# 24 - 95 Primary and Metastatic Tumors of the Nervous System

## 95 Primary and Metastatic Tumors of the Nervous System

Mary Jane Lim-Fat, Patrick Y. Wen

Primary and Metastatic

Tumors of the Nervous

System An estimated 95,000 people will be diagnosed with a primary brain tumor annually in the United States. At least 27,000 of these tumors are malignant, and most of these are gliomas. Meningiomas account for 41% of all central nervous system (CNS) tumors, vestibular schwanno mas 10%, and CNS lymphomas ~2%. Brain metastases are three times more common than all primary brain tumors combined and are diag nosed in ~150,000 people each year. Metastases to the leptomeninges and epidural space of the spinal cord each occur in ~2–12% of patients with systemic cancer and are also a major cause of neurologic disability. APPROACH TO THE PATIENT Primary and Metastatic Tumors of the Nervous System PART 4 Oncology and Hematology CLINICAL FEATURES Brain tumors of any type can present with a variety of symptoms and signs that fall into two categories: general and focal; patients often have a combination of the two (Table 95-1). General symp toms include headache, with or without nausea or vomiting, cog nitive difficulties, personality change, and gait disorder. These symptoms arise when the enlarging tumor and its surrounding edema cause an increase in intracranial pressure or compression of cerebrospinal fluid (CSF) circulation, leading to hydrocephalus. The classic brain tumor headache predominates in the morning and improves during the day, but this pattern is seen in a minority of patients. Headaches are often holocephalic but can be ipsilateral to the side of a tumor. Occasionally, headaches have features of a typi cal migraine with unilateral throbbing pain associated with visual scotoma. Personality changes may include apathy and withdrawal from social situations, mimicking depression. Focal or lateralizing findings include hemiparesis, aphasia, or visual field defect. Later alizing symptoms are typically subacute and progressive; language difficulties may be mistaken for confusion. Seizures are common, occurring in ~25% of patients with brain metastases or malignant

gliomas, and are the presenting symptom in up to 90% of patients with a low-grade glioma. All seizures arising from a brain tumor will have a focal onset whether or not it is apparent clinically. NEUROIMAGING Cranial magnetic resonance imaging (MRI) is the preferred diag nostic test for any patient suspected of having a brain tumor and should be performed with gadolinium contrast administration. TABLE 95-1 Symptoms and Signs at Presentation of Brain Tumors HIGH-GRADE GLIOMA (%) LOW-GRADE GLIOMA (%) MENINGIOMA (%) METASTASES (%) Generalized Impaired cognitive function

Hemiparesis

Headache

Lateralizing Seizures

70+

Aphasia

<5 —

Visual field deficit — — —

Computed tomography (CT) scan should be reserved for those patients unable to undergo MRI. Malignant brain tumors—whether primary or metastatic—typically enhance with gadolinium, have central areas of necrosis, and are surrounded by edema of the neigh boring white matter. Low-grade gliomas usually do not enhance with gadolinium and are best appreciated on fluid-attenuated inver sion recovery (FLAIR) MRI sequences. Meningiomas have a typical appearance on MRI because they are dural-based enhancing tumors with a dural tail and compress but do not invade the brain. Dural metastases or a dural lymphoma can have a similar appearance. Imaging is characteristic for many primary and metastatic tumors and sometimes will suffice to establish a diagnosis when the location precludes surgical intervention (e.g., brainstem glioma). Functional MRI is useful in presurgical planning to define eloquent sensory, motor, or language cortex. Positron emission tomography (PET) is useful in determining the metabolic activity of the lesions seen on MRI; MR perfusion and spectroscopy can provide infor mation on blood flow or tissue composition. These techniques may help distinguish tumor progression from tissue necrosis due to treatment with radiation and chemotherapy. Neuroimaging is the only test necessary to diagnose a brain tumor. Laboratory tests are rarely useful, although patients with metastatic disease may have elevation of a serum tumor marker (e.g., β human chorionic gonadotropin [β-hCG] from testicular cancer). Additional testing such as cerebral angiogram, electroencephalogram (EEG), or lum bar puncture is rarely indicated or helpful. TREATMENT Brain Tumors Therapy of any intracranial malignancy requires both symptomatic and definitive treatments. Definitive treatment is based on the specific tumor type and includes surgery, radiotherapy, and chemo therapy. However, symptomatic treatments apply to brain tumors of any type. Most high-grade malignancies are accompanied by sub stantial surrounding edema, which contributes to neurologic dis ability and raised intracranial pressure. Glucocorticoids are highly effective at reducing perilesional edema and improving neurologic function, often within hours of administration. Dexamethasone has been the glucocorticoid of choice because of its relatively low

mineralocorticoid activity; initial doses are 4–12 mg/d in one to two daily doses. Glucocorticoids rapidly ameliorate symptoms and signs, but their long-term use causes substantial toxicity including insomnia, weight gain, diabetes mellitus, steroid myopathy, and personality changes. Consequently, a taper is indicated as definitive treatment is administered and the patient improves. Patients with brain tumors who present with seizures require antiepileptic drug therapy. Prophylactic antiepileptic drugs are occasionally used in the perioperative setting, but there is no role for extended use in patients who have not had a seizure. The agents of choice are drugs that do not induce the hepatic micro somal enzyme system. These include levetiracetam, topiramate,

lamotrigine, valproic acid, and lacosamide (Chap. 447). Other drugs, such as phenytoin and carbamazepine, are used less fre quently because they are potent enzyme inducers that can interfere with both glucocorticoid and chemotherapy metabolism. Venous thromboembolic disease occurs in 20–30% of patients with HGGs or brain metastases. Prophylactic anticoagulants should be used during hospitalization and in nonambulatory patients. Those who have had either a deep vein thrombosis or a pulmonary embolus can receive therapeutic doses of anticoagulation safely and without increasing the risk of hemorrhage into the tumor. Inferior vena cava filters are reserved for patients with absolute contraindications to anticoagulation such as recent craniotomy. PRIMARY BRAIN TUMORS ■ ■EPIDEMIOLOGY No etiology has been identified for most primary brain tumors. The only established risk factors are exposure to ionizing radiation (menin giomas, gliomas, and schwannomas) and immunosuppression (pri mary CNS lymphoma). There is no proven evidence for any association with exposure to electromagnetic fields including cellular telephones, head injury, foods containing N-nitroso compounds, or occupational risk factors. A small minority of patients have a family history of brain tumors. Some of these familial cases are associated with genetic

