### **Role of Radiation Therapy in Benign Brain Tumors**

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#### **Brain Tumors**

- Worldwide, approximately 238,000 new cases of brain and other CNS tumors with an estimated 175,000 deaths
- Estimated new cases and deaths from brain and other nervous system tumors in the United States in 2015
- ↗ New cases: 22,850.
- **7** Deaths: 15,320.

NCI Database 2015

### Principles of Radiation Treatment in Benign Diseases

- 1. Estimate the *natural course of disease* without therapy.
- 2. Consider potential consequences of **non treatment** of the patient.
- 3. Review data about *alternative therapies* and their therapeutic results.
  - Conduct a *risk-benefit analysis* compared with other possible measures.

#### Principles of Radiation Treatment in Benign Diseases

Proof that the indication is justified
 Conventional therapies have failed
 Risks of other therapies are greater
 Non treatment has unacceptable consequences.

6. Consider the individual *potential long-term radiogenic risks*.

7. Inform *patient* about all details of radiotherapy

## Principles of Radiation Treatment in Benign Diseases

- 8. Written consent of the patient following thorough patient education.
- 9. Assurance of *long-term aftercare* in order to document result.
- *10. Second opinion* in case of doubts and if the provided patient data or treatment decision are uncertain.



#### Benign Brain Tumors Clinical Tip

- Whether primary, metastatic, malignant, or benign, brain tumors must be differentiated from other space-occupying lesions such as abscesses, arteriovenous malformations, and infarction, which can have a similar clinical presentation.
- Seizures are a presenting symptom in approximately 20% of patients with supratentorial brain tumors and may antedate the clinical diagnosis by months to years in patients with slowgrowing tumors.

#### Benign Brain Tumors & Diseases treated by RT

- ↗ Meningioma
- Pituitary tumors
- Craniopharyngioma
- Hemangioblastoma and Hemaniopericytoma
- Glomus Jugulare Tumor
- Pineocytoma
- Chordoma
- Vestibular Schwannoma
- Ganglioglioma
- Central Neurocytoma
- Arteriovenous Malformations

# What are the Radiation Techniques available for treatment of benign brain Tumors?

- Conventional Two Dimensional Planning
- Conventionally fractionated three dimensional conformal radiotherapy (3DCRT)
- Conventionally fractionated intensity-modulated radiation therapy (IMRT)
- Stereotactic radiosurgery (SRS)
- Fractionatied Stereotactic radiosurgery (FRS) 2-5 F
- Frame-based or linear accelerator-based fractionated stereotactic radiotherapy SRT
- ↗ Protons and heavy ions.

## Stereotactic RadioSurgery (SRS) and Radiotherapy (SRT)

- Stereotactic refers to using a precise three-dimensional mapping technique to guide a procedure
- Stereotactic radiosurgery and radiotherapy are techniques to administer precisely directed, high-dose irradiation that tightly conforms to target to create a desired radiobiologic response while minimizing radiation dose to surrounding normal tissue

#### Fractionated Stereotactic RadioSurgery (FSR)

The term fractionated stereotactic radiosurgery (FSR) is limited to stereotactically guided high-dose conformal radiation administered to a precisely defined target volume in two to five sessions. Although it would have been less confusing to refer to this as hypofractionated SRT and reserve the term radiosurgery for single-fraction irradiation, the terminology is already in use.



#### Stereotactic RadioSurgery (SRS) and Radiotherapy (SRT) Techniques

- **7 Gamma Knife Radiosurgery** usually 201 Cobalt sources
- **Rotating Gamma System** 30 Cobalt sources China
- **Proton Radiosurgery**
- **7 LINAC Radiosurgery**

Many LINAC-based systems such as

CyberKnife (Accuray Inc

XKnife (Radionics Inc.),

Novalis (BrainLAB),

Peacock System (NOMOS Corp) are commercially available.

- **Tomotherapy** Slice Therapy, Add 6MV linac Beam to Diagnostic CT Scan
- LINAC Image-Guided Radiotherapy Add Diagnostic CT Scan technology to a Linear accelerator

# Stereotactic Radiosurgery

- Radiation Therapy Oncology Group (RTOG) study 90-05 established the maximum tolerated dose of single faction SRS to be
- 7 24 Gy for ≤20 mm
- 7 18 Gy for 21 to 30 mm
- 15 Gy for tumors 31 to 40 mm in size



#### Fractionated Stereotactic Radiotherapy

- For lesions larger than 4 cm and/or located in critical regions, the delivery of a single large-fraction treatment as in SRS is not desirable because of a high risk of CNS toxicity.
- Fractionated stereotactic radiotherapy (FSRT) is a hybrid between conventionally fractionated radiotherapy and SRS that combines fractionation with stereotactic localization and targeting techniques.
- Various systems for FSRT have been developed, with a reported accuracy of 1 to 3 mm. As for SRS, the use of multiple arcs and circular collimators for irregularly shaped lesions leads to the inclusion of a large amount of normal tissue.
- The use of multiple noncoplanar fixed fields each having a unique entrance and exit pathway is preferable because of better conformality because multileaf collimators are almost always used. With the Perfexion device, the use of the "Extend" frame permits FSRT, as well as targeting of lower cranial lesions.



