Tolerance of the Central Nervous System to Irradiation

The central nervous system (CNS) is a relatively sensitive, often dose-limiting tissue in curative radiation therapy for CNS and adjacent neoplasms. Radiation injury has been documented on the basis of clinical signs, imaging findings, and histopathologic correlations. CNS effects are more pronounced in children and seem to be inversely related to age, with the youngest children having the greatest CNS sensitivity. Of further concern is that numerous chemotherapy agents are associated with unique or enhanced sequelae when given in conjunction with radiation therapy.

Studies of laboratory models of cerebral and spinal cord changes have helped to clarify the pathophysiology of radiation-induced neural damage and to associate the extent of damage with time, dose, delivery, and volume. For example, Caveness reported a detailed investigation of the clinical, histologic, and physiologic findings in primates after irradiation comparable with that used clinically. In that study, a single fraction of 20 Gy was uniformly fatal by week 26; this dose produced increased intracranial pressure and ventriculomegaly with scattered necrotic foci most dramatically affecting the brainstem. A single fraction of 15 Gy produced discrete microfoci of white matter necrosis by 26 weeks, with coalescing areas of white matter necrosis evident by 56 weeks. Pathologic findings were less pronounced in animals killed 78 weeks after irradiation, suggesting that some recovery had taken place. No clinical or histologic abnormalities were observed after whole-brain irradiation with a single fraction of 10 Gy or with 40 Gy delivered in 20 fractions over 4 weeks.

In experiments more relevant to clinical radiation therapy, delivering 60 Gy to the whole brain in fractions of 2 Gy over a period of 6 weeks caused papilledema and anorexia in pubertal monkeys, but no overt clinical findings were apparent in adult primates. Histologically, the adult brains showed discrete microfoci of white matter necrosis with calcifications by 26 weeks; healing of the degenerative foci along with increased microcalcifications was seen by 52 weeks. The radiation-induced changes were quantitatively greater in younger animals. After 80 Gy delivered in 40 fractions, confluent areas of necrosis appeared in the cerebral hemispheres of younger animals by 32 weeks, progressive necrosis was observed at 52 weeks, and coalescent necrotic regions and atrophy were seen by 78 weeks.

Caveness' findings at lower dose levels are similar to the mineralizing microangiopathy seen in children with acute leukemia treated with cranial irradiation (20 to 24 Gy) and methotrexate. Small, coalescent foci of necrosis related to microvascular changes may account for the clinically silent lacunar lesions evident in magnetic resonance imaging (MRI) studies of long-term survivors of childhood brain tumors.

Postirradiation CNS effects are typically classified temporally as acute, subacute, and late reactions. Fractionated radiation rarely produces clinically apparent acute changes, even when the total dose approaches 70 to 80 Gy. Anecdotal reports of transient exaggeration of neurologic signs have been related theoretically to perilesional or intralesional edema that develops at the beginning of irradiation. Young and colleagues found abrupt neurologic deterioration in 50% of patients who were given large (7.5- to 10-Gy) fractions for the treatment of symptomatic cerebral metastases; the investigators attributed this effect to the radiation therapy. Although no similar phenomena were reported in studies by the Radiation Therapy Oncology Group (RTOG) in which 6-Gy fractions were administered, this finding might have been related to the more consistent use of corticosteroids by the RTOG.

Subacute CNS effects are rather common. Jones observed transient, self-limited paresthesias with neck flexion (Lhermitte's sign) that lasted for 1 to 2 months after spinal cord irradiation. These paresthesias, which occur in 15% to 25% of patients after mantle irradiation for Hodgkin disease, are thought to result from transient...
demyelination. Comparable transitory neurologic changes, called the somnolent syndrome, occur after cranial irradiation such as that given for acute leukemia; mild encephalopathy or focal neurologic changes can appear after the treatment of intracranial tumors. The cranial syndrome is thought to stem from a transient demyelinating event and is the result of the effects of radiation on the replicating oligodendrocytes. MRI can detect specific dose-related changes in gray and white matter within several weeks of conventionally fractionated irradiation. The potential for self-limited neurologic deterioration, most often occurring during the second month after irradiation, is important to bear in mind because clinical and radiologic changes can sometimes mimic tumor progression.

Late reactions of the normal brain are the dose-limiting toxicities for radiation treatment. Clinical manifestations of focal neurologic deficits, encephalopathy, or neuropsychological dysfunction accompany various morphologic findings, such as atrophy, calcifications, diffuse white matter degeneration, and focal necrosis. Permanent or progressive myelopathy can result from spinal cord irradiation. Late changes in hypothalamic-pituitary function manifest as specific radiation-induced endocrine deficits.

**Postirradiation Cerebral Necrosis**

Postirradiation cerebral necrosis, the most direct effect of CNS irradiation, is thought to result from direct effects of radiation on the replicating glial cell compartments and the capillary endothelial cells. The theoretical relationship between primary glial cells (i.e., type II astrocytes and oligodendrocytes) and vascular endothelial components is shown in Figure 33-1. Clinical signs of postirradiation cerebral necrosis are seen 6 to 36 months after therapy. Cerebral changes often mimic residual or recurrent tumor, with mass effect, enhancement, or cyst formation evident on computed tomography (CT) scans; these changes occur at or near the site of the primary tumor (i.e., the high-dose volume for intracranial neoplasms).

Cerebral necrosis unrelated to intraparenchymal neoplasms has been described in reviews by Kramer and colleagues and Sheline and coworkers. Necrosis has been observed after therapy for extracranial tumors (predominantly those of the skin and paranasal sinuses) and for noninvasive pituitary tumors or craniopharyngiomas. Postirradiation necrosis is a dose-related phenomenon with a relative threshold radiation dose of 50 to 55 Gy if treatment is given in a conventional fractionation schedule (1.8- to 2-Gy fractions given once daily). Marks and colleagues reported the occurrence of necrosis in 5% of 139 patients with intracranial tumors treated with conventional fractionation to doses higher than 45 Gy; 6 of the 7 patients who had necrosis were given total doses in excess of 63 Gy.

The dose-time relationship is critical in determining CNS tolerance, with fraction size the dominant factor among patients receiving doses of 60 to 63 Gy. Necrosis in patients who receive less than 60 Gy usually has been associated with fractions of greater than 2.5 Gy. Aristizabal and colleagues documented necrosis after treatment for pituitary tumors in 3% of 106 patients given less than 2.2 Gy per day (total dose of about 50 Gy) compared with 15% of 13 patients given doses of greater than 2.2 Gy daily. The influence of fraction size was made apparent in the iso-effect analyses of brain necrosis reported by Sheline and colleagues.

Sheline and coworkers contend that the brain can tolerate a total radiation dose of 50 to 54 Gy given in fractions of 2 Gy once daily. At that dose, cerebral necrosis is estimated to occur in 0.04% to 0.4% of patients. The likelihood of necrosis is higher among patients with primary brain tumors, although the incidence is still estimated to be less than 5% among patients receiving a dose of 55 Gy at 1.8 to 2 Gy per fraction. Tolerance is affected by age; experimental and clinical data indicate that children younger than 2 years can tolerate approximately 10% to 20% less radiation to the brain than those older than 2 years.

**Postirradiation Myelopathy**

Postirradiation myelopathy is the spinal cord equivalent of cerebral necrosis. The myelopathy manifests as sensory and motor signs referable to a single cord level, signs that are often clinically indicative of hemisection of the cord (Brown-Séquard syndrome). Symptoms occur as early as 6 months after treatment (median, 20 months). The pathophysiology of spinal cord myelopathy is similar to that of cerebral necrosis, and there is continued debate concerning the relative importance of vascular endothelial changes (particularly in the spinal cord with end-arterial blood supply to portions of the thoracic cord) and direct effects of the radiation on glial elements.

The time-dose relationship and tolerance of the spinal cord to irradiation have been analyzed in the context of extraspinal tumors. The thoracic spinal cord seems to be the most sensitive portion; few instances of lumbar myelopathy have been reported. Phillips and Buschke suggested that the thoracic spine could tolerate a dose as high as

![Figure 33-1](https://example.com/figure33-1.png)

**FIGURE 33-1.** The direct effects of radiation on glial cells (astrocyte II and oligodendrocyte) and the indirect effects resulting from vascular changes are shown in a scheme developed by van der Kogel. (From van der Kogel AJ. Central nervous system radiation injury in small animal models. In Gustin PH, Leibel SA, Sheline GE [eds]: Radiation Injury to the Nervous System. New York: Raven Press, 1991, pp 91-112.)
50 Gy given in fractions of 2 Gy once daily. Abbatucci and colleagues observed cervical cord myelopathy after doses of 55 Gy or more. The incidence of myelopathy rises rapidly with increasing doses, approaching 50% at 65 Gy. Many clinical trials of large-fraction irradiation for lung cancer have confirmed that the frequency of reactions increases as the fraction size exceeds 2.5 Gy. Fraction size also seems to correlate inversely with the latent interval before the development of myelopathy; however, no experimental evidence exists to suggest improved tolerance to fractions less than 2 Gy. The Continuous Hyperfractionated, Accelerated Radiation Therapy (CHART) regimen for lung cancer was originally based on a presumed cord tolerance of a low dose per fraction, but that regimen initially was associated with an unacceptable risk of myelopathy. Tolerance decreases as the volume or length of cord irradiated increases.

Other Late Effects
A unique late effect of cranial irradiation combined with chemotherapy, called leukoencephalopathy, has been observed in children with acute lymphoblastic leukemia, adults with small cell carcinoma of the lung, and patients with primary CNS tumors. Leukoencephalopathy is a profoundly demyelinating, necrotizing reaction that usually occurs 4 to 12 months after combined treatment with methotrexate and radiation. Dementia and dysarthria may progress to seizures, ataxia, focal long tract signs, or death. Although most of these symptoms regress after systemic, intrathecal, or intraventricular methotrexate therapy is discontinued, patients are left with permanent neurologic deficits. The occurrence of leukoencephalopathy in patients treated with systemic and intrathecal methotrexate without radiation and a dose-effect relationship that is more apparent for methotrexate than for radiation suggest that the clinical leukoencephalopathy is more significantly related to the methotrexate than to the radiation. However, white matter changes interpreted as leukoencephalopathy (and so coded in the NCI Common Terminology Criteria for Adverse Events) must be distinguished from the clinical syndrome previously described.

Decline in intellectual function has been related to cranial irradiation of adults and particularly of children. Neurocognitive changes in children correlate significantly with cranial irradiation, young age at diagnosis and therapy, and functional level at the time the irradiation was begun. The occurrence of dose-related neurocognitive alterations suggests a role for continued, if cautious, reduction in the full cranial radiation dose for patients with medulloblastoma, for example, who exhibit favorable presenting signs. Changes in white matter volume obtained by MRI segmentation constitute an objective variable that is closely tied to intellectual function and that may permit more detailed studies of the effects of radiation therapy and chemotherapy in the current generation of clinical trials. Intellectual impairment in adults has occurred primarily after intensive chemotherapy and radiation for the prevention of metastasis from small cell carcinoma of the lung and for treatment of primary CNS lymphomas.

Peripheral nervous system tissue is relatively resistant to irradiation. Acute and subacute symptoms or signs occur infrequently; transient cranial nerve neuropathies are observed only with high-dose, single-fraction, high-linear energy transfer (LET) radiation for pituitary or parasellar tumors. The optic chiasm is often considered a dose-limiting structure when irradiation for parasellar or adjacent temporal lobe lesions is being planned, and special attention is given to limiting the risk of dose-related visual complications. Optic nerve or chiasm injury has been documented in almost 20% of patients treated with fraction sizes of 2.5 Gy or greater (to total doses of 45 to 50 Gy), compared with 0 of 27 patients and 0 of 500 patients treated with fraction sizes of 1.7 to 2 Gy to the same level. Late injury to the brachial plexus observed after the treatment of breast cancer similarly seems to occur largely after high-dose fractions.

Central Nervous System Neoplasms
Primary tumors of the CNS represent 2% of all cases of cancer in the United States. Approximately 20,500 new cases are diagnosed annually. The incidence of these tumors exceeds that of Hodgkin disease in adults, and they account for 20% of all cases of childhood cancer.

The natural history of tumors of the brain and spinal cord is relatively unusual because aggressive malignant lesions rarely disseminate beyond the neuraxis. Categorizing CNS tumors as benign or malignant is often difficult because histologically low-grade or benign neoplasms are sometimes associated with a poorer prognosis than certain histologically malignant tumors. It is instead the potential for local invasiveness or metastasis along the cerebrospinal fluid (CSF) pathways that determines the “malignancy” of CNS tumors. The challenge for neurosurgeons and radiation oncologists is to remove or devitalize neoplastic tissue in the functionally vital, anatomically confined nervous system.

