Primary Central Nervous System Tumors: Advances in Knowledge and Treatment

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Introduction

Tumors of the central nervous system (CNS) represent a unique, heterogeneous population of neoplasms. The Surveillance, Epidemiology, and End Results (SEER) program estimated 17,400 new cases of brain and other nervous system cancer for 1998 in the United States (9,800 in males and 7,600 in females).\(^1\) For the same period, SEER estimated 13,300 deaths from brain and other nervous system cancer. The estimated incidence rate for all primary tumors, including benign and malignant tumors, is 11.8 per 100,000 person-years, with malignant tumors accounting for 6.5 per 100,000 person-years.

The most common primary malignant neoplasm is glioblastoma multiforme, which is the cause of most deaths attributable to CNS tumors. Meningiomas account for the majority of benign tumors. Overall, CNS tumors are more common in whites than in blacks, and males have higher mortality rates than do females. The incidence of malignant tumors appears to be increasing with increasing age, approximately 1.2% per year, with the greatest rate of increase in the population older than 70 years. Survival decreases with higher age in most tumor types. SEER data for the five leading causes of cancer death in 1994 by age and sex are shown in Table 1. Although CNS tumors are not common, they cause significant morbidity and mortality.

Classification

The World Health Organization (WHO) classified CNS tumors into nine categories in its most recent revision (Table 2).\(^2\)

Tumors of neuroepithelial tissue account for many tumors often thought of as “primary brain tumors” and represent a significant proportion of the CNS tumors for which clinical research is conducted. This category is further subclassified into the tumor types described in Table 3. Astrocytic tumors such as glioblastoma multiforme and anaplastic astrocytomas, commonly called malignant gliomas, are included in this category.

Pathology grading systems for the most common astrocytic tumors have generally followed a three-tiered system: astrocytoma, anaplastic astrocytoma (and mixed tumors), and glioblastoma multiforme. The first such system was described in 1926 by Bailey and Cushing, who used the terms astroblastoma and spongioblastoma multiforme. Since then several other grading systems have been used, including the four-tiered system of Kernohan and colleagues, the Ringertz...
three-tiered system, a previous WHO schema, and several variants of these from individual pathologists and institutions.

Obviously, the various grading systems led to significant confusion about what constituted different tumors and made interpretation of clinical trial results difficult. One pathologist’s definition of glioblastoma differed from that of another, and many different systems were in place. Recently, the trend has been toward using one of two systems for grading malignant gliomas, the WHO definition or the Dumas-Duport grading system.

The WHO definition of astrocytic tumors emphasizes degrees of cellularity, nuclear and cellular pleomorphism, mitosis, endothelial proliferation, and necrosis. Glioblastoma is a highly cellular tumor with nuclear and cellular pleomorphism, endothelial proliferation, mitotic figures, and, often, necrosis. Although necrosis is a hallmark of this tumor and frequently occurs, its presence is not required for a tumor to be identified as a glioblastoma in the WHO classification. Anaplastic astrocytomas are less cellular, with less pleomorphism, less mitosis, and no necrosis. Finally, astrocytomas are glial tumors other than glioblastoma and anaplastic astrocytoma, with little cellularity and minimal pleomorphic changes.

Daumas-Duport and colleagues use a different method of grading based upon the presence or absence of the following four criteria: nuclear atypia, mitosis, endothelial proliferation, and necrosis. Grade I neoplasms have none of these features, grade II have one feature, grade III have two features, and grade IV have at least three criteria present. This system of numerical grades is used by many neuropathologists who do not use the WHO

| Female | Lung | Leukemia | Breast | Breast | Lung | Lung |
|--------|------|----------|--------|--------|------|------|
| Male   | Lung | Leukemia | Leukemia | Lung | Lung | Lung |
| Female | Breast | Brain/ONS | Leukemia | Lung | Breast | Colon |
| Male   | Prostate | Brain/ONS | NHL | Colon | Colon | Prostate |
| Female | Colon | Endocrine | Cervix | Colon | Colon | Breast |
| Male   | Colon | Endocrine | Brain/ONS | NHL | Prostate | Colon |
| Female | Pancreas | Bone | Brain/ONS | Ovary | Ovary | Pancreas |
| Male   | Pancreas | NHL | Colon | Brain/ONS | Pancreas | Pancreas |
| Female | Ovary | Soft tissue | NHL | Cervix | Pancreas | NHL |
| Male   | NHL | Soft tissue | Soft tissue | Pancreas | NHL | Leukemia |

NHL = non-Hodgkin’s lymphoma; ONS = other nervous system tumors.
Adapted from Landis et al.
criteria to describe astrocytic tumors. In clinical practice, tumors classified grade I by the Daumas-Duport system are rare, and thus even this system for all practical purposes is a three-tiered system, similar to the WHO classification.

Much of the difficulty in nomenclature centers on tumors of a lesser grade than WHO grade glioblastoma, which frequently has the features of a Daumas-Duport grade IV tumor. WHO grade III or anaplastic astrocytoma, mixed tumors, and many variants of lower-grade astrocytomas are frequently the subjects of debate and discordant reviews by various pathologists, emphasizing the subjective nature of pathologic diagnoses. More generally agreed upon criteria are needed, as are more objective criteria, such as molecular markers, which, it is hoped, will fill the need for sensitive, specific criteria for tumor designation.

Figure 1 shows the typical pathology of glioblastoma multiforme (Fig. 1A) and low-grade astrocytoma (Fig. 1B). Note the hypocellularity and pleomorphism in the lower-grade tumor compared with the glioblastoma. Also depicted is a typical immunohistochemical stain for glial fibrillary acidic protein (GFAP), a marker of glial origin (Fig. 1C).

**Molecular Considerations**

Malignant transformation of glial or neuronal cells is a complex process that is still...
incompletely understood and is the subject of intense laboratory research. CNS tumor pathogenesis is probably a multistep process in which tumor suppressor gene inactivation and oncogene activation and overexpression play a part, along with alterations in cell cycle progression, abnormalities in signal transduction pathways, glial cell invasion, and angiogenesis. The hope of molecular research is that it will lead to novel, minimally toxic, more specific treatment strategies for malignant CNS tumors.

A detailed review of this topic is beyond the scope of this article, but we will highlight several areas in this section, with an emphasis on astrocytic tumors.

**CHROMOSOMAL ABNORMALITIES**

In astrocytic tumors, many chromosomal abnormalities have been identified, frequently involving chromosomes 7, 10, 17, 19, and 22. The tumor suppressor gene *TP53* is frequently altered, by point mutations and deletions on chromosome 17p13 in more than 30% to 40% of cases, including WHO grade II tumors; this suggests an early, perhaps initiating, event in malignant transformation. Abnormalities at codon 273 are the most common mutations, but many other types of mutation have been described.

The *TP53* gene encodes a protein involved in transcriptional regulation of other genes and ultimately plays a role in cell cycle regulation, response to DNA damage, and apoptosis. Transfection experiments with the wild type of tumor protein p53 into human glioma tumor cells result in cell death via apoptotic pathways. This concept of gene transfer of wild-type p53 into tumor with mutated p53 is a strategy being developed for clinical trials in malignant glioma, and phase I trials will open shortly.

**ONCOGENE AMPLIFICATION**

Oncogene amplification also occurs in malignant glioma. One of the first genes found was the *c-erbB* oncogene, which encodes a receptor for the epidermal growth factor receptor (EGFR). The EGFR is a tyrosine kinase glycoprotein that binds epidermal growth factor and transforming growth factor α (TGF-α). The human *EGFR* gene has been localized to chromosome 7p11-12 and appears to play a role in cell proliferation and transformation.

In human glioblastoma, EGFR is...
amplified in approximately 40% of patients. In some cases, gene rearrangements also occur, leading to a truncated receptor without a ligand-binding domain, and EGFR remains constitutively active. Tumor cell proliferation may occur because of this uncontrolled, autocrine growth stimulus.

