

Primary Brain Tumors in Adults: Diagnosis and Treatment

ALLEN PERKINS, MD, MPH, *University of South Alabama, Mobile, Alabama*

GERALD LIU, MD, *Harvard Vanguard Medical Associates, Weymouth, Massachusetts*

Primary intracranial tumors of the brain structures, including meninges, are rare with an overall five-year survival rate of 33.4%; they are collectively called primary brain tumors. Proven risk factors for these tumors include certain genetic syndromes and exposure to high-dose ionizing radiation. Primary brain tumors are classified by histopathologic criteria and immunohistochemical data. The most common symptoms of these tumors are headache and seizures. Diagnosis of a suspected brain tumor is dependent on appropriate brain imaging and histopathology. The imaging modality of choice is gadolinium-enhanced magnetic resonance imaging. There is no specific pathognomonic feature on imaging that differentiates between primary brain tumors and metastatic or nonneoplastic disease. In cases of suspected or pathologically proven metastatic disease, chest and abdomen computed tomography may be helpful, although determining the site of the primary tumor is often difficult, especially if there are no clinical clues from the history and physical examination. Using fluorodeoxyglucose positron emission tomography to search for a primary lesion is not recommended because of low specificity for differentiating a neoplasm from benign or inflammatory lesions. Treatment decisions are individualized by a multidisciplinary team based on tumor type and location, malignancy potential, and the patient's age and physical condition. Treatment often includes a combination of surgery, radiotherapy, and chemotherapy. After craniotomy, patients should be followed closely for complications, including deep venous thrombosis, pulmonary embolism, intracranial bleeding, wound infection, systemic infection, seizure, depression, worsening neurologic status, and adverse drug reaction. Hospice and palliative care should be offered when appropriate throughout treatment. (*Am Fam Physician*. 2016;93(3):211-217. Copyright © 2016 American Academy of Family Physicians.)



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► **Patient information:** Available at <http://www.aafp.org/afp/2016/0201/p211-s1.html>.

Primary intracranial tumors arising from the meninges, neuroepithelial tissues, pituitary and related structures, cranial nerves, germ cells, blood-forming organs, or a distant subclinical primary tumor are known collectively as primary brain tumors. These tumors in adults are rare with an estimated 23,380 new cases diagnosed in 2014, leading to 14,320 deaths; these accounted for 1.4% of all new cases of cancer and 2.4% of all cancer deaths. The incidence of a new brain tumor is 6.4 per 100,000 persons per year with an overall five-year survival rate of 33.4%. The peak prevalence is between 55 and 64 years of age, with a slightly higher incidence in men than in women. There is an approximate 0.6% lifetime risk of being diagnosed with brain or other nervous system cancer.¹

Risk Factors

There are many hypotheses about the pathogenesis of primary brain tumors; genetics clearly play a role in their development.²⁻⁴

Exposure to high-dose ionizing radiation is the only proven environmental risk factor for primary brain tumors. Other investigated toxins and exposures have not been shown to increase the risk.⁵ *Table 1* includes risk factors for primary brain tumors.²⁻⁵

Classification

The World Health Organization classifies primary brain tumors based on histopathologic criteria and immunohistochemical data; a malignancy grade is also assigned to tumors, defined by a combination of morphological features, growth patterns, and molecular profile (*Table 2*).^{6,7} Nonmalignant tumors of the meninges (meningiomas) and tumors of the pituitary gland are often included. When they are included, they account for 50% of primary brain tumors. Glioblastomas, associated with higher malignancy grade and poor prognosis, account for only 15% of primary brain tumors when these nonmalignant tumors are included.⁶

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	References
Gadolinium-enhanced magnetic resonance imaging is the preferred imaging modality in the diagnosis of suspected brain tumors.	C	15, 16
Fluorodeoxyglucose positron emission tomography should not be used initially to search for a primary tumor when metastatic disease is suspected, unless suggested by history or physical examination findings.	C	19
Treatment decisions should be individualized by a multidisciplinary team (medical oncology, radiation oncology, and neurosurgery) based on tumor type, malignancy potential, tumor location, and the patient's age and physical condition.	C	22
Hospice should be offered if life expectancy is less than six months, and in patients who have poor or worsening performance status, who are not candidates for surgery or chemotherapy, who have deteriorating neurologic functions despite therapy, or who have tumor recurrence.	C	13, 46

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

Diagnosis

Figure 1 is an algorithm for the diagnosis of primary brain tumors in adults.

