

Central Nervous System Tumors in Children



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CNS

- Central nervous system (CNS) tumors account for 20% to 25% of all malignancies that occur in childhood(United States)
- The incidence is highest among children 0 to 4 years (4.6 per 100,000 person-years) and lowest among 10- to 19-year-olds (3.7 per 100,000 person-years).
- Only 2% to 5% can be ascribed to a genetic predisposition [neurofibromatosis types 1 and 2, tuberous sclerosis, nevoid basal cell (Gorlin's) syndrome, the adenomatous polyposis syndromes, and Li-Fraumeni syndrome]

CNS

- An even smaller percentage can be attributed to ionizing radiation used for diagnostic or therapeutic purposes
- For the majority of patients, no predisposing factors can be identified, although many have been suggested, including viral agents, pre- and postnatal environmental exposures, and birth characteristics, such as weight and head circumference

survival

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the 5-year relative survival rate is estimated at 72% for all CNS tumors occurring in the 0- to 19-year age

Radiotherapy for Pediatric Central Nervous System Tumors

□ General Principles

- ✓ The planning and delivery of radiotherapy for children with CNS tumors is technically challenging
- ✓ For children younger than age 4 or 5 years, daily anesthesia will almost always be necessary

Long-Term Effects of Radiotherapy for Central Nervous System Tumors

- ✚ The quality of survival of children with brain tumors may be compromised by long-term sequelae*
- ✚ The magnitude of the deficit depends most importantly on **age** at treatment, but many other host (e.g., **NF-1** or not), tumor (e.g., **location, hydrocephalus** or not), and treatment factors (e.g., **radiotherapy volume and dose, use of chemotherapy**) , the development of other deficits, such as behavioral difficulties related to the location of the tumor and/or **surgery***
- ✚ There is increasing evidence that intervention using cognitive or behavioral therapy or pharmacotherapy may be useful, and that this should start soon after treatment for best results*
- ✚ Endocrine deficits are very common after radiotherapy*

strategies

- A number of strategies have been devised in an attempt to minimize the long-term effects of treatment for pediatric brain tumors. These include the following

strategies

- **Avoidance of radiotherapy altogether (e.g., in patients with low-grade astrocytoma for whom surgery alone may be a good option)**
- **Delay to radiotherapy for young children (i.e., those younger than age 3 to 8 years) by the use of chemotherapy**
- **Use of focal rather than extended-field radiotherapy when evidence suggests that extended field (whole-brain, craniospinal) radiotherapy does not influence survival (e.g., ependymoma)**
- **Use of daily anesthesia and of improved immobilization techniques (e.g., rigid casts or a stereotactic frame for small-volume focal radiotherapy for all or part of the treatment) that allow the use of reduced margins around the target volume**
- **Use of image-based treatment planning using CT, magnetic resonance imaging (MRI) or positron emission tomography (PET) coregistration and better treatment-planning techniques that result in greater sparing of normal brain tissue (e.g., three-dimensional conformal radiation therapy [3DCRT] and intensity-modulated radiation therapy [IMRT])**

strategies

- . Use of new radiation modalities (e.g., proton beams that allow even greater sparing of the surrounding normal brain and organs at risk)
- Reduction of the dose of radiotherapy (e.g., in patients with standard risk medulloblastoma for whom in the North American studies the dose for craniospinal irradiation has been reduced progressively from 35 to 36 Gy to 23.4 Gy and, in current studies, to 18 Gy)
- Use of smaller fraction sizes where appropriate (e.g., a fraction size of 1.5 Gy each day for patients with radiosensitive tumors such as germinoma)
- . Use of hyperfractionated radiotherapy (HFRT) (e.g., as in the current European studies for standard risk medulloblastoma)

Radiation Dose and Dose-Fractionation Regimens

- ❖ The conventional daily fraction size for the treatment of most pediatric CNS tumors is 1.8 Gy
- ❖ typical dose-fractionation regimen is 54 Gy in 30 daily fractions of 1.8 Gy, which carries a very low risk of radionecrosis
- ❖ When treating a primary tumor of the spinal cord it is conventional to use a lower total dose (e.g., 50.4 Gy).
- ❖ It is also usual to reduce the radiotherapy dose for children younger than age 3 years to reduce the risk of neurocognitive deficits
- ❖ When treating radiosensitive tumors such as intracranial germinoma, radiotherapy may be delivered using a lower dose per fraction (e.g., 1.5 Gy) and lower total doses of 30 to 50 Gy
- ❖ When the target contains only a small volume of normal brain tissue, dose escalation may be feasible.
- ❖ HFRT may be a useful strategy in situations where dose escalation cannot be achieved safely using conventional fractionation.

Follow-Up During and After Radiotherapy

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- These days nausea and vomiting secondary to treatment almost always can be prevented by the use of the 5HT-3 antagonists
- Headache is not common in children and should be investigated by physical examination for signs of raised intracranial pressure and by imaging as appropriate
- Steroids, if used, usually can be tapered by the third or fourth week of treatment
- Fatigue is a rather common symptom and is cumulative
- The neurologic status of the patient, especially coordination and gait disorders, may appear to worsen during the last weeks of treatment because of this. Children usually recover relatively quickly, however, and often can get back to their usual routine by 6 weeks to 2 months following completion of
- hormonal deficits, especially growth-hormone deficit secondary to inclusion of the hypothalamicâ€“pituitary axis and primary hypothyroidism when craniospinal irradiation (CSI) is delivered using photons

Specific Tumor Types

- Specific Tumor Types
- There are important differences between tumors seen in childhood and those occurring in adults
- In children, almost half of all tumors arise in the infratentorial compartment
- Low-grade astrocytic tumors as a group account for approximately one third to half of all CNS tumors, but medulloblastoma is the most common distinct entity
- High-grade gliomas, are much less common in children.

Astrocytic Tumors

- Diffusely infiltrating astrocytomas,
 - Diffuse astrocytomas (WHO grade II),
 - Anaplastic astrocytoma (WHO grade III),
 - Glioblastoma multiforme (WHO grade IV) and variants
- Pilocytic astrocytoma (WHO grade I),
- Pleomorphic xanthoastrocytoma (surgery is usually curative)
- Desmoplastic cerebral astrocytoma of infancy (surgery is usually curative)
- Subependymal giant cell astrocytoma. (surgery is usually curative)

Low-Grade Astrocytomas (WHO Grades I and II)

- ➡ overall survival rates at 10 and 15 years as high as 80% to 100%
- ➡ Most LGA occurring in childhood are of one of two types: pilocytic astrocytoma and low-grade astrocytoma of diffuse or fibrillary type (pilocytic astrocytomas are designated as grade I, All other low-grade astrocytomas are designated as grade II)
- ➡ Pilocytic astrocytomas are the most common type in the pediatric age group, accounting for almost all of the LGA at certain sites (e.g., the anterior optic pathway, the cerebellum).
- ➡ Diffuse, or fibrillary, low-grade astrocytomas account for only approximately 15% of all LGA in children
- ➡ Symptoms and signs of raised intracranial pressure may be seen in patients with midline and cerebellar tumors.
- ➡ Patients with posterior fossa tumors may present with neck stiffness and a head tilt as a manifestation of raised intracranial pressure, causing tonsillar herniation, altitudinal diplopia, or spinal-accessory nerve irritation
- ➡ Seizures are present in as many as three quarters of patients with hemispheric lesions

Management of Low-Grade Astrocytomas: General Principles

- Some children with LGA may not require any tumor-specific treatment. These include, for example, patients with NF-1, as many as 15% of whom have optic pathway tumors (Active intervention is reserved for patients who develop progressive disease that is symptomatic)
- Progression-free survival without treatment may be very good as well for patients with tectal lesions who present with hydrocephalus without localizing brainstem signs

Management of Low-Grade Astrocytomas: General Principles

- ▶ The common characteristics of these very indolent tumors are their small size (<1.5 or 2 cm) and the fact that on imaging they are hypodense/hypointense and nonenhancing. Close follow-up with regular MRI is essential to identify patients with progressive lesions as manifested by increasing size and/or enhancement with gadolinium. Treatment (usually radiotherapy but sometimes now surgery) at the time of progression is associated with a high probability of long-term tumor control.
- ▶ If in doubt, a period of surveillance generally will be an acceptable initial approach
- ▶ Surgery is the mainstay of treatment for LGA
- ▶ Currently, complete resection is achieved in approximately 80% of cerebral, cerebellar, and spinal-cord tumors and 40% of diencephalic tumors.

