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Overview of the clinical features and diagnosis of brain tumors in adults

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INTRODUCTION

Brain tumors are a diverse group of neoplasms arising from different cells within the central nervous system (CNS) or from systemic cancers that have metastasized to the CNS. Systemic cancers most likely to metastasize to the CNS include lung cancer, melanoma, and breast cancer. Primary brain tumors include a number of histologic types with markedly different tumor growth rates ([table 1A-G](#)). (See "[Classification and pathologic diagnosis of gliomas, glioneuronal tumors, and neuronal tumors](#)" and "[Epidemiology, clinical manifestations, and diagnosis of brain metastases](#)".)

Brain tumors can produce symptoms and signs by local brain invasion, compression of adjacent structures, and increased intracranial pressure (ICP). In addition to the histology of the tumor, the clinical manifestations are determined by the function of the involved areas of the brain. The proper evaluation of the patient with a suspected brain tumor requires a detailed history, comprehensive neurologic examination, and appropriate diagnostic neuroimaging studies.

An overview of the clinical manifestations and diagnosis of primary and secondary brain tumors in adults will be reviewed here. The evaluation of brain masses in patients with human immunodeficiency virus (HIV) is presented separately. (See "[Approach to the patient with HIV and central nervous system lesions](#)".)

EPIDEMIOLOGY

The age-adjusted incidence rate of primary brain and nervous system tumors in the United States is estimated to be 25 per 100,000 persons [1]. Approximately 30 percent of tumors are malignant, and the remainder are nonmalignant. Meningiomas and glial tumors (eg, glioblastoma, astrocytoma, oligodendrogloma) account for approximately two-thirds of all primary brain tumors in adults ([table 2](#)). (See ["Epidemiology, pathology, clinical features, and diagnosis of meningioma"](#).)

The frequency of various tumor types and grades varies by age group. In adolescents and young adults, primary brain tumors are more common than metastatic tumors, and among primary brain tumors, low-grade gliomas predominate ([figure 1](#)). In adults above the age of 30 to 40 years, metastatic brain tumors become increasingly prevalent, accounting for more than half of all brain tumors. Glioblastoma is the most common malignant primary brain tumor in adults, with a median age at diagnosis of 64 years.

Most primary brain tumors in adults are sporadic, with no identifiable risk factors. Aside from relatively rare genetic syndromes such as neurofibromatosis and cancer predisposition syndromes such as Li-Fraumeni, the only established risk factor for primary brain tumors is exposure to ionizing radiation. (See ["Risk factors for brain tumors", section on 'Ionizing radiation'](#) and ["Risk factors for brain tumors", section on 'Genetic predisposition syndromes'](#).)

CLINICAL MANIFESTATIONS

Patients with brain tumors may present with generalized and/or focal signs and symptoms or they may be asymptomatic ([table 3](#)).

Symptoms of high-grade gliomas and metastases typically progress over days to weeks, whereas symptoms of low-grade gliomas and other indolent tumors may progress over months to years. Absence of symptoms is more common with low-grade tumors and small lesions without surrounding edema.

Headache — Headache is a common manifestation of brain tumors and a presenting symptom in up to half of patients. Conversely, brain tumors are an uncommon cause of headaches and make up a very small proportion of all headaches in general medical practice. (See ["Evaluation of headache in adults", section on 'Classification'](#).)

Headaches associated with brain tumors are usually dull and constant, but occasionally throbbing. The most common headache quality is tension-type (40 to 80 percent), followed by migrainous (10 percent) [2,3]. Headaches are often bifrontal in location, worse on the same side as the tumor.

Symptom severity tends to progress over time. Severe headaches are infrequent unless increased intracranial pressure (ICP) or meningeal irritation is present. The "classic" early morning brain tumor headache appears to be uncommon.

Patients may report worsening of headache after a change in body position, such as bending over, or with maneuvers that raise intrathoracic pressure, such as coughing, sneezing, or the Valsalva maneuver. These activities lead to a period of raised ICP, which uncommonly can cause a loss of consciousness. (See '[Increased intracranial pressure](#)' below.)

Tumor-related headaches may be worse at night and may awaken the patient. This nocturnal pattern is thought to be due in part to transient increases in the partial pressure of carbon dioxide, a potent vasodilator, during sleep. Other possible physiologic explanations include recumbency and decreased cerebral venous return.

Other features suggestive of a brain tumor or other causes of secondary headache in a patient complaining of headaches include new and progressive symptoms, morning nausea and vomiting, a significant change in prior headache pattern, and an abnormal neurologic examination. (See "[Evaluation of headache in adults](#)".)

Brain tumor headaches are discussed in more detail elsewhere. (See "[Brain tumor headache](#)".)

Seizures — Focal seizures are among the most common symptoms of primary and metastatic brain tumors. Seizures affect 50 to 80 percent of patients with primary brain tumors and 10 to 20 percent of patients with metastatic tumors. Among primary brain tumors, low-grade tumors are more likely to cause seizures than high-grade tumors. (See "[Seizures in patients with primary and metastatic brain tumors](#)", section on '[Epidemiology](#)').

The clinical manifestations of focal seizures depend upon tumor location. As an example, frontal lobe tumors may cause focal tonic-clonic movements involving one extremity, while seizures originating within the occipital lobe may cause visual disturbances. Temporal lobe seizures are often the most difficult to diagnose and localize. In this setting, abrupt sudden behavioral changes may occur with or without typical preseizure auras, such as abnormal smell, taste, or gastrointestinal symptoms. (See "[Focal epilepsy: Causes and clinical features](#)", section on '[Clinical features](#)').

Tumor-related seizures are typically repetitive and are stereotyped in a given patient. The ictal event may be preceded by an aura, which is itself a brief focal seizure, and followed by postictal sequelae. The postictal phase can be manifested as a period of fatigue and an urge to sleep. For patients with focal seizures, a postictal paresis (also known as a Todd paralysis) may be present.

Focal-onset seizures in any location can evolve into bilateral tonic-clonic seizures. If seizure propagation is rapid or if the initial phase of the seizure is unwitnessed, the presenting seizure may appear as a generalized tonic-clonic seizure. Subtle or brief focal seizures may go on for months before a generalized seizure brings the patient to medical attention, particularly in the case of low-grade primary brain tumors.

Both primary and metastatic brain tumors can cause status epilepticus, which may occur at the time of tumor diagnosis or subsequently [4]. (See "[Convulsive status epilepticus in adults: Classification, clinical features, and diagnosis](#)".)

Patients who present with seizures usually have smaller primary brain tumors or fewer metastatic lesions in the brain, compared with those who present with other symptoms. This is probably because the diagnosis of a seizure is an indication for neuroimaging, which leads to an earlier diagnosis. (See "[Evaluation and management of the first seizure in adults](#)".)

A seizure should not be confused with a syncopal event that may be caused by an abrupt increase in ICP. This distinction is important since treatment is different in the two conditions. Patients with seizures are high risk for seizure recurrence and should be treated with antiseizure medications. By contrast, patients with increased ICP require urgent glucocorticoids, neurosurgical intervention, or both. (See "[Seizures in patients with primary and metastatic brain tumors](#)", section on 'Approach to management' and 'Increased intracranial pressure' below and "[Management of vasogenic edema in patients with primary and metastatic brain tumors](#)".)

Focal deficits — Focal signs and symptoms of brain tumors vary based on tumor location. Symptoms may be caused by local tissue disruption, mass effect on nearby structures, or vasogenic edema.

- **Weakness** – Muscle weakness is a common complaint in patients with brain tumors. The manifestations may be subtle, particularly in the early stages. For upper motor neuron lesions, weakness is generally more pronounced in the flexors of the lower extremities than in the extensors, and more pronounced in the extensors than the flexors in the upper extremities. Transient weakness may represent a postictal state, as in Todd paralysis. (See "[The detailed neurologic examination in adults](#)" and '[Seizures](#)' above.)

A key feature of tumor-related muscle weakness is its frequent responsiveness to glucocorticoids, particularly with tumors that are near the motor cortex or its descending fibers. A response to steroids usually means that the weakness is caused by edema and not by direct tumor involvement, as is often the case with metastatic tumors. In such patients, tumor resection may relieve mass effect and lessen the glucocorticoid requirement, even if surgery itself is not curative. (See "[Management of vasogenic edema in patients with primary and metastatic brain tumors](#)", section on 'Symptomatic treatment' and "[Overview of the treatment of brain metastases](#)", section on 'Single brain metastasis'.)

- **Sensory loss** – Cortical sensory deficits (abnormalities in graphesthesia or stereognosis) can develop in patients whose tumors involve the primary sensory cortex. These sensory deficits usually do not respect a dermatomal or peripheral nerve distribution. (See "[Approach to the patient with sensory loss](#)", section on 'Sensory examination').

The type of deficit varies in part with location of the tumor. As an example, visual-spatial disconnection syndromes can be found in patients with tumors located in the visual association cortex. Other cortically based sensory deficits include loss of spatial orientation, tingling, and lack of coordination.

- **Aphasia** – Patients with a tumor in the language-dominant hemisphere may present with variable degrees and types of aphasia. The left hemisphere is dominant in >95 percent of right-handed people and in >70 percent of left-handed people [5]. (See "[Approach to the patient with aphasia](#)", section on 'Cerebral dominance').

Symptoms range from occasional word-finding hesitation or word substitutions in routine speech to severe expressive or receptive aphasia. Tumors in the frontal lobe near Broca's area typically produce a nonfluent or expressive aphasia, whereas tumors in the posterior temporal lobe more often cause difficulties with language comprehension (receptive aphasia). Tumors in the dominant parietal lobe and thalamus also commonly cause language dysfunction. (See "[Approach to the patient with aphasia](#)", section on 'Aphasia syndromes').

A formal assessment of language dominance and localization using functional magnetic resonance imaging (fMRI) and other techniques is often required in patients with aphasia to determine the feasibility of surgical resection. (See '[Preoperative planning](#)' below.)

- **Visual-spatial dysfunction** – The visual pathway courses through the brain from the retina and optic chiasm to the occipital poles of the cerebral cortex. Because of its long course through the brain, the visual pathway can be affected by brain tumors that involve any of these areas.

Tumor-related compression of the optic chiasm usually manifests as a bitemporal hemianopsia. However, there may be a unilateral hemianopsia with a central scotoma in the contralateral eye in the early stages, particularly when the compression is on one side. The latter is thought to result from partial compression of the Wilbrand knee in the contralateral optic nerve, although the existence of this pathway has been questioned [6]. (See "[Causes, presentation, and evaluation of sellar masses](#)" and "[Optic pathway glioma](#)".)

Postchiasmatic lesions also may present with visual abnormalities. Because the visual fibers are more spread apart before they converge in the occipital lobe, the more anterior the lesion in the optic radiation, the more asymmetric the hemianopsia (incongruous hemianopsia). Lesions in the occipital cortex cause congruous hemianopsia. (See "[Homonymous hemianopia](#)".)

Cognitive dysfunction — Cognitive dysfunction, which includes memory problems and mood or personality change, is common among patients with primary and metastatic brain tumors.

Most of the neurocognitive deficits associated with brain tumors are subtle. Patients often complain of having low energy, fatigue, an urge to sleep, and loss of interest in everyday activities. They may become abulic and show a lack of spontaneity. This pattern of symptoms can be confused with depression. (See "[Unipolar depression in adults: Assessment and diagnosis](#)".)

Because these symptoms lack specificity, they are often recognized in retrospect by the patient or the treating clinician. Thus, consideration should be given to neuroimaging to rule out a brain tumor in patients without a prior history of depression who experience new onset of depressive symptoms without obvious cause.

Increased intracranial pressure — Increased ICP can arise either from a large mass or from restriction of cerebrospinal fluid (CSF) outflow causing hydrocephalus. Symptoms may be subtle or consist of the classic triad of headache, nausea, and papilledema. (See "[Evaluation and management of elevated intracranial pressure in adults](#)".)

Nausea and vomiting are not specific to high ICP and can occur with more common causes of headache, such as migraine. Several characteristics suggest the possibility of tumor-associated emesis, such as triggering emesis by an abrupt change in body position. More importantly, neurogenic nausea and vomiting usually occur in the context of other neurologic symptoms such as headache or focal neurologic deficit; these signs and symptoms may be subtle, however.

In the presence of a large brain tumor or one associated with hydrocephalus, the ICP may be raised to a level that reduces brain compliance; in this setting, even a further small increase in intracranial fluid volume can result in dramatic elevations in ICP.

A significant rise in ICP can temporarily decrease cerebral perfusion, leading to loss of consciousness. Patients with a baseline elevation in ICP are particularly susceptible to this sequence of events in association with plateau waves, which are sustained increases in ICP caused by activities that transiently raise the ICP. Activities that may trigger a plateau wave include moving from a sitting to standing position and maneuvers that increase intrathoracic pressure, such as the Valsalva maneuver, coughing, sneezing, or vomiting.

A syncopal episode due to high ICP may simulate a seizure, since patients suffer loss of consciousness and may have a few tonic-clonic jerks. Identification of plateau wave-related episodes of loss of consciousness is critical, since these events identify patients who require urgent glucocorticoids and/or neurosurgical intervention to reduce elevated ICP rather than treatment with an antiseizure medication. (See "[Management of vasogenic edema in patients with primary and metastatic brain tumors](#)", section on 'Symptomatic treatment'.)

NEUROIMAGING FEATURES

Magnetic resonance imaging (MRI) with contrast is the optimal study for the evaluation of brain tumors. Computed tomography (CT) has much lower soft-tissue resolution and is relied upon primarily in emergency settings, for a more detailed view of bony structures, and in patients with a contraindication to MRI.

Typical MRI features of the more common brain tumors in adults are reviewed below. None of these imaging findings are specific, however, and histopathologic sampling is required to establish both tumor type and grade in the majority of primary brain tumors and in some cases of suspected brain metastases. However, this may change in the future as technology advances [7,8]. (See '[Diagnosis](#)' below.)

