Chapter 2
Central Nervous System

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INTRODUCTION

This chapter will discuss malignant glioma, low-grade glioma, brainstem glioma, optic glioma, CNS lymphoma, ependymoma, choroid plexus tumor, meningioma, acoustic neuroma, craniopharyngioma, pituitary tumor, pineal tumor, medulloblastoma, primary spinal cord tumor, arteriovenous malformation, and trigeminal neuralgia. Brain metastases will be discussed in the palliative care chapter.

ANATOMY

- Meninges (outer to inner): dura mater → arachnoid mater → subarachnoid space → pia mater.
- Precentral gyrus = primary motor strip; postcentral gyrus = primary somatosensory cortex. Medial = body, lower extremities, feet. Lateral = trunk, arms, head.
- Brain gray matter is peripheral and white matter is central.
- Broca’s (motor) area = dominant frontal lobe just superior to lateral sulcus (Sylvian fissure) = site of expressive aphasia (comprehend but not fluent).
- Wernicke’s (sensory) area = dominant temporal lobe at posterior end of lateral sulcus = site of receptive aphasia (fluent but not comprehend).
- Diencephalon = thalamus, hypothalamus, and pineal gland.
- Telencephalon = olfactory lobes, cerebral hemispheres, basal ganglia, amygdalae.
- Mesencephalon = tectum, crus cerebri, superior and inferior colliculi, cerebral aqueduct.
- Only CN IV exits from dorsal surface of midbrain.
- CSF: choroid plexus produces → lateral ventricles → foramen of Monroe → third ventricle → cerebral aqueduct of Sylvius → fourth ventricle → foramen of Magendie and two lateral foramina of Lushka.
Caverous sinus contains CN III, IV, V1, V2, VI and the internal carotid artery. Cavernous involvement commonly produces CN VI palsy.

Tumors with a high propensity for CSF spread include medulloblastomas, primitive neuroectodermal tumors (PNET), and CNS lymphoma. Germ-cell tumors and ependymomas have a lower propensity for CSF spread.

CN exits:
- Superior orbital fissure = CN III, IV, VI, V1
- Foramen rotundum = V2
- Foramen ovale = V3
- Foramen spinosum = middle meningeal artery and vein
- Internal auditory meatus = CN VII, VIII
- Jugular foramen = CN IX, X, XI
- Hypoglossal canal = CN XII

Lateral plain film.
- Hypothalamus = 1 cm superior to sellar floor.
- Optic canal = 1 cm superior and 1 cm anterior to the hypothalamus.
- Pineal body (supratentorial notch) = 1 cm posterior and 3 cm superior to external acoustic meatus.
- Lens = 1 cm posterior to anterior eyelid, 8 mm posterior to line connecting lateral canthus. Median globe size = 2.5 cm.
- Location of cribiform plate cannot always be correctly identified with lateral plain film alone (Gripp et al. 2004).

Spinal cord.
- Thirty-one pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal.
- Spinal cord white matter is peripheral and gray matter is central.
- Pia mater covers cord and condenses into dentate ligaments.
- Arachnoid contains CSF (normal pressure 70–200 mm H₂O lying down, 100–300 mm H₂O sitting or standing, ~150 mg total volume).
- Dura ends at S2.
- Cord ends at L1 in adults, conus ends at ~L2 in adults, cord ends ~L3–4 in newborns.

**Epidemiology**

- Twenty-one thousand eight hundred and ten new malignant primary brain tumors and 13,070 deaths in the US in 2008.
Malignant tumors comprise ~40% of all primary brain/CNS tumors.

Adult primary CNS tumors: 30–35% meningioma, 20% GBM, 10% pituitary, 10% nerve sheath, 5% low-grade glioma, <5% anaplastic astrocytoma, <5% primary CNS lymphoma.

Of adult gliomas, ~80% are high-grade and ~20% are low-grade.

Children: 20% of all pediatric tumors (second to ALL). Twenty percent JPA, 15–20% malignant glioma/GBM, 15% medulloblastoma, 5–10% pituitary, 5–10% ependymoma, <5% optic nerve glioma.

Possible etiologic associations: rubber compounds, polyvinyl chloride, N-nitroso compounds, and polycyclic hydrocarbons.

Prior ionizing RT has been associated with new meningiomas, gliomas, and sarcomas (~2% at 20-year).

GENETICS

NF-1: von Recklinghausen, chromosome 17q11.2, 1/3,500 live births, NF1 encodes neurofibromin, autosomal dominant, 50% germline, 50% new mutations, peripheral nerve sheath neurofibromas, café au lait spots, optic and intracranial gliomas, and bone abnormalities.

NF-2: chromosome 22, 1/50,000 live births, NF2 encodes merlin, autosomal dominant, bilateral acoustic neuromas, gliomas, ependymomas, and meningiomas.

von Hippel-Lindau: chromosome 3, autosomal dominant, renal clear cell carcinoma, pheochromocytoma, hemangioblastoma, pancreatic tumors, and renal cysts.

Tuberous sclerosis (Bourneville’s disease): TSC1 on chromosome 9, TSC2 on chromosome 16, autosomal dominant, subependymal giant cell astrocytoma, retinal and rectal hamartomas.


Li-Fraumeni syndrome: germline p53 mutation = breast, sarcoma, and brain CA.

Turcot’s syndrome: primary brain tumors with colorectal CA.

Neuroblastoma: N-myc amplification commonly seen and serves as a prognostic factor.

IMAGING

MRI: T1 pre and postgadolinium, T2, and FLAIR (fluid attenuation inversion recovery, removes increased CSF signal on T2).

Tumor Enhancement with gadolinium correlates with breakdown of the blood–brain barrier (BBB).
Tumor: high grade – increased signal on T1 postgadolinium and T2 (T2 also shows edema). Low grade – increased signal on T2/FLAIR.

Acute blood = increased signal on T1 pre-gadolinium.

Post-op MRI should be performed within 48 h to document any residual disease after surgical intervention.

JPA: enhancing nodule, highly vascular, 50% associated with cysts, high uptake on PET.

Grade 2 glioma: nonenhancing, hypointense on T1, hyperintense on T2/FLAIR, well-circumscribed, solid, round, calcifications associated with oligodendroglioma.

Grade 3 glioma: enhancing with gadolinium, infiltrative, less well-defined borders, mass effect (sulcal effacement, midline shift, ventricular dilatation, and vasogenic edema).

GBM: rim enhancing, central necrosis, irregular borders, and mass effect.

Dural tail sign: this could represent tumor or increased vascularity, linear meningeal thickening and enhancement associated with some tumors adjacent to meninges, reported in 60% of meningioma, also seen in chloroma, lymphoma, and sarcoidosis.

MR spectroscopy: NAA = neuronal marker, choline = marker of cellularity and cellular integrity, creatine = marker of cellular energy, lactate = marker of anaerobic metabolism. Tumor = increased choline, decreased creatine, decreased NAA. Necrosis = increased lactate, decreased choline, creatine, and NAA.

Dynamic MR perfusion: astrocytoma = increased relative cerebral blood volume (CBV), generally increasing with grade. Oligodendroglioma = even low-grade, may have high CBV due to hypervascularity. Radiation necrosis and tumefactive demyelinating lesions = low CBV.

The use of gadolinium-based MR contrast has been associated with development of nephrogenic systemic fibrosis (NSF) in patients with chronic kidney disease maintained on dialysis. For patients with GFR < 30, gadolinium-based MR contrast should be avoided. For patients with GFR of 30-100, use of contrast is determined on a case by case basis, based on institutional protocols (Kuo et al. 2007)

**PATHOLOGY**

World Health Organization Grading System of gliomas: WHO Grade 1 = JPA, Grade 2 = fibrillary astrocytoma, Grade 3 = anaplastic astrocytoma, Grade 4 = glioblastoma multiforme.
Astrocytoma grading (AMEN) = nuclear atypia, mitoses, endothelial proliferation, necrosis.

Pearls: pseudopalisading and necrosis = GBM, Rosenthal fibers = JPA, psammoma bodies = meningioma, verocay body = schwannoma, Schiller-Duval body = yolk-sac tumor, Fried-egg = oligodendroglioma, pseudorosette = ependymoma, Homer-Wright rosettes = medulloblastoma, pineoblastoma, Flexner-Wintersteiner rosettes = pineoblastoma.

RADIATION TECHNIQUE
FRACTIONATED EBRT

- Simulate patient with head mask.
- 3DCRT or IMRT for most lesions. 3DCRT provides better dose homogeneity, fewer hot spots. Inverse planning may allow greater sparing of critical structures and/or deliver hot spots in center of (hypoxic) tumor. Must be determined on a case-by-case basis.
- Fuse planning CT and MRI (pre-op vs. post-op) to help delineate target volume. Post-op MRs are better than pre-op MRs in most cases.