Management of Low-Grade Astrocytomas: General Principles

- ✿ Children with LGA who undergo complete resection fare very well, with long-term disease-free and overall survival rates of 80% to 100%, postoperative adjuvant therapy is clearly not indicated.
- ✿ For children who undergo less than complete resection, the progression-free survival rate after surgery alone is less satisfactory,
- ✿ patients who had undergone subtotal resection (<1.5 cm residual tumor) were observed without adjuvant treatment, the 5-year progression-free survival rate was only 65%, However, the majority of patients can be salvaged with a second surgical resection and/or radiotherapy, overall survival at 5 years was 95%
- ✿ Consequently, the usual recommendation following subtotal resection will be close follow-up.
- ✿ The role of postoperative radiotherapy following lesser degrees of tumor resection remains unclear. In most series, the use of radiotherapy in this situation results in improved disease-free survival without any benefit in terms of overall survival

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Algorithm for management

Maximal surgical resection compatible with a good neurological outcome



Follow up with routine imaging

Second surgical resection (if feasible) at time of progressive disease



Radiotherapy (or chemotherapy for children < 10 years and children of all ages with NF-1) at time of progressive disease that is not resectable

Radiotherapy in Low-Grade Astrocytomas

- Indications for Radiotherapy

- Radiotherapy is not indicated after complete resection.
- Radiotherapy may be indicated following incomplete resection in situations when tumor progression would compromise neurologic function (e.g., threat to vision)
- The clearest indication for radiotherapy is in patients with progressive and/or symptomatic disease that is unresectable

Radiotherapy Target Volume

- The radiotherapy target volume (the gross tumor volume or GTV) consists of the tumor bed and any macroscopic disease seen on MRI prior to treatment
- margins that were considered standard practice (i.e., 2 to 3 cm) are overly generous, particularly for the well-circumscribed pilocytic tumors; margins of 0.5 cm around the GTV as seen on T1 weighted gadolinium-enhanced images probably represent an adequate clinical target volume (CTV) for such tumors
- More generous margins of 1 to 1.5 cm around the GTV as seen on T2 weighted or FLAIR images are more appropriate for the more infiltrative diffuse fibrillary tumors.
- With thermoplastic masks it will be necessary to add an additional 3 to 4 mm around the CTV to arrive at the planning target volume (PTV), but the use of rigid or stereotactic localization systems may require an additional margin of only 1 to 2 mm

Radiotherapy Dose

- the recommendation for children with LGA would be a "standard" dose of 50 to 54 Gy depending on the age of the child and the location of the tumor and its relationship to critical normal structures, such as the optic chiasm
- Radiotherapy Technique
- The radiotherapy technique to be used is that which provides homogeneous irradiation of the CTV and spares the greatest volume of normal tissue

Radiosurgery:

- may not be optimal for slowly growing tumors, particularly those comprised of tumor cells embedded in rather than displacing normal brain, as is the case for diffuse or fibrillary LGA
- Although such treatment may be of interest for part or even all of the treatment for pilocytic astrocytomas
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Other options:

- Brachytherapy: Brachytherapy series necessarily select for smaller tumors, and there is no evidence that brachytherapy is a better treatment option than external-beam radiotherapy
- instillation of radioactive solutions such as phosphorus-32 (^{32}P), yttrium-90 (^{90}Y), gold-198 (^{198}Au), and rhenium-186 (^{186}Re): Radioactive solutions may be useful in cystic LGA, particularly for patients with recurrent disease after radiotherapy in whom symptoms not infrequently relate more to the cyst than to the solid component of tumor

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High-Grade Astrocytomas (WHO Grades III and IV)

- anaplastic astrocytoma
- Glioblastoma multiforme (GBM): is the most malignant astrocytic tumor
- Both AA and GBM may develop from diffuse or fibrillary astrocytomas (WHO grade II)
- High-grade astrocytomas (HGA) account for 5% of all CNS tumors in the pediatric age group
- Two thirds of HGA are located in the cerebral hemispheres

High-Grade Astrocytomas (WHO Grades III and IV)

- Patients with HGA usually present with symptoms of short duration (<6 months) that relate to the location of the lesion.
- maximal surgical resection compatible with a good neurologic outcome should be the goal for all patients, regardless of tumor location or histology
- A second surgical procedure should be considered if there is significant residual tumor after the first
- Postoperative radiotherapy is always indicated
- radiotherapy target volume is local with a GTV that consists of the tumor bed and any macroscopic residual disease plus a margin for the CTV of 1.5 to 2 cm

High-Grade Astrocytomas (WHO Grades III and IV)

- to consider a field-size reduction at 50 to 54 Gy to a CTV that consists of the tumor bed and any macroscopic residual disease plus a margin of 1 to 1.5 cm
- The dose to the CTV should be at least 54 Gy given over 6 weeks, but a dose of 59 to 60 Gy is more usual if feasible.
- There is no evidence that higher doses, as delivered using radiosurgery or stereotactic boosts, boosts with brachytherapy, or HFRT, result in improved outcomes, but newer approaches such as IMRT, which allows accelerated treatment to a component of the target volume (such as the GTV), may be of interest if only to decrease the overall treatment time.
- Chemotherapy: The role of chemotherapy remains to be defined
- There have been few phase III randomized trials of chemotherapy in HGA in children

High-Grade Astrocytomas (WHO Grades III and IV)

- ◆ Off study it may be difficult to make a recommendation with respect to adjuvant chemotherapy, although the poor prognosis, particularly for patients with macroscopic residual disease following surgery, usually is given as an argument for the use of the "current best" regimen
- ◆ The prognosis for children with HGA is poor
- ◆ Patients with lesions in the cerebral hemispheres fare better than those with tumors in other locations
- ◆ The prognosis for children with bithalamic lesions is particularly poor , and these patients are managed similarly to patients with diffuse intrinsic pontine tumors

High-Grade Astrocytomas (WHO Grades III and IV)

- infants with HGA appear to fare somewhat better than older children
- histologic grade (AA versus GBM) has not been shown consistently to affect outcome
- p53 overexpression and a high MIB-1 labeling index appear to identify patients with a particularly adverse prognosis who might be appropriate candidates for novel therapeutic approaches

- Astrocytic Tumors
 - . in Specific
 -locations

Optic Pathway Gliomas

- approximately 5% of all CNS tumors in the pediatric age group
- the peak age incidence is between 2 and 6 years
- One third of patients have NF-1
- tumors confined to the optic nerve(s), tumors of the optic chiasm with or without optic nerve involvement , and tumors that involve the hypothalamus or adjacent structures
- Optic nerve gliomas may involve one or both optic nerves. Bilateral involvement is pathognomonic of NF-1
- the optic nerve tumors are incidental findings on routine imaging, and patients may remain asymptomatic with nonprogressive lesions over long periods; even spontaneous regressions are well documented

