Overview of radiosurgery for benign brain tumors

Anuj V. Peddada, M.D.
Department of Radiation Oncology
Penrose Cancer Center
Colorado Springs, CO

Objectives

- Provide overview of benign brain tumors
  - meningiomas
  - acoustic neuromas (Vestibular Schwannoma)
  - pituitary adenomas
- Discuss treatment options for these tumors
- Review the results with radiosurgery

General Comment

- Because of the longevity of these patients, the quality and outcome of treatment for benign disease may not be evident for many years (decades)
- Thus, long-term follow-up is essential in evaluating outcomes

Radiation Induced Neoplasm Criteria

1) Second tumor within the irradiated field used to treat the primary disease
2) Tumor not present prior to irradiation and reasonable interval between XRT and detection of 2nd tumor (usually several years)
3) Histologically different primary and subsequent tumor
4) No known genetic or predisposing conditions to secondary malignancy

Cahan *et al*, 1998

Radiation-induced neoplasm after radiosurgery

- Very small number of cases reported in the literature
- 0 % in 6200 GK procedures in Pittsburgh
- Note: 1-3% risk reported with fractionated radiotherapy

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The Risk of Radiation-Induced Tumors or Malignant Transformation After Single-Fraction Intracranial Radiosurgery: Results Based on a 25-Year Experience

Bruce E. Pollock, MD,*,† Michael J. Link, MD,*,† Scott L. Stafford, MD,† Ian F. Parney, MD, PhD,* Yolanda I. Garces, MD,† and Robert L. Foote, MD†

*Departments of *Neurological Surgery, †Radiation Oncology, and †Otorhinolaryngology, Mayo Clinic College of Medicine, Rochester, Minnesota*

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Summary

The risk of radiation-induced tumorigenesis or malignant transformation after single-fraction intracranial stereotactic radiosurgery (SRS) remains unclear. In this study we found no cases of radiation-induced tumors and a low rate of malignant transformation (0.9%) after single-fraction SRS. The risk of radiation-induced tumors or malignant transformation after SRS is very low and should not be used as a justification for choosing alternative treatment approaches (surgical resection,

Purpose: To determine the risk of radiation-induced tumors or malignant transformation after single-fraction intracranial stereotactic radiosurgery (SRS).

Methods and Materials: We performed a retrospective review of 1837 patients who received single-fraction SRS for arteriovenous malformation or benign tumor (meningioma, vestibular schwannoma, pituitary adenoma, glomus tumor) at a single center between 1990 and 2009. Patients were excluded if they refused research authorization (n = 31), had a genetic predisposition to tumor development (n = 84), received prior or concurrent radiation therapy (n = 79), or had less than 5 years of imaging follow-up after SRS (n = 501). The median imaging follow-up period for the remaining 1142 patients was 9.0 years (range, 5-24.9 years).

Results: No radiation-induced tumors were identified in 11,264 patient-years of follow-up after SRS. The risk of a radiation-induced tumor developing after SRS was 0.0% at 5 years (95% confidence interval [CI], 0.0%-0.4%), 0.0% at 10 years (95% CI, 0.0%-0.9%), and 0.0% at 15 years (95% CI, 0.0%-2.8%). Malignant transformation occurred in 7 of 316 meningioma patients (2.2%) and 1 of 358 vestibular schwannoma patients (0.3%) at a median of 4.9 years (range, 2.8-13.8 years) after SRS. No cases of malignant transformation were noted in patients with pituitary adenomas (n = 188) or glomus tumors (n = 47). The 5-, 10-, and 15-year risk of malignant transformation was 0.5% (95% CI, 0.0%-0.9%), 0.8% (95% CI, 0.0%-1.8%), and 2.4% (95% CI, 0.0%-5.5%), respectively. Patients who underwent prior resection (hazard

Slide 6

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Introduction to benign tumors

- Histological benign
- Functional deficits that can persist for years
- Surgically challenging at times
- Without treatment, significant neurological morbidity and mortality can occur
- Prolonged survival can be expected for most patients
- Both short- and long-term outcomes after treatment must be acceptable

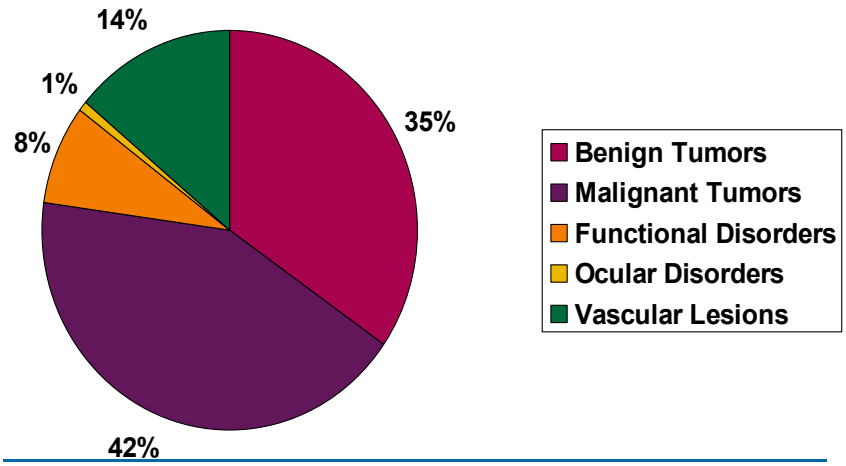
Benign intracranial lesions as radiosurgery targets