CLINICAL PRESENTATION

Clinical signs and symptoms of primary brain tumors may be general or focal. General symptoms, such as headache and seizures, are due to increased intracranial pressure.⁸ Focal symptoms, such as unilateral weakness or personality changes, are due to tissue destruction or compression of specialized regions (Table 3).⁹ Initial symptoms of low-grade tumors or initial stages of disease are often focal, progressing to generalized symptoms as the tumor increases in size and spreads.^{10,11}

The following have been reported by patients as the first symptom of a primary brain tumor: headache (23.5% of patients); generalized seizures (21.3%);

unilateral weakness (7.1%); unsteadiness (6.1%); expressive language disorder (5.8%); visual problems (3.2%); confusion (4.5%); unilateral numbness (2.3%); personality problems (1.6%); diplopia (0.3%); and other symptoms (24.2%), such as anosmia, apraxia, cognitive delay, drowsiness, dysphagia, hallucinations, memory loss, nausea and vomiting, pain, and stiff neck.⁸

The headache associated with a tumor is classically thought of as severe, worse in the morning, and occurring with nausea and vomiting. However, patients with a brain tumor more often report a bifrontal, tension-type headache.¹² In addition, a chronic, persistent headache with nausea, vomiting, seizures, changes in headache pattern, neurologic symptoms, or positional worsening should prompt an evaluation for brain tumor.¹³ Cognitive dysfunction (e.g., language, attention, executive functioning) is common in persons with brain tumors

and may be caused by the tumor, tumor-related epilepsy, treatment, psychological distress, or a combination of these factors. General neurologic symptoms may progress to encephalopathy and dementia, which may be the presenting symptoms.¹⁴ When a tumor is suspected, funduscopy and a focused neurologic examination should be performed in addition to the history and physical examination. This examination should include an assessment of mental status; cranial nerves; and motor, sensory, and cerebellar function.

DIAGNOSTIC IMAGING

Diagnosis of a suspected brain tumor is dependent on appropriate brain imaging and histopathology (eFigures A and B). Gadolinium-enhanced magnetic resonance imaging (MRI) is the preferred modality because of its resolution and enhancement

Table 1. Risk Factors for Primary Brain Tumors

Environmental	Genetic
Proven	Proven
High-dose ionizing radiation exposure	Cowden disease
Unproven or disproven	Gorlin syndrome
Alcohol use	Li-Fraumeni syndrome
Cellular telephone use	Neurofibromatosis types 1 and 2
Chemical agents (e.g., hair dyes, solvents)	Tuberous sclerosis complex
Electromagnetic fields	Turcot syndrome
Infections (e.g., viruses, <i>Toxoplasma gondii</i>)	Von Hippel-Lindau disease
N-nitroso, antioxidant, calcium consumption	Unproven
Occupational exposure (e.g., vinyl chloride)	Genetic polymorphisms (e.g., <i>XRCC1</i>)

Information from references 2 through 5.

with contrast agents.^{15,16} If MRI cannot be performed (e.g., in patients with metallic implants, embedded devices, or claustrophobia), head and spine computed tomography (CT) is acceptable, although the resolution is not as high as MRI and it cannot adequately assess lesions in the posterior fossa and spine.¹⁵ Additional imaging such as magnetic resonance perfusion, magnetic resonance spectroscopy, or fluorodeoxyglucose positron emission tomography may be necessary for diagnosis and staging, and should be ordered only under the direction of the treating physician.^{16,17} Emergent imaging should be performed in patients with red flag symptoms (Table 4).¹⁸

DIFFERENTIAL DIAGNOSIS

Although imaging significantly narrows the differential diagnosis of primary brain tumors, there is no specific pathognomonic feature on imaging that differentiates between primary brain tumors and metastatic or nonneoplastic disease. In cases of suspected or pathologically proven metastatic disease, chest and abdomen CT may be helpful, although determining the site of the primary tumor is often difficult, especially if there are no clinical clues from the history and physical examination. Using fluorodeoxyglucose positron emission tomography is not recommended initially to search for a primary lesion when a metastatic brain tumor is suspected, unless suggested by history or physical examination findings, because of its low specificity for differentiating neoplasms from benign or inflammatory lesions.¹⁹

Even with the extensive range of imaging available, nonneoplastic diseases often present similarly to brain tumors. Once a neoplastic process has been excluded, a directed investigation based on history and physical examination findings should be pursued (Table 5).²⁰

STAGING

Brain cancers do not conform to a standard staging system. Although they may spread to other parts of the brain or spinal cord, they rarely spread beyond that.²¹