Optic Pathway Gliomas

- management of patients with optic nerve tumors will usually consist initially of close follow-up with regular ophthalmologic examinations and MRI, with active intervention, usually chemotherapy, reserved for patients with clear evidence of progression that is symptomatic
- Patients with unilateral optic nerve involvement may not have NF-1. They present most frequently with proptosis that may be relatively long standing
- On MRI, optic nerve tumors are usually relatively small and well circumscribed, with bright enhancement typical for pilocytic astrocytoma. Biopsy is not necessary to make a diagnosis
- Treatment usually, although not always, will be necessary, and the approach will depend on whether there is useful vision
- surgical resection will be the treatment of choice
- If useful vision is preserved, chemotherapy would be the preferred option for infants, very young children up to the age of 3 to 5 years, and for patients of all ages with NF-1
- Radiotherapy could be considered for older children.
- Long-term tumor control approaches 100% with either modality(chemotherapy&radiotherapy)

Chiasmatic gliomas

- Chiasmatic gliomas are tumors that involve the optic chiasm and sometimes one or both optic nerves as well
- Patients typically present with loss of visual acuity and temporal field defects
- Biopsy is usually not necessary
- A period of surveillance is appropriate initial management, particularly for patients with NF-1
- For patients without NF-1, especially those who present before the age of 5, Surgery is rarely an option for tumors in this location
- As for optic nerve tumors, chemotherapy usually will be the treatment of choice for infants and young children and for patients with NF-1
- Radiotherapy is reserved for salvage postchemotherapy and for definitive treatment of older children without NF-1
- Overall survival for patients with chiasmatic tumors is in the 90% to 100% range.

Posterior, or chiasmatic/hypothalamic, gliomas

- Posterior, or chiasmatic/hypothalamic, gliomas account for approximately 70% of all optic pathway gliomas in children
- They are typically rather large lesions that probably arise in the optic chiasm and extend to involve the hypothalamus
- They often fill the third ventricle, eventually causing hydrocephalus
- Early findings consist of nystagmus, impaired visual acuity, and visual field deficits; only later do patients present with increasing head circumference and/or symptoms and signs of raised intracranial pressure
- Treatment consists of CSF diversion, if necessary, and surgical resection particularly if tumor is growing exophytically into the basal cisterns
- In most patients, however, resection will be incomplete
- a period of surveillance is reasonable, although most patients will require adjuvant therapy

Posterior, or chiasmatic/hypothalamic, gliomas

- ◆ The treatment of choice for children younger than 5 and those with NF-1 usually will be chemotherapy, most often now using a carboplatin-based regimen
- ◆ The indications for radiotherapy are (a) progressive disease on chemotherapy for children younger than 10 years and (b) progressive disease at diagnosis or after surgery for older patients
- ◆ given to local fields to a dose of 45 to 50 Gy for younger children and of 50 to 54 Gy for those older than 5 years
- ◆ Overall, however, the results of treatment are less satisfactory for this group of patients than for those with anterior tumors
- ◆ Patients with NF-1 are also at greater risk for Moyamoya syndrome, a progressive vaso-occlusive process involving the circle of Willis, This may be seen without radiotherapy
- ◆ when radiotherapy is used in patients with NF-1 it is important to include MR angiography as part of the regular follow-up imaging protocol and to intervene surgically if necessary to avoid a cerebrovascular accident

Brainstem Gliomas

- Tumors arising in the midbrain, pons, and medulla oblongata account for 10% to 15% of all CNS tumors in the pediatric age group
- improvements in neurosurgical techniques and perioperative care have made surgery not only feasible but the treatment of choice for all except the diffuse intrinsic tumors
- Focal tumors may occur at any level in the brainstem but are most frequently seen in the midbrain and medulla
- Signs and symptoms of raised intracranial pressure are uncommon except in patients with tumors arising in the tectal region that may cause aqueduct stenosis while still small.

Brainstem Gliomas

- ❖ patients with nonenhancing focal tumors in the tectal region who present with only hydrocephalus may do well without any treatment other than CSF diversionary procedures , Active intervention, including biopsy, is reserved for patients with clinical and radiologic evidence of progressive tumor
- ❖ Surgery is the treatment of choice for focal tumors at other locations that are surgically accessible (meaning either that they extend toward the surface of the brainstem laterally or at the floor of the fourth ventricle) and have imaging characteristics suggestive of low-grade histology

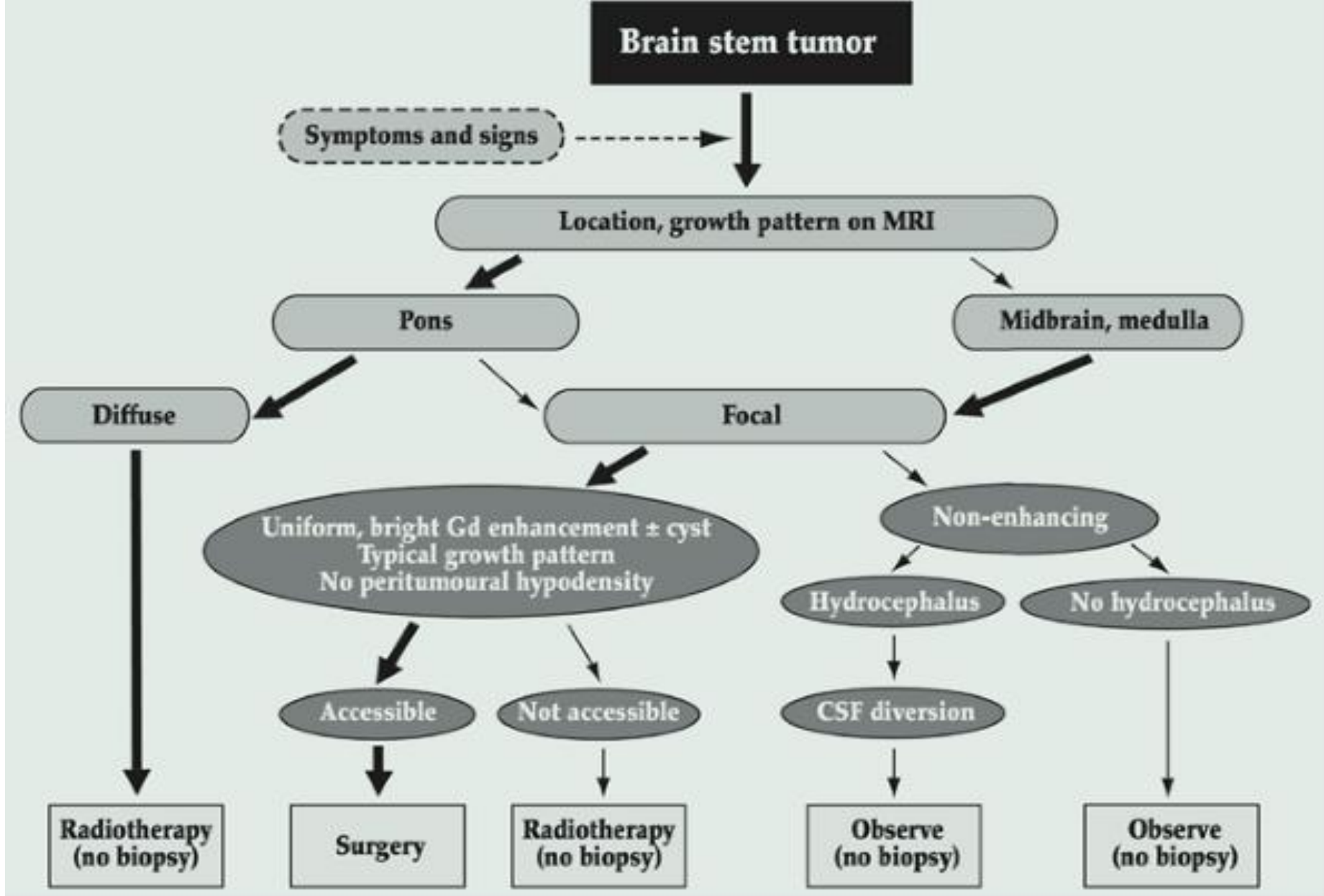


FIGURE 82.7 An algorithm for the management of patients with brainstem tumors. The flowchart starts with the location and growth pattern on MRI. For focal tumors, the presence of hydrocephalus and the accessibility of the tumor are key factors in determining the management strategy. CSF diversion is indicated for focal, non-enhancing tumors with hydrocephalus. Observe (no biopsy) is the recommended management for focal, non-enhancing tumors without hydrocephalus.



