic of a hypercellular (grade IV) tumor.

Molecular alterations seen in some pediatric HGG include *TP53* and *ATRX* mutations, *PDGFRA* amplifications, *BRAF* V600E mutations (commonly with *CDKN2A/B* mutations that differentiate them from LGG), and H3.3G34RV epigenetic changes. Children have relatively few DNA copy number alterations, making targeted therapy more challenging.

Management of HGG includes surgical resection with goal of gross total resection when possible, typically followed by focal radiation (55 to 60 Gy over a 6-week period). Adjuvant chemotherapy is often used, which tends to be alkylator-based, such as temozolomide; enrollment in a clinical trial investigating newer therapies is often recommended. Bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody, has been used to reduce tumor-related edema, but does not improve long-term outcomes in pediatric-aged patients.⁸² Newer treatments include novel molecular-targeted therapies and immunotherapies (vaccines, oncolytic viruses, immune checkpoint inhibitors, adoptive T-cell therapy) given with or after radiotherapy.

Outcomes for HGG are generally poor, with 5-year overall survival 15% to 35%, with the better outcomes for those patients who had at least 90% resection.^{83,84} A subset of infants with malignant glioma and different molecular signature who receive chemotherapy, with or without delayed irradiation, appears to have better survival, closer to 50% at 5 years.⁸⁵

DIFFUSE MIDLINE GLIOMA

Diffuse midline glioma (DMG), including the entity previously termed diffuse intrinsic pontine glioma (DIPG),

is a subtype of glioma that arises in the brainstem, thalamus, or spinal cord, with unique biology. Areas of both LGGs and HGGs are often intermixed on histological assessment.⁸⁶ These WHO grade IV tumors account for about 10% of pediatric brain tumors overall, and about 75% of those that occur in the brainstem. The median age at diagnosis is 6 to 7 years with equal male-to-female predominance.

Depending on the location, patients with brainstem lesions typically present with headache, long motor tract signs, and cranial neuropathies. Diplopia secondary to cranial nerve VI palsy and unilateral facial weakness secondary to cranial nerve VII palsy are common in pontine lesions. Ataxia, dysmetria, and dysarthria indicate involvement of projections to adjacent cerebellum.⁸⁷ In approximately 20% to 30%, inferior extension of the tumor can block CSF flow and cause hydrocephalus.

DMGs are characteristically nonenhancing diffuse mass lesions, although some have heterogeneous enhancement (Figure 9.6). Other gliomas, usually low-grade, may arise in the brainstem, including focal tectal lesions, usually nonenhancing, causing hydrocephalus; enhancing exophytic cervicomedullary masses, which are pilocytic astrocytomas; and intrinsic partially cystic, partially enhancing pilocytic tumors. In total, these variants comprise 10% to 20% of all brainstem gliomas.

The expansion of genomic and epigenomic profiling resulted in the groundbreaking discovery of mutations in the chromatin remodeling pathway, specifically mutations in the histone 3 variant H3.3 (H3K27M), that occur in these tumors. This mutation leads to amino acid substitutions within the histone tail and regulates posttranslational modifications.⁸⁸ Other identified aberrations in

FIGURE 9.6 Diffuse midline glioma (diffuse intrinsic pontine glioma). Axial T2-weighted image (A) and contrast-enhanced T1-weighted image (B) reveal a diffusely infiltrating mass centered in the pons. The mass surrounds the basilar artery anteriorly (arrow, A). A ring-enhancing necrotic component (arrow, B) is evident posteriorly.

some DMGs include *ACVR1*, *TP53*, *PDGFRA*, *PIK3CA*, *EGFR*, and *MYC*.

Significant surgical resection is not possible in diffuse infiltrating tumors due to their location. Management has changed over the past decade in that biopsy was previously avoided due to the ability to make the diagnosis on imaging and the morbidity of the procedure. However, with recent advances in genetic sequencing, biopsies are becoming more common, as tissue removed is sufficient to molecularly characterize lesions and guide therapy.

First-line therapy includes focal radiation (typically 54 Gy over 6 weeks). Radiation typically provides temporary stabilization of symptoms, although local recurrence most often occurs within 6 to 9 months. Adjuvant chemotherapy has not demonstrated efficacy. Ongoing research is being done to evaluate agents targeting epigenetic or transcriptional disruption, ion channel functioning, and receptor signaling.

DMGs have a poor prognosis; median overall survival is 9 to 12 months and overall survival at 5 years is less than 3%. For the other types of nondiffuse brainstem gliomas, management and prognosis are markedly different. Tectal tumors are often indolent and may require no treatment other than CSF diversion. Cervicomedullary lesions carry the same prognosis as other LGGs.

EPENDYMOMA

Ependymomas are neuroepithelial tumors that arise along the ependymal lining of the ventricular system from radial glial stem cells.⁸⁹ They account for 5% to 10% of pediatric CNS tumors, and about 20% of those that occur in the spinal cord. Median age at diagnosis is 5 years old, with a slightly higher incidence in males. While

ependymomas of the posterior fossa are most common in children, ependymomas can also occur in the supratentorial region and spinal cord (Table 9.3). Historically, they have been divided by histology into WHO grade I tumors including myxopapillary ependymoma and subependymoma, WHO grade II ependymomas, and WHO grade III anaplastic ependymomas.

Clinical presentation depends on location of the tumor, with supratentorial ependymomas presenting with headache, seizures, and focal neurological deficits. Posterior fossa ependymomas typically present with cranial nerve palsies (due to their predilection for cerebellopontine angle) and cerebellar dysfunction with or without evidence of increased intracranial pressure. Spinal cord lesions may present with back pain, weakness, sensory changes, and bowel/bladder dysfunction. Imaging typically reveals a fairly well-circumscribed heterogeneous mass with areas of necrosis, calcification, cystic change, or hemorrhage; enhancement is variable. Invasion into the pontine angle is common. Extension caudally, along the upper cervical cord, is frequent and, if present, can help distinguish ependymomas from other posterior-fossa tumors. Histology shows GFAP- and EMA- positive monomorphic cells with round or oval nuclei and a variably dense fibrillary background; there may be perivascular pseudorosettes and ependymal rosettes.