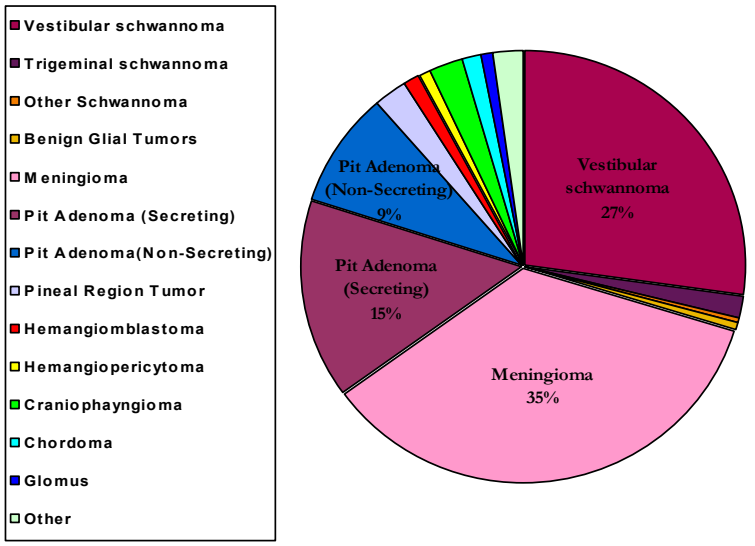
- Well circumscribed targets without infiltration
- Easily visualized with sharp delineation
- Slow growth rate makes high dose single fraction treatment potentially desirable over fractionation
- Late complications have time to occur

Radiosurgery of benign tumors

- Goal of SRS: accurately deliver adequate amount of radiation to the "target" with a minimal dose outside the prescribed area
- Dose to the tumor margin is selected to:
  - Minimize the risk of visual deficits, cranial neuropathies and other complications
  - Provide the highest potential for growth control
  - Provide normalization of hormone production

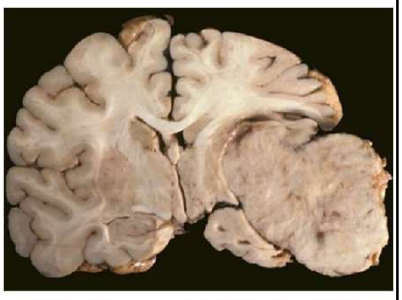
Treatment Statistics (SRS users survey)

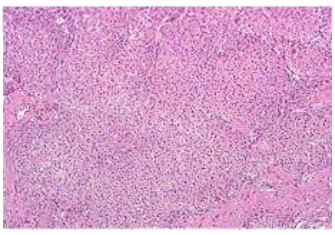




Introduction: Meningiomas

- Second most common CNS neoplasm
- ~18 - 30 % of all intracranial tumors
- Intracranial incidence 2/100,000[2] but 7-8/100,000 at autopsy[3]
- Most common in 5th to 8th decade, with a peak at 6th decade
- F:M – 3:2 supratentorial





1. Russell D *et al*, 1989
2. Rohringer M *et al*, 1989
3. Bondy M *et al*, *1996*

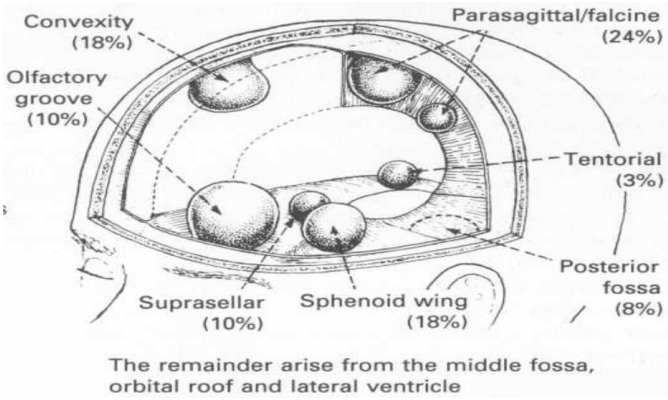
Introduction: Meningiomas

- Imaging: Dural-based enhancing mass w/cortical buckling –often have tail
- Hyperostosis, irregular cortex, intra-tumoral Ca++
- Etiology
  - Radiation exposure
  - Head trama
  - Viral infection
  - Estrogen receptors
  - Genetic predisposition

CLINICAL MANIFESTATIONS

- Many are asymptomatic—found incidentally by MRI
- But may have symptoms:
- Tumor location: by compression of underlying neural structures
- Location
  - Cerebral convexity (Sylvian & parasagittal areas)
  - Falx cerebri
  - Skull base
  - Olfactory groove
  - Sphenoid ridge
  - CP angle
  - Tuberculum sella

