Intracranial neoplasms can arise from any of the structures or cell types present in the cranial vault, including the brain, meninges, pituitary gland, skull, and even residual embryonic tissue. The overall annual incidence of primary brain tumors in the United States is 18.7 cases per 100,000 population.

The most common primary brain tumors are meningiomas, representing 30% of all primary brain tumors, and gliomas, representing 40% of all primary brain tumors; many of these tumors are clinically aggressive and high grade. Primary brain tumors are the most common of the solid tumors in children and the second most frequent cause of cancer death after leukemia in children.

Brain metastases occur in approximately 15% of cancer patients as a result of hematogeneous dissemination of systemic cancer, and the incidence may be rising due to better control of systemic disease. Lung and breast cancers are the most common solid tumors that metastasize to the central nervous system (CNS). Melanoma and testicular and renal carcinomas have the greatest propensity to metastasize to the brain, but their relative rarity explains the low incidence of these neoplasms in large series of patients with brain metastases. Patients with brain metastases from nonpulmonary primaries have a 70% incidence of lung metastases. Although many physicians presume that all brain metastases are multiple, in fact, half are single and many are potentially amenable to focal therapies.

**Epidemiology**

**Gender** There is a slight predominance of primary brain tumors in men.
Primary brain tumors have a bimodal distribution, with a small peak in the pediatric population and a steady increase in incidence with age, beginning at age 20 years and reaching a maximum of 20 cases per 100,000 population between the ages of 75 and 84 years.

**Etiology and risk factors**

The cause of primary brain tumors is unknown, although genetic and environmental factors may contribute to their development.

**Genetic factors** Clear heritable factors play a minor role in the genesis of primary brain tumors; less than 5% of patients with glioma have a family history of brain tumor. Several inherited diseases, such as tuberous sclerosis, neurofibromatosis type I, Turcot syndrome, and Li-Fraumeni cancer syndrome, predispose patients to the development of gliomas. However, these tumors tend to occur in children or young adults and do not account for the majority of gliomas that appear in later life. A large genomic study identified five risk loci for glioma susceptibility: 5p15.33 (TERT), 8q24.21 (CCDC26), 9p21.3 (CDKN2A-CDKN2B), 20q13.33 (RTEL1), and 11q23.3 (PHLDB1).

Loss of heterozygosity (LOH) on chromosomes 9p and 10q and p16 deletions are frequently observed in high-grade gliomas, with low-grade gliomas having the fewest molecular abnormalities. In oligodendrogliomas, 1p and 19q LOH and IDH1 mutations are associated with significantly improved survival.

**Molecular markers** One of the most useful markers, the epigenetic silencing of the *MGMT* (O6-methylguanine-DNA methyltransferase) DNA-repair gene by promoter methylation, is an independent prognostic factor in patients with glioblastoma and has been associated with longer survival in patients who received the alkylating agent temozolomide (Temodar). Epidermal growth factor receptor (EGFR) amplification and overexpression are present in about 60% of glioblastomas. Molecular markers of brain tumors can predict survival and will become increasingly important in the diagnosis and treatment of glioma.

**Environmental factors** Prior cranial irradiation is the only well-established risk factor for intracranial neoplasms.

**Lifestyle characteristics** Brain tumors are not associated with lifestyle characteristics such as cigarette smoking, alcohol intake, or cellular phone use.

**Signs and symptoms**

Brain tumors produce both nonspecific and specific signs and symptoms.

Nonspecific symptoms include headaches, which occur in about half of patients but are rarely an isolated finding of intracranial tumors, and nausea and vomiting, which are caused by an increase in intracranial pressure. Because of the widespread availability of CT and MRI, papilledema is now seen in < 10% of patients, even when symptoms of raised intracranial pressure are present.
Mutations of the isocitrate dehydrogenase genes (IDH1 and IDH2) are early glioma-initiating events and are seen in the majority of low-grade gliomas (Yan H et al: N Engl J Med 360:765–773, 2009).

**Specific signs and symptoms** are usually referable to the particular intracranial location of the tumor and are similar to the signs and symptoms of other intracranial space-occupying masses.

*Lateralizing signs*, including hemiparesis, aphasia, and visual-field deficits, are present in ~50% of patients with primary and metastatic brain tumors.

*Seizures* are a common presenting symptom, occurring in ~25% of patients with high-grade gliomas, at least 50% of patients with low-grade tumors, and 50% of patients with metastases from melanoma, perhaps due to their hemorrhagic nature. Otherwise, seizures are the presenting symptom in 15% to 20% of patients with brain metastases. Seizures may be generalized, partial, or focal.

Several studies have identified glioblastoma subtypes based on gene expression profiles. Proneural, neural, classic, and mesenchymal subtypes were described. Proneural tumors were more likely to carry mutations of *IDH1* and *p53* and were associated with improved overall survival. Classic tumors frequently (95%) showed amplification of *EGFR*. Mesenchymal tumors were most likely to have mutations or deletions of *NF1*, several of which were comutated with *PTEN*. They also had higher activity of mesenchymal and astrocytic markers CD44 and MERTK, as well as high expression of *CHI3L* and *MET*, and had the shortest overall survival (Verhaak RG et al: Cancer Cell 17:98–110, 2010).

*Stroke-like presentation* Hemorrhage into a tumor may present like a stroke, although the accompanying headache and alteration of consciousness usually suggest an intracranial hemorrhage rather than an infarct. Hemorrhage is usually associated with high-grade gliomas, occurring in 5% to 8% of patients with glioblastoma. However, oligodendroglialomas have a propensity to bleed, and hemorrhage occurs in 7% to 14% of these low-grade neoplasms. Sudden visual loss and fatigue may be seen with bleeding into or infarction of pituitary tumors, termed *pituitary apoplexy*.

