Part II

Primary
Central Nervous System
Tumors
Primary Cerebral Tumors

MITCHEL S. BERGER, STEVEN A. LEIBEL, JANET M. BRUNER, JONATHAN L. FINLAY, AND VICTOR A. LEVIN

The intracranial supratentorial compartment is the most common site for central nervous system (CNS) tumors. Understanding tumors that arise within the supratentorial brain is, therefore, of the utmost importance. This chapter provides the reader with a reasonably thorough understanding of (1) the symptoms and signs of tumors that arise within the various supratentorial locations; (2) the various approaches to surgical intervention, from biopsy to cortical mapping, for tumors in eloquent sites of the brain; (3) the pathologic classification and grading schemes used around the world for the various supratentorial tumors; (4) conventional as well as other radiation approaches such as brachytherapy, radiosurgery, three-dimensional conformal radiotherapy, and proton beam treatment for the tumors; and (5) the progress and limitations of chemotherapy used with radiation and as independent therapy. In addition, some major and subtle differences between children and adult patients with primary brain tumors are noted. Therapeutic approaches to tumors in infants are not covered in this chapter as they are rare and too specialized for this text.

SYMPTOMS AND SIGNS

Neurologic symptoms and physical signs reflect the location of tumor rather than tumor histology. Symptoms are at two levels: general symptoms, associated with increased intracranial pressure; and focal symptoms, related to tumor location.

General symptoms are headache, gastrointestinal upset such as nausea and vomiting, personality changes, and slowing of psychomotor function. Because the brain parenchyma does not have pain-sensitive structures, headache has been attributed to local swelling and distortion of pain-sensitive nerve endings associated with blood vessels, primarily in the meninges. Many tumors grow without headache as a prominent symptom, but others rapidly lead to headache either because of the tumor’s proximity to pain-sensitive fibers or due to its rapid growth and the achievement of a critical volume that causes compression and displacement of brain. Under the latter circumstances, the onset and disappearance of headache correlate with changes in intracranial pressure. Headaches can vary in severity and quality; frequently they occur in the early morning hours or upon first awakening. Sometimes patients complain of an uncomfortable feeling in the head rather than headache.

Gastrointestinal symptoms such as loss of appetite, queasiness, nausea, and occasionally vomiting can occur in all patients but are most common in children and in patients harboring infratentorial rather than supratentorial tumors. Changes in personality, mood, mental capacity, and concentration can be noted early or can be the only abnormalities observed. In general, patients with brain tumors tend to sleep longer at night and nap during the day. These symptoms are not unique to individuals with brain tumors and can easily be confused with depression, neurasthenia, and other psychological problems.
Focal symptoms can be episodic (seizures) or progressive. Seizures are important harbingers of brain tumors; although only 10% of patients presenting with seizures are diagnosed with a brain tumor, the association increases with increasing patient age. Seizures are a presenting symptom in approximately 20% of patients with supratentorial brain tumors. Rapidly growing, infiltrative malignant gliomas are likely to produce complex partial motor or sensory seizures, although generalized grand mal seizures are also common. In patients with slowly growing astrocytomas, gangliogliomas, and oligodendrogliomas, generalized seizures may antedate the clinical diagnosis by months to years. The etiology of seizures associated with these tumors is unclear, although experimental evidence implicates a depletion of gamma aminobutyric acid (GABA) and somatostatin-immunoreactive neurons in the adjacent, nontumor-infiltrated epileptogenic brain (Haglund et al., 1992). Focal seizures that occur in patients older than 40 years of age are indicative of a brain tumor until proven otherwise.

The distribution of infiltrative parenchymal tumors in the brain has a direct relationship to the mass of the affected lobe or region. The most frequently involved locations in the cerebrum are, in descending order of frequency, frontal, parietal, temporal, and occipital lobes. Clinical patterns of tumor growth in the various brain locations are less stereotypic than those observed after strokes; nonetheless, understanding the nature of the various syndromes that present will help clinicians to better understand the effect of tumor growth in the CNS.

Frontal lobe tumors can be asymptomatic or can produce mild slowing of contralateral hand movements, contralateral spastic hemiplegia, marked elevation in mood or loss of initiative, and dysphasia (if the involved lobe is the dominant lobe). Bifrontal disease is, unfortunately, all too common and can cause bilateral hemiparesis, spastic bulbar palsy, severe impairment of intellect, lability of mood, and dementia.

Temporal lobe tumors can be clinically silent or can produce impairment of recent memory, homonymous quadrantanopsia, auditory hallucinations, and even aggressive behavior. Involvement of the non-dominant temporal lobe can lead to minor perceptual problems and spatial disorientation. Dominant temporal lobe involvement can lead to dysnomia, impaired perception of verbal commands, and even full-blown, fluent Wernicke-like aphasia. Bilateral disease involving both temporal lobes is rare compared with the common occurrence of bilateral disease in frontal lobe tumors that readily cross through the corpus callosum. However, in some cases, use of opposed lateral field radiation portals can lead to bilateral temporal lobe damage that can be devastating for the patient as it produces impairment of recent memory and can lead to dementia.

Parietal lobe tumors affect sensory and perceptual functions more than motor functions, although mild hemiparesis is sometimes seen with extensive parietal lobe tumors. Abnormalities may range from mild, and observable only by formal testing, to severe sensory loss leading to hemianesthesia and/or other hemisensory abnormalities. In addition to homonymous hemianopsia or visual inattention, involvement of the nondominant parietal lobe can lead to perceptual abnormalities, anosognosia, and an apraxia for dressing oneself; dominant parietal lobe tumors lead to alexia, dysgraphia, and other types of apraxia.

Occipital lobe tumors can produce contralateral homonymous hemianopsia or visual aberrations that take the form of imperception of color, object size, or object location. Bilateral occipital damage rarely occurs as a result of tumor invasion, but it can be produced in herniation syndromes and can lead to cortical blindness.

Thalamic and basal ganglia tumors can reach 3 to 4 cm in diameter before the patient experiences symptoms, which can be nonspecific headaches resulting from hydrocephalus and increased intracranial pressure secondary to trapping of the lateral horn of one of the ventricles. Patients can also present with contralateral sensory abnormalities detected only by testing for sensory extinction or, rarely, with a severe neuropathic pain syndrome. Some patients complain of intermittent paresthesias on the contralateral side; these are at times so episodic that anticonvulsant drugs are prescribed. Contralateral intention tremor and hemiballistic-like movement disorders are uncommon.

**GENERAL SURGICAL METHODS AND TECHNIQUES**

**Biopsy Techniques**

A simple and readily available method that can be used to obtain a biopsy specimen is with computer tomography (CT) or magnetic resonance imaging (MRI) guidance. After a localizing CT or MRI scan is
done, a small twist drill opening is made in the skull and a biopsy needle is placed into it and imaged to ensure correct placement; a tumor sample is then taken and a repeat scan performed to make sure no hemorrhage has occurred. A comparison of the freehand method with one using a stereotactic apparatus, found no significant difference in morbidity and mortality between the two procedures (Wen et al., 1993).

An alternative biopsy approach involves the use of ultrasonography via a burr hole (Berger, 1986; Enzmann et al., 1984; Tsutsumi et al., 1989). This has been performed very accurately on lesions greater than 7 to 10 mm and provides immediate feedback after the procedure to ensure that a hemorrhage has not occurred. In a study comparing this method to CT-guided stereotactic techniques, the diagnostic yield rate was found to be comparable for CT-guided and ultrasound-guided approaches (94% versus 91%) (Di Lorenzo et al., 1991). Both methods resulted in a similar number of complications. The ultrasound biopsy method, however, had a shorter operative time and was significantly less costly.

With the advent of CT-coupled stereotactic frames in the late 1970s and early 1980s, surgeons had the capability of obtaining tissue specimens with millimeter accuracy. The components of the most commonly used apparatus, the Brown-Roberts-Wells frame, included a base ring that was fixed to the skull and a localizing ring with nine graphite rods to allow lesions to be referenced in three dimensions (Heilbrun et al., 1983). An arc guidance system fit into the base ring allows any two points in three-dimensional space to be traversed (e.g., entry and target points). This represented a tremendous step forward in neurosurgical instrumentation and precision. Experience has shown that tumor biopsy accuracy has been greatest when directed to the tumor center and the immediately surrounding contrast-enhancing tissue. The diagnostic accuracy for grade and type of lesion may be enhanced by including cytologic squash preparations with the histology (Cappabianca et al., 1991).

Comparing histologic findings from lesions that were biopsied and subsequently resected, the discrepancy rate was greatest with astrocytic tumors in terms of their grade (Chandrasoma et al., 1989). This is clearly a problem when small samples are obtained, especially when differentiating between low-grade gliomas and reactive gliosis (Taratuto et al., 1991). Notwithstanding that, the stereotactic biopsy technique is the most accurate method for obtaining tissue, regardless of the type of frame used, and this method is the standard against which all other methods of obtaining small tissue samples should be compared.

Stereotactic-Guided Volumetric Resections

Kelly and colleagues (1982, 1983) developed an innovative technique that coupled imaging with computer-assisted stereotactic resection of tumors. Reconstructed tumor sections based on CT and MRI results are displayed to the surgeon on a video terminal during surgery, allowing for precise, stereotactic laser vaporization of any intracranial target. It became apparent early in their experience that this approach was more beneficial for patients with circumscribed lesions (i.e., metastasis, pilocytic astrocytoma, and so forth) than for those with more infiltrative glial tumors (Kelly et al., 1986). The morbidity associated with this procedure is acceptable; however, the outcome for malignant glial tumors was disappointing. Survival data were not significantly different compared with those from conventional radical resections (Kelly, 1988).

The limitations of all surgical approaches have more to do with the infiltrative nature of gliomas than with surgical technique. Stereotactic biopsy samples from brain adjacent to the contrast-enhanced and hypodense areas in high- and low-grade gliomas demonstrated isolated tumor cells well beyond the bulk of the image-defined tumor mass (Kelly et al., 1987; Kelly, 1993). Extending the resection into these areas without consideration for functional white matter tracts will result in unacceptable morbidity, emphasizing the need to consider in the overall treatment plan the infiltrated brain adjacent to the main tumor nidus.

Frameless Navigational Resection Devices

The next generation of image-based computerized localization for tumor resection will not use frames attached to the skull for three-dimensional reference of an intracranial target. The primary components of any contemporary navigational system are registering the surgical target with respect to surrounding structures and physical space, interacting with a localization device, integrating real-time data, and interfacing with a computer. Contemporary frameless
navigation systems include ultrasonic digitizer systems, magnetic field digitizers, multijointed encoder arms, infrared flash systems, and robotic systems (Zakhary et al., 1999). The majority of these newer systems use a localizing arm that initializes and calibrates fiducial markers that are attached to the patient’s head during the preoperative scan and at the time of surgery. Changes in the position of the localizing arm are updated using acoustic transit times between the sound sources and the fiducial markers (Roberts et al., 1986; Barnett et al., 1993); other systems use mechanical sensors (Watanabe et al., 1987) or light emitters.

Regardless of the system employed, surgeons will ultimately use this technology to preoperatively plan incisions and bone flaps as well as to guide the initial phases of the resection. Shifting of the brain contents will necessarily limit the utility of these methods when intra-axial tumors are resected because localization is based on findings from the preoperative scan. This will not, however, be a factor during complex skull base surgery.

**Intraoperative Imaging Techniques**

Unlike frameless and frame-based systems that are limited by their reliance on preoperative imaging, both intraoperative CT and MR scanning provide intraoperative updates of data sets for navigational systems. Intraoperative re-registration of target anatomy eliminates the problem of brain shift that may be caused by resection or brain retractors and allows the surgeon to more precisely achieve resection control and to modify the preplanned surgical approach, if necessary. Use of intraoperative MR requires MR-compatible instruments (i.e., titanium or ceramic) to minimize artifact. Surgical instruments can be tracked with the use of light-emitting diode sensors to provide image guidance during movements and interactive feedback on corresponding images (Black et al., 1997; Tronnier et al., 1997; Steinmeier et al., 1998).

**Intraoperative Localization of Tumor and Margins**

For neurosurgeons, gross visualization for consistency and color has been the sine qua non used to distinguish normal brain from tumor at the time of surgery. Low-grade glial tumors differ from their malignant counterparts in both texture (firmer than normal brain) and color (slightly paler than white matter). Most malignant gliomas have a very soft and often necrotic grayish appearance; characteristic thrombosed veins are almost always seen with glioblastoma. These tumors are usually highly vascular with vascularization corresponding to the contrast-enhancing rim on the imaging studies.

Following the opening of the dura, the cortex is inspected for expanded gyri and red “arterialized” veins, which are pathognomonic for malignant gliomas secondary to reduced oxygen extraction with increased blood flow (Fig. 3–1). Before the resection begins, it is helpful to use ultrasound localization to determine the overall tumor size, depth, and underlying cystic structures. Tumor volumes, as seen on both CT and MRI scans, closely correspond to high- and low-grade gliomas that have been previously unresected and untreated (LeRoux et al., 1989, 1993). Once these are operated on and radiated, gliosis accumulates and increases the echogenic background, which tends to overestimate the true size of the tumor.

Intraoperative verification of tumor and of the transition zone between the tumor and the adjacent tumor-infiltrated brain is best achieved with serial frozen sections or smear preparations (Reyes et al., 1991). This is often a very time-consuming process and is complicated by the need to distinguish reactive astrocytes from infiltrating tumor cells. Alternative ways to intraoperatively document the extent of tumor removal involve imaging with dedicated CT and MRI, laser activation of hematoporphyrin (Perria et al., 1988), fluorescent dyes (Poon et al., 1992), intravenous (IV) indocyanine green (Hansen et al., 1993), and IV fluorescein with ultraviolet photoactivation (Moore, 1947).

**Functional Mapping-Guided Tumor Resection**

As radical resective surgery becomes more commonplace in modern neurosurgical practice and teaching, the risks of functional morbidity will certainly be the rate-limiting factor for most surgeons. Over the past several years, functional mapping of cortical and subcortical regions using both intraoperative and extraoperative techniques has become an indispensable adjunct to avoid morbidity while performing wide, radical tumor resections in eloquent brain areas. For example, in the dominant cerebral
hemisphere, language testing for reading, speech, and naming must be done before tumors that involve the posterior frontal, anterior parietal, and temporal lobes are resected. Preoperative deficits in these language functions could be due either to swelling or to tumor infiltration into essential language sites; a preoperative trial of high-dose dexamethasone will usually distinguish between the two causes. The motor cortex is located within 3 to 5 cm behind the coronal suture superiorly and a similar distance posterior to the outer border of the sphenoid wing. The region is flanked posteriorly by the primary somatosensory cortex and near the vertex by the supplementary motor area anteriorly. The presence of any tumor on either side of the motor cortex should dictate that stimulation mapping be done to identify the cortical motor neurons and also their descending motor tracts in the subcortical white matter. These include the corona radiata, internal capsule, cerebral peduncles, and the corticospinal pathways to the brain stem and spinal cord. Tumors involving the insula, thalamus, and basal ganglia often abut the descending motor tracts, which may be readily stimulated.

Because seizures associated with low-grade gliomas are often medically refractory, neurosurgical approaches have been adapted from epilepsy surgery to provide better seizure control. Intraoperative mapping of seizure foci using electrocorticography will readily identify epileptogenic areas and, combined with the functional brain map, will allow for removal of these regions without associated deficits.

Not all patients will be good candidates for functional mapping resections. Preoperative planning begins with a thorough neurologic assessment to decide whether the patient is a candidate for mapping. If a dense hemiparesis is present despite administration of steroids, it is unlikely that intraoperative stimulation will elicit motor responses. In that setting, somatosensory evoked responses may be used to identify the central sulcus by documenting a phase reversal potential across this sulcus (Woolsey et al., 1979). Because the motor cortex in young children is often unexcitable by direct stimulation mapping, evoked potentials should also be available for this particular patient population (Goldring and Gregorie, 1984). Language function is assessed by having the
patient count to 10 and stick out his or her tongue, which verifies that Broca’s area and the inferior face motor cortex are intact. The patient is then shown a series of picture slides with common objects to name. A baseline naming error rate greater than 25% will prevent functional mapping from providing reliable information.

The MRI scan is used to identify the motor cortex by localizing two mirror image lines on both sides of the midline that represent the central sulcus (Berger, 1990; Berger et al., 1990b). This is best seen on the high T2-weighted axial images (Fig. 3–2). Sagittal and far-sagittal scans may be used to identify the marginal sulcus and an imaginary line drawn from the back of the insular triangle, respectively, which mark the combined sensorimotor (i.e., Rolandic) cortex.

With the patient awake and the cortex exposed, the sensory and motor cortex is easily stimulated using currents as low as 2 mA and usually not greater than 6 mA. The current is produced with a constant current generator, which elicits a train of biphasic square wave pulses (frequency, 60 Hz; duration per phase, 1.25 msec) via a bipolar electrode. Patients who are asleep will require higher currents (i.e., 6 to 16 mA maximum). Using multichannel electromyographic recordings in addition to visual observation of motor activity results in greater sensitivity, allowing the use of lower stimulation levels and facilitating detection.
of stimulation-induced seizure activity (Yingling et al., 1999). A current greater than 16 mA has never been necessary to evoke sensory or motor responses. At this point, cold Ringer’s lactate solution should be immediately available for irrigation of the stimulated cortex if a focal motor seizure develops. The best management of intraoperative stimulation-induced focal motor seizures is rapid cortical irrigation at the stimulation site with ice-cold Ringer’s solution, which will abruptly stop the seizure activity originating from the irritated cortex without using short-acting barbiturates (Sartorius and Berger, 1998). The current should be elevated in 1 and 2 mA increments for awake and asleep patients, respectively. When operating near the vertex, the leg motor cortex will be hidden along the falx. Thus, a strip electrode should be inserted between the midline cortex and the falx to evoke stimulation-induced responses of the leg and foot. The same or a slightly higher current may be used to stimulate subcortical motor tracts without concern for current spread, which remains limited to within 2 to 4 mm of the bipolar electrode contacts.

Figure 3–3 demonstrates the utility of mapping the cortex and the underlying white matter in a patient with an infiltrative astrocytic glioma involving the face motor cortex in the nondominant hemisphere. The cortex was mapped to evoke orofacial movements in addition to finger and wrist flexion and extension (Fig. 3–4). The face motor cortex was resected in its entirety, and the tumor was removed until subcortical stimulation demonstrated hand movements (Figs. 3–5 and 3–6). The patient had a left-sided facial droop, which cleared in 3 weeks, and brief hand weakness, which lasted a few days.

Following localization of Broca’s area based on stimulation-induced counting arrest, naming is tested as a language measure that best predicts postoperative deficits (Penfield and Roberts, 1959). Before testing it is essential to determine the optimal stimulation current based on recording after discharge potentials from the cortex following bipolar stimulation. This is done to ensure that subclinical seizure activity is not the cause of speech dysfunction during the mapping. The current to be used will vary between 2 and 8 mA and should be adjusted to 1 mA below the current that causes after-discharge potentials. A wide surface area is tested after sterile numbered tickets are placed on the cortex for documentation purposes. Approximately 15 to 25 sites are tested, with each site being stimulated at least three times. Errors in naming take the form of hesitation or complete anomia. Hesitation in naming is not con-
considered critical, whereas difficulty with naming is a critical function and denotes an essential language site.

In a series of 117 patients who had language testing when undergoing operation on the left, dominant hemisphere, essential language sites were randomly identified throughout that hemisphere, with the heaviest concentration of sites located around the perisylvian cortex (Ojemann et al., 1989). At least 67% had more than one essential language site, and in 16% of the population tested no temporoparietal language sites could be found. A companion study to this evaluation of temporal lobe language in patients with gliomas in the same region showed a number of findings that again emphasized that language localization cannot be determined anatomically but must rely on stimulation mapping (Haglund et al., 1993). In that study, we failed to identify a language function in the inferior temporal gyrus, whereas the superior temporal gyrus was nearly twice as likely as the middle temporal gyrus to have stimulation-induced language errors. Contrary to accepted neurosurgical teaching,
Figure 3–5. Subcortical hand motor fibers (6, 7) are seen following resection of the overlying cortex. A indicates a tumor margin.

Figure 3–6. Postoperative T₁-weighted axial image showing the resection cavity.
essential naming sites were found in the anterior tempo-
ral lobe (i.e., first 3 cm) in nearly 15% of patients
with temporal lobe gliomas. It was also learned from
this study that resecting the tumor within 7 mm of an
essential language site results in a permanent nam-
ing deficit 40% of the time. However, if the resection
is further than 1 cm from the essential naming cor-
tex, no permanent deficits will result. Knowing this,
we are now able to avoid permanent morbidity while
removing tumors from the dominant cerebral hemi-
sphere when language is mapped before resection.

An example of the utility of speech mapping dur-
ing tumor resection is shown in Figure 3–7. In this
case, the patient had a brief history of seizure activ-
ity accompanied by postictal confusion and naming
errors, which resolved after each seizure. A MRI scan
revealed a non–contrast-enhancing tumor in the pos-
terior parietal lobe on the left side. Intraoperative
speech mapping demonstrated repetitive errors in
naming at three essential sites between 1 and 3 cm
in front of the tumor nidus (Fig. 3–8). The lesion was
resected completely using intraoperative ultrasound
guidance, and the resection cavity did not come closer
than 1 cm to the nearest essential language site (Figs.
3–9 and 3–10). Postoperatively, the patient had a se-
vere dysnomia, which cleared within 4 to 6 weeks fol-
lowing surgery, and his neurologic functions returned
to baseline.

PATHOLOGY OF DIFFUSE
INfiltrATIVE GLIOMAS

The most common tumors of the cranial–spinal axis
are those that infiltrate or displace the brain paren-
chyma of the intracranial supratentorial compart-
ment. Of these tumors, histologically, the most com-
mon belong to the glioma family of tumors.

General Features

The astrocytic gliomas, the most common class of
supratentorial glial neoplasms, are derived from and
have an appearance simulating normal astrocytes.
Astrocytes occur most commonly in the white matter,
but are also found in the cerebral cortex. Astrocy-
tomas are diffusely infiltrating neoplasms of the cere-
bral hemispheres, and there is evidence that their
prognosis and survival depend on the tumor’s histo-
logic grade (Burger et al., 1985; Fulling and Nelson,
1984; Kim et al., 1991). All grades of diffuse infiltrative cerebral astrocytoma should be considered malignant, even if only by virtue of their location within the enclosed bony skull, because almost none of these tumors is cured by surgical excision alone.

Astrocytes are supporting glial cells and generally have small round nuclei with inconspicuous micronucleoli. Under normal circumstances in routinely stained histologic sections, astrocytes do not have visible cytoplasm, but ultrastructural studies reveal short cytoplasmic processes containing intermediate filaments. These filaments are known, through immunohistochemical studies, to be composed of glial fibrillary acidic protein, a specific type of astrocytic protein (Fig. 3–11). Tumors can be confirmed as astrocytomas by specific immunostaining of tumor cells for glial fibrillary acidic protein. Astrocytes can react to brain injury by increasing the amount of their cytoplasm and the complement of filaments filling it. Their cytoplasmic processes become elongated and thickened, their cell bodies become enlarged, and their cytoplasm is then visible in routine sections. These enlarged, reactive astrocytes are called gemistocytes.

Astrocytic neoplasms exhibit a stereotypic range of features that become more prominent with increasing grades of anaplastic malignancy. In general, the features we use to grade tumor malignancy are those that permit us to diagnose the tumors. These features include degree of cellularity, nuclear and cytoplasmic pleomorphism of individual cells, mitotic activity, vascular changes such as small vessel proliferation or vascular mural cell proliferation, and tumor necrosis. None of these features in isolation is specifically diagnostic of malignancy, but the combined spectrum is used for both diagnosis and tumor grading. Other histologic features that suggest a diagnosis of tumor and tend to suggest increasing malignancy, but are not statistically significant in studies of histologic grading, include tumor invasion of the cerebral cortex, microcystic areas (indirectly correlated with grade), presence of tumor gemistocytes, and pial or subpial invasion by tumor cells.

Most astrocytomas are derived from fibrillary astrocytes of white matter and arise in the subcortical white matter. Low-grade astrocytomas show an increased cellularity over normal white matter, and the cell nuclei are slightly enlarged. No mitotic activity is

---

Figure 3–8. Intraoperative photograph of the tumor and adjacent brain following awake stimulation mapping of the cortex. Repetitive errors in naming were documented in numbers 33, 34, and 35. Numbers 24 and 25 overlie the center of the tumor.
Figure 3–9. Post-resection photograph with essential language sites preserved.

Figure 3–10. Postoperative $T_1$-weighted sagittal images of the resection cavity.
seen, vessels are not abnormal, and necrosis is not identified. Small nucleoli may become more prominent, but the nuclei themselves are regular in outline without much pleomorphism. Microcysts may be a distinctive feature and may contain proteinaceous fluid. Astrocytomas derived from the protoplasmic astrocytes of the cerebral cortex are relatively filament-poor and arise within the cortex itself. These tumor cells have short, delicate processes and poor immunoreactivity for glial fibrillary acidic protein.