Where intracranial meningiomas occur



Issues with meningiomas

- Majority are microscopically benign BUT
  - Locally compressive
  - Can invade brain tissue and surrounding structures
  - Recur after resection
  - Spread along the leptomeninges to involve multiple regions or intracranial compartments
  - ~ 10 - 20 % are atypical or anaplastic (malignant) and clinically associated with significant morbidity and mortality

Diagnosis

- Cranial CT Scan
- Isointense or slightly hyperintense
- Hyperostosis—20%
- MR Isointense (65%) or hypointense (35%) in T1 and T2
- Angiography
  - Hypervascular
  - embolization reduce the risk of intraoperative bleeding
- MR Angiography & Venography

Treatment Options

Observation

Surgery

Radiotherapy

Radiosurgery

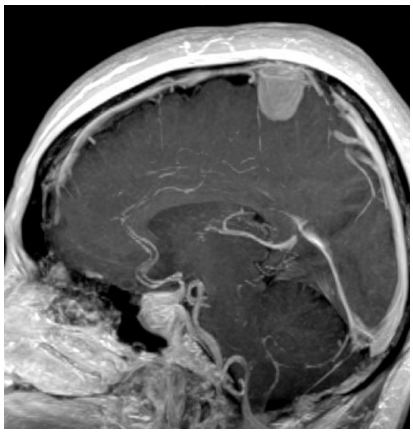
Chemotherapy??

Goals for Surgery

- Surgical resection of a meningioma and its dural base is the treatment of choice

1) Establish diagnosis
2) Maximize resection/ameliorate mass effect
   (Aim: complete resection of the tumor and its dural attachment)
3) Minimize neurological deficits
4) Can be curative

Limitations of Surgery



- Recur despite “complete resection”
- Even with gross total resection, tumor recurrence rates can range from 18% - 25 % at 10 years
- Surgically inaccessible/ uncontrollable
- Invasion of normal neural or vascular structures
- Higher grade lesion have a more aggressive clinical course

Simpson Criteria

Degree of Resection	Recurrence rate
Complete resection with dural margin	9%
Complete resection with coagulation of dura	19 %
Complete resection (no treatment of dura)	29 %
Partial removal leaving tumor *in situ*	40 %
Decompression	NA

Indications for radiosurgery

- Newly diagnosed patients
  - Skull base
  - Convexity
  - Parasaggital
  - CP angle
  - Not used for optic nerve sheath tumors
- Recurrent tumors
- Residual tumor after resection

SRS for meningiomas: Mayo experience

- 330 pts (follow-up data for 297 meningiomas)
- Median age: 57 yrs (20-90)
- 42 % recurrent/residual tumors after prior resection
  - 2.7 % atypical meningiomas
  - 6. 7 % malignant meningiomas
- 58 % newly diagnosed (assumed benign)
- 70 % at skull base; 12 % convexity
- Median tumor volume 7.3 cm^3 (range 0.5-50.5 cm^3)
- Median f/u 43 months (2-138)

Pollock, 2003

SRS in Meningiomas

- Median tumor margin dose was 16 Gy (12-36 Gy) to 50 % isodose line
- Max dose to optic nerves or chiasm 10 Gy
  - Defined as that received by 1% of ON
- At follow-up:
  - Decrease in size by 2 mm – decrease
  - Increase in size by 2 mm – increase
  - < 2 mm change (either direction) – unchanged

Pollock 2003

Tumor control for all meningiomas post SRS

- At follow-up for 297 meningiomas (benign/atypical and malignant):
  - 173 (58 %) decreased
  - 106 (36 %) unchanged

  } 94 % local control
  - 18 (6 %) increased

Tumor Control in Benign Meningiomas s/p SRS

- At follow-up for 267 benign meningiomas:
  - 165 (62 %) decreased
  - 96 (36 %) unchanged

  } 98 % local control
  - 6 (2 %) increased
    5 of 6 had prior surgery
  - Reminder : Benign Residual Meningiomas (Sx ± EBRT):
    92% -- 5 yr and 83% -- 10 yr PFS[2]

Pollock et al, 2003

Nutting et al, 1999

Results of Atypical or Malignant Meningiomas s/p SRS

- At follow-up for 30 atypical or malignant meningiomas:
  - 8 (27 %) decreased
  - 10 (33 %) unchanged

  } 60% local control
  - 12 (40 %) increased
  - Reminder : Atypical & Malignant Meningiomas (Sx + EBRT): 20% -- 5 yr PFS[2]

Pollock, 2003
Kokubo M *et al*, 2000

Complications Related to Meningioma SRS

26 pts (8.7%)

- Cranial nerve deficits affected 17 pts (5.7 %); 4 pts (1.3 %) with multiple cranial neuropathies
- Symptomatic brain edema 5 pts (1.7 %)
- ICA injury 2 pts (0.7 %)
- Cyst adjacent to treated tumor 2 pts (0.7 %)