High-grade glioma — High-grade gliomas are typically hypointense masses on T1-weighted images that enhance heterogeneously following contrast infusion. Enhancing tumor can be distinguished from the surrounding hypointense signal of edema on T1-weighted sequences ([image 1](#)). Vasogenic edema is common and appears as hyperintense signal abnormality in the white matter on T2/fluid-attenuated inversion recovery (FLAIR)-weighted imaging.

Glioblastomas often have thick rim enhancement along the margins of the tumor, with central lack of enhancement indicative of central necrosis or cystic change ([image 2](#)). Gradient-echo

or susceptibility-weighted sequences may show susceptibility artifact consistent with blood products within the center of the tumor. High-grade gliomas often have evidence of increased blood flow and blood volume, as well as elevated permeability, on perfusion imaging. High choline signal, decreased N-acetylaspartate (NAA), and increased lactate on magnetic resonance spectroscopy (MRS) are also notable features. (See "[Clinical presentation, diagnosis, and initial surgical management of high-grade gliomas](#)".)

Low-grade glioma — Low-grade gliomas in adults generally appear as T2/FLAIR hyperintense, expansile lesions involving both cortex and underlying white matter ([image 3](#) and [image 4](#)). Vasogenic edema is usually absent. Most low-grade gliomas are nonenhancing, although the presence or absence of enhancement is not a reliable indicator of tumor grade. Calcification is sometimes present and is suggestive but not specific for oligodendrogloma histology ([image 5](#)). (See "[Clinical features, diagnosis, and pathology of IDH-mutant, 1p/19q-codeleted oligodendroglomas](#)", section on 'Neuroimaging'.)

The imaging appearance of oligodendrogloma and isocitrate dehydrogenase (IDH)-mutant astrocytoma is similar, and both may show evidence of the 2-hydroxyglutarate (2HG) metabolite using specialized MRS techniques. One distinguishing feature on conventional MRI has been termed the T2/FLAIR mismatch sign ([image 6](#)), which is specific for IDH-mutant astrocytoma, although not sensitive [9]. This sign describes the hyperintense tumor rim seen on FLAIR images that is not apparent on T2-weighted images ([image 4](#)).

Most low-grade gliomas involve the cerebral hemispheres or thalamus in adults. The radiographic appearance of brainstem gliomas ([image 7](#)), which are most common in children but can present in early adulthood, is reviewed elsewhere. (See "[Diffuse intrinsic pontine glioma](#)", section on 'Neuroimaging' and "[Focal brainstem glioma](#)", section on 'Diagnostic evaluation').

Primary CNS lymphoma — Primary central nervous system lymphoma (PCNSL) is a rare form of non-Hodgkin lymphoma that occurs in both immunocompetent and immunocompromised adults. In immunocompetent patients, PCNSL can be solitary or multifocal. Lesions are isointense or hypointense on T2-weighted MRI and tend to enhance homogeneously after administration of contrast. Typical locations include periventricular white matter, basal ganglia, and corpus callosum.

Diffusion-weighted imaging often shows prominent diffusion restriction ([image 8](#)). This feature, although not specific for PCNSL, can be useful in raising clinical suspicion for the diagnosis, especially when other suggestive features are also present (eg, homogeneous contrast enhancement, typical location). Glucocorticoids should be withheld if possible when

lymphoma is suspected to maximize diagnostic yield of biopsy. (See '[Role of glucocorticoids](#)' below.)

The clinical features, imaging, and diagnosis of PCNSL are reviewed in detail separately. (See "[Primary central nervous system lymphoma: Clinical features, diagnosis, and extent of disease evaluation](#)" and "[HIV-related lymphomas: Primary central nervous system lymphoma](#)".)

Brain metastases — Brain metastases typically appear as rounded, well-circumscribed masses that enhance after administration of contrast ([image 9](#)). They are single in 20 to 30 percent of patients and multiple in the remaining patients. The masses themselves may be solid, cystic, or centrally necrotic and can be hypointense, isointense, or hyperintense on T1- and T2-weighted images. Contrast enhancement is nearly universal. Occasionally, very thin-walled cystic metastases will not enhance or only enhance minimally.

Metastases larger than 0.5 to 1 cm usually have surrounding edema on T2-weighted and FLAIR sequences, which is often extensive in relation to the size of the tumor. Susceptibility artifact on gradient-echo or susceptibility-weighted sequences may be present and indicates the presence of blood products or less commonly calcification. Hemorrhagic brain metastases can occur with any underlying cancer type but are most common in association with melanoma, renal cell cancer, thyroid cancer, choriocarcinoma, and non-small cell lung cancer. (See "[Epidemiology, clinical manifestations, and diagnosis of brain metastases](#)".)

Meningioma — On MRI, a typical meningioma is an extra-axial, dural-based mass that is isointense or hypointense to gray matter on T1 and isointense or hyperintense on T2-weighted images. There is usually strong, homogeneous enhancement after administration of contrast ([image 10](#)). On noncontrast head CT, meningiomas are often isodense to brain and easily missed unless there is hyperdensity associated with tumor calcification. (See "[Epidemiology, pathology, clinical features, and diagnosis of meningioma](#)", section on '[Neuroimaging](#)').

Others — The clinical and imaging features of a large number of rarer primary brain tumors, as well tumors of the skull base, suprasellar region, and spine, are reviewed separately. (See "[Uncommon brain tumors](#)" and "[Craniopharyngioma](#)" and "[Causes, presentation, and evaluation of sellar masses](#)" and "[Chordoma and chondrosarcoma of the skull base](#)".)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a new brain mass on neuroimaging includes both neoplastic and nonneoplastic conditions ([table 4](#)) [10].

Nonneoplastic conditions most commonly confused with high-grade glioma or other enhancing tumors on magnetic resonance imaging (MRI) include subacute infarction, subacute hemorrhage, vascular malformations, infections, and noninfectious inflammatory disorders [11].

- **Ischemic infarct** – Cortically based embolic infarcts often show enhancement in the subacute phase and, when imaged during this time period, can be mistaken for high-grade glioma or other brain tumors. Clues to an ischemic etiology include gyriform or serpentine pattern of enhancement, location in a typical vascular territory, and clinical history of sudden onset of symptoms days or weeks before the MRI was performed. A short-interval follow-up MRI in four to six weeks can be useful when imaging is equivocal, before proceeding with biopsy.
- **Hemorrhage** – Intraparenchymal hemorrhages can develop enhancement in the subacute phase and thereby mimic the appearance of a hemorrhagic tumor. Conversely, tumors that hemorrhage can be difficult to distinguish from bland hemorrhages on initial imaging. Venous infarctions often have associated hemorrhage or edema and should be considered. Short-interval follow-up MRI and clinical risk factors can be used to help distinguish the two. (See ["Overview of the evaluation of stroke"](#), section on 'Evaluation of patients with intracerebral hemorrhage'.)
- **Venous infarct** – Venous infarcts due to cortical venous sinus thrombosis often have associated edema or hemorrhage and are an occasional mimic of high-grade gliomas or metastases. Risk factors for venous thrombosis include prothrombotic conditions, oral contraceptive use, pregnancy, systemic malignancy, infection, and head injury. Magnetic resonance venography should be performed if venous infarct is suspected. (See ["Cerebral venous thrombosis: Etiology, clinical features, and diagnosis"](#).)
- **Vascular malformation** – Cavernous malformations can usually be distinguished from tumors by the presence of old blood products on gradient-echo or susceptibility-weighted MRI sequences in the absence of mass effect or edema. Large cavernous malformations and those that have recently bled may be harder to distinguish and require short-interval follow-up imaging. Arteriovenous malformations can usually be distinguished from tumors by the presence of prominent dark flow voids on T2-weighted imaging. Cerebral angiography is typically required for diagnosis and to plan treatment. (See ["Vascular malformations of the central nervous system"](#), section on 'Cavernous malformations' and ["Brain arteriovenous malformations"](#).)

- **Abscess** – Bacterial and fungal abscesses, which often appear as ring-enhancing lesions and thereby similarly to glioblastoma or metastases, can often be distinguished from cystic or centrally necrotic brain tumors by their prominent diffusion restriction on diffusion-weighted MRI sequences and clinical risk factors or signs of infection. Magnetic resonance spectroscopy (MRS) can also be useful [12]. (See "[Pathogenesis, clinical manifestations, and diagnosis of brain abscess](#)", section on '[Evaluation and diagnosis](#)').
- **Inflammatory disorders** – Inflammatory and demyelinating lesions of the central nervous system (CNS), including tumefactive multiple sclerosis, may show enhancement and even edema in the acute phase ([image 11](#) and [image 12](#)). Inflammatory etiologies often manifest with multiple lesions or involve more than one compartment (eg, parenchymal and leptomeningeal). Particularly when mass-like brainstem lesions are present, rarer disorders to consider include neuromyelitis optica spectrum disorders, neuro-Behçet disease, chronic lymphocytic inflammation with pontine perivascular enhancement response to steroids (CLIPPERS), and neurosarcoidosis [13]. Lumbar puncture and spine MRI are typically indicated if any of these disorders are suspected. (See "[Evaluation and diagnosis of multiple sclerosis in adults](#)", section on '[Differential diagnosis](#)').

The radiographic differential diagnosis of low-grade gliomas and other nonenhancing, infiltrative primary brain tumors includes demyelination (eg, multiple sclerosis, acute demyelinating encephalomyelitis), posterior reversible leukoencephalopathy syndrome, paraneoplastic or autoimmune encephalitis, and infections such as progressive multifocal leukoencephalopathy (PML). MRS can sometimes be helpful in these cases to raise or lower suspicion for tumor (see '[Role of advanced imaging techniques](#)' below). Lumbar puncture should be performed if PML or encephalitis is suspected to test for JC virus and other inflammatory and infectious markers. PML and other brain lesions in patients with immunodeficiency are reviewed separately. (See "[Progressive multifocal leukoencephalopathy \(PML\): Epidemiology, clinical manifestations, and diagnosis](#)" and "[Approach to the patient with HIV and central nervous system lesions](#)".)

Meningiomas have a largely separate radiographic differential diagnosis ([table 5](#)), which is reviewed elsewhere. (See "[Epidemiology, pathology, clinical features, and diagnosis of meningioma](#)", section on '[Differential diagnosis](#)').

INITIAL EVALUATION

Patients with a suspected brain tumor should undergo history and neurologic examination, brain magnetic resonance imaging (MRI) with contrast, and systemic cancer screening if brain

metastases are suspected ([algorithm 1](#)). Unless imaging features are atypical, additional testing is often not necessary prior to diagnostic biopsy or resection. The urgency of neurosurgical evaluation depends on the clinical stability of the patient, symptom severity, and tumor size and location.

Physical and neurologic examination — All patients with a suspected brain tumor should undergo a physical and neurologic examination to evaluate for neurologic deficits associated with the tumor. The degree of deficits and the clinical stability of the patient guide the urgency of neurosurgical evaluation and treatment and the need for glucocorticoids. (See '[Role of glucocorticoids](#)' below and '[Urgency of neurosurgical evaluation](#)' below.)

Examination of the visual fields, retina, and particularly the optic discs should be performed in patients suspected of having increased intracranial pressure (ICP) and in those with tumors encroaching on the optic pathway. Although gross papilledema is easy to diagnose, evolving papilledema can be difficult to recognize. As an example, only the medial portion of the optic disk may be blurred initially in early papilledema. Venous engorgement and the absence of venous pulsations are also important diagnostic clues. (See "[Overview and differential diagnosis of papilledema](#)".)

Brain MRI with contrast — MRI of the brain with contrast is usually the only test needed to suggest a brain tumor. Standard sequences that should be included to fully characterize brain tumors include T1 and T2, fluid-attenuated inversion recovery (FLAIR), gradient-echo/susceptibility, diffusion-weighted imaging, and postcontrast T1-weighted images. Typical radiographic features of some of the more common brain tumors in adults are reviewed above. (See '[Neuroimaging features](#)' above.)

Patients who have a possible brain tumor detected on head computed tomography (CT) or noncontrast brain MRI should undergo brain MRI with contrast to further characterize the lesion and help rule out nonneoplastic etiologies. Those with a contraindication to MRI should undergo head CT with contrast. (See '[Differential diagnosis](#)' above.)

Role of advanced imaging techniques — Magnetic resonance spectroscopy (MRS) is not routinely indicated in the evaluation of brain tumors but can provide useful additional noninvasive data in selected cases, especially when the imaging appearance is equivocal and nonneoplastic etiologies are under consideration. MRS data also correlate with tumor type and grade but are not sufficiently sensitive or specific to replace histologic diagnosis.

The technique may improve the differentiation of infiltrative primary brain tumors from other nonneoplastic lesions (eg, demyelination, abscess, stroke) by analyzing the chemical composition in an area of interest selected by the radiologist. Voxels need to be appropriately

placed to yield useful information. Spectra suggestive of a glial tumor include decreased N-acetylaspartate and increased choline ([table 6](#)). A lactate peak can be seen in the necrotic center of high-grade gliomas or in association with infarcts and abscesses. One study found that analysis of MRS plus diffusion-weighted imaging sequences had >95 percent sensitivity and specificity for distinguishing bacterial abscess from cystic tumor [12].

In addition to these metabolites, investigational studies have demonstrated that 2-hydroxyglutarate (2HG), which accumulates in gliomas carrying mutations in isocitrate dehydrogenase (IDH) type 1 or type 2, can be detected by MRS and is highly specific for untreated IDH-mutant tumors, with variable sensitivity [14-20]. Performance is more variable in previously treated or recurrent tumors [20]. Data are mixed with regard to whether quantitative 2HG correlates with tumor grade or mitotic index, and larger studies are needed to standardize and validate both diagnostic and prognostic value of 2HG MRS before widespread clinical use [18-20].

Other advanced MRI techniques, including functional MRI (fMRI) and diffusion tensor imaging, are used in selected cases to help plan maximal safe resection but are not part of the routine diagnostic work-up of brain tumors. (See '[Preoperative planning](#)' below.)