GENERAL GUIDELINES FOR TARGET VOLUMES

- Individualize tumor volume based on propensity to infiltrate, follow disease extension along the white matter tracts (e.g., internal capsule and corpus collosum) and use nonuniform margin.
- High-grade gliomas:
  GTV1 = T1 enhancement + T2/FLAIR. CTV1 = GTV1 + 2 cm margin.
  Boost: GTV2 = T1 enhancement. CTV2 = GTV2 + 2 cm.
  PTV = CTV + 0.3–0.5 cm.
- Low-grade gliomas.
  These tumors are often nonenhancing and tumor may be best visualized on FLAIR.
  GTV = T1 enhancement or FLAIR for oligodendrogliomas.
  CTV = GTV + 1–2 cm margin.
  PTV = CTV + 0.3–0.5 cm.
### DOSE TOLERANCE GUIDELINES

<table>
<thead>
<tr>
<th>EBRT using 1.8–2.0 Gy/fx</th>
<th>SRS Max point dose</th>
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<tbody>
<tr>
<td>Whole brain 50 Gy</td>
<td>Brainstem 12 Gy</td>
</tr>
<tr>
<td>Partial brain 60 Gy</td>
<td>Optic nerve and chiasm 8 Gy</td>
</tr>
<tr>
<td>Brainstem 54 Gy</td>
<td>Visual pathway 12 Gy</td>
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<tr>
<td>Spinal cord 45 Gy</td>
<td></td>
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<tr>
<td>Chiasm 50–54 Gy</td>
<td></td>
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<tr>
<td>Retina 45 Gy</td>
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<tr>
<td>Lens 10 Gy</td>
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<tr>
<td>Inner ear 30 Gy (increasing risk of hearing deficit with increasing dose)</td>
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<tr>
<td>Epilation 20–30 Gy</td>
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<tr>
<td>Lacrimal gland: 30 Gy transient, 60 Gy permanent</td>
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</table>

- Fetal dose from cranial RT = 0.05–0.1% of total dose (<0.1 Gy).
- Individual patient dose constraints should be determined based on physicians’ clinical judgment and experience.

### POSSIBLE RADIATION COMPLICATIONS

- **Acute**: alopecia, radiation dermatitis, fatigue, transient worsening of symptoms due to edema, nausea, and vomiting (particularly with brainstem [area postrema] and posterior fossa [PF] radiation), and otitis externa. Mucositis, esophagitis, and myelosuppression are associated with cranio-spinal irradiation. Subside within 4–6 weeks after radiation. Dose-related.
- **Subacute** (6 weeks to 6 months after RT): somnolence, fatigue, neurologic deterioration, perhaps caused by changes in capillary permeability and transient demyelination.
- **Late** (6 months to many years after RT): radiation necrosis, diffuse leukoencephalopathy (especially with chemo, but not necessarily correlated with clinical symptoms), hearing loss, retinopathy, cataract, visual changes, endocrine abnormalities (if hypothalamic-pituitary axis is irradiated), vasculopathy, Moyamoya syndrome, decreased new learning ability, short-term memory, and problem solving skills.

### FUNCTIONAL STATUS

See Appendix A.
MALIGNANT GLIOMAS

PEARLS

- Most common primary malignant CNS tumor in adults.
- Majority are glioblastoma.
- Multicentric tumors in <5% of cases.
- Incidence rises with age, peaks at 45–55-year (bimodal based on primary vs. transformation).
- Presentation: #1 headache (50%), #2 seizures (20%).
- Prognostic factors: age, histology, KPS, extent of surgery, duration of symptoms (see RPA below).
- Survival benefit from the addition of temozolomide to RT seen in patients with MGMT promoter methylation.

RTOG RPA CLASSES FOR MALIGNANT GLIOMA

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>I and II: anaplastic astrocytoma, age ≤50, normal mental status, or age &gt;50, KPS &gt;70, symptoms &gt;3 month</td>
<td>MS: 40–60 months</td>
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<tr>
<td>III and IV: anaplastic astrocytoma, age ≤50, abnormal MS, or age &gt;50, symptoms &lt;3 month; Glioblastoma age &lt;50 or age &gt;50 and KPS ≥70</td>
<td>MS: 11–18 months</td>
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<tr>
<td>V and VI: glioblastoma, age &gt;50, KPS &lt;70 or abnormal mental status</td>
<td>MS: 5–9 months</td>
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- EORTC adaptation of RPA classes III-V, GBM only (based on updated Stupp data):
  - Class III (MS 17 month): age <50, WHO PS 0
  - Class IV (MS 15 month): age <50, WHO PS 1–2; age ≥50, GTR or STR, MMSE ≥27
  - Class V (MS 10 month): age ≥50, MMSE <27, biopsy only

TREATMENT RECOMMENDATIONS

General management
- Dexamethasone before/after surgery when clinically indicated; taper gradually
- Surgical decompression for increased ICP
- Antiseizure medications as indicated, ensure therapeutic levels

Resectable, or partially resectable, operable
- GTR/STR → RT (60 Gy) + concurrent temozolomide qd → temozolomide ×6c monthly (Stupp et al. 2005, 2009)
- Or 40 Gy/15 fx for age ≥60 and KPS >50 (Roa et al. 2004)
Inoperable
- RT (60 Gy) + concurrent temozolomide qd  \( \rightarrow \) temozolomide \( \times 6 \)c monthly (Stupp et al. 2005, 2009)

Recurrence
- Steroids if clinically indicated
- If local and resectable and/or symptomatic: surgery  \( \rightarrow \) chemo
- If local and unresectable: chemo and/or highly conformal RT or SRS
- If diffuse: chemo + best supportive care
- If poor KPS: best supportive care

STUDIES
RT VS. OBSERVATION
- Keime-Guibert (NEJM 2007): randomized 81 patients >70 year with GBM and KPS >70 after surgery (~50% biopsy only, ~30% GTR) to best supportive care ± RT (1.8/50.4 Gy to T1 enhancing + 2 cm). Trial stopped early because RT improved MS (4.3 \( \rightarrow \) 7.3 month; 53% relative reduction in death) and MPFS (1.4 \( \rightarrow \) 3.7 month) independent of the extent of surgery, with no difference in QOL and cognitive evaluations.
- Walker et al. (1979) BTSG: pooled three randomized trials. Compared observation vs. WBRT 45 vs. 50 vs. 55 vs. 60 Gy. MS increased with higher doses, 4 \( \rightarrow \) 7 \( \rightarrow \) 9 \( \rightarrow \) 10 month.
- Walker et al. (1978) BTSG 6901 – phase III: 222 patients (90% GBM, 10% AA)  \( \rightarrow \) surgery  \( \rightarrow \) randomized to observation vs. BCNU alone vs. WBRT 50–60 Gy alone vs. WBRT + BCNU. RT was WB to 50 Gy, then boost to 60 Gy. RT ± BCNU improved MS by 3–6 month vs. observation or BCNU alone.

DOSE AND FRACTIONATION
- Roa et al. (2004) – phase III: 100 patients with GBM age \( \geq 60 \) and KPS \( \geq 50 \) randomized to 60 Gy/30 fx vs. 40 Gy/15 fx. No difference in MS (5.1 vs. 5.6 month). Fewer patients in the short course RT arm required increased steroids (23 vs. 49%).
- Bauman et al. (1994): single arm prospective study. Twenty-nine patients with GBM age \( \geq 65 \) and KPS \( \leq 50 \) treated with WBRT (30 Gy/10 fx). RT increased MS vs. best supportive care (10 vs. 1 month).
- MRC (Bleehen and Stenning 1991) randomized 474 patients to 45 Gy/20 fx vs. 60 Gy/30 fx. No adjuvant chemo. MS 12 month (60 Gy) vs. 9 month (45 Gy, \( p = 0.007 \)).

- RTOG 9305 (Souhami et al. IJROBP 2004): phase III trial of 203 patients randomized to postoperative SRS, followed by EBRT (60 Gy) plus BCNU, vs. EBRT and BCNU alone. Dose of radiosurgery dependent on tumor size (range 15–24 Gy). No difference in survival (MS 13.5 month) or patterns of failure.

- RTOG 0023 (Cardinale et al. IJROBP 2006): phase II trial of 76 patients who were given 50 Gy and four weekly stereotactic radiotherapy boosts, to a cumulative dose of 70–78 Gy. After the RT, 6 cycles of BCNU given. MS 12.5 month, no improvement compared to historical data.

### CHEMO-RT

- EORTC/NCIC (Stupp et al. 2005, 2009) – phase III: 573 patients with newly diagnosed glioblastoma (16% biopsy only, 40% GTR, 44% STR) randomized to RT alone vs. RT + concurrent and adjuvant temozolomide. RT was 60 Gy/30 fx. Temozolomide was concurrent daily (75 mg/m²/day) and adjuvant (150–200 mg/m²/day × 5 days) q4 weeks × 6 month. Concurrent and adjuvant temozolomide significantly improved MS (14.6 vs. 12.1 month) and 5-year OS (9.8 vs. 1.9%). MGMT gene promoter methylation was the strongest predictor for outcome and benefit from temozolomide.

- Walker et al. (1980) BTSG 7201 – phase III: 476 patients (84% GBM, 11% AA) → surgery → randomized to MeCCNU alone vs. RT alone vs. RT + MeCCNU vs. RT + BCNU. RT was WB 60 Gy/30–35 fx. RT ± chemo increased MS compared to chemo alone (37–43 vs. 31 weeks). No difference between MeCCNU and BCNU.

- RTOG 94–02 (Cairncross et al. JCO 2006) – phase III: 289 patients with pure or mixed anaplastic oligodendroglioma → surgery → randomized to PCV chemo ×4c → RT vs. RT alone. RT was 50.4 Gy → boost to 59.4 Gy. No difference in MS (4.9 vs. 4.7 year), but PCV chemo improved PFS (2.6 vs. 1.7 year). Patients with 1p/19q loss had longer PFS and OS. Benefit of PCV only observed for PFS in patients with 1p/19q loss.