Another growth factor important in the pathogenesis of astrocytomas is the platelet-derived growth factor (PDGF) receptor (PDGFR), another member of the receptor tyrosine kinase family. Two isoforms of the receptor exist (α and β) with two ligands (A and B). PDGF-A binds only to the α receptor, whereas PDGF-B can bind to both receptors. Human astrocytomas express high levels of the ligands and receptors, primarily because of overexpression rather than amplification or rearrangements. PDGFR-α overexpression appears to be an early event in pathogenesis and is present in most grades of tumors. Ligand overexpression appears more common in the higher-grade tumors.

Aberrant cellular proliferation and transformation may be consequences of these receptor tyrosine kinase genes via abnormal signaling pathways, such as activation of ras protein and other substrates that control cell growth. Inhibition of cell cycle progression is under the influence of CDK inhibitors (CDKIs). Many CDKs and CDKIs exist, and alteration of the function of these proteins can result in either progression or inhibition of the cell cycle.

Protein kinase C (PKC) is another member of the protein kinase family involved in signal transduction and is frequently highly expressed in malignant gliomas. Several isoforms of PKC exist, and selective inhibition of these isoforms is of interest because growth of glial tumor cells can be modulated based upon PKC activity. Nonselective inhibition has been used as a therapeutic strategy in patients with malignant glioma by treatment with high doses of tamoxifen. More specific inhibitors are being developed, such as UCN-01 and bryostatin.

**Altered N Cell Cycler Regulation**
In addition to the genetic alterations present in CNS tumors, a few of which have been highlighted in this section, alterations in cell cycle regulation are commonly found in these tumors. Cyclins and cyclin-dependent kinases (CDKs) phosphorylate key substrates involved in the activation of the cell cycle, with different CDKs functional at different stages of the cycle. Inhibition of cell cycle progression is under the influence of CDK inhibitors (CDKIs). Many CDKs and CDKIs exist, and alteration of the function of these proteins can result in either progression or inhibition of the cell cycle.

The retinoblastoma gene (RB) was one of the first tumor suppressor genes identified, and phosphorylation of the Rb protein is a key step controlling cell cycle progression in the G1 phase. One of the CDKs, CDK4, phosphorylates Rb protein, which inhibits this protein’s ability to bind to transcription factors such as E2F, which bind to DNA and initiate cell cycle progression. Other CDKIs exist, including p21 and p16. The CDKI p21 mediates p53-induced cell cycle arrest, an important pathway initiated in response to DNA damaging agents. Mutations of any of these protein substrates could abrogate what might normally result in cell cycle arrest, instead allowing cell proliferation to continue with persistent DNA damage. Alterations in this complex pathway are found in CNS tumors and include overexpression of CDK4, deletions in p16 and p21, and mutations in p53 and Rb protein. Drug and gene therapy strategies to modify these abnormal protein factors are currently being developed for clinical trials.

**Tumor Cell Invasion and Angiogenesis**
In addition to growth factor and cell cycle alterations, malignant tumors acquire the ability to invade and to develop a new blood supply by angiogenesis. Gliomas...
are often very invasive tumors. Although local control of tumor is potentially possible for short periods by surgery and radiotherapy, the fact that tumor cells invade beyond macroscopic margins is one reason that cure by local control alone is not possible.

Degradation of the extracellular matrix involves secretion of proteases by tumor cells to break down the adjacent brain substrate, allowing cells to invade. Among the several kinds of proteases secreted by glioma cells are metalloproteinases. Interestingly, inhibitors of metalloproteinases also can be secreted by the same tumor cells, suggesting an elaborate regulatory process that may ultimately control the rate of cell invasion. Clinical trials using protease inhibitors are ongoing in patients with CNS tumors in an attempt to control at least one compartment of the complex process of tumor growth.

Angiogenesis is an important factor in CNS tumor growth. Vascular endothelial growth factor (VEGF) is a mitogen, which induces angiogenesis and vascular permeability. Overexpression of VEGF and its receptors is found in many tumors, including malignant gliomas, which are highly vascularized and often hypoxic tumors.

One hallmark of glioblastoma is the presence of necrosis. Hypoxia can induce VEGF expression, and it is likely that tumor cells that become hypoxic increase VEGF secretion in an attempt to survive. Increased VEGF expression in glioblastoma may regulate both tumor angiogenesis and peritumoral edema. Endothelial cells in the tumor vasculature contain the receptors for VEGF, whereas the ligands for these receptors are expressed on the tumor cell, suggesting a paracrine loop supporting tumor growth. Inhibitors of angiogenesis, including antibodies to VEGF, would be an attractive strategy to use, particularly in glioblastoma, and several studies are now ongoing.

The hope of further research in these and other areas of molecular neurobiology and pathology is that it will lead to improvements in clinical therapy and ultimately survival expectations.
Familial Syndromes
Several familial syndromes exist that involve tumors within the CNS, including neurofibromatosis types 1 and 2, von Hippel-Lindau disease, tuberous sclerosis, Li-Fraumeni syndrome, and Turcot’s syndrome (Table 4).

Neurofibromatosis type 1 is an autosomal dominant disorder, often called von Recklinghausen’s disease. The neurofibromatosis type 1 gene is located on chromosome 17q12, and multiple gene mutations are known to occur. Approximately 50% of cases result from germline mutations.

Patients with this disorder can manifest many abnormalities, including café au lait spots, neurofibromas, nerve sheath tumors, bony abnormalities, and intracranial tumors. Astrocytic tumors predominate, including pilocytic astrocytomas in one or both of the optic nerves, and may involve the chiasm or hypothalamus. Astrocytomas may be in other areas of the brain, and glioblastoma multiforme also may be found.

Neurofibromatosis type 2 is autosomal dominant and is often called central neurofibromatosis. The gene for neurofibromatosis type 2 (NF2) is located at chromosome 22q12 and is believed to be a tumor suppressor gene. Both germline and somatic mutations have been described. Patients with this disorder can present with bilateral eighth nerve schwannomas and tumors involving other cranial nerves. In addition, meningiomas, ependymomas, astrocytomas, and cerebr al hamartomas can occur.

Von Hippel-Lindau disease is also autosomal dominant, and the gene is located at chromosome 3p25-26. Clinical characteristics include the presence of capillary hemangioblastomas in both the CNS and the retina and cysts and adenoma in liver, pancreas, and kidney. Malignant tumors associated with von Hippel-Lindau disease include pheochromocytoma, pancreatic islet cell tumors, and renal cell carcinoma.

Clinical Manifestations
Patients often present with general or focal signs and symptoms, which depend on the size and location of the lesion. General signs and symptoms include headache, nausea or vomiting, and changes in levels of consciousness. None of these events are specific to a brain tumor, and, in fact, few patients with headache are found to have a brain tumor.

Headaches that are associated with intracranial pathology are often intermittent, moderately severe, and more frequently experienced in the early morning, and they may be aggravated by measures that increase intracranial pressure, such as coughing. Often, these headaches are nonfocal. Focal headaches may occur without an increase in intracranial pressure and may localize to the site of the tumor.

Vomiting may be an indication of increasing intracranial pressure, or it may result from a lesion of the posterior fossa.

Seizures can present as the initial manifestation of disease or during the ill-
ness in up to 30% of patients. However, similar to the situation with headaches, most patients with epilepsy do not harbor a tumor. This is particularly true of children. The relationship of seizure to the presence of a brain tumor increases with patient age, and new onset seizures in an adult should prompt an immediate search for intracranial pathology. Patients with slower-growing tumors are likely to present with seizure activity, which occurs in up to 70% of cases, whereas those with more rapidly growing tumors such as glioblastoma have a seizure rate between 30% and 40%.