As cellularity and pleomorphism, either nuclear or cytoplasmic, increase, the tumor becomes more anaplastic. Anaplastic astrocytomas may have moderate degrees of all these features. In addition, mitotic activity is present. Anaplastic astrocytomas are more likely to show cortical invasion or subpial accumulation of neoplastic cells. Any astrocytoma with gemistocytic change involving greater than about 20% of the cells should be graded as an anaplastic astrocytoma (Krouwer et al., 1991), although designation as a gemistocytic astrocytoma requires that approximately 60% of the tumor cells be gemistocytes.

The distinguishing histologic features of glioblastoma, the highest malignant grade of astrocytoma, are the presence of vascular mural cell proliferation or coagulative tumor necrosis (Burger and Green, 1987; Kleihues and Cavenee, 2000). Necrosis may be accompanied by pseudopalisading of neoplastic cells around it, but evidence of palisading is not required by most neuropathologists to make the diagnosis of glioblastoma (Burger et al., 1985).

In addition to specific histologic features of malignancy grades, astrocytomas may have a widely variable histology from one microscopic field to another within the same tumor, a feature known as heterogeneity. Tumor heterogeneity is thought to arise from a predominance of various transformed clones of astrocytes in different regions of the tumor during its progression.
growth. As the name *multiforme* suggests, glioblastomas are especially noted for their variable histology.

**Approaches to Grading Gliomas**

Whereas for most tumors it is recognized that higher grades of malignancy are associated with a poorer patient prognosis, the grading criteria for gliomas in most grading schemes are subjective. Within a single grade, the prognosis for tumors in individual patients may be difficult to predict on the basis of grade alone (i.e., astrocytomas with similar histologic features may behave in widely disparate clinical fashions). Any scheme of histologic grading has two main goals: the tumor grade must predict behavior, and the grading criteria must be sufficiently objective and defined to minimize variation among observers and to maximize reproducibility (Fulling and Nelson, 1984). Numerous grading systems have been used for astrocytomas, most of them utilizing three or four grades of malignancy (Burger et al., 1985, 1991; Fulling and Nelson, 1984; Svien et al., 1949; Kernohan et al., 1949; Ringertz, 1950; Nelson et al., 1983; Burger and Green, 1987; Daumas-Duport et al., 1988b; Kleihues and Cavenee, 2000). Histologic criteria used to define these grades vary somewhat for different schemes (Table 3–1). Increasingly, more malignant tumors show a continuum of histologic features that permits their classification into grades.

The first systems for grading gliomas were presented at about the same time (Svien et al., 1949; Kernohan et al., 1949; Ringertz, 1950). Svien and Kernohan each used a four-grade system (designated as grades 1 through 4) that was patterned after the histologic grading system for epithelial neoplasms used at the Mayo Clinic. Ringertz’s system had three grades of astrocytoma malignancy: astrocytoma, intermediate-type astrocytoma, and glioblastoma multiforme. Necrosis was used to divide the intermediate-type astrocytoma from the glioblastoma. Although the three systems defined histologic grade according to the presence of cellular anaplasia, the systems of Svien and Kernohan determined tumor grade according to the proportion of normal tissue remaining mixed with the invading tumor and on the type of invading edge of tumor into normal tissue. Because of the infiltrative growth pattern of gliomas, this feature is notoriously difficult to distinguish, especially in well-differentiated tumors. Also, it has subsequently been considered that the presence of even a single highly malignant focus of glioblastoma in an otherwise lower-grade astrocytoma portends a grave prognosis. Data from the original publications (Svien et al., 1949; Kernohan et al., 1949) showed no clinical distinction between grades II and III astrocytomas, whereas there was a clear survival difference among the three groups of patients in Ringertz’s study. Thus, the three-tiered grading schemes were popularized.

Three-tiered grading systems have been shown to be closely correlated with the clinical prognosis for astrocytomas and are widely used today in diagnostic neuropathology. These grading systems include those of Ringertz, with its modifications (Ringertz, 1950; Fulling and Nelson, 1984; Nelson et al., 1983; Burger et al., 1985; Burger and Green, 1987), and a scheme widely called the *St. Anne-Mayo system* (Daumas-Duport et al., 1988b). The St. Anne-Mayo scheme designates four histologic features to be used in grading and nominally has four grades of astrocytoma. Their grade 1 tumor, however, is exceedingly rare (<0.25% in one series), and the other three grades produce three distinct survival curves; thus, this scheme should also be considered as a three-tiered scale (Kim et al., 1991).

Histologic features used to grade astrocytomas include increasing cellularity; microcysts (which suggest an improved prognosis); nuclear and cellular

<table>
<thead>
<tr>
<th>Table 3–1. Comparison of Astrocytoma Grading Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified Ringertz</strong></td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Astrocytoma (low grade)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
</tr>
</tbody>
</table>
pleomorphism; vascular mural cell proliferation; mitotic activity; and coagulative tumor necrosis (Fig. 3–12). The St. Anne-Mayo system rates cellular pleomorphism, mitotic activity, vascular endothelial proliferation, and necrosis within a standardized and objective numeric scale. When present, each feature receives one scoring point, and the grades are based solely on the total numeric score. Concordance among individual pathologists who use the St. Anne-Mayo system is reported to be as high as 94% (Kim et al., 1991). That single study examined 251 astrocytoma cases and suggested, because of survival data, that the presence of necrosis should cause a tumor to immediately be classified as grade 4, even using their system. In this discussion, the terms low-grade astrocytoma, anaplastic astrocytoma, and glioblas-


toma are used. In most cases it can be assumed that the glioblastoma is primarily derived from astrocytes, even though its morphology may be so bizarre as to obscure such recognition, and sometimes it follows an earlier diagnosis of oligodendrogloma.

The most recent World Health Organization (WHO) classification also incorporates grading of nervous system neoplasms (Kleihues and Cavenee, 2000). The WHO criteria and general grading for astrocytomas are analogous to the St. Anne-Mayo system, but the terms used are diffuse astrocytoma (low grade), anaplastic astrocytoma, and glioblastoma. They are considered as WHO grades II, III, or IV, respectively (Daumas-Duport et al., 1988b; Kleihues and Cavenee, 2000).

Previous grading schemes for oligodendrogliomas are not as well correlated with patient survival as are those for astrocytomas (Smith et al., 1983; Burger et al., 1987; Shaw et al., 1992; Mork et al., 1985; Kros et al., 1988, 1990). Well-differentiated oligodendrogliomas are considered as WHO grade II neoplasms, whereas anaplastic oligodendrogliomas are WHO grade III (Kleihues and Cavenee, 2000). Grading oligodendrogliomas using WHO criteria has been shown to be clinically significant (Dehghani et al., 1998). Only these two grades of malignancy are accepted by the WHO. Many features used to grade oligodendrogliomas are similar to those for astrocytomas: cellularity, pleomorphism, mitotic activity, vascular changes, and necrosis (Smith et al., 1983; Burger et al., 1987). Sometimes lower grade oligodendrogliomas may have microcysts as well (Mork et al., 1986). Oligodendrogliomas of all histologic grades tend to infiltrate the cortex readily to form clusters of neoplastic cells in the subpial region and around neurons and blood vessels.

Grading systems for the other types of gliomas are much less well defined. For ependymomas, most authors have found little correlation between postoperative survival and tumor grade (Schiffer et al., 1991; Fokes and Earle, 1969; Ross and Rubinstein, 1989; Chiu et al., 1992).

Specific Tumor Characteristics

Low-Grade Astrocytoma

Diffuse low-grade astrocytomas are WHO grade II (Kleihues and Cavenee, 2000). Even though low-grade astrocytomas might be considered slow-growing tumors, most neuropathologists and neurosurgeons do not consider them benign because of their invasive quality and their location within the confines of the bony calvarium. These astrocytomas are rarely cured because they cannot be completely excised and because their ability to expand without damage to the host is limited by the skull. Thus, patients may die from recurrent astrocytomas, sometimes even lower grade ones, because of associated increased intracranial pressure or invasion of vital CNS structures.

Diffuse fibrillary astrocytomas are the most common morphologic subtype and usually arise in the white matter, which is the location of their normal cellular counterparts. The lobar distribution of these tumors is similar to that of the amount of white matter present in each brain lobe, with a higher incidence in the frontal regions (Burger et al., 1991). Grossly, these tumors are slightly discolored yellow or gray and have indistinct margins with the surrounding brain. The usually discrete border between cerebral white matter and gray matter may be blurred by the tumor. The tumor consistency is variably reported as firm, almost rubbery, or soft and gelatinous. This character may depend on the degree of fibrillarity of the individual cells within the neoplasm.

Histologically, low-grade astrocytomas show increased cellularity compared with normal brain tissue and have mild or moderate nuclear pleomorphism. The increase in cellularity may be only slight, producing a challenge for the diagnostic pathologist, and may simulate the slightly increased cellularity of reactive astrocytosis, a repair process. However, reactive astrocytic cells show generally more abundant and luxuriant cytoplasmic processes than do neoplastic astrocytes, with a more even cellular distribution and smaller, darker nuclei. The nuclei of astrocytoma cells are enlarged and show more prominent chromatin granules. Microcysts may be a useful feature for making a differential diagnosis with gliosis because this feature is rare in gliosis but common in low-grade astrocytomas. Astrocytoma cytoplasmic processes may be evident in routine sections but can be better visualized after immunohistochemical staining for glial fibrillary acidic protein. Other features of anaplasia, such as mitotic activity, vascular proliferative changes, and necrosis, are absent. Microcalcifications can be present in as many as 15% of astrocytomas. Although these tumors are diffusely invasive into the surrounding brain, their invasion is largely
limited to white matter. Invasion of the cerebral cortex with perineuronal satellitosis and subpial accumulation suggests a more aggressive astrocytoma or an oligodendroglioma.

Astrocytomas, especially low-grade examples, may occur as mixed tumors with neuronal or other glial components. Mixtures with oligodendroglioma are especially common, but other elements should be present in significant proportions to justify a diagnosis of mixed glioma.

**Anaplastic Astrocytoma**

The gross appearance of anaplastic astrocytomas is similar to that of the lower grade tumors, except that the anaplastic astrocytomas have a softer consistency because they usually lack extreme fibrillarity. Diffuse infiltration remains a feature, without evidence of necrosis in the tumor, although the relatively greater difference with surrounding normal brain tissue may falsely suggest a more discrete lesion.

The histologic features of anaplastic astrocytomas are similar to those of low-grade astrocytomas but these features are more abundant and exaggerated. These tumors are WHO grade III (Kleihues and Cavenee, 2000). Cellularity is more increased, as are nuclear and cellular pleomorphism. These features may be extreme, with back-to-back cells and bizarre, hyperchromatic nuclei. Cytoplasm may be scanty, with nuclear lobation and enlargement indicating anaplasia. Alternatively, the abundant eosinophilic cytoplasm of gemistocytes may be prominent, with relatively small and uniform nuclei. Gemistocytic astrocytic foci generally occur in tumors with more usual fibrillary areas. The presence of more than 20% of gemistocytes in a glial neoplasm is a poor prognostic sign (Krouwer et al., 1991); thus, gemistocytic astrocytomas should be considered anaplastic. Mitotic activity is easily recognized in most anaplastic astrocytomas but inexplicably may be absent in the gemistocytic areas. Despite this seeming anomaly, gemistocytic cells commonly transform to more highly anaplastic small cells.

The range of anaplasia in this grade is broad, with some examples showing low cellularity and pleomorphism with a few mitotic figures and others being highly cellular and pleomorphic with frequent mitoses, lacking only the necrosis required for a histologic diagnosis of glioblastoma. For this reason, it is useful to have a more objective indicator of behavior, and some markers of cell proliferation have been used in an attempt to predict prognosis more accurately. The most used markers in this area have been antibodies to bromodeoxyuridine (BrdU) and Ki-67. The cellular incorporation of BrdU is a specific marker of the DNA synthesis phase of the cell cycle, whereas the Ki-67 antibody labels an antigen that is present in all phases of the cell cycle except G0. Both antibodies can be identified by immunohistochemical staining in paraffin-embedded tissue sections. In longer use, the BrdU labeling index was found to correlate with tumor grade and prognosis in all grades of astrocytoma and oligodendroglioma (Hoshino et al., 1993; Prados et al., 1998b; Lamborn et al., 1999), but not within the glioblastoma multiforme histology (Ritter et al., 1994). The BrdU labeling index appears to be an age-independent predictor of survival only in low-grade and anaplastic astrocytomas (Ito et al., 1994).

Because BrdU must be introduced into the tumor by injection into the patient before surgery, the MIB-1 antibody to the Ki-67 antigen is far more popular today. The MIB-1 antibody can be used in paraffin tissue sections and appears reliable for labeling index prognostications (Key et al., 1993; Davis et al., 1995) in a manner similar to BrdU. Some studies suggest that astrocytomas with MIB-1 labeling indices of $>5\%$ or $>7.5\%$ are associated with shorter survival times and an anaplastic histologic grade (Jaros et al., 1992; Montine et al., 1994).

**Glioblastoma**

Glioblastoma, also known as glioblastoma multiforme, is the glioma with the highest grade of malignancy, WHO grade IV (Kleihues and Cavenee, 2000). It represents 15% to 23% of intracranial tumors and about 50% to 60% of astrocytomas. Most examples are generally considered to arise from astrocytes because glial fibrillary acidic protein can be identified in the cell cytoplasm. Some examples, however, apparently arise from other glial lineages, such as oligodendrocytes. Glioblastoma is the most frequently occurring astrocytoma. Autopsy and serial biopsy studies have shown that some astrocytomas progress through the grades of malignancy with transformation from low-grade to anaplastic astrocytoma to glioblastoma (Muller et al., 1977). But, because some examples of glioblastoma appear to arise rapidly in otherwise normal patients and are recognized when
they are small, it is thought that this variety of glioblastoma can also arise directly from malignant transformation of astrocyte precursor cells without passing through the lower grades of malignancy (Kleihues and Ohgaki, 1997, 1999).

Tumor necrosis is the characteristic gross feature that distinguishes glioblastoma from anaplastic astrocytoma (Fulling and Nelson, 1984; Nelson et al., 1983; Burger et al., 1985; Burger and Green, 1987). Another microscopic feature that is distinctive and diagnostic is the presence of proliferative vascular changes within the tumor. These changes may occur in the endothelial cells (vascular endothelial hyperplasia or proliferation) or in the cells of the vessel wall itself (vascular mural cell proliferation). Both types of change are sometimes considered together as microvascular proliferation. Glioblastomas may show evidence of older or more recent hemorrhage, and their cellularity is usually extremely high. The individual cells may be small, with a high nuclear/cytoplasmic ratio, or very large and bizarre, with abundant eosinophilic cytoplasm. With cell proliferation labeling studies, the small cells are the more proliferative ones, and these small cell glioblastomas have a more aggressive course, with even shorter patient survival times than those of highly pleomorphic or better differentiated astrocytes (Burger and Green, 1987). Some glioblastomas may be so highly cellular that the population of small anaplastic cells simulates primitive neuroectodermal tumors such as the medulloblastoma. These same small cells may appear to condense in rows around areas of tumor necrosis, forming the characteristic pseudopalisades. They also have a propensity to infiltrate the brain extensively, spreading even to distant locations and giving the appearance of a multifocal glioma. Although some examples are truly multifocal (i.e., arising in multiple simultaneous primary sites), many of these multifocal tumors show a histologic connection when the whole brain is examined at autopsy.

The histologic morphology of glioblastoma can be highly variable, conferring the name multiforme. Some tumors are largely spindled and simulate a fibrosarcoma. Others show cytoplasmic lipidization or epithelioid structures that imitate squamous or glandular patterns with positive keratin immunoreactivity (Rosenblum et al., 1991; Gherardi et al., 1986; Galloway and Roessmann, 1986). A myxoid or chondroid type of appearance has also been seen (Kepes et al., 1984). The astrocytic origin of these diverse morphologic cell types can be confirmed by a positive glial fibrillary acidic protein immunostain.

The regional distribution of glioblastomas is similar to that of other astrocytomas, although these neoplasms occur relatively frequently in the brain stem and spinal cord in younger patients. If the tumors gain access to the ventricular system or the subarachnoid space, these pathways become avenues for wide dissemination.

Gliosarcoma

Gliosarcoma is a variant of glioblastoma in which a distinct component of sarcoma is admixed with the glioma. The frequency of gliosarcoma in glioblastoma is reported to be from 2% to 8% (Morantz et al., 1976; Meis et al., 1991). In some cases, this change is recognized at recurrence of an anaplastic astrocytoma or glioblastoma and may also be seen de novo. The sarcoma element may be of any histologic type, with fibrosarcoma being the usual one. Other types include malignant fibrous histiocytoma, osteosarcoma, rhabdomyosarcoma, and chondrosarcoma. Currently, the sarcomatous element is thought to be derived from a mesenchymal cell associated with the vascular adventitia. Differentiation into endothelium, smooth muscle, or pericytes can occur (Miller et al., 1991; Haddad et al., 1991). The prognosis of gliosarcoma is similar to that of glioblastoma.

Oligodendrogial Tumors

Oligodendrogliomas, like astrocytomas, mimic the histology of their presumed cell of origin. They also arise primarily in the white matter but tend to infiltrate the cerebral cortex more than do astrocytomas of a similar grade of malignancy. Like astrocytomas, grading schemes of histologic malignancy have been used for oligodendrogliomas, but these correlate less well with prognosis than those used for astrocytomas. Many of the histologic features used to grade oligodendrogliomas are similar to those used for astrocytomas: cellularity, pleomorphism, mitotic activity, vascular changes, and necrosis. Lower grade oligodendrogliomas may have microcysts. Oligodendrogliomas of all histologic grades tend to infiltrate the cortex readily and to form clusters of neoplastic cells in the subpial region, around neurons, and around blood vessels. In general, the cells of oligodendrogliomas have round, regular nuclei and dis-
Distinct cytoplasmic borders with clearing of the cytoplasm (Fig. 3–13). Their cytologic appearance has been compared to “fried eggs.” The neoplastic cells do not have fibrillary cytoplasmic processes. Another fairly distinctive and diagnostically helpful feature is the vascular pattern of oligodendrogliomas, referred to as “chicken wire” vessels. The blood vessels divide the tumor into discrete lobules. For this reason and because of the not uncommonly seen discrete margin between oligodendrogliomas and adjacent white matter, some are mistaken for metastatic carcinomas. Variants of the usual clear cells are recognized. Some oligodendrogliomas can have cells with a small rim of eosinophilic cytoplasm. These cells are distinctive and are called mini-gemistocytes. Despite the cytoplasm, there are few or no cell processes, and these mini-gemistocytes are believed to be true oligodendrocytes rather than astrocytes (Herpers and Budka, 1984).

As might be expected, this rim of eosinophilic cytoplasm may contain intermediate filaments ultrastructurally (Kros et al., 1992), and it shows positive immunoreactivity for glial fibrillary acidic protein. In addition, most oligodendrocytes show positive nuclear and cytoplasmic reactivity for S-100 protein, a characteristic that can help in distinguishing them from other clear cell tumors in the brain and that can be useful if these tumors are nonimmunoreactive (as might be expected) for glial fibrillary acidic protein. With increasing anaplasia, oligodendrogliomas can become highly cellular and pleomorphic, approaching an appearance of glioblastoma multiforme with the presence of necrosis. Although it is correct to classify these as anaplastic oligodendrogliomas, some would use the term glioblastoma once necrosis is identified in any high-grade glial neoplasm. One justification for separating anaplastic oligodendrogliomas from astrocytic glioblastomas is the slightly better prognosis of the former, even in this highest grade of malignancy (Ludwig et al., 1986; Dehghani et al., 1998). Some authors have reported that an MIB-1 labeling index of >3% to 5% predicts a worse prognosis in oligodendrogliomas (Heegard et al., 1995; Kros et al., 1996; Coons et al., 1997; Cairncross et al., 1998; Dehghani et al., 1998).

**Oligoastrocytomas**

Many, if not most, oligodendrogliomas occur with a regional or intimate cellular mixture of astrocytoma. For the diagnosis of mixed glioma, the proportion of each should be substantial, but authors have differing opinions with respect to exact numbers; usually a mixture with a range from 10% to 25% of the mi-

**Figure 3–13.** Low-grade oligodendroglioma. Proliferation of cells with round nuclei and cleared cytoplasm ("fried egg" cells). The oligodendroglioma cells are more numerous than would be seen in normal brain tissue, but neuropil is present between the neoplastic cells. Small, thin-walled capillaries (arrows) are also a feature. Hematoxylin and eosin. Original magnification, ×200.
nor element is used to diagnose a mixed glioma. Oligoastrocytomas and anaplastic oligoastrocytomas correspond to WHO grade II or grade III, respectively (Kleihues and Cavenee, 2000). Histologic features of anaplasia may be present in either component and will affect the prognosis adversely. Such features include marked cellular pleomorphism, high cellularity, and a high mitotic rate. Microvascular proliferation and necrosis may also be seen. Prognosis and response to therapy have not been shown to depend on the proportion of the oligodendroglial versus the astrocytic component of the tumor (Shaw et al., 1994).

Supratentorial Ependymomas

Ependymomas are tumors that arise from the ependymal cells of the ventricles. Although more common in the posterior fossa of children, they are also well-recognized supratentorial gliomas. In contrast to the posterior fossa examples, supratentorial ependymomas often arise with no direct connection to the cerebral ventricles (Burger et al., 1991; Bigner et al., 1998). They have a distinctive, almost epithelial, appearance and are commonly calcified. One diagnostic feature is the presence of true ependymal rosettes, but these are rare. A feature that serves to suggest the diagnosis is the alternating appearance of zones with fairly uniform round nuclei alternating with eosinophilic anuclear zones. These anuclear zones occur most commonly around blood vessels and represent ependymal cell cytoplasmic processes. True ependymal rosettes may be impossible to find without resorting to ultrastructural studies.

Ependymomas may have some immunoreactivity to glial fibrillary acidic protein and may also react with antikeratin antibodies. Other ultrastructural features that attest to these tumors’ histologic origin are a columnar cell shape, a definite polar orientation with respect to blood vessels, basal lamina near the vessel, and abundant microvilli on the cell surface distant from the vessel. True cilia may be recognized but may be difficult to find. Many supratentorial ependymomas have regions with clear cells, simulating a mixture of oligodendroglial cells. However, these clear cells are thought to be a variant of ependymal cells. Ependymomas are classified with WHO grade II tumors. Anaplastic ependymomas are WHO grade III (Kleihues and Cavenee, 2000). Ominous features that suggest a higher grade include very high cellularity and frequent mitoses. Vascular mural cell proliferation and necrosis do not seem to be predictive of poor prognosis in ependymomas.

**PATHOLOGY OF NONINFILTRATIVE GLIOMAS**

The following sections of this chapter discuss the very low-grade, noninfiltrating gliomas and other low-grade infiltrating gliomas whose prognosis, while quite good for brain tumor patients, is less favorable than that of patients with noninfiltrating gliomas. Most low-grade glioma patients are children, adolescents, or young adults; therefore, special consideration with respect to surgery, perioperative care, radiotherapy, and chemotherapy is discussed.

In addition to the diffuse supratentorial astrocytomas that are histologically graded according to the above scheme, special variants of astrocytoma exist that do not conform to these grades and that occur in specific clinical situations. These include the juvenile pilocytic astrocytoma, which is the most common tumor in this group; the pleomorphic xanthoastrocytoma; the desmoplastic astrocytoma; and the subependymal giant cell astrocytoma of tuberous sclerosis. Other more uncommon variants of mixed neuronal–glial and mature neuronal tumors include the desmoplastic infantile ganglioglioma, the dysembryoplastic neuroepithelial tumor, the central neurocytoma, and the ganglioglioma.

**Characteristics of Specific Tumors**

**Juvenile Pilocytic Astrocytoma**

The most common locations of supratentorial juvenile pilocytic astrocytomas, considered as WHO grade I, are the cerebral hemispheres followed by, in order of decreasing frequency, optic pathways, hypothalamus, and thalamus (Clark et al., 1985; Sutton, 1987). Juvenile pilocytic astrocytomas of the cerebral hemispheres are usually cystic, with a tumor nidus presenting as a mural nodule (Palma and Guidetti, 1985; Tomita et al., 1986). On occasion, the tumor is arranged in a plaque-like fashion at the perimeter of the cyst, which is brightly enhanced on CT following the administration of IV contrast agents (Maiuri, 1988). It should be noted, however, that not all cystic hemispheric lesions, with or without the appear-
ance of a mural nodule, are astrocytic in nature. The clinical differential diagnosis of these tumors includes ependymoma, hemangioblastoma, neuroblastoma, meningoima, and primitive neuroectodermal tumor.