*Altered mental status* Approximately 75% of patients with brain metastases, and as many as half of patients with malignant gliomas, have impairment of consciousness or cognitive function. Some patients with multiple bilateral brain metastases may present with an altered sensorium as the only manifestation of metastatic disease; this finding can be easily confused with metabolic encephalopathy.

**Screening for metastatic brain tumors**

Screening for brain metastases is performed in only a few clinical situations.

**Lung cancer** Approximately 10% of patients with small-cell lung cancer (SCLC) have brain metastases at diagnosis, and an additional 20% to 25% develop such metastases during their illness. Therefore, cranial CT or MRI is performed as part of the initial evaluation for extent of disease.

Occasionally, patients with non–small-cell lung cancer (NSCLC) undergo routine cranial CT or MRI prior to definitive thoracotomy, because the presence of brain metastases may influence the choice of thoracic surgical procedure. This approach is particularly valuable in patients with suspected stage IIB or III disease for whom thoracotomy is considered following neoadjuvant therapy.
Diagnosis

**Radiographic appearance of primary lesions**

MRI The diagnosis of a brain tumor is best made by cranial MRI. This should be the first test obtained in a patient with signs or symptoms suggestive of an intracranial mass. MRI is superior to CT and should always be obtained with and without contrast material such as gadolinium.

![Figure 1](http://www.cancernetwork.com/cancer-management/primary-metastic-brain-tumors/article/10165/1802_718)

FIGURE 1 T1-weighted MRI with gadolinium contrast showing a typical appearance of a glioblastoma. Non–contrast-enhanced images of this lesion (not shown) revealed the presence of some hemorrhage.

High-grade or malignant primary brain tumors appear as contrast-enhancing mass lesions that arise in white matter and are surrounded by edema (Figure 1). Multifocal malignant gliomas are seen in ~5% of patients.

Low-grade gliomas typically are nonenhancing lesions that diffusely infiltrate and tend to involve a large region of the brain. Low-grade gliomas are usually best appreciated on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI scans (Figure 2). As many as 40% of nonenhancing tumors may harbor foci of high-grade glioma.

CT A contrast-enhanced CT scan may be used if MRI is unavailable or the patient cannot undergo MRI (eg, because of a pacemaker). CT is adequate to exclude brain metastases in most patients, but it can miss low-grade tumors or small lesions located in the posterior fossa. Tumor calcification is often better appreciated on CT than on MRI.

![Figure 2](http://www.cancernetwork.com/cancer-management/primary-metastic-brain-tumors/article/10165/1802_718)

FIGURE 2 FLAIR MRI demonstrating a diffusely infiltrating, low-grade oligodendroglioma involving the right frontal and temporal lobes. This lesion did not enhance with gadolinium.

PET Body positron emission tomography (PET) scans performed for staging of systemic malignancies have a sensitivity of only 75% and a specificity of 83% for identification of cerebral metastases. Therefore, they are less accurate than MRI, which remains the gold standard.

**Radiographic appearance of metastatic lesions** On CT or MRI, most brain metastases are enhancing lesions surrounded by edema, which extends into the white matter (Figure 3). Unlike primary brain tumors, metastatic lesions rarely involve the corpus callosum or cross the midline.
The radiographic appearance of brain metastases is nonspecific and may mimic other processes, such as infection. Therefore, the CT or MRI scan must always be interpreted within the context of the clinical picture of the individual patient, particularly as cancer patients are vulnerable to opportunistic CNS infections or may develop second primaries, which can include primary brain tumors.

Other imaging tools Magnetic resonance spectroscopy (MRS) and perfusion imaging can help differentiate low-grade from high-grade brain tumors but cannot distinguish different tumor types of the same grade.

Pathology

Glial tumors arise from astrocytes, oligodendrocytes, or their precursors and exist along a spectrum of malignancy. The astrocytic tumors are graded, using the four-tier World Health Organization (WHO) system. Grade I tumors are localized tumors called pilocytic astrocytomas, which are usually found in children and may be associated with neurofibromatosis type I. Grade II tumors are low-grade diffuse fibrillary astrocytomas. Grade III (anaplastic astrocytoma) and IV (glioblastoma) tumors are high-grade malignant neoplasms. Grading is based on pathologic features, such as endothelial proliferation, cellular pleomorphism, mitoses, and necrosis. The oligodendroglial neoplasms are classified as either the low-grade oligodendroglioma (grade II) or the anaplastic oligodendroglioma (grade III).
Primitive neuroectodermal tumors (PNETs) are high-grade, aggressive tumors that usually occur in children. They include pineoblastoma and neuroblastoma. Histologically, they are identical to medulloblastomas, but their prognosis is usually worse than that for medulloblastomas. Thus, their biology is different, even though they may be similar pathologically.

![Image](image_url)

**FIGURE 4** T1-weighted MRI with gadolinium contrast showing the typical appearance of a meningioma. Note the dural-based 'tail.'

**Extra-axial tumors** The most common extra-axial tumor is the meningioma. Meningiomas are usually benign tumors that arise from residual mesenchymal cells in the meninges. They produce neurologic symptoms by compressing the underlying brain. Meningiomas rarely are malignant or invade brain tissue (Figure 4).

Other common extra-axial tumors include pituitary adenoma, epidermoid or dermoid tumors, and acoustic neuroma (vestibular schwannoma). Most extra-axial tumors have a benign histology but can be locally invasive. Many extra-axial benign tumors are incidentally identified on MRI imaging performed for nonspecific symptoms such as headache. Most of these tumors do not require therapy and do not enlarge. Many benign extra-axial tumors identified in this way can be observed with serial imaging studies alone.

**Metastatic brain tumors** The pathology of metastatic brain lesions recapitulates the pathology of the underlying primary neoplasm. This feature often enables the pathologist to suggest the primary source in patients whose systemic cancer presents as brain metastasis. However, even after a complete systemic evaluation, the site of the primary tumor remains unknown in 5% to 13% of patients with brain metastases.