Molecular profiling of ependymomas has allowed greater understanding of their biology and more robust classification of these tumors. Supratentorial tumors in children frequently harbor fusions in *RELA:C11ORF95*, and this was made a distinct entity in the 2016 WHO classification schema, often associated with *CDKN2A*

TABLE 9.3 EPENDYMOMA SUBTYPES IN CHILDHOOD

TYPE (RELATIVE INCIDENCE)	SUPRATENTORIAL (20%)		INFRATENTORIAL (70%)		SPINAL (10%)	
Median age at diagnosis	6–8 years		3–4 years		12–14 years	
Histology	Moderately cellular, monomorphic cells with round/oval nuclei and salt and pepper chromatin; perivascular pseudorosettes and ependymal rosettes; IHC positive for GFAP, S100, vimentin, EMA					
Molecular features	<i>RELA:C11ORF95</i> fusion	<i>YAP1</i> fusion	PF-A (loss of H3K27 trimethylation)	PF-B (retained H3K27 trimethylation)	Myxopapillary (alterations of <i>HOXB13</i> , <i>NEFL</i> , <i>PDGFRa</i>)	Other
Outcomes	Overall survival 75%	Nearly 100% survival rate	5-year pro- gression-free survival <50%	5-year progres- sion-free survival 60% to 70%	Overall survival 95%	5-year progres- sion-free survival 60% to 70%

EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; IHC, immunohistochemistry; PF-A, posterior fossa group A; PF-B, posterior fossa group B.

deletions and poor outcomes. Less frequently, *YAP1* fusions are seen in other supratentorial ependymomas.⁹⁰ In the posterior fossa, two subgroups have been identified by DNA methylation cluster analysis; “PF-A” and “PF-B,” the former characterized by lack of H3K27 trimethylation and more common in infants and young children.⁹¹

Standard therapy for ependymoma includes surgical resection with the goal of gross total resection, typically followed by focal (often proton beam) radiation therapy within 1 month of surgery (50 to 60 Gy over 6-week period) in children as young as 1 year of age.⁹² Delayed radiation is associated with worse outcomes. For children with anaplastic ependymomas, after gross total resections, maintenance chemotherapy may prolong event-free survival. For those younger than 1 year of age, chemotherapy is often given postoperatively in order to delay irradiation. Some patients can be successfully treated with chemotherapy alone.

Outcomes for ependymoma depend on subtype and extent of surgical resection. Myxopapillary ependymomas have an excellent prognosis with 10-year overall survival greater than 95%.⁹³ For pediatric ependymomas in general, 5-year overall survival is 50% to 60%. Supratentorial tumors with *RELA* fusion have a variable prognosis and overall survival of 75%. In contradistinction, *YAP1* fusion ependymomas have nearly a 100% survival rate.^{94,95} Posterior fossa tumors with PF-A methylation pattern with 1q gain have 5-year progression-free survival of less than 50% and worse overall survival compared to PF-B tumors. Late relapse may occur.⁹⁶

Embryonal Tumors

Embryonal tumors are composed of a variety of different molecular genetic entities characterized by densely packed, small, round, undifferentiated cells with mild to moderate nuclear pleomorphisms and a high mitotic count.¹⁴ In total, comprising 20% to 25% of all tumors arising in childhood, they are far more common in the pediatric age group than in adulthood (Table 9.2).^{12,13,15} Medulloblastoma, the most common embryonal tumor, arises by definition in the posterior fossa, although other embryonal tumors may also arise in the same region of the brain. Nonmedulloblastoma embryonal tumors are diagnosed throughout childhood, but have a propensity to present in the first 3 years of life.¹²

MEDULLOBLASTOMA

Medulloblastoma remains one of the last tumors in the WHO classification to be defined not only by its histological appearance, but also by its site of origin (in the posterior

fossa).¹⁴ Medulloblastomas peak between the ages of 1 and 9, and approximately 10% will arise in infancy.^{12,13}

The majority of medulloblastomas arise in the region of the fourth ventricle, filling the fourth ventricle and causing the relatively acute onset of midline cerebellar deficits such as truncal and gait unsteadiness associated with headaches and vomiting due to obstruction of the fourth ventricle and hydrocephalus.³⁷ Patients are usually diagnosed within 3 months of onset of symptoms, and hydrocephalus is present in greater than 80% of patients at the time of diagnosis.³⁷

Different variants of medulloblastoma may present somewhat differently. The sonic hedgehog (SHH) variant, arising from cerebellar granular cell precursors of the cerebellar external granular layer, are more commonly seen in children younger than 3 years of age, tend to be found in the lateral lobes of the cerebellum, and cause more lateralized cerebellar deficits early in disease.¹⁷ The wingless (WNT) variant, believed to arise from lower rhombic lip progenitor cells of the brainstem and most commonly seen in adolescence, is attached to the brainstem and may result in more acute presentations due to intratumoral hemorrhage.^{16,17} Medulloblastoma is one of the tumor types that can present with acute neurological compromise and coma due to intratumoral bleeding.³⁷

Based on the tempo of presentation, clinical findings, and, to a somewhat lesser degree, age of the patient, medulloblastomas can often be clinically and radiographically distinguished from the other three most common tumor types that occur in the posterior fossa in pediatric patients (Table 9.1). At the time of diagnosis, up to 30% of children with medulloblastoma will have evidence of leptomeningeal dissemination, although in the majority such dissemination is asymptomatic.³⁷