The vast majority of patients with juvenile pilocytic astrocytomas develop symptoms in the first three decades of life, in particular between the ages of 10 and 25 years (Clark et al., 1985; Garcia and Fulling, 1985; Schisano et al., 1963). The duration of symptoms before surgery is usually 3 to 5 years. The most common symptoms of cerebral hemisphere tumors are related to mass effect and location and include headaches, nausea and vomiting, weakness, visual disturbances, and seizures. Tumors of the hypothalamus and thalamus can cause precocious puberty, "diencephalic syndrome" (Scott and Mickle, 1987), and hemiparesis, respectively. Children less than 1 to 2 years of age may also present with macrocephaly. This finding of an enlarged head in an infant or newborn who also is failing to thrive indicates a tumor in the hypothalamic area until proven otherwise (Wisoff et al., 1990). Obstructive hydrocephalus results from a tumor, usually of a pilocytic phenotype, occurring in the posterior optic pathway, optic–hypothalamic region, or the anterior thalamus (Nishio et al., 1993). Anatomically, the tumor occludes the anterior third ventricle, blocking either the aqueduct of Sylvius or the foramen of Monro. Anteriorly located optic pathway tumors are rarely associated with hydrocephalus.

Astrocytomas of the third ventricle region, optic apparatus, and cerebellum in children have a similar histologic appearance and biologic behavior. Their singular common feature is the presence of elongated, spindled astrocytes, the so-called pilocytes or "hair-like" cells (Burger et al., 1991). These cells have spindle-shaped nuclei and long, thin, eosinophilic cytoplasmic processes that extend from the cells in a bipolar array. Another usual histologic feature is the presence of Rosenthal fibers within the tumor or at its periphery and the interface with surrounding brain. These distinctive eosinophilic beaded structures are derived from astrocytic processes. Ultrastructurally, the eosinophilic material is electron dense, and residual intermediate filaments can be distinguished at its periphery. Immunocytochemically, studies for glial fibrillary acidic protein usually show peripheral positive reactivity in Rosenthal fibers, with a largely negative reaction in the center.

In addition to this common feature, tumors of the separate locations have some distinctive features. The parenchymal pilocytic astrocytomas are commonly described as cystic with a mural nodule. This nodule has a fleshy, dark red appearance grossly and is distinguished histologically by its biphasic nature. It appears as an irregular alternating pattern of pilocytic areas and looser microcystic areas (Fig. 3–14). The microcysts contain eosinophilic, acellular, proteinaceous material. The cells in the looser areas are more stellate, with multiple short cell processes and round nuclei. The pilocytic areas are commonly located around blood vessels. The numerous blood vessels can show thickening and hyalinization of their walls, with endothelial cell hypertrophy or proliferation, simulating the vascular mural cell proliferation seen in malignant astrocytomas of the cerebral hemispheres. However, in the pilocytic astrocytomas of children, these vascular changes do not portend an ominous prognosis. Other areas of these tumors may show cells with clear cytoplasm, resembling oligodendroglioma. Individual nuclei of the pilocytes can be enlarged, hyperchromatic, and pleomorphic, but these nuclear features again are not associated with a worse behavior. It is thought that this nuclear pleomorphism represents a degenerative change. The pilocytic astrocytomas with the biphasic pattern have been termed juvenile pilocytic astrocytomas to distinguish them from the diffuse astrocytomas having a pilocytic growth pattern that occurs in the cerebral hemispheres of adults or in the brain stem. These diffuse pilocytic astrocytomas are typically graded according to the usual criteria for malignant astrocytomas and behave as such.

Pilocytic astrocytomas of the optic apparatus and third ventricle region are less commonly biphasic than are the hemisphere parenchymal examples, but have the distinctive pilocytes and lack mitotic activity (Fig. 3–14). These tumors distort the usual organizational pattern of the optic nerves and chiasm, expanding and then obliterating the septate structure. There is an increase in glial cellularity but little pleomorphism. An exuberant growth of connective tissue is also a common feature, and the tumors can grow into the leptomeninges of the optic structures. Rosenthal fibers are a common finding. Metastatic spread in the cerebrospinal fluid has been described, even in the absence of increased histologic anaplasia (Obana et al., 1991).

Pilocytic astrocytomas show strong cytoplasmic glial fibrillary acidic protein immunoreactivity in the pilocytic cells with diffuse reactivity in the stellate
cells. Vascular structures fail to stain with glial fibrillary acidic protein, but can be delineated with a Masson trichrome, reticulin, or Factor VIII immunostain. These three methods label the perivascular collagen, connective tissue fibers, or endothelial cells, respectively.

Tuberous Sclerosis (Bourneville’s Disease)

Tuberous sclerosis is a phakomatosis associated with supratentorial noninfiltrative gliomas. Children and young adults afflicted with this syndrome are typically cognitively retarded and have seizures that are often refractory to medical care and dermatologic manifestations of facial adenoma sebaceum. Cortical hamartomas are the rule and are associated with periventricular calcified nodules (Pinto-Lord et al., 1986). These latter lesions are typically located near the foramen of Monro and histologically are subependymal giant cell astrocytomas (McLaurin and Towbin, 1986), a lesion that has not been documented in patients without tuberous sclerosis (Shep-
herd et al., 1991). If the subependymal nodule grows, it will block the foramen of Monro and cause obstructive hydrocephalus. Often this is a very indolent process with a gradual onset of symptoms.

**Subependymal Giant Cell Astrocytoma**

The subependymal giant cell astrocytoma is a tumor of uncertain histogenesis that is usually included with astrocytomas. It is classified as WHO grade I (Kleihues and Cavenee, 2000). The degree of histologic pleomorphism of the cells may suggest a diagnosis of glioblastoma multiforme, but mitotic activity and necrosis are lacking. The subependymal giant cell astrocytoma generally occurs in the setting of tuberous sclerosis and is located, as its name suggests, in the subependymal region, two features that may be helpful in suggesting the correct diagnosis. However, sporadic examples in patients without a history of tuberous sclerosis do occur (Boesel et al., 1979). The tumor cells are large and bizarre, and the tumor is highly cellular. Abundant eosinophilic cytoplasm is a usual feature. The nuclei are very enlarged and have prominent nucleoli, even suggesting a neuronal origin (Nakamura and Becker, 1983). Ultrastructurally, intermediate filaments are numerous, as are long, thickened cytoplasmic processes. Immunohistochemical studies, however, failed to reveal a defined histogenesis for this neoplasm, as tumor cells may mark poorly for both glial and neuronal antigens or may mark for both. This tumor is usually considered benign and is curable by surgical excision alone (Shepherd et al., 1991).

**Pleomorphic Xanthoastrocytoma**

Another tumor found to involve the cerebral hemispheres in children and young adults is the pleomorphic xanthoastrocytoma. This lesion is almost always superficial in location and often abuts a leptomeningeal surface (Kepes et al., 1979). The temporal lobe is most commonly involved, followed in frequency by the parietal lobe. In our experience, seizures are the most common form of presentation, and the duration of symptoms may extend up to several years before the surgical diagnosis. Although usually described as a benign and indolent lesion and classified as WHO grade II, the clinical course and outcome of this tumor are controversial because of the difficulty in arriving at a histologic diagnosis due to its pleomorphic and giant cell appearance. Nonetheless, cases have been reported with a rapidly progressive tumor growth resulting in death (Weldon-Linne et al., 1983). Xanthoastrocytomas, like other gliomas, have been found in patients with neurofibromatosis (Ozek et al., 1993).

The pleomorphic xanthoastrocytoma is a distinctive astrocytoma variant known for its extreme histologic pleomorphism in the absence of significant mitotic activity and necrosis (Kepes et al., 1979; Kepes, 1993). The importance of recognizing this variant is that it should not be mistaken for glioblastoma multiforme. This superficially located tumor of early adulthood is usually considered benign and is surgically curable. The individual tumor cells, in addition to showing marked pleomorphism tending even toward the bizarre, have a high content of lipid, revealed in frozen sections by staining for neutral fat with oil red O. The astrocytic nature of these foamy, lipidized cells is revealed by positive cytoplasmic immunoreactivity for glial fibrillary acidic protein (Grant and Gallagher, 1986). The finding of mitotic activity or necrosis or the occurrence of this neoplasm in patients beyond the third decade of life should raise caution about the diagnosis and prognosis. These examples may be classified as WHO grade III (Giannini et al., 1999). Some examples have been shown to transform to glioblastoma or to behave in a malignant fashion (Weldon-Linne et al., 1983).

**Desmoplastic Cerebral Astrocytoma**

The desmoplastic infantile astrocytoma is another distinctive variant that occurs in a stereotypical clinical situation. It corresponds to WHO grade I (Kleihues and Cavenee, 2000). This tumor is generally one of infancy and childhood (VandenBerg, 1993; Louis et al., 1992; de Chadarevian et al., 1990). A few examples in adults have been described. The singular histologic feature is the extreme spindling of astrocytes within an extensive collagen matrix. The tumor may be superficially located in the hemisphere, and it has been postulated that the collagen arises from growth of the tumor into the pia with collagen proliferation from that source. These tumors may even resemble a sarcoma, but immunohistochemical studies positive for glial fibrillary acidic protein again reveal their astrocytic nature. The prognosis for these tumors is considered favorable with complete excision, but they occur very infrequently.
A tumor having similar histology but also exhibiting primitive small cells and neuronal differentiation occurs in very young children, generally under 2 years of age (VandenBerg et al., 1987; VandenBerg, 1993). These are the desmoplastic infantile gangliogliomas, which are discussed below.

**Mixed Neuronal−Glial Tumors**

Mixed neuronal–glial tumors include a broad histologic spectrum, ranging from the typical ganglioglioma, with its complement of atypical but well-differentiated neuronal elements, to the more complex examples of desmoplastic infantile ganglioglioma and dysembryoplastic neuroepithelial tumor.

**Dysembryoplastic Neuroepithelial Tumor.** The dysembryoplastic neuroepithelial tumor is found exclusively in patients who undergo cortical resections for intractable epilepsy (Daumas-Duport et al., 1988a). This tumor is described as showing multiple intracortical nodules of glial proliferative elements combined with a dysplastic cerebral cortex and a columnar orientation of a “specific glioneuronal element” composed of oligodendroglia, neurons, and capillaries (Daumas-Duport, 1993). The astrocytic component is generally pilocytic and forms nodules that may be microcystic. Mitotic activity is not seen, and necrosis is not a feature of this tumor. These are considered WHO grade I (Kleihues and Cavenee, 2000). The tumor’s histologic appearance is quite characteristic, with a prominent vascular septa dividing it into a lobular pattern. Mature lymphocytes can be a feature of the vascular component. The glial component is usually astrocytic and low grade, with rare or absent mitotic figures (Haddad et al., 1992). The glial morphology may suggest a pilocytic astrocytoma. Intermingled with the astrocytic component is a population of atypical neurons, which are manifested in their size and shape, arrangement, and neurohistology. Multinucleated forms may be seen. Because large, gemistocytic astrocytes may simulate atypical neurons with their abundant eosinophilic cytoplasm, special immunohistochemical markers of neuronal differentiation, such as synaptophysin or neurofilament protein, may be required to confirm the diagnosis (Miller et al., 1993).

**Desmoplastic Infantile Ganglioglioma.** The desmoplastic infantile ganglioglioma is a distinctive and rare tumor that occurs in infants, generally within the first 2 years of life (VandenBerg, 1993). These tumors are very similar to the superficial cerebral astrocytoma with dural attachment described by Taratuto et al. (1984) and tend to be located in the frontal and parietal regions. These tumors may be large, with a prominent cystic or multicystic appearance, and generally have a superficial hemispheric location. They have a predominant desmoplastic character, resulting in a firm gross consistency, and often have a large amount of proteinaceous fluid. Despite this, they infiltrate into brain. The desmoplasic consists of admixed fibrous collagen and glial elements. The astrocytic component may be moderately pleomorphic but is identified by its positive cytoplasmic immunoreactivity for glial fibrillary acidic protein. The neuronal elements range from mature neurons to primitive small cells and can be recognized by immunohistochemical stains for synaptophysin or neurofilament protein. The neuronal elements are usu-
ally seen in the less desmoplastic areas of the tumor and may be of variable amounts. Mitoses and necrosis are more likely to be found in association with the small cell component. Despite their cellular heterogeneity and primitive small cell component, these tumors are associated with a prolonged survival provided that the tumor is maximally resected. They are WHO grade I (Kleihues and Cavenee, 2000).

Central Neurocytoma

Neurocytomas are neoplasms of small mature neurons that may arise within the ventricles (intraventricular or central neurocytoma) or in the brain parenchyma (cerebral neurocytoma) (Burger et al., 1991; Hassoun et al., 1993; Hessler et al., 1992). The classic central neurocytoma is a supratentorial, often calcified, mass within the lateral ventricle. It may arise from the septum pellucidum (Kim et al., 1992).

Histologically, this neoplasm is characterized by a diffuse proliferation of small, clear cells with round nuclei and finely punctate chromatin. Fibrillary zones may be interspersed and may help to distinguish this tumor from oligodendroglioma. The tumor is not anaplastic, mitotic figures are rare, and necrosis is unusual. It corresponds to WHO grade II. The diagnostic feature is evidence of neuronal differentiation, either immunohistochemically or ultrastructurally (Hessler et al., 1992). Tumor cells are positive for the neuronal markers synaptophysin and neurofilament and negative for glial fibrillary acidic protein. Electron microscopy reveals dense-cored granules within the cell bodies (Hassoun et al., 1993). These diagnostic studies can distinguish neurocytomas from ependymomas and oligodendrogliomas. With complete removal, neurocytomas seem to behave in a benign fashion and generally do not recur (Kim et al., 1992).

OUTCOME VARIABLES

Several patient and tumor characteristics influence outcome in those with astrocytomas. The most important prognostic variables are patient age at diagnosis, functional status, completeness of resection, and tumor histology. Young age (Leibel et al., 1975; Marsa et al., 1975; Laws et al., 1985; Piepmeier, 1987; Medbery et al., 1988; Shaw et al., 1989; North et al., 1990), and more extensive surgery (Leibel et al., 1975; Laws et al., 1985; Shaw et al., 1989; Soffietti et al., 1989; North et al., 1990) are associated with an improved outcome. Patients with mixed oligoastrocytomas have a better prognosis than do those with pure astrocytomas (Shaw et al., 1991). Oligodendrogliomas, however, have a significantly better long-term survival than mixed oligoastrocytomas and astrocytomas (Shaw et al., 1997). While sometimes included with grade II astrocytomas, in general, survival of patients with gemistocytic astrocytoma is similar to those with anaplastic astrocytomas.

SURGICAL TREATMENT AND ITS IMPACT

The belief that most gliomas are infiltrative into adjacent brain has been strengthened in recent years by studies based on diagnostic imaging and neuroimage-guided stereotactic biopsies of these tumors and their surrounding periphery. This, along with technical advances in neurosurgical instrumentation allowing for precise tissue sampling using image-coupled reference frames, has had a significant effect on the role of surgery in managing the patient with a glioma.

In a study correlating results of CT scans with results of postmortem examination for extent of disease in patients with glioblastoma, Burger and colleagues (1988) found tumor beyond the contrast-enhancing rim at autopsy in most cases that had shown hypodense regions on the scan. However, there was a delay of several weeks between the imaging study and death; also the cause of death was the actual tumor in fewer than 50% of cases. Furthermore, the authors stated that the "methodology to identify neoplastic cells (in adjacent brain) has significant limitations."

Daumas-Duport et al. (1987) optimized tissue fixation methods to be able to define in greater detail cells that appeared to be neoplastic and had been obtained stereotactically from peripheral glioma zones. In addition, this group implanted corresponding specimens into nude mice, and the implants formed tumors composed of astrocytes. There was no attempt made to correlate the regions from where these isolated tumor cells were taken and patterns of recurrence in patients on the basis of follow-up imaging.
studies. Making a qualitative interpretation of neoplastic versus reactive astrocytes suffers from the lack of specific tumor cell markers. Extending beyond the CT era, biopsy material obtained from hyperintense, T2-weighted signal regions seen on MR imaging studies also verified isolated tumor cells outside the contrast-enhancing rim in high-grade glial tumors (Kelly, 1993).

Despite the knowledge base surgeons have acquired about the histologic limits of infiltrative gliomas, clinical studies have supported a localized pattern of tumor recurrence. Reports by Liang et al. (1991) and Hochberg and Pruitt (1980) documented recurrent disease within 2 cm of the contrast-enhancing rim in 85% to 90% of their patients. These two studies were done 10 years apart, and even with improvements in imaging, the conclusions were the same. Similarly, in another study Gaspar et al. (1992) found tumor recurrence in all cases within 4 cm of the contrast margin and not beyond this imaging line of demarcation.

Low-Grade Infiltrative Gliomas

Controversy continues to exist with regard to extent of tumor removal and outcome in patients with supratentorial low-grade glial tumors, which, in most circumstances, involve the cerebral hemispheres. Several points regarding the prognostic effect of tumor removal remain unclear, and management strategies are almost always based on class III evidence (i.e., evidence provided by expert opinions, nonrandomized historic controls, or case reports) (Bampoe and Bernstein, 1999; Eddy, 1990). A review by the Guidelines and Outlines Committee of the American Association of Neurological Surgeons (1998), based on data published between 1966 to 1994 on low-grade gliomas showed that the only available standard for adults with suspected or known supratentorial nonoptic pathway low-grade glioma is to obtain tissue diagnosis before active treatment. Several critical issues (e.g., the need for biopsy before observation and the effects of observation, resection, and radiotherapy on outcome) remained unclear. There were no standards or guidelines that could be supported by class I evidence (randomized controlled clinical trial) or class II evidence (case–control or cohort studies). Therefore, all current management strategies were considered as practice options based on class III evidence.

It is generally believed that the survival rate is higher for patients with gross total tumor resections compared with those with biopsy only. Unfortunately, no prospective randomized study has ever been done to evaluate the relationship between amount of tumor removed and subsequent influence on recurrence patterns and survival. Most studies are retrospective. Reports have been based on the surgeon’s impression at the time of surgery, appearance of the postoperative CT or MRI images, or measurement of perpendicular tumor diameters as seen on contrast-enhanced neuroimages. In addition, several studies include pediatric patients and evaluate survival characteristics for a combination of adult and pediatric patients, without taking into account that age is the strongest prognostic indicator within a histologic subgroup. This approach results in longer survival times and better overall outcomes for series incorporating younger patients.

Another common methodologic problem arises when various histologies with different natural histories are combined and evaluated together without manipulating the data to separate individual histologic subtypes. In several studies, pilocytic or gemistocytic astrocytomas are included in the study population. These heterogeneous populations make the data harder to interpret, and conflicting results are often obtained in studies evaluating the efficiency of a particular treatment option. Currently, there are only a few hemispheric low-grade glioma series with more than 75 patients that exclude the pediatric age group as well as gemistocytic and pilocytic histologies. All of these studies with relatively homogeneous patient populations show a statistically significant advantage in terms of survival for low-grade glioma patients who receive the most extensive resections (Leighton et al., 1997; Philippon et al., 1993; Rajan et al., 1993; Soffietti et al., 1989; van Veelen et al., 1998). None of these studies, however, offers class I evidence (randomized controlled clinical trial).

Of additional importance in interpreting surgical results is the fact that a large number of low-grade gliomas recur with a more malignant tumor grade (Afra et al., 1978; Laws et al., 1985; North et al., 1990; Piepmeier et al., 1987).

We previously analyzed our database, using a computerized image analysis technique (Duong et al., 1992) that yields a quantitative, volumetric determination of preoperative and postoperative tumor volumes, including percent of resection, to ascertain...
whether these parameters influence recurrence patterns. By measurement we found a mean preoperative tumor volume of 26.6 cc (based on T2-weighted MR signal) and found no tumor recurrence (mean follow-up, 42 months) when the preoperative volume was <10 cc (Berger et al., 1994). The likelihood of recurrence was greater and the time to tumor progression shorter when the volume increased (e.g., 41% recurrence rate at a median 30 months for patients with tumors >30 cc). Other studies have found radical resection to favorably influence outcome for patients who have a low-grade glioma. Data on the amount of resection were based on the operative report or on the qualitative assessment of the postoperative scans, without an attempt to use volumetric analysis (Guthrie and Laws, 1990; Laws et al., 1985; North et al., 1990). These data are similar to those reported by the Japanese Brain Tumor Registry during the past 25 years (1992), which include 5 year survival rates of 48% for biopsy and subtotal resections of 50% or less versus a 70% survival for those with greater than 90% resections (Brain Tumor Registry of Japan, 1992).

These data also parallel studies that evaluated postoperative tumor volume and survival time for high-grade gliomas (Levin et al., 1980b). Using volumetric measurements (based on tumor measurements in 3 intersecting directions), it was found that when the postoperative tumor volume was >10 cc the chance of recurrence was 46% (median time to tumor progression, 30 months) compared with a tumor volume of <10 cc, which had a chance of recurrence of 15% (median, 50 months); there were no recurrences following complete resection at a mean follow-up time of 54 months.

The timing of surgical intervention following a diagnosis based on imaging studies is also controversial, with some studies recommending immediate intervention (Laws et al., 1985; Morantz, 1987; Weingart et al., 1991) and others advocating a less urgent approach (Cairncross and Laperriere, 1989; Recht et al., 1992). One study that quantified the tumor area as being less than or greater than 25 cc found a significant difference in survival when patients with smaller tumors were operated on earlier (Shibamoto et al., 1993). Another retrospective review of patients whose surgery was deferred until disease progressed demonstrated that in nearly 50% of the cases malignancy was documented at the time of the biopsy even though the lesions had a classic low-grade appearance on the initial imaging studies (Recht et al., 1992). Although controversy will continue about biopsy versus radical resection as well as about the timing of surgery, such data as are presented in this section show a trend toward an increasing risk of early and malignant recurrence when a conservative approach is taken once the presumptive diagnosis of low-grade glioma is made.

Very few data exist on what role extensive surgery plays in determining the outcomes of patients with oligodendroglioma. Survival was positively influenced by total tumor resection in some studies (Chin et al., 1980; Shaw et al., 1992; Varma et al., 1983; Mork et al., 1985; Celli et al., 1994; Schiffer et al., 1997). This contrasts with studies by Sun and colleagues (1988) and others (Kros et al., 1994; Daumas-Duport et al., 1997) in which survival was not affected by the extent of resection. In one analysis, radiotherapy did not affect outcome following total tumor removal, implying that, unlike other infiltrative low-grade gliomas, oligodendroglioma may be more amenable to a complete tumor resection because of its somewhat circumscribed nature associated with macroscopically distinct margins (Lindegaard et al., 1987). As with all low-grade gliomas, the surgical strategy should favor radical tumor removal when at all feasible.

Finally, because low-grade tumors tend to have an indolent growth pattern, they are often associated with seizure activity that is infrequently not refractory to medical care. This is especially true for oligodendrogliomas, gangliogliomas, and astrocytic gliomas (Arseni and Petrovici, 1971; Hirsch et al., 1989; Pilcher et al., 1993). A controversial surgical issue involves the role of intraoperative electrocorticography during tumor resection used to minimize postoperative seizures. For most patients with intermittent seizures that are well controlled with antiepileptic drugs, removing the tumor alone without seizure mapping is sufficient and results in good control of tumor-associated epilepsy (Cascino et al., 1990; Cascino, 1990; Franceschetti et al., 1990; Goldring et al., 1986; Hirsch et al., 1989). In some low-grade glioma patients who have intractable seizures, tumor removal by itself often will not diminish seizure activity (Awad et al., 1991; Cascino et al., 1990; Spencer et al., 1984; Zentner et al., 1997). Our approach has been to use electrocorticography during the tumor resection to identify separate seizure foci adjacent to the tumor nidus (Berger et al., 1993). Of our adult patients,
88% became seizure free with (47%) or without (41%) antiepileptic drugs. Even the few patients who had persistent seizure activity while taking medication benefited from surgery and had fewer seizures that were often less intense. Each child and adolescent in our series was seizure free and not taking medication except for two children who continued therapy with antiepileptic drugs because they had a few seizures following surgery. These data are also supported by other investigators who use electrocorticography to control postoperative seizures in this particular patient population (Awad et al., 1991; Drake et al., 1987; Gonzalez and Elvidge, 1962; Rasmussen, 1975; Ribaric et al., 1991).

Juvenile Pilocytic Astrocytomas and Other Noninfiltrative Gliomas

The goal of surgical intervention in patients with cerebral hemispheric juvenile pilocytic astrocytomas is to evacuate the cyst contents and remove all contrast-enhanced tissue documented on the preoperative CT or MRI studies. This includes the mural nodule and any or all parts of the cyst that are contrast enhanced. Failure to remove the lesion while simply draining the cyst will uniformly result in re-accumulation of the cyst contents. Several studies have documented that the cyst wall is gliotic without neoplastic cells when it does not enhance with contrast administration (Maiuri, 1988; Tomita et al., 1986). If the cyst wall enhances, it must be completely resected to avoid tumor recurrence (Morota et al., 1990). The mural nodule is quite discrete and has a reddish-brown appearance. It is friable and moderately bloody. At the end of the resection, the adjacent, noninfiltrated white matter should be clearly visible. As expected, there is a distinct microscopic margin between the tumor and the contiguous white matter (Garcia and Fulling, 1985). Because the cyst is often in continuity with the ependymal surface of the ventricular system, we do not recommend, as do some authors, that the cyst be fenestrated into the ventricle (Palma et al., 1983; Mercuri et al., 1981). Following removal of the tumor, the cyst will not recur. In addition, debris from the resection cavity may seep into the ventricle and cause a communicating hydrocephalus.

