The National Centre for Stereotactic Radiosurgery

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Radiosurgery

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The National Centre for Stereotactic Radiosurgery

Gamma Radiosurgery Center

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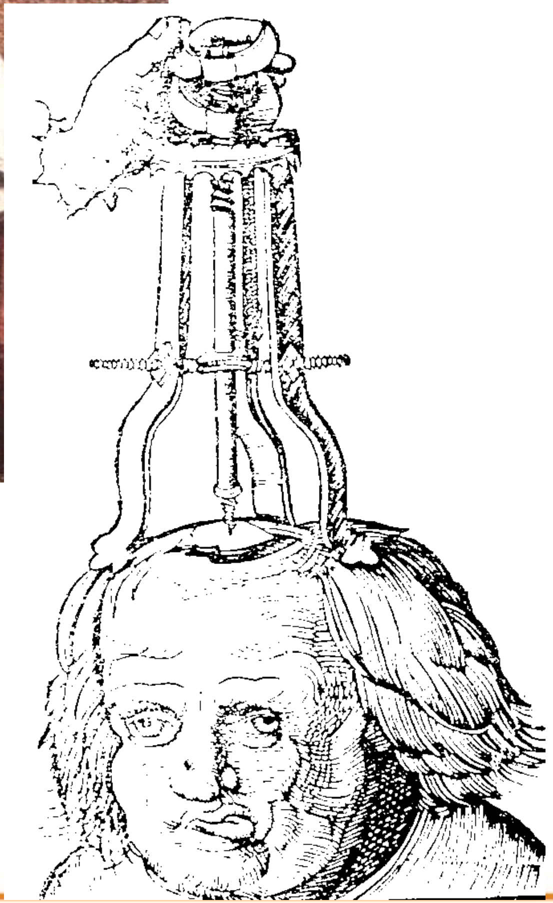
„The history of neurosurgery is the history of its tools"

(Prof Ladislau Steiner)

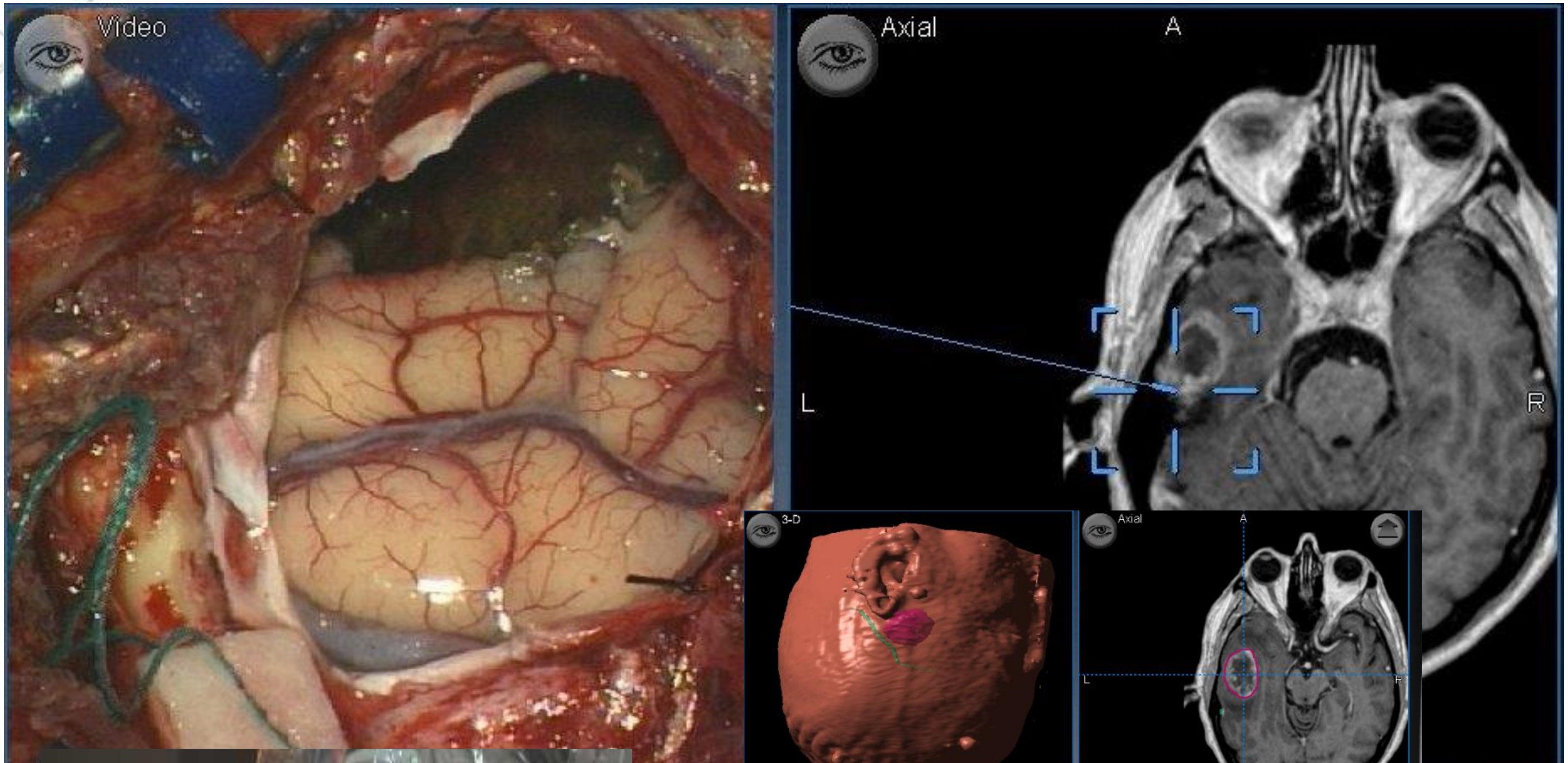
„The development of neurosurgery is a hard way toward minimally invasivity"

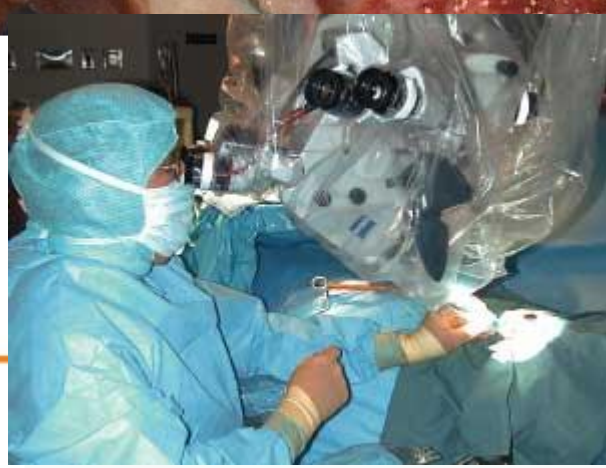
(Prof Emil Pásztor)

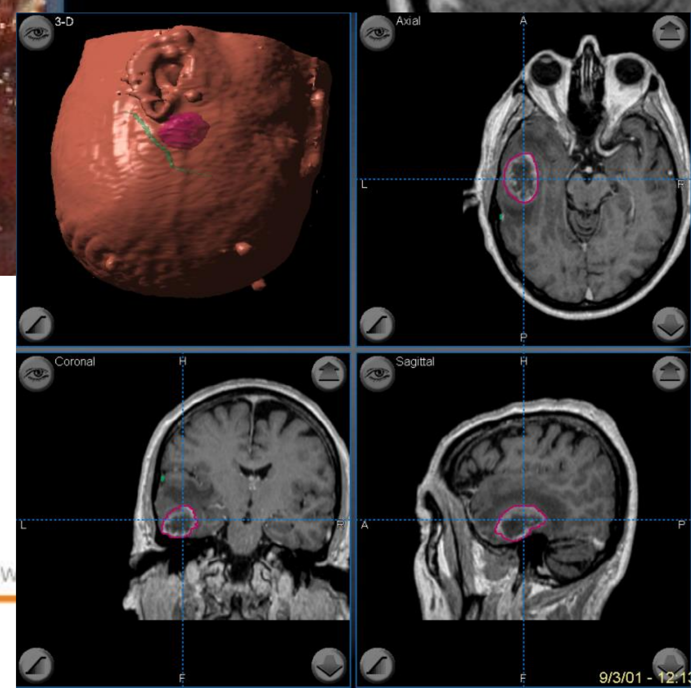
Early Neurosurgery



Microneurosurgery

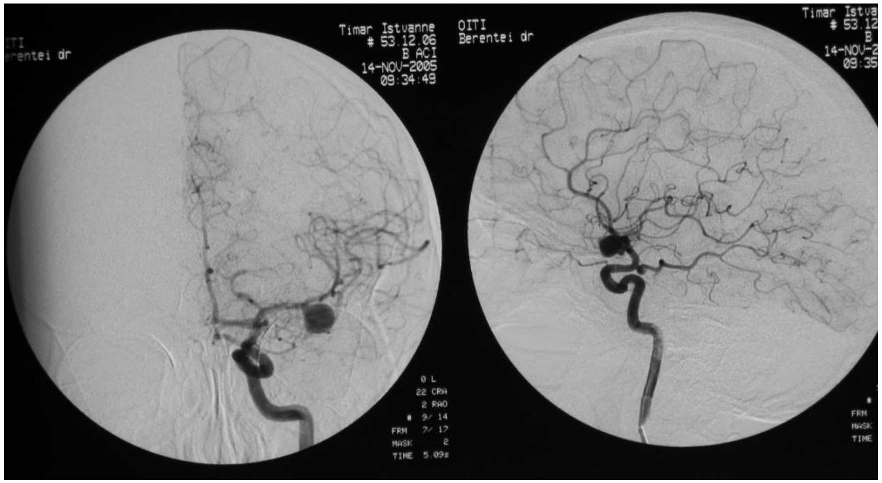


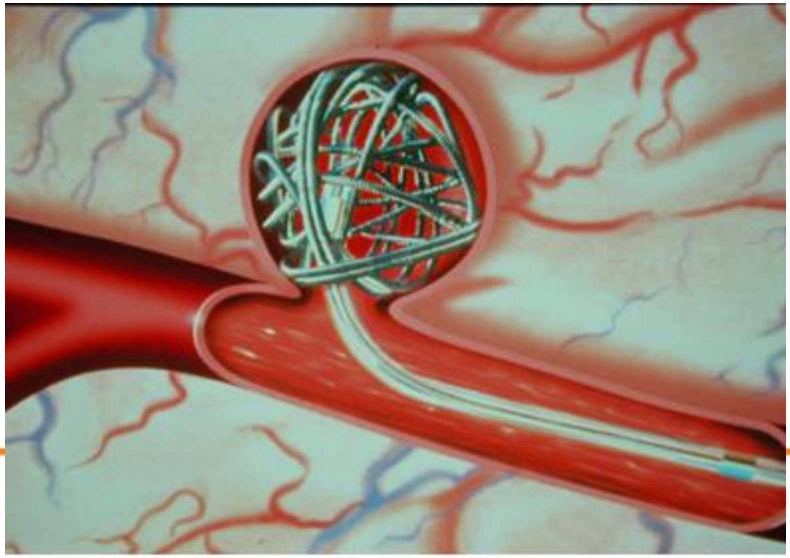




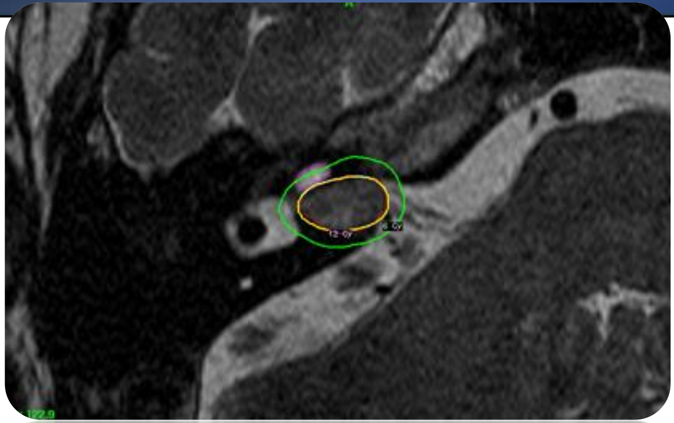
Minimally invasive alternatives

Neurointervention

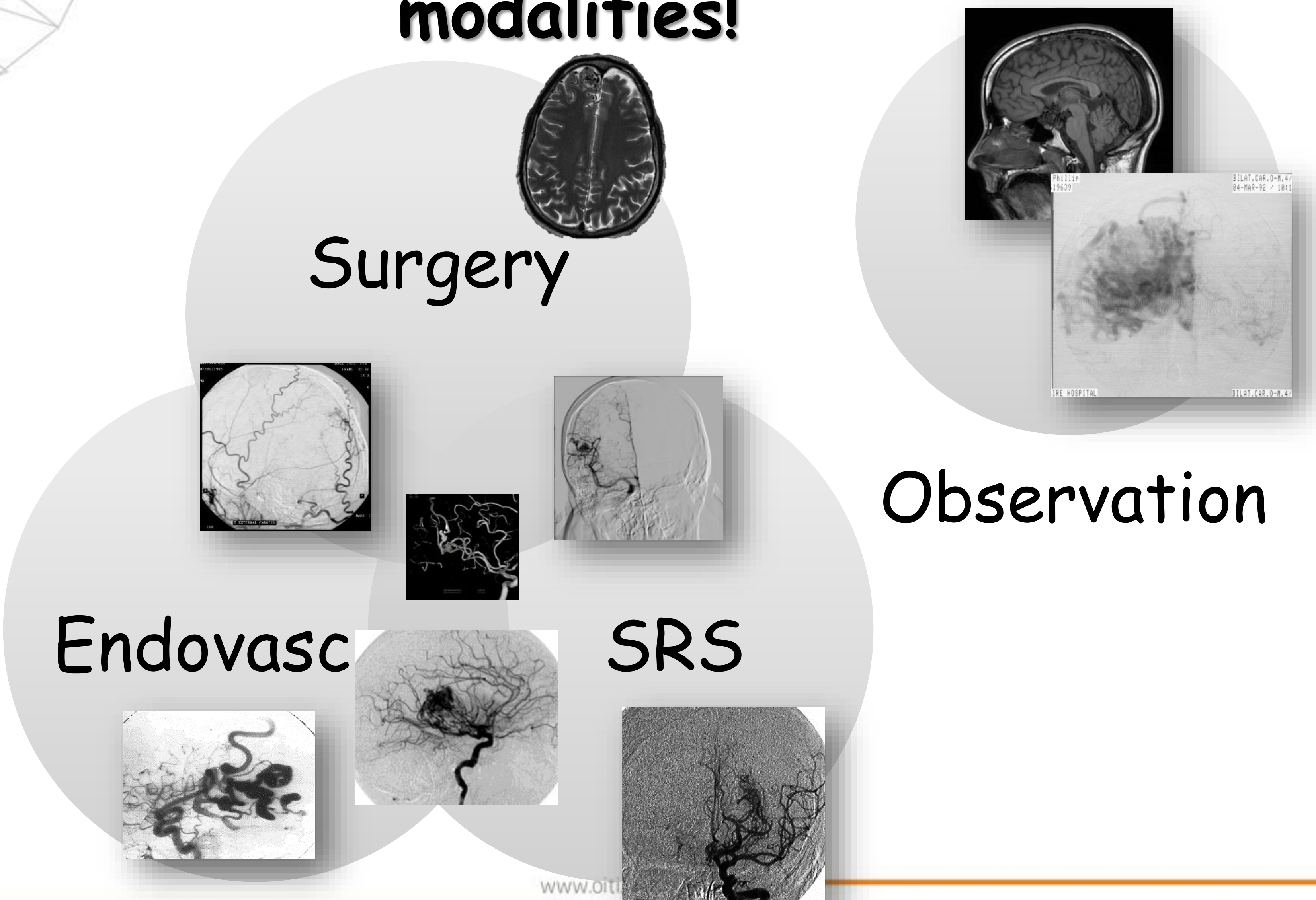




Radiosurgery



Not competitive rather complimentary modalities!



The Syrenes of interventions

Surgery

- Complete removal!
- Immediate cure!
- Well established!

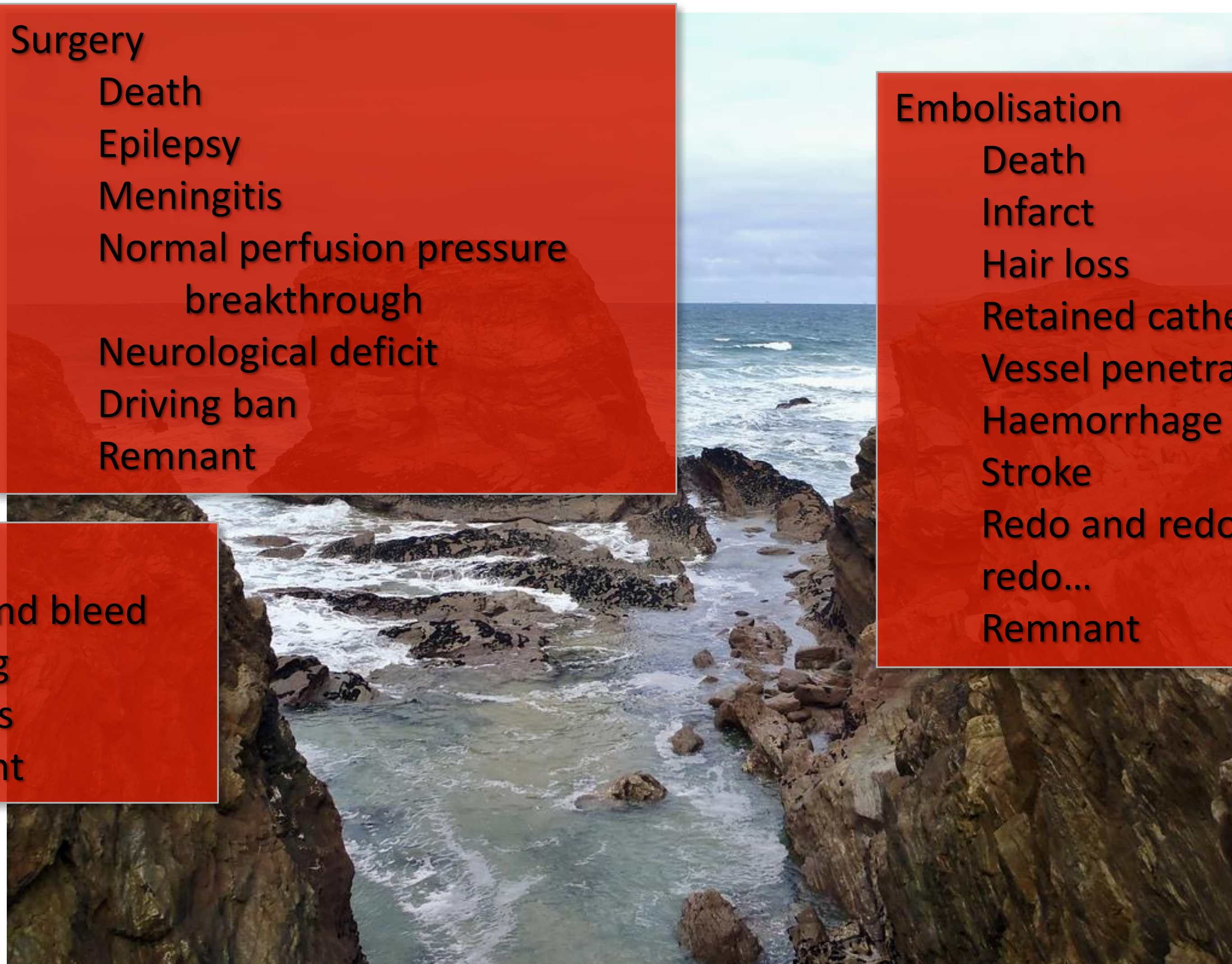
Endovascular

- No wound!
- Daycase procedure!
- New!
- Fancy!
- Minimally invasive!

Radiosurgery

- No wound!
- Daycase procedure!
- New!
- Expensive machine!
- Minimally invasive!