Focal findings are often present and may help the physician localize the tumor. Patients with tumors of the anterior frontal lobes can present with changes in attention span, impaired intellect, difficulty in communication, losses in inhibition, and changes in behavior. More posterior lesions may cause focal findings of weakness or seizure activity.

Lesions of the temporal lobe may cause seizures, weakness, visual field defects, and memory impairment, most often for recent events. Speech and language disturbances are frequent in those with tumors in the dominant temporal lobe. Temporal lobe seizures may include déjà vu, a sense of anger or fear, or hallucinations involving the sense of taste or sound and focal motor seizures.

Patients with occipital lobe tumors often present with visual field disturbances, hallucinations, and failure to recognize familiar objects. Parietal lobe tumors can cause deficits in sensation, inability to recognize letters or numbers, and neglect syndromes such as the lack of awareness of the opposite side of the body. Lesions of the dominant parietal lobe may cause difficulties in calculation, confusion in left-right orientation, and the inability to write.

More midline tumors, such as those of the thalamus, often cause symptoms of intracranial pressure, hydrocephalus, and weakness or sensory loss. Hypothalamic lesions produce endocrine or visual pathway abnormalities, or both. Tumors of the brain stem can cause multiple abnormalities, including motor and sensory weakness of the cranial nerves, weakness or numbness of the extremities (or both), nausea, vertigo, and hiccups. Such tumors may ultimately result in obstructive hydrocephalus. Cerebellar tumors often cause headache, ataxia, neck stiffness, nystagmus, vertigo, and nausea.

The differential diagnosis of these signs and symptoms includes other pathologies such as vascular lesions, inflammatory or infectious processes, and other conditions that may raise intracranial pressure. Often, imaging studies can distinguish these lesions from brain tumors. However, even with a characteristic lesion seen on scans, a biopsy or resection is usually indicated to confirm the diagnosis, specify the tumor type and grade, and improve neurologic symptoms.

**Diagnostic Neuroimaging**

**Magnetic Resonance Imaging**

Magnetic resonance (MR) imaging has become the standard for imaging patients with suspected brain tumors and is used for evaluation of response and tumor status. Although useful in some situations, computed tomography (CT) has largely been replaced by MR imaging, which is preferable because of the superior sensitivity of MR imaging and the relative ease of acquiring multiplanar images without loss of detail. Paramagnetic agents, such as gadolinium, also allow contrast scanning with minimal risk of allergic complications or renal toxicity. Moreover, the patient is not exposed to radiation.

Although very sensitive and relatively specific, MR imaging cannot yet definitively determine specific pathologic diagnoses; tumor biopsy or resection is required for that purpose. The field of MR imaging is changing rapidly, however, with new techniques becoming avail-
able that will increase specificity and reduce scanning time and costs.

Figure 2 shows findings typical for a malignant glioma. Figure 2A is an axial, gadolinium-enhanced image that shows a well-circumscribed tumor in the right frontal lobe. Areas of heterogeneity are seen within the tumor, suggesting some areas of necrosis and varying cellular density and recent hemorrhage. Figure 2B is the same lesion represented in the coronal plane, and Fig. 2C is the T2-weighted
image, showing the various compartments of the lesion and surrounding edema that extends beyond the periphery of the actual lesion.

Figure 2D is a contrast-enhanced image showing the appearance of the lesion site after an extensive resection. In this setting, minimal, if any, residual enhancement remains, and the surgical cavity is now filled with cerebrospinal fluid (CSF). This MR image was made 24 hours after surgery to reduce the effects of surgery and the healing process, which produce imaging artifacts that may appear similar to residual tumor. In this case, the tumor was a glioblastoma multiforme.

MR imaging is particularly useful for assessing response to treatment and aiding in diagnosis. Figure 3 depicts the changes seen after chemotherapy in a patient with a pinealoblastoma. Figure 3A, which was made before treatment, shows a contrast-enhancing lesion in the midbrain. After one cycle of treatment with chemotherapy, the lesion is significantly reduced (Fig. 3B), which qualifies as a partial response.

**Fig. 3.** Findings of magnetic resonance (MR) imaging in a patient treated for pinealoblastoma. (A) Axial, T1-weighted, contrast-enhanced MR image of a tumor in the midbrain. (B) Appearance of the lesion after one cycle of chemotherapy.

**Positron Emission Tomography**

Assessment of response is clearly an important issue in the evaluation of new agents or treatment strategies. However, differentiating the effects of previous therapy, which may cause changes in the MR image, from the effects of tumor progression may be difficult. Differentiation is particularly important when previous treatment includes conventional radiotherapy or high-dose radiotherapy delivered by interstitial brachytherapy or radiosurgery. The MR appearance of radiation necrosis is similar to that of tumor progression.

In these cases, considering the use of metabolic imaging such as positron emission tomography (PET) is important. Fluorine 18 fluorodeoxyglucose is most commonly used in this setting.
nant tumors show hypermetabolism compared with normal surrounding brain, whereas radiation-injured or necrotic brain shows reduced metabolism (Fig. 4). Figure 4A is an MR image of a malignant glioma that previously had been treated with gamma-knife radiosurgery. A small area of new contrast enhance-
ment was noted in the median temporal lobe just adjacent to a resection cavity. PET imaging (Fig. 4B) shows this lesion to be hypermetabolic to normal brain, which is consistent with true tumor progression. Figure 4C is an MR image made after gamma-knife radiosurgery, again showing an area of contrast enhancement, which appeared several months after treatment. With PET imaging (Fig. 4D), no evidence of enhanced metabolic activity was seen within the region of new enhancement, and the patient was considered to have a response to therapy.

In both cases, areas of enhancement may have been considered either tumor progression or radiation injury. Without confirmation with PET, these patients might have been treated inappropriately.

Magnetic Resonance Spectroscopy

Although valuable for the reasons mentioned earlier, PET imaging is not widely available and requires the generation of short half-life isotopes, which must be used quickly. New modalities of noninvasive tumor assessment are currently being evaluated. One of these is magnetic resonance spectroscopy (MRS), which is available with routine MR imaging equipment. Areas of interest may be evaluated for intracellular metabolites, making it possible for late radiation injury to be differentiated from tumor.

When proton MRS is used, three metabolites are of greatest interest: choline-containing compounds, creatine plus phosphocreatine, and N-acetylaspartate. Tumors often show elevated levels of all three metabolites, whereas necrotic brain has reduced levels. Specific ratios of these compounds are used to express the relative changes to normal brain and to determine tumor activity. New machines
are now able to assess these regions using three-dimensional imaging techniques with simultaneous registration to the normal MR imaging data set and with retrospective realignment with previous MR

imaging and MRS data to allow sequential analysis over time.

Figure 5 shows the typical appearance of a normal brain (Fig. 5B), the tumor MRS pattern (Fig. 5C), the pattern seen with necrosis (Fig. 5D), and the corresponding MR image (Fig. 5A). Continued research into this type of image analysis will greatly enhance our ability to assess the response to and toxicity of various modalities of therapy being used today.

FUNCTIONAL MR IMAGING

Neuroimaging is especially important in guiding the surgeon to perform a safe resection. In most cases of suspected or known tumor, one goal of surgery is to remove as much of the tumor as is safely possible. Image-guided resections are frequently used to achieve this goal.

Computer-assisted stereotactic tumor removal requires that data be collected from various imaging modalities and integrated into the three-dimensional coordinate system and that specialized operating instruments be used at the time of surgery. Probes used during the procedure help localize the areas of interest to the three-dimensional images available on monitors in the operating room, allowing the surgeon to have the same three-dimensional field of view.

With this capability, both deep-seated lesions and more superficial tumors are more accessible for extensive resections. Even with this capability, the surgeon also must know where critical functional areas of brain exist within individual patients because some geographic variability is present for motor/sensory cortex and language. Functional MR imaging helps in this regard, and as with the three-dimensional imaging discussed earlier, the data can be integrated and displayed in the operating room.

