Central Nervous System Tumors

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Central nervous system tumors are relatively common in the United States, with more than 40,000 cases annually. Although more than half of these tumors are benign, they can cause substantial morbidity. Malignant primary brain tumors are the leading cause of death from solid tumors in children and the third leading cause of death from cancer in adolescents and adults aged 15 to 34 years. Common presenting symptoms include headache, seizures, and altered mental status. Whereas magnetic resonance imaging helps define the anatomic extent of tumor, biopsy is often required to confirm the diagnosis. Treatment depends on the histologic diagnosis. Benign tumors are usually curable with surgical resection or radiation therapy including stereotactic radiation; however, most patients with malignant brain tumors benefit from chemotherapy either at the time of initial diagnosis or at tumor recurrence. Metastases to the brain remain a frequent and morbid complication of solid tumors but are frequently controlled with surgery or radiation therapy. Unfortunately, the mortality rate from malignant brain tumors remains high, despite initial disease control. This article provides an overview of current diagnostic and treatment approaches for patients with primary and metastatic brain tumors.


PATHOLOGY

Primary malignant central nervous system (CNS) tumors represent about 2% of all cancers but account for a disproportionate rate of morbidity and mortality. An estimated 43,800 new cases of benign and malignant brain tumors are diagnosed annually in the United States, including 3410 cases in children and adolescents. Of these patients, approximately 12,760 will die. The incidence of brain tumors is 14.8 per 100,000 person-years, with approximately half being histologically benign. Even benign tumors, if not amenable to excision or radiation therapy, can be fatal as a result of progressive growth in the closed space of the skull. Females have a slightly higher incidence (15.1/100,000 person-years) than males (14.3/100,000 person-years), likely because of the higher incidence of meningiomas in women. Malignant CNS tumors are the leading cause of death from solid tumors in children and the third leading cause of cancer-related death for adolescents and adults aged 15 to 34 years. The distribution of histologic diagnoses is illustrated in Table 1. Meningiomas are the most common benign brain tumor, and astrocytomas, including glioblastoma multiforme (GBM), are the most common malignant brain tumors.

Genetic predisposition to CNS tumors appears relatively uncommon, although gliomas may be inherited as a part of several familial diseases. Specifically, germline mutation of some known tumor-suppressor genes characterizes several genetic syndromes that carry an increased incidence of developing brain tumors: type 1 neurofibromatosis (mutation of NF1), Turcot syndrome (mutation of APC), basal cell nevus (or Gorlin) syndrome (mutation of PTCH), and Li-Fraumeni syndrome (mutation of TP53 or CHEK2) are associated with the greatest risk of brain tumors.

Environmental factors associated with primary brain tumors have been difficult to identify. One factor, exposure to vinyl chloride, has been associated with an increased incidence of high-grade gliomas. Also, ionizing radiation has been identified as a rare cause of primary brain tumors. For example, radiation treatment for children with tinea capitis or for acute lymphocytic leukemia, craniopharyngioma, or non-Hodgkin lymphoma has been associated with an increased risk of subsequent brain tumors, especially gliomas. Finally, the risk of primary CNS lymphoma, but not other types of primary brain tumors, is increased for patients infected with the human immunodeficiency virus.

Primary CNS tumors comprise a diverse range of pathologic entities, each with a distinct natural history. For simplicity, CNS tumors may be classified as gliomas or nongliomas. The most common gliomas are astrocytomas, oligodendrogliomas (or mixtures of oligodendroglioma and astrocytoma elements), and ependymomas (Table 2). Characteristic morphological and genetic features will be highlighted in the discussion of each tumor type. Uncommon astrocytoma variants, including pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma, tend to be well circumscribed and may be excised with curative intent. Unfortunately, most gliomas are characterized by diffuse infiltration of white matter tracts, making the surgical resection difficult.
DIAGNOSIS AND STAGING

The presenting symptoms of a brain tumor are related to mass effect, parenchymal infiltration, and tissue destruction. Headache, the most common presenting symptom, is related to mass effect and occurs in approximately 35% of patients. The new onset of headaches in a patient who has not previously had headaches is most characteristic, especially if the headaches are more severe in the morning and are associated with nausea, vomiting, or focal neurologic deficits. In patients with preexisting headaches, a change in the characteristics of the headaches or an increase in their frequency and/or intensity can also herald the presence of an intracranial mass. Seizures occur in approximately one-third of patients with gliomas, especially in patients with low-grade tumors. However, seizures may be associated with any CNS tumor. Focal neurologic deficits are related to the location of the tumor. Altered mental status may develop in 15% to 20% of patients with gliomas.4

Computed tomography (CT) of the brain typically reveals a mass that may or may not be enhanced with use of contrast medium. On CT, low-grade gliomas may be isodense with normal brain parenchyma and may not be enhanced with contrast medium. Also, lesions in the posterior fossa may not be identifiable on CT scans. Consequently, CT findings alone may be insufficient for a diagnosis. Magnetic resonance imaging (MRI) is more sensitive than CT for confirming the presence of a brain tumor. On T1-weighted MRI scans, a brain tumor appears as a mass lesion that may or may not be enhanced with contrast medium; there is always a signal abnormality on T2-weighted scans reflective of tumor as well as of vasogenic edema. Increased blood flow in the region of the tumor can be seen on MRI perfusion scans, whereas MRI diffusion shows reduced water movement, presumably secondary to increased cellularity and increased interstitial pressure. As a rule, more contrast enhancement is observed with higher grades of malignant disease. Ring enhancement is characteristic of GBM, with the enhanced portions corresponding to viable tumor and the T1 hypointense region corresponding to necrosis. Both MRI and positron emission tomography provide physiologic information about the tumor. Unfortunately, to date, the sensitivity and specificity of these techniques for particular tumor histology or radiation necrosis are too low to recommend their routine clinical use. Definitive diagnosis still requires a surgical biopsy or resection with histologic examination of the tissue.

Because most primary brain tumors remain localized to the intracranial compartment, systemic staging procedures are unnecessary. Primitive neuroectodermal tumors, such as medulloblastoma, CNS germ cell tumors, and primary CNS lymphoma, frequently spread by way of the subarachnoid space to the leptomeninges. Consequently, MRI of the spine should be performed for all patients with these diagnoses.