The risky sees: The challenge…



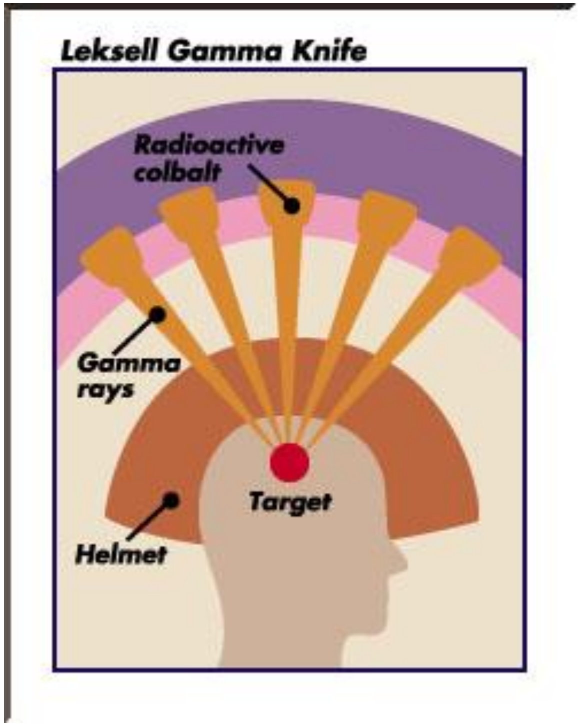
Surgery
- Death
- Epilepsy
- Meningitis
- Normal perfusion pressure breakthrough
- Neurological deficit
- Driving ban
- Remnant

Embolisation
- Death
- Infarct
- Hair loss
- Retained catheter
- Vessel penetration
- Haemorrhage
- Stroke
- Redo and redo and redo…
- Remnant

SRS
- Delay and bleed
- Swelling
- Necrosis
- Remnant

Radiosurgery

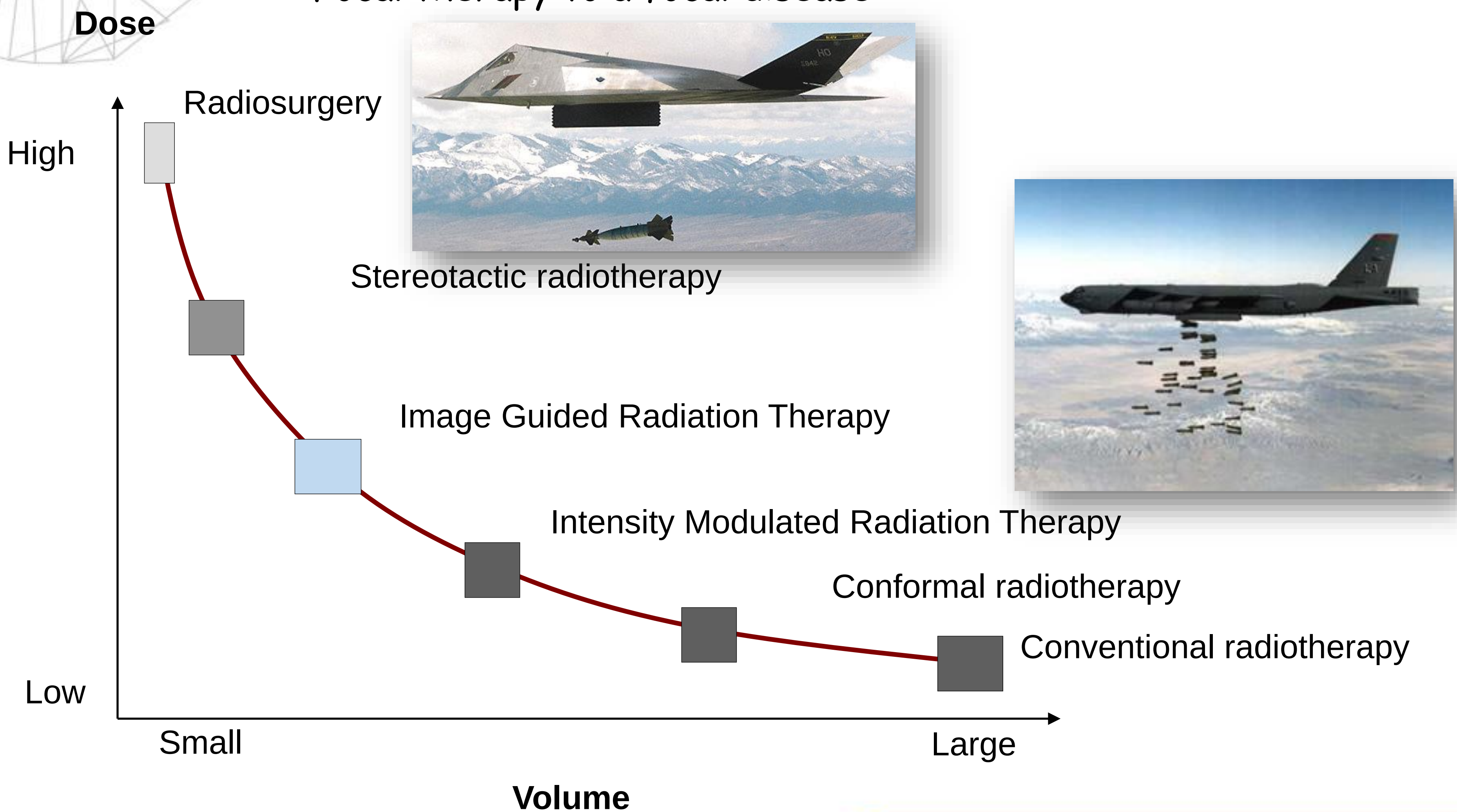
- A **neurosurgical procedure**, which allows non-invasive brain (and spine) surgery without opening the skull, by means of directed high energy beams of ionizing radiation preventing damage of the surrounding healthy structures (submillimeter accuracy)
- The target is the cross section of multiple low dose radiation beams (gamma radiation based: Co^{60}, LINAC based: high energy x-ray)
- Single high dose
- **Not radiotherapy**



- **Predictable**
- **Reproducable (transferable expertise)**

Radisourgery versus radiotherapy

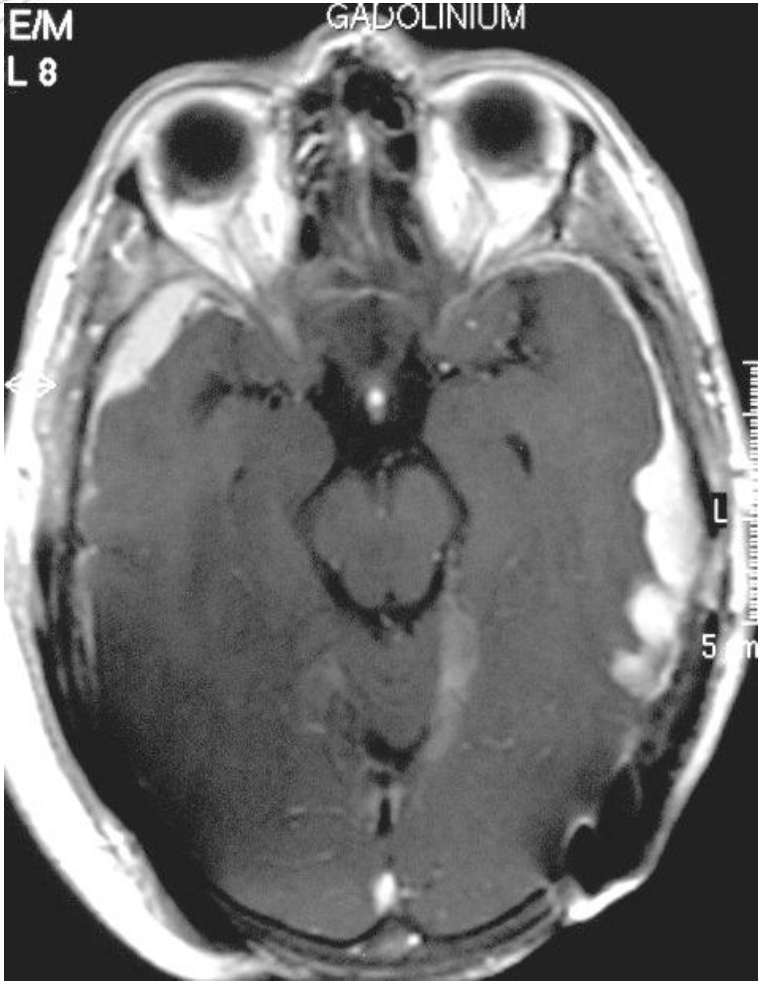
Focal therapy to a focal disease

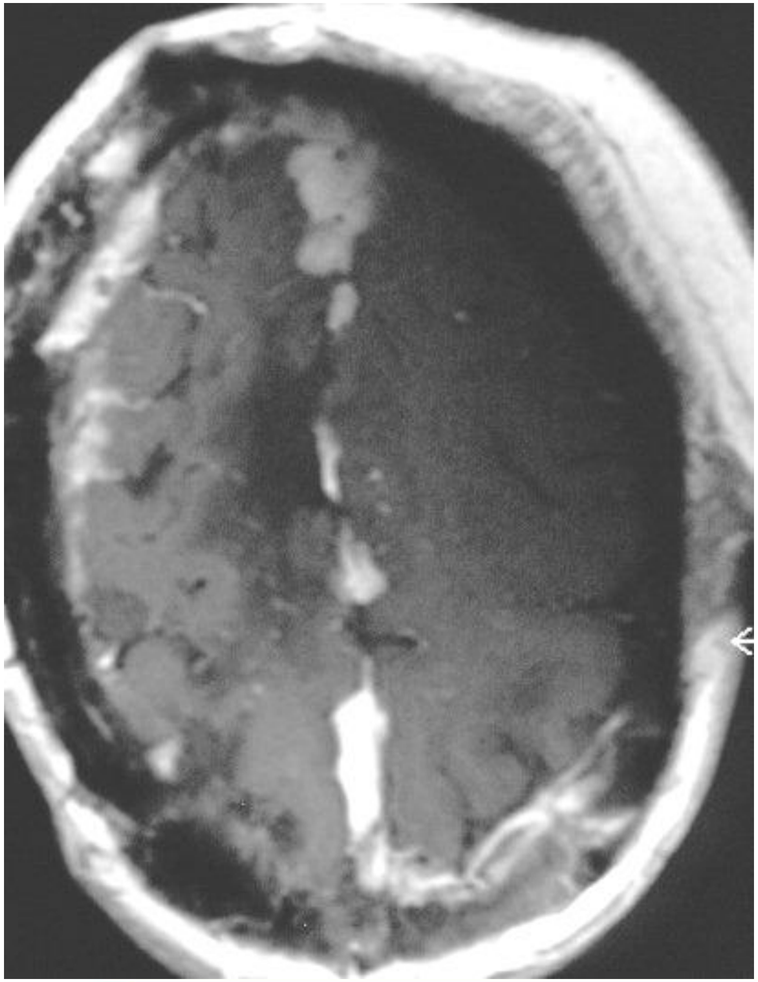


Why is the outcome of radiosurgery good?

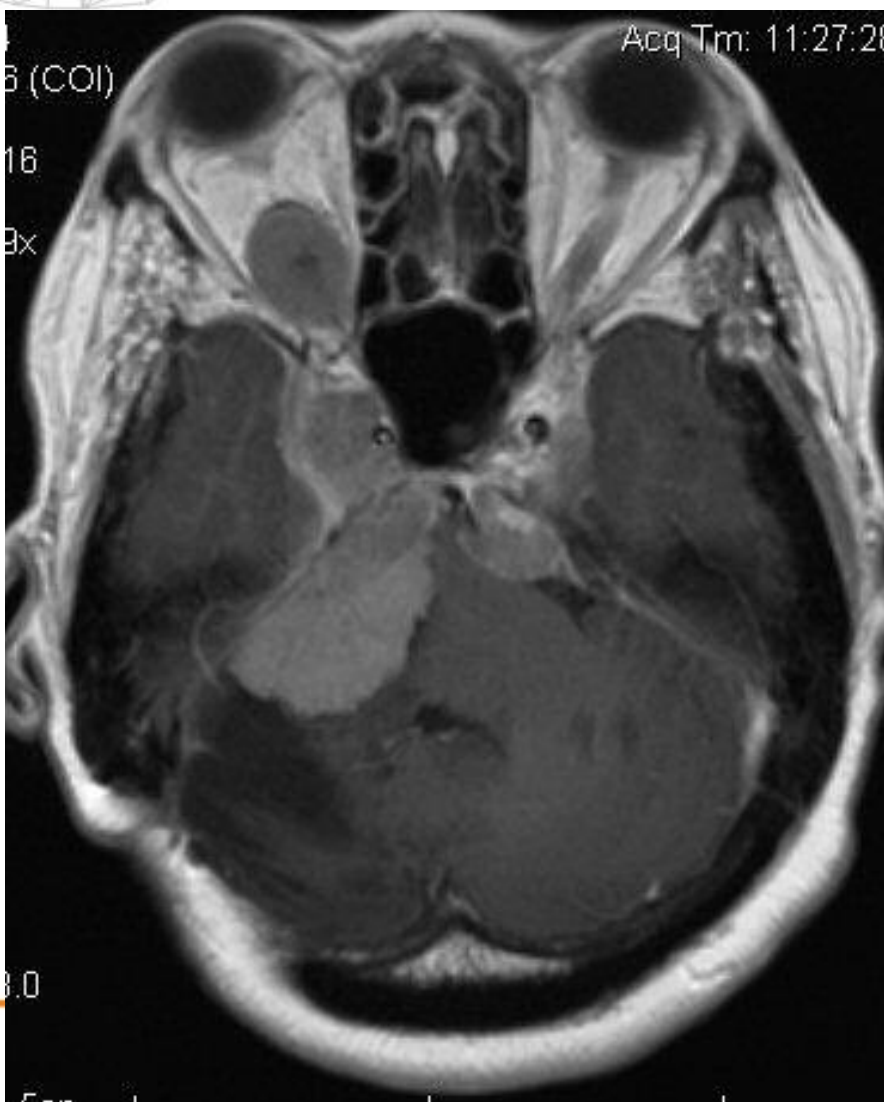
- Patient selection
  - Pathology:
    - Radiosensitivity is not prerequisition
    - Vascular effect
  - Size of lesion
    - "3 cm" diameter is not a limit
    - Volume
- Dose
- Conformal treatment plan

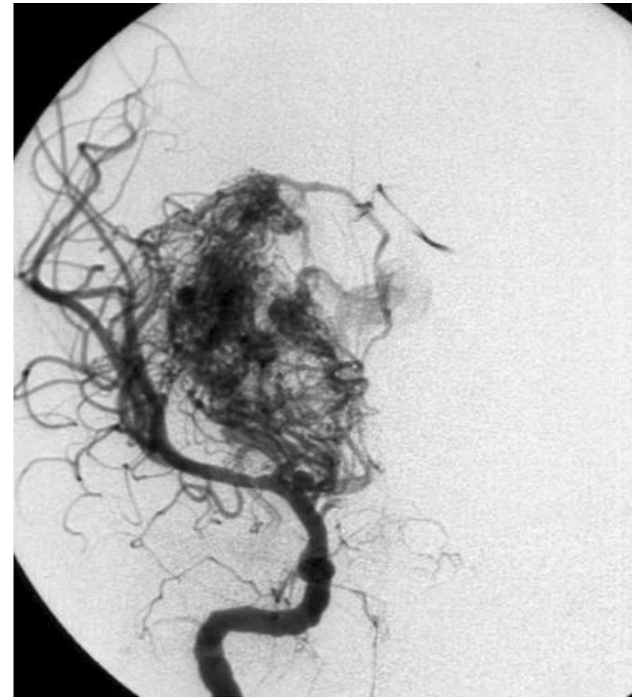
The shape of lesion is not appropriate

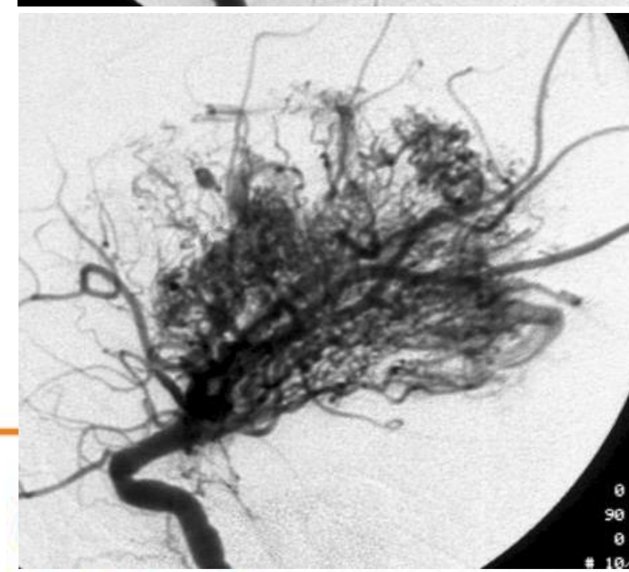




Large, diffuse lesion







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- Conformal treatment plan

Dose: effect and side effect

$$P_{obl}=36 * \ln(D_{min})-40 \quad ; 0 \le P_{obl} \le 100 \qquad \text{Eq.1}$$

where P_{obl} = Probability of obliteration

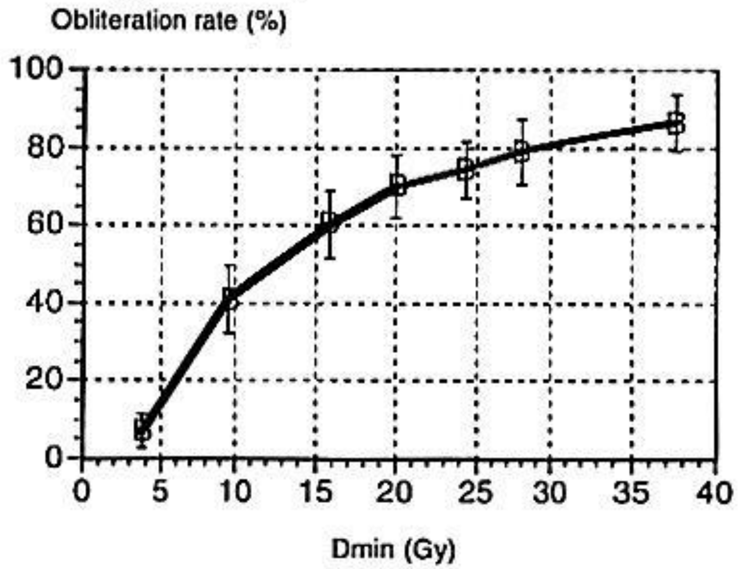
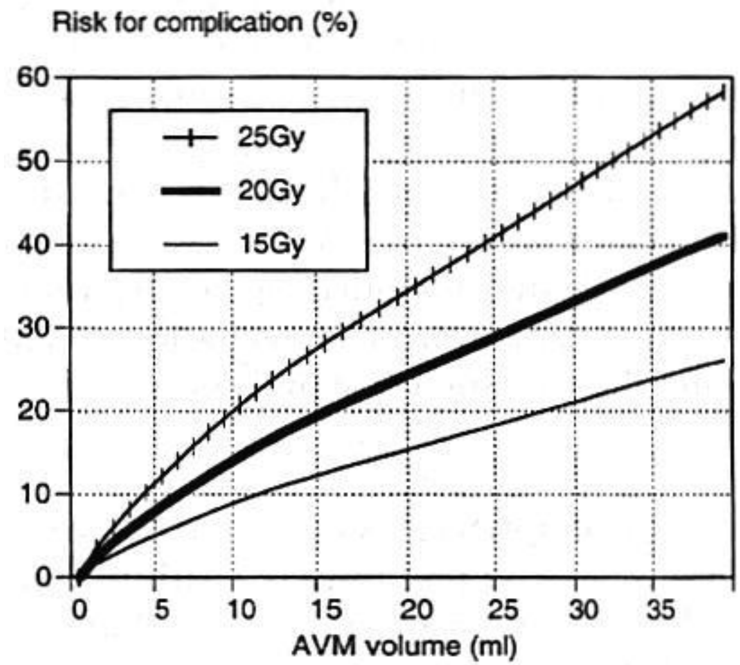


Fig. 5. Obliteration rate plotted against D_{min}. The bars represent the 95% confidence interval.

Proportional to dose



Factors defining complication

- Anatomical location

- Size of target volume
- Marginal (minimal) dose

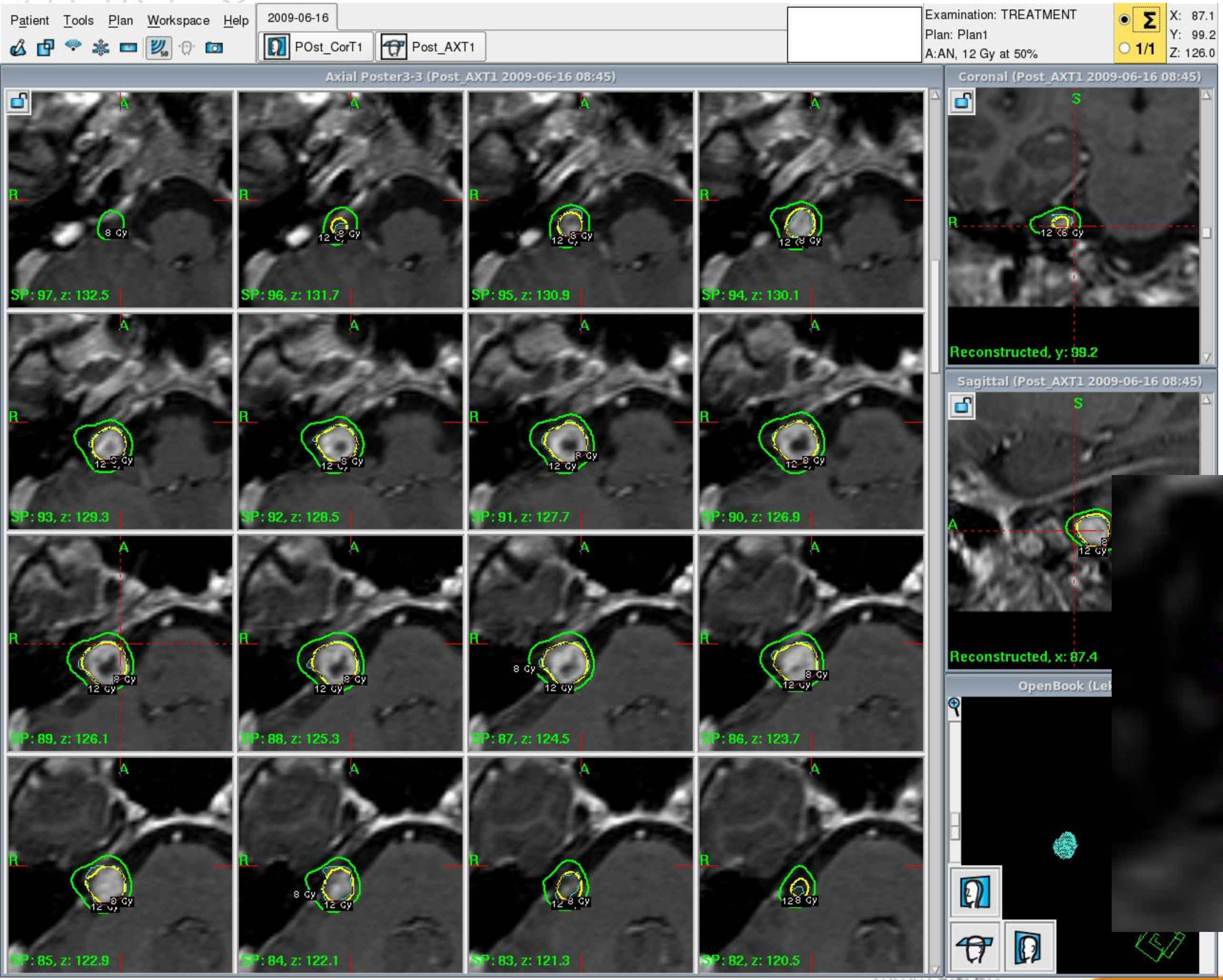
- $Dose_{average}$ to 20 cm^3 (M Soderman)
- Volume receiving 10Gy (B Wowra)

- Quality of treatment plan (conformity index)
  - = therapist's experience

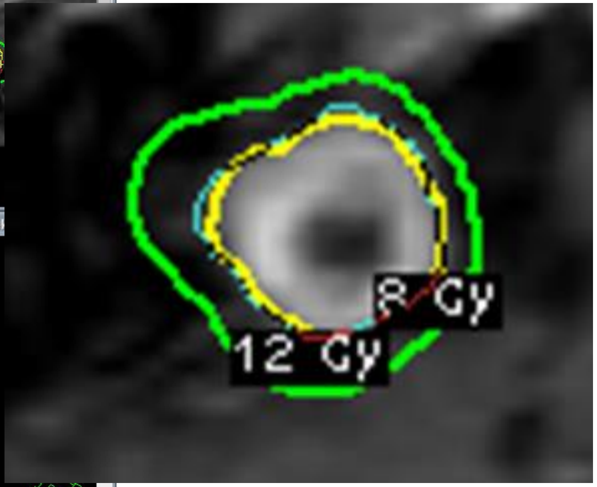
Reducing complication

- Patient selection
- Dose
- Conformal treatment planning
  - Quality of neuroradiology
  - Anatomy!!! (e.g. n VII)
  - Paddick index

