Chapter 3
Intracranial Tumors

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Pearls

Brain Metastases

- Most common intracranial tumor (20–40% of all cancer patients on autopsy); most commonly from lung cancer, breast cancer, or melanoma.
- "Solitary" metastasis: one brain lesion as the only site of disease; "single" metastasis: one brain metastasis, other sites of disease
- Start dexamethasone up to 4 mg q6hrs for neurologic symptoms; no role for steroids in asymptomatic patients. Taper as tolerated once radiotherapy is complete; no evidence for seizure prophylaxis (Table 3.1).
- Prognostic factors include KPS, age, number of brain metastases, and tumor histopathologic characteristics.

Meningioma

- Thirty percent of primary intracranial neoplasms; twofold more likely in women (though with equal incidence rates for anaplastic meningiomas). Pathogenesis

Table 3.1 RTOGRPA for brain metastases (Gaspar et al. 1997)

Class	Characteristics	Survival (months)
I	KPS 70–100	7.1
	Age < 65	
	Primary tumor controlled	
	Metastases to brain only	
II	All others	4.2
III	KPS <70	2.3

Table 3.2 Simpson grading system for meningioma resection

Grade I	Macroscopic complete removal with excision of dural attachment, any abnormal bone, and involved venous sinus(es)
Grade II	Macroscopic complete removal with coagulation of dural attachment
Grade III	Macroscopic complete removal of intradural component(s), without resection or coagulation of dural attachment or extradural extensions
Grade IV	Partial removal with residual intradural tumor in situ
Grade V	Simple decompression with or without biopsy

linked to ionizing radiation, viral infection, sex hormones, NF2, and loss of chromosome 22q.

- Radiosurgery utilized for definitive treatment of WHO grade 1 meningiomas or for adjuvant therapy after subtotal resection (Table 3.2).

Acoustic Neuroma

- Acoustic neuromas (i.e., vestibular schwannomas) arise from myelin sheath Schwann cells surrounding the vestibular nerve; 6–8% of intracranial tumors, overall incidence ~1% on autopsy studies.
- Risk factors include acoustic trauma and coincidence with parathyroid adenoma; bilateral acoustic neuromas pathopneumonic for NF2.
- Both CN VII and VIII may be affected. Symptomatic presentation with hearing loss, tinnitus, vertigo, and unsteady gait. Extension into the cerebellopontine angle may lead to dysfunction of CN V (trigeminal pain) and the facial nerve (facial paresis and taste

disturbances), as well as compression of the posterior fossa (ataxia, hydrocephalus, and death).
- Mean growth rate ~ 2 mm per year, although may remain stable for years.

Paraganglioma

- Rare neuroendocrine tumors with incidence of ~1:1,000,000; sometimes called glomus tumors or chemodectomas as they arise from glomus cells which function as chemoreceptors along blood vessels.
- Can occur in the abdomen (85%), thorax (12%), and the head and neck (3%); usually benign (<5% malignant potential).

Pituitary Adenoma

- Approximately 10% of intracranial tumors (5–25% incidence on autopsy), almost all of which arise in the anterior lobe; 75% functional (30–50% prolactinoma, 25% GH, 20% ACTH, and <1% TSH).
- Microadenoma <1 cm; macroadenoma ≥1 cm.
- Presenting symptoms include headaches, bitemporal hemianopsia and/or loss of color discrimination from optic chiasm compression, hydrocephalus from third ventricle obstruction, and cranial nerve palsies with extension to the cavernous sinus.
- Forbes-Albright syndrome from prolactinoma: amenorrhea-galactorrhea in women, impotence and infertility in men.
- Both mass effect and radiation damage to the pituitary infundibulum can cause an elevation in prolactin due to loss of hypothalamic inhibition (“stalk effect”).

- Hormone levels typically normalize within 1–2 years after radiotherapy.

Arteriovenous Malformation (AVM)

- Abnormal congenital communication between arterial and venous vasculature at a "nidus"; supraphysiologic hydrodynamic gradient.
- Low incidence in the US population (0.14%), but 8% coincidence with cerebral aneurysm.
- Annual rate of spontaneous hemorrhage ~2–6%, with morbidity 20–30% and mortality 10–15% per event; after angiographic obliteration, lifetime risk of hemorrhage ≤1%.
- SRS induces vascular wall hyperplasia and luminal thrombosis, but requires several years to achieve full effect.
- AVMs differ from cavernous malformations insofar as the latter are composed of sinusoidal vessels without a large feeding artery, and therefore have a low-pressure gradient (Table 3.3).

Table 3.3 Spetzler-Martin AVM grading system (total score 1–5)

Size of nidus	<3 cm = 1
	3–6 cm = 2
	>6 cm = 3
Location	Adjacent to non-eloquent brain = 0
	Adjacent to eloquent cortex = 1
Venous drainage	Superficial = 0
	Deep = 1

Neuropathic Facial Pain

Trigeminal Neuralgia

- CN V sensory nucleus disorder resulting in episodic, provokable (i.e., shaving, brushing teeth, wind, etc.), paroxysmal, unilateral, severe, lancinating pain lasting seconds to minutes in the distribution of the trigeminal nerve.
- Predominantly idiopathic, although may be the result of trigeminal nerve compression by an aberrant artery or vein, or demyelination due to multiple sclerosis. Secondary trigeminal neuralgia can develop due to mass effect from meningioma, vestibular schwannoma, AVM, aneurysm, or other lesions.
- Diagnosis of exclusion; obtain MRI to rule out cerebellopontine angle neoplasm.
- Median time to pain relief after SRS is ~1 month; 50–60% CR, 15–20% PR; <10% incidence of facial numbness after treatment.

Cluster Headache

- Sudden onset of unilateral pain typically along the distribution of CN V1; associated with ipsilateral autonomic activity including ptosis, meiosis, lacrimation, conjunctival injection, rhinorrhea, and nasal congestion.
- Etiology unclear; 6:1 male to female predominance.
- GKRS to the trigeminal nerve alone not successful and is associated with much higher rate of toxicity than during SRS for trigeminal neuralgia (Donnet et al. 2006; McClelland et al. 2006). Investigation of SRS to the pterygopalatine ganglion +/− trigeminal nerve root is ongoing (Kano et al. 2011; Lad et al. 2007).

Sphenopalatine Neuralgia (Sluder's Neuralgia)

- Rare craniofacial pain syndrome with 2:1 female predominance associated with unilateral pain in the orbit, mouth, nose, and posterior mastoid process as well as ipsilateral autonomic stimulation from vasomotor activity.
- Etiology unclear, though potentially related to pterygopalatine ganglion irritation from inflammation/infection of the sphenoid or posterior ethmoid sinuses.
- Radiosurgical data limited to case reports of sphenopalatine ganglion treatment (Pollock and Kondziolka 1997).

Other

- Small retrospective series of SRS for residual/recurrent pineal parenchymal tumors, craniopharyngiomas, and neurocytomas with high long-term local control and survival.
- SRS used as salvage treatment for certain functional disorders, including epilepsy, Parkinson disease, and essential tremor with varying efficacy.
- Stereotactic treatment of residual/recurrent glial tumors, medulloblastoma, and other aggressive CNS malignancies has been reported, but outcomes are discouraging. Hypofractionation of recurrent glial tumors is effective as salvage.

Treatment Indications

- In general, SRS+WBRT is associated with longer survival than WBRT alone in patients with single metastases and KPS $\geq$70, improved LC and KPS preservation in patients with 1–4 metastases and KPS $\geq$70, and

potentially, improved survival in patients with KPS <70.

