Advances in Meningioma Management

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MASSACHUSETTS GENERAL HOSPITAL
RADIATION ONCOLOGY

HARVARD MEDICAL SCHOOL

Disclosures

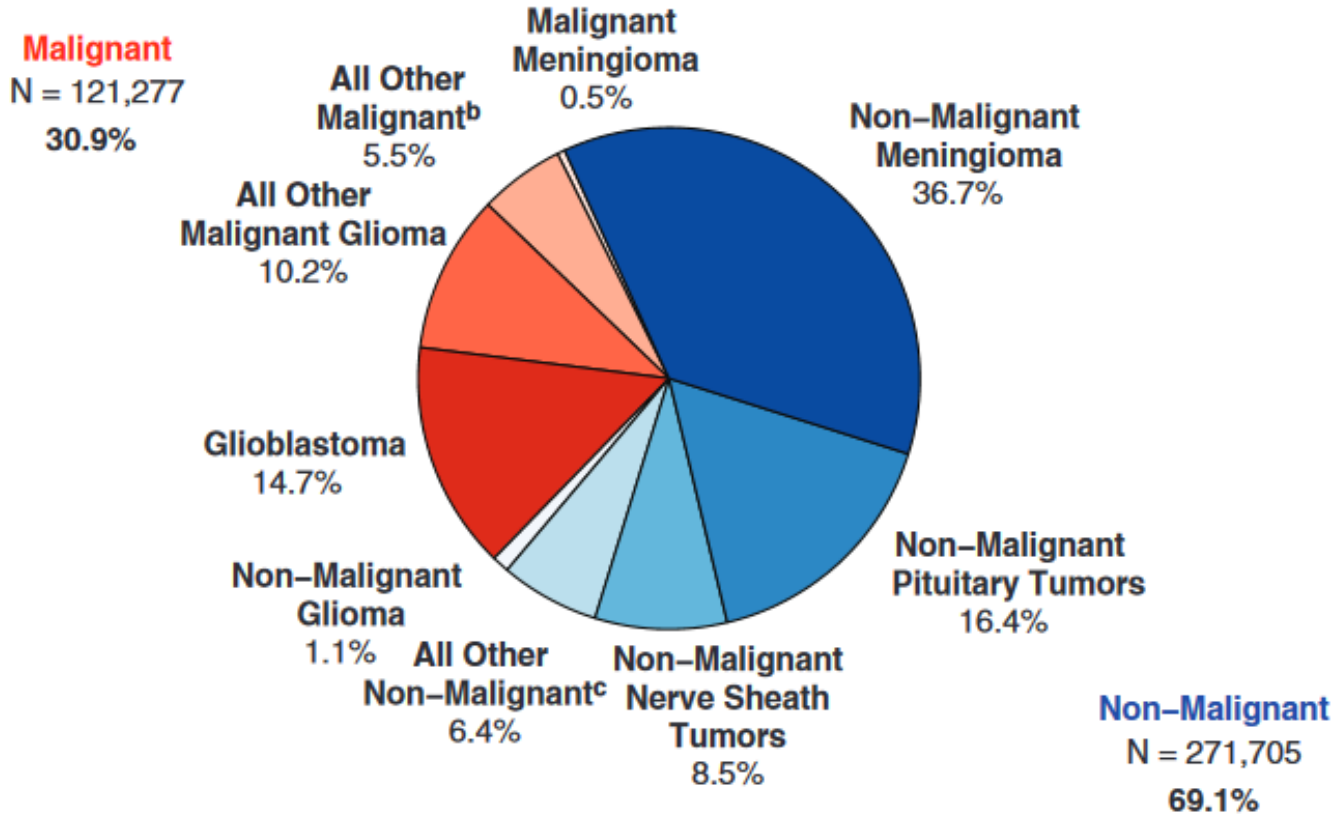
- None relevant
- Others:
  - UpToDate, writer
  - prIME Oncology, symposium speaker
  - Cleveland Clinic, expert consultant

Outline

- The problem of meningiomas
- Overview of standard of care
- Update on benign meningiomas
- Update on high grade meningiomas
- Imaging, pathology and genetics

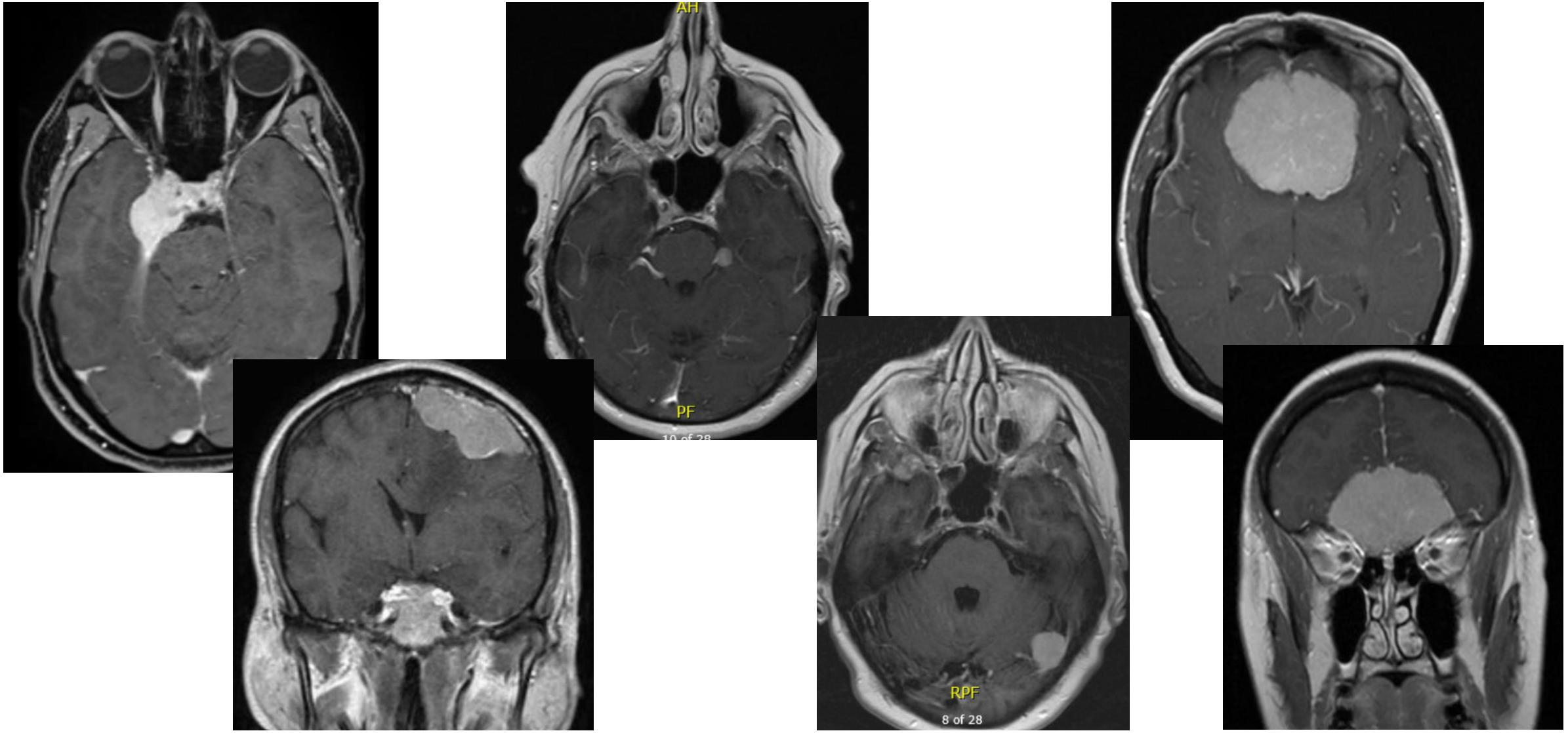
Meningiomas

- Most common primary brain tumor, ~37%
- Range from “benign” to aggressive
- Variety of locations along lining of brain
- Risk factors: hormones, radiation