Radiographically, medulloblastomas tend to be relatively well-defined lesions arising in the medullary velum or the roof of the fourth ventricle (Figure 9.7).^{12,37} There is commonly invasion of the middle cerebellar peduncle. The majority of these tumors will be at least contiguous to the brainstem, and evidence for direct brainstem invasion is probably present in 10% to 20%, especially the WNT variant. Calcification and areas of hemorrhage may also be seen. As stated previously, SHH variant tumors, especially in infancy, are more likely to be laterally placed in the cerebellum. Medulloblastoma is usually hyperdense compared with the normal cerebellum on CT and on MRI has iso- to hypointense signal characteristics on T1-weighted images and hyperintense signal on T2-weighted images.^{12,13} Similar to other embryonal tumors, masses (and their metastases) restrict on diffusion imaging, a reflection of their hypercellularity. After

contrast infusion, the majority of medulloblastomas enhance, although some do so heterogeneously. Up to 25% show minimal to no enhancement. Dissemination may be seen along the cerebellar surfaces and the cerebrum, but leptomeningeal dissemination is more common along the spine. Dissemination can be difficult to visualize in nonenhancing tumors.^{12,13}

Extensive molecular studies of large numbers of children with medulloblastoma have disclosed distinct molecular subgroups.^{17,97–101} Molecular findings have been included, to some degree, in the WHO two-tiered histological and molecular classification schema. As noted in Table 9.4, molecularly medulloblastoma has been separated into WNT, SHH, and non-WNT/SHH-activated subgroups (also divided into groups 3 and 4). The WNT-activated subgroup, comprising approximately 10% of all medulloblastoma, was initially identified by intranuclear beta-catenin immunohistochemical staining.¹⁰² Presently, beta-catenin nuclear staining alone is not considered sufficient for diagnoses of WNT-activated tumors, and demonstration of either a monosomy 6 copy number alteration or a *CTNNB1* mutation is required to confirm diagnosis.

The SHH-activated variant of medulloblastoma, comprising approximately 25% of childhood medulloblastomas, has been further divided into as many as four subtypes.^{17,97–100,103–106} The SHH-TP53 wild-type (WT) variant, which may have a desmoplastic/nodular histology, commonly has *PTCH* mutations, but may also alternatively have *SUFU* or *SMO* mutations and tends to arise in children younger than 3 years of age; it carries an excellent prognosis. SHH-TP53 variant,

which may demonstrate a large-cell anaplastic histology, is more likely to have *GLI2*, in addition to *TP53*, mutations. It usually arises in children older than 3 years of age and, unlike the SHH-TP53-WT, has a poor prognosis.

The non-WNT/non-SHH subgroup of medulloblastoma, which may have as many as eight subtypes, is often split into group 3 and group 4 tumors. Group 3 tumors, which have a 2:1 male predominance, may be histologically classical or large-cell anaplastic tumors.^{101,107,108} The large-cell anaplastic variant is more likely to have *MYC* amplification, dissemination at diagnosis, and poor prognosis. The group 4 tumors, occurring in all age groups, also have a male predominance and may have *MYCN* amplification as well as other genetic abnormalities such as an isochromosome 17q abnormality. Of the non-WNT/non-SHH group, the majority will fall into group 4 tumors.^{101,107,108}

Conventionally, medulloblastomas in children 3 years of age or older have been separated into average-risk and poor/high-risk subgroups. Based on staging studies and histological features, patients with average-risk disease include those whose tumors have been totally or near-totally resected (arbitrarily less than 1.5 cm² residual disease on postoperative imaging), have no evidence of tumor dissemination, and histologically are not anaplastic (less than 50% of the tumor microscopically demonstrating anaplasia).³⁴ Patients with tumors that are partially resected, anaplastic, and/or have any evidence of tumor dissemination, including positive CSF cytology for tumor cells, are considered high/poor risk. In more recent schema, patients are also considered to be high/poor risk, independent of these factors, if their tumors were SHH-TP53 associated or were group 3 with *MYC* amplification.¹⁰⁹ Because of the excellent prognosis of the WNT medulloblastomas, patients with WNT tumors without evidence of dissemination are considered to be of very good risk disease, and separated therapeutically from other medulloblastomas.¹⁰⁹

For patients with average-risk disease, conventional treatment consists of “reduced-dose” craniospinal (2,340 cGy) and local boost radiotherapy (5,500–5,960 cGy) and adjuvant chemotherapy during and after radiation therapy.³⁴ Various chemotherapeutic regimens have been used and the widest experience has been with the use of vincristine during radiotherapy and alkylator plus cisplatin-based therapy following radiation therapy.^{34,110} Delay of initiation of radiation therapy for more than 4 weeks from definitive surgery to allow the use of preradiation chemotherapy has resulted in poorer disease control in children with average-risk disease.¹¹¹

FIGURE 9.7 Medulloblastoma with subarachnoid dissemination. Axial T2-weighted image (A) and contrast-enhanced sagittal T1-weighted image (B) reveal a slightly heterogeneous enhancing mass that occupies the fourth ventricle. The mass invades the region of the right dentate nucleus (arrow, A). The infundibular recess/pituitary stalk region is thicker than a normal (arrow, B) cyst, indicative of a subarachnoid metastasis.

TABLE 9.4 MEDULLOBLASTOMA SUBTYPES IN CHILDHOOD

TYPE/(RELATIVE INCIDENCE)	WNT/(10%)	SHH TP53-WT/ (20%–25%)	SHH TP53-MUTANT/ (5%)	NON-WNT GROUP 3/ (10%–15%)	NON-SHH* GROUP 4/(48%)
Age	Older children; adolescence; adulthood	Infancy	Childhood	Childhood	All ages; later childhood
Gender (M:F)	1:2	1:1	1:1	2:1	2:1
Histology; immunohistochemistry	Usually classical; nuclear beta-catenin staining	Desmoplastic nodular in infancy; early childhood-desmoplastic	Large-cell; anaplastic	Classic; anaplastic	Classic
Molecular features	<i>CTNNB1</i> mutations 85%+ ; <i>APC</i> 5% to 10%; 6q loss 85%+ ; adults no 6q loss	<i>PTCH1</i> , <i>PTCH2</i> , <i>SMO</i> , <i>SUFU</i> mutation; 9q deletions may occur	<i>MYCN</i> amplification; <i>GLI2</i> amplification; <i>TP53</i> mutation	<i>MYC</i> amplification; i17q loss	Some <i>MYCN</i> amplification or overexpression; i17q loss; 11q loss
Metastatic spread	Infrequent <i>APC</i> mutation	May occur	Frequent	Very frequent	Can occur
Predisposition	Turcot	Gorlin	<i>TP53</i> mutation; Li–Fraumeni?	?	?
Outcome	>90% PFS* in childhood and adolescence; lower in adults	>75%–85% PFS in infancy, early childhood	Poor; <40% PFS	Poor if <i>MYC</i> amplification; <40% PFS	Good; >75% PFS, better in non-i17q; excellent with 11q loss? >85% PFS