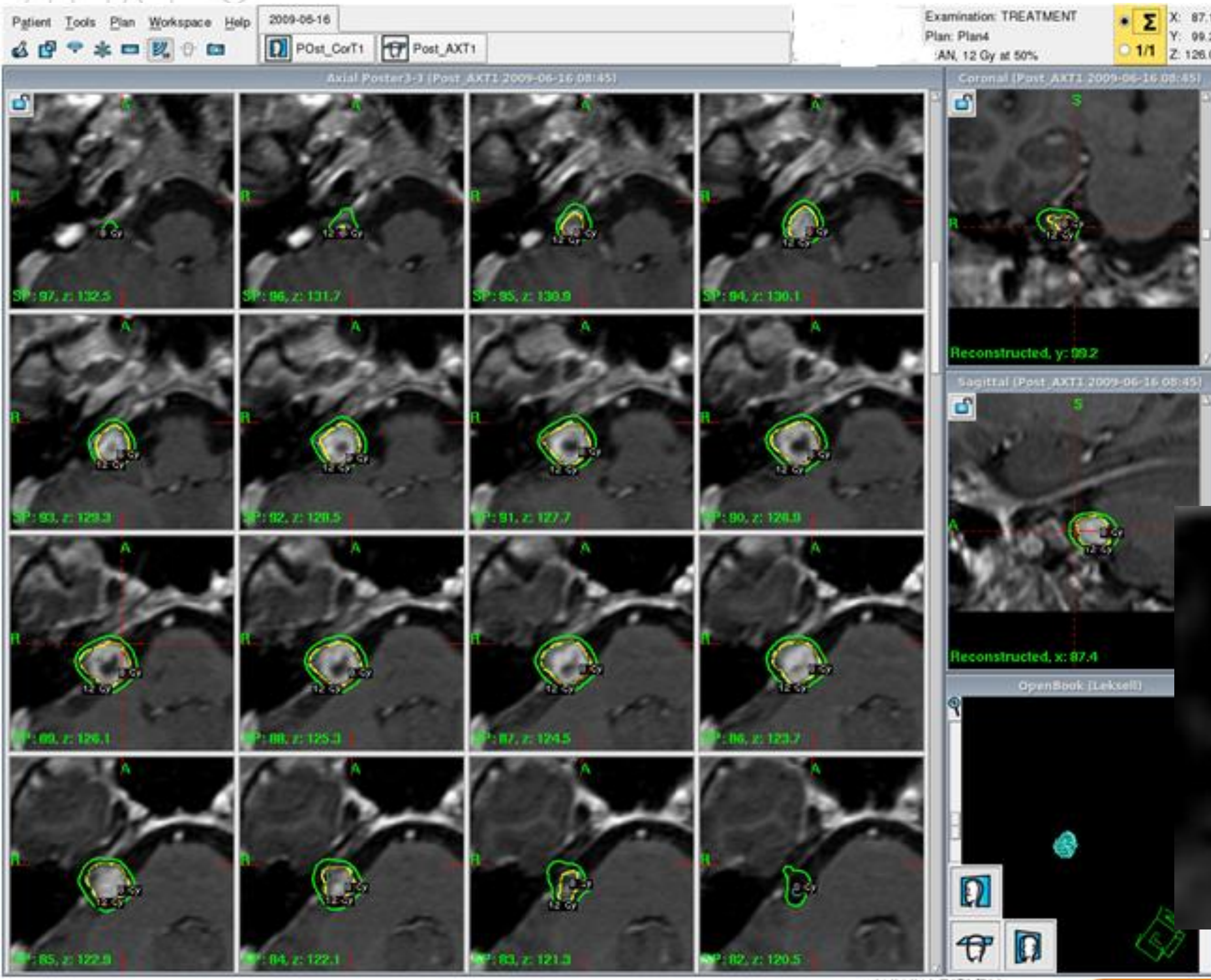
Quality of treatment plan



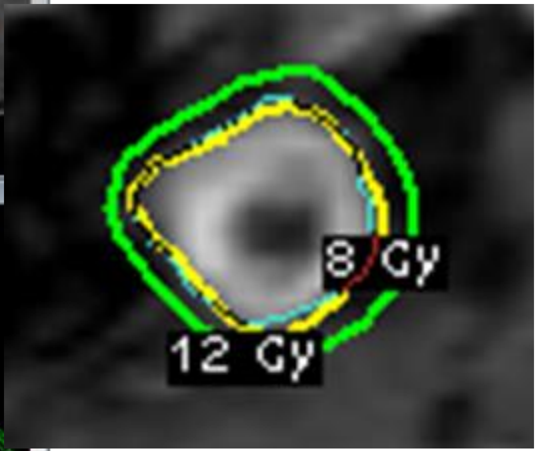
- 12Gy marginal
- 6x8mm
- 19.9 min



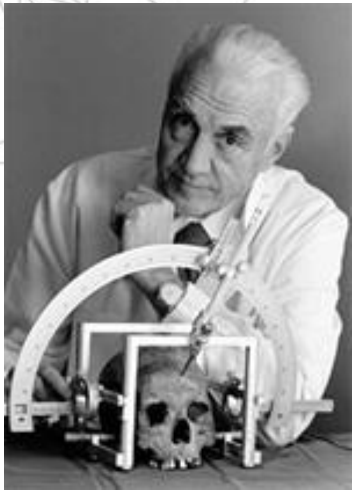
Quality of treatment plan

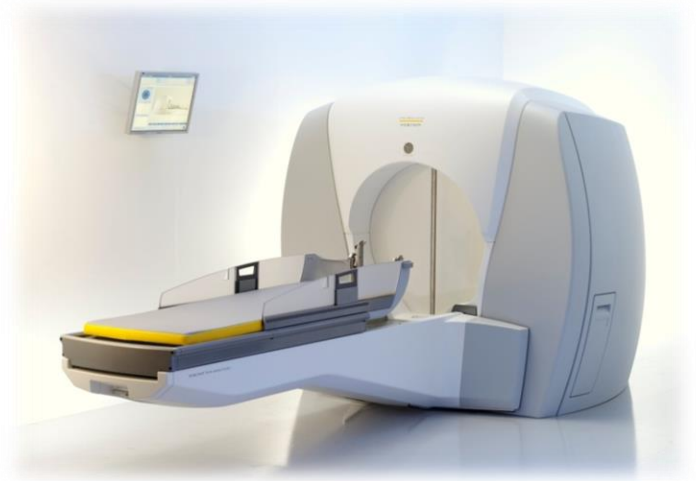


- 12 Gy marginal
- 1x8mm + 13x4mm
- 49 min



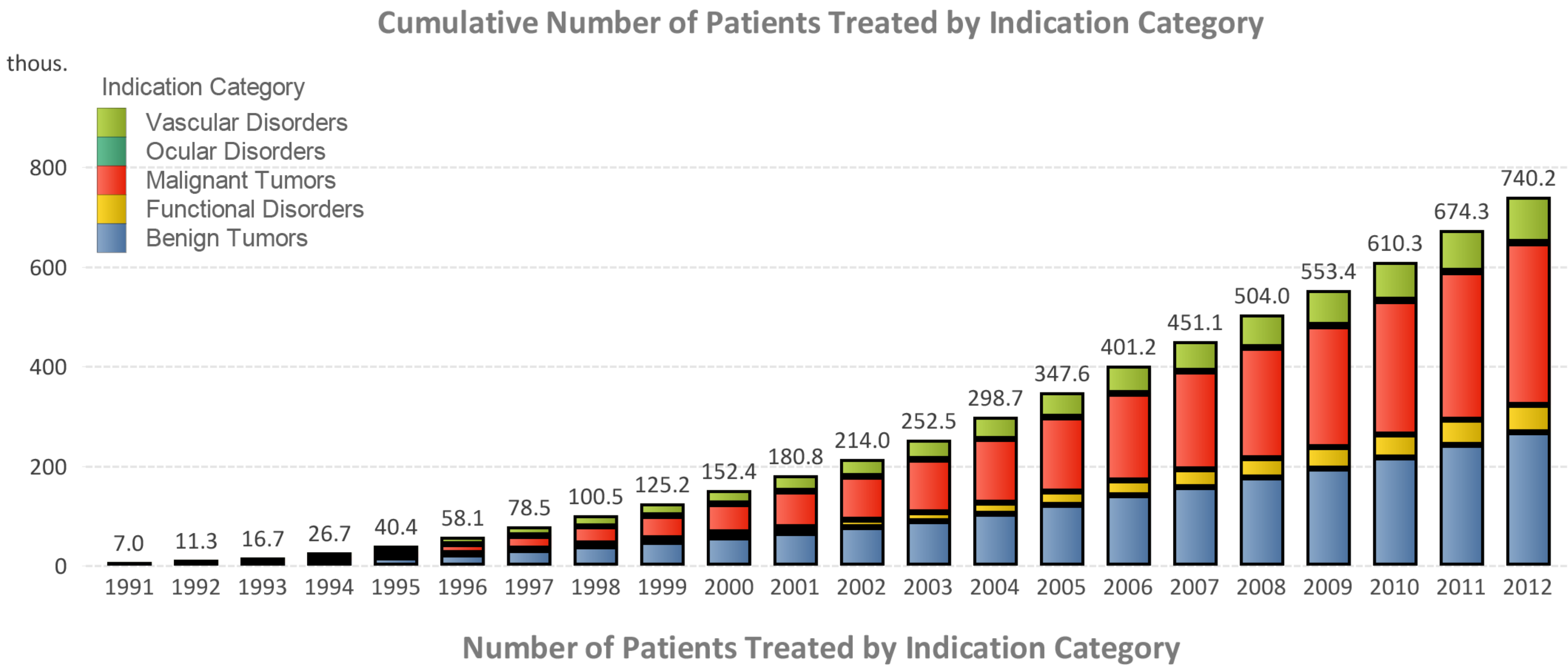
History of radiosurgery



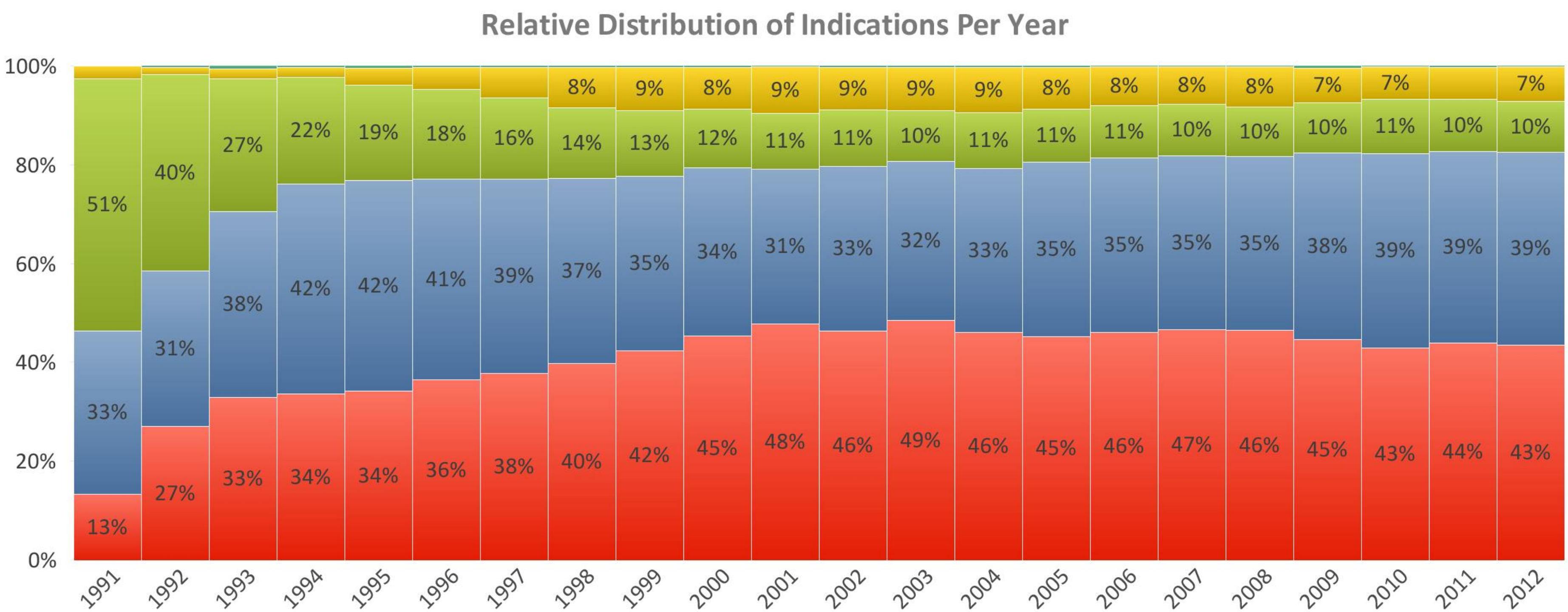


- 1914, 1928: Vilhelm Magnus, later Cushing&Bailey AVM radiotherapy
- 1949: Lars Leksell describes his stereotactic system
- 1951: „stereotactic radiosurgery" (Leksell)
- 1968: first gamma knife (Leksell, Stockholm)
- 1970: first AVM treatent (Ladislau Steiner, Lars Leksell)
- 1985: Sheffield, 1987: Pittsburgh, present >300 gammgamma knife world wide, 80': LINAC adapded to radiosurgery
- Gamma knife: 2012-ben appr. 700 000 treatments annually world wide

Spread of radiosurgery around the world



Change of relative indications

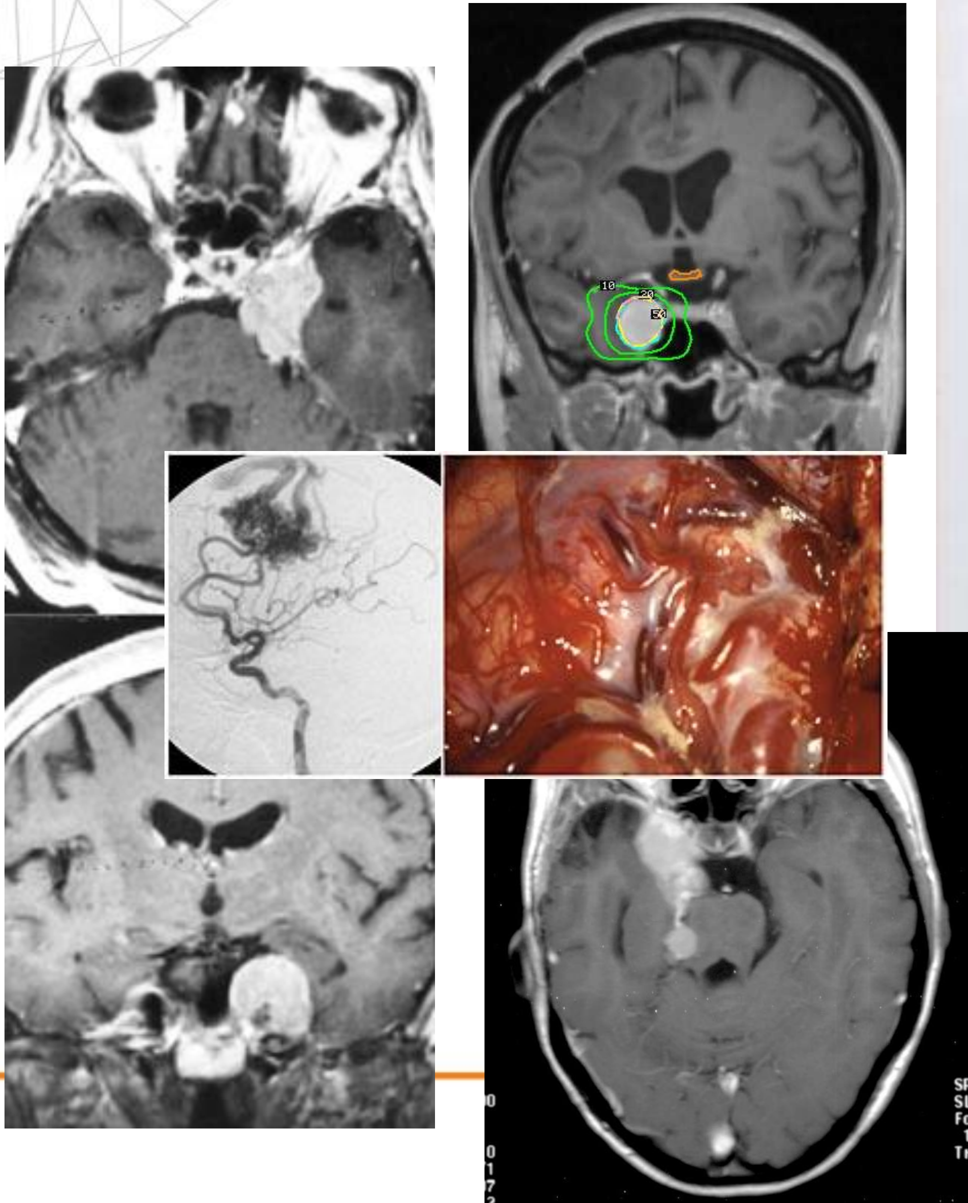


The reason for the success of radiosurgery

- Small intervention
- Outpatient
- Short hospital stay
- Good outcomes
- Quick return to normal life
- …etc

Prefer to send the hard cases!

Am I able to operate on?



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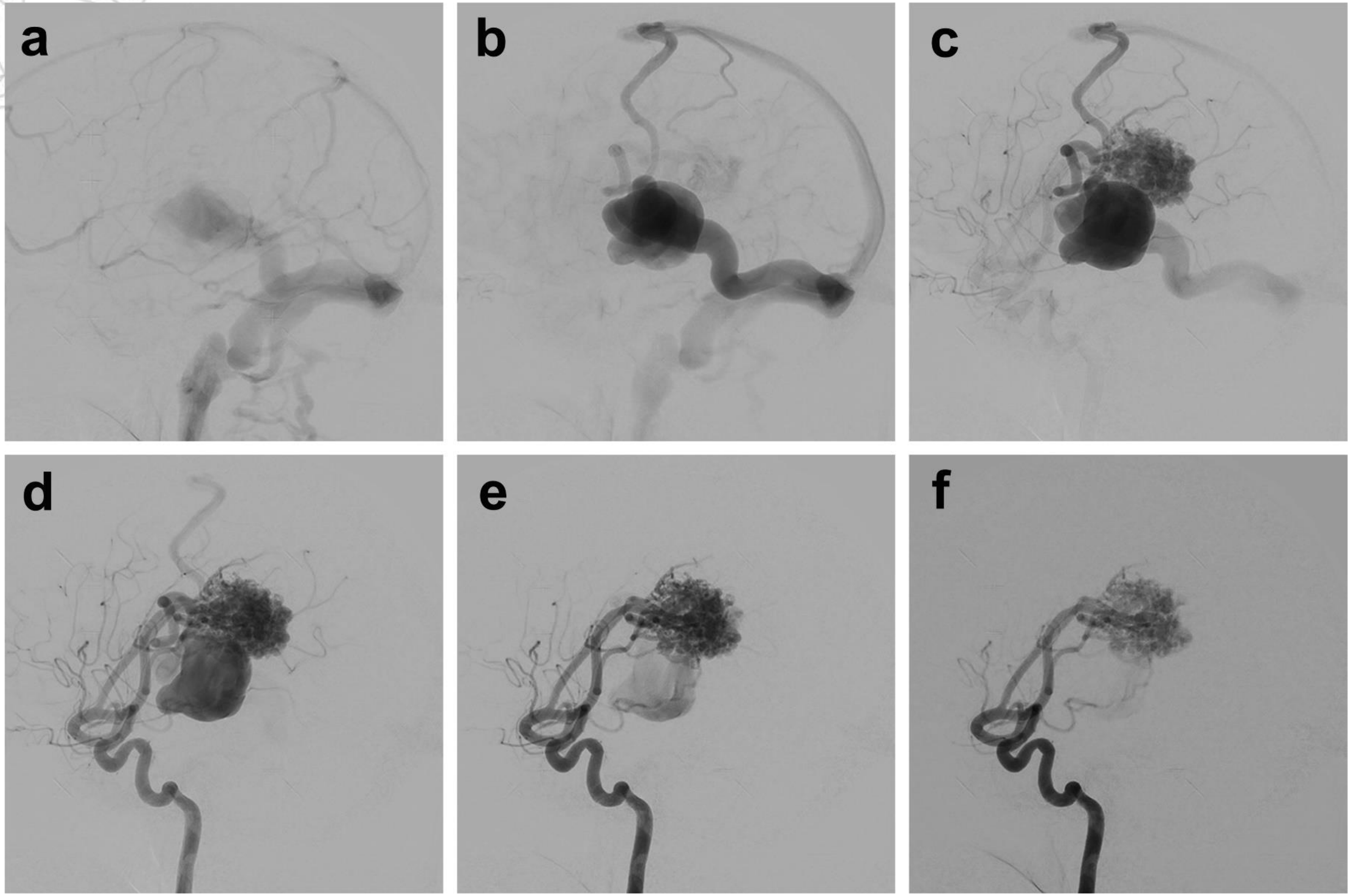
Adverse effects of the success of radiosurgery on neurosurgery

- Lower number of operative cases
- Less surgical experience
- Worse quality of practical surgical education

- More cases sent to radiosurgery

AVM - Planning: nidus definition



Nagy et al. In: Benes&Bradac (eds) 2017

Factors defining treatment of AVMs

- Radiological factors
  - Size
  - Location (eloquence)
  - Draining veins (deep /superficial)
  - Diffuse/compoct nidus
  - Shape of nidus
  - Angio-architecture, aneurysms
- Patient factors
  - Clinical condition (neurological, internal)
  - Presentation
    Bleed? Epilepsy? Steal?
  - Age (lifetime risk of bleeding)
  - Patient's preference
- Institutional factors
  - Available modalities, experience

Microsurgery (Spetzler-Martin)

Radisourgery

Endovascular

Conservative

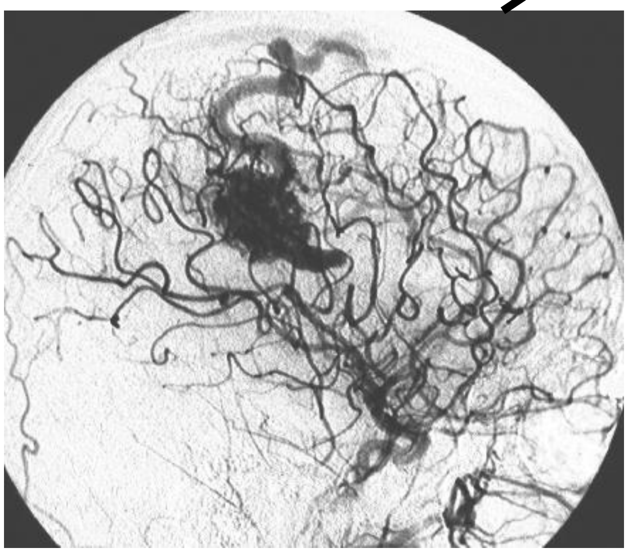
Always individual, recommended by multidisciplinar team!

