

*Medical Progress***BRAIN TUMORS**

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**T**HE term “brain tumor” refers to a collection of neoplasms, each with its own biology, prognosis, and treatment; these tumors are better identified as “intracranial neoplasms,” since some do not arise from brain tissue (e.g., meningiomas and lymphomas) (Table 1). However, for most intracranial tumors, the clinical presentation, diagnostic approach, and initial treatment are similar. This article will focus on general presentation, diagnosis, and specific treatment.

**EPIDEMIOLOGY**

The American Cancer Society estimates that 16,800 new intracranial tumors were diagnosed in 1999, more than double the number of diagnosed cases of Hodgkin’s disease and over half the number of cases of melanoma.<sup>2</sup> In 1999, primary cancer of the central nervous system was the cause of death in approximately 13,100 people. Metastases to the brain from a systemic primary cancer are even more common; one estimate suggests that more than 100,000 patients per year die with symptomatic intracranial metastases.<sup>3</sup>

For the period from 1950 to 1989, the age- and sex-adjusted incidence of primary tumors of the central nervous system at the Mayo Clinic was 19.1 per 100,000 persons per year (11.8 per 100,000 for symptomatic tumors and 7.3 per 100,000 for asymptomatic tumors).<sup>4</sup> This incidence is almost identical to that found in the Central Brain Tumor Registry of the United States, in which the annual rate was 11.47 per 100,000 persons.<sup>5</sup> Although data from the Florida Cancer Registry and other registries showed a significant increase in the incidence of malignant gliomas and central nervous system lymphomas in the elderly during the 1980s, other reports showed little or no change.<sup>6,7</sup> These differences can be attributed to ascertainment bias and to improvements in the management of common illnesses, which result in longer survival and the subsequent emergence of brain tumors that would not have been evident had the patient died at an earlier age of more common problems.<sup>8</sup>

Ionizing radiation is the only unequivocal risk factor that has been identified for glial and meningeal neoplasms. Irradiation of the cranium, even at low

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**TABLE 1. HISTOLOGIC CLASSIFICATION OF TUMORS OF THE CENTRAL NERVOUS SYSTEM.\*****Tumors of neuroepithelial tissue**

Astrocytic tumors  
Astrocytoma  
Anaplastic astrocytoma  
Glioblastoma multiforme  
Pilocytic astrocytoma  
Pleomorphic xanthoastrocytoma  
Subependymal giant-cell astrocytoma  
Oligodendroglial tumors  
Oligodendroglioma  
Anaplastic oligodendroglioma  
Mixed gliomas  
Oligoastrocytoma  
Anaplastic oligoastrocytoma  
Ependymal tumors  
Ependymoma  
Anaplastic ependymoma  
Myxopapillary ependymoma  
Subependymoma  
Choroid-plexus tumors  
Choroid-plexus papilloma  
Choroid-plexus carcinoma  
Neuronal and mixed neuronal–glial tumors  
Gangliocytoma  
Dysembryoplastic neuroepithelial tumor  
Ganglioglioma  
Anaplastic ganglioglioma  
Central neurocytoma  
Pineal parenchymal tumors  
Pineocytoma  
Pineoblastoma  
Embryonal tumors  
Medulloblastoma  
Primitive neuroectodermal tumor

**Meningeal tumors**

Meningioma  
Hemangiopericytoma  
Melanocytic tumor  
Hemangioblastoma

**Primary central nervous system lymphomas****Germ-cell tumors**

Germinoma  
Embryonal carcinoma  
Yolk-sac tumor (endodermal-sinus tumor)  
Choriocarcinoma  
Teratoma  
Mixed-germ-cell tumors

**Tumors of the sellar region**

Pituitary adenoma  
Pituitary carcinoma  
Craniopharyngioma

**Metastatic tumors**

\*This table has been abridged and modified from the World Health Organization classification.<sup>1</sup>

doses, can increase the incidence of meningiomas by a factor of 10 and the incidence of glial tumors by a factor of 3 to 7,<sup>9,10</sup> with a latency period of 10 years to more than 20 years after exposure. No other environmental exposure or behavior has been clearly identified as a risk factor. The use of cellular telephones, exposure to high-tension wires, the use of hair dyes, head trauma, and dietary exposure to *N*-nitro-

sourea compounds or other nutritional factors have all been reported to increase the risk of brain tumors; however, the data are conflicting and unconvincing.<sup>11-14</sup>

### CLINICAL PRESENTATION

Brain tumors can cause either focal or generalized neurologic symptoms. Generalized symptoms reflect increased intracranial pressure and consist of headache and, when the illness is severe, nausea, vomiting, and a sixth-nerve palsy. Focal symptoms and signs, such as hemiparesis and aphasia, reflect the intracranial location of the tumor. The frequency and duration of symptoms vary with the type of tumor (Table 2). For example, a rapidly evolving hemiparesis is more typical of a high-grade than a low-grade glioma.