- EORTC 26951 (van den Bent et al. JCO 2006): 368 patients with anaplastic oligodendroglioma or oligoastrocytoma randomized after resection to RT → PCV ×6c, or RT alone. RT was 45 Gy → boost to 59.4 Gy. Median OS (40 vs. 31 month, \( p = 0.23 \)), PFS (23 vs. 13 month, \( p = 0.002 \)). 1p/19q loss was associated with better PFS and OS. In contrast to RTOG 9402, there was no differential benefit of PCV based on 1p/19q status.
DOSE

- EBRT: 1.8–2 Gy/fx to 45–46 Gy followed by boost to 59.4–60 Gy
- GTV1 = T1 enhancement + T2/FLAIR. CTV1 = GTV1 + 2 cm margin
- Boost: GTV2 = T1 enhancement. CTV2 = GTV2 + 2 cm
- PTV = CTV + 0.3–0.5 cm

FOLLOW-UP

- MRI 2–6 weeks after RT and then every 2 month.

LOW-GRADe GliOMA

PEARLS

- Ten percent of primary intracranial tumors, 20% of gliomas.
- Oligodendrogliomas account for <5% of intracranial tumors.
- Age of onset: 30–40 year for WHO Grade II and 10–20 year for JPA.
- Presentation: seizures (60–70%, better prognosis) > headache > paresis.
- Favorable prognostic factors: age <40 year, good KPS, oligo subtype, GTR, low proliferative indices, 1p/19q deletions for oligodendroglioma.
- MS: low-grade pure oligodendroglioma (120 month) > low-grade mixed oligoastrocytoma > low-grade astrocytoma (60 month) ≥ anaplastic oligodendroglioma (60 month) > anaplastic astrocytoma (36 month) > GBM (12 month).

TREATMENT RECOMMENDATIONS

<table>
<thead>
<tr>
<th>JPA, subependymal giant cell astrocytoma, subependymoma, grade 2 pleo-morphic astrocytoma, dysembryoblastic neuroepithelial tumor</th>
<th>GTR → observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendroglioma, oligoastrocytoma, astrocytoma (adults)</td>
<td>STR → consider observation vs. resection vs. chemo vs. RT vs. SRS, depending on the location of tumor, symptoms, age of patient</td>
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<td>Maximal safe resection (GTR or STR) →</td>
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<td></td>
<td>Observation if age &lt;40 years, oligodendroglioma, GTR, good function. Serial MRIs, if progresses → RT 50–54 Gy (UCSF standard dose for low-grade gliomas is 54 Gy)</td>
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</table>
Or, immediate post-op RT to 54 Gy. No survival benefit, but RT delays time to relapse by ~2 years (EORTC study)

QOL gained by delaying recurrence must be weighted against QOL lost due to late toxicities of RT

Maximal safe resection (GTR or STR) → observation and serial MRIs. Adjuvant chemo may prolong DFS and delay need for RT. Adjuvant RT may improve DFS, but not recommended for children <3 years. Consider second surgery for operable progression and RT for inoperable progression (doses 45–54 Gy)

**STUDIES**

**TIMING OF RT**

- **EORTC 22845** (Karim et al. 2002; van den Bent et al. 2005) – phase III: 311 patients (WHO 1–2, 51% astro., 14% oligo., 13% mixed oligo-astro) treated with surgery (42% GTR, 19% STR, 35% biopsy) randomized to observation vs. post-op RT to 54 Gy. RT improved median progression-free survival (5.3 year vs. 3.4 year), 5-year PFS (55 vs. 35%), but not OS (68 vs. 66%). Sixty-five percent of patients in the observation arm received salvage RT. No difference in rate of malignant transformation (66–72%).

**DOSE**

- **EORTC 22844** (Karim et al. 1996) – phase III: 343 patients (WHO 1–2, astro., oligo. and mixed) treated with surgery (25% GTR, 30% STR, 40% biopsy) randomized to post-op RT 45 Gy vs. 59.4 Gy (shrinking fields). No difference in OS (59%) or PFS (49%). Five-year OS oligo vs. astro = 75 vs. 55%, <40 year vs. ≥40 year = 80 vs. 60%. Age <40 year, oligo histology, low T-stage, GTR, and good neurologic status are important prognostic factors.

- **INT/NCCTG** (Shaw et al. 2002) – phase III: 203 patients (WHO 1–2, astro, oligo, mixed) treated with surgery (14% GTR, 35% STR, 51% Bx) randomized to post-op RT 50.4 Gy vs. 64.8 Gy. No difference in 5-year OS (72% low dose vs. 64% high dose). Best survival in patients <40 year, tumor <5 cm, oligo histology and GTR. Increased Grade 3–5 toxicity (2.5 vs. 5%) with higher dose. Pattern of failure: 92% in field, 3% within 2 cm of RT field.
Shaw et al. (1989) – retrospective study: 5/10-year OS surgery alone = 30/10%, surgery + <53 Gy = 50/20%, surgery + > 53Gy = 67/40%.

ROLE OF CHEMOTHERAPY

- INT/RTOG 9802 (ASCO abstract 2008): phase III of low-grade gliomas. Low-risk (<40 year + GTR) observed until symptoms. Two hundred and fifty one high-risk (≥40 year or STR or biopsy) patients randomized to RT alone vs. RT → PCV ×6 cycles q8 weeks. RT 54 Gy to FLAIR + 2 cm margin. No boost. Five-year OS was 72 vs. 63% (p = 0.33), 5-year PFS was 63 vs. 46% (p = 0.06). For 2-year survivors, OS for 3 additional year was 84 vs. 72% (p = 0.03), and PFS was 74 vs. 52% (p = 0.02), suggesting a benefit to PCV chemo in the high-risk subgroup.
- Ongoing RTOG and EORTC trials investigating the use of temozolomide.

DOSE

- EBRT: 1.8 Gy/fx to 50.4–54 Gy.
- These tumors are often nonenhancing and tumor may be best visualized on FLAIR.
- GTV = T1 enhancement or FLAIR.
- CTV = GTV + 1–2 cm margin.
- PTV = CTV + 0.3–0.5 cm.

FOLLOW-UP

- MRI 2–6 weeks after RT, then every 6 month for 5 years, then annually.

BRAINSTEM GLIOMA

PEARLS

- Most common in young patients.
- Accounts for 5% of adult, and 15% of pediatric CNS tumors.
- Incidence peaks between age 4–6 year.
- Seventy to eighty percent are high-grade astrocytomas, remaining are low-grade astrocytomas, ependymomas, PNETs, and atypical teratoid-rhabdoid tumors.
- Biopsy can be associated with high mortality and morbidity, so sometimes not performed.
- MRI and presentation to determine grade.
High-grade tumors > infiltrative, often originate in the Pons, extend alone white matter tracts into the cerebellum or diencephalon, diffusely expand the brainstem, younger age, rapid onset of symptoms, multiple neurological deficits.

Low-grade tumors > focal lesions in the midbrain or thalamus, or dorsally exophytic lesions, older age, and indolent course.

Differential diagnosis (nondiffuse): abscess, neurofibromatosis, demyelinating diseases, AVM, encephalitis.

Two to five-year OS 45–66% in adults and 20–30% in children overall, but MS only 11 month for high-grade gliomas.

**TREATMENT RECOMMENDATIONS**

**Steroids**  ■ Can help to stabilize or improve neurologic symptoms

**Shunts**  ■ May be necessary in severe hydrocephalus

**Surgery**  ■ Role is limited, generally not indicated in diffuse pontine lesions. Dorsally exophytic tumors and cervicomedullary tumors may be surgically resected

**Radiation**  ■ Conventional fractionation to 54–60 Gy. Recommend 3DCRT
  ■ For diffuse lesions, cover the tumor with 2 cm margin or the entire brainstem (diencephalon to C2) and any cerebellar extension with margin
  ■ No benefit of dose escalation above 72 Gy at 1-Gy b.i.d.
  ■ No benefit of hyperfractionation (Pediatric Oncology Group)

**Chemotherapy**  ■ No benefit of adjuvant CCNU, vincristine, prednisone, temozolomide vs. RT
  ■ No survival benefit of neoadjuvant chemotherapy
  ■ High-dose chemo with stem-cell rescue showed no benefit in Phase I/II trials

**OPTIC GLIOMA**

**PEARLS**

■ Five percent of all CNS tumors in the pediatric age group

■ Subdivided into: optic nerve gliomas, chiasmatic gliomas, and chiasmatic/hypothalamic gliomas (bulky lesions)
Ten to fifteen percent of NF-1 patients have optic glioma; 25–40% of childhood optic pathway tumors have NF-1

Presentation: optic nerve tumors: asymptomatic, long standing proptosis, impaired visual acuity, optic nerve atrophy; chiasmal tumors: decreased visual acuity, temporal field defects chiasmatic/hypothalamic tumors: nystagmus, visual field deficits, impaired visual acuity, hydrocephalus, increased intracranial pressure

MRI: small and well circumscribed, homogenous enhancement

Biopsy not necessary for diagnosis

**TREATMENT RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Optic nerve and chiasmatic tumors</td>
<td>Chemo first for all patients and reserve RT for chemo failures</td>
</tr>
<tr>
<td>Chiasmatic/hypothalamic tumors</td>
<td>CSF diversion if indicated. Maximal safe surgical resection. Chemo. Reserve RT (45–50 Gy) for patients who progress on or after chemo (~50% can avoid RT at 5-years)</td>
</tr>
</tbody>
</table>

**SURVIVAL**

- Long-term OS 90–100%.
- Long-term PFS 60–90%.
- For chiasmatic/hypothalamic gliomas: LC 70–80% and long-term OS 50–80%.