Tumors Common in Children
Brain tumors in children account for one in five cases of childhood cancer. The incidence of primary CNS tumors, particularly the astrocytic lesions, increased in children during the first half of the 1990s; since then, the incidence has leveled off, perhaps because of the added diagnostic sensitivity of MRI. Pediatric brain tumors arise most often in the posterior fossa. Posterior fossa tumors often produce symptoms and signs of increased intracranial pressure because the growing tumor obstructs the flow of CSF through the fourth ventricle. Ataxia often accompanies pressure-related headaches and morning vomiting. Brainstem gliomas cause cranial nerve palsy, ataxia, and long tract signs, including lateralizing weakness and sensory deficits.

Supratentorial tumors occur in the cerebral hemispheres and the central or deep-seated areas of the thalamus, hypothalamus, suprasellar area, and pineal-third ventricular region. Symptoms are local and include lateralizing neurologic deficits and seizures, which are associated with hemispheric and thalamic tumors; visual and endocrine changes; and specific oculomotor findings, which are associated with tumors of the pineal region.

Primary tumors of the spinal cord account for only 5% of tumors in children. Metastasis to the CNS is uncommon...
in childhood cancer. Contiguous extradural compression within the spinal canal or at the base of the skull (e.g., in neuroblastoma, rhabdomyosarcoma, primary bone tumors) is more common than hematogenous metastasis to the brain.

Common primary intracranial tumors diagnosed in children are listed in Table 33-1. The histologic classification of pediatric brain tumors has been relatively standardized by the World Health Organization (WHO). The most common tumors are the astrocytic lesions (i.e., astrocytomas, malignant gliomas, and brainstem gliomas). Medulloblastoma, which accounts for 20% of all childhood CNS tumors, is part of the broader category of supratentorial primitive neuroectodermal tumors (PNETs) and other embryonal CNS tumors (i.e., cerebral neuroblastoma, ependymoblastoma, and pineoblastomas).

Biologic findings increasingly define the nature of CNS tumors in children, providing some associations with tumor aggressiveness and outcome. Medulloblastoma, for example, is often associated with gene deletions in chromosomal region 17p1; expression of the EGFR gene (formerly designated erbB1), which encodes the epidermal growth factor receptor, and NTRK3 (formerly called TRKC), which encodes the neurotrophin tyrosine kinase receptor type 3, are negatively and positively correlated with outcome, respectively. Several other molecular markers, such as cyclin-dependent kinase 6, MYC, apurinic or apyrimidinic endonuclease activity, and members of the WNT pathway, also have prognostic significance. Several investigators have proposed combining information on gene expression patterns and clinical stage for stratifying risk groups in medulloblastoma.

**TABLE 33-1. Relative Incidence of Brain Tumors in Children**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infratentorial</strong></td>
<td></td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>25</td>
</tr>
<tr>
<td>Astrocytoma (cerebellum)</td>
<td>15</td>
</tr>
<tr>
<td>Brainstem glioma</td>
<td>10</td>
</tr>
<tr>
<td>Ependymoma (fourth ventricular region)</td>
<td>6</td>
</tr>
<tr>
<td><strong>Supratentorial</strong></td>
<td></td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>23</td>
</tr>
<tr>
<td>Malignant glioma (anaplastic astrocytoma, glioblastoma multiforme)</td>
<td>6</td>
</tr>
<tr>
<td>Embryonal (primitive neuroectodermal) tumors</td>
<td>4</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>3</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>6</td>
</tr>
<tr>
<td>Pineal region tumors</td>
<td>4</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>2</td>
</tr>
</tbody>
</table>


**Medulloblastoma**

Medulloblastoma represents 20% of childhood brain tumors. Common throughout the pediatric age range, the median age at diagnosis is 6 years, and 25% of tumors occur in children younger than 3 years. Approximately 10% to 20% of medulloblastomas occur in adults, predominantly in the third to fifth decades. The classic presenting triad of posterior fossa tumors such as medulloblastomas consists of headaches and vomiting, which are signs of increased intracranial pressure and ataxia.

Medulloblastoma is by definition a posterior fossa tumor, most often arising in the cerebellar vermis, within the cerebellar hemispheres (typically in adolescents and frequently as the desmoplastic variant) or along the cerebellopontine peduncle. The tumor grows to fill the fifth ventricle and often attaches to the brainstem. Medulloblastoma is the characteristic “seeding” CNS tumor and is associated with subarachnoid dissemination through the CSF; metastasis may be apparent from cytologic findings or from images of radiographic deposits within the intracranial subarachnoid space (i.e., along the convexities or within the basal cisterns, sometimes limited to the region of the pituitary stalk) or within the spinal subarachnoid space. Subarachnoid disease is apparent at diagnosis in 20% to 25% of affected children. Extraneural disease, usually involving the bone or bone marrow, is an uncommon finding at diagnosis or disease recurrence.

The embryonal CNS tumors represent a group of histologically related neoplasms that occur predominantly in children. The WHO classification defines the embryonal tumors as round, blue, small cell tumors that tend to seed the neuraxis and respond to radiation and chemotherapy, although the prognosis varies widely. Less common tumors in this category include the supratentorial PNETs; the rare, primitive medulloepithelioma; and atypical or rhabdoid tumor (see “Tumors in Children Younger than 3 Years”). Pineoblastoma is classified separately (see “Pineal Region and Germ Cell Tumors”). The term posterior fossa PNET is synonymous with medulloblastoma.

**BOX 33-1. Embryonal Central Nervous System Tumors**

- Medulloblastoma
- Central neuroblastoma
- Ependymoblastoma
- Primitive neuroectodermal tumor (PNET)

**Additional Tumors with a Distinct Histology and Different Genetic Pathway of Evolution**

- Medulloepithelioma
- Atypical teratoid or rhabdoid tumor
- Pineal Parenchymal Tumor Classified Clinically as an Embryonal Tumor
- Pineoblastoma

*In the definition proposed by Kleihues and Cavenee, embryonal central nervous system tumors are “histologically identifiable entities that all develop on the background of an undifferentiated round-cell tumor but show a variety of divergent patterns of differentiation.”

**PNET** refers to supratentorial tumors; tumors that occur in the posterior fossa are known as medulloblastomas.
Medulloblastoma is thought to originate from the primitive external granular layer of the developing cerebellum. The tumor is characterized by undifferentiated small, round, blue cells, often including neuroblastic rosettes and with various degrees of neuronal and glial differentiation. The desmoplastic tumors are classically identified by their prominent nodularity and dense areas of reticular fibers. Other histopathologic subsets include medulloblastoma with extensive nodularity or advanced neuronal differentiation and large cell or anaplastic medulloblastoma.

**Surgery and Staging**

Surgery is the initial therapy, with the goal of maximal resection for the sake of therapy and reestablishing CSF flow. Intraoperative ventriculostomy has replaced the routine initial placement of a ventriculoperitoneal shunt; with current surgical approaches, less than 25% of children require postoperative conversion of the temporary ventriculostomy to a permanent ventriculoperitoneal shunt. Gross total resection is limited only by substantial invasion of the tumor into the brainstem or infiltration into the peduncle. Gross total or near-total resection (i.e., more than 90% of the tumor removed, with less than 1.5 cm² of residual disease) is achieved in almost 90% of children older than 3 years in the United States. The operative mortality rate should be less than 1% or 2% for children treated with current approaches, and the postoperative morbidity is typically acceptable, with a small proportion of children left with permanent new cranial nerve deficits or marked ataxia.

The posterior fossa syndrome, marked by severe truncal ataxia, difficulties with speech and swallowing stemming from bulbar effects, and sometimes mutism, seems to be associated with extensive dissection along the lower brainstem; symptoms usually abate considerably over several months after the surgery, although late residual deficits of various degrees of severity have been seen.

Postoperative neuraxis staging is standard in defining risk groups and subsequent therapy for medulloblastoma and the other embryonal tumors. Immediate postoperative cranial MRI or CT (preferably done within 1 to 3 days of surgery) defines the postoperative residual effect, which is a more reliable prognostic factor than the operative coding of the extent of resection. Neuraxis staging begins with a contrast-enhanced spinal MRI (preferably more than 10 days after surgery to eliminate the confusion of findings with postoperative debris) and subsequent lumbar CSF cytologic studies; routine bone scanning and bone marrow assessments are standard only in investigational settings.

Staging is based on the extent of residual tumor (average risk is defined as the presence of ≤1.5 cm² of residual tumor) and the presence or absence of subarachnoid or extraneural metastasis (defined according to a modification of the Chang system (Box 33-2)). Most important from the standpoint of planning therapy is determining whether isolated CSF cytologic evidence of metastatic disease (M1 disease), imaging evidence of intracranial disease outside the posterior fossa (M2 disease), or imaging evidence of spinal metastasis (M3 disease) is present; extraneural disease is classified as M4. Standard or average-risk disease is defined as that which has been totally removed or has residual tumor volume of less than 1.5 cm³ with M0 disease; almost 60% to 65% of children enrolled in U.S. studies at the turn of the century were so classified.

**Box 33-2. Chang Staging System for Medulloblastoma**

<table>
<thead>
<tr>
<th><strong>Primary Tumor (T)</strong></th>
<th><strong>Distant Metastasis (M)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>M0: No evidence of gross subarachnoid or hematogenous metastasis</td>
</tr>
<tr>
<td>T2</td>
<td>M1: Microscopic tumor cells found in cerebrospinal fluid</td>
</tr>
<tr>
<td>T3a</td>
<td>M2: Gross nodule seedings demonstrating in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles</td>
</tr>
<tr>
<td>T3b</td>
<td>M3: Gross nodular seeding in spinal subarachnoid space</td>
</tr>
<tr>
<td>T4</td>
<td>M4: Metastasis outside the cerebrospinal axis</td>
</tr>
</tbody>
</table>

*The T stage is no longer thought to be prognostically related to outcome. Modified from Chang CH, Houser EM, Herbert C Jr. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastoma. Radiology 1969;93:1351-1359.*

The presence of only local residual disease is uncommon in children with high-risk disease; more often, these children have neuraxis dissemination.

**Radiation Therapy**

Postoperative management consists of radiation therapy and chemotherapy. Infants and young children (i.e., those younger than 3 years) are treated in accordance with developing investigational approaches (see “Tumors in Children Younger than 3 Years”). The standard sequence of therapy for children 3 years old or older is to begin radiation therapy within 28 to 31 days of surgery, followed by chemotherapy. Although studies of preirradiation chemotherapy have added significantly to our knowledge of chemosensitivity, randomized trials have shown no benefit from administering chemotherapy before the radiation, and in some instances, results have suggested that this sequence is ultimately detrimental to disease control.

Radiation therapy for medulloblastoma is technically demanding and biologically unforgiving. It requires the systematic inclusion of the entire subarachnoid space (i.e., craniospinal irradiation [CSI]) followed by a boost to the posterior fossa. One standard technique involving immobilization of patients in the prone position is illustrated in Figure 33-2. Lateral craniofacial fields encompass the intracranial and upper cervical spine regions, with particular attention to including the subfrontal and infratemporal regions (at the cribriform plate in the midline subfrontal area and along the infratemporal regions) (Fig. 33-3).

The conventional dose to the neuraxis in patients given surgery and radiation is 36 Gy (delivered in 1.8-Gy
fractions once daily). The progression-free survival rate for patients with localized disease after maximal resection and CSI (36 Gy) is approximately 65% at 5 to 10 years (Table 33-2). A randomized study of patients with average-risk medulloblastoma conducted by the Pediatric Oncology Group (POG) and Children’s Cancer Group (CCG) in the late 1980s established the superiority of a total dose of 36 Gy compared with 23.4 Gy for CSI and the benchmark outcome of more than 90% tumor removal with less than 1.5 cm$^2$ of residual disease. Later findings suggest that the combination of reduced-dose CSI (23.4 Gy) and chemotherapy produces disease control rates comparable with or superior to those for conventional-dose CSI alone. Large-scale prospective studies are documenting the efficacy of what is now considered the standard treatment for localized medulloblastoma, which is radiation (CSI dose of 23.4 Gy) followed by cisplatin-containing chemotherapy.

Reports of outcome from nonrandomized, single-arm trials, further supported by neuropsychological findings from the POG-CCG study previously mentioned, suggest that cognitive function in children with average-risk disease after therapy is superior among those given CSI to 23.4 Gy instead of 36 Gy, especially in children 3 to 8.5 years old. The current Children’s Oncology Group (COG) trial is testing, in children between 3 and 7 years old with average-risk disease, whether the CSI dose can be further reduced from 23.4 Gy to 18 Gy. Children with metastatic disease at presentation (i.e., M1 to M3 disease) require a dose of 36 to 39 Gy to the neuraxis. The use of proton therapy for CSI has a theoretical advantage over photon therapy because of the lack of exit dose from proton therapy. Miralbell and colleagues estimated that the risk of second neoplasms could be reduced with proton therapy relative to photon therapy.

