ARRO*Case*

Meningioma

SRS post Subtotal Resection

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Case: Presentation

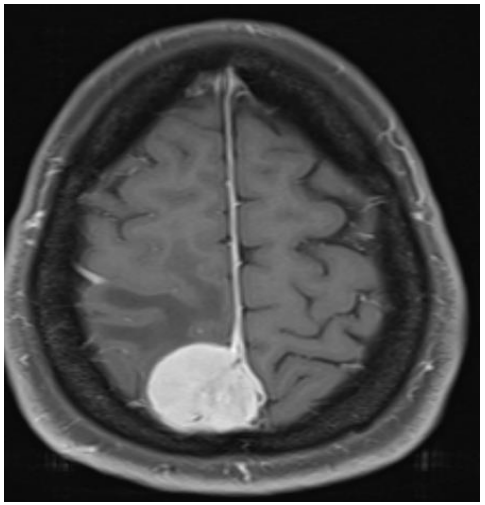
- 39-year-old female presented to emergency department with recent seizure, transient left sided weakness, and syncopal episode.
- **PMH/PSH**: Endometriosis, morbid obesity, asthma, HTN, myomectomy
- **FH**: None relevant
- **Meds:** OCP
- **SH:** Widowed. Former smoker. Social alcohol consumption. Limited exercise.

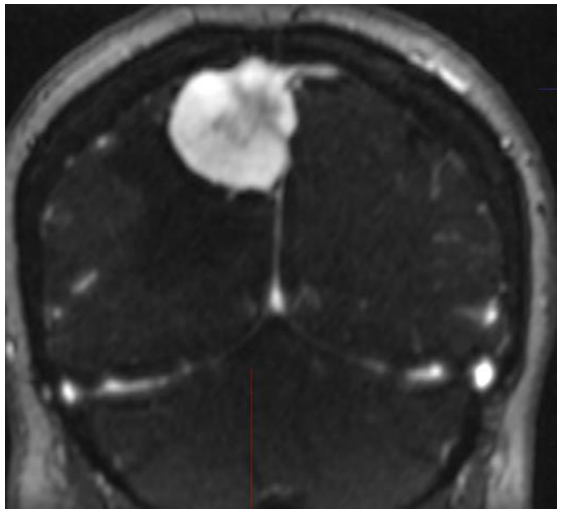
Case: Physical Exam

- **General:** No acute distress. Tearful.
- **CV:** RRR. No m/r/g.
- **Lung:** CTAB. No increased WOB.
- **Abdomen:** Soft, non-tender, non-distended. NABS.
- **Neurologic Exam:**
  - Mental status: Awake, alert, and oriented to person, place, time, and situation. CRANIAL NERVES: Pupils are equally round and reactive to light. CN II-XII grossly intact.
  - STRENGTH: Segmental strength testing revealed 5/5 strength throughout the bilateral upper and lower extremities.
  - REFLEXES: Normal and symmetric with downgoing toes to plantar stimulation.
  - COORDINATION: No ataxia/dysmetria with finger to nose.
  - GAIT: Normal casual and tandem gait with no Romberg.

Case: Diagnostic Workup

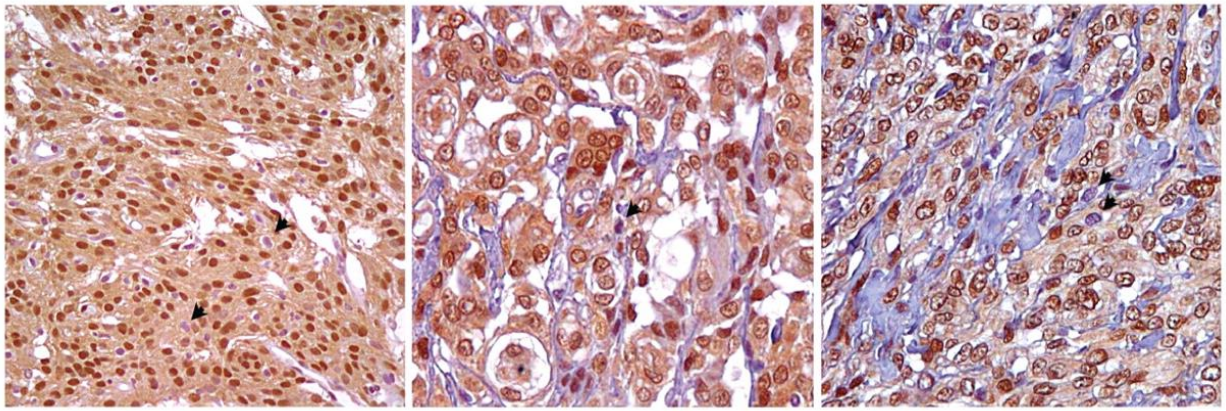
- **Head CT without contrast**
  - Revealed right parietal mass. Borders difficult to distinguish without contrast.
- **Brain MRI with contrast (T1 and Venogram)**
  - Large right parafalcine parietal meningioma with localized mass effect, extensive underlying vasogenic edema
  - MRV suggestive of sagittal sinus invasion and localized occlusion.
    - If venous flow present, surgeon must avoid further sinus injury to prevent venous stroke





Case: Surgical Intervention

- Evaluated by neurosurgery and subsequently underwent maximal safe resection given active symptoms and radiographic appearance of meningioma
- Postoperative MRI demonstrated complete resection of the right side of the parietal mass. Small left parafalcine component still present.
  - Patient not referred to radiation oncology at this time
- Pathology revealed diagnosis of WHO grade I meningioma. No brain invasion. Mitotic figures not elevated.



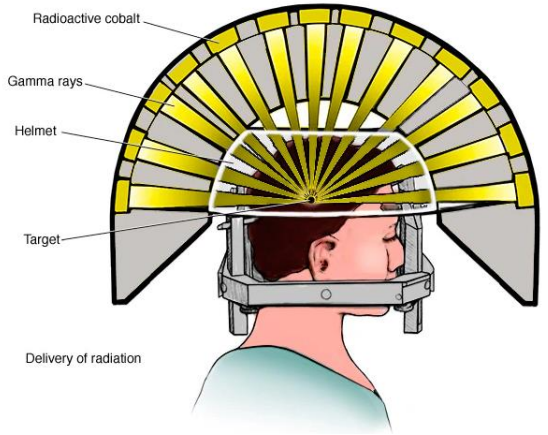
WHO Grade I | WHO Grade II | WHO Grade III

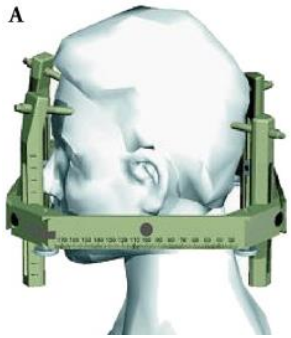
Case: Adjuvant Radiation

- Repeat Brain MRI 1 year post resection demonstrated slight interval increase in the residual parasagittal meningioma, measuring 2.6 cm (from 2.2 cm). Sinus partially patent, stable.
- Radiation Oncology consulted:
  - Patient reported markedly improved left sided paresthesias and weakness. Denied recent seizures.
  - Discussed further management options including continued observation, stereotactic radiosurgery, fractionated external beam radiation therapy, and repeat surgery.
  - Reviewed potential radiotherapy side effects: Radiation necrosis, worsened edema, additional neurologic deficits
- Consensus decision made to proceed with single fraction frame-based SRS based off size (< 3 cm) and location. Total dose: 12 Gy.
  - Observation possible, but further growth would limit SRS as an option and increase risk of radiation necrosis
  - Difficult to surgically remove residual tumor given proximity to sinus