Screening for systemic malignancy — The likelihood that a lesion is metastatic should be assessed prior to proceeding to biopsy or resection. Brain metastases are more common than primary brain tumors in adults. Although brain metastases usually present in the context of overt systemic disease, they can occur as the initial manifestation of a systemic malignancy. (See '[Epidemiology](#)' above.)

If any aspect of the clinical or neurodiagnostic evaluation suggests that a brain tumor is a metastatic rather than a primary lesion, a systemic evaluation should be performed. CT of the chest is the highest-yield study in this setting, and the added utility of abdomen and pelvis CT is very low [21]. Typical neuroimaging clues that a brain lesion may be metastatic include the presence of multiple lesions, a single enhancing tumor that is well circumscribed from surrounding brain and associated with surrounding edema, and involvement of multiple compartments (eg, parenchymal, leptomeningeal, dural). Neurosurgical intervention in a patient with a presumed brain metastasis should balance the risks of the procedure versus the potential benefits (ie, tissue diagnosis, resection of a solitary lesion, relief of neurologic symptoms). (See '[Metastases](#)' below.)

Screening for systemic malignancy is not necessary when clinical and radiographic suspicion for a primary brain tumor is high.

Other tests — Lumbar puncture for cerebrospinal fluid (CSF) sampling and analysis does not typically provide useful diagnostic information for most primary brain tumors unless leptomeningeal seeding is present or suspected by neuroimaging on the basis of leptomeningeal enhancement. This may evolve, however, even for parenchymal tumors, with the development of more sensitive techniques such as cell-free DNA and metagenomic next-generation sequencing on CSF [22-25].

The primary role of lumbar puncture is to explore infectious or inflammatory etiologies in patients with atypical or unusual neuroimaging findings. If lymphoma is considered a possibility on the basis of imaging characteristics, CSF should be sent for cytology, flow cytometry, and immunoglobulin H (IgH) gene rearrangement studies, ideally before the patient is exposed to glucocorticoids to maximize diagnostic yield. Additional testing in patients with suspected primary central nervous system lymphoma (PCNSL) is reviewed separately. (See "[Primary central nervous system lymphoma: Clinical features, diagnosis, and extent of disease evaluation](#)".)

Role of glucocorticoids — High-dose glucocorticoids effectively reduce cerebral edema and can improve headaches and neurologic deficits caused by peritumoral edema. In patients with severe symptoms or threatened herniation, the usual initial dose of [dexamethasone](#) is 10 mg, followed by 4 mg every six hours or 8 mg twice per day. Once neurologic symptoms are stabilized, dexamethasone should be weaned to the lowest effective dose to prevent complications. Lower doses are often sufficient for less severe symptoms ([algorithm 2](#)). (See "[Management of vasogenic edema in patients with primary and metastatic brain tumors](#)", section on '[Dexamethasone dose and schedule](#)').

Glucocorticoids should be avoided if possible when there is high suspicion for lymphoma, as steroids cause acute lysis of lymphocytes and decrease the diagnostic yield of biopsy. (See "[Primary central nervous system lymphoma: Clinical features, diagnosis, and extent of disease evaluation](#)", section on '[Avoidance of glucocorticoids](#)').

Glucocorticoids are not necessary or indicated in patients with minimal symptoms and for tumors that are not associated with surrounding edema. Toxicities of chronic steroid use may contribute to morbidity and decreased quality of life in patients with brain tumors. Glucocorticoids should also be minimized in patients with malignant glioma because they may shorten patient survival [26,27].

Antiseizure medications — Patients presenting with a seizure and those who provide a clinical history suggestive of seizure activity should be treated with an antiseizure medication. [Levetiracetam](#) is commonly used in this setting, but other drugs that can be quickly titrated to

therapeutic levels are equally reasonable. (See "[Seizures in patients with primary and metastatic brain tumors](#)", section on '[Approach to management](#)').

Antiseizure medications are **not** generally recommended in patients who have never had a seizure, aside from perioperative prophylaxis in patients undergoing craniotomy for tumor resection. (See "[Seizures in patients with primary and metastatic brain tumors](#)", section on '[Indications for antiseizure medication therapy](#)').

Urgency of neurosurgical evaluation — The urgency of neurosurgical evaluation for a newly discovered brain tumor depends on the clinical stability of the patient, symptom severity, and tumor size and location.

Patients with large, symptomatic tumors, including those with signs and symptoms of elevated ICP or impending herniation, require emergent evaluation and neurosurgical attention. Patients with smaller tumors and those with minimal symptoms can often be safely and effectively evaluated in the outpatient setting. Patients should be referred to a high-volume center with subspecialty neurosurgical expertise in brain tumors, when possible.

DIAGNOSIS

Accurate diagnosis of a brain tumor requires an adequate tissue sample for histopathologic and molecular study. This may be obtained by stereotactic biopsy or open surgery. Procedure selection is individualized based on suspected tumor type and grade, location, and operability.

Glucocorticoid use should be avoided prior to biopsy or surgery if either a primary central nervous system lymphoma (PCNSL) or an infectious process is part of the differential diagnosis. (See '[Primary CNS lymphoma](#)' above and '[Differential diagnosis](#)' above.)

Preoperative planning — Functional magnetic resonance imaging (fMRI) is an important adjunct in the preoperative planning for patients whose tumor is located near eloquent areas of the brain. In such areas, imaging after activation of speech, sensory function, and motor function by appropriate stimuli may permit separation of tumor from normal brain and surrounding edema preoperatively. Diffusion tensor imaging (tractography) is also commonly used in this setting to better visualize the relationship between tumor and important white matter fiber tracts. (See "[Clinical presentation, diagnosis, and initial surgical management of high-grade gliomas](#)", section on '[Preoperative imaging](#)').

Surgical resection or biopsy — Technical advances have improved the safety of both surgical resection and stereotactic biopsy. Improved diagnostic neuroimaging permits better

preoperative localization of the lesion and separation of the lesion from adjacent normal brain tissue, particularly in eloquent areas of the brain.

A variety of intraoperative techniques allow neurosurgeons to improve the extent of resection while minimizing risk of damage to normal brain, including intraoperative MRI, cortical simulation, and awake craniotomy with repetitive neurologic and language assessments. In addition, for patients with high-grade gliomas, an optical imaging agent (5-aminolevulinic acid) is increasingly used to improve visualization and extent of malignant tissue resection [28,29]. (See "[Clinical presentation, diagnosis, and initial surgical management of high-grade gliomas](#)", section on 'Intraoperative techniques').

Gliomas — For most patients with primary brain tumors, tissue for histologic confirmation is obtained at the time of surgical resection.

For primary glial tumors, maximum surgical resection when possible is usually recommended. In patients with nonresectable lesions or those whose lesions are in a critical location, stereotactic biopsy is an alternative. (See "[Treatment and prognosis of IDH-mutant astrocytomas in adults](#)", section on 'Surgical management' and "[Clinical presentation, diagnosis, and initial surgical management of high-grade gliomas](#)", section on 'Surgery').

A tissue diagnosis of a diffuse intrinsic pontine glioma (DIPG) is usually not required prior to treatment, provided typical clinical and neuroimaging features are present ( [image 7](#)). In equivocal cases, the clinician must weigh the risks of a surgical biopsy versus the diagnostic uncertainty. (See "[Diffuse intrinsic pontine glioma](#)".)

Lymphoma — Patients with primary or secondary central nervous system (CNS) lymphoma are typically not offered surgical debulking, since surgical resection does not improve survival and may be associated with worse outcomes. Stereotactic biopsy is usually recommended, providing a high rate of positive tissue diagnosis with a low rate (<2 percent) of morbidity and mortality. Definitive treatment is usually chemotherapy, radiation, or a combination of these modalities. (See "[Primary central nervous system lymphoma: Clinical features, diagnosis, and extent of disease evaluation](#)" and "[Primary central nervous system lymphoma: Treatment and prognosis](#)" and "[Secondary central nervous system lymphoma: Clinical features and diagnosis](#)" and "[Secondary central nervous system lymphoma: Treatment and prognosis](#)".)

Metastases — Biopsy is not necessary for patients with multiple brain metastases if there is a preexisting primary cancer known to have a propensity for brain metastases. However, if a patient has a primary tumor that does not usually metastasize to the brain (eg, prostate cancer), there is no known primary or the primary is temporally distant without recent relapse, or

neuroimaging is not typical for metastasis, biopsy or resection may be indicated to define the etiology of a brain lesion.

The importance of biopsy in such situations was illustrated in a randomized trial of surgery for the treatment of solitary brain metastases, in which 11 percent of patients had a second primary malignancy, inflammatory process, or infection rather than metastasis [30]. A tissue diagnosis can also be important for the determination of actionable mutations or immunohistochemical characteristics that indicate responsiveness to immunotherapy.

The management of patients with brain metastases is dependent upon the overall condition of the patient, as well as the number, size, and location of brain metastases. Depending on the primary cancer type, the initial treatment approach may include targeted therapy or immunotherapy with or without radiotherapy. The management of patients with brain metastases is discussed separately. (See "[Overview of the treatment of brain metastases](#)" and "[Management of brain metastases in melanoma](#)" and "[Brain metastases in non-small cell lung cancer](#)" and "[Brain metastases in breast cancer](#)".)

Meningioma — The characteristic appearance of dural-based meningiomas often can allow a tentative diagnosis, and many small tumors can be safely observed without surgery or radiation. (See "[Management of known or presumed benign \(WHO grade 1\) meningioma](#)", section on 'Small, asymptomatic tumors'.)

Symptomatic meningiomas and asymptomatic tumors that are large, expanding, infiltrating, or associated with surrounding edema are surgically resected if feasible. Complete surgical resection is preferred when a meningioma is in an accessible location, since complete resection of the tumor and its dural attachment can be curative. (See "[Management of known or presumed benign \(WHO grade 1\) meningioma](#)", section on 'Large or symptomatic tumors').

Empiric radiation therapy without a histologic diagnosis may be warranted in carefully selected cases for lesions in a surgically inaccessible location. (See "[Management of known or presumed benign \(WHO grade 1\) meningioma](#)", section on 'Nonresectable tumors').

Neuropathology — Histopathologic and molecular examination of the tumor specimen remains the most important component of the diagnostic evaluation of brain tumors. A smear or frozen section can be performed rapidly during the surgery for a preliminary interpretation of the histologic subtype. With this information, the neurosurgeon can make a decision whether or not to proceed with a more extensive resection.

A definitive diagnosis requires examination of the permanent tissue sections stained by hematoxylin and eosin and a variety of immunohistochemical stains. Molecular testing is

increasingly important in the diagnosis and classification of brain tumors, especially for diffuse gliomas [31]. For these tumors, routine pathologic evaluation includes IDH mutational testing and a number of additional molecular tests to allow for an integrated diagnosis ([algorithm 3](#) and [table 1A](#)). (See "[Classification and pathologic diagnosis of gliomas, glioneuronal tumors, and neuronal tumors](#)" and "[Clinical presentation, diagnosis, and initial surgical management of high-grade gliomas](#)", section on 'Pathology').

The diagnostic accuracy of small tissue samples, such as those from a stereotactic biopsy, can be lower than those derived from a complete or partial resection. This is particularly true for glial tumors because regional heterogeneity and sampling error may underestimate the histologic grade of malignancy [32]. Molecular studies, including testing for IDH, 1p/19q, telomerase reverse transcriptase (*TERT*) promoter mutation, and H3 K27M, may help to improve diagnostic accuracy in these circumstances. Next-generation sequencing may be of value for identifying pathogenic variants that are susceptible to treatment with specific targeted therapies [33]. (See "[Clinical presentation, diagnosis, and initial surgical management of high-grade gliomas](#)", section on 'Role of tumor genome sequencing').

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "[Patient education: Brain cancer \(The Basics\)](#)")
- Beyond the Basics topics (see "[Patient education: Low-grade glioma in adults \(Beyond the Basics\)](#)" and "[Patient education: High-grade glioma in adults \(Beyond the Basics\)](#)" and "[Patient education: Meningioma \(Beyond the Basics\)](#)")

SUMMARY

- **Epidemiology** – Metastases from a systemic cancer are the most common brain tumors in adults. Among primary brain tumors, meningiomas and gliomas together account for more than two-thirds of all adult primary brain tumors. (See '[Epidemiology](#)' above.)
- **Signs and symptoms** – Brain tumors can produce symptoms and signs by local brain invasion, compression of adjacent structures, and increased intracranial pressure (ICP). In addition to the histology of the tumor, the clinical manifestations are determined by the function of the involved areas of brain. (See '[Clinical manifestations](#)' above.)
- **Neuroimaging** – Magnetic resonance imaging (MRI) with contrast is the optimal study for evaluation of brain tumors. Computed tomography (CT) has much lower resolution and is relied upon primarily in emergency settings, for a more detailed view of bony structures, and in patients with a contraindication to MRI. (See '[Neuroimaging features](#)' above.)
- **Differential diagnosis** – Nonneoplastic conditions that may be confused with high-grade glioma or other enhancing tumors on MRI include subacute infarction, subacute hemorrhage, vascular malformations, infections, and inflammatory disorders ([table 4](#) and [table 5](#)). Additional considerations in low-grade tumors include demyelination, inflammation, and infection. (See '[Differential diagnosis](#)' above.)
- **Initial evaluation** – Patients with a suspected brain tumor should undergo history and neurologic examination and brain MRI with contrast ([algorithm 1](#)). A CT of the chest and abdomen should be performed when metastatic disease is suspected. Unless imaging features are atypical, additional testing is often not necessary prior to diagnostic biopsy or resection. (See '[Initial evaluation](#)' above.)
- **Role of glucocorticoids** – Glucocorticoids are used to decrease peritumoral edema and elevated ICP in patients with severe symptoms or threatened herniation ([algorithm 2](#)). Steroids are not necessary in patients with minimal symptoms and should be avoided when there is high clinical suspicion for lymphoma. (See '[Role of glucocorticoids](#)' above.)
- **Diagnosis** – Accurate diagnosis of a brain tumor requires an adequate tissue sample for histopathologic and molecular analysis. This may be obtained by stereotactic biopsy or open surgery. Procedure selection is individualized based on suspected tumor type and grade, location, and operability. (See '[Preoperative planning](#)' above and '[Surgical resection or biopsy](#)' above.)