Figure 6 depicts the information that can be acquired by this process. In Fig. 6A the positions of motor cortex for various body parts are shown in red, superimposed on a brain MR image surface rendering. Figure 6B shows the relationship of areas of motor cortex to a tumor (shown in green). Figure 6C–F depicts the location of the left second digit of the hand in relation to conventional axial and sagittal MR images. The tumor is shown as a contrast-enhancing lesion with an area of central necrosis (6C and D). In 6E and F, the cortical localization of the finger, which is slightly anterior to the tumor margin, is superimposed on the same images. The availability of this type of imaging facilitates surgical treatment planning.

None of the general signs and symptoms of CNS tumors—headache, nausea or vomiting, and changes in levels of consciousness—are specific to a brain tumor, and few patients with headache are found to have a brain tumor.
Fig. 6. Functional magnetic resonance (MR) imaging. (A) Functional brain MR image shows a surface rendering of a brain, with areas of motor cortex depicted in red and identified by the text. (B) Three-dimensional MR image shows facial structures and brain surface. A tumor is identified in green, and areas of the motor cortex important to the surgeon are depicted in red, showing the relationship of tumor to motor areas. (C–F) MR images of a contrast-enhancing tumor in the frontal lobe shown in the sagittal plane (C) and the axial plane (D). The relationship of the left second digit (LD2) motor cortex to the lesion is shown in the sagittal plane (E) and the axial plane (F).
and enhances the possibility of a more complete resection.

Surgical Considerations

An accurate diagnosis of tumor requires surgery, and except in a few situations, biopsy is at least attempted in each patient. Imaging modalities have improved in recent years but still cannot be relied upon entirely to determine the precise pathology. With the stereotactic procedures currently available, tissue samples should be obtainable from any location in the brain.

Exceptions exist to this approach for tissue sampling, particularly in tumors that arise from the brain stem, which have imaging characteristics that are sufficient to make an accurate diagnosis. Diffuse lesions intrinsic to the pons and medulla are predominately infiltrating astrocytomas, often grade II or III (using the WHO classification), and the clinical outcome for these patients is consistently poor independent of the pathologic grade. Because extensive tumor resections are not possible, the clinical and radiographic findings are so characteristic, and outcome does not depend on tumor grade, biopsies are not recommended. For almost every other situation, however, at least a biopsy is recommended.

In most cases, an attempt at surgical resection is also recommended. Several compelling reasons exist to support this approach, including the problem of sampling error, which may occur with small biopsy specimens. A significant amount of heterogeneity exists in many tumor types, and a small biopsy sample may reveal fewer malignant features of what really may be a more aggressive tumor.

A rationale for tumor resection is also appropriate, whenever possible, to improve symptoms related to mass or pressure effect that the tumor may be causing. Rapid clinical improvement is possible with more extensive resections in symptomatic lesions.

In some cases, a complete tumor removal is possible, and a surgical “cure” is achieved. This is the case for many benign tumors, such as meningiomas and juvenile pilocytic astrocytomas. In these situations, a complete surgical resection is all that is needed from a therapeutic standpoint, and complete resection may preclude the need for radiotherapy, which may have long-term negative consequences, particularly in a very young or very old patient.

Among the familial syndromes that involve tumors of the CNS are neurofibromatosis types 1 and 2, von Hippel-Lindau disease, tuberous sclerosis, Li-Fraumeni syndrome, and Turcot’s syndrome.

In other situations, a biopsy is sufficient to establish the diagnosis, and further resection is not necessary for that purpose or to resolve symptoms or improve survival. In primary CNS lymphoma, for instance, no survival benefit is gained from a tumor resection more extensive than biopsy alone if the response to chemotherapy and radiotherapy is excellent.

In other tumor types, a relationship may exist between the extent of tumor resection and survival expectation. Further research is needed in this area, however. Some controversy still exists, particularly in astrocytic tumors, over whether more extensive resection influences survival. Biopsy alone compared with larger resection is associated with a shorter survival
in patients with glioblastoma multiforme, but whether a 25% resection is “better” than a 50% or 75% resection is not known with certainty. Similar questions exist for low-grade infiltrating astrocytomas other than pilocytic tumors.

With the sophisticated neurosurgical and imaging techniques described earlier, reducing the amount of tumor burden in patients with high-grade tumors is now possible, and the procedure can be done safely.

**Radiotherapy**

Radiotherapy for CNS tumors is usually carried out using x-rays, gamma rays, neutrons, protons, and other heavy particles. DNA damage is the major event in tumor cell kill after radiation. The mechanism of this damage involves the formation of hydroxyl radicals, which may exist for longer periods in the presence of oxic cells. Hypoxic tumor cells, in contrast, are believed to be more resistant to the DNA-damaging effects of radiation. Unfortunately, large numbers of hypoxic tumor cells probably are present in highly malignant tumors such as glioblastoma multiforme, which may in part explain the limited time of tumor control in this CNS tumor.

**Conventional Radiotherapy**

X-rays produced by linear accelerators are most commonly used in patients with CNS tumors. In most settings, three-dimensional treatment planning is used to maximize tumor control and limit treatment to tumor and adjacent brain. Whole-brain radiation is not recommended for most patients with primary astrocytic tumors but is used in other diseases, such as medulloblastoma, other PNETs, and primary CNS lymphoma. Computed tomography is used for dose calculations, but MR imaging also may be needed to improve identification of tumor margins; thus, both modalities may be necessary to achieve local tumor control and reduce toxicity.

In many intracranial tumors, an effective radiation dose may be limited by the normal tissue tolerance of brain white matter, and the treatment planning described earlier is critical to decrease the risks of both acute and long-term complications of treatment. The biologic effect of the radiation dose depends on the time course in which the dose is given and not just on total dose. Thus, fractionation scheme as well as dose is important to the biologic effect, as characterized by the following formula:

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\text{Biologically effective dose (Gy)} = D[1 + d/(\alpha/\beta)]
\]

For this formula, \(D\) = total dose, \(d\) = dose per fraction, and the factors \(\alpha\) and \(\beta\) are used to describe the type of cell being irradiated. Typically, an \(\alpha/\beta\) ratio of 10 is used for early-reacting tissue, such as tumor cells, and an \(\alpha/\beta\) ratio of 3 is used for late-reacting tissue, such as normal brain.

Thus, one may compare the biologically effective dose of various dose-fractionation treatment regimens. For instance, a similar tumor response may be expected when a tumor is treated with a large single fraction of 15 Gy or with 54 Gy delivered over 30 fractions. However, considering a dose-fractionation scheme that protects late-reacting tissue (brain white matter) and is equally effective for tumor control may be advantageous. One such strategy is the use of hyperfractionated techniques, in which more frequent fractions are used each day (two or three times a day), which may allow an overall higher dose to be delivered without necessarily increasing risk to normal brain.

**Brachytherapy**

Another approach to local tumor control in CNS tumors is interstitial brachytherapy. With the use of stereotactic procedures, temporary implants can be placed precisely within the tumor bed, delivering additional radiation to a very focal field. The procedure is done using local anesthesia, after careful dose calculations and
final dosimetry using CT planning techniques. A final tumor dose is determined, and the sources are removed usually within 4 to 5 days.

In malignant glioma, a prescription dose of 50 to 60 Gy is usually planned. With high-activity iodine 125 sources, a dose rate of 40 to 60 cGy/hour is used. The acute risks of the procedure are minimal and well tolerated. However, risks of late radiation injury causing symptomatic necrosis exist, with up to 40% of patients requiring surgical removal of necrotic brain 6 months to 2 years later. In carefully selected patients, however, prolonged disease-free survival is possible.

In contrast to removable, high-activity I sources, permanent sources also can be used. In this procedure, low-activity sources are placed along the tumor margin at the time of surgical resection. The dose rate for these sources is closer to 10 cGy/hour, and a total dose up to 210 Gy is possible, with the peak dose delivered over a 2-month period. The sources are left in place indefinitely. The risk of symptomatic necrosis appears to be reduced with this approach, which permits treatment of larger tumor volumes than can be treated with removable, high-activity sources. To date, controlled clinical trials have not been conducted to compare these two approaches.