**CNS LYMPHOMA**

**PEARLS**

- Approximately 2% of intracranial tumors.
- Rapidly rising incidence (3–10×) in the last two decades in both immunocompetent and immunodeficient populations.
- EBV present in 60–70% of immunodeficient, and 15% immunocompetent patients.
- Median age: 55 year in immunocompetent, and 31 year in immunocompromised patients.
- Multifocal tumors: 25–50% of immunocompetent, and 60–80% of immunodeficient patients.
- MRI: single or multiple periventricular masses, intensely enhancing.
In AIDS patients, smaller lesions may demonstrate ring enhancement. Differential diagnosis includes toxoplasmosis.

- Leptomeningeal involvement in 1/3 of patients.
- Retinal and vitreous seeding in 15–20% of patients.
- In primary intraocular lymphoma, 80% develop CNS involvement within 9 month.
- Histology: 90% are DLBCL.
- Presentation: focal deficits, seizures, headache, lethargy, confusion. Neck or back pain (spinal cord involvement). Blurred vision or floaters (ocular involvement, which presents in ~20% of patients).
- Workup: MRI brain and spine, biopsy, ophthalmologic exam, CXR, CSF cytology, CBC, EBV titer, HIV testing. CT chest, abdomen, and pelvis and bone marrow biopsy, consider testicular ultrasound for elderly men, consider PET scan. Hold steroids, if possible prior to diagnostic procedures.
- Systemic or intrathecal methotrexate given with RT has synergistic neurotoxicity.

**TREATMENT RECOMMENDATIONS**

**Surgery**
- Biopsy for tissue diagnosis. Extensive resection does not improve OS.

**Steroids**
- Should be withheld until after biopsy. Ninety percent have clinical response. Forty percent have shrinkage. Ten percent have complete resolution on imaging. Response is short-lived and tumor recurs within weeks to month after steroids are stopped.

**General management**
- If KPS ≥40 and acceptable renal function → high-dose methotrexate-based regimen followed by WBRT 24–36 Gy at 1.8–2-Gy/fx, If PR → boost gross disease to 45 Gy. If CSF positive or spinal MRI positive, consider intrathecal chemotherapy. If eye exam positive, intraocular chemotherapy or RT to globe.
- If KPS <40 or renal dysfunction → WBRT. If CSF positive or spinal MRI positive, consider intrathecal chemotherapy and focal spinal RT. If eye exam positive, RT to globe. Consider nonmethotrexate chemo alternatives.
- For patients >60, may omit WBRT if CR to chemo and reserve RT for recurrence.
- For leptomeningeal spread, use intrathecal chemo or CSI to 39.6 Gy with additional 5.4–10.8 Gy to gross disease.
- See Chap. 3 regarding ocular lymphoma.
STUDIES

- RTOG 83–15 (Nelson et al. 1992) – phase II: 41 patients with CNS lymphoma treated with 40 Gy WBRT + 20 Gy boost to tumor bed. Eighty-eight percent of recurrences were within the boost field. MS 12.2 month 2-year OS 28%. Better survival in patients with KPS >70 and Age <60.
- RTOG 88–06 (Schultz et al. 1996) – phase I/II: 51 patients with HIV-negative CNS lymphoma treated with CHOD × 2 (cytoxan, adriamycin, vincristine, dexamethasone) → WB to 41.4 Gy and boost to 59.4 Gy. No difference in MS when compared with RTOG 83–15.
- RTOG 93–10 (DeAngelis et al. 2002) – phase II: 102 HIV-negative CNS lymphoma patients treated with chemo ×5 (IV/IT MTX, vincristine, procarbozine) → WBRT 45 Gy → high-dose cytarabine. Fifty-eight percent CR, 36% PR, MPFS 24 month, MS 36.9 month. Fifteen percent patients with severe delayed neurotoxicity. Better survival in patients <60 year (50 vs. 22 month, p<0.001).
- MSKCC experience (Gavrilovic, et al. 2006): 57 patients treated with high-dose MTX ± RT. Five-year OS 74% for patients <60 year treated with RT, but no difference in MS for patients >60 year with or without RT (29 month). 25% neurotoxicity for patients <60 year vs. 75% for >60 year with RT vs. 3% if no RT.

SURVIVAL

- RT alone MS 12 month, 2-year OS 20–30%.
- Chemo (high-dose MTX-based) + WBRT MS 30–60 month, 2-year OS 55–75%.
- Survival recursive partitioning analysis (JCO 2006 Abrey et al. 2006). From MSKCC, confirmed with RTOG data.
  - I: Age <50: MS 8 year, failure-free survival (FFS) 2 year.
  - II: Age ≥50 and KPS ≥70: MS 3 year, FFS 1.8 year.
  - III: Age ≥50 and KPS <70: MS 1 year, FFS 0.6 year.

EPENDYMOMA

PEARLS

- Ependymal cells form the lining of the ventricular system and the central spinal canal.
Less than 5% of adult brain tumors, incidence peaks at 35 years old.

Ten percent of pediatric brain tumors, incidence peaks at 5 years old.

Most intracranial lesions are located in the PF and arise from floor of the fourth ventricle.

Ten to thirty percent of fourth ventricular tumors extend down through the foramen magnum to the upper C-spine.

Sixty percent of primary spinal cord tumors are ependymomas.

Increased frequency of spinal cord ependymomas in patients with NF2.

Less than 7% incidence of CSF spread at diagnosis, up to 15% ultimately, rare without local progression.

CSF relapse 5–15%. More common with infratentorial and high-grade tumors.

Complete resection of the PF tumors is difficult due to proximity to fourth ventricle, CNs, and major vessels.

Complete resection is the single most important prognostic factor.

Other good prognostic factors: low grade and age >2–4 year.

CSF and MRI spine required to assess spine. Lumbar puncture and spine MRI should be delayed 2-3 weeks after surgery to avoid false positive results.

Pediatric patients should be enrolled in clinical trials whenever possible.

**TREATMENT RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Symptomatic hydrocephalus</th>
<th>Steroids and/or CSF diversion</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Ependymoma resectable     | Maximal safe surgical resection | 5-year PFS  
Adults: GTR 50–55%  
STR 0–25%  
Peds (most infratentorial with post-op RT) GTR 60–80%  
STR 30–45%  
5-year OS low-grade 60–90% |
|                           | Negative MRI spine and CSF    |          |
|                           | GTR → limited field RT (54–60 Gy) |          |
|                           | STR → limited field RT        |          |
|                           | Positive MRI spine or CSF → CSI (30–36 Gy, boost gross disease, 54–60 Gy for brain lesions and 45 Gy for spine lesions) |          |

continued
Anaplastic ependymoma resectable
- Maximal safe surgical resection
- Negative MRI spine and CSF
  GTR or STR → limited field RT (54–60 Gy)
- Positive MRI spine or CSF → CSI (30–36 Gy, boost gross disease 54–60 Gy for brain lesions and 45 Gy for spine lesions)

Unresectable
- Negative CSF → limited field RT (54–60 Gy)
- Positive MRI spine or CSF → CSI (30–36 Gy, boost gross disease 54–60 Gy for brain lesions and 45 Gy for spine lesions)

Recurrence
- Maximal surgical resection
- Post-op RT if no prior RT, consider SRS
- Chemotherapy, best supportive care

Children <4 years
- Maximal safe surgical resection. If STR → chemo (platinum-based compounds and cyclophosphamide) and delay RT to avoid toxicities

FOLLOW-UP
- MRI brain and spine (if initially positive) every 3–4 month for the first year, every 4–6 month for the second year, then every 6–12 month.

CHOROID PLEXUS TUMORS

PEARLS
- Less than 2% of all glial tumors.
- Most common location: lateral ventricles in children, the fourth ventricle in adults.
- Benign (WHO grade I) = choroid plexus papilloma, 60–80%, papillary formation, lack of mitosis, and normal tissue invasion.
Malignant (WHO grade III) = choroid plexus carcinoma, 20–40%, nuclear atypia, pleomorphism, frequent mitoses, and invasion of subependymal brain tissue.

Most commonly present with hydrocephalus due to CSF overproduction and flow obstruction.

Up to 30% of children present with metastatic disease at diagnosis.

Workup: MRI brain and spine, CSF cytology.

**TREATMENT RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>General management</th>
<th>Maximal safe resection is first-line therapy for both choroid plexus papilloma and carcinoma</th>
</tr>
</thead>
</table>
| Choroid plexus papilloma | GTR and spine negative → observation  
  | STR and spine negative → RT to post-op bed 50–54 Gy |
|                     | STR and spine positive (rare!) → CSI 36 Gy + LF boost 54 Gy and boost to mets 45–54 Gy  
  | No role for chemotherapy |
| Choroid plexus carcinoma | GTR and spine negative → observation, consider RT  
  | STR and spine negative → RT to post-op bed to 54 Gy |
|                     | STR and spine positive → CSI 36 Gy + LF boost 54 Gy and boost to mets 45–54 Gy  
  | Consider chemotherapy |

**SURVIVAL**

- Choroid plexus papilloma 5-year OS 90–100%.
- Choroid plexus carcinoma 5-year OS 20–30%.