Table 2. WHO Classification of Primary Brain Tumors

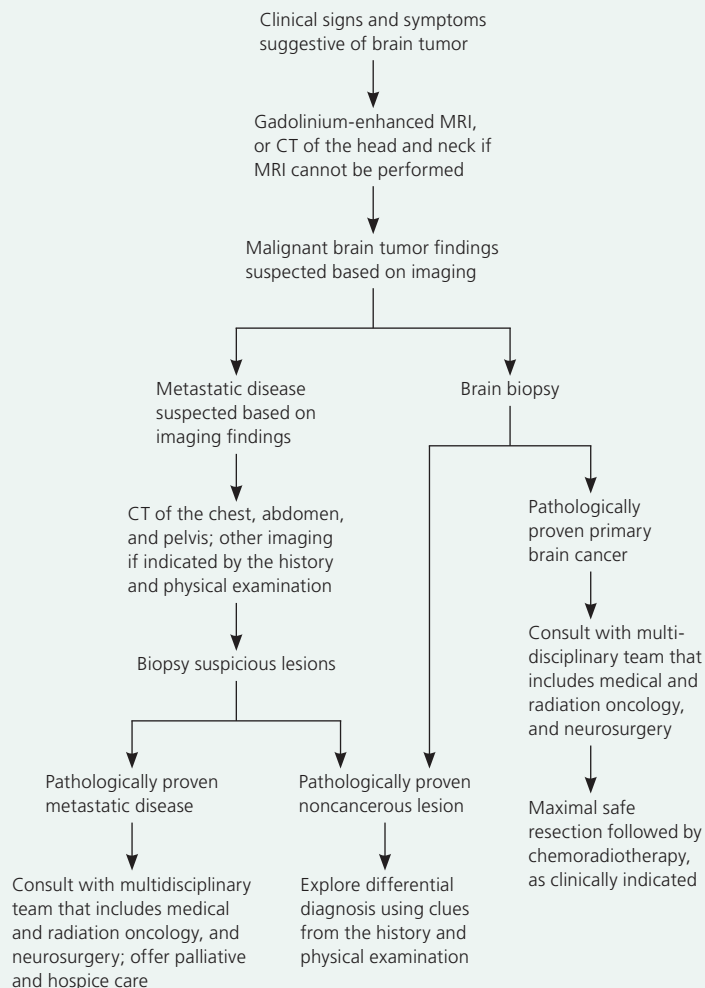
<i>Classification</i>	<i>Average annual U.S. age-adjusted incidence per 100,000</i>
Tumors of the meninges	7.88
Meningioma	7.61
Mesenchymal tumors	0.08
Primary melanocytic lesions	0.01
Other neoplasms related to the meninges	0.18
Tumors of the neuroepithelial tissue	6.61
Glioblastoma	3.19
Diffuse astrocytoma	0.55
Glioma (malignant, not otherwise specified)	0.46
Ependymal tumors	0.42
Anaplastic astrocytoma	0.37
Pilocytic astrocytoma	0.34
Neuronal and mixed neuronal-glial tumors	0.28
Embryonal tumors	0.26
Oligodendroglioma	0.26
Oligoastrocytic tumors	0.21
Anaplastic oligodendroglioma	0.11
Unique astrocytoma variants	0.07
Choroid plexus tumors	0.05
Tumors of the pineal region	0.04
Other neuroepithelial tumors	0.01
Tumors of the sellar region	3.47
Tumors of the pituitary	3.29
Craniopharyngioma	0.18
Tumors of the cranial nerves and spine	1.70
Nerve sheath tumors	1.70
Other tumors of cranial nerves and spine	0.00
Lymphomas and hematopoietic neoplasms	0.46
Lymphoma	0.44
Other hematopoietic neoplasms	0.01
Germ cell tumors and cysts	0.10
Germ cell tumors, cysts, and heterotopias	0.10
Unclassified tumors	1.19
Neoplasm, unspecified	0.88
Hemangioma	0.30
All other	0.00
Total	21.42

NOTE: WHO also assigns a malignancy grade to tumors, defined by a combination of morphological features, growth patterns, and molecular profile. I = low proliferative potential and the potential for cure following surgical resection alone; II = generally infiltrative in nature, and, despite low-level proliferative activity, often recur and may progress to higher grades of malignancy; III = histologic evidence of malignancy; IV = cytologically malignant, mitotically active, necrosis-prone, and associated with a fatal outcome.

WHO = World Health Organization.

Adapted with permission from Ostrom QT, Gittleman H, Liao P, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. *Neuro Oncol.* 2014;16(suppl 4):iv37-iv38, with additional information from reference 7.