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Topic 5180 Version 49.0

GRAPHICS**WHO classification of adult-type and pediatric-type diffuse gliomas**

Tumor type	CNS WHO grade	Characteristic molecular genetic alterations
Adult-type diffuse gliomas		
Astrocytoma, IDH-mutant	2, 3, 4	<i>IDH1, IDH2</i>
Oligodendrogloma, IDH-mutant, 1p/19q-codeleted	2, 3	<i>IDH1, IDH2, 1p/19q</i>
Glioblastoma, IDH-wildtype	4	IDH-wildtype, chromosome 7 and 10, <i>TERT, EGFR</i> , others
Pediatric-type diffuse low-grade gliomas		
Diffuse astrocytoma, <i>MYB</i> - or <i>MYBL1</i> -altered	1	<i>MYB, MYBL1</i>
Angiocentric glioma	1	<i>MYB</i>
Polymorphous low-grade neuroepithelial tumor of the young	1	<i>BRAF, FGFR</i> genes
Diffuse low-grade glioma, MAPK pathway-altered	NA*	MAPK pathway genes
Pediatric-type diffuse high-grade gliomas		
Diffuse midline glioma, H3 K27-altered	4	H3 K27, <i>EGFR, EZHIP</i>
Diffuse hemispheric glioma, H3 G34-mutant	4	H3 G34
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	4	IDH-wildtype, H3-wildtype, methylome, <i>EGFR, PDGFRA, MYCN</i>
Infant-type hemispheric glioma	NA†	RTK genes

WHO: World Health Organization; CNS: central nervous system; IDH: isocitrate dehydrogenase; *TERT*: telomerase reverse transcriptase; *EGFR*: epidermal growth factor receptor; *MYB*: MYB proto-oncogene, transcription factor; *MYBL1*: MYB proto-oncogene-like 1; 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, bHLH transcription factor; NA: not assigned; RTK: receptor tyrosine kinase.

* Low grade.

¶ High grade.

Adapted with permission from: WHO Classification of Tumours Editorial Board. Central nervous system tumours [Internet]. Lyon (France): International Agency for Research on Cancer; 2021 [cited 2022 February 17]. (WHO classification of tumours series, 5th ed.; vol. 6). Available from: <https://tumourclassification.iarc.who.int/chapters/45>.

Graphic 134980 Version 5.0

WHO classification of circumscribed astrocytic tumors

Tumor type	CNS WHO grade	Characteristic molecular genetic alterations
Pilocytic astrocytoma	1	<i>KIAA1549-BRAF, BRAF</i>
High-grade astrocytoma with piloid features	NA	Methylome
Pleomorphic xanthoastrocytoma	2, 3	<i>BRAF, CDKN2A</i>
Subependymal giant cell astrocytoma	1	<i>TSC1, TSC2</i>
Chordoid glioma	2	<i>PRKCA</i>
Astroblastoma, <i>MN1</i> -altered	NA	<i>MN1, BEND2</i>

WHO: World Health Organization; CNS: central nervous system; NA: not assigned; *CDKN2A*: cyclin-dependent kinase inhibitor 2A; *TSC*: tuberous sclerosis complex; *PRKCA*: protein kinase C alpha; *BEND2*: BEN domain containing 2.

Adapted from: WHO Classification of Tumours Editorial Board. Central nervous system tumours. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 6).

Graphic 109511 Version 2.0

World Health Organization (WHO) classification of ependymomas

Location	Tumor classification	CNS WHO grade
Supratentorial	Supratentorial subependymoma	1
	Supratentorial ependymoma, <i>ZFTA</i> fusion-positive	2, 3
	Supratentorial ependymoma, <i>YAP1</i> fusion-positive	2, 3
Infratentorial	Posterior fossa subependymoma	1
	Posterior fossa ependymoma, group PFA	2, 3
	Posterior fossa ependymoma, group PFB	2, 3
Spinal	Spinal subependymoma	1
	Myxopapillary ependymoma	2
	Spinal ependymoma	2, 3
	Spinal ependymoma, <i>MYCN</i> -amplified	NA

CNS: central nervous system; *ZFTA*: zinc finger translocation-associated; *YAP1*: Yes1-associated transcriptional regulator; PFA: posterior fossa group A; PFB: posterior fossa group B; NA: not assigned.

Data from: WHO Classification of Tumours Editorial Board. Central nervous system tumours. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 6).

Graphic 109513 Version 6.0

WHO classification of glioneuronal and neuronal tumors

Tumor type	CNS WHO grade	Characteristic molecular genetic alterations
Ganglioglioma	1	<i>BRAF</i>
Gangliocytoma	1	<i>BRAF</i>
Desmoplastic infantile ganglioglioma/desmoplastic infantile astrocytoma	1	
Dysembryoplastic neuroepithelial tumor	1	<i>FGFR1</i>
Diffuse glioneuronal tumor with oligodendrogloma-like features and nuclear clusters*	NA	Methylome
Papillary glioneuronal tumor	1	<i>PRKCA</i>
Rosette-forming glioneuronal tumor	1	<i>FGFR1, PIK3CA, NF1</i>
Myxoid glioneuronal tumor	1	<i>PDGFRA</i>
Diffuse leptomeningeal glioneuronal tumor	NA	<i>KIAA1549-BRAF, 1p, methylome</i>
Multinodular and vacuolating neuronal tumor	1	MAPK pathway genes
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	1	<i>PTEN</i>
Central neurocytoma	2	
Extraventricular neurocytoma	2	<i>FGFR genes (FGFR1-TACC1), IDH-wildtype</i>
Cerebellar liponeurocytoma	2	

WHO: World Health Organization; CNS: central nervous system; *FGFR*: fibroblast growth factor receptor; NA: not assigned; *PRKCA*: protein kinase C alpha; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *NF1*: neurofibromin 1; *PDGFRA*: platelet-derived growth factor receptor alpha; MAPK: mitogen-activated protein kinase; *PTEN*: phosphatase and tensin homolog; IDH: isocitrate dehydrogenase.

* Provisional tumor.

Adapted from: WHO Classification of Tumours Editorial Board. Central nervous system tumours. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 6).

Graphic 109517 Version 2.0

World Health Organization (WHO) classification of choroid plexus tumors

Tumor classification	Tumor grade
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III

Data from: WHO Classification of Tumours of the Central Nervous System, 4th ed., Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (Eds), IARC, Lyon 2016.

Graphic 109515 Version 1.0

Meningioma subtypes

	WHO grade
Meningiomas with low risk of recurrence or aggressive growth:	
Meningothelial	I
Fibrous (fibroblastic)	I
Transitional (mixed)	I
Psammomatous	I
Angiomatous	I
Microcystic	I
Secretory	I
Lymphoplasmacyte-rich	I
Metaplastic	I
Meningiomas with greater likelihood of recurrence and/or aggressive behavior:	
Atypical*	II
Clear cell (intracranial)	II
Chordoid	II
Rhabdoid	III
Papillary	III
Anaplastic (malignant)	III
Meningiomas of any subtype or grade with high proliferation index	I, II, III

* As of the 2016 edition of the WHO Classification of Tumours of the Central Nervous System [1], atypical meningioma is defined as a tumor with increased mitotic activity (≥ 4 mitoses per ten high powered fields), brain invasion, or three or more of the following features: increased cellularity, small cells with a high nuclear:cytoplasmic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, or foci of spontaneous or geographic necrosis.

WHO: World Health Organization.

Reproduced with permission from: Perry A, Louis DN, Scheithauer BW, et al. Meningiomas. In: WHO Classification of Tumours of the Central Nervous System, Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (Eds), IARC Press, Lyon 2007.

[1] WHO Classification of Tumours of the Central Nervous System, Fourth Edition, Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (Eds), IARC, Lyon 2016.

Graphic 72593 Version 5.0

World Health Organization (WHO) classification of medulloblastoma

Medulloblastomas, genetically defined

Medulloblastoma, Wnt-activated

Medulloblastoma, SHH-activated and *TP53*-mutant

Medulloblastoma, SHH-activated and *TP53*-wildtype

Medulloblastoma, non-Wnt/non-SHH

Medulloblastoma, group 3

Medulloblastoma, group 4

Medulloblastomas, histologically defined

Medulloblastoma, classic

Desmoplastic/nodular medulloblastoma

Medulloblastoma with extensive nodularity

Large cell/anaplastic medulloblastoma

Medulloblastoma, NOS

Wnt: Wingless-related integration site; SHH: sonic hedgehog; *TP53*: tumor protein 53; NOS: not otherwise specified.

Data from: WHO Classification of Tumours of the Central Nervous System (revised 4th ed), Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (Eds), IARC: Lyon 2016.

Graphic 109467 Version 3.0

Distribution of all primary brain and CNS tumors by site

Histology	Percent of total	Annual incidence rate*
Tumors of neuroepithelial tissue	29.9	6.62
Pilocytic astrocytoma	1.4	0.34
Diffuse astrocytoma	2.3	0.53
Anaplastic astrocytoma	1.7	0.38
Unique astrocytoma variants	0.3	0.07
Glioblastoma	15.1	3.20
Oligodendrogioma	1.1	0.25
Anaplastic oligodendrogioma	0.5	0.10
Oligoastrocytic tumors	0.9	0.20
Ependymal tumors	1.9	0.43
Glioma malignant, NOS	2.0	0.47
Choroid plexus	0.2	0.05
Other neuroepithelial tumors	0.03	0.01
Neuronal and mixed neuronal-glial tumors	1.2	0.28
Tumors of the pineal region	0.2	0.04
Embryonal tumors	1.1	0.26
Tumors of cranial and spinal nerves	8.1	1.76
Nerve sheath tumors	8.1	1.76
Tumors of meninges	37.6	8.13
Meningioma	36.4	7.86
Mesenchymal tumors	0.4	0.08
Primary melanocytic lesions	0.04	0.01
Other neoplasms related to the meninges	0.8	0.18
Lymphomas and hematopoietic neoplasms	2.1	0.46
Lymphoma	2.0	0.44
Other hematopoietic neoplasms	0.07	0.01
Germ cell tumors and cysts	0.4	0.10

Germ cell tumors, cysts and heterotopias	0.4	0.10
Tumors of sellar region	16.3	3.68
Tumors of the pituitary	15.5	3.49
Craniopharyngioma	0.8	0.18
Unclassified tumors	5.6	1.23
Hemangioma	1.5	0.34
Neoplasm, unspecified	4.0	0.88
All other	0.03	0.01
TOTAL	365,858	100.0

CBTRUS Statistical Report: NPCR and SEER data from 2008 to 2012.

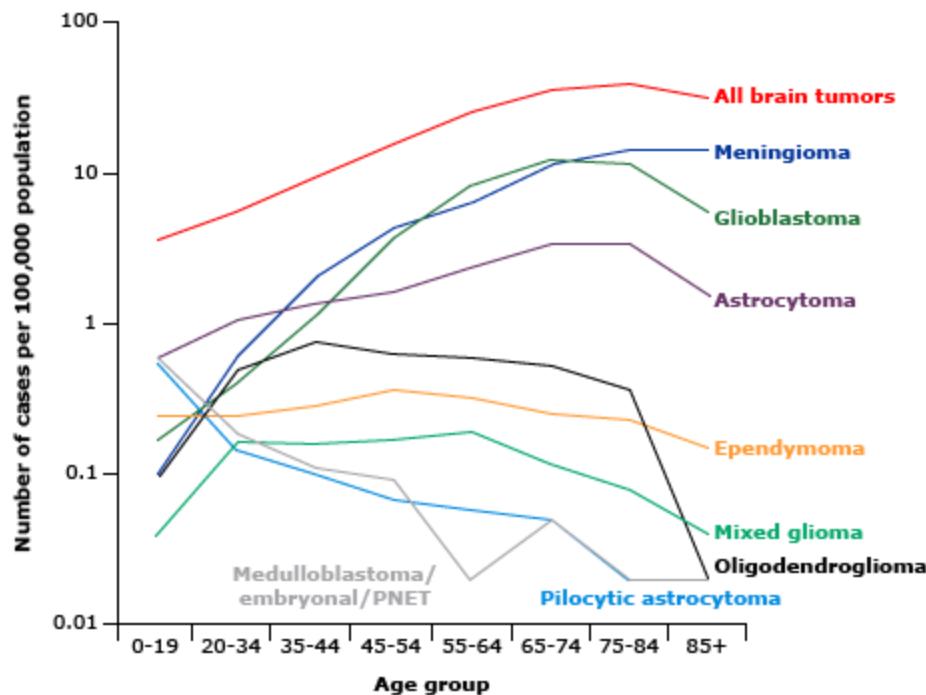
CNS: central nervous system; NOS: not otherwise specified; CBTRUS: Central Brain Tumor Registry of the United States; NPCR: National Program of Cancer Registries; SEER: Surveillance, Epidemiology, and End Results Program.

* Average annual age-adjusted incidence rate.

Data from: Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro Oncol 2015; 17 Suppl 4:iv1.

Graphic 81566 Version 12.0

Incidence rates of primary brain tumors by major neuroepithelial tissue and meningeal histologic types and age group



The category "All brain tumors" includes some specific types not individually shown (tumors of cranial and spinal nerves, hemangioblastomas, primary lymphomas, germ cell tumors, and tumors of the sellar region). The "Astrocytoma" category includes diffuse astrocytomas, anaplastic astrocytomas, unique astrocytoma variants, and astrocytomas not otherwise specified.

PNET: primitive neuroectodermal tumor.