#### **Meningeal Tumors**

- Meningiomas are the most common benign tumors of the CNS.
- ↗ The incidence peaks in the seventh decade of life
- ↗ 2 to 1 female-to-male predominance
- Meningiomas are extraaxial tumors that arise from dura; common locations are cerebral convexity, parasagittal falx, and sphenoid ridge.
- The majority (>90%) of meningiomas are benign and classified by the World Health Organization (WHO) as grade I tumors
- WHO grade II meningiomas (atypical, clear cell, or chordoid) have a higher tendency for local recurrence
- WHO grade III malignant meningiomas (anaplastic, rhabdoid, papillary) are exceedingly rare



#### Meningioma

- ↗ A very long natural history is characteristic, mandating prolonged follow-up.
- More than 90% of these tumors are benign; the remainder exhibit atypical histologic features or frank invasion of brain parenchyma.
- **Primary treatment is surgical, if feasible.**
- Radiation therapy is reserved for tumors that are incompletely resected, recur after surgery, are inaccessible to surgical resection, or have atypical or invasive features.
- The standard radiation dose has been approximately 54 Gy for benign meningiomas and up to 60 Gy for tumors with atypical or invasive features.
- Stereotactic radiation therapy techniques have been used; however, followup is still short in these studies.
- Anecdotal reports exist of responses to medical therapy (hydroxyurea and antiestrogen and antiprogesterone agents

#### Meningeal Tumors Grade I meningiomas

- Active surveillance with deferred treatment, especially for incidentally discovered asymptomatic tumors.
- ↗ Surgery.
- Stereotactic radiosurgery for tumors less than 3 cm.
- Surgery plus radiation therapy is used in selected cases, such as for patients with known or suspected residual disease or with recurrence after previous surgery.
- Fractionated radiation therapy for patients with unresectable tumors.
- WHO grade I meningiomas are usually curable when the mengiomas are resectable. With the increasing use of sensitive neuroimaging tools, there has been greater detection of asymptomatic low-grade meningiomas. The majority appear to show minimal growth and can often be safely observed while therapy is deferred until growth or the development of symptoms.

#### Meningeal Tumors Surgical Resection

- Maximal safe resection
- Relapse rate is as low as 10%
- Local recurrence rates are as high as 40% for patients with incomplete resection, although these rates can be substantially reduced with the use of adjuvant radiotherapy.
- Meningiomas tend to be highly vascularized tumors. In select patients, preoperative embolization is used to decrease blood loss and improve the extent of resection.



### Meningeal Tumors Radiotherapy

- Primary radiotherapy (RT) is indicated for tumors in locations in which complete resection is not feasible (i.e., optic nerve, cavernous sinus, major venous sinus) or for patients who are poor surgical candidates.
- Adjuvant RT is indicated for patients with subtotal resection (STR), Recurrent disease, or for WHO grade II or III tumors.
- RT techniques include conventionally fractionated threedimensional conformal radiotherapy (3D-CRT), conventionally fractionated intensity-modulated radiation therapy (IMRT), frame-based or linear accelerator-based fractionated stereotactic radiotherapy (FSRT), stereotactic radiosurgery (SRS), or protons and heavy ions.



### Meningeal Tumors Radiotherapy

- For 3D-CRT or IMRT treatments, the clinical target volume (CTV) is constructed by adding a 1- or 2-cm symmetric margin around the GTV
- 54 Gy/30F/6weeks given in 1.8 daily fractions.
- For patients with more aggressive histology (WHO grade II or III tumors), the GTV is expanded by at least 2 cm, with a higher dose prescription in the range of 60 Gy.
- Several modern series of radiotherapy show 5-year local control rates >95%



#### Radiosurgery and SRS Meningeal Tumors

- Radiosurgery and SRS are both excellent management options for most small benign meningiomas, with in-field tumor control rates well above 90%, as has been seen with most other benign tumors.
- Marginal recurrence rates as high as 25% may develop because of the tight margins used for radiosurgery or SRT treatment volumes limited to small recurrences or residual tumor after resection of large parasagittal meningiomas.
- Marginal recurrences are far less of a problem with unresected (and usually unbiopsied) meningiomas.



#### Radiosurgery and FSRS Meningeal Tumors

- ↗ 16 Gy to 80% isodose line (IDL) 1 or 2 fractions.
- FSRT dose 30 Gy in 5 fractions near optic nerve (to the 80% IDL) with high rates of tumor control and visual preservation
- Reported results with SRS are excellent, with 5-year local control rates as high as 98% to 100%
- Male gender, conformality index <1.4, and size >10 mL predict for worse outcome after SRS.