Diagnosis of Primary Brain Tumors



Treatment

Treatment decisions are individualized by an experienced multidisciplinary team consisting of medical oncology, radiation oncology, and neurosurgery. Treatment decisions are based on tumor type and location, malignancy potential, and the patient's age and physical condition. Treatment may require only surveillance but commonly includes surgery, radiotherapy, chemotherapy, or a combination, and enrollment in clinical trials should be offered as an option for some high-grade tumors.²² This article provides a brief treatment overview; detailed treatment algorithms are available from the National Comprehensive Cancer Network (<http://www.nccn.org>, membership required).

SURGERY

The preferred treatment for primary brain tumors is the maximal safe surgical removal of the tumor followed by radiotherapy and chemotherapy. Although extent of resection is a prognostic variable, the extent of safe tumor resection is dependent on tumor location, patient performance status, and, most importantly, patient age.²³ Benefits of maximal resection include relief of mass effect, decreased tumor burden, improved diagnosis, and a trend toward prolonged survival.²⁴⁻²⁷

Figure 1. Algorithm for diagnosis of primary brain tumors in adults. (CT = computed tomography; MRI = magnetic resonance imaging.)

Table 3. Presenting Manifestations of Primary Brain Tumors by Location

Tumor location	Neurologic signs
Frontal lobe	Dementia, personality changes, gait disturbances, generalized or focal seizures, expressive aphasia
Parietal lobe	Receptive aphasia, sensory loss, hemianopia, spatial disorientation
Temporal lobe	Complex partial or generalized seizures, quadrantanopia, behavioral alterations
Occipital lobe	Contralateral hemianopia
Thalamus	Contralateral sensory loss, behavioral changes, language disorder
Cerebellum	Ataxia, dysmetria, nystagmus
Brain stem	Cranial nerve dysfunction, ataxia, papillary abnormalities, nystagmus, hemiparesis, autonomic dysfunction

Adapted with permission from Newton HB. Primary brain tumors: review of etiology, diagnosis and treatment. *Am Fam Physician.* 1994;49(4):792.

Table 4. Red Flag Headache Symptoms Warranting Emergent Brain Imaging

- Acute, new, severe; changed significantly from prior headaches
- Associated with fever or other systemic symptoms
- New headache in an adult, especially in those older than 50 years
- Occurs on exertion, onset at night or in early morning
- Occurs with meningismus
- Occurs with new neurologic signs
- Precipitation of pain with the Valsalva maneuver
- Progressive in nature
- Severe or persistent headaches in older persons or children, particularly those with worrisome features

Information from reference 18.

RADIOTHERAPY

Radiotherapy can be used as primary treatment or adjunctively following surgical resection. Standard fractionated external beam radiotherapy is the most common approach, although other options include brachytherapy, fractionated stereotactic radiotherapy, and stereotactic radiosurgery. Hypofractionation of radiotherapy may be considered for older or immunocompromised patients.^{28,29} Radiotherapy can improve progression-free survival and overall survival in patients with high-risk low-grade gliomas, defined as patients younger than 40 years with subtotal resection or biopsy, or patients older than 40 years with any degree of resection.³⁰

CHEMOTHERAPY

Chemotherapy given in combination with radiation has been shown to improve survival in selected cases.³¹ For example, carmustine wafers (Gliadel), or temozolomide (Temodar) in younger patients, placed during surgery have improved survival in patients with high-grade gliomas.^{32,33} Patients with the O6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter and glioblastomas benefit from temozolomide.³⁴ Treatment of anaplastic oligodendrogliomas and anaplastic oligoastrocytomas with the combination of procarbazine (Matulane), lomustine (Gleostine), and vincristine delays progression, especially in patients with *1p/19q* deletions, but does not prolong survival.³⁵

PERI- AND POSTOPERATIVE TREATMENTS

After craniotomy, patients should be followed closely for complications in the perioperative period (the first 21 postoperative days). Common complications include deep venous thrombosis, pulmonary embolism, intracranial bleeding, wound infection, systemic infection, seizure, depression, worsening neurologic status, and adverse drug reaction.³⁶ To help with prognosis and treatment planning, a repeat brain MRI with or without contrast media should be performed within three days of the surgery to determine the extent of resection.^{26,37}

Glucocorticoids, which are the mainstay of postoperative management, help decrease tumor-associated