Irradiation includes a boost to the posterior fossa region, classically defined as the entire infratentorial volume. The use of opposed lateral posterior fossa fields has been standard, but radiation oncologists are increasingly using a three-dimensional conformal radiation therapy approach to spare the auditory apparatus and, when possible, the pituitary-hypothalamic region (Fig. 33-4). Proton therapy for pediatric medulloblastoma is also being considered as a way of maximizing target dose coverage and sparing normal tissues (Fig. 33-5). The cumulative dose delivered to the posterior fossa is typically 54 to 55.8 Gy. A few institutional summaries of patterns of treatment failure for patients with medulloblastoma and descriptions of preliminary experience with target volumes confined

FIGURE 33-2. A, Classic craniospinal irradiation configurations, with a divergent posterior spinal field matching opposed lateral cranioceval fields. The collimator rotation enabling the cranioceval fields to be matched to the divergence of the posterior spinal field is typically modified at least every 5 fractions. Field markings for medulloblastoma are determined by the cribriform plate at the orbital level (see Fig. 32-3). B, The parallel inferior border from the cranioceval fields is achieved by couch rotation, calculated to achieve a three-dimensional match in the depicted plane.

FIGURE 33-3. A conventional fluoroscopic image used for simulating the lateral cranioceval fields used in craniospinal irradiation for medulloblastoma (see Fig. 33-2). The long arrow indicates the margins along the cribriform plate. The radiopaque dot and the small arrows indicate the anterior margins of the lateral orbital rims. Divergence rather than a collimator angle is needed when only the subarachnoid space is to be targeted.
to the operative or tumor bed highlight investigational approaches that are being studied prospectively in a COG study.100,101

**Chemotherapeutic Agents**

Several categories of chemotherapeutic agents have shown efficacy in medulloblastoma: alkylating agents (e.g., cyclophosphamide, lomustine), platinating agents (e.g., cisplatin, carboplatin), topoisomerase II inhibitors (e.g., etoposide), and the vinca alkaloids (e.g., vincristine). The most common adjuvant treatment for standard- or average-risk disease was described by Packer and colleagues87 and consists of concurrent vincristine during irradiation and post-irradiation cycles of lomustine, cisplatin, and vincristine. The addition of concurrent carboplatin or etoposide and high-dose, peripheral stem cell–supporting chemotherapy regimens has been studied in two separate protocols for the treatment of high-risk disease.102 The first report of a multi-institutional phase II trial of this approach showed 5-year event-free survival rates of 83% for children with average-risk disease and 70% for children with high-risk disease.103

Although posterior fossa recurrence previously was regarded as the dominant pattern of failure, later studies have indicated that more patients exhibit neuraxis or combined local and disseminated failure. Approaches to the management of disease recurrence are not standardized but often include chemotherapy, further surgery for localized disease, and the judicious use of additional irradiation. Secondary or salvage therapies are rarely successful.

**Astrocytoma**

Astrocytomas are the most common glial tumors in children, developing in the cerebellum, brainstem, cerebral hemispheres, diencephalon (i.e., thalamus, hypothalamus, and third ventricular region, including the optic chiasm),

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### TABLE 33-2. Survival Rates after Craniospinal Irradiation for Medulloblastoma

<table>
<thead>
<tr>
<th>Study and Reference</th>
<th>Period</th>
<th>Number of Patients</th>
<th>Survival Rate at 5 Years (%)</th>
<th>Survival Rate at 10 Years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloom et al, 196936</td>
<td>1950-1964</td>
<td>71</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Berry et al, 198193</td>
<td>1958-1978</td>
<td>122</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>Hughes et al, 198694</td>
<td>1977-1985</td>
<td>53</td>
<td>64</td>
<td>42</td>
</tr>
<tr>
<td>Jenkin et al, 199096</td>
<td>1977-1987</td>
<td>72</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td>Thomas et al, 200092</td>
<td>1978-1991</td>
<td>42 (CSI = 36 Gy)</td>
<td>67*</td>
<td>67*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46 (CSI = 23 Gy)</td>
<td>52*</td>
<td>52*</td>
</tr>
</tbody>
</table>

*Event-free survival rates at 5 and 8 years.

CSI, craniospinal irradiation.

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**FIGURE 33-4. A,** Treatment plans for a three-dimensional conformal technique demonstrating the ideal dose distribution for a six-field, non-coplanar approach targeting the entire posterior fossa. Anatomically, this approach includes the tentorium as it extends superiorly in the posterior clinoid and then inferiorly to define the anterior and superior margins of the posterior fossa. The inferior and posterior margins are defined by the calvarium and the lower margin of foramen magnum. (Continued)
or spinal cord. In adults, low-grade tumors occur primarily in the cerebral hemispheres and thalamus; however, malignant astrocytomas far exceed the number of histologically benign lesions beyond the age of 20 years.

The WHO grades astrocytomas as grade I (juvenile pilocytic astrocytoma [JPA]) or grade II (fibrillary astrocytoma or astrocytoma not otherwise specified); high-grade lesions are deemed grade III (anaplastic [malignant] astrocytoma) or grade IV (glioblastoma multiforme). Grossly, the tumors are solid with discrete or infiltrating margins or cystic. Pilocytic astrocytomas are biologically nonaggressive lesions that are often cystic, occurring predominantly in the cerebellum and diencephalon in children. The natural history of astrocytomas depends on the age of the patient and the site of origin and histologic classification of the tumor. Pilocytic tumors rarely progress to a more malignant histology; however, fibrillary astrocytomas progress to a more malignant histology in 30% to 50% of cases. The proliferative index, assessed by staining for Ki-67 with the murine monoclonal antibody MIB1, has been reported to influence prognosis.

Cerebellar Astrocytomas

Cerebellar astrocytomas involve the vermis or hemispheres in 75% of patients; in 25% of children, tumors manifest as transitional neoplasms that involve the cerebellum and the cerebellar peduncles or adjacent brainstem. Cerebellar astrocytomas are classically cystic lesions; the textbook appearance consisting of a large cyst associated with a mural nodule occurs in about one fourth of cases. Grossly, most tumors are mixed cystic and solid lesions or apparently solid tumors with small cystic components. Histologically, 75% of astrocytomas in this location are JPAs. Debate continues about whether high-grade gliomas occur in the cerebellum in children; if they do, they are quite uncommon.

Therapy for cerebellar astrocytomas is largely surgical. Reports from institutions indicate that gross total resection is done in 65% to 90% of cases, although this rate has risen to approximately 85% to 90% in recent series. Resection is more often incomplete in patients with tumors involving the cerebellar peduncles or the brainstem. The operative mortality rate should be less than 4%, unlike the rate for patients with medulloblastomas and ependymomas that may invade the adjacent brainstem. Morbidity after radical resection of cerebellar astrocytomas usually is limited.

Recurrence of tumor after radioimaging confirmation of complete surgical removal is uncommon; in the most recent series, the recurrence rate is less than 10%. Prognosis most closely parallels the extent of resection; multivariate analyses have also identified solid (rather than cystic) lesions, transitional lesions (versus those confined to the cerebellum), and lesions showing a fibrillary or diffuse histology (versus JPA) as potentially significant prognostic factors. A direct correlation between the volume of residual tumor and outcome has also been reported.

Indications for radiation therapy are limited in patients with cerebellar astrocytomas. Although radiation therapy has been suggested to be effective for incompletely resected solid lesions, enthusiasm is generally limited for postoperative irradiation for any cerebellar astrocytomas. A small subset of tumors, often those that primarily involve the cerebellar peduncle, will recur after initial surgery; our approach to the treatment of such tumors is to use irradiation only after tumor progression after a second attempt at resection. MRI (T2-weighted or fluid attenuation inversion recovery [FLAIR] sequences) and MRI/CT fusion are
The total dose is 50 to 54 Gy in conventional fractionation.

**Supratentorial Astrocytomas**

Supratentorial astrocytomas include diencephalic or central lesions and lesions of the cerebral hemispheres. In children, total resection can be achieved for up to 90% of astrocytomas in the cerebral hemisphere. Diffuse cerebral lesions, including those labeled gliomatosis cerebri, can arise in several cerebral lobes with an often low-grade histologic appearance (i.e., fibrillary, WHO grade II) but clinically malignant potential. Similarly, thalamic tumors represent a mix of circumscribed JPs and diffuse, sometimes bithalamic fibrillary tumors; up to 40% of thalamic gliomas are histologically malignant (i.e., WHO grade III to IV, anaplastic astrocytoma or glioblastoma).

Biopsy alone has been the standard surgery for most thalamic astrocytomas because knowledge of the tumor histology is important in guiding therapy. However, Bernstein and colleagues reported that major resections were performed in up to 33% of patients with circumscribed thalamic tumors, and the incidence of major operative morbidity was only 7%. Further experience confirmed that limited or aggressive resection might each have a role in the treatment of low-grade thalamic gliomas.

The role of radiation therapy in childhood astrocytomas is evolving. It is thought to depend on tumor histology and site, age of the patient, and presence or absence of clinical signs. Several reviews have shown that radiation therapy...
is effective in terms of tumor response, prolonged progression-free interval, and long-term disease control. A joint CCG-POG prospective trial of postoperative irradiation for incompletely resected astrocytomas was abandoned in the early 1990s because the proportion of children in whom gross total or near-total resection could be achieved had increased substantially and because the wisdom of performing irradiation before symptomatic or radiographic documentation of disease precluded uniform acceptance of irradiation as a randomized option. Preliminary experience in that trial suggested that observation might be appropriate after substantial resection because disease seems to progress in only a minority of such cases 3 to 5 years after surgery (J. Wisoff, personal communication, 2001). For some patients with central low-grade gliomas (e.g., tectal plate or midbrain; less often, hypothalamic or thalamic), cautious observation can identify indolent, stable tumors that may not require immediate intervention if the child is neurologically stable. However, this approach implies a commitment to intervene with surgery or radiation, or both, when clinical or radiographic evidence of tumor progression appears.

The systematic use of postoperative irradiation has also been questioned in adults. Adults more often have sizable peripheral cerebral hemispheric tumors. Outcome at 5 and 10 years seems to be improved for patients given radiation therapy for incompletely (as opposed to completely) resected tumors. A trial by the European Organisation for Research and Treatment of Cancer to evaluate postoperative observation versus irradiation for WHO grade I and II hemispheric lesions in adults showed no convincing advantage for early irradiation or for low-dose (45 Gy) versus high-dose (60 Gy) therapy.

The effect of radiation therapy is well documented for central supratentorial lesions. Neurologic improvement has been observed in 80% of patients after irradiation for diencephalic tumors. Objective reduction in the size of supratentorial astrocytomas has been confirmed in approximately one half of the patients studied by prospective CT assessment. Long-term survival of patients with biopsy-proven diencephalic lesions usually has required irradiation to therapeutic dose levels. Limited-volume, fractionated irradiation has been reported to control most such lesions, with toxicity apparently being more limited in the pediatric age group.

**Optic Pathway Glioma**

Tumors of the optic nerves and chiasm are low-grade astrocytomas that occur predominantly in young children, often younger than 3 to 5 years. In 25% to 30% of cases, the tumors are associated with neurofibromatosis. Tumors of the optic nerve often behave as hamartomatous lesions, although up to 50% may extend proximally toward the chiasm. Chiasmatic gliomas manifest with visual and often
with endocrine signs; it is often difficult to distinguish chiasmatic from hypothalamic tumors. In collected reports of 500 cases, 25% of patients with chiasmatic involvement died of tumor-related events. In an often-quoted series of 36 children, Hoyt and Baghdassarian indicated that chiasmatic tumors were indolent and non-threatening. However, follow-up at a median of 20 years documented a 25% tumor-related mortality rate in a population weighted toward the apparently more benign tumor associated with neurofibromatosis.

The efficacy of radiation therapy for tumors of the optic chiasm with or without hypothalamic involvement has been documented in numerous series. Visual acuity or visual fields are improved in approximately 25% of patients receiving radiation therapy, and neuroimaging shows a reduction in the size of the lesion in these patients. Survival rates after irradiation for chiasmatic gliomas reportedly range between 75% and 100% in large series of patients followed for 5 to 10 years. Controversy regarding management appropriately surrounds the often-benign clinical course of the disease in relation to the potential for treatment-related morbidity with surgery or irradiation. Exophytic JPAs arising in the chiasmatic or hypothalamic region are amenable to incomplete surgical resection; the potential advantage of partial resection lies in delaying more definitive irradiation. Particularly among younger children, a balance between disease progression and the potential risk of adverse endocrine and intellectual effects from irradiation has favored a conservative approach. Packer and colleagues described their experience with chemotherapy, particularly the carboplatin and vincristine regimen. In most young children, previously progressive or symptomatic disease was stabilized with chemotherapy; objective responses were documented in up to 50% of cases, and the median time to disease progression was in excess of 3 years. Initial management with relatively toxicity-free chemotherapy approaches is logical for children with progressive symptomatic chiasmatic or hypothalamic tumors, certainly for those younger than 3 to 5 years and possibly for all children before puberty. The frequency and durability of disease control are not clear for children for whom irradiation is begun when their disease progresses during or after chemotherapy. Outside the investigational setting, the treatment of choice remains primary irradiation for children between 5 and 10 years old because long-term disease control can be achieved in up to 90% of these cases.