### Radiosurgery and SRS Unbiopsied Meningeal Tumors

- A University of Pittsburgh study, analyzed 219 imaging-diagnosed meningiomas (unbiopsied) managed with gamma knife radiosurgery to a prescription dose of 8.9 to 20 Gy (median, 14 Gy)
- The actuarial tumor control rate was 93.2% at 10 years.
- The actuarial rate for developing any postradiosurgical injury reaction was 8.8%
- The risk of postradiosurgery sequelae was lower (5.3%) after 1991
  ■

#### Meningeal Tumors Grade II meningiomas

- ↗ Surgery plus radiation therapy.
- The prognoses for patients with meningiomas (WHO grade II) (i.e., atypical, clear cell, and chordoid), meningiomas (WHO grade III) (i.e., anaplastic/malignant, rhabdoid, and papillary), and hemangiopericytomas are worse than are those for patients with low-grade meningiomas because complete resections are less commonly feasible, and the proliferative capacity is greater.

#### Meningioma Evidence-Based Treatment Summary

- 1. Small asymptomatic meningiomas in noncritical locations, especially in the elderly or in patients with other comorbidities, can be observed.
- 2. The goal of surgery is to completely resect the meningioma with negative margins, as patients with WHO grade I completely resected meningiomas have low rates of relapse and can be observed postoperatively.
- 3. For subtotally resected or unresectable progressive meningioma radiotherapy is frequently used but has not been tested in a prospective clinical trial. Local control appears to be improved with postoperative radiotherapy. Both radiosurgery and radiotherapy have been used in this context but have not been directly compared.
- 4. For grades II and III meningioma, postoperative radiotherapy is routinely recommended.
- 5. Primary radiotherapy or radiosurgery could be used for unresectable, progressive meningiomas.
- 6. Systemic therapy does not have a defined role in meningioma.

#### **Pineal Parenchymal Tumors**

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- ↗ Surgery plus radiation therapy for pineocytoma.
- Surgery plus radiation therapy and chemotherapy for pineoblastoma.
- Pineocytoma (WHO grade II), pineoblastoma (WHO grade IV), and pineal parenchymal tumors of intermediate differentiation are diverse tumors that require special consideration.
- Pineocytomas are slow-growing tumors, and patients with them carry variable prognoses for cure. Pineoblastomas are more rapidly growing tumors, and patients with them have worse prognoses. Pineal parenchymal tumors of intermediate differentiation have unpredictable growth and clinical behavior.



- They are thought to be vestigial remnants of the Rathke's pouch, representing about 2% of intracranial tumors, occurring about half the time in children and young adults.
- Craniopharyngiomas are frequently calcified and can be visualized radiographically.
- They are usually about 3.5 cm in diameter, encapsulated, and solid but can be cystic or multilobulated.
- They can displace cranial nerves and the optic chiasm and protrude into the floor of the third ventricle.
- In children, they can cause growth retardation. Adults usually present with visual disturbances. Both can demonstrate hormonal disturbances and diabetes insipidus.
- Histologically there can be two forms. The adamantinomatous form and papillary craniopharyngioma.



- Standard treatment options:
- Surgery alone if the tumor is totally resectable.
- Debulking surgery plus radiation therapy if the tumor is unresectable.
- Craniopharyngiomas (WHO grade I) are often curable.







Axial, coronal, and sagittal magnetic resonance imaging of a patient with multicystic (*yellow arrows*) craniopharyngioma prior to treatment

↗ 1.Surgical resection is recommended, when feasible.

- 7 2. The use of postoperative radiotherapy has not been tested in prospective trials but reduces the risk of recurrence and improves survival in incompletely resected tumors. Cyst decompression and biopsy followed by radiotherapy may be an acceptable treatment for patients for whom resection is not considered feasible.
- 3. Intracavitary bleomycin or radiocolloids may be useful in cystic tumors.

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## RT in Craniopharyngioma

- Radiation therapy is often used in the adjuvant setting. In select patients (i.e., <3 years old), observation following STR may be an option as local control rates are similar with RT at the time of relapse ("salvage" RT) compared with adjuvant RT with no compromise in overall survival.
- RT techniques include 3D-CRT, IMRT, FSRT, proton therapy, and intralesional RT with β-emitting isotopes (yttrium-90, phosphorous-32). The GTV is the postoperative residual tumor volume, including the cyst wall, if present.
- A margin of 1 to 1.5 cm is added to the GTV to create the PTV. Dose prescriptions for 3D-CRT and IMRT are typically 54 Gy given in 1.8-Gy daily fractions.