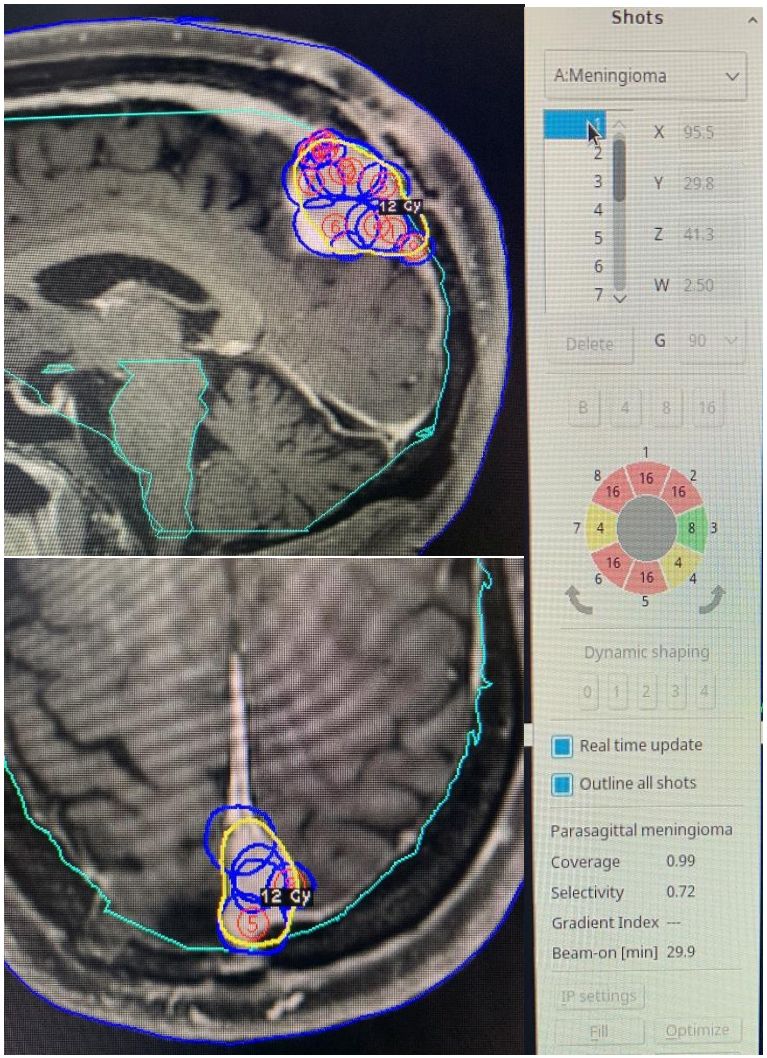
Case: SRS Treatment Delivery

- Leksell Gamma Knife® Icon™
  - 192 60Co sources divided into 8 moveable sectors
    - Each can be collimated to 4mm, 8 mm, 16 mm, or blocked
    - All 192 beams intersect as single point → high dose to conformal target
    - Accommodates both frame and mask-based immobilization with onboard cone-beam CT and intrafraction motion management system





Case: GammaPlan® Treatment Planning



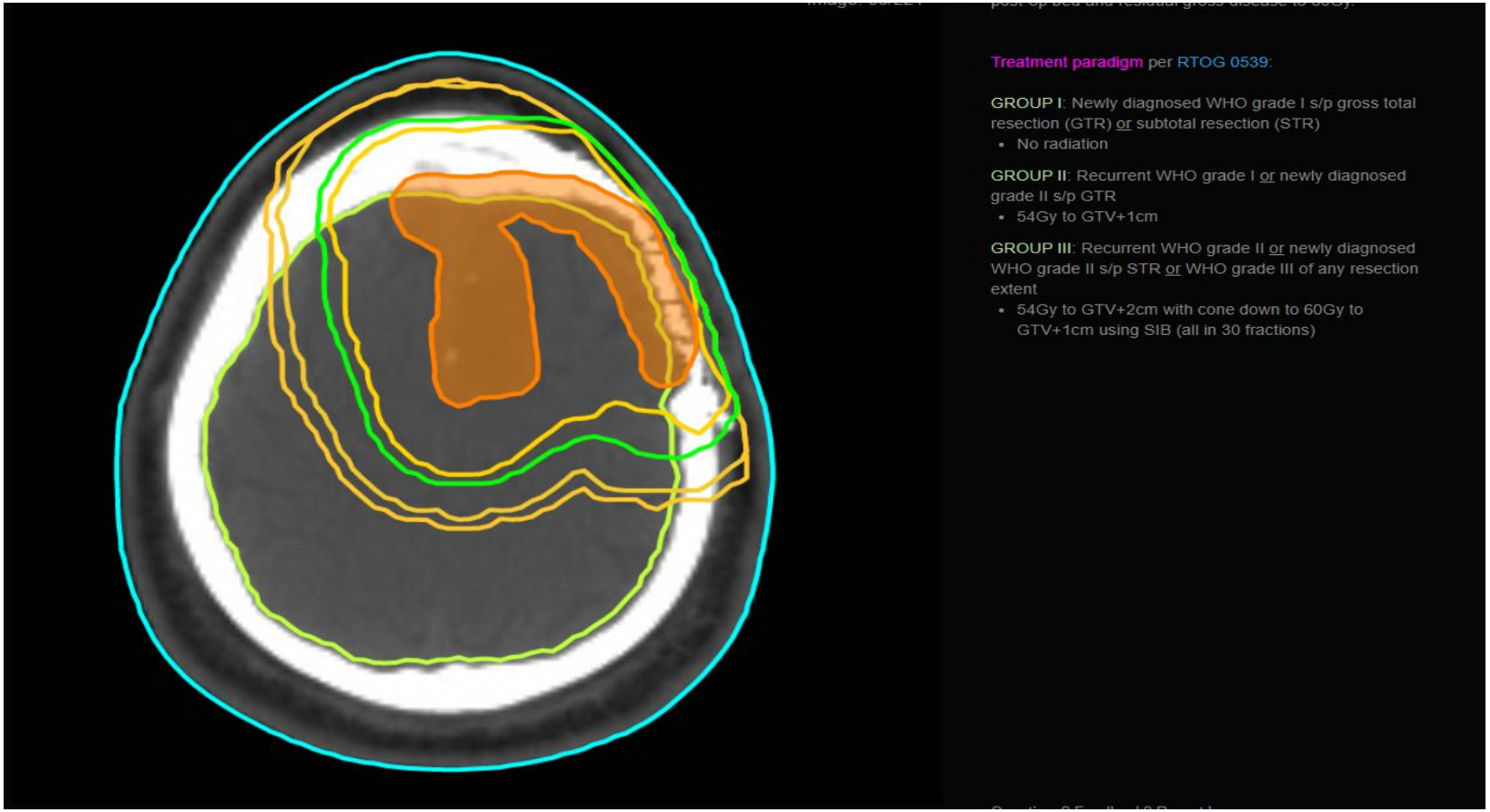
- Forward Planning:
  - Position shots → Adjust collimation (4,8,16mm) and weighting manually
  - Must balance coverage, selectivity, and beam time

- Interactive Inverse Planning Functions:
  - Auto-Fill: Geometrically packs GTV with shots
    - Can customize collimation, composites, etc.
    - Drawback: May use more shots than necessary
  - Optimize: Uses annealing algorithm to optimize shots per user specified:
    - Collimation
    - Weights
    - Coverage vs. Selectivity

eContour

Fractionated RT Example (per RTOG 0539)