### Radiation Therapy Technique

Radiation therapy for low-grade astrocytomas uses local target volumes to encompass the typically discrete primary tumor quite narrowly. Uncommonly, low-grade tumors diffusely infiltrate one or more cerebral lobes, requiring more wide-field or total cranial irradiation (Fig. 33-7). Low-grade, often pilocytic, astrocytomas are associated with multifocal disease or subarachnoid involvement at diagnosis (or, less commonly, at recurrence) in 15% to 20% of patients with childhood astrocytomas. Multifocal or metastatic disease is rarely confined to the spinal subarachnoid region; multiple disease sites are almost always apparent on cranial MRI studies, obviating any requirement for spinal imaging or staging in patients with this tumor. Specific histologic subtypes of tumors (i.e., pleomorphic xanthoastrocytoma and meningocerebral astrocytoma) can directly infiltrate the contiguous meninges, but this seems to be associated with an indolent, benign course after surgery alone.

Establishing the target volume requires detailed MRI. A 1-cm margin beyond the abnormalities shown on T1- or T2-weighted images seems adequate on the basis of early follow-up data from patients for whom three-dimensionally planned and delivered radiation techniques were used. A phase II trial by the COG is using MRI/CT fusion for target delineation, a 0.5-cm margin for clinical target volume, and a 0.3- to 0.5-cm margin for planning target volume. The planning target volume is treated by using a conformal technique to 54 Gy in 30 fractions.
A dose-response relationship for astrocytoma has not been well defined. In most series, a radiation dose of approximately 50 Gy delivered in 1.8-Gy, once-daily fractions has proved adequate. However, in statistical analyses of rather sizable series of patients, Albright and Laws and their associates observed an apparent benefit conferred by doses above 40 Gy. Justifying dose levels above 54 to 55 Gy in children is difficult in view of the increase in risk at radiation levels approaching cerebral tolerance. For adults with supratentorial astrocytomas, Shaw and colleagues, having shown a dose-response relationship indicating improved survival after at least 53 Gy, recommend levels of 55 to 60 Gy. However, two randomized studies of adults with low-grade gliomas testing 50.4 Gy versus 64.8 Gy or 45 Gy versus 59.6 Gy showed no significant difference in outcome between the lower doses and the higher doses.

**Prognosis**

Laws and colleagues reviewed the Mayo Clinic experience with 461 patients of all ages with supratentorial astrocytomas treated between 1915 and 1975. The most important correlates of 10- and 15-year survival were age (86% long-term survival for children and adolescents younger than 20 years versus 33% for those 20 years old or older) and the degree of tumor involvement, reflected by the neurologic deficit and the extent of resection (37% survival rate for patients after biopsy or limited removal compared with 55% for those after subtotal or total resection). In Shaw’s review of the same Mayo experience with adult patients with supratentorial astrocytomas, a role for radiation therapy was clearly indicated for most patients with astrocytomas, with 5- and 10-year survival rates of 68% and 39%, respectively, after at least 53 Gy. Patients treated with less than 53 Gy or no irradiation had a 5-year survival rate of 47% (both groups) and 10-year survival rates of 27% and 11%, respectively.

The long-term potential for radiation therapy to control disease specifically in children with hemispheric astrocytomas has been documented in reviews by Bloom and Jenkin and their colleagues, who independently reported that the survival rate reached a plateau between 5 and 15 years after postoperative irradiation. The benefit of adding irradiation after incomplete resection for children with supratentorial hemispheric tumors was made apparent in the Pittsburgh series reported by Pollack and colleagues.

Site-specific survival rates suggest that patients with hypothalamic and chiasmatic astrocytomas enjoy longer survival times than do patients with most other types of supratentorial astrocytomas. Bloom and colleagues cited 5-year survival rates of 60% to 70% for patients with hypothalamic or hypothalamic tumors after primary irradiation. Albright and colleagues reported a mean survival duration of 5.1 years after radiation therapy for patients with diencephalic gliomas compared with a mean survival time of less than 1 year for patients who did not undergo irradiation. The virtual lack of tumor progression beyond 5 years after radiation therapy further suggests a role for radiation therapy as a curative modality in the primary management of hypothalamic or chiasmatic tumors.

**Brainstem Gliomas**

Tumors of the brainstem most often involve the pons (70%), followed by the medulla (15% to 20%) and the midbrain (10% to 15%). Brainstem gliomas are characterized as diffusely infiltrating or focal, depending on the pattern of involvement; focal tumors are well demarcated, confined to one anatomic segment of the brainstem, and occupy less than one half of the brainstem. Most focal tumors are JPAs histologically; they occur more often in the midbrain or medulla but can arise in the pons.

Pontine gliomas are largely diffuse (Fig. 33-8). Dorsally exophytic lesions are relatively benign tumors that usually arise at the pontomedullary junction or from the medulla; histologically, they are JPAs. In the past, brainstem tumors have been treated conservatively, with histologic confirmation limited to focal or cystic lesions for which knowledge of the histology or drainage might facilitate treatment. Findings from biopsied cases indicate that malignant glioma exists in 40% of patients at diagnosis; the remaining tumors are largely fibrillary astrocytomas. At autopsy, however, malignant gliomas are found in more than 80% of cases.

Radiation therapy is primarily used for diffusely infiltrating brainstem gliomas. Substantial neurologic improvement occurs in 60% to 70% of patients with diffusely infiltrating pontine gliomas, although long-term survival is limited to 10% to 20% of patients with these gliomas.

Dorsally exophytic tumors are usually identified during surgery for a tumor that otherwise fills much of the fourth ventricle. The lesions in more than one half of the patients remain indolent after incomplete resection; the 40% or more of tumors that do progress are most often controlled with radiation (Fig. 33-9).
Radiation Therapy Technique

Brainstem gliomas tend to infiltrate longitudinally, usually extending beyond the pons to involve the midbrain or medulla and extending peripherally into the cerebellum or medial temporal lobes (see Fig. 33-8). Irradiation is limited to the brainstem and immediately adjacent neural tracts. The infiltrative nature of these tumors can be better appreciated on T2-weighted MRI studies. Clinical target volumes are defined with 2-cm margins along the tracts of infiltration (i.e., into the midbrain or medulla, through the peduncles, and into the adjacent cerebellum). Given the poor overall outcome for patients with pontine lesions, many centers continue to use two-dimensional, opposed lateral fields in this setting, providing a margin around the known tumor extent.

The standard dose for brainstem gliomas is 54 to 56 Gy, given in a conventional fractionation scheme. In a series of trials, hyperfractionated doses given to total doses of 66, 70 to 72, and 76 to 78 Gy indicated no real benefit from the higher doses. Most long-term survivors have been adults or children with focal brainstem lesions often located outside the pons (i.e., in the midbrain or medulla). The decade-long experience with hyperfractionated therapy for these tumors has encouraged neurosurgeons, radiation oncologists, and pediatric oncologists to enroll patients in multi-institutional protocols. In a randomized trial conducted by the POG, conventional fractionation to 54 Gy was documented to be as effective as 70 Gy given in twice-daily 1.2-Gy fractions. This trial also documented the apparent negative effect of irradiation in combination with concurrent cisplatin in this setting.

Prognosis

The 5-year overall survival rates are 10% to 20% for children with brainstem gliomas and 20% to 30% for adults. Median survival after irradiation is only 8 months for patients with classic intrinsic tumors in the pons. Hoffman and colleagues initially identified as highly favorable a subset of children in whom exophytic tumors extended into the fourth ventricles. However, it is now understood that these tumors are usually JPAs, survival after surgery, with or without radiation, approaches 90% in this selected group. Intrinsic pontine tumors, constituting most of the classically identified brainstem gliomas, are usually associated with multiple cranial nerve palsies, diffusely hypodense lesions on CT or MRI studies, and a high-grade histologic appearance indicative of an infiltrating, aggressive neoplasm. Long-term survival rates.
for the latter group have consistently been less than 15%. Less common intrinsic tumors that are focal and confined to a segment of the pons or midbrain are associated with slightly better long-term survival rates.\textsuperscript{165}

Chemotherapy regimens have little effect on brainstem gliomas. Adjuvant therapy did not affect outcome in the only published randomized trial.\textsuperscript{177}

\textbf{Ependymomas}

Intracranial ependymomas occur predominantly in young children, but they are also seen in older children and adults. Ependymomas also occur as primary spinal cord neoplasms, but this presentation is more common in adults. Posterior fossa ependymomas typically manifest with the same symptom triad as other posterior fossa tumors in children—headache, vomiting, and ataxia. Associated symptoms include torticollis and lower cranial nerve dysfunction. The median age of children with these tumors is 4 years; however, almost 30% of infant brain tumors (i.e., those in children younger than 3 years) are ependymomas.\textsuperscript{178,179} Infratentorial lesions in younger children may occur more often in girls than in boys. Supratentorial lesions more often manifest with seizures or focal neurologic abnormalities and are most common in adolescents and adults.

Tumors of the posterior fossa occur predominantly in children; these tumors show a predilection for the fourth ventricle in young children and often involve or originate within the region of the foramen of Luschka (Fig. 33-10).\textsuperscript{179,180} Direct extension through the foramen magnum into the upper cervical spinal canal is a characteristic pattern of growth. Ependymomas disseminate into the subarachnoid space in approximately 12% of children.\textsuperscript{95,181-184} However, this manifestation is more often seen at diagnosis or as a primary site of recurrence in very young children and may be associated with an anaplastic histology; in older children, this pattern is more common after local recurrence than earlier in the disease.\textsuperscript{183,184} Supratentorial tumors often arise in regions adjacent to the ventricular system, and growth occurs largely through intraparenchymal extension.\textsuperscript{185}

Ependymomas arise from the ependymal cells lining the ventricular system and the central spinal canal. The tumor characteristically includes ependymal rosettes and perivascular pseudorosettes. Ependymomas are differentiated or low-grade lesions; variants include cellular, clear cell, tanycytic, and papillary types.\textsuperscript{69} In one series, 15% to 30% of ependymomas were classified as anaplastic tumors (i.e., WHO grade III), marked by increased cellularity and mitotic rate. The tumors usually are well demarcated but can show parenchymal invasion.\textsuperscript{69,115} Although ependymomas were regarded by leading neuropathologists in the 1980s as being of little clinical significance, an association has since been recognized between an anaplastic histology and a less favorable outcome.\textsuperscript{186-192} Ependymoblastomas are rare embryonal tumors and are discussed with the other supratentorial PNETs.

Surgery is the initial intervention for most intracranial ependymomas. Even extensive tumors of the fourth ventricle can often be grossly resected; total resection of tumors extending into or arising in the cerebellopontine angle has been achieved.\textsuperscript{180,190} The advantage of near-total or total resection is apparent, with considerable improvement in disease control in children in whom complete resection was achieved.\textsuperscript{189-191} The price of this control is a significant incidence of new postoperative neurologic deficits, including the posterior fossa syndrome and major new bulbar signs (e.g., palsies of cranial nerves IX and X resulting in difficulty with speech and airway protection), sometimes requiring postoperative tracheostomy or the placement of a feeding tube.\textsuperscript{68} Institutional experience shows that gross total resection can be accomplished in 50% to 60% of patients with infratentorial ependymoma; however, a total resection rate as high as 90% has been reported.\textsuperscript{190}

Postoperative irradiation is essentially routine for patients with ependymomas, almost regardless of age, because adjuvant radiation has been shown to increase disease control rates in several major series.\textsuperscript{190,192} However, a single experience suggests that disease could be controlled in a certain subgroup of children with supratentorial ependymomas who are treated with total resection alone; in this ongoing

\textbf{FIGURE 33-10.} A typical ependymoma involving the fourth ventricle. A, Axial CT scan reveals a lesion that fills much of the fourth ventricle and extends through the right foramen of Luschka. B, Sagittal MRI scan shows the tumor extending caudally along the medulla and below the foramen magnum into the upper cervical spinal canal.
COG prospective trial, only a small proportion of patients with such ependymomas is being treated with observation only.193 For all lesions of the fourth ventricle or cerebellolpontine angle, high rates of tumor control have been achieved only for patients treated with local postoperative radiation and radical resection.189-191,194 Long-term disease control was accomplished in approximately 70% of such children, compared with 20% to 30% of those treated with incomplete resection and similar radiation.

Ependymomas respond to a variety of chemotherapeutic agents, including cyclophosphamide and vincristine, cisplatin and carboplatin, and etoposide. A randomized trial of adjuvant lomustine, vincristine, and prednisone conducted by the CCG showed no benefit from this chemotherapy.195 The initial experience in infants with ependymomas indicated an inverse relationship between the duration of chemotherapy (equivalent to the time of initiating radiation therapy) and disease control, encouraging current institutional and cooperative group trials to limit the use of chemotherapy for this tumor; only for the youngest children (<18 months old) has a brief (3 to 4 month) course of chemotherapy been used before radiation (or second resection and radiation if measurable disease is apparent at the completion of chemotherapy).194 For infants, interest in chemotherapy dose escalation continues because of positive preliminary results from the second POG study of infant brain tumors, results that suggested that dose-intensified chemotherapy produced better disease control rates than did standard chemotherapy.196 In older children, the usefulness of limited-duration chemoresponsiveness in facilitating second operative resections before radiation is being examined in a COG trial.