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#### SRS and FRST in Craniopharyngioma

- SRS and FSRT have been used with success in the treatment of craniopharyngioma. In one series from Stanford University using a frameless robotic platform,
- 16 patients were treated postoperatively with doses of 18 to 38 Gy given over 3 to 10 fractions prescribed to mean IDL of 75%. Local control was 91% in this cohort of patients with no visual or neuroendocrine complications.
- Cystic craniopharyngiomas may also be managed by the use of intralesional radioactive isotope injection using a β-emitter. Typical prescriptions range from 200 to 250 Gy prescribed to the cyst wall. Optimal results are seen in patients whose tumors have one cyst and lack a large solid component.

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#### **Arteriovenous malformations AVM**



- AVMs arise in the brain, spine, lungs, kidneys and skin. Brain AVMs are the most common.
- AVMs are an abnormal connection between the arteries and veins. Arteriovenous malformations are most commonly of prenatal origin.
- The overall ratio of AVMs to aneurysms is probably in the range of 1:10.
- Most patients present between the ages of 20 and 60 years of age. The mean age is about 35-40.
- AVMs are equally distributed between male/female.

#### **Arteriovenous malformations AVM**



- ✓ It is estimated that 1 in 200-500 have an AVM in the brain.
- When an AVM bleeds, there is a 10-15% risk of death related to each bleed and a 20-30% chance of permanent brain damage.
- The risk of bleeding is higher in the first years after the first bleed.
- In about 50% of patients the presentation is a sudden hemorrhage, or bleeding into the brain, a form of stroke. Other potential complications include seizures, headaches, and stroke-like symptoms (difficulty with movement, speech, and vision). These complications may occur in conjunction with, or independently of, hemorrhage.
- About 5-10% of AVMs are discovered by accident while the individual is being tested for other unrelated medical problems.

# Arteriovenous malformations AVM before and after Radiosurgery



*Upper row* (before radiosurgery), Lateral right carotid digital subtraction angiogram shows a parietal AVM with arteriovenous shunts and early venous drainage (black arrow); collapsed-view 3D time-of-flight MR angiogram and T1- and T2-wighted transaxial MR images show the AVM (yellow arrows).

*Lower row* (13 months after radiosurgery), MR images show the partially regressed AVM nidus and mild radiation-induced edema (red arrow).

AJNR 2004 25: 1636-1644

#### **Arteriovenous malformations AVM**



AVM size	Adjacent eloquent cortex	Draining veins
Under 3 cm = 1	Non-eloquent = 0	Superficial only $= 0$
3–6 cm = 2	Eloquent* = 1	Deep veins = 1
Over 6 cm = 3		



A common method of grading cerebral AVMs is the Spetzler-Martin grade.<sup>[5]</sup> This system was designed to assess the patient's risk of neurological deficit after open surgical resection (surgical morbidity), based on characteristics of the AVM itself. Based on this system, AVMs may be classified as grades 1 - 5. This system was not intended to characterize risk of hemorrhage.

"<u>Eloquent cortex</u>" is a name used by neurologists for areas of cortex that, if removed will result in loss of sensory processing or linguistic ability, minor paralysis, or paralysis.

The risk of post-surgical neurological deficit (difficulty with language, motor weakness, vision loss) increases with increasing Spetzler-Martin grade.





Effect of location on the risk of developing permanent symptomatic neurologic injury following arteriovenous malformation (AVM) radiosurgery
### Stereotactic RadioSurgery



Phase I Radiation Therapy Oncology Group (RTOG) dose-escalation data for radiosurgery of recurrent brain metastases and glioblastoma fit to logistic dose– response curves. The numbers at each data point indicate the number of patients in each dose/diameter group 37

### Stereotactic RadioSurgery for Arteriovenous Malformation AVM

- Untreated intracranial AVMs have a bleeding risk of approximately 3% per year, or higher if prior bleeds have occurred.
- This results in an average of 1% of untreated AVM patients dying each year from hemorrhage.
- Management options include observation, surgical resection, embolization, and radiosurgery.
- Radiosurgery can dramatically reduce the risk of hemorrhage. Radiosurgery obliterates the AVM nidus in approximately 75% of patients within 3 years of the procedure. Individual obliteration rates vary from 50% to 88%
- Although AVM obliteration rates appear to be optimized with marginal doses of approximately 23 Gy, lower doses are selected for most patients to minimize complications.
- The risk of neurologic sequelae from radiosurgery averages approximately 3% but varies with treatment volume, dose, and location.
- The risk of hemorrhage while waiting for complete obliteration to develop seems unaltered

