Chapter 121

Neoplasms of the Central Nervous System

Epidemiology of Brain Tumors

Incidence and Prevalence

The precise incidence and prevalence of brain tumors is imprecisely documented because benign tumors were not required to be reported prior to 2003, and metastatic disease to the brain remains unreported. The major data sources include the Surveillance, Epidemiology, and End Results (SEER) program and the Central Brain Tumor Registry of the United States (CBTRUS). The SEER registry reports a primary central nervous system (CNS) tumor incidence of 6.4 cases per 100,000 per year (7.6 per 100,000 men and 5.4 per 100,000 women), translating to an estimated case load of 22,070, with an anticipated 12,920 deaths, and an age-adjusted death rate of 4.4 per 100,000. The median age at diagnosis is 55, and an age-dependent bimodal distribution is observed, with the incidence estimated at 3.1 per 100,000 up to age 4, 1.8 per 100,000 from age 15 to 24 years, and a peak of 18 per 100,000 around age 65 years. The CBTRUS database quotes the estimated incidence of new CNS tumors in the United States at 62,930 cases, primarily because it includes both benign and malignant histologies in the assessment.

In 1993, the World Health Organization (WHO) ratified a new classification, assuming that each tumor results from a specific cell type. Most registries do not contain detailed information regarding the distribution of various CNS tumors, as specified in the WHO classification. Many of these tumors are radiographically and clinically diagnosed; examples include infiltrating pontine gliomas, vestibular schwannomas, skull-base meningiomas, and brain metastases. Specific CNS tumor types also differ in incidence based on anatomic location. Figure 121.1 presents a simplified distribution by subtype.

The increased utilization of cranial imaging for headaches, seizures, or trauma has led to an increase in the diagnosis of benign tumors. SEER suggests that between 1975 and 1987 there was a significant increase in the incidence of CNS tumors, which leveled off between 1991 and 2006. Because many patients with CNS tumors survive for several years, the prevalence exceeds the incidence; as of 2004, there were 612,000 Americans alive with CNS tumors, 124,000 with malignant and 488,000 with nonmalignant tumors.

Etiologic Factors

No agent has been definitively implicated in the causation of CNS tumors, and risk factors can be identified only in a minority. Commonly implicated associations described with other malignancies, such as diet,
Environmental Factors

Farmers and petrochemical workers have been shown to have a higher incidence of primary brain tumors. A variety of chemical exposures have been linked. Ionizing and nonionizing radiation has been implicated, with the clearest association coming from the occurrence of superficial meningiomas, in individuals receiving cranial or scalp irradiation, with the association being stronger for young children receiving low doses of irradiation for benign conditions. Exposure to ionizing radiation is a known risk factor for a small percentage of astrocytomas, sarcomas, and other tumors. There is a 2.3% incidence of primary brain tumors in long-term survivors among children given prophylactic cranial irradiation for acute leukemia, a fourfold increase over the expected rate.

There are conflicting reports regarding nonionizing radiation emitted by cellular telephones. Several investigators have reported meta-analyses of case control studies evaluating cell phone use and the development of a brain tumor. Kan et al. reviewed nine studies (5,259 cases and 12,074 controls) and showed an overall odds ratio (OR) of 0.90 for cellular phone use and brain tumor development; the OR was 1.25 for long-term users. An OR of 0.98 for developing malignant and benign tumors of the brain as well as the head and neck was reported by Myung et al. when collating 23 case control studies (12,544 cases and 25,572 controls). The International Commission for Non-Ionizing Radiation Protection Standing Committee on Epidemiology reviewed the epidemiologic evidence and they concluded that there was not a causal association between mobile phone use and malignant glioma, but for slow-growing tumors, the observation period was too short for conclusive statements. A recent report of the INTERPHONE study, an international, population-based case control study, also did not find an increased risk of glioma or meningioma. Further studies continue.

Viral Associations

Although certain canine and feline CNS tumors may have a viral association, the human evidence remains weak. Specifically, no increase in the risk of developing a brain tumor has been associated with previous polio vaccination, which discredits claims that simian virus 40 that contaminated older polio vaccine preparations caused brain tumors. The exception to this is primary CNS lymphoma, which has been shown to be associated with Epstein-Barr virus. An increase in incidence of primary CNS lymphoma is most likely due to the increasing numbers of immunosuppressed patients in the setting of human immunodeficiency virus and posttransplant use of immunosuppressants.
The association between human cytomegalovirus (HCMV) infection and glioblastoma was first described by Cobbs et al.\textsuperscript{18} in 2002. The presence of HCMV was also demonstrated in glioblastoma and in other gliomas.\textsuperscript{19} Further work is needed to evaluate the role of this virus.

**Hereditary Syndromes**

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder associated with intra- and extracranial Schwann cell tumors. Optic gliomas, astrocytomas, and meningiomas also occur at higher frequency in NF1. NF2 is characterized by bilateral vestibular schwannomas and meningiomas. Systemic schwannomas also occur in NF2. Subependymal giant cell astrocytoma commonly occur in children with tuberous sclerosis, an autosomal dominant disorder caused by mutation in the \textit{TSC1} and \textit{TSC2} genes. Other hereditary tumor syndromes affecting the CNS include Li-Fraumeni syndrome (germ line mutation in one p53 allele; malignant gliomas); von Hippel-Lindau syndrome (germ line mutation of the \textit{VHL} gene; hemangioblastomas), and Turcot's syndrome (germ line mutations of the adenomatous polyposis gene; medulloblastoma).\textsuperscript{20} The nevoid basal cell carcinoma syndrome (Gorlin's syndrome) is associated with medulloblastomas (and possibly meningiomas) and represents mutations in the \textit{PTCH} suppressor gene or other members of the Sonic hedgehog pathway.\textsuperscript{21,22}

Meningiomas and schwannomas are more common in females; gliomas, medulloblastomas, and most other CNS tumors are more common in males. Meningiomas are more common in African Americans and gliomas and medulloblastomas in whites. It has been suggested that there is a lower incidence of meningiomas and...
a higher incidence of gliomas and vestibular schwannomas in higher socioeconomic groups.\textsuperscript{23,24,25,26,27}

**Classification**

Primary CNS tumors are of ecto- and mesodermal origin and arise from the brain, cranial nerves, meninges, pituitary, pineal, and vascular elements. The WHO classification lists approximately 100 subtypes of CNS malignancies in seven broad categories (Table 121.1).\textsuperscript{3,28,29} A listing of tumors of glial origin is summarized in Table 121.2. In spite of the low proliferation rate within the meninges, meningiomas are among the most common CNS tumors. Astrocytes are among the most mitogenically competent cells, and astrocytomas, also referred to interchangeably as gliomas, are among the more common primary CNS tumor. The precise cell of origin of gliomas, however, remains unclear.

The WHO classification can be reduced to a simpler working formulation, categorizing the neoplasms into tumors presumably derived from glia, neurons, or from cells that surround the CNS or form specialized anatomic structures. Glial cells are believed to give rise to astrocytomas, oligodendrogliomas, and ependymomas. Neuronal cells are involved in the development of medulloblastoma and primitive neuroectodermal tumors (PNETs). In PNETs, anatomic location is pivotal; transformation of cortical neuroblasts leads to cortical PNETs; retinal neuroblasts form retinoblastoma; and pineal neuroblasts form pineoblastomas. Specialized anatomic structures within the CNS give rise to pituitary adenomas, pineocytomas, chordomas, hemangioblastomas, germ cell tumors, and choroid plexus papillomas and carcinomas.

This working formulation is speculative, based on scanty phenotypical and immunohistochemical evidence. For example, oligodendrogliomas are diagnosed based on cellular morphology, including prominent nuclei surrounded by a cytoplasmic halo with a characteristic “fried egg” appearance, and many have codeletions of 1p and 19q. However, no definitive markers for oligodendrogliomas currently exist; these tumors can stain both for glial fibrillary acidic protein, an astrocytic marker, and for synaptophysin, a presumptive neuronal marker.\textsuperscript{30} A third of all gliomas have morphologic characteristics of both astrocytoma and oligodendroglioma, leading some to separate gliomas based on their molecular and genetic characteristics.\textsuperscript{31} Evidence that suggests that some oligodendrocytes derive from a neuronal lineage, whereas some neuron-derived tumors (embryonal tumors) can show significant areas of glial differentiation, highlights the uncertainly.\textsuperscript{32,33}

An alternative hypothesis is that all neuroepithelial cells are derived from a common precursor cell (i.e., a multipotent neural stem cell), and hence all neuroepithelial tumors are derived from neural stem cells or their committed progeny.\textsuperscript{34} The recent discovery, isolation, and characterization of cancer stem cells from human brain tumors provides supportive evidence.\textsuperscript{35}

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### Table 121.1 Classification of Tumors of the Central Nervous System: Selected from the 2007 World Health Organization Classification

1. Neuroepithelial tumors
   - Astrocytic tumors
     a. Pilocytic Astrocytoma
     b. Subependymal giant cell astrocytoma
     c. Pleomorphic xanthroastrocytoma
     d. Diffuse astrocytoma
       a. Fibrillary astrocytoma

b. Gemistocytic astrocytoma
  c. Pro-oplasmic astrocytoma
e. Anaplastic astrocytoma
f. Glioblastoma
  a. Giant cell glioblastoma
  b. Gliosarcoma
g. Glionatosis cerebri
Oligodendroglial tumors
  a. Oligodendroglioma
  b. Anaplastic oligodendroglioma
Ependymal tumors
  a. Subependymoma
  b. Myxopapillary ependymoma
c. Ependymoma
d. Anaplastic ependymoma
Choroid plexus tumors
  a. Choroid plexus papilloma
  b. Atypical choroid plexus papilloma
c. Choroid plexus carcinoma
Other neuroepithelial tumors
  a. Astroblastoma
  b. Chordoid glioma of the third ventricle
c. Angiocentric glioma
Neuronal and mixed neuronal-glial tumors
  a. Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
  b. Desmoplastic infantile astrocytoma/ganglioglioma
c. Dysembryoplastic neuroepithelial tumor
d. Gangliocytoma
e. Ganglioglioma
f. Anaplastic ganglioglioma
g. Central neurocytoma
h. Extraventricular neurocytoma
i. Cerebellar liponeurosytoma
j. Papillary glioneuronal tumor
k. Rosette-forming glioneuronal tumor of the fourth ventricle
l. Paraganglioma
Tumors of the pineal region
  a. Pineocytoma
  b. Pineoblastoma
Embryonal tumors
  a. Medulloblastoma
  b. Primitive neuroectodermal tumors
c. Atypical teratoid/rhabdoid tumor
2. Tumors of cranial/spinal nerves
  a. Schwannoma (neurilemmoma, neurinoma)
  b. Neurofibroma
c. Perineurinoma
d. Malignant peripheral nerve sheath tumor
3. Tumors of the meninges
  A. Tumors of meningothelial cells
4. Meningioma
5. Fibrous
6. Psammomatous
7. Clear cell
8. Atypical
9. Anaplastic (malignant)

B. Mesenchymal tumors
9. Lipoma
10. Solitary fibrous tumor
11. Rhabdomyosarcoma
12. Malignant fibrous histiocytoma
13. Chondrosarcoma
14. Osteoma
15. Hemangioma
16. Hemangiopericytoma
17. Kaposi sarcoma

4. Lymphomas and Hematopoietic neoplasms
9. Malignant lymphomas
10. Plasmacytoma

5. Germ cell tumors
9. Germinoma
10. Yolk-sac tumor
11. Choriocarcinoma
12. Teratoma
13. Mixed-germ cell tumors

6. Sellar tumors
9. Pituitary adenoma
10. Craniopharyngioma

7. Metastatic tumors

Approximately 15% of all primary CNS tumors arise in the spinal cord, where the distribution of tumor types is significantly different from that in the brain (Table 121.3). Tumors of the lining of the spinal cord and nerve roots predominate (50% to 80% of all spinal tumors); schwannomas and meningiomas are most common, followed by ependymomas. Primary gliomas of the spinal cord are uncommon.4,5

Anatomic Location and Clinical Considerations

Intracranial Tumors

Intracranial tumors produce four categories of symptoms: those arising from increased intracranial pressure (ICP), physiologic deficits specific to location, higher order neurocognitive deficits, and endocrinologic dysfunction. Headache arises from irritation of the dura or intracranial vessels or due to elevated ICP from tumor bulk, edema, or obstruction of a cerebrospinal fluid (CSF) pathway. Slow-growing tumors may grow remarkably large without producing headache, whereas rapidly growing tumors can cause headache early in their course. Small tumors can cause headache by growing in an enclosed space that is richly innervated with pain fibers, such as the cavernous sinus, or by causing obstructive hydrocephalus. Nausea and vomiting, gait and balance alterations, personality changes, and slowing of psychomotor function or even...
somnolence may be present with increased ICP. Because ICP increases with recumbency and hypoventilation during sleep, early-morning headaches that awaken the patient are typical. Sometimes the only presenting symptoms are changes in personality, mood, or mental capacity or slowing of psychomotor activity. Such changes may be confused with depression, especially in older patients. Although fewer than 6% of first seizures result from brain tumors, almost one-half of patients with supratentorial brain tumors present with seizures. An adult with a first seizure that occurs without an obvious precipitating event should undergo magnetic resonance imaging (MRI).

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**Table 121.2 the Variety of Central Nervous System Glial Tumors (Based on 2007 World Health Organization Classification)**

- **Astrocytic Tumors:**
  - Pilocytic astrocytoma
  - Pilomyxoid astrocytoma
  - Subependymal giant cell astrocytoma
  - Pleomorphic xanthoastrocytoma
  - Fibrillary astrocytoma
  - Gemistocytic astrocytoma
  - Protoplasmic astrocytoma
  - Glioblastoma
  - Giant cell glioblastoma
  - Gliosarcoma
  - Gliomatosis cerebri
- **Oligodendroglial Tumors:**
  - Oligodendroglioma
  - Anaplastic oligodendrogloma
- **Oligoastrocytic Tumors:**
  - Oligoastrocytoma
  - Anaplastic oligoastrocytoma
- **Ependymal Tumors:**
  - Subependymoma
  - Myxopapillary ependymoma
  - Ependymoma
  - Anaplastic ependymoma
- **Choroid Plexus Tumors:**
  - Choroid plexus papilloma
  - Choroid plexus carcinoma
- **Other Neuroepithelial Tumors:**
  - Astroblastoma
  - Anaplastic astroblastoma
  - Chordoid glioma of the third ventricle

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**Table 121.3 Primary Spinal Tumors**
<table>
<thead>
<tr>
<th>Histology</th>
<th>Sloof et al. (5)</th>
<th>Preston-Martin(4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwannoma</td>
<td>29.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Meningioma</td>
<td>25.5</td>
<td>42.0</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>12.8</td>
<td>15.1</td>
</tr>
<tr>
<td>Sarcomas</td>
<td>11.9</td>
<td>—</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>6.5</td>
<td>11.2</td>
</tr>
<tr>
<td>Other gliomas</td>
<td>—</td>
<td>1.9</td>
</tr>
<tr>
<td>Vascular tumors</td>
<td>6.2</td>
<td>—</td>
</tr>
<tr>
<td>Chordomas</td>
<td>4.0</td>
<td>—</td>
</tr>
<tr>
<td>Epidermoids</td>
<td>1.4</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>2.7</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*a These two references provide data regarding tumor type.

Tumors are sometimes associated with location-specific symptoms. Frontal tumors cause changes in personality, loss of initiative, and abulia (loss of ability to make independent decisions). Posterior frontal tumors can produce contralateral weakness by affecting the motor cortex and expressive aphasia if they involve the dominant (usually left) frontal lobe. Bifrontal disease, seen with “butterfly” gliomas and lymphomas, may cause memory impairment, labile mood, and urinary incontinence.

Temporal tumors might cause symptoms detectable only on careful testing of perception and spatial judgment, but can also impair memory. Homonymous superior quadrantanopsia, auditory hallucinations, and abnormal behavior can occur with tumors in either temporal lobe. Nondominant temporal tumors can cause minor perceptual problems and spatial disorientation. Dominant temporal lobe tumors can present with dysnomia, impaired perception of verbal commands, and ultimately fluent (Wernicke's-like) aphasia. Seizures are more common from tumors in this location.

Parietal tumors affect sensory and perceptual functions. Sensory disorders range from mild sensory extinction or stereognosis, observable only by testing, to a more severe sensory loss such as hemianesthesia. Poor proprioception in the affected limb is common and is sometimes associated with gait instability. Homonymous inferior quadrantanopsia, incongruent hemianopsia, or visual inattention may
occur. Nondominant parietal tumors may cause contralateral neglect and, in severe cases, anosognosia and apraxia. Dominant parietal tumors lead to alexia, dysgraphia, and certain types of apraxia. Occipital tumors can produce contralateral homonymous hemianopsia or complex visual aberrations, affecting perception of color, size, or location. Bilateral occipital tumors can produce cortical blindness.

Classic corpus callosum disconnection syndromes are rare in brain tumor patients, even though infiltrative gliomas often cross the corpus callosum in the region of the genu or the splenium. Interruption of the anterior corpus callosum can cause a failure of the left hand to carry out spoken commands. Lesions in the posterior corpus callosum interrupt visual fibers that connect the right occipital lobe to the left angular gyrus, causing an inability to read or name colors.

Thalamic tumors can cause local effects and also obstructive hydrocephalus. Headaches from hydrocephalus or trapping of one lateral ventricular horn are common. Either sensory or motor syndromes or, on the dominant side, aphasia is possible. “Thalamic” pain disorders or motor syndromes from basal ganglia involvement may also occur.

The brainstem, composed of the midbrain, pons, and medulla, has both nuclear groups and traversing axons. The most common brainstem tumor is the pontine glioma, which presents most frequently with cranial nerve VI and VII palsies. Long tract signs usually follow, with hemiplegia, unilateral limb ataxia, gait ataxia, paraplegia, hemisensory syndromes, gaze disorders, and occasionally hiccups.

The midbrain, juxtaposed between the pons and the cerebral hemispheres, encompasses the tectum, the cerebral peduncles, and the cerebral aqueduct. Tectal involvement causes Parinaud syndrome, peduncular lesions cause contralateral motor impairment, and obstruction of the aqueduct causes hydrocephalus.

Tumors in the medulla can have a fulminant course, including dysphagia, dysarthria, and deficits in cranial nerves IX, X, and XII. Involvement of the medullary cardiac and respiratory centers can result in a rapidly fatal course. Fourth ventricular tumors, because of their location, cause symptomatic obstructive hydrocephalus at a relatively small size, with associated disturbances of gait and balance. Rapidly enlarging lesions may end in cerebellar herniation.

Cerebellar tumors have variable localizing presentations. Midline lesions in and around the vermis cause truncal and gait ataxia, whereas more lateral hemispheric lesions lead to unilateral appendicular ataxia, usually worst in the arm. Abnormal head position, with the head tilting back and away from the side of the tumor, is seen often in children but rarely in adults. Bilateral sixth cranial nerve palsies are uncommon and reflect hydrocephalus.

Mass lesions within or abutting the brain or spinal cord can cause displacement of vital neurologic structures. This can lead, in the brain, to herniation syndromes with respiratory arrest and death and, in the spine, to paraplegia or quadriplegia. Subfalcine herniation, usually from a unilateral frontal tumor, is often asymptomatic. In transtentorial (temporal lobe) herniation, the medial temporal lobe shifts into the tentorial notch, compressing cranial nerve III and the ipsilateral cerebral peduncle, resulting in pupillary dilation and lack of response to light. Coma usually follows. In tonsillar herniation, increasing posterior fossa mass effect displaces one or both cerebellar tonsils into the foramen magnum, causing posturing, coma, and respiratory arrest. Both tonsillar and transtentorial herniation are rapidly fatal without prompt intervention.

Hemorrhage into a tumor can also cause acute neurologic deterioration. This is often associated with iatrogenic coagulopathies such as thrombocytopenia due to chemotherapy or anticoagulation therapy for deep venous thrombosis. Primary tumors that most often bleed de novo are glioblastoma and oligodendrogliomas; of the metastatic tumors, lung cancer, melanoma, renal cell cancer, thyroid cancer, and choriocarcinoma most often show hemorrhage.
Lumbar puncture should not be performed in any of the acute herniation syndromes or when herniation is imminent. In fact, lumbar puncture should be avoided in the setting of significantly elevated ICP associated with a brain tumor.

**Spinal Axis Tumors**

For the clinical presentation of tumors of the spinal axis to be understood, the local anatomy must be appreciated (Fig. 121.2). Intracranially, the dura is adherent to the skull, and there is normally no extradural space. In the spinal canal, the extradural space contains fat and blood vessels. Through the intervertebral foramina, the extradural space communicates with the mediastinum and the retroperitoneum. Nearly all extradural tumors are metastases or locally invasive non-CNS neoplasms (e.g., carcinomas, sarcomas), with direct extension from adjacent vertebral bodies or through the foramina.

<table>
<thead>
<tr>
<th>Location</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Foramen magnum</td>
<td>11th and 12th cranial nerve palsies; ipsilateral arm weakness early; cerebellar ataxia; neck pain</td>
</tr>
<tr>
<td>Cervical</td>
<td>Ipsilateral arm weakness with leg and opposite arm in time; wasting and fibrillation of ipsilateral neck, shoulder girdle, and arm; decreased pain and temperature sensation in upper cervical regions early; pain in cervical distribution</td>
</tr>
<tr>
<td>Thoracic</td>
<td>Weakness of abdominal muscles; sparing of arms; unilateral root pains; sensory level with ipsilateral changes early and bilateral with time</td>
</tr>
<tr>
<td>Lumbosacral</td>
<td>Root pain in groin region or sciatic distribution, or both; weakened proximal pelvic muscles; impotence; bladder paralysis; decreased knee jerk, and brisk ankle jerks</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>Unilateral pain in back and leg becoming bilateral when the tumor is quite large; bladder and bowel paralysis</td>
</tr>
</tbody>
</table>
Intradural spinal tumors arise from the spinal cord (intramedullary) or from surrounding structures (extramedullary). The two common extramedullary intradural tumors, schwannoma and meningioma, arise from nerve roots and from the dura, respectively. A spinal tumor can produce local (focal) and distal (remote) symptoms, or both. Local effects indicate the tumor's location along the spinal axis, and distal effects reflect involvement of motor and sensory long tracts within the cord. Table 121.4 summarizes the clinical findings useful in localizing a spinal cord tumor.

Distal symptoms and signs are confined to structures innervated below the level of the tumor. Neurologic manifestations often begin unilaterally, with weakness and spasticity, if the tumor lies above the conus medullaris, or weakness and flaccidity if the tumor is at or below the conus. Impairment of sphincter and sexual function occurs later unless the tumor is in the conus. The upper level of impaired long-tract function usually is several segments below the tumor's actual site. Local manifestations may reflect involvement of bone (with axial pain) or spinal roots, with radicular pain and loss of motor and sensory functions of the root or roots.

Figure 121.2 Cross-section of thoracic spinal cord shows relation of spinal nerves to intraspinal tracts.
Neurodiagnostic Tests

**Magnetic Resonance Imaging**

The imaging modality of choice for most CNS tumors is MRI, which can demonstrate anatomy and pathologic processes in detail. Computed tomography (CT) is generally reserved for those unable (implanted pacemaker, metal fragment, paramagnetic surgical clips) or unwilling (because of claustrophobia) to undergo MRI. Because of the link of nephrogenic systemic fibrosis to the infusion of gadolinium-based contrast agents, there are new preventative guidelines regarding the administration of gadolinium in patients who may be at high risk.

The most useful imaging studies are T1-weighted sagittal images, gadolinium (Gd)-enhanced and unenhanced T1 axial images, and T2-weighted axial images (Fig. 121.3). Contrast-enhanced MRI provides an improved ability to discern tumors from other pathologic entities, one tumor type from another, and putatively higher- from lower-grade malignancies. There are, however, limitations in anatomic MRI to definitively diagnose a mass lesion as a tumor. Other confounding diagnoses include bacterial abscess, tumor refractive demyelination, and acute ischemic disease. It is conventionally believed that most low-grade gliomas (except pilocytic astrocytomas and pleomorphic xanthoastrocytoma) do not enhance, but in reviewing imaging studies of patients enrolled in several clinical trials, it is apparent that this may not be so categorical, in that even low-grade gliomas may frequently contain areas of enhancement, raising the concern that these areas might represent high-grade or malignant transformation (Fig. 121.4).

**Neuraxis or Spinal Imaging**

In the evaluation of spinal cord tumors, MRI is also the preferred modality, providing superb visualization of the spinal cord contour and (with gadolinium contrast) of most intrinsic tumors (such as ependymomas, astrocytomas, meningiomas, and schwannomas), as well as facilitating the diagnosis of leptomeningeal dissemination. Tumor cysts are readily identified on MRI, and spinal cord tumors can often be distinguished from syringomyelia. Ideally, neuraxis imaging should be performed before surgery. In the immediate
postoperative period, spinal MRI scans may be difficult to interpret because arachnoiditis and blood products can mimic leptomeningeal metastasis. Delayed spinal MRI (more than 3 weeks after surgery) combined with an increased dose of gadolinium is a sensitive imaging study for leptomeningeal disease.

**Newer Imaging Modalities**

Newer MRI techniques include magnetic resonance spectroscopy, dynamic contrast-enhanced MRI, diffusion-perfusion MRI, and functional MRI. In addition, metabolic imaging using positron emission tomography using various tracers is being explored.\(^{38,39}\) These newer techniques remain to be validated as biomarkers of biological behavior or clinical outcome. Posttreatment metabolic scans may help distinguish recurrence from treatment-related changes, although most modalities have a relatively high false-negative rate. A modification of the standard MRI is quick brain MRI, which uses single-shot fast-spin echo imaging to allow adequate demonstration of ventricular anatomy and appropriate evaluation of shunt function.\(^{40}\)

**Pseudoresponse and Pseudoprogression**

In malignant gliomas treated with combined modality therapy, it is speculated that 25% to 40% or even more may experience imaging changes relatively early in the course of therapy, usually within a few months, which appears consistent with radiographic progression. However, with time, and without any therapy, many of these changes actually improve or even resolve, and in patients operated on with a presumptive diagnosis of tumor, the histopathology often reveals large areas of tumor necrosis.\(^{41,42}\) With the advent of antiangiogenic therapies for malignant glioma, rapid resolution of tumor enhancement is visualized on MRI, sometimes, within days. This is consistent with the traditional definition of response, but in several instances, especially with time, even in the absence of contrast enhancement, tumor progression and clinical deterioration occurs, which is sometimes appreciated as T2 or fluid-attenuated inversion recovery (FLAIR) changes; this phenomenon is labeled as *pseudoresponse*.\(^{42}\)

**Figure 121.4** A: Low-grade astrocytomas often do not enhance and contrast-enhanced T1-weighted magnetic resonance sequences considerably underestimate the true infiltrative extent of these
neoplasms. B: The fluid-attenuated inversion recovery (FLAIR) sequence is considerably more useful in appreciating the true extent of such neoplasms.

**Cerebrospinal Fluid Examination**

Typically, medulloblastoma, ependymoma, choroid plexus carcinoma, lymphoma, and some embryonal pineal and suprasellar region tumors have a high enough likelihood of spreading to justify CSF examinations to look for malignant cells (cytology) and specific markers, such as human chorionic gonadotropin-β and α-fetoprotein.

CSF spread of tumor may be associated with several possible findings, including CSF pressure above 150 mm H₂O at the lumbar level in a laterally positioned patient, elevated protein, typically greater than 40 mg/dL, reduced glucose (below 50 mg/mL), and tumor cells by cytologic examination. A high protein concentration with normal glucose levels and normal cytology is also seen with base of skull tumors, such as vestibular schwannoma, and with spinal cord tumors that obstruct the subarachnoid space and produce stasis of the CSF in the caudal lumbar sac. Sampling of the CSF in the immediate postoperative period may lead to false-positive results, however, and is best done before surgery or more than 3 weeks after surgery, as long as there is no uncontrolled raised intracranial pressure.

**Surgery**

**Preoperative Considerations**

The major objectives of surgery are to maximally remove bulk tumor, reduce tumor-associated mass effect and elevated ICP, and provide tissue for pathologic analysis in a manner that minimizes risk to neurological functioning. For some tumors complete resection can be curative. However, most brain tumors are diffusely infiltrative; for these, surgical cure is rarely possible. Surgery can rapidly reduce tumor bulk with potential benefits in terms of mass effect, edema, and hydrocephalus. The requirement for histopathologic confirmation of diagnosis is not necessary in certain well-defined situations, but a tissue diagnosis is still required to determine the appropriate treatment course in most circumstances. As molecularly targeted therapies become useful, tissue removal for molecular analysis will become more necessary to guide therapy. Pseudoprogression may make tissue-based confirmation necessary before changes in therapy are instituted.  

Technologic advances in surgical approaches, techniques, and instrumentation have rendered most tumors amenable to resection; however, for some tumor types or locations, the risk of open operation supports the choice of biopsy for obtaining diagnostic tissue. Biopsy techniques include stereotactic biopsy (with or without a stereotactic frame) using CT, MRI, or both, to choose the target. Metabolic or spectroscopic imaging can be coregistered with anatomic images to choose targets that may be of higher biologic aggressiveness within a tumor that appears homogeneous on standard imaging. In certain settings, an approach using simple ultrasonic guidance can also be considered for obtaining diagnostic tissue.

Unless lymphoma is being considered, patients are given corticosteroids, usually dexamethasone, immediately preoperatively and often for several days before surgery to reduce cerebral edema and thus minimize secondary brain injury from cerebral retraction. Steroid administration is then continued in the immediate postoperative period and tapered off as quickly as possible. Antibiotics are given just before making the incision to decrease the risk of wound infection.

**Anesthesia and Positioning**

The routine use of prophylactic anticonvulsants in the perioperative period is less commonly...
recommended, although practice patterns seem to indicate their widespread use.\textsuperscript{44,45} Patients with a history of seizures need to have their anticonvulsants maintained at therapeutic dose levels. Under certain circumstances, such as for awake craniotomies with electrocorticography, the use of anticonvulsants for a short time might be warranted.

Either general endotracheal anesthesia or local anesthesia with sedation can be used for craniotomies. Specific techniques to reduce patient discomfort during surgery are required when local anesthesia is used. Most craniotomies today are performed under general anesthesia. Inhalational agents, such as isoflurane, may be used, but total intravenous anesthesia, with agents such as propofol and dexmedetomidine, is becoming a more widespread practice as there may be a lower risk of producing fluctuations in cardiac function and ICP.

Ordinarily, cranial fixation is used to minimize patient movement during surgery, although rigid fixation may be less desirable during awake procedures. Steps are taken during the procedure to minimize ICP. The patient’s head is placed slightly above the level of the heart to increase venous drainage, and jugular vein compression is avoided. Mild hyperventilation is used. These measures, along with the use of image-guided minimal access craniotomies, are generally sufficient to avoid the routine use of mannitol and furosemide. However, should ICP remain elevated, mannitol (between 0.25 and 1.0 g/kg of body weight) can be administered and may be followed by furosemide to potentiate its action.

**General Surgical Principles**

In the past, localization of the surgical incision and craniotomy were most often performed by a surgeon’s understanding of cranial anatomy and interpretation of preoperative imaging. More recently, image-guided navigation systems have been employed to more effectively localize tumor margins, as they project to the cranial surface and thus allow for smaller, precisely positioned craniotomies.\textsuperscript{46,47} Once the dura has been opened, the tumor should once again be localized and most tumors are approached through an incision in the crest of an overlying gyrus or through a sulcus. The selection of the cortical entry site is aided by cortical mapping when appropriate, intraoperative ultrasonographic images, and the frameless image-guided stereotactic system, or with intraoperative MRI. If the tumor presents to the surface, its surface margins should be identified and dissection should begin at the margins. If the tumor does not present on the surface, often a fissure or sulcus may be split to gain access to it, reducing the distance through which the brain must be dissected. If this is not possible or desirable, the pia-arachnoid may be coagulated and incised and a transcortical route taken to the tumor. The operating microscope may be used for the approach through the subcortical white matter to the tumor, although use of surgical loupe magnifiers is commonly used for tumors that do not involve vascular structures or are not adjacent to the brainstem. The glistening peritumoral white matter is seen easily through the microscope as each of the tumor’s margins is reached, and at this interface the resection is stopped. Hemostasis is sometimes difficult to achieve but must be perfect. Hemispheric tumor cysts can be drained and, when possible, fenestrated into an adjacent ventricle to prevent reaccumulation. For tumors not resectable because of their location or diffuseness, biopsy can be performed stereotactically using frameless or frame-based technique. Tumors that are limited to the cortical surface may be best sampled with an open biopsy, under direct vision, due to the risk of inadvertent injury to a cortical vessel with a more limited, needle-based approach.