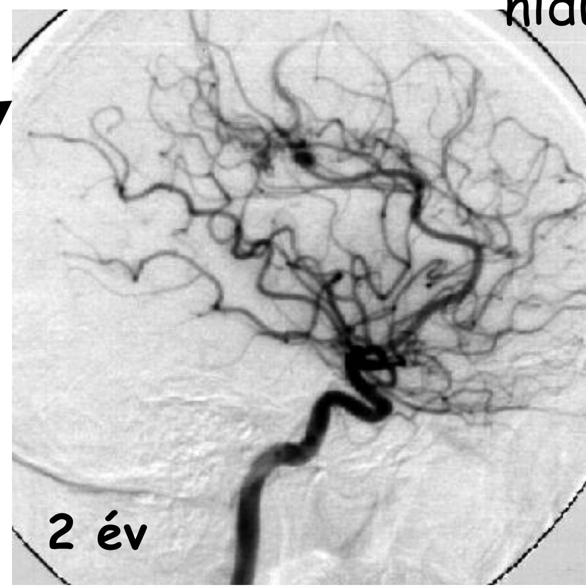
Kemeny et al., Acta Neurochir Suppl 2004

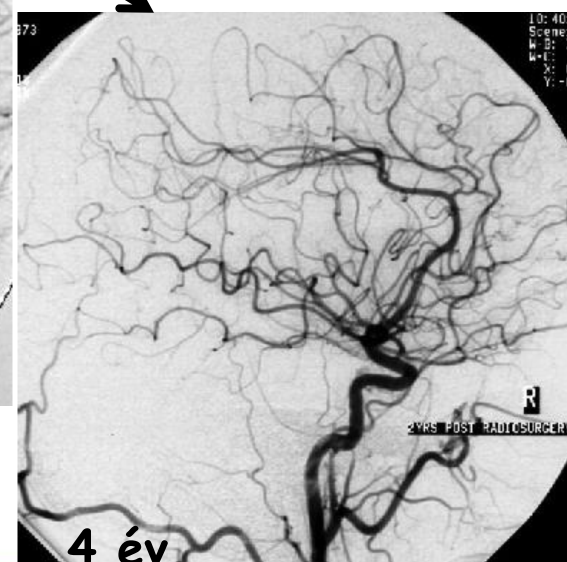
Advantages and disadvantages of radiosurgery

- Noninvasive
- Day-case treatment
- No acute side effect
- Low risk of radiation
- High obliteration rate

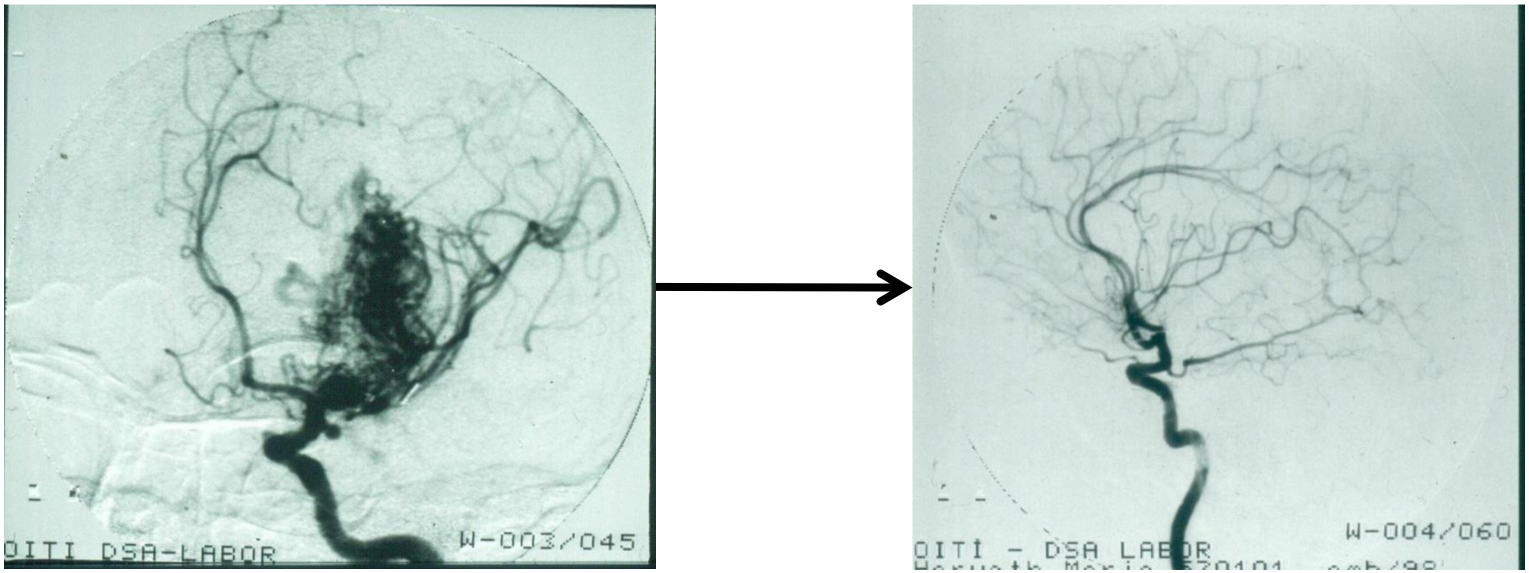
- During the 2-4 year latency period the risk of bleeding is unchanged
- Not appropirate for all AVM (fistulosus, diffuse nidus, radioresistence)



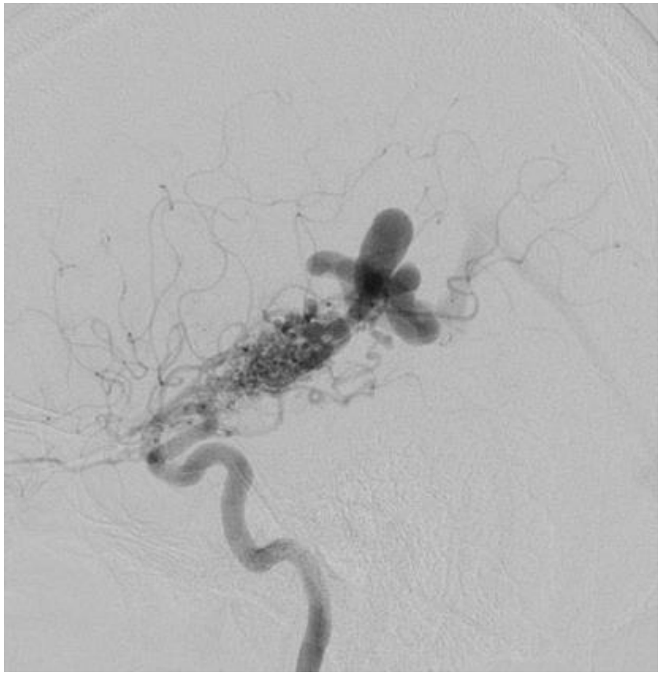
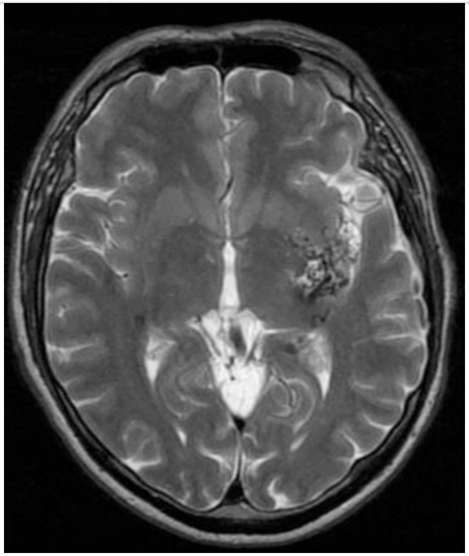
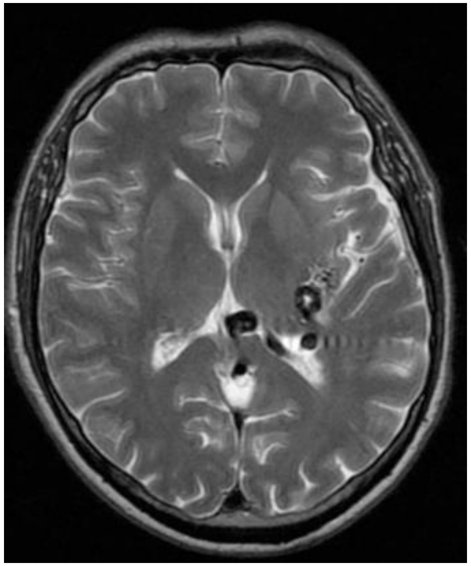




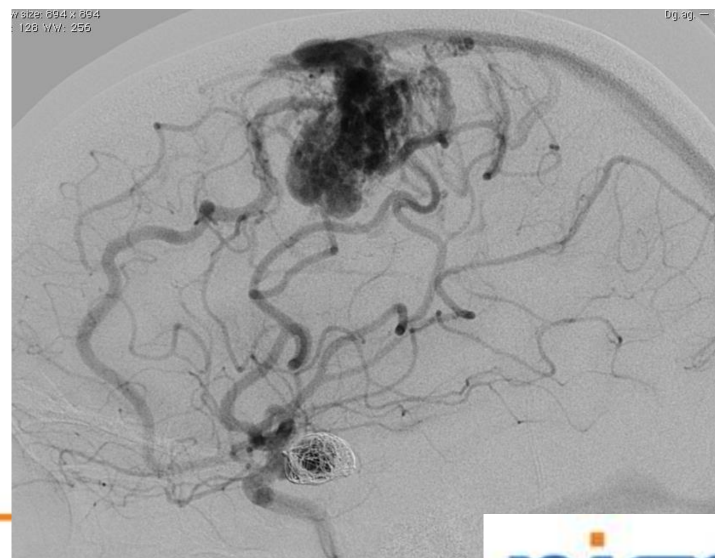
Ideal for radiosurgery



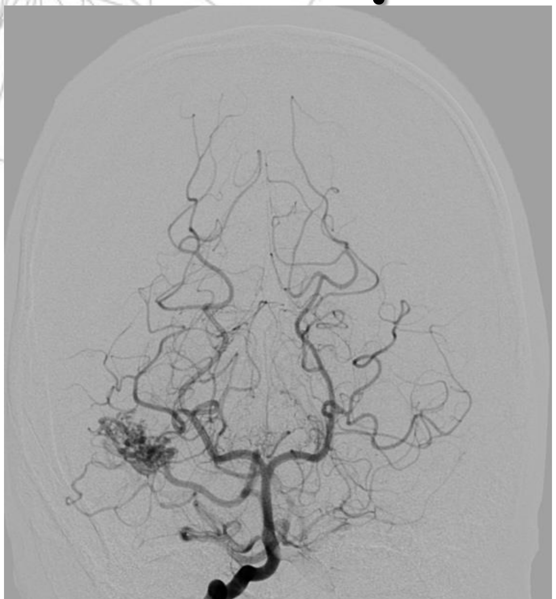
Ideal for radiosurgery

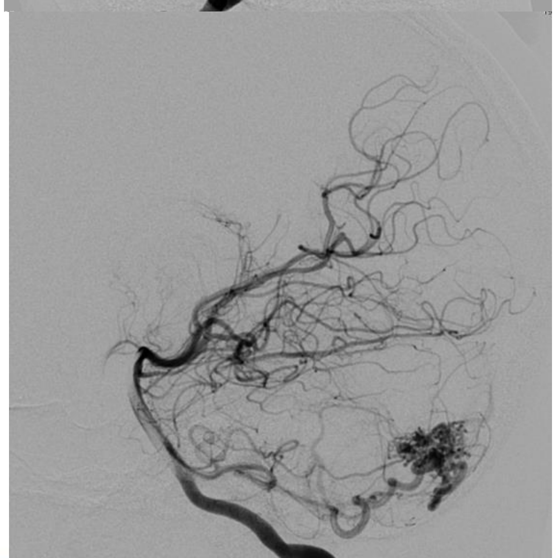





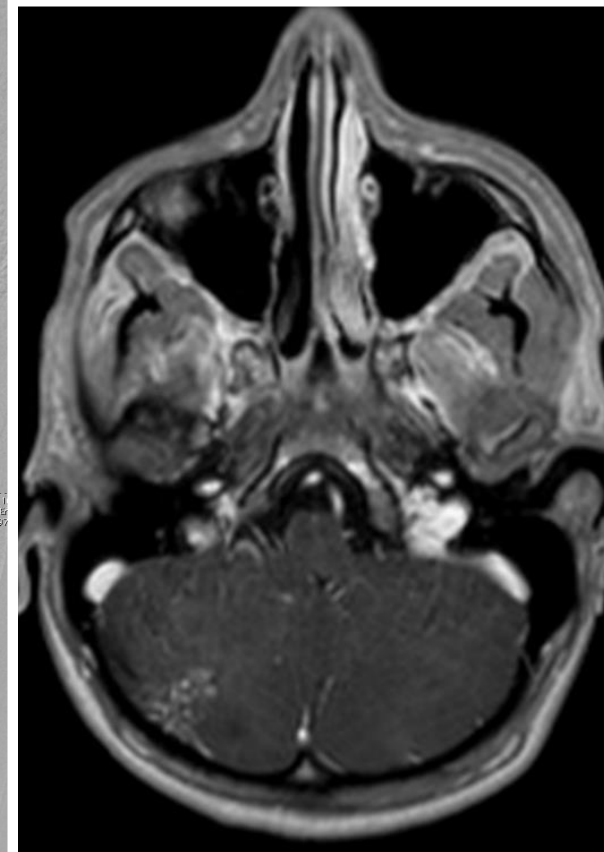
Ideal for radiosurgery



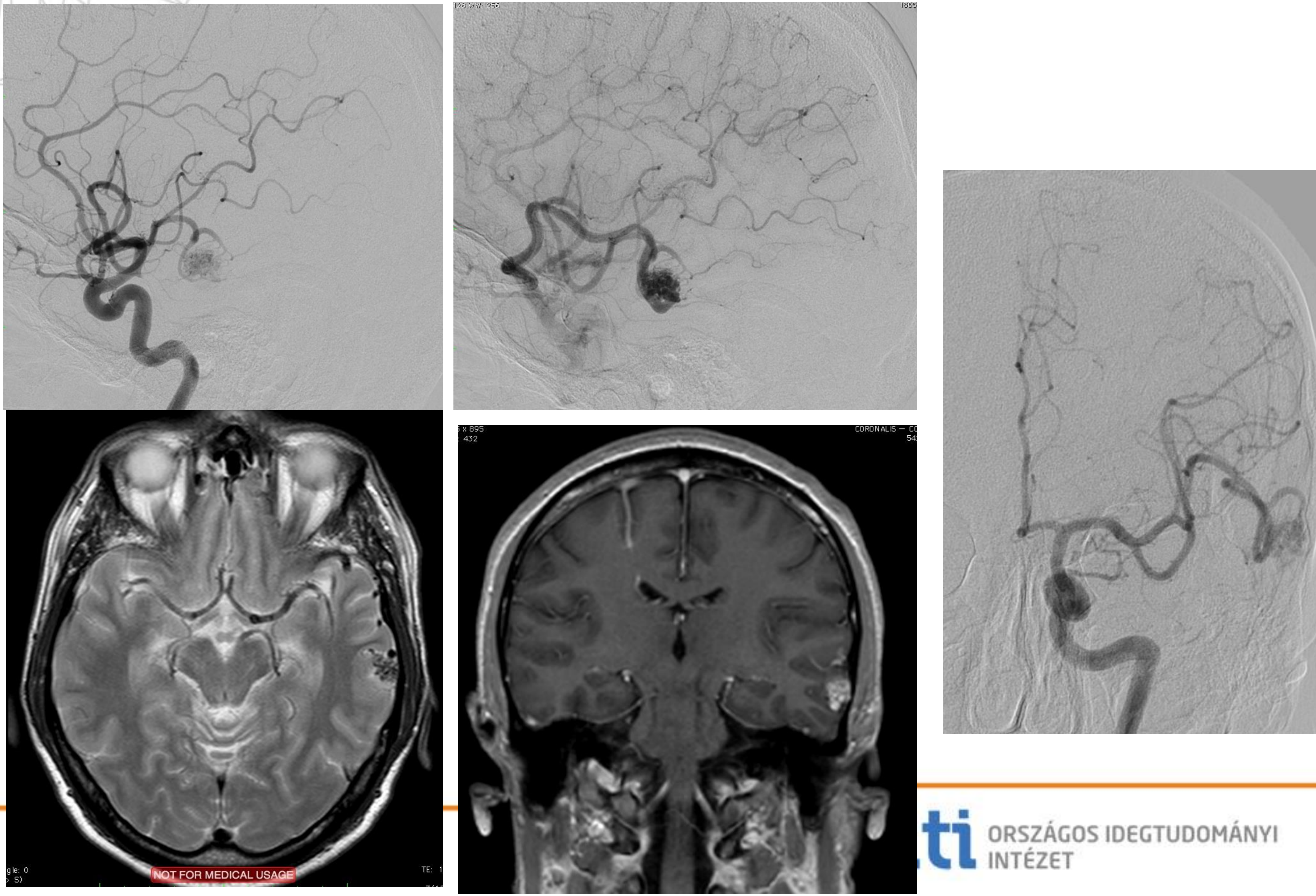
Optimal for all – endovascular



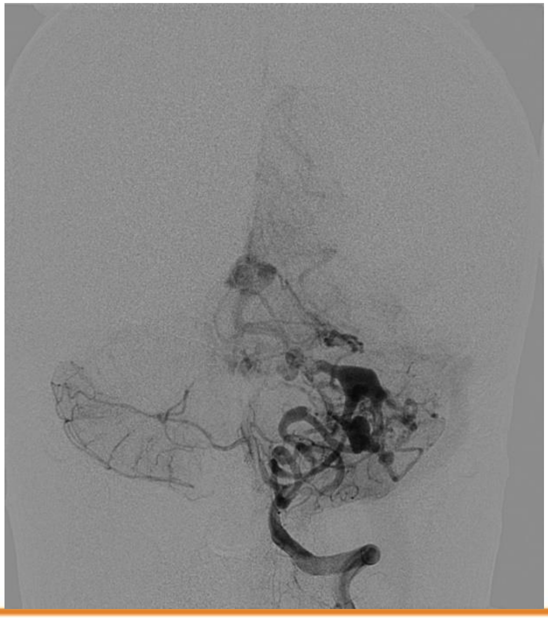


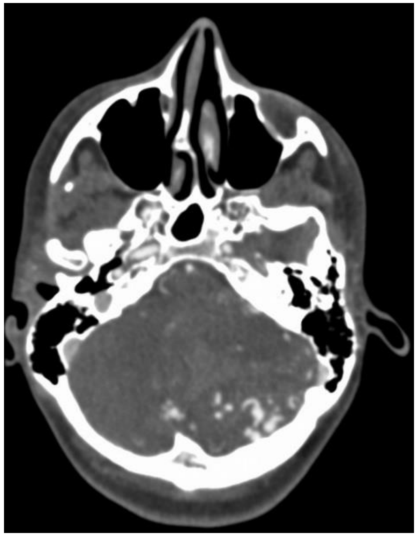


Both radiosurgery are microsurgery

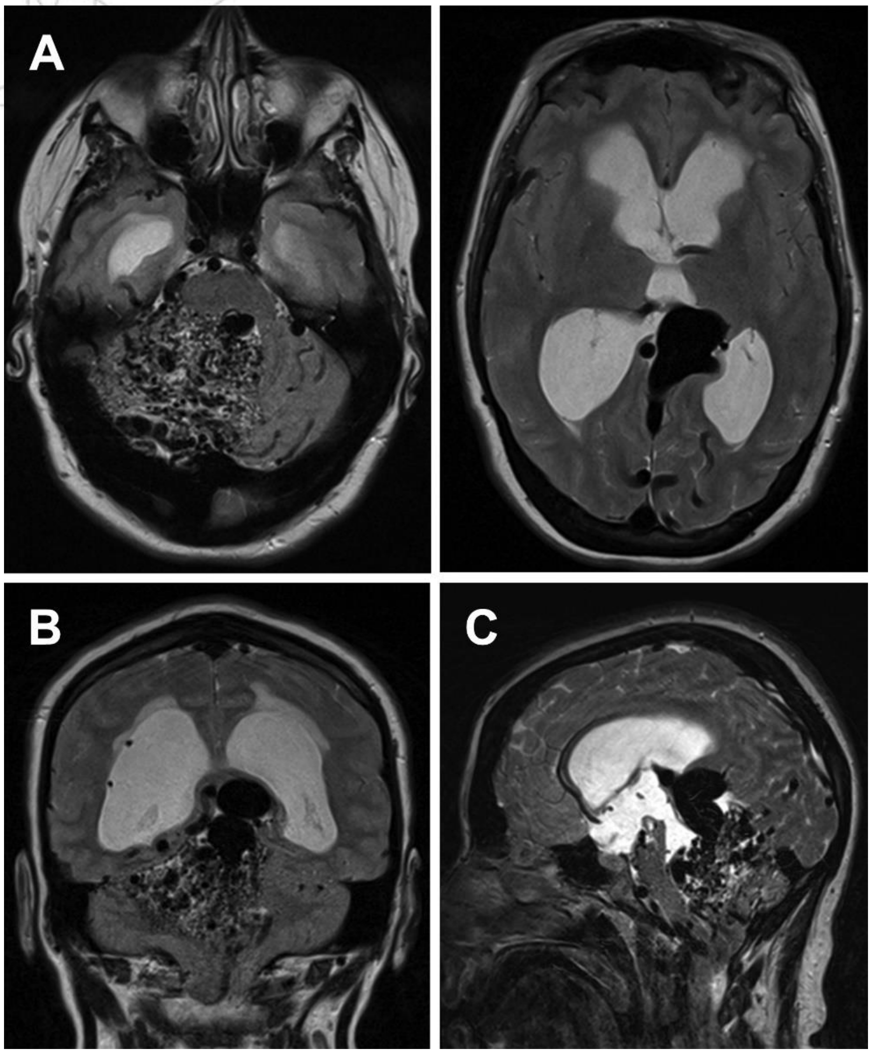


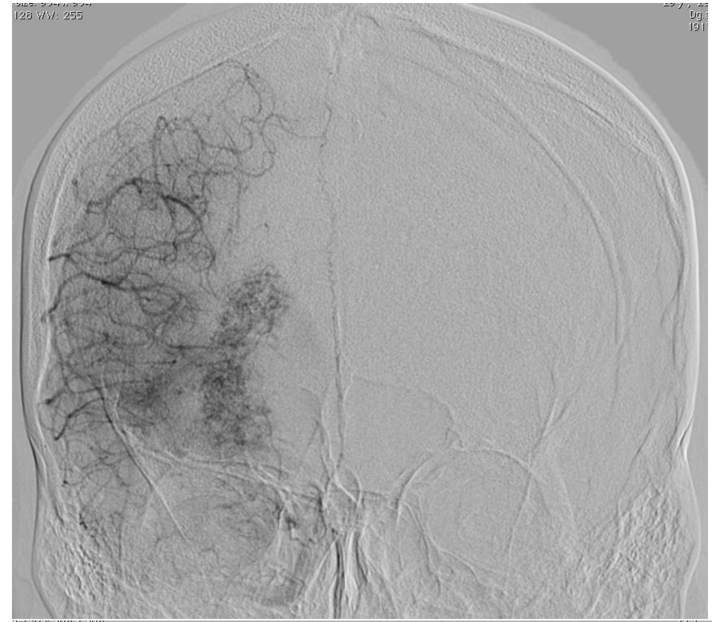
Not good for radiosurgery

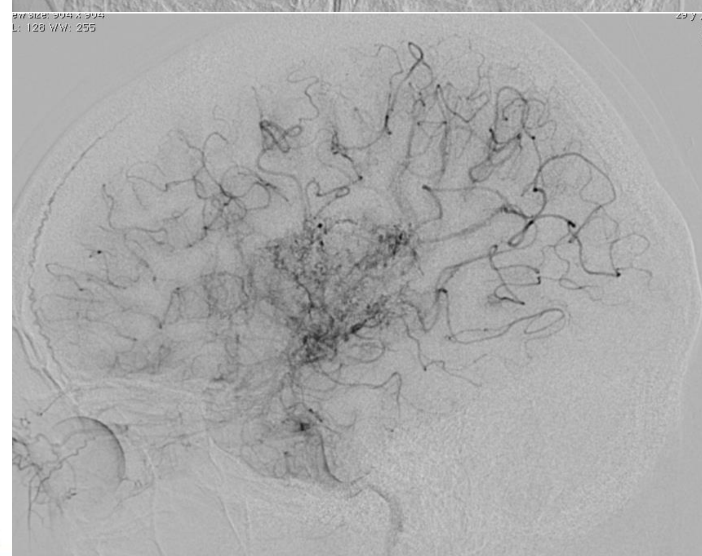




Conservative





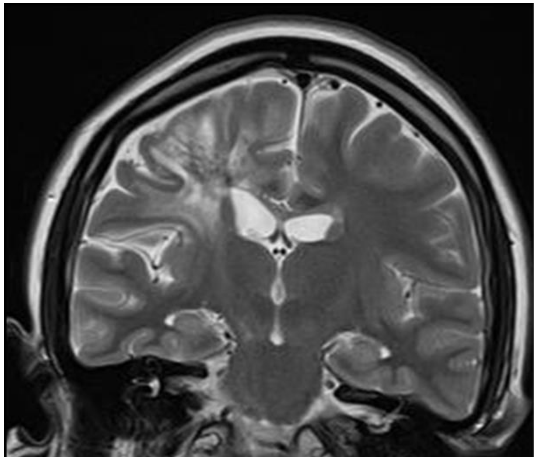


Outcomes of AVM radisourgery

- Outcome is the result obliteration, adverse radiation effects, and the morbidity of bleeding during latency period
- Obliteration depends on size, and delivered dose (50% isodose, or marginal dose is typically 17-25 Gy for AVMs)
- Adverse radiation effect depends on size, location (superficial/deep), and dose
- The risk of bleeding until complete obliteration is similar to untreated AVMs (2-4%/year), typically higher in the case of associated aneurysms