### Fractionated Stereotactic RadioSurgery for Arteriovenous Malformation AVM

- SRS is indicated mostly for lesions in deep or eloquent regions of the brain and is particularly safe and successful for lesions that are <3 cm.</p>
- Unlike surgery, the time to obliteration ranges from 1 to 4 years after SRS, so the patient remains at a continued bleeding risk. Even with time, Maruyama et al demonstrated that the bleeding risk is not completely eliminated but reduced by approximately 88%.
- Based on the Flickinger et al dose-response data, typical prescriptions for treatment of AVM are 21 to 22 Gy prescribed to the 50% IDL for frame-based radiosurgery. The prescription should be lowered for AVMs near the brainstem or larger lesions (>3 cm). For linac-based SRS, prescriptions generally range from 16 to 24 Gy in a single fraction to 20 to 22 Gy in 2 fractions for spinal AVMs

### Stereotactic RadioSurgery for Arteriovenous Malformation AVM

- When an AVM nidus fails to completely obliterate by 3 years after radiosurgery, irradiation can be repeated with acceptable morbidity.
- Although some residual radiation injury effect would be expected within the previously irradiated, unobliterated AVM nidus vasculature, retreatment appears to require similar, if not higher, doses to achieve similar rates of complete obliteration as initial radiosurgery.

### Stereotactic RadioSurgery for Large Arteriovenous Malformation AVM

- Management of large AVMs is presently difficult because radiosurgery may be associated with high complication risks and low obliteration rates.
- Recent improvements in embolization with liquid glue (ev3, Inc.) or polymer can sometimes help reduce the target volume but adds to the total risks of the overall management.
- Another promising approach is staged radiosurgery, in which large AVMs are treated in two or three sections separated by 4- to 6-month intervals to reduce acute toxicity. Whether there is any benefit to fractionating stereotactic irradiation of AVMs is presently unclear

### Stereotactic RadioSurgery for Cavernous Arteriovenous Malformation AVM

- Cavernous malformations do not show detectable flow on angiography but nevertheless are vascular lesions with annual hemorrhage risks of 0.5% per year with no prior bleed, 4.5% with one prior hemorrhage, and approximately 32% per year after a history of two or more hemorrhages.
- Lower pressures in these lesions lead to smaller bleeds than are typically seen with AVM. Repeated bleeds from brainstem cavernous malformations can cause considerable neurologic morbidity. Symptomatic, surgically accessible lesions should be resected.
- Radiosurgery of brainstem cavernous malformations with a history of two or more prior hemorrhages appears to reduce the risk of subsequent bleeds to approximately 1% per year with acceptable morbidity

### Fractionated Stereotactic RadioSurgery for Arteriovenous Malformation AVM

Minimum Dose to Target (Gy)	Predicted AVM Obliteration Rate (%)
27	99
25	98
22	95
20	90
17	80
16	70
13	50

AVM, arteriovenous malformations.

Adapted from Flickinger JC, Pollock BE, Kondziolka D, et al. A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. Int J Radiat Oncol Biol Phys 1996;36:873–879.

FLICKINGER'S PREDICTED RATES OF IN-FIELD ARTERIOVENOUS MALFORMATIONS OBLITERATION BASED ON THE MINIMUM DOSE WITHIN THE TARGET VOLUME



### Vestibular Schwannoma and Neurofibroma





- Vestibular schwannomas, also known as acoustic neuromas, are benign tumors arising from Schwann cells.
- Acoustic neuromas (AN) represent 5% to 8% of primary CNS brain tumors.
- They are associated with loss of genetic information on chromosome 22.
- Vestibular schwannomas either occur on one side as spontaneous mutations or bilaterally as the hallmark of type 2 neurofibromatosis (NF-2).
- Vestibular schwannomas usually arise within the internal auditory canal and later extend intracranially into the cerebellar pontine angle.
- Symptoms include sensorineural hearing loss, tinnitus, and vertigo.
- The differential diagnosis of a cerebellar pontine angle tumor includes vestibular schwannoma (90%), meningioma (close to 10%), cholesteatomas, facial or trigeminal schwannoma, and rare primary or metastatic malignant tumors.

# Vestibular Schwannoma and Neurofibroma

### Evidence-Based Treatment Summary

- 1. Small nonprogressive tumors can be observed.
- 2. Surgical resection is generally considered the standard of care for symptomatic lesions.
- 3. Radiosurgery produces outcomes equivalent to surgery, although these modalities have not been prospectively compared.
- 4. Fractionated stereotactic radiotherapy is being increasingly employed, with institutional reports suggesting a lower incidence of cranial neuropathies than radiosurgery, but this has not been prospectively validated.
- 5. The role of bevacizumab in NF-2-associated progressive bilateral vestibular schwannomas is being explored.

### Stereotactic RadioSurgery for Vestibular Schwannoma

The University of Pittsburgh 313 acoustic schwannoma patients who underwent gamma knife radiosurgery

SRS Dose of 12 to 13 Gy Tumor control rate, free of surgical intervention, was 98.6% at 7 years.