Headache occurs in about half of all patients with brain tumors. Typically, the headache is diffuse, but it can accurately indicate the hemisphere in which the tumor is located.<sup>15</sup> Generally, the headache is more noticeable on awakening in the morning and, even without treatment, dissipates within a few hours. The headache can occasionally be unilateral and throbbing and can mimic migraine or even cluster headaches.<sup>16</sup>

Seizures occur at presentation in 15 to 95 percent of patients with brain tumors, depending on the type of tumor (Table 2). Typically, the seizures are focal but may become generalized and cause loss of consciousness. Postictal hemiparesis or aphasia (Todd's phenomenon) may indicate the location of the tumor.

Other symptoms that reflect the location of the tumor, such as hemiparesis or aphasia not associated with seizures, typically have a subacute onset and are progressive. The exception is a visual-field deficit that may develop progressively but that often goes unnoticed by the patient until it contributes to an accident (frequently an automobile accident).

### DIAGNOSIS

The only test needed to diagnose a brain tumor is cranial magnetic resonance imaging (MRI). Computed tomography (CT) can miss structural lesions, particularly in the posterior fossa, or nonenhancing tumors such as low-grade gliomas. Therefore, if a brain tumor is a diagnostic consideration, MRI with gadolinium enhancement is the test of choice; a normal contrast-enhanced MRI scan essentially rules out the possibility of a brain tumor.

### GLIAL TUMORS

Glial tumors are divided into two main categories: astrocytic and oligodendroglial.<sup>1</sup> Both can be either low grade or high grade. High-grade (malignant) glial neoplasms can arise either alone (primary glioblastoma) or from a preexisting low-grade tumor (secondary glioblastoma); in secondary glioblastoma, low-grade tumor may be immediately adjacent to highly malignant disease. Error can occur when a small sample is taken for biopsy and the examined tissue does not

TABLE 2. SYMPTOMS OF BRAIN TUMORS.

SYMPTOM	TUMOR TYPE			
	LOW-GRADE GLIOMA	MALIGNANT GLIOMA	MENINGIOMA	PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA
	percent with symptom			
Headache	40	50	36	35
Seizure	65-95	15-25	40	17
Hemiparesis	5-15	30-50	22	24
Mental-status abnormalities	10	40-60	21	61

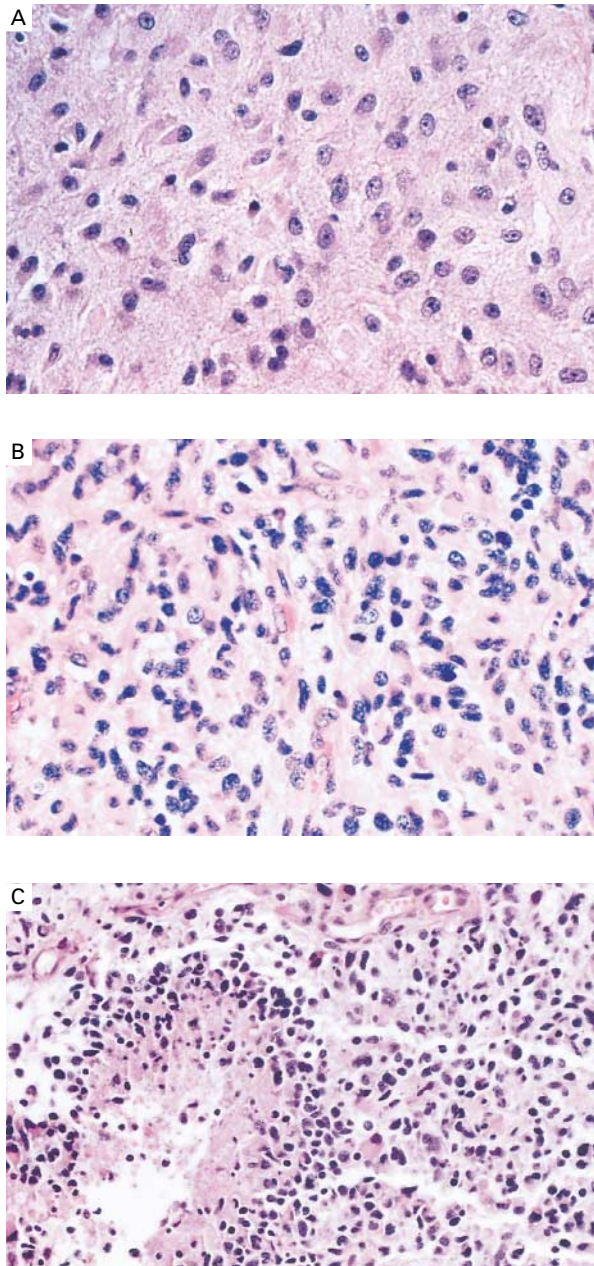
reflect the biology of the entire tumor, particularly if features indicative of malignancy are missed. All gliomas, particularly the astrocytic neoplasms, are histologically, genetically, and thus therapeutically heterogeneous.<sup>1,17,18</sup>