- SRS alone may provide equivalent survival and LC, plus improved neurocognitive outcomes when compared to SRS + WBRT or WBRT alone in patients with ≤3 metastases; close surveillance and salvage treatment are essential.
- After resection, both SRS+WBRT and WBRT alone are acceptable adjuvant strategies, although SRS alone may be used in select cases with minimal intracranial disease and close surveillance (Linskey et al. 2010) (Tables 3.4 and 3.5).

Table 3.4 Radiosurgical treatment indications for brain metastases

Single lesion	Surgical resection + SRS to cavity
RPA class I–II	SRS alone for medically/surgically inoperable cases
2–4 Lesions RPA class I–II	SRS +/− surgical resection with excellent prognosis/KPS
KPS ≤60, extensive intracranial/extracranial disease, and in combination with SRS as described above	WBRT

Table 3.5 Radiosurgical treatment indications for benign intracranial neoplasms

Meningioma	• Recurrent/residual disease after surgery
	• Recurrent disease after prior SRS/RT
	• Medically or surgically inoperable
Acoustic neuroma	• STR (LF 45% without adjuvant RT vs. 6% with postoperative SRS)
	• Patient desire for greater preservation of useful hearing (30–50% with surgery)
Pituitary adenoma	• Adjuvant therapy after STR of macroadenoma with persistent postoperative hypersecretion or residual suprasellar extension
	• Consider medical management with bromocriptine or cabergoline for prolactin-secreting microadenoma
	• Medically inoperable, surgically inaccessible, or anticipated high morbidity due to Spetzler-Martin grade
Neurofacial pain	• Failure of medical management (carbamazepine, phenytoin, gabapentin, baclofen, etc.)
	• Failure of surgical management (radiofrequency rhizotomy, balloon compression, microvascular decompression, etc.)

Workup

- H&P with emphasis on neurologic components.
- Review of systems including any sensory changes, neurologic symptoms, and endocrine abnormalities.
- Laboratories:
  - No routine serum tests necessary for the evaluation of brain metastases, meningioma, AVM, neurofacial pain syndromes, etc.
  - Acoustic neuroma: Audiometry is the best initial screening and typically shows sensorineural hearing loss (as will the Rinne and Weber tests).
  - Pituitary adenomas: Endocrine evaluation with prolactin, basal GH, serum ACTH, free cortisol, dexamethasone suppression, TSH, T3, T4, FSH, LH, plasma estradiol, and testosterone levels.
- Imaging:
  - Thin-cut MRI with T1 pre- and post-gadolinium, T2, and FLAIR (fluid attenuation inversion recovery) sequences; tumor enhancement after gadolinium correlates with breakdown of the blood–brain barrier, abnormal T2 signal indicative of gliosis and/or edema.
  - Can consider increased dose gadolinium at the time of radiosurgery to improve sensitivity of detection of brain metastases.
  - Hemorrhagic metastases most often seen with renal cell cancer, choriocarcinoma, and melanoma.
  - Magnetic resonance spectroscopy: tumors characterized by increased choline (cellularity marker), decreased *N*-acetylaspartic acid (NAA; neuronal marker), and decreased creatinine (cellular energy marker); necrosis associated with increased lactate (anaerobic metabolism), and decreased choline/NAA/creatinine.
  - Dynamic magnetic resonance perfusion: relative cerebral blood flow (CBV) elevated in tumors

(often in concert with grade), and decreased in areas of radiation necrosis and tumefactive demyelination.

- Postoperative MRI should be performed within 48 h of surgery to document residual disease; acute blood appears as increased intrinsic T1 signal pre-contrast.
- "Dural tail sign" can be indicative of either tumor extension or vascular congestion associated with tumors adjacent or intrinsic to the meninges (seen with 60% of meningiomas).
- Meningiomas are isointense on T1 and T2 and intensely enhance with gadolinium; evidence of bony destruction or hyperostosis in 15–20% of cases. Acoustic neuroma: seen as enhancing "ice cream cone" in the internal acoustic canal or as "dumbbell" projecting into the foramen magnum.
- Pituitary adenomas: X-ray skeletal survey should be performed in cases of acromegaly to evaluate growth plates.
- AVM: Co-registration of cerebral angiography and time of flight MRI sequences helpful for target delineation.
- Neuropathic facial pain: Thin slice (1 mm) MRI/MRA has sensitivity and specificity of 89% and 50%, respectively, for identifying vascular compression of the trigeminal nerve.

Radiosurgical Technique

- Simulation and treatment planning.
  - Simulation with stereotactic frame or mask depending on treatment modality.
  - Primary MRI planning with thin cuts (1–2 mm) preferred for intracranial radiosurgery, with fusion of preoperative scans if available.

- If necessary, CT slices no thicker than 2 mm should be obtained and co-registered with MRI images.
- Target volumes:
  - Brain metastases: GTV alone for intact lesions. For resection cavities, a 1–2 mm margin may increase local control (Soltys et al. 2008). Consensus guidelines recommend 5–10 mm expansion along the dura underlying the bone flap to account for microscopic disease.
  - Meningioma, acoustic neuroma, pituitary adenoma, and other benign intracranial tumors: GTV with 0–2 mm margin depending on degree of immobilization and stereotaxis.
  - Trigeminal neuralgia: Target ipsilateral trigeminal nerve adjacent to the pons in the retrogasserian cistern with a single, 4 mm shot. Retreatment isocenter should be located 2–3 mm away from initial target if possible.

- Dose prescription:
  - See Table 3.6.
  - Consider hypofractionation in select cases if dose constraints to critical structures cannot be met with single-fraction treatment.
- Dose delivery.
  - Multiple treatment modalities available, but most centers employ GK SRS, frameless robotic radiosurgery, and/or linac-based SRS.

Table 3.6 Dose recommendations and outcomes for intracranial stereotactic radiosurgery

Presentation	Recommended dose	Outcomes
Brain metastases	• 13–24 Gy/1 fraction depending on tumor volume/location • Dose reduction or hypofractionation (21–30 Gy/3–5 fractions) with larger lesions and/or resection cavities • Consider dose reduction (15–16 Gy) for brainstem lesions	
Meningioma	• Individualize dose based on tumor volume/location/ surgical/radiosurgical history • 15 Gy/1 fraction for WHO grade I–III lesions; hypofractionation to 25–30 Gy/5 fractions possible, although long-term results unknown (UCSF experience). • Grade III lesions may require higher dose	Long-term LC >90% for WHO grade I lesions

(continued)

Table 3.6 (continued)

Presentation	Recommended dose	Outcomes
Acoustic neuroma	• 12–13 Gy/1 fraction	LC and preservation of CNs V and VII in excess of 95%; hearing preservation ~75%
	• 18–25 Gy/3–5 fractions	Appears safe and effective, but long-term results are unknown
Paraganglioma	• 15 Gy/1 fraction or hypofractionation to 25 Gy/5 fractions	LC ~100%
Pituitary adenoma	• Nonfunctioning tumors: 12–20 Gy/1 fraction	
	• Functioning tumors: 15–30 Gy/1 fraction (maximal safe dose); discontinue medical therapy 4 weeks prior to radiosurgery.	
	• Single-fraction optic apparatus tolerance: 8 Gy	
	• 21–25 Gy/3–5 fractions	Appears safe and effective, but long-term results unknown

(continued)

Table 3.6 (continued)