Specialized technology can be used to help define the completeness of resection. Image-guided navigation systems are almost always employed, but the guidance may lose accuracy over the course of an operation due to brain shift or cyst decompression. Intraoperative imaging with ultrasound, CT, or MRI may be used to determine the extent of residual tumor and to further localize areas where additional tumor may be removed safely.\textsuperscript{48} There has been growing use of 5-aminolevulinic acid (5-ALA), a prodrug which is converted by glioma cells into fluorescent porphyrins that can be visualized with an operating microscope.
equipped with a fluorescent imaging package. The impact of the use of 5-ALA to guide resection of glioblastoma multiforme (GBM) on completeness of surgical resection and progression-free survival has been demonstrated in a phase 3 trial.\textsuperscript{49} Its use is limited to tumors that enhance with contrast on MRI (or CT), as low-grade tumors do not appear to convert the prodrug to a fluorescent porphyrin that can be visualized intraoperatively.

Intraoperative cortical-stimulation mapping facilitates resection of tumors in or adjacent to functionally critical areas. Motor functions can be mapped even under general anesthesia; however, anesthetic agents may increase the threshold to response and hence decrease the sensitivity of mapping. Sensory and speech-associated cortex are typically mapped during an awake craniotomy. Often preoperative mapping of functional areas and their connections with MRI-based techniques are used to delineate both cortical areas and important subcortical white matter tracts that subserve speech and motor function.\textsuperscript{50}

Reresection of recurrent cerebral astrocytomas can be modestly efficacious.\textsuperscript{51} When the initial tumor was low grade, histologic resampling may be necessary to guide further treatment at recurrence. Reoperation offers a chance to implant polymer wafers containing carmustine (BCNU) or to administer experimental agents, such as gene therapy agents or immunotoxins. Smaller volume of disease at initiation of chemotherapy predicts longer survival, thus, reoperation may improve the efficacy of adjuvant treatment as well as relieve mass effect in some patients.\textsuperscript{52} An increasingly important aspect of resection is the need for tumor sampling to allow molecular marker analysis, which might provide and aid in assessing of prognosis as well as probability of benefit from both chemotherapeutic and targeted therapies.

**Craniotomy for Supratentorial Tumors**

The bony opening is designed to be generous enough to facilitate surgery but small enough to avoid possible injury to the surrounding normal brain, particularly if the brain is under pressure, and there is risk of intraoperative herniation into the cranial opening. A frameless stereotactic neuronavigation system is commonly used to design the craniotomy flap, to localize subcortical tumors, and to estimate progress during tumor resection. For this, a preoperative MRI or CT is done with fiducials on the scalp, which are used along with a reference array to register the patient's head and thereby map the images onto the operative area as localized by a handheld probe. The craniotomy is centered over the tumor or positioned to give access to the route of approach. The scalp flap is designed to surround the bone flap fully; the scalp's vascular supply is given careful consideration in the design. After the scalp incision is made and periosteum cleared, burr holes are drilled and connected with an air-powered saw or craniotome. The bone flap can then be removed. The dura is opened and reflected, and the approach to the tumor is made. A peripherally located lesion may be immediately seen. However, when the lesion is subcortical, the exposed field may appear normal. If critical functional cortex is in the field, motor and speech can be mapped intraoperatively using electrical cortical stimulation or somatosensory evoked potential techniques.\textsuperscript{53} A preoperative functional MRI scan or magnetoencephalography can serve as a guide. Motor mapping can be done under general anesthesia if muscle relaxants are avoided; however, many anesthetic agents can raise the threshold to electrical response and some surgeons favor awake mapping or monitoring of function. Glioma resections in the dominant hemisphere are often done under local anesthesia to allow speech mapping.

Localization of subcortical tumors can often be accomplished using intraoperative ultrasonography, as well as with frameless image-guided neuronavigation systems.\textsuperscript{54} Because preoperative images are used, brain shift that occurs during the operation can cause discrepancy. Intraoperative imaging with ultrasonography, CT, and MRI can now be used to provide an immediate estimate of the progress of the resection and can be used to update the navigation system. Although neuronavigation systems do increase
the degree of resection achieved, the impact on patient outcome has not yet been clarified. For contrast-enhancing tumors, there is growing use of 5-ALA and a suitably equipped fluorescent operating microscope. When technically possible, it is preferable to perform a circumferential dissection of the tumor.

Patients are monitored in the specialized care unit overnight after surgery, and an MRI is done within 24 to 48 hours to evaluate the extent of any remaining tumor.

**Craniotomy for Posterior Fossa Tumors**

Patients may be positioned prone, three-quarters prone, or lateral, depending on lesion location, surgeon preference, and patient body habitus. A linear incision is used for a midline approach, and a paramedian or retromastoid linear incision is used for more laterally located lesions. Bony removal is often performed with a high speed drill, rather than as a bone flap. With larger and more caudal lesions, it is common to open the foramen magnum and even to remove the arch of C1 to allow room for postoperative brain swelling, which otherwise can cause tonsillar herniation through the foramen magnum. A low exposure allows drainage of CSF from the cisterna magna to relax the brain. After resection, the dura is tightly closed. A dural patch is often used, but some dural substitutes may suffice. Some surgeons also replace a craniectomy defect with a methylmethacrylate cranioplasty or with titanium mesh.

**Stereotactic Tumor Biopsy**

For deeply situated intrinsic tumors, multicentric tumors, or diffuse nonfocal tumors, resection is not practical and stereotactic needle biopsy is used for diagnosis. Open, stereotactically guided biopsy is reserved for unusual situations, such as a lesion abutting a large blood vessel or one that is restricted to the cortical surface.

Many image-guided stereotactic systems are available and frame-based or frameless techniques may be used. Typically, the patient undergoes a CT or an MRI with either a rigid array of fiducial bars fixed tightly to the skull to minimize movement or skull-implanted or scalp-applied surface fiducials in the case of frameless stereotaxy. For cooperative adults, local anesthesia may be used; for children, general anesthesia is usually required. The images are loaded into a navigation system that can be used preoperatively to plan an entry point and target combination, which will provide a safe trajectory with the opportunity to sample multiple parts of a lesion along a single path. After the entry point is localized, a scalp incision is made and either a burr hole or a stereotactically guided twist drill craniostomy is made. The dura is perforated and the stereotactic biopsy needle is advanced to the target. A small tissue core is obtained from the target using a side-biting needle. Hemorrhage at the biopsy site, the principal risk of the surgery, occurs in few patients and a CT may be performed to evaluate for the presence of blood. Occasionally, cerebral edema is exacerbated by biopsy.

**Radiation Therapy**

**General Concepts**

Radiation therapy plays an integral role in the treatment of most malignant and many benign primary CNS tumors. It is often employed postoperatively as adjuvant treatment to decrease local failure, to delay recurrence, and to prolong survival in gliomas, as definitive treatment in more radiosensitive diseases such as PNET and germ cell tumors, or as therapy to halt further tumor growth in schwannomas, meningiomas, pituitary tumors, and craniopharyngiomas, and as ablative therapy to abrogate hormonal overproduction in secretory pituitary adenomas. Radiation therapy is also the primary modality in palliating brain metastases.
Radiobiologic and Toxicity Considerations

Most neoplasms can potentially be cured if the correct radiation dose can be delivered to the entire tumor and its microscopic extensions. This is not always feasible as the maximum radiation dose deliverable is limited by the tolerance of the surrounding normal tissues, and the identification of regions of microscopic extension remains vague. Radiation tolerance of the CNS depends on several factors, including total dose, fraction size, volume irradiated, underlying comorbidities (particularly hypertension and diabetes), and innate sensitivity. Adverse reactions to cranial irradiation differ in pathogenesis and temporal presentation and are not discussed here.

A major radiobiologic consideration revolves around the selection of total dose and the fractionation schedule. Late or long-term toxicities are generally a function of fraction size, and therefore, as the fraction size is increased, such as with radiosurgery, higher late toxicity rates must be anticipated. These late toxicities from larger fraction sizes can be minimized by sharply targeting the dose, which can drastically reduce dose to normal tissues, and by minimizing the volume irradiated, which explains the limited size of tumors treated with radiosurgery. In conventional radiotherapy, fraction sizes of 2 Gy are routinely utilized and may be lowered to 1.8 Gy per fraction in proximity to the visual apparatus or may be increased to 3 Gy per fraction in patients in whom shorter palliative schedules, with lesser concern regarding long-term morbidities, exist. For radiosurgery, doses in the order of 12 to 21 Gy in single fractions are often utilized. In general, the entire target is treated with a relatively uniform dose, but with the advent of newer delivery methods, it is possible to create dose gradients or dose inhomogeneities within the tumor to match the differential radiosensitivity, but this concept of dose painting remains investigational.

Treatment Planning and Delivery Methods

High-resolution MR fusion with CT planning images has allowed more precise delineation of targets, although a significant margin, particularly with gliomas, is still necessary to cover microscopic extension. Patient immobilization devices limit intrafraction motion and provide precision in positioning, decreasing the margin required for setup variability. Image-guided radiotherapy (IGRT), using biplanar orthogonal x-ray imaging systems, cone beam CT, or megavoltage CT, further improves setup reproducibility and allows decreased margins. For the cranium, IGRT localization approaches utilize either external fiducials, such as those mounted on a bite-block system, with in-room monitoring cameras, or imaging, which principally relies on comparing baseline bony anatomy to the anatomy visualized on the images obtained for each treatment fraction. IGRT therefore offers the opportunity to precisely and accurately set the patient up with millimeteric precision (less than 1 to 3 mm) prior to daily treatment, and several systems also allow for continuous monitoring while the patient is being treated. Newer systems in development incorporate MRI on-board.

The primary benefit of incorporating IGRT into treatment delivery is that by improving daily patient setup, it allows a decrease in the margin of delivery error, effectively reducing the total volume irradiated. IGRT can be incorporated with any radiotherapy method, such as fractionated external-beam radiotherapy and stereotactic radiosurgery (SRS), and is practically mandatory for charged-particle therapy, frameless radiosurgery, fractionated stereotactic radiotherapy (FSRT), and intensity-modulated radiotherapy (IMRT). CT-based three-dimensional conformal radiation (3DCRT) in which noncoplanar fields with unique entrance and exit pathways can be mapped on the target has improved normal tissue sparing. This allows avoidance of critical structures, such as the brainstem, optic apparatus, and spinal cord. In IMRT, the photon flux of a beam is modulated in multiple directions during treatment, aimed at mimicking the shape of the target from various viewpoints, thereby producing improved conformity and nonuniform dose distribution. IMRT is increasingly being utilized for CNS tumors, based primarily on dosimetric studies, which suggest superior
tumor coverage and reduction in the dose to critical structures (Fig. 121.5). This can be beneficial in specific instances, such as to preserve cochlear function, vision, or pituitary activity. Huang et al. were able to show a reduction in cochlear dose from 54.2 to 36.7 Gy and a reduction of grade 3 or 4 hearing loss from 64% to 13% with the use of IMRT compared to conventional radiation therapy.

Figure 121.5 Intensity-modulated radiotherapy allows dose shaping to avoid critical structures. In this treatment plan of a right frontal oligodendroglioma (orange), tight target coverage and excellent conformal avoidance of the optic chiasm (red) and pituitary (purple) are achieved, as evidenced by the dose-volume histogram (DVH).

In FSRT, the concepts of 3DCRT or IMRT are merged with the accuracy and precision in delivery that characterizes SRS, and, typically, the radiation fraction size is considerably increased, so that the total course of therapy is reduced from the typical 20 to 30 or more fractions to five or fewer fractions. Various FSRT systems have been developed, with reported precision between 1 to 3 mm. FSRT is often used for larger lesions (e.g., 4 cm or more) and for lesions located in critical regions where single fraction SRS is disadvantageous because of a higher risk of toxicity, such as larger vestibular schwannomas or meningiomas.
SRS is used to treat a diverse group of lesions. Stereotactic treatments generally reference the target lesion to a reproducible Cartesian coordinate system outside the patient, although frameless systems may utilize fiducials directly on the patient or the bony anatomy itself as a surrogate. The coordinate system is generally affixed to the patient, most commonly in the form of a head frame. Treatment can be carried out using either a modified or dedicated linear accelerator, cobalt-60 units, or charged particle devices. Several commercial devices have now been developed, each with slightly unique features, including robots that position the linear accelerator at various angles, collimation systems that provide prefixed circular collimators of various sizes, or shaped collimated beams, and even intensity modulated delivery from one or multiple directions, delivered serially, helically, or volumetrically.62 Radiosurgery plays a dominant role in the treatment of oligometastases to the brain, arteriovenous malformations, schwannomas, and meningiomas and is occasionally used to treat malignant recurrences (Fig. 121.6).

Figure 121.6 Example of radiosurgery dose distribution. This schwannoma is being treated with radiosurgery; the 12.5-Gy prescription isodose line very conformally covers the lesion.

Charged-particle beams deposit the majority of their dose at a depth dependent on the initial energy, avoiding the exit dose of photon therapy. This localized dose is known as the Bragg peak. Although pencil-scanning proton beams have narrow Bragg peaks, in order to cover larger volumes, proton beams have traditionally been modified by passive range modulators that disperse the Bragg peak and broaden the dose deposition. Charged-particle radiotherapy has been particularly utilized to treat tumors of the skull base to doses higher than can be achieved conventionally. In particular, chordomas and chondrosarcomas require high radiation doses for local control. Proton beams have also been advocated for the childhood tumors as they decrease integral radiation dose, although concern about incidental neutron production exists.63,64

Brachytherapy has a limited role in the CNS, although it has enjoyed some resurgence and is occasionally used for recurrent gliomas. A liquid colloid of organically bound $^{125}$I in a spherical balloon is one of the newer innovations.65 At least two randomized trials using seed implants have failed to demonstrate a survival advantage in malignant glioma. The injection of radioisotopes within the cystic craniopharyngiomas allows ablation of the secretory lining. A select group of patients with cystic tumors may benefit from the
direct instillation of colloidal $^{32}$P, $^{90}$Y, or $^{198}$Au. This technique will deliver between 200 to 400 Gy to the cyst wall.

Radiolabeled therapy is in the developmental phase. The most commonly used antigenic targets for CNS malignancies are the epidermal growth factor receptor (EGFR), neural cell adhesion molecule (NCAM), tenascin, placental alkaline phosphatase (PLAP), and phosphatidylinositide. Institutions using this technique have utilized murine, chimeric, or humanized monoclonal antibodies attached to $^{131}$I, $^{90}$Y, $^{188}$Re, and $^{211}$At. The evolution of the trials has seen the delivery route move from systemic (intra-arterial or intravenous) to local instillation of the agent into a surgically created resection cavity. Even though the blood-brain barrier is often disrupted by a rapidly growing CNS malignancy, 150 kDa antibodies would still not likely cross to a significant degree. Most of the trials to date are of “dose searching pilot” or phase 1 design. Using $^{131}$I-81C6 (antitenascin monoclonal antibody), a trend toward significant improvement in median survival was shown for patients receiving 40 to 48 Gy versus less than 40 Gy. Unlike brachytherapy, there appears to be a very low rate of CNS toxicity and a minimal need for surgical intervention for removal of necrotic regions.

**Chemotherapy and Targeted Agents**

Drug therapies alone are effective for only a few types of CNS tumors (i.e., primary CNS lymphoma) but are useful as adjunctive therapy for many CNS tumors. Among the reasons for the poor efficacy of chemotherapeutic and targeted agents is the low concentration of drug penetration to the tumor because of the difficulty of agents to cross the blood-brain barrier, active transport mechanisms of drug efflux, and high plasma protein binding of agents, thereby lowering the volume of distribution of agents in the brain parenchyma. Intrinsic and acquired resistance remains an important reason for the lowered efficacy of chemotherapy. Although targeted agents are in early testing, multiplicity and alternate signaling pathways limit their efficacy.

**The Blood–Brain Barrier**

Central to treating CNS tumors is the issue of drug delivery, due to the blood-brain barrier (BBB), a physiologic and functional barrier. The CNS microvasculature has several unique features, including the lack of fenestrations between adjacent endothelial cells and relatively fewer pinocytotic and endocytotic endothelial vesicles. Additionally, adjacent BBB endothelial cells are connected by a continuous extension of tight junctions, which limit passive diffusion between endothelial cells and through capillary structures. Tight junctions within the BBB are also enveloped by astrocytic foot processes, which increase the barrier to passive diffusion across the BBB. These unique tight junctions result in a high transendothelial electric resistance and diminished paracellular resistance.

Brain microvasculature selectively transports nutrients through 20 or more active or facilitated carrier transport systems expressed on the endothelial surface. The endothelium is also rich with efflux pumps, including the multidrug resistance (MDR) gene-encoded P-glycoprotein. These and other efflux pumps actively remove substrate molecules that may have passed the BBB. The hydraulic conductivity of brain capillaries, and thus the oncotic pressure driving protein influx across endothelium, is 500, 1,000, and 3,000 times less than in heart, muscle, and intestinal capillaries, respectively.

The coadministration of chemotherapeutic agents with inhibitors of efflux transporters has been performed to increase the BBB permeability of anticancer agents, but to date, the results have largely been disappointing.
The Blood-Tumor Barrier
The microvascular differences between the blood-tumor barrier (BTB) and the normal BBB range from a subtle increase in endothelial fenestrations to a dramatic breakdown of tight junctions, enlargement of the perivascular space, and swelling of the basal lamina. Different tumors display different degrees of disruption of the BTB. Most low-grade gliomas do not enhance with contrast and have BTBs that are similar to the normal BBB. In contrast, highly malignant tumors such as glioblastoma have significant disruption of most barrier functions within the avidly contrast-enhancing portion of the tumor. Even in these tumors, however, drug delivery is not normal because the tumor-induced neovasculature is often poorly perfused or not patent, and there is a relatively long distance between tumor-induced angiogenic vessels and individual tumor cells. Furthermore, even in these highly malignant and angiogenic tumors, the leading front of infiltrating tumor cells is located in normal brain parenchyma with a relatively intact BBB. Several strategies are being explored to improve delivery of anticancer drugs to brain tumors and range from disruption of the BBB to noninvasive or direct delivery of agents into the brain.

Disrupting the Blood-Brain Barrier
Physicochemical characteristics largely determine a drug's ability to cross the BBB. Smaller, ionically neutral, lipophilic drugs, with a high octanol or water coefficient, are more likely to penetrate the BBB and BTB. Unfortunately, most drugs lack these characteristics and are excluded by the barrier. This has led to the development of alternate drug administration techniques. The most widely used method for disrupting the BBB is through an intravascular osmotic load using mannitol, which results in cerebral endothelial shrinkage and disruption of endothelial tight junctions. More refined attempts to disrupt the BBB have focused on specific drugs that selectively target cerebral endothelial cellular signaling pathways, such as the bradykinin pathway, and result in transient BBB disruption. Unfortunately, clinical studies have not demonstrated convincing improvements in patient outcome.

Another strategy to enhance drug delivery to brain tumors while minimizing systemic exposure is intraarterial administration. After the first pass of the drug through the brain, it becomes diluted into the total-body blood volume. Most clinical experience suggests slightly higher response rates at the expense of significant neurotoxicity. Another drawback of selective arterial drug delivery is that tumors often obtain their vascular supply from multiple arteries. Finally, intraarterial drug delivery has been associated with significant morbidity, including strokes from arterial dissection and embolism. Thus, there is currently limited enthusiasm for this strategy, with the potential exception of primary CNS lymphomas.

Noninvasive delivery systems using specialized carriers with favorable pharmacokinetic and pharmacodynamic properties are being explored. Use of nanosystems (colloidal carriers) focus on liposomes and polymeric nanoparticles, which allow for sustained, gradual release of drug. Conventional liposomes, however, are rapidly cleared from the circulation by macrophages of the reticuloendothelial system, thereby limiting the potential for drug delivery to the brain. Modification of the liposomes through a decrease in the size or surface modification and use of monoclonal antibodies for specific tumor targeting are some mechanisms used to optimize this technology.

Intracranial or Intratumor Drug Delivery
Another strategy to circumvent the BBB is to deliver drugs directly into the brain through local administration. One way to do this is surgical placement of biodegradable synthetic polymers impregnated with a drug. The prototype for this is the Gliadel Wafer (Eisai Inc, Woodcliff Lake, New Jersey), which contains BCNU. BCNU is highly lipid-soluble and crosses the BBB readily in both directions. BCNU that diffuses out of the polymer therefore passes into the local bloodstream, where the BCNU concentration is
low. This carries the drug away from the brain, a phenomenon known as the *sink effect*. Another limitation is that drug penetrates the surrounding brain only by passive diffusion, a slow and inefficient process. High concentrations of BCNU are thus found only within a few millimeters of the wafers, which makes it unlikely that cytotoxic drug concentrations will reach distant infiltrating tumor cells. Implantations that contain other chemotherapeutic agents (e.g., paclitaxel and cisplatin) have also been evaluated.

Convection-enhanced delivery (CED) is another strategy for local drug delivery. CED requires the implantation of catheters directly into the brain, followed by continuous infusion of the drug under a constant pressure gradient. CED offers several theoretical advantages such as the ability to move very large molecules (i.e., immunoglobulins, liposomes, small virions) through the interstitial space and the ability to achieve homogeneous concentrations of the drug even at the leading edge of the infusate. This results in much larger volumes of distribution with CED. CED also theoretically offers the ability to target a specific anatomic zone of cerebral tissue for treatment while sparing other areas. The efficiency of CED depends on the physicochemical characteristics of the administered drug and the volume of distribution of the agent. Because an invasive procedure is required, multiple administrations may be impractical, and the lack of efficacy of some of the initial clinical trials may be explained by these factors. Current research focuses on optimizing convection parameters (i.e., type of agent, volume, infusion rate, pressure), technology (catheters and pumps), and finding methods to allow the imaging of the convected infusate.

Another approach is direct administration of the agent into the CSF. Because the CSF has the pharmacokinetic characteristics of a closed (albeit dynamic) compartment, drugs given directly into the CSF can reach high levels. Because this compartment is separate from systemic circulation, drugs given in this way must be in their active form. Given the high CSF drug levels that can be attained through direct administration, intra-CSF treatment can be highly effective in treating tumor cells that are in the CSF and are lining the leptomeninges. Unfortunately, there is a significant delay in equilibration between the CSF and extracellular space of the brain even for small soluble molecules given directly into the CSF. For larger, less diffusible molecules, equilibrium between the two compartments never occurs. This pharmacologic phenomenon, referred to as the *CSF-brain barrier*, explains why intra-CSF drug administration is an inefficient and ineffective delivery strategy for parenchymal tumors. Additionally, intra-CSF delivery is limited by significant neurologic morbidity. With a few exceptions (i.e., methotrexate, cytarabine, thiotepa), most compounds cause unacceptable neurologic toxicity, including death, when given into the CSF. Because of this, intrathecal chemotherapy is used principally to treat leptomeningeal metastases and for CNS prophylaxis for high-risk leukemia.

**Challenges Specific for Targeted Agents**

Despite the availability of targeted agents specific to aberrant signaling pathways in high-grade glioma, the results of phase 2 studies of many agents have been disappointing. In addition to the difficulty of delivery of agents across the BBB, there are other challenges that limit the efficacy of these agents. These include accounting for the heterogeneity of tumors, redundancy of pathway interactions, lack of accurate and reproducible biomarkers to select patients for specific therapies, and difficulty in assessing target modulation.

**Other Systemic Therapy Considerations**

Many antiepileptic agents, including phenytoin, carbamazepine, and phenobarbital, induce the hepatic cytochrome P-450 isoenzyme and glucuronidation drug elimination systems. The specific isoenzymes
induced by these drugs are often capable of metabolizing many agents. For example, standard paclitaxel
doses commonly result in subtherapeutic serum levels in patients also using phenytoin. In fact, the
maximally tolerated paclitaxel dose in patients using enzyme-inducing P-450 antiepileptics is nearly
threefold higher than in patients not using such agents. Similar observations have been made with regard
to 9-aminocamptothecin, vincristine, teniposide, irinotecan, and targeted agents. In addition to
different MTDs being established depending on the use of enzyme-inducing antiepileptics, the side effect
profile and dose-limiting toxicities can also differ. Most phase 1 clinical trials in brain tumor patients
now use separate arms for patients who are or are not taking enzyme-inducing antiepileptic drugs or limit
enrollment to patients not taking enzyme-inducing antiepileptic drugs. It may be preferable to change to a
non–enzyme-inducing antiepileptic agent (e.g., levetiracetam [Keppra]), although it may take days to make
the switch and some time for the P-450 enzyme induction to resolve.

Specific Central Nervous System Neoplasms

Cerebral Glioma

Pathologic Classification

The histological subtypes of glioma include tumors of astrocytic, oligodendroglial, ependymal, and
neuroepithelial origin. The first widely used classification system was devised by Kernohan et al. Unfortunately, there was little reproducible prognostic significance among the four grades. Recognizing
this limitation, Ringertz  established a three-tiered system that allowed for easier distinction between
low- and high-grade tumors, but the system suffered from significant intraobserver variability. A more
useful approach was suggested by Daumas-Duport et al., who reintroduced a four-tiered system based
on a set of objective criteria: nuclear pleomorphism, mitoses, endothelial proliferation, and necrosis.
Although the classification initially appeared to demonstrate good separation in survival among patients by
grade, it did not provide adequate prognostic differentiation between grades 2 and 3 in a validation
study.

To resolve these controversies, the WHO convened an international panel of neuropathologists to define a
new classification system, which has since garnered worldwide acceptance. In this revised WHO schema,
noninfiltrative glioma are classified as grade I and infiltrating glioma are subsequently categorized from
grades II to IV. Infiltrative astrocytic tumors are divided into three categories: astrocytoma (including
grade II fibrillary, gemistocytic, and protoplasmic), anaplastic astrocytoma (grade III), and glioblastoma
(including grade IV giant cell glioblastoma and gliosarcoma). Oligodendroglioma and ependymoma are either
grade II or anaplastic (grade III).

Grade I Astrocytoma

Low-grade astrocytomas (grade I) such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and
subependymal giant cell astrocytoma are typically circumscribed and indolent tumors. Complete surgical
resection, whenever feasible, is the curative mainstay therapy for such tumors. Despite aggressive near
total resection, delayed recurrence and eventual malignant transformation are unfortunately common.
However, resection of a low-grade glioma can be difficult in locations such as the optic pathway,
hypothalamus, and in those involving deep midline structures. In these instances, asymptomatic patients
can be observed carefully for a prolonged period of time and undergo a maximally safe resection only at
the time of progression.

In patients who have recurrent tumor that are not amenable to further resection or who have residual
tumor causing significant morbidity, adjuvant chemotherapy or radiotherapy can improve recurrence-free
survival, although the role of chemotherapy in adults remains controversial. Immediate postoperative adjuvant therapies may be appropriate in some cases depending on the location of the tumor, the extent of residual disease, the impracticability of repeated surgical excision, and availability for follow-up. Generally, radiotherapy is the primary adjuvant treatment used in older children and adults with low-grade glioma. In young children with unresectable progressive low-grade glioma, there is a desire to avoid or delay radiotherapy owing to the long-term radiation related sequelae; chemotherapy is often utilized here as the initial therapeutic option. Some responses from chemotherapy can last for years, and nearly half of all children treated with chemotherapy ultimately require radiotherapy for tumor progression.

In terms of radiotherapy used with curative intent, in children, the most common situation is with cerebellar and optic-pathway pilocytic astrocytoma, typically after progression on chemotherapy, whereas in adults, this tends to occur most commonly with hypothalamic pilocytic astrocytoma. The typical radiation dose used in this setting is 50.4 to 54.0 Gy, in 1.8 Gy fractions. There is evidence of improved progression-free survival in this situation.

Grade II Infiltrating Low-Grade Glioma

Nonpilocytic or diffusely infiltrating low-grade gliomas are classified as WHO grade II tumors. They may arise from astrocytic, oligodendrocytic, or mixed lineage. Like astrocytomas, oligodendrogliomas display various degrees of clinical aggressiveness. In addition to histology and molecular characteristics, several variables have been found to be of prognostic importance in low-grade glioma. Pignatti et al. performed the most comprehensive of these analyses and developed a scoring system to identify patients at varying level of risk for mortality. Multivariate analysis showed that age 40 or older, astrocytoma histology, maximum diameter 6 cm or greater, tumor crossing the midline, and presence of neurologic deficits negatively impacted survival.

Patients with up to two factors were considered low risk (median survival, 7.7 years) and patients with three or more were considered high risk (median survival, 3.2 years).

Surgery for Low-Grade Glioma

Retrospective analyses have suggested that the extent of resection is a significant prognostic variable. The Radiation Therapy Oncology Group (RTOG) performed a prospective evaluation of the natural history of completely resected low-grade gliomas (RTOG-9802), evaluating the recurrence risk in 111 patients with surgeon-defined gross total resections (GTR) and found that the extent of postoperative residual disease was an important variable for time to first relapse. Five-year recurrence rates were 26% versus 68% for patients with less than 1 cm residual tumors versus 1 to 2 cm residual tumors.

Radiation Therapy

The role of radiotherapy, in particular the timing, remains controversial. Early intervention is indicated for patients with increasing symptoms and radiographic progression. In younger patients (less than 40 years) who have undergone complete resection, observation with imaging is an option. In RTOG-9802 median time to progression in 111 good-risk patients defined as younger than 40 and a gross total tumor resection was 5 years. In those who have undergone a subtotal resection or those with high-risk features, postoperative radiotherapy may be recommended, typically 50.4 Gy in 1.8 Gy fractions.

Three phase 3 trials provide the best evidence with respect to the indications for radiotherapy as well as the dose (Table 121.5). In a study by the European Organisation for Research and Treatment of Cancer (EORTC-22845), 314 patients were randomized to postoperative radiotherapy to 54 Gy (n = 157) or...
radiotherapy at progression (n = 157).\textsuperscript{114} Statistically significant improvement in progression-free survival was associated with early radiotherapy, 5.3 versus 3.4 years (\(P < .0001\)), without a difference in median survival, 7.4 versus 7.2 years. Malignant transformation occurred in 65\% to 72\% of patients with no difference between the two groups.

Two other trials investigated the dose question. In EORTC-22844, 379 patients were randomized to 45 Gy versus 59.4 Gy.\textsuperscript{115} With a median follow-up of 74 months, overall survival (58\% vs. 59\%) and progression-free survival (47\% vs. 50\%) were similar. In an Intergroup study, 203 patients were randomized to 50.4 Gy (n = 101) or 64.8 Gy.\textsuperscript{116} There was no significant difference in progression-free or overall survival.

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Study} & \textbf{Treatment Arm} & \textbf{No. of Patients} & \textbf{5-Y Survival (\%)} \\
\hline
EORTC-22845 & Observation\textsuperscript{a} & 157 & 66 \\
 & 54 Gy (30 fractions) & 157 & 68 \\
EORTC-22844 & 45 Gy (25 fractions) & 171 & 58 \\
 & 59.4 Gy (33 fractions) & 172 & 59 \\
NCCTG & 50.4 (28 fractions) & 101 & 72 \\
 & 64.8 (36 fractions) & 102 & 64 \\
\hline
\end{tabular}
\caption{Phase 3 Radiotherapy Trials in Low-Grade Glioma}
\end{table}

EORTC, European Organisation for Research and Treatment of Cancer; NCCTG, North Central Cancer Treatment Group.