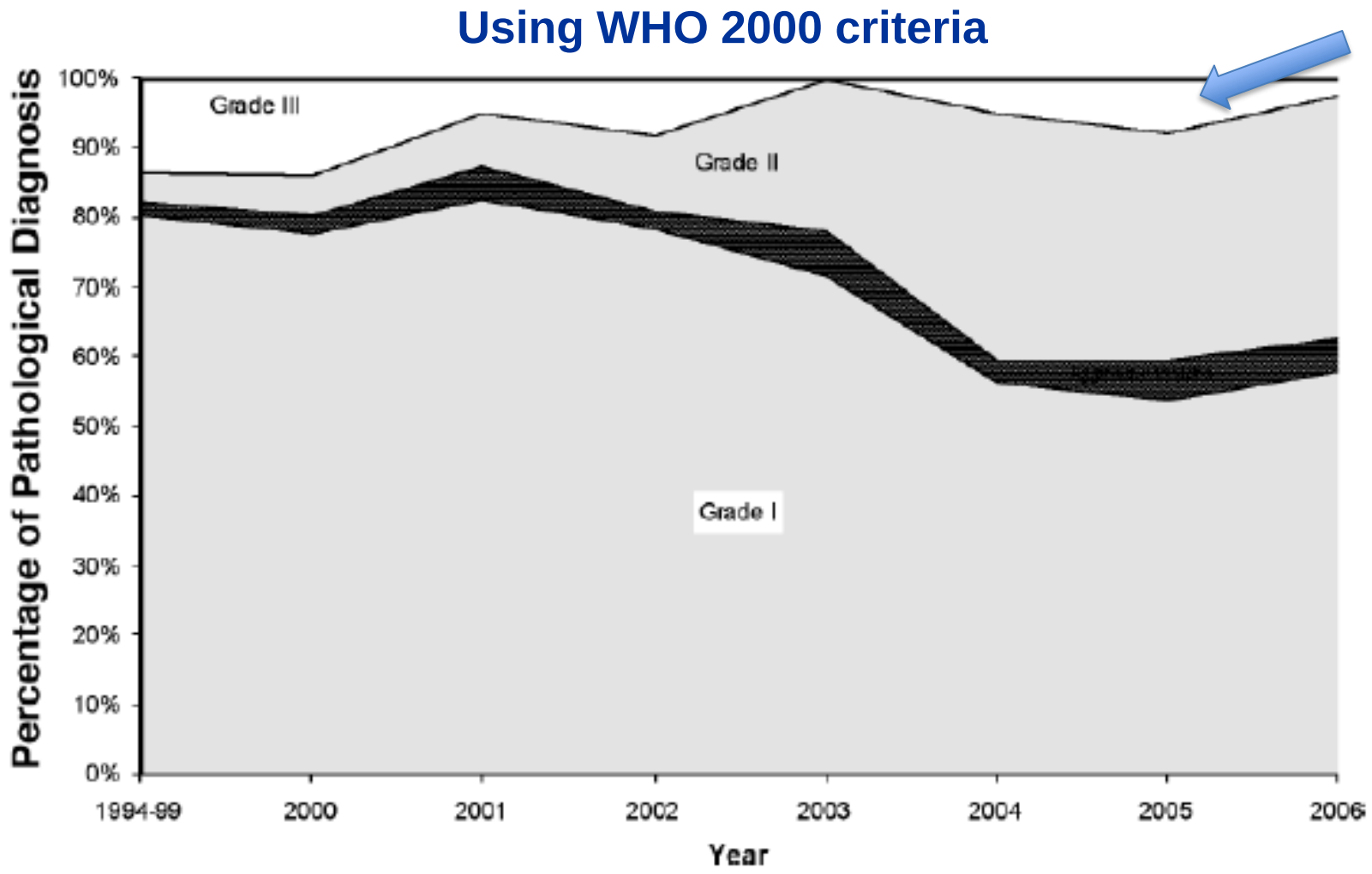


CBTRUS 2011-2015
Ostrom QT et al. Neuro Oncol 2018

Meningiomas: A Variety of Shapes & Sizes



Distribution of Meningioma by Grade



Grade 3 Anaplastic or Malignant — **2-3%**

Grade 2 Atypical — **25-30%**

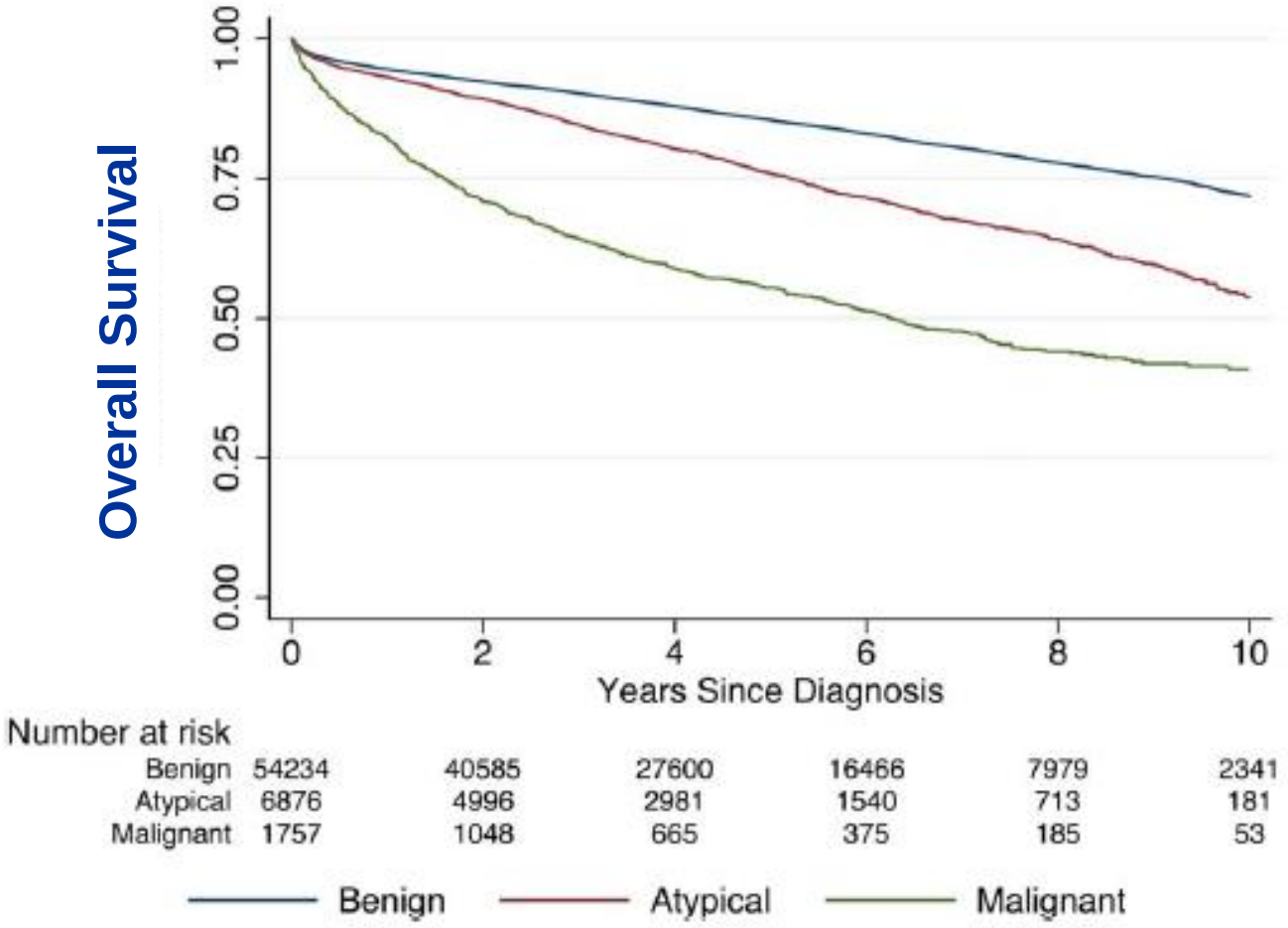
Grade 1 Benign — **70-75%**

Pearson BE et al. Neurosurg 2008

Survival of Meningioma Patients

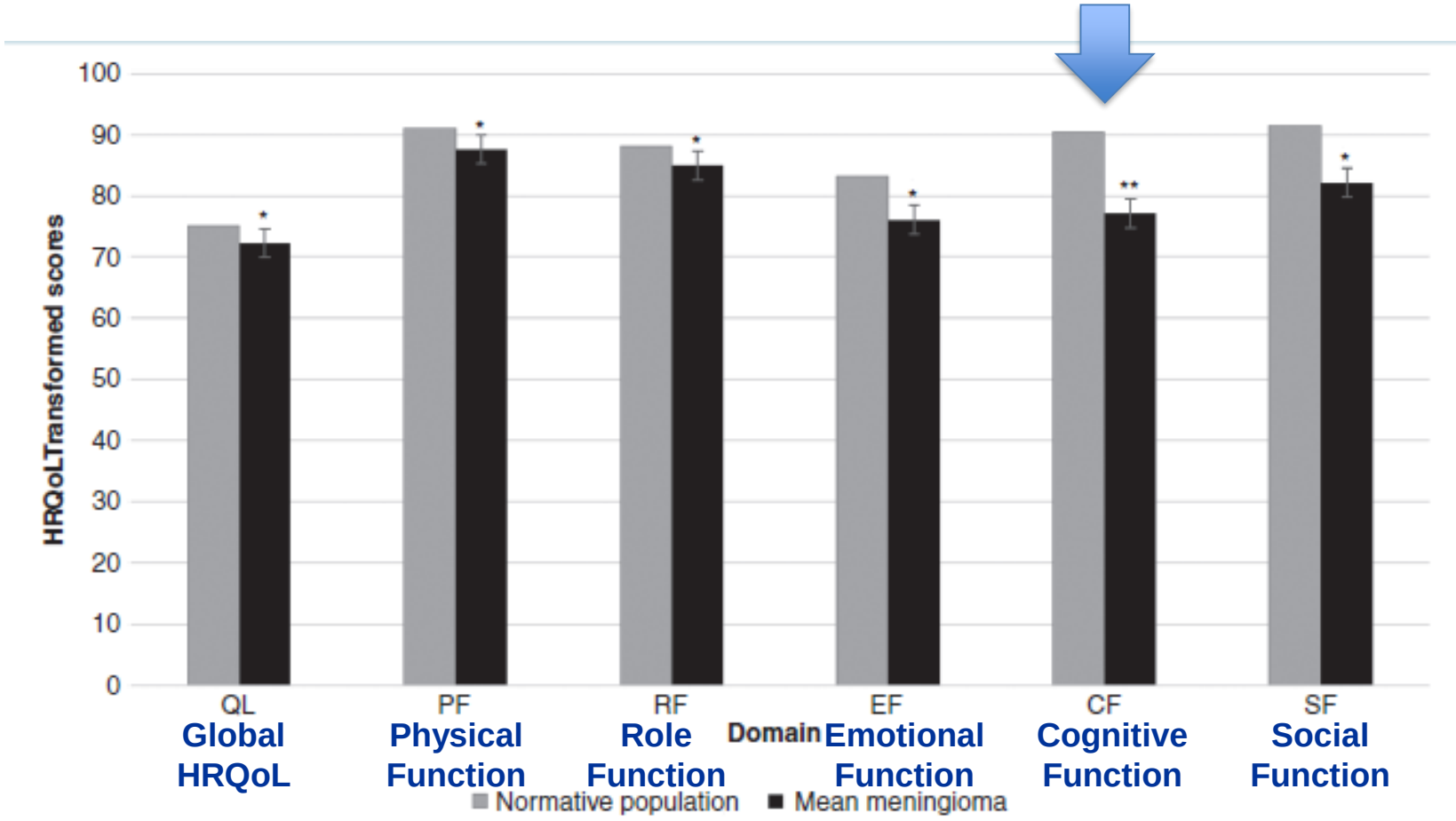
NCDB 2004-2014:
62,867 meningioma patients

Benign 86%
Atypical 11%
Malignant 3%



Rydzewski NR et al. Cancer 2018

Health Related Quality of Life (HRQoL)



291 patients, all benign meningiomas
455 EORTC QLQ-C30 completed postop annually to 10 years
181, 71, 28, 11 completed 1, 2, 3, 4 times, respectively

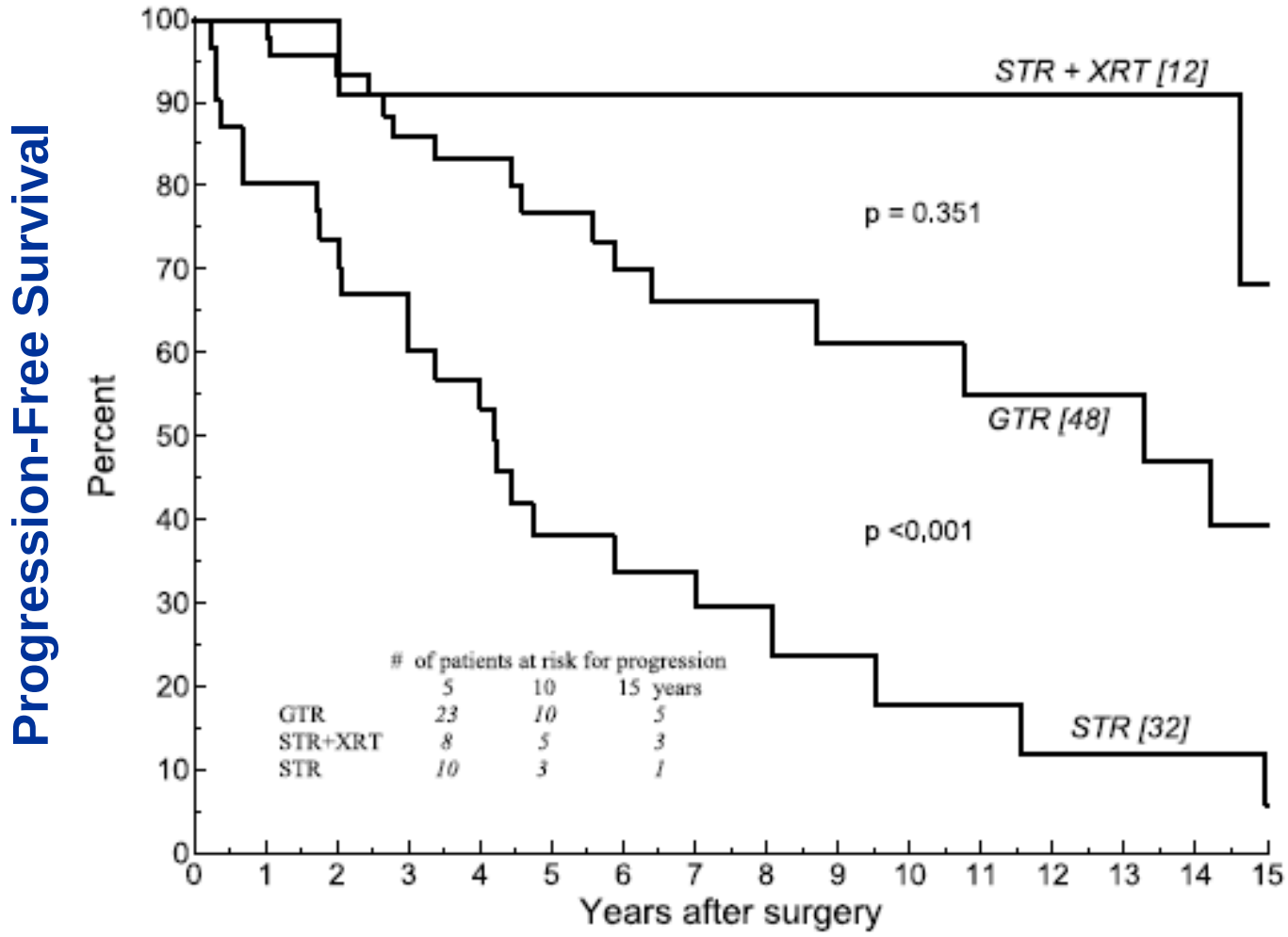
Nassiri F et al. Neuro-Oncol 2019

STANDARD OF CARE FOR MENINGIOMAS

Standard of Care for Meningiomas

- **Do nothing**: if not causing symptoms, not growing, and likely benign
- **Surgery**: take out as much as possible if causing symptoms or growing
- **Radiation therapy**:
  - After surgery if at risk of causing symptoms or of growing back
  - Alone if small or if surgery not possible
- No good drugs

Benign (Grade I) Meningiomas: Surgery and Radiation Define Standard Treatment



Partial resection + Radiation therapy

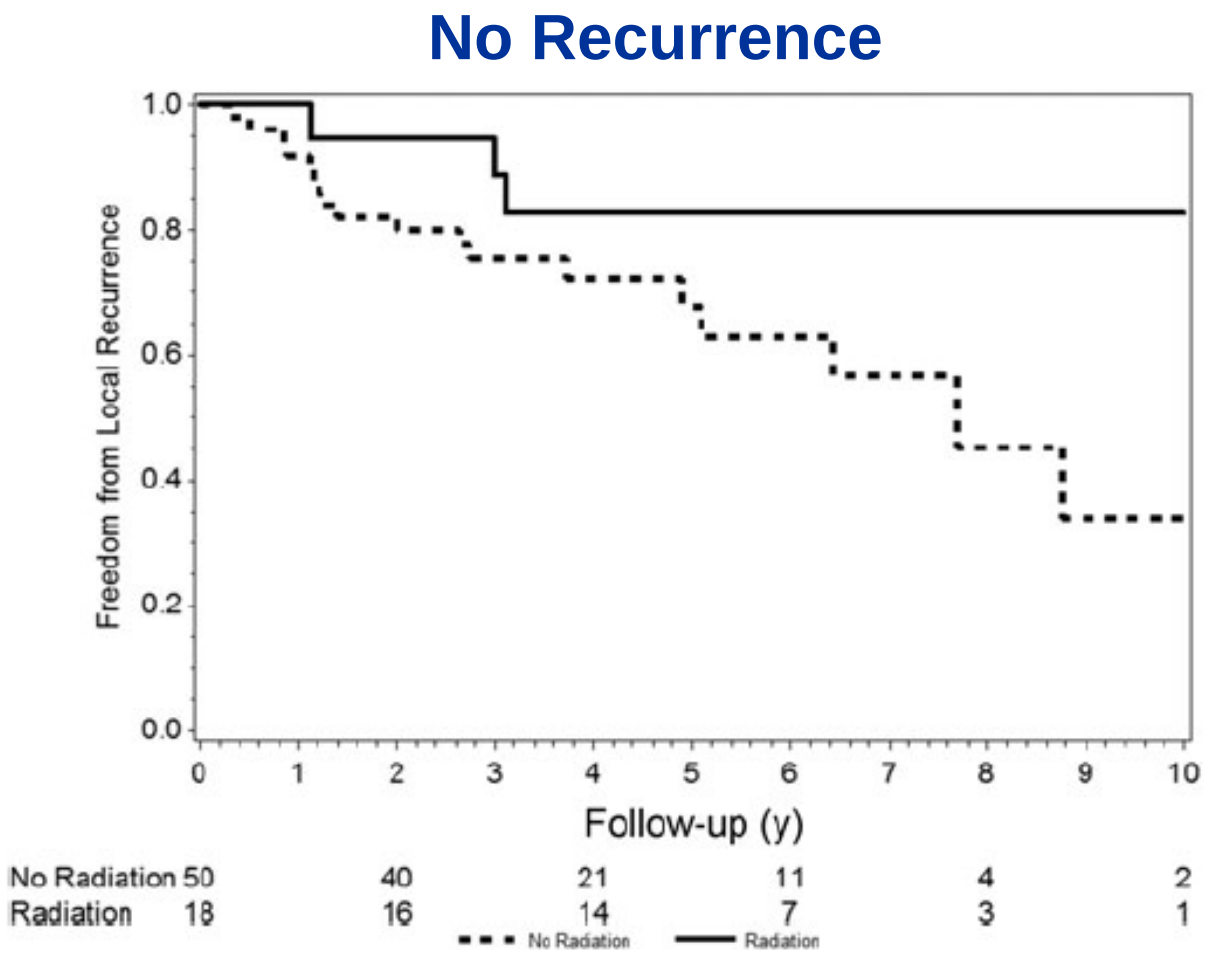
Complete resection (Gross total resection)

Partial resection (Subtotal total resection)

Soyuer S et al. Radiother Oncol 2004

Atypical (Grade 2) Meningiomas: Radiation Therapy after Surgery Reduces Tumor Recurrence

- 68 atypical meningioma
- All complete surgical removal
- Some with postoperative radiation (RT)



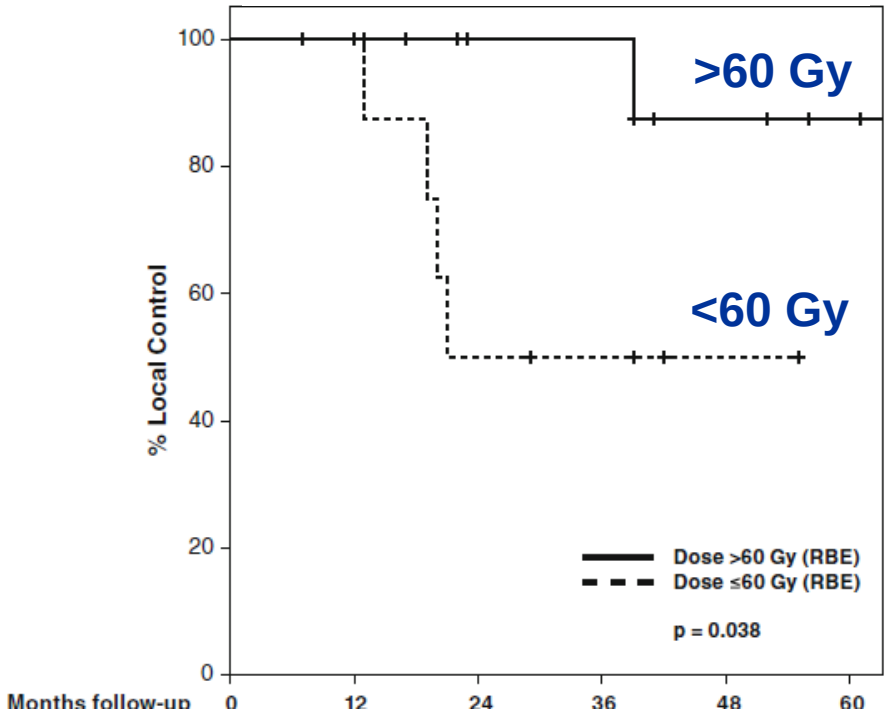
Surgery + RT

Surgery only

Aizer AA et al. NeuroOncol 2014 BWH

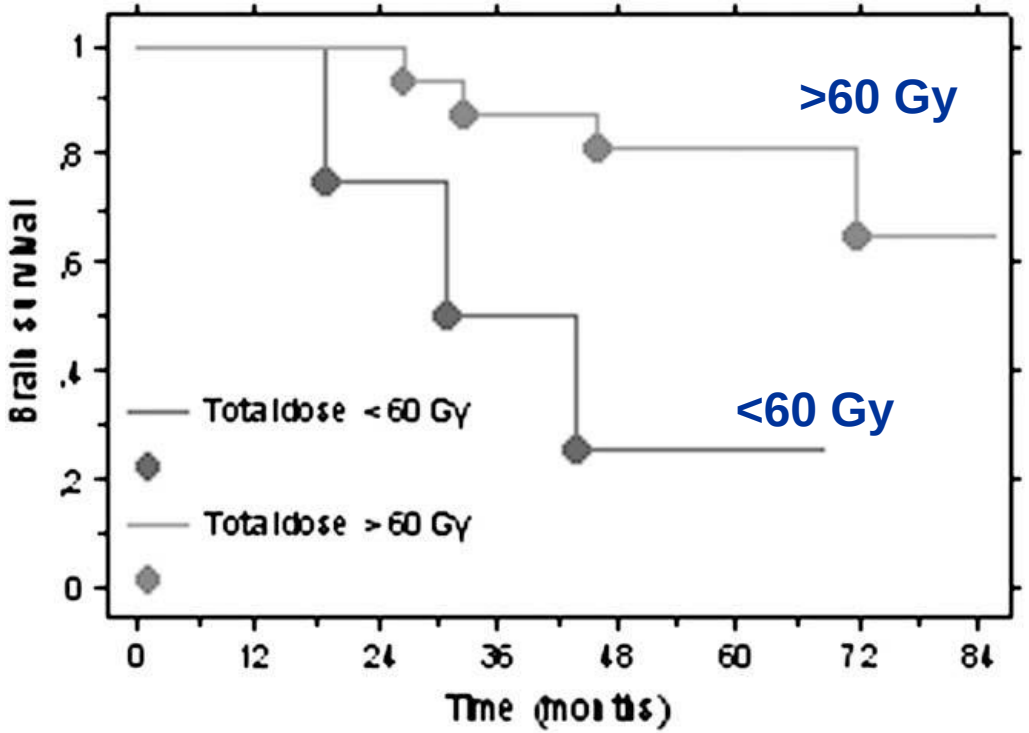
High Grade (Grade 2-3) Meningiomas: Do Better with Higher Radiation Dose