*5-year progression-free survival.

PFS, progression-free survival.

After conventional treatment, children with average-risk medulloblastoma have a greater than 80% likelihood of disease control 5 years from diagnosis, with the majority cured of their disease. Late disease relapse may occur, but more commonly secondary malignancies occur, especially HGGs.^{34,110}

For children 3 years of age or older with high-risk disease, treatment remains problematic.^{34,37,110} Most children receive 3,600 cGy of craniospinal radiation, 5,960 cGy of local-site radiation therapy, and boost radiation to sites of metastatic disease. Chemotherapy is often also intensified; despite these modifications, survival from 5 years from diagnosis has ranged between 50% and 65%.^{37,111}

Because of concerns over the likely deleterious effects of craniospinal radiation therapy in children younger than 3 years of age and, in some studies, in children younger than 4 or 5 years of age, craniospinal radiation therapy has been delayed and in some cases completely removed from treatment regimens. This has been most successfully accomplished in infants and young children with SHH–TP53–WT nodular desmoplastic medulloblastoma because the use of higher dose chemotherapeutic regimens supported by peripheral stem cell rescue or bone marrow rescue has resulted in survival rates of

75% to 80% or higher without radiation therapy.^{112,113} Other chemotherapy regimens have also been successful in young children with medulloblastoma with SHH-activated tumors, including therapies using intrathecal chemotherapy. For the non-SHH-activated tumors, chemotherapy alone regimens have not been as successful, resulting in disease control in less than 50% of children. For these patients, radiation therapy is often given after the completion of chemotherapy and focal radiation therapy has been used in those patients without disseminated disease at time of diagnosis. The management of infants and young children with disseminated disease at the time of diagnosis is highly problematic, as disease control after chemotherapy alone is less than 25%.^{112–114}

The management of relapsed medulloblastoma is suboptimal. Although these tumors may be both chemotherapy and radiation therapy sensitive, they are usually not curable.

For long-term survivors, neurocognitive sequelae can be severe, especially after higher doses of craniospinal radiation therapy (see Late Effects section).¹¹⁵ Endocrinologic sequelae are also common and after 3,600 cGy of craniospinal radiation and, to a lesser extent, 2,340 cGy of craniospinal radiation, approximately 80% of prepubertal patients will be growth-hormone deficient; associated thyroid and gonadal hormone deficiencies occur

at a lower incidence.^{44,116,117} The use of cisplatin-containing treatment regimens have led to hearing compromise in 30% to 50% of those treated.^{117,118}

ATYPICAL TERATOID/RHABDOID TUMORS

Atypical teratoid/rhabdoid tumors (AT/RTs) are defined as embryonal tumors, which are composed predominantly of poorly differentiated elements, including rhabdoid cells with inactivation of *SMARCB1* (*INI1*) or (rarely) *SMARCA4* (*BRG1*).¹⁴ These tumors were first identified as a separate entity in the mid-1980s.¹¹⁹ Although uncommon, comprising less than 2% of all primary CNS tumors, AT/RTs do make up 10%, or more in some series, of embryonal tumors in children younger than 3 years of age. Rarely diagnosed in adulthood, they can present all throughout childhood.^{1,14}

The molecular subclassification of AT/RTs remains in flux; three molecular subtypes have been identified: one marked by overexpression of tyrosinase (AT/RT-TYR) occurring primarily infratentorially in children younger than 1 year of age; the second marked by both increased SHH and NOTCH signaling (AT/RT-SHH) arising in children between 2 and 5 years of age; and the third demonstrating MYC overexpression (AT/RT-MYC) presenting in older patients.^{120–122} Germline *SMARCB1* may be present in 40% or possibly more of patients.¹²³ Rarely, in those children with germline mutations, rhabdoid tumors of the kidney may arise concurrently with intracranial tumors.

AT/RTs may occur throughout the nervous system, with a slight supratentorial predilection (Figure 9.8).¹²⁴ Infants and young children with large cortical tumors are likely to present with lethargy, vomiting, focal neurological deficits, and seizures.¹²⁴ Posterior fossa tumors are more common in the cerebellar hemispheres than the ventricular system and present like medulloblastomas, often in a relatively acute fashion due to intratumoral bleeding.¹²⁴ AT/RTs cannot be definitively radiographically distinguished from other embryonal brain tumors; however, in addition to medulloblastoma-like features, frequent cystic and/or necrotic regions manifest as areas of hemorrhagic heterogeneous signal intensity, which are clues to diagnosis.^{12,124} Leptomeningeal dissemination occurs in approximately 25% of patients.

Histopathologically, AT/RTs are hallmarked by variability in histological appearance.^{14,119} The majority of the tumors are usually relatively undifferentiated, but the most pathognomonic features are the classical rhabdoid regions of tumor-containing large cells with eccentric nuclei, prominent eosinophilic nucleoli, and abundant cytoplasm. Rhabdoid cells immunohistochemically

demonstrate expression of EMA, SMA, and vimentin. Immunohistochemical staining demonstrates lack of expression of the *SMARCB1* (*INI1*) protein. Much less frequently *SMARCB1* is maintained, and there is a loss of nuclear expression of *SMARCA4* (*BRG1*).