- ith bulky tumors and for patients with tumors in the medulla with lower cranial nerve deficits who are at high risk of developing postoperative complications.
- There are several treatment options for patients with surgically inaccessible focal lesions (conventional radiotherapy, HFRT and with interstitial irradiation using iodine-125, radiosurgery and stereotactic irradiation)
- with the advent of improved treatment planning and conformal radiotherapy treatment techniques, standard treatment for these lesions should be considered to be external-beam radiotherapy, using limited treatment volumes with a margin for the CTV of 0.5 cm, to a total dose of the order of 54 Gy given over 6 weeks, as for LGA at other locations

Dorsal exophytic tumors

- Dorsal exophytic tumors arise from the floor of the fourth ventricle
- They are usually large, filling the fourth ventricle, but do not invade the brainstem to any significant extent
- Surgery is the treatment of choice for dorsal exophytic tumors
- Ultrasound guidance is essential to achieve a maximal degree of tumor resection
- the majority of children do well following surgery, and routine postoperative adjuvant therapy is not indicated
- Radiotherapy should be considered for the rare patient who is found to have a high-grade lesion or for patients with low-grade tumors who are found to have progressive disease in the early (0 to 9 months) postoperative period
- For patients whose tumors recur later, further surgery should be considered and radiotherapy should be reserved for those with inoperable disease
- The radiotherapy volume and dose should be similar to those used for LGA in other locations.
- the prognosis for patients with

Cervicomedullary tumors

- Cervicomedullary tumors arise in the upper cervical cord and grow rostrally beyond the foramen magnum.
- Most are low-grade lesions
- Surgery is the treatment of choice
- no indication for routine postop

Diffuse intrinsic brainstem tumors

- ❑ Diffuse intrinsic brainstem tumors account for 70% to 80% of all brainstem tumors
- ❑ They arise in the pons and cause diffuse enlargement of the brainstem
- ❑ In contrast to the other types of brainstem tumors, the majority of diffuse intrinsic tumors are fibrillary astrocytomas with a propensity for malignant change and a very poor prognosis.
- ❑ Diffuse intrinsic tumors typically present with a short duration of symptoms (median 1 month) consisting of multiple, bilateral, cranial nerve deficits (especially VI and VII) as well as long tract signs and ataxia
- ❑ Only 10% of patients have hydrocephalus at diagnosis
- ❑ Surgery has no role in the management of patients with diffuse intrinsic lesions

Diffuse intrinsic brainstem tumors

- ❑ Even biopsy, a relatively nonmorbid procedure now, no longer is considered necessary because in the context of a typical clinical presentation, the MRI findings are characteristic and histology does not influence treatment
- ❑ Treated with conventional radiotherapy, the majority (75% or more) of patients with diffuse intrinsic tumors will improve clinically
- ❑ the progression-free interval is short (median <6 months) and survival is poor, with median survival <1 year and survival rates at 2 years <20%.
- ❑ Alternative approaches that use chemotherapy in combination with radiotherapy also have been disappointing
- ❑ New agents and novel chemotherapy“radiotherapy combinations are under investigation by the pediatric cooperative groups in North America and Europe
- ❑ standard treatment for diffuse intrinsic brainstem tumors consists of radiotherapy given to the GTV as demonstrated by T2-weighted or FLAIR MRI with a margin for the CTV of 1 to 1.5 cm to a dose of 54 Gy given in 30

Low-Grade Astrocytomas of the Spinal Cord

- Intramedullary spinal cord tumors account for 3% to 6% of all CNS tumors in the pediatric age group
- About 60% are astrocytomas, the majority of which are of low histologic grade
- Patients typically present with symptoms of long duration, usually pain and motor deficits
- Resection is more difficult and less likely to be complete in patients with grade II astrocytoma because of the more infiltrative nature of these tumors and the absence of a plane of cleavage .
- Since outcome following complete or subtotal resection for LGA is very good, with long-term progression-free survival in the 70% to 90% range , routine postoperative adjuvant therapy is not indicated
- For children in whom complete or subtotal resection is not possible, options will be as for patients with LGA in other locations, that is, early second surgery or close follow-up with second surgery and/or radiotherapy at the time of progression

Low-Grade Astrocytomas of the Spinal Cord

- ▶ As for LGA in other locations, chemotherapy may be an alternative to radiotherapy for infants and very young children in this situation
- ▶ Immediate treatment would be indicated for patients with a high-grade astrocytoma
- ▶ The radiotherapy target volume for LGA usually will consist only of the solid portion of the tumor (including intratumoral cysts) with a margin for the CTV of 0.5 to 1 cm around the GTV
- ▶ The usual dose would be 50.4 Gy given in 28 daily fractions over approximately 6 weeks
- ▶ patients with high-grade lesions, most of whom will have had only a biopsy; a margin beyond the entire lesion of 1.5 cm would be more appropriate , The dose prescription usually will be as for low-grade lesions because of a substantial risk of morbidity at higher doses, but often chemotherapy will be given as well

Ependymal Tumors

- ⓐ *Ependymomas account for 5% to 10% of all brain tumors in the pediatric age group*
- ⓐ *with a predilection for infants and children younger than age 5 years*
- ⓐ *two-thirds arise in the ependymal lining of the fourth ventricle*
- ⓐ *gadolinium-enhanced MRI of the whole CNS and CSF cytology are essential components of the work-up for all patients,*
- ⓐ *the risk of leptomeningeal seeding at diagnosis is at most 5% to 10%.*
- ⓐ *The completeness of the surgical resection is the factor that has the greatest impact on the outcome of children with ependymoma, regardless of tumor location*
- ⓐ *complete resection is possible in 70% to 85% of supratentorial ependymomas and in a similar percentage of spinal ependymomas*
- ⓐ *complete resection is lower in patients with infratentorial ependymo*

Ependymal Tumors

- Since residual disease is associated with a much worse outcome, “second-look” surgery should be considered, if feasible, either after the realignment of structures that takes place following resection of an initially bulky tumor or after chemotherapy
- Postoperative radiotherapy is the standard of care for all children with ependymoma
- Radiotherapy for patients who have undergone complete resection: such a strategy results in worse disease-free and perhaps also overall survival and therefore can be considered acceptable only for (a) patients with ependymoma of the spinal cord who have undergone complete resection for whom disease-free survival in contemporary series approaches 100% and (b) selected patients with supratentorial ependymoma, such as those with intraventricular tumors or with extraventricular tumors that are solid and located in noneloquent areas and can be resected with a wider margin

Ependymal Tumors

- optimal radiotherapy target volume, dose, and dose-fractionation schedule:
using a GTV that is a composite of the tumor bed, based on preoperative imaging , and including any macroscopic residual disease, with a margin for the **CTV of 1 cm**
the current standard is a dose of at least 54 to 55 Gy for lesions in the brain
- because failure most often occurs at the site of macroscopic residual disease, even higher doses may be desirable , HFRT has been explored in ependymoma for this reason

Ependymal Tumors

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- ◆ The role of chemotherapy in ependymoma remains to be defined , Response rates to chemotherapy are quite poor
- ◆ In infants and very young children chemotherapy has been used because of the desire to delay or even avoid altogether radiotherapy
- ◆ local treatment consisting of the tumor bed and any macroscopic residual disease with a margin for the CTV of 1.5 cm is used for patients with localized disease; only patients with leptomeningeal seeding at diagnosis receive CSI
- ◆ As for ependymomas, the dose should be 54 to 55 Gy, with a boost to macroscopic residual disease, if feasible, to 59 to 60
- ◆ Patients with leptomeningeal dissemination at diagnosis fare extremely poorly despite aggressive treatment with craniospinal radiotherapy and systemic chemotherapy.