Oucomes of AVM radiosurgery: Obliteration and side effect

- <u>Obliteration</u>:
  - 4 years after treatment:
    <1 cc: >90%
    1-4 cc: 70-80%
    4-10 cc: 60%
    >10 cc: 30-60%
  - Repeat treatment: 60-70%

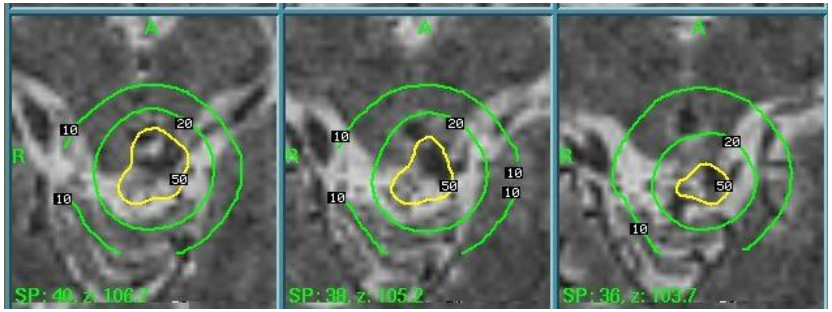


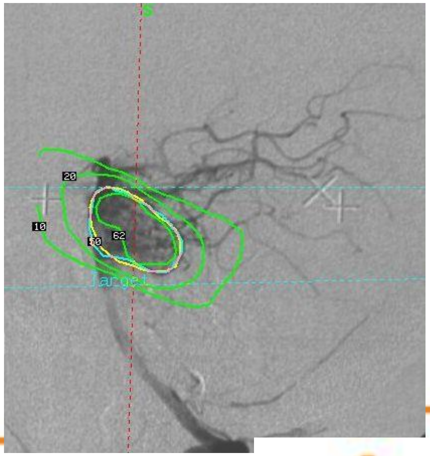
- <u>Adverse radiation effect</u>:
  - Superficial, <10 cc: 2-5%

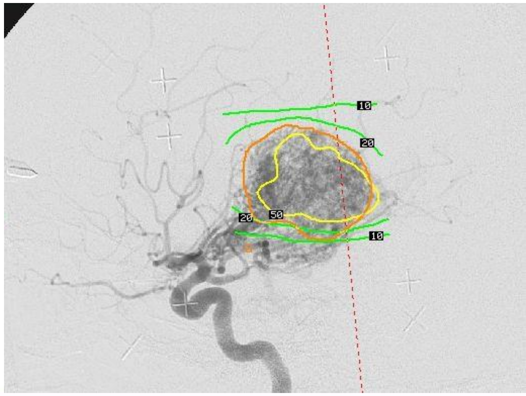
Friedman, Neurosurg Clin N Am 24:561–574, 2013

Outcomes of AVM radiosurgery: Deep AVMs

- ≤4 cc can be treated effectively with an obliteration rate of 70-80%, and acceptable morbidity/mortality (6-15%)
- >4 cc in the brainstem has too high morbidity
- >8 cc thalamus/basal ganglia AVMs: treatment results in 50-60% obliteration with 20-25% morbidity/mortality in optimal situation (This group is not ideal for any modality)





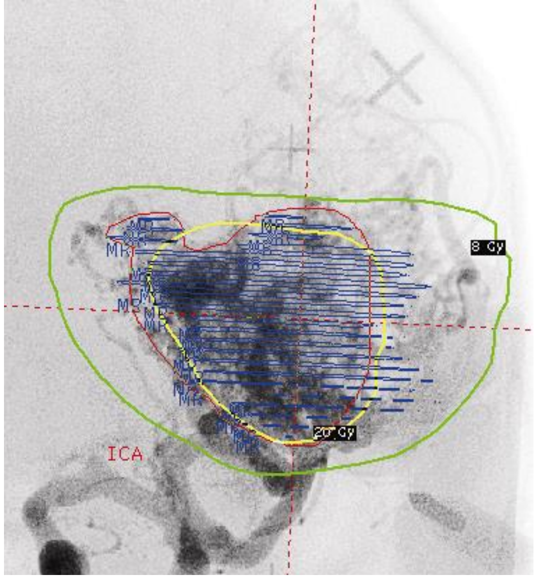


Nagy et al., Neurosurgery 70:1458–1471, 2012

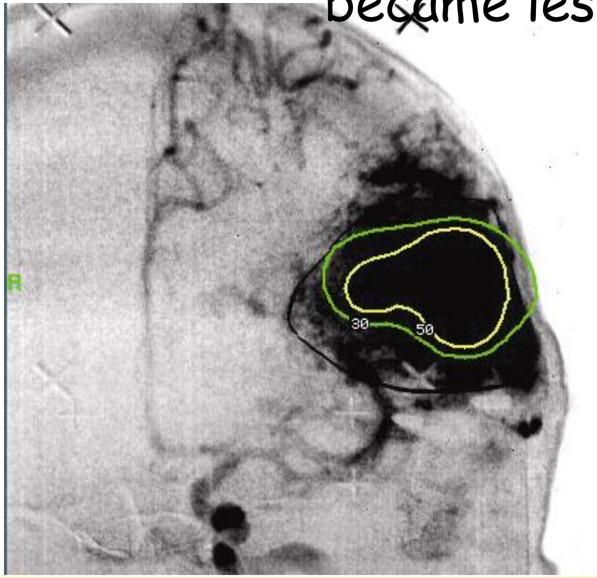
Treatment dilemma: Large AVMs (SM IV-V)

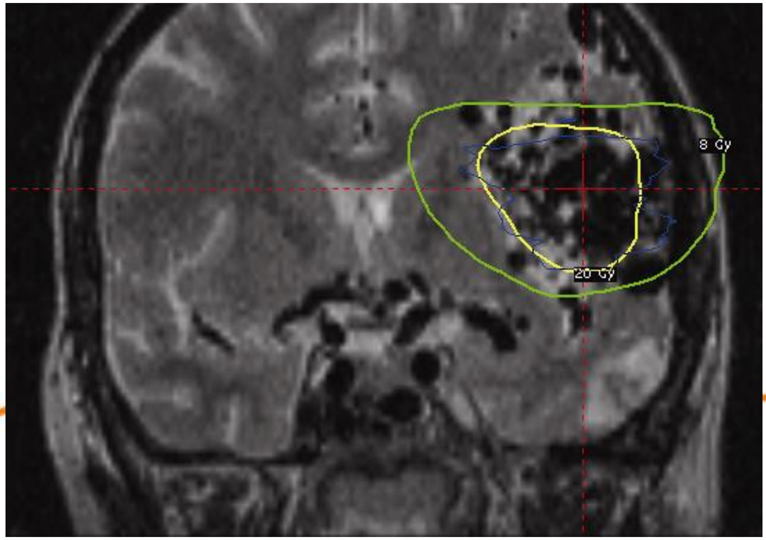
- Partial obliteration does not reduce bleeding risk, therefore it is recommended only in selected cases
- Do not treat, except for agressive cases (Spetzler)
- Treat them because of poor natural history (Steinberg)
- >10 cc (3 cm) was traditionally considered not ideal for radiosurgery because of low obliteration rate and high morbidity

Outcome of AVM radiosurgery: Evolution of the treatment of large AVMs



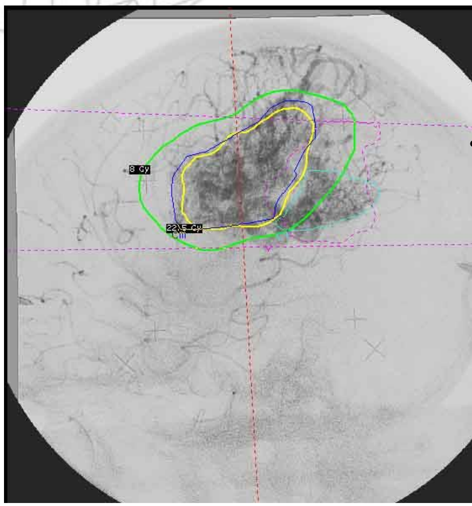
- Early angio only based treatment plan was changed by MRI+angiography based planning in the 90s
- Obliteration increased form 30 to >60%
- However, 10-15% adverse radiaton effect rate did not decreased, only severe cases became less frequent





Nagy et al., Acta Neurochir 154:383–394, 2012

Outcome of AVM radiosurgery: Treatment of large AVMs today

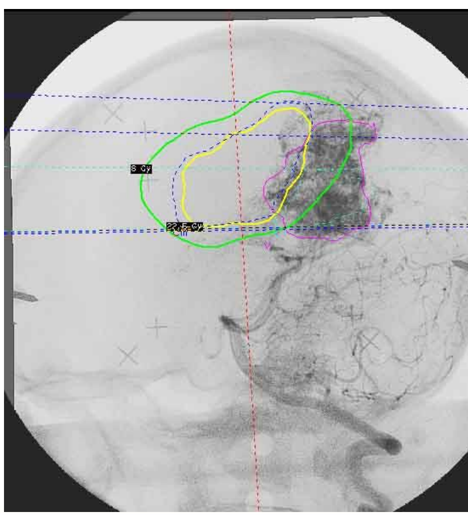


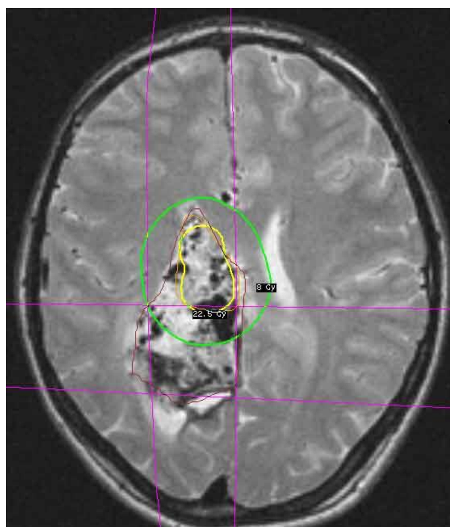
- <u>Staged Volume Radiosurgery)</u>

Treatment in 2-3 volume fractions with 6-12-week interval (17,5 Gy)

- 60% obliteration
- 6,5% adverse radiation effect (5% MRS1)
- Risk of bleeding is not reduced during latency period

(3% morbidity, 4,5% mortality)

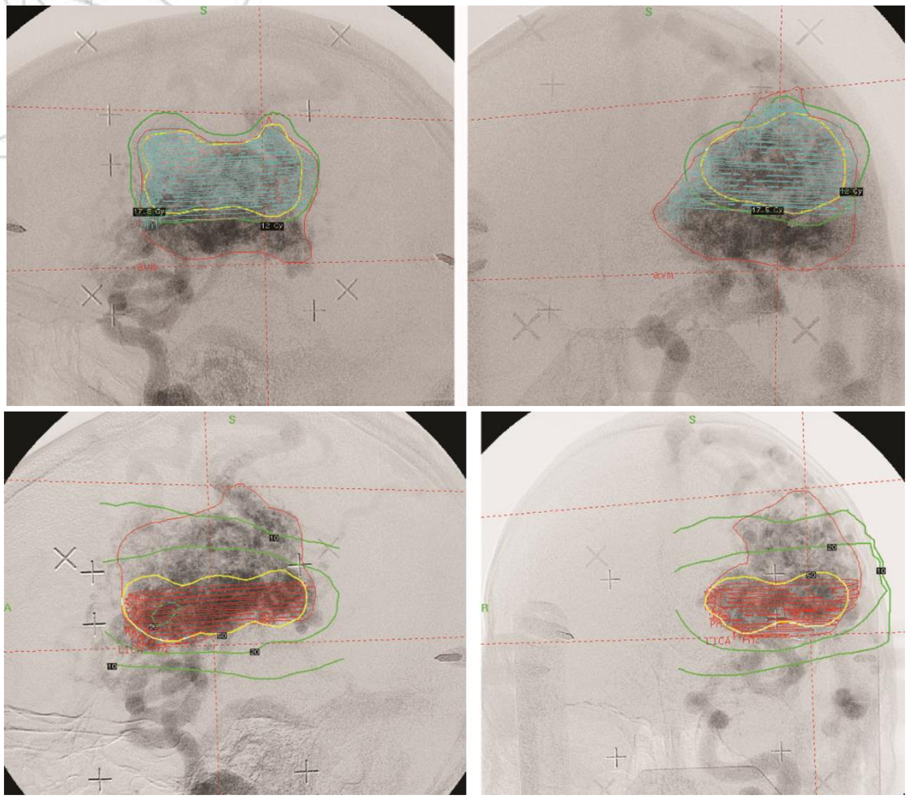




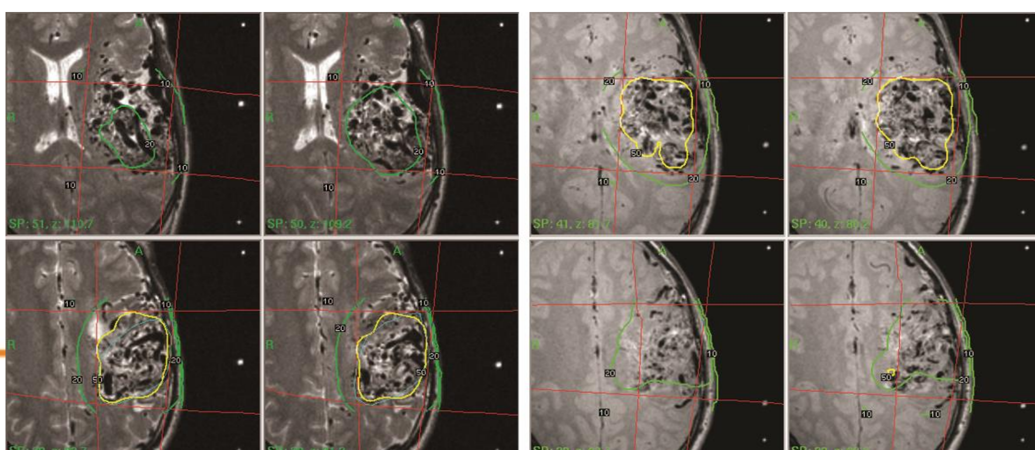
17 + 20 cc

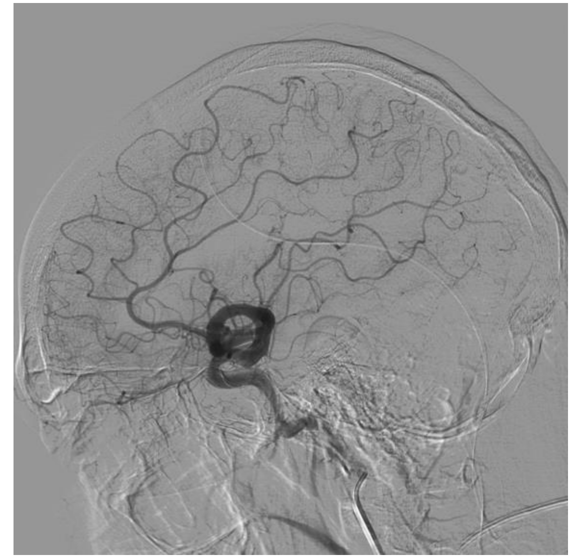
Nagy et al., Neurosurgery 80:180-192, 2017

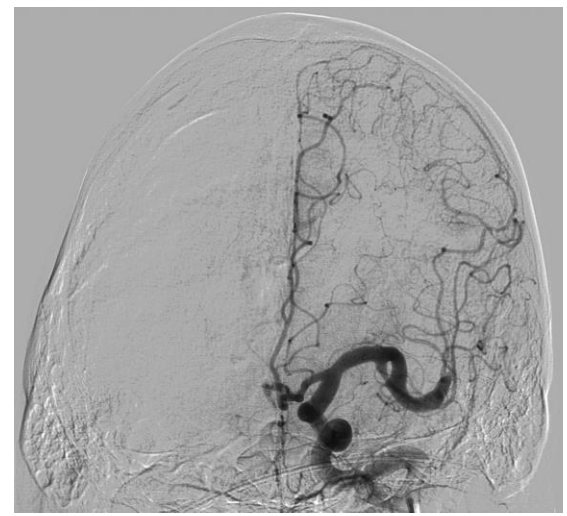
Staged volume radiosurgery



40 + 25 cc







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Multimodality treatment: Surgery and radiosurgery

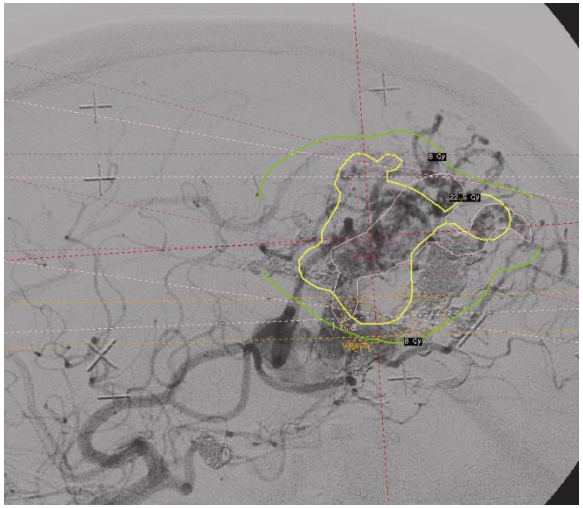
- Each modality adds its own morbidity, therefore single modality is oreferred. It is a realistic goal for smaller AVMs (a multidisciplinar team should decide on treatment after diagnosis!)

- After surery: after hematoma evacuation or residual nidus
-
- Rezidual nidus can be removed after radiosurgery („downgrading") : less preoperative embolization, less blod loss, shorter operation time, shorter hospital stay, lower morbidity

Sanchez-Mejia et al., Neurosurgery 64:231–240, 2009

Multimodality treatment: Radiosurgery and embolization

- Embolization prior to radiosurgery usually reduces obliteration rate (because it is not volume, but flow reduction in most the cases), so it is out of fashion recently
- Embolization of associated aneurysms and fistules before/after radisourgery is an option



Hodgson et al., AJNR Am J Neurorad 30:109-110, 2009
Nagy et al., Acta Neurochir 154:383–394, 2012
Rubin et al., Neurosurgery 74:S50–S59, 2014

Radiosurgery of cavernomas

- **Is it effective?**

  - No radiological evidence of „cure" Nincs radiológiai bizonyíték a „gyógyulásra", it is suggested only by statistics of patient population (of heterogenous quality of publications)

- **Is it a real alternative for surgery?**

- **Is it safe?**
  - Conflicting reports on side effects

- **Is it a real alternative for observation in case of inoperable cases?**

Is there evidence?

CCM CARE GUIDELINES

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Tania Rebeiz, MD[§]
Elisabeth Tournier-Lasserve, MD[¶¶]
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Guidelines for the Clinical Management of Cerebral Cavernous Malformations: Consensus Recommendations Based on Systematic Literature Review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel

BACKGROUND: Despite many publications about cerebral cavernous malformations (CCMs), controversy remains regarding diagnostic and management strategies.

OBJECTIVE: To develop guidelines for CCM management.

METHODS: The Angioma Alliance (www.angioma.org), the

CONCLUSION: Current evidence supports recommendations for the management of CCM, but their generally low levels and classes mandate further research to better inform clinical practice and update these recommendations.

Akers et al., Neurosurgery 2017

Contemporary radiosurgery of CCMs

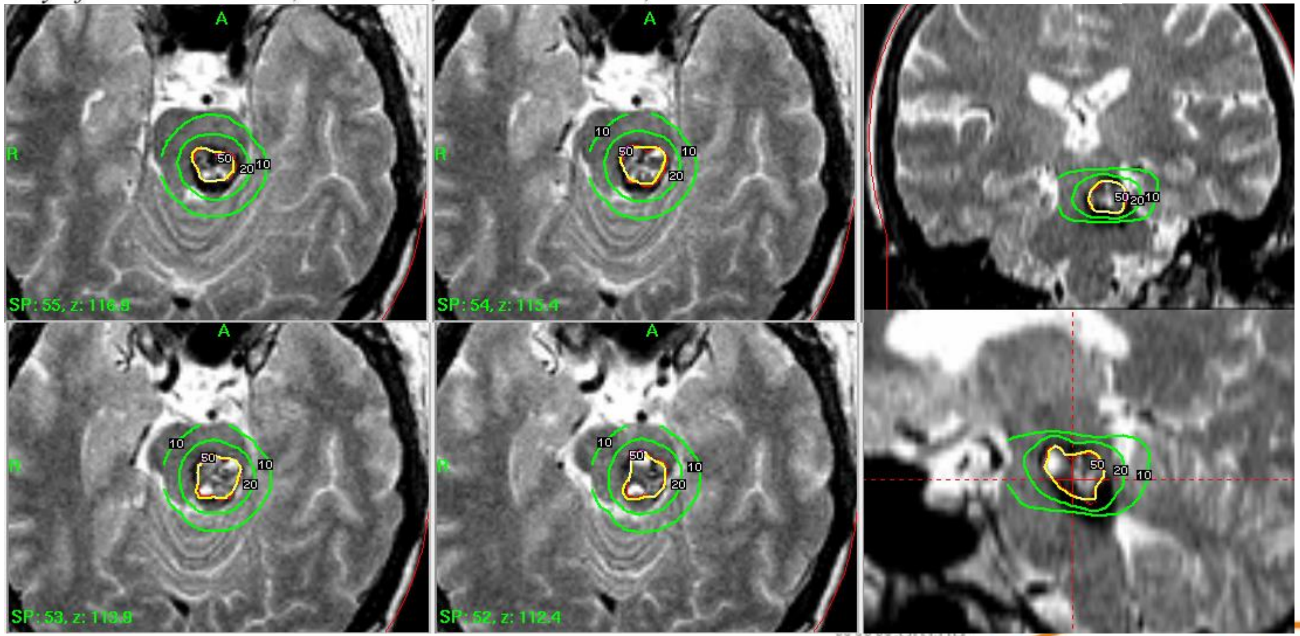
8. Radiosurgery may be considered in solitary CCM lesions with previous symptomatic hemorrhage if the CCM lies in eloquent areas that carry an unacceptable high surgical risk (Class IIb, Level B).