Presentation	Recommended dose	Outcomes
AVM	• Individualize dose based on tumor volume; staged radiosurgery for larger lesions	2-Year obliteration rate for single-fraction treatment: <2 cm 90–100%, >2 cm 50–70%
	• 18 Gy/1 fraction for 8 cm^3 target(s); dose escalation when feasible and safe (UCSF experience)	
Trigeminal neuralgia	• Primary: 70–90 Gy (100% isodose line)	Pain relief in ~30–80% of patients, although retreatment common; dose related to both relief from symptoms and development of new symptoms
	• Retreatment: 50–70 Gy (100% isodose line)	
Pineal tumors	• Fractioned neuraxial RT for high-grade lesion; 15 Gy SRS reserved for residual tumor or local recurrence after RT	

Toxicities and Management

- Stereotactic frame:
  - Mild headache immediately following frame removal, usually subsiding within 60 min.
  - Minimal bleeding from pin insertion sites requiring compression.
  - Peri-orbital edema resolving with head elevation and warm compress.
  - <1% Risk of superficial skin infection.
- Acute (1 week to 6 months):
  - Alopecia and skin changes following treatment of superficial lesions.
  - Mild fatigue.
  - Transient worsening of neurologic symptoms due to edema potentially requiring steroids.
- Late (>6 months):
  - Radiation necrosis: Overall five-percent rate of symptomatic brain necrosis after SRS; typically resolves with steroids, but may require surgical intervention.
  - Endocrine abnormalities.
  - Cranial nerve dysfunction following treatment of skull base tumors.
  - Rare: memory impairment and cavernous malformations.
  - Isolated case reports of stroke, facial palsy/hyperesthesia, vision loss, and eye dryness after SRS for trigeminal neuralgia, all of which are very rare.

Recommended Follow-Up

- Brain metastases and other high-grade lesions:
  - MRI 4–12 weeks after treatment, then every 2–3 months for the first 2-years, followed by imaging

every 6 months for the next 3 years, and yearly thereafter; imaging intervals should be individualized according to clinical symptoms and lesion trajectory.

- Low-grade lesions (meningioma, acoustic neuroma, paraganglioma, etc.):
  - MRI every 6–12 months for the first 2-years, then annually; imaging intervals should be individualized according to clinical symptoms and lesion trajectory.
- Pituitary adenoma and other peri-sellar lesions:
  - Endocrine testing every 6–12 months with visual field testing annually.
- Acoustic neuromas and cerebellopontine angle tumors:
  - Formal audiometry annually.
- AVM:
  - MRI up to once per year for 3 years after treatment, with angiogram to confirm response after 3 years.
- Neuropathologic facial pain and functional disorders:
  - Clinical follow-up only.

Evidence

Brain Metastases

SRS Boost with WBRT

- RTOG 95-08 (Andrews et al. 2004): Randomized, multi-institution trial including 333 patients with 1–3 brain metastases and KPS ≥70 treated with WBRT (37.5 Gy/15 fractions) plus SRS (15–24 Gy/1 fraction) vs. WBRT alone. Significant survival advantage with SRS in patients with a single metastasis on univariate analysis (6.5 vs. 4.9 months), RPA class I on multivariate analysis (11.6 vs. 9.6 months), and trends for advantage with lung histology (5.9 vs. 3.9 months), and tumor size >2 cm (6.5 vs. 5.3 months). WBRT+SRS also associated with significantly higher 1-year LC (82% vs. 71%), and

improved KPS (13% vs. 4%) with decreased steroid use at 6 months. Minimal acute- and long-term toxicity.

- University of Pittsburgh (Kondziolka et al. 1999a, b): Randomized trial of 27 patients with 2–4 brain metastases and KPS ≥70 treated with WBRT (30 Gy/12 fractions) plus SRS (16 Gy/1 fraction) vs. WBRT alone. Study stopped early due to significant interim benefit in LC for WBRT+SRS (100% vs. 8%); median time to LF 6 months with WBRT vs. 36 months with WBRT+SRS. No difference in OS (8 vs. 11 months), and survival equal (~11 months) when accounting for SRS salvage in WBRT arm. No difference in OS or LC depending on histological type, number of brain metastases, or extent of extracranial disease.

SRS Alone or With WBRT

- RTOG 90-05 (Shaw et al. 2000): Dose escalation study including 156 patients (36% recurrent primary brain tumors, median prior dose of 60 Gy; 64% recurrent brain metastases, median prior dose of 30 Gy). Maximum tolerated doses of 24 Gy, 18 Gy, and 15 Gy for tumors ≤20 mm, 21–30 mm, and 31–40 mm in diameter, respectively; MTD for tumors <20 mm likely higher, but investigators reluctant to escalate further. Tumor diameter ≥2 cm significantly associated with increasing risk of grade ≥3 neurotoxicity on multivariate analysis; higher dose and KPS also associated with greater neurotoxicity. Actuarial 24-month risk of radionecrosis 11%. Patients with primary brain tumors and those treated on linear accelerators (as opposed to GKRS) had ~2.8-fold greater chance of local progression.
- JROSG 99-1 (Aoyama et al. 2006): Randomized, multi-institution trial including 132 patients with 1–4 brain metastases (diameter < 3 cm) and KPS ≥70, treated with SRS (18–25 Gy/1 fraction) vs. WBRT (30 Gy/10 fractions) followed by SRS. Trial stopped

early due to low probability of detecting a difference between arms. Addition of WBRT reduced rate of new metastases (64% vs. 42%) and need for salvage brain treatment, and improved 1-year recurrence rate (47% vs. 76%). No difference in OS (~8 months), neurologic or KPS preservation, or MMSE score.

- MDACC (Chang et al. 2009): Randomized trial including 58 patients with 1–3 brain metastases and KPS ≥70 treated with SRS (15–24 Gy/1 fraction) vs. SRS + WBRT (30 Gy/12 fractions) and followed with formal neurocognitive testing. Trial stopped early due to significant decline in memory and learning at 4 months with WBRT by Hopkins Verbal Learning Test (52% vs. 24%). However, WBRT also associated with improved LC (100% vs. 67%) and distant brain control (73% vs. 45%) at 1 year. Significantly longer OS with SRS alone (15 vs. 6 months), but patients in this arm received more salvage therapy including repeat SRS (27 vs. 3 retreatments).
- UCSF (Sneed et al. 1999): Retrospective review of GKRS (n = 62) vs. GKRS+WBRT (n = 43); treatment characteristics individualized according to physician preference. OS (~11 months) and 1-year local FFP (71% vs. 79%) equivalent. Although brain FFP significantly worse for SRS alone (28% vs. 69%), no difference when allowing for first salvage (62% vs. 73%) after 1 year.
- Sneed et al. (2002): Retrospective, multi-institution review of 569 patients with brain metastases treated with SRS alone (n = 268) vs. WBRT+SRS (n = 301); exclusion criteria included resection of brain metastasis and interval from end of WBRT to SRS >1 month. Median and overall survival no different among respective RPA statuses (I: 14 vs. 15 months; II: 8 vs. 7 months; class III: ~5 months). Twenty-four percent WBRT salvage rate in SRS patients.
- EORTC 22951-26001 (Kocher et al. 2011): Randomized, multi-institution trial of WBRT (n = 81, 30 Gy/10

fractions) vs. observation (n = 79) following either surgery or SRS for 1–3 brain metastases in patients with stable systemic disease and ECOG performance status 0–2. Median time to ECOG performance status deterioration >2: 10 months with observation and 9.5 months with WBRT. OS similarly equivalent (~11 months), although WBRT reduced 2-year relapse at both new and initial sites. Salvage therapies used more frequently in the observation arm.