SURGERY

The goals of surgery are to obtain tissue for histologic diagnosis and analysis of molecular markers, to reduce surgical extirpation impossible. Nongliomas consist of typically benign tumors, such as meningiomas and pituitary adenomas, as well as malignant tumors, such as primitive neuroectodermal tumors (medulloblastomas), primary CNS lymphomas, and the rarely occurring CNS germ cell tumors.  

Accurate pathological diagnosis requires the review of an experienced tumor neuropathologist because the rate of discordance between general pathologists and neuropathologists is high. The diagnosis may change substantially for at least one-third of patients when pathological review is performed by an experienced neuropathologist.

### TABLE 1. Distribution of All Primary Brain and CNS Tumors by Histology, CBTRUS 1998-2002 (N=63,698)*

<table>
<thead>
<tr>
<th>Histology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>3.1</td>
</tr>
<tr>
<td>Nerve sheath</td>
<td>8.0</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>0.7</td>
</tr>
<tr>
<td>Pituitary</td>
<td>6.3</td>
</tr>
<tr>
<td>Glioblastoma†</td>
<td>20.3</td>
</tr>
<tr>
<td>Astrocytomas</td>
<td>9.8</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>2.3</td>
</tr>
<tr>
<td>Oligodendrogliomas</td>
<td>3.7</td>
</tr>
<tr>
<td>Embryonal, including medulloblastoma</td>
<td>1.7</td>
</tr>
<tr>
<td>Meningioma</td>
<td>30.1</td>
</tr>
<tr>
<td>All other</td>
<td>13.9</td>
</tr>
</tbody>
</table>

*CBTRUS = Central Brain Tumor Registry of the United States; CNS = central nervous system.

### TABLE 2. Distribution of All Primary Brain and CNS Gliomas by Histology Subtypes, CBTRUS 1998-2002 (N=25,539)*

<table>
<thead>
<tr>
<th>Histology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymomas</td>
<td>5.6</td>
</tr>
<tr>
<td>Oligodendrogliomas</td>
<td>9.2</td>
</tr>
<tr>
<td>Pilocytic astrocytomas†</td>
<td>5.7</td>
</tr>
<tr>
<td>Diffuse astrocytomas</td>
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<tr>
<td>Anaplastic astrocytomas</td>
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<tr>
<td>All other astrocytomas</td>
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</tr>
<tr>
<td>Glioblastomas</td>
<td>50.7</td>
</tr>
<tr>
<td>All other gliomas</td>
<td>10.1</td>
</tr>
</tbody>
</table>

*CBTRUS = Central Brain Tumor Registry of the United States; CNS = central nervous system.
mass effect while preserving neurologic function, to promote cytoreduction of the tumor, and to treat hydrocephalus, if present. Advances in neuroanesthesia, microneurosurgical techniques, and instrumentation have decreased the risk of surgery. When therapeutic intervention is deemed appropriate, surgery remains the initial therapy for nearly all patients with brain tumors and can be curative for most benign tumors, including meningiomas. Because of the infiltrative nature of most primary brain tumors, relief of mass effect and debulking result in symptomatic improvement and permit time for the safe administration of subsequent treatment. In low-grade infiltrative gliomas, an aggressive resection of the tumor appears to improve prognosis, provided neurologic risk is within acceptable limits. Current stereotactic technique allows for biopsy specimens to be obtained from nearly any part of the brain, including the brainstem. Biopsy is generally reserved only for patients with tumors in critical functional portions of the brain, where resection would result in unacceptable neurologic deficit. Patients with primary CNS lymphoma or CNS germ cell tumors may need biopsy only because primary treatment usually involves radiation therapy or chemotherapy or both.

For the aggressive resection of a tumor, surgical tools and technologies have been developed that facilitate tumor removal with low perioperative neurologic risk. For example, infiltrative gliomas in and around functioning brain regions can be more aggressively removed if the surgery is performed with the patient awake during segments of the operation. This technique allows the surgeon and attending neurology team to map brain cortical regions and their radiating white matter tracts, hence limiting injury. Another useful tool is computer-guided surgery, termed stereotaxis. Image-guided stereotaxis orients the tumor in 3-dimensional space, thereby allowing the neurosurgeon to plan a safer trajectory for tumor access. The most recent advance in stereotaxis is the development of intraoperative MRI, which provides the neurosurgeon with real-time updated data on tumor volume and location.

RADIATION THERAPY

External beam radiotherapy is an essential component of treatment for many patients with brain tumors. It can be curative for some patients and prolongs survival for most. Radiation is often the primary treatment modality for patients with metastatic brain tumors, epidural spinal cord compression, and leptomeningeal metastases. Whereas whole-brain radiation may be administered for certain tumors, such as medulloblastomas or primary CNS lymphomas, involved-field radiation using multiple field techniques has become the standard of treatment for most patients with gliomas. Involved-field radiation has been as effective as whole-brain radiation and reduces the dose of radiation to normal brain tissue, potentially reducing radiation-related damage. To have a therapeutic effect, radiation must cause less damage to normal tissue than to the tumor. Radiation treatments have been designed to deliver higher doses of radiation to tumor than to surrounding normal structures. The therapeutic ratio can also be improved biologically by exploiting the different radiosensitivities of normal tissues and tumors with fractionated radiotherapy. In general, normal tissues are better able to repair DNA damage than tumors because of aberrant cell cycle control mechanisms in tumors. However, a single large dose of radiation is able to overcome these repair mechanisms and damage normal tissues along with tumor (ie, radiosurgery). Given that normal cells are inherently superior to tumor cells at repairing sublethal damage, the therapeutic ratio could be improved by delivering multiple small doses of radiation.

An extreme form of focal radiotherapy used to treat many benign and neoplastic cranial conditions is stereotactic radiosurgery (SRS). The goal of SRS is to deliver a high radiation dose in a single fraction to an image-defined target while minimizing the radiation exposure to the adjacent tissues. In contrast to conventional fractionated radiation therapy, SRS does not rely on the increased radiation sensitivity of the target compared to the normal brain. Rather, SRS treatment spares normal structures by using conformal dose plans that deposit large radiation doses into the target with a rapid fall-off of radiation at the edges of the dose plan. Stereotactic radiosurgery uses multiple radiation beams and is able to encompass treatment volumes in the high-dose region with small margins because of stereotactic imaging and immobilization. The resulting rapid dose fall-off minimizes damage to normal brain tissues, thereby reducing risk to the surrounding structures. Stereotactic radiosurgery techniques have demonstrated efficacy for well-circumscribed lesions such as meningioma or limited brain metastases. However, for the infiltrative malignant tumors, the role of SRS remains under investigation. In a phase 3 trial, investigators found no survival advantage for patients who received radiation with stereotactic boost compared with patients who received standard radiation. Similarly, the clinical benefits of other focal radiation therapy techniques, such as interstitial brachytherapy or the use of radioactive isotopes, are still being investigated and are not recommended for routine clinical use.