Reduction of hemorrhage risk after stereotactic radiosurgery for cavernous malformations

DOUGLAS KONDZIOLKA, M.D., M.SC., F.R.C.S.(C), L. DADE LUNSFORD, M.D., JOHN C. FLICKINGER, M.D., AND JOHN R. W. KESTLE, M.D., M.SC., F.R.C.S.(C)

Departments of Neurological Surgery and Radiation Oncology, Presbyterian University Hospital, and the Center for Image-Guided Neurosurgery, University of Pittsburgh, Pittsburgh, Pennsylvania; and Division of Neurosurgery, Research Consulting Unit, British Columbia's Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

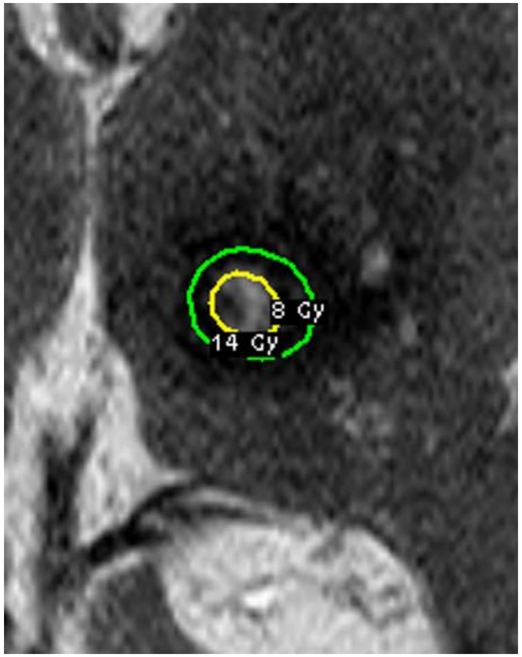
J Neurosurg 83:825–831, 1995



Principles of modern CCM radisourgery

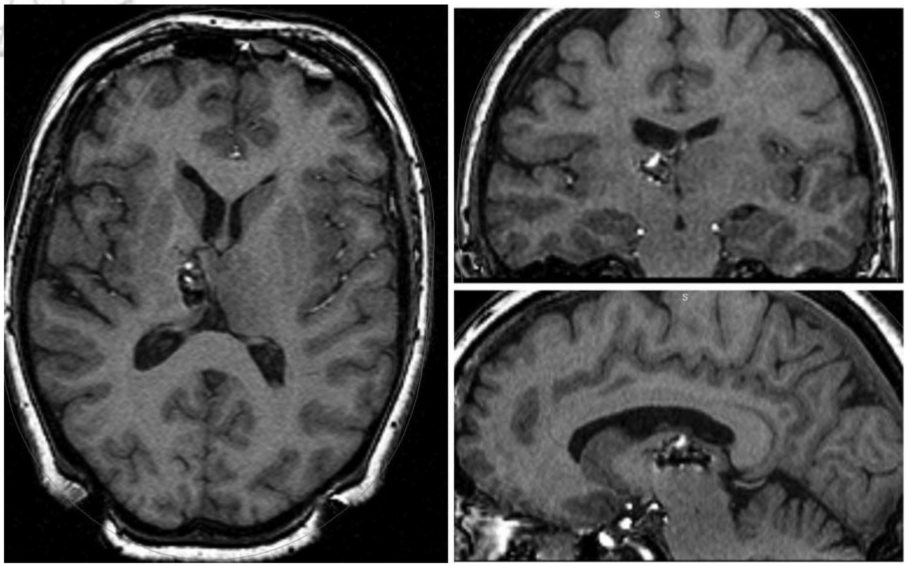
- Adequate patient selection and analysis (proper knowledge of natural history)
  - Difference between hemispheric and deep seated
  - Definition of bleed/rebleed

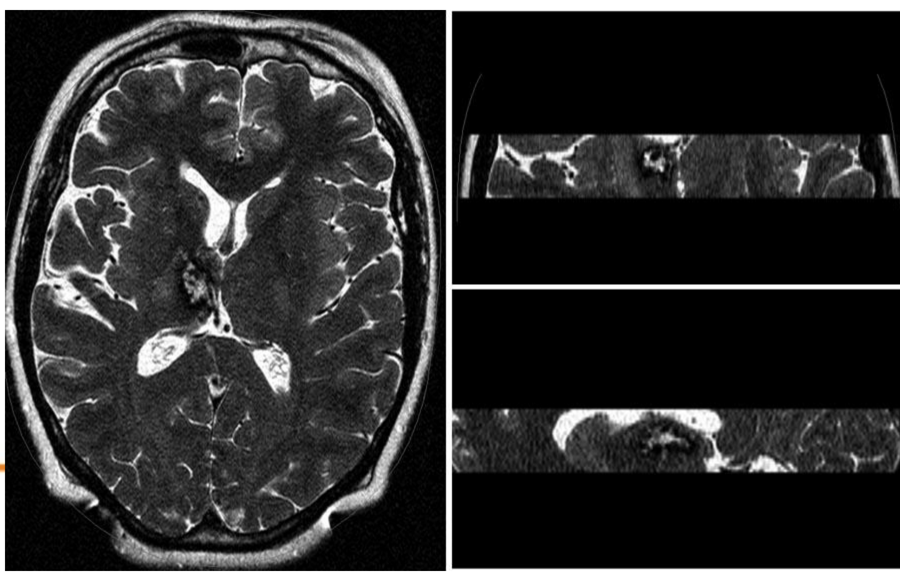
- Modern treatment protocols
  - Conformity (GK, MRI-based planning)
  - 12-15 Gy (<20 Gy) marginal dose
  - Within hemosiderine ring
  - Avoid DVA
  - After resolution of bleed (3 months)



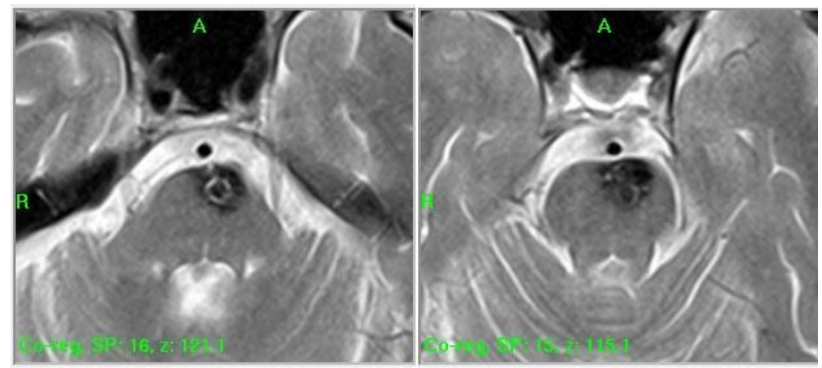
Nagy&Kemeny, J Neurosurg Sci 2015

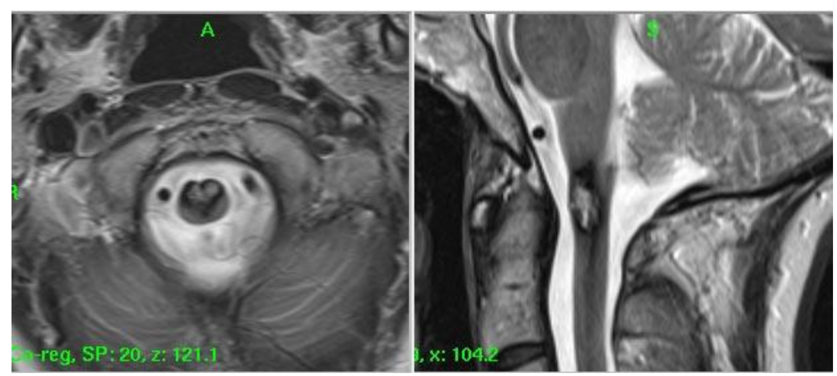
CCMs ideal for radisourgery





Small, bled 1x
Not ideal surgical corridor





Results of modern CCM radisourgery The Sheffield experience

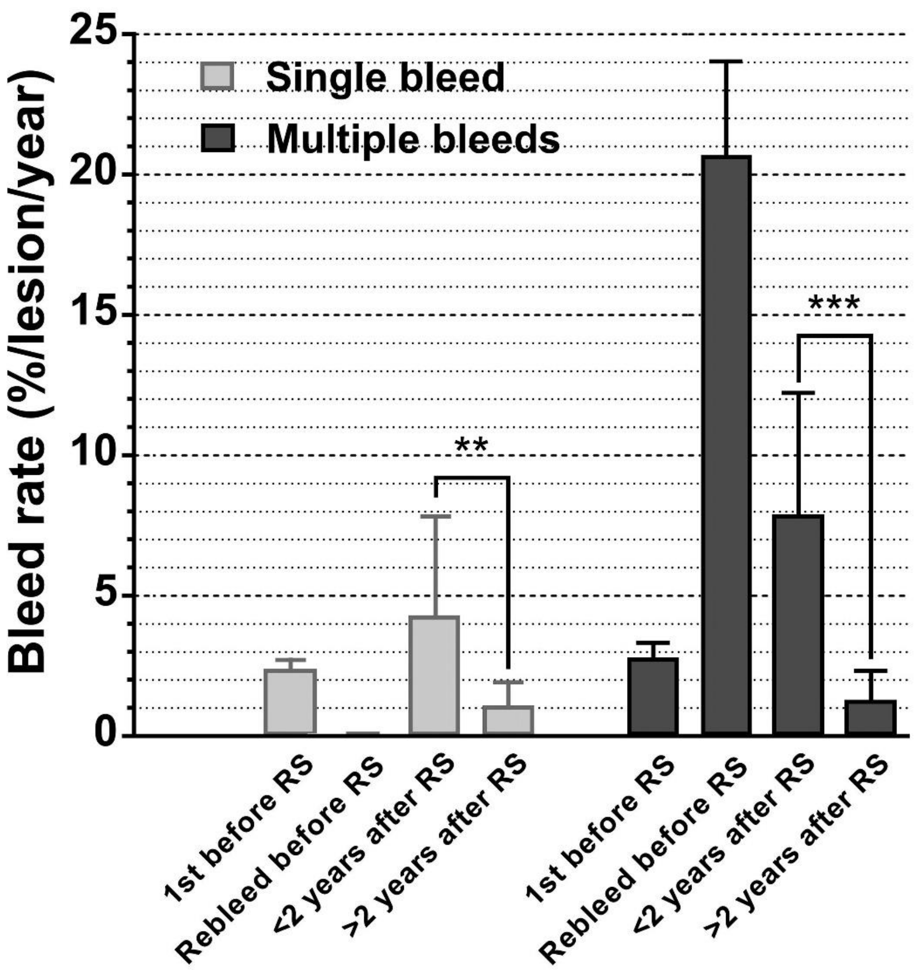
- 236 deep eloquent lesions in 231 patients (168 brainstem, 68 thalamus/basal ggl)
- 109 felssuperficial lesions in 96 patients
- Median follow-up 5,5 yrs (1-20) (227 patients)
- Deep eloquent: 26 lesions unbled, 126 bled 1x, 83 multiple bleeds
- Superficial: 71 lesions unbled, 52 bled 1x, 15 multiple bleeds
- Median volume

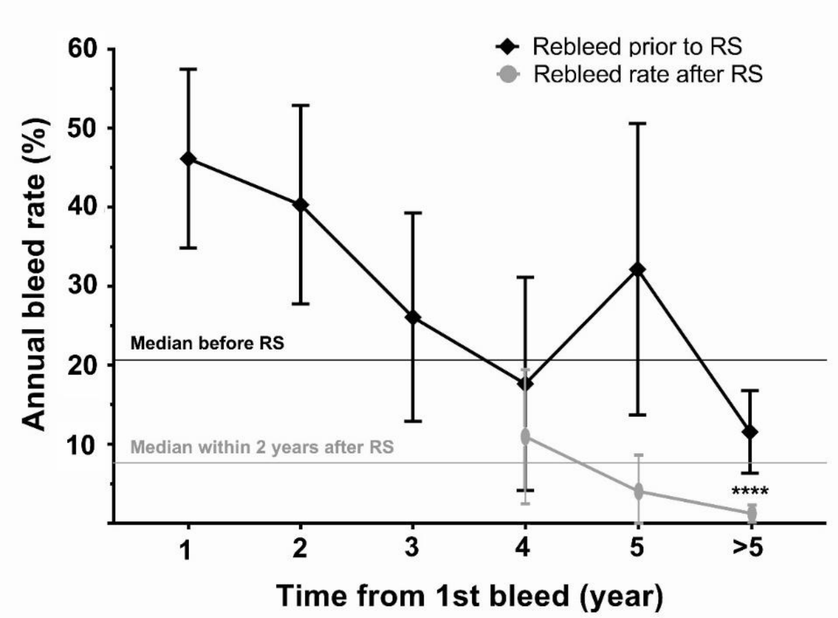
  Lesion: brainstem 240, thalamus/basal ggl 537, superficial 604 mm^3

  Treatment: brainstem 260, thalamus/basal ggl 620, superficial 638 mm^3
- Median marginal dose (50 % isodose): brainstem 12 Gy, thalamus/basal ggl 13 Gy, superficial 15 Gy

Nagy et al., J Neurosurg 2018

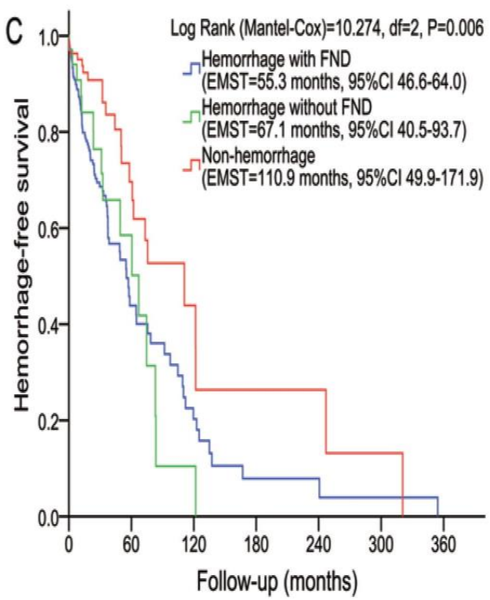
Rebleed after radisourgery

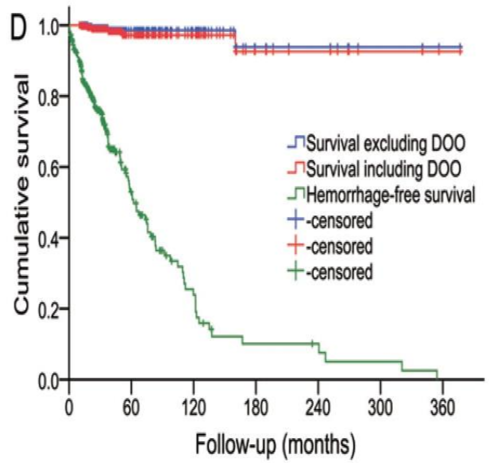




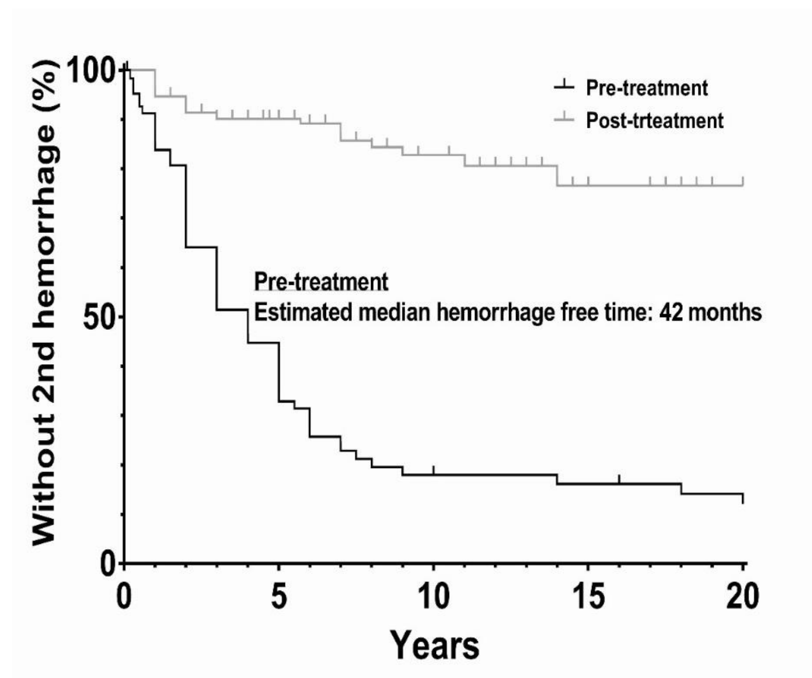
Nagy et al., J Neurosurg 2018

Rebleed after radiosurgery





	6 mo (%)	1 yr (%)	3 yr (%)	5 yr (%)	7 yr (%)	10 yr (%)	15 yr (%
(blue)	100	100	99.2	98.5	98.5	98.5	93.8
(red)	100	99.7	98.9	97.2	97.2	97.2	92.6
(green)	92.9	87.2	70.6	53.0	36.4	23.9	10.1



Li et al., J Neurosurg 2014

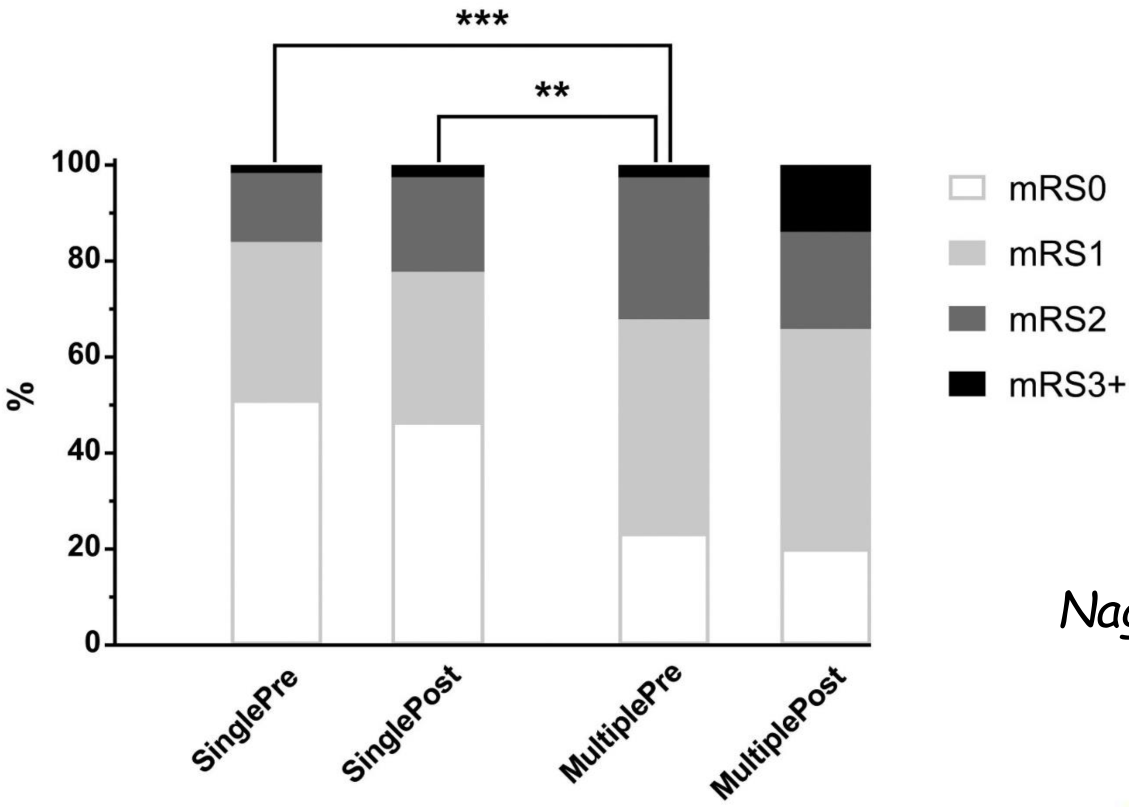
Nagy et al., J Neurosurg 2018

Persisting morbidity

- Prior to RS: “low risk” 43%, “high risk” 72 ($p < 0.001$)
- After RS:

  - Adverse radiation effect (ARE): 7,3% (only MRS1)

  - Hemorrhage related: 7,2% (4,8% MRS1, 2,4% MRS2)