Glial tumors are graded pathologically, on the basis of the most malignant area identified, according to either the World Health Organization (WHO) system or the St. Anne-Mayo system, both of which are based on the presence or absence of nuclear atypia, mitosis, microvascular proliferation, and necrosis<sup>1</sup> (Fig. 1). Accurate pathological grading is essential because it defines treatment and prognosis. The histologic features of the tumor and the patient's age and performance status are major prognostic factors and have more influence than any specific therapy on the outcome.<sup>19,20</sup>

### Astrocytic Tumors

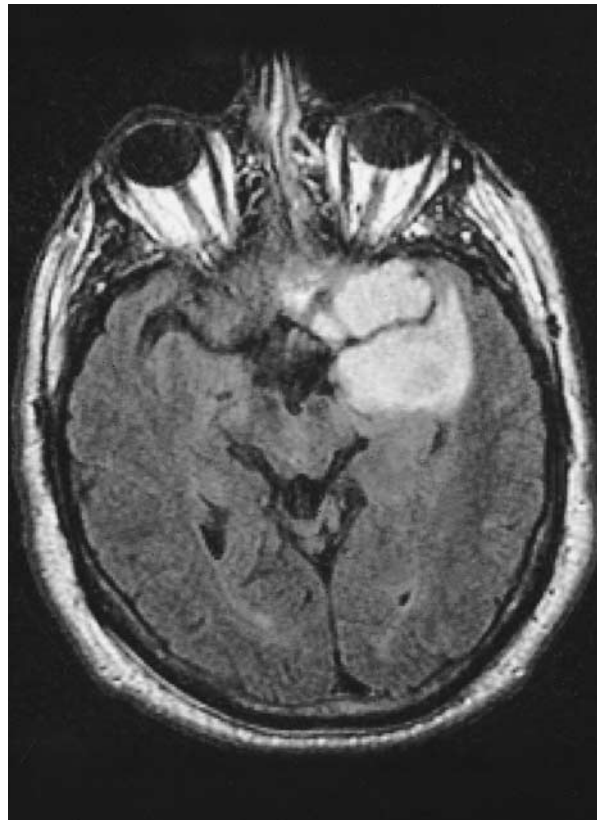
#### *Astrocytoma*

The low-grade fibrillary astrocytoma (WHO grade II)<sup>1,21</sup> must be distinguished from its more benign counterparts, such as the pilocytic astrocytoma (WHO grade I) and pleomorphic xanthoastrocytoma (WHO grade II). Astrocytomas are tumors found in young adulthood, with a peak incidence in the third to fourth decade of life. Typically, the first clinical manifestation is a seizure, which may be accompanied or followed by other neurologic symptoms or signs. The diagnosis is usually established when neuroimaging is performed to evaluate the seizure. The characteristic appearance of an astrocytoma on MRI is that of a diffuse, nonenhancing mass that is hypointense on T<sub>1</sub>-weighted images and best seen on T<sub>2</sub>-weighted images or those obtained with the use of fluid-attenuated inversion recovery, on which the mass is brightly outlined against normal brain tissue (Fig. 2). Typically, the lesion has a local mass effect, and there is evidence of cortical infiltration, with abnormal signal reaching the surface of the brain. Although the



**Figure 1.** Histologic Criteria of the World Health Organization for the Classification of Gliomas.

Fibrillary astrocytoma is characterized by increased cellularity with a monomorphic population of cells infiltrating the neuropil (Panel A, hematoxylin and eosin). Anaplastic astrocytoma is characterized by nuclear atypia and mitoses (Panel B, hematoxylin and eosin). Glioblastoma multiforme is characterized by necrosis with cells arranged around the edge of the necrotic tissue (pseudopalisading cells) (Panel C, hematoxylin and eosin); vascular proliferation is apparent at the top of the image.



**Figure 2.** MRI (Obtained with Fluid-Attenuated Inversion Recovery Sequence) of a Low-Grade Astrocytoma Involving the Left Frontotemporal Region.

pathological hallmark of an astrocytoma is that of a highly infiltrative and nondestructive neoplasm, the radiologic borders of this tumor are usually distinct. These lesions have no surrounding edema and, in young adults, frequently involve the insular cortex.