Table 5. Clinical Clues to Nonmalignant Brain Lesions

<i>Clinical clues</i>	<i>Suggested etiology</i>
Abnormalities found on more extensive imaging that are suggestive of an etiology	Cysticercosis, fungal infections, sarcoidosis, tuberculosis
Chronic fever; recent dental procedure; recent ear, nose, throat infections	Brain abscess
History of transient neurologic deficits, including visual symptoms	Multiple sclerosis
History of tuberculosis exposure	Tuberculosis
Immunosuppression, including diabetes mellitus	Opportunistic infections
Oral candidiasis	AIDS, immunosuppression
Personal or family history of autoimmune or inflammatory disease, age younger than 40 years	Behçet syndrome, multiple sclerosis, sarcoidosis, other inflammatory illnesses
Presence or history of oral and genital ulcers or skin rashes	AIDS, Behçet syndrome, sarcoidosis, syphilis
Risky sexual behavior, intravenous drug use, age younger than 40 years	AIDS, brain abscess, syphilis
Travel to countries with endemic infectious disease	Amebiasis, cysticercosis, hydatidosis

Information from reference 20.

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vasogenic edema and prevent postoperative and radiation-associated edema. Because long-term use is often necessary, patients should be monitored for potential adverse effects of glucocorticoids (e.g., hyperglycemia, weight gain, immunosuppression, gastritis and bowel perforation, insomnia, psychological disturbances). Glucocorticoids should be tapered after one week if possible to minimize adverse effects, although an increase in neurologic symptoms may occur with an early taper, requiring a slower taper.³⁸

Despite perioperative anticoagulation with heparin, thromboembolic disease is common, with an incidence as high as 60% within six weeks after surgery in patients with malignant gliomas.³⁹ The American Society of Clinical Oncology recommends against routine thromboprophylaxis in the outpatient setting and against the use of novel oral anticoagulants. Patients undergoing surgery should receive prophylaxis before surgery and continuing for at least seven to 10 days.⁴⁰

Although approximately 30% of patients with resection of brain tumors will develop seizures,⁴¹ prophylactic use of anticonvulsants is not recommended beyond the initial postoperative period. Anticonvulsants may be tapered and discontinued after the initial week in patients who are medically stable and experiencing anticonvulsant-related adverse effects.^{42,43}

Cognitive deficits are problematic and common post-treatment. Function may be improved with a multifaceted cognitive rehabilitation program, which includes computer-based attention retraining and compensatory skills training of attention, memory, and executive functioning. Mood problems, including depression, may be improved with psychosocial and supportive care.^{44,45}

Hospice and palliative care should be made available when appropriate throughout treatment. Hospice should be offered if life expectancy is less than six months, and in patients who have poor or worsening performance status, who are not candidates for surgery or chemotherapy, who have deteriorating neurologic deficits despite therapy, or who have tumor recurrence.^{13,46}

Prognosis

The five-year survival rate for primary brain tumors is 33.4%,¹ although this rate varies widely among the specific types of tumors: 100% for pilocytic astrocytoma, 58% for low-grade astrocytoma, 11% for anaplastic astrocytoma, and 1.2% for glioblastoma.⁴⁷

Prognostic factors associated with better outcomes in low-grade gliomas include age younger than 40 years, a tumor that is less than 6 cm at its largest diameter, a tumor that does not cross the midline of the brain,

histology subtype (oligodendroglioma or mixed types have better outcomes than astrocytomas), and no neurologic deficits before surgery.⁴⁸ Prognostic factors associated with better outcomes in high-grade gliomas include lower tumor grade, younger age, better functional status, greater extent of resection, and hypermethylation of the *MGMT* gene promoter.^{46,49,50}

Further Information

More information on primary brain tumors is available from the National Cancer Institute (<http://www.cancer.gov/types/brain/hp>) and the National Brain Tumor Society (<http://braintumor.org/brain-tumor-information>).

Data Sources: A PubMed search was completed in Clinical Queries using the key terms primary, brain, and tumor. The search included meta-analyses, randomized controlled trials, and reviews. Also searched were Agency for Healthcare Research and Quality clinical guidelines, Cochrane Database of Systematic Reviews, Google Scholar, National Guideline Clearinghouse database, and Essential Evidence Plus. A scoping review of pertinent articles was used to expand the search of relevant articles. Search dates: November 1, 2014, and November 22, 2015.

NOTE: This review updates a previous article on this topic by Chandana and colleagues.¹³

The Authors

ALLEN PERKINS, MD, MPH, is chairman of the Department of Family Medicine at the University of South Alabama, Mobile.