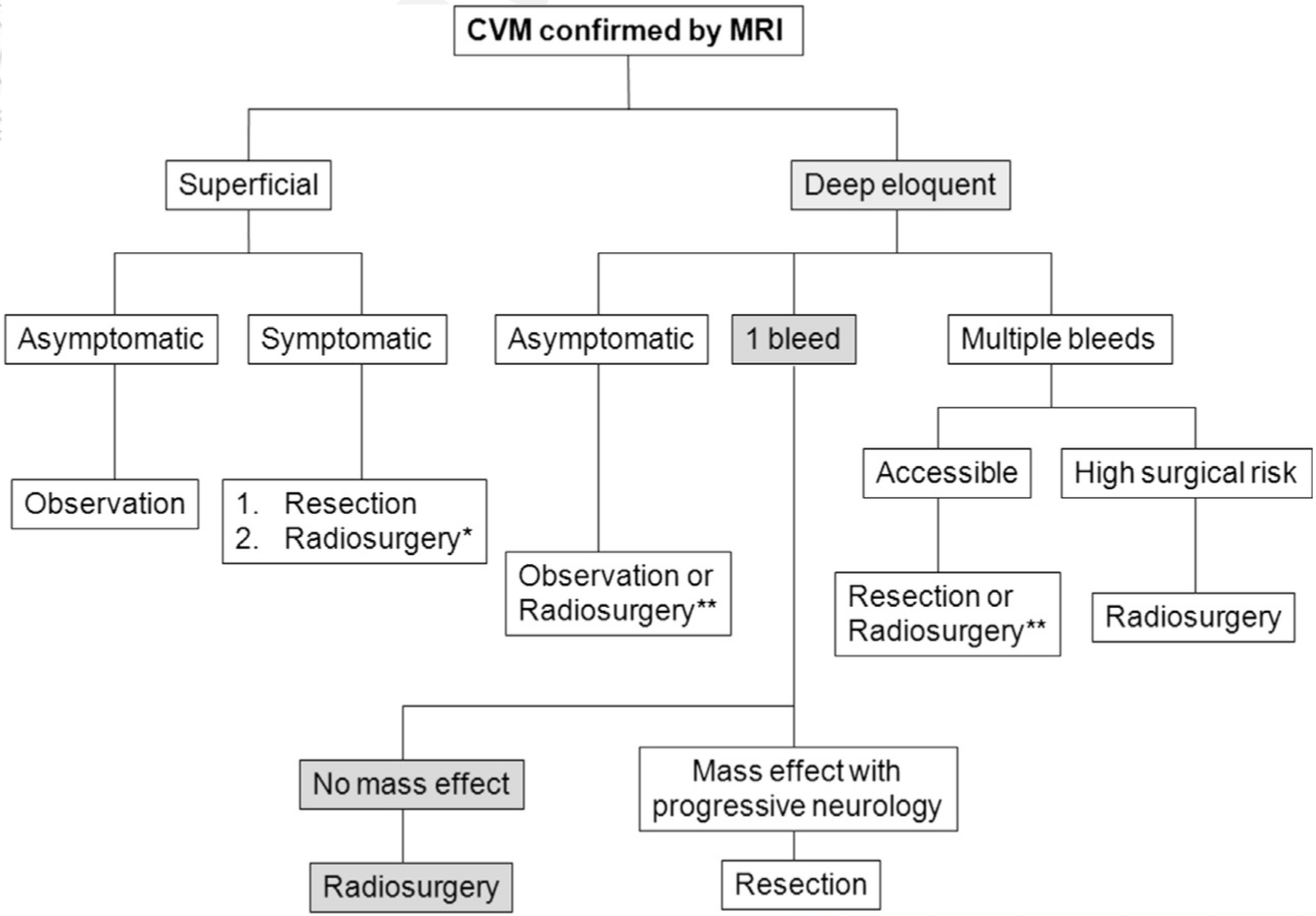
Nagy et al., J Neurosurg 2018

Epilepsy

- 61 of 319 patients (19%) had seizure associated to CCM
- 13% (9/68) in supratentiorial deep seated, 55% (52/94) in supratentorial hemispheric
- 87% improved in the hemorrhagic, 78,6% in non-hemorrhagic CCMs (ILAE class 1-3)
- Independent of the time interval between presentation and treatment

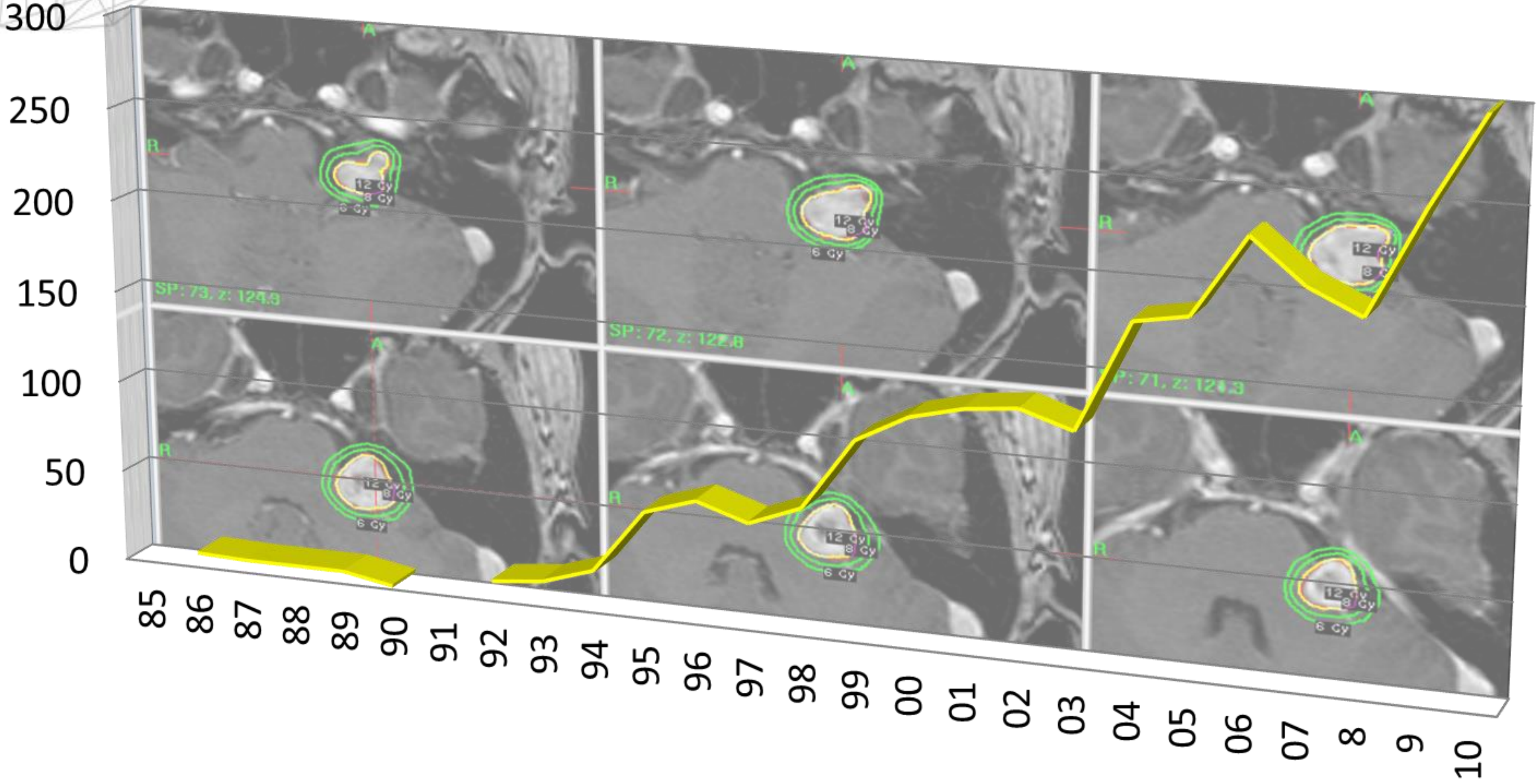
Nagy et al., J Neurosurg 2018

Proposed treatment algorithm

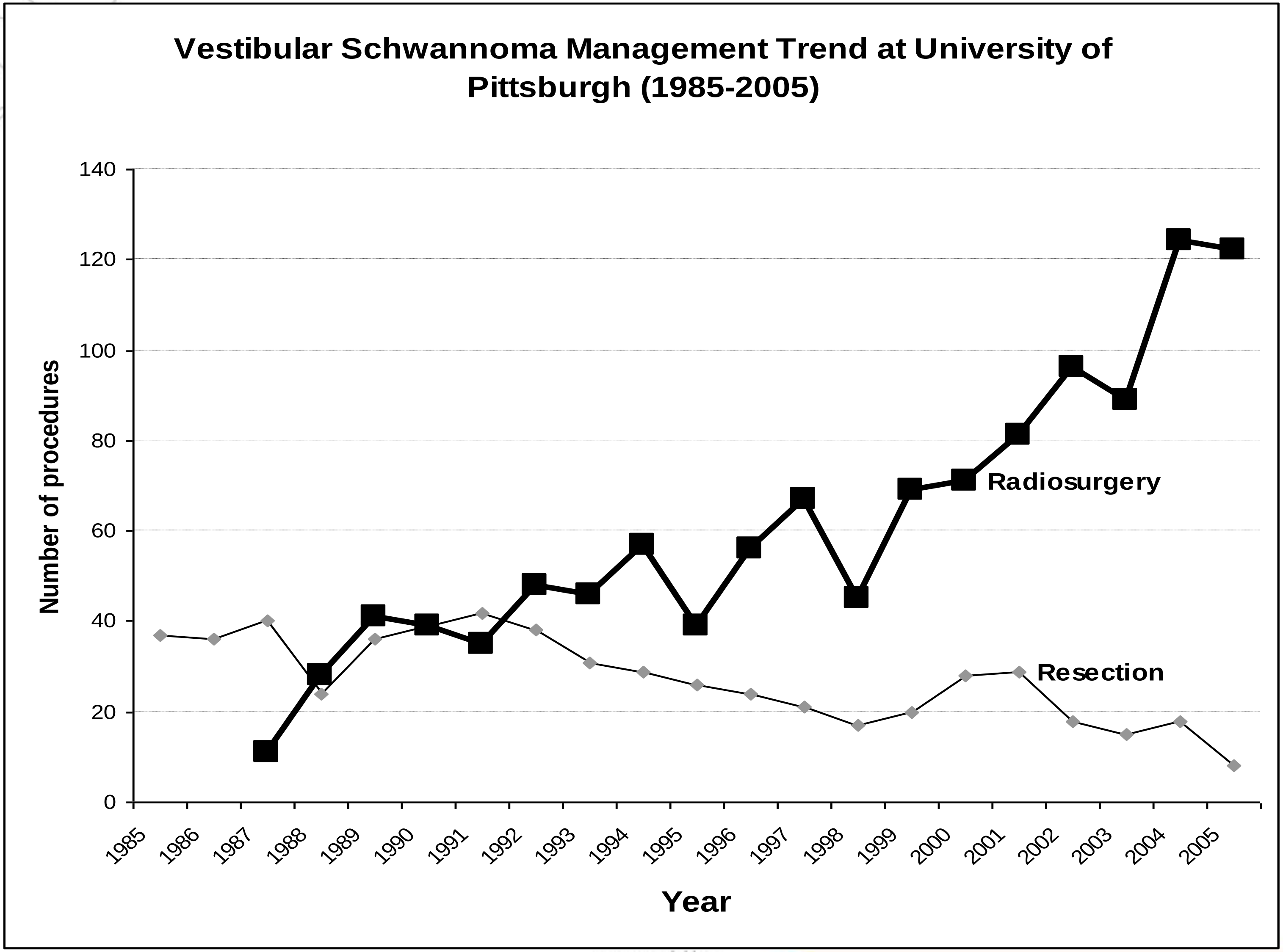


Nagy&Kemeny, Neurosurg Clin N Am 24:574–89, 2013

Vestibular schwannomas in Sheffield



Vestibular schwannomas in Pittsburg

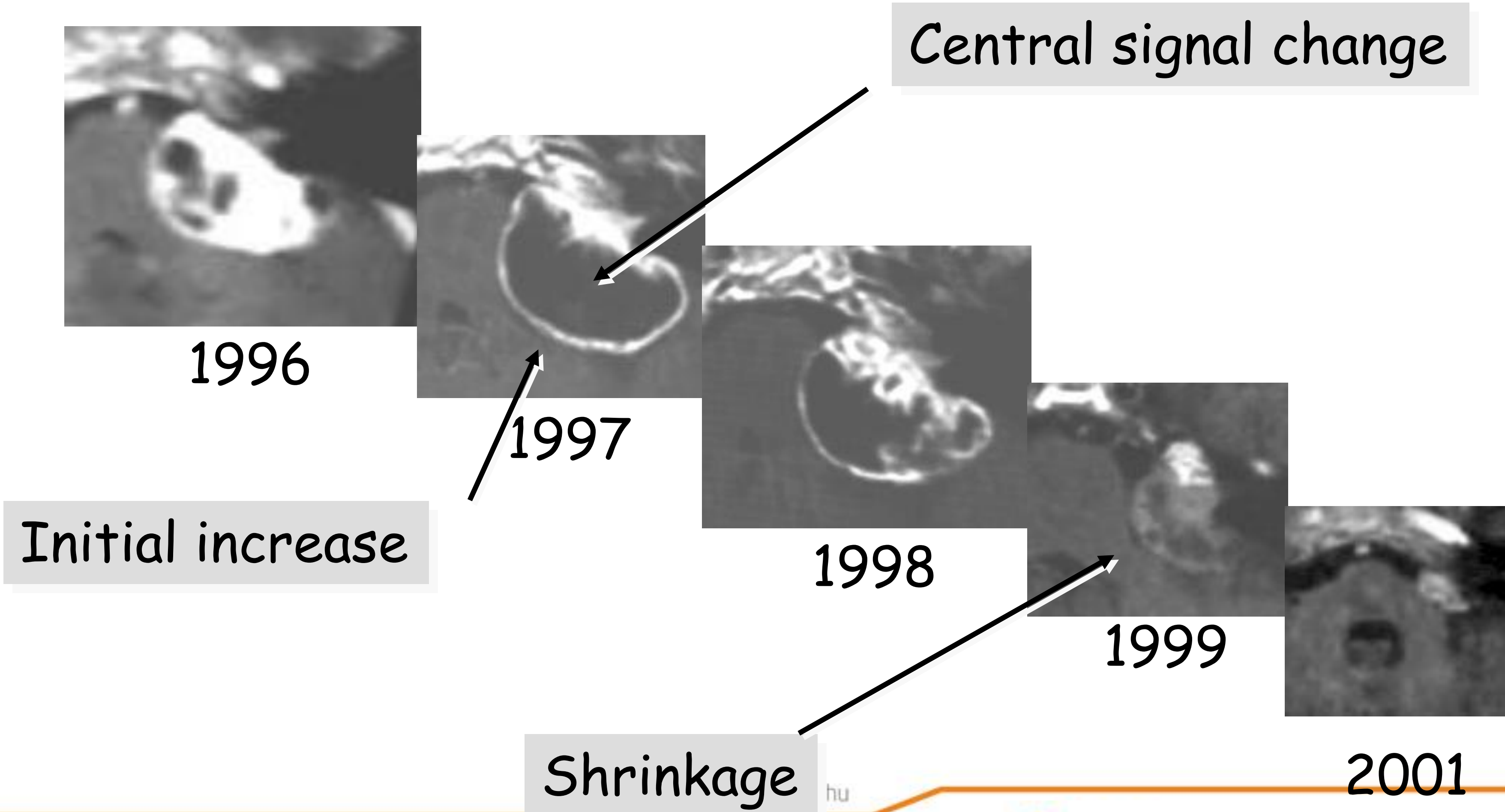


Evolution of patient selection

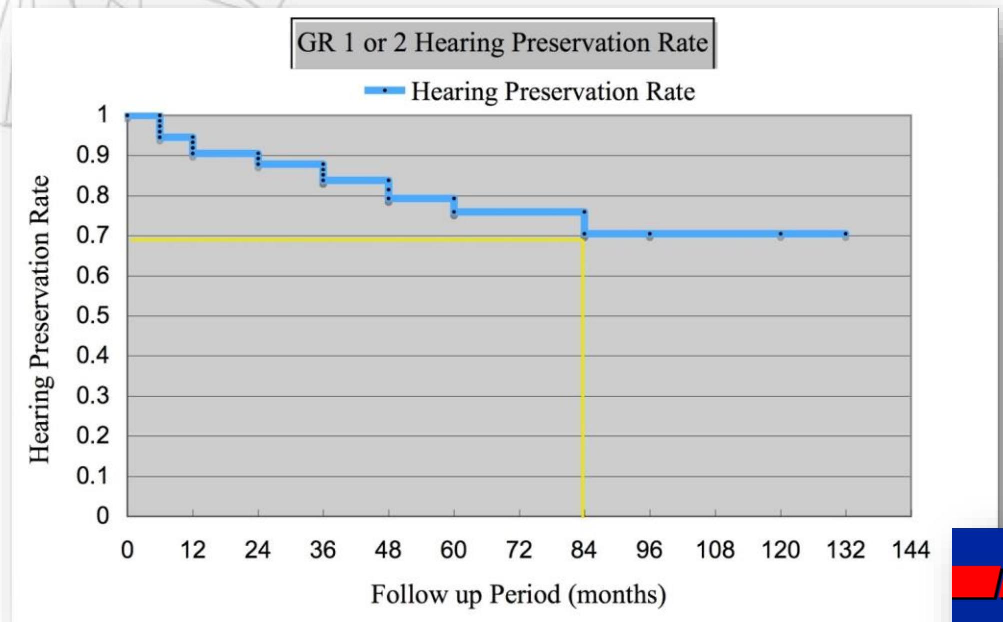
- Recidive/reziduum (even at present 25%)
- Elderly, general contraindication
- Contralateral deafness
- "VIP" (collegaues, politicain, actors...)

- Patient decision
- First option (90%)

Tipical response



Hearing preservation



Marseille

Sheffield

Hearing preservation after radiosurgery (Sheffield)

Gardner Robertson Grades before Radiosurgery	Nº	Hearing preserved	Grade decreased	Deaf
Grade I-II	50	38 (76%)	10	2
Grade III-IV	64	48 (75%)	5	11
Grade V	112			112

Journal of Neurology, Neurosurgery & Psychiatry. 74(11):1536-42, 2003

Meningioma

- Challenging or“inoperable” cases
  - Sinus cavernosus, clivus etc

- Radiosurgery and microsurgery are not competitors!

British Journal of Neurosurgery, February 2005; 19(1): 13 – 20

Taylor & Francis
Taylor & Francis Group

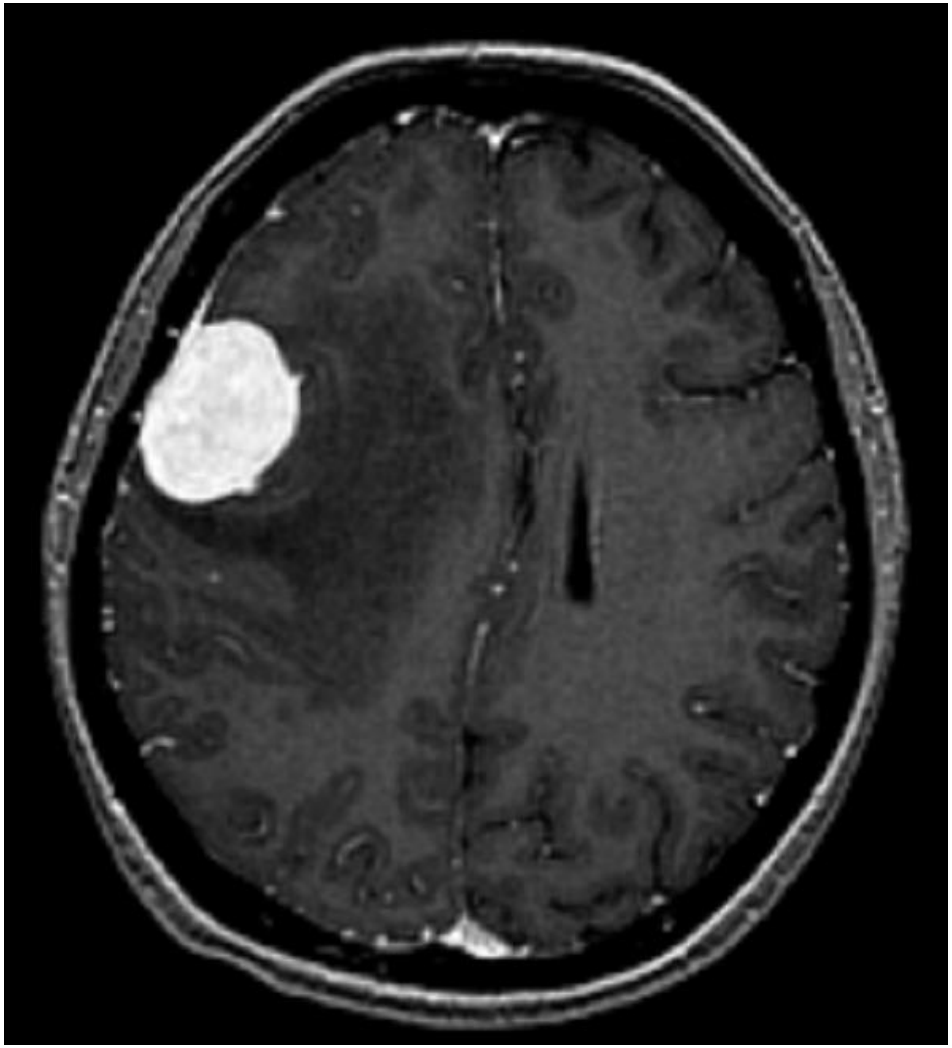
ORIGINAL ARTICLE

The use of stereotactic radiosurgery in the management of meningiomas

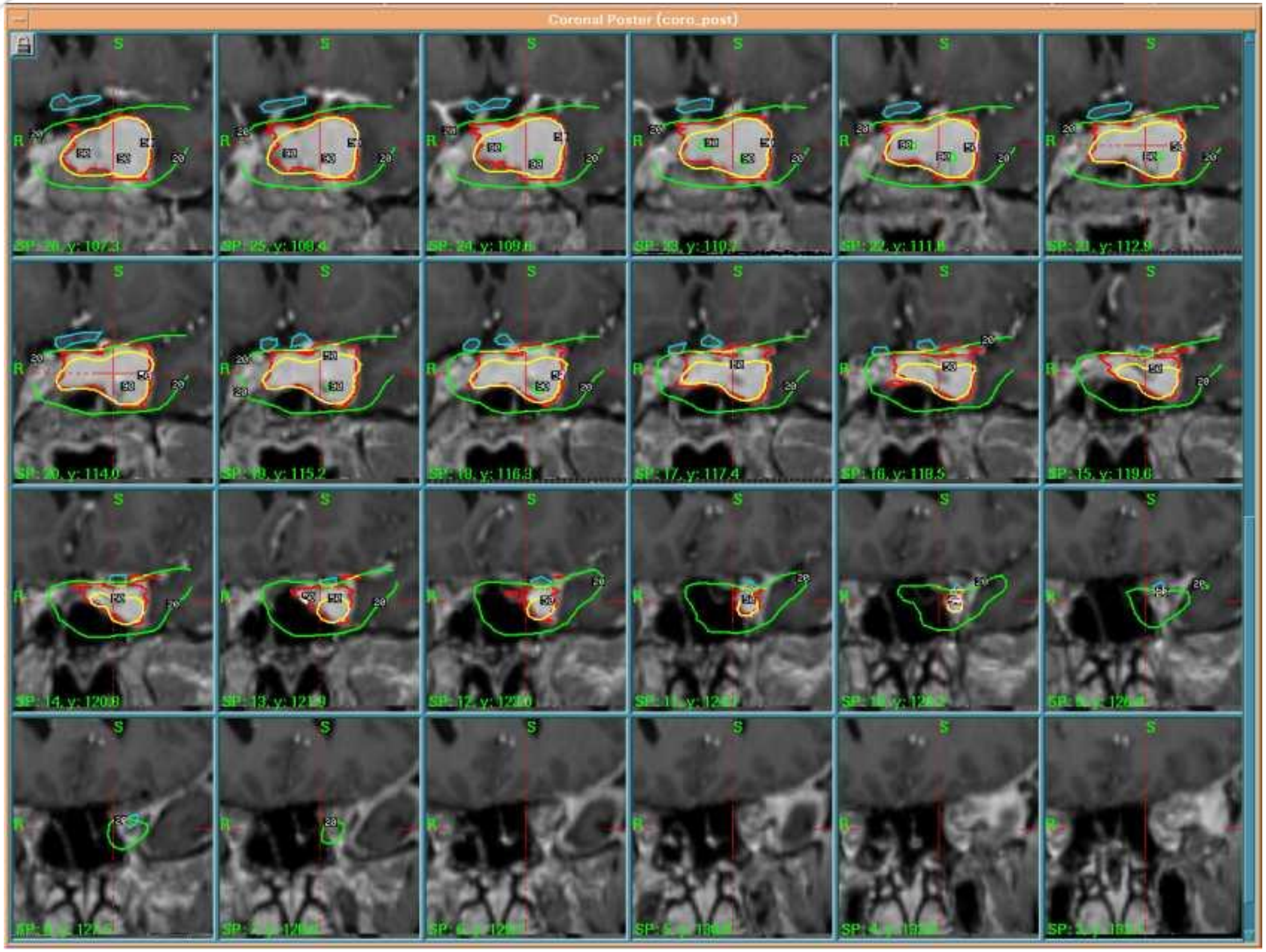
IRFAN MALIK, J. G. ROWE, L. WALTON, M. W. R. RADATZ & A. A. KEMENY