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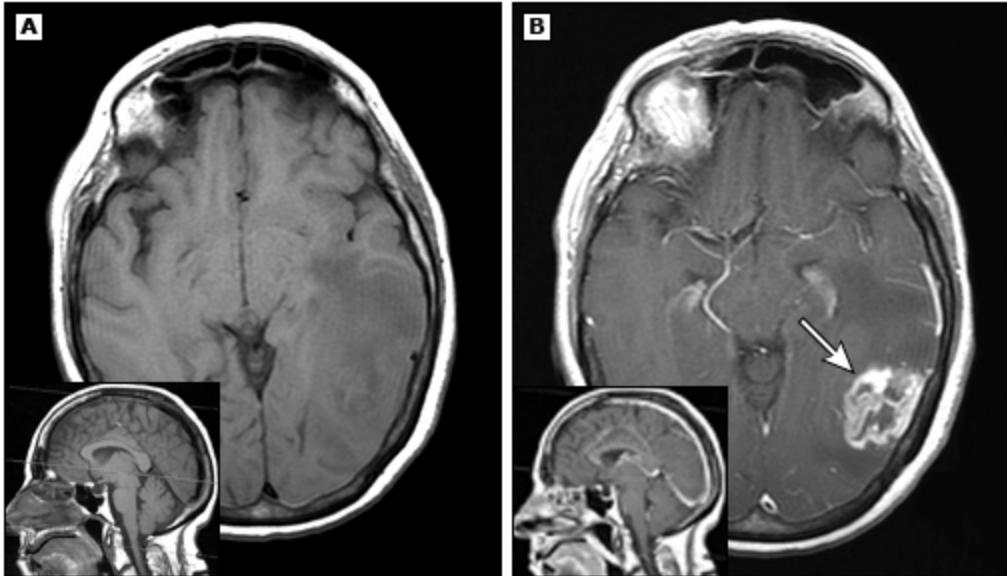
Graphic 72275 Version 6.0

Neurologic presentation of brain tumors

Generalized	Focal
Headaches	Seizures
Seizures	Weakness
Nausea/vomiting	Sensory loss
Depressed level of consciousness	Aphasia
Neurocognitive dysfunction	Visual spatial dysfunction

Graphic 52235 Version 1.0

Magnetic resonance imaging features of glioblastoma



(A) Axial T1-weighted MRI showing edematous left temporal lobe with loss of sulci and gray-white demarcation.

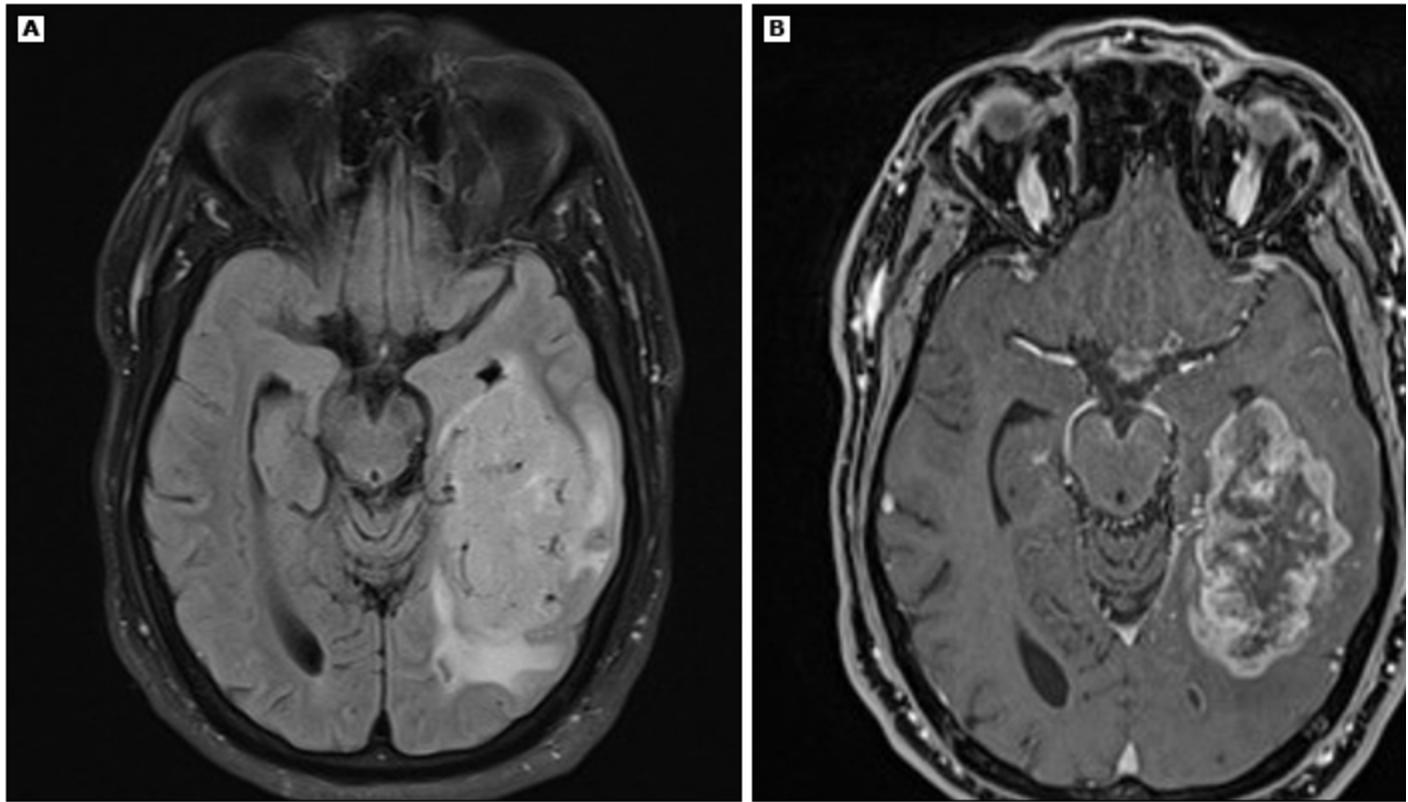
(B) After gadolinium infusion, a circular $2.5\text{ cm} \times 2.5\text{ cm}$ area of irregular contrast enhancement is seen in the left temporal lobe (arrow).

MRI: magnetic resonance imaging.

Courtesy of Harry Greenberg, MD.

Graphic 65860 Version 7.0

Left temporal glioblastoma

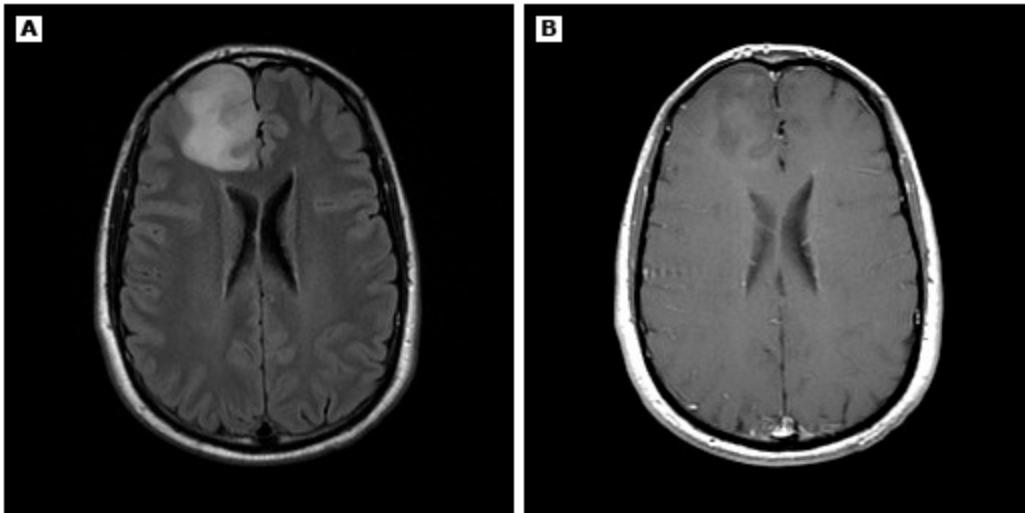


Brain MRI in a 53-year-old male presenting with several weeks of headaches and word-finding difficulties. FLAIR (A) and postcontrast T1-weighted images (B) show a large, T2-hyperintense mass in the left temporal lobe with heterogeneous enhancement and central necrosis. Pathology confirmed a WHO grade IV glioblastoma.

MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery; WHO: World Health Organization.

Graphic 113733 Version 2.0

MRI appearance of low-grade oligodendroglioma



Brain MRI in a 40-year-old male presenting with first-time generalized tonic-clonic seizure. Pathology confirmed a WHO grade 2 oligodendro glioma, IDH-mutant, 1p/19q-codeleted.

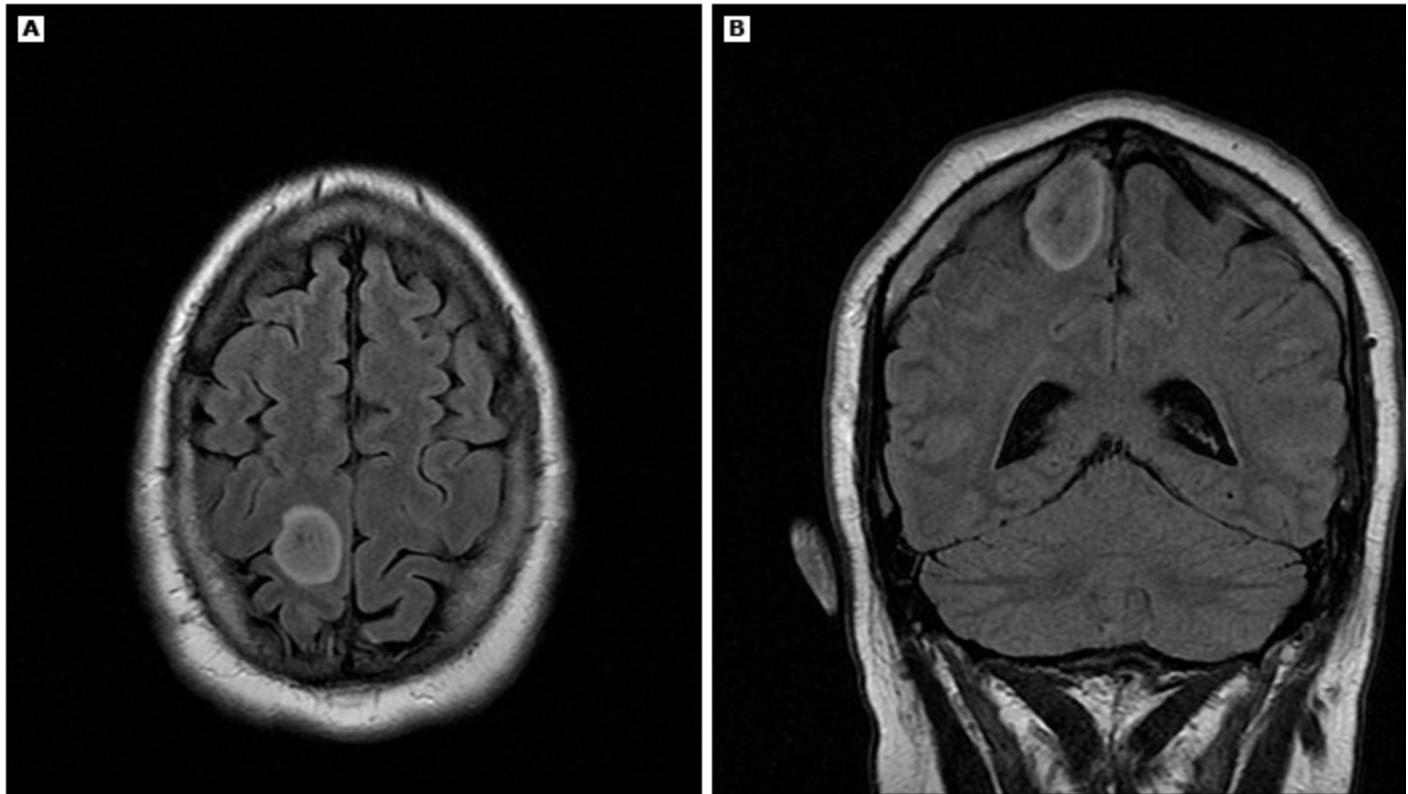
(Panel A) Axial FLAIR image showing a T2-hyperintense, expansile mass in the right frontal lobe.

(Panel B) Postcontrast axial T1-weighted image showing no appreciable contrast enhancement.

MRI: magnetic resonance imaging; WHO: World Health Organization; IDH: isocitrate dehydrogenase; FLAIR: fluid-attenuated inversion recovery.