When initially recognized as a separate entity, AT/RTs were predominantly diagnosed in infants and survival was infrequent.^{124,125} With the understanding of the wider spectrum of the disease, survival rates as high as 60% have been reported in older children with AT/RTs who undergo aggressive surgical resections followed by preradiation chemotherapy, adjuvant radiation therapy (usually craniospinal with local boost as is given for high-risk medulloblastomas), and then additional chemotherapy.^{126,127} For infants and very young children, there is reluctance to use craniospinal therapy. Hybrid chemotherapeutic regimens combining drugs used for medulloblastoma and high-risk sarcomas are frequently used. Although not as favorable as the survival rate noted in older patients,^{128,129} with these more aggressive chemotherapeutic regimens often supplemented with focal

FIGURE 9.8 Atypical teratoid/rhabdoid tumor (AT/RT). Axial T2-weighted image shows a large, well-defined left insular mass with mix of hemorrhage (very low T2 signal, long arrow), hypercellular solid components (less T2 hypointense content, short arrows), and central/peripheral necrosis (T2 hyperintense components). Mild amount of surrounding edema evident in left frontal lobe anterior to the mass.

radiation therapy after completion of chemotherapy, 5-year survival rates are 30% to 40%.

OTHER EMBRYONAL PRIMARY CENTRAL NERVOUS SYSTEM TUMORS

Other embryonal primary CNS tumors are a histologically and molecularly mixed group of embryonal tumors.¹⁴ In some ways almost a diagnosis of exclusion in the past, these tumors were termed by different nomenclatures including primitive neuroectodermal tumors and supratentorial primitive neuroectodermal tumors.^{14,130–132} They have different molecular alterations than do medulloblastomas or atypical teratoid/rhabdoid tumors. Adding to the complexity of diagnosis, some tumors with similar histological features have different molecular signatures, while other histologically apparently divergent tumors share the same molecular aberrations. Entities such as the embryonal tumor with multilayered rosettes are more clearly delineated, usually harboring *C19MC*-amplification or *LIN28A* expression, while for others distinct molecular signatures are not known.^{14,133,134} Molecularly defined subtypes that are not yet included in the WHO classification, such as those with *BCOR* mutation or mutations in the *FOX* family of genes, have been identified.^{130,131} Terms such as “medulloepithelioma,” “CNS neuroblastoma,” and “CNS ganglioneuroblastoma” remain in the WHO classification, but are likely to be replaced or at least be part of a tiered system incorporating molecular characterization in the near future.^{130,131,135}

Overall these “other” embryonal tumors constitute up to 3% of all childhood brain tumors and a greater percentage of those younger than 3 years of age.^{1,14} Predominantly located in the cerebral hemispheres, they share imaging features with medulloblastomas and AT/RTs.¹⁴ Leptomeningeal dissemination occurs in over one-quarter of patients.

Because of the noted cellular and molecular heterogeneity and the young age of patients, management of these tumors remains highly problematic. In most small series, those patients undergoing a total or near-total resection have a greater likelihood of long-term survival.^{136–139} Embryonal tumors in older patients are usually managed similarly to high-risk medulloblastoma patients, although the need for craniospinal radiation therapy plus tumor site boost radiotherapy rather than focal radiation therapy alone in this grouping of patients is unclear. Younger children with more localized tumors are often initially treated with high-dose chemotherapeutic regimens usually followed by focal radiation therapy. Children with localized disease who undergo total or near-total resection can survive, but the overall prognosis

is poor, with nearly no survivors among individuals with disseminated disease and as high as 50% survival among those with more localized tumors.

Pineal Region Tumors

The pineal region includes the structures of the pineal gland, splenium of the corpus callosum, third ventricle, midbrain tegmentum, and tectum. Tumors in the pineal region comprise less than 4% of all childhood brain tumors and usually consist of germ cell tumors, tumors that arise from the pineal parenchyma, and tumors that arise from adjacent structures including astrocytoma. Germ cell tumors include germinomas and non-germinomatous germ cell tumors such as mixed germ cell tumors and teratomas. Pineal parenchymal tumors include pineoblastoma, pineocytoma, and pineal parenchymal tumors of intermediate differentiation.

The clinical presentation of pineal region tumors is usually due to mass effect on adjacent structures. If the tumor is blocking the cerebral aqueduct, pineal tumors typically present with symptoms of increased intracranial pressure (headache, nausea/vomiting, lethargy) secondary to hydrocephalus. If there is compression of the tectum, patients will likely demonstrate components of Parinaud syndrome, which includes impaired upgaze, pupils that react better to accommodation than light, lid retraction, and convergence or retraction nystagmus. Germinomas and other germ cell tumors may also concurrently arise in the suprasellar region (bifocal lesions) with associated endocrinopathies (e.g., diabetes insipidus, precocious puberty, isolated growth failure, pan-hypopituitarism).

In differentiating subtypes of pineal region tumors, there are some notable imaging features.^{140,141} Calcification of a germ cell tumor on CT is often central (Figure 9.9) versus the exploded/peripheral calcification seen in pineoblastoma. Germinomas are most commonly heterogeneous solid or solid/cystic masses with decreased T2 signal and heterogeneous enhancement on MRI. Mature teratomas appear on MRI as a cystic and solid, lobulated mass with heterogeneous enhancement.

Laboratory markers in the CSF, and less frequently serum, including alpha fetoprotein (AFP), beta human chorionic gonadotropin (B-HCG), and placental alkaline phosphatase (Table 9.5) can be diagnostic for secreting germ cell tumors, including up to 50% of germinomas, and, if elevated, avoid the need for tissue confirmation.