MRI is often supplemented by positron-emission tomography (PET), particularly in patients who are presumed to have low-grade gliomas, which are characterized by glucose hypometabolism.<sup>22</sup> PET images showing diffuse hypometabolism may support a decision to defer surgery or radiation therapy. If hypermetabolic areas are present, indicating the presence of a high-grade tumor, biopsy or resection should target those areas in an effort to include the most malignant tissue in the pathological specimen.<sup>23</sup>

Because most patients with astrocytoma are young and neurologically normal, except for having had an isolated seizure, treatment is particularly challenging. When the lesion is amenable to complete surgical excision, resection should be performed. Most neurooncologists believe that resection improves the outcome for patients with low-grade tumors, although

others have argued that resection may be deferred safely in patients who are otherwise asymptomatic and whose seizures are well controlled with anticonvulsant drugs.<sup>24,25</sup> The majority of low-grade tumors are not amenable to resection, however, because they involve too large an area of the brain or critical structures such as the language areas.

Radiation therapy is the most effective nonsurgical therapy for astrocytomas; however, early diagnosis and treatment do not necessarily improve survival and may cause disability. Three randomized, controlled trials have addressed the effect of radiotherapy on low-grade astrocytomas. Two multicenter trials have demonstrated equivalence in survival and time to disease progression between patients who received focal radiotherapy at a low dose (50.4 or 45.0 Gy) at the time of diagnosis and those who received a high dose (64.8 or 59.4 Gy).<sup>26,27</sup> However, higher doses of radiation were associated with a higher incidence of fatigue or malaise, insomnia, and poor emotional functioning months after radiotherapy, suggesting that lower doses are the superior treatment.

Another definitive trial addressed the timing of radiotherapy. After surgery or biopsy, patients were randomly assigned to immediate radiotherapy or deferral of radiotherapy until there was clinical progression.<sup>28</sup> Immediate radiotherapy significantly delayed the time to progression, but overall survival was identical in the two groups. The implication is that it makes no difference whether patients with low-grade astrocytomas receive radiation therapy immediately or only after they have had a clear progression of symptoms. Consequently, patients who are neurologically normal and whose seizures are well controlled with anticonvulsant therapy, whether or not they have undergone tumor resection, should be followed until there is clear evidence of progressive neurologic symptoms or signs or of tumor progression on subsequent MRI or PET scans.

Some astrocytomas, such as those causing hemiparesis or impaired cognitive function, require immediate intervention. Patients with such astrocytomas should be treated with surgical debulking, followed by radiotherapy of the involved field, with a total dose of no more than 54 Gy. There is no indication for the routine use of chemotherapy in the treatment of astrocytomas.

All patients, whether they have received treatment at presentation or not, must be followed clinically and radiographically. Most astrocytomas progress to high-grade malignant gliomas, which are often marked by the appearance of contrast-enhanced areas on MRI scans or hypermetabolic areas on PET scans. When progression occurs, treatment usually includes radiotherapy, if it has not previously been administered, and chemotherapy.

The median survival of patients with low-grade astrocytomas is five years, and most patients die from

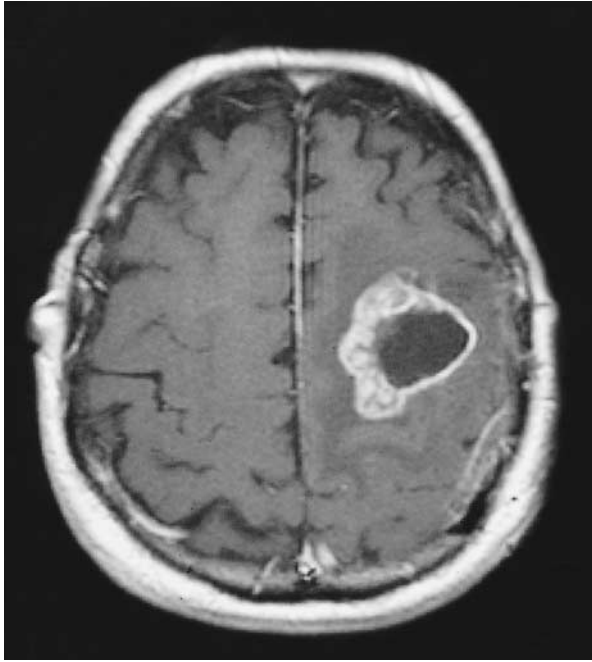
progression of their disease to a high-grade malignant glioma.<sup>29,30</sup> The range of survival times is broad and unpredictable; some patients die early and others survive for a decade or more.<sup>31</sup>

#### **Malignant Astrocytoma**

The malignant astrocytomas, the anaplastic astrocytoma and glioblastoma multiforme, are the most common glial tumors, with an annual incidence of 3 to 4 per 100,000 population. At least 80 percent of malignant gliomas are glioblastomas.<sup>4</sup> Gliomas can occur anywhere in the brain but usually affect the cerebral hemispheres. The male-to-female ratio among affected patients is about 3:2. The peak age at onset for anaplastic astrocytomas is in the fourth or fifth decade, whereas glioblastomas usually present in the sixth or seventh decade. Most malignant astrocytomas are sporadic, but they can occasionally complicate genetic syndromes such as neurofibromatosis type 1, neurofibromatosis type 2, Li-Fraumeni syndrome, and Turcot's syndrome.<sup>21</sup> There are also examples of familial brain tumors in the absence of any known genetic syndrome.