With solid juvenile pilocytic astrocytomas it is somewhat more difficult to achieve a gross total resection, especially when the tumor is deep or attached to subcortical functional tracts. Solid tumors should be aggressively resected, however, unless excessive or unacceptable morbidity would result. The long-term results without radiotherapy or chemotherapy are excellent following a complete resection. Nevertheless, as a precautionary measure we advocate careful and routine follow up every 6 to 12 months for the first several years after surgery. The 10 year survival rate for a completely resected pilocytic hemispheric astrocytoma, verified with postoperative imaging studies, should approach 100% (Wallner et al., 1988a; Shaw et al., 1989). This favorable outcome also pertains to adult patients with this diagnosis (Garcia and Fulling, 1985). Although incompletely resected tumors may have a protracted course, recurrence is likely over a period of several years, necessitating routine follow up (Palma and Guidetti, 1985).

Thalamic juvenile pilocytic astrocytomas tend to be well circumscribed and may be associated with a cyst (Wald et al., 1982). Anterior thalamic tumors are best resected via a parasagittal incision in front of the premotor cortex, thus entering the ventricle anteriorly. These lesions displace the internal capsule laterally, whereas posterior thalamic masses push the posterior limb of the internal capsule forward. Therefore, the best approach in the latter circumstance is through the posterior ventricle (i.e., the atrium). It is critical to localize the capsular motor fibers using subcortical stimulation methods to avoid morbidity while maximizing the extent of resection (Berger et al., 1990). An alternative surgical approach is to volumetrically resect the pilocytic tumor using computer-assisted stereotactic methods (Lyons and Kelly, 1992). This technology is very accurate and effective, but is expensive and is not available to most neurosurgeons.

Because subependymal giant cell astrocytomas are always located within the anterior horn of the lateral ventricle, the preferred approach to them depends on the ventricular size. Ventricular dilatation is the rule for symptomatic patients because of the relationship between the tumor and the foramen of Monro. Therefore, in most circumstances a frontal transventricular approach is performed to gain the necessary exposure, taking advantage of the large ventricles. However, some surgeons still recommend a transcortical exposure because there is less brain re-
traction and less potential risk of postoperative epilepsy, although this latter point is debatable (McLaurin and Towbin, 1986). Regardless of approach, virtually all surgeons agree that these lesions should only be removed when symptoms of ventricular obstruction exist.

The supratentorial ependymoma and pleomorphic xanthoastrocytoma appear grossly as an encapsulated mass distinct from the adjacent brain. However, the latter lesion tends to have more of a contiguous relationship with the leptomeninges (Kepes et al., 1989), making its resection more difficult, especially when the tumor occurs within the sylvian fissure. With both lesions, a superficial (i.e., pial-based) attachment should alert the surgeon that these tumors are circumscribed and amenable to complete resection. One review of the literature, however, revealed that even with complete resection of a pleomorphic xanthoastrocytoma, there is a 30% chance of recurrence (Macaulay et al., 1993); thus, routine surveillance with postoperative imaging studies is mandatory.

While there is universal agreement among surgeons that cerebral hemispheric gangliogliomas should be completely resected (Silver et al., 1991; Otsubo et al., 1992), controversy exists regarding the extent of resection as it pertains to optimal tumor control. If the literature is reviewed with respect to seizure control and extent of surgical resection, it appears that a complete tumor resection results in a 50% seizure-free condition, a rate not greatly dissimilar to that with incomplete tumor removal (Hadad et al., 1992). However, when intraoperative electrocorticography is used to map epileptogenic foci so as to include them as part of the operative procedure, the likelihood that patients with a gross total tumor resection would achieve complete seizure control was 92% (Pilcher et al., 1993). This outcome is significantly better than that for removing only the tumor. Even when the tumor was removed and the epileptic focus incompletely resected, a 95% reduction in postoperative seizures was demonstrated. Therefore, intraoperative electrocorticography is indispensable for patients who have intractable epilepsy associated with gangliogliomas or other similar, yet less frequently occurring, lesions (e.g., desmoplastic infantile gangliogliomas and dysembryoplastic neuroepithelial tumors). For the latter two noninfiltrative, circumscribed tumor types, the goal of surgery is complete resection, which positively influences outcome for control of recurrence and seizures (VandenBerg, 1993; Daumas-Duport, 1993).

High-Grade Gliomas

Unlike for low-grade gliomas, surgeons have been much more willing to use cytoreductive surgery for bulky malignant gliomas to alleviate mass effect associated with symptoms and signs of increased intracranial pressure. Moreover, areas of necrosis are more amenable to surgical aspiration than is firm white matter infiltrated with a low-grade glial tumor. However, the idea that the extent of resection sufficiently influences survival of patients with malignant gliomas is still not universally accepted; thus, treatment recommendations will vary among surgeons. For example, in a retrospective study that analyzed outcome after a limited (i.e., stereotactic) biopsy, the median survival times for patients with glioblastoma and anaplastic astrocytoma were each less than 30 weeks; if deep midline tumors were excluded, the median survivals improved to 47 and 129 weeks, respectively. In this study, the few patients who received cytoreductive surgery exhibited no statistical difference in outcome when biopsy was compared with a more aggressive surgery, although in the latter situation no information was provided about the extent of resection (Coffey et al., 1988). Kelly (1990) demonstrated a survival advantage for those patients with glioblastoma who underwent complete stereotactically guided resection (48 weeks) over those patients who had a biopsy or a standard craniotomy and resection (30 and 38 weeks, respectively). Comparing results from these two studies suggests that biopsy is not a substitute for a good tumor resection.

A number of radiographic studies have shown an inverse relationship between postsurgical tumor volume and survival (Levin et al., 1980b; Wood et al., 1988). Volumetric analysis of 107 operations on patients with hemispheric glioblastoma multiforme showed that patients who underwent a total tumor resection with no residual disease had a significantly longer time to tumor progression and survival (Keles et al., 1999). In this study, as volume of residual tumor increased, a shorter time to progression and a longer survival were observed. Most cooperative prospective multimodality trials show a survival advantage for subtotal and gross total resection compared with biopsy.
In addition to the concept that an aggressive resection, as opposed to limited tumor removal, will positively influence outcome (Chang et al., 1983; Levin et al., 1980b; Walker et al., 1978; Dinapoli et al., 1993), quality of life also becomes a critical issue, which is influenced by surgery. It has been recognized for quite some time that removal of a very small tumor or biopsy specimen may result in excessive morbidity from swelling or hemorrhage (Fadul et al., 1988). Studies (Ammirati et al., 1987; Ciric et al., 1987; Keles et al., 1999) have demonstrated that patients usually improve neurologically or remain the same with aggressive tumor removal. This has also been our experience, and, combined with neurophysiologic cortical and subcortical mapping methods, the likelihood of creating a permanent deficit with current surgical techniques should be less than 3% to 5%.

The role of radical resection for children with malignant supratentorial gliomas has not been as rigorously examined as for adults. In the few studies that address this issue without any reference to how extent of resection was determined, it appears that children who received a radical resection rather than a biopsy survived longer (Allen et al., 1986; Artico et al., 1993). In a study evaluating extent of resection on survival conducted by the Childrens Cancer Group (CCG-945), the 5 year progression-free survival (PFS) rates for anaplastic astrocytoma were 44% following gross total resection and 22% for less radically resected tumors; for glioblastoma the 5 year PFS rates were 26% for gross total resection and only 4% for children with less radical resections (Wisoff et al., 1998).

Gliosarcoma continues to be a difficult problem for the surgeon because of its highly invasive nature. Often, the lesion may appear somewhat circumscribed (Maiuri et al., 1990), but it is extremely vascular and frequently invades the overlying dura (Morantz et al., 1976). Too few studies have been done to determine whether the extent of surgery influences survival for this tumor type, although the data will likely be similar to those for glioblastoma.

Gliomatosis cerebri is mentioned in this section, although it is an unusual finding. These very extensive, diffusely infiltrating gliomas usually present with symptoms and signs of increased intracranial pressure. A biopsy is mandatory and will suffice along with the MRI sequences (Spagnoli et al., 1987). There is no indication for extensive resection, and a stereotactic procedure should be directed at any contrast-enhancing tissue when present. Because of the intracranial hypertension associated with a large tumor mass, a biopsy may result in rapid neurologic deterioration (Ross et al., 1991); therefore, the patient should be observed in the intensive care unit overnight following biopsy.

In summary, radical tumor resections performed under the proper conditions will usually preserve or improve a patient’s functional status and augment survival for a longer period of time than when more limited tumor resections are performed (Mornex et al., 1993; Chandler et al., 1993; Kornblith et al., 1993; Kaplan, 1993). This applies not only to glioblastoma but to other anaplastic (including gemistocytic), astrocytic, and oligodendrogial tumors (Krouwer et al., 1991; Winger et al., 1989; Prados et al., 1992a). However, in the anaplastic subtypes, the advantage of surgery must be considered to be strongly influenced by age at diagnosis because that is a known key prognostic variable for malignant gliomas (Curran et al., 1992a; Winger et al., 1989) in terms of tumor biology and in biasing the surgeon to be more aggressive.

**Ependymomas**

Few reports are available that describe the rationale for surgical resection of supratentorial ependymomas. Similar to other tumors that arise within the ventricle and extend into the cerebral hemispheres, surgical excision is designed to relieve mass effect and unblock the ventricular system. By itself, total tumor removal for ependymomas and mixed ependymoma astrocytomas will often result in long-term survival without the need for radiation (Palma et al., 1993). However, this is not the case with the malignant variant of this lesion, which requires focal radiation and sometimes chemotherapy to achieve similar results. Unfortunately, most studies that comment on survival in relation to extent of tumor removal do so without separating supratentorial from fourth ventricular tumors. Nonetheless, there is a distinct survival advantage for a radical tumor resection in the majority of series (Kovalic et al., 1993; Vanuytsel et al., 1992; Undjian and Marinov, 1990; Papadopoulos et al., 1990).

In a series from Boston that combined tumors in both supratentorial and fourth ventricular locations, it is important to note a discrepancy between the op-
operative report and the postoperative imaging study (i.e., overestimation in 33% of the cases) (Healey et al., 1991). This discrepancy will certainly change as MRI replaces CT scans in the postoperative analyses of future studies. In the Boston study, the survivals at 10 years after surgery were 75% for those patients without radiographic evidence of residual tumor and 0% for patients with residual disease. Two other series, incorporating multivariate analyses, reported significantly longer PFS and overall survival rates for patients who underwent gross total resections (Rousseau et al., 1993; Pollack et al., 1995).

In the Italian Pediatric Neuro-oncology Group study, which included 92 patients, radical surgery was the only prognostic factor found in multivariate analysis to have a statistically significant effect in predicting both PFS and overall survival (Perilongo et al., 1997). Recently, in a multi-institutional study, including patients from 11 United States pediatric oncology centers, less than gross total resection was a significant adverse risk factor for event-free and overall survival (Horn et al., 1999).

Two studies dispute these findings, however. The authors claim that, in their collective experience, radical surgery is not prognostically important (Goldwein et al., 1990; Rawlings et al., 1988). Only in the Goldwein et al. (1990) study were postoperative imaging scans obtained. Notwithstanding these two studies, current neurosurgical management of ependymomas, regardless of histology, involves achieving a radical resection of the lesion without removing more than 5 to 10 mm of adjacent white matter. The prevailing consensus is that greater extent of resection seems to improve outcome and can be maximized by careful preoperative planning, a meticulous but aggressive surgical strategy, and excellent postoperative care (Smyth et al., 2000).

RATIONALE FOR REOPERATION

With heightened interest in treating patients who have failed first-line therapy, the role of reoperation must be critically evaluated in terms of the benefits versus risks. Clearly, for those patients who have mass effect, cytoreductive surgery is an important therapeutic modality that can be carried out if the patient is to have a good quality of life during the retreatment phase. Historically, a few important retrospective studies have analyzed patients who had malignant gliomas; these studies defined important clinical parameters that predicted a good outcome (survival advantage and an improved quality of life) following reoperation. Prognostically significant factors included duration of time from initial resection to tumor progression, age, and Karnofsky performance status (KPS) (Wilson, 1975; Young et al., 1981; Salcman et al., 1982). Overall, patients with glioblastoma and anaplastic astrocytoma may expect median survivals of 56 weeks and 88 weeks, respectively, following reoperation and subsequent chemotherapy (Harsh et al., 1987). Somewhat better figures have been reported by Berger et al. (1992) when the interval of time between initial surgery and reoperation is long, the KPS is 70 or greater, and the age of the patient at the time of reoperation is less than 60 years. They found for glioblastoma a mean survival time of approximately 70 weeks when the Karnofsky score before reoperation was 70 or better; for a small group of patients with anaplastic astrocytoma, the mean survival time after reoperation was 135 weeks. The interval between initial surgery and diagnosis to reoperation was predictive: patients with disease progression within 6 months of the initial operation had a mean survival of 40 weeks after reoperation versus 150 weeks if the tumor did not recur until 1 year following the original surgery. From these studies we conclude that patients who benefit most from reoperation with a malignant glioma are younger than 60 years old, have a good functional status, and have a prolonged period of disease stability following the initial operation.

RADIOThERAPY AND CHEMOTHERAPy TREATMENT

Approaches for Low-Grade Infiltrating Gliomas

Radiotherapy

Until recently, there have been no randomized trials to clarify many of the issues surrounding the treatment of low-grade astrocytomas; thus, therapeutic decisions generally have been based on information obtained from retrospective reports. Some series do not separate patients with pilocytic astrocytomas from those with nonpilocytic tumors, although this distinction is important in the therapeutic decision-mak-
ing process. Representative survival rates for supratentorial astrocytomas treated with surgery or surgery and radiation therapy are summarized in Table 3–2. The outcomes of patients diagnosed and treated in the era of modern neuroimaging are notably better than those reported in older studies when the conditions for making a diagnosis were less sophisticated (Philippon et al., 1993).

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Cases</th>
<th>Treatment</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 Year</td>
</tr>
<tr>
<td>Levy and Elvidge (1956)</td>
<td>42</td>
<td>S</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>S + RT</td>
<td>36</td>
</tr>
<tr>
<td>Bouchard (1980)</td>
<td>105</td>
<td>S + RT</td>
<td>49</td>
</tr>
<tr>
<td>Leibel et al. (1975)</td>
<td>35</td>
<td>S</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>S + RT</td>
<td>35</td>
</tr>
<tr>
<td>Marsa et al. (1975)</td>
<td>40</td>
<td>S + RT</td>
<td>40</td>
</tr>
<tr>
<td>Fazekas (1977)</td>
<td>18</td>
<td>S</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>S + RT</td>
<td>50</td>
</tr>
<tr>
<td>Laws et al. (1984)</td>
<td>461</td>
<td>S, S + RT</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>S</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>74</td>
<td>S + RT</td>
<td>49</td>
</tr>
<tr>
<td>Garcia et al. (1985)</td>
<td>23</td>
<td>S</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>S + RT</td>
<td>50</td>
</tr>
<tr>
<td>Medbery et al. (1988)</td>
<td>50</td>
<td>S + RT</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50 Gy</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50 Gy</td>
<td>22</td>
</tr>
<tr>
<td>Shaw et al. (1989)</td>
<td>19</td>
<td>S</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>S + RT ≥53 Gy</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>S + RT &lt;53 Gy</td>
<td>47</td>
</tr>
<tr>
<td>Whitton and Bloom (1990)</td>
<td>60</td>
<td>S + RT</td>
<td>36</td>
</tr>
<tr>
<td>North et al. (1990)</td>
<td>77</td>
<td>S, S + RT</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>45–59 Gy</td>
<td>66</td>
</tr>
<tr>
<td>McCormack et al. (1992)</td>
<td>53</td>
<td>S + RT</td>
<td>64</td>
</tr>
<tr>
<td>Shibamoto et al. (1993)</td>
<td>71</td>
<td>S + RT</td>
<td>54 (age ≥30)</td>
</tr>
<tr>
<td>Philippon et al. (1993)</td>
<td>179</td>
<td>S</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S + RT</td>
<td>55</td>
</tr>
<tr>
<td>Eyre et al. (1993)</td>
<td>54</td>
<td>S + RT</td>
<td>50</td>
</tr>
<tr>
<td>Karim et al. (1996)</td>
<td>391</td>
<td>S + RT (45 Gy)</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S + RT (59.4 Gy)</td>
<td>59</td>
</tr>
<tr>
<td>Leighton et al. (1997)</td>
<td>167</td>
<td>S, S + RT</td>
<td>72</td>
</tr>
<tr>
<td>Shaw et al. (1998)</td>
<td>203</td>
<td>S + RT (50.4 Gy)</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S + RT (64.8 Gy)</td>
<td>68 (p = 0.57)</td>
</tr>
<tr>
<td>Karim et al. (1998)</td>
<td>311</td>
<td>S + immediate RT</td>
<td>63 (PFS 44%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S + delayed RT</td>
<td>66 (PFS 37%)</td>
</tr>
</tbody>
</table>

S, surgery alone; S + RT, surgery and postoperative irradiation; N, data not available; PFS, 5 year progression-free survival.

*Difference significant, p = 0.02.

Median survival times in recent series range from 7.2 to 12.9 years, raising concerns over the value today of the older literature in making treatment decisions. The improved outcome appears to be related to the earlier diagnosis of neurologically intact patients who exhibited only seizures at the time of diagnosis (Piepmeier, 1987; Cairncross and Laperriere, 1989; McCormack et al., 1992; Philippon et al.,
As mentioned, survival is significantly affected by the age of the patient at diagnosis, presence of seizures at presentation, KPS, as well as whether the lesion enhances with IV contrast administration. Using a recursive partition analysis, Bauman et al. (1999a) were able to distinguish four distinct prognostic subgroups of adult, supratentorial, low-grade glioma (including oligodendroglioma) patients: group I (<70, age >40 years), median survival time 1 year; group II (≥70, age >40 years, the tumor enhances on CT/MRI), median survival time 3.8 years; group III (<70, age 18 to 40 years or ≥70, age >40, the tumor does not enhance), median survival time 7.2 years; and group IV (≥70, age 18 to 40 years), median survival time 10.7 years.

Using a BrdU labeling index, Hoshino et al. (1988) found that 10% (3/29) of patients with tumors exhibiting a labeling index <1% died within a 3.5 year follow-up period, whereas 50% (9/18) of patients with a labeling index >1% died within the same time interval. This concept has been corroborated in subsequent studies as well (Ito et al., 1994; Lamborn et al., 1999). These data emphasize that low-grade astrocytomas may vary considerably in their biologic behavior even though they have similar histologic appearances. Repeat biopsy specimens and autopsy studies indicate that over time at least 50% of astrocytomas transform into more anaplastic lesions (Laws et al., 1985; Muller et al., 1977; Rubinstein, 1972; Soffietti et al., 1989). Thus, whereas astrocytomas are generally considered to be benign, slow-growing tumors, in some cases they may be highly lethal.

Opinions differ regarding the need for postoperative irradiation when a complete surgical resection has been performed. The 5 year recurrence-free survival rates for patients with supratentorial astrocytomas or mixed oligoastrocytomas who undergo total or radical subtotal tumor resection range from 52% to 95% (Fazekas, 1977; Garcia et al., 1985; Hirsch et al., 1989; Leibel et al., 1975; Medbery et al., 1988; Shaw et al., 1989). The variations in outcome reflect prognostic differences related to age, the inclusion of patients with radical subtotal resections, and the reliance on retrospective evaluations of operative reports to determine the completeness of resection in the era before the availability of CT and MRI studies. Because recurrences are infrequent in children whose astrocytomas have been completely resected, postoperative irradiation is generally not recommended (Hirsh et al., 1989; Nishio et al., 1989; Mercuri et al., 1981). In contrast, the outcomes in adult patients after total or radical subtotal resection have been found in some series to be similar to those of patients undergoing less extensive surgery (Fazekas, 1977; Garcia et al., 1985; Shaw et al., 1989). Thus, some authors have recommended postoperative irradiation after complete resection in adults (Garcia et al., 1985; Shaw et al., 1989, 1991), whereas others suggest that radiation therapy be withheld until there is evidence of tumor recurrence (Leibel et al., 1975; Morantz, 1987; Soffietti et al., 1989; Wara, 1985).

Postoperative irradiation appears to prolong the survival of patients with incompletely excised supratentorial astrocytomas (Fazekas, 1977; Garcia et al., 1985; Leibel et al., 1975; Morantz, 1956; Shaw et al., 1989). On average, the 5 and 10 year survival rates for patients who receive radiation therapy are 52% and 26%, respectively, compared with 26% and 12% for patients who do not (Table 3–2). Leibel et al. (1975) reported the outcomes of 108 patients of all ages with incompletely resected lesions. Of those, 71 patients received postoperative irradiation and 37 did not only. 6% of tumors were pilocytic, whereas 78% arose in the cerebral hemispheres. The age distribution and performance status of the patients in the two groups were similar. The 5 year recurrence-free survival rate after incomplete resection alone was 19%, whereas it was 46% after incomplete resection and irradiation. For adult patients, the 5 year survival rate was 10% after surgery alone, compared with 32% when radiation therapy was added. The survival of patients undergoing incomplete resection and postoperative irradiation was superior to that of patients treated by surgery alone at all follow-up time intervals from 3 to 20 years. All patients not receiving radiation therapy had died by 20 years, whereas 23% of those who did remained alive and free of disease.

In their series of adult patients with cerebral astrocytomas, Garcia et al. (1985) reported an actuarial 5 year survival rate of 21% after resection alone compared with 50% after resection and postoperative irradiation (p = 0.02). Shaw et al. (1989) found that patients receiving high-dose postoperative irradiation had a significantly longer survival than those receiving low-dose irradiation or surgery alone. The 5 year survival rate was 68% for patients receiving a dose of at least 53 Gy, 47% for those receiving less than 53 Gy, and 32% for those receiving none (p = 0.04).
Older patients appear to benefit most from postoperative irradiation (Garcia et al., 1985; Laws et al., 1985; Shaw et al., 1989). Shaw et al. (1989) found that patients 35 years of age or older who received postoperative irradiation had 5 and 10 year survival rates of 67% and 45%, respectively, compared with 37% and 5% for patients treated with low-dose irradiation or surgery alone (p = 0.008). For patients 34 years of age or less, the 5 year survival rate was 70% with high-dose irradiation compared with 53% with low-dose irradiation or surgery alone (p = 0.69).

The fact that low-grade astrocytomas are diagnosed earlier in their natural history has raised questions regarding whether radiotherapy should be administered immediately after surgery or be delayed until recurrence or progression has been demonstrated. It is generally agreed that patients with intractable seizures or those with large, progressive, symptomatic, unresectable or incompletely resected tumors should undergo immediate radiotherapy. However, radiotherapy is commonly deferred in patients with medically controlled seizures who present with asymptomatic, indolent tumors (MacDonald, 1994). Proponents of this approach argue that it is unclear whether early irradiation provides an outcome advantage over delayed irradiation or whether such treatment delays or prevents tumor dedifferentiation (Cairncross and Laperriere, 1989; Whitten and Bloom, 1990).

This issue was clarified in a clinical trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) and British Medical Research Council Brain Tumour Working Party (MRC). Patients with low-grade astrocytomas (65%), oligodendrogliomas (25%), or mixed tumors (10%) were randomized to receive immediate postoperative irradiation to a dose of 54 Gy or no further treatment until there was evidence of disease progression. Among those in the deferred treatment arm, 65% of patients received subsequent radiotherapy, 19% underwent surgery and/or chemotherapy, and the remainder received only supportive care. A preliminary analysis of the study demonstrated that immediate irradiation significantly improved the 5 year PFS (44% versus 37%, p = 0.02). However, there was no improvement in overall 5 year survival (63% versus 66%) (Karim et al., 1998). The outcomes of patients with astrocytomas strongly correlate with the proliferative potential of the tumor as measured by an antibody to BrdU incorporation into tumor cells (Hoshino et al., 1988) and the MIB-1 antibody to the Ki-67 protein (Shibuya et al., 1993). The development of such immunohistochemical and molecular markers to better predict the prognosis for an individual patient may provide an opportunity for earlier intervention and improvement in outcome for the prognostically more unfavorable subsets of patients.

Limited radiation fields are used in the treatment of low-grade astrocytomas. Recurrences are nearly always found at the original primary tumor site (Medbery et al., 1988; Shaw et al., 1989), and there is no difference in the survival distributions or patterns of failure between patients receiving partial and those receiving whole-brain irradiation (Medbery et al., 1988; North et al., 1990; Shaw et al., 1989). Fields should encompass the T2-weighted MRI abnormality, which tends to be larger than the CT-defined lesion, with a margin of 1 to 2 cm (Kun, 1992; Shaw et al., 1991; Karlsson et al., 1992). Complex three-dimensional treatment plans are used whenever appropriate to limit the high-dose volume and to minimize the risk of long-term radiation sequelae (Ellenberg et al., 1987).