\textsuperscript{a}Treatment with resection, radiotherapy, or both, at progression (for most patients).

Consequently, low-dose radiotherapy, 50.4 to 54.0 Gy in 1.8 Gy fractions, has become an accepted practice for selected patients with low-grade gliomas. The target volume is local, with a margin of 2 cm beyond changes demonstrated on traditional MRI sequences. FLAIR images usually show considerable abnormality beyond any enhancing or nonenhancing tumor and whether a smaller margin may be used for planning if FLAIR sequences are utilized is unknown.

Brown et al.\textsuperscript{117} reviewed the results of the Mini-Mental Status Examination for 203 adults irradiated for low-grade gliomas. Most patients maintained stable neurocognitive status after radiotherapy, and patients with abnormal baseline results were more likely to have improvement in cognitive abilities than to deteriorate after therapy; few patients showed cognitive decline. In a more in-depth analysis of formal neurocognitive testing, 20 patients were analyzed before radiotherapy and then every 18 months for 5
years, and cognitive function remained stable; these results suggest that the tumor itself has the most deleterious effect on cognitive function.118

Chemotherapy
Low-grade gliomas have historically been considered chemotherapy resistant. With the recent demonstration of the chemotherapy responsiveness of some low-grade astrocytomas and oligodendrogliomas has come renewed interest in investigating chemotherapy for low-grade glioma.119,120 It has been demonstrated that some low-grade gliomas, especially optic pathway and hypothalamic tumors, can be responsive to chemotherapy.121,122 In children, various single and multichemotherapeutic and biological agents are effective in controlling the growth of a low-grade glioma in a setting of a newly progressive lesion, multiply recurrent, or unresectable residual tumors.107,108,109,110,123,124 Platinum-containing regimens result in radiographic response rates greater than 60%.123 A national randomized phase 3 trial by the Childrens' Cancer Group (CCG-9952) tested the efficacy of vincristine/carboplatin versus 6-thioguanine, procarbazine, lomustine, vincristine (TPCV) in children less than 10 years of age with unresectable or progressive low-grade gliomas, the results of which are currently not available. In the recently completed pediatric national trial by the Children's Oncology Group (ACNS-0223), temozolomide was added to the vincristine and carboplatin backbone. Vinblastine has also demonstrated substantial activity in recurrent low-grade gliomas and is a commonly used second-line agent after treatment failure with vincristine and carboplatin.125,126 Other second- and third-line therapies for multiply recurrent tumors include TPCV and temozolomide. Irinotecan and bevacizumab are currently being investigated in a multi-institutional phase 2 trial for the treatment of progressive low-grade gliomas. Rapamycin, an oral immunosuppressive agent, has been effective in reducing the growth of astrocytoma associated with tuberous sclerosis.127 Most of the chemotherapy responses seen in children with low-grade gliomas are for contrast-enhancing masses that probably represent pilocytic astrocytomas. Nonenhancing, diffusely infiltrating astrocytomas in children appear to be much less responsive to chemotherapy. Some of these responses can last for years, although nearly half of all children treated with chemotherapy ultimately require radiotherapy.

Data on the use of chemotherapy for low-grade glioma in adults are sparse. In a small Southwest Oncology Group trial, adults with incompletely excised low-grade gliomas were randomly assigned to radiation therapy alone or radiation therapy and lomustine (CCNU). There was no difference in survival between the two arms.128 The role of adjuvant procarbazine, CCNU, and vincristine (PCV) for “high-risk” patients (less than total resection, age older than 40 years) with low-grade gliomas was evaluated in RTOG-9802. Results suggest potential improvement in progression-free, but not overall, survival with adjuvant chemotherapy.113 Several studies have evaluated PCV in the recurrent setting, and, more recently, temozolomide has also been evaluated (Tables 121.6 and 121.7).119,120,129,130,131,132,133,134,135,136,137,138 In general, approximately half the patients treated with either temozolomide or PCV experienced imaging stability or improvement of neurologic symptoms. Although results are encouraging, the number of patients treated in these studies was small, and there are questions regarding the criteria used for radiographic response.

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>Disease</th>
<th>N</th>
<th>Path</th>
<th>Enhancing (%)</th>
<th>Prior RT</th>
<th>RR (%)</th>
<th>1-Y PFS (%)</th>
</tr>
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<td></td>
</tr>
</tbody>
</table>

Table 121.6 Pcv for Chemotherapy Naive Low-Grade Glioma
Stege et al. (132)  
Recurrent 5 O, OA 0 Y 60 N/A  
Newly diagnosed 16 0 N 81 N/A  

Buckner et al. (134)  
Newly diagnosed 28 O, OA 46 N 52 91  

Soffieti (131)  
Recurrent 26 O, OA 73 Y 62 80  

Lebrun et al. (133)  
Newly diagnosed 33 O, OA 18 N 27 N/A  

PCV, procarbazine, CCNU (lomustine), and vincristine; O, oligodendroglioma; OA, oligoastrocytoma; RT, radiotherapy; RR, response rate; PFS, progression-free survival, N/A, not available.

Patients with low-grade oligodendroglial tumors with 1p/19q deletion or t(1p;19q) have longer progression-free and overall survival than those without. Consequently, 1p/19q determination is important in patient counseling and in assessing the results of outcomes in future clinical trials. In fact, an ongoing randomized phase 3 EORTC trial is stratifying patients with low-grade glioma by 1p status prior to randomization to radiotherapy versus temozolomide, and an Intergroup trial in the United States is also collecting tissue for molecular analysis.

**Grade III Anaplastic Astrocytoma**

Randomized evidence for gross total resection is lacking, but retrospective analysis reaffirm the value of this in prolonging survival. However, almost all of these tumors are characterized by postoperative residual disease, and radiotherapy is used adjunctively, resulting in a 3-year survival of approximately 55%.

**Radiation Therapy**

Partial brain fields are used for the treatment of anaplastic astrocytoma; the initial gross tumor volume (GTV) is defined as the T2 or FLAIR abnormality; the boost GTV is defined as the contrast-enhancing volume or the surgical bed; for smaller, nonenhancing tumors, the initial and the boost GTV are often equivalent. The clinical tumor volume (CTV) is defined as an approximately 2 cm margin surrounding the GTV, but not expanding across natural barriers. The initial volume is typically treated to 46 Gy, with the boost volume to 60 Gy.

Prados et al. reported results from an RTOG study that randomized patients with anaplastic astrocytomas to conventional radiotherapy with or without bromodeoxyuridine (B UdR) with adjuvant PCV. The study was closed before full accrual based on an interim analysis that predicted no survival advantage for the B UdR arm.
Chemotherapy

The role of chemotherapy remains controversial. Most phase 3 trials have demonstrated no benefit compared with radiation alone. Both single-agent carmustine and PCV are associated with minimal improvement in survival. Although for a period of time PCV was considered the “superior” regimen, database analysis has belied this claim.\(^{140}\) A meta-analysis by the Glioma Meta-Analysis Trialists’ group demonstrated an approximate 6% absolute increase in 1- and 2-year survival for patients who received chemotherapy (2-year survival of 37% vs. 31%).\(^{143}\) A large randomized trial by the Medical Research Council found no benefit of adjuvant PCV compared with radiation therapy alone.\(^{144}\) Although temozolomide is effective for the treatment of recurrent anaplastic astrocytoma, its role as an adjuvant to radiation therapy has not been rigorously assessed. Based on these results in recurrent anaplastic astrocytoma, the RTOG initiated a phase 3 trial (RTOG-9813) to compare radiation with BCNU to radiation with temozolomide, and the results are pending.

<table>
<thead>
<tr>
<th>Author (Ref.)</th>
<th>N</th>
<th>Path</th>
<th>Enhancing (%)</th>
<th>Prior RT/Chemo</th>
<th>RR (%)</th>
<th>1-Y PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinn et al. (120)</td>
<td>46</td>
<td>A, O, AA</td>
<td>70</td>
<td>Y/Y</td>
<td>61</td>
<td>76</td>
</tr>
<tr>
<td>Pace et al. (130)</td>
<td>43</td>
<td>A, O, AA</td>
<td>60</td>
<td>Y/Y</td>
<td>47</td>
<td>39</td>
</tr>
<tr>
<td>Brada et al. (136)</td>
<td>30</td>
<td>A, O, AA</td>
<td>0</td>
<td>N/N</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Hoang-Xuan et al. (119)</td>
<td>60</td>
<td>O, OA</td>
<td>11</td>
<td>N/N</td>
<td>31</td>
<td>73</td>
</tr>
<tr>
<td>Van den Bent (135)</td>
<td>28</td>
<td>O, OA</td>
<td>100</td>
<td>Y/Y</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Pouratian et al. (138)</td>
<td>28</td>
<td>O, OA</td>
<td>24</td>
<td>N/N</td>
<td>52</td>
<td>72</td>
</tr>
<tr>
<td>Murphy et al. (137)</td>
<td>13</td>
<td>O, OA</td>
<td>0</td>
<td>N/N</td>
<td>100</td>
<td>N/A</td>
</tr>
<tr>
<td>Van den Bent (129)</td>
<td>39</td>
<td>O, OA</td>
<td>100</td>
<td>Y/N</td>
<td>53</td>
<td>40</td>
</tr>
</tbody>
</table>

A, astrocytoma; O, oligodendroglioma; AA, anaplastic astrocytoma; RT, radiotherapy; RR, recurrence rate; PFS, progression-free survival, N/A, not available.
A comparison of the efficacy and safety of radiotherapy versus chemotherapy with either PCV or temozolomide as initial therapy on patients with newly diagnosed anaplastic glioma showed comparable results in terms of time to treatment failure. Because of the potential prognostic and predictive value of hypermethylation of the O6-methylguanine DNA-methyltransferase (MGMT) promoter and mutations of the isocitrate dehydrogenase (IDH1) gene in malignant glioma, analysis of these was a correlative part of the study. Hypermethylation of MGMT promoter and mutations of IDH1 gene as well as oligodendroglioma histology reduced the risk of progression. Hypermethylation of MGMT promoter was associated with prolonged progression-free survival in the chemotherapy and radiotherapy arms.

Difluoromethylornithine (DFMO), an inhibitor of ornithine decarboxylase, was evaluated in a phase 3 trial. Of 228 patients, the majority had anaplastic astrocytoma. Following radiotherapy, patients were randomized to PCV or PCV plus DFMO. There was a difference in survival during the first 2 years, but this did not continue after 2 years.

**Chemotherapy for Recurrent Anaplastic Astrocytomas**

Chemotherapy for anaplastic astrocytomas that recur following radiation is of benefit, and both nitrosourea-based regimens and temozolomide have efficacy. The U.S. Food and Drug Administration granted accelerated approval for temozolomide on the basis of its activity in recurrent anaplastic astrocytoma; the response rate was 35% for patients who had not received chemotherapy and 20% for patients who had received nitrosourea-based therapy. Many patients are being treated with temozolomide early in the course of their illnesses, so for recurrent anaplastic astrocytoma, nontemozolomide regimens used in glioblastoma are often considered. Several clinical trials to evaluate targeted agents in recurrent malignant glioma often include recurrent grade III histology. Based on documented activity of the antivascular endothelial growth factor antibody in glioblastoma, this agent has also been used in patients with recurrent anaplastic astrocytoma. A small retrospective study reported a 64% radiographic response and 6-month progression-free survival rate of 60% in 25 patients. Prospective studies are pending.
Figure 121.7 Kaplan-Meir survival curves for the two arms of the Intergroup 9402 trial, demonstrating no survival benefit from chemoradiotherapy (radiation and PCV [PCV, procarbazine, CCNU (lomustine), and vincristine] chemotherapy), compared with radiation alone. Patients are stratified by 1p19q codeletions, and although codeleted patients have superior survival, there is no obvious survival benefit from chemotherapy. (From ref. 156, with permission.)

**Grade 3 Anaplastic Oligodendroglioma**

**Surgery**

Surgery retains its role as the principal modality of treatment, as with other glial neoplasms, and maximum safe resection is considered the standard of care. However, the consideration of risks versus benefits of an aggressive surgical resection should take into account the 1p/19q deletional status of the tumor and potential for a more favorable natural history and response to medical therapy.

**Radiation Therapy**

No randomized trials that focus only on these tumors comparing radiation versus no radiotherapy have been completed. In general, patients with pure and mixed anaplastic oligodendrogliomas receive postoperative irradiation to 60 Gy in conventional daily fractions of 1.8 to 2.0 Gy using an approach similar to that used for other malignant gliomas.
Chemotherapy

Retrospective series and phase 2 trials first suggested that oligodendrogliomas are chemosensitive. In two phase 3 trials, radiation alone was compared with radiation plus PCV. In the North American trial (RTOG-9402) patients received PCV for four cycles prior to radiation or no upfront PCV. Survival in the two groups was the same. Patients with 1p and 19q deletions had significantly better outcomes, regardless of treatment (Fig. 121.7). An unprespecified analysis of progression-free survival demonstrated that the benefit from PCV was most notable in patients with 1p and 19q deletions. In the European trial, patients received PCV or no immediate chemotherapy after radiation. PFS was better in the PCV group, but overall survival was not different. Patients with 1p and 19q deletion had superior survival, regardless of treatment. Further molecular analysis of this cohort demonstrated that MGMT promoter methylation was of prognostic value. Taken together, these studies demonstrate that chemotherapy potentially improves progression-free survival (with the caveat that progression-free survival was not the primary end point of either trial), but the effect on survival is not statistically obvious, possibly because salvage treatment at recurrence results in equivalent survival. Importantly, both trials confirm the prognostic value of 1p and 19q.

Temozolomide has produced high response rates in patients with anaplastic oligodendroglioma. Chinot et al. treated 48 PCV-failed patients with anaplastic oligodendroglioma/oligoastrocytoma with temozolomide. The objective response rate was 44%. Vogelbaum et al. reported the results of RTOG-0131, a phase 2 trial in which temozolomide was given before radiotherapy to newly diagnosed patients with anaplastic oligodendroglioma/oligoastrocytoma. In 27 patients, the objective response rate was 33%. The 6-month progression rate was 10%. Response to temozolomide has also been shown to be significantly associated with loss of 1p in a small retrospective study.

Chemotherapy for Recurrent Anaplastic Oligodendroglioma

Prospective trials have demonstrated that approximately 50% to 70% of patients with anaplastic oligodendrogliomas that recur after radiotherapy respond to chemotherapy. Although there is no evidence that the sequence of temozolomide and PCV is superior in terms of efficacy, the absence of cumulative myelosuppression with temozolomide argues for its use initially in the setting of recurrent disease.

Ongoing Clinical Trials for Newly Diagnosed Grade 3 Glioma

Two international trials are being conducted in patients with newly diagnosed grade 3 glioma stratified by 1p 19q status rather than histology. Nondeleted patients are randomized to radiation with or without temozolomide; following radiotherapy there is a second randomization to adjuvant temozolomide or not. Codeleted patients are randomized to three arms, a phase 2 temozolomide alone arm, and two phase 3 arms, radiotherapy alone or radiotherapy and concurrent and adjuvant temozolomide.

Grade IV Glioblastoma

Surgery

Gliomas are heterogeneous, and therapy is guided by the most aggressive grade in the specimen. Resection provides the best opportunity to obtain an accurate diagnosis. Studies have shown that more complete resections are more likely to provide a high-grade diagnosis and to detect an oligodendroglial component. Resection relieves mass effect, and more extensive resections are associated with greater
neurologic improvement. Response to postoperative radiation therapy is more favorable, and deterioration during treatment is less likely after resection. Finally, it is likely that resection has a modest survival benefit through cytoreduction. Two randomized trials of resection of malignant gliomas have been published. In a study by Vuorinen et al., survival was twice as long with resection. Stummer et al. reported that patients without contrast-enhancing tumor had a higher overall median survival time than did those with residual enhancing tumor (17.9 months vs. 12.9 months, respectively; \( P < .001 \)). Many retrospective studies of both low- and high-grade glioma have shown longer survival with resection, after adjustment for age, performance score, histologic type, and other prognostic factors. Although selection bias accounts for some of the difference, most surgeons believe resection is beneficial. Complete resection of an enhancing tumor enhances certain approved or investigational adjuvant therapies (e.g., carmustine wafers, immunotherapy).

**Radiotherapy**

Randomized trials have demonstrated a survival benefit with radiotherapy. Localized radiation volumes are recommended based on evidence from several sources that GBM typically recur locally, and the bulk of the infiltrative disease is within a few centimeters of the enhancing rim. However, the wide and somewhat unpredictable degree and direction of dissemination, which is not visualized well with any imaging technique, renders radiotherapy field definition difficult. Dandy, for example, identified recurrences in the contralateral hemisphere even after hemispherectomy, showing the capability of malignant gliomas to spread along white matter tracts. Such findings as well as autopsy studies that show diffuse dissemination have led to some recommendations that the entire intracranial contents should be irradiated.

However, Hochberg and Pruitt reported that in 35 GBM patients who had a CT scan within 2 months prior to autopsy, 78% of recurrences were within 2 cm of the margin of the initial tumor bed and 56% were within 1 cm or less of the volume outlined by the CT. Halperin et al. reviewed CT scans and multiple pathologic sections of 15 brains of patients with GBM who received minimal or no radiotherapy. If radiation treatment portals had been designed to cover the contrast-enhancing volume and peritumoral edema with a 1 cm margin, the portals would have covered histologically identified tumor in only 6 of 11 cases. On the other hand, treatment of the contrast-enhancing area and all surrounding edema with a 3 cm margin around the edema would have covered histologically identified tumors in all cases.

Standard therapy uses a total dose of 60 Gy in 30 to 33 fractions. Walker et al. reported a dose-response relationship using data from 420 patients treated on Brain Tumor Cooperative Group protocols. Doses ranged from less than 45 to 60 Gy, using daily fractions of 1.7 to 2.0 Gy. A significant improvement in median survival from 28 to 42 weeks was found in the groups treated to 50 to 60 Gy. A Medical Research Council study in 443 patients showed a survival advantage in patients who received 60 compared to 45 Gy (12 months vs. 9 months; \( P = .007 \)). A benefit for doses greater than 60 Gy has not been shown. The RTOG and ECOG randomized 253 patients to either whole-brain irradiation to 60 Gy with or without a 10-Gy boost to a limited volume. There was no benefit shown from the higher dose.

For patients with poor prognostic factors and for those who are not able to tolerate conventional treatment, a shorter course may provide palliation. Older patients (older than 65 years), especially those with poor performance status, have been shown to have limited posttreatment improvement following conventional radiotherapy. Phillips et al. randomized 68 patients to standard radiotherapy to 60 Gy in 30 fractions or a shorter course of 35 Gy in 10 fractions. There was no significant survival difference between the two arms. In another trial, Roa et al. randomized 100 patients older than 60 years of age with GBM to 60 Gy in 30 fractions or 40 Gy in 15 fractions. Overall survival between the two arms was not
different. Keime-Guibert et al.\textsuperscript{178} randomized 85 patients older than 70 years to radiotherapy or supportive care only, but aborted the trial early because of significantly superior survival in the radiotherapy arm.

**Dose Intensification**

Dose intensification using 3DCRT or IMRT has not been shown to improve survival. Chan et al.\textsuperscript{179} published the results of 34 patients with high-grade gliomas treated using 3DCRT conformal IMRT radiation to 90 Gy. At median follow-up of 11.7 months, 1- and 2-year survivals were 47% and 13%, respectively, not superior to historic expectations.

Several groups have used hyperfractionated or accelerated regimens to escalate dose. In a randomized phase 1 and 2 study, RTOG-8302 examined escalation using twice-daily fractionation. Hyperfractionated doses were 64.8, 72.0, 76.8, and 81.6 Gy given in 1.2 Gy fractions twice daily and accelerated hyperfractionated regimens were 48.0 and 54.4 Gy given in 1.6 Gy twice-daily fractions. In the final report on 747 patients, there were no survival differences between the arms.\textsuperscript{180}

**Dose Escalation Using Radiosurgery and Fractionated Stereotactic Radiotherapy**

In a prospective randomized trial, Souhami et al.\textsuperscript{181} compared conventional radiotherapy and BCNU with or without radiosurgery in 203 patients with GBM. The radiosurgery dose depended on tumor size, ranging from 15 to 24 Gy. No significant improvement in survival was identified. There was also no difference in failure patterns between the groups, and quality of life and cognitive decline were comparable.

The use of a boost using FSRT was tested in RTOG-0023. Seventy-six patients with GBM with postoperative tumor plus cavity less than 60 mm were treated with 50 Gy radiotherapy in daily 2-Gy fractions, plus four FSRT treatments given once weekly. The FSRT dose was either 5 or 7 Gy per fraction for a cumulative dose of 70 or 78 Gy in 29 treatments during 6 weeks. Overall, no survival advantage was seen when compared with the historical database. However, subset analysis showed that patients who had undergone gross total resection had a median survival time of 16.6 compared to 12 months for controls, suggesting that patients with minimal disease may benefit from dose escalation.\textsuperscript{182}

**Dose Escalation Using Brachytherapy**

Laperriere et al.\textsuperscript{183} used brachytherapy as a boost to conventional radiotherapy. Patients were randomized to external-beam radiotherapy with or without a temporary \textsuperscript{125}I implant. Median survival was not different between the two arms (13.8 months vs. 13.2 months). The results of the Brain Tumor Cooperative Group Trial 87-01 reported by Selker et al.\textsuperscript{184} mirror these findings.

Radiotherapy delivered by an inflatable balloon is a newer approach. Tatter et al.\textsuperscript{185} evaluated the safety and performance of one such device (GliaSite, Proxima Therapeutics, Inc, Alpharetta, Georgia). Twenty-one patients with recurrent malignant glioma underwent resection and device placement. At 1 to 2 weeks following implantation, the balloon was filled with an aqueous solution of organically bound \textsuperscript{125}I, delivering 40 to 60 Gy during 3 to 6 days. This was well tolerated with no serious adverse effects. Median survival was 12.7 months. Prospective, randomized trials are needed for further evaluation.

**Radiosensitizers**

Studies using radiation modifiers to overcome the hypoxia present in malignant gliomas have generally
yielded disappointing results. Chang reported no benefit in 38 patients treated with hyperbaric oxygen and irradiation using schedules ranging from 36 Gy given in 3 weeks to 60 Gy given in 6 to 7 weeks. Miralbell et al. reported the results of an EORTC trial examining the addition of carbogen and nicotinamide to overcome the effects of hypoxia. In this phase 1 and 2 trial, 107 patients received radiotherapy with carbogen, breathing during each treatment or a daily oral dose of nicotinamide, or both. Patients who received nicotinamide had higher rates of acute toxicity. Overall survival was similar in all groups (median survival, 10.1 months vs. 9.7 months vs. 11.1 months) and did not differ from historic controls. RSR-13, an agent that specifically delivers oxygen to hypoxic tumor regions, has been evaluated in phase 1 and 2 clinical trials, but due to the limited activity observed, further phase 3 development is not currently being pursued.

Nitroimidazoles such as misonidazole (MISO) are oxygen-mimetic agents. A double-blind randomized trial conducted by the Medical Research Council found no difference in survival between patients treated with radiotherapy to 45 Gy in combination with either MISO or placebo. Tirapazamine is a bioreductive agent with enhanced toxicity for hypoxic cells. In a phase 2 trial of tirapazamine given with 60 Gy in newly diagnosed GBM (RTOG-9417), patients at two dose levels of tirapazamine were observed to have median survivals of 10.8 and 9.5 months, not superior to historic controls.

Halogenated pyrimidines are incorporated into the DNA of dividing cells due to their biochemical similarity to thymidine. After being incorporated, cells are much more susceptible to single-strand breaks from radiation-induced free radicals and have impaired ability to repair DNA. Early clinical trials focused on intra-arterial BUdR, but later it was determined that prolonged intravenous infusion could achieve equivalent radiosensitization with fewer complications. Phase 1 and 2 studies to evaluate continuous infusion iododeoxyuridine (I UdR) with hyperfractionated radiotherapy reported median survivals of 11 to 15 months. This led to a single-institution trial investigating higher doses of BUdR with hyperfractionated radiotherapy. Median survival was not improved, and significant toxicities were observed. The NCOG later published data comparing survival from pooled data within the NCOG (patients treated with BUdR with radiotherapy) with a similar population of patients from the RTOG database (patients who did not receive BUdR). They reported a median survival of 16.9 months for the NCOG patients (BUdR) compared with 9.8 months for the non-BUdR group (P < .0001). However, there were many limitations with this comparison, including wide variations among radiotherapy fractions, total radiotherapy dose, use of chemotherapy, and use of other potential radiosensitizers, severely limiting the interpretation of this data set.

Motexafin gadolinium (MGd) is a redox-active drug that selectively accumulates in tumor cells. It is thought to sensitize tumors through the production of reactive oxygen species that destabilize cellular metabolism. In a phase 1 clinical trial, MGd was shown to be a radiosensitizer for GBM. A phase 2 RTOG trial has been completed, but results are not available to date.

**Radiosensitizers and Radiation-Synergistic Cytotoxics**

Camptothecins are systemic agents able to effectively penetrate the BBB and are hypothesized to act as radiation sensitizers by preventing DNA repair through inhibition of the topoisomerase-I enzyme. RTOG-9513 evaluated topotecan as a radiosensitizer in GBM, but the median survival of 9.3 months was not significantly different from matched historical controls from the RTOG database. Preclinical studies with platinum agents have suggested that these drugs are able to inhibit the repair of radiation-induced damage and potentially exert a direct cytotoxic effect on glioma cells. A phase 3
Intergroup trial to evaluate continuous infusion cisplatin in combination with radiotherapy compared with conventional radiotherapy found no significant difference in survival between the groups.\(^\text{195}\)

Based on preclinical studies showing paclitaxel as a radiosensitizer in malignant glioma cell lines, the RTOG performed a phase 2 study (RTOG-9602) to evaluate the feasibility and efficacy of conventional radiotherapy and concurrent weekly paclitaxel in newly diagnosed GBM. An objective response was observed in 23% of the patients, with an observed median survival of 9.7 months, not improved compared with historical controls.

**Radioimmunotherapy**

Radioimmunotherapy, using monoclonal antibodies against EGFR tagged with \(^{125}\)I, has been evaluated. In a phase 2 trial, 25 patients with malignant gliomas were treated with resection or biopsy followed by definitive external-beam radiotherapy and one or multiple doses (35 to 90 mCi per infusion) of \(^{125}\)I-labeled monoclonal antibody-425. The total cumulative dose ranged from 40 to 224 mCi. At 1 year, 60% of patients were alive and the median survival was 15.6 months. In an updated report on 180 patients with a minimum follow-up of 5 years, median survival was 13.4 months.\(^\text{196}\)

Radiolabeled antibodies to tenascin have been evaluated in phase 1 and 2 trials showing activity against newly diagnosed and recurrent malignant gliomas. In a phase 2 trial \(^{125}\)I-labeled murine antitenascin monoclonal antibody was injected into the resection cavity in 33 patients with malignant glioma, followed by external-beam radiotherapy and 1 year of chemotherapy. Median survival (87 weeks) was longer than that of historical controls. Only one patient required reoperation for radionecrosis.\(^\text{197}\)

**Particle Beam Therapy**

Alternate radiation modalities used in the treatment of gliomas include neutrons, protons, helium ions, other heavy nuclei, negative pi-mesons, and thermal neutrons in conjunction with boronated compounds (boron neutron capture therapy). To date, most studies have been designed to determine optimal dose scheduling, efficacy, and safety. Despite theoretical advantages with respect to dose distribution and radiobiologic effect, most trials have failed to demonstrate improved survival.

In a pilot study, Griffin et al.\(^\text{198}\) did not find a difference in survival in patients treated with fast neutrons to 14 Gy versus external-beam photons to 50 Gy, and in an RTOG study, 166 patients with GBM were randomized to receive a neutron boost or a photon boost after 50 Gy external-beam radiotherapy with no significant difference in median survival (9.8 months vs. 8.6 months). A randomized neutron dose searching study was performed by the RTOG to test the efficacy of neutron boost following whole-brain photon irradiation in patients with malignant glioma. There was no difference in overall survival in the groups tested.\(^\text{199}\)

**Chemotherapy**

In a landmark international trial, patients were randomized to radiotherapy with or without concurrent and adjuvant temozolomide. Median and 2-year survival were increased by 2.5 months and 16.1%, respectively, in patients receiving temozolomide, and long-term follow-up showed a persistent survival benefit.\(^\text{200}\) A companion correlative study demonstrated that methylation of the promoter region of the \(\text{MGMT}\) gene in the tumor was associated with superior survival, regardless of treatment received, but the benefit was maximal for methylated patients.\(^\text{146}\) MGMT removes the methyl group from the O6 position of guanine, reversing the cytotoxic effects of methylating agents (such as temozolomide), making the tumor...
resistant to treatment, while methylation of the promoter region of MGMT results in inactivation of MGMT. MGMT status was strongly associated with survival (Fig. 121.8). Recognizing that a different schedule of temozolomide may overcome chemotherapy resistance, there have been several studies of alternative dosing of temozolomide both at the time of recurrence and in the newly diagnosed setting.²⁰¹,²⁰² A large phase 3 randomized international study led by the RTOG has completed accrual to standard treatment versus a 21- or 28-day adjuvant temozolomide schedule. Results are pending. Strategies to increase the therapeutic ratio of existing chemotherapies, such as the inhibition of DNA repair enzymes (i.e., poly[ADP-ribose] polymerase [PARP]) are being evaluated. These agents are being combined with radiation and chemotherapy to increase the cytotoxicity of the combination approach.²⁰³,²⁰⁴,²⁰⁵

Figure 121.8 Kaplan-Meir survival curves for the two arms of the international glioblastoma trial, demonstrating a significant survival benefit from chemoradiotherapy, compared with radiotherapy. The patients are evaluated by methylguanine DNA-methyltransferase (MGMT) gene promoter methylation status, and the maximum survival benefit is seen in the combination arm when the gene promoter is silenced. (From ref. 146, with permission.)

Although nitrosourea-based chemotherapy is modestly effective for patients with GBM, its use has been supplanted by temozolomide. There is evidence that carmustine-impregnated wafers implanted into the brain at the time of resection provide modest improvement in outcomes in selected patients compared with patients who received placebo wafers.²⁰⁶

**Chemotherapy for Recurrent Glioblastoma**

Treatment options for recurrent GBM must be tailored to the individual. Few agents have proven activity. A randomized phase 2 trial of temozolomide versus procarbazine in 225 patients with GBM at first relapse
demonstrated that treatment with temozolomide improved median progression-free survival (12.4 weeks vs. 8.3 weeks; *P* < .006).\(^{207}\) Radiographic responses were disappointing (5.4% vs. 5.3%).