**MENINGIOMA**

**PEARLS**

- Thirty percent of primary intracranial neoplasms
- Most common benign intracranial tumor in adults
- Eight thousand six hundred new cases in the US in 2002
- Incidence increases with age, peaks in the sixth and seventh decades
- F:M = 2:1 for all meningiomas and 1:1 for anaplastic meningiomas (rhabdoid and papillary)
Locations: cerebral convexities, falx cerebri, tentorium cerebelli, cerebellopontine angle, sphenoid ridge, and spine

Possible risk factors: ionizing radiation, viral infection, sex hormones, NF2, loss of chromosome 22q.

WORKUP

- H&P: historically, most common presentation was headaches > personality change/confusion > paresis. Symptoms correlate with location: cranial neuropathy (cerebellopontine angle), headaches or seizures (convexities, falx), visual loss (sphenoid ridge wing or optic nerve involvement). Increased use of CT/MRI brain scans has led to a rising incidence, particularly for asymptomatic lesions (autopsy series suggest prevalence of 2–3%).
- CT: extraaxial, well-circumscribed and smooth, with moderate to intense homogenous enhancement with contrast, often minimal edema (consistent with slow growth). Bony changes (destruction or hyperostosis, reflects disease involvement and not reactive change) in 15–20%. Malignant meningiomas may frequently invade the brain.
- MRI: isointense on T1 and T2, intensely enhance with gadolinium.
- Dural tail sign: linear meningeal thickening and enhancement adjacent to a peripherally located cranial mass, reported in 60% of meningiomas, also seen in chloroma, lymphoma, and sarcoidosis.
- Slower tumor growth has been linked to calcification, homogeneous enhancement and iso to hypointense T2 signal.

TREATMENT RECOMMENDATIONS

Resectable, operable
- Observation, if asymptomatic and slow-growing.
- GTR (often facilitated by pre-op angiography ± embolization) → observation and serial MRIs.
- If recurrence → RT. Alternative, definitive RT, or SRS

Unresectable, operable
- STR → RT. Alternative, definitive RT, or SRS

Inoperable
- RT alone or SRS alone

Malignant meningioma
- GTR or STR → RT to 60 Gy with 2–3 cm margin

Recurrence
- RT or SRS or surgery as salvage therapy
STUDIES

POST-OP EBRT

- Goldsmith et al. (1994): 140 patients from USCF with STR + post-op RT for benign (84%) and malignant (16%) meningiomas. Five-year OS 85% for benign, 58% for malignant. Improved PFS in patients who received >52 Gy (95 vs. 65% benign, 65 vs. 15% malignant). No benefit of aggressive STR vs. biopsy alone if post-op RT given. Patients with benign tumors treated after 1980 (when CT and MRI were used for treatment planning) had better 5yr PFS compared to those treated before 1980 (98% vs. 77%, P=0.002).

SRS

- Kondziolka et al. (1999): 99 patients from U. Pittsburgh, 43% SRS alone, 57% surgery + SRS, median tumor margin dose 16 Gy, max dose 32 Gy, median tumor volume 4.7 cc. LC 95%, PFS 93% at 5–10-year.
- Stafford et al. (2001): 190 patients from Mayo Clinic, 59% had prior surgery, 12% with atypical or malignant histology. Median tumor margin dose was 16 Gy. Median prescription isodose volume was 8.2 cm³. Five-year LC for patients with benign, atypical, and malignant tumors were 93, 68, and 0%, respectively. Five-year CSS for patients with benign, atypical, and malignant tumors were 100, 76, and 0%, respectively.
- EORTC 26021–22021: phase III study randomizing benign Grade I incompletely resected intracranial meningiomas to observation vs. EBRT or SRS. Trial closed in 3/2006, Results pending.

DOSES

- EBRT: 54 Gy for benign, 60 Gy for malignant.
- SRS or FSRT: individual dose chosen based on tumor volume, location, surgical history, and radiosensitivity of nearby structures.

SURVIVAL

- WHO I: 5-year PFS for GTR 88–98%, for STR alone 43–83%, and for STR + RT 88–98%. 5/10/15-year OS 85/75/70%.
- Malignant: surgery + RT, 40–50% 5-year PFS.
FOLLOW-UP

- MRI every 4 months for 1 year, every 6 months for 2 years, then annually.

ACOUSTIC NEUROMA

PEARLS

- Six percent of intracranial tumors.
- Arise from Schwann cells of myelin sheath of peripheral nerves.
- Sporadic (unilateral, age 40–50 year) or associated with NF 2 (bilateral).
- Slow growing, well-circumscribed, expansile, displace adjacent nerves.
- Symptoms: progressive sensorineuronal hearing loss and vestibular deficits. May affect CN VII function. Expansion into cerebellopontine angle may lead to CN V symptoms. Hydrocephalus may occur.
- Screening: pure tone and speech audiometry (selective loss of speech discrimination common).
- Thin slice, gadolinium-enhanced MRI through the cerebellopontine angle is the imaging modality of choice.
- Suspected NF should have neuraxis imaging.

TREATMENT RECOMMENDATIONS

- Surgery: 90% are total or near-total resection (<10% LF). STR without post-op RT (45% LF) vs. STR with post-op RT (6% LF). Preservation of CN VII function >60%. Preservation of useful hearing 30–50%, depending on lesion size and surgical technique.
- SRS: >90% LC. Dose 12–13 Gy single fraction, increased complications with >14 Gy. Similar outcome with fractionated and single fraction SRS. Preservation of CN VII function >90%. Preservation of useful hearing ~75%. Preservation of CN V function =90%.
- EBRT: dose 54 Gy/1.8 Gy fx. Preservation of CN VII function >95%. Preservation of useful hearing ~75%. Preservation of CN V function ~95%.
STUDIES

- Koh et al. (2007): 60 patients treated with FSRT (50 Gy/2 Gy fx). Five-year LC 96%, useful hearing preservation 77%. No new cranial nerve toxicity.
- Chopra et al. (2007): 216 patients treated with SRS (12–13 Gy marginal dose). Ten-year LC 98%. Preservation of serviceable hearing among hearing patients was 74%. CN V function preservation was 95%, CN VII was 100%.

CRANIOPHARYNGIOMA

PEARLS

- Benign, partially cystic, epithelial tumors.
- Arise from Rathke’s pouch in the sellar region.
- Five to ten percent of pediatric intracranial tumors, ages 5–14 year.
- Bimodal distribution: 55% occur in children and 45% are over age 20 year with another peak between 55 and 65 year.
- Present with neuroendocrine deficits such as diabetes insipidus or growth failure, visual field cuts, decreased acuity, increased ICP, cognitive and behavioral changes.
- MRI: solid nodule (calcified and contrast enhancing) with cystic component filled lipoid, cholesterol laden fluid (“crankcase oil”).
- May develop invaginations into adjacent brain, causing a glial reaction.

TREATMENT RECOMMENDATIONS

- Maximal safe resection.
- If GTR → observation (LC 85–100%).
- If STR → post-op EBRT to 54 Gy at 1.8-Gy/fx (LC 75–90%), or observation (LC 30%).
- Cyst decompression for nonresectable lesions prior to RT may ease sparing of critical structures and sometimes may be required during the course of RT.
- SRS: for small primaries or recurrent tumors.
- Intralesional bleomycin and intracavitary injection of radioactive colloid are effective in shrinking and fibrosing cysts,
although data are limited. Treatment toxicity can mimic disease progression with multiple endocrinopathies, visual loss, seizures, other cranial neuropathies, motor neuropathies, and neurocognitive deficits.

- For children <3 year, limited surgery and close follow-up, defer RT.

**SURVIVAL**

- Long-term event-free survival 80–100%.