syndromes (Table 95-2). ■ ■MOLECULAR PATHOGENESIS As with other neoplasms, brain tumors arise as a result of a multistep process driven by the sequential acquisition of genetic alterations. These include loss of tumor-suppressor genes (e.g., p53, cyclindependent kinase inhibitor 2A and 2B [CDKN2A/B], and phosphatase TABLE 95-2 Genetic Syndromes Associated with Primary Brain Tumors SYNDROME INHERITANCE GENE/PROTEIN ASSOCIATED TUMORS Cowden’s syndrome AD Mutations of PTEN (ch10p23) Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), meningioma, astrocytoma Familial schwannomatosis Sporadic Hereditary Mutations in INI1/SNF5 (ch22q11) Schwannomas, gliomas Gardner’s syndrome AD Mutations in APC (ch5q21) Medulloblastoma, glioblastoma, craniopharyngioma Gorlin syndrome (basal cell nevus syndrome) AD Mutations in Patched 1 gene (ch9q22.3) Medulloblastomas Basal cell carcinoma Li-Fraumeni syndrome AD Mutations in p53 (ch17p13.1) Gliomas, medulloblastomas Sarcomas, breast cancer, leukemias, others Lynch syndrome AD Mutations in MSH2, MSH1, MSH6, PMS2 Glioblastoma and other gliomas Gastrointestinal, endometrial, and other cancers Multiple endocrine neoplasia 1 (Wermer’s syndrome) AD Mutations in Menin (ch11q13) Pituitary adenoma, malignant schwannomas Parathyroid and pancreatic islet cell tumors NF1 AD Mutations in NF1/neurofibromin (ch17q12-22) NF2 AD Mutations in NF2/merlin (ch22q12) Bilateral vestibular schwannomas, astrocytomas, multiple meningiomas, ependymomas TSC (Bourneville disease) AD Mutations in TSC1/TSC2 (ch9q34/16) Subependymal giant cell astrocytoma, ependymomas, glioma, ganglioneuroma, hamartoma Turcot syndrome AD Mutations in APCa (ch5) Gliomas, medulloblastomas AR hMLH1 (ch3p21) Adenomatous colon polyps, adenocarcinoma VHL AD Mutations in VHL gene (ch3p25) Hemangioblastomas aVarious DNA mismatch repair gene mutations may cause a similar clinical phenotype, also referred to as Turcot syndrome, in which

there is a predisposition to nonpolyposis colon cancer and brain tumors. Abbreviations: AD, autosomal dominant; APC, adenomatous polyposis coli; AR, autosomal recessive; ch, chromosome; NF, neurofibromatosis; PTEN, phosphatase and tensin homologue; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau.

and tensin homolog on chromosome 10 [PTEN]) and amplification and overexpression of protooncogenes such as the epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptors (PDGFR). The accumulation of these genetic abnormalities results in uncontrolled cell growth and tumor formation. Many brain tumors, including glioblastomas, are characterized by significant molecular heterogeneity, which contributes to the difficulty in developing effec tive therapies.

Important progress has been made in understanding the molecular pathogenesis of several types of brain tumors, including glioblastoma and medulloblastoma, allowing them to be separated into different subtypes with different prognoses. This has led the World Health Organization (WHO) to issue an update on the classification of CNS tumors in 2016 that for the first time incorporated molecular param eters in addition to traditional histology into the diagnosis of brain tumors. The most recent 2021 WHO Classification of Tumors of the CNS further stressed the use of integrated diagnoses based on both molecular diagnostics and histology. This has improved the classifica tion of brain tumors, allowing for better understanding of the progno sis and optimal therapy for patients. INTRINSIC “MALIGNANT” TUMORS CHAPTER 95 ■ ■DIFFUSE GLIOMA Gliomas are the most common type of malignant primary brain tumor. The 2021 WHO Classification now differentiates gliomas as “adult type” or “pediatric type” based on molecular genetic differences. Both adult-type and pediatric-type diffuse gliomas can be subclassified into high- or low-grade glioma based on histology and are further charac terized by key molecular alterations (Table 95-3). Although uncom mon, pediatric-type diffuse gliomas also occur in adults, hence their inclusion here. Primary and Metastatic Tumors of the Nervous System
Breast, endometrial, thyroid cancer, trichilemmomas Familial polyposis, multiple osteomas, skin and soft tissue tumors Schwannomas, astrocytomas, optic nerve gliomas, meningiomas Neurofibromas, neurofibrosarcomas, others Retinal angiomas, renal cell carcinoma, pheochromocytoma, pancreatic tumors and cysts, endolymphatic sac tumors of the middle ear

TABLE 95-3 Summary of Gliomas and Relevant Molecular Alterations CHARACTERISTIC MOLECULAR ALTERATIONS TUMOR TYPE Adult-Type Diffuse Gliomas Astrocytoma, IDH-mutant IDH1, IDH2 Oligodendroglioma, IDH-mutant, 1p/19q-codeleted IDH1, IDH2, 1p/19q Glioblastoma, IDH wild type Chromosome 7 gain and 10 loss, TERT, EGFR Pediatric-Type Diffuse High-Grade Gliomas Diffuse midline glioma, H3 K27-altered H3 K27M, H3K27me3, EGFR, EZHIP Diffuse hemispheric glioma, H3 G34-mutant H3.3 G34R/V Diffuse pediatric-type high-grade glioma, H3 wild type and IDH wild type EGFR, PDGFRA, MYCN Pediatric-Type Diffuse Low-Grade Gliomas Diffuse low-grade glioma, MAPK pathway-altered MAPK pathway genes (BRAF V600E mutation, BRAF fusion, FGFR mutation) Abbreviations: IDH, isocitrate dehydrogenase; TERT, telomerase reverse transcriptase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; MAPK, mitogen-activated protein kinase; EZHIP, EZH inhibitor protein; PDGFRA, platelet-derived growth factor receptor alpha; MYCN, MYCN proto-oncogene. PART 4 Oncology and Hematology ■ ■ADULT-TYPE DIFFUSE GLIOMA Adult-type diffuse gliomas are classified based on the presence of a mutation in a key driver, the isocitrate dehydrogenase (IDH) gene, followed by the presence of 1p/19q co-

deletion. Both of these molecu lar alterations have significant prognostic impact and lead to the emergence of three distinct groups: IDH-mutant astrocytoma (1p/19q intact), IDH-mutant oligodendroglioma (1p/19q co-deleted), and IDH wild-type glioblastoma. Diffuse gliomas can present rarely as widespread infiltration of the brain tissue without a focal mass. Such tumors usually present with cognitive problems, and the MRI demonstrates confluent, typically nonenhancing areas of increased signal on FLAIR sequences without significant mass effect. Formerly known as gliomatosis cerebri, these lesions are now categorized by the pathology identified on biopsy, but they can be diagnostically challenging when the nature of the imaging abnormalities is unclear. Often diagnosis is delayed until the patient develops worsening deficits or there is clear progression on imaging. Treatment is then determined by the pathology. Astrocytoma, IDH-Mutant IDH-mutant astrocytoma can be further classified into grade 2, 3, or 4 based on histologic features, with higher grade tumors incorporating additional features of malignancy. CDKN2A/B homozygous deletion is associated with poor prognosis, and its presence confers a grade 4 to IDH-mutant astrocytomas with lower-grade histologic features. Low-grade (grade 2) IDH-mutant astrocytomas are infiltrative tumors that usually present with sei zures in young adults or can be detected incidentally. They appear as nonenhancing tumors with increased T2/FLAIR signal (Fig. 95-1). If feasible, patients should undergo maximal surgical resection, although complete resection is rarely possible because of the invasive nature of the tumor. In patients at higher risk for recurrence (subtotal resection or above the age of 40 years), there is evidence that radiation therapy (RT) followed by PCV (procarbazine, lomustine, and vincristine) or temozolomide chemotherapy may be of benefit. The tumor transforms to a higher-grade astrocytoma in most patients, leading to variable survival with a median of ~10 years. The IDH-inhibitor vorasidenib has been showed to be effective in delaying the progression-free sur vival and time to next intervention, and IDH inhibitors may become an integral part of the management for both IDH-mutant low-grade glioma astrocytoma and oligodendroglioma. High-grade IDH-mutant astrocytoma includes grade 3 astrocytoma (formerly termed anaplas tic astrocytoma) and grade 4 astrocytoma (previously IDH-mutant glioblastoma) and generally presents in the fourth and fifth decades