- University of Cologne (Kocher et al. 2004): Retrospective review of patients with 1–3 previously untreated cerebral metastases treated with linac-based SRS (n = 117, median dose 20 Gy/1 fraction) or WBRT (n = 138, 30–36 Gy/10 fractions) stratified by RPA class. Rate of salvage WBRT: SRS group 22%, WBRT group 7%. Significantly longer survival after SRS in RPA class I (25 vs. 5 months) and class II (6 vs. 4 months) patients; no difference in RPA class III patients (4 vs. 2.5 months).
- NCCTG (Brown et al. 2016): Prospective phase III trial randomizing participants to SRS alone or SRS plus WBRT for 1–3 brain metastases with primary endpoint of neurocognitive deterioration at 3 months. Overall 213 participants showed less cognitive deterioration at 3 months after SRS alone (63.5%) compared to SRS and WBRT (91.7%) $p < 0.001$. Time to intracranial failure was significantly shorter for SRS alone (HR 3.6; $p < 0.001$), with no significant difference in OS at 10.4 months for SRS alone and 7.4 months for SRS plus WBRT ($p = 0.92$).

SRS for >4 Brain Metastases

- University of Pittsburgh (Bhatnagar et al. 2006): Retrospective review of 105 patients with ≥4 brain metastases (median 5, range 4–18) treated with single-session GKRS (median marginal dose 16 Gy/1 fraction) plus WBRT (46%), after failure of WBRT (38%), or

alone (17%). Median OS 8 months (RPA class I: 18 months, class II: 9 months, and class III: 3 months), 1-year LC 71%, and median time to progression or new brain metastases 9 months. Total treatment volume, age, RPA classification, and median marginal dose (but not the total number of metastases treated) are all significant prognostic factors on multivariate analysis.

- JLGK0901 (Yamamoto et al. 2014): Prospective observational cohort of 1194 patients treated with SRS to 1–10 brain metastases, analyzed by number of metastases (1, 2–4, and 5–10). Median OS for 1 brain metastasis 13.9 months, 2–4 metastases 10.8 months, 5–10 metastases 10.8 months, with non-inferiority being demonstrated between SRS treatment of 5–10 lesions compared to 2–4 ($p < 0.0001$ uskom for non-inferiority). No significant difference demonstrated the number of treatment related adverse events in either group with multiple brain metastases ($p = 0.89$).

SRS Boost After Resection

- Stanford (Soltys et al. 2008): Retrospective review of 76 resection cavities treated with SRS (median marginal dose 18.6 Gy, mean target volume 9.8 cm^3). Actuarial LC at 6 and 12 months: 88 and 79%, respectively. Conformality index significantly correlated with improved LC on univariate analysis; LC 100% for the least conformal quartile, and 63% for all others. Target volume, dose, and number of fractions are not significant. Recommendation for 2 mm margin around resection cavities.
- NCCTG N107C (Brown et al. 2017): Prospective phase III trial of patients with resected brain metastasis randomized to SRS versus WBRT, primary outcomes were neurocognitive deterioration free survival and OS. Accrued 194 patients with median follow-up of 11.1 months (IQR 5.1-18), SRS associated with less

frequent neurocognitive decline at 6 months (52% vs. 85%; $p = 0.00031$), with no significant difference in OS between the two groups (12.2 m vs. 11.6 m; $p = 0.70$).

- MDACC (Mahajan et al. 2017): Single-institution phase III trial of 132 patients randomized to postoperative SRS versus observation for 1–3 resected brain metastases. Median follow-up of 11·1 months (IQR 4·8-20·4) with 12-month FFLR of 43% (95% CI 31–59) for the observation group and 72% (60–87) for the SRS with HR 0·46 [95% CI 0·24–0·88]; $p = 0·015$) favoring SRS. No significant difference in OS was seen between observation and SRS (HR 1.26; 95% CI 0·84–1·98).
- Soliman et al. (2018): Expert consensus guidelines for target delineation of postoperative surgical cavity, using ten example clinical scenarios. High level of agreement between experts with recommendation for inclusion of the entire surgical tract, extension of CTV 5–10 mm along overlaying dura due to risk of microscopic disease, ≤5 mm extension into venous sinus when there is preoperative contact.

Brainstem Lesions

- Chen et al. (2021): Systematic review and comparative meta-analysis of SRS to brainstem metastases. Inclusive of 32 retrospective studies comprising 1446 patients with 1590 brainstem metastases treated to a median marginal dose of 16 Gy (range 6–39 Gy) in a median of 1 (range 1–13) fractions. Rate of local control at 1-year was 86% (95% CI 83–88%), with symptomatic improvement in 55% (95% CI 47–63%), and OS at 1-year was 33% (95% CI 30–37%). Toxicity of any grade was found in 5.6% of patients, with 2.4% (95% CI 1.5–3.7%) developing grade 3–5 toxicity including 1.1% of patients developing symptomatic radionecrosis.

Salvage After SRS

- Zindler et al. (2014): Retrospective review of 443 patients with 1–3 brain metastases treated with RS alone. Salvage treatment for distant brain recurrence (DBR) in 25% of patients, 70% of which had ≤3 lesions. Actuarial DBR rates at 6, 12, and 24 months after primary SRS were 21, 41, and 54%, respectively. Median time to DBR: 5.6 months. DBR-RPA classes: I = WHO 0 or 1, ≥6 months from RS (OS 10 months); II = WHO 0 or 1, <6 months from RS (OS 5 months); III = WHO ≥2 (OS 3 months).
- Wake Forest (Farris et al. 2017): Retrospective evaluation of 737 patients treated with brain metastases with SRS alone, proposed metric of brain metastasis velocity (BMV) equal to the number of new brain metastases after SRS over time in years. Low-, intermediate-, and high-risk categories had significant difference in OS at 12.4 months (95% CI: 10.4–16.9), 8.2 months (95% CI, 5.0–9.7), and 4.3 months (95% CI: 2.6–6.7) respectively. Lower BMV was associated with decreased use of salvage WBRT ($p = 0.02$) and lower risk of neurological death (p = 0.008).

Meningioma

- Mayo Clinic (Stafford et al. 2001): Retrospective review of 190 consecutive patients with 206 meningiomas treated by SRS (median marginal dose 16 Gy; median target volume 8.2 cm^3). Prior surgery in 59% of patients; 12% of lesions with atypical or anaplastic histology; 77% of tumors involved the skull base. Five-year CSS for benign, atypical, and anaplastic tumors was 100, 76, and 0%, respectively; LC 93, 68, and 0%, respectively. Complications attributed to SRS in 13% of patients (CN deficits in 8%, symptomatic parenchymal changes in 3%, carotid artery stenosis in

1%, and cyst formation in 1%); decrease in functional status related to radiosurgery in six patients.

- University of Pittsburgh (Kondziolka et al. 1999a, b): Retrospective review of 99 consecutive patients treated with SRS (43%) or surgery followed by SRS (57%). Median marginal dose 16 Gy; median target volume 4.7 cm^3. Five patients previously treated with conventional RT; 89% of tumors adjacent to the skull base. At 10 years, 11% LF; PFS worse in patients with prior resections and multiple meningiomas. New or worsening neurologic symptoms in 5% of patients. By survey, 96% of patients considered treatment a success.