Several agents such as the platinoids, taxanes, 5-fluorouracil (5-FU), and irinotecan have been tested, most demonstrating very little activity. In a review of eight clinical trials with 225 recurrent malignant gliomas, the 6-month survival was 15% versus 31% for GBM versus anaplastic astrocytoma.\(^{208}\)

### Targeted Therapies

As the genetic and molecular pathogenesis of gliomas is better understood, new targets are being identified and inhibitors of associated signaling pathways are being developed. One example is EGFR as a frequently deregulated signaling molecule in GBM, prompting phase 1 and 2 trials of erlotinib and gefitinib for recurrent high-grade gliomas. Both have shown limited activity.\(^{100,209,210,211}\) Patients whose tumors demonstrate the variant 3 mutant (EGFRvIII), with resulting constitutive activation of EGFR tyrosine kinase activity, along with intact phosphatase and tensin analogue (PTEN), appear to be more responsive to EGFR inhibitors.\(^{212}\) There are two reports of the combination of erlotinib with radiation and chemotherapy for newly diagnosed glioblastoma showing modest additional benefit to standard radiochemotherapy, and an additional completed but as yet unreported RTOG trial (0211), none of which show convincing survival improvement.\(^{213,214}\) Preliminary reports using other targeted agents including the mammalian target of rapamycin (mTOR) inhibitor, temsirolimus, and the farnesyl transferase inhibitor, tipifarnib, have shown objective responses in a few high-grade gliomas.\(^{215,216,217,218,219}\)

The most promising results have been seen for angiogenic inhibitors. The most important mediator of angiogenesis in GBM is vascular endothelial growth factor (VEGF). Antiangiogenic therapies such as the anti-VEGF monoclonal antibody bevacizumab have produced dramatic radiological responses and prolonged progression-free survival relative to historical controls.\(^{220,221}\) Based on the results of a randomized phase 2 study of 167 patients who received bevacizumab with or without irinotecan, the U.S. Food and Drug Administration granted accelerated approval to bevacizumab for recurrent glioblastoma in 2009.\(^{152}\) The progression-free survival at 6 months was 43% for single agent bevacizumab and 50% for the combination arm. The objective response rates were 28% and 38% for the two arms, and median survival times were 9.2 months and 8.7 months, respectively. The most common side effects associated with bevacizumab include fatigue, headache, and hypertension; proteinuria and poor wound healing are also seen. There are several reports of small single-arm phase 2 studies of the combination of bevacizumab with radiation and temozolomide in the newly diagnosed setting and two large randomized placebo-controlled trials are ongoing.\(^{222}\) Recognizing that tumors ultimately evade the effect of antiangiogenic agents through various mechanisms, other strategies include the evaluation of the combination of bevacizumab with chemotherapeutic and targeted agents, and the investigation of other VEGF targeted agents. Batchelor et al.\(^{223}\) reported reduction in contrast enhancement and edema in 12 of 16 GBM patients who received cediranib (AZD2171), an orally administered pan-VEGF receptor inhibitor, with median progression-free survival of 3.7 months. VEGF Trap (afiblercept), a recombinantly produced fusion protein that captures circulating VEGF and CT-322 (Angiocept, Adnexus Therapeutics, Waltham, Massachusetts), a pegylated recombinant peptide with a high affinity for VEGF, are currently being tested in both the recurrent and newly diagnosed setting. Other promising antiangiogenic agents under investigation include celengitide (EMD121974),\(^{224,225}\) an integrin inhibitor; XL184 a multitargeted tyrosine kinase inhibitor that acts on the VEGFR, hepatocyte growth factor receptor (MET) and c-KIT; and enzastaurin, an inhibitor of protein kinase C-beta that targets VEGF as well as the mTOR pathway.\(^{226}\)

Other mechanisms of cell growth that are being targeted include epigenetic modulation through histone deacetylase inhibitors, the proteasome inhibitor bortezomib, and the glutamate receptor inhibitor
Convection-Enhanced Delivery

CED is designed to circumvent the BBB and BTB and deliver even large molecules to discrete areas of the brain and spinal cord by direct infusion of an agent into the brain under positive pressure. Proof of principle for CED has been demonstrated in several studies, but unfortunately phase 3 results have been disappointing.\(^{230,231}\) Significant challenges of optimizing the volume of distribution of the agent to the infiltrating tumor will need to be addressed before the ultimate therapeutic potential of this approach can be realized. The initial experience has demonstrated the need for more reliable delivery technology and methods for demonstrating the success and extent of drug delivery.

Issues in Study Designs for Novel Agents

Several key issues confront the incorporation of new agents in the upfront management of malignant glioma. First, there is the issue of defining the appropriate end point. In recurrent malignant glioma, progression-free survival is frequently employed, but because of insufficient evidence linking this to survival in newly diagnosed malignant glioma, survival remains the gold standard. However, there is considerable heterogeneity in survival outcomes, based on clinical and possibly molecular prognostic variables. An adequate staging system has never been developed. The RTOG has analyzed an extensive database of prospectively treated patients (primarily with surgery, radiotherapy, and alkylating chemotherapy), and, using a statistical method known as recursive portioning analysis, has developed six prognostic groups, referred to as RTOG recursive portioning analysis classes I to VI. Patients can be segmented into classes using eight variables: age, histology, Karnofsky performance score, mental status, neurologic function, symptom duration, extent of resection, and radiotherapy dose. GBM patients fall in classes III through VI, and their median survival ranges from 4.6 months to 17.9 months (Table 121.8).\(^{232}\)

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>No. of Patients</th>
<th>Median Survival (mo)</th>
<th>2-Y Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>139</td>
<td>58.6</td>
<td>76</td>
</tr>
<tr>
<td>II</td>
<td>34</td>
<td>37.4</td>
<td>68</td>
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<tr>
<td>III</td>
<td>175</td>
<td>17.9</td>
<td>35</td>
</tr>
<tr>
<td>IV</td>
<td>457</td>
<td>11.1</td>
<td>15</td>
</tr>
<tr>
<td>V</td>
<td>395</td>
<td>8.9</td>
<td>6</td>
</tr>
<tr>
<td>VI</td>
<td>263</td>
<td>4.6</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 121.8 Radiation Therapy Oncology Group Recursive Portioning Analysis (Rpa) Classification: Survival By Class
Gliomatosis Cerebri

Gliomatosis cerebri is a rare condition with diffuse involvement of multiple parts of the brain (greater than two lobes). On MRI, there is typically diffuse increased signal on T2-weighted and FLAIR images and low or absent signal in the affected areas on T1-weighted images (Fig. 121.9). Treatment remains undefined. Perkins et al.\textsuperscript{233} reviewed the outcomes of 30 patients. Transient improvement or stabilization was achieved in 87% of patients with clinical improvement in 70%. Patients younger than 40 and those with nonglioblastoma histology had better overall survival.

In a French trial, 63 patients were treated with PCV or temozolomide.\textsuperscript{234} Objective responses were observed in 26% of patients with no significant difference between the two regimens. Median progression-free and overall survival were 16 months and 29 months, respectively. Patients with an oligodendrogial component had better progression-free and overall survival.

A retrospective review of 296 patients from the literature and the Association des Neuro-Oncologues d'Expression Francaise (ANOCEF) network was recently published.\textsuperscript{235} Median survival was 14.5 months. Patients younger than 42, with better Karnofsky performance score, low-grade histology, or oligodendrogial subtype had better outcomes. The impact of radiotherapy on survival remained unclear.

Optic, Chiasmal, and Hypothalamic Gliomas

**Clinical Considerations**

Nearly all gliomas of the optic nerve and chiasm are discovered in patients younger than 20 and most occur in those under 10 years of age. Twenty percent to 50% of patients with optic pathway glioma (OPG)
are affected by NF1. Patients with NF1 are more likely to have lesions involving one or both optic nerves (anterior), whereas chiasmatic or hypothalamic (posterior) involvement is commonly seen among non-NF1 patients (sporadic). Lewis et al. found that gliomas along the anterior visual pathway occurred in 15% of NF1 patients and were occasionally bilateral; 67% of these were neither suspected clinically nor obvious on ophthalmologic examination. In one series, 25% involved the chiasm alone, 33% the chiasm and hypothalamus, and 42% the chiasm and optic nerves or tracts. Clinically, they cause loss of visual acuity (70%), strabismus and nystagmus (33%), visual field impairment (bitemporal hemianopsia, 8%), developmental delay, macrocephaly, ataxia, hemiparesis, proptosis, and precocious puberty. Funduscopic evaluation demonstrates a range of findings from normal optic discs, to venous engorgement, to disc pallor because of atrophy. Chiasmal tumors often grow to involve the hypothalamus, causing a diencephalic syndrome characterized by emaciation (especially in children between 3 months and 2 years of age), motor overactivity, and euphoria. In general, optic nerve gliomas have a better prognosis than those involving the chiasm, and tumors confined to the anterior chiasm have a better outcome than posterior chiasmal tumors.

The natural history of these tumors ranges from indolent growth or spontaneous regression (with NF1) to rapid progression or dissemination (with hypothalamic lesions). Generally, the prognosis of OPG is good with overall 5-year survival rates ranging between 70% and 90%; however, the long-term morbidity is high. NF1 and age less than 5 years at diagnosis have better progression-free survival.

Pathologic Considerations

Histopathologically, a majority of these tumors are low-grade gliomas, typically pilocytic or fibrillary astrocytomas. They range from primarily piloid and stellate astrocytes (most common), with or without oligodendroglia, through the gamut of malignant astrocytomas to GBM (rarely). Typically, optic gliomas appear as fusiform expansions of any part of the nerve. They may bridge through the optic foramen and expand as dumbbell tumors. The nerve can be infiltrated by tumor originating in the chiasm, the walls of the third ventricle, or the hypothalamus.

Imaging Findings

Diagnosis is best made by MRI, which demonstrates enlargement of the affected optic pathway, often with enhancement.

T2 signal may extend posteriorly along the optic tracts as far as the visual cortex, which may represent tumor infiltration or edema. Cysts and calcification are uncommon, but the hypothalamic component can be cystic.

Treatment Decision Making

In general, children with asymptomatic lesions of the optic pathways found by MRI are not treated unless clinical or radiographic progression is documented. Tumors in children with NF1 tend to be more indolent than sporadic tumors. Only one-third to one-half of children with NF1 with asymptomatic optic pathway tumors found on screening MRIs require treatment for increasing visual symptoms. Most children with sporadic tumors undergo imaging because of symptoms and should be treated. Sporadic tumors often present with advanced findings such as hydrocephalus, decreased visual acuity, and endocrinopathies. Rarely, both sporadic and NF-associated optic pathway gliomas can regress spontaneously.

Surgery
Surgery is indicated only for some optic pathway gliomas. In appropriate patients, surgery may decrease the recurrence rate and increase the time to recurrence. Patients treated with surgery, followed by radiation and chemotherapy, appear to have the highest long-term control. In patients with progressive symptoms (e.g., severe visual loss and proptosis), unilateral anterior tumors that do not involve the optic chiasm may be resected. Biopsy or subtotal resection can be performed for posterior optic pathway gliomas that involve the hypothalamus and optic tract, particularly if they are symptomatic because of local compression and mass effect.

A transcranial approach to orbital tumors allows sparing of the globe and improves the cosmetic result. Initially a craniotomy is performed ipsilateral to known tumor, and the nerve and chiasm are examined directly. If the tumor is limited to the nerve, then the nerve can be sectioned just anterior to the chiasm. The orbit is unroofed, and the remainder of the nerve extending into the globe is resected. Resection of the chiasm is not indicated due to resultant bilateral blindness.

If the tumor involves the chiasm and the MRI raises suspicion of another tumor type, such as an optic nerve sheath meningioma or another parasellar mass, a confirmatory biopsy can be performed. This is rarely needed in patients with NF1, in whom there is a high index of suspicion for an optic nerve glioma. Subtotal resection is indicated if mass effect produces dysfunction of adjacent structures such as the hypothalamus or the nerve itself. Hydrocephalus can be produced by more posteriorly situated tumors and may be alleviated by debulking. If hydrocephalus persists after debulking, CSF shunting (which may need to be biventricular or require fenestration of the septum) becomes necessary.

**Radiation Therapy**

Untreated optic gliomas, especially those involving the chiasm or extending into the hypothalamus or optic tracts, progress locally or are fatal in 75% of patients. Tenny et al. found that only 21% of patients who were followed after biopsy or exploration survived compared with 64% of those who received radiation therapy.

Routine postoperative irradiation is not indicated for gliomas confined to the optic nerve, which can be completely resected. Radiation therapy can prevent tumor progression, improve disease-free survival, and stabilize or improve vision in patients with chiasmal lesions, for whom postoperative residual is the rule. Wong et al. reported that 86% of chiasmal gliomas not treated with radiation therapy progressed locally, whereas treatment failure occurred in 45% that underwent radiation therapy. Furthermore, control was achieved in 87% of the irradiated patients who received a dose of 50 to 55 Gy compared to 55% of those who received 46 Gy or less.

The prognosis for patients with optic nerve tumors may be better than for those with chiasmal-hypothalamic lesions. In a literature review, local control was found to be achieved for 154 of 189 irradiated anterior chiasmal tumors (81%), whereas 92 of 142 posterior tumors (65%) were controlled. Vision improved in 61 of 210 evaluable patients (29%) and remained stable in 118 of 210 patients (56%). For chiasmal-hypothalamic tumors, radiation therapy produced radiographic shrinkage in 11 of 24 (46%) with a median progression-free survival of 70 months compared with 30 months for patients who did not receive radiation therapy. Age and tumor location were important prognostic factors, with younger children (less than 3 years), and children with lesions posterior to the chiasm faring less well after radiotherapy.

Three-dimensional conformal radiotherapy, IMRT, and stereotactic techniques are used to minimize the dose to adjacent structures. A report by Debus et al. summarized results in patients treated with FSRT (52.2 Gy median dose at 1.8 Gy/d). All patients remained disease free, and no significant complications or marginal failures were seen despite highly conformal radiation fields. Because these tumors are often focal, techniques like FSRT can offer both excellent local control and decreased late effects.
Chemotherapy

In recent years, chemotherapy has played a pivotal role in the management of OPG in young children in order to spare the developing brain from the adverse effects of irradiation.\textsuperscript{242,254,255,256,257} This is especially important in patients with NF1 who are at significant risk of developing vasculopathy such as moyamoya syndrome and second malignancy after receiving radiotherapy.\textsuperscript{256,258} Retrospective series suggest that cognitive function is preserved better in children who receive initial chemotherapy compared with radiation therapy.\textsuperscript{242,259} Although the appropriate agents are still evolving, vincristine plus carboplatin remains the most common first-line regimen.\textsuperscript{121} Gnekow et al.\textsuperscript{260} reported a 5-year progression-free survival of 73\% in 55 patients who were treated with this regimen. The randomized Children's Oncology Group A9952 study showed a 5-year progression-free survival of 35\% using carboplatin with vincristine and 48\% using thioguanine, procarbazine, lomustine, and vincristine regimen in children with newly diagnosed progressive low-grade glioma.\textsuperscript{261} Cisplatin-based regimens have shown responses between 50\% and 60\% and 5-year progression-free survival of 50\%.\textsuperscript{262,263,264} Other studies have shown temozolomide to be effective.\textsuperscript{265,266,267} Results from a phase 2 trial of temozolomide for progressive disease showed imaging improvement in 4 of 26 patients, and stable disease in 54\% for a median of 34 months.\textsuperscript{266} Vinblastine has also been active in these tumors and is generally a second-line agent.\textsuperscript{125,126} Collectively, these data suggest that chemotherapy is helpful in delaying tumor progression in a significant portion of children.

Whether chemotherapy alone can improve vision is controversial. Most studies in the literature lack objective data on visual outcome prior and after chemotherapy. Recently Moreno et al.\textsuperscript{268} conducted a systematic review of eight reports and found only 14.4\% of the children treated with chemotherapy had improvement in their vision. Due to the risk of second malignancy, alkylator-based chemotherapies are generally avoided in patients with NF1. Current studies are evaluating rapamycin, an oral mTOR inhibitor; erlotinib, an EGFR Inhibitor; and bevacizumab and irinotecan.\textsuperscript{124}

Brainstem Gliomas

Clinical and Pathological Considerations

Brainstem gliomas account for 15\% of all pediatric brain tumors but are rare in adults. They can be divided into several distinct types. The diffuse intrinsic pontine tumors are generally high-grade astrocytomas, either anaplastic astrocytomas or GBM, and focal, dorsally exophytic or cervicomedullary lesions are usually low grade with a better prognosis. Although rare, ependymomas, PNETs, and atypical teratoid-rhabdoid tumors also occur in the brainstem. Nonneoplastic processes that may be confused with a brainstem tumor include neurofibromatosis, demyelinating diseases, arteriovenous malformations, abscess, and encephalitis.

The diagnosis is usually based on a short history of rapidly developing neurologic findings of multiple cranial nerve palsies (most commonly VI and VII), hemiparesis, and ataxia. The initial manifestations of a brainstem glioma are unilateral palsies of cranial nerves VI and VII in approximately 90\% of patients. The classic MRI finding is diffuse enlargement of the pons with poorly marginated T2 signal involving 50\% or greater of the pons (Fig. 121.10).\textsuperscript{269} Most are nonenhancing; in children, enhancing lesions could have either a pilocytic or malignant component; in adults, enhancement is worrisome for a malignant glioma.\textsuperscript{270} Cervicomedullary tumors are nonenhancing, well-circumscribed lesions with an exophytic component. Tectal gliomas are nonenhancing and enlarge the tectal plate, often expanding it into the supracerbellar cistern with associated hydrocephalus. Overall, the prognosis is poor, with 5-year survival varying between 0\% and 38\%
and a median survival of less than 1 year.271

Figure 121.10 Typical magnetic resonance appearance of a diffuse pontine glioma. Diffuse
enlargement of the pons is visualized on the T2-weighted image (A); a small amount of hemorrhage is
visualized on the noncontrast T1-weighted image (B).

Surgery
Complete resection is almost never possible, and even biopsy is restricted because of substantial morbidity
and mortality.272,273 When a biopsy is thought to be necessary because atypical imaging findings or clinical
characteristics suggest another diffuse brainstem disorder, stereotactic needle biopsy is used, usually with
an entry point on the frontal convexity or over the lateral cerebellar convexity if the lesion is accessible
via the middle cerebellar peduncle without crossing pial planes. Resection has no place in the treatment
of diffuse pontine gliomas in children or adults. For the rare focal astrocytic lesions of the adult or
pediatric brainstem, surgery may play a larger role. Tectal gliomas have a typical imaging appearance, and
biopsy is neither necessary nor safe. However, the accompanying noncommunicating hydrocephalus (from
compression of the aqueduct of Sylvius) can be treated with CSF diversion, either by third
ventriculocisternostomy or by ventriculoperitoneal shunting.274 Dorsally exophytic astrocytomas within the
fourth ventricle or at the cervicomedullary junction are often resectable with low morbidity and excellent
long-term results, if a complete removal is achieved.275 Intrinsic astrocytomas or ependymomas at the
cervicomedullary junction can often be completely removed through a posterior midline approach.276
Kestle et al.277 treated 28 patients with juvenile pilocytic astrocytoma of the brainstem with resection in
25 cases and biopsy in 3. The 5- and 10-year progression-free survival rates were 74% and 62%, respectively,
after gross total resection or resection with linear enhancement and 19% and 19%, respectively, when solid
residual tumor was present; thus, long-term survival after resection of these tumors seems to relate to the
extent of initial excision.
Radiation Therapy

Radiation therapy, the primary treatment for brainstem tumors, improves survival and can stabilize or reverse neurologic dysfunction in 75% to 90% of patients. The GTV is usually best defined using T2-weighted or FLAIR MRI. A margin of 1.0 to 1.5 cm is added to create a CTV. These lesions should be treated to 54 to 60 Gy using daily fractions of 1.8 to 2.0 Gy. In a multi-institutional survey by Freeman and Suissa, the 1-, 2-, and 5-year survival rates of children treated with conventional radiation therapy techniques were 50%, 29%, and 23%, respectively. Hyperfractionation, designed to deliver higher tumor doses, has been evaluated, without a significant survival advantage (median survival, 8.5 months vs. 8.0 months for conventional vs. hyperfractionated regimens). Several drugs, such as topotecan, and motexafin-gadolinium have been investigated as radiosensitizers, without clear evidence of benefit, and therefore, the role of sensitizers remains investigational.

Fewer data exist with respect to brainstem glioma in adults, but there is some evidence that these tumors may be less aggressive in adults, with overall survival that ranges from 45% to 66% at 2 to 5 years, perhaps because of a greater frequency of more favorable tumor types. In the series from ANOCEF, 48 adult patients with brainstem gliomas were grouped on the basis of their clinical, radiological, and histologic features. Nearly half had nonenhancing, diffusely infiltrative tumors and had symptoms that were present for longer than 3 months. Eleven of these 22 patients underwent biopsy, and 9 had low-grade histology. Nearly all underwent radiotherapy and had a median survival of 7.3 years. A second group of 15 patients who had presented with rapid progression of symptoms and had contrast enhancement on MRI were described. Fourteen of these patients underwent biopsy, and anaplasia was identified in all 14 specimens. Despite radiotherapy, the median survival in this group was 11.2 months, which approximates the survival in pediatric series.

Chemotherapy

In one study, radiation therapy was compared with radiation therapy followed by CCNU, PCV, and prednisone; chemotherapy did not improve survival. Another study by the CCG randomly assigned 32 patients to preradiation chemotherapy with three courses of carboplatin, etoposide, and vincristine; and 31 patients to preradiation cisplatin, etoposide, cyclophosphamide, and vincristine. Response rates and overall survival were not substantially different in either arm. Clinical trials using temozolomide during and after radiation therapy have not shown improvement in the outcome. Thus, no agent used either during or after radiation treatment has been shown to have benefit over radiation alone.

Various molecularly targeted therapies such as EGFR antagonists, or antiangiogenic therapies are being explored, but no definitive data support their routine use.

Cerebellar Astrocytomas

Clinical and Pathological Considerations

Cerebellar astrocytomas, which occur most often during the first two decades of life, arise in the vermis or more laterally in a cerebellar hemisphere. They are usually well circumscribed and can be cystic, solid, or some combination of both. It is not uncommon to have a small tumor (mural nodule) associated with a large cystic cavity.

Histologically, most are low-grade juvenile pilocytic astrocytomas that lack anaplastic features. In a series of 451 children, cerebellar astrocytomas accounted for 25% of all posterior fossa tumors, and 89% of the
111 cerebellar astrocytomas were low grade. Approximately 75% of these tumors are located only in the cerebellum, with the remainder involving the brainstem as well. Because these tumors usually arise in the vermis or median cerebellar hemisphere, the clinical presentation is similar to that of medulloblastoma, with truncal ataxia, headache, nausea, and vomiting. In infants, head enlargement from hydrocephalus is seen.

**Surgery**

Cystic cerebellar astrocytomas are exposed through a posterior fossa craniotomy. The cyst is located with ultrasonography or stereotaxy, cannulated, and then exposed by an incision through the cerebellar folia. With the operating microscope, the cyst is examined and the vascular, firm mural nodule is identified, dissected, and removed. The nonneoplastic cyst wall is not excised. Solid cerebellar astrocytomas are separated carefully from surrounding white matter, again using the improved visualization offered by the operating microscope. Ordinarily, the tumor has a distinctive appearance and is easily separated from surrounding white matter; the only barriers to complete resection are penetration of the tumor into the dentate nucleus, cerebellar peduncles, or brainstem. Gross total resection is tantamount to a cure for these lesions.

**Radiation Therapy**

Most completely resected cerebellar astrocytomas do not require radiation therapy. The management of partially resected pilocytic astrocytomas remains controversial because many remain stable for years without additional treatment. Even when they progress, repeat resection is reasonable if a majority of the tumor can be removed. The overall prognosis for diffuse cerebellar astrocytomas in children tends to be poorer than for pilocytic tumors, with only 30% to 40% of patients free of progression at 5 years. Thus, radiation is often used after surgery for partially resected diffuse cerebellar astrocytomas. Doses of 50 to 60 Gy are delivered, depending on the histologic features and the age of the patient.

**Chemotherapy**

In general, chemotherapy is not indicated. Based on the experience with optic pathway glioma, several of which have pilocytic features, carboplatin has been used for recurrent tumors. There is limited experience with the use of temozolomide in this setting. High-grade gliomas that arise in the cerebellum are treated with regimens identical to their supratentorial counterparts.

**Gangliogliomas**

**Clinical and Pathological Considerations**

Gangliogliomas, along with pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and subependymal giant cell astrocytomas, are considered “astroglial variant” forms of low-grade glioma. They are more circumscribed than diffuse low-grade gliomas, are classified as grade 1 or 2, and do not typically invade normal brain. Because they do not generally progress to higher-grade lesions, surgery alone is frequently curative. Gangliogliomas are more common in children than adults. They are the most common neoplasms to cause chronic focal epileptic disorders, and they typically arise in the temporal lobe but may also occur in the brainstem, spinal cord, and diencephalon. They may include a cystic component, and the solid portion is free of normal brain parenchyma. Unlike diffuse low-grade gliomas, gangliogliomas enhance on MRI scans. They contain both glial and neuronal elements. The glial elements, which stain for glial fibrillary acidic protein, are almost always astrocytic and often pilocytic, but fibrillary...
Astrocytes are also common. The glial elements dictate whether the lesion is grade 1 or 2. The neurons in the tumor are neoplastic and are characteristically large and relatively mature (i.e., they contain ganglion cells). The presence of neoplastic neurons may be confirmed by immunostaining for neuron-specific enolase and synaptophysin. Grade 2 lesions have rarely been observed to progress to a higher grade.295,296

Table 121.9 Outcomes Following Treatment in Patients with Ganglioglioma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>10-Y Local Control Rate (%)</th>
<th>10-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross total resection</td>
<td>188</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>Gross total resection with postoperative radiotherapy</td>
<td>21</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>Subtotal resection</td>
<td>113</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>Subtotal resection with postoperative radiotherapy</td>
<td>80</td>
<td>65</td>
<td>74</td>
</tr>
</tbody>
</table>

Surgery

Surgical resection is directed at removal of the contrast-enhancing portion of the tumor. Nevertheless, although lesions located within eloquent brain regions are resectable, they may present significant surgical challenges because the boundary between tumor and functional brain may be difficult to define, even with the aid of modern surgical adjuncts (e.g., operating microscope, computer-assisted navigation, functional brain mapping). Although no phase 3 prospective studies have documented the superiority of surgery over other approaches (e.g., radiotherapy), retrospective studies have indicated that complete resection is associated with long-term survival.295,296 Resection of gangliogliomas also can result in seizure control.297 Grade 2 gangliogliomas may recur, and some patients do poorly. The degree of anaplasia determines the prognosis.

Radiation Therapy

Because resection has the potential to cure most of these lesions, radiotherapy is generally reserved for subtotally resected cases or for recurrences.298 It is also used for lesions in complex locations where further resection may result in significant morbidity. To determine the optimal strategy for ganglioglioma, Rades et al.299 conducted a literature-based retrospective study of more than 400 patients treated for ganglioglioma. They examined four different treatment strategies (GTR or subtotal resection [STR] with or without radiotherapy) in 402 patients identified from reports published between 1978 and 2007. Surgery was found to be the mainstay of therapy, with 209 patients undergoing GTR and 193 undergoing STR. Adjuvant radiotherapy was used in 101 patients (20 following GTR and 81 following STR). Patients who underwent GTR had higher rates of overall survival and progression-free survival advantage than individuals who underwent STR (Table 121.9). For patients undergoing GTR, the 10-year rates of local control and...
overall survival were 89% and 95%, respectively, better than the 52% and 62% observed for patients undergoing STR. This indirectly indicates that GTR is the most effective treatment strategy for ganglioglioma. For patients undergoing STR followed by postoperative radiotherapy, the 10-year rate of local control was 62%, better than the 52% for patients undergoing STR without postoperative radiotherapy; although the 10-year survival also improved from 65% to 74% with the use of postoperative radiotherapy in patients with subtotally resected tumors, this did not reach statistical significance. For the 40 patients undergoing STR for whom radiotherapy details were known, local recurrence was observed in 6 of 22 (27%) receiving 54 Gy, compared to 7 of 18 (39%) receiving greater than 54 Gy, implying no specific dose-response relationship.

Chemotherapy

Chemotherapy for gangliogliomas is generally reserved for young children who have undergone subtotal resection and who demonstrate disease progression. In older patients, it is typically used as salvage therapy to treat recurrent tumors after the failure of surgery and radiation therapy. In general, for astroglial variants such as ganglioglioma, no optimal chemotherapeutic regimens have been defined, and most researchers consider disease stabilization (rather than a complete tumor response) to be a successful outcome.

Ependymoma

Clinical and Pathologic Features

Ependymomas arise from the ependymal cells lining the cerebral ventricles and the vestigial central canal of the spinal cord. As a result, they arise in the periventricular area, as intramedullary spinal cord tumors, and in the filum terminale. Approximately 60% of intracranial ependymomas are infratentorial and 40% are supratentorial. The most frequent location is in the fourth ventricle (Fig. 121.11). Tumor extension through the foramina of Luschka or Magendie into the basal cisterns is common. Other locations include the walls of the lateral and third ventricles. Half of supratentorial ependymomas are intraventricular and half are parenchymal, likely arising from embryonic ependymal rests retained within white matter. Grade 2 or differentiated ependymomas make up the majority. Rosette formation is a hallmark of ependymoma on pathologic examination. Less often, they may have grade 3 anaplastic features. The difference in prognosis between differentiated ependymomas and anaplastic ependymomas is not clear, and histologic features of malignancy do not always imply short survival. Individual ependymomas do not tend to progress from grade 2 to 3 as do other gliomas. Seeding of CSF pathways has been reported to occur more frequently with anaplastic tumors and heralds a poorer prognosis. Myxopapillary ependymomas generally arise in the conus, cauda equina, or filum terminale; they are considered grade 1, and resection is often curative.
Figure 121.11 Typical magnetic resonance appearance of a posterior fossa ependymoma. The tumor arises from the floor of the fourth ventricle and rapidly expands to occupy it, compress the pons/medulla ventrally, and the vermis of the cerebellum dorsally. The enhancement is typically heterogenous.

Clinical presentation depends on location. Tumors with ventricular involvement often cause increased ICP and hydrocephalus by obstruction of CSF pathways. Headaches, nausea and vomiting, papilledema, ataxia, and vertigo are frequent. Focal neurologic signs and symptoms are seen with supratentorial ependymomas that involve the parenchyma. The presence of calcification in a fourth ventricular tumor on CT is very suggestive of an ependymoma. Supratentorial parenchymal tumors cannot be readily distinguished from other gliomas by imaging. For anaplastic ependymomas, a staging spinal MRI with gadolinium and CSF cytologic examination are essential.

In a literature review, Vanuytsel and Brada found that the overall incidence of spinal seeding in ependymomas was 6.9%. Infratentorial lesions were more likely to seed (9.7%) than were supratentorial lesions (only 1.6%), and anaplastic ependymomas seeded at a higher rate (8.4%) than low-grade tumors (4.5%). In total, 15.7% of those with high-grade infratentorial tumors developed spinal dissemination, whereas none with supratentorial anaplastic lesions did. For low-grade tumors, 2.7% of supratentorial lesions showed seeding compared with 5.5% of infratentorial lesions. Spinal seeding was directly related to local progression, regardless of tumor grade. The incidence of spinal dissemination was 3.3% in patients with locally controlled primary lesions and 9.5% in those with uncontrolled primary lesions.

Ependymoblastomas, an aggressive subtype of embryonal cell neoplasm, are distinct from anaplastic
ependymomas. They tend to disseminate throughout the neuraxis, and inclusion of these tumors in series evaluating leptomeningeal spread of ependymomas tends to overestimate the risk of seeding.\textsuperscript{301,303}

Subependymomas are benign tumors with an admixture of fibrillary subependymal astrocytes. They are distinct from subependymal giant cell astrocytomas, which occur in the lateral ventricles in tuberous sclerosis. Subependymomas occur most often in the floor or walls of the fourth ventricle in older men. Most are asymptomatic and slow growing, and treatment is rarely needed except for hydrocephalus or demonstrated growth. They are often incidentally found at autopsy.

**Surgery**

Several retrospective studies support the relationship between postsurgical residual ependymoma and a poorer outcome, and therefore maximal safe resection is the goal.\textsuperscript{304,305,306} Ependymomas arising from the floor of the fourth ventricle are approached through a unilateral suboccipital craniectomy and laminectomy of C1. The inferior subarachnoid space is occluded to minimize the possibility of CSF dissemination of tumor cells to the spine. The tumor is exposed by retracting the cerebellar tonsils laterally and splitting the inferior vermis or by opening the cerebellomedullary fissure on one or both sides. Often a tongue of tumor is visible over the dorsal aspect of the medulla and upper cervical spinal cord before the tonsils are retracted. The dorsal tumor surface is seen as the vermis is divided, and its attachment to the floor of the fourth ventricle can then be exposed and evaluated. Firm attachment precludes complete removal because the floor of the fourth ventricle must be carefully protected from injury. Tumor is removed to the extent possible using illumination and magnification afforded by the operating microscope. Residual tumor is often simply amputated flush with the floor. These tumors may also extend through the foramen of Luschka, entangling the cranial nerves in the basal cisterns, which also precludes a complete resection. The less common supratentorial tumors are removed as with any glioma. Avoidance of bleeding into the ventricular system is important to prevent postoperative hydrocephalus.