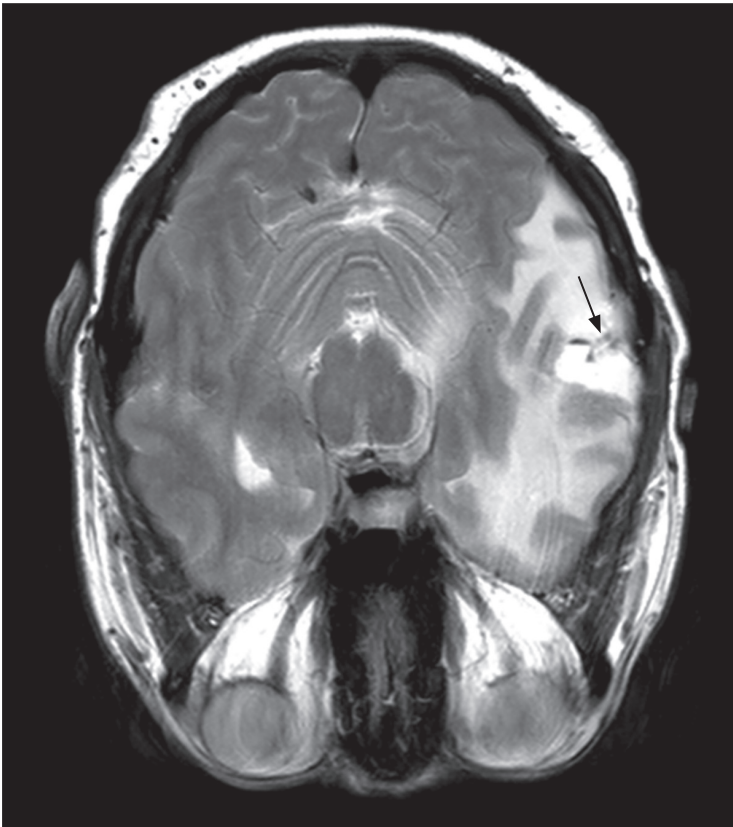
GERALD LIU, MD, is a physician with Harvard Vanguard Medical Associates in Weymouth, Mass. At the time this article was written, he was an assistant professor in the Department of Family Medicine at the University of South Alabama.

Address correspondence to Allen Perkins, MD, MPH, University of South Alabama, 1504 Springhill Ave., Ste. 3414, Mobile, AL 36604. Reprints are not available from the authors.

REFERENCES

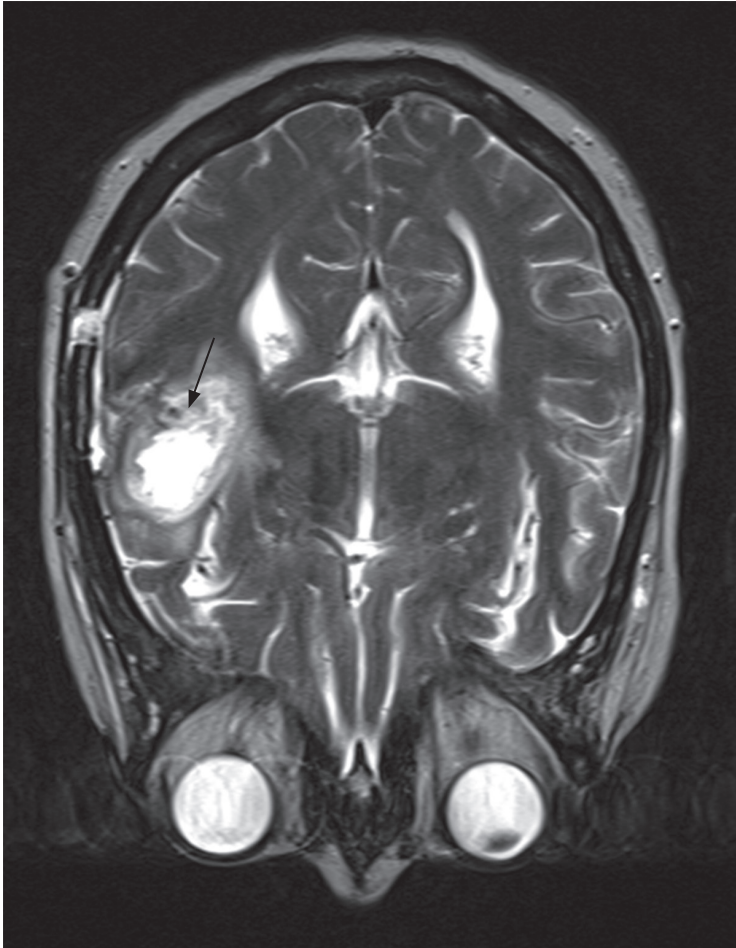
1. Howlader N, et al. SEER cancer statistics review, 1975-2012. http://seer.cancer.gov/csr/1975_2012. Accessed November 18, 2015.
2. Farrell CJ, Plotkin SR. Genetic causes of brain tumors. *Neurol Clin.* 2007;25(4):925-946, viii.
3. Lu Q, Dai D, Zhao W, et al. Association between MTHFR 677C>T polymorphism and risk of gliomas. *Tumour Biol.* 2013;34(5):2801-2807.
4. Zhang H, Liu H, Knauss JL. Associations between three XRCC1 polymorphisms and glioma risk. *Tumour Biol.* 2013;34(5): 3003-3013.
5. Fisher JL, Schwartzbaum JA, Wrensch M, Berger MS. Evaluation of epidemiologic evidence for primary adult brain tumor risk factors using evidence-based medicine. *Prog Neurol Surg.* 2006;19:54-79.
6. Ostrom QT, et al. Primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. *Neuro Oncol.* 2014;16(suppl 4): iv1-iv63.
7. Louis DN. WHO classification of tumours of the central nervous system. 4th ed. Lyon, France: International Agency for Research on Cancer; 2007.
8. Grant R. Overview: brain tumour diagnosis and management/Royal College of Physicians guidelines. *J Neurol Neurosurg Psychiatry.* 2004; 75(suppl 2):ii18-ii23.