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## PITUITARY TUMORS

**PEARLS**

- Ten to fifteen percent of primary brain tumors.
- 2.5: 1 incidence (female to male).
- Long natural history with insidious onset of symptoms; often slow (or no) detectable radiologic progression.
- The pituitary gland is surrounded by anterior and posterior clinoids; superiorly by anterior cerebral arteries, the optic nerves, and chiasm; laterally by cavernous sinuses (CN III, IV, V1, V2, VI, internal carotid artery); inferiorly by sphenoid sinus.
- Nearly all pituitary tumors arise from the anterior lobe, which is derived from Rathke’s pouch (an evagination of ectodermal tissue from NPX).
- Anterior lobe produces GH, PRL, ACTH, TSH, FSH, LH, controlled by hypothalamic portal system hormones.
- Posterior lobe produces ADH and oxytocin.
- Seventy-five percent functional, 25% nonfunctional.
- Tumors secreting prolactin are the most common secreting tumors (30%), followed by GH (25%) → ACTH → TSH (rare).
- Macroadenomas: ≥1 cm; microadenomas: <1 cm.
- MEN-1: autosomal dominant, pituitary, parathyroid, pancreatic island cell tumors.
- Mass effect on stalk (infundibulum) causes increased PRL because of the loss of inhibition from hypothalamus. A similar effect after radiation of the stalk can be observed with persistent PRL elevation.
- Immunohistochemistry to identify subtype.
- After radiation therapy, prolactin and growth hormone levels normalize over several year. ACTH usually normalizes within 1 year.
WORKUP

- H&P: headache, visual field testing (bitemporal hemianopsia, superior temporal deficits, homonymous hemianopsia, central scotoma, etc), CN deficits (involvement of cavernous sinus), sleep/appetite/behavior changes (compression of hypothalamus), growth abnormalities, cold or heat intolerance.
- Imaging: MRI (thin cuts with contrast) or CT (look for bone destruction), skeletal survey when indicated.
- Complete endocrine evaluation.
  - Prolactin
  - Basal GH, IGF-1, glucose suppression, insulin tolerance, TRH stimulation
  - Serum ACTH, 24-h urine 17-hydroxycorticosteroids and free cortisol, dexamethasone suppression
  - Gonadal: LH, FSH, plasma estrodial, testosterone
  - Thyroid: TSH, T3, T4
  - Basal plasma or urinary steroids; cortisol response to insulin-induced hypoglycemia and plasma ACTH response to metyrapone
- Acromegaly = headache, changes in facial/skull/hand bones, heat intolerance, wt gain. Dx = GH >10 ng/mL, not suppressed by glucose, or elevated IGF-1.
- Prolactinoma = amenorrhea, infertility, decreased libido, impotence galactorrhea, PRL >20 ng/mL.
- Cushing’s disease = bilateral adrenal hyperplasia, central obesity, HTN, glucose intolerance, hirsutism, easy bruising, osteoporosis. Diagnosis = elevated cortisol, not suppressed with low-dose dexamethasone, partially suppressed with high-dose dexamethasone, normal or moderately elevated plasma ACTH. In adrenal tumors, ACTH is depressed.

TREATMENT RECOMMENDATIONS

TREATMENT MODALITIES

Medical management

- Bromocriptine for prolactinomas, somatostatin analogs and pegvisomant (GH receptor antagonist) for GH-secreting tumors, and ketoconazole, metapyone, mitotane for ACTH-secreting tumors may be used
- Frequent relapse when discontinued
- Provide temporary control of remission while awaiting response to RT

continued
### TREATMENT AND OUTCOME BY TUMOR TYPE

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Treatment Options</th>
</tr>
</thead>
</table>
| Nonfunctioning pituitary tumors | Surgery → observation or RT vs. definitive RT alone  
                          | 10-year DFS 90% (S+RT) vs. 80% (RT alone)                                          |
| GH-secreting                | Surgery → observation → RT 45–50 Gy for recurrent GH elevation. Or, RT alone 45–50 Gy for inoperable patients  
                          | 10-year DFS 70–80% (S+RT) vs. 60–70% (RT alone)                                    |
| Prolactin-secreting         | Observation vs. medical management vs. surgery vs. RT, individualize treatment based on symptoms, side effect profile, and patient preferences. Ten-year DFS 80–90% |
| ACTH-secreting              | Surgery → observation → RT 45–50 Gy for recurrent ACTH elevation. RT alone 45–50 Gy for inoperable patients. Surgery results in more rapid normalization of hormones than RT alone. Ten-year remission rate 50–60% |
| TSH-secreting               | Aggressive, always treat with post-op RT                                             |
| Histiocytosis X             | 5–15 Gy in 3–8 fx                                                                   |

### DOSE

- 1.8 Gy/fx to 45–50 Gy for nonfunctioning, or 50.4–54 Gy for functioning.
- No more than 5% of dose inhomogeneity in tumor volume.
- 1.8–54 Gy for TSH and to 50.4 Gy for ACTH-secreting tumors.

### SURVIVAL

- No difference in OS between surgery, surgery + RT, or RT alone; best therapy based on minimizing side effects.
FOLLOW-UP

- Post-RT contrast-enhanced MRI every 6 month ×1 year, then annually.
- Endocrine testing every 6 month – 1 year. Assess hormonal response and monitor gonadal, thyroid and adrenal function for hypopituitarism.
- Formal visual field testing before RT for baseline and annually.

PINEAL TUMORS

PEARLS

- Adults: 1% of adult brain CA. Thirty to forty percent are germinomas and 10–20% NGGCTs.
- Nongerminomatous germ-cell tumors (NGGCTs) include embryonal carcinoma (produces both β-HCG and AFP), endodermal sinus tumor (elevated AFP), choriocarcinoma (elevated β-HCG), malignant teratoma.
- Pineoblastoma and NGGCTs more commonly have CSF dissemination.
- Presenting symptoms: sellar (visual field cut), suprasellar (endocrinopathies), and pineal (hydrocephalus, Parinaud’s (see below)).
- Classic triad = diabetes insipidus, precocious or delayed sexual development, visual deficits.
- Workup = MRI brain and spine, baseline ophthalmologic exam, CSF cytology and serum markers (β-HCG and AFP).

PINEOBLASTOMA

- Highly malignant primitive embryonal tumor, variant of PNET, WHO grade IV.
- Associated with bilateral retinoblastoma = trilateral retinoblastoma.
- Presents with rapidly raised ICP and enlarged head circumference.
- MRI: multilobulated, heterogeneous enhancement, with areas of necrosis and/or hemorrhage.
- Leptomeningeal spread at diagnosis in up to 50% cases.
PINEOCYTOMA
- Slow-growing tumor. WHO grade II.
- Most common in teens. Present with raised ICP.
- Parinaud’s syndrome: limited upward gaze, lid retraction, retraction nystagmus, pupils that react more poorly to light than to accommodation.
- MRI: spherical, well-circumscribed, homogeneous enhancement, hypointense on T1, hyperintense on T2.

PINEAL PARENCHYMAL TUMOR OF INTERMEDIATE DIFFERENTIATION
- Moderately high cellularity, mild nuclear atypia, occasional mitoses.
- No pineocytomatous rosettes.
- Rare tumor, optimal treatment need to be decided on an individual basis.

GERMINOMAS
- Germinoma = like seminoma in men, dysgerminoma in women
- MRI: hypodense, well-circumscribed, homogeneous enhancement
- Mildly elevated β-HCG, but not AFP

NGGCT
- Elevated serum or CSF AFP and marked elevated B-HCG
- Less radiosensitive than germinoma
- Extent of resection correlates with survival

TREATMENT RECOMMENDATIONS AND OUTCOME

<table>
<thead>
<tr>
<th>Histology</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pineoblastoma</td>
<td>Treat like medulloblastoma: maximal safe resection (to determine risk category) → CSI (23.4–39 Gy) + local boost to 54–55.8 Gy + chemo (5-year OS 50–70%). Radiosurgery boost possible for gross residual. If no CSI, poor outcome. MPFS 11–14 month. Five-year OS 50–70%</td>
</tr>
</tbody>
</table>

continued
Pineocytoma  
- Treat like low-grade glioma: surgery when possible.
- If GTR, observe. If STR → post-op RT (residual + 1–1.5 cm margin; 50–55 Gy). Five-year OS 60–90%

Germinoma  
- MRI of neuraxis. RT alone or chemo followed by RT. Prophylactic neuraxis RT is controversial, not done at UCSF. Consider partial cranial field: whole ventricular irradiation to 24–30 Gy, boost to primary to 45–50 Gy. If there is neuraxis or subependymal spread, or multiple midline tumors → CSI 24–36 Gy + primary disease to 45–50 Gy. Five-year OS 80–90%, spinal relapse 10–20%

NGGCT  
- Maximal safe resection → platinum-based chemo. MRI and lumbar puncture. If negative neuraxis, consolidative local RT. If positive neuraxis, CSI 30–36 Gy + primary disease 50–54 Gy. Five-year OS 20–40%

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**MEDULLOBLASTOMA**

**PEARLS**

- Twenty percent of pediatric CNS tumors, 40% of all PF tumors.
- The second most common pediatric CNS tumor: low-grade glioma 35–50%, medulloblastoma 20%, brainstem glioma 10–15%, high-grade glioma 10%.
- Median age 5–6 year in children and 25 year in adults.
- Thirty to forty percent of patients have CSF spread at the time of diagnosis.
- Bad prognostic factors: male, age <5 year, M1 disease.
- At diagnosis, 2/3 of patients are standard risk and 1/3 are high risk.
- Common presentation: vomiting, nausea, ataxia, headaches, papilledema, CN palsy, and motor weakness.
- Differential diagnosis of Posterior Fossa (PF) mass: medulloblastoma, ependymoma, astrocytoma, brainstem glioma, JPA, and metastasis.
- PF syndrome = difficulty swallowing, truncal ataxia, mutism, respiratory failure in 10–15% of children after PF craniotomy for medulloblastoma.
- PCV chemo = cisplatin, CCNU, vincristine.
WORKUP
- H&P
- MRI of the brain (pre-op and post-op within 24–48 h after surgery)
- MRI of the spine to rule-out leptomeningeal spread
- CSF cytology
- Bilateral bone marrow biopsy
- Consider bone scan and CXR
- Baseline audiometry, IQ, TSH, CBC, and growth measurements