Local control



McDonald MW et al. JNO 2015 Indiana
22 pts, all Grade 2

Cause specific survival



Boskos et al. IJROBP 2009 CPO
24 pts, 19 Grade 2, 5 Grade 3

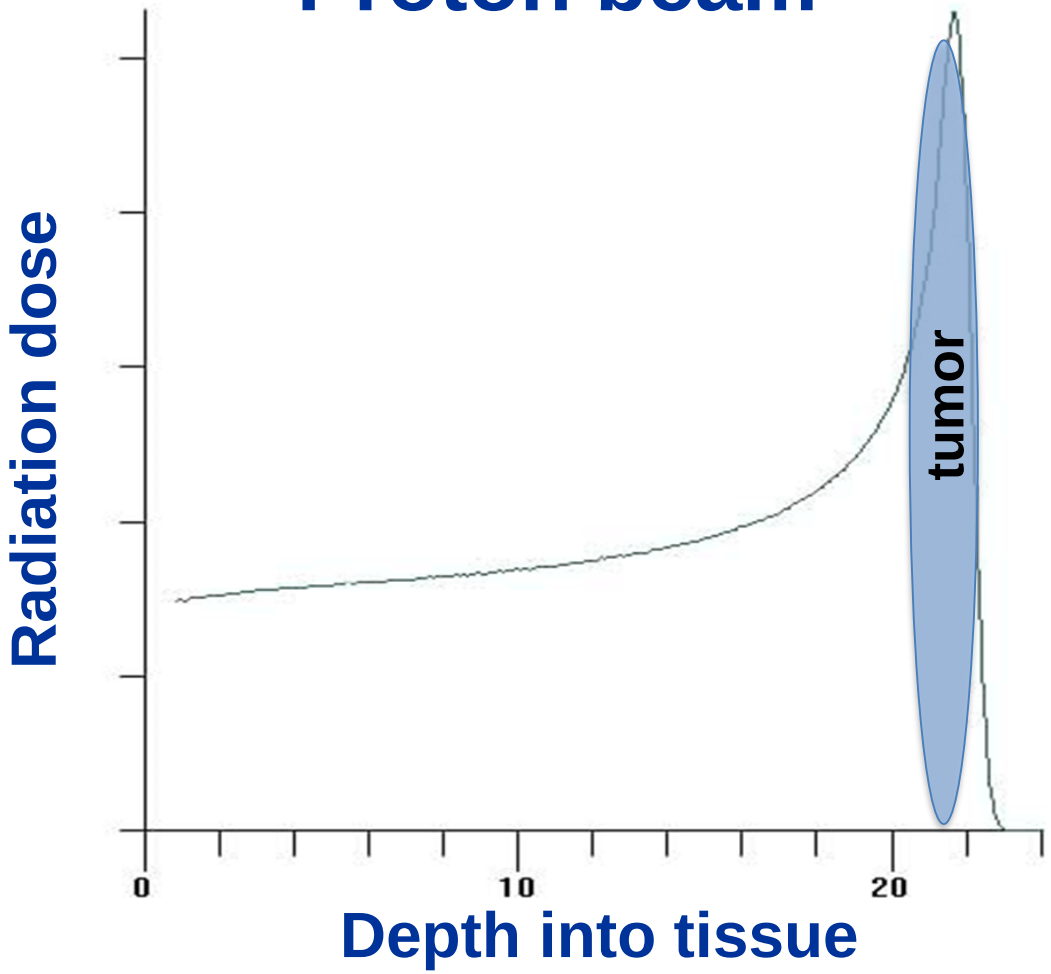
UPDATE ON BENIGN MENINGIOMAS

Proton Radiation

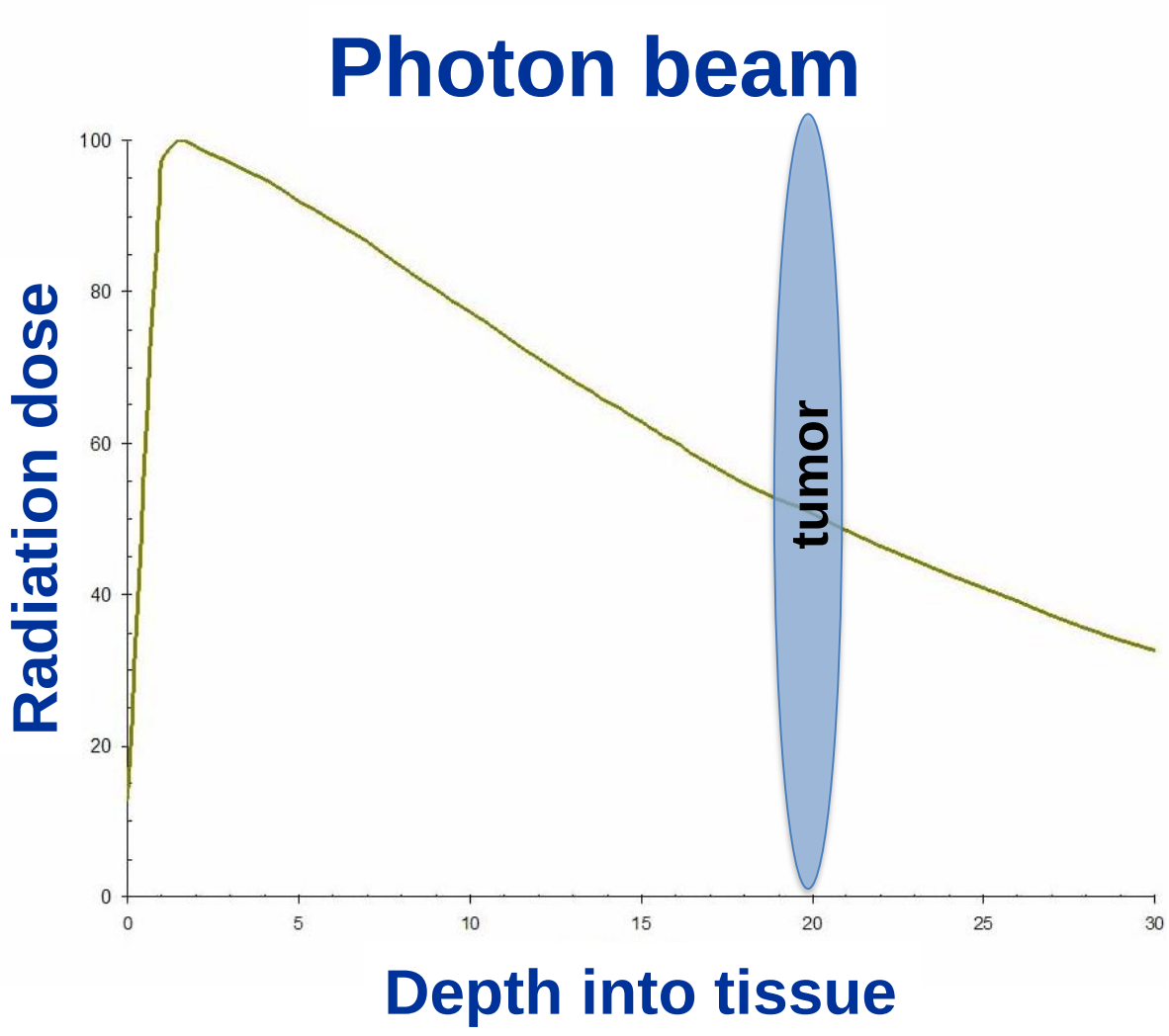
- A radiation beam that stops
- A radiation beam that concentrates the radiation dose at the end of the beamlength
- As compared to standard (photon) radiation, protons may be able to achieve both:
  - Higher dose to tumor target and
  - Lowest dose to normal tissues

Protons vs Photons

Proton beam

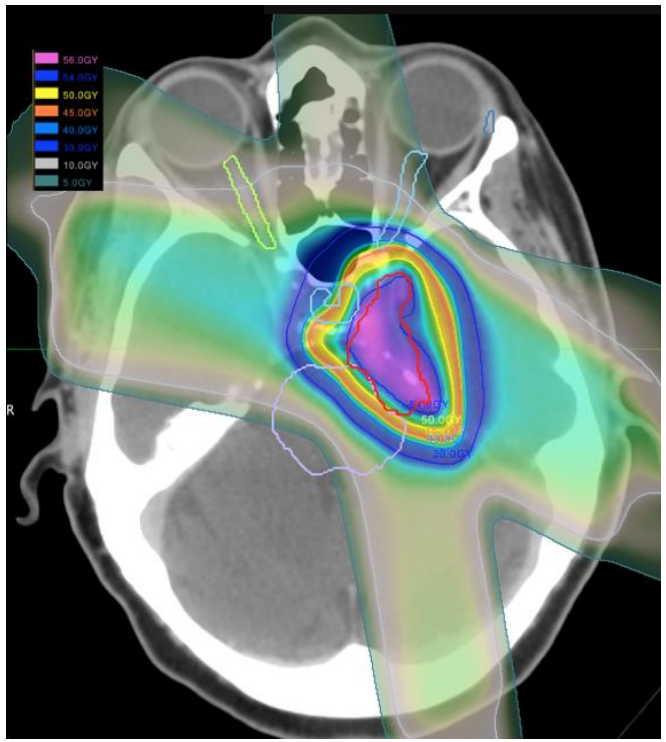


Photon beam

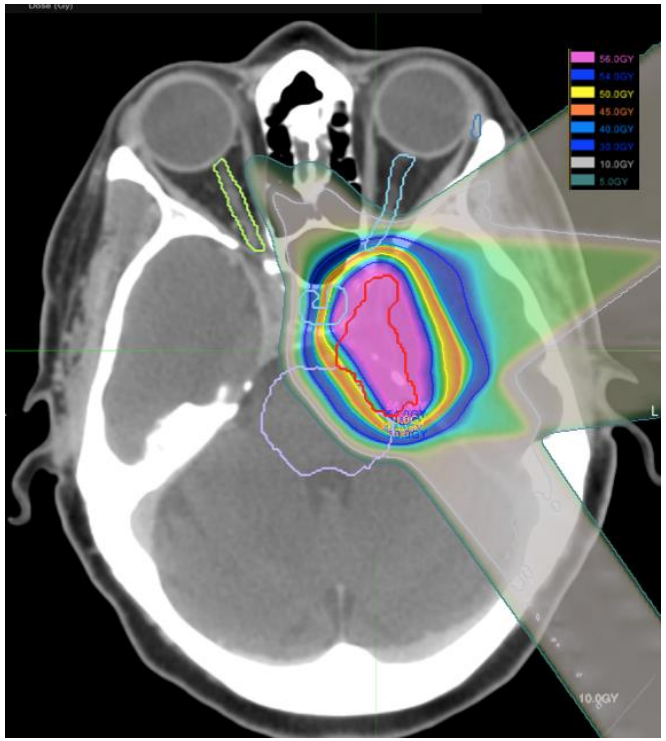


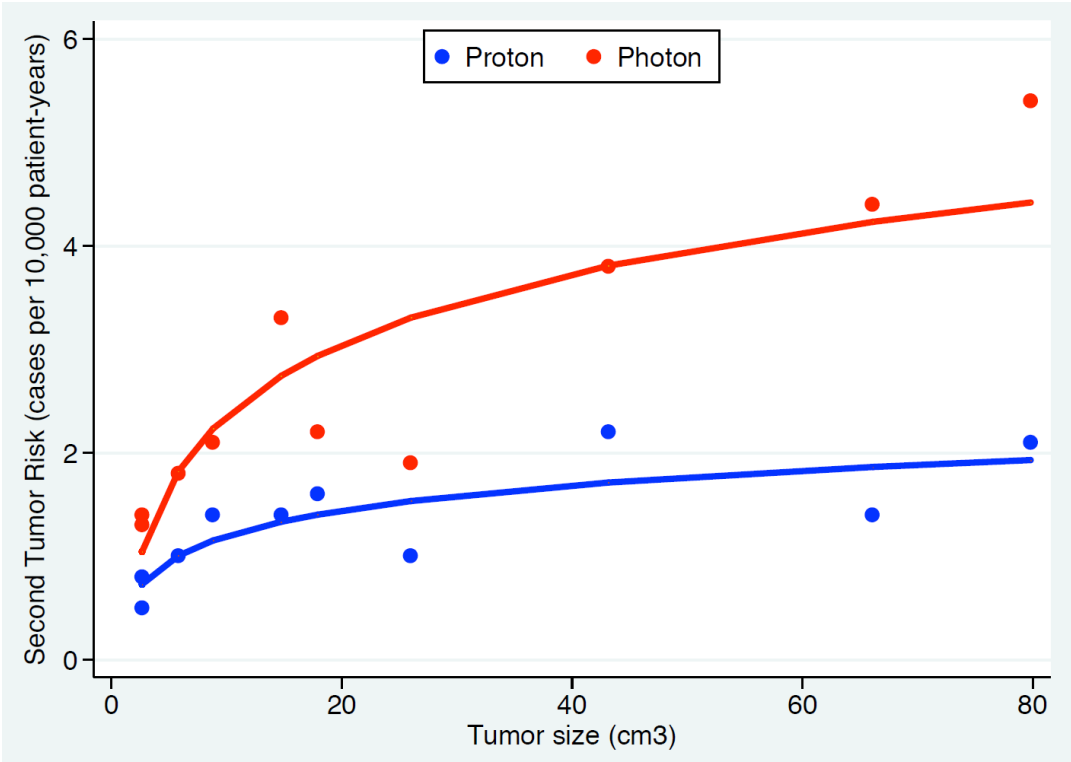
Second Tumor Risk after Radiation Therapy for Meningioma: Always Lower with Protons

Photon



Proton





Arvold N et al. IJROBP 2011 MGH

First Prospective Randomized Study on Benign Meningiomas

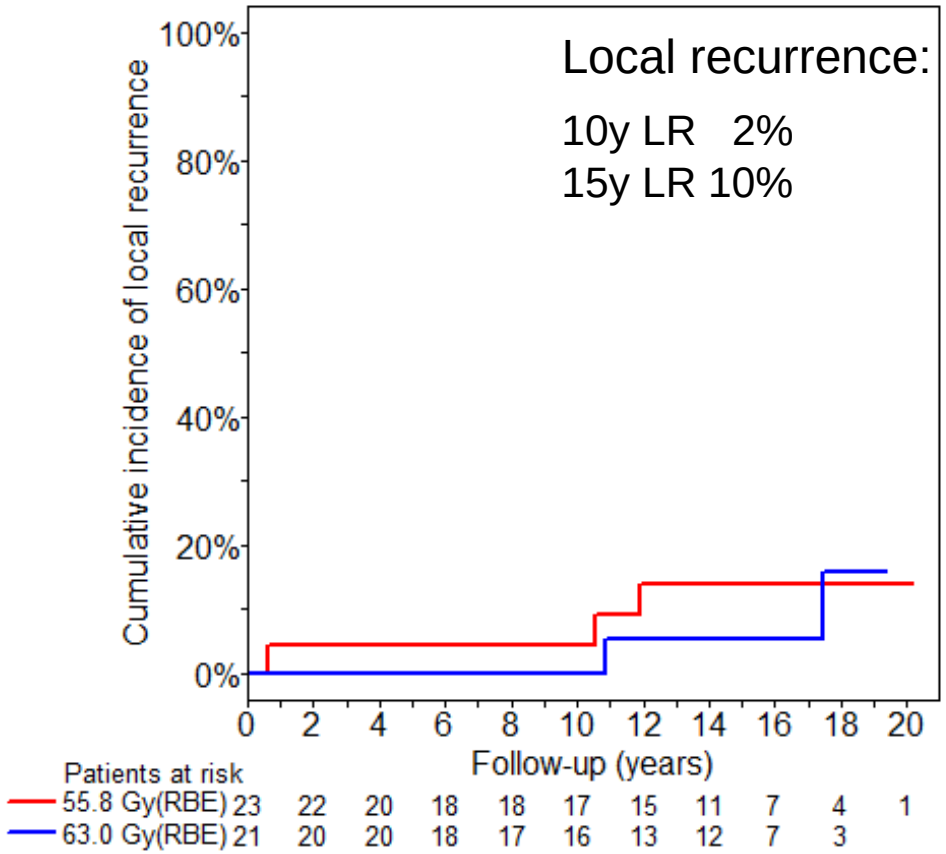
Benign meningioma

47 subjects
1991-2000

RANDOMIZE

55.8 Gy(RBE)

63.0 Gy(RBE)

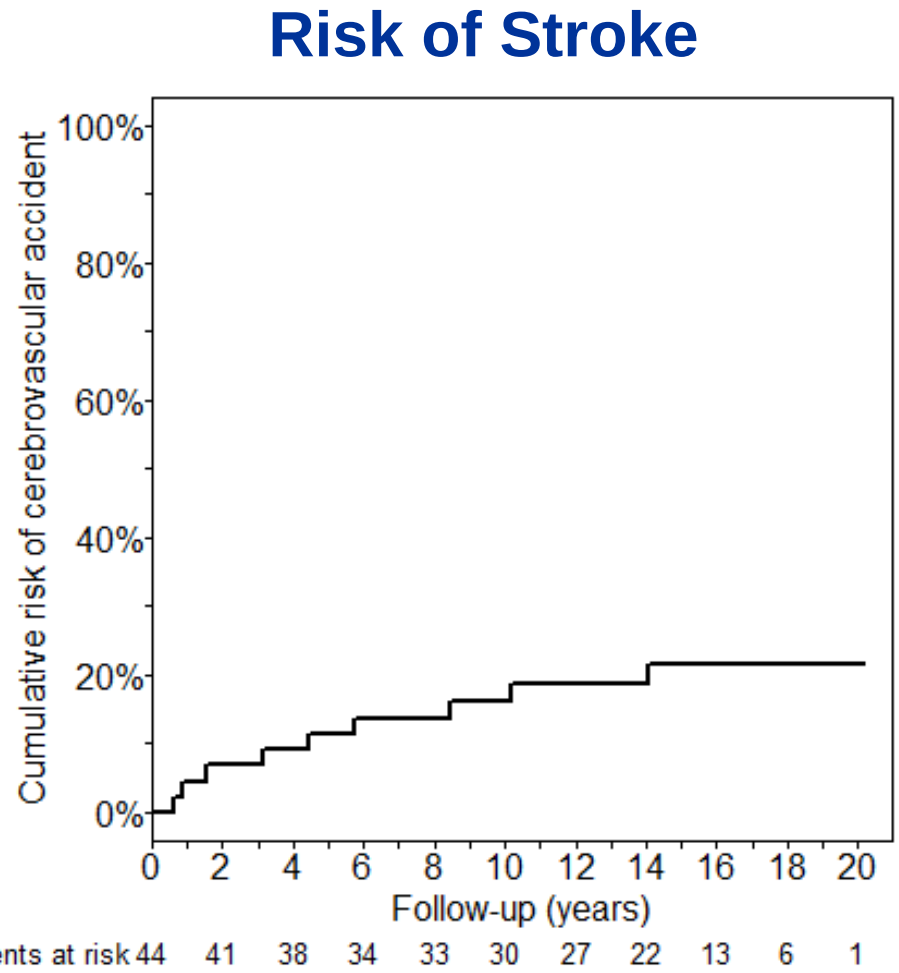


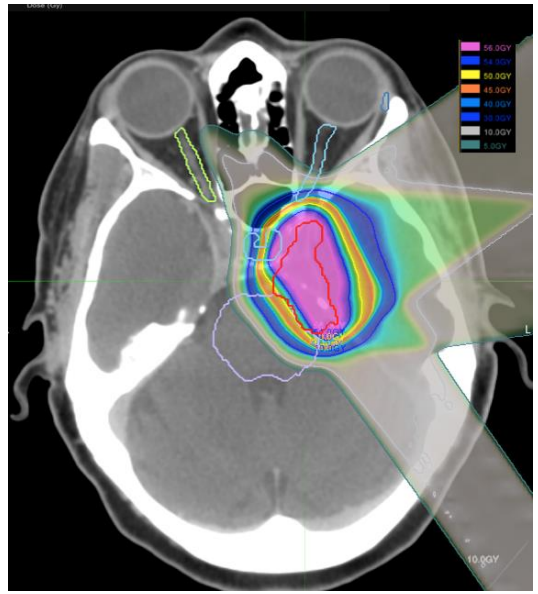
80/20 protons/photons
Median follow up 14.8 years