Most clinical experience with ependymomas is based on treatment volumes for infratentorial lesions that include the entire posterior fossa and often the upper cervical spinal canal to one to two vertebral levels below the caudal tumor extent. Because recurrent disease is almost always localized to the initial tumor bed and often the site of attachment and because minimal residual disease is left adjacent to the brainstem or peduncle, current prospective investigations are targeting only the local tumor bed (with margins as tight as 1 cm) using three-dimensional conformal or intensity-modulated radiation therapy (Fig. 33-11).159 However, findings during an as yet insufficient follow-up period indicate that the limited treatment volumes should be used with caution outside a controlled setting. For supratentorial lesions, a 1- to 2-cm margin around the initial tumor extent is indicated, with potential modifications when the normal brain is reconfigured by tumor resection. Treatment volumes for differentiated and anaplastic ependymomas usually are not different.197,198 Previous interest in CSI for anaplastic infratentorial lesions has not continued into contemporary protocols or treatment standards, except in cases in which neuraxis involvement is documented at diagnosis.

Classically, radiation doses of 45 to 54 Gy have been used.182,189,192 However, doses of 54 to 55.8 Gy have been reported to achieve superior results and are indicated even after gross total resection.199,200 Despite apparently encouraging results from a small POG trial of hyperfractionated radiation (70 Gy given twice daily in 1.2-Gy fractions) for patients with posterior fossa ependymomas, no substantiated role has been established for altered fractionation. The potential value of dose escalation is being explored in trials testing cumulative doses approaching 60 Gy.193

**Pineal Region and Germ Cell Tumors**

A unique group of tumors occur in the pineal region: germ cell tumors, pineal parenchymal tumors, and glial and ependymal tumors (Table 33-3).69,116,201 Intracranial germ cell tumors occur predominantly in the pineal region, although they can also arise in the anterior third ventricular (suprasellar) region and, less commonly, in thalamic or deep cerebral hemispheric areas.

This unique group of tumors manifests with clinically and histologically linked syndromes. Pineal region germinomas occur predominantly in adolescent boys and are associated with multifocal or metastatic disease in the anterior third ventricular region in 10% to 40% of cases.202-206 Suprasellar (anterior third ventricular) germ cell tumors occur more broadly throughout the pediatric age group and about equally in girls and boys; these tumors are often germinomas but also include other germ cell types. Pineal parenchymal tumors in children are overwhelmingly malignant pineoblastomas, with a considerable proportion occurring in infants and children younger than 2 to 3 years as highly aggressive, widely metastasizing, small, round, blue cell tumors. Pineocytomas are decidedly less common in children occurring more often in adults.69,207-209

Regardless of histology, pineal region tumors typically manifest with Parinaud’s syndrome, consisting of near-light dissociation (i.e., pupillary responses are diminished to

**FIGURE 33-11.** The treatment plan shows the isodose volumes for a three-dimensional conformal approach, using multiple non-coplanar 6-MeV photon fields to encompass the tumor within the lower aspect of the posterior fossa and the uppermost spinal canal. The target volume in contemporary protocols more often addresses the tumor bed or surgical bed than the full posterior fossa.
light but are maintained with attempted accommodation), lack of upward gaze, and incomplete ability to accommodate. Obstructive hydrocephalus often occurs when the tumors are near the sylvian aqueduct. Suprasellar lesions can also manifest as hydrocephalus when the growing tumor obstructs the foramen of Monro; diabetes insipidus can also manifest as hydrocephalus when the growing tumors are near the sylvian aqueduct. Suprasellar lesions have usually been biopsied because of their relative accessibility and the broad differential diagnosis that includes astrocytomas of the hypothalamic or chiasmatic region and craniopharyngioma. Germ cell tumors can occasionally be definitively diagnosed on the basis of chemical markers. Any significant elevation of the alpha-fetoprotein level in the serum or CSF is diagnostic of a malignant germ cell histotype (typically embryonal carcinoma, yolk sac tumor, or teratocarcinoma), and marked elevation of β-human chorionic gonadotrophin level (β-HCG; typically more than 100 to 1000 mIU/mL) is diagnostic of a choriocarcinoma or malignant mixed germ cell tumor (with choriocarcinomatous elements). Modification of the β-HCG level (50 to 100 mIU/mL) is compatible with a germinoma, but cytologic or histologic evidence is required to confirm the diagnosis. After a diagnosis is established, neuraxis staging (e.g., spinal MRI, lumbar CSF cytology) is mandatory for any of the germ cell tumors and pineoblastoma.

An open craniotomy is usually required to biopsy suprasellar tumors. Biopsy has been possible during third ventriculosity, often at the time of ventriculoperitoneal shunt insertion or third ventriculostomy. Pineal region tumors can be approached stereotactically, but their challenging location adjacent to the major draining intracranial veins has led many neurosurgeons to prefer an open approach. Tumor resection is feasible in the pineal region, although done in only a few instances because of the high rate of potential complications. Although insertion of a ventriculoperitoneal shunt is often necessary, the notable incidence of shunt metastasis (with tumor arising throughout the peritoneal cavity), although low in absolute terms, is relatively more common for this group of tumors than for any other intracranial lesions. Performance of a third ventriculostomy, rather than placement of a ventriculoperitoneal shunt, is encouraged for accomplishing internal decompression.

### Radiation Therapy Technique

Radiation therapy is highly curative in patients with germinomas in the pineal region, anterior third ventricle, or multiple midline locations. Considerable debate, however, surrounds the appropriate radiation volume for these tumors. Given the recognized incidence of intraventricular and subarachnoid dissemination, craniospinal (or less often, full cranial) irradiation has been recommended for pineal region and suprasellar germinomas. The outcome in many series indicates that disease is controlled in up to 95% of patients treated with full neuraxis radiation as a component of their therapy (Table 33-4). Local irradiation, variably defined as encompassing the primary tumor site with a margin or the entire third ventricular region, has been associated with long-term disease-free survival rates of more than 80% (see Table 33-4). Considerable debate, however, surrounds the appropriate radiation volume for these tumors. Given the recognized incidence of intraventricular and subarachnoid dissemination, craniospinal (or less often, full cranial) irradiation has been recommended for pineal region and suprasellar germinomas. Local irradiation, variably defined as encompassing the primary tumor site with a margin or the entire third ventricular region, has been associated with long-term disease-free survival rates of more than 80% (see Table 33-4). The incidence of neuraxis dissemination varies from less than 10% to 35%. No consensus has been reached regarding the appropriate radiation volume because cure rates are relatively high for local and full-neuraxis irradiation, and the toxic effects associated with the relatively low doses necessary for this disease are exquisitely age related.

Evidence is increasing that 45 Gy delivered to the primary tumor site is adequate to ensure virtually uniform control of pineal region and suprasellar germinomas. Wider-field components (craniospinal or, as done at some institutions, full cranial irradiation) can be limited to doses of 25 Gy. CSI doses as low as 18 to 19.8 Gy in children with no detectable leptomeningeal metastasis from germinomas at diagnosis have been reported to be effective in preventing leptomeningeal recurrence.

Considerable interest has been expressed in chemotherapy for intracranial germinomas. Although a high rate of response has been documented, durable control of disease has been achieved in only about one half of the patients treated with chemotherapy only, including some of the more rigorous treatment regimens that carry a 5% to 10% rate of toxicity-related death. CSI is often a successful salvage treatment for germinomas that recur after such therapy.

Early studies conducted by Allen and colleagues established that disease control was excellent after combined

### TABLE 33-3. Histologic Classification and Relative Incidence of Pineal Region Tumors

<table>
<thead>
<tr>
<th>Histologic Type*</th>
<th>Relative Frequency†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumors of Germ Cell Origin</strong></td>
<td></td>
</tr>
<tr>
<td>Germinoma</td>
<td>60% to 80%</td>
</tr>
<tr>
<td>Teratoma (differentiated, immature, malignant)</td>
<td>65%</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>18%</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>7%</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Tumors of Pineal Parenchymal Origin</strong></td>
<td>14%</td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td></td>
</tr>
<tr>
<td>Pineocytoma</td>
<td></td>
</tr>
<tr>
<td><strong>Tumors of Glial Origin</strong></td>
<td>15%</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Malignant glioma</td>
<td></td>
</tr>
<tr>
<td>Ganglioglioma (ganglioneuroma)</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
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chemotherapy (with cyclophosphamide or carboplatin) followed by limited-volume, reduced-dose radiation. Strategies incorporating moderately aggressive chemotherapy and local radiation (to 30 to 36 Gy for patients showing a good partial or complete response, as shown on imaging studies and by normalization of any elevated markers) or limited-dose CSI (for those with disease dissemination) result in disease control rates exceeding 90%, with limited toxic effects.220,222,224,228 Whether such an approach offers any advantage over radiation therapy alone is unclear; prospective trials of this approach are being conducted in Europe and by the COG. It is difficult to improve on the disease control rates produced by primary irradiation, although prepubertal patients and those who require CSI before completion of skeletal growth may benefit from a combined-modality approach.

In patients with malignant germ cell tumors (i.e., embryonal or yolk sac carcinoma, choriocarcinoma), treatment with radiation therapy alone has rarely controlled disease in more than 25% to 40% of cases.213,220 Combined radiation and chemotherapy seems to be beneficial in such cases, but the chemotherapy must be relatively aggressive, and the radiation dose to the craniospinal axis is usually 24 to 36 Gy, followed by a boost dose to the tumor bed of 9 to 25 Gy, depending on the response to prior chemotherapy.230,231

**Prognosis**

A fairly favorable outcome has been observed for patients with pineoblastomas treated with radiation therapy (including CSI) and chemotherapy (including alkylating agents or nitrosoureas in conjunction with vincristine).232 Disease has been controlled in up to 60% of patients, compared with the 0% to 10% survival rates for infants treated with prolonged chemotherapy with or without radiation.178

### Craniopharyngioma

Craniopharyngiomas are histologically benign tumors derived from squamous cell rests in the region of the pituitary stalk. More than one half of these tumors occur in patients younger than 18 years, and craniopharyngiomas represent 3% to 9% of the intracranial tumors of children. The tumor arises as an extra-axial lesion, typically a densely calcified, solid tumor in the suprasellar region with large cystic components (Fig. 33-12). These histologically classic adamantine tumors occur in children and adults.233 Less common are the noncalcified, squamous papillary type, which usually occur in adults.69,115

Total surgical resection is usually curative in patients with craniopharyngiomas.5,33-240 The decision about whether to use surgery or radiation therapy depends on the site of origin and growth of the tumor, which often damages the hypothalamus or optic chiasm and sometimes damages the adjacent major vessels. Although encapsulated, the lesion usually adheres to these vital structures, even though it does not infiltrate to the level of the tuber cinereum.234-236 Modern microsurgical techniques allow total resection in up to 75% of cases, with operative mortality rates of 1% to 3%.236,241-243 The incidence of long-term functional deficits may be higher among patients who undergo radical resection than among those treated with radiation.237,244-247

**TABLE 33-4. Therapy and Outcome in Intracranial Germinomas**

<table>
<thead>
<tr>
<th>Radiation Therapy</th>
<th>Chemotherapy</th>
<th>5-Year NED Rate (%)</th>
<th>Study and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT only +</td>
<td>+ 50-55</td>
<td>85</td>
<td>Shibamoto et al, 1988&lt;sup&gt;221&lt;/sup&gt;</td>
</tr>
<tr>
<td>+ 45-55</td>
<td>86</td>
<td>Rich et al, 1985&lt;sup&gt;203&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>+ 45-59</td>
<td>97</td>
<td>Hardenbergh et al, 1997&lt;sup&gt;219&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>+ 45-50</td>
<td>91</td>
<td>Bamberg et al, 1999&lt;sup&gt;222&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>CrI, VtI 50-54</td>
<td>87</td>
<td>Wolden et al, 1995&lt;sup&gt;206&lt;/sup&gt;</td>
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<tr>
<td>0 40-50</td>
<td>90</td>
<td>Haddock et al, 1997&lt;sup&gt;215&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>0 44</td>
<td>100</td>
<td>Merchant et al, 2000&lt;sup&gt;218&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy and reduced RT 0 30 Cyclophosphamide</td>
<td>91</td>
<td>Allen et al, 1987&lt;sup&gt;223&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>0 40 VP-16/CBCDA; VP-16/ ifosfamide</td>
<td>96&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Bouffet et al, 1999&lt;sup&gt;224&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>0 30 (CBCDA or CDDP); vinblastine; bleomycin</td>
<td>92</td>
<td>Calaminus et al, 1994&lt;sup&gt;220&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy only 0 0 CDDP, VP-16, bleomycin</td>
<td>42</td>
<td>Balmaceda et al, 1996&lt;sup&gt;225&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

*Includes cases from Rich et al, 1985<sup>203</sup> (CSI or CrI, dose of 15 to 44 Gy).
†Event-free survival at 3 years.