Tumor-focused therapy depends on the tumor type and staging. Within the germ cell tumor group, germinomas are the most common, occur more often in males, and

carry an excellent prognosis. Over 90% of children with germinomas are cured through a combination of chemotherapy, radiation, or both. As nonencapsulated tumors, germinomas may spread along the surface of the brain or through the CSF. Treatment consists of craniospinal and local boost radiation therapy, or with radiation-reduction strategies such as preradiation chemotherapy and whole ventricular plus local boost radiation therapy. Nongerminomatous germ cell tumors also respond to preradiation chemotherapy, but have lower survival rates of 60% to 70%. For mature teratomas, surgical resection is the treatment of choice. Pineoblastomas are malignant, WHO grade IV tumors; treatment and outcome are discussed in the text that follows. Pineoctyomas are well-marginated low-grade tumors usually treated with total surgical resection or with partial resections and local radiation therapy and carry a favorable prognosis. Pineal parenchymal tumors with intermediate differentiation are problematic without a consensus on optimal treatment.

PINEOBLASTOMA

Pineoblastomas are by definition poorly differentiated highly cellular malignant embryonal neoplasms arising in the pineal region.¹⁴ Although an embryonal tumor, they are classified by WHO separately from the other embryonal tumors in the pineal subgrouping of tumors.

FIGURE 9.9 Germinoma. Unenhanced axial CT study shows a pineal region mass causing obstructive hydrocephalus (*dilated frontal horns). The mass is hyperdense, indicative of hypercellularity; central calcification (arrow) represents the engulfed pineal gland.

TABLE 9.5 ONCOLOGIC MARKERS IN CEREBROSPINAL FLUID* OF GERM CELL TUMORS AND PROGNOSIS

TYPE OF GERM CELL TUMOR	ALPHA FETOPROTEIN (AFP)	BETA HUMAN CHORIONIC GONADOTROPIN (B-HCG)	PLACENTAL ALKALINE PHOSHATASE	PROGNOSIS
Germinoma				
Pure germinoma	-	+/-	+/-	Excellent
Syncytiotrophoblastic germinoma	-	+	+/-	Excellent
Nongerminomatous germ cell				
Embryonal GCT	+/-	-	+	Intermediate to poor
Mixed GCT	+/-	+/-	+/-	Intermediate
Choriocarcinoma	-	++	+/-	Intermediate
Yolk sac tumor	+/-	-	+/-	Intermediate to poor
Teratoma				
Mature teratoma	+/-	+/-	-	Excellent
Immature teratoma	+/-	+/-	+	Intermediate to poor

*At times detected in serum
GCT, germ cell tumor.

Per this classification schema, they overlap with pineal parenchymal tumors of intermediate differentiation.^{14,130} Pineoblastomas are molecularly different from medulloblastomas and other embryonal tumors. Pineoblastomas can occur at any age, but are more common in childhood, especially in the first 10 years of life.¹⁴ Pineoblastomas can be associated with germline mutations in both the *RBI* gene and in *DICER1*.^{142–144}

Pineoblastomas are radiographically characterized as multilobulated masses that compress or invade the tectum, which are associated with hydrocephalus; the tumor usually enhances readily.¹⁴ Leptomeningeal dissemination occurs in approximately 20% to 30% of patients at the time of diagnosis.

Treatment is usually similar to medulloblastoma therapy. Because of the location of the tumor, gross total resection is difficult, but in those patients with localized disease at diagnosis who undergo total or near-total resections followed by adjuvant radiation therapy and chemotherapy, 5-year disease-free survival is 50% or greater.^{132,137} Survival is much poorer in infants and young children, especially those who have disseminated disease, those who undergo partial resection, and those, because of age, who are treated with chemotherapy alone.

CRANIOPHARYNGIOMA

Craniopharyngiomas are sellar/suprasellar tumors that are histologically benign, but are often associated with significant morbidity and sometimes mortality due to close proximity to critical structures including the optic pathway, pituitary, hypothalamus, intracranial vasculature, brainstem, and temporal lobes. Presenting symptoms include visual impairment, headaches with or without increased intracranial pressure, polydipsia/polyuria, and sometimes poor growth or delayed puberty. Comprising up to 5% of all pediatric tumors, there are multiple histological subtypes, with the adamantinomatous subvariety predominating in childhood and the papillary subtype in adulthood; the former is associated with *CTNNB1* mutations and the latter with *BRAF* V600E mutations.¹⁴⁵

Initial treatment is surgery, and the approach to surgical resection has evolved over time. While complete resection was once the goal for cure, it is now only attempted if the tumor is not anatomically involved with the hypothalamus or optic pathway.¹⁴⁶ Residual tumor may be treated with radiation, but radiotherapy may also result in long-term sequelae, especially in young children. Systemic chemotherapy has not been found to be effective. Intracystic interferon-alpha can delay disease progression and is used as an alternative to aggressive surgeries

or radiotherapy in primary cystic lesions.¹⁴⁷ When radiation is needed, initial experience with proton-beam therapy has shown promise in reducing sequelae.

Pediatric craniopharyngioma and its treatment often lead to neurological and neurocognitive sequelae. Adverse consequences include endocrinopathies requiring hormone replacement, progressive hypothalamic obesity, vision impairment, severe physical fatigue, and headaches. Neurocognitive deficits secondary to frontal lobe damage from the tumor or its treatment (primarily surgery) can be impairing, especially to working memory and executive functioning.¹⁴⁸ Concerns have been raised about risks of tumor growth after growth hormone replacement; however, a meta-analysis of 10 studies and 3,487 patients demonstrated a lower recurrence rate of craniopharyngioma among children treated with growth hormone replacement therapy than those who did not receive replacement.¹⁴⁹ Overall, craniopharyngioma is often a chronic disease and requires multidisciplinary care including neurosurgery, neurology, endocrinology, oncology, psychiatry, and psychology.