FIGURE 95-1 Fluid-attenuated inversion recovery (FLAIR) MRI of a left frontal lowgrade astrocytoma. This lesion did not enhance. of life as variably enhancing tumors. Treatment is the same as for glio blastoma, consisting of maximal safe surgical resection followed by RT and adjuvant temozolomide alone or RT with concurrent and adjuvant temozolomide. The median survival for high-grade anaplastic astrocy toma can range from 3 to 9 years. Oligodendroglioma, IDH-Mutant and 1p/19q Co-deleted

Oligodendrogliomas account for ~15–20% of gliomas. They are characterized by co-deletion of 1p/19q and have IDH mutations. Oli godendrogliomas are classified by the WHO into grade 2 or grade 3 oligodendrogliomas (formerly anaplastic oligodendrogliomas). Oligo dendrogliomas have distinctive pathologic features such as perinuclear clearing—giving rise to a “fried egg” appearance—and a reticular pattern of blood vessel growth. Some tumors have both an oligoden droglial as well as an astrocytic component. With molecular testing, it is now clear that almost all of these mixed tumors (oligoastrocytomas) are genetically either astrocytomas or oligodendrogliomas. As a result, the diagnosis of oligoastrocytoma is now rarely made unless molecular testing is not available. Grade 2 oligodendrogliomas are generally more responsive to therapy and have a better prognosis than pure astrocytic tumors. These tumors present similarly to

grade 2 astrocytomas in young adults. The tumors are nonenhancing and often partially calcified. They should be treated with surgery and, in patients with residual disease or aged

> 40 years, RT and chemotherapy. Targeting mutant IDH with inhibi tors such as vorasidenib to delay progression and transformation to higher grade may become an effective strategy in low-grade oligoden droglioma. Patients with oligodendrogliomas have a median survival in excess of 10 years. Grade 3 oligodendrogliomas present in the fourth and fifth decades as variably enhancing tumors. They are more responsive to therapy than grade 3 astrocytomas. Treatment involves maximal safe resection followed by RT and PCV or temozolomide chemotherapy. Median survival of patients is in excess of 10 years. Glioblastoma Glioblastomas account for the majority of high-grade astrocytomas and are now defined by the absence of IDH mutations. With the new WHO classification, grade 2 and 3 astrocytomas without the classic histologic features of glioblastoma (necrosis and endothe lial proliferation) but harboring molecular features of glioblastoma

FIGURE 95-2 Postgadolinium T1 MRI of a large cystic left frontal glioblastoma. (epidermal growth factor amplification, combined with whole chromo some 7 gain and 10 loss, or telomerase reverse transcriptase [TERT] promoter mutations) are considered molecular glioblastomas. Glioblastomas are the most common malignant primary brain tumor, with >12,000 cases diagnosed each year in the United States. Patients usually present in the sixth and seventh decades of life with headache, seizures, or focal neurologic deficits. The tumors appear as ring-enhancing masses with central necrosis and surrounding edema (Fig. 95-2). These are highly infiltrative tumors, and the areas of increased T2/FLAIR signal surrounding the main tumor mass contain invading tumor cells. Treatment involves maximal surgical resection followed by involved-field external-beam RT (6000 cGy in thirty 200-cGy fractions) with concomitant temozolomide, followed by 6 months of adjuvant temozolomide. With this regimen, median survival is increased to 15–18 months compared to only 12 months with RT alone, and 5-year survival is ~10%. Efforts to increase the dose of RT locally using brachytherapy or stereotactic radiosurgery (SRS) have failed to improve the outcome, and these treatments are not recommended. Patients whose tumor contains the DNA repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) are relatively resistant to temozolomide and have a worse prognosis compared to those whose tumors contain low levels of MGMT as a result of silenc ing of the MGMT gene by promoter hypermethylation. Implantation of biodegradable polymers containing carmustine chemotherapy into the tumor bed after resection of the tumor or addition of tumor treat ing fields (scalp electrodes delivering low-intensity electric currents) produces a modest improvement in survival. For elderly patients aged >65–70 years, a hypofractionated RT regi men of 40 Gy over 3 weeks with temozolomide is well tolerated and likely leads to similar outcomes as the 6-week standard RT regimen. Despite optimal therapy, glioblastomas invariably recur. Treatment options for recurrent disease may include reoperation, reirradiation, and treatment with bevacizumab and standard chemotherapeutic regi mens. Bevacizumab, a humanized vascular endothelial growth factor (VEGF) monoclonal antibody, has activity in recurrent glioblastoma, increasing progression-free survival but not overall survival and reduc ing peritumoral edema and glucocorticoid use (Fig. 95-3). Immune checkpoint inhibitors have

been successful in a variety of solid tumors but have failed to demonstrate substantial activity in glioblastoma. A recent phase 3 trial comparing bevacizumab with nivolumab in recur rent glioblastoma demonstrated an identical median overall survival

CHAPTER 95 A Primary and Metastatic Tumors of the Nervous System
B FIGURE 95-3 Postgadolinium T1 MRI of a recurrent glioblastoma before (A) and after (B) administration of bevacizumab. Note the decreased enhancement and mass effect. of approximately 10 months in the two arms, with similar toxicities. Treatment decisions for patients with recurrent glioblastoma must be made on an individual basis, taking into consideration such factors as previous therapy, time to relapse, performance status, and quality of life. Whenever feasible, patients should be enrolled in clinical trials. Novel therapies undergoing evaluation in patients with glioblastoma include targeted molecular agents directed at receptor tyrosine kinases and signal transduction pathways; immunotherapy using vaccines, novel checkpoint inhibitors, or chimeric antigen receptor (CAR) T cells; oncolytic viruses; antiangiogenic agents; chemotherapeutic agents that cross the blood-brain barrier more effectively than cur rently available drugs; and infusion of radiolabeled drugs and targeted toxins into the tumor and surrounding brain by means of convectionenhanced delivery. The most important adverse prognostic factors in patients with glioblastomas are older age, unmethylated MGMT promoter, poor Karnofsky performance status, and unresectable tumor.

Gliosarcomas are a variant of glioblastoma containing both an astro cytic and a sarcomatous component and are treated in the same way as glioblastomas.

■ ■PEDIATRIC-TYPE DIFFUSE HIGH-GRADE GLIOMA Pediatric-type diffuse high-grade gliomas (HGGs) are clinically and biologically distinct and are further classified based on their location, which also corresponds to specific molecular alterations. These tumors are typical in younger patients, including young adults, and prior to the recognition of these specific molecular drivers, many pediatric-type HGGs, which do not harbor IDH mutations, were often diagnosed and treated as glioblastoma. Diffuse Midline Glioma, H3K27-Altered These tumors arise from midline structures including the pons, thalamus, or spinal cord and have an infiltrative appearance, often without contrast enhance ment on MRI. They harbor mutations in the H3F3A gene, resulting in lysine-to-methionine substitution in amino acid residue 27 (K27M). H3K27-altered glioma can occur both in children and adults and car ries a poor prognosis regardless of grade. As gross total resection is not feasible in these tumors, treatment mostly consists of RT, while sys temic therapy options remain limited in efficacy. The median overall survival is about 1 year. Diffuse Hemispheric Glioma, H3 G34-Mutant Another HGG that preferentially occurs in young adults is the diffuse hemispheric glioma with the histone variant H3.3 glycine to arginine or valine (H3.3-G34R/V) mutation. These tend to occur in a hemispheric loca tion, and the progression remains poor, with median overall survival of 18–22 months. No standard-of-care treatment exists for these tumors, which are often treated similar to GBM with RT and chemotherapy. PART 4 Oncology and Hematology ■ ■PEDIATRIC-TYPE LOW-GRADE GLIOMA While most common in pediatric patients, pediatric-type low-grade gli omas can also arise in young and older adults. They include avian myelo blastosis viral oncogene (MYB)-altered or MYB proto-oncogene like 1 (MYBL1)-altered diffuse gliomas and mitogen-activated protein kinase (MAPK)-altered diffuse gliomas (commonly v-Raf murine sarcoma viral oncogene homolog B [BRAF] or fibroblast growth factor receptor [FGFR] alterations). Gross total resection can be curative in many cases, and systemic therapy can provide durable response