Myxopapillary Ependymoma

- ❁ Myxopapillary ependymomas are slowly growing lesions almost always located in the conus-filum terminale region of the spinal cord
- ❁ They are the most common spinal cord tumor in this location
- ❁ Surgical resection is the treatment of choice
- ❁ If the tumor is not resected en bloc or if there is macroscopic residual tumor, postoperative radiotherapy should be used since outcome appears to be significantly worse in these situations
- ❁ The radiotherapy target volume is local (macroscopic disease plus a margin cephalad and caudad of 1.5 cm for the CTV) and the dose, 50.4 Gy
- ❁ Leptomeningeal seeding: patients should be treated with curative intent with CSI followed by a boost to the primary site

Choroid Plexus Tumors

- ✦ The WHO classification lists two different entities: choroid plexus papilloma (WHO grade I) and choroid plexus carcinoma (WHO grade III).
- ✦ Surgery is the treatment of choice for choroid plexus papillomas both for the primary lesion and for macroscopic metastatic deposits, if feasible
- ✦ Blood loss may be considerable
- ✦ The role of radiotherapy following incomplete resection is unclear(choroid plexus papillomas) , close follow-up would seem

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Ganglioglioma and Anaplastic Ganglioglioma

- Gangliogliomas are well-differentiated, slowly growing tumors composed of mature ganglion cells in combination with neoplastic glial cells WHO grade I or II.
- Although these tumors can arise anywhere within the CNS, most in children arise in the temporal region and typically present with seizures.
- Surgery is the treatment of choice
- The indications for radiotherapy would be as for patients with LGA, that is, for patients with progressive or recurrent disease that is not resectable
- postoperative radiotherapy:
for patients with anaplastic gangliogliomas who have undergone less than complete resection

Pineal Parenchymal Tumors

- ❑ Pineal region tumors account for 2% to 8% of intracranial tumors in children.
- ❑ Approximately half are germ-cell tumors, one-fourth to one-third are pineal parenchymal tumors, and most of the remainder are astrocytic tumors.
- ❑ WHO classification: pineoblastoma (WHO grade IV), pineocytoma (WHO grade II), and pineal parenchymal tumor of intermediate differentiation.

Pineoblastoma

- ✿ Pineoblastoma is a highly malignant primitive embryonal tumor
- ✿ Leptomeningeal spread is seen in as many as 50% of patients at diagnosis
- ✿ Surgery for lesions in the pineal region is particularly delicate, and complete resection is often not possible
- ✿ Postoperatively, older children are treated with CSI and chemotherapy, as for medulloblastoma and supratentorial primitive neuroectodermal tumor (S-PNETs)
- ✿ infants who are treated with chemotherapy without radiotherapy

Pineocytoma

- ❑ Pineocytoma is a slow-growing tumor
- ❑ They account for approximately half of pineal parenchymal tumors and in childhood most commonly occur in the teenage years
- ❑ Some will have symptoms of upper mesencephalic tegmental dysfunction (Parinaud's syndrome)
- ❑ Treatment consists of surgical resection
- ❑ If complete or subtotal resection is accomplished, the outcome is probably quite favorable even without any adjuvant treatment
- ❑ Following lesser degrees of resection, postoperative radiotherapy usually is recommended using local fields consisting of macroscopic residual disease, with a margin of 1 to 1.5 cm and a dose of 50 to 55 Gy over 6 weeks

Embryonal Tumors

- # Embryonal tumors as a group are the second most common type of CNS tumor in the pediatric age group
- # Ependymoblastoma
- # Medulloblastoma,
- # Supratentorial PNET.
- # Medulloepithelioma,
- # Atypical teratoid/rhabdoid tumor

Medulloblastoma

- Medulloblastoma accounts for 15% to 20% of all CNS tumors in the pediatric age group
- The median age at presentation is 6 years
- In the majority of cases the tumor arises in the cerebellar vermis and projects into the fourth ventricle
- Patients typically present with symptoms and signs of raised intracranial pressure, that is, headache and morning vomiting
- The frequency of spinal seeding at diagnosis is approximately 30% to 35%, and investigation at diagnosis must include a gadolinium-enhanced MRI of the spinal axis and CSF cytology.

Medulloblastoma

- The former should be obtained whenever possible preoperatively or else at least 2 to 3 weeks postoperatively to avoid misinterpretation resulting from artifactual changes seen in the later postoperative period
- CSF cytology: which should be obtained by lumbar puncture, often cannot be obtained preoperatively because of the presence of raised intracranial pressure and more commonly is obtained at approximately 3 weeks postoperatively
- Medulloblastoma is one of the few CNS tumors to spread outside the CNS (to lymph nodes, bone), although this is an uncommon event.

Table 82.2 Chang Staging System for Metastases in Patients with Medulloblastoma

M0	No metastases
M1	Tumor cells found in cerebrospinal fluid
M2	Gross nodular seeding in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M3	Gross nodular seeding in the spinal subarachnoid space
M4	Metastases outside the central nervous system

risk categories

- ❑ Patients are allocated to one of two risk categories: standard and high risk
- ❑ **Standard risk:** Those who have undergone complete or subtotal resection with $<1.5 \text{ cm}^2$ of residual tumor and no evidence of CSF dissemination (M0)
- ❑ complete or near-total resection is accomplished in approximately 80% of cases
- ❑ two thirds of patients will be Standard risk and one third will be high risk.

Management of Standard-Risk Medulloblastoma

- Several treatment strategies designed to reduce the morbidity associated with the use of radiotherapy have been tested
- Until relatively recently, the standard of care for patients older than 3 years with standard-risk disease consisted of postoperative radiotherapy to the craniospinal axis to a dose of 35 to 36 Gy followed by a boost to the whole posterior fossa to a total dose of 54 to 55.8 Gy
- reduce the radiotherapy target volume to avoid supratentorial radiation produced disastrous results
- HFRT to a CSI dose of 36 Gy without chemotherapy
- reduced-dose CSI (23.4 Gy) followed by a boost to the posterior fossa to a total dose of 55.8 Gy in combination with systemic chemotherapy

Management of Standard-Risk Medulloblastoma

- reduced-dose (23.4 Gy) CSI in combination with weekly vincristine, followed by adjuvant systemic chemotherapy consisting of vincristine 1.5 mg/m², CCNU 75 mg/m², and cisplatin 75 mg/m²
- CCNU was replaced by cyclophosphamide
- such an approach is now considered to be the standard of care for children with standard-risk medulloblastoma in North America.
- Current studies are testing the safety of an even lower dose of CSI (18 Gy) in children aged 3 to 8 years and of a reduced-volume posterior fossa boost in children of all ages