CBCDA, carboplatin; CDDP, cisplatin; CrI, full cranial irradiation; CSI, craniospinal irradiation (dose levels 24 to 30+ Gy for localized tumors); NED, no evidence of disease; RT, radiation therapy; VP-16, etoposide; VtI, full ventricular volume irradiation (typically to doses of 20 to 36 Gy), +, used; 0, not used.
Kramer and colleagues established the effectiveness of high-dose radiation after limited cyst aspiration, initially reporting 5-year survival for 9 of 10 patients and with later follow-up showing 13- to 15-year survival for 6 of 6 children. Subsequent series showed similarly impressive long-term survival data. Bloom and colleagues updated Kramer’s initial findings, reporting a 10-year survival rate of 85% for the children and a 10-year relapse-free survival rate of 80%. Disease control is even better in young adults: 92% at 20 years for patients 16 to 39 years old at the time of diagnosis. These latter figures are equal to the best results observed in primary surgical series when corrected to account for cases with incomplete resection.

**Radiation Therapy Technique**

Radiation therapy for craniopharyngioma is designed to narrowly encompass the solid and cystic components of a well-delineated, central neoplasm. Much of the published information involves treatment using coronal arcs of 180 to 220 degrees; three-dimensional conformal or fractionated stereotactic radiation therapy is being used to improve dose conformity.

Craniohypophygiomas show a radiation dose-response relationship. Bloom and colleagues reported a superior outcome in response to 50 to 55 Gy compared with the response to less than 50 Gy. Doses of 50 to 54 Gy at 1.8 Gy per fraction are recommended for children. It is not clear that higher doses are necessary or desirable for adults. Doses in excess of 60 Gy are associated with significantly greater toxicity, especially in the visual system, with little improvement in survival.

Single-fraction radiosurgery has been used more broadly in Europe than in the United States. Radiosurgery may be appropriate for children with small foci of residual disease, particularly disease that is limited to intrasellar deposits or foci of disease remote from the hypothalamus and chiasm.

**Prognosis**

Excellent long-term survival rates have been attained for patients who undergo total resection or planned limited surgery and radiation. The proportion of patients in recent series who underwent successful resection approximates 75%, However, even the most vociferous advocates of surgery acknowledge the existence of residual calcifications or apparently viable, radiographically obvious tumor in up to 50% of postoperative CT studies of patients who have undergone gross total resection. The rate of disease recurrence after complete resection ranges from 10% to 30%. Despite the benign nature of craniopharyngioma, tumor progresses in 70% to 90% of patients after incomplete resection and without radiation at a median of 2 to 3 years.

Primary radiation after cyst decompression or partial resection has been associated with progression-free survival rates of 80% to 95% at 5 to 20 years. Survival rates of 90% to 100% are common among children and adults.

The relative toxicity of primary surgery and radiation for craniopharyngioma are becoming increasingly apparent. Diabetes insipidus occurs in 75% to 100% of patients after complete surgical resection. Endocrine dysfunction involving other pituitary-hypothalamic hormones has occurred in 40% to 80% of patients after surgery. Hypothalamic obesity is apparent in more than 50% of long-term survivors; it is less common among those who undergo limited surgery and radiation. Undesirable personality changes are associated with resections that damage the hypothalamus.

An increased endocrine deficit has been identified in patients whose primary treatment was surgery compared with those who underwent limited resection and radiation. Up to 25% of children show significant decreases in vision after resection; reports of visual complications from radiation therapy have been anecdotal. Overall performance, intellectual function, and memory seem to be equal or better in the population treated by conservative surgery and radiation than in those treated surgically.

**Primitive Neuroectodermal Tumors**

In 1973, Hart and Earle described the cerebral PNET as a malignant embryonal tumor that affects children and young adults. The tumor accounts for approximately 3% of supratentorial neoplasms. PNETs are large, often cystic hemispheric tumors characterized histologically by a highly cellular, undifferentiated infiltrate that includes vascular endothelial hyperplasia and necrosis. In classic descriptions, focal areas of glial or neuronal differentiation constitute less than 5% to 10% of the tumor. The clinically similar cerebral neuroblastoma is distinguished from the Hart/Earle PNET by its degree of neuronal differentiation. The specific cerebral PNET encountered in a patient, however, must be distinguished from the broad concept of PNETs advanced by Rorke and colleagues, as discussed earlier in this chapter.

Cerebral PNETs infiltrate widely despite their circumscribed gross appearance. The tumor can also arise multifocally. About one third of cases involve ventricular or spinal subarachnoid dissemination. The more...
differentiated cerebral neuroblastoma has been associated with CSF metastasis in an equal proportion of patients at autopsy, although isolated involvement of the subarachnoid space is uncommon.263,264,266,268

Studies conducted by the CCG have documented the efficacy of combining chemotherapy (the tested regimen included lomustine, prednisone, and vincristine) with CSI for children with cerebral PNETs who are more than 3 or 4 years old.232,263,267,269-271 Long-term survival approached 60% in this group. For infants and young children, therapeutic approaches are comparable with those used for other embryonal CNS lesions in this age group (see “Tumors in Children Younger than 3 Years”). Despite anecdotal reports of disease control after cranial irradiation, CSI is considered standard therapy for supratentorial PNETs, including cerebral neuroblastoma and pineoblastoma.232,268 The doses and techniques used for supratentorial PNETs are similar to those described for medulloblastoma, with typically a 2-cm margin planned around the tumor bed to define the clinical target volume.

**Tumors in Children Younger than 3 Years**

Between 15% and 20% of pediatric brain tumors occur in infants and children younger than 3 years. The most common tumors in this age group are astrocytomas (primarily optic chiasmatic or hypothalamic tumors; cerebellar astrocytomas are uncommon), embryonal tumors (medulloblastoma, PNET, and pineoblastoma), ependymoma, and malignant gliomas.272-274 Tumors occurring almost uniquely in this age group include atypical teratoid or rhabdoid tumors and choroid plexus neoplasms (papillomas and carcinomas).275-279 Desmoplastic infantile astrocytoma and ganglioglioma are uncommon, and when they do occur, they are typically large tumors that are biologically benign.280 The operative mortality is relatively high in this age group because of tumor presentations (often sizable, midline or multilobed supratentorial lesions) and the relative lack of elasticity of the still-myelinating brain.

The infant brain is particularly vulnerable to the effects of radiation therapy, particularly with regard to neurocognitive development.281 Survival rates for patients in this age group with ependymoma or medulloblastoma are significantly lower than those for other age groups because the tumor in these very young patients is often advanced at presentation and because tumoricidal radiation doses cannot be used.95,177,181,271,282-284

The use of prolonged chemotherapy after surgery to delay or obviate the use of radiation therapy for very young children has been studied for almost 20 years (Fig. 33-13).178,285-281 Trials of treatment for medulloblastoma in infants conducted by the POG, CCG, and International Society of Paediatric Oncology (SIOP) have documented that chemotherapy is effective in only a minority of patients; durable disease control has been achieved in 20% to 30% of patients with chemotherapy alone and in only 35% of those treated with response-defined consolidative radiation.178,288-292 Salvage radiation has achieved a surprising degree of secondary control after progression during chemotherapy, but the dose required to overcome chemotherapy resistance produces late changes in intelligence quotient that make this an ethically unacceptable alternative.291,293 A trial from Germany in which postoperative intravenous and intraventricular chemotherapy without radiation therapy was used for infants with medulloblastoma showed 5-year progression-free survival rates of 82%, 50%, and 33% for infants who had complete resection, residual tumor, and macroscopic metastases, respectively.294 Because these results seem to be better than those in any previous report, they will need confirmation. For infants with ependymoma, earlier intervention with radiation after prolonged chemotherapy may help control disease; however, this strategy too seems to work in only a minority of cases.194 Chemotherapy alone has been an unsuccessful postoperative intervention.205 Reports of survival of patients with pineoblastoma and atypical teratoid or rhabdoid tumors treated with this approach have been anecdotal.178,194,232,296

The current generation of infant brain tumor trials focuses on the judicious use of irradiation. Based on preliminary data for children with recurrent medulloblastoma, the frontline approach in the Pediatric Brain Tumor Consortium and COG trials is to introduce early, limited-volume, three-dimensional conformal radiation therapy to the posterior fossa and primary tumor site alone for patients with M0 medulloblastoma and to the local tumor bed only for those
Tumors Common in Adults

Malignant Gliomas: Anaplastic Astrocytoma and Glioblastoma Multiforme

The dominant primary intracranial tumors that occur in adults in terms of frequency and mortality are the malignant gliomas. These tumors occur in the cerebral hemispheres as sizable, rapidly growing lesions with a characteristic ringlike, enhancing appearance on CT or MRI, with central necrosis, infiltrating margins, and surrounding low-density changes (Fig. 33-14). Malignant gliomas occur in all age groups but predominate in the fifth and sixth decades, and they account for 35% to 45% of all adult brain tumors.

Histologically, malignant gliomas are heterogeneous neoplasms composed of fibrillary astrocytes; gemistocytes; large, bizarre glial cells; and small anaplastic cells. In Kernohan and Sayre’s classic categorization of astrocytic neoplasms, which defined these tumors as grade III and grade IV astrocytomas, malignant gliomas were thought to represent progressively dedifferentiated astrocytic tumors marked by a certain degree of pleomorphism, hyperchromaticism, and mitosis. In contemporary neuropathology, malignant gliomas are classified as anaplastic astrocytoma or the more malignant glioblastoma multiforme, with the latter identified by the presence of tumor necrosis. Anaplastic astrocytomas account for 10% to 15% of malignant gliomas; more than 85% are glioblastomas.

Malignant gliomas typically infiltrate the adjacent normal brain. Detailed comparisons of imaging and histologic findings have established the anatomy of malignant gliomas. Histologically, the central low-density region seen on neuroimaging studies is a necrotic and hypocellular area. The surrounding ring of enhancing tissue is composed of densely cellular tumor. The hypodense area beyond the enhancing tissue seen on CT scans is hypocellular and edematous but infiltrated by small anaplastic T cells. In 50% of cases, scattered tumor cells immediately surrounding the hypodense volume are evident histologically. The often sizable area of increased signal on T2-weighted MRI similarly contains infiltrates of viable T cells. Tumor cells characteristically extend along neural tracts and across the corpus callosum. Distant subarachnoid or subependymal extension occurs in 5% to 9% of patients with malignant gliomas.

Surgery for malignant gliomas is usually limited to subtotal resection. Macroscopically, complete removal is achieved in only 10% to 20% of cases. The extent of residual tumor visualized on postresection CT scans seems to correlate with outcome, with increased time to progression and survival being associated with smaller residual tumor volumes among adults and children.

Radiation therapy has been the most effective treatment for these aggressive lesions, but it usually can only delay disease progression or recurrence. Early clinical trials conducted by the Brain Tumor Study Group confirmed the clinical efficacy of radiation. Median survival increased from 14 weeks after surgery to 36 weeks for patients given postoperative radiation. The survival rate at 1 year was 24% for patients also treated with radiation therapy, compared with only 3% for patients who had surgery only. One fourth to one half of patients who receive radiation therapy show clinical improvement. Up to 60% of patients are able to return to work and achieve full function.
Despite documented improvement in time to progression and survival, the response to radiation illustrated by imaging studies is complex and rarely indicative of rapid or significant disease reduction. Essentially all glioblastomas and 65% to 80% of anaplastic astrocytomas recur within 2 to 5 years and result in rapid death, causing malignant gliomas to live up to their reputation of being one of the most aggressive and lethal tumors. Although the anatomy of malignant gliomas suggests that disease extension or metastasis is the source of recurrence, recurrent disease almost always arises from within the central or enhancing portion of the tumor. The central tumor is relatively radiosensitive, perhaps because of an inherent lack of radiosensitivity or a hypoxic, relatively radioresistant necrotic core. This pattern of intracerebral recurrence has stimulated several lines of clinical investigation to overcome hypoxic cell resistance; considerable interest has also been expressed in exploiting the time-dose relationship to identify an altered fractionation regimen of value in treating this tumor. Several trials have tested modifications in radiation delivery, including physical modalities other than photons and local boost techniques incorporating interstitial brachytherapy or stereotactic radiosurgery.

Early trials of radiosensitizers focused on the nitroimidazoles misonidazole and etanidazole. Later studies have investigated carbogen and nicotinamide. Despite some improvement realized from use of these agents with suboptimal radiation, clinically meaningful benefit was not achieved. Long-standing interest in the halogenated pyrimidines bromodeoxyuridine and iododeoxyuridine has resulted in several trials of their use with conventional and altered fractionation, but only a marginal benefit has been suggested by the results.