**Staging and prognosis**

**Staging** is not applicable to most primary brain tumors because they are locally invasive and do not spread to regional lymph nodes or distant organs. Staging with an enhanced complete spinal MRI and cerebrospinal fluid (CSF) evaluation is important for a few primary tumor types, such as medulloblastoma, ependymoma, and PNET, because they can disseminate via the CSF. All systemic cancers are stage IV when they present with brain metastasis.

**Prognostic factors** For patients with primary brain tumors, prognosis is inversely related to several important factors, including pathologic grade and patient age, and is directly related to the overall clinical condition at diagnosis. Several molecular markers that correlate well with prognosis have been identified recently, such as \( IDH1 \) mutations and LOH on chromosomes 1p and 19q in anaplastic oligodendroglioma.
With conventional treatment, including surgical resection, radiotherapy, and 40 years old with low-grade glioma generally have a more aggressive disease; their median survival is usually < 5 years.

For a large proportion of patients with brain metastases, median survival is only 4 to 6 months after whole-brain radiotherapy. However, some patients (ie, those who are < 60 years old, have a single lesion, or have controlled or controllable systemic disease) can achieve prolonged survival, and these individuals warrant a more aggressive therapeutic approach. Furthermore, most of these patients qualify for vigorous local therapy for their brain metastases, such as surgical resection or, stereotactic radiosurgery. These approaches can achieve a median survival of 40 weeks or longer, and rarely some patients are cured.

Treatment

Treatment of primary brain tumors and brain metastases consists of both supportive and definitive therapies.

SUPPORTIVE THERAPY

Supportive treatment focuses on relieving symptoms and improving the patient's neurologic function. The primary supportive agents are anticonvulsants and corticosteroids.

Anticonvulsants

Anticonvulsants are administered to the 25% of patients who have a seizure at presentation. Traditionally, phenytoin was the most commonly used medication, but carbamazepine and valproic acid are equally efficacious. Doses of all these anticonvulsants can be titrated to the appropriate serum levels to provide maximal protection.

Newer anticonvulsants, such as levetiracetam (Keppra), gabapentin, lamotrigine (Lamictal), and topiramate (Topamax), are preferred and have become the first choice in many patients. Most of these agents have the advantages of causing fewer cognitive side effects, and because they do not induce the hepatic microsomal system, they do not alter the metabolism of chemotherapeutic agents. Serum levels of these agents are less reliable than those of older drugs. These agents should replace the older drugs as first-line antiepileptic therapy in most patients.

Prophylaxis

Prospective studies have failed to show the efficacy of prophylactic anticonvulsants for patients with brain tumors who have not had a seizure. Consequently, prophylactic anticonvulsants should not be administered, except during the perioperative period, when their use may reduce the incidence of postoperative seizures; the drugs can be tapered off within 2 weeks of surgery. Increasingly, the new agents are being used for prophylaxis.

Corticosteroids

Corticosteroids reduce peritumoral edema, diminishing mass effect and lowering intracranial pressure. This effect produces prompt relief of headache and improvement of lateralisiting signs. Dexamethasone is the corticosteroid of choice because of its minimal mineralocorticoid activity. The starting dose is ~16
mg/d, but this dose is adjusted upward or downward to reach the minimum dose necessary to control neurologic symptoms. In patients whose MRI is suggestive of CNS lymphoma, urgent biopsy should precede the initiation of steroids.

Long-term corticosteroid use is associated with hypertension, diabetes mellitus, a nonketotic hyperosmolar state, myopathy, weight gain, insomnia, and osteoporosis. Thus, the steroid dose in patients with a brain tumor should be tapered as rapidly as possible once definitive treatment has begun. Most patients can stop taking steroids by the time they have completed cranial irradiation. All patients taking corticosteroids for more than 6 weeks should be on antibiotic prophylaxis for *Pneumocystis jiroveci* (formerly *carinii*) pneumonia. Prophylaxis should continue for 1 month after the steroids have been discontinued. This practice is without supporting evidence (as shown in a large Cochrane review), although it is routinely used.

DEFINITIVE THERAPY: primary brain tumors

Definitive treatment of brain tumors includes surgery, radiation therapy, and chemotherapy. The first step is to devise an overall therapeutic plan that should outline the sequence and elements of multidisciplinary therapy.

**Surgery**

Various surgical options are available, and the surgical approach should be carefully chosen to maximize tumor resection while preserving vital brain structures and minimizing the risk of postoperative neurologic deficits. The goals of surgery include (1) obtaining an accurate histologic diagnosis; (2) reducing tumor burden and associated mass effect caused by the tumor and/or peritumoral edema; (3) maintaining or re-establishing pathways for CSF flow; (4) achieving a potential "cure" by gross total removal; and (5) reducing tumor burden prior to adjuvant irradiation or chemotherapy. Surgery for a primary brain tumor rarely achieves cure but can reduce tumor burden so that the tumor becomes more amenable to adjuvant irradiation or chemotherapy. In glioblastomas, resection of greater than 98% of tumor, as measured by postoperative MRI, is associated with improved survival. Similarly, improved survival has also been demonstrated for low-grade gliomas when gross total resection is achieved.

**Surgical tools** A variety of tools are available to help the neurosurgeon achieve these goals, including stereotactic and image-based guidance systems and electrophysiologic brain mapping.

Stereotactic frames provide a rigid, three-dimensional (3D) coordinate system for accurate targeting of brain lesions identified on CT or MRI scans and are particularly well suited for obtaining tissue for biopsy from tumors located in sites where aggressive tissue removal would produce unacceptable neurologic deficits. Limitations of stereotactic biopsy are that small volumes of tissue are obtained and that tissue sampling errors may result in a failure to reach a correct diagnosis. Stereotactic biopsy may be nondiagnostic in 3% to 8% of cases and has a surgical morbidity of approximately 5%.