**Radiation Therapy**

No definitive trials exist to make absolute recommendations regarding postoperative radiotherapy. Postoperative irradiation improves the recurrence-free survival of patients with intracranial ependymomas, and 5-year survival rates with doses of 45 Gy or more range from 40\% to 87\%.\textsuperscript{307}

Historically, for posterior fossa tumors, the entire craniospinal axis and later the entire posterior fossa has been irradiated.\textsuperscript{308} Modern series document that local recurrence is the primary pattern of failure and that the incidence of isolated spinal relapses is low even among the highest-risk patients, with the majority of spinal failures associated with local recurrences.\textsuperscript{303,309} Paulino\textsuperscript{310} has shown that the pattern of failure is predominantly local. In nine patients who received radiation therapy to the tumor bed plus a 2-cm margin, the two failures in this group were within the tumor bed, and there were no failures within the posterior fossa outside the tumor bed. For most patients, a more usual volume now consists of the tumor bed and any residual disease plus an anatomically defined margin of 1 to 1.5 cm to create a CTV. Larger margins may be required in areas of infiltration, and special attention must be paid to areas of spread along the cervical spine since 10\% to 30\% of fourth ventricular tumors extend down through the foramen magnum to the upper cervical spine.\textsuperscript{311,312} Patients with neuraxis spread (positive MRI or positive CSF cytology) should receive craniospinal irradiation (40 to 45 Gy) with boosts to the areas of gross disease and to the primary tumor to total doses of 50 to 54 Gy.

Craniospinal irradiation for low-grade, nondisseminated ependymomas has largely been abandoned in the United States.

In their literature review, Vanuytsel and Brada\textsuperscript{302} found that risk of seeding was independent of whether
Prophylactic spinal irradiation was given. For high-grade lesions, spinal dissemination occurred in 9.4% of patients who received craniospinal axis irradiation (CSI) and in 6.7% of those treated with local radiation therapy only. Similarly, for low-grade tumors, spinal seeding occurred in 9.3% after craniospinal irradiation, whereas 2.2% developed seeding without prophylactic treatment.

The treatment volumes recommended for low-grade supratentorial ependymomas vary from generous local fields to fields encompassing the whole brain, whereas for low-grade infratentorial tumors they include local fields, the whole brain with cervical spine extension, and the craniospinal axis. Wallner et al.\textsuperscript{312} reviewed data for 20 patients with supratentorial and infratentorial low-grade ependymomas treated with partial or whole-brain postoperative irradiation. Of 16 patients, only 1, who was eventually found to have a local recurrence, developed spinal dissemination. The 5- and 10-year survival rates for those who received greater than 45 Gy were 67% and 57%, respectively. Because local failure dominated the recurrence patterns, whole-brain treatment was thought unnecessary. Based on this series and others, low-grade supratentorial ependymomas are treated using partial brain fields with a dose of approximately 54 Gy. Low-grade infratentorial ependymomas are also treated using limited fields. The craniospinal axis is irradiated only if pretreatment CSF cytologic studies reveal malignant cells or if radiographic studies show evidence of tumor spread.

Rogers et al.\textsuperscript{313} studied outcomes in 45 patients with nondisseminated posterior fossa ependymomas (low grade in 43) who underwent either gross total resection (n = 32) or subtotal resection (n = 13) with or without subsequent radiation therapy (median = 54 Gy). The 10-year actuarial local control rate was 100% for patients who underwent gross total resection and radiotherapy, 50% for those who underwent gross total resection alone, and 36% for those who underwent both subtotal resection and radiotherapy. The 10-year overall survival rate was superior in patients who underwent both gross total resection and radiotherapy: 83% compared with 67% in those who underwent gross total resection alone and 43% in those who underwent both subtotal resection and radiotherapy. In their smaller series, Massimino et al.\textsuperscript{314} recommended adjuvant radiotherapy after gross total resection of ependymomas especially with posterior fossa tumors.

Some authors recommend CSI in the treatment of anaplastic ependymomas, whereas others recommend only whole-brain irradiation with a boost to the tumor for supratentorial lesions located away from the CSF pathways.\textsuperscript{302,303,308,312} A dose of 54 Gy is given to the primary tumor and 36 Gy to the remainder of the axis if CSI is to be given. If spread within the brain is demonstrated, the entire brain receives 45 to 54 Gy, based on age. Spinal imaging studies are routinely performed, and areas of gross involvement are boosted to 50 Gy. Local recurrence is the primary pattern of failure with high-grade ependymomas.\textsuperscript{302,303,308,312} Subarachnoid seeding is uncommon in the absence of local recurrence. Furthermore, the patterns of failure are similar in patients treated with local fields or with CSI, and prophylactic treatment may not prevent spinal metastases. In one series of 28 patients with anaplastic ependymomas, 12 received CSI, 2 received treatment to the whole brain, and 14 received treatment to limited fields.\textsuperscript{315} Actuarial 5- and 10-year survival rates were 56% and 38%, respectively. All 19 radiotherapy failures were local, and in one of these cases CSF seeding also developed. A benefit from CSI could not be demonstrated. Based on these and other data, CSI is generally not recommended for patients with anaplastic (high-grade) ependymomas unless CSF seeding is pathologically or radiographically documented. Prophylactic CSI for patients with infratentorial high-grade lesions is still advocated by some.\textsuperscript{316}

Clinical trials are examining more aggressive local therapies to improve local control in ependymoma. In a recent trial, 3DCRT was employed in localized ependymoma to reduce treatment volume. Eighty-eight patients were treated to 59.4 Gy, targeting only the resection bed and a modest margin, and the 3-year local failure rate was under 15%. These patients also underwent neurocognitive evaluation, and with 24-month follow-up, no major deficits were identified.\textsuperscript{317,318}
**Chemotherapy**

There is no evidence that chemotherapy improves survival in these cases. The CCG tested carboplatin and found a response plus stable disease rate of 28%. In a CCG evaluation of cisplatin, the overall median time to progression was only 3.8 months. A small trial of etoposide in ten adult patients with recurrent spinal cord ependymoma showed a 20% response rate, a median time to progression of 15 months, and overall survival of 17.5 months. A multicenter trial conducted by the French Society of Pediatric Oncology used alternating courses of three different regimens (procarbazine plus carboplatin, etoposide plus cisplatin, vincristine plus cyclophosphamide) as adjuvant postsurgical treatment in 72 children younger than 5 years of age. Forty percent of patients were spared radiotherapy 2 years after treatment and 23% at 4 years after treatment. Chemotherapy has a potential role in deferring radiotherapy, although patients spared radiation with this strategy might also have been progression free with surgery alone, especially because no chemotherapy responses were seen in patients with measurable disease after surgery.

Thus, to date, few if any drugs have shown even modest consistent activity in ependymomas. Although, a complete removal of the ependymoma has a positive impact on the outcome, a complete resection is achieved in only 40% to 60% of cases. Responsiveness to preirradiation chemotherapy was therefore investigated in a Children's Oncology Group (COG) study. Garvin et al. reported an objective response rate of 58% to preirradiation chemotherapy, consisting of cisplatin, etoposide, cyclophosphamide, and vincristine, in children with incompletely resected ependymoma. The 3-year event-free survival in patients assigned to preirradiation chemotherapy because of incomplete resection was 58% and was comparable to those who had a complete resection and were assigned to irradiation alone. However, 15% of the children who received preirradiation chemotherapy experienced progression prior to radiation therapy. Therefore, a subsequent COG study was carried out that aimed to decrease the progression rate prior to radiotherapy by employing a strategy of “second-look” surgery following the preirradiation chemotherapy in children with residual disease. In this study, patients who had a complete resection of a differentiated supratentorial ependymoma were observed without any further therapy. The results of this study are pending. The recently opened randomized COG study is exploring whether maintenance chemotherapy following radiation will improve event-free and overall survival.

The primary application of chemotherapy, therefore, is investigational and it is within the realm of neoadjuvant therapy to improve resectability as primary adjuvant therapy in young children to delay radiotherapy and as possible salvage. In the Baby Pediatric Oncology Group study a 48% response rate was reported to two cycles of vincristine and cyclophosphamide in 25 children younger than 3 years of age with ependymoma, allowing a delay in radiotherapy by 1 year without impacting the outcome. However, the use of chemotherapy to delay radiotherapy has to be approached cautiously. In a trial of 34 patients with anaplastic ependymoma, 25 patients relapsed relatively rapidly and only 3 patients who did not receive radiotherapy survived.

Despite multimodal therapy, 50% of the patients with ependymoma will experience a relapse. The majority of the recurrences are local, and prognosis is poor after relapse. Resection, reirradiation, and chemotherapy are the common treatment modalities for relapsed ependymoma. Various antineoplastic agents such as etoposide, cyclophosphamide, temozolomide, cisplatin, and irinotecan have failed to improve survival in these patients. Novel therapies to target molecular pathways are currently under investigation. Coexpression of ERBB2 and ERBB4 has been described in over 75% of pediatric ependymoma and impacts prognosis. Consequently, inhibitors of ERBB are being evaluated in both pediatric and adult patients with recurrent ependymoma. As in other malignant glioma, tumor vasculature represents an attractive target. Agents that directly inhibit or indirectly dysregulate this target...
(bevacizumab, ZD6474, metronomic therapy) are being examined. In a study reported by Kiernan et al., three of the five patients with recurrent ependymoma were alive at 2.5 years after treatment with a metronomic regimen consisting of oral thalidomide and celecoxib with alternating oral etoposide and cyclophosphamide every 21 days for a 6-month period.

**Meningiomas**

**Clinical and Pathological Considerations**

Meningiomas are believed to arise from epithelioid cells on the outer surface of arachnoid villi in the meninges, also known as arachnoidal cap cells. The most frequent locations are along the sagittal sinus and over the cerebral convexity (Fig. 121.12). Meningiomas are extra-axial, intracranial, and sometimes intradural, extramedullary spinal tumors that produce symptoms and signs through compression of adjacent brain tissue and cranial nerves. They often also produce hyperostosis; bony invasion does not indicate malignancy. They rarely metastasize except after multiple resections when they may spread to the lung, where growth is typically slow.

Figure 121.12 These five images show various appearances of meningioma. The most common location is parasagittal (A). Some meningiomas remain small (B), whereas others achieve a massive size with midline shift (C). An optic nerve meningioma (arrow) is illustrated in (D), whereas spinal locations are also possible (E).

The WHO updated its grading criteria recently, categorizing this tumor into three grades. Benign (WHO
grade I) meningiomas comprise about 70% to 85% of intracranial primaries. With appropriate treatment, approximately 80% of WHO grade I meningiomas remain progression-free at 10 or more years. Atypical (WHO grade II) meningiomas account for 15% to 25% of patients. These have greater proliferative capacity, and a seven- to eightfold increased recurrence risk within 5 years. Only about 35% patients with WHO grade II meningiomas remain disease-free at 10 years. About 1% to 3% of intracranial meningiomas are anaplastic (WHO grade III). These aggressive malignant tumors have a median overall survival of less than 2 years.

**Surgery**

The goal is total resection, including a dural margin, because this is often curative for WHO grade I tumors. The risks of resection must be balanced against the advantages of less-aggressive removal because these tumors are typically slow-growing, and the patients are sometimes elderly. Observation is appropriate for some, especially small tumors that are incidentally discovered. In a series of 603 patients who had asymptomatic meningiomas that were treated conservatively, Yano and Kuratsu found that approximately 63% exhibited no growth, and only 6% ultimately experienced symptoms.

**Simpson Grades of Resection**

The completeness of surgical removal is a crucial prognostic factor, and historically, the definitions provided by Donald Simpson have served as a useful guideline. By following 470 patients during a 26-year span, he described five “grades of resection,” based on recurrence. Grade 5 resection refers to a biopsy only and is associated with near-universal progression. A partial tumor resection is labeled Simpson grade 4 and is associated with a recurrence rate of 44%. A Simpson grade 3 resection refers to gross total resection of the tumor, without addressing hyperostotic bone or dural attachments, and is associated with a 29% rate of relapse. A Simpson grade 2 resection includes gross tumor removal, and the dural attachments are either removed or coagulated and the relapse rate drops to 19%; and finally, when hyperostotic bone is also removed for a Simpson grade 1 resection, the relapse rate is 9%.

This definition has subsequently been expanded to include a category referred to as grade 0 resection. Kinjo et al. reported on 37 convexity meningioma patients who underwent gross total resection of the tumor, any hyperostotic bone, and all involved dura with a 2-cm dural margin, and observed no local recurrences, with over half of the patients followed beyond 5 years; this is now widely termed the grade 0 resection. However, apart from convexity primaries, resection to this extent is usually not feasible in other locations.

The likelihood of gross total resection varies considerably among primary sites, with convexity lesions most amenable to complete resection and skull-base lesions least likely to be completely resected. In most surgical series, at least a third of meningiomas reported are not fully resectable.

**Preoperative Planning**

Meningioma surgery requires a detailed knowledge of surgical anatomy. A preoperative angiogram to assess vascularity and to identify or embolize surgically inaccessible feeding arteries is sometimes indicated. Typically, embolization is done within 24 to 96 hours of surgery so that collateral vascular supply to the tumor does not develop. Normally, only the vascular supply from the external carotid artery can be embolized safely. In meningiomas that receive more than 50% of their blood supply from this artery, Kai et al. found the optimum interval between embolization and surgery to be 7 to 9 days, which allowed the greatest degree of tumor softening. For convexity and parafalcine tumors, preoperative imaging may be performed to allow use of a neuronavigation system to aid in planning the scalp incision and bony opening.
Surgical Principles and Impact of Location

The arterial supply to the tumor is addressed first, if accessible. The tumor capsule is then carefully dissected, as the central portion of the tumor is removed by the use of an ultrasonic aspirator, an electrocautery cutting loop, scissors or bipolar electrocautery, and suction.

At the cerebral convexity, a large bone flap is made around the tumor's dural base, which is then circumscribed with a dural incision. Microdissection frees the tumor from surrounding brain as the tumor is lifted away. Overlying hyperostotic bone, which contains tumor cells, can be replaced with a cranioplasty. This results in a Simpson grade 1 or 0 resection, and these tumors rarely recur.

Parasagittal meningiomas abut the midline. Critical draining veins from adjacent brain, invasion or occlusion of the sagittal sinus by the tumor, and massive overlying bony erosion or hyperostosis are the surgical challenges. Preoperative vascular imaging defines sagittal sinus patency and relations between cerebral veins and the tumor. A patent sagittal sinus cannot be transected except in its anterior one-third. Further posteriorly, the involved sagittal sinus may be opened to remove tumor within, or the involved sinus wall may be resected and replaced by a graft. Sindou and Alvernia achieved gross total resection in 93% of instances in 100 consecutive patients, with meningiomas arising primarily in the superior sagittal sinus. The overall recurrence rate was 4%, with a mean follow-up period of 8 years. Use of sinus reconstruction with wall and lumen invasion led to significantly less clinical deterioration after surgery relative to the subgroup not undergoing venous repair, leading them to conclude that venous flow restoration is justified when not too risky. Because recurrence-free survival after subtotal resection of these lesions can be lengthy and because residual tumor may grow to occlude the sinus completely, which makes complete resection possible later with a lesser risk, subtotal resection is also an option. Alternatively, residual tumor within the sagittal sinus can be treated in a delayed manner with the use of stereotactic radiosurgery. Falx meningiomas do not involve the sagittal sinus but occupy the falx below, often becoming bilateral. Surgical interruption of adjacent cerebral veins can cause cerebral edema and venous infarction. Overzealous retraction of the adjacent brain to provide a surgical access corridor can also cause postoperative neurologic deficits.

Olfactory groove meningiomas typically grow extremely large before personality change or headache leads to their discovery. Anosmia is the rule but is rarely noted. Surgery is carried out through a large bifrontal exposure. The broad sessile tumor base is divided first to interrupt feeding arteries from the skull base. The tumor is then debulked by internal coring and dissection, while the optic nerves, carotid arteries, and anterior cerebral arteries on the tumor's posterior aspect are protected. Reconstruction of the skull-base dura is often performed with a vascularized pericranial graft to reduce the risk of CSF leakage into the frontal and ethmoid sinuses.

Tuberculum sellae meningiomas become symptomatic at a smaller size through compression of optic nerves and chiasm. Attention to the safety of the optic apparatus and the anterior cerebral and carotid arteries is axiomatic.

The approach to sphenoid ridge meningiomas varies with their origin on the lateral, middle, or medial third of the sphenoid bone. Lateral-third tumors can present as an intracranial tumor, as massive temporal bone hyperostosis, or often as both. Removal of the intracranial mass through a frontotemporal craniotomy can be complicated by adherence to sylvian veins and the middle cerebral artery. Bony hyperostosis of the sphenoid wing can cause proptosis, requiring removal and orbital reconstruction. Middle-third tumors grow intracranially. Surgical cure through a frontotemporal craniotomy is likely. Medial-third tumors arise from the anterior clinoid process, compress the optic nerve, and encase the carotid and middle cerebral arteries. They can grow diffusely into the cavernous sinus and optic canal and even the orbit proper. Total removal is feasible only when the tumor presents early, because of optic nerve compression; for
larger tumors, the surgeon stops when the risk of further removal exceeds the potential benefit. Many tumors occupy the cavernous sinus with little or no tumor mass in the temporal fossa itself. Few surgeons advocate radical resection for these lesions; they may be observed or, if growing or symptomatic, treated with radiosurgery or FSRT.

Cerebellopontine angle meningiomas arise from the petrous bone and if small and laterally situated are exposed through a posterior fossa craniectomy, with the cerebellum retracted medially. Tumors arising more ventrally, from the petroclival junction or clivus, require a combined approach above and below the tentorium, which affords better exposure with less brain retraction. Posterior fossa meningiomas may engulf critical blood vessels and cranial nerves and may adhere to the brainstem, so surgical removal must proceed cautiously.

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**Recurrence Following Resection**

Gross total resection for benign meningiomas remains the preferred treatment and is generally considered definitive. Three large series with extended follow-up are available (Table 121.10). These have remarkably similar rates of local recurrence after gross-total resection: 7% to 12% at 5 years, 20% to 25% at 10 years, and 24% to 32% at 15 years. As expected, recurrence following subtotal resection is more frequent. Outcomes following subtotal resection alone, from four single institutions with up to 20 years of follow-up, are available. Collectively, the rates of progression following subtotal resection at 5, 10, and 15 years are 37% to 47%, 55% to 63%, and 74%, respectively.

**Radiation Therapy**

Given the long natural history of meningiomas and the relatively late recurrences, radiotherapy has not been routinely adopted in the adjuvant context. Further, there is a paucity of clinical trials on which to base recommendations. However, in almost every retrospective series, cohort comparisons suggest that radiotherapy leads to a decrease in recurrence.
The need for adjunctive radiation therapy is determined by the extent of resection, tumor grade, patient age, and performance status. The risk of recurrence following resection has been outlined previously. In general, it is common practice to not use adjunctive radiotherapy after Simpson grade 0, 1, 2, and sometimes 3 resection for benign histology.

The risk of relapse after subtotal resection is high, as previously mentioned. Several reports, now numbering more than 50, suggest that postoperative irradiation prolongs the time to recurrence. As an illustrative series, Barbaro et al. compared 54 patients treated with subtotal resection and radiation therapy with 30 patients undergoing subtotal resection alone. The absolute rates of recurrence were 60% versus 32% in favor of radiotherapy, with the median recurrence times being 10.4 years for the irradiated patients and 5.5 years for the nonirradiated group. Goldsmith et al. reported the results for 140 patients (117 with benign and 23 with malignant tumors) treated with subtotal resection and postoperative irradiation. For patients with benign meningiomas, the 5- and 10-year progression-free survival rates were 89% and 77%, respectively. Patients who received at least 52 Gy had a 20-year progression-free survival rate of greater than 90%. The 5-year progression-free survival of patients treated after 1980 was 98%, compared to 77% for those treated prior to 1980. This improvement was attributed to the availability of cross-sectional imaging for tumor localization and 3D treatment planning. Condra et al. found that at 15 years, 70% of their patients had experienced relapse after subtotal excision alone, whereas only 13% of those treated with subtotal excision and postoperative irradiation experienced recurrence. The 15-year cause-specific survival rate was 86% for patients treated with adjuvant radiation, compared to 51% for nonirradiated patients. The actuarial relapse-free survival rates at 5, 10, and 15 years for patients undergoing subtotal resection and irradiation in another series were 78%, 67%, and 56%, respectively.

The size of the residual tumor as well as grade affect the outcome after radiotherapy. Connell et al. showed that for tumors 5 cm or larger, the 5-year progression-free survival rate was 40%, significantly lower than the 93% observed for smaller tumors. Among patients irradiated for unresectable tumors and in those with residual disease, the volume of visible tumor on imaging studies rarely decreases by more than 15% and often only after many years.

**Radiation Therapy for Anaplastic and Malignant Meningioma**

Atypical and malignant meningiomas behave more aggressively. Chan and Thompson found that the median survival of six patients treated with surgery alone was only 7.2 months, compared with 5.1 years for 12 patients treated with surgery and postoperative irradiation. Six of the nine patients with malignant histology reported by Glaholm et al. died within 5 years. Goldsmith et al. reported a 5-year progression-free survival of 48% for 23 patients treated by subtotal resection and irradiation. The recurrence rate among 53 patients with malignant meningiomas collected from six series in the literature was 49%. The recurrence rates were 33% for patients treated with complete resection alone, 12% for those undergoing complete resection and radiation therapy, 55% for patients treated by subtotal resection and irradiation, and 100% for those treated by subtotal resection alone. These and other data suggest that all patients with atypical and malignant meningiomas should be offered postoperative irradiation, regardless of the extent of resection.

**Primary Radiotherapy**

Radiation therapy has been used as primary treatment following biopsy, or on the basis of imaging findings alone, in several small series. An early report from the Royal Marsden Hospital found 47% disease-free survivorship at 15 years in 32 patients. In a recent series, Debus et al. noted no recurrences in patients treated by radiotherapy alone (n = 59).
Optic nerve sheath meningiomas are rare tumors, generally not resected, but treated with radiotherapy as primary management. Narayan et al.\textsuperscript{361} found no radiographic progression in any of 14 optic nerve sheath meningioma patients treated with conformal radiotherapy, with more than 5 years of median follow-up. In a study by Turbin et al.,\textsuperscript{362} radiation therapy alone provided more favorable outcome than observation or surgery alone.

**Radiation Dose and Volume Considerations**

For benign meningiomas, the planning target volume consists of the residual tumor with a modest margin of normal tissue, defined by MRI and modified by the neurosurgeon’s description of the site of residual disease. Extensive tumors of the base of the skull and malignant meningiomas require more generous margins, with special attention to dural extensions toward and through skull foramina. The preoperative tumor volume is used for planning for completely resected malignant lesions. A dose of 54 Gy in daily fractions of 1.8 Gy is recommended for benign meningiomas, and 60 Gy or higher for atypical and malignant tumors. Complex 3DCRT treatment planning and delivery techniques and IMRT are used to restrict the dose to normal tissues.

**Radiosurgery**

Numerous retrospective reports describe the use of radiosurgery for small meningiomas, either residual or progressive after resection, or untreated, skull-base lesions. Local control rates range from 75% to 100% at 5 to 10 years. Kondziolka et al.\textsuperscript{363} found that 93% of their patients treated with radiosurgery and followed for 5 or more years required no further therapy. Nearly 85% of patients treated by Hakim et al.\textsuperscript{364} were free of progression with a median follow-up of 22.9 months.

Pollock and Stafford\textsuperscript{365} treated 49 patients with radiosurgery for cavernous sinus meningiomas. With mean follow-up of 58 months, no tumor enlarged, and event-free survival rates were 98%, 85%, and 80% at 1, 3, and 7 years, respectively. Zachenhofer et al.\textsuperscript{366} treated 36 subtotaly resected skull-base meningiomas with radiosurgery, and with a mean follow-up period of 8.5 years, the neurologic status improved in 44% of patients, remained stable in 52%, and deteriorated in 4%. In contrast, Couldwell et al.\textsuperscript{367} reported 13 cases of skull-base meningiomas that progressed after radiosurgery, with some demonstrating rapid growth immediately after radiosurgery and others progressing up to 14 years later; the denominator for this series is ill-defined. They cautioned that regrowth can be aggressive and suggested careful extended follow-up.

**Radiosurgery Complications**

Cranial neuropathies, transient neurologic deficits, radiation necrosis, and significant edema have been reported in 6% to 42% of patients treated with radiosurgery.\textsuperscript{368,369} Complications are more frequent in patients with large or deep-seated tumors and in those treated with high single doses.\textsuperscript{363,370} Fractionated radiotherapy may be preferable for larger tumors.

**Chemotherapy**

There is currently no defined role for chemotherapy for newly diagnosed or nonirradiated meningiomas. Chemotherapy is generally reserved for recurrent meningioma not amenable to further surgery or radiotherapy. Responses are anecdotal, with no drug or combination yielding consistent responses. Because many meningiomas express estrogen and progesterone receptors, there have been unsuccessful attempts to use agents such as tamoxifen. Grunberg et al.\textsuperscript{371} reported the use of mifepristone (RU-486), an antiprogestosterone, in 14 patients with recurrent meningiomas. Five of 14 patients showed objective
response after 6 or more months; a subsequent Southwest Oncology Group phase 3 trial of mifepristone for meningiomas showed no benefit.\textsuperscript{372}

Preliminary data suggest that hydroxyurea may have activity.\textsuperscript{373} Mason et al.\textsuperscript{374} reported stabilization in 12 patients with unresectable or progressive meningiomas with a median duration of treatment of 122 weeks.

Kaba et al.\textsuperscript{375} reported on six patients with either a recurrent malignant or an unresectable meningioma treated with interferon-alfa-2B. Five of six patients exhibited response, with stabilization in four and slight regression in one for 6 or more months. Targeted agents such as STI-571 (imatinib), angiogenesis inhibitors, and EGFR inhibitors have been evaluated, without clear efficacy.\textsuperscript{376,377}

**Primitive Neuroectodermal or Embryonal Central Nervous System Neoplasms**

These tumors of putative embryonal origin predominantly arise in children and include supratentorial primitive neuroectodermal tumors (PNETs), pineoblastoma, medulloblastoma, ependymoblastoma, and atypical teratoid or rhabdoid tumors. They are characterized by sheets of small, round, blue cells with scant cytoplasm. Supratentorial PNETs, medulloblastomas, and pineoblastomas have a similar appearance with differentiation based on location, although there is accumulating evidence of different cytogenetics.\textsuperscript{378} Historically, small round cell tumors arising in the posterior fossa were called medulloblastomas. Given the cytologic similarity between all these tumors regardless of location, it was suggested in the 1980s that they all be designated as PNETs. Although still controversial, the current WHO classification retains medulloblastoma as a distinct type of PNET within the larger group of “embryonal” tumors that includes medulloepithelioma, neuroblastoma, and ependymoblastoma. Pineoblastoma also retains a separate position within the category of pineal parenchymal tumors. Regardless of formal classification, these tumors are viewed as developmentally aberrant early neural (glial or neuronal or both) progenitor or stem cell neoplasms.

Supratentorial PNETs and medulloblastomas continue to be treated with similar regimens. The embryonal neoplasms are grouped together, given their tendency to spread within the neuraxis, infrequent extracranial dissemination, an aggressive natural history, and a treatment approach that combines aggressive resection, chemotherapy, and both local and craniospinal irradiation in noninfants. Most of the experience has been accumulated with medulloblastoma and extrapolated to the other tumors.

**Medulloblastoma**

**Epidemiology**

Medulloblastomas comprise 15\% to 30\% of CNS tumors in children and an estimated 350 to 400 cases are diagnosed in the United States annually. There is a 1.5:1 male-to-female predominance, and 70\% are diagnosed by age 20. Medulloblastomas become progressively more rare with increasing age, with few cases found in those older than 50.\textsuperscript{379,380} Gorlin and Turcot syndromes have increased rates of medulloblastoma, but account for only 1\% to 2\% of medulloblastomas.\textsuperscript{21,381}

**Pathology**

Medulloblastomas classically have Homer-Wright (neuroblastic) rosettes, although these are found in less than 40\% of the cases.\textsuperscript{382} Mitoses are frequent, representing a high proliferative index. Immunohistochemical analysis is positive for synaptophysin, most prominent in nodules and within the centers of the Homer-Wright rosettes, correlating with a presumed neuronal progenitor origin.\textsuperscript{383} According to the WHO classification, medulloblastomas are histologically grade IV and classified into five
variants: classical, desmoplastic/nodular, medulloblastoma with extensive nodularity, anaplastic, and large cell. The desmoplastic subtype has collagen bundles interspersed with the densely packed undifferentiated cells of the classic subtype as well as nodular, reticulin-free “pale islands,” or follicles. Inactivation mutations of the \( \text{PTCH} \) gene, the underlying genetic anomaly in Gorlin syndrome, are seen in the desmoplastic subtype, which is more common. Medulloblastoma with extensive nodularity is similar to the desmoplastic variant except that the reticulin-free zones are large and rich in neuropilike tissue. Anaplastic medulloblastoma is relatively rare, accounting for approximately 4% of cases, and has marked nuclear pleomorphism, nuclear moulding, cell-cell wrapping, and high mitotic activity, with high degree of atypia. It has a high rate of amplification of the \( \text{myc} \) oncogene, a known negative prognostic factor, and correlates with a worse clinical outcome. Gene expression profiles for medulloblastomas have been correlated with outcome independent of clinical factors.

**Radiographic and Clinical Features**

Childhood medulloblastoma typically arises within the vermis, expanding into the fourth ventricle. In older patients, tumors in the lateral cerebellar hemispheres are more common (greater than 50% in adults compared with 10% in children).

Clinical signs and symptoms depend on both age, with infants having less specific symptoms, and the anatomic location within posterior fossa. Midline tumors usually present with symptoms of increased intracranial pressure, including nocturnal or morning headaches, nausea and vomiting, irritability, and lethargy, manifestations of progressive hydrocephalus from fourth ventricle compression. Truncal ataxia may be present because of involvement of the vermis, and sixth nerve palsies are the most common nerve deficit. In younger children, bulging of open fontanelles may occur. Tumors of a lateral origin more frequently have ataxia and unilateral dysmetria. On CT, medulloblastomas are classically discrete vermian masses that are hyperattenuated compared with the adjacent brain and enhance avidly. Imaging variance is common with frequent cyst formation and calcification (59% and 22% of cases, respectively). MRI is the gold standard. Medulloblastomas are typically iso- to hypointense on T1-weighted images, of variable signal intensity on T2-weighted images, and enhance heterogeneously. MRI provides improved evaluation of foraminal extent beyond the fourth ventricle, invasion of the brainstem, and subarachnoid metastases. Diffusion-weighted images exhibit restriction, allowing PNETs to be distinguished from ependymomas.

**Staging and Risk Groups**

A modified version of the Chang staging system is currently used. \( T \) stage has been made less relevant than the extent of residual disease due to advances in neurosurgical techniques. \( M \) stage remains crucial. \( M0 \) represents no tumor dissemination, whereas \( M1 \) represents tumor cells in the CSF. \( M2 \) represents presence of gross tumor nodules in the intracranial, subarachnoid, or ventricular space, and \( M3 \) represents gross tumor nodules in the spinal subarachnoid space. \( M4 \) represents systemic metastasis.