The use of radiation with high-LET particles has been examined in clinical trials as a possible way of overcoming the apparent oxygen-related radiosensitivity of these tumors. However, the use of fast-neutron beam radiation has produced no significant improvement over conventional photon radiation. The rationale for using proton radiation stems more from the ability to restrict the volume of tissue irradiated than from its being less affected by oxygenation; trials of doses as high as 90 Gy suggest a potential benefit in terms of central tumor control, but no early demonstration of improvement in outcome has been seen.

Stereotactic interstitial implantation of radioactive sources has been done at several European centers since the 1950s. Over the past 2 decades, prospective studies of temporary stereotactic brain implants using high-activity iodine 125 (125I) have evaluated the toxicity and efficacy of volume-limited, high-dose radiation delivery. Among selected patients with limited-volume recurrent malignant gliomas, geometrically planned implantations of radiation sources delivering an average of 60 Gy to the enhancing lesion over 6 days resulted in survival durations of approximately 1 year for those with glioblastomas and 1.5 years for those with anaplastic astrocytomas. Results of the Brain Tumor Cooperative Group’s prospective randomized trial suggested that interstitial boost radiation could be beneficial in appropriately selected cases.

Patients with malignant gliomas who are potentially suitable for local types of therapy (e.g., brachytherapy, radiosurgery) are those with a relatively favorable prognosis, constituting 20% to 40% of cases. The criteria for implantation include Karnofsky performance status scores above 70, unifocal supratentorial lesions less than 6 cm in the greatest diameter, and no involvement of the midline, corpus callosum, or subependyma. A retrospective review of unselected patients treated with standard external beam radiation therapy to the brain (EBRT) revealed that outcome was significantly better among implant-eligible patients with glioblastoma (median survival of 14 months) than among those who were ineligible (median survival of less than 6 months), indicating that any perceived improvement in outcome in patients attributed to the brachytherapy may be artificial. However, median survival duration and 2- and 3-year survival rates for patients with glioblastoma treated with 125I brachytherapy seem to be superior in single-institution experiences and in comparison with the previously described findings. Comparable data for anaplastic astrocytomas are less convincing.

Symptomatic local necrosis occurs in 40% to 50% of patients with interstitial implants, and this often requires surgical intervention. Ultimate survival has been reported to be superior in patients who require a second operation, which presumably reflects the combination-treatment effect.

Stereotactic radiosurgery has been used to achieve a high-dose boost. Eligibility criteria are selective, typically including single lesions less than 4 to 5 cm in diameter without subependymal extension and more than 5 mm away from the optic chiasm or brainstem. In the initial U.S. series, which included a high proportion of patients who had undergone limited surgical resection, the median survival time was at least equal to that among patients with implants: 26 months for those with glioblastoma and more than 36 months for those with anaplastic astrocytoma. In a multi-institutional trial of 189 patients, the median survival time was 86 weeks for those with glioblastoma who met all criteria for gamma knife intervention, compared with 40 weeks for those with more extensive tumors or a less favorable performance status score. The incidence of symptomatic necrosis may be less than that for patients with interstitial implants.

Several trials in the United States, Europe, and Japan have assessed modifications in the radiation time-dose relationship. Despite an early suggestion that hyperfractionation delivered to higher doses might be beneficial, subsequent studies conducted by the RTOG have shown no substantial benefit from such therapy. A large randomized dose-escalating trial conducted by the RTOG tested hyperfractionated doses of 64.8 to 81.6 Gy, given in 1.2-Gy fractions twice daily with an interfractional interval of 4 to 8 hours. The results indicated that the ideal dose response occurred at 72 Gy, although the superiority of this schedule over 60 Gy delivered in conventionally fractionated radiation therapy was apparent. Patients who received doses of 75 to 81.6 Gy fared less well. Without documentation of any reduction in neurotoxicity from hyperfractionated delivery, few objective data indicate that the therapeutic ratio and effect of hyperfractionation are greater than those for conventional fractionation.

Alternative time-dose regimens have included accelerated hyperfractionation (1.5- or 1.6-Gy fractions given twice daily), accelerated fractionation (1.9- or 2.0-Gy fractions given three times daily), and hypofractionation (fractions...
of 2.5 to 6 Gy). \(^{332,334-347}\) Although the hypofractionation regimens may expedite palliation in patients with advanced or unfavorable conditions, these regimens have provided no overall benefit.

Chemotherapy has been investigated extensively for the treatment of glioblastomas. As sole adjuvants to surgery, nitrosoureas have been ineffective.\(^{306}\) When combined with radiation, nitrosoureas or combinations of agents (e.g., carmustine-hydroxyurea plus procarbazine-teniposide, carmustine-hydroxyurea, vincristine-procarbazine) have been associated with only marginally improved survival times for patients enrolled in prospective studies.\(^{306,311,330}\) Despite one report of encouraging early results with penciclovir,\(^{351}\) a randomized trial conducted by the Medical Research Council in the United Kingdom of more than 670 patients showed no survival benefit for patients given penciclovir in addition to standard radiation therapy.\(^{352}\) Two randomized trials testing concurrent temozolomide plus radiation therapy with radiation therapy alone demonstrated a significant survival benefit for the combination.\(^{353-354}\) In a trial by the European Organisation for Research and Treatment of Cancer, the survival benefit from temozolomide was more apparent when the MGMT gene was epigenetically silenced.\(^{355}\) The current RTOG trial uses MGMT status in the tumor as one of the criteria for stratification. Many biological agents are available for the treatment of malignant gliomas, including compounds with specific biological targets (e.g., epidermal growth factor, platelet-derived growth factor) and antiangiogenesis agents.\(^{350}\) One ongoing trial is using a vaccine against a truncated form of the epidermal growth factor receptor (EGFRvIII) for patients whose glioblastomas have undergone gross total resection and demonstrate overexpression of EGFRvIII. Studies of local chemotherapy, specifically carmustine-impregnated wafers (Gliadel), have yielded inconclusive results in patients with malignant gliomas, producing an apparent response but being of uncertain value as an adjuvant therapy.\(^{357}\)

**Radiation Therapy Technique**

Radiation therapy remains the most effective single agent in prolonging survival in patients with malignant gliomas. It should consist of standard EBRT with wide local coverage of the neoplasm.\(^{310,314}\) Anatomic studies of tumor extent, imaging analyses of patterns of recurrence, and clinical trials have shown that the appropriate initial target volume should extend 2 to 3 cm beyond the low-density periphery shown on CT scans or 2 cm beyond the abnormal signal shown on T2-weighted MRI studies.\(^{301,302,314,315,350}\) Margins of less than 2 cm are theoretically inadequate because of the histologic nature of the tumor\(^{301}\) and the way in which the initial sites of disease progress.\(^{315}\)

The use of limited high-dose treatment volumes delivered by three-dimensional conformal or proton radiation may be associated with a relative increase in the peripheral failure rate.\(^{338,358}\) Central or intracranial disease progression is less common in patients with interstitial implants. Studies of patterns of failure in series of patients treated with brachytherapy have shown that disease recurs primarily in the tumor margin, often within 2 cm of the high-dose implant; the incidence of distant intracranial recurrence is also relatively high.\(^{316,317}\)

Dose-response data were established early in clinical trials involving patients with malignant gliomas. Walker and colleagues\(^{306}\) showed that median survival time improved from 28 weeks for patients given 50 Gy in 25 to 28 fractions to 42 weeks for patients given 60 Gy in the first Brain Tumor Study Group studies (Fig. 33-15).\(^{306}\) Three-dimensional conformal and proton-based regimens have made it possible to escalate doses to 70 to 90 Gy; however, although central tumor control may be improved, no increase in survival has been found.\(^{338,358}\) As summarized earlier, none of the altered fractionation regimens has been shown to improve outcome over that achieved with conventionally fractionated radiation to 60 to 65 Gy (in 1.8- to 2-Gy fractions given once daily).\(^{345}\) No data exist to suggest that these recommendations for radiation therapy for adults be adjusted for children; however, the requirement for high-dose radiation to reasonably large volumes limits the use of this modality in young children with malignant gliomas.

**Prognosis**

Reports of survival beyond 2 years for adults with glioblastoma remain anecdotal.\(^{359}\) However, approximately 15% to 25% of patients with anaplastic astrocytoma survive 5 years, with gradually decreasing survival beyond that time documented in most series. Levin and colleagues\(^{351}\) reported that adjuvant penciclovir chemotherapy is associated with a 35% survival rate at 3 to 5 years for patients with anaplastic lesions; however, these and similar results seen in other small series were not substantiated in a Medical Research Council trial.\(^{314,352,360}\) Other factors influencing prognosis include age (survival is progressively better among younger patients, with the best among 18 to 39 year olds, the next best among 40 to 59 year olds, and the worst among those 60 years old or older) and initial performance status.\(^{309,325}\) Among children with malignant gliomas, the overall progression-free survival rates at 3 to 5 years range from 15% to 20%; for the small subset with completely resected lesions, corresponding survival rates of up to 75% have been reported.\(^{309,361,362}\)
Oligodendroglioma

Oligodendroglioma is a relatively uncommon tumor that occurs in all age groups. The tumor arises most often in the frontal lobes and occasionally involves the infratentorial or spinal regions. The most common symptom is seizures. The relatively nonaggressive nature of this tumor is indicated by the median survival time, which is more than 5 years from the onset of symptoms and diagnosis. The co-deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) has been associated with less aggressive behavior of the tumor and better response to therapy.

Primary surgical resection is the initial therapy for low-grade oligodendrogliomas. The role of postoperative radiation has been poorly defined. In a small, retrospective study, Sheline and colleagues found an improvement in 5-year survival rates for patients who underwent irradiation compared with those who did not (85% versus 55%), but the survival rate at 10 years was not statistically improved. Chin and colleagues reported a progression-free survival rate of 100% at 5 years for 24 patients completing postoperative radiation. Lindegaard and colleagues observed a benefit from radiation only among those who had undergone incomplete surgical resection. In a study of a similar group of patients treated during roughly the same period, Reedy and colleagues found no survival advantage from radiation therapy.

In the absence of a prospective trial assessing the efficacy of radiation therapy, it seems justified and prudent to use postoperative radiation for subtotally resected lesions. Local fields to doses of 50 to 54 Gy approximate the treatment recommended for other low-grade tumors.

Although 5-year survival rates in excess of 65% to 90% have been observed in major clinical series, the ultimate survival rate beyond 15 or 20 years was only 30% in two large reviews from an earlier era that examined the pathologic behavior of tumors from more than 500 patients. Late tumor progression and death take place more than 5 to 10 years after diagnosis. Histologic grading is of increasing importance because a role for penciclovir chemotherapy in the treatment of anaplastic oligodendrogliomas has been established. Long-term survival is higher for patients younger than 40 or 50 years.

Meningioma

Meningiomas are common CNS tumors, most often occurring as intracranial tumors along the convexities or in parasagittal regions. The usually benign meningioma constitutes 15% of adult CNS tumors, with a female-to-male ratio of 2.5 to 1. The natural history of this tumor was elegantly described in Cushing and Eisenhardt’s 1938 monograph, in which they identified the broad dural attachment (or local infiltration), growth along or into the venous sinuses, and osseous invasion or overlying reactive bone formation that typify these lesions. Angioblastic meningiomas have a less favorable outcome than the other so-called benign tumors. Less than 10% of meningiomas are malignant, and these lesions seem to be associated with an unfavorable outcome.

Surgery is the primary treatment for most peripherally located intracranial meningiomas. Local tumor recurrence after complete resection occurs in 10% to 20% of cases, related in part to the extent of dural and sinus excision. Symptomatic tumor recurrence or progression takes place in approximately 50% of patients with subtotally excised lesions, most often in patients with meningiomas of the sphenoid ridge and parasellar areas, which represent almost 30% of all meningiomas (Fig. 33-16). The efficacy of radiation therapy for incompletely resected meningiomas has been well documented. Wara and colleagues reported local tumor recurrence in 74% of patients after incomplete resection and in 29% of patients given postoperative radiation. Progression-free survival rates beyond 5 years average 70% to 90% for patients undergoing incomplete resection and radiation; disease control rates in excess of 70% to 80% at 8 to 10 years are associated with survival rates exceeding 90%. Similar outcomes have been observed among patients who receive radiosurgery alone or as an adjunct to incomplete surgery. Neurologic improvement has occurred in 44% of patients after radiation for unresected primary lesions. Serial CT studies have confirmed the regression of neoplasms in response to radiation therapy (see Fig. 33-16). In sites such as the optic nerve sheath, operative intervention may be associated with a significant functional deficit. Primary irradiation can improve tumor-related defects in visual acuity and visual fields in these patients.

Radiation Therapy Technique

Because meningiomas are locally infiltrating tumors that produce local tissue changes by means of direct tumor extension or have subclinical, limited multicentricity, local irradiation should include a reasonable margin despite the circumscribed appearance of these tumors on CT scans. Large tumors of the sphenoid ridge may extend beyond the cranial vault into the orbit or the facial or cervical regions. Optimal radiologic assessment of tumor extent and the use of wide inferior treatment margins are important in these cases. Three-dimensional conformal techniques, intensity-modulated radiation therapy, and proton therapy are suitable for the treatment of meningiomas.