WHO Grade 1 Meningioma

- Germany (Fokas et al. 2014): Retrospective review of 318 patients with histologically confirmed (45%) or radiographically presumed (55%) benign meningioma treated with fractionated stereotactic RT (80%; median dose 55.8 Gy/31 fractions), hypofractionated stereotactic RT (15%; 40 Gy/10 fractions or 25–35 Gy/5–7 fractions), or SRS (5%) based on tumor size and proximity to critical structures. With median follow-up 50 months, 5- and 10-year LC, OS, and CSS were 93, 89, and 97%; and 88, 74, and 97%, respectively. On multivariate analysis, tumor location and age >66 years were significant predictors of LC and OS, respectively. Acute worsening of neurologic symptoms and/or clinically significant acute toxicity after RT in 2% of patients; no late grade ≥3 toxicity.
- University of Pittsburgh (Kondziolka et al. 2014): Retrospective review of 290 benign meningioma patients treated with GKRS (median marginal dose 15 Gy, median target volume 5.5 cm^3). Prior fractionated RT in 22 patients, STR in 126 patients, and recurrence after GTR in 22 patients. Overall tumor control 91%; 10- and 20-year actuarial PFS from the treated lesion were both 87%. Among symptomatic patients, 26%

improved, 54% remained stable, and 20% had a gradual worsening. No significant difference in control with prior craniotomy vs. primary GKRS; PFS worse in those with prior RT and higher-grade lesions.

- Santacroce et al. (2012): Retrospective, multicenter review of 4565 consecutive patients with 5300 benign meningiomas treated with GKRS (median marginal dose 14 Gy; median target volume 4.8 cm^3). Results of 3768 lesions with >24 months follow-up reported. Tumor size decreased in 58% of cases, remained unchanged in 34%, and increased in 8%; overall control rate 92%. Five- and 10-year PFS 95 and 89%, respectively. Tumor control higher for presumed meningiomas vs. histologically confirmed grade I lesions, female vs. male patients, sporadic vs. multiple meningiomas, and skull base vs. convexity tumors. Permanent morbidity in 6.6%.
- Prague (Kollová et al. 2007): Retrospective review of 400 benign meningiomas in 368 patients treated with SRS (median marginal dose 12.5 Gy; median target volume 4.4 cm^3). With median follow-up of 5 years, 70% of tumors decreased in size, 28% remained stable, and 2% increased in size. Actuarial LC 98%; worse in men and with <12 Gy. Temporary toxicity in 10% and permanent in 6%. Peritumoral edema worse with >16 Gy, age >60 years, no prior surgery, preexisting edema, tumor volume >10 cm^3, and anterior fossa location.
- Mayo Clinic (Pollock et al. 2003): Retrospective review of 198 benign meningiomas <3.5 cm^3 in mean diameter treated surgically (n = 136) or with primary SRS (n = 62; mean marginal dose 18 Gy). No statistically significant difference in 3- and 7-year PFS for Simpson Grade I resections (100 and 96%, respectively) and SRS (100 and 95%, respectively). SRS associated with superior PFS relative to Simpson Grade ≥2 resections, and relative to surgery in general, fewer adjuvant treatments (3% vs. 15%) and fewer complications (10% vs. 22%).

- RTOG 0539 Low Risk (Rogers et al. 2020a, b): Phase II prospective cohort of observation after GTR or STR of a WHO grade 1 meningioma. Overall 60 patients eligible for analysis with 58 (93.4%) having undergone GTR, the 5-year and 10-year PFS were 89.4% and 85.0%. In patients with confirmed STR, 10-year PFS was 72.7%, with no incidence of grade 4 or 5 adverse events, reflecting the good outcomes for low-risk GTR meningioma but raise questions about management after STR.

WHO Grade 2 and 3 Meningioma

- Northwestern University (Kaur et al. 2014): Systematic review from 1994 to 2011 analyzing 21 English-language studies reporting tumor characteristics, treatment parameters, and clinical outcomes for atypical and malignant (anaplastic) meningiomas treated with adjuvant RT or SRS. Median 5-year PFS and OS for atypical lesions after adjuvant RT were 54 and 68%, respectively; anaplastic lesions: 48 and 56%, respectively. Outcomes data identified for only 23 patients treated with SRS (median marginal dose 18–19 Gy), generally with poor outcomes.
- UCSF (Kaprealian et al. 2016): Retrospective analysis of 280 patients with 438 meningioma. 5-year FFP for WHO grade 2 and 3 meningioma were 56% and 47%, respectively. Of WHO grade 3 meningiomas 87% failed within the prior SRS target volume, with 13% failing immediately adjacent to the volume. On MVA poorer FFP was associated with larger target volume and SRS after prior radiotherapy versus after prior surgery alone. No association was demonstrated between SRS dose and improved FFP for any grade meningioma.
- RTOG 0539 Intermediate Risk (Rogers et al. 2018): Phase II trial of conventionally fractionated RT (54 Gy in 30 Fx) for recurrent WHO grade 1 meningioma, and

WHO grade 2 meningioma with a GTR. Primary outcome 3-year PFS, actuarially 93.8% with no significant difference in PFS between participants with benign or atypical tumors ($p = 0.52$, HR 0.56), with no grade 3+ reported adverse events.

- RTOG 0539 High Risk (Rogers et al. 2018): Phase II trial of adjuvant radiation for recurrent atypical, STR atypical, or anaplastic meningioma. All participants received 60 Gy in 30 fractions, with large margins (1–2 cm) including extension beyond anatomic boundaries. Overall 57 patients enrolled with median follow-up of 4 years, with primary outcome being 3-year PFS at 58.8%, LC at 3-years was 68.9%, and OS was 78.6%. Overall, 1 patient (1.9%) experienced a late grade 5 AE due to radionecrosis. Adjuvant radiotherapy showed acceptable rates of toxicity with ongoing need for improvement in outcomes in this cohort of patients.

Skull Base

- NAGKC (Sheehan et al. 2014): Multi-institutional, retrospective review of 763 patients with sellar and/or parasellar meningiomas treated with GKRS (median marginal dose 13 Gy; median target volume 6.7 cm^3); 51% prior resection, and 4% prior RT. Median follow-up 67 months. Actuarial PFS at 5 and 10 years 95 and 82%, respectively; significant predictors of progression included >1 prior surgery, prior RT, and tumor marginal dose <13 Gy. Stability or improvement in neurologic symptoms in 86% of patients; CN V and VI improvement in 34% with preexisting deficits. Progression of existing neurologic symptoms in 14% of patients; new or worsening CN deficits in 10% (most likely CN V dysfunction). New or worsening endocrinopathy in 1.6% of patients.
- NAGKC (Starke et al. 2014): Multi-institution, retrospective review of 254 patients with radiographically

presumed (55%) or histologically confirmed (45%) benign petroclival meningioma treated with GKRS upfront (n = 140) or following surgery (114). Mean marginal dose 13.4 Gy; mean target volume 7.5 cm^3. With mean follow-up of 71 months, 9% of tumors increased in size, 52% remained stable, and 39% decreased; 94% of patients had stable or improved neurologic symptoms. PFS at 5 and 10 years was 93 and 84%, respectively. Multivariate predictors of favorable outcome included small tumor volume, female gender, no prior RT, and lower maximal dose.

- Park et al. (2014): Retrospective review of 74 patients with cerebellopontine angle (CPA) meningioma treated with GKRS; median marginal of dose 13 Gy, median target volume 3 cm^3. With median follow-up 40 months, 62% of tumors decreased in size, 35% remained stable, and 3% increased. PFS at 1 and 5 years was 98 and 95%, respectively. Neurological improvement in 31%, stability in 58%, and worsening of symptoms in 11% of patients (most likely trigeminal neuralgia); rate of improvement 1, 3, and 5 years after GKRS was 16, 31, and 40%, respectively. Asymptomatic peritumoral edema in 5% of patients; symptomatic adverse radiation effects in 9%.