**Image-based guidance system** "Frameless" or "image-guided" stereotactic systems use computer technology to coregister preoperative imaging studies with intraoperative head position, thereby establishing stereotactic accuracy without the need for a frame. These systems are useful for stereotactic biopsy or achieving maximal resections of predefined tumor volumes and minimizing surgical morbidity. Intraoperative MRI accomplishes similar goals but is limited by a requirement for specialized operating suites.
Intraoperative brain mapping, also termed cortical mapping, uses electrical stimulation of the cortical surface to define the primary motor, sensory, or speech cortex. By identifying the exact location of these areas prior to tumor resection, the surgeon can avoid these structures, thereby preserving neurologic function. These tools enable the neurosurgeon to perform more complete removal of tumors with less morbidity. Intraoperative MRI is being used in a number of centers to facilitate the complete removal of a tumor. Images are obtained before the operation is completed to assure removal of all visible tumor.

Pathology-based surgical approach for primary brain tumors The surgical approach to an intracranial lesion is strongly influenced by the suspected or previously confirmed pathology. Guidelines for the management of the most common tumors are discussed.

Meningiomas and other extra-axial tumors Benign extra-axial tumors, such as meningiomas, usually have a well-defined plane separating them from the surrounding brain parenchyma. In general, total extirpation can be achieved by open craniotomy, particularly when the tumor is located over the convexity. Firm attachment of the tumor to the dura, cranial nerves, vascular structures, or skull base may make this impossible. Subtotal resections that preserve neural or vascular structures while reducing mass effect are often favored for extensive skull base tumors.

The surgical management of other benign extra-axial tumors, such as acoustic neuroma, pineocytoma, choroid plexus papilloma, and pituitary adenoma, closely parallels that of meningiomas. Gross total resection is generally curative and should be attempted whenever safe.

Low-grade gliomas Gross total resection, whenever possible, is the goal of surgery for low-grade gliomas and mixed neuronal-glial tumors (eg, astrocytoma, oligodendroglioma, pilocytic astrocytoma, and ganglioglioma). Long-term survival is better in patients who have undergone gross total resection than in those who have had subtotal resection (5-year survival rates > 80% for gross total resection vs ~50% for subtotal resection).

If radiographically proven gross total resection is attained, postoperative irradiation or chemotherapy can often be withheld until there is evidence of tumor progression (see section on "Radiation therapy"). If a postoperative scan reveals a small but surgically accessible residual lesion, immediate reoperation should be considered, particularly in children or in those with pilocytic astrocytomas (WHO grade I).

When low-grade tumors are found in patients with medically refractory chronic epilepsy, surgical management should be oriented toward curing the epilepsy, as well as achieving total tumor removal.

Ependymomas Gross total resection is the goal of surgery whenever possible for ependymomas. Because ependymomas arise in the ventricular system, they can disseminate in the CSF. Therefore, all patients should be assessed for subarachnoid metastases with complete cranial and spinal MRI performed with gadolinium.

High-grade gliomas More extensive resections improve the quality of life and neurologic function of patients with high-grade gliomas (glioblastoma, anaplastic astrocytoma, and anaplastic oligodendroglioma) by reducing mass effect, edema, and steroid dependence. Resection of > 98% of the tumor volume prolongs survival relative to subtotal or partial resections, but extensive subtotal resections do not appear to confer any survival advantage over biopsy. For this reason, most neurosurgeons attempt to achieve maximal resection while minimizing the risk to critical areas of the brain.

Recurrent or progressive tumors When a brain tumor recurs or enlarges, reoperation is often necessary to reduce mass effect. Although rarely curative, these procedures can improve quality of life and
modestly extend survival. In general, reoperation is not considered in patients with a Karnofsky performance status (KPS) score > 60 or in those patients who are not candidates for additional therapy following surgery.

_Pseudoprogression_ describes an increase in contrast enhancement independent of tumor growth in patients who have recently received radiation therapy. It occurs most frequently (58%) within the first 3 months following radiation therapy and is more commonly seen after concurrent chemoradiation therapy. It is estimated that up to 50% of patients with an increase in enhancement have true tumor progression. However, in practice, current treatment is usually continued for at least 3 months to avoid discontinuing an effective therapy. Pseudoprogression may represent a more robust response to therapy and may correlate with _MGMT_ promoter methylation and a better therapeutic outcome. A recurrent tumor cannot be distinguished from radiation necrosis on routine MRI. Both disorders may cause severe mass effect and edema, and resection is the optimal treatment for both if the patient is symptomatic. Occasionally, PET or MRS can distinguish tumor from treatment effect, but these imaging modalities are unreliable.

Initial resection or reoperation followed by intracavitary or intraparenchymal administration of chemotherapy, immunotherapy, or liquid I-125 radiotherapy (GliaSite) is being explored but is still investigational. Carmustine (BiCNU)-impregnated wafers (Gliadel) are the only form of intracavitary chemotherapy currently approved by the FDA for glioblastoma.

**Radiation therapy**

Radiation therapy plays a central role in the treatment of brain tumors in adults. It is the most effective nonsurgical therapy for patients with malignant gliomas and also has an important role in the treatment of patients with low-grade gliomas and metastatic brain tumors.

_Whole-brain vs partial-brain irradiation_ Whole-brain irradiation is reserved for multifocal lesions, lesions with significant subependymal or leptomeningeal involvement, and metastatic brain tumors. For the majority of patients with unifocal disease, limited-field treatment results in less morbidity and appears to produce equal, albeit poor, overall survival.

Intensity-modulated radiotherapy (IMRT) is an advanced technique to deliver high-precision radiotherapy to a tumor. Treatment is planned using 3D CT images to design a dose that will conform to the 3D shape of the tumor. Using multiple beams, a uniform dose of RT is delivered to the whole tumor while sparing normal tissues.