Diagnosis is easily established by cranial MRI. Malignant astrocytomas typically have irregular contrast enhancement, which is often ring-like (Fig. 3). The lesion is surrounded by edema, and the mass effect can be severe enough to cause herniation. The tumor typically involves white matter and can spread across the corpus callosum and involve both hemispheres. Although contrast-enhanced MRI suggests the presence of a discrete border to the lesion, these tumors are widely infiltrative. Tumor cells typically extend microscopically several centimeters away from the obvious area of disease and, in some cases, can extend throughout the entire hemisphere or large portions of the brain — a condition known as gliomatosis cerebri.<sup>32,33</sup>

Primary glioblastomas tend to occur in older patients (mean age, 55 years), whereas secondary glioblastomas tend to occur in younger adults (45 years of age or less).<sup>1</sup> The difference between these two entities can occasionally be recognized radiographically, when regions of nonenhancing tumor are evident in secondary glioblastomas, as well as pathologically, when a surgical specimen contains low-grade disease. The two types of glioblastoma arise through different molecular pathways.<sup>1</sup> Primary glioblastomas are associated with a high rate of overexpression or mutation of the epidermal growth factor receptor, *p16* deletions, and mutations in the gene for phosphatase and tensin homologues (*PTEN*).<sup>34-36</sup> Secondary glioblastomas have genetic alterations involving the *p53* gene and overexpression of platelet-derived growth factor A and its receptor, platelet-derived growth factor receptor  $\alpha$ .<sup>37</sup> These two pathways clearly demonstrate that the glioblastoma phenotype can arise by at least two mechanisms.



**Figure 3.** MRI of a Glioblastoma Multiforme in the Left Frontal Lobe, Obtained after the Administration of Gadolinium.

The irregular enhancing margin with central necrosis is characteristic of the tumor.

The treatments for anaplastic astrocytoma and glioblastoma multiforme are identical. Resection is the initial intervention. Gross total excision is associated with longer survival<sup>38,39</sup> and improved neurologic function<sup>40</sup>; therefore, every effort should be made to remove as much tumor as possible.

Surgery is followed by involved-field radiotherapy up to a total dose of 60 Gy, which significantly prolongs survival.<sup>41</sup> There have been many efforts to intensify radiotherapy, including the use of radiosensitizers, brachytherapy, and radioactive seeds implanted in the tumor bed that deliver an additional 60 Gy, but none have improved survival.<sup>42,43</sup> Brachytherapy has been supplanted by stereotactic radiosurgery, which is noninvasive and easier to administer. Only tumors 3 cm or less in diameter are amenable to stereotactic radiosurgery, and only if they are not located immediately adjacent to critical structures such as the optic nerve or brain stem.<sup>44</sup> A randomized controlled study to assess the benefits of this technique is under way.

The routine use of chemotherapy in addition to cranial irradiation is controversial. Individual randomized, controlled studies have demonstrated no significant improvement in median survival with single-agent or multiagent chemotherapy, although a significant increase in survival has been noted in a meta-analy-

sis.<sup>45</sup> However, chemotherapy consistently increases the proportion of long-term survivors from less than 5 percent to approximately 15 to 20 percent. The clinical relevance of this increase has been debated, although the finding is consistent in every study. A recent analysis established that there is a significant increase in the proportion of long-term survivors with the addition of chemotherapy, regardless of the patient's performance status, the histologic features of the tumor, the duration of symptoms, or age (up to 65 years).<sup>46</sup> The numbers were too small to determine whether patients over the age of 65 benefit. No clinical feature can identify the patients who are likely to benefit from chemotherapy. However, recent data demonstrate that methylation of the promoter region of the gene for the DNA-repair enzyme O<sup>6</sup>-methylguanine-DNA methyltransferase predicts tumor responsiveness to alkylating agents.<sup>47</sup>

The chemotherapeutic agent best studied has been carmustine. To date, no other drug has proved superior. The combination of procarbazine, lomustine, and vincristine was reported to improve the survival of patients with anaplastic astrocytomas; however, a large retrospective comparison of carmustine and this regimen of combination chemotherapy found no difference in survival between the two treatments, and more acute toxicity was associated with the combination.<sup>48</sup> Other data also suggest that patients who receive combination chemotherapy do not respond as well as those who receive a single agent as part of the initial treatment.<sup>49</sup>