Management of High-Risk Medulloblastoma

- for patients with residual disease, M0, it would be logical to consider using a radiotherapy dose to residual disease in the posterior fossa higher than the standard 55.8 Gy, and this may be feasible using stereotactic radiotherapy or 3D conformal technique
- Patients with M1 disease may do well using a standard CSI dose of 35 to 36 Gy;
- results for patients with M2 , 3 disease remain quite poor, although the use of a higher radiotherapy dose (40 Gy CSI plus a boost of 5 Gy to macroscopic disease) produced excellent early results in POG 9031, approaching those for patients with less advanced disease.
- The hyperfractionated accelerated radiotherapy (HART) regimen under investigation by the U.K. group may prove to be an equally efficacious and safer way to deliver high dose CSI.
- Preradiotherapy chemotherapy may also be of interest in this group of patients
- preradiotherapy chemotherapy may allow identification of patients who do not respond and who might benefit from more aggressive chemotherapy, such as high-dose chemotherapy with stem cell rescue in combination with conventional radiotherapy, HFRT, or HART

Management of Medulloblastoma in Infants

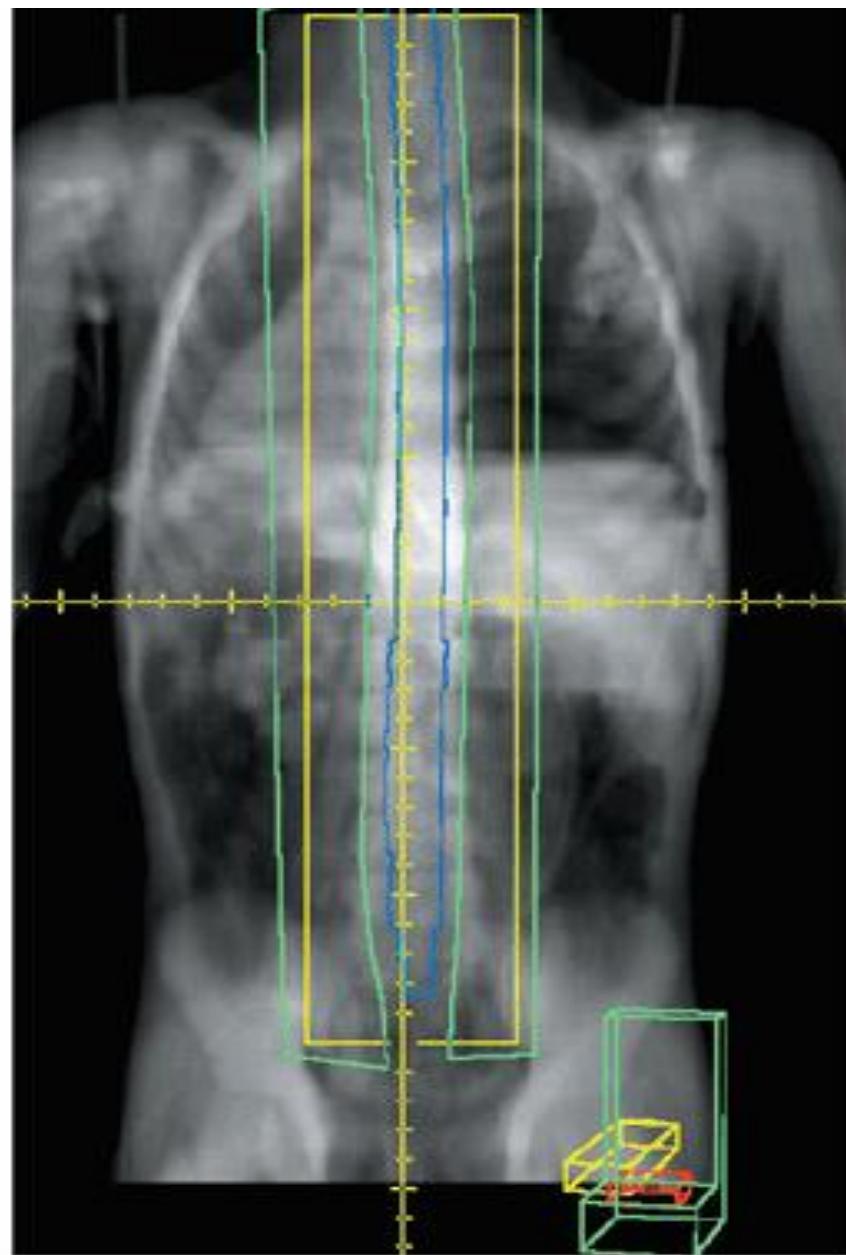
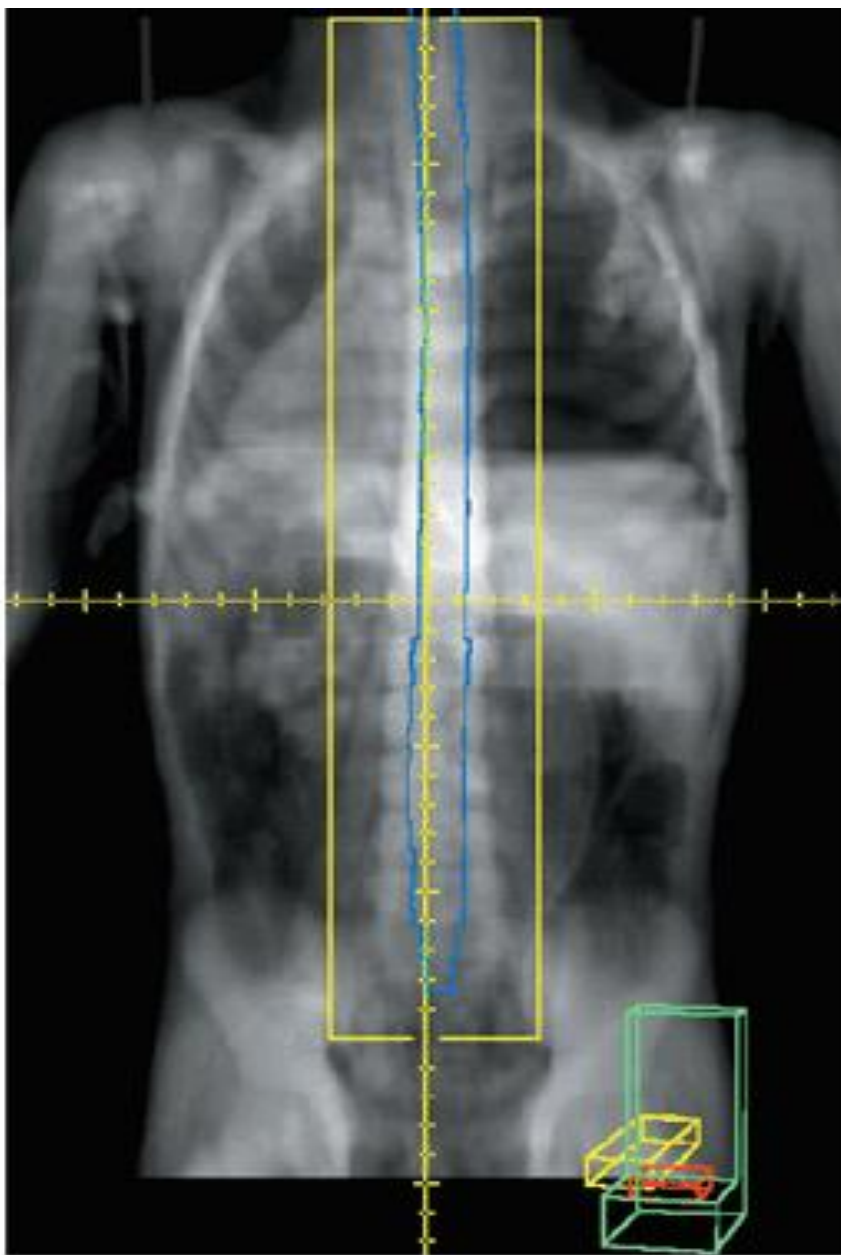
- Medulloblastoma accounts for 20% to 40% of all CNS tumors in infants and carries a worse prognosis than in older children
- Medulloblastoma accounts for 20% to 40% of all CNS tumors in infants and carries a worse prognosis than in older children
- Infants with M0 disease who have undergone total resection may do well with chemotherapy alone
- Infants with M2-3 disease fare poorly and require more aggressive treatment such as high-dose chemotherapy with stem cell rescue and/or chemotherapy given using alternative routes of administration, such as intrathecal or intraventricular, with or without radiotherapy.