## Stereotactic Radiation Therapy for Vestibular Schwannoma

Various fractionation schemes FSR 18 Gy/3, 20 Gy/4 to 5, 25 Gy/5 SRT 45 to 50 Gy/25, and 54 Gy/30 have been used with vestibular schwannoma with minor differences in results

As compared to SRT better hearing preservation (upto 98% actuarial hearing preservation)

similar facial and trigeminal neuropathy rates for the radiosurgery and fractionated radiotherapy groups



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### Chordoma

- Chordomas are rare, slowly growing midline tumors originating from the embryonal notochord rests in the skull base (35%), vertebral column (15%), or sacral regions (50%). The most common sites of skull-based tumors include the clivus, dorsum sella, and nasopharynx
- Complete surgical resection is the mainstay of treatment. However, due to location, GTR is often not possible. Relapse rates are as high as 50% even after surgical resection with negative margins



### Chordoma

- Adjuvant radiation therapy is indicated to reduce recurrence rates for skull-based chordomas. Retrospective data suggest that salvage RT is inferior to adjuvant RT
- RT techniques for treatment of skull-based chordomas include conventionally fractionated 3D-CRT or IMRT, fractionated charged particle therapy (protons, carbon ions), and FSRT.
- Determination of the GTV should be made by coregistration of the preoperative and/or postoperative MRI to the treatment planning CT scan.
- Margins for CTV should be 1 to 2 cm with an additional 3 to 5 mm for the PTV. Dose prescriptions to the PTV for patients receiving photonbased treatment should be at least 60 Gy given in 1.8- to 2.0-Gy daily fractions



### **Glomus Jugulare Tumors**



- RT is indicated for patients with tumors in unsuitable locations (i.e., skull base), as adjuvant therapy after STR, or as salvage therapy at the time of relapse after surgery. RT techniques include conventionally fractionated 3D-CRT or IMRT, SRS, and FSRT.
- The diagnostic MRI should be coregistered with the treatment planning CT scan. The GTV is delineated and 1 to 1.5 cm is added for clinical and setup margin. With conventional techniques, doses are often 45 to 55 Gy given in 1.8-to 2.0-Gy daily fractions with local control rates near or >90% in several series.
- Results with SRS have been comparable to that of conventionally fractionated RT. Using a frame-based platform, reported tumor margin doses range from 12.5 to 20 Gy prescribed to the 50% IDL
- Tumor control more than 90%



### Hemangioblastoma

- Hemangioblastomas are benign vascular tumors that present during the third and fourth decades of life.
- They account for 1% to 2% of primary CNS tumors in adults.
- Most arise in the cerebellum, constituting the most common primary cerebellar tumors in adults.
- An association with von Hippel-Lindau disease is noted in 10% of patients.
- Histologically, the tumor consists of closely packed, thin-walled blood vessels in a stroma of large, oval foamy cells. The lesions are intensely enhancing on CT and MRI, and angiography confirms the vascular nature of the lesion. Imaging of the craniospinal axis often documents multiple lesions in patients with von Hippel-Lindau disease.
- **Treatment is surgical, and complete resection is curative.**
- Radiosurgery has also been shown to be useful in patients with unresectable disease but is associated with higher rates of recurrence 51

# Hemangiopericytoma



- Hemangiopericytoma is a sarcomatous lesion developing from smooth muscle in blood vessels usually along the base of the skull, although intraparenchymal lesions may be seen.
- In contrast to other primary CNS tumors, hemangiopericytomas commonly develop systemic metastases.
- There is a 90% 9-year actuarial risk for local failure following surgical resection only.
- Postoperative radiotherapy to total doses of 50 to 60 Gy reduces the risk of recurrence rate and improves overall survival.
- Tumor control is dose dependent, with doses >50 Gy associated with superior outcomes. Radiographic response is slow.
- Radiosurgery has been used for recurrent hemangiopericytomas, with reported local control rates of approximately 80% following treatment.

### Hemangioblastoma and Hemangiopericytoma

### Evidence-Based Treatment Summary

- 1. Surgical resection is recommended, when feasible, for both of these diseases.
- 2. Radiotherapy is generally reserved for subtotally resected progressive hemangioblastoma, but there are no prospective data.
- 3. Postoperative radiotherapy is recommended for subtotally resected hemangiopericytoma, but there are no prospective data.
- 4. Radiotherapy or radiosurgery may be considered for unresectable tumors.