Clinical staging requires the assessment of tumor dissemination and includes CSF cytologic examination. This is frequently not performed prior to surgery because of concern for cerebellar herniation from increased pressure within the posterior fossa. Ventricular fluid is not as sensitive as lumbar fluid in detecting dissemination within the neuraxis. Negative CSF cytology does not preclude more advanced leptomeningeal disease. MRI examination of the spine has supplanted conventional myelography. CSF dissemination is identified on MRI scans as diffuse enhancement of the thecal sac, nodular enhancement of the spinal cord or nerve roots, or nerve root clumping, predominantly seen along the posterior aspect
of the spinal cord based on CSF circulatory patterns. Spine MRI is ideally performed prior to surgery if medulloblastoma is suspected and the patient is stable; otherwise 10 to 14 days should elapse after surgery to avoid a potential false-positive interpretation from surgical cellular debris and blood products. Metastases outside the CNS are less common and occur in less than 5% of patients and correlate with advanced disease within the neuraxis. Eighty percent of systemic metastases are osseous. A bone scan, chest x-ray, and bilateral marrow biopsies should be routinely performed for M2 and M3 stages.

Patients with medulloblastomas are currently classified as “average” or “high risk” based on age, M stage, extent of residual disease, and pathology. Average-risk patients have M0 stage arising within the posterior fossa, are more than 3 years old, and have less than 1.5-cm tumor residual. Due to the poor prognosis, all patients with anaplastic medulloblastoma are classified as high risk. Patients less than 3 years old have particularly poor prognoses. This may represent the presence of more primitive, aggressive tumors, but could also be due to the higher likelihood metastatic disease, subtotal resection, and reduced-dose or withholding of radiotherapy. Between 20% and 30% of patients present with neuraxial dissemination, most commonly along the spinal cord. The presence of metastatic disease is prognostically significant, with 5-year progression-free survival rates of 70% for M0 disease, to 57% for M1, and to 40% for M2 or higher in CCG-921. The disease-free survival of high-risk patients treated with CSI with or without chemotherapy is 25% to 30%. Average-risk patients have historically had a 5-year disease-free survival of 66% to 70%, which has increased to 70% to 80% in recent reports.

Surgery

In one study, 3-year survival was reduced by 60% in patients who had incomplete resection of their primary tumor. Although hydrocephalus associated with medulloblastoma obstructing the fourth ventricle can be relieved with a ventriculostomy, ICP may be controlled with corticosteroids, and in most patients aggressive tumor resection is sufficient to relieve hydrocephalus. An occipital burr hole is commonly placed at surgery, before the posterior fossa is exposed, to allow cannulation of the ventricles for drainage of CSF if needed to lower the increased ICP so the dura can be opened safely.

Surgery for medulloblastoma is usually carried out with the patient prone. The incision and bony exposure are usually in the midline, but a paramedian incision and unilateral bony removal are done when the tumor is limited to one hemisphere, particularly in adults. The more common midline craniotomy includes the ring of the foramen magnum, and a laminectomy of C1 (and rarely C2) is performed to decompress herniated cerebellar tonsils or to remove a caudally extending tongue of tumor.

After opening the dura, the cerebellar tonsils are retracted laterally. The tumor is usually first seen in the midline foramen of Magendie. The floor of the fourth ventricle is separated from the tumor by a cottonoid pledget, which is advanced to protect the floor as the tumor is resected. The thinned vermis is incised in the midline as the dorsum of the tumor is exposed. Alternatively, the naturally occurring corridor through the cerebellomedullary fissure between the tonsils and medulla is opened and exploited for exposure on one or both sides. The tumor is usually soft and moderately vascular and is readily removed under the operating microscope with suction or ultrasonic aspirator. Dissection is continued laterally to remove tumor from the cerebellar hemispheres and ventrally to remove tumor from the fourth ventricle.

When the obstructive hydrocephalus has been relieved, CSF can be seen flowing from the aqueduct of Sylvius. Watertight closure is obtained. Following surgery, gradual weaning of the ventriculostomy is attempted, with internalization 7 or more days after surgery, if clamping is untenable. Postoperative shunting for hydrocephalus is necessary in approximately 35% to 40% of patients because of scarring and decreased capacity to resorb CSF. Patients who require long-term shunting are younger and have larger ventricles and more extensive tumor at presentation. Concern has existed that a VP shunt may cause
peritoneal seeding, but this has not been upheld.\textsuperscript{405}

With advances in neurosurgical technique, the number of patients not undergoing a gross total or near-total resection is dwindling. MRI should be performed to evaluate the extent of residual disease within 48 to 72 hours following surgery to prevent postsurgical changes from influencing interpretation. Patients with either gross total resection or subtotal resection have better 5-year overall survival and posterior fossa local control rates than patients who undergo biopsy alone. Although retrospective data infer that a total resection is prognostically favorable, the majority of trials have found that patients who undergo substantial subtotal resection with minimal residual disease treated with both chemotherapy and radiation do just as well as those who undergo total resection.\textsuperscript{406} This justifies opting for a near-total resection, particularly when there is invasion of the floor of the fourth ventricle or envelopment of cranial nerves or the posterior inferior cerebellar artery. It is clear, however, that the extent of resection does not impact survival in patients with disseminated disease.\textsuperscript{406}

The value of an aggressive resection must be balanced against surgical complications, interchangeably referred to as posterior fossa syndrome or cerebellar mutism syndrome. These conditions consist of diminished speech and can include emotional lability, hypotonia, long-tract signs, bulbar dysfunction, decreased respiratory drive, urinary retention, and ataxia. These changes can be seen in up to 25\% of patients who have undergone resection of a midline posterior fossa tumor.\textsuperscript{407} Although thought to be a temporary, a significant number have persistent deficits.

**Radiation Therapy**

The aims of radiotherapy are to treat residual posterior fossa disease (or gross deposits of disease anywhere in the craniospinal axis) and treat microscopic disease in the craniospinal axis. Historically, CSI has been delivered to 36 Gy with a posterior fossa boost of 54 Gy using conventional fractionation of 1.8 Gy/d.\textsuperscript{408} Radiation is typically initially withheld in patients younger than 3 years of age because of the higher risk of neurocognitive damage. Supratentorial PNETs and other embryonal tumors have been treated with the same CSI regimen, with a boost to the tumor bed and residual disease. Supratentorial PNETs treated with an appropriate dose and volume of radiotherapy were found to have a 49\% progression-free survival at 3 years compared with 7\% with major violations of radiotherapy.\textsuperscript{409}

Various alterations to the radiotherapy regimen have been made endeavoring to limit late toxicities. Hyperfractionation has been examined, with one study showing no improvement in survival and an excess of failures outside the primary site, although this was likely attributable to a reduced craniospinal dose of 30 Gy.\textsuperscript{410} A recent trial showed adequate disease-free survival with possible preservation of intellectual function with short follow-up.\textsuperscript{411} IMRT has been used to provide radiation to the posterior fossa, with a 32\% reduction in dose to the cochlear apparatus, reducing the risk of grade 3 or 4 hearing loss from 64\% to 13\%.\textsuperscript{59} Improved imaging methods have allowed more precise delineation of tumor within the posterior fossa, providing the possibility of avoiding treatment to the entire posterior fossa with the boost dose. Although standard practice has been to boost the entire posterior fossa, retrospective data have shown isolated recurrences outside the tumor bed to be rare.\textsuperscript{412,413} Encompassing the tumor bed and a 2-cm margin only for the boost led to less than 5\% isolated posterior fossa recurrences.\textsuperscript{414}

A combined CCG/Pediatric Oncology Group trial compared standard and reduced dose CSI (36 vs. 23.4 Gy) with a posterior fossa boost to 54 Gy in average-risk patients. All patients received concurrent vincristine during radiation with no adjuvant chemotherapy. Patients who received the lower dose had a higher rate of early relapse, lower 5-year event-free survival (67\% vs. 52\%), and lower overall survival.\textsuperscript{415} Comparison of CSI doses of 35 versus 25 Gy in International Society of Paediatric Oncology (SIOP) II yielded similar
Strong advocates for proton therapy have emerged as a result of the sharply diminished exit dose from spinal irradiation and the more conformal treatment of the posterior fossa. Dosimetric analysis that compared photons to protons has demonstrated a decrease in the dose to 50% of the heart volume from 72.2% to 0.5%, and the dose to the cochlea was reduced from 101.2% of the prescribed posterior fossa boost dose to 2.4%. Proton-based radiotherapy also demonstrated decreased radiation dose to normal tissues compared with IMRT. However, this area remains controversial, as some recent analyses contend that the current generation of proton-beam machines might in fact pose a greater risk of second malignancies because of a higher rate of neutron production and contamination, which is more carcinogenic.

Chemotherapy

Chemotherapy has been used in medulloblastoma with the dual goals of reducing radiation dose while maintaining optimal disease-free survival rates in average-risk patients and improving disease-free survival in high-risk patients.

Tait et al. in SIOP I compared radiotherapy alone versus radiotherapy with concurrent vincristine followed by maintenance vincristine and CCNU. Overall, there was no survival benefit from chemotherapy, but un prespecified post hoc subgroup analysis identified subgroups that appeared to benefit from chemotherapy, including T3 or T4 disease, and subtotal resection. Similar results were seen in a CCG study. The 5-year disease-free survival rates in the CCG and SIOP studies were 59% and 55%, respectively, for radiation therapy plus chemotherapy, and 50% and 43%, for radiation therapy alone. Based on these results, routine use of chemotherapy for “high”-risk medulloblastoma has become standard.

For “standard”-risk patients, chemotherapy has been postulated to lead to a reduction in the CSI dose necessary to control microscopic disease. A phase 2 trial of CCNU, vincristine, and cisplatin for eight cycles following the reduced CSI prescription of 23.4 Gy had a progression-free survival rate of 86% and 79% at 3 and 5 years, respectively. This was superior to historical controls, and CSI to 23.4 Gy with chemotherapy was adopted as the standard of care and reference dose for further trials.

The most recent COG trial for average-risk patients compared cisplatin and vincristine with either CCNU or cyclophosphamide and 23.4 Gy CSI. No differences in outcome were noted, with a 5-year event-free and overall survival rates of 81% and 86%, respectively. The overall outcomes indirectly validated the use of reduced-dose CSI in conjunction with chemotherapy. The ongoing COG trial for average-risk patients is investigating a CSI dose of 18 Gy in patients between 3 to 7 years of age. The 2 × 2 randomization also compares boosting the entire posterior fossa versus a local boost.

Current approaches for high-risk medulloblastoma focus on chemotherapy dose intensification. Vincristine, CCNU, and prednisone had a 63% 5-year progression-free survival rate, better than an “8-in-1” chemotherapy regimen. High-dose cyclophosphamide with autologous stem cell rescue is feasible and provided a 5-year event-free survival of 70% in patients with high-risk disease. In a pilot study involving 57 children, the COG incorporated carboplatin as a radiosensitizer with CSI to 36 Gy and a posterior fossa boost followed by six cycles of maintenance cyclophosphamide, vincristine, and cisplatin. Four-year overall survival and progression-free survival rates were 81% and 66%, respectively, with an inferior outcome in patients with anaplastic medulloblastoma.

The ongoing COG trial for high-risk medulloblastoma includes a randomization to full dose CSI with and without...
carboplatin followed by a second randomization to maintenance therapy with or without a proapoptotic agent, isotretinoin.

As the risk of cognitive deficits increases with decreasing patient age, extensive effort has been made to develop regimens that can delay or potentially eliminate the need for radiation in patients younger than 3 years of age. The avoidance of radiation has proved to be more feasible for patients with M0 disease. Addition of intraventricular methotrexate following surgery in a five-drug chemotherapy regimen provided 5-year progression-free and overall survival rates of 58% and 66%, respectively. Although asymptomatic leukoencephalopathy was detected by MRI and mean intelligence quotient (IQ) scores were lower than healthy controls, the mean IQ scores were significantly higher than previous cohorts who had received radiation. A prospective randomized trial of supratentorial PNETs in children younger than 3 years old treated with chemotherapy and omitted or delayed radiation yielded less promising results, with a progression-free and overall survival rates at 3 years of 15% and 17%, respectively. Administration of radiation was the only positive prognostic variable for progression-free and overall survival. The Head Start I trial for young children with localized medulloblastoma consisted of five cycles of cisplatin, vincristine, etoposide, and cyclophosphamide followed by a single high-dose myeloablative chemotherapy regimen of thiotepa, carboplatin, and etoposide. The 5-year survival was 79%. With the addition of methotrexate, children with disseminated disease had a 5-year progression-free survival of 45% and overall survival of 54%.

Recurrent medulloblastomas is essentially an incurable and lethal disease. Although it is responsive to a variety of neoplastic agents, including vincristine, nitrosoureas, procarbazine, cyclophosphamide, etoposide, and cisplatin, with several regimens yielding relatively high response rates, durability is limited. A CCG trial to evaluate carboplatin, thiotepa, and etoposide with peripheral stem cell rescue showed 3-year event-free and overall survival of 34% and 46%, respectively.

Long-term effects from treatment can be categorized as neurocognitive, neuropsychiatric, neuroendocrine, and growth retardation. Hypothalamic and pituitary endocrinopathies such as delayed hypothyroidism and decreased growth hormone secretion may occur. Growth retardation can also be secondary to delayed or reduced bone growth, leading to reduction in sitting height. Neurocognitive deficits have long been recognized secondary to surgery, radiotherapy, and chemotherapy. In one study, 58% of children showed an IQ above 80 at 5 years after treatment, but by 10 years after treatment, only 15% of the patients had an IQ that remained above 80. A prospective study of cognitive function showed an average decline of 14 points in mean IQ, with an average decline of 25 points in patients younger than 7 years. Even with risk-adapted radiation therapy patients had a significant yearly decrease in mean IQ, reading, spelling, and math. Psychologic secondary effects are partially attributable to the diminished cognitive function as well as the social challenges caused by the physical manifestations of CSI (hearing loss, decreased truncal stature, and thin hair) and potential ataxia and abnormal speech patterns. Risk for secondary malignancies also exists. A population-based study tabulated a 5.4-fold increased rate of malignancy when compared with the general population, although this only affected 20 of 1,262 patients at risk.

Pineal Region Tumors and Germ Cell Tumors

Clinical and Pathological Considerations

Pineal and germ cell tumors account for less than 1% of intracranial tumors in adults and 3% to 8% of brain tumors in children. Germinomas are the most common type, accounting for 33% to 50% of pineal tumors. The peak incidence of germ cell tumors is in the second decade, and few present after the third decade. Gliomas are the next most common pineal region tumor (approximately 25%). Pineal parenchymal tumors...
are nearly as common as glial tumors and are called pineocytomas if benign and pineoblastomas (a variant of PNET) if malignant; a rare intermediate form also exists.

Germ cell tumors commonly involve the two midline sites, suprasellar and pineal regions, and occasionally are found in other areas such as basal ganglia, ventricles, cerebral hemispheres, and spinal cord. Germinomas can occur bilocally or rarely even multifocally; the most common bifocal presentation is synchronous involvement of the suprasellar region and the pineal gland. Based on histology and the presence of tumor markers in the serum or CSF, the WHO classification system divides intracranial germ cell tumors into germinomas and nongerminomatous germ cell tumors. Nongerminomatous germ cell tumors are further divided into embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma (mature, immature or teratoma with malignant transformation). A quarter of the intracranial germ cell tumors have more than one histologic component and are known as mixed germ cell tumors. Alpha-fetoprotein (elevated in yolk sac tumors) and β-human chorionic gonadotropin (elevated in choriocarcinoma, and to a modest extent in germinoma) are generally secreted by these tumors. Mature teratomas do not have elevated tumor markers.

Neurologic signs and symptoms are caused by obstructive hydrocephalus and involvement of ocular pathways. Major symptoms are headache, nausea and vomiting, lethargy, and diplopia. Signs are primarily ocular but can include ataxia and hemiparesis. The major ocular manifestation is paralysis of conjugate upward gaze (Parinaud syndrome), but pupillary and convergence abnormalities are seen, as are skew deviation and papilledema. Some patients with pineal germ cell tumor can present with symptoms of diabetes insipidus (DI) without any radiological evidence of overt suprasellar disease.

On CT, these lesions are hyperdense. On MRI the mass is hypointense on T2-weighted sequences (due to the high cellularity of the mass) and shows enhancement with gadolinium. Calcification and fat may be seen in teratomas or mixed malignant germ cell tumors. Germinomas tend to surround a calcified pineal gland, whereas pineal parenchymal tumors tend to disperse the calcification into multiple small foci. The potential for leptomeningeal dissemination requires imaging of the neuraxis before surgery. Determination of histology, tumor markers, and extent of disease is critical for optimal management of pineal region tumors. The prognosis varies depending on the histologic type, the size of the tumor, and the extent of disease at presentation.

Surgery

Because pineal tumors are near the center of the brain, they are among the most difficult brain tumors to remove. The application of modern surgical technology with superb illumination, magnification, surgical guidance, and neuroanesthesia has made this region much more accessible. Surgeons can choose from several approaches depending on preference and the tumor’s position and extent. The current recommendation is to obtain tissue when a diagnosis cannot be made from serum tumor markers, CSF tumor markers, cytologic examination, or both. Whenever possible the tumor is completely excised, except when a germinoma is found at open surgery; a biopsy suffices in this situation because germinomas respond well to radiation. Resection is important when tumors are radioresistant or when excision may be curative (teratomas, arachnoid cysts, and pineal parenchymal tumors).

The most commonly used microsurgical approaches are the infratentorial supracerebellar approach, in which the surgical corridor is in the midline between the tentorium above and the superior surface of the cerebellum below, and the occipital transtentorial approach, under the occipital lobe and through an incision in the tentorium to reach the pineal region from above and to the side. Both have been associated with low morbidity and mortality in experienced hands.

The place of stereotactic biopsy in the diagnosis of pineal region tumors is unclear. Although biopsies have
been described as safe, particularly for large tumors, some avoid it because of the risk of damaging large veins that flank the pineal gland.\textsuperscript{433} In addition, there is a risk that tissue sampling of these heterogeneous tumors may not depict the correct histologic nature of all parts of the tumor. Without an accurate diagnosis, treatment planning may be erroneous or inadequate. In favor of biopsy are the advantages of a rapid tissue diagnosis and shortened hospital stay. Transventricular endoscopic biopsy can also be performed, which reduces the risk of hemorrhage because the trajectory is mostly traversed under direct vision.

In patients with a pineal mass and obstructive hydrocephalus from blockage of the aqueduct of Sylvius, endoscopic surgery can play a special role. Through a frontal burr hole, the endoscope can be passed through the foramen of Monro into the third ventricle. An endoscopic third ventriculostomy is performed by making a fenestration in the floor of the third ventricle, which relieves hydrocephalus, and the mass in the posterior third ventricle can be viewed and biopsied through a flexible endoscope. A rigid endoscope can also be safely used by placing a second burr hole for the biopsy. CSF for cytology and marker studies can also be obtained and the walls of the third ventricle inspected for tumor studding. There is a small risk of intraventricular hemorrhage.\textsuperscript{434}

**Radiation Therapy**

With certain exceptions, such as benign teratomas, radiation therapy has an established role in the curative treatment of pineal germ cell and parenchymal tumors. The location and infiltrative nature of these lesions often does not allow complete resection. In the past, the risk of biopsy or attempted resection often led to the use of radiation therapy without histologic confirmation. In such instances, response to low-dose radiation therapy, measurement of α-fetoprotein and human chorionic gonadotropin-β, and CSF cytology were used to provide diagnostic information. There is a tendency to increase the use of biopsy and resection, and treatment without histology is less common.

Five-year survival rates with radiation therapy range from 44% to 78% and vary with histology, extent of disease, age, radiation volume, and dose to the primary.\textsuperscript{307} In a multi-institutional survey by Wara and Evans,\textsuperscript{435} the survival of patients with pineal parenchymal cell tumors or malignant teratomas was 21% (3 of 14) compared with 72% (26 of 36) for those with germinomas. Wolden et al.\textsuperscript{436} reported 5-year disease-free survival rates of 91% for germinomas, 63% for unbiopsied tumors, and 60% for nongerminomatous germ cell tumors irradiated to 50 to 54 Gy to the local site with or without treatment to the whole brain or ventricular system. Patients younger than 25 to 30 years old have survival rates of 65% to 80% compared with 35% to 40% for older patients. This may reflect the increased incidence of germinomas in younger patients.

Germinomas are infiltrative tumors that tend to spread along the ventricular walls or throughout the leptomeninges. The incidence of CSF seeding ranges from 7% to 12%. For this reason, fields encompassing the entire ventricular system, the whole brain, and even the entire craniospinal axis have been recommended. The appropriate treatment volume for pineal germinomas was evaluated by Haas-Kogan et al.\textsuperscript{437} in 93 patients treated at the University of California-San Francisco (UCSF) or at Stanford. The UCSF group favored whole ventricular irradiation; the Stanford group included CSI. Five-year survival for the combined cohort was 93%, with no difference in survival or distant failure regardless of whether CSI or whole ventricular radiation was given. In some institutions, 25.5 Gy (1.5 Gy/d) whole-brain or whole-ventricular radiation is followed by a boost to the primary to 45 to 50 Gy. CSI is reserved for patients with disseminated disease at presentation.

Neoadjuvant chemotherapy and low-dose (30 to 40 Gy) focal irradiation is employed by some.\textsuperscript{438,439} Chemotherapy might be useful in the young child to defer irradiation. For disseminated or multiple midline germinomas, systemic chemotherapy or CSI is given. CSI doses of 20 to 35 Gy have been used when CSF...
cytology results are positive. When response to primary chemotherapy is incomplete or the tumor recurs, salvage radiotherapy yields good results.440

Nongerminomatous malignant germ cell tumors, whether localized or disseminated, are treated with chemotherapy followed by restaging. After restaging, localized tumors receive focal radiation therapy to 54 to 60 Gy, and disseminated tumors receive CSI (54 to 60 Gy to the primary, 45 Gy to the ventricular system [controversial], 35 Gy to the spinal cord, and 45 Gy to localized cord lesions).436 In a German study 63 supratentorial PNETs were treated with chemotherapy before or after radiation (35 Gy CSI with a boost to the primary of 54 Gy).409 The 3-year survival was 49.3% in those for whom treatment was delivered as prescribed, but only 6.7% in those with major protocol violations. This indicates the importance of CSI in pineoblastoma, analogous to the situation with medulloblastoma.

Tumors that tend not to metastasize to the cord, such as teratomas, pineocytomas, and low-grade gliomas, are treated by resection, with localized radiotherapy reserved for patients with residual disease.441 For selected patients with small residual disease, radiosurgery has been shown to be effective in terms of local control.

Chemotherapy

Chemotherapy for pineal glial neoplasms is similar to that for gliomas elsewhere. Germinomas are chemosensitive and responsive to cisplatin, carboplatin, ifosfamide, cyclophosphamide, bleomycin, and etoposide. Adjuvant multidrug therapy with radiotherapy has produced encouraging disease-free and overall survival. Newly diagnosed germinomas treated with two courses of high-dose cyclophosphamide showed a complete response rate of 91%.442 Building on this, Allen et al.443 reduced the radiation dose and volume. Of the ten patients with a complete response treated with reduced radiation, only 10% failed within 5 years. A comparable approach that used carboplatin produced an 88% response rate, and radiation dose was reduced in five of eight patients. Bouffet et al.438 reported 3-year event-free survival of 96% in 57 patients with germinoma using four courses of alternating etoposide/carboplatin and etoposide/ifosfamide followed by 40 Gy localized radiation therapy for nondisseminated patients and CSI for those with dissemination. Despite reducing the dose of involved-field radiation to 24 Gy Aoyama et al.444 achieved a 5-year overall survival of 100% and an event-free survival of 86% in patients with pure germinomas with addition of a few cycles of cisplatin-based induction chemotherapy. Similar results were seen in other trials where lower doses of irradiation (24 to 35 Gy) were combined with chemotherapy.445,446

Given the poor outcome of CNS nongerminomatous germ cell tumors after radiotherapy alone, there is significant interest in the use of chemotherapy. Balmaceda et al.447 reported the results from using four cycles of carboplatin, etoposide, and bleomycin without radiation. Of 71 patients (45 germinoma and 26 nongerminomatous), 68 were assessable for response; after four cycles, the complete response rate was 57%. The 29 patients with less than a complete response received dose-intensiﬁed chemotherapy or surgery, and a further 16 achieved a complete response, for an overall complete response rate of 78%. Despite these high response rates, only 28 of 71 (39%) patients were alive and progression free within 31 months. Subsequently, they treated 20 patients with two cycles of cisplatin, etoposide, cyclophosphamide, and bleomycin, and the 16 patients achieving a complete response received two additional cycles of carboplatin, etoposide, and bleomycin.448 Nine of the 14 survivors received radiation therapy. The chemotherapy response rate was 94%, 5-year overall survival was 75%, and 36% of patients were event free. Although the complete response rate was high, approximately half the patients developed recurrent disease, suggesting that a multimodal therapeutic approach of surgery, chemotherapy, and radiotherapy is necessary to improve the overall
outcome of these tumors. Matsutani et al.\textsuperscript{449} analyzed 153 germ cell tumors treated with surgery and radiation therapy with or without chemotherapy. The 10-year survival rates for mature and malignant teratoma were 92.9\% and 70.7\%, respectively. Patients with pure malignant germ cell tumors (embryonal carcinoma, yolk sac tumor, or choriocarcinoma) had a 3-year survival rate of 27.3\%. The mixed tumors were divided into three subgroups: (1) mixed germinoma and teratoma; (2) mixed tumors whose predominant characteristics were germinoma or teratoma combined with some elements of pure malignant tumors; and (3) mixed tumors with predominantly pure malignant elements. The 3-year survival rates were 94.1\%, 70.0\%, and 9.3\%, respectively, for the three groups.

High-dose chemotherapy with autologous stem cell rescue has been used for pineoblastoma.\textsuperscript{450} Twelve patients were treated with induction chemotherapy followed by CSI with a pineal boost (36 Gy CSI, 59.4 Gy to primary), then with high-dose chemotherapy with stem cell support. Nine of the 12 patients remained disease free, including two infants who never received radiation. The actuarial 4-year progression-free and overall survivals were 69\% and 71\%, respectively. Although still considered investigational, the survival results are impressive. The use of high-dose chemotherapy and autologous bone marrow support has not been as promising for patients with recurrent tumors, although reported data are few.\textsuperscript{450}

**Pituitary Adenomas**

**Clinical and Pathological Considerations**

Pituitary tumors are identified incidentally or present through symptoms of local mass effect or as a result of endocrine effects. Pituitary adenomas almost always arise from the anterior pituitary, the adenohypophysis. The tumor initially compresses the gland and, subsequently, the optic chiasm and nerves. Tumors less than 10 mm, microadenomas, rarely compress the optic apparatus. Larger macroadenomas can involve the cavernous sinus bilaterally, the third ventricle (sometimes producing hydrocephalus), and, less commonly, the middle, anterior, or even posterior fossae. The classic ophthalmologic finding is visual loss, typically starting with bitemporal hemianopsia and loss of color discrimination. Automated visual field testing is more sensitive than simple confrontation. Occasionally, extraocular palsies can result from compression or invasion of the nerves in the cavernous sinus. Tumors that present with mass effect are often nonsecreting, but prolactin, growth hormone, thyrotropin, and gonadotropin-producing tumors may also present in this way.

Neuroendocrine abnormalities are usually from tumors that oversecrete hormones but can also result from compression of the pituitary gland and the stalk. The most commonly secreted hormones are prolactin, adrenocorticotropic hormone, or growth hormone. The incidence of the various types of adenoma is variable. In 800 patients operated on at UCSF between 1970 and 1981, 79\% were endocrinologically active. Of these, 52\% were prolactin secreting, 27\% were growth hormone secreting, 20\% were corticotropin secreting, and only 0.3\% were thyroid-stimulating hormone secreting.\textsuperscript{451} Sexual impotence in men and amenorrhea and galactorrhea in women are hallmarks of a prolactin-secreting tumor. Hypogonadism, infertility, and osteopenia are also common.\textsuperscript{452} Growth hormone hypersecretion causes acromegaly or, in the rare patient with a tumor occurring before epiphyseal closure, gigantism. The secondary production of insulin-like growth factor-1 (IGF-1; primarily from the liver) or somatomedin C produces skeletal overgrowth changes (e.g., increased hand and foot size, macroGLOSSIA, frontal bossing). Soft tissue swelling, peripheral nerve entrapment syndromes, and arthropathies may occur. Hypertension, cardiomyopathy, diabetes, and an increased risk of colon cancer are prevalent with acromegaly. Adrenocorticotropic hormone hypersecretion by a pituitary tumor results in Cushing's disease, with weight gain, hypertension, striae, hyperglycemia, infertility, osteoporosis, increased skin pigmentation, and psychiatric symptoms. Rarely, pituitary adenomas can present acutely with headache, visual loss, and confusion, which can progress to obtundation. This potentially life-threatening condition is termed pituitary apoplexy. The
etiology of apoplexy is thought to involve tumor infarction due to interruption of its blood supply, but the exact mechanism is not known. Symptomatic pituitary apoplexy is a surgical emergency and patients need to be carefully medically managed with judicious fluid and salt replacement and administration of high-dose corticosteroids. A need for prolonged hormone replacement therapy is often a consequence of apoplexy.

On MRI, pituitary microadenomas are generally seen within the gland according to the distribution of normal cells. For example, prolactinomas tend to be located laterally within the sella. Microadenomas show subtle hypointensity to the normal gland on T1-weighted sequences and are often more difficult to detect on T2 sequences. Immediately after administration of contrast, adenomas show less enhancement than adjacent normal gland (Fig. 121.13). On delayed views, the tumor enhances more than the normal gland. Indentation of the sellar floor, stalk deviation, and mass effect on adjacent structures also provide evidence of the presence of tumor.

**Surgery**

There are two primary goals of surgery for macroadenomas: to decompress the visual pathways by reducing tumor bulk and, for secreting tumors, to normalize hypersecretion, with preservation of remaining normal pituitary function.

The standard surgical approach for the majority of pituitary tumors is transsphenoidal, which is safer and better tolerated than the transcranial (frontotemporal craniotomy) approach. The transsphenoidal approach is used for microadenomas that occupy the sella turcica and for many macroadenomas. Image-guided neuronavigation and intraoperative fluoroscopy are essential to reduce the risk of injury to the carotid arteries. Even when the majority of tumor is actually suprasellar, transsphenoidal resection can be safely accomplished if the tumor consistency is soft (and tumor aspiration and curettage can thus easily be performed) and if the tumor is situated so that it can drop into the sella with progressive resection. Tough, fibrous suprasellar tumors and those that extend laterally into the middle fossa, anteriorly beneath the frontal lobes, or into the posterior fossa may require a craniotomy for resection. Tumor that invades the cavernous sinus is generally not removed. The role of endoscopic transsphenoidal surgery for pituitary adenomas is currently being expanded. Potential advantages include a less-invasive surgical approach with a wider field of view and quicker postoperative recovery. Moreover, Cappabianca et al. observed a decreased incidence of complications in a series of 146 consecutively treated patients who underwent an endoscopic endonasal transsphenoidal approach to the sellar region for resection of these tumors, compared with large historical series that employed the traditional microsurgical transsphenoidal approach.
Pituitary adenomas are usually isointense to the gland on noncontrast T1-weighted magnetic resonance images; on contrast administration, the normal gland enhances early, as visualized on this sagittal image, whereas the adenoma (arrow) continues to remain unenhanced. With late imaging, the adenoma enhances.

Current surgical cure rates for hormonally active adenomas are 80% to 90% if there is no involvement of the cavernous sinus, suprasellar region, or clivus. Patients with microadenomas have a higher surgical cure rate than patients with macroadenomas. Patients cured of their endocrine disease can expect to have a normal lifespan; however, those with persistent endocrinopathies, and particularly those with acromegaly, may not enjoy a normal lifespan due to the impact of the high hormone levels on multiple organ systems. In patients not biochemically cured with initial surgery, tumor is often found at the time of second surgery just next to the original site. Patients with persistent acromegaly, however, may not be amenable to biochemical cure with a second surgery as the residual growth hormone secreting cells can be difficult to visualize. Growth through the dura into the adjacent cavernous sinus is often found at repeat surgery even when no tumor is seen preoperatively on MRI. Benveniste et al. found that, although repeated transsphenoidal surgery to treat recurrent or residual tumor mass was associated with a 93% rate of clinical remission, its use to treat recurrent or persistent hormone hypersecretion produced only a 57% rate of initial endocrinological remission, with a 37% likelihood of sustaining such remission at a mean of 31 months. Thus, they suggested that for treatment of residual or recurrent adenomas that cause persistent or recurrent hormone hypersecretion, radiosurgery may be a better option.