Radiosurgery

One other method available to treat local tumor is radiosurgery. A misnomer, radiosurgery does not involve surgery other than the placement of a stereotactic frame on the skull of the patient. The technique, initially developed Lars Leksell, essentially allows multiple source beams (more than 200) to converge and focus on a small target isocenter.

One apparatus designed to accomplish this process is the gamma knife, but linear accelerators have been modified to achieve the same endpoint. The gamma knife uses cobalt 60 as the source, but other sources, such as protons, also may be used. Small, deep-seated malignant lesions are often treated with radiosurgery, and high local control rates are possible. Nonmalignant lesions, such as arteriovenous malformations, are also treated using this technique.

As with interstitial brachytherapy, the risk of radiation injury has to be taken into account, and the risk increases as the size of the tumor volume increases. Usually, small lesions are ideal candidate lesions for radiosurgery, with what appears to be a smaller risk of symptomatic necrosis compared with that of interstitial brachytherapy using high-activity sources. Local tumor control rates are believed to be equal with the two approaches. Lesions too large for radiosurgery still may be treated with removable or permanent brachytherapy sources.

Chemotherapy

Chemotherapy for brain tumors is most often used as part of a multimodality approach that includes surgery and radiotherapy. It may be given before, during, or after radiation and again at the time of tumor progression.

Drug delivery remains a challenge for oncologists treating these tumors. Tight junctions between endothelial cells normally control the blood–brain barrier. Large molecules with low lipid solubility and extensive plasma protein binding are unable to pass through an intact barrier. Unfortunately, many chemotherapeutic agents have these characteristics and would not be expected to enter the tumor bed. Although disruption of the blood–brain barrier is commonly seen within areas of greatest tumor bulk, particularly in the higher-grade tumors, this barrier protects other areas of tumor.

Intraarterial drug delivery alone or with osmotic blood–brain barrier disruption has been used as a strategy to overcome this limitation. Higher drug concentrations can be used with intraarterial
delivery than with intravenous delivery, and intraarterial delivery may be further enhanced by the use of hyperosmotic solutions of mannitol. Nonosmotic agents also have been developed and tested recently. The results of these trials are still being evaluated. It is not yet clear that intraarterial therapy offers survival results superior to those seen with standard intravenous chemotherapy.

Chemotherapeutic drugs also may be delivered directly into the tumor, either at the time of surgical resection or via stereotactic procedures. Again, the strategy is to increase drug concentration to tumor and bypass the blood–brain barrier. Also, biodegradable polymers may be impregnated with chemotherapeutic drugs and the polymer “wafers” placed into the tumor bed during surgery. Over time, drug diffuses out of the wafer and penetrates into the tumor. Each of these approaches has been tested in clinical trials and may be appropriate to consider as a therapeutic option in carefully selected patients.

High-dose chemotherapy also has been used in malignant tumors. Autologous bone marrow is used to support patients through the toxicity of myeloablative therapy; more recently, peripheral blood stem cell support has been administered. This approach appears more successful in chemosensitive tumors, such as medulloblastoma and PNETs, with a minimal tumor burden. More resistant tumors, such as glioblastoma multiforme, are less likely to respond to such treatment, in part because of other mechanisms of resistance inherent to those tumors and, again, in part because of the blood–brain barrier. Carefully controlled phase III studies have yet to be done with sufficient numbers of patients to assess the true response rate in selected tumor types or the impact of this therapy on survival.

The most commonly used chemotherapeutic drugs are alkylating agents, particularly the nitrosoureas. These drugs have been used as single agents or in combination with other drugs such as procarbazine and vincristine. Although these drugs are used successfully to control growth or reduce tumor burden in some tumors, in many cases the benefit is short lived or not apparent.

Many mechanisms of drug resistance exist to limit the cytotoxic effects of these classes of agents. One mechanism of resistance includes repair of alkylator-based DNA crosslinks by O6-alkylguanine DNA alkyltransferase, which mediates the repair process.23 This repair protein is present in tumor cells, and strategies to inhibit the protein are now available and being tested in phase I and II trials. Other mechanisms of resistance are known to be present in tumor cells, including increased levels of P-glycoprotein, glutathione S-transferase, and other enzymes. Much of the ongoing research in CNS tumors is designed to either find new chemotherapeutic agents or specifically improve tumor cell delivery of currently available drugs.

The commonly used drugs for CNS tumors are listed in Table 5. New drugs being developed and biologic and gene therapy approaches are discussed later in this article.

Treatment of Specific Tumor Types

A brief description of some clinical and therapeutic features of the most common CNS tumors follows. Readers are encouraged to refer to specific texts for a comprehensive review of each subject.

Malignant Astrocytomas

Glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic mixed gliomas are generally referred to as malignant astrocytomas. However, each of these entities has different clinical behavior and survival expectations. In most cases, clinical trials attempt to distinguish these tumors in terms of describing treatment effect ei-
Glioblastoma Multiforme

The mean age at diagnosis for patients with glioblastoma multiforme is 54 years. These patients most often have a single, large, supratentorial, contrast-enhancing lesion seen on MR imaging and a short history of neurologic findings noted before diagnosis.

Most patients are treated with surgery and radiotherapy. When adjuvant chemotherapy is used, it is usually given at the initiation of radiotherapy and again after the completion of radiotherapy. The agent most commonly used is single-agent BCNU (carmustine). The goal of surgery is to make a specific diagnosis, relieve symptoms, and reduce tumor bulk to the maximum extent possible.

With this approach, the median survival expectation is approximately 50 weeks, which, unfortunately, has not changed significantly in more than 30 years. Various prognostic factors influence survival, with younger age being one of the strongest predictors of longer survival (Table 6).

In some cases, the role for any additional therapy beyond a biopsy to determine the diagnosis is probably not indicated. Older patients with large, nonresectable lesions that cause significant neurologic impairment may not achieve a meaningful prolongation in survival and may not recover any useful function despite therapy. This situation is

| Drug                     | Mechanism                                      |
|--------------------------|------------------------------------------------|
| Nitrosureas              |                                                |
| BCNU (carmustine)       | DNA crosslinks, carbamoylation of amino groups  |
| CCNU (lomustine)        |                                                |
| ACNU (nimustine)        |                                                |
| Procarbazine             | ? DNA alkylation, interference with protein synthesis |
| Carboplatin              | Chelation via intrastrand crosslinks           |
| Cisplatin                |                                                |
| Cyclophosphamide        | DNA alkylation, carbonium ion formation        |
| Ifosfamide               |                                                |
| Paclitaxel               | Microtubule function inhibitors               |
| Vincristine              |                                                |
| Etoposide                | Topoisomerase II inhibitors                    |
| Teniposide               |                                                |
| Topotecan                | Topoisomerase I inhibitors                     |
| Irinotecan (CPT-11)     |                                                |
| Tamoxifen                | Protein kinase C inhibitor (at high doses)     |
not common, however. Typically, patients can undergo at least a partial tumor removal and remain ambulatory and able to care for most of their daily needs.

The use of radiotherapy clearly has been proved to increase survival time beyond that achieved by the best palliative care measures. In many earlier studies, whole-brain radiation was used despite the appearance of a local/regional tumor burden. The most common site of relapse is within the original tumor site or within 2 to 4 cm of the margin. Although tumor cells are known to exist well beyond that margin, morbidity and mortality are generally consequences of local/regional failure. Whole-brain radiation has not been shown to increase survival compared with focal radiotherapy. In fact, whole-brain radiation can cause significant negative side effects, particularly in older patients or in patients who survive beyond the median survival time of 1 year.25

Currently, patients are treated with focal radiotherapy, using three-dimensional conformal techniques to reduce the dose to the noninvolved brain. More intensive radiation is possible in selected patients using interstitial brachytherapy or radiosurgery techniques. Indeed, these patients have been shown to survive longer when additional radiation “boost” procedures are used.