Link: https://econtour.org/cases/102

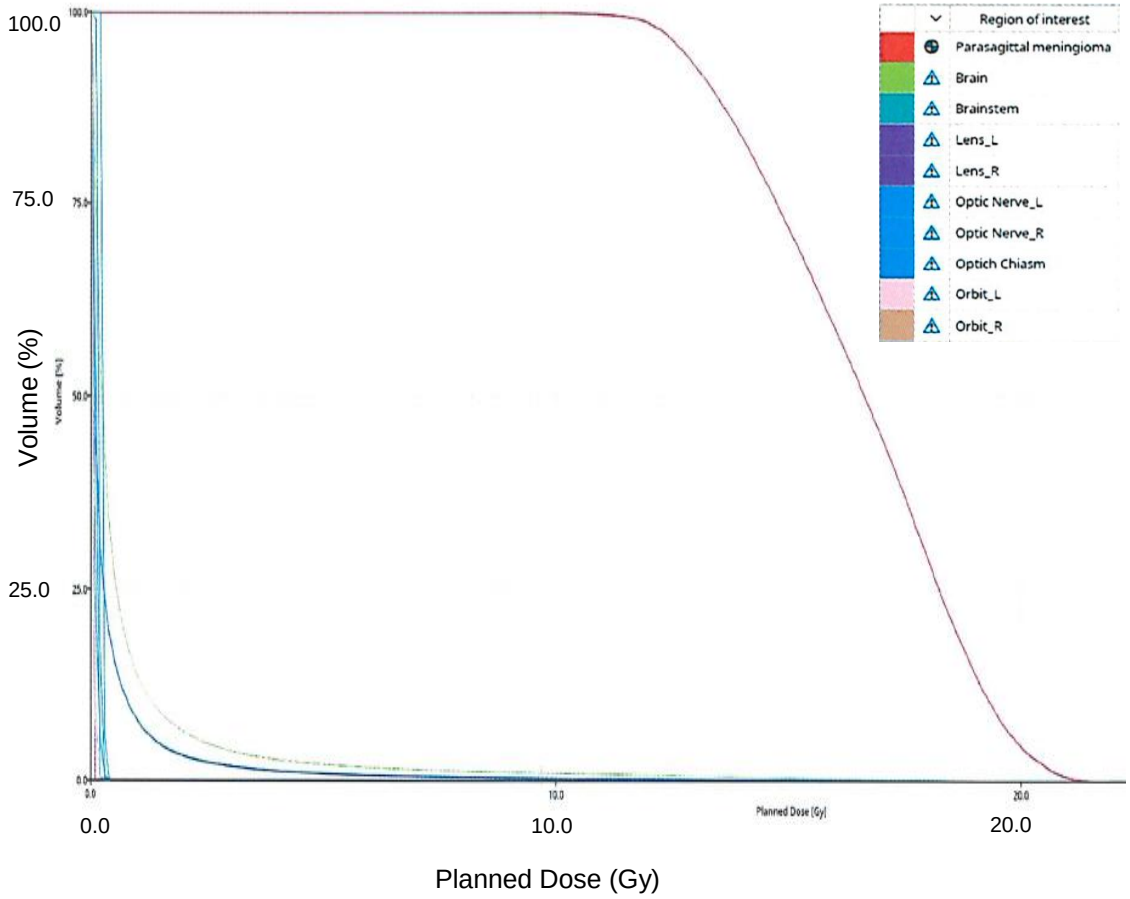


Dosimetric Guidelines

Target/OAR	Fractionated	SRS
GTV	D100% ≥ 95%	D100% ≥ 95%
Brain	50 Gy (whole brain)	12 Gy (5-10cc)
Brainstem	54-60 Gy	15 Gy
Cord	45-50 Gy	14 Gy
OC/ON	55 Gy	10 Gy
Cochlea	45 Gy (Mean)	4 Gy (Mean)
Lens	7 Gy	1.5 Gy
Orbit	55 Gy	8 Gy

****Max point dose unless otherwise specified

Case: DVH Evaluation

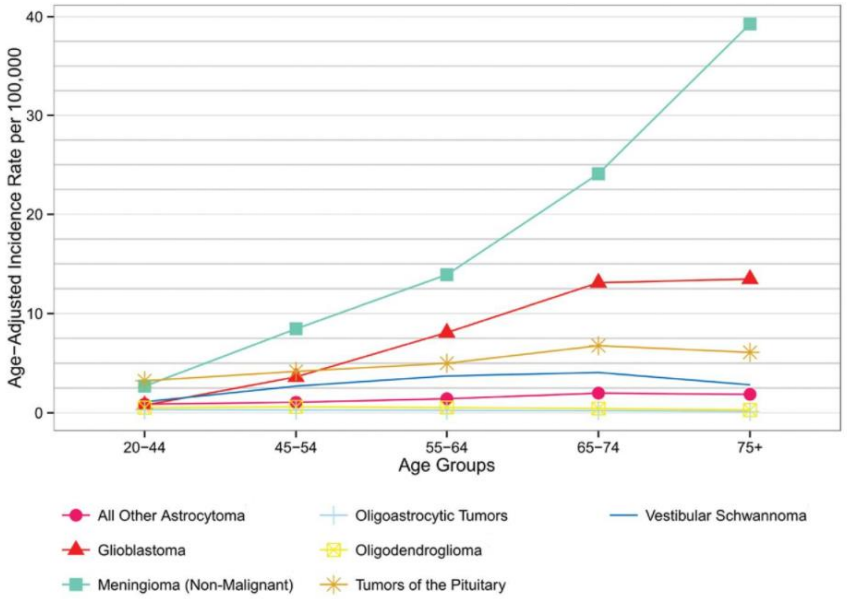


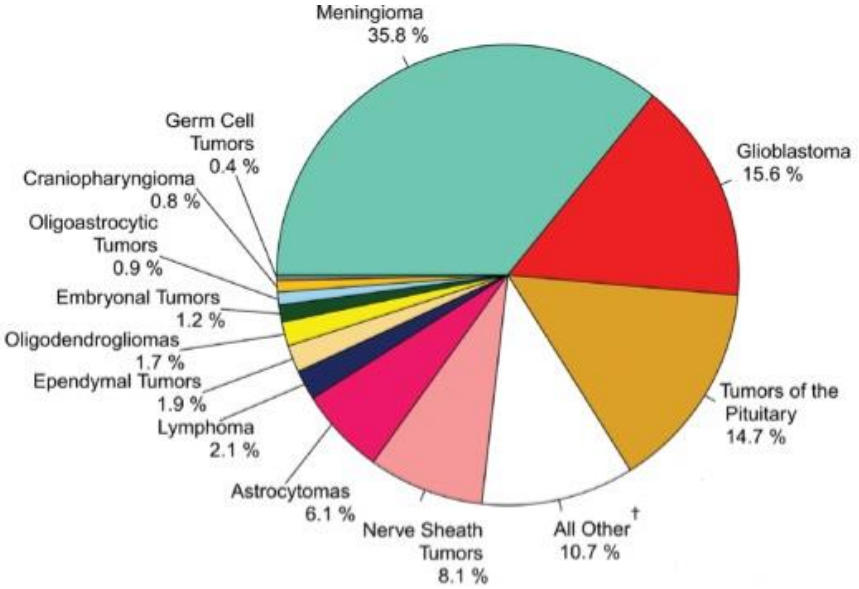
GTV	98.6%≥ 12 Gy
Brain	12 Gy (9.8 cc)
Brainstem	Max: ≤0.5
ON_L	Max: ≤0.5
ON_R	Max: ≤0.5
OC	Max: ≤0.5
Orbit_L	Max: ≤0.1
Orbit_R	Max: ≤0.1
Lens_L	Max: ≤0.1
Lens_R	Max: ≤0.1