Sanford NN et al. IJROBP 2017 MGH

Recognizing a Long-Term Risk of Radiation: Stroke

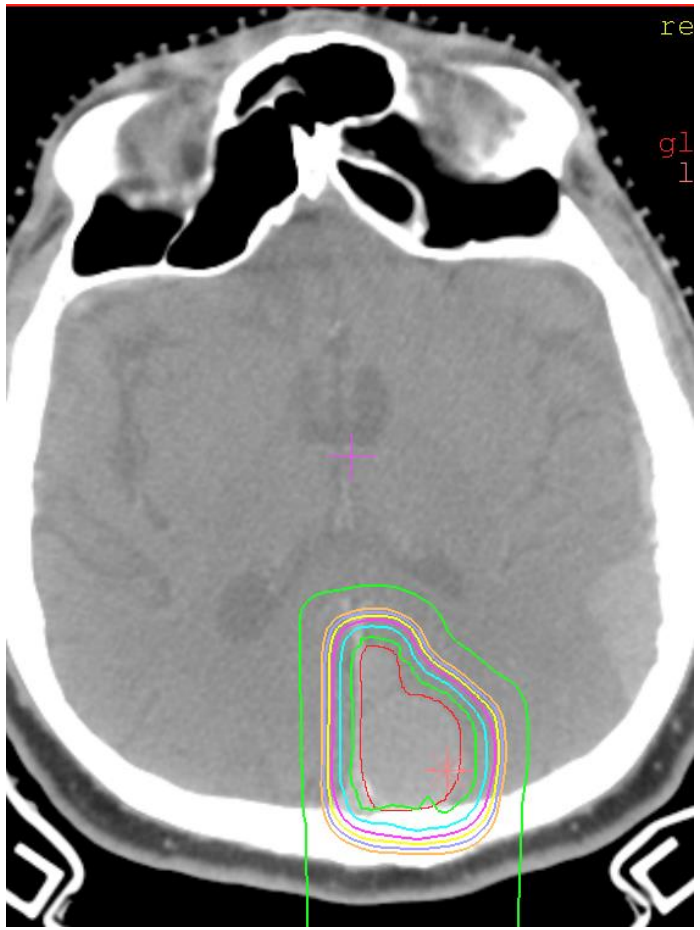
- Cumulative stroke risk at 15 years of 20%
- All cases with tumor encasing middle cerebral artery or close branch



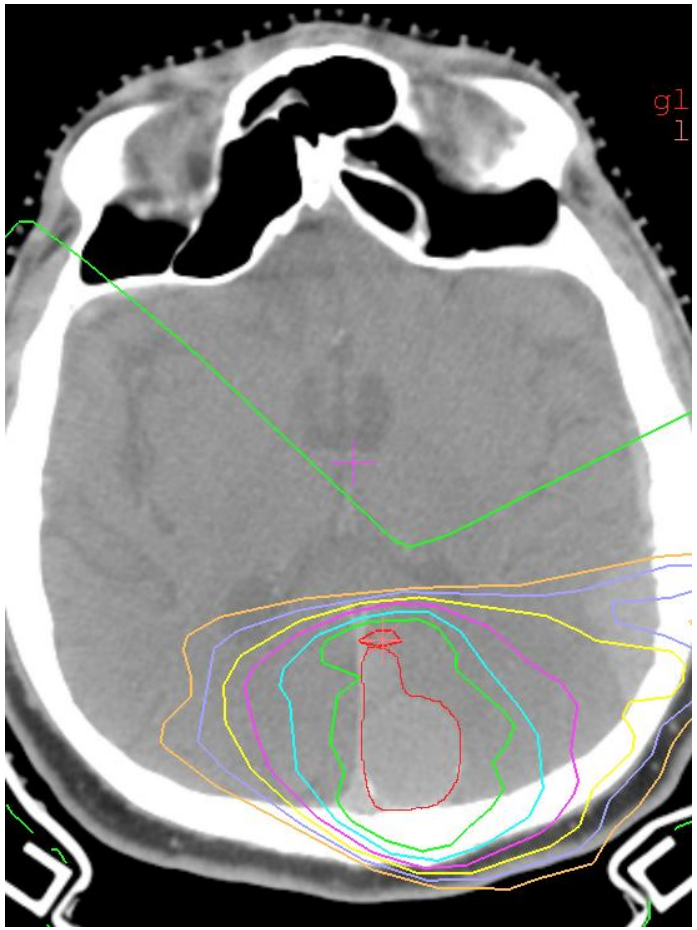


Sanford NN et al. IJROBP 2017 MGH

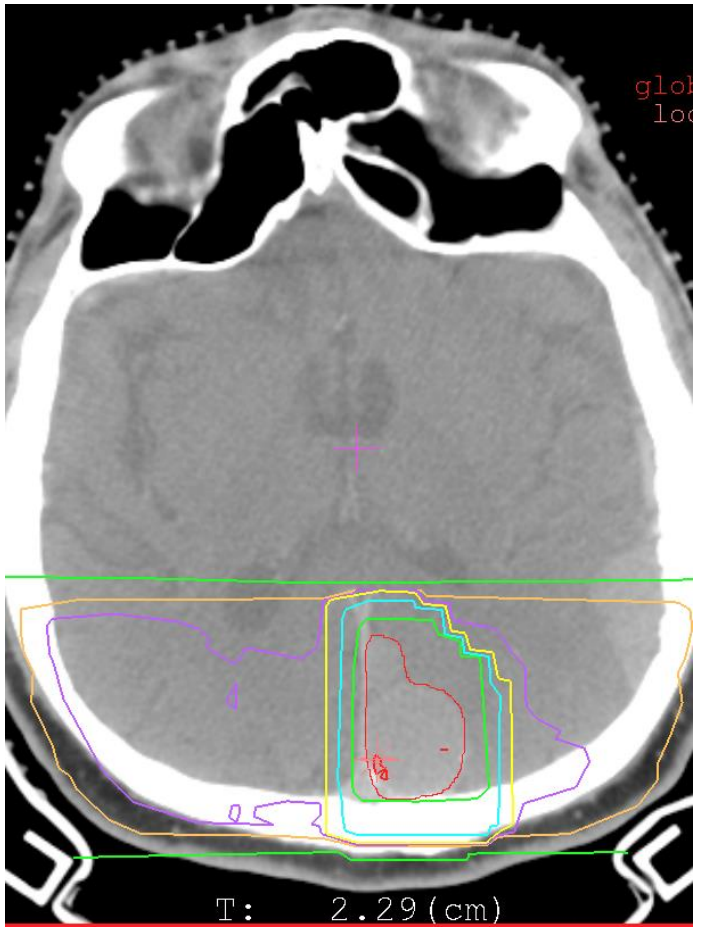
Multiple Meningiomas: Protons Spare Normal Brain Radiation Exposure Which Increases Safety & Opportunity for Re-Treatments



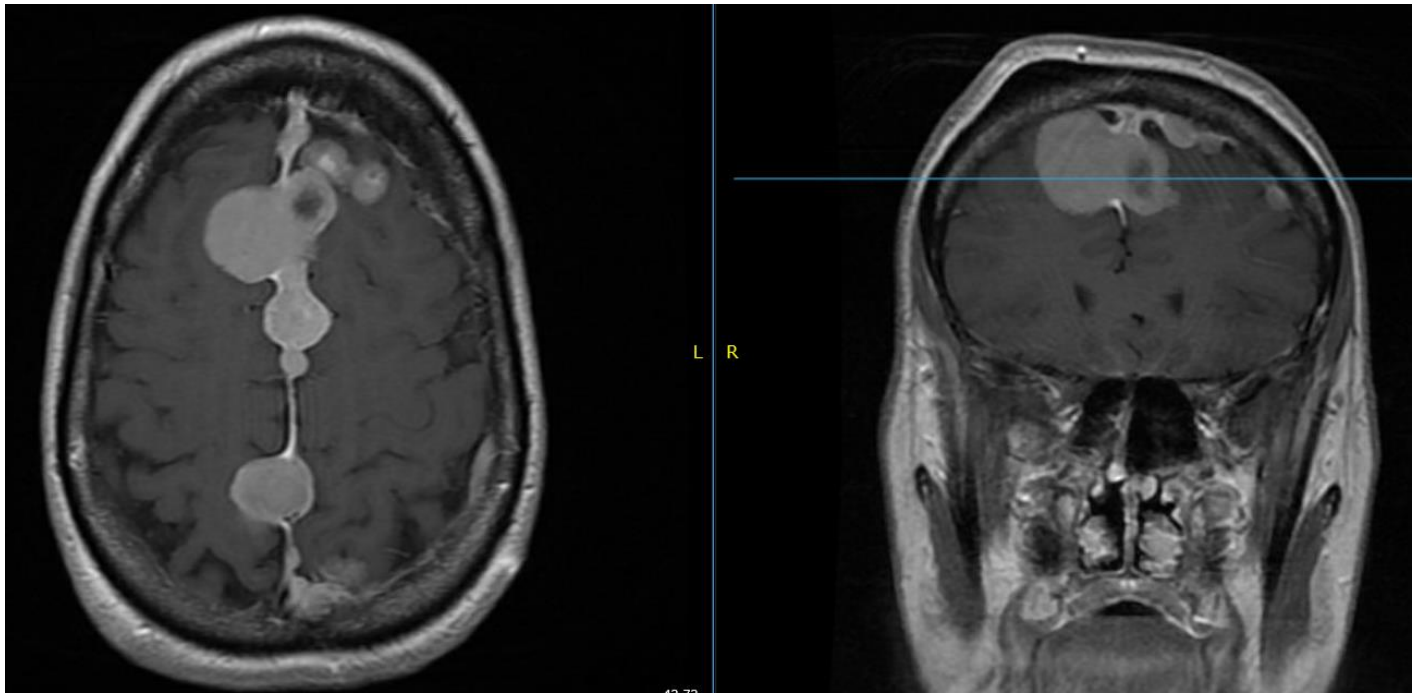
Protons



Photons (IMRT)

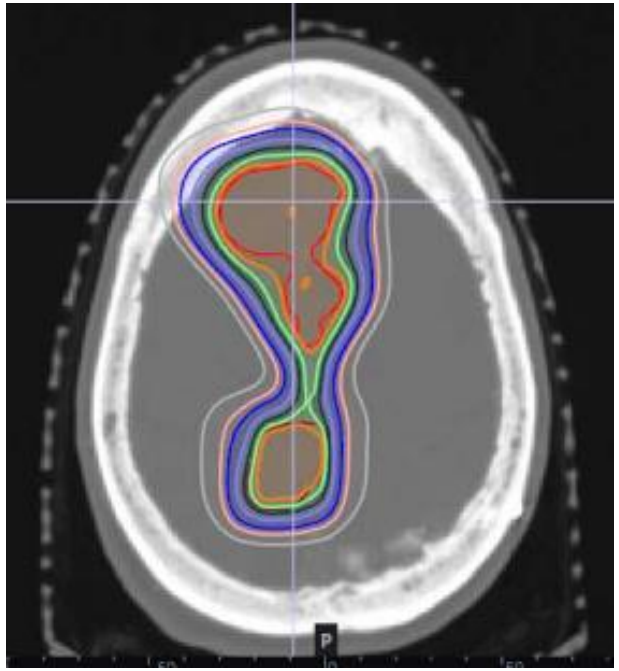


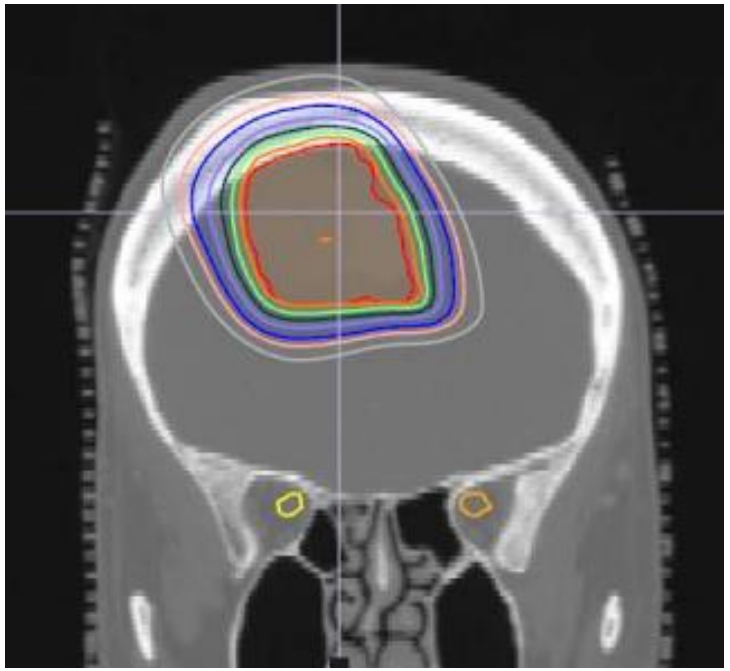
Photons (3D-CRT)