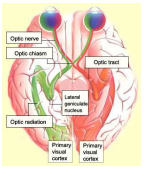
Pollock 2003

Cranial Neuropathies s/p SRS

- Cranial nerve deficits affected 17 pts (5.7%)
- 4 pts (1.3%) with multiple cranial neuropathies
  - Trigeminal nerve n = 10
  - Abducent nerve n = 3
  - Optic nerve n = 2
  - Oculomotor nerve n = 2
  - Facial nerve n = 2
  - Vestibulocochlear nerve n = 2
- Median time to onset: 6 months (1 – 98 months)
- 14 pts no change at last follow-up
- 3 pts complete resolution

Pollock, 2003

Radiation optic neuropathy



- Significant complications to optic apparatus with dose[1]
  - 4/17 pts (24 %) receiving > 8 Gy optic apparatus
  - 0/35 pts receiving < 8 Gy (p=0.009)
- Develops 7- 30 months post SRS[2]
- Abrupt change in vision
- Clinically anterior visual pathway involvement, typically decreased VA or homonymous hemianopia[2]
- MRI Gd shows swelling and enhancement in 3/ of 4 pts
- Only 1 partial improvement with systemic steroids

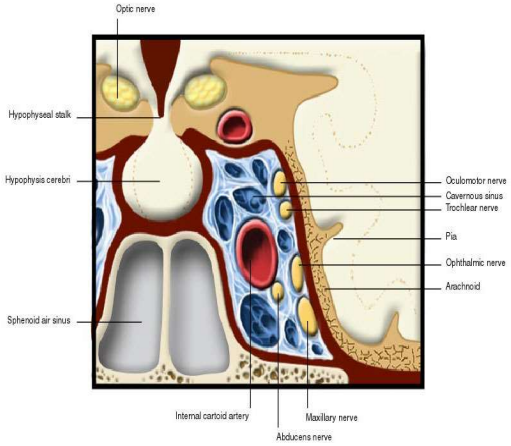
Tishler RB *et al*, 1993
Girkin CA *et al*, 1997

Optic Nerve Radiation Tolerance

- Tishler (1996) 8 Gy
- Duma (1993) 9 Gy
- Leber (1998) 10 Gy
- Stafford (2003) 12 Gy

SRS and Cranial Nerves of the Cavernous Sinus

- No relationship of dose to cavernous sinus and neuropathy in CN III-VI (range 5-40 Gy) [1,2]



Tishler RB *et al*, 1993
Leber KA *et al*, 1998

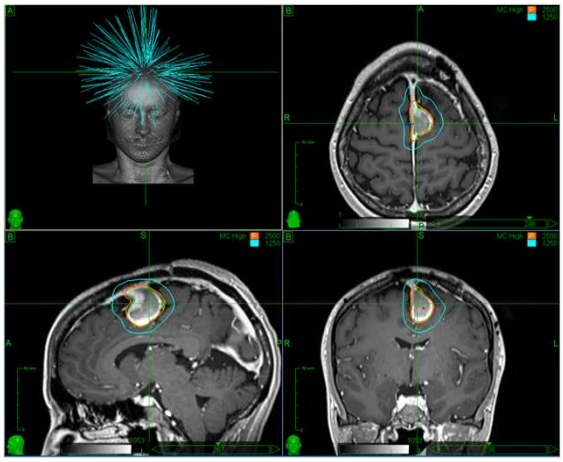
Cranial nerve complications secondary to SRS

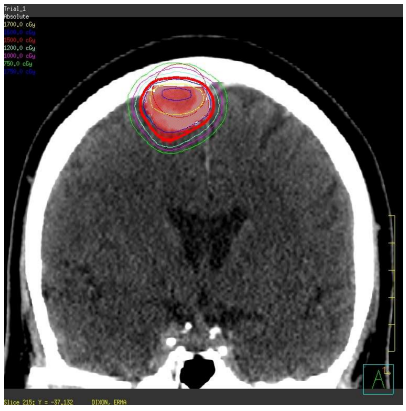
- Special sensory nerves (optic and vestibulococlear) are the most radiation sensitive
- No relationship of dose to cavernous sinus and neuropathy in CN III-VI (range 10-40 Gy) [1]
- Significant increase in complications to optic apparatus with dose

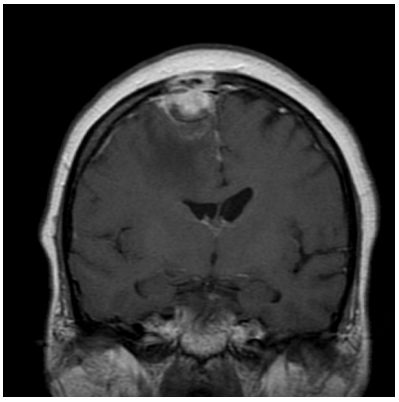
Surgery vs SRS for cavernous sinus meningiomas