Patient selection factors may influence these survival expectations, and phase III studies have been inconclusive thus far, both favoring brachytherapy and showing no additional benefit. Further studies are ongoing, particularly with the use of radiosurgery. Adjuvant chemotherapy also may increase survival in some patients. Although most patients appear to have the same median survival with or without adjuvant BCNU, younger patients with otherwise favorable prognostic factors do appear to have a slight survival advantage when chemotherapy is used as an adjuvant to radiotherapy.26 Unfortunately, most patients still die within 2 years despite intensive radiotherapy and adjuvant chemotherapy.

Treatment strategies used at the time of tumor recurrence include additional surgery, interstitial brachytherapy or radiosurgery, and chemotherapy. Patients are generally believed to be good candidates for surgery if a substantial resection is possible, they have good perfor-

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**Table 6**

| Favorable Prognostic Factors in Malignant Astrocytomas |
|---------------------------------------------------------|
| **Glioblastoma Multiforme**                              |
| Younger age                                             |
| Higher Karnofsky performance status                     |
| Extent of resection (more than biopsy)                  |
| Use of postoperative radiation                          |
| Adjuvant chemotherapy (possibly)                        |
| Long duration of symptoms                               |
| Response to radiation (possibly)                        |
| **Anaplastic Gliomas**                                  |
| Younger age                                             |
| Higher Karnofsky performance status                     |
| Extent of resection (probably)                           |
| Use of postoperative radiation                          |
| Adjuvant chemotherapy (probably)                        |
| Oligodendrogliarial component                           |

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Primary CNS tumors

Glioblastoma Multiforme

Anaplastic Gliomas

Younger age

Higher Karnofsky performance status

Extent of resection (more than biopsy)

Use of postoperative radiation

Adjuvant chemotherapy (possibly)

Long duration of symptoms

Response to radiation (possibly)

Table 6

Favorable Prognostic Factors in Malignant Astrocytomas

| Glioblastoma Multiforme | Anaplastic Gliomas |
|-------------------------|-------------------|
| Younger age             | Younger age       |
| Higher Karnofsky performance status | Higher Karnofsky performance status |
| Extent of resection (more than biopsy) | Extent of resection (probably) |
| Use of postoperative radiation | Use of postoperative radiation |
| Adjuvant chemotherapy (possibly) | Adjuvant chemotherapy (probably) |
| Long duration of symptoms | Oligodendrogliarial component |
| Response to radiation (possibly) | |
mance status, and additional therapy is available beyond that of surgery alone. An additional reason for surgery is to treat with local therapies, such as interstitial brachytherapy or polymer-based drug delivery. Again, these salvage therapies are most useful in well selected patients in whom enhanced survival is expected.

**MR imaging has become the standard for imaging patients with suspected brain tumors and is also used to evaluate the status of the tumor and the patient’s response to therapy.**

Unfortunately, many patients are not candidates for additional surgery or radiotherapy because they have a large tumor burden or their tumor is located in areas of brain where surgery, focal radiation, or chemotherapy would be dangerous. Systemic chemotherapy is often used in these patients, either as an adjuvant to additional surgery or radiotherapy or alone as the single modality of therapy. Survival expectation at the time of initial relapse is poor, often only 4 to 6 months.

**Other Anaplastic Tumors**

Patients with anaplastic tumors other than glioblastoma multiforme have a much different prognosis, with median survival expectations of 4 to 5 years. Although some of the same prognostic variables that are important for glioblastoma multiforme are also important for these tumors, other factors appear to play a role in improving survival.

The evidence supporting additional radiotherapy beyond conventional external beam therapy is not as compelling as that seen in patients with glioblastoma multiforme. In one phase II study, for instance, the use of interstitial brachytherapy after external beam radiation was associated with more toxicity and was not shown to improve survival over that seen in historical studies that did not use brachytherapy. No studies have been conducted that address the use of radiosurgery as a boost after external radiotherapy, and the modality is not routinely used in this patient group.

Although longer survival with multimodality treatment including adjuvant chemotherapy has not been proved in the setting of phase III studies, retrospective evaluation of patient outcomes with these unique tumor types suggests this is the case. Because of these results, most patients are currently treated with chemotherapy after focal radiotherapy.

One small randomized phase III study compared the use of single-agent BCNU with the combination of procarbazine, CCNU (lomustine), and vincristine (PCV) in patients with glioblastoma multiforme and anaplastic gliomas. The investigators found a statistically significant survival advantage in patients with anaplastic gliomas treated with the three-drug combination. No such advantage was seen in patients with glioblastoma multiforme. The sample sizes were small, however, and other studies have suggested that no advantage exists with PCV compared with BCNU alone.

Patients with pure anaplastic oligodendrogliomas or mixed anaplastic oligoastrocytomas also appear to have a more favorable response to treatment than do patients with pure anaplastic astrocytomas. Indeed, it has been shown that patients with pure anaplastic oligodendrogliomas often have a complete response to chemotherapy before radiotherapy or at the time of relapse. The chemotherapy used in those studies was PCV.
These lines of evidence strongly suggest that adjuvant chemotherapy is an appropriate modality for patients with anaplastic gliomas. Specific phase III studies still need to be conducted to determine whether chemotherapy does or does not benefit newly diagnosed patients with anaplastic gliomas.

As was discussed for patients with recurrent glioblastoma multiforme, patients with recurrent anaplastic glioma should be considered for a second surgical resection, interstitial brachytherapy or radiosurgery, other chemotherapy approaches, or some combination of these treatments. In patients who did not receive adjuvant chemotherapy earlier, PCV chemotherapy is frequently used. New chemotherapy agents (discussed later in this article) are often tested in this patient group.

Patients in first relapse may be retreated successfully for 1 to 2 years but eventually become resistant to treatment, and their biologic behavior is similar to that of patients with recurrent glioblastoma multiforme, with a short survival expectation after successive relapses. Because median survival expectations (measured from the initial diagnosis) are 4 to 5 years, we have now seen more of the long-term effects of treatment, such as treatment-related second tumors, vascular abnormalities believed to be secondary to radiotherapy, and chronic neuropsychological deficits.

Low-Grade Gliomas
Low-grade gliomas include grade 2 fibrillary or protoplasmic astrocytomas, oligodendrogliomas, mixed oligoastrocytommas, juvenile pilocytic astrocytomas, gangliogliomas, gangliocytomas, pleomorphic xanthoastrocytomas, dysembryoplastic neuroectodermal tumors (DNETs), and others.

Obviously, with such a diverse spectrum of histologic subtypes, variations exist in clinical presentation and treatment approach. In general, however, patients with these tumors are young adults or children, are often diagnosed after a history of seizures, and may have either nonenhancing or enhancing tumors on MR imaging. Clinical and imaging characteristics may strongly suggest one tumor type over another, but most cases require at least a biopsy to confirm the specific pathology.

Patients with ependymomas who are treated with radiotherapy after incomplete surgical resection fare much better than do those treated with surgery alone.

Complete surgical resection may be all that is necessary for treatment of some of these tumors and should be considered whenever possible. For instance, a completely resected pilocytic astrocytoma in the cerebellum requires no further therapy. Pilocytic astrocytomas in the hypothalamus or involving the optic nerves and chiasm, however, can be completely resected only rarely. Often these tumors cause functional deficits such as visual loss or endocrine abnormalities. Additional therapy is needed in this setting. In younger children, chemotherapy is frequently the first therapy used and can successfully control tumor growth for many years, deferring the need for external beam radiotherapy. Other tumors, such as the recently described dysembryoplastic neuroectodermal tumor, have a favorable outcome, even with partial resection, and treatment beyond surgery is not recommended. The same is true for most cases of pleo-
morphic xanthoastrocytoma or ganglioglioma. Tumor may grow slowly over many years before treatment is considered. In these cases, repeat resections should be considered.