Meningioma Overview

Epidemiology

- > 26,000 new cases per year
- Roughly 1/3 of all primary brain tumors
- Increased incidence with age
- 50% diagnosed incidentally



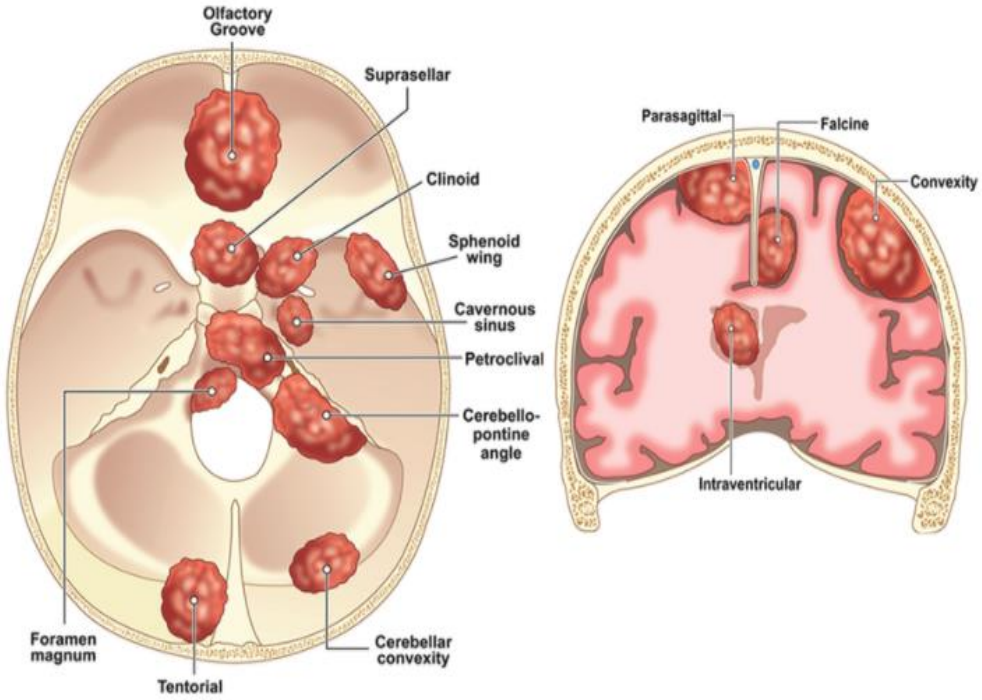


Risk Factors

- Intrinsic
  - Female (2:1), African American, breast and thyroid cancer, uterine fibroids, genetic polymorphisms (GLTSCR1, BRCA1, NF2, etc.), BMI
- Extrinsic
  - Ionizing radiation (pediatric radiotherapy, tinea capitis treatment)
    - No known association with low energy electromagnetic fields (cell phones, power lines)
  - Exogenous hormones? Controversial
    - ~ 80% of meningiomas have progesterone receptors, 40% estrogen receptors
    - No definitive association with oral contraceptives, HRT, etc.

Anatomic Sites

- Originate from arachnoid cap cells
- Common sites: parasagittal, falcine, cerebral convexity, sphenoid wing
- < 10% found in spinal meninges



WHO Classification

- Grade 1 (> 80%), benign
  - Features: Calcifications, psammoma bodies
- Grade 2 (5-15%), atypical, still benign
  - Brain invasion OR
  - 4-19 mitoses/10 HPF OR
  - ≥ 3 atypical features:
    - Small cell + high nucleus to cytoplasm ratio, increased cellularity, large nucleoli, patternless or sheet like growth, focal of necrosis
- Grade 3 (1-2%), malignant/anaplastic
  - ≥ 20 mitoses/10 HPF OR
  - Sarcomatous/Carcinomatous/Melanomatous features

WHO Classification Subtypes

Grade 1 (Benign)	Grade II (Atypical)	Grade III (Malignant)
Psammomatous	Atypical (criteria)	Anaplastic (criteria)
Fibroblastic	Clear Cell	Papillary
Meningothelial	Choroid	Rhabdoid
Transitional		
Angiomatous		
Secretory		
Metaplastic		
Microcystic		
Lymphoplasmacyte rich		

Simpson Grade

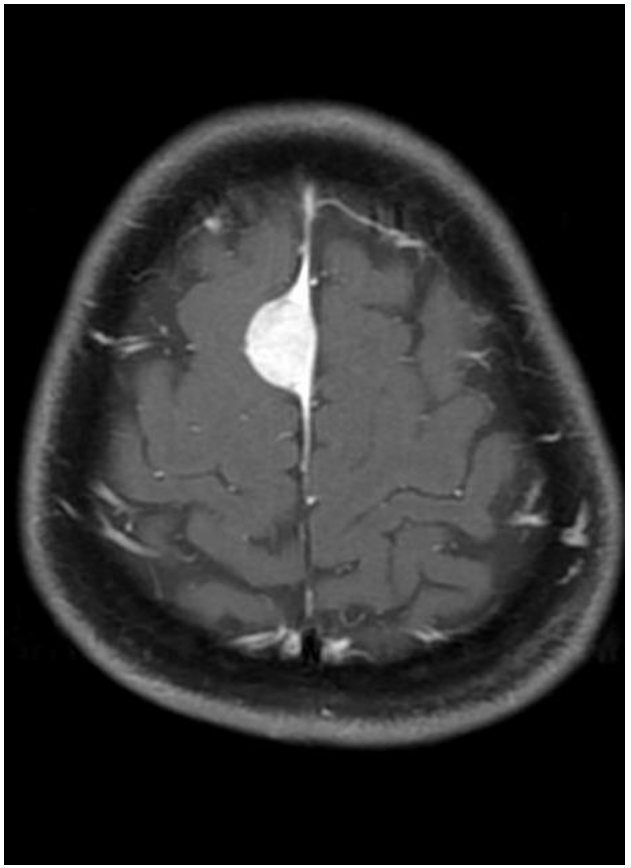
- *The recurrence of intracranial meningiomas after surgical treatment. Simpson D. 1957.*
  - Evaluated recurrence rates after resection alone, 265 pts

Gross total resection

Grade	Resection Extent	Recurrence Rate (10 year)
1	Complete removal including resection of underlying bone and associated dura	9%
2	Complete removal and coagulation of dural attachment	19%
3	Complete removal without resection of dura or coagulation (e.g., invaded sinus)	29%
4	Subtotal resection	44%
5	Simple decompression with or without biopsy	100%

Standard Workup

- H&P with full neurological exam
  - Presentation: Headache or asymptomatic most common. May present with various focal deficits based on anatomic location
- CT Head (with contrast)
  - Homogenously contrast enhances and isodense without contrast
  - Hyperostosis (5%), differs from skull invasion
- MRI Brain/Skull Base (T1 with contrast)
  - Homogenously contrast enhances and isotense without contrast
  - Broad dural base “tail” common
  - > 50% with vasogenic edema, positively correlated with aggressiveness
  - T2 hyperintensity seen in hypervascular tumors (choroid, angiomatous)
- Radiographic findings sufficient for final diagnosis