9. Newton HB. Primary brain tumors: review of etiology, diagnosis and treatment. *Am Fam Physician*. 1994;49(4):787-797.
10. Chang SM, Parney IF, Huang W, et al. Patterns of care for adults with newly diagnosed malignant glioma. *JAMA*. 2005;293(5):557-564.
11. Youland RS, Schomas DA, Brown PD, et al. Changes in presentation, treatment, and outcomes of adult low-grade gliomas over the past fifty years. *Neuro Oncol*. 2013;15(8):1102-1110.
12. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. *Neurology*. 1993;43(9):1678-1683.
13. Chandana SR, Movva S, Arora M, Singh T. Primary brain tumors in adults. *Am Fam Physician*. 2008;77(10):1423-1430.
14. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol*. 2004;3(3):159-168.
15. Bradley WG Jr, Waluch V, Yadley RA, Wycoff RR. Comparison of CT and MR in 400 patients with suspected disease of the brain and cervical spinal cord. *Radiology*. 1984;152(3):695-702.
16. Jacobs AH, Kracht LW, Gossman A, et al. Imaging in neurooncology. *NeuroRx*. 2005;2(2):333-347.
17. Treister D, Kingston S, Hoque KE, Law M, Shiroishi MS. Multimodal magnetic resonance imaging evaluation of primary brain tumors. *Semin Oncol*. 2014;41(4):478-495.
18. Purdy RA, Kirby S. Headaches and brain tumors. *Neurol Clin*. 2004;22(1):39-53.
19. Soffietti R, Cornu P, Delattre JY, et al. EFNS Guidelines on diagnosis and treatment of brain metastases. *Eur J Neurol*. 2006;13(7):674-681.
20. Omuro AM, Leite CC, Mokhtari K, Delattre JY. Pitfalls in the diagnosis of brain tumours. *Lancet Neurol*. 2006;5(11):937-948.
21. National Cancer Institute. Adult central nervous system tumors treatment (PDQ). Updated August 25, 2015. <http://www.cancer.gov/cancertopics/pdq/treatment/adultbrain/Patient/>. Accessed November 18, 2015.
22. National Institute for Health and Care Excellence. Guidance on cancer services. Improving outcomes for people with brain and other CNS tumours. The manual. June 2006. <https://www.nice.org.uk/guidance/csgbraincns/evidence/improving-outcomes-for-people-with-brain-and-other-cns-tumours-the-manual-2>. Accessed October 13, 2015.
23. Fadul C, Wood J, Thaler H, et al. Morbidity and mortality of craniotomy for excision of supratentorial gliomas. *Neurology*. 1988;38(9):1374-1379.
24. Hentschel SJ, Sawaya R. Optimizing outcomes with maximal surgical resection of malignant gliomas. *Cancer Control*. 2003;10(2):109-114.
25. Tsitlakidis A, Foroglou N, Venetis CA, et al. Biopsy versus resection in the management of malignant gliomas: a systematic review and meta-analysis. *J Neurosurg*. 2010;112(5):1020-1032.
26. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. *Neurosurgery*. 2008;62(4):753-764.
27. Sanai N, Berger MS. Operative techniques for gliomas and the value of extent of resection. *Neurotherapeutics*. 2009;6(3):478-486.
28. Keime-Guibert F, Chinot O, Taillandier L, et al.; Association of French-Speaking Neuro-Oncologists. Radiotherapy for glioblastoma in the elderly. *N Engl J Med*. 2007;356(15):1527-1535.
29. Walker MD, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. *J Neurosurg*. 1978;49(3):333-343.
30. Mehta MP, Won M, Shaw EG, et al. Mature survival data from RTOG 9802: A phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) for adult patients with high-risk low-grade glioma (LGG). *Int J Radiat Oncol*. 2014;90(1 suppl):S37-S38.
31. Rock K, McArdle O, Forde P, et al. A clinical review of treatment outcomes in glioblastoma multiforme. *Br J Radiol*. 2012;85(1017):e729-e733.
32. Hart MG, Grant R, Garside R, et al. Chemotherapy wafers for high grade glioma. *Cochrane Database Syst Rev*. 2011;(3):CD007294.