**Radiation therapy for low-grade gliomas** Retrospective studies suggest a limited radiation dose response in low-grade gliomas. However, selection bias may play a role in these studies.

Several randomized studies addressed the question of optimal timing and dose of radiotherapy in patients with low-grade gliomas. An American intergroup randomized trial compared 50.4 vs 64.8 Gy of radiation in patients with low-grade glioma. An EORTC trial compared 45.0 vs 59.4 Gy of radiation in patients with low-grade astrocytoma. Both studies confirmed the superiority or equivalent efficacy of the lower radiation dose and less toxicity.

A second EORTC trial tested immediate vs delayed radiotherapy in individuals with low-grade glioma. Although immediate radiotherapy significantly improved 5-year progression-free survival, overall survival was identical in the two treatment arms. Furthermore, quality of life was better in patients whose radiotherapy was deferred until clinical or radiographic disease progression was evident.
**Recommended treatment approach for low-grade astrocytomas**

The role of postoperative radiotherapy in the management of incompletely resected low-grade astrocytomas has not been firmly established. However, based on the available data, the following principles appear reasonable:

- Complete surgical resection of hemispheric astrocytomas should be attempted.
- If complete surgical resection has been attained, radiation therapy can be withheld until MRI or CT studies clearly indicate a recurrence that cannot be approached surgically.
- When complete surgical resection is not performed, postoperative irradiation may be recommended, depending upon the patients' clinical condition.
- Radiation therapy should be delivered, using a megavoltage machine, in 1.7- to 2.0-Gy daily fractions, to a total dose of about 50 Gy. The treatment fields should include the primary tumor volume only, as defined by MRI, and should not encompass the whole brain.
- In low-grade astrocytomas, radiation therapy can be expected to produce a 5-year survival rate of 50% and a 10-year survival rate of 20%. Patients with low-grade oligodendrogliomas survive even longer.
- Cognitive impairment may develop in long-term survivors of low-grade gliomas. This may be due to the disease itself, surgical resection, antiepileptic drug use, and radiotherapy if used.

**Radiation therapy for high-grade gliomas**

An analysis of three studies of high-grade gliomas performed by the BTSG showed that postoperative radiotherapy doses > 50 Gy were significantly better in improving survival than no postoperative treatment and that 60 Gy resulted in significantly prolonged survival compared with 50 Gy. Doses greater than 60 Gy used in the American intergroup protocol resulted in competing morbidity.

Based on these data, involved-field radiotherapy to 60 Gy in 30 to 33 fractions is standard treatment for high-grade histologies; this amount corresponds to a dose just above the threshold for radionecrosis. About half of patients with anaplastic astrocytomas exhibit radiographic evidence of response following 60 Gy of radiation, compared with 25% of patients with glioblastoma. Complete radiographic response is rare in either case. Elderly patients with glioblastoma have a particularly poor prognosis, with a median survival of 4 to 6 months in most series. Some of these patients are not treated at all, but a randomized controlled study demonstrated that 50 Gy yields a significantly longer survival than supportive care alone (median of 29.1 weeks vs 16.9 weeks; \( P = .002 \)) without compromising quality of life. Such an abbreviated course of radiotherapy should be considered in patients older than 70 years of age.

**Alternatives to conventional radiotherapy**

The results of standard radiation treatment in patients with malignant gliomas are poor. Patients with glioblastoma have a median survival of 12 to 15 months, whereas patients with anaplastic astrocytomas survive a median of 3 years. To improve these poor results, a number of new approaches have been tried, including hyperfractionated radiotherapy (HFRT), focal dose escalation with interstitial brachytherapy, and radiosurgery, but none improved survival. Brachytherapy and HFRT have been abandoned.

Antiangiogenic therapy was found to be a highly effective treatment for radiation necrosis. All 5 of the 14 patients with radionecrosis initially randomized to receive bevacizumab (Avastin) and the 7 patients
who crossed over from the placebo arm had significant radiographic response and clinical improvement (Levin VA et al: Int J Radiat Oncol Biol Phys Apr 15, 2010 [E-pub ahead of print]).

**Radionecrosis** Both brachytherapy and stereotactic radiosurgery can induce focal radionecrosis. This complication produces symptoms of mass effect in about 50% of patients with malignant glioma, requiring resection to remove the necrotic debris. Occasionally, treatment with corticosteroids can control the edema around the radionecrotic area, but often the patient becomes steroid-dependent, with all of the attendant complications of chronic steroid use. Radionecrosis can be a significant limitation of the focal radiotherapy techniques.

**Recommended approach for extra-axial tumors** Surgery alone is curative in the vast majority of patients with benign tumors. However, in certain subsets of patients, postoperative radiotherapy may control further growth of these lesions.

*Pituitary adenomas* For hormonally inactive pituitary adenomas that persist or recur after surgery, 45 to 50 Gy is delivered in 25 to 28 fractions to the radiographic boundaries of the tumor. For Cushing disease and acromegaly, higher doses are required for biochemical remission. Coronal-enhanced MRI is critical for treatment planning, because CT often does not visualize the skull base and the entire extent of disease.

The most common indications for radiotherapy are invasion of the cavernous sinus or the suprasellar space and incomplete resection of macroadenomas (> 1.5 cm). Most pituitary lesions do not grow following radiotherapy, and hormonally active tumors usually demonstrate a hormonal response, with a reduction in hormone hypersecretion in 1 to 3 years. Following radiation therapy, 20% to 50% of patients develop panhypopituitarism, requiring hormone replacement therapy. Other significant complications (ie, damage to the visual apparatus) are rare today.

*Meningiomas* are readily curable with complete surgical resection. However, base of skull lesions and lesions involving a patent venous sinus often cannot be resected completely. For some patients with these lesions, a course of postoperative radiotherapy is indicated. In general, 54 Gy is delivered in 30 fractions to the radiographic tumor region utilizing 3D treatment planning. Malignant meningiomas always require postoperative radiotherapy, even after gross total resection. Radiosurgery may also be useful in treating meningiomas, and doses of 13 to 18 Gy are associated with a high rate of control 10 years following therapy.