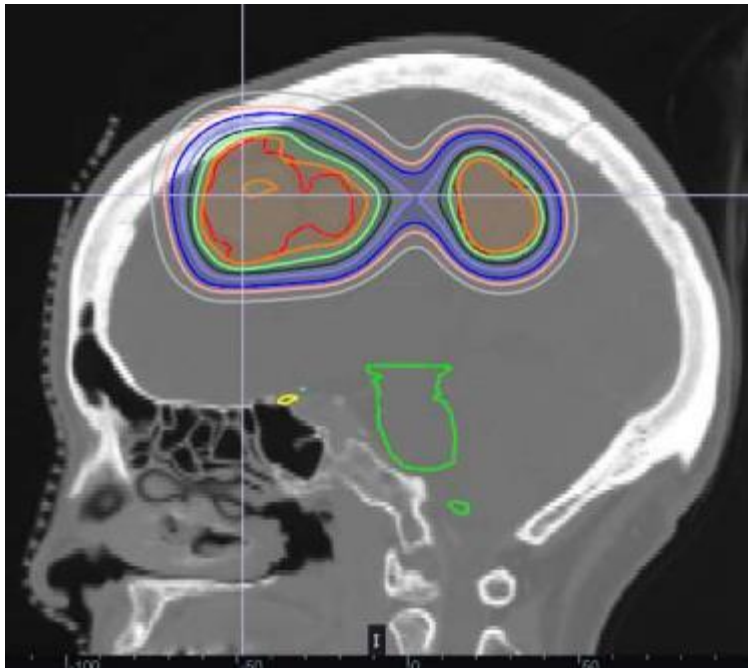


50 year old woman with multiple meningiomas with multiple recurrences

Doing well after 2 courses of protons separate by 10 years

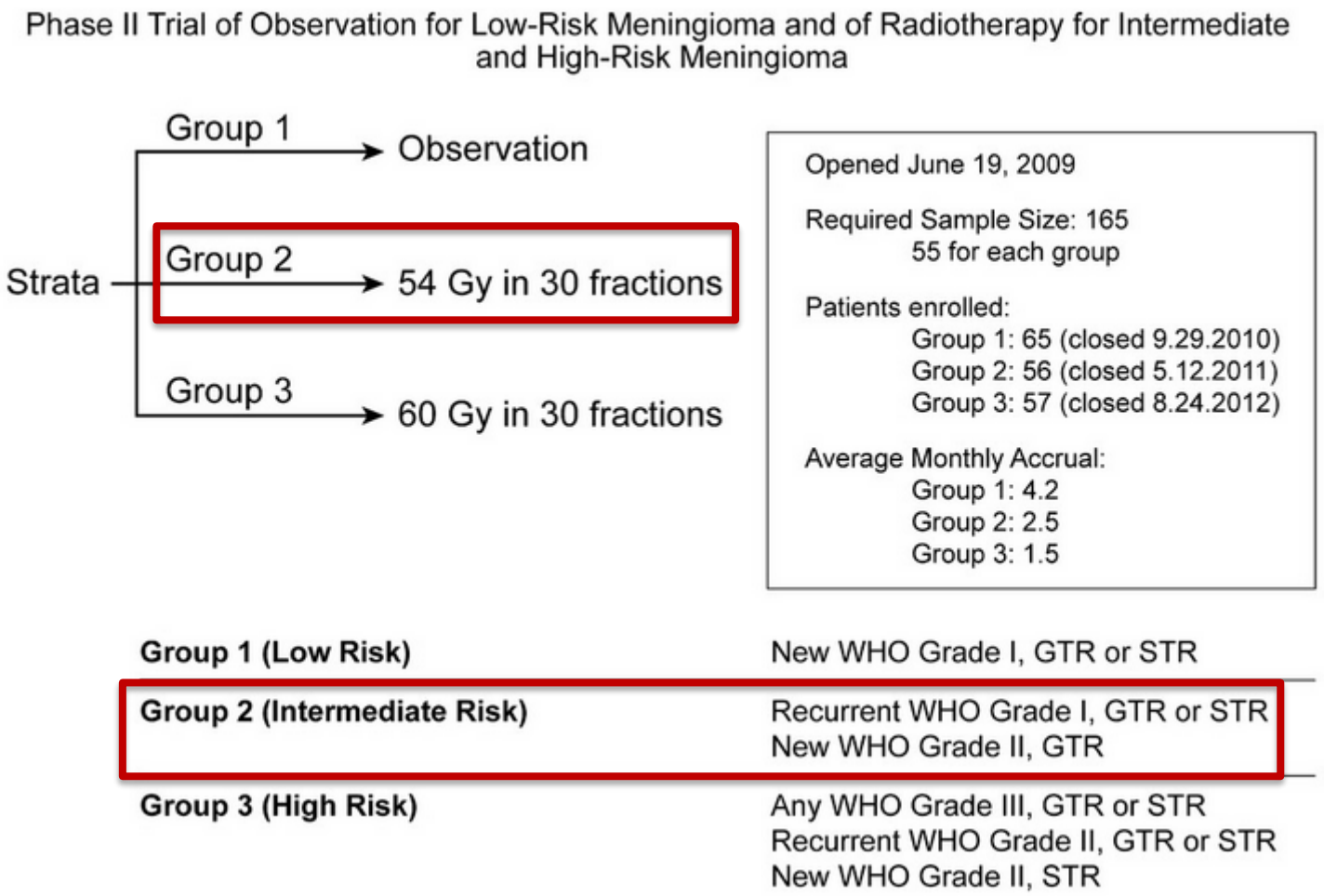






UPDATE ON HIGH GRADE MENINGIOMAS

US Study NRG Oncology/ RTOG 0539: Intermediate Risk Meningiomas



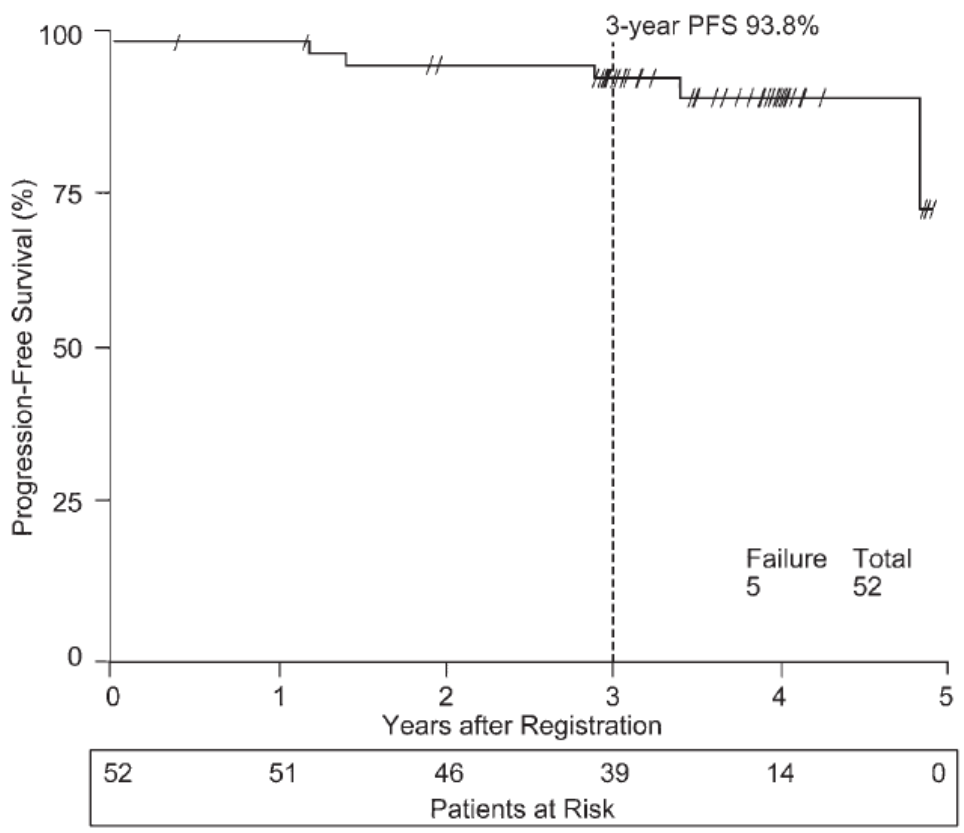
Group 2:

- **Recurrent benign (Grade 1)**
- **Completely resected atypical (Grade 2)**

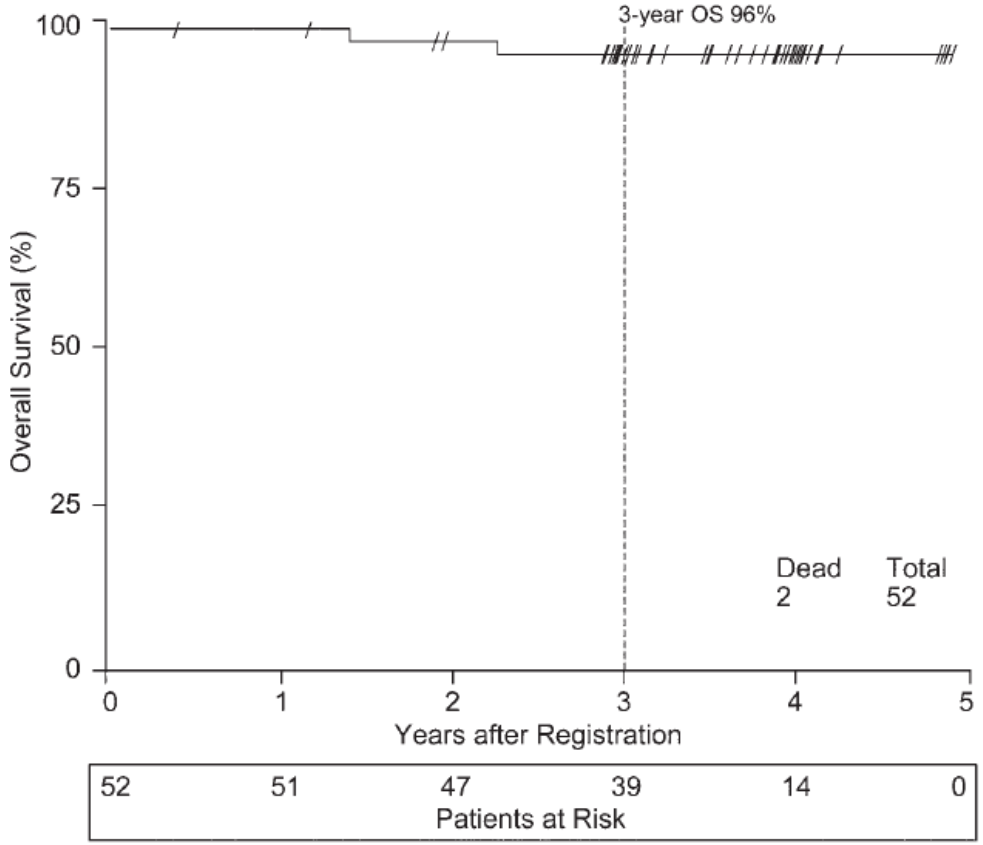
Rogers L et al. JNS 2018

RTOG 0539: Intermediate Risk Meningiomas Do Well at 3 Years after Radiation Therapy

Progression free survival



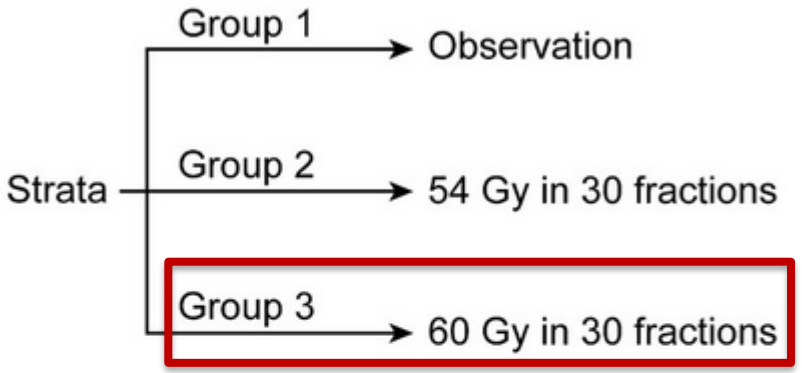
Overall survival



Rogers L et al. JNS 2018

US Study NRG Oncology/RTOG 0539: High Risk Meningiomas

Phase II Trial of Observation for Low-Risk Meningioma and of Radiotherapy for Intermediate and High-Risk Meningioma



Opened June 19, 2009

Required Sample Size: 165
55 for each group

Patients enrolled:
Group 1: 65 (closed 9.29.2010)
Group 2: 56 (closed 5.12.2011)
Group 3: 57 (closed 8.24.2012)

Average Monthly Accrual:
Group 1: 4.2
Group 2: 2.5
Group 3: 1.5

Group 1 (Low Risk)	New WHO Grade I, GTR or STR
Group 2 (Intermediate Risk)	Recurrent WHO Grade I, GTR or STR New WHO Grade II, GTR
Group 3 (High Risk)	Any WHO Grade III, GTR or STR Recurrent WHO Grade II, GTR or STR New WHO Grade II, STR

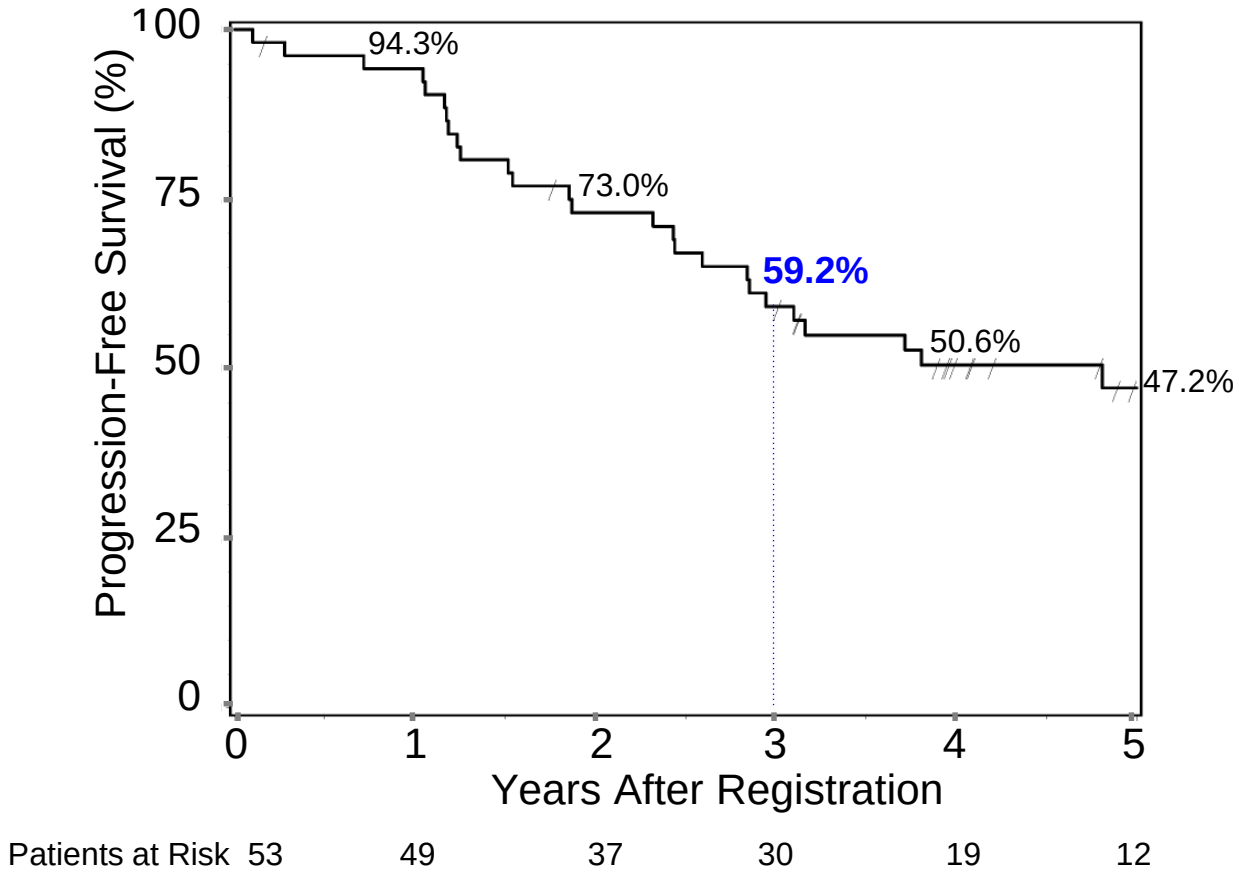
Group 3:

- **Recurrent atypical (Grade 2)**
- **Incompletely resected atypical (Grade 2)**
- **Any anaplastic (Grade 3)**