Another innovation, stereotactic radiotherapy, combines the advantages of SRS (ie, minimizing damage to normal tissue by carefully targeting radiation) with the biological benefit of fractionation (ie, exploiting the differing radiosensitivities of normal tissues and neoplasms). These advantages are helpful when treating lesions near dose-limiting structures such as the optic nerves (Figure 1).
Intra-arterial chemotherapy, with or without blood-brain barrier disruption, appears to be effective for patients with chemosensitive tumors such as medulloblastomas or primary CNS lymphomas. However, intravenous or oral administration of effective drugs appears to offer comparable benefit. The use of high-dose chemotherapy and local administration of chemotherapy into the brain tumor have generally been disappointing. However, the US Food and Drug Administration has approved the use of carmustine-impregnated degradable polymers for the treatment of newly diagnosed gliomas and recurrent GBM. Even so, the median survival associated with that treatment is only slightly better than that associated with placebo, and the benefits are not long-lasting.

ANCILLARY THERAPEUTIC AGENTS

Corticosteroids, anticonvulsant drugs, and anticoagulant drugs are important ancillary agents for the treatment of patients with brain tumors. Corticosteroids are indispensible for controlling increased intracranial pressure and mass effect. Unfortunately, the long-term use of these agents can result in substantial toxic effects. Anticonvulsant drugs are sometimes administered prophylactically in the perioperative period. The use of anticoagulants is clearly indicated in patients who have had seizures; however, routine prophylactic anticonvulsant therapy should be discouraged in patients with no history of seizure because it has not been shown to benefit them in prospective randomized trials. Clinical trials have shown that some anticonvulsant agents, including phenytoin, phenobarbital, and carbamazepine, induce hepatic enzymes such as cytochrome P450 (especially CYP3A4/5) and glucuronidation enzymes. Induction of these enzymes substantially alters bioavailability of many chemotherapeutic agents and other drugs metabolized by the same enzyme systems, such as warfarin. The use of enzyme-inducing anticonvulsant drugs clearly reduces the blood concentration of camptothecins (topotecan and irinotecan) and taxanes (paclitaxel), but it is not known whether this reduction in drug concentration affects efficacy. In contrast, other more novel anticonvulsant drugs, such as levetiracetam, do not cause hepatic enzyme induction or inhibition and hence do not result in drug interactions, thereby simplifying other pharmaceutical interventions.

Clinically apparent deep vein thrombosis or pulmonary emboli that require anticoagulation drugs may occur in 20% to 30% of patients with primary brain tumors. Presumably, injury to brain parenchyma results in the release of tissue thromboplastins and increases the risk for clotting. Conventional therapy with heparin and warfarin is usually effective and well tolerated. Patients receiving anticoagulant agents that are maintained within the therapeutic range.
do not appear to have a greater risk of intracranial bleeding than those who do not need anticoagulant drugs.

**GLIOMAS**

**ASTROCYTOMAS**

Different grading systems have been used for astrocytomas, leading to considerable confusion. Since 1993, the 4-tiered grading system of the World Health Organization (WHO) has been the most widely accepted, if variably used, system. This grading system documents 4 key histologic features: increased cellularity, mitoses, endothelial proliferation, and necrosis.

According to the WHO classification system, grade 1 astrocytomas such as pilocytic astrocytoma are typically benign, grade 2 astrocytomas are diffuse infiltrating low-grade tumors with only increased cellularity, grade 3 (anaplastic) astrocytomas have mitoses, and grade 4 astrocytomas (GBM) have evidence of endothelial proliferation and/or tumor necrosis.

**Low-Grade Astrocytomas.** Low-grade astrocytomas may be either well circumscribed (grade 1, WHO) or diffusely infiltrating (grade 2, WHO). The circumscribed tumors include pilocytic astrocytomas, pleomorphic xanthoastrocytomas, subependymal giant cell astrocytomas, and subependymomas. These uncommon tumors can often be cured by resection. Even if resection is incomplete, the tumor may remain indolent or be successfully treated with radiation. In the rare instances in which local treatment fails, the value of chemotherapy is unclear, although the combination of carboplatin and vincristine has been reported to benefit children.

On CT scans, diffuse infiltrating low-grade astrocytomas typically appear as lesions with low attenuation or with isointensity. On MRI, the preferred diagnostic procedure, contrast agents may not enhance the imaging of these tumors or the enhancement may be wispy and faint. Focal intense enhancement may indicate areas of increased anaplasia. When feasible, biopsy should be performed to obtain a sample of the contrast-enhanced portion because the prognosis is typically related to the most anaplastic part of the tumor.

Most patients with low-grade astrocytomas are young adults (in their 20s and 30s) and typically present with seizures. Favorable prognostic features include younger age at diagnosis, tumor size of less than 5 cm, and, possibly, greater extent of tumor resection. The median survival is approximately 5 years. Late recurrences are relatively common, and patients should be followed up for at least 15 years.

Therapy for patients with low-grade astrocytoma is controversial. Despite their relatively indolent course, most astrocytomas eventually evolve into more anaplastic lesions and cannot be cured by surgery and radiation therapy. The role of complete surgical resection has been debated. The findings of some studies suggest that maximum tumor debulking is optimal. However, complete resection may be limited to a select group of patients with small unilateral tumors or tumors that do not involve critical brain structures. A practical approach is to resect as much of the abnormal tissue as possible without causing substantial neurologic deficit. Radiation therapy that begins immediately after diagnosis has been shown to extend the time to recurrence compared with radiation that is delayed until the time of tumor progression. However, currently, there is no convincing evidence that early radiation therapy improves overall survival (Figure 2).