At the time of recurrence, a second resection should be considered. By itself, repeated resection has been shown to prolong survival for a median of six months. If it has not been used earlier, stereotactic radiosurgery may be considered for discrete, focal recurrences. Additional chemotherapy can also be useful. Traditional agents have included nitrosourea drugs, if not used initially, and procarbazine. The efficacy of temozolomide in the treatment of recurrent malignant gliomas has been demonstrated.<sup>50</sup> Temozolomide, which is administered orally, has a favorable side-effect profile and thus is well tolerated by most patients. Thalidomide has been tested as an antiangiogenic agent, but the results have been disappointing<sup>51</sup>; its weak antiangiogenic effect indicates that stronger agents may be more successful. Other approaches, such as gene therapy with the herpes simplex thymidine kinase gene, have also been ineffective,<sup>52</sup> but the trials were conducted early in the development of gene-therapy technology.

Despite aggressive treatment, most patients die of the disease, with median survival of about three years for anaplastic astrocytoma and one year for glioblastoma. The few long-term survivors of glioblastoma are usually young, in good health, and able to undergo gross total resection of their lesion, followed by radiotherapy and chemotherapy.<sup>19</sup>

### Oligodendroglial Tumors

Oligodendrogliomas and oligoastrocytomas are tumors of oligodendrocytes or their precursors, or they have composite histologic features, reflecting both oligodendrocytic and astrocytic cells. Formerly, the distinction between an oligodendroglial tumor and an astrocytic tumor had no therapeutic importance, and in earlier series of tumors, oligodendrogliomas represented approximately 5 percent of glial neoplasms. However, with the recent recognition that oligodendrogliomas are uniquely sensitive to chemotherapy, neuropathologists have made a greater effort to identify these uncommon neoplasms. The consequence is that they are now found to represent approximately 20 percent of glial neoplasms, and this is probably a more accurate estimate.<sup>53</sup> Oligodendrogliomas are divided into two categories, low grade and high grade (anaplastic), which are of both prognostic and therapeutic use.<sup>21</sup>

The distinction between an astrocytoma and an oligodendrogloma, when made purely on histologic grounds, can be difficult. However, many oligodendrogliomas have deletions of 1p and 19q,<sup>54</sup> and molecular changes such as these may prove to be the defining criteria for this type of tumor. New data now link chemosensitivity to the loss of heterozygosity at 1p and 19q in low-grade and high-grade oligodendrogliomas.<sup>55,56</sup>

#### Low-Grade Oligodendrogloma

The majority of oligodendrogliomas are low grade and radiographically indistinguishable from astrocytomas, although oligodendrogliomas are more likely to be calcified. These oligodendroglial tumors are prone to spontaneous hemorrhage, as a result of their delicate vasculature; even a low-grade tumor may present as an intracranial hemorrhage. Most patients present with a seizure or progressive hemiparesis or cognitive impairment. Those who have a hemorrhage generally present with hemiparesis, headache, and lethargy, all of acute onset.

The issues concerning diagnosis and treatment are identical to those for low-grade astrocytomas. Treatment is deferred until there is clinical or radiologic evidence of progression, unless patients have disabling symptoms or signs at presentation. However, once the decision to initiate treatment is made, the therapy differs from that used for astrocytomas.

Conventional treatment with focal radiotherapy, up to a total dose of 54 Gy, improves symptoms and probably prolongs survival. However, in 1988 it was recognized that malignant oligodendrogliomas are sensitive to chemotherapy.<sup>57</sup> A regimen of procarbazine, lomustine, and vincristine resulted in marked shrinkage of tumors, as shown by neuroimaging. Subsequent studies established the beneficial effect of chemotherapy in malignant oligodendrogliomas, with 75 percent of patients responding to treatment and

roughly 50 percent of these patients recovering completely.<sup>58,59</sup> Procarbazine, lomustine, and vincristine were then used for low-grade oligodendrogliomas, and again responses were observed.<sup>59,60</sup> Chemotherapy is probably not curative in patients with this disease, but it can produce sustained remissions with durable clinical improvement.

Earlier studies of patients with oligodendrogliomas reported a median survival of about 10 years, which is much longer than the median survival of patients with astrocytomas. MRI has led to earlier diagnosis, and a recent series of 106 patients with oligodendrogliomas yielded a median survival of 16 years.<sup>61</sup> Many patients can be followed for years without intervention. When treatment is implemented, it appears that the outcomes are equivalent regardless of the type of treatment, be it chemotherapy, radiotherapy, or both. I prefer to use chemotherapy initially, because it delays the administration of radiotherapy and thus postpones the long-term cognitive consequences of radiotherapy in patients who survive for lengthy periods.