The benefit of adding temozolomide (Temodar) to radiotherapy in newly diagnosed glioblastoma persists throughout 5 years of follow-up (Stupp R et al: Lancet Oncol 10:459–466, 2009).

*Acoustic neuroma* has classically been considered a surgical disease. Following total resection, recurrence rates are < 5%. When only subtotal resection is possible, disease recurs in at least 60% of patients.

Radiosurgery has been used as an alternative to surgery for acoustic neuroma. Tumor control rates of > 80% at 20 years have been reported. For patients with useful hearing prior to radiosurgery, that function is preserved in < 50%. After radiosurgery, 10% of patients experience facial weakness, and 25% have trigeminal neuropathy. The risk of cranial neuropathies is related to the size of the lesion treated.

*Chemotherapy*
The NOA-04 trial randomized patients with newly diagnosed anaplastic gliomas to receive either radiation (RT) followed by chemotherapy (randomized to either temozolomide [Temodar] or PCV) or chemotherapy followed by RT at the time of disease progression. Neither initial treatment selection nor chemotherapy type adversely affected progression-free survival, although time to disease progression after RT may be longer than after chemotherapy. In this study, IDH1 mutations more strongly influenced survival than codeletion of 1p/19q or MGMT methylation (Wick W et al: J Clin Oncol 27:5874–5880, 2009).

Malignant gliomas Chemotherapy has a limited but measurable benefit in the treatment of patients with malignant gliomas, and temozolomide is the most active agent.

In a large phase III trial, patients with newly diagnosed glioblastoma were randomized to receive radiotherapy alone or radiotherapy with concurrently administered temozolomide followed by adjuvant temozolomide. A total of 573 patients were studied, and median survival was significantly prolonged from 12.1 months to 14.6 months with the addition of temozolomide to radiotherapy. The 2-year survival rate was only 10% in those treated with radiotherapy alone compared with 27% in those who received radiotherapy plus temozolomide. The combined-modality regimen was well tolerated and associated with minimal additional toxicity. This regimen has now become the standard for all newly diagnosed patients with glioblastoma and combines the potential radiosensitizing effect of concurrent temozolomide with the benefit of adjuvant chemotherapy.

This study demonstrates clear benefit in patients with glioblastoma, and many investigators have extrapolated this regimen for use in patients with gliomas of all grades. Current practice varies from treating anaplastic astrocytoma with radiation therapy alone, to sequential radiotherapy and chemotherapy, to concurrent chemoradiation therapy. Two ongoing phase III trials are addressing this question.

Studies designed to improve upon the standard of care for newly diagnosed glioblastoma add another agent to chemoradiation therapy with temozolomide. Based on data that the glutaminergic system plays a role in glioblastoma cell proliferation and migration, talampanel, an alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor blocker, was given in addition to standard radiation and temozolomide. Median survival was 18.3 months, and those younger than 71 years had a median survival of 20.3 months. This finding compares favorably with a median survival in the EORTC study of radiation therapy and temozolomide of 14.6 months, despite having fewer patients on study with methylated MGMT.

Patients with newly diagnosed glioblastoma were given standard chemoradiation with temozolomide (Temodar) and were then randomized to receive 6 cycles of dose-dense (150 mg/m² on days 1–7 and 15–21) or metronomic (50 mg/m² daily) temozolomide. This regimen was followed by maintenance cis-retinoic acid. Median overall survival was 17.1 months, with an 80% 1-year survival in the dose-dense group, compared with 15.1 months and 69%, respectively, in the metronomic arm (Clarke JL et al: J Clin Oncol 27:3861–3867, 2009).

Despite initial treatment, all malignant gliomas eventually recur. At relapse, patients may benefit from re-resection or different chemotherapeutic agents such as procarbazine or lomustine (CeeNU). However, re-challenging with temozolomide at higher doses and using an alternate schedule may improve outcome. Patients with progressive grade III or IV glioma after standard temozolomide (150 to 200 mg/m² days 1–5) were given metronomic temozolomide at 50 mg/m² daily for up to 1 year or until disease progression. Six-month progression-free survival was 24%, and 1-year survival was 27% for
glioblastoma and 36% and 61%, respectively, for anaplastic glioma. Those deriving the greatest benefit from temozolomide re-challenge were patients whose disease progressed in the first 6 months of therapy and those whose disease progressed after initial treatment discontinuation.

Molecularly targeted agents have been a major focus of glioblastoma treatment in recent years. Randomized phase II trials have generated attention for their ability to expedite clinical testing of new agents. Unfortunately, targeted therapy has not been shown to be effective as single-agent therapy.

Cilengitide, an integrin receptor inhibitor, was given in a randomized phase II trial to patients with recurrent glioblastoma. Those receiving a dose of 2,000 mg twice weekly had an overall survival of 9.9 months. In another randomized phase II trial, patients with progressive glioblastoma were given either erlotinib (Tarceva) or cytotoxic chemotherapy with temozolomide or carmustine. Erlotinib compared unfavorably, with progression-free survival at 6 months of only 11% vs 24% in the control group. EGFRvIII mutation did not correlate with efficacy.

Recently, a phase III trial randomized patients to receive enzastaurin, a PKC-beta inhibitor, or lomustine for progressive glioblastoma. The 6-month progression-free survival rate was 11% for enzastaurin and 19% for lomustine.