For patients with few or no symptoms or with seizures that are controlled with anticonvulsant drugs, it is acceptable to defer radiation until symptomatic tumor growth is evident. The rationale for delaying radiation is to reduce the risk of radiation-induced neurologic damage. However, this rationale is questionable because of emerging evidence...
Anaplastic Astrocytomas. Patients with anaplastic astrocytoma may present with seizures, focal neurologic deficits, headaches, or changes in mental status. The median age at diagnosis is approximately 45 years. Magnetic resonance imaging usually indicates a contrast-enhanced mass lesion, although enhancement of some lesions may not be possible. Biopsy or surgical resection is necessary to establish the diagnosis. Anaplastic astrocytomas can be distinguished from low-grade astrocytoma by the presence of mitoses. These lesions have a high propensity to undergo anaplastic transformation, and so sufficient tissue must be removed for thorough pathological evaluation if anaplastic astrocytoma is to be distinguished from GBM. In particular, histologic diagnosis of anaplastic astrocytoma in patients with ring-enhancing mass lesions on MRI suggests glioblastoma; such a finding may indicate that tissue representative of the true diagnosis has not been obtained.

Poor prognostic variables include older age, poor performance score, and severe neurologic impairment. In general, the outcome is better for more complete surgical resection, but it remains unclear whether the better outcome is associated with the surgery itself or is a result of the clinical scenario that permitted more complete resection.

The standard initial treatment is maximum surgical debulking without increasing neurologic deficit. In this setting, radiation therapy has been shown to prolong survival and is a standard component of treatment. The role of adjuvant chemotherapy remains controversial; some phase 3 trials have shown that patients benefit from adjuvant chemotherapy compared with radiation alone, whereas others have shown no such benefit. Both single-agent carmustine and the combination regimen of PCV are associated with prolonged survival in some series and meta-analyses. Most recently, a meta-analysis by the Glioma Meta-Analysis Trialists Group showed an approximate 6% absolute increase in 1-year and 2-year survival for patients with anaplastic astrocytoma who received chemotherapy. Two-year survival was better in patients receiving radiation plus chemotherapy (37%) than in those receiving radiation alone (31%). However, a large randomized trial by the Medical Research Council found no benefit of adjuvant PCV compared with radiation therapy alone. In general, the median survival has ranged from 24 months to more than 36 months. The breadth of the range in survival likely reflects patient selection criteria, which are influenced by the interpretation of pathological analyses, patient age, performance score, and referral bias. Currently, clinical trials do not confirm a therapeutic benefit for adjuvant chemotherapy. Although temozolomide is effective for the treatment of recurrent anaplastic astrocytoma, its role as an adjuvant to radiation therapy has not been rigorously assessed.

Chemotherapy also benefits patients with anaplastic astrocytoma that recurs after radiation; both nitrosourea-based regimens and temozolomide have shown efficacy. In fact, the Food and Drug Administration granted accelerated approval for temozolomide on the basis of its activity in recurrent anaplastic astrocytoma; the response rate to temozolomide was 35% for patients who had not received chemotherapy and 20% for patients who had received nitrosourea-based therapy.

Glioblastoma Multiforme. Glioblastoma multiforme is the most common and most malignant of the primary brain tumors. Although this tumor can occur in all age
groups, including children, the average age at which it is
diagnosed is 55 years. The onset of symptoms is often
abrupt and is most commonly related to mass effect and
focal neurologic symptoms. Seizures are also relatively
common. Intracranial bleeding may be the presenting
symptom in less than 3% of patients. The duration of
symptoms before diagnosis is usually short, ranging from a
few days to a few weeks.

T1-weighted MRI scans using gadolinium as con-
trast agent typically show a ring-enhanced mass lesion,
with low signal intensity at its center and surrounding the
ring-enhanced component (Figure 4). In biopsy speci-
mens, tumor necrosis is often observed in the central
portion and increased vascularity in the ring-enhanced
portion; the surrounding low-signal component corre-
sponds to intact brain parenchyma that has been diffuse-
ly infiltrated by tumor cells. Studies involving the use of
serial stereotactic biopsies have shown isolated tumor
cells well beyond any signal abnormality visible on T2-
weighted scans.

Pathological features include increased cellularity with
marked nuclear pleomorphism, frequent mitoses, endothe-
lial proliferation, and areas of palisading necrosis. Epider-
mal growth factor receptor amplification and mutation or
loss of the PTEN tumor suppressor gene are characteristic
genetic alterations. Both of these abnormalities are charac-
teristic of older patients with GBM but are less commonly
found in GBMs that arise in younger patients. Anaplastic
astrocytomas with these genetic alterations may behave
more like GBM.19 Poor prognostic clinical variables in-
clude increasing age, poor performance status, increased
severity of neurologic deficits at diagnosis, and the inabili-
ty to achieve substantial tumor resection.

Surgical removal remains the mainstay of treatment,
provided that unacceptable neurologic deficit can be
avoided. The extremely infiltrative nature of this and other
infiltrating astrocytomas makes complete surgical removal
impossible. Radiotherapy has been the standard treat-
ment since the early phase 3 clinical trials in which the
Brain Tumor Study Group compared treatment with post-
operative supportive care only, carmustine alone, radiation
therapy alone, and radiation therapy plus carmustine.20 The
1-year survival for each of these treatment arms was 3%,
12%, 24%, and 25%, respectively. In summary, although
radiotherapy rarely cures glioblastoma, prospective ran-
donized studies show that it doubles the median survival
vs supportive care alone. Currently, radiation is commonly
administered to a total dose of 60 Gy delivered in 2 Gy
fractions over 30 treatment days. Multiple attempts to im-
prove the therapeutic efficacy of radiation by using higher
doses, altered fraction schemes, and radiation sensitizers
have been unsuccessful. A phase 3 randomized trial of
patients with GBM showed no benefit to adding SRS to
radiation plus carmustine.21 Moreover, such a radiosurgical
boost can result in tumor and brain necrosis with resultant
increased focal deficit and increased intracranial pressure,
sometimes requiring surgical debulking.

Recently, the benefit of adjuvant temozolomide for pa-
tients with GBM was convincingly shown. In a landmark
trial, patients were randomized after surgery to receive ra-
diotherapy alone or radiotherapy plus concurrent temozo-
لومide followed by 6 cycles of adjuvant temozolomide. In
patients who received temozolomide, median survival was
increased by 2.5 months and 2-year survival by 16.1%
(Figure 5).21 These results changed the standard of care for
treatment of patients with GBM. Moreover, a companion
correlative laboratory study demonstrated that methylation
of the promoter region of the MGMT gene in the tumor
specimen is associated with superior survival, regardless of
treatment received (Figure 6).22 The MGMT protein re-
moves the methyl group from the O6 position of guanine,
reversing the cytotoxic effects of methylating agents (such
as temozolomide) on tumor cells, making the tumor resis-
tant to treatment; methylation of the promoter region of
MGMT results in its inactivation.