with oral BRAF or MAPK inhibitors when a targetable mutation or fusion is found. ■ ■CIRCUMSCRIBED ASTROCYTOMA AND OTHER GLIONEURONAL TUMORS These tumors regroup several histologies of more circumscribed tumors, with a typically more indolent natural history. Pilocytic astro cytomas (WHO grade 1) are the most common tumor of childhood. They occur typically in the cerebellum but may also be found elsewhere in the neuraxis, including the optic nerves and brainstem. Frequently they appear as cystic lesions with an enhancing mural nodule. Often, they have BRAF fusions or mutations. These are well-demarcated lesions that are potentially curable if they can be resected completely. Subependymal giant cell astrocytomas (SEGAs) are usually found in the ventricular wall of patients with tuberous sclerosis, discussed later. Gangliogliomas and pleomorphic xanthoastrocytomas occur in young adults. They behave as more indolent forms of grade 1 gliomas and are usually treated with surgery. Frequently they will have BRAF V600E mutations, which can be targeted with BRAF inhibitors. ■ ■EPENDYMOMAS Ependymomas are tumors derived from ependymal cells that line the ventricular surface. They arise in three different compartments and are classified according to location as supratentorial, posterior fossa, or spinal ependymomas. Further molecular stratification within each location (supratentorial ependymoma with ZFTA or YAP1 oncogenic fusion; posterior fossa A or posterior fossa B; and spinal with or with out MYCN amplification) and grading can help guide management. Children typically present with posterior fossa ependymoma followed by supratentorial ependymoma. Although adults can have intracranial ependymomas, they occur more commonly in the spine, especially in

the filum terminale of the spinal cord where they have a myxopapillary histology. Ependymomas that can be completely resected are poten tially curable. Partially resected ependymomas will recur and require irradiation. The less common anaplastic ependymoma is more aggres sive and is treated with resection and RT; chemotherapy has limited efficacy. Subependymomas are slow-growing benign lesions arising in the wall of ventricles that often do not require treatment. ■ ■PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA Primary central nervous system lymphoma (PCNSL) is a rare nonHodgkin’s lymphoma accounting for <3% of primary brain tumors. For unclear reasons, its incidence is increasing, particularly in immu nocompetent, older individuals. PCNSL in immunocompetent patients is usually a diffuse large B-cell lymphoma. Immunocompromised patients, especially those infected with the human immunodeficiency virus (HIV) or organ transplant recipients, are at risk for PCNSL that is typically large cell with immunoblastic and more aggressive features. Epstein-Barr virus (EBV) plays an important role in the pathogenesis of PCNSL in this population. These patients are usually severely immunocompromised, with CD4 counts of <50/mL. Immunocompetent patients with PCNSL are older (median age, 60 years) than those with HIV-related PCNSL (median age, 31 years). PCNSL usually presents as a mass lesion, with neuropsychiatric symptoms, lateralizing signs, or seizures. Ocular and leptomeningeal involvement each occur in 15–20% of patients, and involvement of these compartments may be asymptomatic. Rarely, it may present as isolated ocular lymphoma or as primary leptomeningeal lymphoma. When restricted to the leptomeninges, it may present as a subacute or chronic meningitis that causes progressive cranial and spinal nerve dysfunction. CSF cytologic examination or flow cytometry is required to establish the diagnosis. On contrast-enhanced MRI, PCNSL usually appears as a densely enhancing tumor (Fig. 95-4). Immunocompetent patients have solitary lesions more often than immunosuppressed patients. Frequently, there is involvement of the basal ganglia, corpus callosum, or periventricular region. Stereotactic biopsy is necessary to obtain a histologic diagno sis. Whenever possible, glucocorticoids should be withheld until after the biopsy has been obtained

because they have a cytolytic effect on FIGURE 95-4 Postgadolinium T1 MRI demonstrating a large bifrontal primary central nervous system lymphoma (PCNSL). The periventricular location and diffuse enhancement pattern are characteristic of lymphoma.

lymphoma cells and may lead to nondiagnostic tissue. In addition, patients should be tested for HIV, and the extent of disease should be assessed by performing PET or CT of the body, MRI of the spine, CSF analysis, and slit-lamp examination of the eye. Bone marrow biopsy and testicular ultrasound are occasionally performed. TREATMENT Primary Central Nervous System Lymphoma PCNSL is more sensitive to glucocorticoids, chemotherapy, and RT than other primary brain tumors. Durable complete responses and long-term survival are possible with these treatments. High-dose methotrexate, a folate antagonist that interrupts DNA synthesis, produces response rates ranging from 35 to 80% and median survival of up to 50 months. The combination of methotrexate with other chemotherapeutic agents such as cytarabine increases the response rate to 70–100%. The addition of whole-brain RT (WBRT) to methotrexate-based chemotherapy prolongs progres sion-free survival but not overall survival, but it is associated with delayed neurotoxicity, especially in patients aged >60 years. As a result, full-dose RT is frequently omitted, but there may be a role for reduced-dose RT. The anti-CD20 monoclonal antibody rituximab is often incorporated into the chemotherapy regimen, although there are studies questioning its benefit. For some patients, highdose chemotherapy with autologous stem cell rescue may offer the best chance of preventing relapse. At least 50% of patients will eventually develop recurrent disease. Treatment options include RT for patients who have not had prior irradiation, retreatment with methotrexate, and other chemotherapeutic agents such as temo zolomide and pemetrexed. High-dose chemotherapy with autolo gous stem cell rescue may be appropriate in selected patients with relapsed disease. Bruton’s tyrosine kinase (BTK) inhibitors such as ibrutinib, immunomodulatory drugs such as pomalidomide and lenalidomide, and immune checkpoint inhibitors have shown promising preliminary activity and are being evaluated in clinical trials, as are CAR-T cells. PCNSL IN IMMUNOCOMPROMISED PATIENTS PCNSL in immunocompromised patients often produces multiple ring-enhancing lesions that can be difficult to differentiate from metastases or infections such as toxoplasmosis. The diagnosis is usually established by examination of the CSF for cytology and EBV DNA; toxoplasmosis serologic testing; brain PET imaging for hypermetabolism of the lesions, which, although nonspecific, can be consistent with tumor; and, if necessary, brain biopsy. Since the advent of highly active antiretroviral drugs, the incidence of HIV-related PCNSL has declined. These patients are preferably treated with high-dose methotrexate-based regimens and initiation of highly active antiretroviral therapy; WBRT is reserved for those who cannot tolerate systemic chemotherapy. In organ transplant recipients, reduction of immunosuppression may improve outcome. ■ ■MEDULLOBLASTOMA Medulloblastomas are the most common malignant brain tumor of childhood, accounting for ~20% of all primary CNS tumors among chil dren. They arise from granule cell progenitors or from multipotent pro genitors from the ventricular zone. Approximately 5% of children with medulloblastoma have an inherited syndrome, such as Gorlin, Turcot, or Li-Fraumeni, which predisposes to the development of medulloblas toma. Histologically, medulloblastomas are highly cellular tumors with abundant dark staining, round nuclei, and rosette formation (HomerWright rosettes). In the 2016 WHO pathologic classification, they have been divided into four molecular subgroups: (1) WNT-activated (pri marily affects children and has the best outcome); (2) SHH-activated (affects adults, infants, and children, with the younger patients having the better outcome and adults doing poorly); (3) non-WNT/non-SHH, group 3 (frequently has disseminated CNS disease at diagnosis and has the worst outcome); and (4) non-WNT/non-SHH,