Ongoing

- EORTC-1308/ROAM: Multicenter randomized controlled trial running in the United Kingdom evaluating the use of adjuvant radiation therapy versus observation in WHO grade II meningioma after GTR. Radiation therapy consists of 60 Gy in 30 fractions within 8–12 weeks of resection. Target accrual of 190 patients, currently enrolling.
- NRG-BN003: Multicenter randomized phase III trial evaluating observation versus adjuvant radiation therapy after GTR of WHO grade II meningioma.

Primary end point is PFS with radiation therapy consisting of 59.4 Gy in 33 fractions with target accrual of 148 patients, currently enrolling.

Acoustic Neuroma

- University of Pittsburgh (Lunsford et al. 2005): Retrospective review of GKRS outcomes for 829 vestibular schwannoma patients; median marginal dose 13 Gy, mean target volume 2.5 cm^3. Ten-year tumor control rate 97%; hearing preservation 77%. Toxicity notable for <1% facial neuropathy and <3% trigeminal symptoms.
- University of Pittsburg (Johnson et al. 2019): Retrospective review of long-term outcomes for 871 vestibular schwannoma patients, median follow-up 5.2 years (range 1–25). PFS 97% at 3 years, 95% at 5 years, and 94% at 10 years, with rates of serviceable hearing preservation of 68.4% at 5 years and 51.4% at 10 years. Overall 51 patients (5.8%) developed trigeminal neuropathy and 11 patients (1.3%) required surgical intervention for progression after SRS.

Surgery vs. SRS

- Marseille, France (Régis et al. 2002): Non-randomized, prospective series of GKRS (n = 97) vs. microsurgery (n = 110) for vestibular schwannoma with preoperative and postoperative questionnaire assessment. Median follow-up 4 years. GKRS universally superior in terms of facial motor function (0% vs. 37%), CN V disturbance (4% vs. 29%), hearing preservation (70% vs. 38%), overall functionality (91% vs. 61%), duration of hospitalization (3 vs. 23 days), and mean time missed from work (7 vs. 130 days).

Hypofractionated Stereotactic RT vs. SRS

- Amsterdam (Meijer et al. 2003): Prospective trial of single-fraction (n = 49) vs. fractionated linac-based SRS (n = 80) for acoustic neuroma; mean tumor diameter ~2.5 cm. Dentate patients treated with 20–25 Gy/5 fractions, and edentate patients treated with 10–12.5 Gy/1 fraction to the 80% isodose line. Median follow-up 33 months. Excellent tumor control (100% vs. 94%), preservation of hearing (75% vs. 61%), preservation of CN V (92% vs. 98%, statistically significant difference), and preservation of CN VII (93% vs. 97%) with both modalities.
- Japan (Morimoto et al. 2013): Retrospective review of 26 vestibular schwannomas treated with hypofractionated robotic radiosurgery to 18–25 Gy/3–5 fractions (median target volume 2.6 cm^3). Progression defined as ≥2 mm 3D post-treatment tumor enlargement. Seven-year PFS and LC were 78 and 95%, respectively. Six reports of late grade ≥3 toxicity. Formal audiometric testing demonstrated 50% retention of pure tone averages.

Proton Beam Radiosurgery

- Harvard (Weber et al. 2003): Eighty-eight consecutive patients with vestibular schwannoma treated with 3 converging beams aligned to fiducial markers in the calvarium; maximum dose 13 Gy RBE, median target volume 1.4 cm^3. Actuarial 5-year tumor control 94%, and preservation of CN's V and VII 89 and 91%, respectively, but serviceable hearing preservation 33%. Proton beam radiosurgery now only used for tumors <2 cm, and in patients without functional hearing.

Paraganglioma

- Pollock (2004): Retrospective, single-institution review of 42 patients with glomus jugulare tumors treated with single-session GKRS; mean marginal dose of 15 Gy, mean volume 13 cm^3. With median follow-up of 3.7 years, 31% decreased in size, 67% remained stable, and 2% progressed. Seven- and 10-year PFS were 100 and 75%, respectively. Hearing preservation 81% at 4 years, with 15% of patients developing new deficits including hearing loss, facial numbness, vocal cord paralysis, and vertigo.
- Mayo Clinic (Patel et al. 2018): Single-institution retrospective review of 85 patients treated from 1990 to 2017 with GKSRS with median follow-up of 66 months (range 7–202) and a median tumor volume of 11.6 cm^3. Five-year PFS was 98% with median marginal dose to the tumor of 16 Gy (range 12–18 Gy) in a single fraction. Overall, 1 (1%) patient required salvage with EBRT, and 2 (3%) patients experienced clinically worsening neuropathy resulting in vocal cord paralysis (CN X).

Hypofractionation

- Chun et al. (2014): Retrospective, single-institution review of 31 patients with skull base paragangliomas treated with robotic radiosurgery to a total dose of 25 Gy/5 fractions. With median follow-up 24 months, OS and LC were both 100%; tinnitus improved in 60% of patients. Overall tumor volume decreased by 37% (49% when analyzing subset of patients with ≥24-month follow-up). No grade ≥ 3 toxicity.

Surgery vs. SRS

- Gottfried et al. (2004): Meta-analysis of 7 surgical series (374 patients) and 8 GKRS series (142 patients) of glomus jugulare tumors; mean follow-up 4 and 3 years, respectively. LC 92% with surgery, 97% with GKRS. Complications notable for 8% morbidity from GKRS, 8% CSF leak from surgery, and 1.3% surgical mortality. Conclusion that both treatments are safe and efficacious, although inaccessibility of skull base limits selection of surgical candidates.

Pituitary Adenoma

- Sheehan et al. (2005a, b)): Systematic review of 35 peer-reviewed studies involving 1621 patients with pituitary adenoma treated with SRS. LC >90% achieved in most studies, with mean marginal dose ranging from 15 to 34 Gy/1 fraction. Weighted mean tumor control rate for all published studies 96%. Sixteen cases of damage to the optic apparatus with doses ranging from 0.7 to 12 Gy. Twenty-one new neuropathies from CN dysfunction, nearly half of which were transient. Risks of hypopituitarism, RT-induced neoplasia, and cerebral vasculopathy lower with SRS than historical rates with fractionated RT. Heterogeneous quantification of endocrinological remission for Cushing disease, acromegaly, prolactinoma, and Nelson syndrome, with wide variation of endocrine control. Hormone improvement anywhere from 3 months to 8 years after SRS, although levels typically normalize within 2 years.

Hypofractionation

- Iwata et al. (2011): Single-institution retrospective review of 100 patients with recurrent/residual nonfunctioning pituitary adenomas without a history of prior RT treated with SRS to 21–25 Gy/3–5 fractions; median target volume 5.1 cm^3. Three-year OS and LC both 98%. One case of visual disturbance after treatment, three cases of hypopituitarism in patients not previously on hormone replacement therapy, and three cases of transient cyst enlargement.