Carmustine-impregnated wafers that are implanted
into the brain at the time of resection have been shown
to modestly improve outcomes in selected patients, al-
though the magnitude and duration of benefit are relatively
modest.23

Treatment options for glioblastoma that recurs after
radiation and use of temozolomide must be carefully
weighed given the needs of each patient. Because all ther-
apies have limited benefits, symptom control with end-of-
life care may be appropriate. For patients with resectable disease, good neurologic status, and good performance score, a second resection, with or without placement of carmustine-impregnated wafers, can be performed. The value of additional radiotherapy or chemotherapy remains under investigation. Participation in a well-designed clinical trial should be considered.

OLIGODENDROGIOMAS

Tumors that contain oligodendroglial elements are relatively uncommon, probably accounting for no more than 10% of primary brain tumors. Nevertheless, they are notable because of their unique natural history and sensitivity to chemotherapy. These tumors are classified as either low-grade or anaplastic. Anaplastic oligodendrogliomas are characterized by high cellularity, nuclear pleomorphism, frequent mitoses, abundant endothelial proliferation, and tumor necrosis. Approximately half of oligodendrogliomas are characterized by loss of heterozygosity of chromosomes 1p and 19q, a pathognomonic diagnostic feature. Recently, the loss of heterozygosity was shown to be secondary to an unbalanced pericentromeric translocation.24

Most oligodendrogliomas originate as low-grade tumors. Mixed oligoastrocytomas contain both oligodendrogial and astrocytic elements.

Low-Grade Oligodendrogliomas/Oligoastrocytomas.

For patients with pure low-grade oligodendroglioma, median survival is approximately 10 years; for patients with mixed oligoastrocytoma, approximately 8 years (intermediate between pure oligodendroglioma and pure astrocytoma). Deletion or translocation of 1p and 19q in the tumor is associated with superior survival (Figure 7).24 The average age at diagnosis is 35 years. Patients typically present with seizures, although focal neurologic deficits, changes in mental status or personality, or symptoms of increased intracranial pressure can occur. Because these tumors may not be visible on CT scans, MRI is the preferred imaging modality. The tumor is
most visible as increased signal intensity on T2-weighted scans. On T1-weighted scans, the signal may be decreased and contrast enhancement may occasionally be scant. Signal void from calcification may or may not be present.

As with low-grade astrocytomas, controversy exists regarding optimal management. Because these tumors are even more indolent than astrocytomas, symptom control with anticonvulsant drugs without additional antitumor therapy has been common. More complete surgical resection has been suggested to be beneficial, although selection bias for smaller tumors in nonessential brain tissue is evident. The early results of a European trial\(^7\) did not show a survival benefit for immediate vs delayed radiation, although immediate radiation was associated with a longer time to tumor progression. Two other trials\(^11,12\) showed no benefit to high- vs intermediate-dose radiation. Data from several studies\(^25-27\) indicate that initial therapy with temozolomide or PCV may shrink tumors in 31% to 61% of patients with either oligodendroglioma or oligoastrocytoma. Whether such tumor response improves time to progression or overall survival remains to be determined. A clinical trial\(^13\) designed to compare radiation alone with radiation followed by PCV found superior PFS in the PCV treatment arm but no difference in overall survival between the 2 groups. Presumably, treatment at recurrence is effective, resulting in similar outcomes regardless of the timing of chemotherapy. Because temozolomide induces tumor responses and is less toxic, many practitioners advocate its use rather than PCV. Thus, current options for initial treatment include symptom control only with anticonvulsant agents, radiation therapy alone, chemotherapy alone, or a combination of chemotherapy and radiation.

FIGURE 7. Overall survival (OS) and progression-free survival (PFS) in low-grade oligodendroglioma/oligoastrocytoma by 1p/19q status. CI = confidence interval; NR = not reached. From Cancer Res.,\(^{24}\) with permission.
For recurrent low-grade oligodendroglial tumors, surgery, radiation, and chemotherapy may each play an important role. Primary or secondary debulking may reduce symptoms. If radiation therapy was not administered initially, it is likely to be effective for recurrent disease. Response to temozolomide has occurred in approximately 50% of patients with low-grade oligodendroglioma that recurs after radiation.28,29

Anaplastic Oligodendroglioma/Oligoastrocytoma. Mass effect or seizures are typically seen at presentation with anaplastic oligodendroglioma/anaplastic oligoastrocytoma. Bottom, Overall survival in patients receiving RT vs 4 cycles of PCV as initial treatment for anaplastic oligodendroglioma/anaplastic oligoastrocytoma. MST = median survival time. Adapted from J Clin Oncol,30 with permission from the American Society of Clinical Oncology.

For recurrent low-grade oligodendroglial tumors, surgery, radiation, and chemotherapy may each play an important role. Primary or secondary debulking may reduce symptoms. If radiation therapy was not administered initially, it is likely to be effective for recurrent disease. Response to temozolomide has occurred in approximately 50% of patients with low-grade oligodendroglioma that recurs after radiation.28,29

Anaplastic Oligodendroglioma/Oligoastrocytoma. Mass effect or seizures are typically seen at presentation with anaplastic oligodendroglial tumors. Despite the chemosensitivity of these tumors, the median survival is only 3 to 5 years. Current treatment includes optimal surgical debulking followed by radiation therapy. In 2 recent phase 3 trials, one conducted in North America30 and the other in Europe,31 radiation alone was compared with radiation plus PCV. In the North American trial, patients received PCV for 4 cycles before radiation. Although PFS was better in the PCV arm, overall survival in the 2 groups was the same (Figure 8). Notably, patients with 1p and 19q deletions had significantly better outcomes, regardless of treatment. They showed the most notable improvement in PFS, but the PFS of patients without 1p and 19q deletions had significantly better outcomes, regardless of treatment. They showed the most notable improvement in PFS, but the PFS of patients without 1p and 19q deletion also improved with PCV (Figure 9).30 In the European trial, patients received PCV after radiation, and results were nearly identical to those in the North American study. Progression-free survival was better in the PCV group, but overall survival did not differ between the 2 groups. Patients with 1p and 19q deletions had superior survival, regardless of the treatment arm. No significant difference was noted in the survival by treatment arm in patients with or without 1p and 19q deletions.31 Taken together, these studies show that chemotherapy improves PFS but that salvage treatment at recurrence results in equivalent survival. Importantly, both trials confirm the prognostic value of 1p and 19q but do not clearly show that only patients with 1p and 19q deletions benefit from chemotherapy.