The optimal dose of radiation for astrocytomas is not well defined. The standard dose for adult patients is 54 Gy, administered in daily fractions of 1.8 to 2.0 Gy. This dose level is relatively conservative so as to decrease the risk of excessive treatment-related morbidity (Bloom, 1982). At this dose level about 75% of patients will improve neurologically, and the maximum radiographic improvement occurs within a median of 2.8 months (Bauman et al., 1999b). Two randomized trials have shown that higher dose levels do not improve patient outcome (at least at 5 years). In a trial conducted by the EORTC, patients were randomized to receive 45 Gy in 25 fractions or 59.4 Gy in 33 fractions. No difference in survival was observed between the two dose levels. The 5 year survival rates were 58% for 45 Gy and 59% for 59.4 Gy. The PFS rates were also similar (47% versus 50%, respectively) (Karim et al., 1996).

Similarly, a combined North Central Cancer Treatment Group (NCCTG), Radiation Therapy Oncology Group (RTOG), and Eastern Cooperative Oncology Group (ECOG) trial randomized adult patients with supratentorial astrocytomas to receive 50.4 Gy in 28 fractions or 64.8 Gy in 36 fractions. As in the EORTC study, the 5 year survival rates were similar for the two dose levels studied: 73% for 50.4 Gy and 68%
for 64.8 Gy (Shaw et al., 1998). An increase in functional sequelae (Kiebert et al., 1998) and radiation necrosis (Shaw et al., 1998) was observed in patients treated in the high-dose arms of these studies. These data support the use of lower radiation levels for low-grade gliomas.

The 4 year overall survival of children with cerebral hemispheric astrocytomas is 90% (Gajjar et al., 1997). Radiation therapy is likely to lead to unacceptable sequelae in children younger than 3 to 5 years of age. Therefore, in this age group, radiation therapy is postponed for as long as possible provided that no significant neurologic deficits or changes indicative of rapid tumor progression are present. Periodic imaging studies are performed to monitor the disease status. The radiation dose is reduced to 50 Gy for children under 5 years of age. Management decisions are also frequently individualized in older children with incompletely resected astrocytomas who, compared with adults, have a generally better prognosis, a less pronounced survival improvement with postoperative irradiation, and a greater risk of late radiation sequelae (Hirsch et al., 1989; Mercuri et al., 1981; Nishio et al., 1989; Yule et al., 2001).

Chemotherapy

Low-grade astrocytomas account for 40% to 50% of brain tumors in childhood. The use of chemotherapy in the management of children and adults with low-grade astrocytomas is currently evolving. It is unclear how great an effect chemotherapy will have on patients with low-grade astrocytomas as these tumors have a history of being relatively indolent, and uncertainty remains as to the timing of radiation therapy as well as chemotherapy. Because of concern about the toxic effects of radiation in young children, several studies have focused on the use of chemotherapy in an attempt to delay the need for radiation therapy in young children with low-grade astrocytomas in general (Pons et al., 1992; Packer et al., 1993) and optic/chiastic/hypothalamic astrocytomas in particular (Packer et al., 1988). These studies have each used a weekly “back-bone” therapy of IV vincristine, with the addition of actinomycin-D, or etoposide, or carboplatin. Results have demonstrated that (1) objective radiographic responses can be observed in patients with either recurrent or newly diagnosed low-grade astrocytomas; (2) prolonged disease stabilization, often for several years, can be achieved even in the absence of objective radiographic responses; and (3) radiation therapy can be delayed for up to several years with the use of such therapeutic strategies, either alone or combined with judicious surgical debulking.

The actual effect of chemotherapy on overall survival and on quality of survival will take many years to establish. At least for children with low-grade astrocytomas, it is hoped that to address this question the Pediatric Oncology Group and the Childrens Cancer Group (of North America) will conduct randomized trials of observation versus chemotherapy in children less than 5 years of age who have newly diagnosed low-grade astrocytomas. To date, prospective trials of chemotherapy for astrocytoma in adults have been impossible to conduct because of the small numbers of patients with low-grade astrocytoma available for study.

With increasing patient age, histologically low-grade astrocytomas assume a biologic malignancy that leads many clinicians to treat those who present with these tumors after age 45 years more aggressively than younger patients with higher dose radiation (60 Gy instead of 54 Gy) and to add chemotherapy. Other clinicians adhere to the histologic criteria of malignancy and withhold chemotherapy until tumor recurrence. Even more controversial is the use of chemotherapy for those patients under the age of 45 years. In a Southwest Oncology Group trial, patients with incompletely excised low-grade gliomas were randomized to receive radiation therapy alone (n = 19; median age 36 years) or radiation therapy and CCNU (n = 35; median age 39 years). The median survival time of the 54 evaluable patients was 4.4 years with no difference between the two treatment arms (Eyre et al., 1993).

Based on the observation of Piepmeier (1987) that patients with contrast-enhancing low-grade astrocytomas have shorter survival times than those with non–contrast-enhancing low-grade astrocytomas (3.9 versus 7.8 years), Levin et al. (1995) treated a subset of the CT-based contrast-enhanced low-grade glioma group with aggressive chemoradiation and adjuvant chemotherapy. Twenty-two consecutive patients received BrdU during radiation therapy followed by combination chemotherapy with procarbazine, lomustine, and vincristine (PCV) for 1 year after irradiation (Levin et al., 1995). Seventy percent of patients survived nearly 7 years. As a result of this study, during the last 10 years, Levin et al. have treated
most histologically low-grade infiltrating astrocytomas in adults younger than 45 years with three courses of lomustine and procarbazine followed by limited-field radiation. Controversy surrounds this practice.

One of the problems with adjuvant chemotherapy programs for patients with low-grade astrocytoma is that it is difficult to conduct randomized trials because of the relative rarity of the tumor in the general population, the bias of clinicians with respect to its management, and the length of time required to conduct trials. When low-grade astrocytomas recur, approximately 50% do so with the original low-grade histology, whereas the rest recur as a more aggressive anaplastic astrocytoma or glioblastoma multiforme (Afra et al., 1978; Laws et al., 1984; Muller et al., 1977; Rubinstein, 1972; Soffietti et al., 1989).

When the recurrence is either a low- or mid-grade astrocytoma, chemotherapy is frequently beneficial, although cure at that point is not a likely outcome. The drugs and schedules cited in the section on anaplastic gliomas and in Tables 3–3 and 3–4 should be referred to for chemotherapeutic approaches for the patient with recurrent low-grade astrocytoma.

### Juvenile Pilocytic Astrocytomas

**Radiotherapy**

Because the long-term survival of patients with supratentorial juvenile pilocytic astrocytomas approaches 100% when a complete or near-complete (>90%, equivalent to 1 log of cells) surgical resection has been performed, postoperative irradiation is not in-

<table>
<thead>
<tr>
<th>Table 3–3. Single-Agent Chemotherapy for Recurrent and Progressive Supratentorial Glioblastoma Multiforme and Anaplastic Astrocytomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Carmustine (Levin, 1985; Wilson et al., 1976)</td>
</tr>
<tr>
<td>PCNU (Levin et al., 1984)</td>
</tr>
<tr>
<td>Procarbazine (Rodriquez et al., 1989)</td>
</tr>
<tr>
<td>Diaziquone, 5 day bolus (Schold et al., 1984; Decker et al., 1985)</td>
</tr>
<tr>
<td>Diaziquone, 5 day bolus (EORTC Brain Tumor Cooperative Group, 1985)</td>
</tr>
<tr>
<td>Melphalan, oral (Chamberlain et al., 1988)</td>
</tr>
<tr>
<td>Cisplatin (Bertolone et al., 1989)*</td>
</tr>
<tr>
<td>Cisplatin (Sexauer et al., 1985)*</td>
</tr>
<tr>
<td>Carboplatin (Yung et al., 1991a)</td>
</tr>
<tr>
<td>Eflornithine (Levin et al., 1992)</td>
</tr>
<tr>
<td>Betaseron (Yung et al., 1991b)</td>
</tr>
<tr>
<td>Cis-retinoic acid (Yung et al., 1993)</td>
</tr>
<tr>
<td>Trans-retinoic acid (Kaba et al., 1997)</td>
</tr>
<tr>
<td>Ifosfamide/mesna (Elliott et al., 1991)</td>
</tr>
<tr>
<td>Temozolomide (Yung et al., 1999, 2000)</td>
</tr>
<tr>
<td>Tamoxifen (Chamberlain and Kormanik, 1999)</td>
</tr>
<tr>
<td>Irinotecan (Friedman et al., 1999)</td>
</tr>
</tbody>
</table>

GBM, glioblastoma multiforme; AA, anaplastic astrocytoma; % R + SD, percent of all treated patients who responded or had stable disease; MTP, median time to tumor progression; EORTC, European Oncology Radiation and Treatment Committee; NA, not available; PCNU, 1-(2-chloroethyl)-3-(2,6-dioxo-1-piperidyl)-1-nitrosourea.

*Report combined GBM and AA groups because histologies were not separated or there were too few patients in each group to separate activity by histology.

†Childhood tumor data.
The efficacy of radiation therapy for incompletely resected pilocytic astrocytomas is not well established (Shaw et al., 1989; Wallner et al., 1988a). Shaw et al. (1989) found that patients who underwent subtotal resection or biopsy and postoperative irradiation survived longer than those who did not, although the number of patients treated with surgery alone was small. The 5 year survival rate for patients who did not receive radiation therapy was 50% compared with 85% for those who received postoperative irradiation ($p = 0.08$). Therefore, after subtotal resection the recommendation may be either immediate irradiation or close follow up, deferring treatment until there is clinical or radiographic evidence of disease progression.

Chemotherapy

Chemotherapy in the treatment of juvenile pilocytic tumors is generally limited to recurrent disease in patients previously treated with surgery and irradiation. Frequently, chemotherapy is initiated after reoperation. The dearth and diversity of these tumors has led to anecdotal experience but no prospective studies. The most commonly used therapies have been with cell-cycle phase nonspecific drugs such as alkylating agents. In our experience, nitrosourea-based drug combinations have been capable of long-term palliation. Therapies such as procarbazine, lomustine (CCNU), and vincristine (Rodriguez et al., 1990; Petronio et al., 1991) and a combination of 6-thioguanine, dibromodulcitol, lomustine, 5-fluorouracil, hydroxyurea (Levin et al., 1993) 

### Table 3–4. Combination Chemotherapy for Recurrent and Progressive Supratentorial Glioblastoma Multiforme and Anaplastic Astrocytomas

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GBM % R + SD</th>
<th>GBM MTP (Weeks)</th>
<th>AA % R + SD</th>
<th>AA MTP (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procarbazine, lomustine, vincristine (Gutin et al., 1975; Levin et al., 1980a)</td>
<td>45</td>
<td>15</td>
<td>65</td>
<td>27</td>
</tr>
<tr>
<td>Carmustine, 5-fluorouracil, hydroxyurea, 6-mercaptopurine (Levin et al., 1986a)</td>
<td>55</td>
<td>23</td>
<td>71</td>
<td>46</td>
</tr>
<tr>
<td>Elflornithine, carmustine (Prados et al., 1989)</td>
<td>30</td>
<td>8</td>
<td>57</td>
<td>76</td>
</tr>
<tr>
<td>Elflornithine, methyl bisguanylhydrazone (Levin et al., 1987)</td>
<td>72</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Thioguanine, procarbazine, dibromodulcitol, lomustine, 5-fluorouracil, hydroxyurea (Levin et al., 1993)</td>
<td>61</td>
<td>40</td>
<td>92</td>
<td>65</td>
</tr>
<tr>
<td>Diaziquone, carmustine (Schold et al., 1987; Yung et al., 1989)</td>
<td>0–28</td>
<td>9</td>
<td>80</td>
<td>37</td>
</tr>
<tr>
<td>Diaziquone, procarbazine (Schold et al., 1987)</td>
<td>31</td>
<td>25</td>
<td>53</td>
<td>42</td>
</tr>
<tr>
<td>Cyclophosphamide, vincristine (Longee et al., 1990)</td>
<td>60</td>
<td>15</td>
<td>78</td>
<td>35</td>
</tr>
<tr>
<td>Carboplatin, 5-fluorouracil, procarbazine (Flowers et al., 1993)</td>
<td>32</td>
<td>20</td>
<td>57</td>
<td>36</td>
</tr>
<tr>
<td>Carboplatin, etoposide (Jeremic et al., 1992)</td>
<td>50</td>
<td>43</td>
<td>75</td>
<td>38</td>
</tr>
<tr>
<td>Mechlorethamine, vincristine, procarbazine (Goyle et al., 1990)</td>
<td>38</td>
<td>43</td>
<td>100</td>
<td>54</td>
</tr>
<tr>
<td>Etoposide, cisplatin (Buckner et al., 1990)</td>
<td>39</td>
<td>NA</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>6-Thioguanine, procarbazine, CCNU, hydroxyurea (Kyritsis et al., 1996)</td>
<td>33</td>
<td>21</td>
<td>77</td>
<td>38</td>
</tr>
<tr>
<td>Nitrogen mustard, vincristine, procarbazine (Galanis et al., 1998)</td>
<td>4</td>
<td>11</td>
<td>18</td>
<td>16–19</td>
</tr>
<tr>
<td>Carboplatin, cis-retinoic acid (Kunschner et al., 1999)</td>
<td>52</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GBM, glioblastoma multiforme; AA, anaplastic astrocytoma; % R + SD, percent of all treated patients who responded or had stable disease; MTP, median time to tumor progression; NA, not available.
berlain and Levin, 1989) have been quite active. Based on the low level of activity of cisplatin and etoposide in infiltrative low-grade astrocytomas, these are not the first choice for the treatment of recurrent noninfiltrating gliomas.

Malignant Astrocytomas

Radiation Therapy

The importance of radiation therapy for malignant gliomas was demonstrated in prospective clinical studies conducted by the Brain Tumor Cooperative Group (BTCG) (formerly the Brain Tumor Study Group) (Walker et al., 1978, 1980) and the Scandinavian Glioblastoma Study Group (Kristiansen et al., 1981). Patients who received postoperative irradiation had a longer survival time than those treated with either supportive care or chemotherapy alone.

The practice of prescribing a radiation dose of 60 Gy in conventional fractionation schemes is based on data from clinical studies and on limitations imposed by the radiation tolerance of normal brain tissue (Leibel and Sheline, 1991). A randomized trial conducted by the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG) compared 60 Gy whole-brain irradiation with 60 Gy delivered to the whole brain plus an additional 10 Gy delivered to the tumor volume. No survival improvement was noted with the 70 Gy regimen (Chang et al., 1983; Nelson et al., 1988). Thus, it is customary to treat anaplastic astrocytomas and glioblastoma multiforme to 60 Gy given in single daily fractions of 1.8 to 2.0 Gy for 5 days per week (Leibel and Sheline, 1987).

With conventional radiation radiotherapeutic techniques the median survival time for patients with glioblastoma multiforme is 9 to 10 months, whereas the 3 year survival rate is only 2% to 6% (Leibel et al., 1975, 1994; MRC Working Group, 2001). Less firm is the median survival time for patients with anaplastic astrocytoma treated with irradiation only. Estimates of median survivals of 13 to 19 months have been reported (Leibel et al., 1975; MRC Working Group Party, 2001). In a mixed group of high-grade glioma patients treated between 1974 and 1989 with radiation therapy and variable types and amounts of chemotherapy on RTOG protocols, a recursive partition analysis based on age, histology, mental status, duration of symptoms, neurologic functional status, extent of surgery, and radiation dose identified six prognostic classes of malignant glioma patients with median survival times ranging from 4.6 to 58.6 months (Curran et al., 1993) (Table 3–5).

The amount of tissue to include within the treatment volume has been a subject of considerable discussion. Studies that compared cerebral angiography and pneumoencephalography interpretations of tumor extent with autopsy findings demonstrated that malignant gliomas were usually more extensive than had been determined clinically (Concannon et al., 1960; Kramer, 1969; Salazar et al., 1976). Although patients included in these series had very advanced tumors and often died soon after diagnosis, the conclusion that treatment failure could be due to inadequate tumor coverage led to a recommendation that the whole brain be irradiated (Kramer, 1969; Salazar and Rubin, 1976).

Other studies comparing CT and MRI scans with pathologic findings and patterns of failure after radiation therapy support treating malignant gliomas with limited-field rather than with whole-brain irradiation. These investigations have shown that (1) malignant gliomas are localized, and microscopic invasion of the peritumoral brain tissue is limited at the time of initial diagnosis (Burger et al., 1983); (2) only 1.1% to 7.3% of patients with glioblastoma and 4.4% of all patients with astrocytomas present with multifocal lesions (Choucair et al., 1986; Kyritsis et al., 1992); (3) after initial treatment, most tumors recur at or within 1 to 2 cm of their original location (Hochberg and Pruitt, 1980; Wallner et al., 1989; Gaspar et al., 1992); (4) following resection of recurrent tumors, second tumor recurrences develop at the original primary tumor location (Massey and Wallner, 1990); and (5) cognitive impairment and frank dementia occurred all too frequently in patients treated with whole-brain radiation fields. On the other hand, in biopsy (Kelly et al., 1987) and autopsy (Burger et al., 1988) studies, isolated tumor cells have been found to infiltrate into edematous brain tissue surrounding the primary lesion. These observations have suggested that radiation fields should extend to the periphery of CT-defined peritumoral hypodense regions or should encompass tissues that have a prolonged T2-weighted MRI signal. However, analyses of recurrence patterns after conventional irradiation have not demonstrated a propensity for tumors to recur within edematous areas at a distance from the primary tumor site (Wallner et al., 1989). It is possible that all the observed
isolated tumor cells were not tumorigenic because a critical mass of tumor cells was not present.

As there is no apparent survival advantage to irradiating the whole brain compared with irradiating more limited fields (Leibel and Sheline, 1990; Levin et al., 1995) and because many patients who survive for prolonged periods after whole-brain irradiation and chemotherapy develop significant treatment-related sequelae (Shapiro, 1986), partial brain field irradiation is accepted as a standard approach in the treatment of malignant gliomas. The fields are designed to encompass the perimeter of the contrast-enhancing tumor with a 2.5 to 3.0 cm margin of tissue based on preoperative diagnostic imaging studies. If the tumor and associated edema are limited, the surrounding edema may initially be included in the treatment volume (Leibel et al., 1991b). However, if the tumor is extensive and accompanied by a large volume of peritumoral edema, coverage of the entire hypodense region would require treatment of a large volume of brain tissue for what will probably be minimal or no therapeutic gain (Wallner, 1991). Radiation portals should, when possible, be designed with three-dimensional conformal techniques to spare, to the extent possible, the surrounding normal tissues.

The response of malignant gliomas to standard radiation therapy techniques is limited by their striking inherent radioresistance and the radiosensitivity of the surrounding normal brain tissue. Accordingly, a considerable amount of research has been directed

<table>
<thead>
<tr>
<th>Class</th>
<th>Characteristics</th>
<th>Median Survival (Months)</th>
<th>2 Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>AAF, age &lt;50 years, normal mental status</td>
<td>58.6</td>
<td>76</td>
</tr>
<tr>
<td>II</td>
<td>AAF, age ≥50 years, KPS 70–100, time from first symptom to diagnosis ≥3 months</td>
<td>37.4</td>
<td>68</td>
</tr>
<tr>
<td>III</td>
<td>AAF, age &lt;50 years, abnormal mental status</td>
<td>17.9</td>
<td>35</td>
</tr>
<tr>
<td>IV</td>
<td>AAF, age ≥50 years, time from first symptom to diagnosis ≤3 months</td>
<td>11.1</td>
<td>15</td>
</tr>
<tr>
<td>V</td>
<td>GBM, KPS 70–100, ≥partial resection, “work” neurologic functional status</td>
<td>8.9</td>
<td>6</td>
</tr>
<tr>
<td>VI</td>
<td>GBM, KPS &lt;70, normal mental status</td>
<td>4.6</td>
<td>4</td>
</tr>
</tbody>
</table>

AAF, astrocytoma with atypical or anaplastic features; GBM, glioblastoma multiforme; KPS, Karnofsky performance status. Data from Curran et al. (1993).
at improving the efficacy of radiotherapy. In addition to incorporating chemical radiation-response modifiers and pursuing more effective chemotherapy programs (see below), areas of investigation have included the use of altered fractionation schemes, dose escalation with interstitial brachytherapy, radiosurgery, and three-dimensional conformal radiotherapy and the application of heavy particle irradiation.

Hyperfractionated irradiation differs from conventionally fractionated irradiation in that with the former, two or more treatments are given daily with fraction sizes smaller than the usual dose fractions. The goal of this approach is to deliver a higher total radiation dose in the same overall time (6 to 6.5 weeks) as a conventional treatment schedule. Compared with rapidly proliferating glioma cells, normal neural tissues exhibit a slow rate or absence of cell division and have a greater capacity to repair sublethal radiation damage. The size of the radiation dose per fraction has a predominant effect on the incidence of late toxic effects in neural tissue (Leibel and Sheline, 1991). Therefore, the tolerance of these tissues to radiation should be improved by reducing the size of the fractional dose (Nelson et al., 1986). Because rapidly proliferating tumor cells are less affected by the reduction in fraction size, tumor control probability should improve with hyperfractionation, whereas late toxic effects should be equivalent to those observed with conventional fractionation schedules. The 6 to 8 hour interval between dose fractions allows the normal tissues to repair sublethal radiation damage. On the other hand, rapidly proliferating tumor cells progress into more radiosensitive phases of the cell cycle during the interval between fractions. Target cells for late sequelae proliferate slowly; thus, for these tissues little cell cycle reassortment or “self-sensitization” occurs during irradiation (Withers, 1985).

A randomized phase II dose-escalation study conducted by the RTOG found that patients receiving 72 Gy in 1.2 Gy fractions twice daily had a longer median survival time (14.2 months) and a higher 18 month survival rate (44%) than patients who received 81.6 Gy (11.7 months and 28%, respectively). The inferior outcome in the 81.6 Gy arm of the study was attributed in part to excess neurotoxicity. On the basis of findings from a randomized phase II dose-escalation study (Werner-Wasik et al., 1996), the RTOG carried out a randomized trial comparing the hyperfractionated irradiation to 72 Gy with conventional fractionated irradiation to 60 Gy with carmustine (BCNU) given in both study arms. Hyperfractionation did not lead to an improved outcome. The median survival times for patients with glioblastoma multiforme in the two treatment arms were similar—10.2 months with the hyperfractionated regimen and 11.2 months with conventional fractionation (\(p = 0.44\)). Similarly, for patients with anaplastic astrocytoma the median survival times were 43.5 months with hyperfractionation and 49.5 months with conventional fractionation (\(p = 0.81\)) (Scott et al., 1998).

Another fractionation option, accelerated fractionation, attempts to improve radiation-induced tumor cell kill in rapidly proliferating tumors by reducing the length of time needed to complete the course of treatment (Fowler, 1990). Conventional size dose fractions (1.6 to 2.0 Gy) are given two or three times daily. This treatment schedule may also improve the therapeutic ratio by reducing tumor cell repopulation during treatment, thereby increasing the probability of tumor control for a given dose level (Withers, 1985). Several trials using accelerated regimens have been conducted, but none has shown a survival benefit over conventional irradiation for these regimens (Simpson and Platts, 1976; Keim et al., 1987; Shenouda et al., 1991; Prados et al., 2001). These studies, however, indicate that the overall treatment time can be shortened, which may be especially appropriate for patients with relatively short survival expectations (Simpson and Platts, 1976).

Because most gliomas are localized to a single area of the brain (Choucair et al., 1986; Hochberg and Pruitt, 1980; Kyritsis et al., 1992), they should be controllable if sufficiently high radiation doses can be delivered without damaging the surrounding normal brain tissue. Therefore, as a second strategy for improving the outcome of malignant gliomas, interstitial brachytherapy, radiosurgery, and three-dimensional proton beam and photon radiation therapy are being used as an adjunct to conventional irradiation to augment the dose to the primary tumor. Interstitial brachytherapy has been extensively studied as an approach for increasing the tumor dose. Unlike conventional radiation therapy, the intratumoral placement of encapsulated radioactive sources results in maximal doses to the tumor while the surrounding normal tissues receive considerably lower radiation doses (Leibel et al., 1989a,b). 125-Iodine and 192-Iridium sources have most frequently been
used in clinical practice, and stereotactic techniques have been devised for the placement of afterloading catheters, which are removed after the prescribed dose has been given.

Well-circumscribed, peripheral supratentorial tumors measuring up to 5 cm are best suited to receive implantation. Patients with multifocal tumors or lesions with poorly defined borders, as well as those with corpus callosum involvement and subependymal spread, and tumors of the cerebellum, midbrain, and brain stem are not considered for this technique. To be eligible for radiation implantation, the patient should have good neurologic function and a KPS of at least 70. Based on these criteria, approximately 33% of patients with newly diagnosed malignant gliomas are candidates for brachytherapy (Florell et al., 1992).