group 4 (30% have

metastases at diagnosis, but 5-year progression-free survival is 95%). Regardless of subtype, patients present with headache, ataxia, and signs of brainstem involvement. On MRI, they appear as densely enhanc ing tumors in the posterior fossa, sometimes associated with hydro cephalus. Treatment involves maximal surgical resection, craniospinal irradiation, and chemotherapy with agents such as cisplatin, lomustine, cyclophosphamide, and vincristine. Approximately 70% of patients overall have long-term survival but usually at the cost of significant neu rocognitive impairment. A major goal of current research is to improve survival while minimizing long-term complications, and clinical trials are now being designed for specific molecular subgroups.

■ ■PINEAL REGION TUMORS A large variety of tumors can arise in the region of the pineal gland. These typically present with headache, visual symptoms, and hydroceph alus. Patients may have Parinaud's syndrome characterized by impaired upgaze and accommodation. Some pineal tumors such as pineocytomas and benign teratomas can be treated by surgical resection. Germinomas respond to irradiation, whereas pineoblastomas and nongerminomatous germ cell tumors require craniospinal RT and chemotherapy. EXTRINSIC "BENIGN" TUMORS CHAPTER 95 ■ ■MENINGIOMA Meningiomas are diagnosed with increasing frequency as more people undergo neuroimaging for various indications. They are now the most common primary brain tumor, accounting for ~35% of the total. Their incidence increases with age. They tend to be more common in women and in patients with neurofibromatosis type 2 (NF2). They also occur more commonly in patients with a history of cranial irradiation. Primary and Metastatic Tumors of the Nervous System Meningiomas arise from the dura mater and are composed of neoplastic meningothelial (arachnoidal cap) cells. They are most com monly located over the cerebral convexities, especially adjacent to the sagittal sinus, but they can also occur in the skull base and along the dorsum of the spinal cord. Meningiomas are classified by the WHO into three histologic grades of increasing aggressiveness: grade I (benign), grade II (atypical), and grade III (malignant). Many meningiomas are found incidentally following neuroimaging for unrelated reasons. They can also present with headaches, seizures, or focal neurologic deficits. On imaging studies, they have a charac teristic appearance usually of a densely enhancing extra-axial tumor arising from the dura (Fig. 95-5). Typically they have a dural tail, con sisting of thickened, enhanced dura extending like a tail from the mass. The main differential diagnosis of meningioma is a dural metastasis. If the meningioma is small and asymptomatic, no intervention is necessary and the lesion can be observed with serial MRI studies. Larger, symptomatic lesions should be resected. If complete resection is achieved, the patient is cured. Incompletely resected tumors tend to recur, although the rate of recurrence can be very slow with grade I tumors. Tumors that cannot be resected or can only be partially removed may benefit from external-beam RT or SRS. These treatments may also be helpful in patients whose tumor has recurred after surgery. Hormonal therapy and chemotherapy are currently unproven. Rarer tumors that resemble meningiomas include hemangiopericy tomas and solitary fibrous tumors. Since they share similar molecular alterations (NAB2-STAT6 fusion), the 2016 WHO classification intro duced the combined term solitary fibrous tumor/hemangiopericytoma for this entity. These tumors are treated with surgery and RT but have a higher propensity to recur locally or metastasize systemically. ■ ■SCHWANNOMA These are generally benign tumors arising from the Schwann cells of cranial and spinal nerve roots. The most common schwannomas, termed vestibular schwannomas or acoustic neuromas, arise from the vestibular portion of the eighth cranial nerve and account for ~9% of primary brain tumors. Patients with NF2 have a high

incidence of vestibular schwannomas that are frequently bilateral. Schwannomas arising from other cranial nerves, such as the trigeminal nerve (cranial nerve V), occur with much lower frequency. Neurofibromatosis type 1

PART 4 Oncology and Hematology FIGURE 95-5 Postgadolinium T1 MRI demonstrating multiple meningiomas along the falx and left parietal cortex. (NF1) is associated with an increased incidence of schwannomas of the spinal nerve roots. Vestibular schwannomas may be found incidentally on neuroim aging or present with progressive unilateral hearing loss, dizziness, tinnitus, or, less commonly, symptoms resulting from compression of the brainstem and cerebellum. On MRI, they appear as densely enhancing lesions, enlarging the internal auditory canal and often extending into the cerebellopontine angle (Fig. 95-6). The differential diagnosis includes meningioma. Very small, asymptomatic lesions can be observed with serial MRIs. Larger lesions should be treated with surgery or SRS. The optimal treatment will depend on the size of the tumor, symptoms, and the patient’s preference. In patients with small vestibular schwannomas and relatively intact hearing, early surgical intervention increases the chance of preserving hearing. FIGURE 95-6 Postgadolinium MRI of a right vestibular schwannoma. The tumor can be seen to involve the internal auditory canal.

■ ■PITUITARY TUMORS These are discussed in detail in Chap. 392. ■ ■CRANIOPHARYNGIOMAS Craniopharyngiomas are rare, usually suprasellar, partially calcified, solid, or mixed solid-cystic benign tumors that arise from remnants of Rathke’s pouch. They have a bimodal distribution, occurring pre dominantly in children but also between the ages of 55 and 65 years. They present with headaches, visual impairment, and impaired growth in children and hypopituitarism in adults. Treatment involves surgery, RT, or a combination of the two. The papillary subtype of craniopha ryngiomas often has BRAF V600E mutations and can be treated with RAF/MEK inhibitors. ■ ■OTHER BENIGN TUMORS Epidermoid Cysts These consist of squamous epithelium sur rounding a keratin-filled cyst. They are usually found in the cerebel lopontine angle and the intrasellar and suprasellar regions. They may present with headaches, cranial nerve abnormalities, seizures, or hydrocephalus. MRI demonstrates an extra-axial lesion with charac teristics that are similar to CSF but have restricted diffusion. Treatment involves surgical resection. Dermoid Cysts Like epidermoid cysts, dermoid cysts arise from epithelial cells that are retained during closure of the neural tube. They contain both epidermal and dermal structures such as hair follicles, sweat glands, and sebaceous glands. Unlike epidermoid cysts, these tumors usually have a midline location. They occur most frequently in the posterior fossa, especially the vermis, fourth ventricle, and supra sellar cistern. On MRI, dermoid cysts resemble lipomas, demonstrating T1 hyperintensity and variable signal on T2. Symptomatic dermoid cysts can be treated with surgery. Colloid Cysts These usually arise in the anterior third ventricle and may present with headaches, hydrocephalus, and, very rarely, sud den death. Surgical resection is curative, or a third ventriculostomy may relieve the obstructive hydrocephalus and be sufficient therapy. NEUROCUTANEOUS SYNDROMES (PHAKOMATOSES) A number of genetic disorders are characterized by cutaneous lesions and an increased risk of brain tumors. Most of these disorders have an autosomal dominant inheritance with variable penetrance. ■ ■NEUROFIBROMATOSIS TYPE 1