Initial Management Options

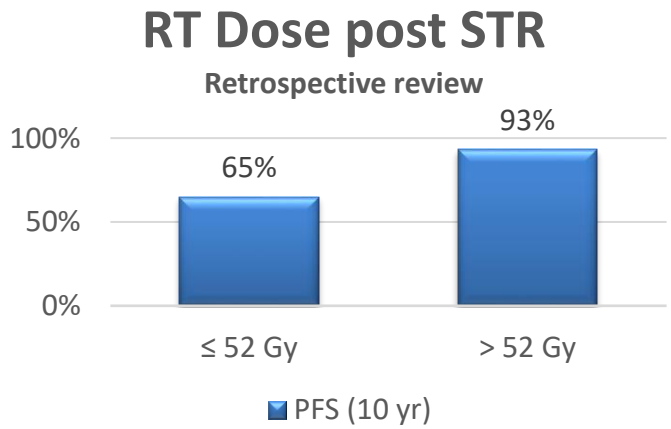
Following radiographic diagnosis

1. Observation
   - Preferred for small asymptomatic tumors (≤ 3cm)
   - Consider potential for future symptoms (E.g., proximity to optic nerve)
   - Annual MRI for surveillance; 1-2 mm growth per year is typical
2. Maximal Safe Resection
   - Preferred intervention if accessible, especially if acutely symptomatic
   - Consider patient's age, ECOG/KS, preference, comorbidities
   - Consider likelihood of complete resection, potential for neurologic consequence
   - Post operative RT dependent on WHO grade and resection extent
3. Definitive Radiotherapy
   - Typically reserved for unresectable disease
   - Fractional RT or stereotactic radiosurgery
   - Dose dependent on WHO grade and size

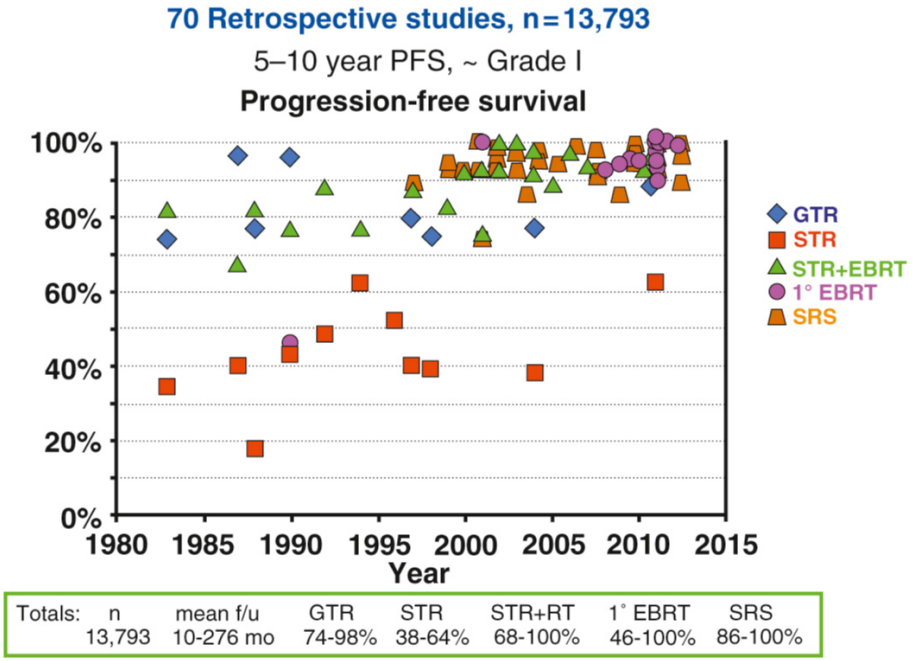
NCCN National Comprehensive Cancer Network®

Treatment Approach: WHO Grade I

- Preferred primary treatment is resection
  - GTR → Observation
  - STR → Observation OR Adjuvant RT
  - Unresectable → Definitive RT
- Fractionated RT Dose
  - 50.4-54 Gy/28-30fx for all Grade I
  - Suggested PFS advantage over 52 Gy



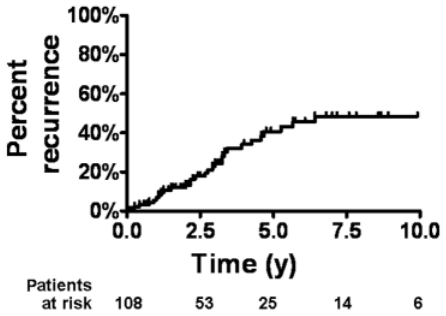
Goldsmith et al. Postoperative irradiation for subtotally resected meningiomas. Columns above include only 'benign' meningiomas (n = 117)



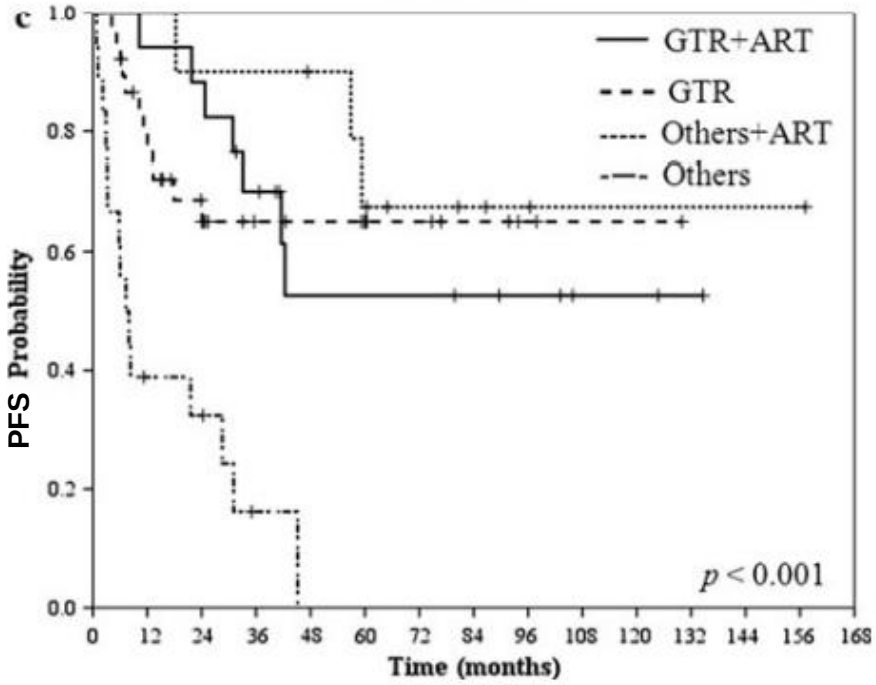
Treatment Approach: WHO Grade II

- Preferred primary treatment is still resection
  - GTR or STR → Adjuvant RT
  - Unresectable → Definitive RT
- Fractionated RT Dose
  - GTR: 54 Gy/30fx
  - STR/Unresectable: 59.4-60 Gy/30-33fx

Atypical meningioma post GTR alone (2009)



The role of adjuvant RT in atypical meningioma (2013)