The limiting aftereffect associated with interstitial brachytherapy is focal peritumoral radiation injury to the brain. The clinical and radiographic changes caused by implanted radioactive sources may be indistinguishable from signs of tumor progression. Brachytherapy-induced neurologic deterioration and steroid dependency may be effectively reversed by resection of the necrotic tissue, a step necessary in approximately 40% of implanted patients (Leibel et al., 1991a).

Initially, interstitial implantation was used for re-treating previously irradiated patients who had recurrent malignant gliomas. When improvements in survival and quality of life were demonstrated (Gutin et al., 1987; Leibel et al., 1989a), this treatment was integrated into the primary management of patients with newly diagnosed malignant gliomas. As shown in Table 3–6, early phase II studies demonstrated survival improvements in patients with glioblastoma multiforme who received a combination of external beam irradiation and interstitial brachytherapy to total doses of 110 to 120 Gy compared with patients treated with conventional radiation therapy (alone or with chemotherapy) but who otherwise satisfied the criteria for implantation (Florell et al., 1992; Gutin et al., 1991; Loeffler et al., 1990; Prados et al., 1992b; Scharfen et al., 1992). Such comparisons, however, are subject to considerable patient selection bias (Florell et al., 1992).

The brachytherapy approach was studied in three randomized trials. The BTCG compared interstitial implantation (60 Gy at 10 Gy per day) preceding external irradiation (60.2 Gy at 1.72 Gy per fraction) and BCNU with external irradiation and BCNU alone. Implanted patients experienced a significant improvement in median survival (16 versus 13 months) and 18 month survival (47% versus 32%) compared with those who did not receive brachytherapy (Green et al., 1994). However, in another trial, Laperriere et al. (1998) found no difference in outcome of patients randomized to receive external beam irradiation alone to 50 Gy or external beam irradiation and a $^{125}$I implant delivering a minimum tumor dose of 60 Gy. The median survival time of patients receiving external beam irradiation and brachytherapy was 13.8 months compared with 13.2 months for those treated with external beam irradiation alone ($p = 0.49$).

A randomized trial testing the addition of interstitial microwave hyperthermia to the brachytherapy boost after external irradiation in newly diagnosed patients with glioblastoma multiforme was conducted at the University of California, San Francisco. Time to progression and survival (median survival 85 versus 76 weeks; 2 year survival 31% versus 15%) were significantly longer in patients receiving hyperthermia than in those treated with external beam irradiation and brachytherapy alone ($p = 0.045$ and $p = 0.02$, respectively) (Sneed et al., 1998).

### Table 3–6. Effect of $^{125}$I Implantation on Survival of Patients with Glioblastoma Multiforme

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Cases</th>
<th>Treatment</th>
<th>Dose (Gy)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florell et al. (1992)</td>
<td>68</td>
<td>Ext RT</td>
<td>60</td>
<td>14 months</td>
</tr>
<tr>
<td>Loeffler et al. (1990)</td>
<td>40</td>
<td>Ext RT</td>
<td>60</td>
<td>NR</td>
</tr>
<tr>
<td>Loeffler et al. (1990)</td>
<td>35</td>
<td>Ext + $^{125}$I</td>
<td>110</td>
<td>NR</td>
</tr>
<tr>
<td>Scharfen et al. (1992)</td>
<td>106</td>
<td>Ext + $^{125}$I</td>
<td>110–120</td>
<td>22 months</td>
</tr>
</tbody>
</table>

Ext RT, external beam irradiation; Ext + $^{125}$I, external beam irradiation plus $^{125}$I implantation; NR, not reached.
Stereotactic radiosurgery has also been used to increase the tumor dose. Radiosurgery is a method of focused, closed-skull external beam irradiation that uses an imaging-compatible stereotactic device for precise target localization. The relationship between the stereotactic coordinate system and the radiation source allows accurate delivery of radiation to the target volume (Larson et al., 1992). Radiosurgery may be delivered using multiple cobalt beams (as in the "gamma knife"), modified linear accelerators, or charged particle beams. The radiation beams intersect at one (sometimes two or more) point(s) within the skull after entering through numerous points or arcs distributed over the surface of the skull (Larson et al., 1990). This technique was designed to deliver a high radiation dose to an intracranial target in a single session without delivering significant radiation to adjacent normal tissues. To maintain a steep dose gradient at the edges of the field, the target volume must be small. Furthermore, because the dose that can be safely administered in a single fraction is limited by the volume irradiated, the application of radiosurgery in effective single doses is restricted to lesions measuring approximately 4 cm or less in diameter (Wilson et al., 1992).

Stereotactic radiosurgery techniques have been used to treat a variety of benign intracranial processes, most frequently small arteriovenous malformations as well as benign tumors such as pituitary adenomas, acoustic neurinomas, and meningiomas. The role of radiosurgery as a boost after conventional radiation therapy for malignant gliomas is currently an area of active research (Loeffler et al., 1992). Shrieve et al. (1999) used radiosurgery as a boost after standard external beam irradiation (59.4 Gy) in 78 patients with newly diagnosed glioblastoma multiforme. Patients with discrete, geometrically spherical lesions measuring 4 cm or less in diameter and a KPS of 70 or higher were selected for radiosurgery. The median tumor volume at the time of radiosurgery was 9.3 cm³, and the median minimum tumor dose was 12 Gy. The median survival time was 19.9 months, and the 1 and 2 year survival rates were 88.5% and 35.9%, respectively. Similar to brachytherapy, 50% of the patients required reoperation to resect necrotic tissue or recurrent tumor. Based on tumor size and geometry and functional status criteria (Loeffler et al., 1992), only 9% of patients are eligible for this procedure (Curran et al., 1992b). The median survival time for radiosurgery-eligible glioblastoma multiforme patients was 12.5 months compared with 10.5 months for ineligible patients (p = 0.07). A comparison of these data with those reported by Shrieve et al. (1999) suggests that for glioblastoma multiforme a survival advantage of approximately 7 months is conferred when radiosurgery is actually given. The benefit of radiosurgery diminishes when broader selection criteria are used (Mehta et al., 1994), whereas a better outcome is associated with lower pathologic grade, younger age, higher KPS, smaller tumor volume, and unifocal tumors. (Larson et al., 1996) Although radiosurgery is biologically at the opposite end of the fractionation spectrum from brachytherapy, the therapeutic ratios of these two modalities appear to be similar (Larson et al., 1993). Stereotactic radiosurgery offers several advantages over brachytherapy. Radiosurgery is noninvasive, thus avoiding the risks of hemorrhage, infection, and tumor seeding. Furthermore, prolonged hospitalization is not required. Thus, for the most part, radiosurgery has replaced brachytherapy for selected patients to augment the tumor dose.

Radiosurgery may also be used to re-treat patients with small, previously irradiated tumors. In one series, the median survival time of 86 patients with recurrent glioblastoma multiforme was 10 months from the time of radiosurgery, similar to the published experience with brachytherapy at recurrence (Shrieve et al., 1995).

Three-dimensional conformal photon radiation therapy is another method of treatment planning and delivery designed to enhance the conformation of the radiation dose to the target volume while maximally restricting the dose delivered to normal tissue outside the treatment volume. When applied to cerebral tumors, conformal treatment planning techniques have permitted a 30% to 50% reduction in the volume of normal brain tissue irradiated at high doses (Thornton et al., 1991, 1992). This new approach to treatment planning may not only decrease the risk of normal tissue injury but may allow higher than traditional radiation doses to be safely administered to patients with malignant gliomas. In an ongoing study at the University of Michigan, doses as high as 90 Gy have been administered using three-dimensional techniques (Lee et al., 1999; AS Lichter, personal communication, 2000).

Protons and helium ion beams, which feature sharp lateral beam edges and have a finite range in tissue, may also be used to deliver higher radiation doses to limited tumor volumes while keeping the dose to neighboring critical structures at a safe level.
The depth of radiation penetration can be tailored to the tumor target by varying the energy of the beam or by interposition of bolus material in the beam path. Proton beam arrangements designed with three-dimensional treatment planning systems are being used as boost therapy for glioblastoma multiforme (approximately 60 cc in volume) after conventional radiation therapy (Suit and Urie, 1992). Fitzek et al. (1999) treated 23 patients with glioblastoma multiforme using combined photon and proton beams to administer a tumor dose of 90 cobalt gray equivalent (CGE) with an accelerated fractionation approach. The median survival time was 20 months (a 5 to 11 month improvement compared with patients with comparable risk factors treated with conventional radiotherapy). The 2 and 3 year actuarial survival rates were 34% and 18%, respectively. Tumor regrowth, demonstrated by histologic tissue examination, occurred most commonly in regions that received dose levels of 70 CGE or less, whereas tumor was found in the 90 CGE dose volume in only one case.

Chemotherapy with Irradiation

For patients with malignant astrocytomas, chemotherapy has been given before, during, and after radiotherapy to improve survival. In the past, the most common forms of chemotherapy have been cytotoxic drugs. The earliest question asked was whether the use of chemotherapy added to the survival benefit already achieved by surgery and radiotherapy. Historically, the nitrosoureas (carmustine and lomustine) have been the most frequently studied agents (Chang et al., 1983; Walker et al., 1978, 1980). A meta-analysis of the results of eight randomized trials reported between 1976 and 1985 showed that the addition of a nitrosourea agent to radiation therapy provided a significant, albeit limited, benefit over radiation therapy. The 1 year survival rate was increased by only 9% (p = 0.002) and the 2 year survival rate by only 3.5% (p = 0.046) (Stenning et al., 1987). Patients younger than 60 years of age (p < 0.01) appear to benefit most from carmustine, whereas carmustine is less beneficial for older patients (Chang et al., 1983; Nelson et al., 1988). Based on these studies, the combination of conventional irradiation and carmustine became the standard treatment regimen for malignant gliomas (Deutsch et al., 1989).

In an effort to improve on these data, a number of chemotherapy combinations were evaluated in clinical trials. The most widely used combination of procarbazine, lomustine, and vincristine (PCV) was reported by Levin and colleagues (1990, 1995) in trials where PCV was given after surgery and radiation therapy. Tables 3–7 and 3–8 summarize some of the adjuvant chemotherapy trials conducted and published through 1999.

### Table 3–7. Comparison of Survivals of Patients with Anaplastic Glioma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>50% Survival (Weeks)</th>
<th>25% Survival (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT, HU, carmustine</td>
<td>37</td>
<td>82</td>
<td>157</td>
</tr>
<tr>
<td>WBRT, HU, PCV (Levin et al., 1990)</td>
<td>36</td>
<td>157</td>
<td>NA (≥317)</td>
</tr>
<tr>
<td>WBRT, mPCV (Jeremic et al., 1992)</td>
<td>31</td>
<td>148</td>
<td>NA</td>
</tr>
<tr>
<td>LFRT, PCNU versus</td>
<td>50</td>
<td>74</td>
<td>20½</td>
</tr>
<tr>
<td>LFRT, carmustine (Dinapoli et al., 1993)</td>
<td>46</td>
<td>88</td>
<td>208</td>
</tr>
<tr>
<td>BrdU, LFRT, PCV (Levin et al., 1995)</td>
<td>138</td>
<td>208</td>
<td>NA</td>
</tr>
<tr>
<td>LFRT, 6TG, carmustine (Prados et al., 1998b)</td>
<td>110</td>
<td>&gt;28½</td>
<td>NA</td>
</tr>
<tr>
<td>WB/LFRT, carmustine</td>
<td>257</td>
<td>168</td>
<td>NA</td>
</tr>
<tr>
<td>WB/LFRT, PCV (RTOG retrospective study reported by Prados et al., 1999a)</td>
<td>175</td>
<td>&gt;168</td>
<td>NA</td>
</tr>
<tr>
<td>LFRT, PCV versus</td>
<td>92</td>
<td>?</td>
<td>NA</td>
</tr>
<tr>
<td>LFRT, BrdU, PCV (Prados et al., 1999b)</td>
<td>97</td>
<td>?</td>
<td>NA</td>
</tr>
</tbody>
</table>

WBRT, whole-brain radiotherapy; LFRT, limited-field radiation therapy; HU, hydroxyurea; PCV, procarbazine, lomustine, vincristine; mPCV, dose-modified PCV; BrdU, bromodeoxyuridine; 6TG, 6-thioguanine; NA, not available.
The two variables having the most impact on chemotherapy studies are age at diagnosis and tumor histology. As an approximation, survival appears to be inversely correlated to age and grade of malignancy: young patients survive longer than the elderly, and patients with low-grade gliomas live longer than those with high-grade gliomas. In a randomized trial conducted by the Childrens Cancer Group, children receiving radiation therapy and the combination of lomustine (CCNU), vincristine, and prednisone had a 5 year event-free survival rate of 46% compared with 17% for children who received radiation therapy alone ($p = 0.026$). When patients who underwent at least a partial resection were separated by pathology groups, chemotherapy was found to be beneficial to children with glioblastoma multiforme (5 year event-free survival, $p = 0.011$; 5 year survival, $p = 0.044$) but not to those with anaplastic astrocytomas. This is comparable to our experience with adults with glioblastoma for whom 5 year survival is closer to 5%.

There is no doubt that patients with anaplastic gliomas respond better to chemotherapy than those with glioblastoma (Levin et al., 2001). In addition, there are data that show that adjuvant (after surgery and radiotherapy) combination chemotherapy of procarbazine, CCNU, and vincristine (PCV) or 6-thioguanine and BCNU leads to longer survival for patients with anaplastic astrocytoma and other anaplastic gliomas (see Tables 3–7 and 3–8) than does monotherapy with adjuvant nitrosourea or procarbazine. The median survival in three studies ranges between 3 and 5 years (Levin et al., 1990, 1995; Prados et al., 1998a).

In addition to pursuing more effective chemotherapy programs, investigational research efforts are directed at improving the therapeutic efficacy of external irradiation. One strategy has focused on techniques designed to selectively enhance tumor cell killing using methods to overcome tumor cell hypoxia, halogenated pyrimidine analogue radiation sensitizers, and modified radiation time–dose frac-

---

**Table 3–8. Comparison of Survival Among Studies that Evaluated Glioblastoma Patients as a Distinct Histology**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>50% Survival (Weeks)</th>
<th>25% Survival (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT, HU, carmustine (Levin et al., 1990)</td>
<td>29</td>
<td>57</td>
<td>71</td>
</tr>
<tr>
<td>WBRT, HU, PCV (Levin et al., 1990)</td>
<td>31</td>
<td>50</td>
<td>94</td>
</tr>
<tr>
<td>WBRT, mPCV (Jeremic et al., 1992)</td>
<td>62</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>LFRT, PCNU versus LFRT, carmustine (Dinapoli et al., 1993)</td>
<td>118</td>
<td>42</td>
<td>62</td>
</tr>
<tr>
<td>5FU, lomustine, LFRT, MISO, HU, PCB, VCR, BCNU, 5FU (Levin et al., 1986b)</td>
<td>64</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td>BrdU, LFRT, PCV (Phillips et al., 1991)</td>
<td>160</td>
<td>62</td>
<td>104</td>
</tr>
<tr>
<td>CARBO, AFLFRT, PCV (Levin et al, 1995)</td>
<td>74</td>
<td>55</td>
<td>91</td>
</tr>
<tr>
<td>LFRT and PCV versus LFRT and PCV, DFMO (Levin et al., 2000b)</td>
<td>138</td>
<td>58</td>
<td>78</td>
</tr>
<tr>
<td>BrdU, AFLRT, PCV (Groves et al., 1999)</td>
<td>70</td>
<td>57</td>
<td>79</td>
</tr>
<tr>
<td>AFLRT versus LFRT versus AFLRT and DFMO during RT versus LFRT and DFMO during RT (Prados et al., 2001)</td>
<td>231</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>LFRT and PCV versus LFRT and PCV, DFMO (Levin et al., 2000b)</td>
<td>226</td>
<td>39</td>
<td>57</td>
</tr>
<tr>
<td>LFRT and PCV (MRC Working Group Party, 2001)</td>
<td>223</td>
<td>40</td>
<td>61</td>
</tr>
</tbody>
</table>

**Notes:**
- WBRT: whole-brain radiotherapy; LFRT: limited-field radiation therapy; HU: hydroxyurea; PCV: procarbazine, lomustine, vincristine; mPCV: dose-modified PCV; MISO: misonidazole; BrdU: bromodeoxyuridine; CARBO: carboplatin; DFMO: difluoromethylornithine (eflornithine); AFLRT: accelerated fractionated radiation therapy; VCR: vincristine; NA: not available.

---
tionation schedules such as hyperfractionation and accelerated fractionation.

Hypoxia protects cells against the effects of radiation. Hypoxic but viable cells may be found in regions of coagulation necrosis that are present in glioblastoma multiforme (Nelson et al., 1986). Even when only 2% to 3% of such resistant cells are present, the radiation dose required to completely eradicate a tumor may double (Dische, 1991). Various methods to modify the effects of hypoxia have been studied, including irradiation under hyperbaric oxygen conditions (Chang, 1977) and combining radiation therapy with electron-affinic hypoxic cell radiation sensitizers such as misonidazole (Bleehen, 1990). To date, neither of these approaches has resulted in an improvement in outcome over that produced by conventional radiation therapy alone. Treatment with high-linear energy transfer radiations (i.e., neutrons and heavy ions) that are less dependent on oxygen tension than conventional (low-linear energy transfer) photon irradiation has also not improved survival rates (Castro et al., 1982; Laramore et al., 1988).

The halogenated pyrimidine analogues are radiation sensitizers that are incorporated into rapidly dividing cells undergoing DNA synthesis because of their similarity to the DNA precursor thymidine. When the analogue is substituted for thymidine in the DNA chain, the cell becomes more susceptible to radiation injury (Djordjevic and Szybalski, 1960). These analogues appear to enhance the effects of a given dose of radiation by a factor of 1.5 to 2 (Mitchell et al., 1983). Tumors located in the brain are ideally suited for halogenated pyrimidine radiosensitization because the clonogenic cells undergo division more rapidly and, therefore, incorporate more drug into DNA than do the surrounding normal neural tissues. Two analogues, BrdU and iododeoxyuridine, have been evaluated in patients with malignant gliomas. The initial impression from these studies was that BrdU with radiation therapy produced survival improvement for patients who had anaplastic astrocytomas (Levin et al., 1995) but not for those with glioblastoma multiforme (Goffman et al., 1992; Phillips et al., 1991; Groves et al., 1999).

Unfortunately, recent publications bring this conclusion into question. First, a retrospective analysis of RTOG and Northern California Oncology Group (NCOG) databases since 1974 suggested that there might be a subset of relatively younger glioblastoma patients who were most likely to benefit from BrdU therapy during irradiation. The data from that study were, however, inconclusive (Prados et al., 1998b). Disappointing was the recent closure of a multigroup open-label randomized phase III trial in newly diagnosed patients with anaplastic glioma comparing radiotherapy plus adjuvant PCV chemotherapy with or without BrdU given as a 96 hour infusion each week of radiotherapy. The study was closed early because a conditional power analysis indicated that even with an additional 12 months of accrual and follow up the probability of detecting a difference between the two arms was less than 0.01% (Prados et al., 1999b). The final report of this study will be available in 2002.

Chemotherapy of Malignant Astrocytomas of Childhood

Although the major effect of chemotherapy on the outcomes of adult patients with malignant astrocytomas has, to date, been limited to anaplastic gliomas, therapeutic trials during the last 15 years in children with these tumors have demonstrated some benefit, even for those with glioblastoma multiforme. This finding suggests that high-grade astrocytomas have a somewhat different biology in adults and children.

In 1976, the Childrens Cancer Group embarked on a randomized trial in children newly diagnosed with high-grade astrocytomas in which involved-field irradiation alone was compared with involved-field irradiation plus adjuvant chemotherapy (vincristine, CCNU, and prednisone) for a duration of approximately 1 year. Although the number of fully evaluable patients accrued to this randomized study was small (n = 58), an advantage for adjuvant chemotherapy was observed for patients with glioblastoma multiforme: those receiving radiation alone died of progressive disease, whereas 49% of patients receiving the adjuvant chemotherapy remained free of tumor progression beyond 5 years. Because of the small numbers of patients enrolled in the study, no advantage for chemotherapy could be statistically confirmed in patients with anaplastic astrocytoma despite a 20% 5 year PFS rate for children with radiation alone versus 45% for children with radiation plus chemotherapy. The most powerful factor predictive of outcome, in addition to the use of chemotherapy, was extent of resection (Sposto et al., 1989).

Based on results from the above study, in 1985 the Childrens Cancer Group embarked on a second ran-
domized therapeutic trial in which the regimen of CCNU and PCV from the earlier study served as the “standard therapy” arm and was compared with the “eight drugs in one day” regimen, a chemotherapeutic regimen that actually incorporated seven drugs (vincristine, CCNU, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside, and either cyclophosphamide or dacarbazine) in addition to methylprednisolone for antiedema and antiemetic effects. In 1991, when the study closed, 185 children had been entered and randomized to a treatment group, and an additional 40 children younger than 3 years of age were nonrandomly assigned to receive the experimental treatment in addition to radiation. Results showed no benefit for the more intensive experimental therapy compared with control arm therapy; nevertheless, the study reaffirmed the benefit of adjuvant chemotherapy for childhood high-grade astrocytomas. Again, the prognostic impact of extent of resection is observed in this study, with virtually all patients who underwent a biopsy or a partial resection having died of disease progression (Finlay et al., 1995).

Of children younger than 3 years treated with the “8-in-1” chemotherapy regimen with the intent of delaying or avoiding irradiation, 35% were alive without disease progression beyond 3 years after diagnosis, a finding similar to that for older children. This more favorable outcome in young children may reflect an idiosyncratic biologic behavior of these tumors to certain cytotoxic chemotherapy agents in very young children. Certainly the time to disease progression is much shorter for younger children (less than 6 months) than for older ones. Young children also display a more dramatic radiographic response to chemotherapy than older children, indicating the promising potential of chemotherapeutic strategies without irradiation for the treatment of younger children with high-grade astrocytomas. These children have traditionally fared poorly with any therapy and are particularly vulnerable to the devastating consequences of cranial irradiation (Geyer et al., 1995).

Results of phase II trials evaluating new agents or older drugs used in new, more dose-intensive strategies have been most encouraging for the medulloblastoma/primitive neuroectodermal family of tumors but far less so for children or adults with high-grade astrocytomas. In trials a decade ago, ifosfamide alone demonstrated no activity in eight patients with recurrent astrocytoma (Chastagner et al., 1993). Partial and minor response rates varying from 0% to 38% have been reported in children with recurrent high-grade astrocytomas treated with carboplatin (Allen et al., 1987) or cisplatin (Bertolone et al., 1989). The original experience with the “8-in-1” regimen showed overall response rates of 22% to 44% in 27 patients with recurrent high-grade astrocytoma treated in three studies. In the Childrens Cancer Group protocol 945 discussed above, however, the partial response rate was less than 10% in 80 children (Finlay et al., 1994). Clearly, these chemotherapeutic agents, alone or in combination and at conventional or dose-intensive strategies, have a minimal ability to produce significant tumor shrinkage in high-grade astrocytomas in children.

An approach initiated in the mid-1980s for children with recurrent brain tumors was the use of myeloablative doses of chemotherapy followed by bone marrow rescue with the patient’s own previously cryopreserved marrow. One initial regimen utilized thiotepa plus etoposide (Finlay et al., 1990); this regimen demonstrated a 20% 2 year disease PFS rate among patients with recurrent high-grade astrocytomas. Among patients so treated following radical surgical resection and who had no gross evidence of residual disease or had achieved a complete response to the myeloablative chemotherapy, approximately 33% were alive beyond 2 years post-diagnosis. Because of these early results, the regimens were subsequently intensified for patients with recurrent tumor, and high-dose carboplatin was added (Finlay, 1992b). Additionally, children with newly diagnosed anaplastic astrocytoma or glioblastoma multiforme were treated with high-dose chemotherapy (thiotepa, etoposide, and carmustine) followed by marrow rescue and subsequent involved-field irradiation; this was the basis for a Childrens Cancer Group multicenter trial in North America for such children and young adults between the ages of 3 and 25 years (CCG-9921; Groves et al., 1999).

Chemotherapy for Malignant Astrocytomas in Adults

Chemotherapy for glioblastoma multiforme is, for the most part, a frustrating experience for both the physi-
ian and the patient. During the last 25 years, chemotherapy has provided small gains measured in added months rather than years of life. Most agents found to be active in phase II clinical trials produce short-duration responses of 3 to 9 months in patients with progressive or recurrent glioblastoma. Response rates vary from 0% to 70%, depending on the criteria used to define response. For anaplastic astrocytomas, the gains have been much greater: Response rates of 25% to 90% have been reported, with median times to progression of 6 to 15 months depending on the drugs and drug combinations used.

Because the most important measure of the activity of a chemotherapeutic drug or regimen is time to treatment failure (when the tumor grows), what is needed to assess the value of therapy are precise, reliable criteria to define and determine tumor progression. Even though clinical considerations are important in good patient management, clinical stability or deterioration alone is insufficient to guide treatment.

Over the years, a variety of methods have been used to assess response. These have included electroencephalography, radionuclide brain scans, CT scans, and, most recently, MRI. Of these, MRI is the most informative method, providing precise anatomic localization as well as information on tumor growth, associated edema and mass effect, hydrocephalus, brain atrophy, radiation damage, leptomeningeal spread of tumor, and intracranial (or tumoral) bleeding.