Rogers L et al. ASTRO 2017

NRG Oncology / RTOG-0539, Group 3

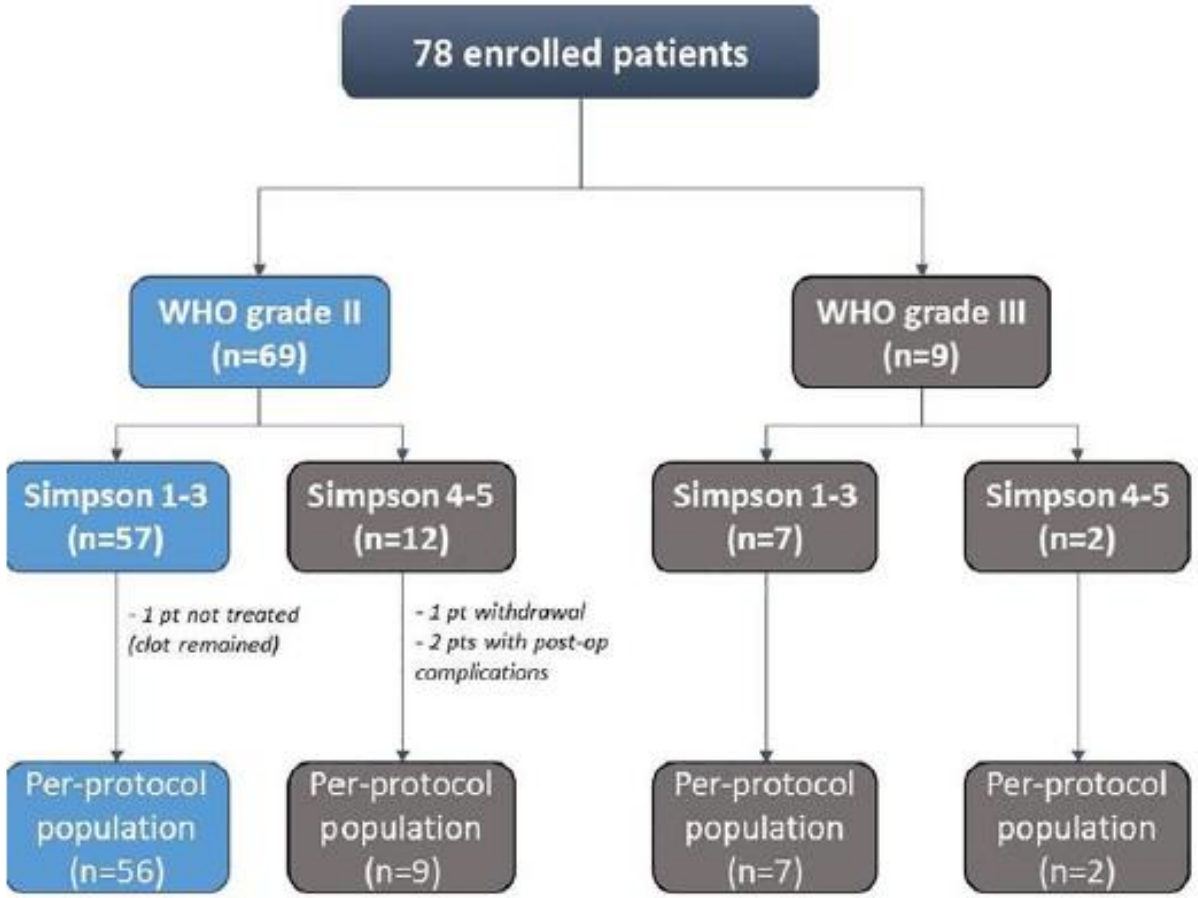
Primary Endpoint: 3y PFS



NRG ONCOLOGY™

Rogers L et al. ASTRO 2017

European Study EORTC 22042: High Grade Meningiomas



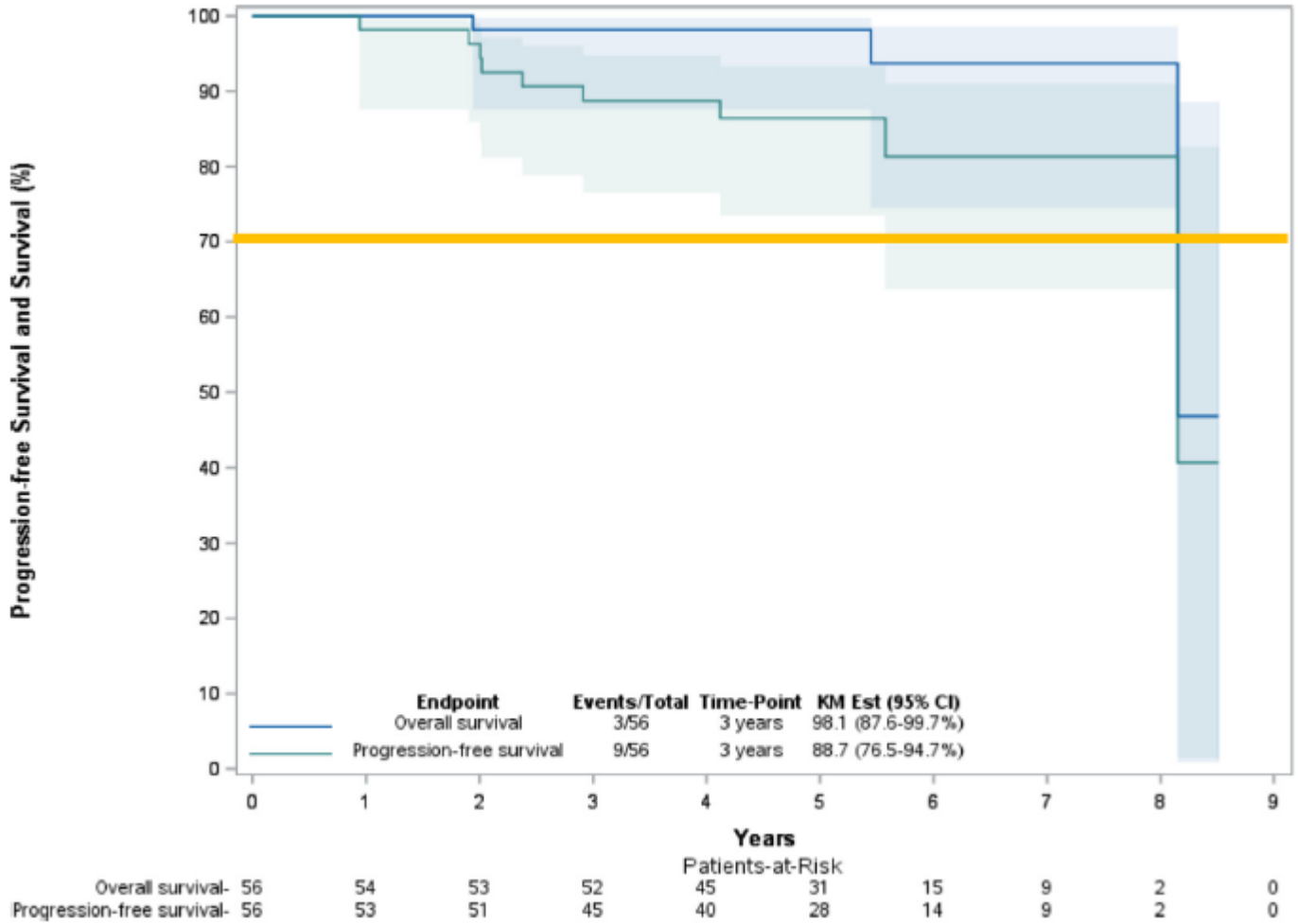
Fully accrued

First report of Arm 1

- 56 patients with grade 2 meningiomas with complete resection
- All received 60 Gy

Weber D et al. Radiother Oncol 2018

EORTC 22042: Grade 2 Meningiomas Complete Resection + Radiation Do Well

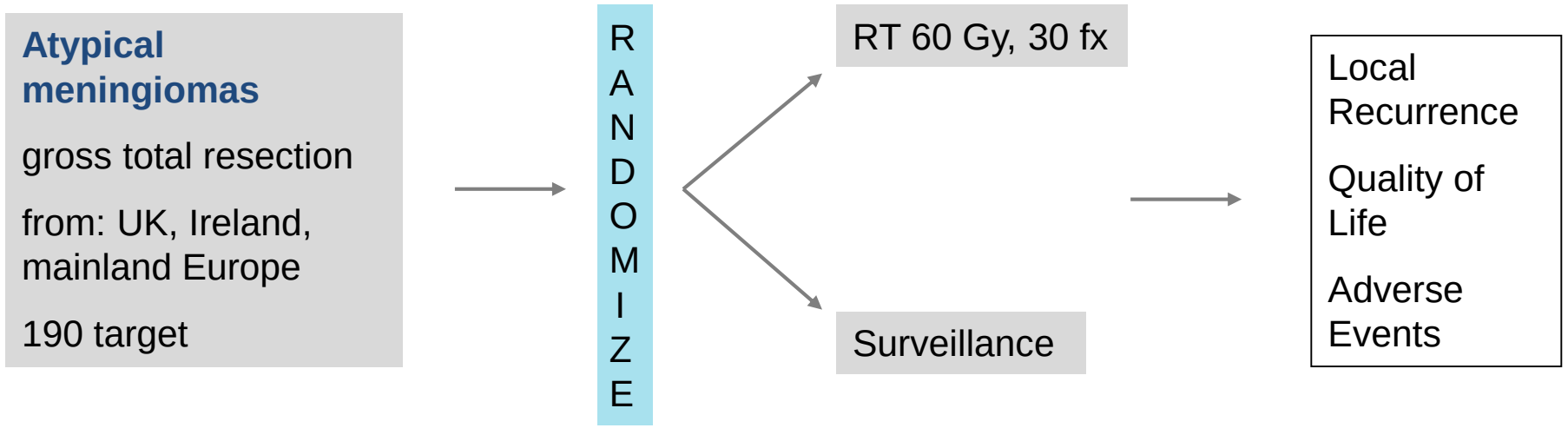


Complete surgical resection
+ RT 60 Gy
3 year data:

- Recurrence 89%
- Survival 98%
- Severe side effects 14%

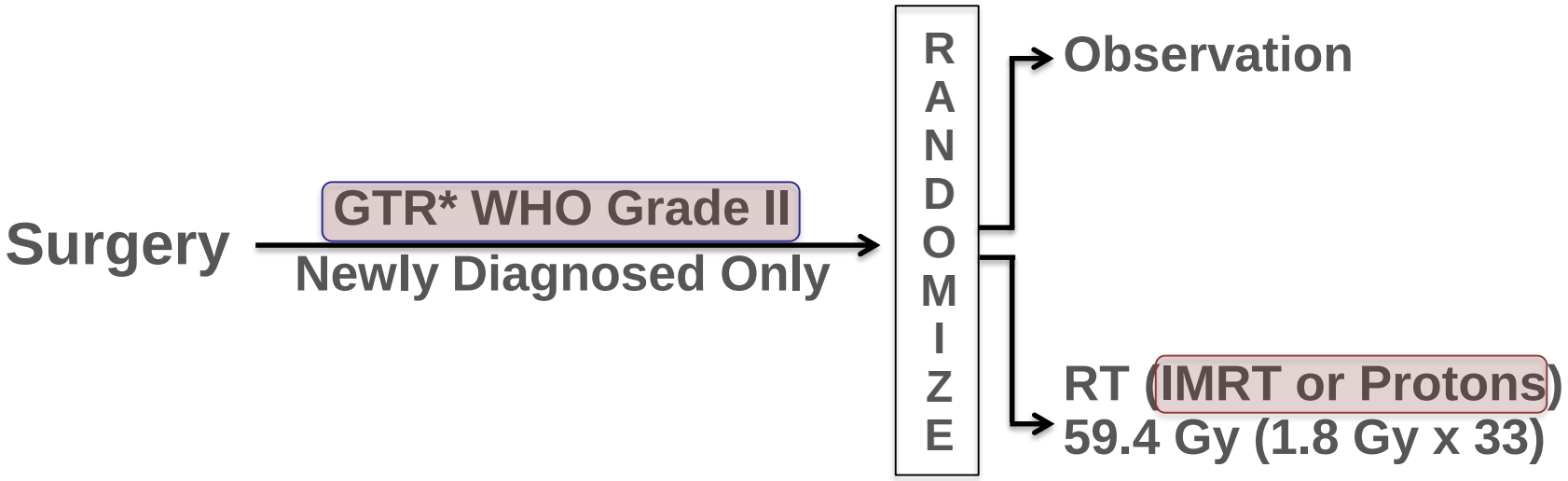
Weber D et al. Radiother Oncol 2018

ROAM/EORTC 1308: Atypical Meningioma with Complete Resection: Radiation or Observation



Jenkinson MD et al. Trials 2015

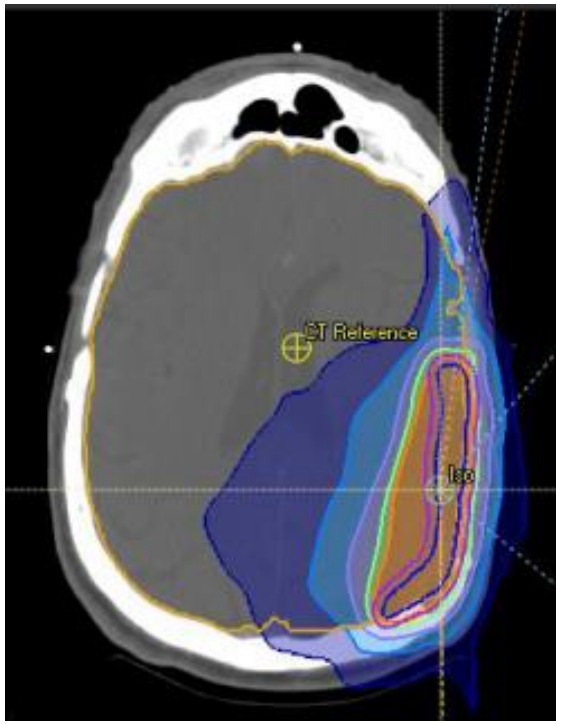
US Study NRG BN003: Atypical Meningioma with Complete Resection: Radiation or Observation

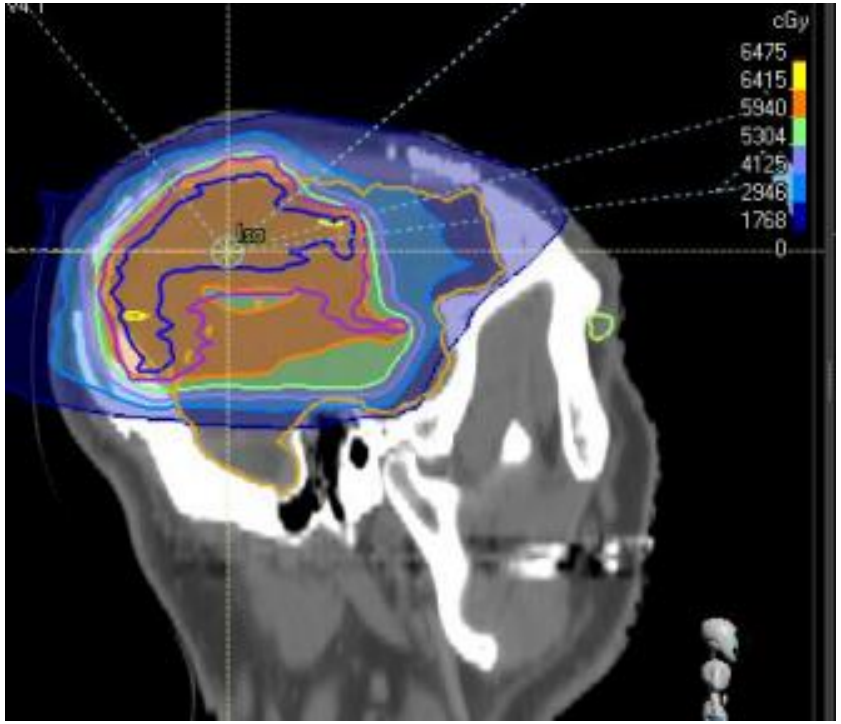


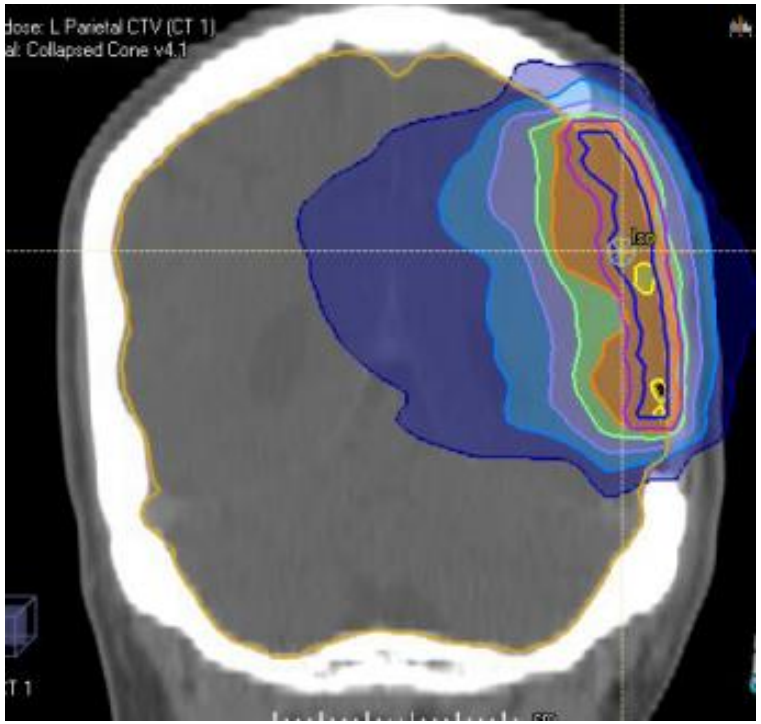
Rogers L et al. ASTRO 2017

Recurrent Atypical Meningioma: VMAT Photons

Volumetric Modulated Arc Radiotherapy: Fast, highly conformal, much better skin sparing