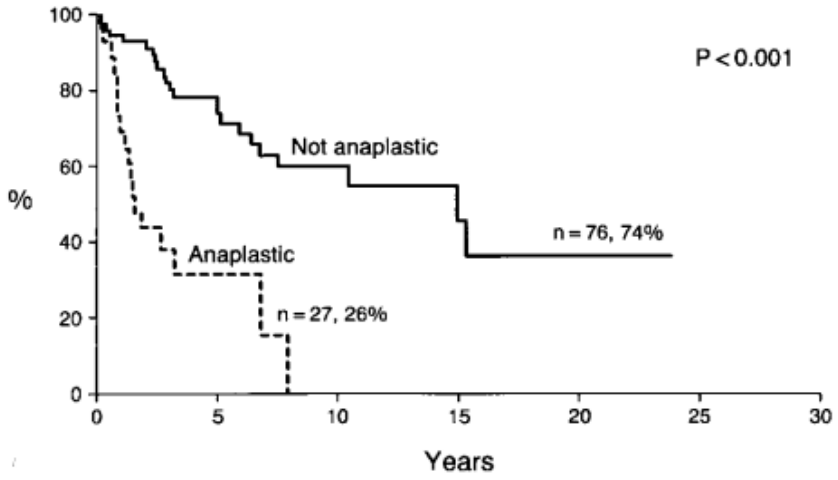


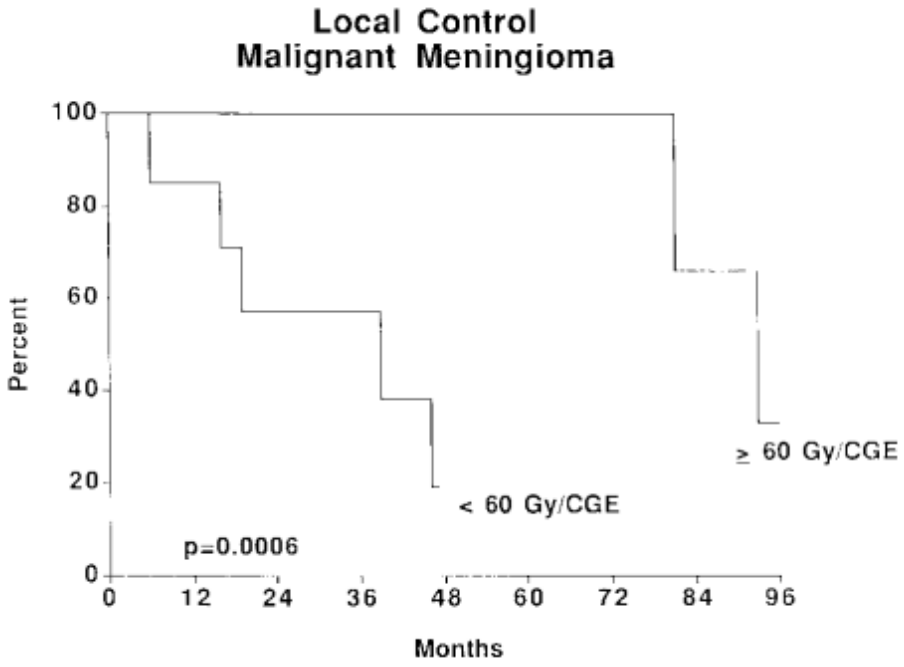
PFS advantage in Others + ART vs. Others (Others = STR + unknown)

Treatment Approach: WHO Grade III

- Resection if accessible
  - GTR or STR → Adjuvant RT
  - Unresectable → Definitive RT
- Fractionated RT Dose
  - 59.4-66 Gy/30-33fx for all grade III

Anaplastic Meningioma OS (1999)

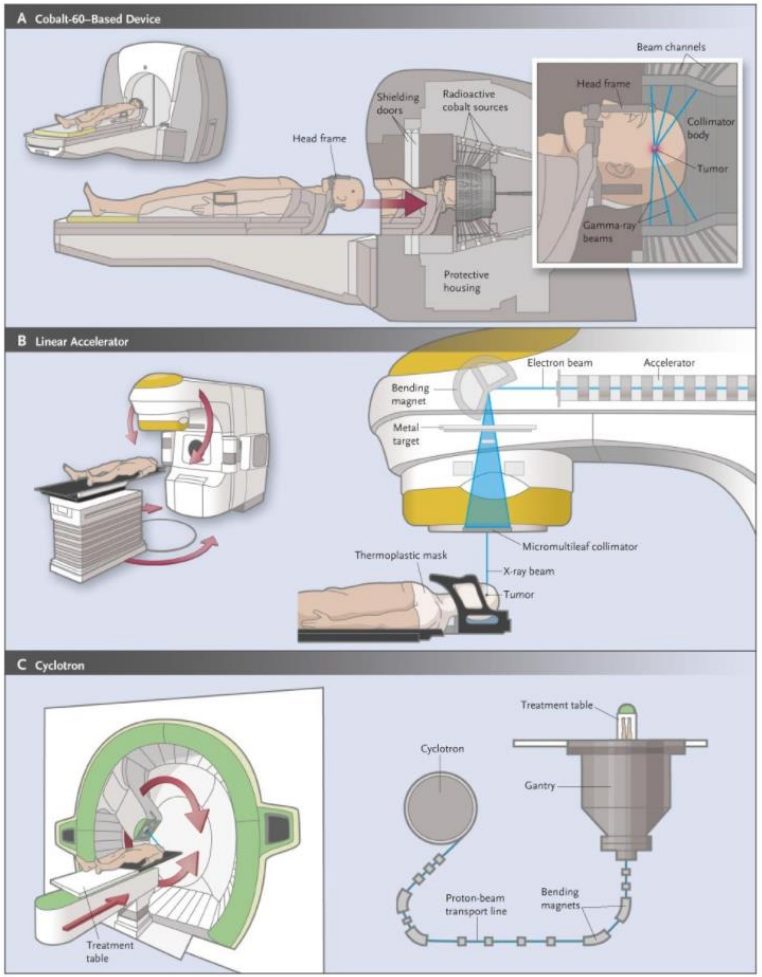




Hug et al. Management of atypical and malignant meningiomas: role of high-dose 3D-CRT. (n = 13). 2000.

When To Consider SRS

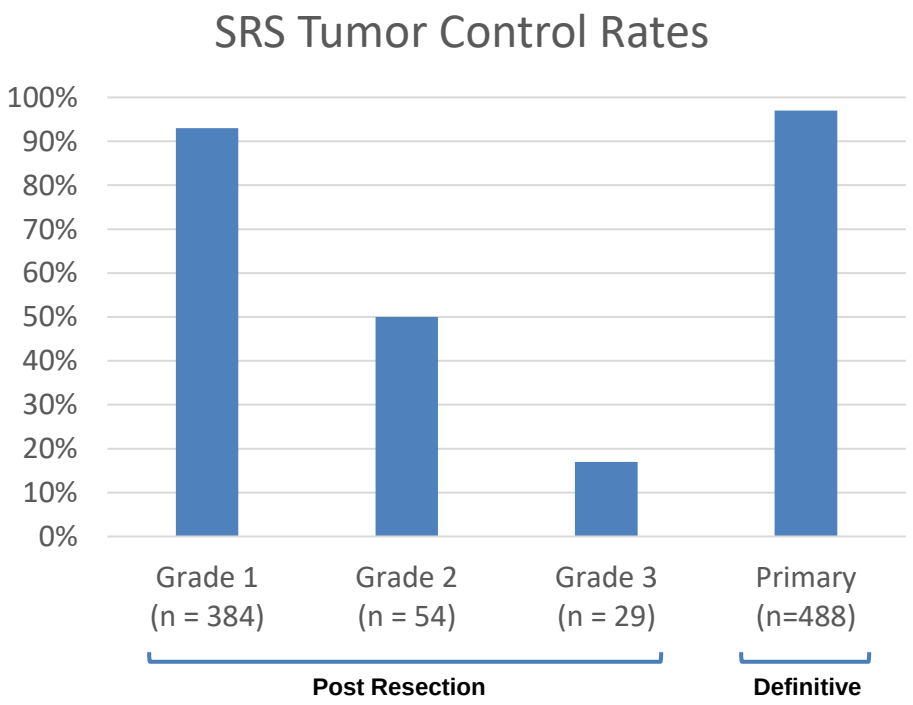
- Suitability Criteria:
  1. Small tumor volume (≤ 3cm)
  2. Well defined GTV margins (**no CTV/PTV needed**)
  3. Maintains dose constraints for proximal OARs
  4. WHO Grade I
- Consider FSRT (2-5 fractions) if:
  1. Tumor volume 2-5cm
  2. Very close proximity to OARs
  3. Reirradiation
- Consider conventional fractionation if GTV < 3mm from optic chiasm/nerves or parasagittal (edema risk)[25]