33. Hart MG, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. *Cochrane Database Syst Rev*. 2013;(4):CD007415.
34. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10):997-1003.
35. Quon H, Abdulkarim B. Adjuvant treatment of anaplastic oligodendrogliomas and oligoastrocytomas. *Cochrane Database Syst Rev*. 2008;(2):CD007104.
36. Chang SM, et al. Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. *J Neurosurg*. 2003;98(6):1175-1181.
37. McGirt MJ, Chaichana KL, Attenello FJ, et al. Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. *Neurosurgery*. 2008;63(4):700-707.
38. Deutsch MB, Panageas KS, Lassman AB, Deangelis LM. Steroid management in newly diagnosed glioblastoma. *J Neurooncol*. 2013;113(1):111-116.
39. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. *Cancer*. 2000;89(3):640-646.
40. Lyman GH, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014. *J Clin Oncol*. 2015;33(6):654-656.
41. van Breeem MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours. *Lancet Neurol*. 2007;6(5):421-430.
42. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. *Neurology*. 2000;54(10):1886-1893.
43. Sirven JI, Wingerchuk DM, Drazkowski JF, et al. Seizure prophylaxis in patients with brain tumors. *Mayo Clin Proc*. 2004;79(12):1489-1494.
44. Catt S, Chalmers A, Fallowfield L. Psychosocial and supportive-care needs in high-grade glioma. *Lancet Oncol*. 2008;9(9):884-891.
45. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol*. 2009;27(22):3712-3722.
46. Krex D, Klink B, Hartmann C, et al. Long-term survival with glioblastoma multiforme. *Brain*. 2007;130(pt 10):2596-2606.
47. Ohgaki H, Kleihues P. Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol*. 2005;64(6):479-489.
48. Pignatti F, van den Bent M, Curran D, et al.; European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group; European Organization for Research and Treatment of Cancer Radiotherapy Cooperative Group. Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol*. 2002;20(8):2076-2084.
49. Jeremic B, Milicic B, Grujicic D, Dagovic A, Aleksandrovic J, Nikolic N. Clinical prognostic factors in patients with malignant glioma treated with combined modality approach. *Am J Clin Oncol*. 2004;27(2):195-204.
50. Laws ER, Parney IF, Huang W, et al.; Glioma Outcomes Investigators. Survival following surgery and prognostic factors for recently diagnosed malignant glioma. *J Neurosurg*. 2003;99(3):467-473.



eFigure A. A 56-year-old woman with an 80 pack-year smoking history presented with a 2-week history of sinus fullness, congestion, and new-onset frontal headaches, which she attributed to a sinus infection. Following 2 weeks of conservative therapy, magnetic resonance imaging was obtained. Findings included a large heterogeneous enhancing mass (*arrow*) within the right temporal lobe, with extensive edema, several satellite lesions, and a 1-cm midline shift consistent with metastatic disease. Pathology obtained at emergency decompression showed metastatic adenocarcinoma of the lung. Chest computed tomography revealed a primary lesion on the right upper lobe.

Primary Brain Tumors



eFigure B. A 52-year-old woman with a history of cerebrovascular accident presented with a nonspecific headache. Conservative measures were unsuccessful, and she developed vertigo over the next 6 weeks. Magnetic resonance imaging revealed a 3.8- × 3.2-cm, well marginated, left-sided mass with surrounding edema (*arrow*). Differential diagnosis included metastasis, lymphoma, and glioblastoma. Subsequent brain biopsy revealed glioblastoma (World Health Organization grade IV).