STAGING

Chang system (Chang et al. 1969)
- T1: ≤3 cm
- T2: >3 cm
- T3a: >3 cm with extension into the aqueduct of Sylvius and/or the foramen of Luschka
- T3b: >3 cm with unequivocal extension into the brainstem
- T4: >3 cm with extension up past the aqueduct of Sylvius and/or down past the foramen magnum
- M0 No metastases
- M1 Microscopic cells in CSF
- M2 Gross Nodular seeding in cerebellar, cerebral subarachnoid space, third or lateral ventricles
- M3 Gross Nodular seeding in spinal subarachnoid space
- M4 Extraneuraxial metastasis

Risk categories
- Standard risk: age >3 years and GTR/STR with <1.5 cm² residual and M0
- High risk: age <3 years or >1.5 cm² residual, or M+

Survival
- Standard-risk DFS 60–90%
- High-risk DFS 20–40%, increased to 50–85% with adjuvant chemo

TREATMENT RECOMMENDATIONS

General management
- Hydrocephalus and increased ICP: steroids and VP shunt before attempting resection

Standard risk
- Surgical resection → CSI 23.4 Gy at 1.8-Gy/fx with PF boost to 54 Gy with concurrent vincristine → PCV chemo. DFS ~80%

High risk
- Surgical resection → post-op CSI 36–39 Gy at 1.8-Gy/fx, with entire PF and mets >1 cm boosted to 54 Gy with concurrent vincristine → PCV chemo. DFS ~60%

Infants
- Surgery → intensive chemo. Reserve RT for salvage (Duffner et al. 1993; Rutkowski et al. 2005). DFS ~30–40%
STUDIES
ROLE OF CHEMOTHERAPY

- Evans et al. (1990) CCGS/RTOG – phase III: 233 patients with medulloblastoma → surgery → randomized to post-op RT vs. post-op chemo-RT followed by chemo × 1 year. RT was CSI 35–40 Gy with PF boost to 50–55 Gy + spinal mets to 50 Gy. Chemo was concurrent vincristine, adjuvant vincristine, CCNU, and prednisone × 1 year. Five-year OS 65% in both arms. Chemo improved EFS in T3–4, M1–3 (46% for chemo-RT vs. 0% for RT alone).

- Tait et al. (1990) SIOP I – phase III: 286 patients with medulloblastoma → surgery → randomized to post-op RT vs. post-op chemo-RT followed by chemo × 1 year. RT was CSI 30–35 Gy/PF boost to 50–55 Gy. Five-year/10-year OS 53/45%. Initial DFS and OS benefit of chemo disappeared with longer F/U secondary to late failures in chemo arm. Subgroups T3–4 and gross residual disease still benefited from chemo.

- PNET 3 (Taylor et al. 2003) – phase III: 217 patients with M0–1 medulloblastoma → surgery → randomized to post-op RT vs. post-op chemo-RT. Chemo was vincristine/etoposide/carboplatin/cyclophosphomide. Patients 3–16-year old received CSI 35 Gy + 20 Gy PF boost. Trial closed early due to low accrual in RT-alone arm. Five-year OS 71%. Five-year EFS significantly better for chemo-RT arm (74 vs. 60%, \( p = 0.04 \)). Follow-up QOL paper reported poorer outcomes in behavior and quality of life for chemo-RT arm (Bull et al. 2007).

TIMING OF CHEMOTHERAPY

- Bailey et al. (1995) SIOP II: 364 patients with low-risk (GTR/STR, no brainstem involvement, M0) and high-risk (gross residual, brainstem invasion, or M+) medulloblastoma. All low-risk patients randomized to surgery + chemo → RT vs. surgery → RT. Chemo was vincristine, procarbazine, and methotrexate. RT was randomized to either standard dose 35 Gy CSI + 20 Gy PF boost vs. low-dose 25 Gy CSI + 30 Gy PF boost. All high-risk patients received 35 Gy CSI + adjuvant vincristine and CCNU. Results: pre-RT chemo did not improve 5-year EFS (58% with chemo and 60% without chemo). For low-risk, no difference with RT alone for 35 vs. 25 Gy (5-year EFS 75 vs. 69%).
STANDARD/AVERAGE/LOW RISK

- Thomas et al. (2000) *POG8631/CCG923*: 88 low-risk (age 3–21, Chang T1–3a, residual <1.5 cm, M0) medulloblastoma randomized to CSI 23.4 Gy/PF 54 Gy vs. CSI 36 Gy/PF 54 Gy. No chemo. A trend toward improved outcome with 36 Gy. However, overall EFS is suboptimal in the absence of chemo.

- *POG A9961* (JCO 2006): 379 average-risk medulloblastoma patients (age 3–21, no disseminated disease, residual <1.5 cm) → CSI 23.4 Gy/PF 55.8 Gy randomized one of two adjuvant chemotherapy regimens (CCNU, cisplatin, vincristine vs. CPM, cisplatin, vincristine). Five-year EFS 82% vs. 80%, 5-year OS 87% vs. 85%, respectively.

- Merchant et al. (2008): 86 newly diagnosed, average-risk medulloblastoma. RT began within 28 days of definitive surgery, and consisted of CSI (23.4 Gy), conformal RT to PF (36 Gy), and primary site RT (55.8 Gy). Five-year EFS 83%, comparable to historical CSI + PF RT.

HIGH-RISK

- Zeltzer et al. (1999) *CCG 921*: high-risk patients (age 1.5–21, or M1–4, or T3–4, or residual >1.5 cm²) randomized to CSI 36 Gy/PF 54 Gy/spinal mets 50.4–54 Gy (age <3 received CSI 23.4 Gy/PF 45 Gy) + vincristine → VCP ×8 vs. “8 in 1” chemo × 2 → RT → “8 in 1” chemo × 8. “8 in 1” chemo was vincristine, prednisone, lomustine, hydroxyurea, procarbazine, cisplatin, cyclophosphamide, and cytarabine. Better 5-year PFS with VCP (63% vs. 45%, p = 0.006). Seventy-eight percent 5-year PFS for M0, >3-year old, ≤1.5 cm² residual.

- Tarbell et al. (2000) *POG 9031*: 226 high-risk patients. randomized to chemo1 → RT → chemo2 vs. RT → chemo1 → chemo2. Chemo1 was cisplatin/etoposide × 7 weeks. Chemo2 was vincristine/cyclophosphamide. RT was CSI 35.2–44 Gy/PF 53.2–56.8 Gy. Results: no difference in 5-year EFS (70% RT first vs. 66% chemo first).

- (Gajjar et al. 2006) St. Jude *Medullo-96*: 134 patients (age 3–21). Low-risk patients received CSI (23.4 Gy)/PF (36 Gy)/primary bed (55.8). High-risk patients received CSI 39.6 Gy/boost to 55.8 Gy. All patients received dose-intensive chemo × 4 cycles. Low-risk 5-year EFS 83%; high risk 70%.

INFANTS

- Duffner et al. (1993): this study addressed whether RT can be delayed by giving chemo post-op and delay RT until >3 year
age. Patients <3 year with malignant brain tumors (including medulloblastoma, malignant glioma, brainstem glioma, ependymoma, PNET, etc.) underwent surgery → age <2 years, 24 month of chemo; age >2 year, 12 month of chemo → if disease progression → reresect or RT. Chemo was cyclophosphamide + vincristine × 2 → cisplatin + etoposide × 1. RT was CSI 35.2 Gy/PF 54 Gy (reduced to 24 Gy/50 Gy if complete response after surgery/chemo). Thirty-nine percent CR after the first 2 cycles of chemo. No difference in 2-year PFS (39 vs. 33%) and OS (53 vs. 55%) between two groups (<2 vs. >2 years). Thirty-four percent PFS and 46% OS for medulloblastoma at 2 year. These results suggest that it is safe to delay RT until age >3 year.

- Rutkowski et al. (2005) German BTSG – phase II: 43 patients (age <3) with medulloblastoma → surgery (40% GTR, 32% STR, 28% macro mets) → intensive chemo ×3c (cyclophosphamide, vincristine, methotrexate, carboplatin, and etoposide) and intrathecal methotrexate. Five-year PFS was 82 vs. 50 vs. 33% and 5-year OS was 93 vs. 56 vs. 38% for GTR vs. STR vs. macro mets. For M0 patients, 5-year PFS and OS were 68% and 77%, respectively. Sixty-two percent chemo response rate in patients with measurable disease after surgery. Age >2, desmoplastic histology and M0 were good prognostic factors. Mean IQ after treatment was lower than healthy controls, but higher than those who received RT. This study shows that lengthy remission can be obtained with intensive post-op chemo in children <3 year, reserving RT for salvage.

- Geyer (JCO 2005) CCG 9921: 284 patients <3-year-old w malignant brain tumors → surgery (167 <1.5 cm residual, 117 >1.5 cm residual) → randomized to two induction chemo regimens (no difference in response rate or EFS). Patients with residual dz after induction chemo or w mets at presentation received RT (tumor + 1.5 cm margin or CSI, respectively) at age 3 year (18 month for medullo or supra PNET) or after 8 cycles chemo. Five-year EFS 27%, OS 43%. Fifty-eight percent of patients alive at 5-year did not receive RT. For medullo, 5-year EFS 32%. For supra PNET, 5-year EFS 17%.