**Radiation Therapy**

Radiation therapy may be indicated for hormone-secreting adenomas that are not surgically cured and are refractory to pharmacologic management. After subtotal resection of a macroadenoma, more than 50% of...
patients demonstrated radiographic evidence of progression during a 5-year period. Younger patients (less than 50 years old) with residual disease have faster tumor regrowth than older counterparts. Ki-67 antigen labeling of more than 1.5% predicts more rapid growth of residual disease. For these patients, immediate postoperative radiotherapy should be considered.

Radiation therapy decreases serum growth hormone concentrations to normal levels in 80% to 85% of acromegalic patients. Growth hormone levels decrease at a rate of 10% to 30% per year, so several years may be required for the levels to normalize. The probability of endocrine cure is highest for tumors with relatively low preradiation therapy growth hormone elevations (30 to 50 ng/mL); response is less reliable for tumors that produce higher growth hormone levels. In contrast, serum IGF-1 levels remain elevated after radiotherapy, and long-term treatment with somatostatin or its analogues may be required. Radiation therapy controls hypercortisolism in 50% to 75% of adults and 80% of children with Cushing's disease. Response occurs within 6 to 9 months of treatment.

Pituitary adenomas may be treated using several different techniques. The most commonly used techniques include 3DCRT, IMRT, and stereotactic radiotherapy. Treatment with charged-particle beams and radiosurgery is emerging. The total dose used for nonfunctioning lesions is 45 to 50 Gy in 25 to 28 fractions of 1.8 Gy. Slightly higher total doses are recommended for secretory lesions. This controls tumor growth in 90% of cases at 10 years. Radiation-induced injury to optic apparatus or adjacent brain with this dose-fractionation scheme is rare, whereas larger fractions or greater total doses lead to a higher incidence of injury. Hypopituitarism may develop, often years after radiation treatment. It is more common in patients who have had both surgery and radiation therapy than in those treated with either modality alone. Hypopituitarism is largely correctable by hormone-replacement therapy, and patients treated for pituitary adenomas should have lifelong endocrine follow-up. One publication suggests that patients treated with surgery and radiation have an elevated risk for late cerebrovascular mortality. Possible contributing factors include hypopituitarism, radiotherapy, and extent of initial surgery. The risk of developing a radiation-induced brain tumor after treatment is 1.3% to 2.7% at 10 years and 2.7% at 30 years.

Radiosurgery is increasingly being used for treating small residual adenomas. In general, patients are eligible for radiosurgery only if the superior extent of the lesions is more than 3 to 5 mm from the optic chiasm. Doses of more than 10 Gy in a single fraction to the optic pathways can cause visual loss. Radiosurgery results in excellent tumor control and appears to cause more rapid biochemical normalization than is seen with conventional radiation therapy, with the caveat that it is used primarily for smaller tumors. In a comparison of radiosurgery with fractionated radiotherapy, Landolt et al. found the median time to normalize IGF-1 levels in acromegaly was 1.4 years after radiosurgery and 7.1 years after fractionated therapy. In a series of 67 patients treated with radiosurgery for growth hormone-producing pituitary adenomas, Kobayashi et al. found that, although safe and effective tumor control was obtained, normalization of growth hormone and IGF-1 secretion was difficult to achieve in cases with large tumors and low-dose radiation. Losa et al. found that radiosurgery was effective in controlling the growth of residual nonfunctioning pituitary adenomas after prior surgical debulking and that the risk of side effects with radiosurgery, especially of hypopituitarism, was lower compared with fractionated radiotherapy. Cranial nerve injury after radiosurgery is seen in fewer than 5% of the cases treated.

Reirradiation can be considered for patients with recurrent pituitary adenomas when there has been a long interval after the first course of radiotherapy and other therapeutical methods have been
unsuccessful. Schoenthaler et al.\textsuperscript{483} reported the outcomes of 15 patients who were retreated (median dose, 42 Gy) after a median of 9 years from the initial course of radiation therapy (median dose, 40.8 Gy). At a median follow-up of 10 years, 80% of patients had local control. No visual complications were observed, but all patients developed hypopituitarism and two sustained temporal lobe injury.

**Medical Therapy**

Medical therapy is very important and effective for patients with secreting pituitary tumors.\textsuperscript{484} Dopamine agonists (e.g., bromocriptine or cabergoline) are the most effective therapy for prolactinomas and are often used as primary treatment, with definitive treatment reserved for patients who either cannot tolerate or do not respond to a dopamine agonist. Somatostatin analogues (e.g., octreotide and lanreotide) are effective for patients with acromegaly and are usually reserved when there is persistent growth hormone hypersecretion after resection. Control rates with octreotide are approximately 50%; dopamine agonists can control growth hormone production in 10% to 34%.\textsuperscript{485} A recently approved growth hormone receptor antagonist (pegvisomant) can be used for patients for whom somatostatin analogues fail. Rates of IGF-1 level normalization as high as 97% have been reported with this agent, but concerns persist that because it acts at the end-organ receptor level, tumor growth may continue in some patients, and the lifetime cost of the agent is prohibitive.\textsuperscript{486} Medical therapy for patients with Cushing's disease is directed at the adrenal glands to reduce cortisol hypersecretion (ketoconazole). Unfortunately, no known drug effectively reduces pituitary corticotropin production.

**Craniopharyngiomas**

**Clinical and Pathological Considerations**

Craniopharyngiomas are the most common nonglial brain tumors in children, occurring primarily in the late first and second decades, although they can present at any age.\textsuperscript{487} Craniopharyngiomas arise from epithelial cell rests that are remnants of Rathke's pouch at the juncture of the infundibular stalk and the pituitary gland. Most have a significant associated cystic component with only 10% being purely solid (Fig. 121.14). Most craniopharyngiomas become symptomatic because of effects of the combined tumor and cyst on the optic apparatus or hypothalamus or both. They may also compress the pituitary gland or extend superiorly into the third ventricle. Cyst fluid is proteinaceous, and this can be seen on MRI. CT shows calcification in 30% to 50% of cases.

Common presenting symptoms include headache, visual complaints, nausea, vomiting, and intellectual dysfunction (especially memory loss). Specific visual signs include optic atrophy, papilledema, hemianopsia, unilateral or total blindness, and diplopia with associated cranial nerve palsies. Endocrine abnormalities at presentation can include growth retardation, menstrual abnormalities, and disorders of sexual development or regression of secondary sexual characteristics (or both). Diabetes insipidus is uncommon at presentation.\textsuperscript{488}
Figure 121.14 Craniopharyngiomas usually have both solid and cystic components, with significant suprasellar extension as visualized in this coronal postcontrast T1-weighted magnetic resonance imaging; the tumor shows typical enhancement in the solid portions.

**Surgery**

Craniopharyngiomas are generally resected using a microsurgical subfrontal or pterional approach. Larger tumors may require bifrontal or skull-base approaches, including supraorbital craniotomy. Endoscopically assisted surgery is sometimes used, although outcome advantages have not yet been clearly shown. In a series of 36 patients treated with radical resection for craniopharyngiomas using a combination of endoscopic-assisted and microsurgical techniques, all 27 patients who had no previous treatment developed diabetes insipidus, among minor neurologic deficits, with or without degrees of panhypopituitarism.\(^\text{489}\) Although complete resection remains the optimal surgical goal, the risk of devastating long-term effects on hypothalamic function and quality of life cannot be ignored. In some cases, there is no clearly defined plane between tumor and surrounding hypothalamus, which makes aggressive resection dangerous. Aggressive removal is frequently associated with some injury to the pituitary stalk, with subsequent temporary or permanent diabetes insipidus and elements of hypopituitarism.\(^\text{490,491}\) These patients require lifelong replacement hormones and inhaled desmopressin acetate spray for the control of diabetes insipidus. Most patients with preoperative visual loss can expect at least some improvement after surgery. The reported mortality rates for craniopharyngioma resection range from 2% to 43%, with severe morbidity in 12% to 61%.\(^\text{492}\) Complications are less likely with experienced surgeons. Alternative approaches include placement of an Ommaya reservoir for largely cystic
tumors through which one can instill sclerosing agents (e.g., bleomycin) or radioisotopes. There is also a developing interest in the use of radiosurgery, which may be associated with a lower risk of endocrinologic morbidity.

**Radiation Therapy**

**Radioisotope Therapy**

Predominantly cystic craniopharyngiomas can be treated with stereotactic or endoscopic instillation of colloidal therapeutic radioisotopes, particularly yttrium-90 or phosphorus-32.\(^{490,493}\) The short penetrance of the beta-particles emitted by these isotopes allows the epithelial cells lining the cyst to be treated without significant dose to neighboring structures. Intracystic therapy may have a role in treating cysts that recur after conventional external-beam irradiation, or even as a primary cyst treatment. Although most cysts shrink with intracystic therapy, one-third of patients require further surgery later.

**External-Beam Radiation Therapy**

Numerous reports demonstrate that subtotal removal and irradiation produce local tumor control and survival rates comparable to those after radical excision.\(^{494,495,496}\) The local control rates after complete resection, subtotal resection alone, and subtotal resection with postoperative irradiation are 70%, 26%, and 75%, respectively. A study at Children's Memorial Hospital in Chicago found 32% recurrence after complete resection and none after subtotal resection and adjuvant radiotherapy.\(^{497}\) Ten-year survival rates range from 24% to 100% for complete resection, 31% to 52% for subtotal resection, 62% to 86% for incomplete resection and irradiation, and 100% after radiotherapy alone.\(^{492,494,495,497,498}\) Patients who undergo conservative treatment, including biopsy and cyst drainage and irradiation, appear to enjoy a better quality of life and demonstrate less psychosocial impairment than those initially treated with more extensive resections.\(^{494}\) Furthermore, conservative therapy is associated with less hypothalamic and pituitary dysfunction and a lower incidence of persistent diabetes insipidus than when a total or near-total excision is attempted. More extensive resections, using a subfrontal approach, may be associated with frontal lobe and visual perceptual dysfunction. The negative impact on IQ is greater in patients treated with aggressive resection than in those treated with conservative surgery and postoperative irradiation.\(^{499}\)

The radiation treatment volume is based on CT and MRI scans, with relatively small margins. Generally, more sophisticated 3DCRT and IMRT approaches and stereotactic radiotherapy techniques are increasingly being used to spare surrounding normal tissues.\(^{498}\) One report showed excellent tumor control (100%) with minimal late toxicity when FSRT (mean dose, 52.2 Gy in 29 fractions) was used.\(^{500}\) No significant effect on cognition or visual injury was reported. The total dose is 50 to 55 Gy, given in daily 1.8-Gy increments. One review suggested better local control when doses of 55 Gy or more are delivered.\(^{501}\)

**Radiosurgery**

The use of radiosurgery is limited by the proximity of most lesions to the optic chiasm and brainstem. In a long-term analysis by the Karolinska Hospital, 9 of 11 children treated (82%) ultimately experienced recurrence after radiosurgery.\(^{502}\) This was thought to be due to the required low marginal dose of 6 Gy to parts of the tumor abutting the optic chiasm. These results suggest that radiosurgery plays a limited role in the treatment of most craniopharyngiomas and should be reserved for those uncommon tumors confined to the pituitary fossa and away from the chiasm and hypothalamus.\(^{503}\)
Kobayashi et al.504 reviewed long-term results (follow-up of 65.5 months) of radiosurgical treatment for residual or recurrent craniopharyngiomas after microsurgery in 98 consecutive patients and found only a 20.4% tumor progression rate. They used a tumor margin dose of 11.5 Gy at the retrochiasm and ventral stalk area, which decreased the rate of visual and pituitary function loss so that deterioration both in vision and endocrinological functions occurred in only six patients (6.1%). Similarly, Albright et al.490 used radiosurgery as the initial treatment for the solid component of craniopharyngiomas in five children, limiting radiation to the optic chiasm to 8 Gy, and reported no operative morbidity or mortality, whereas 5 of 27 children who underwent microsurgical tumor resection suffered worsened vision postoperatively.

Vestibular Schwannomas

Clinical and Pathological Considerations

Schwannomas, also known as neurilemmomas or neurinomas, are benign neoplasms derived from Schwann cells that show a predilection for sensory nerves. Most intracranial schwannomas arise from the vestibulocochlear nerve, with trigeminal nerves being a distant second in frequency. Previously called acoustic neuromas, these neoplasms are more correctly termed vestibular schwannomas as they arise from both the superior and inferior portions of the vestibular nerve rather than the cochlear nerve. Vestibular schwannomas are equally common between genders and median age at diagnosis is approximately 50, with an overall increased incidence between 45 and 64 years of age. Vestibular schwannomas account for approximately 6% to 8% of intracranial neoplasms. The incidence of vestibular schwannomas is between 0.8 and 1.7 per 100,000, with an increasing incidence since the early 1980s.505,506 This increased incidence may represent the discovery of asymptomatic lesions by a rising number of cranial imaging studies, predominantly MRI. The rate of incidental vestibular schwannomas detected on MRI ranges from 0.02% to 0.07%.507,508 More than 90% of vestibular schwannomas are sporadic and unilateral. Bilateral vestibular schwannoma is virtually pathognomonic for NF2 and is one of the key components of the Manchester criteria for the diagnosis of NF2.509 When associated with NF2, vestibular schwannomas have a significantly earlier disease manifestation and tend to occur in the second or third decade of life.

Vestibular schwannomas arise along the zone of transition between the central and peripheral myelin located near the medial aperture of the internal auditory canal (IAC). Macroscopically, they are typically lobulated, with the eighth cranial nerve located eccentrically along the surface as these tumors grow in an expansile fashion, displacing rather than invading nerves. Vestibular schwannomas in NF2 tend to embed within the seventh and eighth cranial nerve bundles more frequently.510 As with peripheral schwannomas, microscopic examination yields Antoni A and B tissue patterns. Vestibular schwannomas are benign, with few case reports of malignant dedifferentiation.

Although vestibular schwannomas arise from the vestibular portion of cranial nerve VIII, cochlear symptoms predominate, with the two most common being hearing loss and tinnitus.511 Progressive unilateral sensorineural hearing loss is characteristic. Evaluation is typically delayed, with the duration of hypacusis averaging 3.7 years prior to diagnosis. Vertigo and unsteadiness are the most common vestibular symptoms. Facial nerve paresis or spasm may be seen. Large tumors can compress the trigeminal nerve, with paresthesias or neuralgia. Impingement of the brainstem or cerebellum may lead to ataxia and long-tract signs as well as involvement of the lower cranial nerves. Most ominous is the rare patient with nausea and vomiting from fourth ventricular compression and obstructive hydrocephalus.

MRI with thin-section, high-resolution, gadolinium-enhanced T1- and T2-weighted images of the cerebellopontine angle is the study of choice (Fig. 121.6). Vestibular schwannomas typically enhance along the course of the eighth cranial nerve with variable intra- and extracanalicular components. Cystic
changes are frequently identified in larger lesions. MRI allows identification of the lesion and potential differentiation from other masses of the cerebellopontine angle such as meningiomas, epidermoid cysts, arachnoid cysts, and, rarely, lipomas. Auditory brainstem response audiometry is less sensitive than MRI. \(^{512}\)

Pure tone and speech audiometry continue to be performed to document hearing loss. Hearing loss is more pronounced at higher frequencies, and the degree of speech discrimination loss is disproportionately worse than the pure tone hearing loss.

**Treatment**

Treatment revolves around the dual goals of local control and cranial nerve function preservation. Factors that influence treatment choice include tumor size, location, patient age, the presence and degree of symptoms such as tinnitus and vertigo, whether a patient has NF2, the status of contralateral hearing, and patient preference. Consultation with a multidisciplinary team is essential.

**Observation**

Vestibular schwannomas are typically slow-growing, and various studies have shown an increase in size ranging from 0.35 to 2.2 mm/y (mean, 1.42 mm/y). \(^{513}\) Chalabi et al. \(^{514}\) reported that with mean follow-up of 4.2 years, 85% of observed vestibular schwannoma were noted to have exhibited measurable growth. Given the slow growth pattern and the recognition that neither surgery nor radiation therapy restore hearing lost to a vestibular schwannoma, and both pose risks to cranial nerve function, observation is a reasonable choice for some patients. Such an approach requires that the patient be willing to undergo regular annual or semiannual clinical and imaging follow-up. This course may be selected by many patients with small acoustic neuromas, particularly older patients and patients with multiple medical comorbidities. Patients with functional hearing must understand that further hearing loss, including sudden hearing loss, can occur while under observation.

**Surgery**

Surgery has the unique advantage of removal of the schwannoma, with a low risk of recurrence following complete resection. Microsurgical resection has been the mainstay of treatment for many years and was previously recommended as the standard of care in a 1991 consensus statement. \(^{515}\) The three standard surgical approaches are translabyrinthine, middle cranial fossa, and retrosigmoid. The translabyrinthine approach uses a retroauricular excision and traverses the mastoid with removal of the petrous bone using a high-speed drill. The facial nerve is best visualized with this approach, being seen in the lateral IAC and separated from the tumor. The dura of the posterior fossa is then exposed and opened to remove the intradural tumor portion. Historically, this approach has sacrificed hearing due to destruction of the labyrinth. More recent techniques have allowed hearing preservation with a partial labyrinthectomy or avoidance of the bony labyrinth altogether. \(^{516,517}\) The translabyrinthine approach is generally used when patients have significant ipsilateral hearing loss and the chance of maintaining usable hearing is low. A commonly used cutoff is less than 50 db speech reception and 50% speech discrimination. \(^{518}\) The middle cranial fossa and retrosigmoid approaches both allow hearing preservation but suffer from poor visualization of small segments of the IAC. \(^{519,520}\) These “blind spots” can be visualized by adding endoscopy to the microsurgical resection. The middle cranial fossa approach starts with a supra-auricular incision and temporal craniotomy. The middle fossa floor is exposed and drilled to reveal the IAC, which is opened for tumor removal. This approach is limited in the size of tumors that can be removed (15 to 20 mm) and retraction of the temporal lobe is also required. The retrosigmoid approach uses a unilateral posterior fossa craniectomy, dural opening, and medial retraction of the cerebellum to expose the cerebellopontine angle. The lower cranial nerves are protected while the IAC is unroofed with a drill. The approach offers the ability to resect all tumor sizes and potential functional preservation of all cranial nerves, including a
Slightly diminished risk of facial nerve injury compared to the middle cranial fossa approach. Surgical risks include the inherent risk of general anesthesia, CSF leak, meningitis, headache, hearing loss, and facial nerve paralysis. Hearing preservation is influenced by preoperative hearing acuity, location of the tumor, and size. Loss of facial nerve function is the most significant surgical concern, as well as morbidity. Again, tumor size is a factor, as is the relationship between the facial nerve and tumor. Surgery is made particularly challenging by the increased adherence and infiltration in NF2. The risk of facial nerve injury has decreased since the advent of facial nerve electromyography for intraoperative monitoring. Auditory brainstem response may also be used to evaluate the integrity of the cochlear portion of the eighth cranial nerve intraoperatively, improving the odds of potential avoidance and preservation.

Most modern surgical series achieve complete resection in more than 90% of patients, with some reporting significantly higher rates. Subtotal resections are frequently deliberate to preserve hearing or provide emergent, life-saving decompression of the brainstem and fourth ventricle. Results appear to be both surgeon- and volume-dependent, leading to questions of the widespread applicability of results obtained by subspecialty surgeons in academic institutions. There also appears to be a significant learning curve of 20 to 60 patients with new surgical teams. An extensive surgical series of 962 patients undergoing 1,000 vestibular schwannoma operations has been compiled by Samii and Matthies, who reported a 98% complete resection rate with fewer than 1% of non-NF2 patients having a recurrence. The facial and cochlear nerves were preserved in 93% and 68% of patients, respectively, and functional preservation was 39% for patients with intact hearing preoperatively. Mortality was 1.1%, although this included several individuals who were disabled with advanced disease prior to surgery. If hearing is to be preserved, the auditory nerve is also identified and preserved; preservation of hearing is more likely in patients lacking severe adhesion in the interface between the cochlear nerve and the tumor. Life-threatening complications of acoustic neuroma resections are rare except in patients with extremely large tumors. The tendency of postoperative CSF leaks to develop in patients (10% to 13%) is independent of the surgical approach employed and tumor size and may stem from factors such as transient postoperative increases in CSF pressure. Postoperative headache was a significant morbidity in a cohort of 1,657 patients who underwent surgery for acoustic neuroma. Patients who underwent tumor resection by the retrosigmoid approach (82.3%) were significantly more likely to report their worst postoperative headache as “severe” than those resected using the translabyrinthine (75.2%) or middle fossa approaches (63.3%). In another quality-of-life study, hearing loss was perceived as the most disabling symptom among 386 patients who underwent acoustic neuroma surgery.

Radiosurgery
The most substantial experience in radiation-based treatment is with SRS. Both Gamma Knife (Elekta Corp, Stockholm) units and SRS-compatible linear accelerators may be used to perform SRS. The University of Pittsburgh published a review of 162 consecutive patients treated with SRS to a mean dose of 16 Gy with a tumor control rate of 98%. Subsequent surgical resection was required in four patients. Normal facial function was preserved in 79% and normal trigeminal function was preserved in 73% of patients. Because of the unacceptable cranial nerve morbidity in this and other series, the prescription dose for radiosurgery was lowered to 12 to 13 Gy. Results from the decreased prescription dose have a similarly low rate of recurrence, with 97% tumor control at a mean dose of 13 Gy. The risk of facial nerve weakness dropped to 1% and hearing preservation improved to 71%. These results were confirmed with longer follow-up. Recently, a prospective cohort study of 82 patients with unilateral vestibular schwannomas smaller than 3 cm compared surgical and SRS and provided level 2 evidence favoring SRS over microscopic surgical
resection. Tumor control was not statistically different (100% for surgery vs. 96% for SRS). Normal facial movement and preservation of serviceable hearing was more frequent in the SRS group at all time points, and no quality-of-life decline was seen in the SRS group.535

New incomplete trigeminal and facial cranial neuropathies typically develop at approximately 6 or more months after radiosurgery. These tend to be mild and usually improve within a year after onset. Approximately half of patients with useful hearing before radiosurgery maintain their pretreatment hearing level, and hearing lost before treatment is not regained. The risk of treatment-induced cranial neuropathy is directly related to the volume of the lesion, the dose given, and the length of nerve irradiated.

Fractionated Radiation Therapy

Different fractionation regimens have been tried to capitalize on theoretical radiobiologic differences between the neoplastic vestibular schwannoma and surrounding normal tissue. Multiple fractions also allow treatment of lesions that would otherwise not be amenable to treatment with SRS based on size (more than 3 cm) or location (direct compression of the brainstem). Hypofractionation was examined in a series that compared 25 Gy in five fractions and 30 Gy in ten fractions. Actuarial hearing preservation rate was 90% at 2 years, and no recurrence or facial nerve weakness occurred.536 A nonrandomized prospective trial from the Netherlands, however, had a nonstatistically inferior outcome in hearing preservation when comparing hypofractionation to SRS at 10 to 12 Gy.537 Comparison of FSRT (50 Gy in 25 fractions) to SRS in a prospective trial showed comparable high control rates and minimal cranial nerve injury, with the exception of retention of useful hearing, which was 81% versus 33% at 1 year (in favor of FSRT) when followed by serial audiometry.538 Similar rates of tumor control and hearing preservation have been reported by single-institution experiences elsewhere.539,540,541 Koh et al.540 treated 60 acoustic neuromas with FSRT and at a median follow-up of 31.5 months, the 5-year actuarial local tumor control rate was 96.2%, the overall hearing preservation rate was 77.3%, and there were no cases of new cranial nerve toxicity after treatment. FSRT appears to reduce cranial neuropathy rates compared to radiosurgery and allows treatment of larger tumors, but no randomized comparisons have been made.

Several issues confound radiation outcomes assessment for vestibular schwannoma. First, documentation of recurrences can be confounded by inherently slow growth rates and transient postprocedure lesion enlargement.542,543 Second, ionizing radiation does carry a small inherent risk of inducing secondary neoplasms or malignant transformation of the vestibular schwannoma.544,545 The risk of a secondary neoplasm can be particularly concerning in tumor-prone genetic conditions such as NF2. However, given the immense number of individuals who have undergone SRS worldwide, the number of presumed radiation-induced malignancies is only a handful and represents at most 1 per 1,000 patients. This is substantially lower than the rate of surgery-related mortality. Malignant transformation can also be seen in resected vestibular schwannoma patients who did not receive radiation.546 Finally, because of increased adherence of the facial nerve to the tumor, eighth nerve preservation rates are lower when excision is performed for regrowth after radiation when compared to a nonirradiated control group.547

Targeted Therapy for Vestibular Schwannoma

There is significant interest in the development of medical therapy for patients with refractory vestibular schwannoma. Aberrant signaling pathways are known to be present, and there are now reports of the use of targeted agents in this disease. In a single patient case report, the EGFR inhibitor erlotinib was associated with radiographic response of the tumor and improved audiologic function.548 There are also two reports of the use of bevacizumab in the treatment of vestibular schwannoma in the setting of NF1 in patients with a single hearing ear.549,550 These studies consisted of a small number of patients, but the demonstration of objective regression of tumors and improvement in hearing was impressive, highlighting
the need for larger prospective trials of antiangiogenic agents for this disease.

Glomus Jugulare Tumors

Clinical and Pathological Considerations

Glomus jugulare tumors (paragangliomas) arise from glomus tissue in the adventitia of the jugular bulb (glomus jugulare) or along Jacobson’s nerve in the temporal bone, sometimes multifocally. The tumor invades the temporal bone diffusely, but growth is characteristically slow. Sometimes these tumors are endocrine active, with a carcinoid- or pheochromocytoma-like syndrome. Because glomus jugulare tumors occur in the jugular foramen, they commonly cause lower cranial nerve palsies and early symptoms of hoarseness and difficulty swallowing. Facial weakness, hearing loss, and atrophy of the tongue from hypoglossal palsy can follow. Pulsating tinnitus also may be a presenting symptom, and a red pulsating mass is often visible behind the eardrum. A presumptive diagnosis of glomus tumor can be made by CT or MRI scanning, with jugular schwannoma and meningioma being the main differential diagnoses. On CT scans, glomus tumors show a characteristic salt-and-pepper appearance in involved bone; MRI often discloses large blood vessels within the mass. Glomus tumors give positive results on octreotide scintigraphy. These tumors incite a tremendous blood supply, particularly by way of the ascending pharyngeal artery.

Radiography provides the definitive diagnosis. Because preoperative tumor embolization is essential to surgical removal of glomus tumors, the diagnostic angiogram should be taken just before surgery. Histopathologically, numerous vascular channels are distinctive. The background is composed of clear cells clumped in a fibrous matrix. A small percentage of glomus tumors are malignant. There is a familial form in which the tumors are multiple.

Surgery

The treatment of glomus jugulare tumors is controversial, with advocates for surgery, radiation therapy, radiosurgery, and combined approaches. Although surgery can often provide a cure for these benign tumors, especially for small lesions, radiation therapy and radiosurgery avoid the morbidities that may follow surgical removal (lower cranial nerve and facial palsies). Surgery for glomus tumors is most often jointly performed by a neurosurgeon and an otorhinolaryngologist, after preoperative embolization, which may decrease intraoperative blood loss during resection of these extremely vascular tumors. Because these tumors often have intra- and extracranial components, surgery is usually conducted in two parts. The base of the skull in the region of the jugular foramen is first exposed, and neurovascular structures are identified and mobilized through a high transverse cervical incision. When the incision is extended behind the pinna and a mastoidectomy is completed, the facial nerve can be identified and protected, and the entire tumor bulb, jugular bulb, and internal jugular vein can be seen passing through the base of the skull. Finally, suboccipital craniectomy is performed, which allows the sigmoid sinus above and the jugular vein to be ligated, and the segment between them excised with the attached tumor. Complications of this procedure can include swallowing and aspiration problems, CSF leak, and facial palsy.

Liu et al. have recently described a single-stage transjugular posterior infratemporal fossa approach that allows radical resection of glomus jugulare tumors that are located around the jugular foramen, the lower clivus, and the high cervical region from an anterior direction. This approach allows exposure of the infratemporal carotid artery without transection of the external ear canal, permanent rerouting of the facial nerve, or mandibular translocation, and avoids morbidity from these procedures.

Radiation Therapy

Even though glomus tumors are histologically benign, radiation therapy is effective and has been...
recommended for symptomatic lesions that cannot be totally resected, even as primary treatment. These tumors regress slowly after irradiation, and the success of radiation therapy is measured by the amelioration of symptoms and the absence of disease progression. A review of the literature demonstrated local control rates with radiation in excess of 90% with or without surgery. A dose of 45 to 50 Gy in 5 weeks is recommended.

**Radiosurgery**

A literature review by Gottfried et al. showed that the use of SRS to treat glomus jugulare tumors has increased. Compared with conventional radiotherapy, radiosurgery involves a shorter treatment time, precise stereotactic localization, and irradiation of a small volume of normal tissue, which results in a reduced incidence of complications. Among 142 patients treated radiosurgically in eight series reviewed by Gottfried et al., tumors diminished in 36.5%, tumor size was unchanged in 61.3%, and subjective or objective improvements occurred in 39%. Although residual tumor was present in all of these patients, only 2.1% experienced progression, the morbidity rate was 8.5%, and no deaths occurred; however, the incidence of late recurrence is unknown. In another study of eight patients who underwent radiosurgery (median dose of 15 Gy to the tumor margin) for recurrent, residual, or unresectable glomus jugulare tumors, all remained stable without cranial nerve palsies at a median follow-up of 28 months. The authors suggested treatment of small glomus tumors (3 cm or less in average dimension) with radiosurgery and treatment of young patients with large tumors (3 cm or more in average dimension) and patients with symptomatic tumors with surgical resection.

**Hemangioblastomas**

**Clinical and Pathological Considerations**

Hemangioblastomas account for 1% to 2% of intracranial tumors, arising most often in the cerebellar hemispheres and vermis. Although usually solitary, these tumors can be multiple and may also occur in the brainstem, spinal cord, and, less often, the cerebrum. Cerebellar hemangioblastoma can be sporadic or occur as part of the autosomal dominant von Hippel-Lindau complex, which is transmitted with more than 90% penetrance. Other entities associated with von Hippel-Lindau disease are retinal angiomiomatosis, polycystic kidneys, pancreatic cysts, pheochromocytoma, and renal cell carcinoma. Identification of the VHL gene on chromosome band 3p25-26 allows individuals who are at risk for the syndrome, or who have some of its components as an apparent sporadic case, to undergo genetic testing with a high degree of accuracy.

Cerebellar hemangioblastomas usually are recognized in the third decade in patients with von Hippel-Lindau disease and in the fourth decade or later in patients with sporadic tumors. These tumors can cause symptoms and signs of cerebellar dysfunction, especially gait disturbance and ataxia, and hydrocephalus from obstruction of CSF pathways. These tumors tend to enlarge slowly, but patients may become symptomatic from tumor cysts, which can grow quickly.