Graphic 113599 Version 2.0

MRI appearance of low-grade astrocytoma

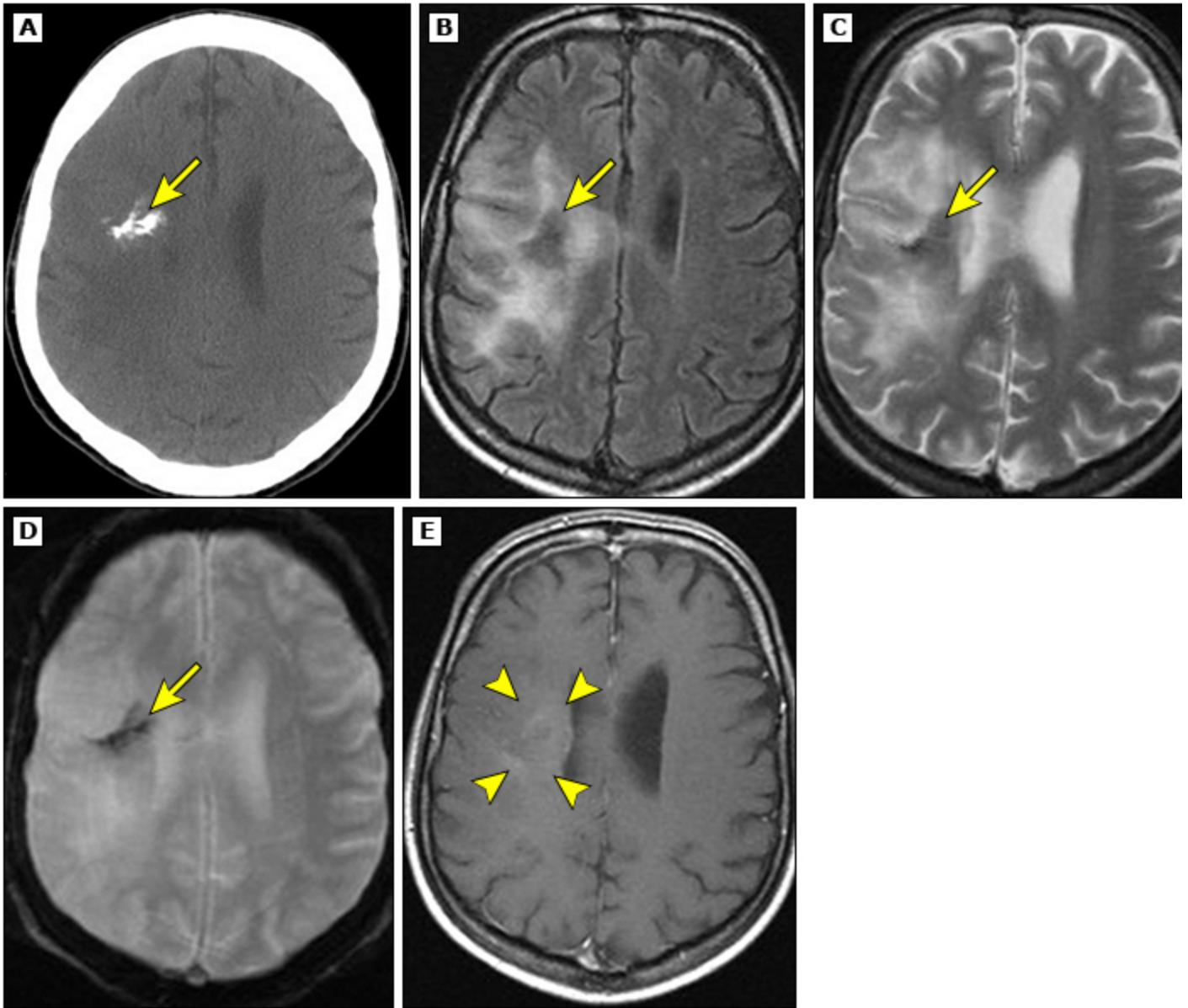


Brain MRI in a 34-year-old male presenting with left leg focal motor seizure. Axial (A) and coronal (B) FLAIR images show a T2-hyperintense, expansile mass in the right posterior frontal lobe, centered in the precentral gyrus, with no surrounding edema. Contrast imaging showed no enhancement. Pathology confirmed a WHO grade II astrocytoma, IDH1 mutant.

MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery; WHO: World Health Organization; IDH: isocitrate dehydrogenase.

Graphic 113730 Version 1.0

Imaging features of IDH-mutant, 1p/19q-codeleted oligodendrogloma, grade 3



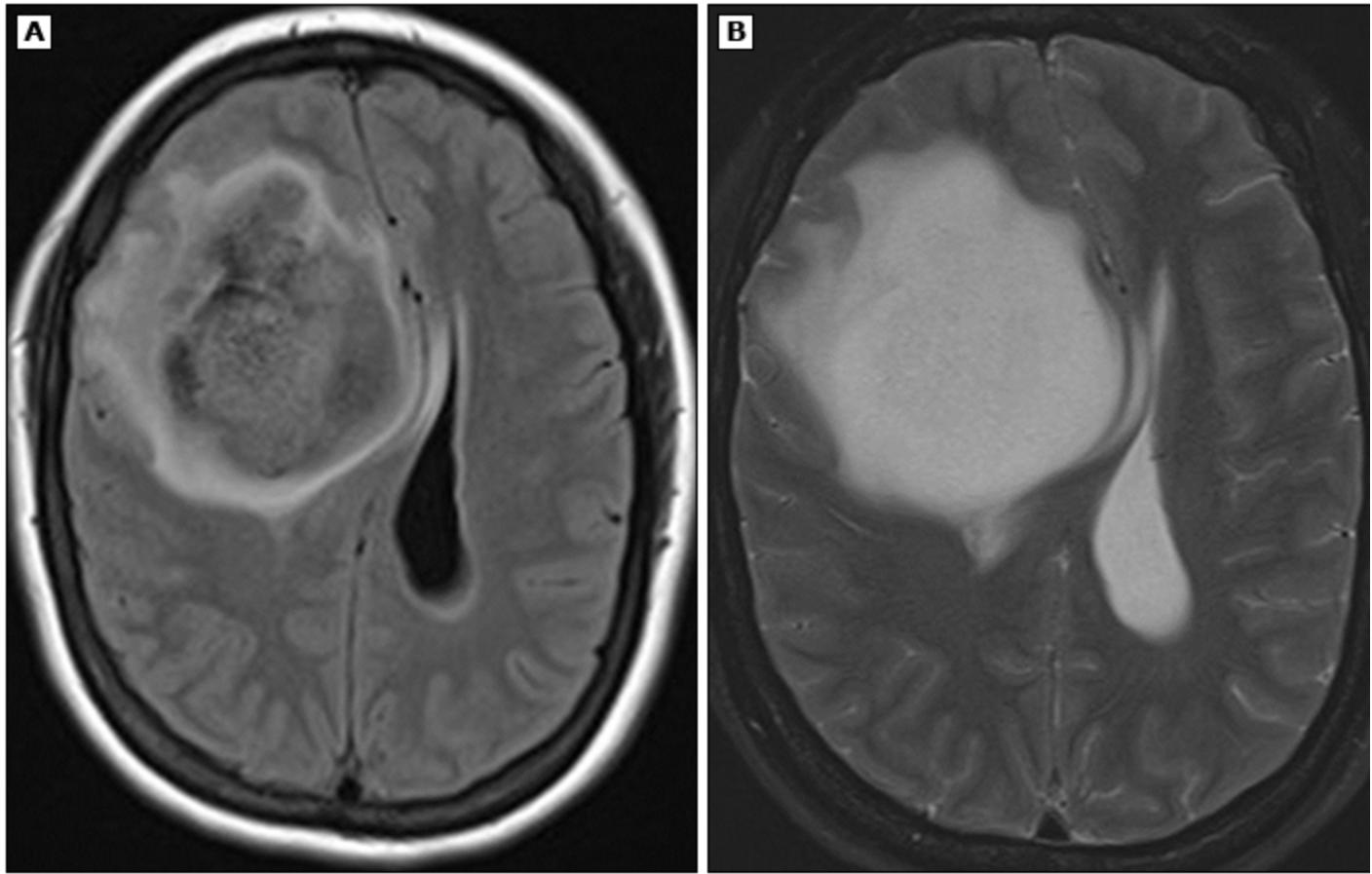
42-year-old male with an IDH-mutant, 1p/19q-codeleted, grade 3 oligodendrogloma. (A) Noncontrast CT shows hyperdense calcification (arrow) within a faintly-hypodense mass in the white matter of the right frontal operculum. Transverse-axial FLAIR (B) and T2-weighted (C) MR images show an ill-defined, infiltrative, hyperintense mass centered in white matter but extending to cortex. Hypointense signal in the center of mass (arrow), better demonstrated on T2*-weighted gradient-echo imaging (D), corresponds to tumoral calcification. (E) Faint contrast enhancement is visualized on postcontrast T1-weighted imaging (arrowheads).

IDH: isocitrate dehydrogenase; CT: computed tomography; FLAIR: fluid-attenuated inversion recovery; MR: magnetic resonance.

Courtesy of Glenn A Tung, MD, FACP.

Graphic 140794 Version 1.0

Imaging features of IDH-mutant astrocytoma, grade 2



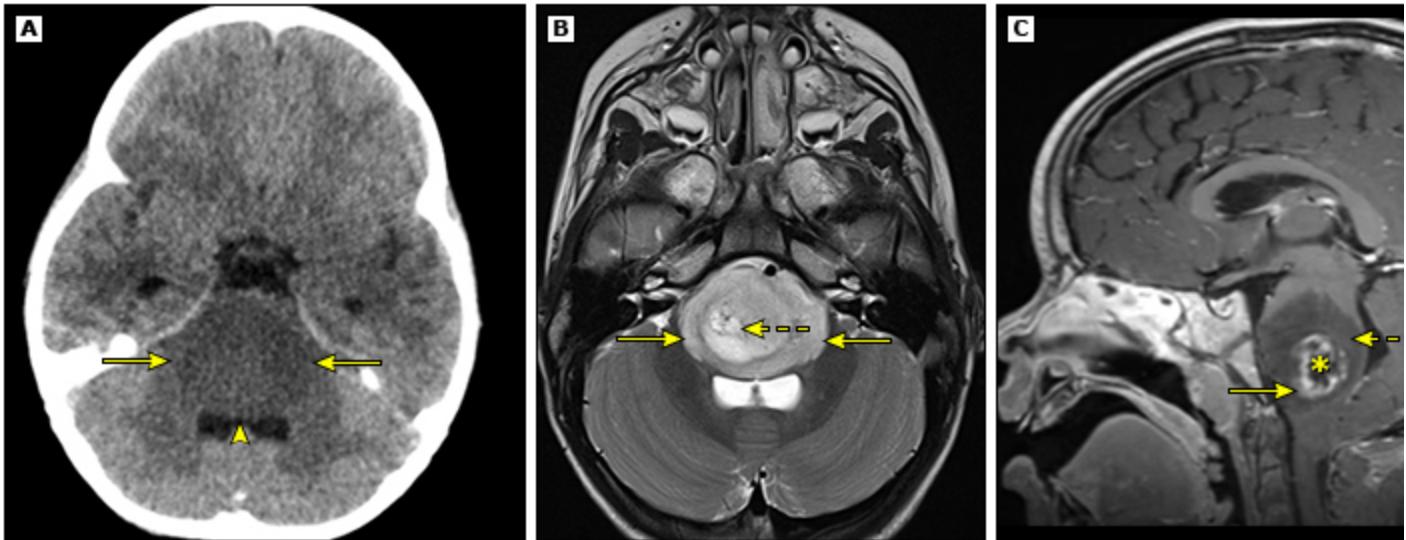
38-year-old with an IDH-mutant astrocytoma, grade 2. On FLAIR MRI (A), a large right frontal mass has relatively hypointense signal except for a peripheral rim of hyperintense signal and vasogenic edema. On T2-weighted MRI (B), the mass has nearly-uniform hyperintense signal. The difference in the signal intensity of the center of a mass on T2-weighted and FLAIR MRI is termed the "T2-FLAIR mismatch" sign and has been attributed to the presence of multiple intratumoral microcysts.

IDH: isocitrate dehydrogenase; FLAIR: fluid-attenuated inversion recovery; MRI: magnetic resonance imaging.

Courtesy of Glenn A Tung, MD, FACP.

Graphic 140796 Version 1.0

CT and MRI appearance of diffuse intrinsic pontine glioma



(A) Axial unenhanced CT of the brain shows diffuse, symmetric low attenuation expansion of the pons (arrows). There is mass effect on the ventral aspect of the fourth ventricle (arrowhead).

(B) An axial T2-weighted image reveals a large pontine mass associated with diffuse high signal intensity (arrows). An area of signal heterogeneity within the tumor likely reflects necrosis (dashed arrow).

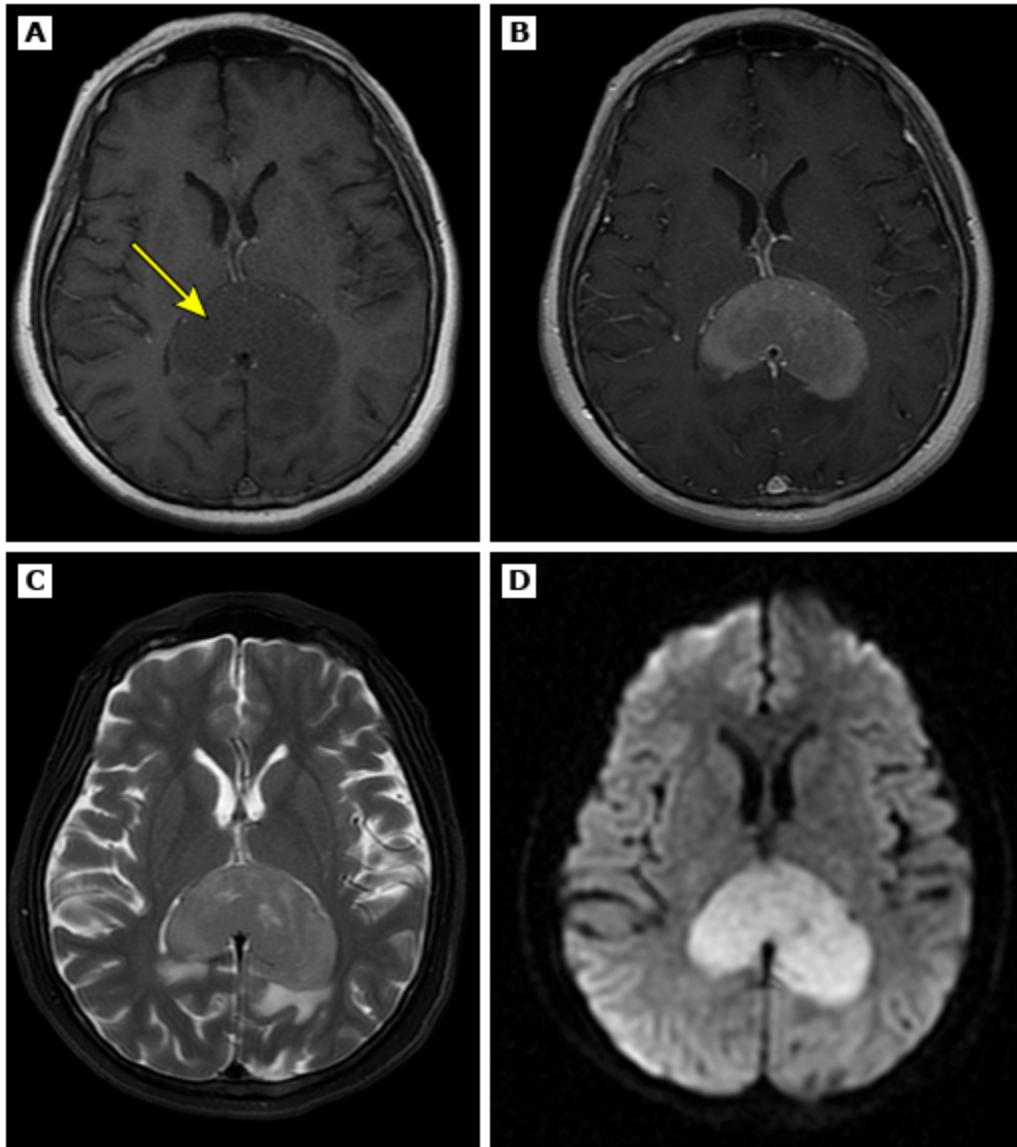
(C) A sagittal Gd-enhanced T1-weighted image shows non-enhancement of the central necrotic region (asterisk), enhancement of the region surrounding the necrosis (arrow), and non-enhancement of the rest of the tumor (dashed arrow).