- Complete resection in 76 % of cavernous sinus meningiomas[1]
- Mortality : 2.4 %
- Morbidity : 4.8 %
- Preoperative cranial nerve deficits:
  - Improved – 14 %
  - Unchanged – 80 %
  - Worse 6 %
- Incomplete resection
  - 40 % 5 yr tumor progression[2]
  - 89 % 15 year tumor progression[3]
- Complications post SRS 8.7%,
- Tumor control 94 % [4]
- ICA injury 2 pts (0.7 %)
- Cyst adjacent to treated tumor 2 pts (0.7 %)

DeMonte F, *et al* 1994
Jung H, *et al* , 2000
Klink DF, *et al*, 2000
Pollock, 2003





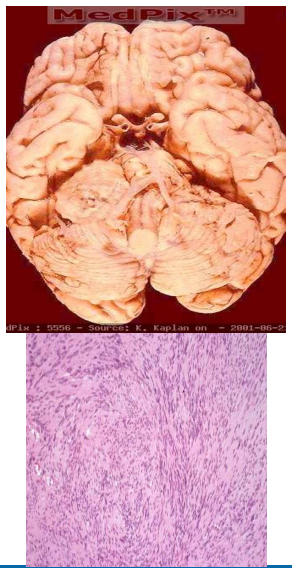


Meningioma treatment recommendations

- Target definition using volume MRI or T1W Gd enhanced
- Typically 12 – 16 Gy to the margin of the lesion
- Located at least 3-5 mm from optic nerve or chiasm (preferably 5 mm)
- Fractionated schedules
  - larger lesions
  - impinging on the optic apparatus
  - < 1cm Parasagital/parafalcine location

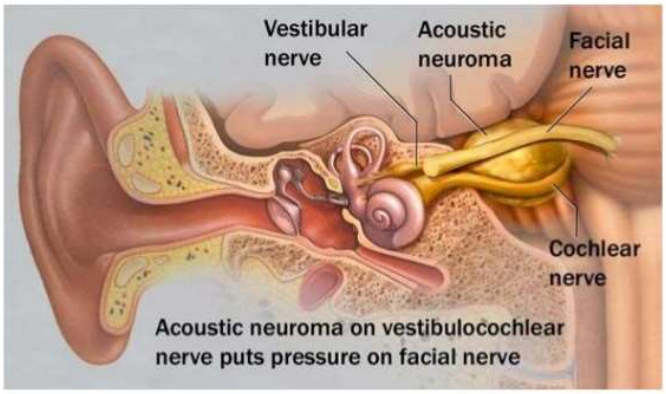
Acoustic Neuroma (AN) introduction

- Vestibular schwannoma
- ~10 % of all intracranial tumors
- Incidence 0.78-1.15/100,000
- 95 % unilateral
- Bilateral is pathognomonic for NF2



Acoustic Neuroma (AN) introduction

- Risk factors:
  - NF2 – bilateral vestibular schwannomas
  - Loud noise (Edwards et al. AM J. Epidemol 2006; 163: 327-33)
- Histopathology
  - Equal frequency on superior and inferior branches of the vestibular portion of the VIII nerve



Acoustic neuroma treatment options

- Observation
- Microsurgery
- Radiation therapy
  - SRS
  - FSRT (3-5 fx)
  - Conventionally fractionated radiation (25-30 fx)

Goals of treatment

- Long-term tumor control
- Preservation of CN function
  - hearing
  - balance
- Maintenance of QOL

Observation

- An acceptable option for certain patients
  - Elderly
  - Contraindications for Surgery
  - Small incidentally found asymptomatic tumors
  - Evidence of slow tumor growth
- Growth
  - Less than 30% of untreated acoustic neuromas have growth greater than 2.0 mm/year on MR imaging
  - Tumors larger than 2.0 cm are more likely to grow
  - Rate of growth is usually constant, but may have sudden increase in size

Fucci et al., *Am J Otol* 1999; 20:495-499

Observation

- Regis et al

  54 patients with small AN and useful hearing
  - 72% had tumor enlargement and were treated with SRS
  - Useful hearing was preserved in only 20%
- Recommendations
  - Serial MR imaging and audiometric tests
- Meta-analysis 1345 pts with median FU 3.2 yrs
  - 51%-no growth
  - 43%-exhibited growth (avg 1.9 mm/year)
  - 6%- showed regression!!
  - Hearing loss occurred in 51%

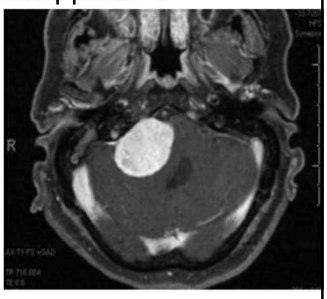
Smouha et al. Laryngoscope 2005, 115 (3) 450-4

Vestibular schwannoma–surgery

- Approaches
  - Retromastoid (retrosigmoid), suboccipital
    - Best for large tumors compressing the brain stem
  - Trans-labyrinthine
    - Small tumors-will sacrifice hearing
  - Middle cranial fossa
    - Small tumors, with the goal of hearing preservation