Choroid Plexus Tumors

Tumors of the choroid plexus epithelium are rare intraventricular lesions accounting for less than 1% of pediatric brain tumors. They usually affect children under 2 years of age, with 10% to 20% diagnosed within the first year of life, and are usually supratentorial. WHO differentiates between benign choroid plexus papillomas (CPP; WHO grade I), atypical choroid plexus papillomas (aCPP; WHO grade II), and aggressive malignant choroid plexus carcinomas (CPC; WHO grade III). Mutations in the tumor suppressor 53 (*TP53*) gene are found in 50% of patients with CPC and alternative mechanisms of *TP53* dysfunction in over 90% of patients.^{150,151} CPC comprise between 12% and 50% of choroid plexus tumors, dependent on the series reviewed.

Outcome is not only related to histological grade, but also dependent on size, location, and disturbances of CSF circulation. Resection is the mainstay of treatment in CPP and aCPP, whereas surgery with adjuvant treatment is frequently recommended for CPC. Most children with CPP and aCPP can be cured by total resection alone; however, there may be high perioperative morbidity due to the young age, intraventricular location, and high-tumor vascularization. Most patients will also require CSF shunting.¹⁵² Another frequent complication is postsurgical subdural hygroma, which may cause macrocephaly or cortical compression, sometimes requiring a subdural peritoneal shunt. After total resection, those

with aCPPs have a higher risk of recurrence than CPPs, and malignant transformation is possible.¹⁵³

Prognosis for choroid plexus carcinomas is poor.¹⁵⁴ Gross total resection is the most important predictor of overall survival, and “second-look” surgery is recommended, sometimes after chemotherapy, if the first surgery is subtotal.^{155,156} CPCs are usually treated, especially if only subtotally resected, with postsurgical adjuvant chemotherapy and cranial or craniospinal radiation therapy if the tumor is metastatic. In patients with germline *TP53* mutations and Li–Fraumeni syndrome, there are risks of secondary malignancy.¹⁵⁷

Schwannomas

Schwannomas, WHO grade I peripheral nerve sheath tumors, which comprise 5% or less of pediatric tumors, arise from Schwann cells and are considered benign, but can cause morbidity due to their location and associated mass effect. These lesions are often sporadic, but can be associated with underlying predisposition syndromes such as neurofibromatosis type 2 (NF2), schwannomatosis, or Carney complex. Schwannoma variants include cellular schwannoma, which can cause local bone erosion; plexiform schwannomas, which are typically cutaneous or subcutaneous and occur in children with NF1; and melanotic schwannomas, which do have malignant potential.¹⁵⁸

Schwannomas are usually diagnosed due to local compression of a peripheral nerve causing pain or nerve dysfunction. Patients with NF2 have bilateral vestibular schwannomas often leading to progressive hearing loss in one or both ears. They are more likely to become first symptomatic in older childhood or adulthood. Imaging reveals well-circumscribed lesions that displace adjacent structures without direct invasion, often with cystic and fatty degeneration and rare hemorrhage or calcification. Histology reveals strong expression of S100 protein with compact spindled areas (Antoni A) and hypocellular microcystic areas (Antoni B), Verocay bodies, macrophages, collagen fibers, and hyalinized vessels.

Most understanding of the molecular biology of schwannomas has come from NF2 research. Loss of merlin, the protein product of *NF2*, leads to disorganization of intracellular signaling pathways and upregulates the PI3K/AKT/mTOR pathway. Genetic alterations seen in schwannomatosis include *LZTR1*, *SMARCB1*, and *COQ6* mutations.¹⁵⁹

Management typically includes observation and consideration of surgical resection or focal radiation therapy if there is significant functional impairment. For NF2-associated vestibular schwannomas, bevacizumab

(anti-VEGF monoclonal antibody) has been shown to improve hearing loss in pediatric patients, but there may be limited durability of this response.^{160,161}

Overall prognosis with schwannomas is good, although functional morbidity, not only hearing loss but also other focal neurological deficits, can occur due to brainstem compression, such as facial palsy, balance difficulties, and hemiparesis. In those with NF2, in addition to bilateral acoustic schwannomas, schwannomas may also form along other cranial nerves, causing additional neurological deficits including cavernous sinus thrombosis. Malignant transformation is uncommon.

Nonprimary Central Nervous System Tumors

Nonprimary CNS tumors, other than leukemia, are infrequent. About 3% to 5% of children with leukemia will have CNS involvement, and brain metastases secondary to childhood lymphoma and other hematopoietic tumors comprise less than 1% of all childhood brain tumors.

LEUKEMIA

Acute lymphocytic leukemia (ALL) is the most common form of leukemia that involves the CNS in childhood.^{43,162–164} With earlier diagnosis and the present treatments, leukemic brain masses, termed “chloromas,” are infrequent. Patients with CNS leukemia may have no symptoms referable to CNS involvement or may present with fairly nonspecific manifestations such as headaches, irritability, lethargy, nausea, and vomiting. Less frequently there may be cranial nerve deficits or other neurological manifestations of disease. Diagnosis is usually made by CSF analysis. The presence of CNS involvement at diagnosis or relapse has prognostic importance and CNS leukemia requires aggressive potentially neurotoxic treatment, including the use of methotrexate.^{43,162–164}

Methotrexate has been associated with leukoencephalopathy when given orally, intravenously at high doses, or intrathecally; concomitant radiation therapy increases the risk of this complication. Arterial and venous strokes have also been associated with ALL therapy, often secondary to L-asparaginase, which is used in induction regimens for ALL and causes a rebound hypercoagulable state. L-asparaginase-associated strokes usually occur 7 to 10 days after completion of induction therapy and tend to present abruptly with seizures and/or focal neurological deficits.^{43,162,165}

Other forms of leukemia can affect the CNS, especially acute promyelocytic leukemia (APML).^{43,162,165} APML, especially at the time of initial treatment, can result in

acute intracranial disseminated intravenous coagulation with resultant intracranial hemorrhage and stroke believed to be secondary to the release of procoagulants as part of acute tumor lysis.