Eventually, most oligodendrogliomas, like astrocytomas, progress by becoming malignant. Patients with worsening clinical symptoms and the appearance of enhancement on MRI scans or hypermetabolism on PET scans warrant reevaluation. Resection or biopsy is often performed, and further therapy is chosen on the basis of histologic features and prior treatment.

#### Anaplastic Oligodendrogloma

Like malignant astrocytic tumors, anaplastic oligodendrogliomas require immediate treatment after diagnosis. Extensive resection should be performed if feasible. Many physicians initiate treatment with chemotherapy, using the combination of procarbazine, lomustine, and vincristine, followed by radiotherapy.<sup>62</sup> The use of chemotherapy before radiotherapy allows one to measure a response to treatment if there is residual tumor. Agents that appear to have some efficacy against recurrent oligodendroglial tumors include melphalan, thiotepa, temozolomide, carboplatin, cisplatin, and etoposide.

### MENINGIOMA

Meningiomas are not strictly brain tumors, since they arise from meningotheial cells that form the external membranous covering of the brain. However, because they arise within the intracranial cavity and present with neurologic symptoms and signs, they are usually classified as brain tumors. They constitute approximately 20 percent of intracranial neoplasms<sup>4,21</sup> and have a total annual incidence of 7.8 per 100,000<sup>4</sup>; however, the majority are asymptomatic tumors discovered incidentally at autopsy. Their incidence in symptomatic patients is about 2 per 100,000. Meningiomas occur more frequently in women, with a female-to-male ratio of 3:2 or even 2:1 in some series.<sup>1</sup> Multiple meningiomas are found in patients with

neurofibromatosis type 2 or can develop sporadically, usually from contiguous spread from a clonal tumor<sup>63,64</sup>; sporadic multiple meningiomas are found in less than 10 percent of patients. Patients with breast cancer have an increased frequency of meningiomas, which need to be distinguished from metastases to the brain.<sup>65</sup>

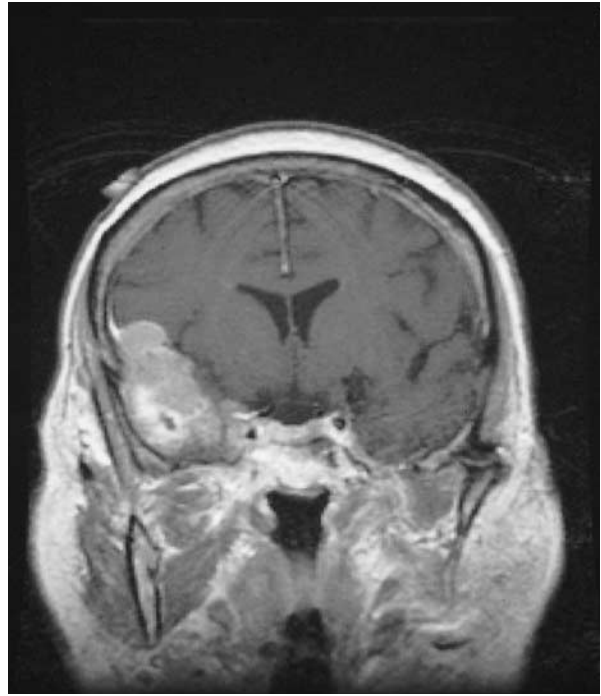
Meningiomas occur primarily at the base of the skull, in the parasellar regions, and over the cerebral convexities. Thus, symptoms and signs directly reflect the location of the tumor. Most meningiomas are slow growing and are not associated with substantial underlying brain edema; they cause symptoms by the compression of adjacent neural structures. Patients with tumors of the hemispheric convexities often present with a seizure or progressive hemiparesis. Patients with skull-based lesions typically present with cranial neuropathy, whereas meningiomas in any location may cause headache.

The diagnosis of meningioma is established by neuroimaging. On MRI, meningiomas are adjacent to bone and usually have a “dural tail,” which indicates that the tumor is anchored to the dura and growing along it (Fig. 4). They have a characteristic diffuse pattern of enhancement. If substantial brain edema is evident, it usually indicates a higher-grade tumor or a secretory meningioma.<sup>66</sup>

The majority of meningiomas are histologically benign. Approximately 5 percent are atypical, and 2 percent are frankly malignant. Several histologic variants exist, but only a few have prognostic importance. Apart from the meningiomas that have atypical or frankly malignant features, clear-cell, chordoid, rhabdoid, and papillary meningiomas have a greater propensity to recur and exhibit aggressive behavior.<sup>1,21</sup> Radiation-induced meningiomas are more commonly atypical or malignant.<sup>9,67</sup> All meningiomas are characterized by the loss of chromosome 22q, which is also the molecular characteristic of neurofibromatosis 2.<sup>68</sup>

Small meningiomas, which are often detected incidentally on images obtained for other reasons, may simply be followed, particularly in older patients.<sup>69,70</sup> Many remain static and never cause neurologic symptoms. In those that grow, intervention can be instituted as needed.