Surgery

- Recommended for large tumors compressing the brain stem and 4th
- Allows for Hearing Preservation, mostly with small tumors (<1.5cm) and through a middle fossa approach (45-82%)
- Complications:
  - CN VII weakness
  - 43-72 % of patients with large tumors
  - 3-7% of patients with small tumors
  - CSF leak 5-15 %
  - Headaches 23-46%



Gormley et al. Neurosurg 1997; 41(1), 50-8

Acoustic Neuroma

	Microsurgery	SRS
Tumor control rate	97 % (GTR)	98.6 ± 1.1 %
Facial nerve function preservation	67 %	100 %
Useful hearing preservation (Class I or II)	24 %	78.6 ± 5.1 %
Hydrocephalus or CSF leak	6.5 %	0.8 %
Death (perioperative or d/t delayed progression)	0.5 %	0.1 %

Gardener-Robertson Classification

Auditory Grade	Pure Tone Loss dB	% Speech Discrimination
1. Good	0-30	70-100
2. Serviceable	31-50	50-69
3. Nonserviceable	50-90	5-49
4. Poor	91 maximum	1-4
5. None	Nontestable	0

Adapted from Kaplan, DM et al., *Otolaryngology* 2003; 32:23-32

Facial and Trigeminal Nerve Preservation

- Prior to 1991, tumor margin dose were 18-20 Gy preserving:
  - 21% facial weakness at 5 yrs
  - 27% trigeminal sensory loss at 5 yrs
- At 14 Gy – 2.5% risk of new but temporary risk of facial weakness
- At 13 Gy
  - < 1 % new facial weakness
  - 3.1 % trigeminal sensory loss
  - 0 % facial or trigeminal neuropathies for intracanalicular tumors

Lunsford LD, *et al* 2005

Long term results: University of Pittsburgh

≥ 10 years (n = 252)

- 98 % tumor control rate (no further surgery or radiosurgery)
- 6 % initially increased 1-2 mm during the first 6-12 months and lost central enhancement, thereafter regressing
- < 2% required subsequent resection

10 -15 yrs (n = 157)

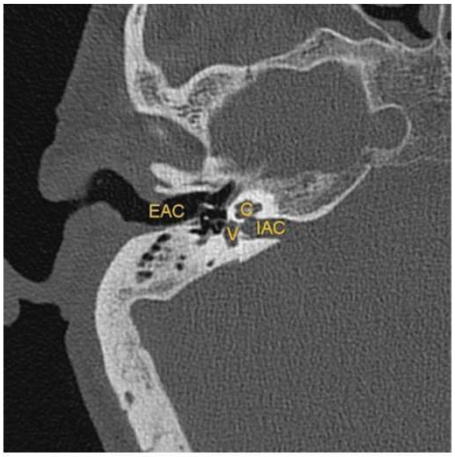
98% local control

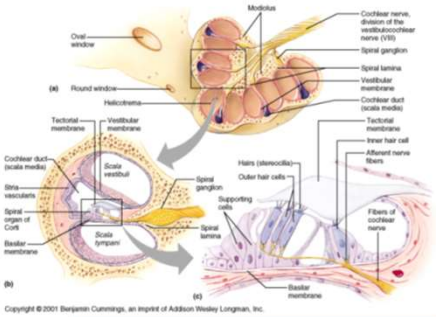
- 73 % reduction in tumor volume
- 25.5% no further change
- 3 % delayed resection
- 0.8 % required management of hydrocephalus

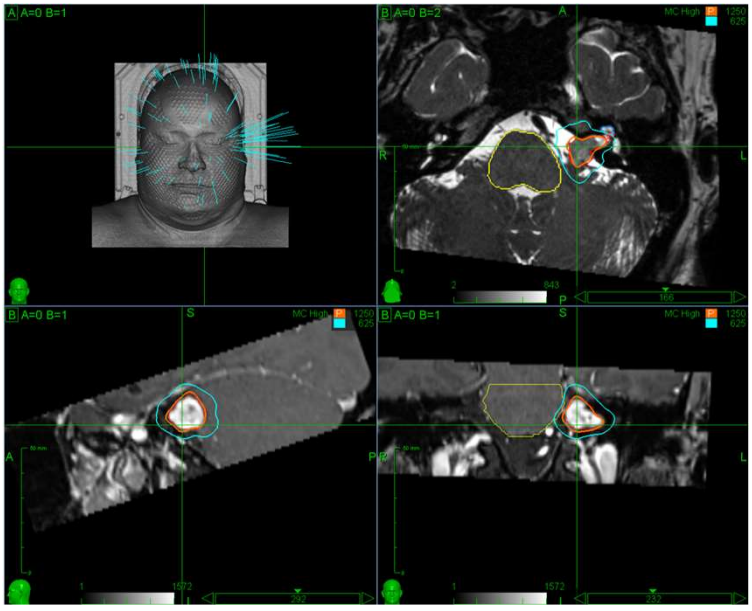
Lunsford LD, *et al* 2005

Treatment planning

- Critical Anatomy for treatment planning:
  - Internal Auditory Canal
  - Cochlea
  - Brainstem
  - Vth Cranial nerve