LYMPHOMA

Lymphoma can metastasize directly to the brain and spine, but may also cause neurological complications by metastasis to vertebral bodies with resultant secondary spinal cord compression.^{43,162,166} Primary CNS lymphoma can rarely occur in severely immunosuppressed children, such as those who have undergone bone marrow transplant or those with HIV infections.

HISTIOCYTOSIS

Histiocytosis can infiltrate any region of the brain. It has a proclivity to involve the pituitary stalk and gland, resulting in diabetes insipidus secondary to posterior pituitary damage.^{43,162,167,168} Sellar involvement can be difficult to distinguish from other forms of CNS cancer, especially nonsecreting germinomas.

Focal neurological deficits may also occur either due to direct brain infiltration or secondary to paraneoplastic involvement of the brainstem, hippocampus, cerebellum, and basal ganglia. Treatment of the latter can be difficult, and it is difficult to distinguish tumor infiltration from paraneoplastic complications.

SARCOMAS

Sarcomas may metastasize to the CNS, usually after metastatic spread to other organs, especially the lungs.^{43,162,169} Tending to occur in children greater than 10 years of age, metastatic sarcoma may present like any brain mass, with nonspecific symptoms such as headaches, nausea, and vomiting. Metastases may also result in seizures and focal neurological deficits. Different forms of sarcoma may metastasize to the brain including osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma. Parameningeal rhabdomyosarcoma has a proclivity to contiguously invade the leptomeninges, and prophylactic CNS therapy is often employed for head and neck tumors.¹⁷⁰ As is the case with lymphomas, sarcomas may involve the vertebral bodies and secondarily compress the spinal cord.

NEUROBLASTOMAS

Neuroblastomas, arising from the sympathetic ganglia, may involve the nervous system by invading through neuroforamina (“dumbbell” lesions) and cause spinal cord compression.^{43,162,171} Another presentation may be dural venous thrombosis associated with seizures and even coma secondary to torcular involvement; direct

intracranial metastasis can also be seen. Neuroblastomas are chemosensitive and radiosensitive, and even those children with extensive CNS involvement may make an excellent recovery and experience long-term disease control. Neuroblastomas and a more mature form of the disease, ganglioneuroblastomas, are also associated with paraneoplastic complications, including opsoclonus myoclonus. In patients with opsoclonus myoclonus, a search for occult neuroblastomas is warranted.

SEQUELAE OF TREATMENT: LATE EFFECTS OF CENTRAL NERVOUS SYSTEM TUMORS

Pediatric cancer survivors are at risk for long-term medical, psychosocial, and neurocognitive problems due to treatment. Late effects are generally defined as occurring 5 or more years after diagnosis and are numerous in pediatric brain tumor survivors (see Table 9A.4 in the online appendix for this chapter, accessible on Springer Publishing Connect: connect.springerpub.com/content/book/978-0-8261-4399-0/chapter/ch09).^{44,172,173} Risk factors include brain tumor type and location, age at treatment, radiation dosimetry if radiation was used, chemotherapy type and intensity, and tumor progression and recurrence. Individual differences are poorly understood, and the pathophysiology of sequelae is likely both direct cell toxicity and response to injury (oxidative stress and/or inflammation). Cumulative incidence of late neurological effects continues to increase over time in long-term survivors, and the strongest risk factors for new adverse effects are history of radiation, strokes, secondary brain (often malignant) tumor, and tumor recurrence.¹⁷⁴ The Children’s Oncology Group offers frequently updated guidelines about late effects screening on their webpage: www.survivorshipguidelines.org.

Pediatric brain tumor survivors are at increased risk for stroke and recurrent strokes, particularly if they received whole-brain radiation with doses greater than 30 Gy.^{175–177} After an initial stroke, survivors have a 10-year recurrent cumulative incidence of 21%.¹⁷⁸ Usually, cancer treatment causes a small vessel vasculopathy; however, large vessel vasculopathy may also occur, and MRAs are often helpful in identifying large vessel disease. The time to arteriopathy on MRI after the start of cranial radiation is usually less than 6 years.¹⁷⁹ Severe recurrent headache may herald neurovascular events.¹⁸⁰ Antiplatelet therapy has not been studied in brain tumor survivors; however, in practice it is often used as primary stroke prevention in those with an abnormal MRA and as secondary prevention in patients who have had one stroke or transient ischemic attack. Stroke-like migraine after radiation

therapy (SMART) syndrome is a vascular syndrome with severe headaches and transient ischemic event symptoms. On imaging, there is focal cortical T2 hyperintensity and gyral enhancement.¹⁸¹ Antiplatelet agents and calcium channel blockers may be useful to prevent recurrent attacks.

Neurocognitive deficits are well recognized in brain tumor survivors and can include an array of memory difficulties, specific learning disabilities, executive function challenges, frank reductions in overall intelligence, and attentional disorders.¹⁸² School difficulties are common, especially after whole-brain radiotherapy. Appropriate educational support is mandatory. Methylphenidate is the most studied stimulant in this population; it often results in increased attention, faster processing speed, and improved short-term memory, but minimal gains in academics.^{183,184} Cognitive remediation for childhood cancer survivors has demonstrated modest gains in achievement, attention, and memory as well as significant improvement in writing samples and social skills.¹⁸⁵ In addition, clinical trials of exercise training have demonstrated cognitive improvement and increased white matter anisotropy in pediatric brain tumor survivors.¹⁸⁶ Cognitive strategies are now being introduced during treatment to attempt to strengthen vulnerable cognitive skills during or shortly after cancer treatment and remediate or prevent those late effects.

Pediatric cancer survivors are also at risk for depression, anxiety, posttraumatic stress disorder, and suicidal ideation. Compared with other cancer survivors, brain tumor survivors struggle with making and keeping friends and with being integrated in their community, and psychosocial support is needed. Routine clinical screening for late sequelae and, in selected situations, surveillance testing, counseling to promote a healthful lifestyle, and early symptom management can sometimes ameliorate or prevent sequelae. Such services are often provided as part of a formal multidisciplinary “late-effects” program.

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