Treatment Approach: SRS

Kondziolka et al. Radiosurgery as Definitive Management of Intracranial Meningiomas (2008)

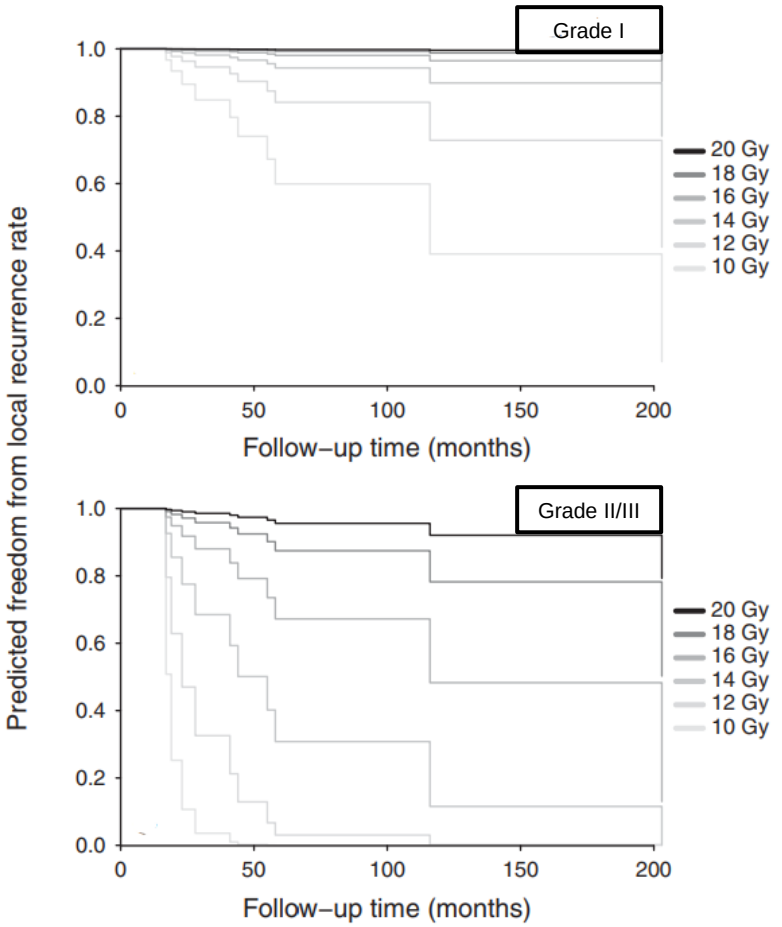
- > 900 pts, prospective review, 18-year interval
- Mean dose: 14 Gy/1fx
- Adjuvant SRS Rationale
  - Small volume (< 3.5cm), residual/recurrent tumor post resection
- Definitive SRS Rationale
  - Small volume (< 3.5cm)
  - Symptomatic and unresectable
  - Significant comorbidities
  - Patient preference



Treatment Approach: SRS

Sethi et al. Dose-Response Relationships for Meningioma Radiosurgery (2015)

- Dose analysis of WHO Grade I-III meningiomas post GKSRS
  - n = 101, 1998-2001
- Median Dose (single fraction)
  - Grade I: 14 Gy (r, 10-18 Gy)
  - Grade II/III: 16 Gy (r, 12-20 Gy)
    - Mostly recurrent post resection
- Local failure association:
  - Lower GKSRS dose
  - Higher grade



Treatment Approach: SRS

Treatment of WHO Grade II Meningiomas with SRS: Identification of an Optimal Group for SRS Using RPA (2021)

- Multi-institutional retrospective review of 233 pts
- All pts with WHO grade II meningioma treated with SRS
  - All with recurrent or persistent disease
  - Prior surgery: GTR (48.3 %), STR (51.7%)
- RPA prognostic group model, 1 point for each of the following:
  - Age > 50
  - Treatment volume > 11.5 cc
  - Prior radiation or multiple surgeries
- “Good” = 0-1 points; “Poor” = 2-3 points
- “Good” prognostic group: 3-year PFS = 63.1%
  - Authors suggest this group should be considered for SRS specifically

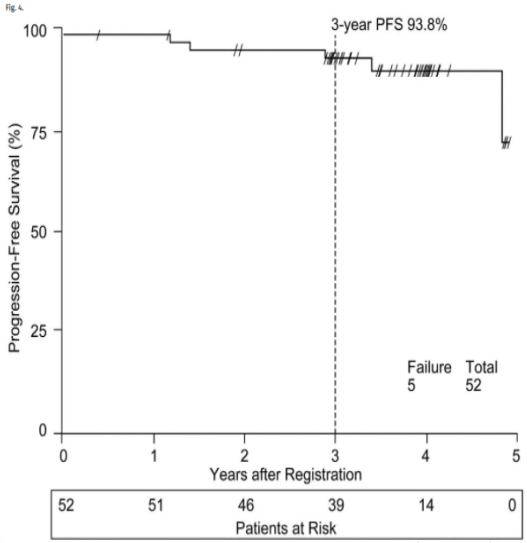
Prospective Trials: RTOG 0539

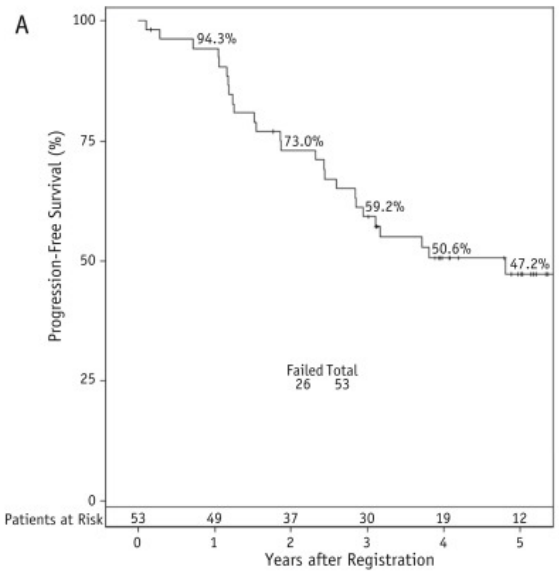
RISK GROUPS		
LOW (n=65)	**INTERMEDIATE (n=56)**	**HIGH (n =57)**
WHO Grade I → GTR or STR	Recurrent WHO Grade I *OR* WHO Grade II → GTR	WHO Grade II → STR *OR* Recurrent WHO Grade II *OR* WHO Grade III
Observation	**54 Gy/30 fx**	**60Gy/30 fx (HD PTV)** **54 Gy/30 fx (LD PTV)**

HD PTV = Gross tumor + resection bed + 1 cm
LD PTV = Gross tumor + resection bed + 2 cm