Tables 3–3 and 3–4, respectively, summarize single-agent and combination phase II chemotherapy trial results for many, but not all, published trials. It is our belief that an effective treatment must be durable in at least a subset of patients. Response alone is insufficient as a measure of benefit unless it can be maintained. For single agents, a “good” therapy for glioblastoma multiforme should produce a median time to tumor progression of 20 to 30 weeks in 30% to 40% of patients. For anaplastic astrocytomas, a “good” median time to progression is 30 to 50 weeks in 40% to 60% of patients.

Two recent publications have addressed response covariates and study approaches that address the issue of durability of treatment benefit. In the first, the authors analyzed eight consecutive phase II trials that included 225 glioblastoma and 150 anaplastic astrocytoma patients (Wong et al., 1999). The data are summarized in Table 3–9. Based on their data, the investigators propose that phase II studies could utilize PFS at 6 months for glioblastoma as an outcome measure and be quite comfortable with a new therapy that substantially exceeded the 15% observed in their study. On the other hand, for anaplastic astrocytoma patients the PFS at 6 months was 31%, and this group of patients responds longer to chemotherapy than glioblastoma patients. This suggests that PFS at 9 months or 1 year would be a better study endpoint for anaplastic astrocytoma. This approach is addressed in a recent paper by Hess et al. (1999).

Excluding studies utilizing radiosurgical approaches, the best published results today for the treatment of glioblastoma by surgery, radiation, and chemotherapy have included chemotherapy during radiation therapy to potentiate radiation followed by the PCV combination after radiation. Table 3–8 summarizes current data. There certainly have been no giant steps made in the success of any one therapy. This is important to keep in mind because many of the approaches being proposed today have public appeal because they utilize twenty-first century technology: gene therapy, radiosurgery, the gamma knife, bone marrow transplantation, osmotic opening of the blood–brain barrier to improve drug access to the brain and tumor, and toxin immunoconjugates. Perhaps in the future one or more of these approaches will have a place in the therapy for malignant gliomas.

Table 3–9. Outcome Analysis of Phase II Studies for Recurrent Malignant Gliomas

<table>
<thead>
<tr>
<th>Variable</th>
<th>CR, PR, MR, and SD 6 Months</th>
<th>PFS 1 Year</th>
<th>OS 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic astrocytoma</td>
<td>150</td>
<td>14%</td>
<td>48%</td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
<td>225</td>
<td>6%</td>
<td>33%</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; MR, minor response; SD, stable disease; PFS, progression-free survival; OS, overall survival.

Data from Wong et al. (1999).
but currently their benefits are inconsistent and for the most part problematic. One must be wary of referring patients for costly and marginally effective treatments without sound scientific principles underlying the proposed treatment plan.

Another concern is that current treatments add little to the survival or quality of life of older patients (Grant et al., 1995), particularly those older than 60 years. All clinical trials to date have found precipitous declines in survival after 60 to 65 years of age. This is not to say that surgery should not be carried out aggressively in these patients, but rather to inject caution about expectations from radiation and chemotherapy. Cytotoxic chemotherapy especially is not likely to improve survival for older patients.

For anaplastic gliomas, the story is quite different. Although advanced age is an important variable that negatively influences survival, chemotherapy can increase survival substantially. Treatment advances are in part due to (1) drugs such as the nitrosoureas (CCNU, carmustine), procarbazine, carboplatin, temozolomide, and cis-retinoic acid; and (2) some drug combination schedules. Table 3–7 summarizes some of the gains made in adjuvant chemotherapy for anaplastic gliomas. Survival gains have increased from 1.5 to 5 years during the last decade. It is likely that temozolomide (Temodar), an alkylating agent approved by the U.S. Federal Drug Administration in August 1999, will create new opportunities for drug combination therapy against malignant gliomas as well as medulloblastomas. In appears to be well tolerated with less morbidity than many of the drugs currently used to treat brain tumors.

The future will likely be characterized by slow increases in the length of patient survival unless there is a research breakthrough that will provide a new chemotherapeutic approach. Tumor-specific and selective therapies at the genetic and chemical levels will be required for any truly meaningful progress in lengthening survival times. Achieving this task will require major research commitments and a good deal of luck.

**Oligodendrogliomas and Oligoastrocytomas**

**Radiation Therapy**

The infrequent occurrence of oligodendrogliomas as well as their variable and often long prediagnosis and post-treatment natural history make it difficult to evaluate the effect of radiation therapy on these tumors (Sheline, 1983). Representative survival data for oligodendrogliomas are summarized in Table 3–10. Ten year survival rates vary, ranging from 8% to 59%. In contemporary series, median survival times of as long as 16 years have been reported (Olson et al., 2000).

The role of postoperative irradiation for patients with oligodendrogliomas is controversial, and conclusions regarding its value are contradictory. Some authors recommend immediate postoperative irradiation for patients with incompletely resected lesions (Chin et al., 1980; Griffin et al., 1992; Lindegaard et al., 1987; Wallner et al., 1988b), whereas others have been unable to show that postoperative irradiation is of benefit (Bullard et al., 1987; Sun et al., 1988). It has also been suggested that radiation therapy be deferred until there is evidence of tumor progression or recurrence (Reedy et al., 1983; Olson et al., 2000) or that only patients with anaplastic tumors or mixed oligoastrocytomas should receive radiation treatment.

Caution should be exercised when drawing firm conclusions from retrospective studies. For example, most retrospective studies comparing surgery alone with surgery plus radiation therapy do not contain analyses to ensure that the distribution of patients in the two treatment groups are comparable with respect to prognostic variables such as age (Bullard et al., 1987), completeness of resection (Mork et al., 1985; Whitton and Bloom, 1990), neurologic signs and symptoms (Bullard et al., 1987; Griffin et al., 1992), and histopathologic features (Bullard et al., 1987; Griffin et al., 1992; Mork et al., 1986). Furthermore, treatment selection factors are either not stated or are unknown (Lindegaard et al., 1987), and changes in the quality of surgery, radiation therapy, and patient management over the long time intervals spanned by the studies are not taken into consideration. In addition, carefully performed pathologic studies suggest that certain histologic and cytologic features have a significant effect on prognosis (Mork et al., 1986; Ludwig et al., 1986), making it important that pathologic material be independently reviewed.

Taken together, the data shown in Table 3–10 suggest that there may be a benefit to radiation therapy for oligodendrogliomas during the first 5 years after treatment, but this effect appears to diminish over time. Gannett et al. (1994) found a significant improvement in survival with postoperative irradiation.
Patients treated with surgery alone had 5 and 10 year survival rates of 51% and 36%, respectively, compared with 83% and 46%, respectively, for patients who received radiation therapy (p < 0.032). Lindegaard et al. (1987) reported that radiation therapy prolonged the median survival time of patients with incompletely resected tumor (37 months with radiotherapy versus 26 months for surgery alone; p = 0.0089) but did not influence the overall cure rate. The studies by Wallner et al. (1988b) and Shaw et al. (1992) suggested a survival advantage for patients with incompletely resected tumors who received at least 45 to 50 Gy. However, the advantage of irradiation versus nonirradiation did not reach statistical significance. On the other hand, Bullard et al. (1987) found no improvement in the time to clinical deterioration, time to tumor recurrence, or median survival time with the addition of radiation therapy, although the percentage of patients surviving with radiation therapy was consistently higher than those surviving without radiation therapy during the first 5 years after treatment. A meta-analysis on reports from the current literature concluded that postoperative ir-

radiation conferred a 14% improvement in 5 year survival (p < 0.01) (Shimizu et al., 1993). The data presented in these studies suggest that more effective therapies are needed to improve the long-term outcomes of patients with oligodendrogliomas.

As for low-grade astrocytomas, it is also difficult to take a categorical position regarding the role of radiation therapy in the treatment of oligodendrogliomas. Patients with completely resected low-grade oligodendrogliomas as well as those with small, asymptomatic (except for seizures controlled with anticonvulsant medication), incompletely resected lesions can be observed, deferring radiotherapy until the time of recurrence. Large, symptomatic, unresectable or incompletely resected tumors should receive postoperative irradiation (Macdonald, 1994). Proliferation markers such as the MIB-1 labeling index may help to distinguish patients who require aggressive treatment from those who can merely undergo observation (Schiffer et al., 1997).

Radiation therapy is given using fields that encompass the tumor volume with a 2 to 2.5 cm margin. A dose of 54 Gy in daily 1.8 Gy fractions is given

### Table 3–10. 5 Year and 10 Year Survival Rates for Patients with Oligodendroglioma

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Cases</th>
<th>Treatment</th>
<th>Survival Rate (%)</th>
<th>5 Year</th>
<th>10 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsa et al. (1975)</td>
<td>14</td>
<td>S + RT</td>
<td>74</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Chin et al. (1980)</td>
<td>11</td>
<td>S</td>
<td>82</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Reedy et al. (1983)</td>
<td>21</td>
<td>S</td>
<td>67</td>
<td>46*</td>
<td></td>
</tr>
<tr>
<td>Lindegaard et al. (1987)</td>
<td>62</td>
<td>S</td>
<td>27</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Bullard et al. (1987)</td>
<td>34</td>
<td>S</td>
<td>48†</td>
<td>17†</td>
<td></td>
</tr>
<tr>
<td>Wallner et al. (1988b)</td>
<td>11</td>
<td>S</td>
<td>55†</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Sun et al. (1988)</td>
<td>16</td>
<td>S</td>
<td>31</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Shaw et al. (1991)</td>
<td>8</td>
<td>S</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Griffin et al. (1992)</td>
<td>14</td>
<td>S</td>
<td>45</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

S, surgery alone; S + RT, surgery and postoperative irradiation; —, data not available.

*Percent survival at 8 years.
†Data estimated from graphs.
to adults, and that dose is reduced to 50.4 Gy for children (Karlsson et al., 1992). The dose is increased to 59.4 Gy with a reduced field for patients with anaplastic oligodendrogliomas (Bauman and Cairncross, 2001). Complex three-dimensional techniques should be used for treatment planning and delivery when appropriate. PCV chemotherapy (see next section) may be useful in reducing the size of large tumors before radiotherapy is begun (Streffer et al., 2000).

Chemotherapy for Oligodendrogliomas

As previously discussed, oligodendroglial tumors can be categorized by histologic features that correlate with survival. Table 3–11 summarizes survivals for low-grade and high-grade oligodendrogliomas using the “A to D” and the St. Anne-Mayo grading schemes. From the reports cited it can be concluded that patients with low-grade tumors survive 108 months (9 years) compared with 26 months (2.2 years) for those with high-grade tumors. In general, the patients reported (Smith et al., 1983; Shaw et al., 1989, 1992) were treated with surgery and irradiation; few were formally treated with chemotherapy. It is clear from Table 3–12, given the sensitivity of oligodendrogliomas to chemotherapy, that the survival of anaplastic oligodendroglioma patients treated with adjuvant chemotherapy (or chemotherapy at tumor progression) will easily exceed the median 2.2 years.

Table 3–12 summarizes adjuvant chemotherapy (pre-radiation and/or post-radiation) with two different dose schedules of procarbazine, CCNU, and vincristine (PCV and slightly higher dose mPCV). The response and stable disease rates are nearly 100%, and the number of patients without progression at 2 years range from 50% to 85%. PCV combinations have been used widely in the treatment of recurrent oligodendroglioma and oligoastrocytoma tumors with complete response rates of 12% to 33%, partial response rates of 40% to 50%, and stable disease rates of 19% to 31% (Cairncross et al., 1994; Soffietti et al., 1998; van den Bent et al., 1998). Taken together, the three studies yield PFS values of 31 months for complete response, 16 months for partial response, and 14 months for stable disease.

There is little doubt that other chemotherapy approaches that utilize combinations of cytotoxic agents such as carboplatin and temozolomide would be expected to be active against oligodendrogliomas. As a

Table 3–11. Effects of Histologic Classification Schemas on Median Survival Time for Patients with Oligodendrogliomas

<table>
<thead>
<tr>
<th>Series</th>
<th>Histologic Type</th>
<th>Low Grade (Months)</th>
<th>High Grade (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. (1983)</td>
<td></td>
<td>94</td>
<td>17</td>
</tr>
<tr>
<td>Kros et al. (1988)</td>
<td></td>
<td>113</td>
<td>15</td>
</tr>
<tr>
<td>Shaw et al. (1992)</td>
<td></td>
<td>117</td>
<td>47</td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td></td>
<td>108 (±12)</td>
<td>26 (±18)</td>
</tr>
</tbody>
</table>

Mean, mean of reported median survival duration; SD, standard deviation.

*Smith type A and St. Anne-Mayo low grade.
†Smith type D and St. Anne-Mayo high grade.

Table 3–12. Initial treatment of Oligodendrogliomas, Anaplastic Oligodendrogliomas, and Oligoastrocytomas

<table>
<thead>
<tr>
<th>Series</th>
<th>Treatment</th>
<th>No.</th>
<th>% R + SD</th>
<th>% 2 Year TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass et al. (1992)</td>
<td>mPCV + RT</td>
<td>5</td>
<td>100</td>
<td>50*</td>
</tr>
<tr>
<td>Kyritsis et al. (1993)</td>
<td>PCV + RT</td>
<td>8</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass et al. (1992)</td>
<td>mPCV + RT</td>
<td>14</td>
<td>92</td>
<td>85†</td>
</tr>
<tr>
<td>Kyritsis et al. (1993)</td>
<td>PCV + RT</td>
<td>12</td>
<td>100</td>
<td>75</td>
</tr>
</tbody>
</table>

PCV, procarbazine, lomustine, and vincristine; mPCV, different PCV schedule; RT, radiation therapy; TTP, time to tumor progression, % R + SD, percent of all patients who respond or have stable disease.

*Three pre-radiation PCV courses.
†Three no radiation at evaluation; 10 pre-radiation PCV; 2 year survival projected because no patient has been evaluated long enough.
conservative approach, while we wait for newer drugs and better approaches to chemotherapy for oligodendrogliomas, it is reasonable to advocate using a combination of procarbazine, CCNU, and vincristine or simply the combination of CCNU and procarbazine for patients with recurrent tumors and to anticipate that adjuvant chemotherapy with surgery and radiation may also turn out to be efficacious.

**Chemotherapy for Mixed Oligoastrocytomas**

Although most high-grade astrocytic tumors in adults and children are either glioblastoma multiforme or anaplastic astrocytoma, a few patients have mixed malignant gliomas. These are usually anaplastic astrocytoma with oligodendroglioma or, less commonly, anaplastic astrocytoma and ependymoma. Only limited information on chemotherapy for children with these tumors is available. In the Childrens Cancer Group protocol 945, 14 patients were considered to have mixed gliomas, with PFS and overall survival at 5 years of 64% and 71%, respectively.

Adjuvant chemotherapy trials for adults with mixed oligoastrocytomas are also listed in Table 3–12. As with oligodendrogliomas, response to therapy in these tumors is high, with more of these patients than those with anaplastic oligodendroglioma having no tumor progression at 2 years (80% versus 56%). Most patients received the PCV combination. Based on these data, it seems most appropriate to treat children as well as adults with a PCV combination until a better therapy comes along. As part of the initial treatment, we normally advocate that a nitrosourea-based chemotherapy regimen such as PCV be used after limited-field irradiation.

**Ependymoma**

**Radiation Therapy**

Most supratentorial ependymomas cannot be completely excised because of their location and growth characteristics (Marks and Adler, 1982; Kricheff et al., 1964). Historically, 0% to 15% of patients with supratentorial tumors treated with surgery survived 5 years (Ringertz and Reymond, 1949; Mork and Loken, 1977). More recently, with improved surgical techniques, survival gains have been realized. Palma et al. (1993) reported on 20 patients between the ages of 1 and 20 years. Of the 18 who survived surgery, 12 (67%) were alive and disease free at a mean follow-up of 12 years (range 5.2 to 21 years); there were nine ependymoma, one anaplastic ependymoma, and two subependymoma patients in this surviving group.

Radiation therapy significantly improves tumor control and survival and is an accepted part of the standard treatment for ependymomas. As shown in Table 3–13, 5 year survival rates for patients who re-

<table>
<thead>
<tr>
<th>Studies</th>
<th>Cases</th>
<th>Treatment</th>
<th>5 Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringertz and Reymond (1949)</td>
<td>13</td>
<td>S</td>
<td>15</td>
</tr>
<tr>
<td>Mork and Loken (1977)</td>
<td>14</td>
<td>S</td>
<td>0</td>
</tr>
<tr>
<td>Phillips et al. (1964)</td>
<td>12</td>
<td>S + RT</td>
<td>80</td>
</tr>
<tr>
<td>Kim and Fayos (1977)</td>
<td>11</td>
<td>S + RT</td>
<td>46</td>
</tr>
<tr>
<td>Bouchard (1980)</td>
<td>17</td>
<td>S + RT</td>
<td>65</td>
</tr>
<tr>
<td>Marks and Adler (1982)</td>
<td>20</td>
<td>S + RT</td>
<td>35</td>
</tr>
<tr>
<td>Pierre-Kahn et al. (1983)</td>
<td>15</td>
<td>S + RT</td>
<td>51</td>
</tr>
<tr>
<td>Salazar et al. (1983)</td>
<td>20</td>
<td>S + RT</td>
<td>35</td>
</tr>
<tr>
<td>Read (1984)</td>
<td>19</td>
<td>S + RT</td>
<td>40 (adults)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17 (children)</td>
</tr>
<tr>
<td>Goldwein et al. (1990)</td>
<td>18</td>
<td>S + RT</td>
<td>35</td>
</tr>
<tr>
<td>Vanuytsel et al. (1992)</td>
<td>40</td>
<td>S + RT</td>
<td>48</td>
</tr>
</tbody>
</table>

S, surgery alone; S + RT, surgery and postoperative radiation therapy.
ceived radiation therapy range from 30% to 80%. The correlation between survival and histopathologic grade is controversial, although we found it to be an important predictor of tumor behavior and outcome (Leibel and Sheline, 1987).

Supratentorial tumors generally have a poorer prognosis than their infratentorial counterparts, probably because a greater proportion of them are high grade (Chin et al., 1982) and because there is a tendency for larger volumes of residual disease to be present after surgical resection at this location (Marks and Adler, 1982). Unlike other brain tumors, young children with ependymomas tend to have a poorer outcome than older children or adults (Garrett and Simpson, 1983; Goldwein et al., 1990; Shaw et al., 1987). This may reflect the practice of reducing the dose of radiation for very young children (Goldwein et al., 1990, 1991; Marks and Adler, 1982).

The amount of normal CNS tissue that should be included in the treatment volume is a major area of controversy. Differences in opinion are based on the potential for ependymomas to spread into the ventricular system and to disseminate into the spinal subarachnoid space. In some reports, the inclusion ofependymoblastomas, which are known for their propensity to disseminate throughout the CNS, tends to overestimate the risk of seeding of the spinal subarachnoid space (Goldwein et al., 1991; Ross and Rubinstein, 1989). Autopsy and clinical studies show that patients who develop intracranial and intraventricular spread also have recurrent or persistent disease at the primary tumor site (Marks and Adler, 1982; Salazar et al., 1983; Wallner et al., 1986). Spinal seeding is uncommon in supratentorial ependymomas, occurring in only 1.6% of cases in a literature review by Vanuytsel and Brada (1991). In that review, no patient with high-grade supratentorial lesions developed spinal subarachnoid seeding, whereas the incidence of seeding in low-grade supratentorial lesions was 2.7%. Relapse of the primary tumor had the greatest effect on the subsequent development of spinal seeding, regardless of tumor grade or site. Spinal dissemination occurred in 3.3% of patients with locally controlled tumors, whereas 9.5% with uncontrolled primary lesions developed seeding ($p < 0.05$). The frequency of seeding was not affected by whether prophylactic spinal irradiation was given.

The treatment volumes recommended for low-grade supratentorial ependymomas vary from generous local fields (Goldwein et al., 1990; Leibel and Sheline, 1987; Pierre-Kahn et al., 1983; Shaw et al., 1987; Wallner et al., 1986; Vanuytsel et al., 1992) to fields encompassing the whole brain (Salazar et al., 1983). However, the survival and local tumor control rates achieved by partial brain irradiation (Goldwein et al., 1990; Vanuytsel et al., 1992; Wallner et al., 1986) are comparable with those obtained with whole-brain irradiation (Salazar et al., 1983). As nearly all recurrences are limited to the original primary tumor site, whole-brain irradiation would not be expected to improve the chance of cure. Patients are treated using a generous target volume, based on operative and radiographic findings, to a dose of at least 54 Gy. Pretreatment myelography, spinal MRI, and CSF evaluation are not performed unless there is evidence of ventricular involvement or signs of subarachnoid metastases.

In the past most authors recommended inclusion of the entire craniospinal axis in the treatment of anaplastic supratentorial ependymomas (Salazar et al., 1983; Wallner et al., 1986; Vanuytsel et al., 1992), although some recommended whole-brain irradiation with an additional boost for high-grade supratentorial lesions located away from the CSF pathways (Pierre-Kahn et al., 1983; Goldwein et al., 1990) if there was no evidence of leptomeningeal spread. However, despite the apparent superiority of craniospinal radiation therapy noted in some series (Salazar et al., 1983), the findings that (1) local recurrence is the primary pattern of failure (Goldwein et al., 1991; Salazar et al., 1983; Marks and Adler, 1982; Shaw et al., 1987; Vanuytsel et al., 1992; Merchant et al., 1997; McLaughlin et al., 1998; Schild et al., 1998), (2) spinal seeding is uncommon in the absence of local recurrence (Leibel and Sheline, 1987; Marks and Adler, 1982; Vanuytsel and Brada, 1991; Schild et al., 1998), (3) the patterns of failure are similar in patients with high-grade tumors treated with local fields or with craniospinal axis irradiation (Goldwein et al., 1991a; Vanuytsel et al., 1992; McLaughlin, 1998), and (4) prophylactic treatment may not prevent spinal metastases have led many investigators to question whether the routine use of craniospinal or whole-brain irradiation leads to improved survival (Goldwein et al., 1991; Vanuytsel and Brada, 1991; Vanuytsel et al., 1992).

Merchant et al. (1997) reviewed the outcomes of 28 pediatric patients with anaplastic ependymoma treated either with or without craniospinal irradiation. The actuarial 5 and 10 year survival rates were
56% and 38%, respectively. A benefit from craniospinal irradiation could not be demonstrated. All 19 patients who failed radiotherapy relapsed at the primary site, and one of these also developed subarachnoid dissemination. On the basis of these and other data, craniospinal irradiation is generally not recommended for patients with supratentorial anaplastic (high-grade) ependymomas unless evidence of leptomeningeal spread is pathologically or radiographically documented (Vanuytsel and Brada, 1991; Goldwein et al., 1991; Goldwein and Lefkowitz, 1991; Merchant et al., 1997; McLaughlin, 1998). Although dose levels of 54 Gy have typically been used to treat anaplastic ependymomas, the administration of 59.4 Gy with conformal techniques would appear to be warranted.

Because the inability to eradicate the primary tumor remains the single most important factor leading to treatment failure (Vanuytsel et al., 1992), more aggressive local therapies to improve local tumor control, in both low- and high-grade ependymomas, are being explored. These include the use of boosts with stereotactic radiotherapy or conformal radiotherapy techniques as well as hyperfractionated radiation schedules (McLaughlin, 1998; Schuller et al., 1999).

Chemotherapy

Supratentorial ependymomas are uncommon tumors, probably representing fewer than 30% of all ependymomas. While firm data on age incidence for these supratentorial tumors are unavailable, in our experience these tumors are most often seen in the first two decades of life. Also, there may be a higher proportion of anaplastic (or malignant) ependymomas than of the more common cellular (or low-grade) ependymomas. In most series, supratentorial ependymomas occur nearly as frequently as infratentorial ependymomas. When supratentorial ependymomas recur, they almost always do so at the primary tumor site, regardless of pathology.

The value of chemotherapy for ependymomas in general and for supratentorial ependymomas in particular remains unclear (Puccetti and Finlay, 1992). No distinction has been made in phase II chemotherapy trials between supratentorial and infratentorial ependymomas. Table 3–14 summarizes therapies for ependymomas in both locations. Single agents vary in the quality of responses and the durability of responses that they produce. Those yielding good responses and longer duration of response activity are carmustine (Levin et al., 1993), dibromodulcitol (Levin et al., 1984), and diaziquone (Ettinger et al., 1990). Cisplatin and carboptatin appear less effective; more recent trials with ifosfamide have shown similar activity.