CT: computed tomography; MRI: magnetic resonance imaging; Gd: gadolinium.

Courtesy of Caroline Robson, MBChB.

Graphic 100714 Version 3.0

MRI of primary CNS lymphoma

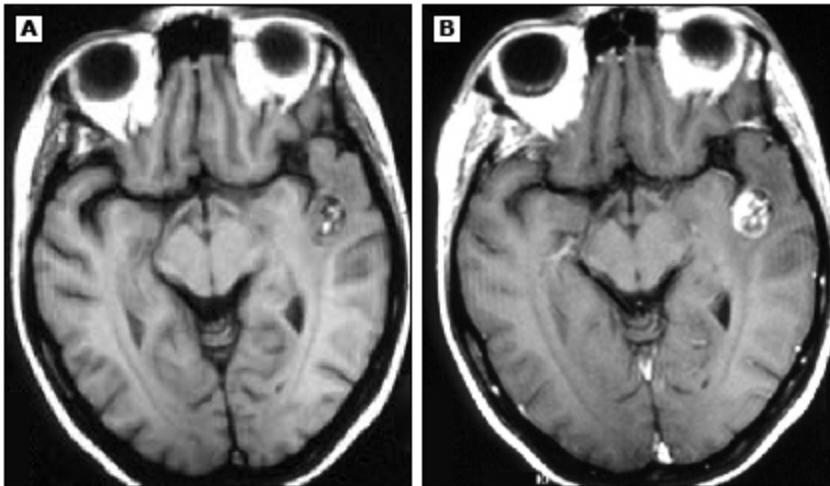


The MRI examination in the transverse plane is from a 63-year-old female with primary CNS lymphoma. The T1-weighted sequence (A) reveals a single mass that infiltrates the splenium of corpus callosum (a relatively common location for primary CNS lymphoma; arrow), abutting the third ventricle anteriorly. The mass enhances homogeneously following gadolinium administration (B), is relatively dark on T2-weighted images (C), and reveals restricted diffusion on the diffusion-weighted sequence (bright, D). The reader should note the relative lack of edema on FLAIR studies. These features are consistent with the diagnosis of primary lymphoma of the brain.

MRI: magnetic resonance imaging; CNS: central nervous system; FLAIR: fluid-attenuated inversion recovery.

Graphic 83271 Version 4.0

CNS metastasis from melanoma



Axial images of a brain magnetic resonance imaging (MRI) study demonstrating an intracerebral metastasis in a patient with melanoma. Following the injection of contrast (B) the lesion enhances with a ring-like pattern.

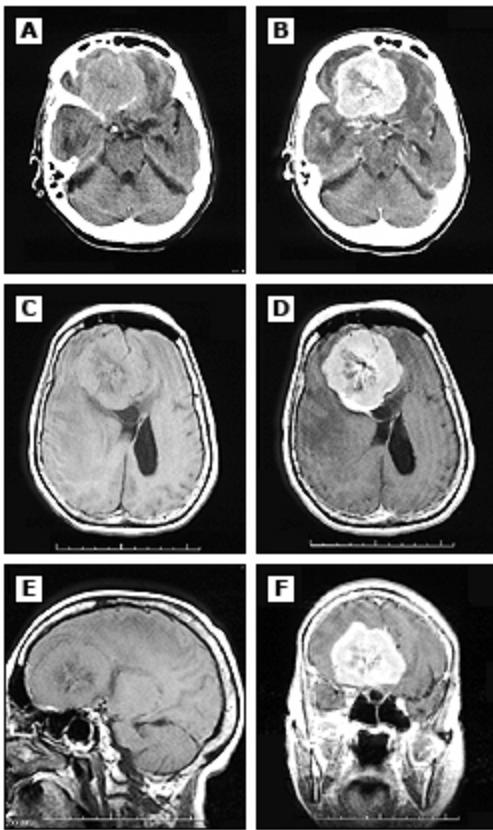
(A) Pre-contrast.

(B) Post-contrast.

Courtesy of Kevin Donohoe, MD.

Graphic 56550 Version 4.0

Intracranial meningioma



A 70-year-old female presented with a several-week history of confusion. (Panels A, B): Noncontrast and contrast-enhanced head CT shows a large bifrontal lesion with calcifications and surrounding edema. (Panels C, D): Noncontrast and contrast-enhanced T1-weighted axial MR images of the head also demonstrate large flow voids representing blood vessels in the center of the tumor. (Panel E): Noncontrast T1-weighted sagittal MR image. (Panel F): Contrast-enhanced T1-weighted coronal MR image.

CT: computed tomography; MR: magnetic resonance.

Courtesy of John Park, MD, PhD.

Graphic 59777 Version 6.0

Differential diagnosis of a brain mass

Primary brain tumors

Glioma

Meningioma

Pituitary adenoma

Vestibular schwannoma

Primary central nervous system lymphoma

Other

Metastatic brain tumors

Vascular disease

Cerebral hemorrhage

Vascular anomaly

Hypertensive

Intratumoral

Cerebral infarct

Reversible posterior leukoencephalopathy syndrome

Infections

Abscess (bacterial, fungal)

Viral infection

Progressive multifocal leukoencephalopathy

Inflammatory

Multiple sclerosis

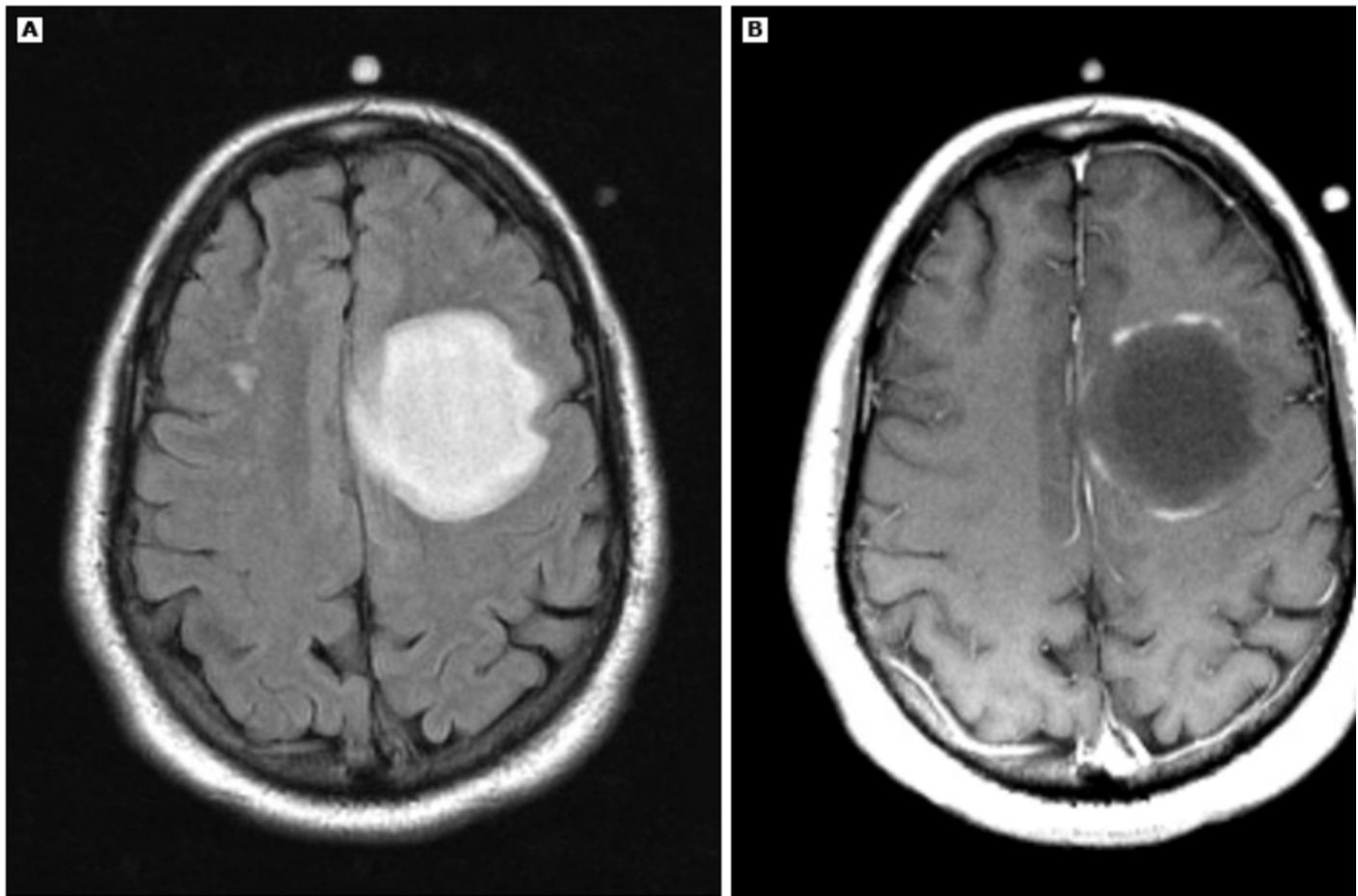
Post-infectious encephalomyelitis

Granulomatous disease

Vasculitis

Textiloma

Brain MRI tumefactive demyelination

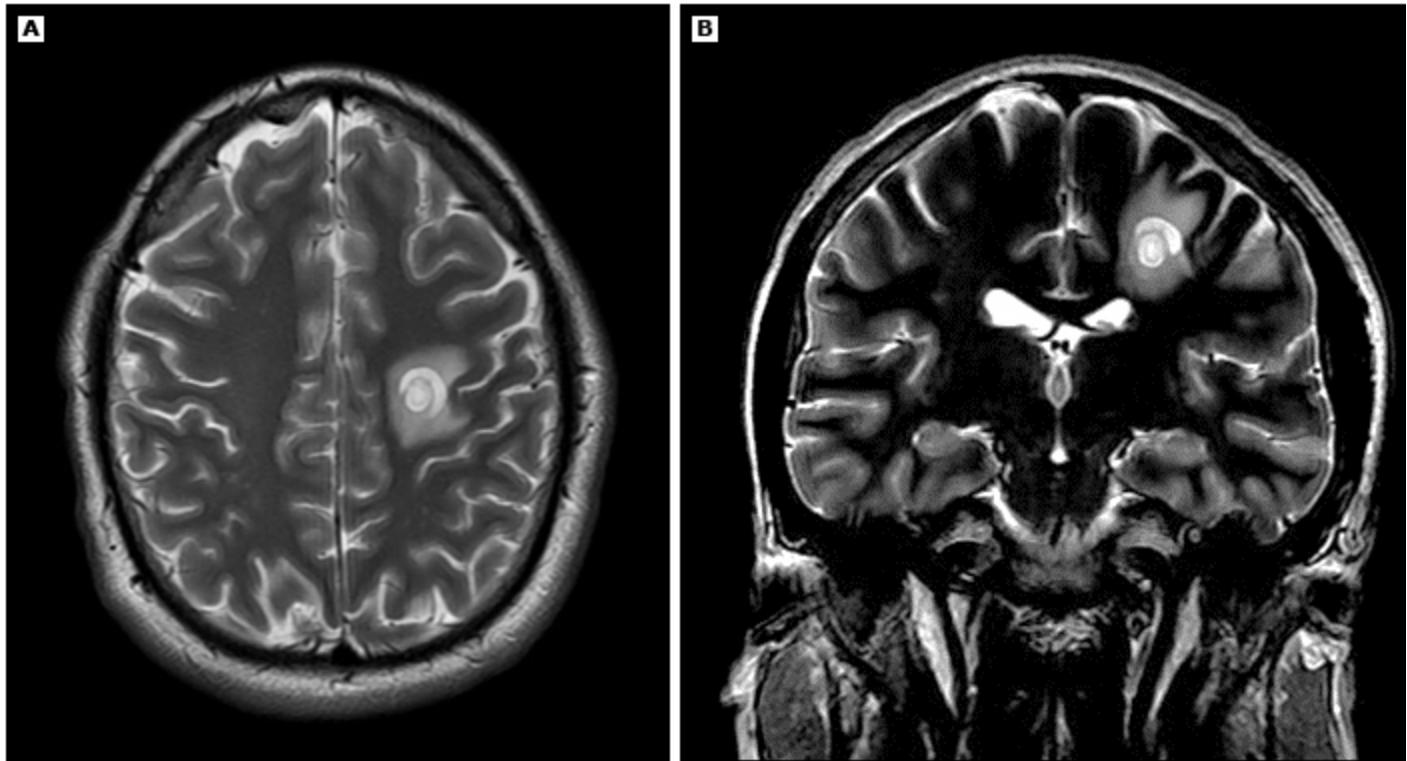


Axial FLAIR image (A) demonstrates a large demyelinating lesion in the left frontal lobe with mass effect that shows peripheral enhancement on post-contrast T1-weighted image (B).

MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery.

Graphic 119492 Version 1.0

Brain MRI showing demyelinating lesion consistent with Balo concentric sclerosis



Axial (A) and coronal (B) T2-weighted images demonstrate a Balo lesion in the left frontal lobe.

MRI: magnetic resonance imaging.

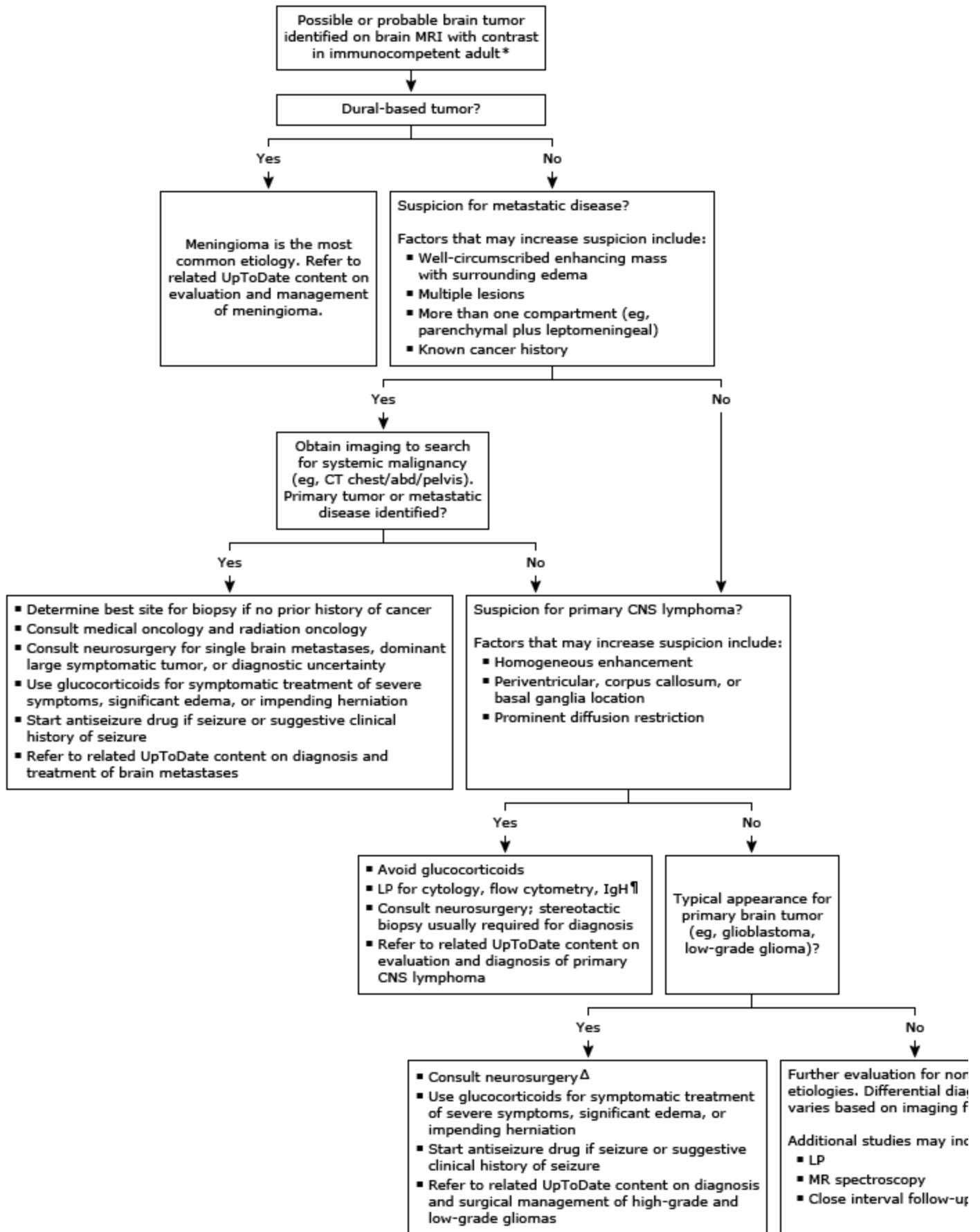
Graphic 119493 Version 1.0

Differential diagnosis of meningioma

Neoplastic	Clinical and imaging clues
▪ Solitary fibrous tumor/hemangiopericytoma	▪ Homogeneously enhancing dural-based tumors; usually indistinguishable from meningioma by imaging
▪ Lymphoma	▪ Lack of hyperostosis; low apparent diffusion coefficient
▪ Plasmacytoma	▪ Abnormal SPEP, UPEP; anemia; renal insufficiency
▪ Metastatic carcinoma	▪ Edema; adjacent skull metastasis; known breast, prostate, or lung cancer
▪ Melanocytic neoplasms	▪ Posterior fossa or spinal cord location
▪ Gliosarcoma	▪ Heterogenous enhancement, local invasion
▪ Leiomyosarcoma	▪ Rare, primarily seen in HIV-positive patients
Non-neoplastic	Clinical clues
▪ Sarcoidosis	▪ Uncommon manifestation of neurosarcoidosis; systemic disease may or may not be present
▪ Granulomatosis with polyangiitis	▪ Constitutional symptoms, renal insufficiency
▪ Histiocytic disorders (eg, Langerhans cell histiocytosis, Erdheim-Chester disease)	▪ Bone lesions, multiorgan involvement, diabetes insipidus
▪ IgG4-related disease	▪ Orbital location; multiple tumors; elevated serum IgG4
▪ Rosai-Dorfman disease	▪ Massive painless cervical lymphadenopathy and fever
▪ Tuberculosis	▪ Endemic regions; immunocompromise; chronic cough and constitutional symptoms

SPEP: serum protein electrophoresis; UPEP: urinary protein electrophoresis; HIV: human immunodeficiency virus; IgG4: immunoglobulin G4.

Evaluation of possible or probable brain tumor in adults



MRI: magnetic resonance imaging; CT: computed tomography; abd: abdomen; CNS: central nervous system; LP: lumbar puncture; IgH: immunoglobulin heavy chain; MR: magnetic resonance.

* MRI with contrast is the optimal study for resolution of brain tumors. CT with contrast should be obtained in patients with a contraindication to MRI (eg, pacemaker). Refer to related UpToDate content for the evaluation of brain masses in patients with human immunodeficiency virus (HIV).

¶ Lumbar puncture is not advised for large lesions associated with midline shift, obstructive hydrocephalus, or mass effect on the fourth ventricle.

Δ Urgency of neurosurgical evaluation for newly discovered brain tumor depends on the clinical stability of the patient, symptom severity, tumor size and location, and suspicion for malignancy. Patients should be referred to a high-volume center with subspecialty neurosurgical expertise in brain tumors, when possible.

◊ Differential diagnosis of brain tumors on neuroimaging varies based on location and whether the lesion is enhancing or nonenhancing. Refer to related UpToDate content on the evaluation and diagnosis of brain tumors in adults for additional details.

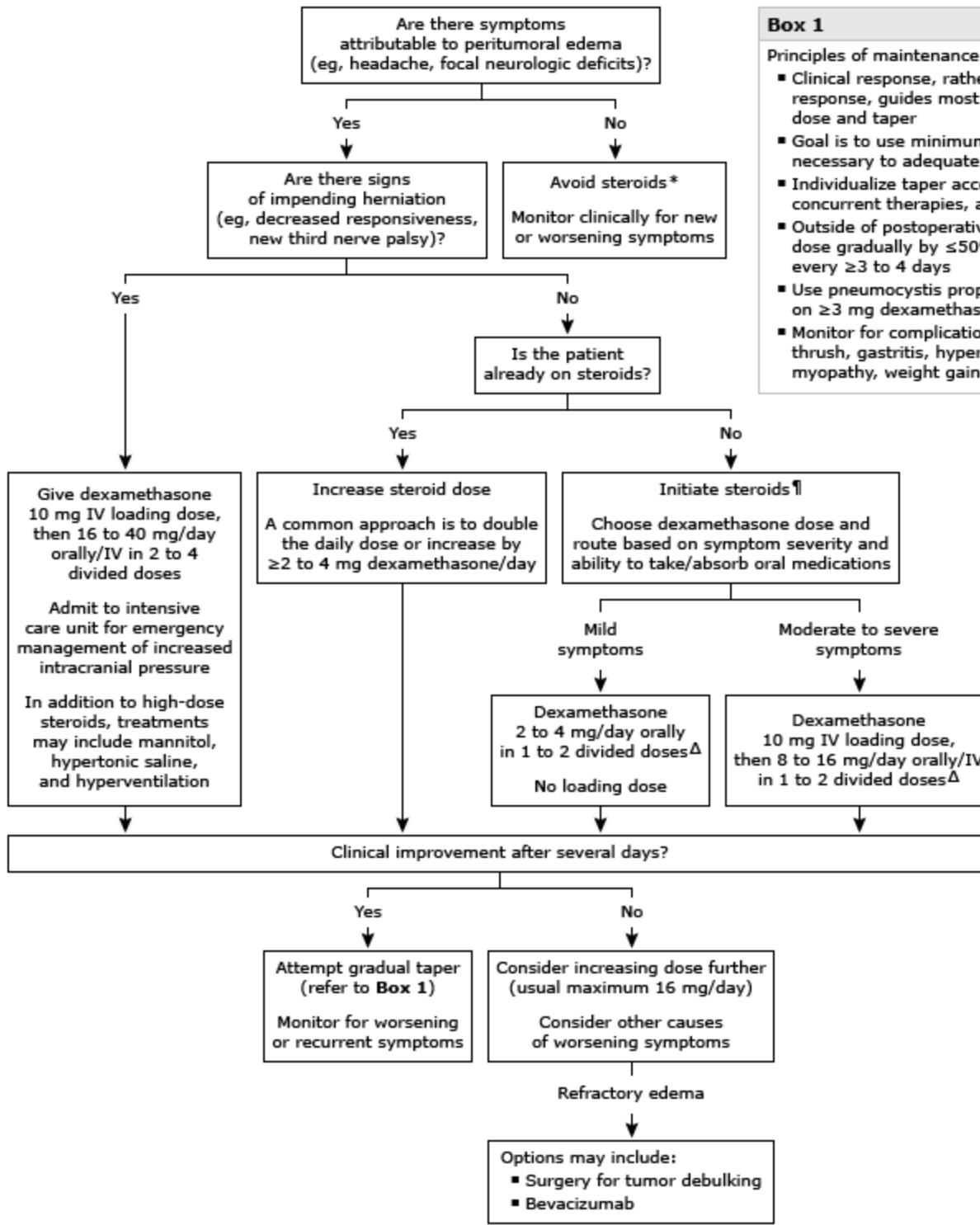
Graphic 113770 Version 2.0

MR spectroscopy parameters

Brain process	N-Acetylaspartate	Choline	Lactate
Neoplasm	↓	↑	↑
Infarction	↓	↓	↑
Infection	↓	-	↑

Graphic 79098 Version 1.0

Management of vasogenic edema in adult patients with brain tumors



Systemic glucocorticoids are the mainstay of symptomatic therapy for peritumoral brain edema. They play a role in stabilizing patients awaiting definitive treatment of the tumor as well as in palliative management of edema related to treatment-refractory tumors. Refer to the UpToDate topic on management of vasogenic edema in patients with brain tumors for additional information on evaluation of symptoms and attribution to vasogenic edema.

IV: intravenous.

* Clinical judgment is required in patients with large amounts of edema, particularly when antitumor therapy has the potential to worsen edema. Increased caution is also required for posterior fossa tumors and edema, which can be associated with rapid deterioration.

¶ If lymphoma is on the differential diagnosis in a patient with a new brain mass, avoid steroids if possible while pursuing urgent neurosurgical consult for biopsy.

Δ Although it has been customary to administer dexamethasone in 4 divided daily doses, its biologic half-life is sufficiently long (36 to 54 hours) to allow once- or twice-daily dosing. This approach is preferred for maintenance therapy because it is easier for patients and has not been associated with diminished efficacy. Use once-daily morning dosing when possible and avoid late evening and middle-of-the-night dosing to help reduce insomnia.

Graphic 139921 Version 2.0

Classification of diffuse gliomas in adults



Shaded nodes indicate final integrated pathologic diagnoses.

IDH: isocitrate dehydrogenase; ATRX: ATRX chromatin remodeler; TP53: tumor protein p53; EGFR: epidermal growth factor receptor; TERT: telomerase reverse transcriptase; CDKN2A/B: cyclin-dependent kinase inhibitor 2A/B; CNS: central nervous system; WHO: World Health Organization; NEC: not elsewhere classified.

* Immunohistochemical staining for the most common mutant form of *IDH1* (R132) should be performed on all diffuse glioma specimens for diagnostic purposes. Less common mutations in *IDH1* and all *IDH2* mutations will not be identified using this antibody but can be detected using DNA sequencing approaches. If immunohistochemistry for mutant *IDH1* R132H is negative, sequencing of *IDH1* (codon 132) and *IDH2* (codon 172) should be performed in patients with grade 2 and grade 3 diffuse gliomas and in younger patients (<55 years) with glioblastomas, as the distinction between IDH-mutant and IDH-wildtype is central to an integrated diagnosis.

¶ For tumors in midline location and in younger patients, assumes testing for H3 K27M and H3 G34 (respectively) has been performed and is negative.

Δ Tumors with none of these alterations receive a provisional diagnosis of astrocytoma, IDH-wildtype, NEC. The biologic behavior of such tumors is uncertain. Further molecular testing may lead to a more definitive diagnosis.

Graphic 134946 Version 2.0

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