The natural history of other tumors, particularly WHO grade II infiltrating astrocytomas in young adults, differs from that of pilocytic astrocytomas. Treatment options for those tumors include the spectrum of no treatment, radiation, chemotherapy, and, in some cases, the combination of radiation and chemotherapy. Adults with these tumors can present in their early twenties or thirties after a seizure. In many cases, complete surgical resection is impossible because of the extent and location of the tumor. Surgical biopsy or partial resection is recommended, however, to confirm the diagnosis.

The drugs most commonly used to treat CNS tumors are alkylating agents, particularly the nitrosureas, which are used as single agents or in combination with other drugs.

Patients without symptoms may be treated at the time of diagnosis or followed with routine neurologic assessment and serial MR images. If the lesion grows in size or begins to produce symptoms, treatment can be considered. One approach is not clearly superior to the other. Some studies strongly suggest that early intervention with radiotherapy is appropriate, whereas others take the approach that intervention later in the course of the disease does no harm.

Again, prognostic factors influence the outcome of these patients and should be considered when treatment decisions are made. Tumors in patients older than 50 years tend to have more aggressive biologic behavior than do similar tumors in younger patients and should be considered for immediate treatment, particularly if bulky residual disease is present. Small surgical biopsies may underestimate the true malignant nature of some of these tumors because of sampling error or the difficulty of accurate pathologic grading as a result of the small tissue specimen. Thus, older or younger patients with a short clinical history and a large contrast-enhancing tumor who undergo a small biopsy procedure may actually have a higher-grade tumor. These patients should be treated.

In addition to age, the extent of surgical resection may be an important predictor of survival. Several small retrospective studies of patients followed over long periods suggest that patients who undergo a complete resection have an increased survival compared with those who have partial removal or biopsy alone. Patient selection factors, however, make it impossible to confirm these observations, and no controlled studies are available that randomize patients to treatment with biopsy alone or resection (either complete or subtotal) with uniform treatment after surgery. It is unlikely that such a study would ever be conducted. However, an attempt at maximal surgical resection should at least be considered in these patients.

Radiotherapy is given to the tumor area and a margin surrounding it rather than to the whole brain. The optimal treatment dose is not clear. In most cases, a dose of 54 Gy is used. In some recent prospective studies, lower doses appear to have an efficacy similar to that of 54 Gy, whereas other retrospective series suggest that higher doses are superior. Further studies are needed to resolve this issue.

Chemotherapy is generally reserved
for tumor progression, and PCV chemotherapy is frequently used. Patients with oligodendrogial tumors often respond to this regimen with a reduction in tumor size, whereas those with pure astrocytomas more often stabilize or show no change for prolonged periods. Eventually, relapses occur, with shorter periods of progression-free survival at each relapse. Although it is true that many of these patients have a long natural history, most patients eventually die of tumor progression or transformation to a more malignant phenotype. Often, at the time of repeat resection of what initially was called a grade 2 astrocytoma, pathologic features characteristic of glioblastoma multiforme are found.

EPENDYMOMAS

Ependymomas arise from ependymal cells lining the ventricles of the brain and the central canal of the spinal cord. They can arise in the brain or spine along these surfaces or in adjacent parenchyma, but they appear most often in the posterior fossa.

Pathologically, these lesions are classified as either low-grade or anaplastic tumors, and they display several variants, such as cellular, papillary, clear cell, tanyctic, and myxopapillary types. It is unclear whether the degree of anaplasia really predicts clinical outcome. Children with posterior fossa ependymomas are often found to have anaplastic tumors and tend to have a higher risk of neuroaxis spread than do adults with spinal cord ependymomas. Most tumors are found below the tentorium, within the fourth ventricle of the posterior fossa or in the spine. Tumor can spread via CSF pathways, and the neuroaxis and CSF are staged to assess the extent of disease.

Treatment decisions are based on the patient’s age, extent of resection, and tumor spread. Many series have shown that young age is a predictor of poor outcome. In several series, the 5-year survival rate for children with posterior fossa ependymoma was less than 20%, whereas adults with a similar tumor location had up to an 80% survival rate. The youngest children seem to fare the worst, particularly those less than 2 years of age.

In addition to age, the extent of surgery is important. Patients with partially resected lesions have a much greater likelihood of recurrence than do patients whose tumors can be completely resected. An attempt at complete resection should be considered whenever possible. Patients who are diagnosed based on a small biopsy should have a more extensive resection completed soon thereafter. Unfortunately, in some cases, complete resection is not possible because of tumor location or the degree of invasion of adjacent structures.

Patients with primitive neuroectodermal tumors who have good-risk features have a 5-year survival rate of more than 75%.

Patients treated with radiotherapy after surgery fare much better than do those treated with surgery alone. Five-year survival rates for those with surgery alone range from 20% to 40%, but the rates increase to 40% to 80% if radiation is given after surgery. Thus, radiotherapy also is believed to be a predictor of survival and is accepted as standard treatment after surgery.

The major controversy with radiation appears to center on the extent of radiation to be used, i.e., focal treatment versus treatment of the entire neuroaxis. Perhaps because of the small number of patients with this disease, carefully
controlled phase III studies addressing this question have not been done.

It appears that the greatest risk of relapse for patients without disseminated disease at initial diagnosis is focal failure, and subsequent neuroaxis spread is probably a consequence of this lack of local control. Thus, most patients are now treated with focal radiotherapy unless dissemination is documented at initial diagnosis. In general, a patient with a single lesion and no evidence of spread along the neuroaxis or tumor cells in the CSF can be treated with focal radiotherapy. Whole-brain or spinal radiotherapy is not given typically. Patients with disseminated disease should be treated with neuroaxis radiation. Again, the risk of recurrence appears highest in those with partially resected tumors.

Unfortunately, chemotherapy appears to have little if any impact on newly diagnosed patients. Chemotherapy given at the time of relapse may halt disease progression for short periods but is unlikely to cause tumor regression. Much more research is needed in this area of treatment. Both of the large cooperative groups treating children with these diseases are undertaking phase I and II studies to find specific new agents or combinations of drugs to treat these tumors.

**MEDULLOBLASTOMAS/PRIMITIVE NEUROECTODERMAL TUMORS**

Primitive neuroectodermal tumors include many malignant tumors commonly seen in children and young adults. Lesions of the cerebellum are called medulloblastomas, those arising from the pineal region are called pinealoblastomas, and those arising from the cerebrum are called cerebral PNETs. Other rare sites include the brain stem and spinal cord. The cerebellum is the most common location for these tumors. Despite the various sites of origin within the CNS, these tumors appear to have similar morphologic and clinical features. The cell of origin is unknown. Histologically, these tumors can show areas of glial, neuronal, or ependymal differentiation, or they can be undifferentiated. The most common cytogenetic abnormality is isochromosome 17q.

PNETs can disseminate widely throughout the CNS, and treatment is planned to include the entire brain and spine. Other intracranial tumors in addition to PNETs can spread beyond the CNS to include bone and other organs, although the incidence of such spread is low.

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**The risk of relapse in meningioma is directly related to the extent of resection, which can be used to guide additional therapy**

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Patients with PNETs are classified as having either good-risk or poor-risk features, based on the extent of residual disease after resection and the presence of disease beyond the primary site. Staging is done either before surgery or 2 to 3 weeks thereafter and includes MR imaging of the spine and examination of the CSF for malignant cells.