(von RECKLINGHAUSEN’S DISEASE) NF1 is an autosomal dominant disorder with variable penetrance and an incidence of ~1 in 2600–3000. Approximately one-half of cases are familial; the remainder are caused by new mutations arising in patients with unaffected parents. The NF1 gene

is located on chromo some 17q11.2 and encodes neurofibromin, a guanosine triphosphatase (GTPase) activating protein (GAP) that is a negative regulator of the RAS–mitogen-activated protein (MAP) kinase signaling pathway, which includes the downstream kinase MEK. It is a classic tumor suppressor, and biallelic loss can result in a variety of nervous system tumors including neurofibromas, plexiform neurofibromas, optic nerve gliomas, astrocytomas, and meningiomas. In addition to neuro fibromas, which appear as multiple, soft, rubbery cutaneous tumors, other cutaneous manifestations of NF1 include café-au-lait spots and axillary freckling. NF1 is also associated with hamartomas of the iris termed Lisch nodules, pheochromocytomas, pseudoarthrosis of the tibia, scoliosis, epilepsy, and intellectual disability. The MEK inhibi tor selumetinib has activity against inoperable plexiform neurofibro mas and is the only treatment that targets the dysregulated signaling pathway. ■ ■NEUROFIBROMATOSIS TYPE 2 NF2 is less common than NF1, with an incidence of 1 in 25,000– 40,000. It is an autosomal dominant disorder with full penetrance. As with NF1, approximately one-half of cases arise from new mutations.

The NF2 gene on 22q encodes a cytoskeletal protein, merlin (moesin, ezrin, radixin-like protein), that functions as a tumor suppressor. NF2 is characterized by bilateral vestibular schwannomas in >90% of patients, multiple meningiomas, and spinal ependymomas and astro cytomas. Treatment of bilateral vestibular schwannomas can be chal lenging because the goal is to preserve hearing for as long as possible. These patients may also have diffuse schwannomatosis that may affect the cranial, spinal, or peripheral nerves; posterior subcapsular lens opacities; and retinal hamartomas. ■ ■TUBEROUS SCLEROSIS (BOURNEVILLE DISEASE) This is an autosomal dominant disorder with an incidence of ~1 in 5000–10,000 live births. It is caused by mutations in either the TSC1 gene, which encodes a protein termed hamartin, or the TSC2 gene, which encodes the protein tuberin. Hamartin forms a complex with tuberin, which inhibits cellular signaling through the mammalian tar get of rapamycin (mTOR), and acts as a negative regulator of the cell cycle. Patients with tuberous sclerosis may have seizures, intellectual disability, adenoma sebaceum (facial angiofibromas), shagreen patch, hypomelanotic macules, periungual fibromas, renal angiomyolipomas, and cardiac rhabdomyomas. These patients have an increased inci dence of subependymal nodules, cortical tubers, and SEGAs. Patients frequently require anticonvulsants for seizures. SEGAs do not always require therapeutic intervention, but the most effective therapy is with the mTOR inhibitors sirolimus or everolimus, which often decrease seizures as well as SEGA size. TUMORS METASTATIC TO THE BRAIN Brain metastases arise from hematogenous spread and frequently origi nate from a lung primary or are associated with pulmonary metastases. Most metastases develop at the gray matter–white matter junction in the watershed distribution of the brain where intravascular tumor cells lodge in terminal arterioles. The distribution of metastases in the brain approximates the proportion of blood flow such that ~85% of all metastases are supratentorial and 15% occur in the posterior fossa. The most common sources of brain metastases are lung and breast carcino mas; melanoma has the greatest propensity to metastasize to the brain, being found in 80% of patients at autopsy (Table 95-4). Other tumor types such as ovarian and esophageal carcinoma rarely metastasize to the brain. Prostate and breast cancers also have a propensity to metas tasize to the dura and can mimic meningioma. Leptomeningeal metas tases are common from hematologic malignancies and also breast and lung cancers. Spinal cord compression primarily arises in patients with prostate and breast cancer, tumors with a strong propensity to metas tasize to the axial skeleton. ■ ■DIAGNOSIS OF METASTASES Brain metastases are best visualized on MRI, where they usually appear as well-circumscribed lesions (Fig. 95-7). The amount of perilesional edema can be highly variable, with large lesions causing minimal edema

and sometimes very small lesions causing extensive edema. Enhance ment may be in a ring pattern or diffuse. Occasionally, intracranial TABLE 95-4 Frequency of Nervous System Metastases for Common Primary Tumors BRAIN (%) LM (%) ESCC (%) Lung

Breast

Melanoma

Prostate

GIT

—

Renal

Lymphoma <1

Sarcoma

Other

—

Abbreviations: ESCC, epidural spinal cord compression; GIT, gastrointestinal tract; LM, leptomeningeal metastases.


B FIGURE 95-7 Postgadolinium T1 MRI of multiple brain metastases from non-smallcell lung cancer involving the right frontal (A) and right cerebellar (B) hemispheres. Note the diffuse enhancement pattern and absence of central necrosis. metastases will hemorrhage; melanoma, thyroid, and kidney cancer have the greatest propensity to hemorrhage, but the most common cause of a hemorrhagic metastasis is lung cancer because it accounts for the majority of brain metastases. The radiographic appearance of brain metastasis is nonspecific, and similar-appearing lesions can occur with infection including brain abscesses, demyelinating lesions, sarcoidosis, radiation necrosis in a previously treated patient, or a primary brain tumor that may be a second malignancy in a patient with systemic cancer. Biopsy is rarely necessary for diagnosis because imaging alone in the appropriate clinical situation usually suffices. However, in ~10% of patients, a systemic cancer may present with a brain metastasis, and if there is not an easily accessible systemic site to biopsy, a brain lesion must be removed for diagnostic purposes.

TREATMENT Tumors Metastatic to the Brain DEFINITIVE TREATMENT The number and location of brain metastases often determine the therapeutic options. The patient’s overall condition and current or potential control of systemic disease are also major determinants. Brain metastases are single in approximately one-half of patients and multiple in the other half. RADIATION THERAPY The standard treatment for brain metastases has previously been WBRT usually administered to a total dose of 3000 cGy in 10 frac tions. This affords rapid palliation, and ~80% of patients improve with