Prospective trials have shown that approximately 50% to 70% of patients with anaplastic oligodendroglioma that recurs after radiotherapy respond to chemotherapy with either PCV or temozolomide.32,33 Although there is no evidence that the sequence of temozolomide and PCV has superior efficacy, the absence of cumulative myelosup-

FIGURE 8. Top, Progression-free survival in patients receiving radiation therapy vs 4 cycles of procarbazine, lomustine, and vincristine (PCV), followed by radiation therapy (RT) as initial treatment for anaplastic oligodendroglioma/anaplastic oligoastrocytoma. Bottom, Overall survival in patients receiving RT vs 4 cycles of PCV as initial treatment for anaplastic oligodendroglioma/anaplastic oligoastrocytoma. MST = median survival time. Adapted from J Clin Oncol,30 with permission from the American Society of Clinical Oncology.

FIGURE 9. Survival distributions by 1p/19q status and treatment arm. MST = median survival time. From J Clin Oncol,30 with permission from the American Society of Clinical Oncology.
pression with temozolomide argues for its use initially in the setting of recurrent disease.

**Ependymomas**

Ependymomas may occur anywhere in the spinal axis. In children, they are more commonly found in the posterior fossa and spinal cord; in adults, they are somewhat more common in the supratentorial brain. The tumors can be classified as either low-grade or anaplastic. For low-grade lesions, surgical resection alone may provide cure. Both the low-grade and anaplastic lesions may disseminate along the leptomeningeal surfaces. Low-grade resectable ependymomas in the spine are usually treated with surgery alone. Whereas the role of postoperative radiotherapy for intracranial low-grade ependymomas remains controversial, anaplastic or incompletely resected low-grade tumors are usually treated with postoperative radiation therapy. Studies have shown that ependymomas may respond to platinum-based chemotherapy regimens, but the clinical benefit of chemotherapy remains speculative. Overall, the response to chemotherapy is less than 20%.

**Meningiomas**

Meningiomas are usually benign and originate in the dura that covers the brain and spinal cord. The incidence rate for the tumor is approximately 2 cases per 100,000 individuals. They are most common for women in the sixth and seventh decades of life. Loss of chromosome 22 is characteristic of meningiomas, although the prognostic significance of this finding is unclear. The frequency of meningioma is increased for patients with type 2 neurofibromatosis. Although meningiomas can express receptors for androgen, estrogen, progesterone, and somatostatin, therapies directed at these receptors have not yet shown therapeutic efficacy.

Patients with meningiomas may present with features typical of mass lesions in the brain, including seizures or focal neurologic deficits. Meningiomas, which may be asymptomatic, are also detected incidentally on CT or MRI scans that are obtained for other reasons. The tumors have a characteristic MRI appearance, usually consisting of uniform contrast enhancement along the dura, with distinct separation from the brain parenchyma. Also characteristic, although not present in all cases, is the “dural tail,” i.e., contrast enhancement extending from the mass lesion. There may be marked parenchymal edema, which is the consequence of vascular endothelial growth factor secreted by the tumor cells, leading to local mass effect.

Many meningiomas that are noted incidentally do not require treatment at the time of original diagnosis. For patients with asymptomatic meningioma, observation may be appropriate. Epidemiological evidence suggests that as many as two-thirds of these patients will not have symptoms over time. If substantial mass effect is observed in patients with or without symptoms, the treatment of choice is usually complete resection. Surgery is often feasible if the meningioma is located over the cortical convexity, olfactory groove, anterior sagittal sinus, or posterior fossa. However, resection may be more difficult for tumors at other sites, such as sphenoidal, parasagittal, orbital, tentorial, or clivus locations. Under those circumstances, external beam radiotherapy or focal stereotactic radiotherapy may be extremely useful for tumor control. In a Mayo Clinic study that compared tumor control rates after surgical resection or SRS for patients with small- to medium-size intracranial meningiomas without symptomatic mass effect, SRS achieved better tumor control (98% vs 88%) with fewer complications (10% vs 22%) than surgical resection. With regard to the choice of radiotherapy modality, SRS is usually reserved for the smaller lesions (ie, <3-4 cm), whereas fractionated stereotactic radiotherapy is used for larger lesions or meningiomas near critical structures such as the optic nerves. No pharmaceutical interventions have reproducibly demonstrated antitumor efficacy for meningiomas.

Rarely, meningiomas may have atypical histologic features or may be frankly malignant. Meningiomas can be highly aggressive, and the approach to such tumors is identical to that for benign meningiomas, although postoperative radiation is typically delivered.

**Pituitary adenomas**

Pituitary tumors are typically either functional or nonfunctional adenomas. Endocrine abnormalities may be found at presentation if the tumors are producing peptides such as prolactin, growth hormone, or adrenocorticotropic hormone. Modest elevations in prolactin levels may occur with nonsecreting tumors because the mass effect exerted by the tumor on the pituitary stalk can perturb the hypothalamic inhibition of prolactin-secreting cells in the pituitary. Ocular manifestations, particularly bitemporal hemianopsia, may result from the compression of the medial and posterior aspects of the optic chiasm. A diagnosis may be confirmed by an assay of pituitary hormones, CT scans, or MRI scans of the sella. Neuroimaging studies usually reveal a mass lesion that arises in or just above the sella turcica, displacing or obliterating the normal pituitary gland. Also, these tumors may be noted incidentally on scans obtained for other reasons.