Targeting anigogenesis has proven to be an effective approach to prolong progression-free survival at recurrence. Bevacizumab (Avastin), a monoclonal antibody that targets vascular endothelial growth factor (VEGF), recently received accelerated FDA approval for recurrent glioblastoma based on two studies. In the one study, patients with recurrent glioblastoma were given either bevacizumab alone or with irinotecan. Six-month progression-free and overall survival rates were 43% and 9.2 months, respectively, in the bevacizumab-alone group and 50% and 8.7 months in the combination group. Although bevacizumab frequently is combined with irinotecan, it is not clear how much benefit chemotherapy adds to bevacizumab alone. AZD2171 (cediranib), a VEGF receptor inhibitor, demonstrated a high radiographic response rate and was shown to normalize tumor vessels in recurrent glioblastoma patients and is undergoing further study.

Disease progression after vascular targeted agents may occur at the primary tumor site or a distant site in the brain. It may have an atypical imaging pattern with diffuse infiltration that is nonenhancing and seen only on MRI FLAIR sequences or more recently described on diffusion-weighted sequences. There has been no increase in intratumoral hemorrhage with the antiangiogenic agents, which makes them safe for use in patients with malignant gliomas. Hydroxyurea and imatinib (Gleevec) may also provide antitumor activity in some patients at recurrence. Current studies are using multitargeted approaches to enhance efficacy.

Astrocytomas Chemotherapy has no role in the initial treatment of low-grade astrocytomas, and often they have progressed to malignant tumors at the time of recurrence.

Oligodendroglioma In contrast, the oligodendroglioma is now recognized as a particularly chemosensitive primary brain tumor. This finding was first observed with the anaplastic oligodendroglioma but has recently been seen with the more common low-grade oligodendroglioma. Chemosensitivity of anaplastic and low-grade tumors is associated with loss of chromosomes 1p and 19q.

Several alkylating agents are active, but the best studied regimen is procarbazine (Matulane), lomustine, and vincristine (PCV), which produces response rates of 75% and 90% in malignant and low-grade oligodendrogliomas, respectively. However, two randomized controlled studies of newly diagnosed patients with anaplastic oligodendroglioma showed a significant delay in progression-free survival with
the addition of PCV to radiotherapy but no prolongation of overall survival. PCV is an active regimen but has largely been supplanted by temozolomide because of the significant myelosuppression, neuropathy, and asthenia associated with PCV. Consequently, chemotherapy is an important therapeutic modality and may be used as initial treatment in patients with low-grade tumors who require therapeutic intervention. This approach defers or eliminates the late cognitive toxicity associated with cranial irradiation in patients with low-grade tumors who can have relatively prolonged survival. Patients with malignant oligodendroglialomas require radiotherapy with or without chemotherapy for initial treatment.

**Definitive therapy: brain metastases**

**Surgery**

**Surgical approach for metastatic tumors** Most patients with brain metastases have a life expectancy of < 6 months, but the majority who undergo resection of a metastatic lesion followed by irradiation will die of systemic rather than intracranial disease.

Excision of metastatic brain tumors is rarely curative, however, as microscopic cells may be left behind. Nevertheless, the reduced tumor burden becomes more amenable to adjuvant irradiation and/or chemotherapy.

**Criteria** The decision whether to recommend surgery for metastatic brain tumors should be based on the following factors:

**Extracranial oncologic status** A comprehensive workup of the patient's extracranial oncologic status is necessary. Extensive critical organ metastases preclude surgery in favor of palliative irradiation as the sole therapy. Brain surgery should not be performed in patients with limited expected survival (3 to 6 weeks) based on extracranial disease.

**Number of metastases** In general, only patients harboring a single metastasis are considered for resection. Occasionally, a large tumor will be removed in the presence of multiple smaller nodules if the edema and mass effect of this lesion are causing a substantial neurologic deficit that could be improved by tumor removal.

If brain metastasis is the presenting sign of systemic cancer and no clear primary source can be identified with routine staging, surgery may be required to establish a tissue diagnosis and plan further therapy.

In addition, surgical removal of a brain metastasis often reverses the neurologic deficits caused by compression of local structures by the tumor and reduces intracranial hypertension. After complete excision of a single brain metastasis, postoperative whole-brain radiotherapy improves control of neurologic disease but does not prolong survival.

Three studies have concluded that when multiple (up to three distinct locations) metastases are resected, either with or without radiotherapy, survival times are identical to those in patients with a surgically resected single metastasis and almost twice as long as those in patients treated by radiation therapy or radiosurgery alone. These studies suggest that a more aggressive surgical approach may be justified in patients with multiple brain metastases who have stable systemic disease.
**Recurrence of solitary metastases** Up to 20% of single metastases may recur in long-term survivors. In these cases, a second operation may be warranted to remove the recurrent lesion and confirm the histologic diagnosis (ie, exclude radionecrosis).

**Radiotherapy**

**Radiation therapy for metastatic brain tumors** For symptomatic patients with brain metastases, median survival is about 1 month if untreated and 3 to 6 months if whole-brain radiation therapy is delivered, with no significant differences among various conventional radiotherapy fractionation schemes (20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in 20 fractions). A more protracted schedule is used for patients who have limited or no evidence of systemic disease or for those who have undergone resection of a single brain metastasis, as these patients have the potential for long-term survival or even cure. The use of hypofractionated regimens is associated with an increased risk of neurologic toxicity.

The addition of the radiosensitizer motexafin gadolinium to whole-brain radiotherapy did not improve survival or time to neurologic disease progression in a randomized phase III trial. Subgroup analysis suggested a prolonged time to neurocognitive disease progression in patients with brain metastases from lung cancer. A new study has confirmed these findings.

**Relief of neurologic symptoms** The major result of whole-brain radiation therapy is an improvement in neurologic symptoms, such as headache, motor loss, and impaired mentation. The overall response rate ranges from 70% to 90%. Unfortunately, symptomatic relief is not permanent, and symptoms recur with intracranial tumor progression.

**Multiple lesions** Patients with multiple lesions are generally treated with whole-brain radiation therapy alone. Retreatment with a second course of whole-brain radiation therapy can provide further palliation for patients with progressive brain metastases (who have at least a 6-month or longer remission of symptoms after the initial course of cranial irradiation).