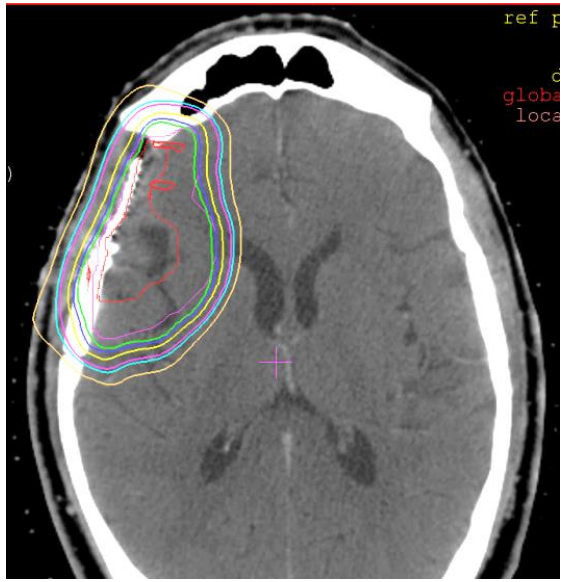


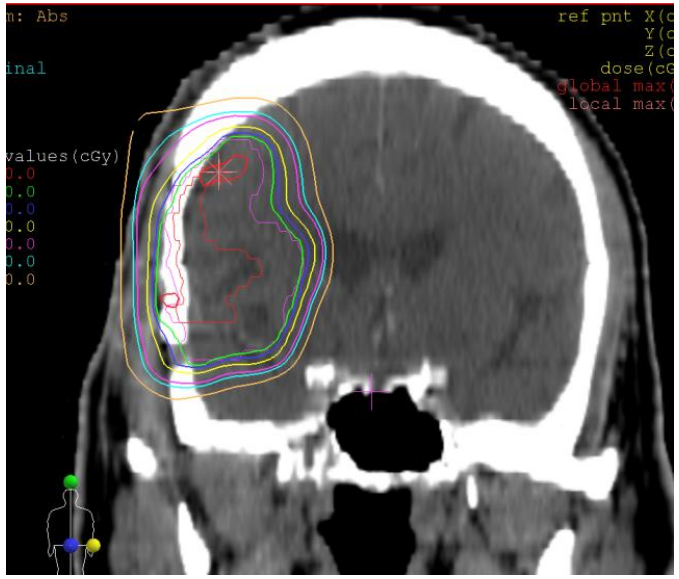




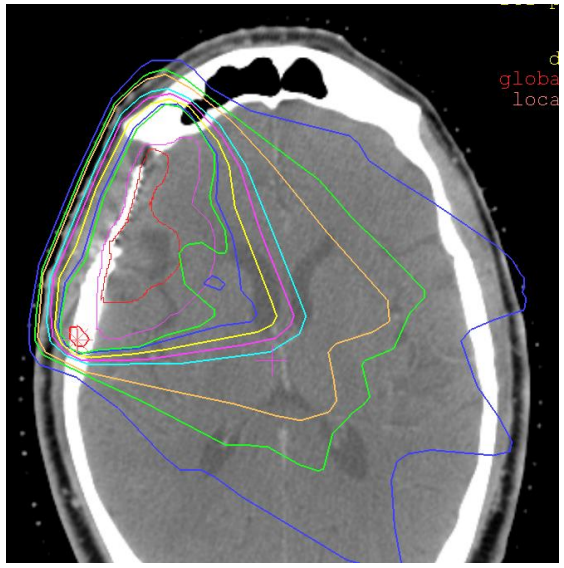
Malignant (Grade 3) Meningioma

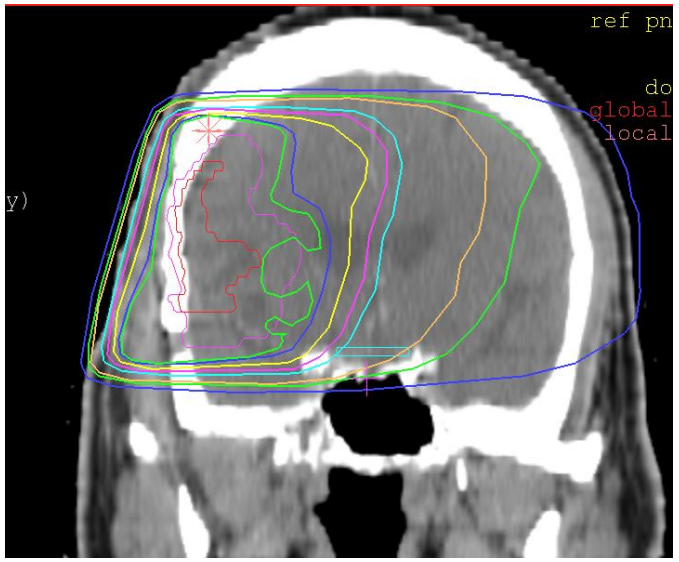
Protons

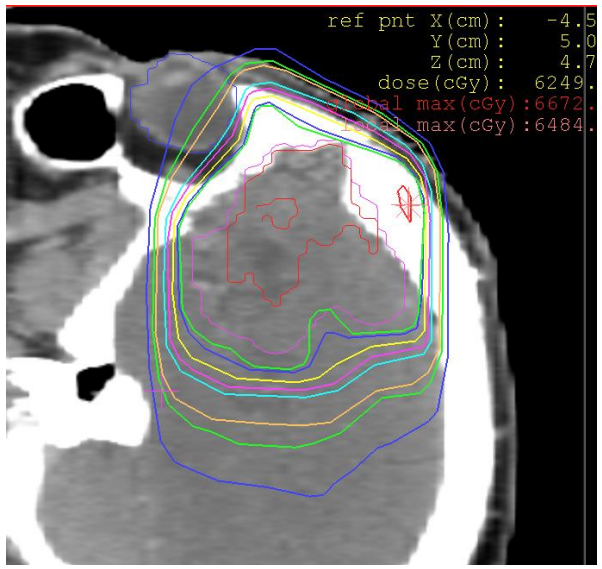




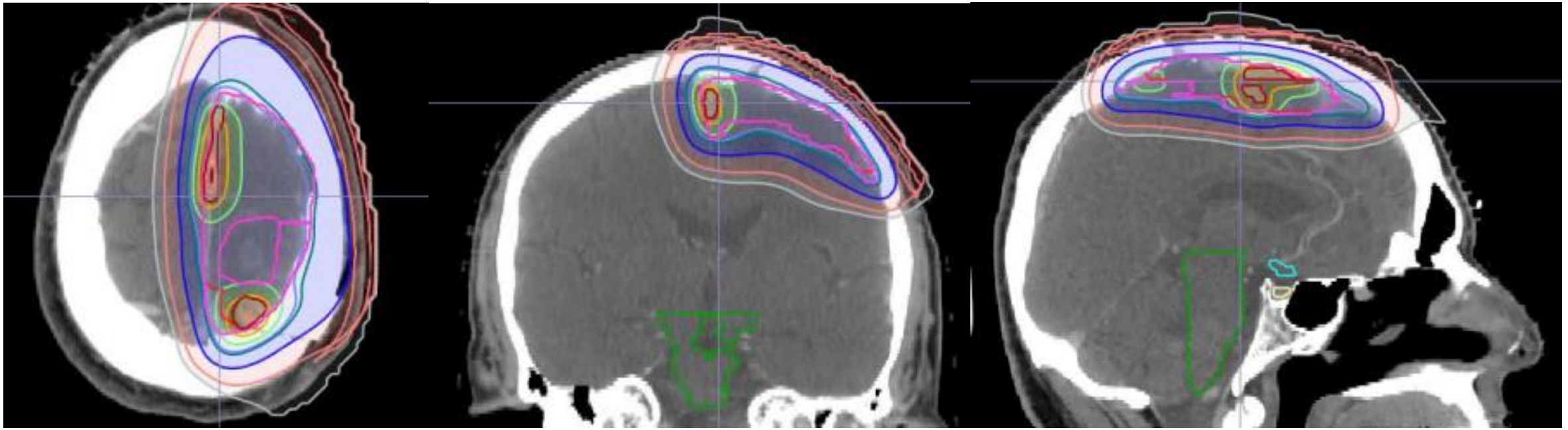
Photons







MGH/MDA Atypical Meningioma Proton Study



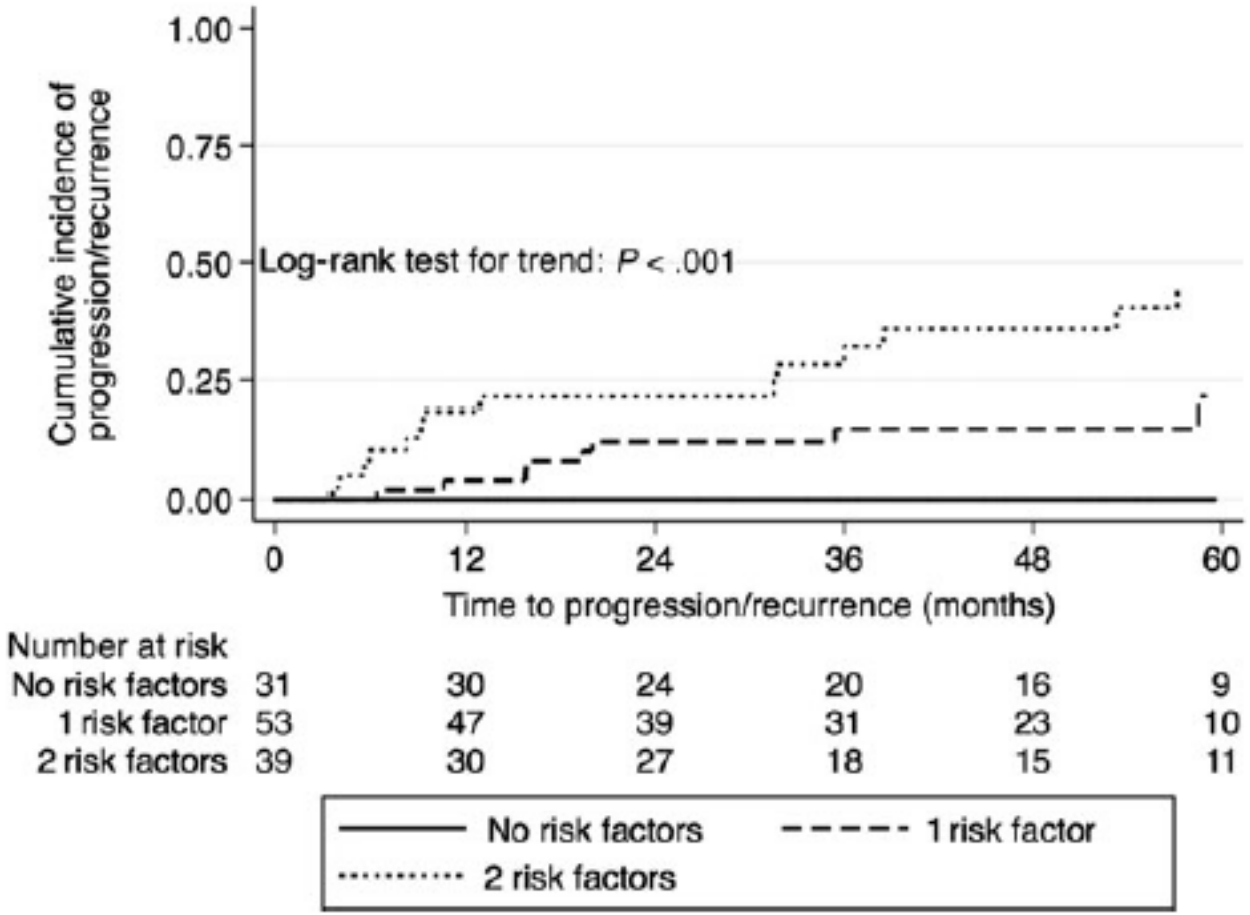
Atypical (grade 2) meningiomas	Microscopic disease	Visible tumor
	59.4 Gy(RBE)	66 Gy(RBE)

MORE ON MENINGIOMAS: IMAGING, PATHOLOGY & GENETICS

Meningioma Model for Recurrence

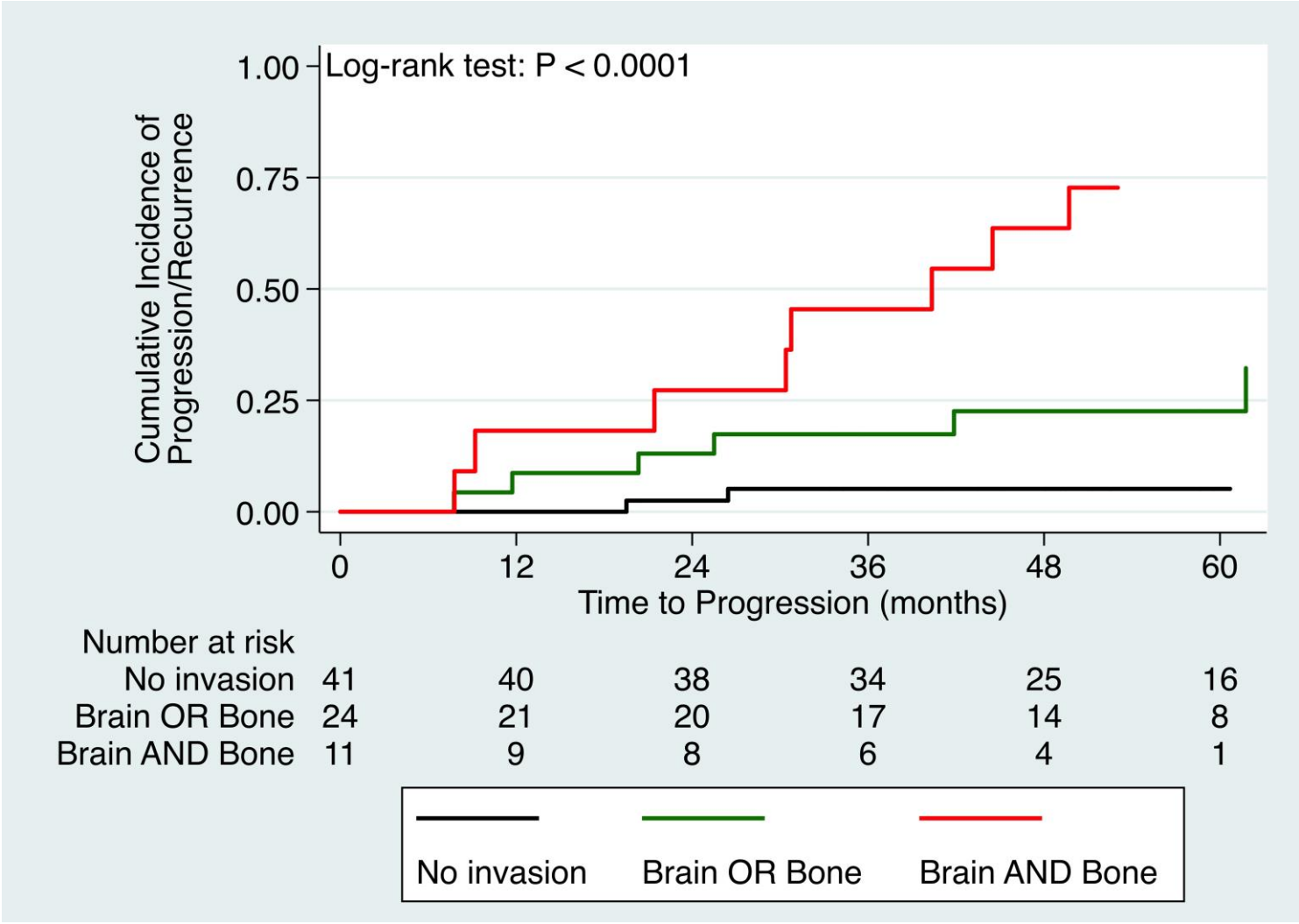
Risk factors:

- Surgery: Incomplete resection (non-Simpson grade I)
- MRI: Low ADC



Hwang WL et al. Neuro Onc 2015 MGH

Brain and/or Bone Invasion is Associated with Recurrence

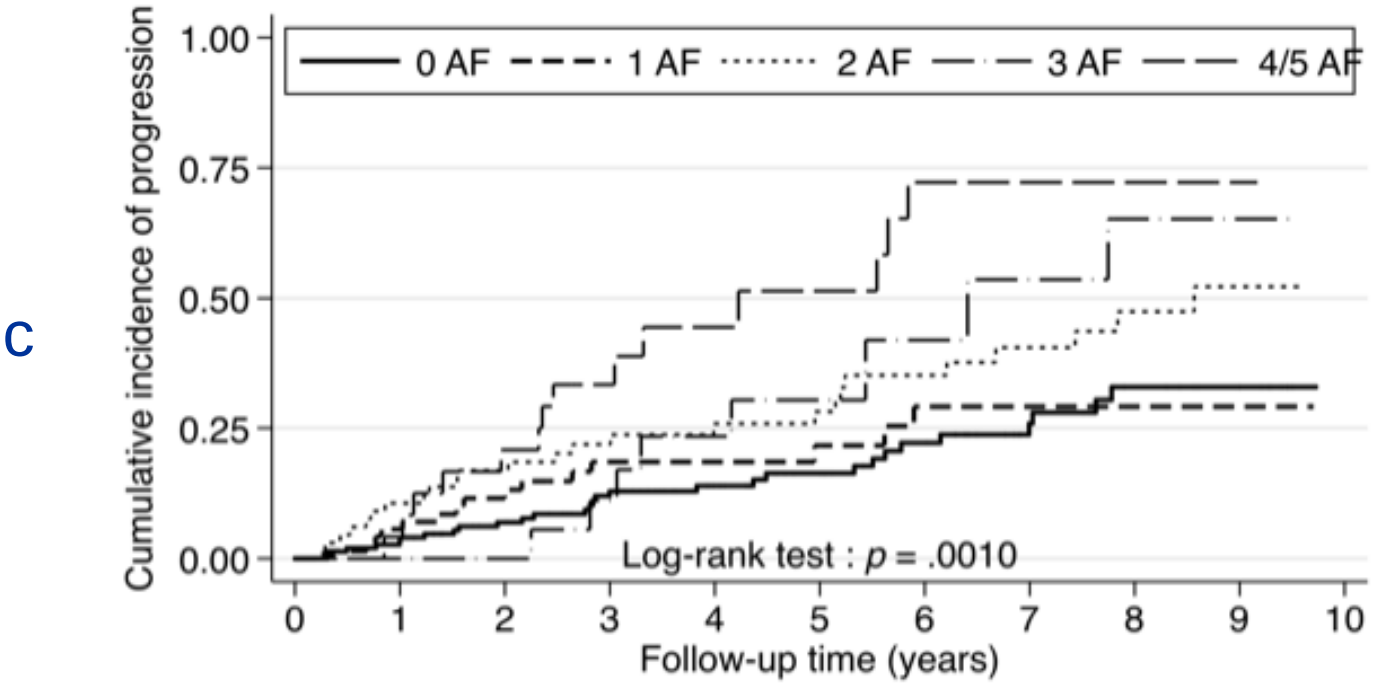


Kim D et al. JNS 2017

More Atypia Features is Associated with Recurrence

Atypia features (AF):