Therapy should be tailored to the individual. For patients with asymptomatic microadenomas, observation only may be appropriate. Patients with prolactin-producing lesions may benefit from bromocriptine, the dopaminergic activity of which inhibits prolactin secretion and can lead to
dramatic reduction in tumor size and improved neurologic symptoms. Surgery should be considered for either functional or nonfunctional lesions that threaten the visual pathways. Patients with inoperable, recurrent, or difficult-to-control endocrine abnormalities should be considered for stereotactic radiotherapy or SRS. Because stereotactic radiotherapy can take years to normalize hormone levels, whereas SRS requires only months, SRS is preferred over radiotherapy, especially for functional adenomas. However, if the tumor encroaches on the optic nerves, stereotactic radiotherapy is the treatment of choice, achieving local control in more than 90% of patients.37

### PRIMARY CNS LYMPHOMAS

Central nervous system lymphomas constitute approximately 2% to 3% of all brain tumors in patients who have an adequate immune system. The tumor is more common in men aged 55 to 60 years; nearly half of all CNS lymphomas occur in patients older than 60 years and nearly a quarter in patients older than 70 years. The incidence appears to be increasing, although it is unclear whether this apparent increase is real or merely reflects ascertainment bias. At increased risk for CNS lymphoma are patients with a compromised immune system, including those who have undergone solid organ transplant, who have congenital immunodeficiency or an autoimmune disorder, or who are infected with human immunodeficiency virus. Human immunodeficiency virus–associated CNS lymphomas are related to the Epstein Barr virus, particularly with a CD4 count of fewer than 500 cells/mm³. Most CNS lymphomas are of the large B-cell variety.

Patients present with a variety of symptoms characteristic of either focal or multifocal mass lesions. The MRI scan usually shows homogeneous contrast-enhanced tumors within the periventricular deep white matter. Multifocality and inhomogeneous contrast enhancement are typical in patients with a compromised immune system. It is extremely important to consider CNS lymphoma in the differential diagnosis of brain tumors. Administration of corticosteroids may result in complete disappearance of the contrast-enhanced lesion, making the diagnosis difficult. Consequently, when CNS lymphoma is considered in the differential diagnosis, corticosteroids should be avoided, unless mass effect is causing serious and immediate injury to the patient. Obtaining biopsy specimens of suspected lesions is critically important, as many malignant and nonmalignant CNS conditions can mimic CNS lymphoma. Unlike systemic large B-cell lymphomas, for which both chemotherapy and radiation therapy are effective and treatment for localized disease is curative, CNS lymphoma typically responds to initial therapy and then relapses. As with systemic lymphoma, the role of surgery is restricted primarily to obtaining appropriate tissue for diagnosis.

Whole-brain radiation therapy was once the mainstay of treatment. Unfortunately, even with localized lesions, the median survival with radiation alone is approximately 1 year. Relapse at sites other than the primary lesion is common. Studies in which high-dose methotrexate was incorporated into the treatment regimen (single-agent methotrexate; methotrexate plus high-dose cytarabine, procarbazine with or without intrathecal methotrexate; or intra-arterial chemotherapy after blood-brain barrier modification with mannitol) have shown better overall survival than the historical results for radiation therapy alone. With methotrexate-containing regimens, the median survival (range, 24-40 months) exceeded that associated with radiation therapy alone (Table 3).39 In some cases, radiation therapy was used only at recurrence if complete regression had been achieved with chemotherapy; long-term survival was reported for some patients without the use of radiation therapy.38-40

Because the diffuse nature of CNS lymphoma requires whole-brain radiation therapy, the risk of later neurologic toxicity with dementia secondary to leukoencephalopathy is relatively high. That risk could be reduced with the development of strategies for effective tumor control that avoid whole-brain radiation. Initial therapy for patients with a compromised immune system is reduction of the cause of immunosuppression. The prognosis for such patients is usually worse than that for patients with an adequate immune system. Because of comorbid infections and generally poor performance status, chemotherapy is often not feasible for patients with a compromised immune system. As with other primary brain tumors, response to treatment correlates with age and performance status.

### MEDULLOBLASTOMAS

Medulloblastoma and other CNS primitive neuroectodermal tumors, such as pineoblastoma and cerebral neuroblastoma, are very uncommon primary CNS malignant tumors in the adult population (>21 years). Medulloblastoma is

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**TABLE 3. Survival for 98 Patients With Primary Central Nervous System Lymphoma Who Were Treated With Chemotherapy and Whole-Brain Radiation Therapy**

<table>
<thead>
<tr>
<th>No. of years after treatment</th>
<th>Progression-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (%)</td>
<td>Rate (%)</td>
</tr>
<tr>
<td></td>
<td>No. of patients at risk</td>
<td>No. of patients at risk</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
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<td>2</td>
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<td>4</td>
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<td>5</td>
<td>25</td>
<td>32</td>
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From J Clin Oncol,39 with permission from the American Society of Clinical Oncology.
more common in children, but young adults are also at risk. The peak incidence of medulloblastoma occurs in children aged 2 to 7 years. This tumor, which occurs in the posterior fossa, may be located in either the cerebellar hemisphere or the vermis and may involve the fourth ventricle. Because of the proximity of the fourth ventricle, obstructive hydrocephalus is relatively common. Symptoms at presentation include loss of balance, lack of coordination, diplopia, dysarthria, and signs of hydrocephalus, including headache, nausea, vomiting, and gait instability.

Magnetic resonance imaging usually reveals a contrast-enhanced mass lesion involving the cerebellum. Other locations of primitive neuroectodermal tumors include the pineal region and supratentorial sites. Patients with supratentorial primitive neuroectodermal tumors have a less favorable long-term survival rate of approximately 50%. These tumors have a high propensity to seed the leptomeninges focally as well as to spread through the subarachnoid space to involve the ventricles, cerebral convexity, and spinal leptomeningeal surfaces. Consequently, MRI of the entire craniospinal axis is necessary.

The goal of surgery should be the removal of as much of the mass lesion as possible; residual tumor after surgery confers a worse prognosis. Also associated with a worse prognosis are positive findings on cytologic analysis of cerebrospinal fluid (CSF) or the presence of leptomeningeal metastases on an MRI scan. Surgery alone is not curative. However, radiation to the craniospinal axis with a boost to the site of the primary tumor can be curative in some cases. Adjuvant chemotherapy (after radiation therapy) with a platinum-based drug (cisplatin or carboplatin), etoposide, and an alkylating agent (cyclophosphamide or lomustine) plus vincristine has increased the cure rate compared with the use of radiation therapy alone. With appropriate initial therapy, long-term survival is achieved in 60% to 80% of patients with medulloblastoma.