Carella and colleagues were unable to identify a dose-response relationship for meningiomas between 50 and 75 Gy. However, excellent local tumor control has been achieved at doses approaching CNS tolerance, and the recommended treatment is a total dose of 50 to 55 Gy given in 25 to 30 fractions. The use of radiosurgery as the primary treatment for selected lesions has produced equally positive results; at many centers, radiosurgery is the treatment of first choice for limited-volume lesions that are difficult to approach surgically or are residual or recurrent after initial resection.

Prognosis

The benign nature of meningiomas is confirmed by the limited number of recurrences seen in patients after total surgical resection. After incomplete resection, however, the median time to clinically apparent tumor progression is 4 years after surgery. The median intervals to tumor progression in patients given radiation therapy exceed 5 to 10 years.

Initial postoperative irradiation for incompletely resected or biopsied meningiomas has achieved excellent local tumor control, as described in the previous paragraphs.
Indications for initial or delayed radiation therapy remain controversial, although increasing information suggests that incompletely resected lesions along the cavernous sinus and those with malignant histologic features may warrant immediate postoperative irradiation. No apparent decrease in tumor control has been observed in most series of patients who undergo repeat surgery and radiation therapy for disease that recurs after initial incomplete resection. A more rapid rate of tumor regrowth after subtotal excision has been indicated in children, raising some concern about the advisability of delaying radiotherapeutic intervention in this age group.

Identifying the histologic subtype of meningioma is important because the local recurrence rate is higher for malignant (anaplastic) meningiomas and because postoperative radiation therapy can effectively control these tumors. For example, Dziuk and colleagues have reported 15% to 80% differences in 5-year progression-free survival rates related to radiation. A long-term disease control rate of only 25% at 5 years has been observed for patients who receive single-fraction radiosurgery, in most cases for recurrent malignant meningiomas.

**Primary Malignant Lymphoma of the Central Nervous System**

Primary malignant lymphoma of the CNS was previously a rare neoplasm, occurring spontaneously in conjunction with immunosuppression. However, the frequency with which it occurs has increased greatly in conjunction with the acquired immunodeficiency syndrome (AIDS) epidemic. The tumor occurs primarily in the supratentorial region, most often as an isodense, diffusely enhancing lesion involving the basal ganglia or thalamus, the periventricular white matter, or the corpus callosum. Up to 15% to 40% of tumors are multifocal intracranial lesions. The CSF contains tumor cells in 10% to 20% of cases; involvement of the ocular vitreous at diagnosis or metachronously occurs in 10% to 25% of cases.

The lesion is usually classified as an immunoblastic or lymphoblastic diffuse, large cell, malignant lymphoma, most often of a B-cell immunophenotype. Systematic evaluation is necessary to distinguish primary lymphoma of the brain from secondary CNS manifestations of malignant lymphoma, although intraparenchymal deposits occur more often with primary tumors than with secondary tumors.

Surgery is limited, often to biopsy alone, but radiation therapy produces a high rate of objective response. Neurologic improvement can be achieved in up to 70% of patients, but median survival has been only 7 to 8 months. Long-term survival after radiation alone has been limited. Chemotherapy has shown increasing efficacy in patients with CNS malignant lymphoma, with rates of objective response often exceeding 50% to 70% in those treated with regimens including high-dose methotrexate or, less often, with conventional systemic chemotherapy regimens (e.g., cyclophosphamide, doxorubicin, vincristine, and prednisone). The combination

**FIGURE 33-16.** CT scans of an orbital sphenoidal meningioma demonstrate residual disease after surgery (top row) and 2 years after irradiation (bottom row). (From Petty AM, Kun LE, Meyer GA. Radiation therapy for incompletely resected meningiomas. J Neurosurg 1985;62:502-507.)
Intracranial metastasis, primarily in the cerebrum, occurs in 60% of patients. Of the primary tumor, and absent or controlled extracranial metastases. In a classic autopsy series, solitary metastases were found in approximately 40% of cases, two to three lesions in 25% of cases, and four or more foci in 35%. 

Treatment of brain metastases is palliative; long-term survival can be achieved for up to 20% of patients with favorable presenting characteristics, such as age younger than 60 to 65 years, favorable performance status (typically, a Karnofsky performance status score of at least 70), control of the primary tumor, and absent or controlled extracranial metastasis. Corticosteroids alone can transiently reduce symptoms in 60% of patients. However, cranial irradiation achieves more prolonged palliation, with objective improvement in neurologic function in 50% to 70% of patients treated in this manner.

Radiation Therapy Technique

Given the size and often the multiplicity of most primary CNS lymphomas, the minimal target volume is often full cranial irradiation. Isolated subarachnoid spinal recurrence after cranial radiation occurs in 4% to 25% of patients. The inability to control the primary tumor within the cranium in a high proportion of patients and the need to coordinate radiation with chemotherapy have led clinicians away from considering CSI. This raises a valid argument for avoiding spinal irradiation in deference to the potential benefits conferred by chemotherapy.

A radiation dose-response relationship has been suggested in the treatment of primary malignant lymphoma of the CNS. Murray and colleagues reviewed 198 cases reported in the literature and found a statistically significant improvement in the 5-year survival rate for patients given doses of more than 50 Gy (42% versus 13%) (Fig. 33-17). However, an analysis at Memorial Sloan-Kettering Cancer Center did not find additional benefit from doses higher than 45 Gy. Recurrence of tumor at the primary site even in patients treated with doses of 50 to 55 Gy led to a major RTOG trial, the results of which failed to demonstrate a significant added benefit from high-dose cranial irradiation. In small series of patients, however, the addition of radiation therapy seems to have prolonged disease control and improved survival relative to the outcome for patients given chemotherapy only.

Prognosis

Overall survival in patients with primary malignant lymphoma seems to have increased among those treated with combined, sequential chemoradiotherapy; median survival times have increased several-fold to approximately 4 to 5 years. However, most patients do die of the disease, sometimes as long as 5 years after diagnosis.

Carcinoma Metastatic to the Brain

Intracranial metastasis, primarily in the cerebrum, occurs in 10% to 15% of patients with cancer. Of the types of cancer that metastasize preferentially to the brain, cancer of the lung and breast predominate, and gastrointestinal and renal carcinomas are less common. Brain metastasis often occurs at multiple sites. In a classic autopsy series, solitary metastases were found in approximately 40% of cases, two to three lesions in 25% of cases, and four or more foci in 35%.

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Earlier time-dose studies showed the relative equivalence of the following treatment regimens: 30 to 36 Gy given in 10 to 12 fractions; 20 Gy given in 5 fractions; and 40 Gy given in 15 fractions. The current standard therapy is 30 Gy given in 10 fractions; however, randomized trials to assess the benefit of surgery or radiosurgery in selected settings favor 37.5 Gy given in 15 fractions.

For patients with a solitary metastasis, the addition of surgical resection or radiosurgery has significantly improved survival time (from a median of 15 weeks to a median of 40 weeks in a randomized trial reported by Patchell and colleagues) and the rate of local control at metastatic sites (from less than 50% for patients treated with cranial irradiation alone to 80% for patients undergoing resection). This increase in survival also has been associated with improved functional outcome. In several series, the outcome from radiosurgery has been similar to that from operative removal; in all of these series, the patients with favorable factors (e.g., age, performance status, absence of disease at other sites) are the ones who benefit the most from the addition of local therapy. Surgery and radiosurgery seem to achieve equivalent results in most reports. Detailed analyses have shown that the addition of full cranial irradiation improves survival and local tumor control and may be associated with long-term survival of a small but meaningful number of patients undergoing aggressive local therapy. One randomized trial comparing radiosurgery alone...
with the combination of radiosurgery and whole-brain irradiation showed significantly fewer intracranial recurrences with the combination therapy, although survival times were similar in both groups. Results for patients with malignant melanoma that has metastasized to the brain have generally paralleled those seen for patients with other carcinomas; however, local therapy may be particularly advantageous for patients with few metastatic sites and favorable performance status. The treatment selected for patients with brain metastasis depends on the absence or presence of the clinical features consistently associated with improved outcome (i.e., age younger than 60 to 65 years, Karnofsky performance status score of 70 or higher, and the lack of apparent or symptomatic disease at the primary site or other extracranial locations). However, there does seem to be a definite advantage to surgery or radiosurgery for patients with only one metastatic focus; a similar advantage seems to exist for those with only two or three metastatic foci. In all of these patients and in those with more advanced cranial or extraneural disease, the addition of full cranial irradiation is an important and worthwhile palliative intervention.

**Spinal Cord Tumors**

Primary tumors of the spinal cord represent 10% to 15% of CNS neoplasms. Extramedullary tumors, including schwannomas and meningiomas, account for almost one half of the lesions in the spinal canal. Primary intramedullary neoplasms are most often gliomas or vascular tumors. Intramedullary gliomas include ependymomas (60%) and astrocytomas (30%). Ependymomas occur more often in the lumbar region, affecting the conus and cauda equina. Spinal ependymomas usually are low-grade neoplasms; those occurring in the cauda equina usually are well-differentiated myxopapillary tumors. The ependymomas tend to develop as discrete lesions, facilitating subtotal or gross total resection.

Gross total resection led to systemic disease control in recent series with a 5-year follow-up. Aggressive surgery, however, is associated with postoperative neurologic deterioration in 15% of patients. Response to radiation is well documented, with 75% of patients showing improvement in neurologic status and progression-free survival rates of 70% to 100% at 10 years. A local tumor control rate of 80% with no identifiable long-term neurologic toxicity despite doses in excess of 45 Gy indicates that radiation has a role in the treatment of patients whose spinal tumors are incompletely resected. Patients with tumors of the cauda equina region and conus have particularly high survival rates after radiation or surgical resection.

Spinal astrocytomas are evenly distributed along the length of the spinal cord. These lesions often contain cystic components and most are low-grade fibrillary tumors. Astrocytomas are more infiltrating than ependymomas, limiting surgery to cyst decompression and partial resection. However, described operative techniques that can be used to completely resect many low-grade astrocytomas in children and adults. Aggressive operative intervention is not advantageous for high-grade spinal astrocytomas. Long-term control in patients with spinal astrocytomas treated with radiation is less predictable than that in patients with ependymomas despite frequent neurologic improvement. The disease-free survival rate at 5 to 10 years ranges from 25% to 60% among patients with spinal astrocytomas. However, the histologic grade affects outcome, in that patients with low-grade astrocytomas enjoy a short-term (5-year) survival rate of as high as 89%, compared with 0% among patients with higher-grade tumors (e.g., glioblastoma).

Spinal cord tolerance is an important consideration when reviewing results of patients with intramedullary tumors treated with radiation. Doses of approximately 50 Gy are recommended for most spinal cord tumors; however, higher doses and the suggestion of a dose-response effect at or above 50 Gy have been reported for localized spinal cord lesions.

Extradural metastasis is the most common oncologic diagnosis for patients with spinal cord disease. An estimated 5% of patients who die of cancer have clinical signs of epidural metastases. Extradural involvement usually results from the contiguous extension of a vertebral metastasis, most often in patients with primary cancer of the breast, lung, or prostate. Less common are vertebral metastases from malignant lymphomas and myeloma or carcinomas of the kidney and gastrointestinal tract.

Early evaluation with spinal MRI has been advocated for patients with pain and radiographic evidence of vertebral metastasis without objective neurologic signs. The treatment of epidural metastases is controversial, largely with respect to the use of surgery before radiation. Conventional procedures have included decompressive laminectomy, at least for patients with rapidly evolving signs or complete block shown by myelography; patients for whom the diagnosis is uncertain or the diagnosis of malignancy is not established require surgical intervention.

Retrospective and prospective studies comparing laminectomy and postoperative radiation with radiation alone confirm an apparent advantage to surgical intervention only for patients with nonambulatory symptoms; however, there has been little difference in outcome for most patients. Experience with vertebral body resection in selected cases indicates improved neurologic outcome after a more aggressive operative approach. Primary irradiation is often the treatment of choice for certain histologic types of tumors known to respond relatively rapidly and for patients with residual functional deficits.

Irradiation for spinal cord compression is considered a radiotherapeutic emergency. Prompt initiation of dexamethasone and high-dose (2- to 4-Gy) fractions are indicated. After two or three treatments, the dose per fraction and total dose depend on the type of malignancy and clinical status of the patient.

Carcinomatous meningitis or diffuse leptomeningeal infiltration is a relatively uncommon late manifestation of systemic cancer. Primary tumors are usually carcinomas of the breast or lung; small cell lung cancer in particular is often associated with intracranial metastasis. Symptoms and signs referable to the spine predominate in 25% of patients; signs related to spinal root infiltration are often apparent. Treatment consists of cranial irradiation or CSI (depending on the histologic findings and coordinated use of chemotherapy), with or without intrathecal or systemic chemotherapy. Responses to treatment are common, but long-term survival results are largely anecdotal.
REFERENCES

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References