- High cell density
- High nuclear:cytoplasmic ratio
- Prominent nucleoli
- Sheeting
- Necrosis



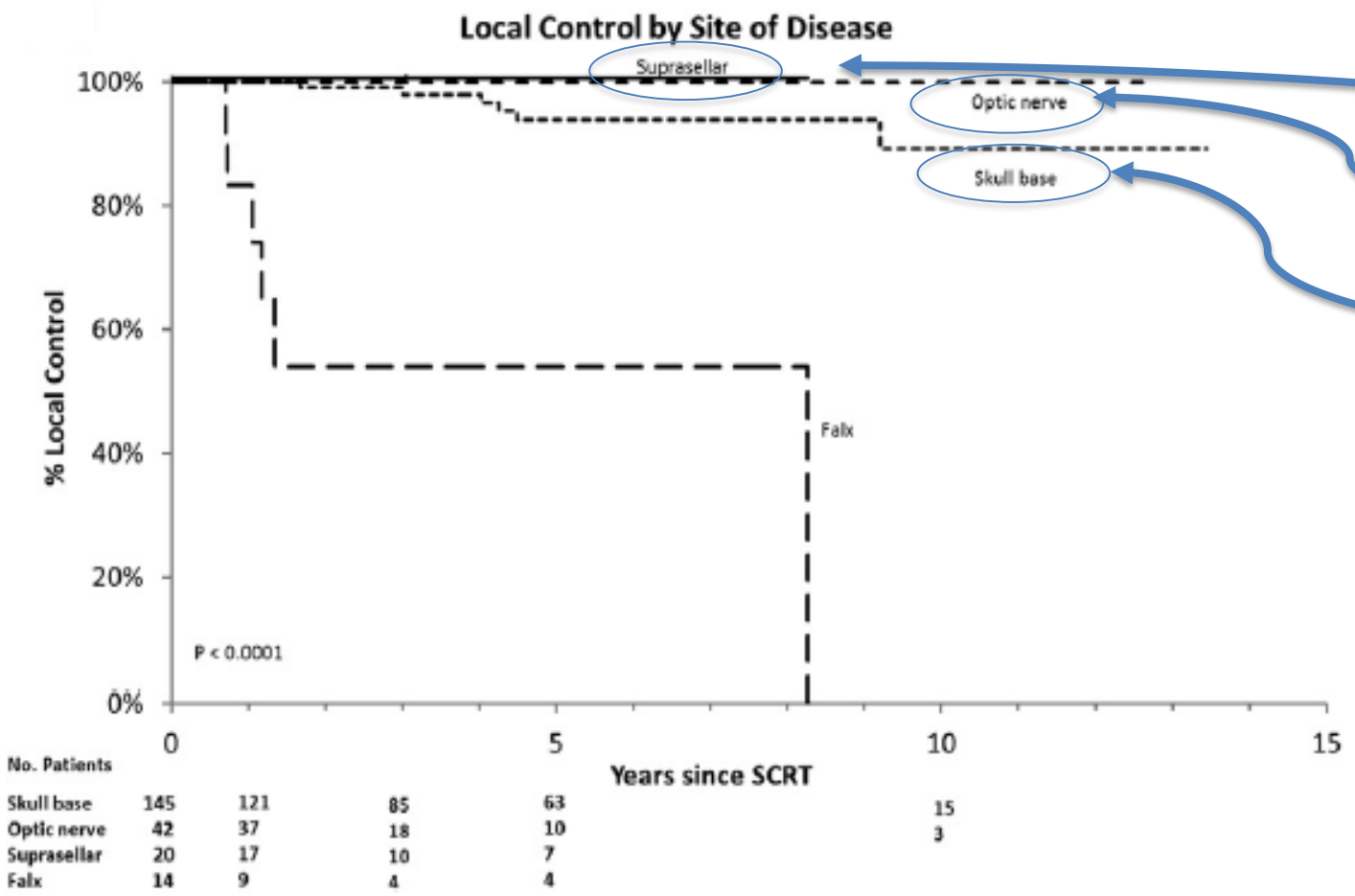
Number at risk

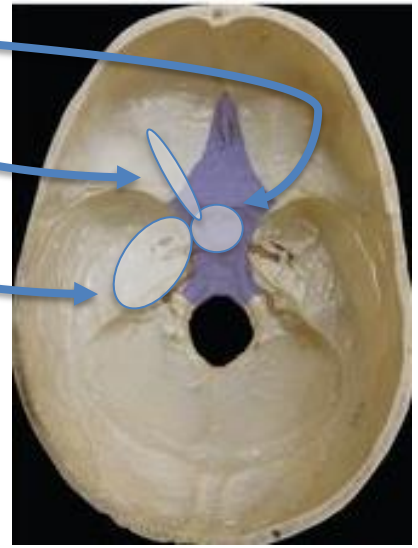
0 AF	149	143	123	98	79	65	50	35	25	21	12
1 AF	71	67	54	41	31	25	18	12	6	6	3
2 AF	66	58	52	42	35	31	25	20	13	4	2
3 AF	22	22	19	16	11	8	5	4	2	2	1
4/5 AF	24	23	19	12	9	7	4	4	4	2	1

AF = Atypical Feature

Lamba N et al. World Neurosurg accepted 2019

Benign Meningiomas Treated with Radiation Vary in Local Control by Anatomical Location

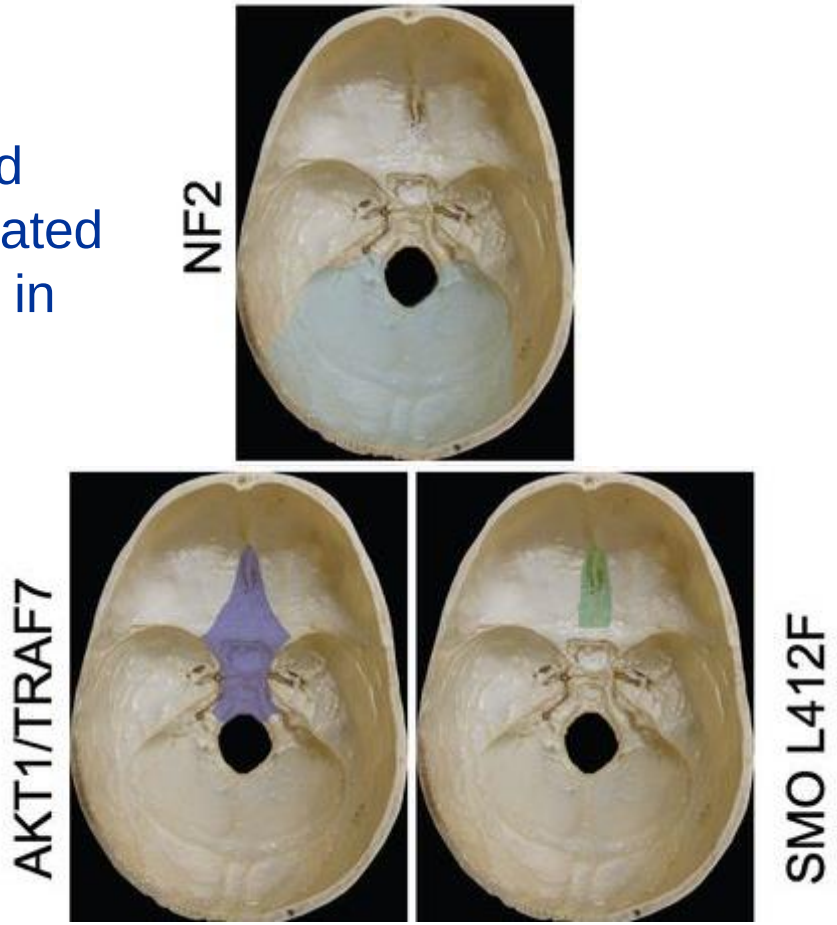




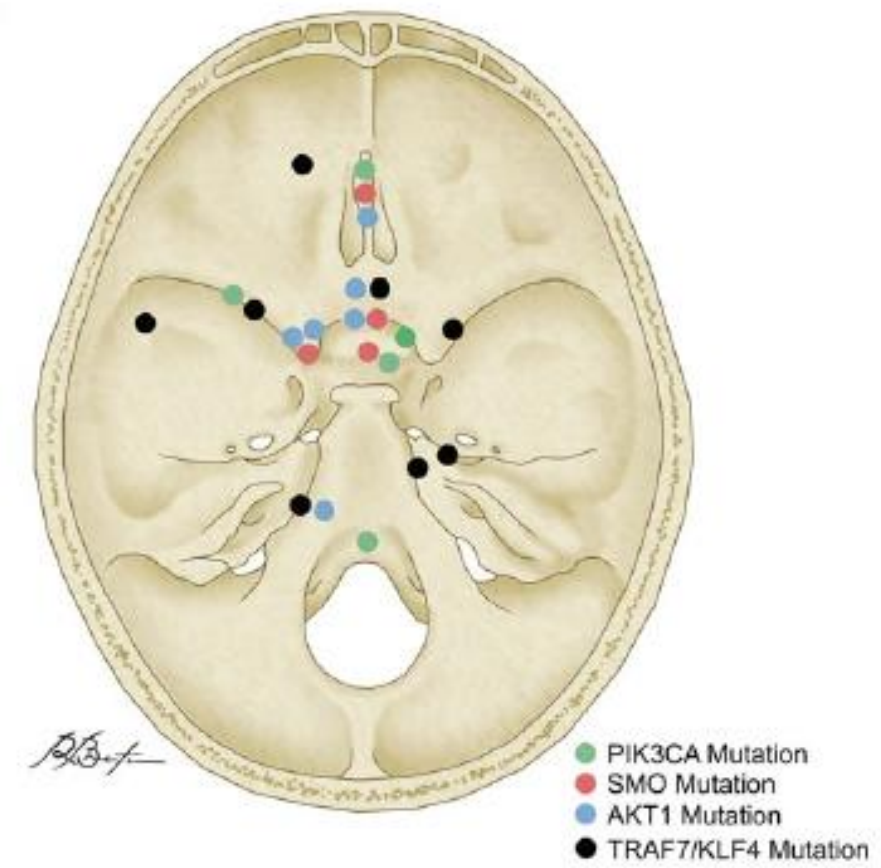
Solda F et al. Radiother Oncol 2013

Distribution of Meningiomas by Mutations in the Skull Base

68% of AKT1- and
64% of SMO-mutated
meningiomas are in
the skull base

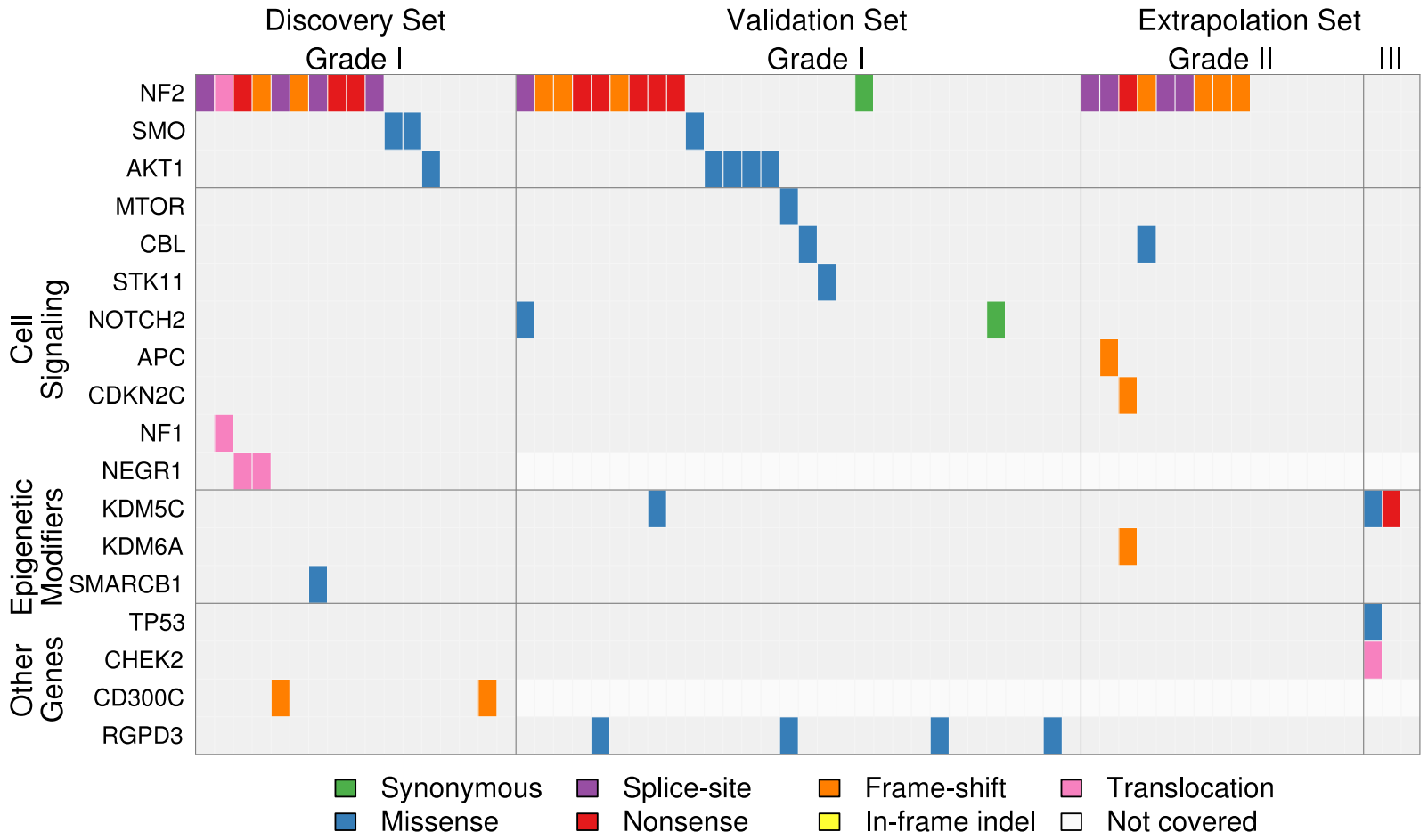


Clark et al. Science 2013



Abedalthagafi et al. NeuroOncol 2016

Specific Mutations Occur in Meningiomas



Brastianos P et al. Nature Genet 2013

Targeted Therapy Studies for Meningioma

- mTORC1/2 inhibitor (AZD2014/vistusertib)
  - For recurrence after surgery/RT

- Alliance Oncology, 3 arm mutation specific trial, any tumor, upfront or recurrence:
  - SMO inhibitor (vismodegib)
  - FAK inhibitor (GSK2256098)
  - AKT1 inhibitor (Afuresertib)

Immunotherapy Studies for High Grade Meningioma

- PD-1 inhibitor pembrolizumab
  - For any recurrence

- PD-1 inhibitor nivolumab
  - For recurrence after surgery/RT

Meningioma Key Points

- Span a range of indolent to aggressive behavior
- Small to large, round to flat, & variety of locations and symptoms
- Maximal safe surgical resection is the single most important factor for tumor control
- Radiation therapy improves tumor control
  - More effective with less residual disease
  - For high grade tumors, higher doses are associated with higher control
  - Late side effects such as stroke can likely be minimized with reducing collateral dose to major blood vessels
  - Proton therapy reduces normal tissue radiation exposure and may be helpful

Meningioma Key Points

- Imaging & pathological features will increasingly help in guiding treatment
- Molecular genetics will offer further understanding of tumor variations
- Targeted therapies and immunotherapy may provide for new treatments

THANK YOU FOR YOUR ATTENTION