SRS vs FSR

- Fractionated radiotherapy relies on differences in radiosensitivity and repair capability between normal and neoplastic tissue to achieve a reasonable therapeutic index
  - Allows for treatment of large tumors indenting the brain stem
- Stereotactic radiosurgery relies on the physical parameters of accuracy of targeting and steepness of radiation fall off at the edge of the treatment volume for its therapeutic index
  - Efficient treatment delivery

Linskey, M., *J Neurosurg* (Suppl 3) 2000;93:90-95

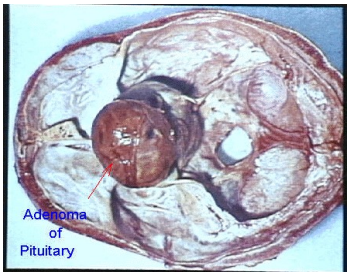
SRS vs FSR

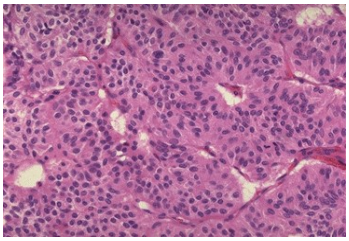
- AN have a very low proliferative index
- The doses of SRS are high enough to affect even benign neoplastic cells regardless of their current stage within the cell cycle
- Three Roles for Fractionated Radiotherapy
  1. Malignant schwannomas
  2. Tumors larger than 3.5cm
  3. NF2 acoustic neuromas (higher proliferative indices)
  4. Hearing preservation???

Linskey, M., *J Neurosurg* (Suppl 3) 2000;93:90-95

Introduction: Pituitary adenomas

- 10–20% of all primary brain tumors
- Often asymptomatic
- Benign sellar tumors
- Most common in adults
  - 3rd – 4th decade
- Subtypes:
  - Excess secretion of normal pituitary hormones (2/3)
  - Non secreting (1/3)

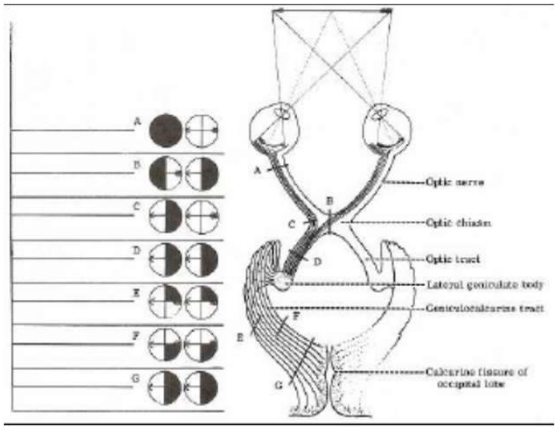




CLINICAL MANIFESTATIONS OF TUMORS OF THE PITUITARY GLAND

- Compression of neural and vascular structures
- Headache
- Hypopituitarism
- Visual symptoms
  - visual field abnormality: bitemporal hemianopsia is the most common
- Papilledema is rare
- May enlarge with pregnancy
- 5% of pituitary adenoma present with pituitary apoplexy

Visual field pathways

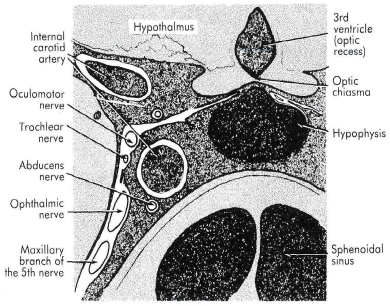


PATHOLOGY

- Endocrine Active (Secretory)-
- Prolactinoma-
  - Most common secretory intrasellar endocrine active tumor
- Growth hormone
  - Before closure of epiphysis gigantism
  - After closure of epiphysis acromegaly
- ACTH:
  - Cushing's Syndrome
- Endocrine Inactive (Non-secretory or null cell adenoma)
- 10% mixed secretory tumor

Treatment options for pituitary adenomas

- Microsurgery
- Medical
- Radiosurgery
- Radiation therapy
- Multimodality approach



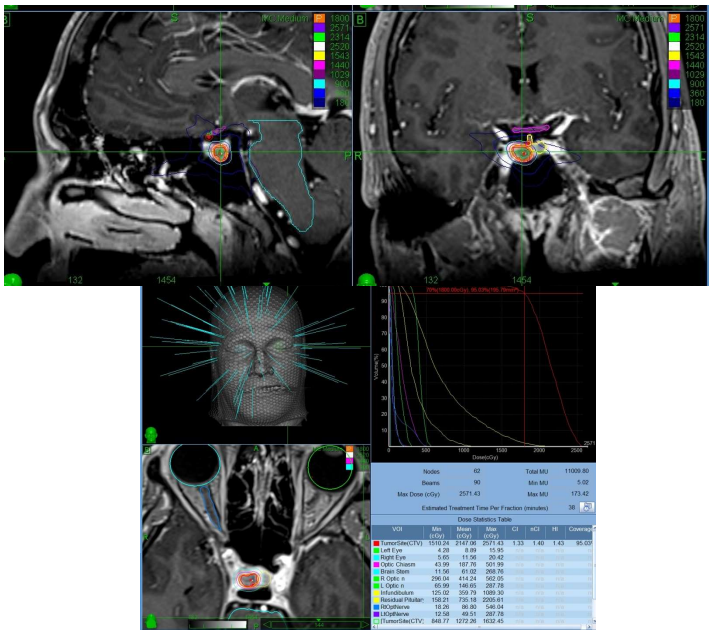
Depends on type of adenoma, symptoms, size at presentation, involvement of adjacent structures, and vicinity to optic apparatus