glucocorticoids and RT. However, it is not curative, is associated with neurocognitive toxicity, and produces median survival of only 4–6 months. Hippocampal avoidance during WBRT can preserve cognitive function without increasing the risk of an intracranial relapse. The use of WBRT has declined with the development of more effective systemic options and access to SRS. If feasible, SRS has become the primary radiation oncology approach to brain metastases. It can be delivered through a variety of equally effective techniques including the gamma knife, linear accelerator, proton beam, or CyberKnife, all of which can deliver highly focused doses of RT, usually in a single fraction. SRS can effectively sterilize the visible lesions and afford local disease control in 80–90% of patients. Some patients have been cured of their brain metastases using SRS, whereas this is distinctly rare with WBRT. Traditionally SRS was used only for patients with 1–3 metastases, but recent data suggest that SRS can effectively treat 10 or more lesions. It is, however, confined to lesions of ≤3 cm and is most effective in metastases of ≤1 cm. The addition of WBRT to SRS improves disease control in the nervous system but does not prolong survival and thus is rarely employed. PART 4 Oncology and Hematology SURGERY Randomized controlled trials have demonstrated that surgical extir pation of a single brain metastasis followed by WBRT is superior to WBRT alone. Removal of two lesions or a single symptomatic mass, particularly if compressing the ventricular system, can also be useful. This is particularly important in patients who have highly radioresistant lesions such as renal carcinoma. Surgical resection can produce rapid amelioration of symptoms, improve control of edema, and result in prolonged survival. WBRT administered after complete resection of a brain metastasis improves disease control but does not prolong survival. There is increasing use of focal RT or even SRS to a resected cavity, especially if there is concern that tumor has been left behind, but most avoid postoperative WBRT because of its cognitive effects. CHEMOTHERAPY Chemotherapy and targeted therapy are becoming increasingly useful for brain metastases. Metastases from tumor types that are highly chemosensitive, such as germ cell tumors or small-cell lung cancer, may respond to chemotherapeutic regimens chosen accord ing to the underlying malignancy. Increasingly, data demonstrate responsiveness of brain metastases to targeted therapeutics, such as for patients with lung cancer harboring EGFR mutations that sensitize them to EGFR inhibitors. Immunotherapy is also effective against those primary tumors that are sensitive to this approach, such as melanoma. Antiangiogenic agents such as bevacizumab are effective in the treatment of CNS metastases in those primary tumors for which it is approved. LEPTOMENINGEAL METASTASES Leptomeningeal metastases are also described as carcinomatous men ingitis, meningeal carcinomatosis, or, in the case of specific tumors, leukemic or lymphomatous meningitis. Among the hematologic malignancies, acute leukemias most commonly metastasize to the

subarachnoid space, followed in frequency by aggressive diffuse lym phomas. Among solid tumors, breast and lung carcinomas and mela noma most frequently spread in this fashion. Tumor cells reach the subarachnoid space via the arterial circulation or occasionally through retrograde flow in venous systems that drain metastases along the bony spine or cranium. In addition, leptomeningeal metastases may develop as a direct consequence of prior brain metastases and occur in almost 40% of patients who have a metastasis resected from the cerebellum. ■ ■CLINICAL FEATURES Leptomeningeal metastases are characterized by multilevel symptoms and signs along the neuraxis. Combinations of lumbar and cervi cal radiculopathies, cranial neuropathies, seizures, confusion, and encephalopathy from hydrocephalus or raised intracranial pressure can be present. Focal deficits such as hemiparesis or aphasia are rarely due to leptomeningeal metastases unless there is direct brain infiltra tion. New-onset limb pain in patients

with breast cancer, lung cancer, or melanoma should prompt consideration of leptomeningeal spread. ■ ■LABORATORY AND IMAGING DIAGNOSIS Leptomeningeal metastases are particularly challenging to diagnose because identification of tumor cells in the subarachnoid compart ment may be elusive. MRI can be definitive when there are clear tumor nodules adherent to the cauda equina or spinal cord, enhancing cranial nerves, or subarachnoid enhancement on brain imaging (Fig. 95-8). Imaging is diagnostic in ~75% of patients and is more often positive in patients with solid tumors. Demonstration of tumor cells in the CSF is definitive and often considered the gold standard. However, CSF cytologic examination is positive in only 50% of patients on the first lumbar puncture and still misses 10% after three CSF samples. New technologies, such as rare cell capture, enhance identification of tumor cells in the CSF; molecular profiling of the CSF can also identify tumor-specific mutations, indicating malignancy in the leptomeninges. CSF cytologic examination is most useful in hematologic malignancies, especially when combined with flow cytometry to identify a clonal population. Accompanying CSF abnormalities include an elevated protein concentration and an elevated white blood cell count; hypo glycorrhachia is noted in <25% of patients but is useful when present. Identification of tumor markers may be helpful in some solid tumors. TREATMENT Leptomeningeal Metastases The treatment of leptomeningeal metastasis is palliative because there is no curative therapy. RT to the symptomatically involved areas, such as skull base for cranial neuropathy, can relieve pain and sometimes improve function. Craniospinal irradiation (CSI) was previously avoided because it has significant toxicity with myelosup pression and gastrointestinal irritation as well as limited effectiveness. However, recent data on proton beam CSI suggest better disease con trol with fewer systemic toxicities. Systemic chemotherapy, targeted therapeutics, and immunotherapy have all demonstrated limited efficacy in the appropriate setting. Alternatively, intrathecal chemo therapy can be effective, particularly in hematologic malignancies. This is optimally delivered through an intraventricular cannula (Ommaya reservoir) rather than by lumbar puncture. Few drugs can be delivered safely into the subarachnoid space, and they have a limited spectrum of antitumor activity, perhaps accounting for the relatively poor response to this approach, particularly in solid tumors. In addition, impaired CSF flow dynamics can compromise intrathecal drug delivery. Surgery has a limited role in leptomen ingeal metastasis. A ventriculoperitoneal shunt can relieve raised intracranial pressure but complicates the use of intrathecal drugs. EPIDURAL METASTASIS Epidural metastasis occurs in 3–5% of patients with a systemic malig nancy and causes neurologic compromise by compressing the spinal cord or cauda equina. The most common cancers that metastasize to

FIGURE 95-9 Postgadolinium T1 MRI showing circumferential epidural tumor around the thoracic spinal cord from esophageal cancer. A B FIGURE 95-8 Postgadolinium MRI images of extensive leptomeningeal metastases from breast cancer. Nodules along the dorsal surface of the spinal cord (A) and cauda equina (B) are seen. the epidural space are those malignancies that spread to bone, such as breast and prostate. Lymphoma can cause bone involvement and com pression, but it can also invade an intervertebral foramen and cause spinal cord compression without bone destruction. The thoracic spine is affected most commonly, followed by the lumbar and then cervical spine. ■ ■CLINICAL FEATURES Back pain is the presenting symptom of epidural metastasis in virtu ally all patients; the pain may precede neurologic findings by weeks or months. The pain is usually exacerbated by lying down; by contrast, arthritic pain is often relieved by recumbency. Leg weakness is seen in ~50% of patients, as is sensory dysfunction. Sphincter problems are present in ~25% of patients at diagnosis.

CHAPTER 95 ■ ■DIAGNOSIS Diagnosis is established by imaging, preferably with an MRI of the entire spine (Fig. 95-9). Any patient with cancer who has severe back pain should undergo an MRI. Plain films, bone scans, or even CT scans may show bone metastases, but only MRI can reliably delineate epidural tumor. For patients unable to have an MRI, CT myelography should be performed to outline the epidural space. The differen tial diagnosis of epidural tumor includes epidural abscess, acute or chronic hematomas, epidural lipomatosis, and, rarely, extramedullary hematopoiesis. Primary and Metastatic Tumors of the Nervous System
TREATMENT Epidural Metastasis Epidural metastasis requires immediate treatment. A randomized controlled trial demonstrated the superiority of surgical resection followed by RT compared to RT alone. However, patients must be able to tolerate surgery, and the surgical procedure of choice is a complete removal of the mass, which is typically anterior to the spinal canal, necessitating an extensive approach and resection. Otherwise, RT is the mainstay of treatment and can be used for patients with radiosensitive tumors, such as lymphoma, or for those unable to undergo surgery. SRS or stereotactic body radiotherapy is increasingly being used, especially for radioresistant tumor types or for reirradiation. Chemotherapy is rarely used for epidural metas tasis unless the patient has minimal to no neurologic deficit and a highly chemosensitive tumor such as lymphoma or germinoma. Patients generally fare well if treated before there is a severe neu rologic deficit. Recovery from paraparesis is better after surgery than with RT alone, but survival is often short due to widespread metastatic tumor. NEUROLOGIC TOXICITY OF THERAPY ■ ■TOXICITY FROM RADIOTHERAPY RT can cause a variety of toxicities in the CNS. These are usually described based on their relationship in time to the administration of RT: acute (occurring within days of RT), early delayed (months), or late delayed (years). In general, the acute and early delayed syndromes resolve and do not result in persistent deficits, whereas the late delayed toxicities are usually permanent and sometimes progressive.