Hormone Control and Risk of Hypopituitarism

- Xu et al. (2013): Retrospective, single-institution review of 262 pituitary adenoma patients treated by SRS with thorough endocrine assessments immediately before treatment, and then again at regular follow-up intervals. Tumor control 89% and remission of endocrine abnormalities in 72% of functional adenoma patients. Thirty percent rate of new hypopituitarism; increased risk with suprasellar extension and higher marginal dose, but not with tumor volume, prior surgery, prior RT, or age at SRS.
- Mayo Clinic (Graffeo et al. 2018): Retrospective review of 97 patients with pituitary adenoma undergoing single-fraction SRS with at least 24 months of endocrine follow-up. Overall median follow-up of 48 months (IQR 34–68) with 27 (28%) patients developing pituitary insufficiency at a median of 22 months. Hypopituitarism with a mean gland dose of <11.0 Gy was 5% (95% CI 0–11%) at 5 years and for a mean gland dose of ≥11.0 Gy was 51% (95% CI 34–65%) at 5 years. Pituitary dysfunction increases in a time and dose-dependent manner after SRS for pituitary adenoma.

Vascular Malformations

Arteriovenous Malformation (AVM)

- Tokyo, Japan (Maruyama et al. 2005): Retrospective, single-institution review of 500 AVM patients status post-definitive treatment with GKRS (mean dose 21 Gy; median Spetzler-Martin grade III). Pre-GKRS rate of spontaneous hemorrhage ~6%; cumulative 4-year obliteration rate 81%, 5-year rate 91%. Hemorrhage risk reduced by 54% during the latency period post-GKRS/pre-obliteration, and 88% after obliteration; greatest risk reduction in those who initially presented with hemorrhage.
- University of Maryland (Koltz et al. 2013): Retrospective review of 102 patients treated with single-fraction or staged SRS for AVM's stratified by Spetzler-Martin grade. With mean follow-up of 8.5 years, overall nidus obliteration was 75% with 19% morbidity, both of which correlated with Spetzler-Martin grade. For Grade I–V lesions, obliteration achieved in 100, 89, 86, 54, and 0% of cases. For AVMs that were not completely obliterated, the mean reduction in nidus volume was 69%.
- University of Virginia (Ding et al. 2014): Retrospective review of 398 Spetzler-Martin grade III AVMs treated with SRS (median target volume 2.8 cm^3, median prescription 20 Gy). With median 68 months clinical follow-up, complete obliteration in 69% of lesions after median of 46 months from SRS. Significant predictors of response included prior hemorrhage, size <3 cm, deep venous drainage, and eloquent location. Annual risk for hemorrhage during the latency period was 1.7%. Symptomatic radiation-induced complications in 12% of patients (permanent in 4%); independent predictors included absence of pre-SRS rupture and presence of a single draining vein.

Conclusion: SRS for Spetzler-Martin grade III lesions is comparable to surgery in long term.

- Harvard (Hattangadi-Gluth et al. 2014): Retrospective review of 248 consecutive patients with 254 cerebral AVMs treated with single-fraction proton beam stereotactic radiosurgery; median target volume 3.5 cm^3, 23% in eloquent/deep locations, and median prescription dose 15 Gy RBE. With median 35 months follow-up, 65% obliteration rate, median time to obliteration 31 months; 5- and 10-year cumulative incidence of total obliteration was 70 and 91%, respectively. Univariate and multivariate analyses showed location and smaller target volume to be independent predictors of total obliteration; smaller volume and higher prescription dose also significant on univariate analysis.
- Harvard (Barker et al. 2003): Retrospective review of toxicity data in 1250 AVM patients treated with stereotactic proton beam radiosurgery. Median follow-up 6.5 years, median dose 10.5 Gy, median target volume 33.7 cm^3 (23% <10 cm^3). Permanent radiation-related deficits in 4% of patients; median time to complications 1.1 years. Complication rate related to dose, volume, deep location, and age; rate <0.5% with <12 Gy.
- Nagasaki, Japan (Matsuo et al. 2014): Median 15.6-year results of 51 AVM patients treated with linear accelerator-based radiosurgery; median prescription 15 Gy, median target volume 4.5 cm^3, median Spetzler-Martin grade II. Actuarial obliteration rates after 5 and 15 years were 54 and 68%, which increased to 61 and 90% when allowing for salvage treatments. Obliteration rate significantly related to target volume ≥4 cm^3, marginal dose ≥12 Gy, and Spetzler-Martin grade I (vs. others) on univariate analysis (target volume also significant on multivariate analysis). Post-treatment hemorrhage observed in 7 cases (14%), predominantly within latency period; actuarial post-

treatment bleeding rate ~5% during the first 2 years, and 1.1% upon final observation. Actuarial symptomatic radiation injury rates at 5 and 15 years were 12 and 19%, respectively; target volume ≥4 cm^3 and location (lobular vs. other) were significantly associated with radiation injury on univariate and multivariate analysis. Cyst formation in five cases (9.8% of patients; three asymptomatic, two treated with resection, and one resolved with steroids).

Staged AVM Treatment

- Yamamoto et al. (2012): Thirty-one patients retrospectively identified who underwent intentional 2-stage GKRS for 32 AVMs with nidus >10 cm^3 (mean target volume 16 cm^3, maximum 56 cm^3). Low radiation doses (12–16 Gy) given to the lesion periphery during the first treatment; second session planned 36 months after the first. Complete nidus obliteration in 65% of patients, and marked shrinkage in the remaining 35%. Mild symptomatic GKRS-related complications in 2 patients.
- Ding et al. (2013): Eleven patients with large AVMs (31 ± 19 cm^3) divided into 3–7 cm^3 sub-targets for sequential treatment by robotic radiosurgery at 1–4-week intervals. Forward and inverse planning used to optimize 95% coverage for delivery of 16–20 Gy; mean conformality index 0.65.

AVM Treatment Versus Medical Management

- ARUBA Trial (Mohr et al. 2020): Prospective randomized control trial of medical management versus neurologic intervention (surgery or radiosurgery) for

unruptured AVM. Overall 226 patients randomized with cessation at interim analysis due to futility. Primary outcome was death from any cause or symptomatic stroke, long-term results with 50.4 months follow-up showed 3.4 events per 100 patient in years in the medical management arm versus 12.3 per 100 patients years in the intervention arm (HR 0.31; 95% CI 0.17–0.56). Primary critique of this trial is the short follow-up time at cessation of accrual and the number of early events in the intervention arm.

Cavernous Malformation

- Poorthuis et al. (2014): Systematic review and meta-regression analysis of 63 cohorts involving 3424 patients. Composite outcome of death, nonfatal intracranial hemorrhage, or new/worse persistent focal neurological deficit was 6.6 per 100 person-years after surgical excision ($n = 2684$), and 5.4 after SRS ($n = 740$; median dose 16 Gy). However, lesions treated with SRS significantly smaller than those treated surgically (14 mm vs. 19 mm).
- University of Pittsburgh (Hasegawa et al. 2002a, b): Retrospective review of 82 consecutive patients treated with SRS for hemorrhagic cavernous malformations; annual hemorrhage rate 34%, excluding the first hemorrhage. Mean marginal dose 16.2 Gy, mean volume 1.85 cm^3. With mean follow-up of 5 years, average hemorrhage rate for the first 2 years after radiosurgery was 12%, followed by <1% from years 2 through 12. Eleven patients (13%) had new neurological symptoms without hemorrhage after radiosurgery.