Radiotherapy for Medulloblastoma

- ❑ The CTV for CSI has an irregular shape that consists of the whole of the brain and spinal cord and overlying meninges
- ❑ Patients have traditionally received CSI in the prone position, but modern technology allows safe treatment in the supine position that in general is more comfortable
- ❑ CT simulation is invaluable for target volume definition for patients with medulloblastoma
- ❑ With current cataract surgical techniques, it is preferable to cover the target volume, keeping shielding of the lenses a secondary objective
- ❑ MRI is required to determine the lower limit of CTV for the spine field

- ❑ Traditionally the lower border of the spine field was placed at the lower border of the second sacral vertebra, but it is well documented that the lower border of the thecal sac can be as high as L5 or as low as S3

- ❑ In the interest of both CTV coverage and normal tissue sparing it is important that the lower border be individualized according to the MRI findings.



B

Type & dose of energy

- In general, photons in the 6 to 10 MV range provide satisfactory coverage of the PTV
- Care is required if using electrons to treat the spinal axis
- The use of electrons to treat the spinal axis most often is justified by reduced acute gastrointestinal toxicity
- Because available data regarding late effects suggest that there may be little or no advantage to the use of electrons
- Traditionally, the entire posterior fossa has been treated to a total dose of 54 to 55.8 Gy

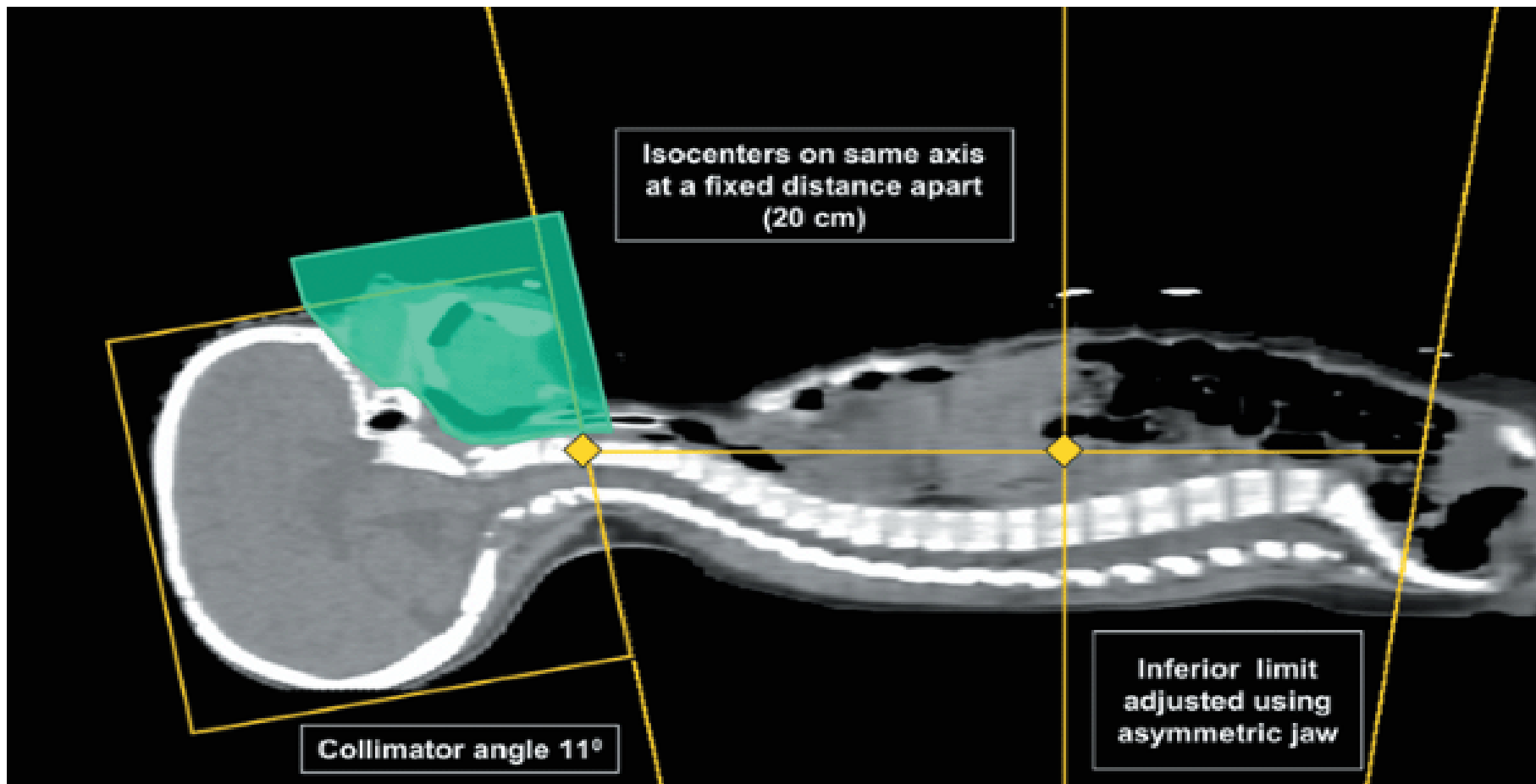


FIGURE 82.12 To cover the clinical target volume for craniospinal irradiation, lateral oblique fields are used to treat the brain and a direct posterior field is used to cover the spinal cord. Correlation with magnetic resonance imaging is necessary to identify the caudal extent of the thecal sac. The field junction, which is over the cervical cord at a level that avoids the inclusion of the teeth in the exit of the spinal field, usually is moved weekly to avoid overdosage. The supine position is more comfortable for the patient and safer if sedation or anesthesia is required. In the technique shown, fixed field parameters are used, which

Radiotherapy for Medulloblastoma

- The optimal CTV for a reduced-volume posterior fossa remains to be defined, although it probably consists of a composite of any macroscopic residual tumor and the surgical bed plus a margin of 1 to 1.5 cm
- A few centers have reported their results using protons for treatment of medulloblastoma
- Delay to radiotherapy may be associated with poorer outcomes and CSI ideally should start within 28 days following surgery

Supratentorial Primitive Neuroectodermal Tumor

- ❑ S-PNETs account for <5% of all CNS tumors in the pediatric age group. The median age at presentation is 3 years
- ❑ Leptomeningeal seeding is present at diagnosis in up to 40% of patients, and MRI of the spinal axis and CSF cytology are mandatory prior to treatment.
- ❑ often using the same protocols as for high-risk medulloblastoma
- ❑ often using the same protocols as for high-risk medulloblastoma
- ❑ For now, the standard of care for children older than 3 years with S-PNETs without leptomeningeal spread consists of maximal surgical resection followed by postoperative radiotherapy (CSI plus a boost to doses similar to those used for high-risk medulloblastoma) followed by chemotherapy
- ❑ Experimental regimens such as preradiotherapy chemotherapy and high-dose chemotherapy with rescue are used in infants and young children and in patients with M2&3 disease

Atypical Teratoid/Rhabdoid Tumor

- highly malignant embryonal tumor unique to childhood
- outcome was very poor and the majority of patients died within 1 year of diagnosis
- Radiotherapy is an important component of treatment
- radiotherapy should be delivered early even in infants, and this may mean using a modified radiotherapy target volume (i.e., tumor bed and any macroscopic residual disease plus a margin)
- Children older than 3 years should receive early CSI.