**Concomitant steroid therapy** Because the radiographic and clinical responses to whole-brain irradiation take several weeks, patients with significant mass effect should be treated with steroids during whole-brain radiation therapy. Dexamethasone (16 mg/d) is started prior to therapy, and the dose may be tapered as tolerated during treatment. Occasionally, higher doses are necessary to ameliorate neurologic symptoms. However, most patients can be safely tapered off corticosteroids at the completion of whole-brain radiotherapy.

**Radiosurgery for metastatic brain tumors** In patients with one to three brain metastases, aggressive local therapy (surgical resection or radiosurgery) produces superior survival and quality of life compared with whole-brain radiation therapy alone. Radiosurgery may be the optimal choice for elderly patients at greater risk for surgical morbidity. Radiosurgery has been used as sole therapy, as a boost to whole-brain radiation therapy, or for recurrent lesions in patients with brain metastases. Radiosurgery has the advantage of delivering effective focal treatment, usually in a single dose, without irradiating the normal brain. Radiosurgery of brain metastases < 1 cm achieves 1- and 2-year local tumor control rates of 86% and 78%, respectively, significantly better than 56% and 24% for lesions > 1 cm. It is particularly useful for patients who have one to three lesions, each < 4 cm in diameter. Patients with numerous lesions are not good candidates for radiosurgery because some of the ports may overlap, and, more importantly, these patients likely harbor other microscopic lesions in the brain that are not being treated effectively with such focal therapy.
Brain metastases are particularly amenable to treatment with radiosurgery. Metastatic tumors do not infiltrate the brain and tend to have well-circumscribed borders; therefore, they can be targeted effectively with highly focused irradiation techniques that maintain a sharp delineation between the enhancing tumor seen on neuroimaging and normal brain. Furthermore, radiosurgery does not have the operative morbidity that may be associated with resection of a brain metastasis. Consequently, it can be used safely in many patients who are not surgical candidates, and it can even treat lesions in surgically unapproachable locations such as the brainstem.

Radiosurgery can achieve crude local tumor control rates of 73% to 98% over a median follow-up of 5 to 26 months. Radiosurgery was initially used as a boost after treatment with whole-brain radiotherapy. Three randomized trials have reported on the value of radiosurgery in addition to whole-brain radiotherapy for patients with multiple brain metastases. Although all three studies show a local tumor control advantage and an improvement in quality-of-life endpoints with the addition of a radiosurgical boost, none shows a statistical advantage in survival. For patients with multiple brain metastases, adding radiosurgery to whole-brain radiotherapy only offers an improved neurologic quality of life with no impact on survival.


A prospective, randomized RTOG trial compared whole-brain radiotherapy alone vs whole-brain radiotherapy plus radiosurgery in patients with one to three metastases. Although there was no statistical improvement in overall survival in the two arms of the trial, a subset analysis showed improved survival for those patients with a single lesion. Local tumor control, neurologic function, and steroid doses were improved in patients with a single lesion treated with radiosurgery.

Radiosurgery is often considered an alternative to standard surgical resection, but it is unclear whether they are equivalent. Most retrospective studies suggest that the two techniques produce similar results; however, some reports indicate that surgery offers improved local tumor control, whereas others suggest that radiosurgery is superior.

Increasingly, radiosurgery is being used as the sole therapy for one to three brain metastases. A prospective randomized trial compared radiosurgery with or without whole-brain radiotherapy in patients with one to four brain metastases. Results were similar to those of the phase III trial of surgical resection of a single brain metastasis with or without radiotherapy: improved local tumor control but no survival benefit. Therefore, whole-brain radiotherapy reduced CNS relapse but had no impact on survival.

Median survival from the time of radiosurgery is 6 to 15 months, and some patients can live for years without recurrence. Most patients exhibit clinical improvement and decreased steroid requirement after radiosurgery, and only 11% to 25% of patients eventually die of neurologic causes.

**Chemotherapy**

**Metastatic brain tumors** Chemotherapy usually has a limited role in the treatment of brain metastases and has not proven to be effective as adjuvant therapy after irradiation or surgery. However, it may have some efficacy in patients with recurrent brain metastases who are not eligible for further whole-brain radiation therapy or stereotactic radiosurgery. In addition, chemotherapy has proven active in patients...
with asymptomatic brain metastases (discovered on screening neuroimaging) who are scheduled to receive chemotherapy for their systemic disease. We have seen patients with brain metastases from a variety of primary tumors respond in this situation. A recent phase III trial of chemotherapy with early vs delayed whole-brain radiotherapy in NSCLC patients with brain metastases showed an identical intracranial response rate and survival. Thus, systemic chemotherapy had some efficacy against brain metastases.

A recently completed phase II trial of temozolomide (75 mg/m²/d) and concurrent whole-brain radiotherapy (40 Gy in 20 fractions) vs whole-brain radiotherapy alone demonstrated improved response rates and neurologic improvement in the combined-modality arm. In addition, there is growing recognition that systemic chemotherapy, including targeted agents, can be effective against brain metastases when the drugs are selected based on the primary tumor. Capecitabine (Xeloda) is effective against brain metastases from breast cancer. High-dose methotrexate has activity against a number of primaries. Temozolomide has activity against recurrent brain metastases, particularly from NSCLC and melanoma.

Erlotinib has efficacy against brain metastases from lung cancer with the appropriate EGFR mutations.

**SUGGESTED READING**

**ON PRIMARY INTRACRANIAL TUMORS**


ON PRIMARY EXTRA-AXIAL TUMORS


ON METASTATIC BRAIN TUMORS


Abbreviations in this chapter
BTSG = Brain Tumor Study Group; EORTC = European Organisation for Research and Treatment of Cancer; RTOG = Radiation Therapy Oncology Group