**BRAIN METASTASES**

Metastases to the brain, the most common intracranial tumors in adults, are 10 times more common than primary tumors. Substantial advances have been made in the diagnosis and treatment of these lesions, improving survival and symptom control. Brain metastases occur in 20% to 40% of adults with cancer and are most commonly associated with cancers of the lung and breast and melanoma. These lesions result from hematogenous spread and are most common at the junction of the gray and white matter where the caliber of blood vessels changes, thereby trapping tumor emboli. Eighty percent of the brain lesions occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brainstem. Approximately 80% of patients have a history of a systemic cancer and 70% have multiple brain metastases that are evident on MRI scans.

The presenting signs and symptoms of these lesions are similar to those of other mass lesions in the brain. The best diagnostic test is MRI with use of a contrast medium; however, not all brain lesions in patients with cancer are metastases. In one prospective study of patients with systemic cancer who were thought to have single brain metastasis, 11% of biopsy specimens of brain tissue showed primary brain tumors or infections. Two randomized prospective studies have shown that surgery plus whole-brain radiation therapy produces better outcomes vs surgery alone in selected patients, ie, those with good performance status, stable or limited systemic disease, and surgically accessible single brain metastasis. Surgery plus radiation results in fewer deaths from neurologic causes vs surgery alone (Figure 10). However, the
addition of whole-brain radiation therapy does not improve overall survival compared with surgery alone.43 Other techniques for delivering focal radiation therapy such as SRS may be effective in treating unresectable lesions. Two randomized prospective studies44,45 showed that selected patients with a limited number of brain metastases improved more when treated with SRS plus whole-brain radiation therapy than with whole-brain radiation therapy alone. Only 1 small prospective trial46 has compared the efficacy of surgery vs radiosurgery, randomizing patients with small single metastasis to either surgery followed by whole-brain radiation therapy or radiosurgery alone; no significant difference in outcomes was found. Retrospective analyses have reported conflicting results.47,48

On the whole, the literature suggests equivalent outcomes for SRS and surgery. The currently available data suggest that radiosurgery is more convenient, effective, and safe for smaller lesions and for lesions in inaccessible locations. Also, SRS offers a reasonable option for patients who are not surgical candidates for medical reasons. However, surgery is clearly the optimal modality for tissue diagnosis or for lesions that cause a mass effect. In summary, SRS and surgical resection should be seen as complementary, but different, modalities to be used in the treatment of select patients with brain metastases.49

Unfortunately, nearly 50% of patients with 1 or 2 brain metastases are not candidates for surgery because of the inaccessibility of the tumor, the extensiveness of the systemic disease, or other complicating factors. These patients and others with multiple brain metastases should receive whole-brain radiation therapy as standard therapy. With whole-brain radiation therapy, up to 50% of these patients show an improvement in neurologic symptoms, and 50% to 70% have an objective response.50-52 Chemotherapy is rarely used as primary therapy for brain metastases. Many tumors that metastasize to the brain (for example, non–small cell lung cancer, a tumor of an unknown primary site, and melanoma) are not sensitive to chemotherapy or have been heavily pretreated with potentially effective agents.

LEPTOMENINGEAL METASTASES

Involvement of the leptomeninges occurs in approximately 5% of patients with cancer and is being recognized more commonly as patients with cancer live longer and as diagnostic studies improve. Leptomeningeal involvement is most commonly seen in melanoma and breast and lung cancer. The tumor reaches the leptomeninges by hematogenous spread or by direct extension from preexisting parenchymal tumor deposits. Tumor cells are then disseminated throughout the neuroaxis by the flow of the CSF. Patients present with signs and symptoms referable to 1 or more of the following: local injury to nerves traveling through the spinal fluid (cranial nerve palsies, radicular weakness, paresthesias, or pain); direct invasion into the brain or spinal tissues or interruption of blood supply to those tissues (focal findings or seizures); obstruction of normal CSF flow pathways (headache and increased intracranial pressure); interference of normal brain function (encephalopathy); or perivascular infiltration by tumor cells, leading to local ischemia and hence stroke-like symptoms.

The diagnosis is made by examination of the CSF or MRI scan of the brain and spinal cord. Initial analysis of CSF reveals the presence of malignant cells in 50% of affected patients; however, in at least 10% of patients with leptomeningeal involvement, the findings on cytologic examination remain persistently negative. Increasing the number of lumbar punctures (up to 6) and the volume of CSF removed (10 mL per lumbar puncture) increases the yield of positive diagnosis. In the CSF, the protein concentration is usually elevated, the glucose concentration may be low, and there is a pleocytosis. Radiographic studies may show hydrocephalus without a mass lesion or diffuse contrast enhancement of the leptomeninges.

Without therapy, the median survival is 4 to 6 weeks, with death the result of progressive neurologic dysfunction. Often, leptomeningeal metastases are a manifestation of end-stage disease, and symptom management may be the most appropriate care. Corticosteroids and analgesics may offer temporary palliation. For patients who have minimal systemic disease and an acceptable performance status, treatment may improve symptoms and prolong survival. Median survival can be increased 3 to 6 months by radiation therapy to symptomatic sites and to areas of bulky disease identified on neuroimaging studies and by intrathecal therapy (delivery by way of lumbar puncture or via an Ommaya reservoir) with methotrexate, cytarabine, or thiopeta. Although intrathecal chemotherapy can substantially prolong the survival of patients with hematologic malignancies such as leukemias and perhaps lymphomas, its benefit in the setting of CSF seeding by solid tumors is equivocal, at best. In such instances, many patients die of advanced systemic disease. The major complication of intrathecal methotrexate therapy is a necrotizing leukencephalopathy that may develop after months of therapy in those few patients who do have prolonged survival. This devastating toxic effect is most common for patients who receive radiation therapy before or concurrently with intrathecal methotrexate therapy.

CONCLUSION

Brain tumors, both primary and metastatic, cause substantial morbidity and mortality. The prognosis of patients with
benign brain tumors overall is very favorable, whereas pa-

tients with primary malignant or metastatic brain tumors

terally die of disease. Nevertheless, multimodal therapy

to surgery, radiation, and chemotherapy clearly reduces

morbidity, prolongs survival, and may be curative in some

patients. Given the limitations of current therapies, efforts to

improve outcomes in patients with malignant brain tumors

should remain a high priority in cancer research.

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