Trigeminal Neuralgia

Primary Treatment

- Marseille, France (Régis et al. 2006): Phase I prospective trial of GKRS (median dose 85 Gy) in 100 patients with trigeminal neuralgia; 42% with history of prior surgery. At 12 months, 83% pain free, 58% pain free and off medication; salvage rate 17%. Side effects included mild facial paresthesia in 6% and hyperesthesia in 4%.
- University of Virginia (Sheehan et al. 2005a, b): GKRS used to treat trigeminal neuralgia in 151 consecutive patients with median 19 months follow-up. Median time to pain relief was 24 days; at 3 years, 34% of patients were pain free, and 70% of patients had improvement in pain. Twelve patients experienced new onset of facial numbness after treatment, which correlated with repeat GKRS. Right-sided neuralgia and prior neurectomy correlated with pain-free outcomes on univariate analysis; multivariate analysis similarly significant for right-sided neuralgia.
- Brussels, Belgium and Marseilles, France (Massager et al. 2007): Retrospective stratification of 358 trigeminal neuralgia patients into 3 dosimetric groups: <90 Gy (no blocking), 90 Gy (no blocking), and 90 Gy with blocking. Excellent pain control in 66% vs. 77% vs. 84%; good pain control in 81%, 85%, and 90%. Mild trigeminal toxicity in 15% vs. 21% vs. 49%; bothersome toxicity in 1.4% vs. 2.4% vs. 10%.
- Brisman (2007): Review of 85 patients with trigeminal neuralgia treated with microvascular decompression (MVD, $n = 24$) or GKRS ($n = 61$) and followed prospectively. Complete pain relief at 12 and 18 months achieved in 68% of MVD patients, and 58 and 24% of GKRS patients; partial pain relief more equivalent. No permanent complications.

- Tuleasca et al. (2018): Systematic review including 65 retrospective and prospective studies of 6461 patients treated with radiosurgery (GK, linac, CK) for trigeminal neuralgia. Maximal doses were 60–97 Gy for GK, 50–90 Gy for linac, and 66–90 Gy for CK within this series of studies. Actuarial pain relief was a median of 52.1% (range 28.6–100%), with median rate of recurrence of 23% (range 0–52.2%).

Retreatment

- UCSF (Sanchez-Mejia et al. 2005): Retrospective review of 32 patients retreated for trigeminal neuralgia with MVD (n = 19), radiofrequency ablation (RFA, n = 5), or SRS (n = 8) from an initial cohort of 209 patients. Retreatment rate with RFA (42%) significantly greater than the rate of retreatment with either MVD (20%) or SRS (8%).
- Columbia (Brisman 2003): Retrospective review of 335 patients with primary trigeminal neuralgia treated to a maximum dose of 75 Gy by GKRS, and then 45 retreated to a maximum dose of 40 Gy GKRS (mean interval 18 months). Final pain relief was 50% or greater in 62% of patients; absence of prior surgery was an independent predictor of response to retreatment. Significant dysesthesias in 2 patients; no other serious complications.
- Zhang et al. (2005): Retrospective study of 40 trigeminal neuralgia patients initially treated with 75 Gy GKRS, and then retreated with 40 Gy GKRS. Landmark-based registration algorithm used to determine spatial relationship between primary and retreatment isocenters. Trend toward better pain relief with farther distance between isocenters; however, neither placing the second isocenter proximal or distal to the brainstem was significant. Mean distance 2.9 mm

in complete or nearly complete responders vs. 1.9 mm in all others.

- Dvorak et al. (2009): Retrospective study of 28 trigeminal neuralgia patients initially treated to median 80 Gy GKRS, then retreated to median 45 Gy GKRS after a median 18-month interval. Univariate analysis showed no significant predictors of pain control or complication. However, when combining peer-reviewed retreatment series (215 total patients), both improved pain control and new trigeminal dysfunction were associated with greater dose: cumulative dose >130 Gy likely to result in >50% pain control as well as >20% risk of new dysfunction.
- University of Pittsburgh (Park et al. 2014): Retrospective review of a single institution to evaluate outcomes after repeat GK radiosurgery for trigeminal neuralgia. Overall 119 patients identified with median interval of 26 months between initial and repeat GKSRS, and median maximal target dose at retreatment was 70 Gy (range 50–90 Gy). Overall 87% of patients received initial pain relief (BNI score I-IIIb), with 44.2% having continued relief after 5 years. Sensory deficits occurred in 25 (21%) of patients between 2 and 18 months, with 76% being classified as mild or not bothersome.

Pineal Tumors

- University of Pittsburgh (Hasegawa et al. 2002a, b): Retrospective review of 16 patients treated with SRS for pineal parenchymal tumors (10 pineocytomas, 2 mixed pineocytoma/pineoblastoma, and 4 pineoblastoma). Mean dose 15 Gy, mean target volume 5 cm^3. Actuarial 2 and 5 year OS 75 and 67%, respectively; CR 29%, PR 57%, SD 14%. LC 100%

although 4 patients died from leptomeningeal or extracranial spread. Two cases of gaze palsy 7 and 13 months after SRS attributed to treatment, one resolved with steroids and the other persisted until death.

- Marseille, France (Reyns et al. 2006): Retrospective review of 13 patients with pineal parenchymal tumors (8 pineocytomas and 5 pineoblastomas) treated with SRS (mean marginal dose 15 Gy). With mean follow-up 34 months, LC 100%; 2 pineoblastomas progressed outside of SRS field resulting in death. No major mortality or morbidity related to SRS.
- United Kingdom (Yianni et al. 2012): Retrospective review of 44 patients with pineal tumors treated with SRS (11 pineal parenchymal tumors, 6 astrocytomas, 3 ependymomas, 2 papillary epithelial tumors, and 2 germ cell tumors). Mean dose 18.2 Gy, mean target volume 3.8 cm^3. One- and 5-year PFS 93 and 77%, respectively, but separating aggressive tumors from indolent lesions showed 5-year PFS 47 and 91%, respectively. Tumor grade, prior RT, and radionecrosis associated with worse outcome.

Functional Disorders

Epilepsy

- UCSF (Chang et al. 2010): Prospective, randomized trial involving 30 patients with intractable medial temporal lobe epilepsy treated with 20 Gy/1 fraction vs. 24 Gy/1 by GKRS to the amygdala, 2 cm of the anterior hippocampus, and parahippocampal gyrus. Nonsignificant difference in seizure control between arms (59% vs. 77%), although early MRI alterations predictive of long-term seizure remission.

Parkinson Disease and Essential Tremor

- Japan (Ohye et al. 2012): Prospective, multicenter study of 72 patients with intractable Parkinson disease or essential tremor treated with selective thalamotomy by GKRS with a single 130 Gy shot to the lateral part of the ventralis intermedius nucleus (located 45% of the thalamic length from the anterior tip). Excellent or good response with improved tremor in 43 of 53 patients (81%) who completed 24 months of follow-up. No permanent clinical complications.
- University of Pittsburgh (Kondziolka et al. 2008): Retrospective review of GKRS thalamotomy in 31 patients with medically refractory essential tremor. Nucleus ventralis intermedius treated with 130–140 Gy in a single fraction. With median follow-up of 26 months, mean tremor score improved by 54%, and mean handwriting score improved by 39%, with the majority of patients (69%) seeing improvement in both. Permanent mild right hemiparesis and speech impairment in 1 patient 6 months after radiosurgery; 1 patient with transient right hemiparesis and dysphagia.
- Martinez-Moreno et al. (2018): Systematic review of 34 studies on SRS for tremor, 3 prospective studies and 31 retrospective studies. SRS thalamotomy to a dose of 130–150 Gy in a single fraction resulted in mean rate of tremor reduction of 88% with a mean complication rate of 17%. Most studies limited by lack of long-term follow-up; however, treatments were effective and well tolerated and recommended as a treatment option by the ISRS.

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