Hemangioblastomas are composed of capillary and sinusoidal channels lined with endothelial cells. Interspersed are groups of polygonal stromal cells with lipid-laden cytoplasm and hyperchromatic nuclei. Immunohistochemical study of these cells shows expression of neuron-specific enolase, vimentin, and S100 protein but not epithelial membrane antigen or glial fibrillary acidic protein. Grossly, the tumor is often cystic, containing proteinaceous, xanthochromic fluid, with an orange-red, vascular, firm mural nodule. The cyst wall is a glial nonneoplastic reaction to fluid secreted by the nodule. Some hemangioblastomas lack cysts, especially in the brainstem and spinal cord, but cystic lesions are more often symptomatic, at least in patients with von Hippel-Lindau disease.
The natural history of spinal hemangioblastomas has been described. The authors reviewed the clinical records and MRIs of 160 consecutively treated patients with 331 spinal hemangioblastomas. Most lesions were located in the posterior cord. Cysts were commonly associated with the lesions, often showing faster growth than the solid portion of the tumor. When symptoms appeared, the mass effect derived more from the cyst than from the tumor. These tumors often have alternating periods of tumor growth and stability, and some remain stable in size for many years. These factors have to be considered in the timing and choice of treatment.

**Surgery**

Complete resection of a hemangioblastoma is often curative. Patients with preoperative hypertension should be evaluated for the presence of a pheochromocytoma, which can be associated with von Hippel-Lindau disease. Hemangioblastomas are very vascular lesions, and biopsy of a suspected hemangioblastoma, either through an open approach or stereotactically, is usually ill advised because of the high risk of hemorrhage. Surgical resection should be carried out *en bloc* with avoidance of entry into the lesion, which can result in fierce bleeding reminiscent of that of an arteriovenous malformation. Embolization is rarely safe. Fortunately, these lesions can be resected with minimal bleeding if resection is carried out entirely in the gliotic plane that surrounds the mass. This is straightforward in most cerebellar tumors, for which a margin of gliotic tissue can be resected with the lesion with little neurologic risk. In contrast, brainstem hemangioblastomas are immediately adjacent to critical structures. Sometimes, dissection immediately adjacent to the tumor can cause significant bleeding, with a high risk of inducing neurologic deficits. A report of 12 patients with von Hippel-Lindau disease confirmed that brainstem hemangioblastomas can be safely resected in some instances. In another study of 13 pediatric patients, successful surgical treatment of all patients, including 2 with brainstem tumors, was achieved. Morbidity was low and there were no recurrences during the follow-up period (mean, 24.6 months).

These tumors are often associated with significant cysts. Surgery is the optimal treatment for rapid relief of mass effect. The cyst wall is not lined with tumor cells, and drainage, rather than excision of the cyst lining, is required. The mural tumor nodule must be entirely resected to avoid cyst recurrence. Cysts can be drained before opening the dura completely to provide brain relaxation, but great care must be taken not to disturb the tumor nodule during this maneuver to avoid inducing significant bleeding. The risk of hemorrhage during the resection is minimized by coagulating and dividing arterial feeders before tumor removal.

Finally, hemangioblastomas that occur in patients known to have von Hippel-Lindau disease need not be resected or otherwise treated unless they have demonstrated active growth or are symptomatic from mass effect or hydrocephalus. Because many of these patients harbor multiple tumors, other approaches, including radiosurgery, should also be considered, although surgery remains a viable option.

**Radiation Therapy**

Radiation therapy is recommended for patients with unresectable, incompletely excised, and recurrent hemangioblastomas and for those who are medically inoperable. Smalley et al. reported outcomes of 25 patients treated with radiation therapy. Nineteen patients had gross residual disease after initial surgery or recurrent tumors; six had only microscopic disease. The overall 5-, 10-, and 15-year survival rates were 85%, 58%, and 58% and the recurrence-free survival rates were 76%, 52%, and 42%, respectively. In-field disease control rates were significantly higher in patients who received at least 50 Gy of radiation than in those who received lower doses. Based on these data, doses of at least 50 to 55 Gy in 5.5 to 6 weeks appear to be warranted. Because of the noninvasive nature of these lesions, conformal radiotherapy or radiosurgery is indicated.
Patrice et al.\textsuperscript{564} summarized the outcomes for 38 lesions in 22 patients who received radiosurgery as definitive treatment or for recurrent tumors after surgery with or without conventional radiotherapy. The median tumor volume was 0.97 cc and the median radiation dose was 15.4 Gy. With a median follow-up time of 24.5 months, 31 of 36 evaluable tumors (86%), including all tumors treated definitively with radiosurgery, remained locally controlled. The five lesions that relapsed after radiosurgery had all been treated for recurrence after initial surgery. Better control rates were associated with higher doses and smaller tumor volumes. The 3-year actuarial progression-free survival rate was 86%. Of 29 hemangioblastomas treated by Chang et al.\textsuperscript{565} only one (3%) progressed. Jawahar et al.\textsuperscript{566} reported treatment of 29 lesions in 27 patients. The actuarial control rate was 84.5% at 2 years and 75.2% at 5 years. In multivariate analysis, smaller tumor volume and higher dose (more than 18 Gy) were favorable. Radiosurgery should be considered for surgically unresectable hemangioblastomas, as adjuvant treatment for incompletely excised tumors, as definitive treatment for multifocal disease, and as salvage therapy for discrete recurrences after surgery.\textsuperscript{564,565}

Nevertheless, based on a series of 30 hemangioblastomas arising in 14 patients with von Hippel-Lindau disease, Rajamaran et al.\textsuperscript{567} concluded that, although radiosurgery offered reasonable local control rates (reaching 83% at 6 years), the greater problem is the tendency for intracranial disease progression, the average time for this being 3 to 4 years (both before and after radiosurgery). To determine the effectiveness of radiosurgery for CNS hemangioblastomas, Asthagiri et al.\textsuperscript{568} analyzed long-term results in von Hippel-Lindau disease patients treated with SRS. Patients were enrolled in a prospective von Hippel-Lindau disease natural history study, undergoing SRS treatment of CNS hemangioblastomas. Treatment regimens, serial clinical evaluations, and longitudinal imaging data were analyzed. Twenty von Hippel-Lindau disease patients (10 males and 10 females) underwent SRS treatment of 44 CNS hemangioblastomas (39 cerebellar and 5 brainstem), with a mean dose of 18.9 Gy. At a mean follow-up of 8.5 years, all patients were alive, and local control rates at 2, 5, 10, and 15 years after SRS were 91%, 83%, 61%, and 51%, respectively. Thirty-three percent of SRS-treated small (less than 1.0 cm diameter) asymptomatic tumors progressed over long-term follow-up. There were no long-term adverse radiation effects. Although SRS treatment of hemangioblastomas in von Hippel-Lindau disease has a low risk for adverse radiation effects, it is associated with diminishing control over a long-term follow-up. These results indicate that SRS should not be used to prophylactically treat asymptomatic tumors and should be reserved for the treatment of tumors that are not surgically resectable.

Because stromal cells in hemangioblastomas secrete VEGF, there is much interest in evaluating small-molecule inhibitors of the VEGF-2 (KDR, FLK-1) receptor as medical management for these tumors, especially for patients with von Hippel-Lindau disease, who routinely harbor multiple hemangioblastomas. Unfortunately, the extreme heterogeneity of tumor growth, with periods of spontaneous stability and a slow overall growth rate, makes it extremely difficult to design trials to test rigorously the efficacy of any systemic therapy.

\textbf{Chordomas and Chondrosarcomas}

Chordomas and chondrosarcomas are rare, locally destructive, slow-growing, malignant bone tumors. Although skull-base chordomas and chondrosarcomas are sometimes pooled together, recent studies have shown important differences between these entities.

\textbf{Clinical and Pathological Considerations}

Chordomas arise within aberrant chordal vestiges along the pathway of the primitive notochord that extends from the tip of the dorsum sellae to the coccyx.\textsuperscript{569} One-third of chordomas arise cranially, with this location more common in women and younger individuals.\textsuperscript{570} Chordomas are extradural, pseudoencapsulated, multilobulated tumors, with a gelatinous consistency centered in the bone, classically with soft tissue extension. Microscopically, the typical chordoma is characterized by cordlike
rows of “physaliferous” cells with multiple round, clear cytoplasmic vacuoles that impart a bubbly appearance to the cytoplasm. Two pathologic variants have been described. The chondroid chordoma has areas with cartilaginous features but a genetic profile distinct from chondrosarcomas.\textsuperscript{571} The dedifferentiated chordoma contains areas of typical chordoma admixed with components that resemble high-grade or poorly differentiated spindle cell sarcoma. In typical chordomas, mitotic figures and atypia are rare; a higher mitotic rate and Ki-67 more than 6\% are associated with a shorter doubling time.\textsuperscript{572}

Chondrosarcomas are cartilage-producing neoplasm that arise within any of the complex synchondroses in the skull base, with the most common sites of origin being the temporo-occipital synchondrosis (66\%), the sphenop-occipit synchondrosis (28\%), and the sphenoethmoid complex (6\%).\textsuperscript{573} Thus, chondrosarcomas predominantly originate in more lateral skull-base structures, unlike most chordomas, which originate in the midline. Chondrosarcomas can be difficult to differentiate from chordomas on pathologic examination. Immunohistochemical advances have improved differentiation between chordomas and chondrosarcomas. In one series of 200 chondrosarcomas, 99\% stained positive for S100, 0\% for keratin, and epithelial membrane antigen was expressed in 8\%.\textsuperscript{573} These immunohistochemical studies allow a chondrosarcoma to be differentiated from a chordoma, which is reactive for keratin and epithelial membrane antigen. The same series confirmed the low-grade nature of base of skull chondrosarcomas as a majority were grade 1, with no grade 3 tumors identified. Mesenchymal chondrosarcomas may have a separate, more aggressive natural history.\textsuperscript{574}

Symptoms that prompt evaluation are typically cranial nerve deficits with the precise deficit dependent on the location and extent of the tumor. In one series, the most common presentation was headaches with intermittent abducens nerve palsy.\textsuperscript{575} Additional symptoms can be caused by intracranial extension with compression of the brainstem, pituitary gland, or optic apparatus. Neck pain may develop in lower clival tumors, possibly the result of pathologic fracture or periosteal expansion.

Chondrosarcomas and chordomas cannot be reliably distinguished from each other based on imaging features or location alone.\textsuperscript{576} High-resolution CT images with bone and soft tissue algorithms show a discrete, expansile soft tissue mass with extensive bony destruction.\textsuperscript{577} On MRI scanning, both chordomas and chondrosarcomas are hyperintense on T2-weighted sequences, with variegated enhancement. The location may be useful in distinguishing chordomas (midline clivus) from chondrosarcomas (petrous apex), although there is considerable overlap. Given the low risk of nodal or hematogenous dissemination, imaging beyond the primary site other than a chest x-ray is typically not indicated unless metastatic disease is suspected clinically.\textsuperscript{578} A baseline endocrine evaluation and neuro-ophthalmologic examination are both recommended if diagnostic imaging or symptoms suggest involvement.

**Surgery**

Surgery for cranial chordomas and chondrosarcomas provides the backbone of treatment and is obligatory to obtain diagnostic tissue, to enhance the effectiveness of subsequent radiation therapy, and to improve the patient’s clinical condition. An aggressive initial approach may improve overall outcome.\textsuperscript{579} Intracranial chordomas occur at the base of the skull, a region relatively remote from surgical access. Approaches to skull-base chordomas and chondrosarcomas often involve teams that include both neurosurgeons and otolaryngologists. For chordomas in the upper clivus that extend into the sella or sphenoid sinus, or both, a transseptal, transsphenoidal approach (as for pituitary tumors) is best. Large, compressive, transdural extensions of these upper clivus tumors into the interpeduncular cistern can be removed using a
transcranial, subtemporal, intradural approach. For more lateralized upper clival tumors and some lateralized midclival tumors, an approach through a sphenosethmoidectomy (to which may be added a maxillectomy) is useful. For midline tumors of the midclivus and lower clivus, a transoral resection is often used. The palate or mandible and tongue can be split if upward or downward extension of the approach is necessary. There is developing interest in the use of endoscopy for primary removal of chordomas or to assist in the removal of these tumors via traditional open approaches. Although most series remain small, excellent results have been reported in appropriately selected patients not having extension lateral to the carotid arteries. A combination of exposures and procedures can be used for extremely large tumors. One goal of surgery is to remove as much tumor from the optic system and brainstem as possible so that very high doses of radiation can be delivered safely. Optimal treatment of these lesions is complete resection, if possible.

A potentially serious complication of the transsphenoidal, transsphenothmoid, and transoral approaches is CSF leakage into the nose or oropharynx and consequent meningitis. Therefore, every attempt is made to keep the dura intact during these procedures. Because dural invasion by cranial chordomas may occur 50% of the time, dural entry during tumor resection is sometimes unavoidable. Careful intraoperative patching of the leak with fat and muscle grafts followed by postoperative spinal CSF drainage should be undertaken to decrease the risk of infection in these cases. This may be more challenging in the setting of a total endoscopic tumor removal, although some techniques appear to be associated with reasonably low rates of CSF leak. Surgical series have reported gross total resection rates of 43% to 72%, with the most recent series using modern imaging and microsurgical techniques reporting the highest gross total resection rate. In this series there was a 31% recurrence-free survival at 10 years, which was improved for those without previous intervention, and a 35% recurrence after gross total resection. Extent of resection correlated with both recurrence rates and survival. Surgical morbidity can be significant, with Gay et al. reporting a significant transient (53%) and permanent (43%) worsening of Karnofsky performance score following surgery.

Approaches for chondrosarcomas are different because of the paramedian location of the tumors. Like chordomas, chondrosarcomas begin as extradural tumors, and maintaining the intact dural barrier is paramount. Most commonly, a variation of the subtemporal middle fossa approach to the upper clivus is used to approach the petroclival synchondrosis. Extradural tumors can be removed through both the middle fossa and presigmoid avenues combined with a presigmoid and retrosigmoid approach. Complete tumor excision, which is paramount in chordoma surgery, is less critical for chondrosarcomas because tumor control rates with adjuvant high-dose radiation are high. Surgery is often tailored to emphasize removal of tumor portions abutting critical structures such as the chiasm or brainstem to allow adequate radiation treatment.

Cranial chordomas often recur after surgery and radiation therapy. In this situation, reoperation directed toward symptomatic improvement is the only treatment option. Reoperations are complicated by surgical scarring and tissue compromise from irradiation, and CSF leaks and other complications are more frequent.

**Radiation Therapy**

Radical excision with negative margins is often not feasible, and even gross excision is often obtained piecemeal with the risk of persistent microscopic disease. As relentless extension is typical of chordomas and chondrosarcomas and recurrence is a strong predictor of overall survival, adequate local control is paramount in determining outcome. Radiotherapy is a mainstay of treatment in preventing recurrence or progression of tumor. Local control of chordomas appears to be dose dependent. Conventional radiation at doses of 50 to 55 Gy does not offer satisfactory local control. A median dose of 50 Gy to chordomas of the skull, sacrum, and
mobile spine provided only a 27% local control rate with a median time to progression of 35 months. Durable control was worse in base of skull disease, with only 1 of 13 clival chordomas remaining disease free. FSRT to 37 sphen-occipital chordomas to a mean dose of 66.6 Gy provided local control rates of 82% at 2 years and 50% at 5 years. Despite a median tumor volume of 55.6 cc, complications were limited with one patient developing a pontine infarct 25 months posttreatment. No instances of optic neuropathy were identified. Chondrosarcomas treated with the same fractionation scheme had 100% 5-year local control.

**Radiosurgery**

SRS has been used to treat chordomas and chondrosarcomas of the skull base, although its application is limited because of size constraints and proximity to critical structures. In one series, candidates were limited to less than 3 cm in greatest diameter and 5 mm from the optic chiasm, with a mean treatment volume of 4.6 cc and a maximum volume of 10.3 cc. With a mean margin dose of 18 Gy, more than 50% of patients in this mixed series of chondrosarcomas and chordomas had symptomatic improvement and, at a mean follow-up of 40 months, 20% had recurred locally outside the treatment field. Krishnan et al. reported a similar local control rate (24%) with both in-field and out-of-field recurrences, although no recurrences occurred in patient with chordoid chordoma or chondrosarcomas. The risk of significant radiation-related complication was high at 34%, although complications were seen only in patients who had received prior fractionated radiotherapy.

**Particle-Beam Therapy**

Charged-particle therapy, because of its innate dose-distribution advantages, has been used for many years to escalate dose to chordomas and chondrosarcomas while minimizing radiation-related side effects. The most extensive experience in treating base of skull chordomas and chondrosarcomas with proton therapy arises from the experience at the Harvard Cyclotron Laboratory. Chordoma relapse-free survival was 59% at 4 years and 44% at 10 years, with similar rates seen in other series. Mean dose ranged from 67 to 70.7 CGE (cobalt gray equivalent). Female gender, dose heterogeneity, large tumor size (more than 25 to 75 cc), brainstem invasion, and dose constrained by proximity to critical structures were all associated with higher rates of recurrence. In a study of skull-base chordomas in 73 children and adolescents (mean age, 9.7 years), patients were treated with partial or gross surgical excision and postoperative proton beam irradiation. The mean follow-up period was 7.25 years, and the overall patient survival rate was 81% among 42 patients with conventional chordomas, 17 with chondroid chordomas, and 14 with cellular chordomas, 6 of which were poorly differentiated and highly aggressive. Chondrosarcomas of the skull base had remarkably high local control rates of 99% and 98% at 5 and 10 years, respectively. Pituitary dysfunction and hearing loss were the most common side effects, with depression, memory loss, temporal necrosis, hearing loss, and blindness being less common. Given the relative lack of morbidity and the suboptimal local control for chordomas, dose escalation has been proposed. Recent radiotherapeutic advances include spot-scanning proton radiation, which creates a near-monoenergetic Bragg peak and improved radiation dose falloff. Carbon ion radiotherapy, charged-particle therapy using a heavier ion, has also been used with good local control with short follow-up and better than expected radiographic responses. Amichetti et al. recently conducted a systematic review of the scientific literature published between 1980 and 2008 on data regarding irradiation of chondrosarcoma of the skull base with proton therapy. From 49 reports retrieved, there were no prospective trials and 9 uncontrolled single-arm studies mainly related to advanced and frequently incompletely resected tumors. According to the inclusion criteria, only four articles, reporting the most recent updated results of the publishing institution, were included in the analysis, providing clinical outcomes for 254 patients. The major findings corroborated the high control rates with low morbidity described above.
Choroid Plexus Tumors

Clinical and Pathological Considerations

Primary tumors of the choroid plexus (CP) are classified according to the World Health Organization as CP papilloma (CPP, WHO grade I), atypical CPP (grade II), and choroid plexus carcinoma (CPC, grade III).29 These are rare tumors that occur most often in children younger than 12 years of age. They appear irregular and lobulated, often very red because of underlying vasculature. Histopathologic examination of papilloma often shows apparently normal choroid plexus, with increased cellular crowding and elongation. Rarely, these tumors show malignant features such as increased cellularity, high mitotic activity, loss of typical cellular architecture, and invasion of the brain parenchyma, and are then classified as choroid plexus carcinoma. Bridging the CPP and CPC is the entity called atypical CPP. Histologically atypical CPP retains the architecture of the CPP but has high mitotic activity and an increase probability for recurrence after surgical resection.

CPC is commonly seen in families who carry a germline mutation in either the TP53 gene (Li-Fraumeni syndrome) or INI1 gene (rhabdoid predisposition syndrome).596 However, most patients with CPP and sporadic CPC do not harbor a germ-line TP53 mutations.

In children, choroid plexus papillomas most often occur in the lateral ventricles. In adults, the fourth ventricular papilloma is most common. Third ventricle tumors are exceedingly rare. Because papillomas tend to grow slowly within ventricles, they expand to fill the ventricle and block CSF flow. In addition, papillomas can secrete CSF. Choroid plexus papillomas and carcinomas can produce hydrocephalus secondary to obstruction of the CSF, CSF overproduction by the tumor, or damage to the CSF resorptive bed from recurrent hemorrhages. As a result, increased ICP without focal findings is the most common presentation. Fourth ventricular tumors can also be associated with focal findings of ataxia and nystagmus. Although choroid plexus papillomas rarely seed throughout the CSF spaces, seeding from carcinomas is frequent and often symptomatic.

Choroid plexus tumors are seen easily by MRI. Imaging demonstrates a lobulated, well-circumscribed, enhancing, intraventricular lesion, often with associated hydrocephalus. Calcification is not common. Choroid carcinoma may show areas consistent with necrosis and brain invasion.597 Staging of the craniospinal axis with brain and spinal MRI and CSF analysis is recommended for patients with choroid tumors with anaplastic features.

Surgery

The treatment of choroid plexus papillomas is total excision. Tumors in the lateral ventricle are approached through the ventricular trigone using a high parietal incision or a low temporal approach, depending on the degree of cortical mantle thinning and the location of the tumor. The predilection of these tumors for the left (usually dominant) side can make the approach worrisome. Hydrocephalus is the rule and simplifies the exposure once the ventricle is opened. Tumor associated branches of the choroidal vessels are coagulated and divided as early as is feasible in the procedure as this greatly reduces hemorrhage. Smaller tumors are removed intact and larger tumors piecemeal. Perioperative CSF drainage is used to prevent subdural hygromas. In half of patients, hydrocephalus is relieved by tumor resection, but persistent hydrocephalus requires shunting. Endoscopy is increasingly used for intraventricular surgery. A review of 75 cases treated between 1985 and 2000 showed 84% survival in patients who had complete resections, compared with 18% survival in those undergoing less than a gross resection.598 This significant survival difference was seen regardless of adjuvant therapies. Unfortunately, total resection is not possible
in many patients. The ability to perform a complete resection depends on histologic type, with nearly a 100% complete resection rate for papillomas versus only a 33% complete resection rate for choroid plexus carcinoma. A meta-analysis of all individual cases of choroid plexus carcinoma reported as of 2004 (347 patients) showed that in the subgroup of incompletely resected carcinomas, 22.6% of patients required a second surgery. The prognosis for these patients appeared better than for those with incomplete resections who did not undergo a second surgery (2-year overall survival times were 69% and 30%, respectively). Often, tumor hypervascularity is the limiting surgical factor, especially in infants, who have small total blood volumes. When carcinoma is suspected before surgery, the tumor can be embolized or neoadjuvant chemotherapy given to shrink it and reduce its vascularity, which facilitates resection.

**Radiation Therapy**

Because choroid plexus papillomas are often cured by complete resection, radiotherapy is infrequently employed. Further, in a study of 41 patients, Krishnan et al. noted that reoperation for recurrence was required only half the time after initial subtotal resection, suggesting that adjuvant radiotherapy may not be necessary after initial subtotal resection in all patients. Because local control outcome at first relapse was poor after subtotal resection, they concluded that the most reasonable role for radiation therapy is after subtotal resection of a recurrence.

Radiation therapy may be beneficial in some patients with choroid plexus carcinomas even after gross total resection. A review of 566 choroid plexus tumors suggested that adjuvant radiotherapy increased survival in patients with choroid plexus carcinoma regardless of the extent of surgery. All of the long-term survivors had complete resection and adjuvant radiotherapy. Another study analysed choroid plexus tumors in 64 patients and found 50% of the CPCs harbored TP53 mutation; 14 of the 16 patients who did not have mutated TP53 were long-term survivors after complete resection and no irradiation. The 5-year survival rate was 0% after resection and irradiation in patients whose tumors showed TP53 immunopositivity.

Because CSF seeding occurs in up to 44% of cases, craniospinal axis irradiation has been proposed, although no significant studies support this practice. Chow et al. recommend that patients with completely excised localized choroid plexus carcinomas be treated with limited field irradiation if their spinal MRI and CSF cytologic study results are negative. They advised CSI for those with incompletely excised tumors or evidence of leptomeningeal spread.

**Chemotherapy**

Chemotherapy is not used for choroid plexus papillomas, although it has been attempted for choroid plexus carcinomas. As with many of the less-common CNS tumors, there are no firm guidelines. Anecdotal reports have cited moderate responses to the platinum compounds, as well as to alkylating agents, etoposide, methotrexate, and possibly anthracyclines. A Pediatric Oncology Group study of eight infants with choroid plexus carcinoma suggests that radiation can be forestalled by using chemotherapy in some infants with these tumors. In a meta-analysis conducted by Wrede et al. 347 CPCs were analysed; 104 cases with CPC received chemotherapy and had a statistically better survival that those without chemotherapy. Chemotherapy remained beneficial in the subgroup who did not receive irradiation and who had an incomplete resection. There is scarcity of data on optimal chemotherapy. The SIOP is conducting a study for choroid plexus tumors. In the study patients with CPP tumors will be observed while CPC tumors will be randomized to receive maintenance chemotherapy consisting of cyclophosphamide, etoposide, and vincristine versus carboplatin, etoposide, and vincristine. Radiation therapy is recommended for children older than 3 years of age.
Spinal Axis Tumors

Clinical and Pathological Considerations

Most primary spinal axis tumors produce symptoms and signs as a result of cord and nerve root compression rather than parenchymal invasion. The frequency of primary spinal cord tumors is between 10% and 19% of all primary CNS tumors. Parenthetically, the majority of neoplasms that affect the spine are extradural metastases, whereas most primary tumors are intradural. Of the intradural neoplasms, extramedullary schwannomas and meningiomas are the most common. Schwannomas and meningiomas are normally intradural, but occasionally may present as extradural tumors. Other intradural, extramedullary neoplasms include vascular tumors, chordomas, and epidermoids. Intramedullary tumors include ependymomas, comprising approximately 40% of intramedullary tumors; the remainder are astrocytomas, oligodendrogliomas, gangliogliomas, medulloblastomas, and hemangioblastomas.

Approximately half of spinal tumors involve the thoracic spinal canal (the longest spinal segment), 30% involve the lumbosacral spine, and the remainder involve the cervical spine, including the foramen magnum. Schwannomas occur with greatest frequency in the thoracic spine, although they can be found at other levels. They often extend through an intervertebral foramen in a dumbbell configuration. Meningiomas are dural based and arise preferentially at the foramen magnum and in the thoracic spine. Most patients are women. Astrocytomas are distributed throughout the spinal cord, and most ependymomas involve the conus medullaris and the cauda equina. Spinal chordomas are characteristically sacral and only rarely affect the cervical region or the rest of the mobile spine.

Patients may present with a sensorimotor spinal tract syndrome, a painful radicular spinal cord syndrome, or a central syringomyelic syndrome. In the sensorimotor presentation, symptoms and signs reflect compression of the cord (Table 121.4). The onset is gradual during weeks to months, initial presentation is asymmetric, and motor weakness predominates. The level of impairment determines the muscle groups involved. Because of external compression, dorsal column involvement results in paresthesia and abnormalities of pain and temperature on the side contralateral to the motor weakness.

Radicular spinal cord syndromes occur because of external compression and infiltration of spinal roots. The main symptom is sharp, radicular pain in the distribution of a sensory nerve root. The intense pain is often of short duration, with pain that is more aching in nature persisting for longer periods. Pain may be exacerbated by coughing and sneezing or other maneuvers that increase ICP. Local paresthesia and numbness are common, as are weakness and muscle wasting. These findings often precede cord compression by months. Often the pain is difficult for the clinician to differentiate from ordinary musculoskeletal symptoms, which causes diagnostic delay.

Intramedullary tumors in particular can give rise to syringomyelic dysfunction by destruction and cavitation within the central gray matter of the cord. This produces lower motor neuron destruction with associated segmental muscle weakness, atrophy, and hyporeflexia. There is also a dissociated sensory loss of pain and temperature sensation with preservation of touch. As the syrinx increases in size, all sensory modalities are affected.

Surgery

The operating microscope is essential for spinal cord tumor surgery. Ultrasonography can be used to examine the spinal cord through either intact or open dura to find the level of maximum tumor involvement or to differentiate tumor cysts from solid tumors. Intraoperative monitoring of somatosensory evoked potentials is commonly used, although some surgeons think that changes in somatosensory evoked potentials...
potentials may occur only after irretrievable damage has occurred, and this remains a topic of controversy. Motor-evoked potentials are used in some centers to guide resection and have retrospectively been shown by some to decrease long-term motor deficits.

MRI is invaluable for the diagnosis, localization, and characterization of spinal tumors. For extremely vascular tumors, notably hemangioblastoma, angiography may provide important preoperative delineation of the tumor blood supply. CT scanning is useful for tumors of the bony axis. Determination of the spinal level of the tumor and its exact relation to the cord is important. Corticosteroids are given before, during, and after spinal cord tumor surgery to help control spinal cord edema.

Meningiomas and schwannomas occur in the intradural, extramedullary spinal compartment. Most of these tumors can be completely resected through a laminectomy. They can be easily separated away from the cord, which is displaced but not invaded by tumor. Schwannomas arise most often in the dorsal spinal rootlets, and their removal includes the rootlets involved. They can grow along the nerve root in a dumbbell fashion through a neural foramen. Some of these can be removed by extending the initial laminectomy exposure laterally, whereas others require a separate operation (thoracotomy, costotransversectomy, or a retroperitoneal approach). Strictly anteriorly situated cervical tumors can successfully be removed via an anterior approach using corpectomy of the appropriate vertebral levels, followed by strut grafting after the tumor resection.

The most common intramedullary tumors are ependymoma and astrocytoma. Except for malignant astrocytomas, resection is the principal treatment for these tumors. Intramedullary tumors are approached through a laminectomy. After dural opening, a longitudinal myelotomy is made, usually in the midline or dorsal root entry zone. The incision is deepened several millimeters to the tumor surface. Dissection planes around the tumor are sought microsurgically and, in the case of ependymomas, usually found and extended gradually around the tumor's surface, whereas removal of the central tumor bulk (by carbon dioxide laser or ultrasonic aspirator) causes the tumor to collapse. Such tumors are usually completely removed, with good long-term outcome. Some patients later develop spinal deformity, requiring stabilization procedures. Tumors without clear dissection planes (usually astrocytomas) cannot be removed completely, but bulk reduction can cause long-term palliation. If frozen-section analysis shows a tumor to be a malignant glioma, a less aggressive surgery is typically performed due to increased risk of morbidity with little benefit achieved from an extensive debulking procedure.

**Radiation Therapy**

Radiation therapy is recommended for unresectable and incompletely resected neoplasms of the spinal axis. In general, doses of 50 to 54 Gy (1.8 Gy/d) are used so that the risk of injury to the cord from radiation is minimized. When lesions involve only the cauda equina or when complete, irreversible myelopathy already has occurred, higher doses are used.

Ependymomas have a longer natural history than astrocytomas. Recurrence of ependymomas may be delayed for as long as 12 years. Radiation therapy is not necessary when ependymomas are removed completely in an en bloc fashion. All nonirradiated patients with incompletely excised lesions reported by Barone and Elvidge and by Schuman et al. experienced recurrence. Postoperative irradiation appears to improve tumor control for incompletely resected ependymomas. Five- and 10-year survival rates in irradiated patients with localized ependymomas range from 60% to 100% and 68% to 95%, respectively, whereas 10-year relapse-free survival rates vary from 43% to 61%. Tumor grade has a significant effect on outcome. Waldron et al. found that for patients with well-differentiated tumors, the 5-year cause-specific survival was 97% compared with 71% for patients with intermediate or poorly differentiated tumors (P = .005). Myxopapillary ependymomas that arise in the conus medullaris and filum terminale have a better prognosis than the cellular ependymomas that arise in the cord. Local recurrence is the predominant
pattern of treatment failure, occurring in 25% of irradiated patients.\textsuperscript{612}

The 5- and 10-year survival rates for irradiated patients with low-grade astrocytomas of the spinal cord vary from 60% to 90% and 40% to 90%, respectively; 5- and 10-year relapse-free survival rates range from 66% to 83% and 53% to 83%, respectively.\textsuperscript{610,612} Fifty percent to 65% of astrocytomas are controlled locally. Good neurologic condition at the time of irradiation, lower histologic grade, and younger age are favorable factors.\textsuperscript{617} Patterns of recurrence for malignant astrocytomas of the spine have been analyzed by MRI.\textsuperscript{618} Despite surgery and full-dose radiation, spinal or brain dissemination is the predominant mode of failure.

**Chemotherapy**

There are no significant controlled clinical trials of chemotherapy for primary spinal axis tumors. Drugs active against intracranial tumors logically may be assumed to be equally efficacious against histologically identical tumors in the spinal cord. Temozolomide is being increasingly used in this setting.

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