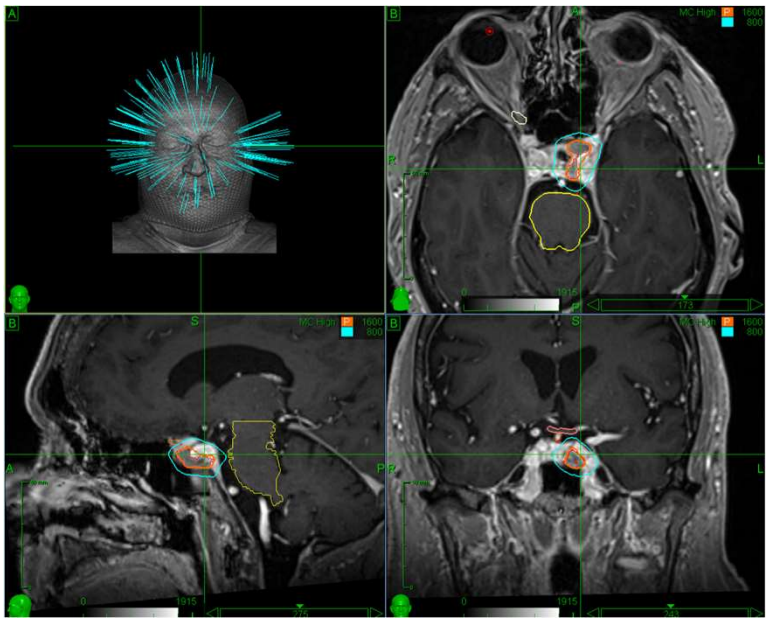
Goals of Pituitary Surgery

- Decompression
- Stop growth of remaining tumor
- Normalize hypersecretion
- Maintain normal pituitary function
- Avoid injury to surrounding structures
  - Hypothalamus
  - Optic nerves
  - Mesial temporal lobes

Indications for SRS of the Pituitary

- Extension into the cavernous sinus
- Incomplete surgical extirpation
- Recurrence post external beam radiation
- Inoperable patients
- Reverses endocrinopathies faster and more reliably than fractionated radiation therapy
- Local control rates 90 -100%





Contraindications for SRS of the Pituitary

- Optic nerve impingement
- Tumor < 3.5 – 4 mm from optic nerve or chiasm
- Does not consistently reduce macroadenomas – not preferred if optic decompression necessary
- Tumor too large - fractionated schedules for larger lesions

Secretory Pituitary Adenomas

- Oversecretion of hormones results in significant incidence of morbidity and reduced life expectancy (acromegaly 4.1 x higher risk to die compared to cured pts or normal population)
- Goals:
  - Tumor control
  - Preservation of normal pituitary function
  - Correction of endocrinopathies is essential to good outcome

Secreting Pituitary and SRS – Special Considerations

- Need higher margin doses than other benign skull base lesions
- Endocrine hypersecretion is difficult to control
- Optic nerves and chiasm are near target, limiting the dose of radiation that can be prescribed
- Pts are younger (fertility and prolonged survival)
- Antisecretory drugs interfere with radiation
- Target (esp post op) can be difficult to define

SRS vs Fractionated Radiotherapy for Acromegaly

	Mean time to N	Cumulative N
SRS	1.03 years	86% after 3.4 yrs
Fractionated radiotherapy	6.52 years	82 % after 12.4 yrs

Landolt AM *et al*, 1998

Sevearingen B *et al*, 1998

Persistent Endocrinopathies post SRS

- Follow-up too short
- Wrong target
- Incomplete target coverage
- Insufficient dose (d/t tumor size or optic apparatus proximity)
- Radioresistance of adenoma at chosen dose
- Radioprotection by drugs

Complications of radiosurgery

Evaluate for endocrine dysfunction (>60 % at 17 yrs)

Vascular injury (4/1621)

Vision loss (16/1621)

Radiation necrosis (13/1621)

Second malignancies (0/1621)

Injury to cranial nerves(21/1567)

Sheehan JP et al. J Neurosurg 102:678-691, 2005
Laws ER et al. J Neuro-oncol 69:257-27, 2004

Summary

- Radiosurgery is an safe and effective treatment option for a variety of benign tumors
- Results appear similar to surgical series
- Treatment complications are the same or lower than surgery for the properly selected patients
- Longer term follow-up will be needed to determine if the local failure and toxicities remain low