### NEURONAL AND MIXED NEURONAL-GLIAL TUMORS

- These are uncommon tumors that are characterized by the presence of both neuronal and glial elements in variable amounts. They include entities such as desmoplastic infantile astrocytoma and dysembryoplastic neuroepithelial tumor. Most will be cured by surgery, but radiotherapy may be indicated in two tumor types:
- Ganglioglioma and anaplastic ganglioglioma
- Central neurocytoma

# Ganglioglioma and Anaplastic Ganglioglioma

- Gangliogliomas are well-differentiated slowly growing tumors composed of mature ganglion cells in combination with neoplastic glial cells (WHO grade I or II). Tumors in which the glial component shows anaplastic features (WHO grade III) are called anaplastic gangliogliomas.
- Although these tumors can arise anywhere within the CNS, most in children arise in the temporal region and typically present with seizures. Surgery is the treatment of choice. When resection is complete, the probability of longterm tumor control in patients with ganglioglioma is excellent.
- The indications for radiotherapy are as for patients with LGAs, that is, for patients with progressive or recurrent disease that is not resectable, and the radiotherapy target volume and dose likewise.
- The indications for postoperative radiotherapy remain undefined except for patients with anaplastic gangliogliomas who have undergone less than complete resection in whom the use of radiotherapy has been shown to result in improved progression-free survival.

### **Central Neurocytoma**



- This is a neoplasm composed of uniform round cells with neuronal differentiation that arises in the lateral or third ventricles, typically the former, that is seen predominantly in adolescents and young adults.
- Patients usually present with symptoms and signs of raised intracranial pressure.
- Surgery is the treatment of choice, and when complete resection is achieved long-term tumor control is excellent without adjuvant treatment.
- Patients in whom complete resection cannot be achieved as well as those with tumors with atypical histology or a high mitotic rate fare less well, and postoperative radiotherapy should be considered in these situations. While a dose of 50 Gy appears adequate for patients with typical neurocytomas, there is evidence of improved tumor control at doses of at least 54 Gy in patients with atypical neurocytoma.



### **Pituitary Adenoma**

Туре	Frequency (%)
Prolactinoma	2030
Growth hormone adenoma	5
Mixed growth/prolactin adenoma	5
Adrenocorticotrophic hormone adenoma	10-15
Gonadotroph adenoma	10-15
Null cell adenoma	20
Thyroid-stimulating hormone adenoma	1
Plurihormonal adenoma	15

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### Pituitary Adenoma Functional Adenoma

Patients with functional adenomas present with signs and symptoms that correspond to the excess hormone: galactorrhea, amenorrhea, diminished libido, and infertility in patients with prolactinomas; acromegaly or gigantism in patients with GH-secreting adenomas; Cushing disease in adrenocorticotropic hormone (ACTH)–secreting adenomas; hyperthyroidism in patients with thyroid-stimulating hormone (TSH)–secreting adenomas. In patients who have had bilateral adrenalectomy, up to 40% will develop Nelson syndrome, which is characterized by an ACTH-secreting adenoma and increased skin pigmentation secondary to increased release of  $\alpha$ -melanocyte–stimulating hormone.





### Pituitary Adenoma workup

- → History and detailed physical examination (H&P)
- Laboratory analysis of pituitary hormone levels
- Contrast enhanced MRI with thin slices through the pituitary
- Tissue diagnosis to rule out other causes of pituitary masses, including craniopharyngioma, meningioma, suprasellar germ cell tumor, metastatic disease, or a benign lesion (i.e., cyst).

### **Pituitary Adenoma**

- Symptomatic adenomas present for medical attention as a result of hormone secretions, compression of nearby normal structures with neurologic symptoms, or compression of the pituitary stalk causing hypopituitarism.
- An initial therapy for most prolactinomas is with a dopamine agonist such as bromocriptine, lysuride, or pergolide. Medical intervention usually decreases adenoma function and size.
- Initial therapy for other pituitary adenomas is transsphenoidal surgical resection. Surgery is generally safe and reverses neurologic symptoms, with most patients normalizing hormone levels. It is mostly useful to cure microadenomas.
- Radiation therapy is often reserved for patients with residual disease after surgery, such as after a debulking surgery. It is also considered for recurrence after definitive surgery or for medically inoperable patients.
- Typically, conventional radiation delivers a dose of 45 Gy at 1.8 Gy daily fractions. At this dose, good control can usually be achieved with a very low risk of optic neuropathy.
- Normalization of hormone levels, however, can take months to years to achieve.



### Pituitary Adenoma Management

- Management of pituitary adenomas requires a multidisciplinary approach to properly select which patients are suitable for different approaches with
- Medical therapy
- Surgery
- Fractionated radiotherapy
- Radiosurgery,
- ↗ or combinations of these.
- Most patients with visual compromise, particularly with a hemianopia or greater, will do better with initial surgical decompression.
- Prolactinomas are usually initially managed with medical therapy.



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### Surgery for Pituitary Adenoma

- Surgery is generally the treatment of choice for pituitary adenomas. Surgery provides immediate relief of compressive symptoms and helps to decrease hormone secretion.
- The most common surgical technique is through a transsphenoidal approach. In some cases, a more aggressive surgery (i.e., frontal craniotomy) may be indicated for patients with extensive intracranial and skull-based involvement.
- Overall, local control rates range from 50% to 80% after surgery alone for both functioning and nonfunctioning adenomas.
- In patients who continue to have abnormally elevated hormones after surgical resection, adjuvant treatment with pharmacotherapy or radiation therapy is pursued.