When treatment is necessary, surgery is the definitive therapy. However, even among tumors that are completely resected, 20 percent recur within 10 years, and more than 80 percent recur after a partial resection. Tumors at the skull base are frequently impossible to remove because they are intertwined with vital structures. Stereotactic radiosurgery is another initial treatment option for tumors less than 3 cm in diameter and not adjacent to the optic nerve or other critical structures. At the time of a recurrence, a second resection should be followed by external-beam radiotherapy, which slows regrowth.<sup>71</sup> If a focal area of disease remains, stereotactic radiosurgery may be use-



**Figure 4.** Coronal MRI Showing a Meningioma Involving the Middle Fossa and Extending into the Cavernous Sinus, Obtained after the Administration of Gadolinium.

Despite the large size of the tumor, there is no edema in the overlying brain.

ful.<sup>72</sup> Patients with multiple recurrences typically undergo craniotomy many times and exhaust their radiotherapeutic options. Chemotherapy for meningiomas has been disappointing. Although initial reports of hydroxyurea and doxorubicin-based regimens were enthusiastic, most studies found these regimens to be ineffective.<sup>73,74</sup> Patients with atypical and anaplastic tumors require radiotherapy as part of the initial treatment; despite this vigorous approach, however, most aggressive meningiomas recur.<sup>75</sup>

#### PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Primary central nervous system lymphoma was believed to represent 1 percent or less of all primary brain tumors, but in the past two decades its incidence has tripled in the United States.<sup>76,77</sup> Congenital or acquired immunosuppression, particularly the acquired immunodeficiency syndrome, markedly increases the risk of primary central nervous system lymphoma.<sup>76</sup> There are no known environmental or behavioral risk factors associated with this disease that might explain its rising incidence in immunocompetent patients.

The incidence of primary central nervous system lymphoma in immunocompetent persons, the focus of this discussion, peaks in the sixth to seventh decade. The incidence is slightly greater in men. This type of lymphoma is multifocal in about 40 percent of patients and is usually subcortical. Behavioral and cognitive changes, the most common presenting symptoms, occur in about two thirds of patients.<sup>78</sup> Hemiparesis, aphasia, and visual-field deficits are present in about 50 percent of patients at diagnosis, and seizures in 15 to 20 percent.<sup>79</sup>

On MRI, lesions are typically periventricular in location and usually have a diffuse and homogeneous pattern of enhancement. Almost all are B-cell tumors, predominantly of the diffuse, large-cell subtype. Cerebral lymphoma can disseminate within the cerebrospinal fluid, and tumor cells can be identified there in about 25 percent of patients.<sup>80</sup> In addition, there is lymphomatous infiltration of the eye in 20 percent of patients at presentation.

In primary central nervous system lymphoma, unlike other brain tumors, resection does not have a therapeutic role, and the diagnosis is usually established by stereotactic biopsy. Chemotherapy should be the first treatment for all patients with the disease. The best regimens include high-dose methotrexate, which can penetrate the blood-brain barrier and is associated with complete-response rates of 50 to 80 percent.<sup>81-83</sup> Standard regimens of combination chemotherapy, useful for systemic lymphomas, are ineffective in the treatment of cerebral lymphoma.<sup>84,85</sup> In the past, radiotherapy was the mainstay of treatment, resulting in a median survival of 12 to 18 months.<sup>86</sup> When methotrexate-based regimens are used in addition to cranial irradiation, the median survival is increased to at least 40 months, with almost 25 percent of patients surviving for 5 years or more. However, chemotherapy combined with radiotherapy results in substantial delayed neurotoxic effects, particularly in patients over 60 years old.<sup>87</sup> Consequently, chemotherapy-only regimens are being explored, with some success. Regimens that rely on disruption of the blood-brain barrier, followed by intraarterial chemotherapy, have resulted in a median survival of 40 months without the use of radiotherapy; however, high-dose systemic regimens can achieve similar results without the morbidity associated with this procedure.<sup>88</sup>

### CONCLUSIONS

Brain tumors are a heterogeneous group of neoplasms, each with its own biology, treatment, and prognosis. New therapies are needed, especially for the astrocytic gliomas. The present focus of research on cancer is to understand a specific cancer at the molecular level and to exploit the genetic aberrations of the malignant cell by means of highly specific and effective therapy. In no brain tumor has this yet been

done; however, it is the primary focus of current laboratory and clinical research. The heterogeneity of individual tumors, the delivery of drugs or other agents into the central nervous system, and the neurotoxic effects of therapy are the chief, unique challenges in the treatment of brain tumors. Nevertheless, this approach will lead to an understanding of the biology of brain tumors and make possible new therapeutic opportunities that will help meet the primary goal of improving the care of patients with brain tumors.

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