Acute Toxicity Acute cerebral toxicity may occur during RT to the brain. RT can cause a transient disruption of the blood-brain barrier, resulting in edema and elevated intracranial pressure. This is usually manifest as headache, lethargy, nausea, and vomiting and can be both prevented and treated with the administration of glucocorticoids.

Early Delayed Toxicity Early delayed toxicity is usually apparent weeks to months after completion of cranial irradiation and is likely due to focal demyelination. Clinically it may be asymptomatic or take the form of worsening or reappearance of a preexisting neurologic deficit. At times, a contrast-enhancing lesion can be seen on MRI/CT that can mimic the tumor for which the patient received the RT. For patients with a malignant glioma, this has been described as “pseu doprogression” because it mimics tumor recurrence on MRI, but it represents inflammation and necrotic debris engendered by effective therapy. This is seen with increased frequency when chemotherapy, particularly temozolomide, is given concurrently with RT. Pseudopro gression can resolve on its own or, if very symptomatic, may require glucocorticoids, resection, or bevacizumab. In the spinal cord, early delayed RT toxicity is manifest as a Lher mitte symptom with paresthesias of the limbs or along the spine when the patient flexes the neck. Although frightening, it is benign, resolves on its own, and does not portend more serious problems. PART 4 Oncology and Hematology Late Delayed Toxicity Late delayed toxicities are the most serious because they are often irreversible and cause severe neurologic deficits. In the brain, late toxicities can take several forms, the most common of which include radiation necrosis and leukoencephalopathy. Radiation necrosis is a focal mass of necrotic tissue that is contrast enhancing on CT/MRI and may be associated with

significant edema. This may appear identical to pseudoprogression but is seen months to years after RT and is always symptomatic. Clinical symptoms and signs include seizures and findings referable to the location of the necrotic mass. The necrosis is caused by the effect of RT on cerebral vasculature with fibrinoid necrosis and occlusion of blood vessels. It can mimic tumor radiographically, but unlike tumor, it is typically hypometabolic on a PET scan and has reduced cerebral blood volume on perfusion MR sequences. It may require resection for diagnosis and treatment unless it can be managed with glucocorticoids. There are reports of improve ment with bevacizumab and laser interstitial thermal therapy. Leukoencephalopathy is seen most commonly after WBRT as opposed to focal RT. On T2 or FLAIR MR sequences, there is dif fusely increased signal seen throughout the hemispheric white matter, often bilaterally and symmetrically. There tends to be a periventricular predominance that may be associated with atrophy and ventricular enlargement. Clinically, patients develop cognitive impairment, a gait disorder, and later urinary incontinence, all of which can progress over time. These symptoms mimic those of normal pressure hydrocephalus, and placement of a ventriculoperitoneal shunt can improve function in some patients but does not reverse the deficits completely. Increased age is a risk factor for leukoencephalopathy but not for radiation necro sis. Necrosis appears to depend on an unidentified predisposition. Other late neurologic toxicities include endocrine dysfunction if the pituitary or hypothalamus was included in the RT port. An RT-induced neoplasm can occur many years after therapeutic RT for either a prior CNS or a head and neck tumor; accurate diagnosis requires surgical resection or biopsy. In addition, RT causes accelerated atherosclerosis, which can cause stroke either from intracranial vascular disease or carotid plaque from neck irradiation. The peripheral nervous system is relatively resistant to RT toxici ties. Peripheral nerves are rarely affected by RT, but the plexus is more vulnerable. Plexopathy develops more commonly in the brachial than in the lumbosacral distribution. It must be differentiated from tumor progression in the plexus, which is usually visualized by CT/MRI or PET scan demonstrating tumor infiltrating the region. Clinically, tumor progression is usually painful, whereas RT-induced plexopathy is painless. Radiation plexopathy is also more commonly associated with lymphedema and myokymia of the affected limb. Sensory loss and weakness are seen in both.

TABLE 95-5 Neurologic Toxicities Caused by Agents Commonly Used in Patients with Cancer Acute encephalopathy (delirium) Methotrexate (high-dose IV, IT) Cisplatin Vincristine Asparaginase Procarbazine 5-Fluorouracil (± levamisole) Cytarabine (high-dose) Nitrosoureas (high-dose or arterial) Ifosfamide Etoposide (high-dose) Bevacizumab (PRES) CAR-T cells Chronic encephalopathy (dementia) Methotrexate Carmustine Cytarabine Fludarabine Visual loss Tamoxifen Gallium nitrate Cisplatin Fludarabine Cerebellar dysfunction/ataxia 5-Fluorouracil (± levamisole) Cytarabine Procarbazine Seizures Methotrexate Etoposide (high-dose) Cisplatin Vincristine Asparaginase Nitrogen mustard Carmustine Dacarbazine (intraarterial or high-dose) Busulfan (high-dose) Myelopathy (IT drugs) Methotrexate Cytarabine Thiotepa Peripheral neuropathy Vinca alkaloids Cisplatin Procarbazine Etoposide Teniposide Cytarabine Taxanes Suramin Bortezomib Abbreviations: CAR, chimeric antigen receptor; IT, intrathecal; IV, intravenous; PRES, posterior reversible encephalopathy syndrome. ■ ■TOXICITY FROM CHEMOTHERAPY Neurotoxicity is second to myelosuppression as the dose-limiting tox icity of chemotherapeutic agents (Table 95-5). Chemotherapy causes peripheral neuropathy from many commonly used agents, and the type of neuropathy can vary depending on the drug. Vincristine causes paresthesias but little sensory loss and is associated with motor dys function, autonomic impairment (frequently ileus), and, rarely, cranial nerve compromise. Cisplatin causes large-fiber sensory loss resulting in sensory ataxia but little cutaneous sensory loss and no weakness. The taxanes also cause a predominately sensory

neuropathy. Agents such as bortezomib and thalidomide also cause neuropathy. Sometimes a severe neuropathy emerges after multiple neurotoxic agents have been used together or in sequence. Encephalopathy and seizures are common toxicities from che motherapeutic drugs. Ifosfamide can cause a severe encephalopathy, which is reversible with discontinuation of the drug. Fludarabine also causes a severe global encephalopathy that may be permanent. Beva cizumab and other anti-VEGF agents can cause posterior reversible encephalopathy syndrome. Cisplatin can cause hearing loss and less frequently vestibular dysfunction. Immunotherapy with monoclonal antibodies such as ipilimumab or nivolumab can cause an autoimmune hypophysitis, Guillain-Barré syndrome, or an autoimmune encephali tis. CAR-T cells frequently cause a reversible encephalopathy due to an immune effector cell–associated neurotoxicity syndrome (Chap. 318). ■ ■FURTHER READING Aizer AA et al: Brain metastases: A Society for Neuro-Oncology (SNO) consensus review on current management and future direc tions. Neuro Oncol 24:1613, 2022. Grommes C et al: Comprehensive approach to diagnosis and treatment of newly diagnosed primary CNS lymphoma. Neuro Oncol 21:296, 2019.

---

Revision #1
Created 2026-01-06 16:31:53 UTC by Omar Ayman
Updated 2026-01-06 16:31:54 UTC by Omar Ayman