Unfortunately, no studies to date have demonstrated a survival advantage with single-agent chemotherapy plus irradiation compared with irradiation alone in children or adults with newly diagnosed ependymomas (Goldwein and Lefkowitz, 1991). Levin and colleagues (2000a) reported on 17 patients with malignant ependymoma treated with a combination of 6-thioguanine, procarbazine, dibromodulcitol, CCNU, and vincristine (TPDCV) chemotherapy and craniospinal radiation. With the combined chemotherapy–radiotherapy protocol, 65% of patients failed, with a median time to progression of 141 weeks and a median survival of 42 months, and there

| Table 3–14. Chemotherapy for Recurrent Ependymoma and Anaplastic Ependymoma Regardless of Location |
|---------------------------------|--------|-------|--------|--------|
| Series                         | Drug               | No.   | % R + SD | 50% TTP (Months) | 25% TTP (Months) |
| Levin et al. (1984)            | Dibromodulcitol    | 12    | 75       | 16     | 20     |
| Levin et al. (1987)            | Carmustine        | 14    | 78       | 13     | 24     |
| Bertolone et al. (1989)        | Cisplatin         | 8     | 75       | 3.8    | 4.3    |
| Goldwein et al. (1990)         | Various*          | 37 trials/16 patients | 22 | 9 | 10 |
| Gaynon et al. (1990)           | Carboplatin       | 14    | 28       | 14     | NA     |
| Ettinger et al. (1990)         | Diaziquone        | 12    | 42       | 10     | 16     |
| Prados et al. (1991)           | TPDCV             | 11    | 82       | 21.6   | NA     |

% R + SD, percent of patients who responded or had stable disease; TTP, time to tumor progression; TPDCV, 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine (MD Prados and VA Levin, personal communication); NA, not attained yet.

*Various combinations of vincristine, cisplatin, lomustine, procarbazine, etoposide, and ifosfamide combinations.
were 8 patients alive at a median of 9 years after study entry.

Therapy for ependymomas relies first on surgery, second on radiation, and third on chemotherapy. In most cases, failure of the first two approaches forces consideration of chemotherapy. Although we advocate no specific chemotherapy at this time, we believe that platinum-based therapies are not particularly active and should be avoided. Unfortunately, few adjuvant chemotherapy studies of the treatment of anaplastic ependymoma are ongoing at this time.

**PRIMITIVE NEUROECTODERMAL TUMORS**

**Pathology**

The term *primitive neuroectodermal tumor* (PNET) was originally used to describe small cell, predominantly undifferentiated, tumors occurring in the cerebral hemispheres of young patients (Hart and Earle, 1973). Some tumors showed minor components of glial or neuronal differentiation. The common histologic feature of all of these tumors is, however, some component of immature, small embryonal-like cells. Most have frequent mitotic activity and zones of necrosis. Subsequently, the term *cerebral neuroblastoma* has been used for those morphologically similar tumors that show evidence of primitive or more advanced neuronal differentiation. The features of neuronal differentiation include the presence of Homer-Wright fibrillary rosettes and large neuron-like cells with more abundant eosinophilic cytoplasm, large round nuclei, and prominent nucleoli. Cerebral neuroblastomas also tend to have an abundant component of connective tissue and a desmoplastic appearance. Small cell, undifferentiated tumors that show astrocytic differentiation or both neuronal and astrocytic differentiation may be called PNET with glial or with divergent differentiation.

Most pathologists accept positive immunoreactivity for glial fibrillary acidic protein (GFAP) in neoplastic cells as evidence of astrocytic differentiation. Positive immunoreactivity for synaptophysin or for neurofilament protein confirms neuronal or neuroblastic components. Examples with definite epithelial ependymal rosettes are designated ependymoblastomas, or PNET with ependymal differentiation. Tumors arising in the pineal region are pineoblastomas.

**Clinical Features**

Primitive neuroectodermal tumors occur most commonly in the first two decades of life, although they are increasingly recognized in adults into the sixth decade. Following the initial description of primary cerebral neuroblastoma by Horten and Rubinstein (1976), a distinction in clinical behavior and outcome between that entity and supratentorial PNET (Hart and Earle, 1973) has been emphasized by some authors but not by others. Both types of tumors demonstrate similar clinical and diagnostic features, although the in vivo appearance of each may be somewhat different. Either lesion may be cystic, grayish-granular, sharply demarcated, and hemispheric in location (Kosnik et al., 1978). In addition to being cystic, the cerebral neuroblastoma may also have a mural tumor nodule that is not seen in PNET. The latter lesion often shows gross areas of necrosis, which are not typical of the cerebral neuroblastoma.

Staging for extent of tumor is similar to that for infratentorial medulloblastoma, although the yield of positive studies at initial diagnosis is lower. Patients must undergo imaging of the entire neuraxis by brain and spine MRI, as well as a diagnostic lumbar puncture within 2 to 3 weeks following surgery for cytologic evaluation of CSF for malignant cells.

**Surgery**

The goal of surgery is complete tumor resection whenever feasible. Because of the tumor’s hemispheric location, it may be necessary to utilize physiologic mapping to achieve that goal, as previously described. There are sparse data on how extent of resection affects outcome. Although several reports of long-term survival appear to coincide with radical resection of either tumor type (Duffner et al., 1981; Halperin et al., 1993; Gaffney et al., 1985), this is not always the case (Tomita et al., 1988). The patients who benefit most from total resection have cystic cerebral neuroblastomas (Berger et al., 1983).

Although PNET may occur in the first three decades of life (unlike neuroblastomas, which always affect younger children), both lesions must be distinguished from the adult central neurocytoma, which is an intraventricular, neurally derived tumor originating from the septum pellucidum (Hassoun et al., 1993). Central neurocytomas are histologically distinct from the neuroblastic and neuroectodermal tumors de-
scribed above. Complete resection of the central neurocytoma is usually curative without further adjuvant therapy (Kim et al., 1992).

**Radiation Therapy**

The general consensus is that patients with PNET should receive postoperative radiation therapy (Humphrey et al., 1981). Although radiation therapy appears to increase survival time (Duffner et al., 1981; Jenkin, 1981), the outcome is usually poor, and most patients develop local or regional recurrences. Because of their propensity to spread throughout the subarachnoid space (Kosnik et al., 1978; Parker et al., 1975; Knapp et al., 1981; Ashwal et al., 1984; Humphrey et al., 1981), PNET are treated with craniospinal axis irradiation (Jenkin, 1981; Gaffney et al., 1985). The primary tumor is given 54 to 55 Gy, and the remainder of the axis receives 36 Gy. The dose should be reduced for very young children (Gaffney et al., 1985).

Chemotherapy is usually a part of the treatment program. Although primitive neuroectodermal tumors are included in pediatric cooperative group protocols designed for high-risk medulloblastoma patients, they are less radiocurable than medulloblastomas (Gaffney et al., 1985; Humphrey et al., 1981). In some series 1 year survival rates are as low as 10% (Kosnik et al., 1978), whereas others report 5 year survival rates of 20% to 47% (Gaffney et al., 1985; Humphrey et al., 1981). The disparity in survival figures reflects the heterogeneity of malignancies that are classified under the term *primitive neuroectodermal tumors* (Rubinstein, 1985). For example, in a series of 14 patients reported by Gaffney et al. (1985), the 3 year survival rate was 29%. None of the patients with tumors containing more than 90% undifferentiated elements were alive at 3 years, whereas 60% of those with less primitive tumors survived 3 years.

An important question is raised by the relative infrequency of neuraxis dissemination at diagnosis of supratentorial nonpineal region PNET compared with infratentorial medulloblastoma. Because the outcome for patients with residual tumor in the absence of metastases remains so poor even in the face of full-dose craniospinal irradiation, one might argue that for such patients restricting irradiation to involved fields might permit greater tolerance of dose intensification of chemotherapy with improved outcome. It is important to remember that almost 40% of the body’s bone marrow resides in the spinal vertebrae and that, following craniospinal irradiation at the standard dose of 36 Gy, the patient’s ability to tolerate even modest doses of chemotherapy is significantly impaired. For patients with pineoblastomas, who are known to experience a very high rate of neuraxis dissemination at diagnosis and relapse, restricting the irradiation field (especially in older children and adults) is probably inappropriate; however, in patients with other supratentorial PNET this may be appropriate within the conduct of a formal clinical trial. One other approach to permit intensification of chemotherapy is to deliver such treatment in a therapeutic window before the delivery of craniospinal irradiation.

Cerebral neuroblastomas are biologically distinct from other PNET. They tend to be less malignant, have a better outcome, and are less likely to disseminate throughout the craniospinal axis (Cohen and Duffner, 1984). This tumor may present as a cystic lesion with a peripheral nodule or as a solid mass, and the tumor’s morphologic nodule is related to prognosis. Berger et al. (1983) reported the outcomes of 11 patients with cerebral neuroblastoma. Six patients presented with cystic tumors, and five had solid lesions. Gross total resection was achieved in only two patients, both with cystic tumors. All patients received postoperative irradiation. Seven of the 11 patients, all treated with local irradiation to an average of 52 Gy, remained alive with no evidence of tumor progression. None of the six patients with cystic tumors developed recurrent disease, whereas four of the five patients with solid tumors had a relapse at the primary site within 8 to 31 months after treatment. The only patient with a solid lesion who did not have a tumor recurrence received adjuvant chemotherapy. Although subarachnoid dissemination is found in autopsied cases (Horten and Rubinstein, 1976), this pattern of spread does not represent a significant clinical problem. Thus, localized cerebral neuroblastomas are treated with limited-field irradiation to 54 Gy. The craniospinal axis is included only if there is evidence of tumor dissemination beyond the site of origin by imaging studies or CSF cytology.

**Chemotherapy**

Although the mainstay of therapy for PNET is surgery and irradiation, young patient age, incomplete resec-
tion, and recurrent tumor require the addition of chemotherapy. Several single-institution reports on supratentorial PNET have indicated a poor prognosis following surgical resection alone or combined with postoperative irradiation; this reflects a high incidence of primary site recurrence as well as neuraxis dissemination throughout the leptomeninges, even in the face of prophylactic craniospinal irradiation. This is particularly true of pineoblastomas, which have a high rate of neuraxis dissemination at both initial presentation and subsequent recurrence. Patient age at onset of these tumors may also have a powerful prognostic importance; most studies indicate that very young children fare worse than older patients, with higher rates of dissemination at diagnosis and recurrence and a shorter time to recurrence. Chemotherapy alone is now generally employed for children younger than 3 years with supratentorial PNET.

The site of origin of PNET has been documented as an important prognostic indicator in a large phase III trial conducted by the Childrens Cancer Group in North America (the CCG-921 study). In that study, both posterior fossa and supratentorial PNET were randomized to one of two chemotherapy-containing regimens; all patients underwent maximal surgical resection of the primary site tumor and were given postoperative craniospinal irradiation with a boost to the primary tumor site. Chemotherapy with CCNU, vincristine, and prednisone was compared with the 8-in-1 regimen of CCNU, vincristine, cytosine arabinoside, cyclophosphamide, and methylprednisolone. The most recently published reports from this study (Jakacki et al., 1995; Cohen et al., 1995; Zeltzer et al., 1999) demonstrate some surprising differences between patients with pineal region PNET, other nonpineal region PNET, and infratentorial PNET or medulloblastoma. For patients with pineal PNET, the 3 year PFS was 61% ± 13%, whereas the corresponding 3 year PFS for patients with nonpineal supratentorial PNET was only 33% ± 9%, a statistically significant difference. Considering both extent of resection and tumor stage, patients with supratentorial PNET have a poorer PFS and overall survival rate than do patients with infratentorial PNET.

In the above cooperative group study, the infratentorial PNET were primarily medulloblastoma, whereas the supratentorial PNET carried other diagnostic labels; no differentiation was made between cerebral neuroblastomas and other supratentorial PNET. Interestingly, greater than 40% of infratentorial tumors showed evidence of neuraxis dissemination at diagnosis (either positive CSF cytology and/or radiographic evidence of intracranial or spinal leptomeningeal dissemination on head CT scan or myelogram), whereas only 21% of patients with supratentorial PNET showed such dissemination. The outcome for patients with supratentorial PNET was significantly affected by neuraxis dissemination; patients without neuraxis dissemination had a 3 year PFS of 56%, whereas all patients with evidence of neuraxis dissemination at diagnosis ultimately relapsed.

An additional effect of volume of residual tumor was observed in patients with nonpineal PNET treated in the CCG-921 study; those with residual tumor volume less than 1.5 cm³ on postoperative scans had a 4 year survival of 40% ± 22% compared with 13% ± 8% for those with greater residual tumor volume. Because of small patient numbers, however, this difference did not attain statistical significance (Albright et al., 1995). The even smaller patient numbers with pineal PNET obviated any valid comparisons, but suggest that patients with bulky residual disease relapsed at a higher rate and earlier following diagnosis (Jakacki et al., 1995). Subsequent pediatric cooperative group trials attempted to improve upon the poor results for patients with supratentorial PNET with either significant residual tumor postoperatively and/or neuraxis dissemination. The studies employed intensification of chemotherapy with agents known to be efficacious against PNET (e.g., alkylating agents such as cyclophosphamide or ifosfamide at high doses, and cisplatin or carboplatin). Again, however, evidence of benefit over conventional chemotherapy is lacking.

Because the occurrence of supratentorial PNET is not uncommon within the first 3 years of life, and because children with these tumors are particularly vulnerable to the deleterious effects of whole-brain irradiation on the developing brain, chemotherapy is now routinely used instead of irradiation either to avoid entirely or to at least delay the need for or restrict the volume and dose of radiation to the brain. In the Childrens Cancer Group CCG-921 study, children younger than 18 months with medulloblastoma/PNET were nonrandomly assigned to receive the 8-in-1 chemotherapy regimen with the intent of delaying irradiation until the completion of at least 1 year of chemotherapy. In a publication reporting the
CG-921 study, all children younger than 18 months of age at diagnosis of pineoblastoma died following tumor recurrence at a median of just 4 months from diagnosis (Jakacki et al., 1995).

The outcome for young children with nonpineal region supratentorial PNET is less clear. All nine children aged 19 to 36 months treated with reduced-dose irradiation to the spine (23.4 Gy) and the primary site (45 Gy) as well as with chemotherapy relapsed and died (Albright et al., 1995). However, those children younger than 18 months of age treated with 8-in-1 chemotherapy without irradiation achieved a 55% ± 16% 3 year PFS, comparable with the survival rate of children older than 36 months of age treated with full-dose irradiation and the same chemotherapy regimen (Geyer et al., 1994). This unusually favorable outcome in a small number of patients (n = 11) contrasts with other reports indicating equally poor outcomes for infants with pineal and nonpineal supratentorial PNET treated with chemotherapy alone (Duffner et al., 1993).

To avoid irradiation for children younger than 6 years of age with supratentorial PNET and for children younger than 3 years of age with PNET in any location, the “Head Start I” chemotherapy regimen was developed (Mason et al., 1998). This regimen uses five cycles of intensive induction chemotherapy (cisplatin, vincristine, high-dose cyclophosphamide, and etoposide) followed by a single cycle of myeloablative chemotherapy (thiotepa, etoposide, and carboplatin) with autologous hemopoietic stem cell rescue. The most recent update (Golomb et al., 1999) indicates a 4 year PFS of almost 50% for patients with supratentorial PNET, with avoidance of irradiation for more than 80% of patients. The more recent protocol, “Head Start II,” being conducted in a multinational setting, employs the same regimen as Head Start I but with intensification in induction using high-dose methotrexate for patients with neuraxis dissemination at diagnosis and increasing the age of eligibility for patients with supratentorial tumors to 10 years.

For recurrences of supratentorial PNET, the subsequent course of management must be tailored to the individual patient, depending on the extent of disease at recurrence, prior exposure to irradiation and/or chemotherapy, the patient’s general condition, and specific organ function at time of recurrence. For those with localized recurrence, radical surgical resection should be considered as a first step. In the presence of leptomeningeal dissemination, surgical debulking of mass lesions is more problematic, although at times it can contribute toward an improved level of palliation.

Postoperative chemotherapy approaches for patients with tumor recurrence range from the use of new investigational agents to myeloablative chemotherapy regimens with autologous hemopoietic stem cell rescue if the patient can be brought to a state of minimal residual tumor either through surgical resection of localized tumor or through reinduction chemotherapy. This intensive approach is particularly warranted for young children who have not received irradiation before recurrence and for the small proportion of patients for whom myeloablative chemotherapy with autologous stem cell rescue followed by irradiation may afford cure of disease (Guruangan et al., 1998).

**CHOROID PLEXUS PAPILLOMAS AND CARCINOMAS**

**Pathology**

Benign or malignant proliferations of choroid plexus epithelium are termed papillomas or carcinomas, respectively. Both are rare, occurring most often in the first decade of life (Matson and Crofton, 1960; Bigner et al., 1998). Congenital examples have been described (Tomita and Naidich, 1987). The papilloma is usually cured surgically (McGirr et al., 1988). These tumors may arise at any choroid plexus site, but the lateral and third ventricles are more common sites in children, whereas the fourth ventricle is more common in adults (Burger et al., 1991; Bigner et al., 1998). Symptoms are usually referable to hydrocephalus, a sequela either of ventricular outflow obstruction by the mass or of active oversecretion of CSF by the proliferating choroid plexus epithelium, or both (Boyd and Steinbok, 1987; Eisenberg et al., 1974).

The diagnosis of choroid plexus papilloma hinges on the presence of an unusually large mass of choroid plexus tissue and some cellular crowding and pseudostratification (Burger et al., 1991) with almost no mitotic activity. The histologic features are remarkably similar to those of normal choroid plexus epithelium. Foci of bone, cartilage, or oncocytic...
change may be seen (Bonnin et al., 1987). Even histologically benign lesions have been reported to seed the subarachnoid space, but they do not invade the cerebral parenchyma (Bigner et al., 1998).

Choroid plexus carcinomas are highly anaplastic, malignant, and invasive neoplasms (Lewis, 1967; Packer et al., 1992; Paulus and Janisch, 1990). They appear as poorly differentiated carcinomas, with ultrastructural features of adenocarcinomas, such as cilia, microvilli, and well-formed cytoplasmic junctions (Burger et al., 1991; Bigner et al., 1998). The differential diagnoses are intraventricular ependymoma and metastatic carcinoma. The distinction from ependymoma can usually be made by identifying the neoplastic stroma as either glial (ependymoma) or mesenchymal (choroid plexus neoplasm). Immunostaining for glial fibrillary acidic protein is usually strongly and diffusely positive in an ependymoma but focal in a choroid plexus tumor (Coffin et al., 1986; Mannoji and Becker, 1988; Miettenen et al., 1986; Bigner et al., 1998). In contrast, cytokeratins are present in choroid plexus tumors as carcinoembryonic antigen may be present in carcinomas, whereas both agents are focal or absent in ependymomas (Coffin et al., 1986; McComb and Burger, 1983).

The role of transthyretin (prealbumin) immunostaining in making a diagnosis is still controversial (Herbert et al., 1990; Paulus and Janisch, 1990). Although this substance is produced in normal choroid plexus and immunoreactivity is seen in most papillomas, the extent and intensity of reactivity decrease with increasing anaplasia (Matsushima et al., 1988). However, this approach is not always possible due to the massive size of the tumor. In this setting, the tumor must be removed piecemeal with bipolar coagulation (Tomita and Naidich, 1987) as opposed to an en bloc delivery, which is the ideal surgical approach. In neonates and infants, the blood volume may range between 250 and 500 ml, thus requiring massive transfusions to replete the rapid bleeding that often occurs with piecemeal removal.

Tumor in the third ventricle will protrude through the foramen of Monro (Fig. 3–15) and derives its vascular pedicle from the roof of the third ventricle. It may be necessary to split both fornices or to maneuver under the lateral ventricle choroid plexus to enter the mid to posterior third ventricle. Venous drainage also becomes a problem because of massive distention due to increased tumor blood volume and the fragility of the draining veins in a young child. Once the tumor is removed, a drain should be left in place for 2 to 3 days to remove all bloody CSF and tumor debris. In most circumstances, a larger subdural effusion will develop, although some surgeons claim that this can be obviated by sealing the cortical opening with fibrin glue (Boyd and Steinbok, 1987). The treatment of choice for this problem if it is symptomatic or does not resolve within 3 to 6 months is to place a subdural–peritoneal shunt.

The etiology of the hydrocephalus is thought to be secondary to overproduction of CSF (Eisenberg et al., 1974), although the altered flow of CSF along with its elevated protein concentration may also be implicated (Rekate et al., 1985). Usually, removal of the tumor

Surgery

Choroid plexus tumors present a difficult challenge to the surgeon because of their large size and enormous blood volume. These lesions are often found in the lateral and third ventricles during childhood and in the fourth ventricle in adults. The goals of surgery include gross total resection and management of the massive ventriculomegaly that often results. In the past, the mortality from surgery approached 20% to 30% as a result of excessive bleeding (Hawkins, 1980), and neurologic morbidity was unacceptably high.

The approach to the lesion depends on the position it occupies in the ventricle. Lateral ventricular tumors are best approached through the posterior temporal lobe, inferior to the middle gyrus (dominant hemisphere), and via the middle to superior gyrus in the nondominant hemisphere (Spallone et al., 1990). Tumors situated in the third ventricle may be approached by a transcortical (superior frontal gyrus) incision or through the transcallosal route (Schijman et al., 1990). The tumor must be mobilized to find the arterial pedicle from the anterior choroidal artery in the case of a lateral ventricular lesion entering into its inferomedial surface (Raimondi and Gutierrez, 1975). In neonates and infants, the blood volume may range between 250 and 500 ml, thus requiring massive transfusions to replete the rapid bleeding that often occurs with piecemeal removal.

In adults, the rarity of choroid plexus neoplasms mandates that metastatic carcinoma be the preferred diagnosis unless it is absolutely and rigorously eliminated (Gottschalk et al., 1993; Bigner et al., 1998).
will reduce the hydrocephalus and the need for permanent ventriculoperitoneal shunting, which is required in 20% or more of cases (Hawkins, 1980).

Choroid plexus carcinomas should likewise be completely resected if possible, as this has been more effective in determining long-term outcome than has adjuvant therapy (Ellenbogen et al., 1989; St. Clair et al., 1991).

Radiation
Because choroid plexus papillomas are often cured by total surgical excision (McEvoy et al., 2000), not much information exists about their response to irradiation (Cohen and Duffner, 1984). The studies that are available do not provide sufficient detail or data to allow an assessment of the value of radiation therapy for these lesions. Pathology specimens from patients who received low-dose preoperative irradiation (approximately 30 Gy) demonstrated a significant reduction in tumor size, obliteration of the tumor capillary bed, and necrosis, although at this dose level there was little change observed in neoplastic choroidal cells (Carrea and Polak, 1977). Naguib et al. (1981) reported a case of an inoperable cerebellopontine angle choroid plexus papilloma that extensively involved the adjacent mastoid bone. This patient received 49.5 Gy in 32 treatment fractions over a period of 33 days. Within 16 months after completion of radiation therapy, the mass was markedly reduced in size. Such anecdotal reports suggest that it is reasonable to offer local irradiation to patients with inoperable or recurrent choroid plexus papillomas (Cohen and Duffner, 1984).

Radiation therapy may be beneficial for patients with choroid plexus carcinomas (Ausman et al.,

Figure 3–15. Choroid plexus papilloma (CPP) protruding through the foramen of Monro.
Chemotherapy

The role of chemotherapy in the management of choroid plexus tumors remains ill defined. Several phase II trials of chemotherapeutic agents in recurrent pediatric brain tumors have included occasional patients with choroid plexus carcinomas, and objective radiographic responses to such agents have been observed. A small number of reports have focused on the efficacy of chemotherapy for choroid plexus carcinomas and have demonstrated objective radiographic responses to (1) a combination of cisplatin and etoposide, (2) myeloablative doses of thiopeta and etoposide, (3) the 8-in-1 regimen (J Finlay, personal communications, 1993), and (4) cyclophosphamide-based therapies with or without intraventricular chemotherapy (VA Levin personal communications, 1993; Souweidane et al., 1999).

Even though chemotherapy has produced objective responses in patients with choroid plexus carcinoma, it does not follow that such drugs have a clear role in improving the outcome for newly diagnosed tumors in children. It seems clear that the single most powerful prognostic factor of a favorable outcome for children with choroid plexus tumors is extent of surgical resection; children who undergo a successful gross total resection of tumor at diagnosis have an excellent survival; it is unclear whether such children require any additional therapy, either irradiation or chemotherapy. Volumetric reduction with preoperative chemotherapy may improve the ability to perform a complete resection (Souweidane et al., 1999). However, the outcomes for patients with incompletely resected or metastatic choroid plexus carcinoma is poor, even with the addition of radiation therapy and/or conventional chemotherapy. Given that the carcinomas have shown sensitivity to chemotherapy, it is appropriate to advocate intensive chemotherapy regimens for children with newly diagnosed, incompletely resected, and/or metastatic choroid plexus carcinoma, with avoidance of irradiation, as most of these children will be younger than 6 years of age and at greatest risk for tumor recurrence and profound developmental and psychosocial dysfunction if subjected to cranial irradiation. In light of the importance of radical surgical resection, any child with localized but incompletely resected primary choroid plexus papilloma or carcinoma should be considered for reoperation to achieve gross total resection.

REFERENCES


Primary Cerebral Tumors


Primary Cerebral Tumors

141


McCormack BM, Miller DC, Budzilovich GN, Voorhees GJ, Ran-


Primary Cerebral Tumors