Germ Cell Tumors

- In the West, CNS germ cell tumors are relatively rare, accounting for 3% to 5% of all CNS tumors in the pediatric age group. They are more common in Asia
- The peak age incidence is 10 to 12 years. Boys are affected more frequently than girls, with a ratio of approximately 3:1
- CNS germ cell tumors arise from primordial germ cells in structures about the third ventricle, with the region of the pineal gland being the most common site of origin, followed by the suprasellar region
- Nongerminomatous germ cell tumors (NGGCT) are the most common tumor type in the former area, and germinomas in the latter.
- Tumors in the pineal region cause obstruction to CSF flow at the aqueduct of Sylvius,

Germ Cell Tumors

- Another characteristic presentation of tumors in this region is Parinaud's syndrome as a result of dorsal midbrain compression
- Measurement of serum and CSF tumor markers is another essential part of the initial work-up
- In the past, many lesions arising in or about the third ventricle were treated without histologic confirmation of diagnosis
- all patients should undergo biopsy unless CSF and/or serum markers confirm the presence of a NGGCT (elevated AFP and/or B-hCG >100 IU/mL) or unless a histologic diagnosis is made by other means (e.g., CSF cytology)
- Occasionally complete resection will be possible; this would be a reasonable strategy for patients with NGGCT, particularly for mature teratomas if it can be accomplished without major morbidity because in that situation it would obviate the need for adjuvant treatment

Germinoma

- In the past, standard treatment for patients with germinoma was radiotherapy alone
- Whole ventricle irradiation alone may be acceptable for a patient with a unifocal lesion with no evidence of leptomeningeal dissemination
- a number of reasonable options for patients with unifocal germinoma without evidence of leptomeningeal dissemination. These include craniospinal radiotherapy, limited volume (whole-ventricle) radiotherapy alone, and chemotherapy followed by whole ventricle or local radiotherapy
- regardless of the target volume so that patients at increased risk for systemic failure (e.g., those with ventriculoperitoneal shunts) may be best treated with a combined chemotherapy&radiotherapy approach
- For patients with bi- or multifocal disease by imaging or by inference (for example, in a patient with a pineal region primary who has diabetes insipidus) and those with leptomeningeal spread at diagnosis, radiotherapy alone using CSI with boosts to macroscopic disease is certainly an option,
- although in North America a combination chemotherapy and radiotherapy regimen consisting of two cycles of chemotherapy followed by CSI followed by a boost to all sites of involvement would be the more usual approach.

Germinoma

-
- ✘ Because subependymal spread is common, such treatment logically would include the lateral, third, and fourth ventricles with a margin of 1 to 1.5 cm
- ✘ Better sparing can be achieved using CT planning and a four-field arrangement
- ✘ Better sparing can be achieved using CT planning and a four-field arrangement
- ✘ Results are excellent with a CSI dose as low as 21 Gy even in patients with leptomeningeal spread.
- ✘ The total dose to the primary site has typically been 40 to 45 Gy but probably can be reduced to 30 Gy in patients who have undergone complete resection or those who have been treated with a combined chemotherapy and radiotherapy regimen with a complete response to chemotherapy
- ✘ The total dose to the primary site has typically been 40 to 45 Gy but probably can be reduced to 30 Gy in patients who have undergone complete resection or those who have been treated with a combined chemotherapy"radiotherapy regimen with a complete response to chemotherapy

Nongerminomatous Germ Cell Tumors

- For NGGCTs the diagnosis can be made in as many as one third of all patients on the basis of imaging findings (location, appearance) plus tumor markers.

Table 82.4 Classification of Nongerminomatous Germ Cell Tumors

Good prognosis

Mature teratoma

Intermediate prognosis

Immature teratoma

Mixed germ cell tumors consisting of germinoma with either mature or immature teratoma

Poor prognosis

Teratoma with malignant transformation

Embryonal carcinoma

Yolk sac tumor

Choriocarcinoma

Mixed germ cell tumors including a component of embryonal carcinoma, yolk sac tumor, choriocarcinoma, or teratoma with malignant transformation

teratomas

- Patients with mature teratomas without any associated malignant elements can be managed with surgery alone, while those with mature teratoma with germinomatous elements will be treated as germinomas
- the current standard of care therefore consists of platinum-based chemotherapy followed by radiotherapy
- There is controversy with respect to the radiotherapy target volume for NGGCT

NGGCT

- In the current North American study, CSI is used for all patients with NGGCT. A dose of 36 Gy is used, followed by a boost to the primary site to a total dose of 54 Gy
- Patients who have less than a complete response to chemotherapy: Second-look surgery may be useful to both exclude the possibility that the residual imaging abnormality represents mature teratoma and/or resect residual viable tumor,
- If the latter, this would be followed by CSI and then more aggressive chemotherapy, such as high-dose chemotherapy with stem cell rescue

Tumors of the Sellar Region

Craniopharyngioma

Xanthogranuloma,
anuloma,

Pituitary
adenomas

Pituitary adenomas

- craniopharyngiomas are benign partly cystic epithelial tumors that arise in the sellar region from remnants of Rathke's pouch
- with a peak incidence between the ages of 5 and 14 years.
- In the majority of patients, craniopharyngiomas have both suprasellar and intrasellar components
- Children typically present with neuroendocrine deficits, especially diabetes insipidus and growth failure
- Visual-field deficits often go unnoticed initially
- patients with tumors that are smaller and/or subdiaphragmatic in location and without hypothalamic symptoms would be managed surgically, while other patients at higher risk for complications secondary to surgery would be managed with biopsy, cyst decompression, if necessary, and radiotherapy

Pituitary adenomas

- A lesion with a small solid component and a simple cyst, for example, may be treated with intracavitary injection of liquid radioactive material
- A lesion with a small solid component and a simple cyst, for example, may be treated with intracavitary injection of liquid radioactive material
- conventionally fractionated external-beam irradiation using modern techniques may be a better option with a lower risk of morbidity for all except very small tumors
- External-beam radiotherapy also will be the treatment of choice for patients with residual disease following surgery who are at high risk for progressive disease even relatively early following surgery or for those in whom surgical resection is not feasible.

Pituitary adenomas

- A margin of 0.5 cm seems reasonable using contemporary planning and delivery techniques.
- A dose of 54 to 55 Gy given in 30 daily fractions over 6 weeks appears to be necessary to achieve a high
- A margin of 0.5 cm seems reasonable using contemporary planning and delivery techniques. A dose of 54 to 55 Gy given in 30 daily fractions over 6 weeks appears to be necessary to achieve a high, usually consisting of cyst decompression, is essential
- When complete resection is not feasible, biopsy, subtotal resection, or simply cyst decompression followed by external-beam radiotherapy is a better choice
- There is equal if not better probability of tumor control in this situation with a lower risk of potentially devastating sequelae than with "heroic" surgery, particularly in less-experienced hands.

Pituitary Adenomas

- Pituitary adenomas are rare in childhood
- Most are functioning adenomas that present with endocrine dysfunction, most often menstrual irregularities and galactorrhea in girls and delayed puberty in boys
- Transphenoidal surgery appears to be feasible and safe in children, even in those with poor pneumatization of the sphenoid sinus, using neuronavigational tools
- Radiotherapy is indicated if surgical resection is not possible or if hormone levels remain elevated following surgery
- Conformal fields with a margin of 0.5 cm beyond macroscopic residual disease (the GTV) are used
- The usual dose, as in the adult population, will be 45 to 50 Gy over 5 to 6 weeks
-

Management of Low-Grade Astrocytomas