ONGOING TRIALS

- P9934: A phase I/II study evaluating the safety and efficacy of systemic chemo, second look surgery and IFRT for children ≥8 month and ≤36 month with nonmetastatic (M0) medulloblastoma.
- **ACNS0331**: A phase III randomized study comparing limited target volume boost irradiation and reduced dose CSI to 18 Gy to standard dose RT in children with newly diagnosed standard-risk medulloblastoma.
- **ACNS0334**: Phase III randomized trial for children <36 month with high-risk medulloblastoma or PNET. Trial designed to evaluate the addition of high-dose methotrexate to the four drug induction chemo regimen of vincristine, etoposide, cyclophosphamide, cisplatin. Patients then undergo second surgery, followed by consolidation and PBSC rescue. RT at discretion of individual institution.

**TREATMENT PLANNING**

**TRADITIONAL PRONE TECHNIQUE**

- Simulate patient prone, hyperextend the neck to avoid PA beam exiting through mouth. Head mask for immobilization. Use CT for treatment planning. Anesthesia may be required for patients unable to cooperate.
- Simulate the spine field first.
  - Superior border: C2 without exiting through mouth (slight neck hyperextension may help minimize exit through mouth).
  - Inferior border: bottom of S2 or lowest level of the thecal sac as seen on MRI.
  - Lateral borders: 1 cm lateral to the lateral edge of pedicles, increase by 1–2 cm in sacrum to cover spreading of neural foramen inferiorly.
  - Field length <35 cm, use 100 cm SSD; >35 cm, use 120 cm SSD.
  - In some patients, two adjacent spinal fields may be required to encompass the spine. When two spinal fields are used, match at depth of mid spinal cord.
  - Use CT or MRI to determine depth of spinal cord.
- Simulate the cranial field second. Two parallel-opposed lateral fields.
  - Superior border flash the skin. Inferior border 0.5–1 cm on cribiform plate, 1 cm on middle cranial fossa. One centimeter anterior to the vertebral bodies, 2–2.5 cm posterior to eye markers. May angle gantry to align eyelid markers to avoid radiation to the lens.
  - **Collimator angle** (of the cranial field) to match diverging spinal fields = arctan(1/2 length superior spine field/SSD).
- **Couch angle** (of the spinal field) to match diverging cranial fields = arctan(1/2 length cranial field/SAD). The foot of couch is rotated toward the side treated. Alternative to couch angle is to beam split lower border of the cranial field to avoid any overlaps at any depth with upper border of the spinal field.
- Various beamsplit techniques may be utilized to avoid overlaps at depth (see Fig. 2.1).
- **Gap shift** = For every 9 Gy, extend the cranial field inferiorly by 1 cm, shift the upper spine field inferiorly by 1 cm, and shorten the lower spine field by 1 cm. Need to recalculate couch angle each time.
- **PF boost**: use 3DCRT and CT/MRI for planning.

**SUPINE TECHNIQUE (SOUTH ET AL. 2008)**

- Patient simulated supine on CT with thermoplastic mask immobilization. Isocenter set at level of C2 vertebral body and marked on mask. Two CT scans then obtained, both covering the isocenter: one of head with 3 mm spacing, one of spine with 5 mm spacing.
- Brain, spinal cord, and OARs outlined on planning CT.
- Brain lateral fields are half-beam blocked and set with Y2 = 20 cm, Y1 = 0 cm.
- An 11° collimator rotation is used to match the beam divergence of the superior border of the spinal field because the spine field isocenter is always located 20 cm inferior to the C2 brain field isocenter. If an inferior spinal field is required, its iso is always located 30 cm inferior to the superior spine field iso. The length of the superior portion of the inferior spine field is adjusted with asymmetric jaws in order to match the inferior limit of the superior spine field at the depth of the posterior surface of the vertebral body at that level. The length of the inferior portion of the inferior spine field is adjusted with asymmetric jaws to cover the caudal extent of the thecal sac.
- All fields use a common 100 cm SAD, so only the couch need be moved longitudinally to treat each field.
- Surface gaps are confirmed with the spine fields in the anterior position as measured from the reconstructed sagittal CT images obtained from the treatment planning system.
- Feathering is accomplished with the use of asymmetric jaws. The inferior jaw of the brain fields is opened by 1 cm every 9 Gy, while the superior border of the superior spinal field is
decreased by 1 cm. The small change in FS is a negligible difference in divergence, so 11° collimation can still be used. With an inferior spine field, the inferior border of the superior spine field is decreased by 1 cm every 9 Gy and the superior border of the inferior field is increased by 1 cm.

Fig. 2.1 Various techniques of cranio-spinal irradiation
All fields are imaged on a daily basis the first week, then weekly thereafter. The anterior surface gaps are checked daily. If the cranial field length exceeds 20 cm, the half-beam blocked fields may be treated at extended SAD with a fixed lateral couch translation.

ALTERNATIVE DELIVERY METHODS

- Protons may be employed to reduce exit dose.
- Tomotherapy may avoid the need to match fields, but greater whole body dose exposure.

PRIMARY SPINAL CORD TUMORS

PEARLS

- Primary spinal cord tumors account for 4% of all CNS tumors overall, and 6% of CNS tumors in children.
- 2/3 extramedullary, 1/3 intramedullary.
- Intramedullary = astrocytoma (most common), ependymoma, and oligodendroglioma.
- Intradural-extramedullary = meningioma, ependymoma, nerve sheath tumors.
- Extradural = metastasis, bone osteogenic sarcoma, chondrosarcoma, chordoma, myeloma, epidural hemangiomas, lipomas, extradural meningiomas, and lymphomas.
- Astrocytomas are more common in C/T spine and frequently associated with cysts.
- Ependymomas are more common in L/S spine.
- Presentation: focal pain, segmental or nerve root weakness, sensory deficit in dermatomal distribution, incontinence.
- Brown-Séquard Syndrome = ipsilateral loss of motor function and fine touch sensation, and contralateral loss of pain and temperature sensation.
- Workup: MRI spine, CSF cytology, MRI brain for ependymoma, lymphoma, AA, metastases and GBM, CT chest for sarcomas, no LP before MRI.
- MRI: nearly all spinal cord tumors enhance with gadolinium, including low-grade gliomas.
- CSF: increased protein, possible xanthochromia (with extradural compression).
### TREATMENT RECOMMENDATIONS

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<td>Observation</td>
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<tr>
<td>Low-grade glioma, STR</td>
<td>RT to 50–54 Gy</td>
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<tr>
<td>High-grade glioma</td>
<td>RT to 54 Gy. Consider adjuvant chemo</td>
<td>5-year OS 0–30% MS 6–24 month</td>
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<td>Ependymoma</td>
<td>RT to 50–54 Gy ± CSI (for documented neuraxis dissemination)</td>
<td>5-year OS 60–100% 5-year DFS 60–90% Low-grade OS: 85–100% High-grade OS: 25–70%</td>
</tr>
<tr>
<td>Meningioma, GTR</td>
<td>Observation</td>
<td></td>
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<tr>
<td>Meningioma, STR</td>
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<tr>
<td>Spinal cord sarcomas, vertebral body chondrosarcomas, chordomas, osteogenic sarcomas</td>
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### ARTERIOVENOUS MALFORMATION

### PEARLS

- Average age 30 year.
- Annual rate of spontaneous hemorrhage ~2–4% with morbidity 20–30% per bleed and mortality 1%/year or 10–15% per bleed.
- There is a period of decreased risk of hemorrhage during latent interval after SRS treatment before complete angiographic resolution.
- After angiographic obliteration, lifetime risk of hemorrhage is ≤1%.
- SRS produces progressive thickening of the vascular wall and luminal thrombosis.
Obliteration takes several years.

Treatment.
- Microsurgical resection or SRS are both options.
- Treat entire nidus, but not feeding arteries or draining veins.
- Tailor dose according to volume and location.
- Maruyama et al. (2005) reviewed 500 patients treated with SRS who were followed with serial exams, MRI and/or angiography. Mean dose 21 Gy. Cumulative 4-year obliteration rate 81%, 5 year 91%. Hemorrhage risk reduced by 54% during latency period and by 88% after obliteration compared to before SRS.
- Obliteration rate at 2-year for lesions <2 cm is 90–100% and for >2 cm is 50–70%.
- F/U: MRI every 6 month × 1–3 year, then annually. Once MRI shows obliteration, obtain angiogram to confirm (gold standard).

TRIGEMINAL NEURALGIA

PEARLS
- Disorder of the sensory nucleus of CN V causing episodic, paroxysmal, severe pain lasting seconds to minutes, followed by a pain free period in the distribution of one or more of its divisions.
- Peak age 60 year. F:M 2:1.
- Often precipitated by stimulation (e.g., shaving, brushing teeth, wind).
- Obtain MRI to rule-out neoplasm in cerebellopontine angle.
- Medical management is standard treatment (carbamazepine, gabapentin, antidepressants, etc.).
- Surgical options include nerve blocks, partial sensory rhizotomy, balloon decompression of the Gasserian ganglion, microvascular decompression, and peripheral nerve ablation (radiofrequency, neurectomy, cryotherapy).
- SRS may also be used with dose of ~80 Gy to 100% isodose line.
- Median time to pain relief with SRS is ~1 month. Approximately 50–60% become pain free, ~10–20% have decreased severity or frequency of pain, and ~5–10% have slight improvement only. Less than 10% developed facial numbness.
REFERENCES


FURTHER READING