Patients without residual disease based on postoperative MR imaging and negative results of CSF cytologic studies are believed to be good-risk patients. More than 75% of these patients survive for 5 years.\(^{40,41}\) Patients with bulky residual disease and dissemination in the brain, spine, or CSF have a much worse prognosis, with only 35% to 50% of these patients being disease-free at 5 years.\(^{40,41}\)

Treatment includes an attempt at gross total resection of the primary site if
possible. Patients with good-risk features are treated with radiation that includes the entire neuroaxis, with a larger dose given to the primary site. In general, children older than 3 years are treated with a dose of 54 Gy to the primary site and 36 Gy to the rest of the brain and spine. Patients with poor-risk features are treated with the combination of radiation and chemotherapy. Children younger than 3 years are treated primarily with chemotherapy in the hope that chemotherapy alone will achieve long-term control or defer craniospinal radiation until the patient is older.

A major risk for young children with good-risk features is the potential for late neurocognitive and endocrine deficits as a consequence of whole-brain radiation. Attempts to reduce this risk have included a reduction in the dose given to the brain and spine and the addition of chemotherapy as adjuvant treatment after low-dose craniospinal radiation. Recent research suggests that this strategy may indeed be possible without lowering survival expectations.

Unfortunately, children with poor-risk features who relapse despite the therapy outlined are rarely cured with second-line therapies. One approach to this group of children is the use of high-dose chemotherapy with autologous peripheral stem cell support. Even in this setting, most patients are not retreated successfully.

**MENINGIOMAS**

Meningiomas occur later in life, peaking at the sixth decade. Most grow slowly and have benign features on histopathologic evaluation. Atypical or malignant tumors account for less than 10% of these tumors. The most common cytogenetic finding is loss of chromosome 22, and mutations of $\text{NF2}$ are found in a high proportion of tumors. Meningiomas may occur as single lesions or in multiple sites, and they may be found incidentally at the time of MR imaging for other reasons or at autopsy for other diseases.

Symptomatic lesions should be resected, with the goal of complete resection if possible. A schema developed by Simpson to describe the extent of resection is shown in Table 7. The risk of relapse is directly related to the extent of resection, which can be used to guide additional therapy. In cases of grade 1 complete surgical resection, no additional therapy is needed, and the risk of relapse is minimal. Approximately 20% of resected lesions of grade 2 or 3 recur focally within 10 to 20 years if no addi-

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**Table 7**

**Classification of Extent of Resection of Meningioma**

| Grade   | Description                                                                 |
|---------|-----------------------------------------------------------------------------|
| Grade One | Gross total resection of tumor, dural attachments, and abnormal bone        |
| Grade Two | Gross total resection of tumor, coagulation of dural attachments            |
| Grade Three | Gross total resection of tumor without resection or coagulation of dural extensions or, alternatively, of its extradural extensions |
| Grade Four | Partial resection of tumor                                                  |
| Grade Five | Simple decompression (biopsy)                                               |

Adapted from Simpson.44
tional therapy is given.

Patients with persistent symptoms and partially resected tumors should be treated with radiotherapy. Patients with malignant meningioma have the highest rate of relapse and, unfortunately, the poorest response to treatment. Radiotherapy is commonly used in these cases, independent of the extent of resection. Re-irradiation is possible in some instances using stereotactic or gamma-knife radiosurgery, particularly in smaller lesions. Large recurrences that are not considered surgically resectable present the greatest challenge, with few options available.

**Accurate diagnosis of a CNS tumor requires surgery, and biopsy is attempted in every patient, with few exceptions.**

Approaches to these tumors have included the use of endocrine manipulations, chemotherapy, and treatment with inhibitors of growth factors. Progesterone and androgen receptors have been identified in these tumors, and clinical trials using inhibitors to these receptors have been initiated. Results of these trials are still pending. The use of conventional chemotherapy with agents commonly used for sarcomas in other sites has been unsuccessful, often at the expense of excessive toxicity and minimal response. The expression of PDGF and its receptor is a common event in meningiomas, suggesting an autocrine loop that may contribute to the growth of these lesions. Inhibitors to these growth factors have become available recently and need further clinical research.

**Investigational Approaches**

As previously mentioned, the pace of laboratory research for CNS tumors has increased over the last 10 to 15 years, particularly in molecular biology. A greater awareness of specific genetic abnormalities and their cellular consequences gives the hope that this research will ultimately translate into novel, more specific treatment strategies for patients with these disorders. Among the specific areas of ongoing clinical research are the testing of new agents, the modulation of mechanisms of resistance to standard chemotherapeutic agents, the inhibitors of growth factors and their receptors, the modification of angiogenesis and invasion, and gene therapy.

The new drugs currently being tested in phase I or II trials include temozolomide, an imidazotetrazine derivative with good oral bioavailability and minimal myelosuppression. This agent has shown activity in recurrent malignant gliomas and also is undergoing testing in newly diagnosed tumors.

Inhibitors of angiogenesis also have completed several phase I and II trials. The two agents in this category include TNP-470 and thalidomide.

Antibodies to VEGF have become available and will soon undergo phase I testing. Inhibitors of the matrix surrounding tumor cells also are being tested. An oral metalloproteinase inhibitor is currently in phase II and III clinical trials. The goal with this agent is reducing the invasive nature of these tumors.

Inhibition of signal transduction, via multiple pathways, has become another area of research. Inhibition of protein kinase C is one such strategy, and the drugs bryostatin, UCN-01, and tamoxifen are being used in this regard.

Inhibition of cell cycle progression by regulation of the cyclin-dependent kinase family of genes by the use of flavopiridol is to begin testing this year.
Other trials targeting PDGF and fibroblast growth factor as substrates for inhibitors of these growth factors have also begun phase I and II testing.

The herpes simplex thymidine kinase gene (HSVtk) was the first gene to be used in humans with recurrent malignant brain tumors. In this trial, a mouse retrovirus was used as the vector-producing cell. The goal of this line of research was to transfer the HSVtk gene into tumor cells and then to treat patients with the antiviral drug ganciclovir. HSVtk encodes for the viral enzyme thymidine kinase that phosphorylates ganciclovir. The phosphorylated metabolite is then toxic to the tumor cell. Phase I and II testing has now been completed, and a phase III study is currently under way.

Drug delivery remains a challenge for the oncologist treating brain tumors.

Early results of phase I trials show that some patients had regression of tumor, suggesting that gene transfer occurred. However, it is still not clear whether the antitumor effect was specifically caused by gene transfer or some other, yet unexplained, effect. A nonspecific inflammatory response is possible as well. A new gene therapy trial has recently opened using an adenovirus as the vector-producing cell for the HSVtk gene.

A new study will soon open with the goal of transferring the p53 gene into tumor cells, again using an adenoviral vector.

Intratumor injection of toxins represents another line of research being developed. In this strategy, various toxins are infused into the tumor-bearing area of brain using catheters and pump systems that can cause slow diffusion of the agent over a time. To select for tumor cells, the toxin is conjugated to substrates that ideally are able to bind to tumor only rather than to normal brain. Various strategies are being developed, including the use ofseudomonas exotoxin conjugated to interleukin-4 (IL-4) or to TGF-α. Receptors to both factors are highly expressed in tumor cells but not in normal brain. Phase I studies are just beginning.

Trials using tumor-specific vaccines also are in progress. In general, tumor cells removed from patients are modified using gene transfer techniques ex vivo, then irradiated, and finally injected subcutaneously back into the patient. Various cytokines are used for this purpose, such as granulocyte-macrophage colony-stimulating factor (GM-CSF). One variation includes the further step of removing draining regional lymph nodes after subcutaneous vaccination, then harvesting and expanding ex vivo autologous “stimulated” lymphocytes, which are then infused back into the patient. Results of these studies are eagerly awaited.

It is beyond the scope of this article to discuss all of the many novel ideas being tested in the clinic. Readers are also encouraged to review general textbooks on the subject of primary CNS tumors for more detailed information and discussion. Clearly, patients with malignant CNS tumors have many more options for participation in clinical research than was possible several years ago. Referral to specialized centers to discuss these options is highly recommended.
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