### **RT for Pituitary Adenoma**

- Except for medically inoperable patients in which RT is used in the primary setting, the role of RT is generally in the adjuvant setting with the following indications: recurrent tumor after surgery; persistence of hormone elevation after surgery; residual disease after STR or debulking procedure.
- Tumor growth control is excellent, particularly for patients with nonfunctioning adenomas.
- Endocrine control after treatment of functioning adenomas, as demonstrated by normalization of pituitary hormone levels, takes years to develop. At a median of 2 years after RT, growth hormone levels stabilize quickest; normalization is slowest for TSH-secreting adenomas.
- Pharmacologic therapy should be discontinued 1 to 2 months prior to the initiation of RT based on evidence demonstrating lower RT sensitivity with concurrent medical treatment.

### **RT for Pituitary Adenoma**









A recurrent nonfunctioning pituitary adenoma 7 years after surgical resection in the axial (A) and coronal (B) planes. The yellow arrows denote invasion into the left cavernous sinus. Rapid arc intensity-modulated radiotherapy treatment plan for the same patient in the axial (C), coronal (D), and sagittal (E) planes. The planning target volume (purple shaded area) was prescribed at 50.4 Gy in 28 fractions.



### **RT for Pituitary Adenoma**

- RT techniques include 3D-CRT, IMRT, single-fraction SRS, and FSRT. Delineation of the GTV (or preoperative GTV in the case of GTR) should be performed by coregistration of the postoperative MRI to the treatment planning CT scan.
- For 3D-CRT and IMRT, the CTV is constructed by adding 1 to 1.5 cm to the GTV; an additional 3 to 5 mm is added to the CTV to create the PTV.
- These margins may be modified based on institutional policy and other considerations, such as the availability of daily image guidance.
- Nonfunctional adenomas are typically prescribed a dose of 45/25F to 50.4 Gy/28F given in 1.8Gy daily fractions.
- Higher doses in the range of 54 Gy /30F/6wks are recommended for secretory adenomas.



### Radiosurgery and FRS for Pituitary Adenoma

Small pituitary adenomas, where the target volume can be separated from the optic nerves, are reasonable candidates for radiosurgery.

### Radiosurgery and FSRS for Pituitary Adenoma

- SRS remains an attractive option for the treatment of pituitary adenomas. General principles apply in that FSRT is used over SRS for large lesions (>3 cm) or lesions near critical structures (<1 or 2 mm from the chiasm). Similar to 3D-CRT or IMRT, higher doses are needed for functional adenomas compared with nonfunctional adenomas.
- Commonly used prescriptions are 16 to 20 Gy in a single fraction for nonfunctional adenomas and 20 to 25 Gy in a single fraction for functional adenomas using a frameless robotic radiosurgery
- Sheehan et al performed a review of 35 peer-reviewed reports of radiosurgery for pituitary adenoma that included 1,621 patients. Most studies reported >90% control of tumor size (range, 68% to 100%). The weighted average tumor control rate for all published series (encompassing 1,283 patients) was 96%. In eight published series with mean or median patient follow-up periods of ≥4 years, tumor growth control rates varied from 83% to 100%.





### Radiosurgery and SRS for Pituitary Adenoma Cushing's disease

- Twenty-two series have published radiosurgery results for 314 Cushing's disease patients. The mean radiosurgical prescription (margin) doses for these series varied from 15 to 32 Gy. In those series with at least 10 patients and a median follow-up of 2 years,
- endocrinologic remission rates range from 17% to 83%. Many of the patients in older series were treated in the pre-CT and MR imaging era of radiosurgery, sometimes as many as four times before their Cushing's disease went into remission.






## Stereotactic RadioSurgery for Benign Intracranial Tummors

- Most small benign intracranial tumors are well managed with radiosurgery, FSR, or SRT. Radiosurgery control rates are high with radiosurgery, with prescription doses on the order of 12 to 14 Gy
- Kondziolka et al. evaluated long-term tumor control in 285 patients who underwent radiosurgery for benign intracranial tumors with a median follow-up period of 10 years. These included
  - 157 patients with vestibular schwannomas,
  - 10 with other cranial nerve schwannomas,
  - 85 with meningiomas,
  - 28 with pituitary adenomas
  - 5 with craniopharyngiomas.
- Forty-four percent of the patients had prior surgical resection and 5% had prior fractionated radiotherapy.
- They found that 95% of the 285 patients had imaging-defined local tumor control (63% had tumor regression and 32% had no further tumor growth).
- The crude tumor control was 95% with a 15-year actuarial tumor control rate of 93.7%.
- In 5% of the patients, delayed tumor growth was identified. Resection was performed after radiosurgery in 13 patients (5%) for tumor growth.