Prospective Trials: RTOG 0539

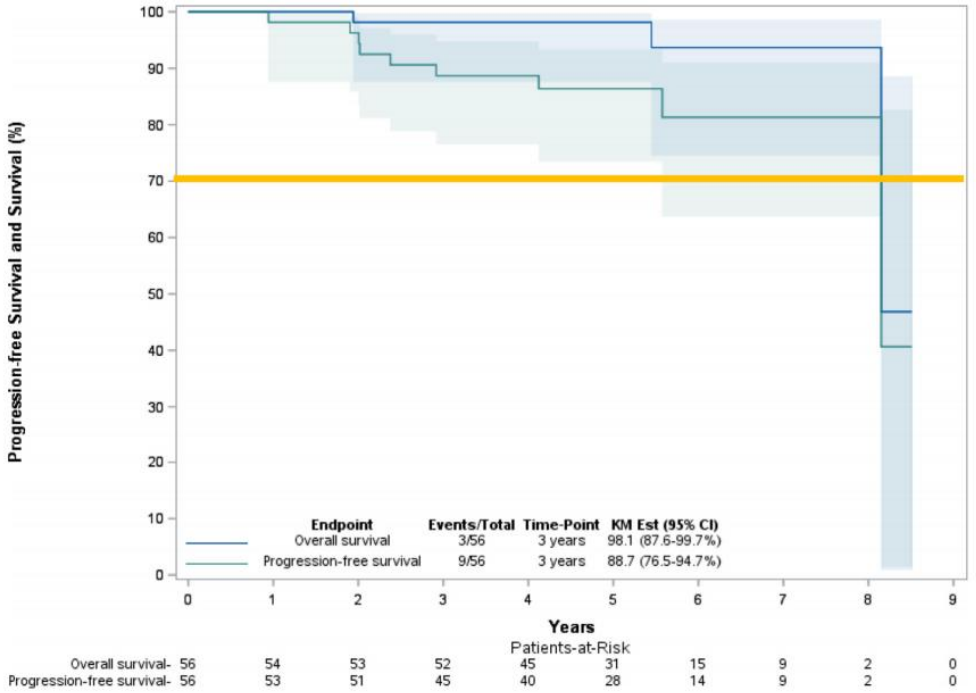
Primary Endpoint = Three Year PFS		
LOW	**INTERMEDIATE**	**HIGH**
3-year PFS: 91.8% 3-year LC: 93.5% 3-year OS: 98.4%	3-year PFS: 93.8% 3-year LC: 95.9% 3-year OS: 96.0%	3-year PFS: 58.8% 3- year LC: 68.9% 3-year OS: 78.6%
40% 5-year LF post STR		92.9% of recurrences within the RT PTV





Prospective Trials: EORTC 22042-26042

- WHO Grade II post GTR (n=56)
  - Observation Cohorts: WHO GII post STR and WHO GIII
- Escalated dose: 60 Gy
  - 50% IMRT, 46 % 3DCRT, 4% FSRT
- Primary Endpoint: 3-year PFS > 70%
- Results:
  - 3-year PFS: 88.7%
  - 3-year OS: 98.2%
  - Late Toxicity ≥ G3: 14.3%



Ongoing Phase III Trials

WHO Grade II post GTR

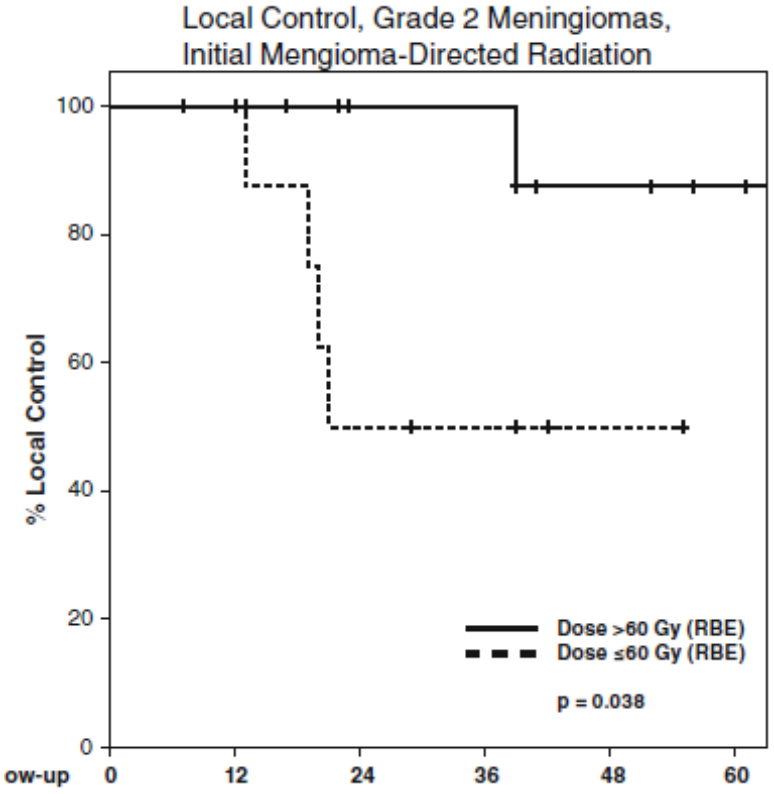
- NRG BN-003 Oncology
  - 59.4 Gy/33fx vs. Observation
  - Primary endpoint: PFS
- ROAM/EORTC-1308
  - 60 Gy/30fx vs. Observation
  - Primary endpoint: DFS

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Role of Heavy Ions

Proton Therapy

- 2005-2013, 22 pts WHO Grade II Meningioma
  - 12 adjuvant
  - 10 recurrence/progression of residual
- Median dose 63 Gy (RBE) proton
- Local Control 71.1% Overall
  - **87.5%** if >60 Gy (RBE)
  - 50.0% if <60 Gy (RBE)



Role of Heavy Ions

Systemic Review of Heavy Ions

Table 1. Summary of the Studies Using Ion Radiotherapy in Treatment of Atypical and Anaplastic Meningiomas

Study	Experimental Design	Country	Meningioma World Health Organization Grade, n*	Type of Ion Therapy	Median Time of Follow-Up (months)	Reported Local Control (Grade, %, months)
Boskos et al., 2009[22]	Retrospective cohort	France	II, 19 III, 5	Proton	48	II/III, 46.7, 60
Slater et al., 2012[29]	Retrospective cohort	United States	II, 4	Proton	74	II, 50, 60
Rieken et al., 2012[28]	Retrospective cohort	Germany	II, 3 III, 1	Carbon	4.5	II/III, 100, 3
Chan et al., 2012[23]	Prospective case series	United States	II, 4 III, 2	Proton	145	II/III, 83, 145
Weber et al., 2012[30]	Retrospective case series	Switzerland	II, 9 III, 2	Proton	54.8	II/III, 49.1, 60
Adeberg et al., 2012[21]	Prospective cohort	Germany	II, 62 III, 23	Carbon	73	II, 95, 24 III, 63, 24
Combs et al., 2013[9]	Retrospective cohort	Germany	II/III, 36	Carbon	12	II/III, 54, 12, 33, 24
Combs et al., 2013[24]	Prospective cohort	Germany	II, 23 III, 4	Carbon	6	II/III, 67, 6
Mozes et al., 2017[26]	Retrospective cohort	Germany	II, 17 III, 5	Carbon	49.5	II/III, 100, 48
Murray et al., 2017[27]	Retrospective cohort	Switzerland	II, 33 III, 2	Proton	56.9	II/III, 68.0, 60
El Shafie et al., 2018[25]	Retrospective cohort	Germany	II, 25† 4/25 proton III, 6 0/6 proton	Proton Carbon	49.7	II, 50, 34.3 III, 50, 10.2
El Shafie et al., 2018[1]	Retrospective cohort	Germany	II, 7 III, 1	Proton Carbon	46.8	II/III, 75, 60

RT Dose Summary

	WHO Grade I	WHO Grade II	WHO Grade III
GTR	Observation	54-60 Gy/30fx *OR* Observation	59.4-66 Gy/30-33 fx
STR	Observation *OR* 50.4-54 Gy/28-30fx *OR* SRS 12-14/1fx Gy	59.4-60 Gy/30-33 fx SRS controversial, consider prognostic group	59.4-66 Gy/30-33 fx SRS controversial
Unresectable *OR* Recurrence	50.4-54 Gy/28-30fx *OR* SRS 12-14/1fx Gy	59.4-60 Gy/30-33 fx *OR* SRS 14-18/1fx Gy	59.4-66 Gy/30-33 fx *OR* SRS 18-24/1fx Gy

References

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