National Centre for Stereotactic Radiosurgery, Royal Hallamshire Hospital, Sheffield, UK

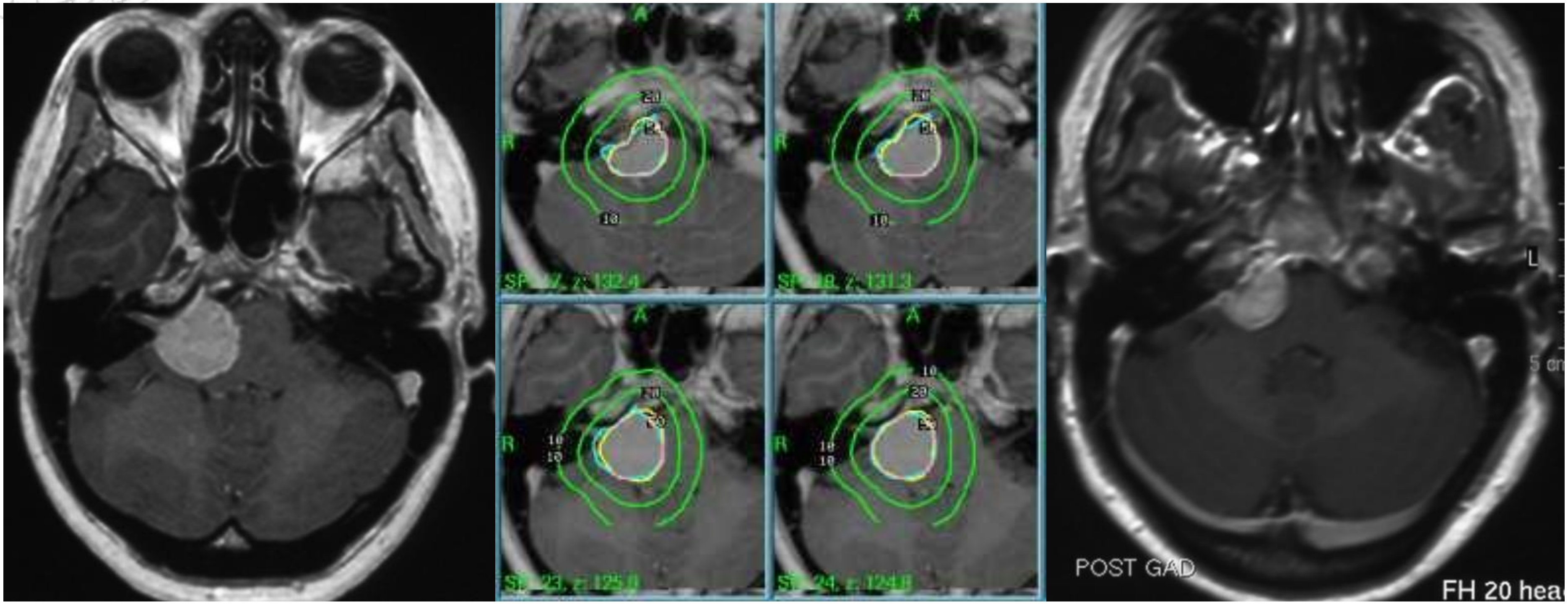
Meningioma: ideal surgical case



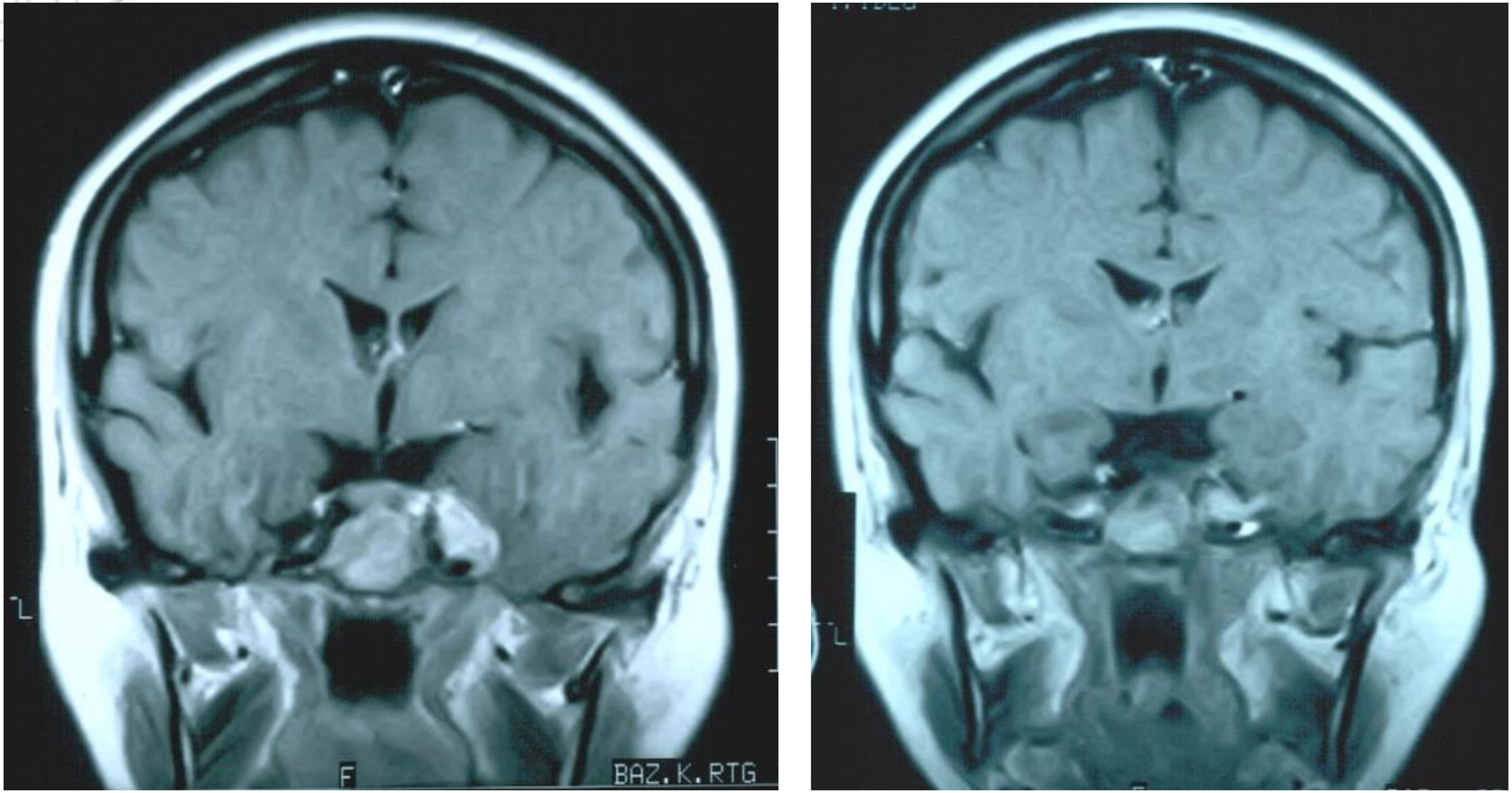
Meningioma: ideal for radiosurgery



Meningioma: ideal for radiosurgery



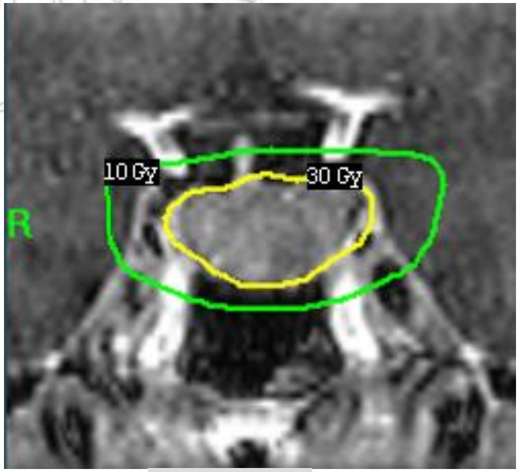
Meningioma: ideal for radiosurgery



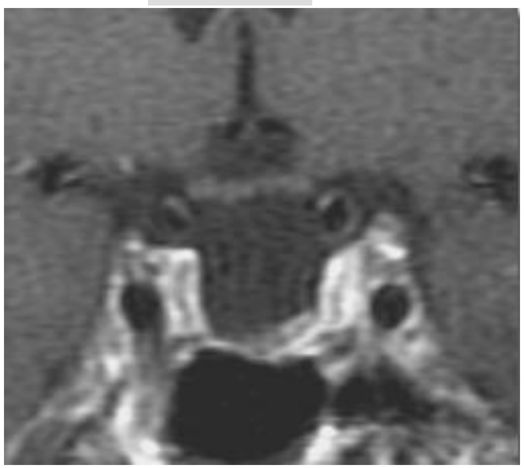
Complication after radiosurgery of meningiomas (n = 301, 70% basis) 90% tumor controll

• VII (worsening)	1
• V (tranzient)	3
• Diplopia	3
• Hemiparesis	3
• Sum of neurological complications	3%

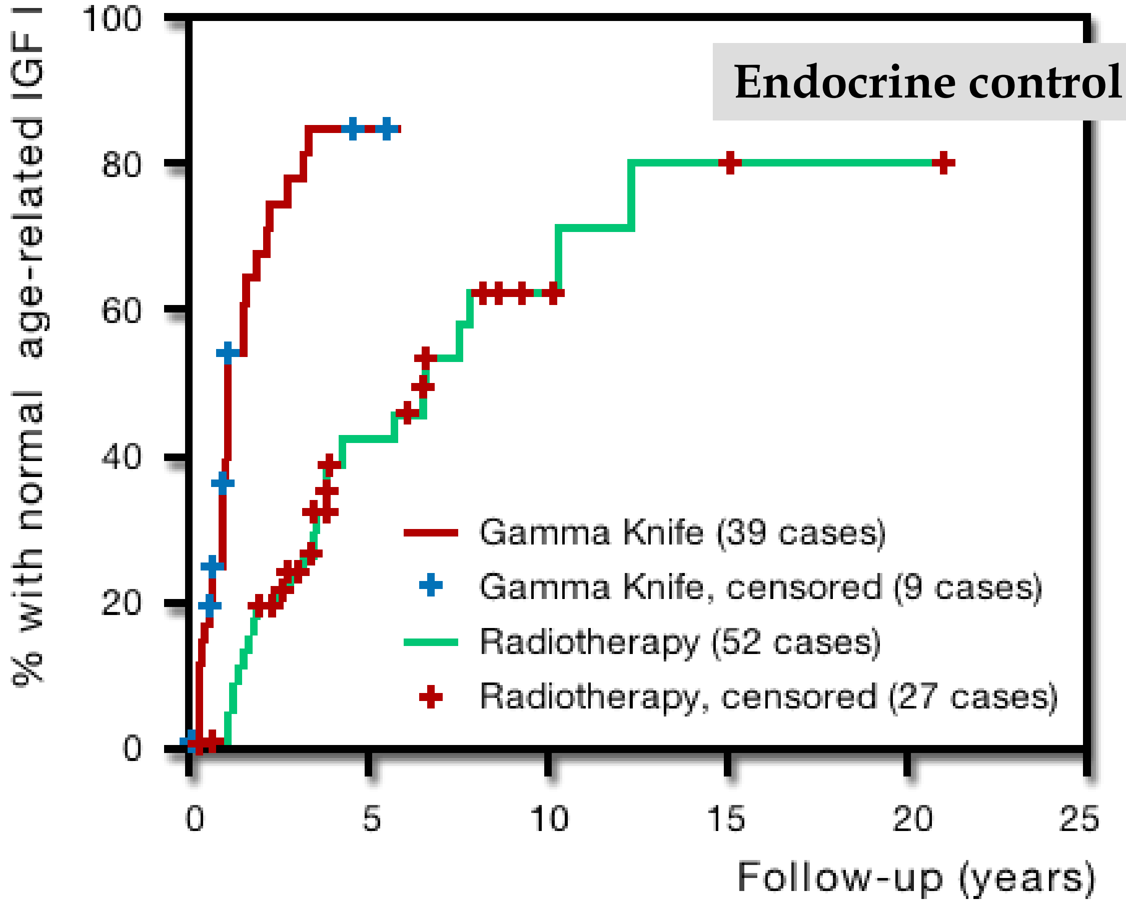
Hypophysis



STRS



19/12 FU



	Median time to normal	Cumulative normal
Gamma Knife	1.03 yrs	86% after 3.4 yrs
Fractionated radiotherapy	6.52 yrs	82% after 12.4 yrs

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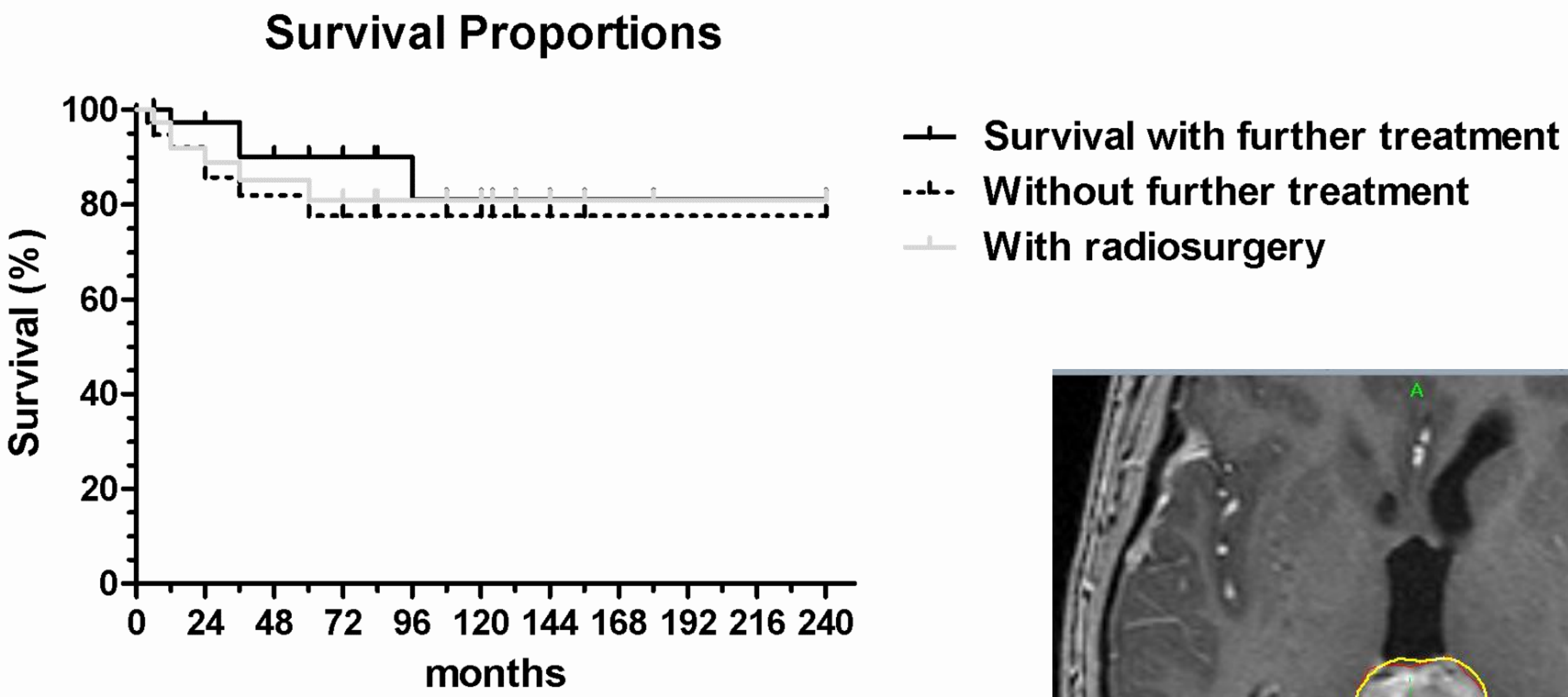
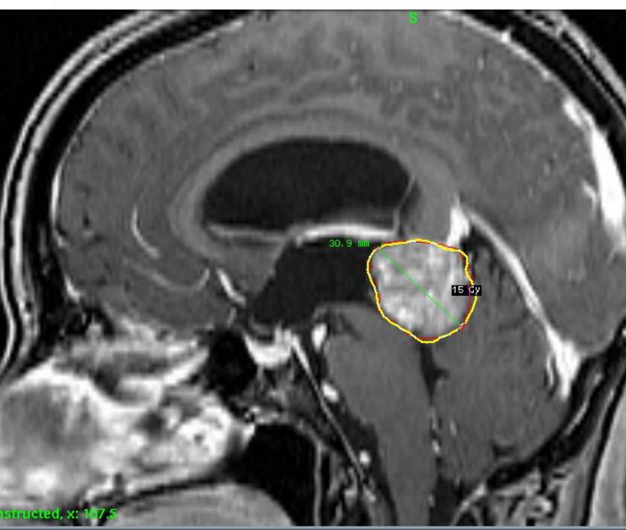
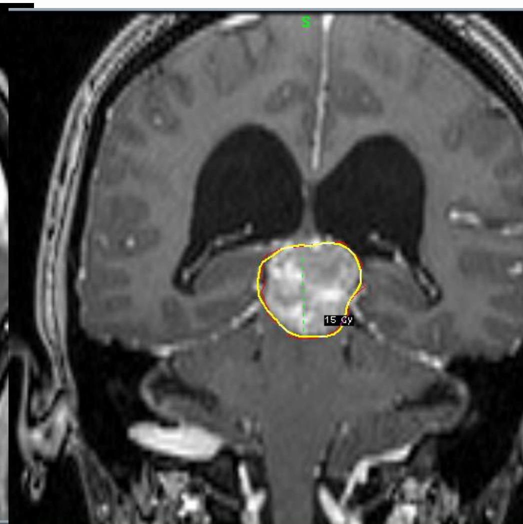
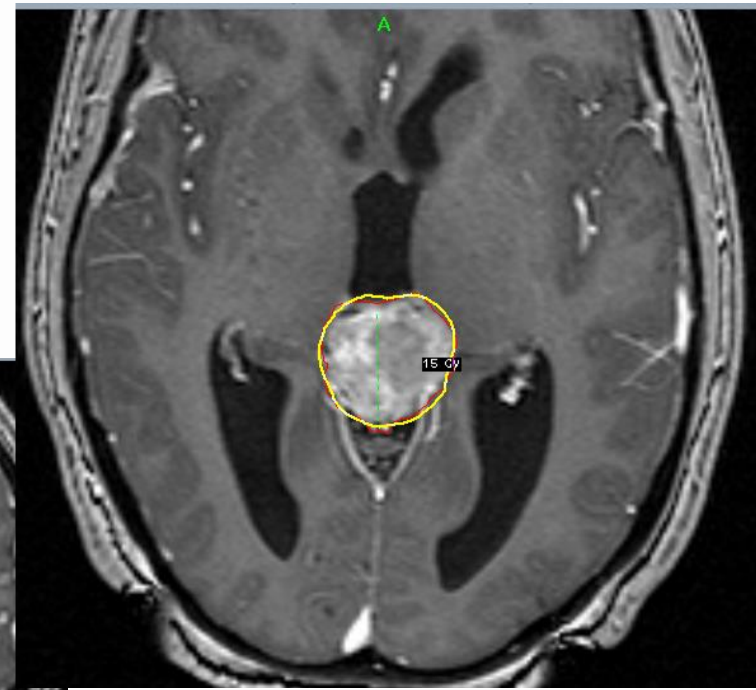
Pineal region









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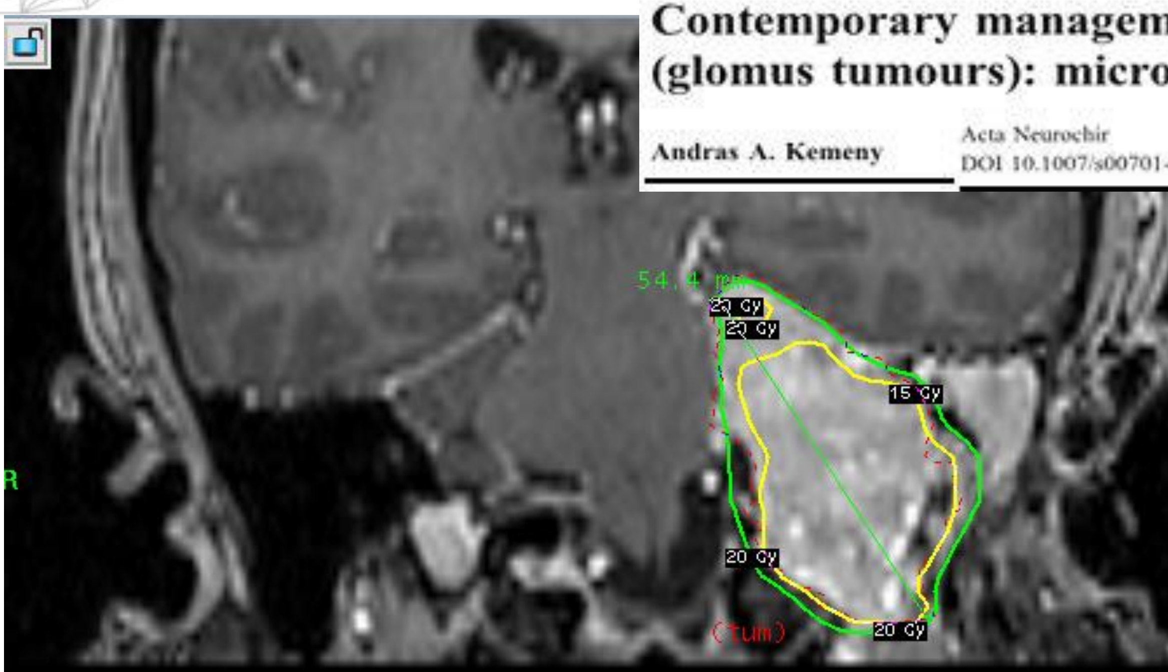
Glomus jugulare tumor

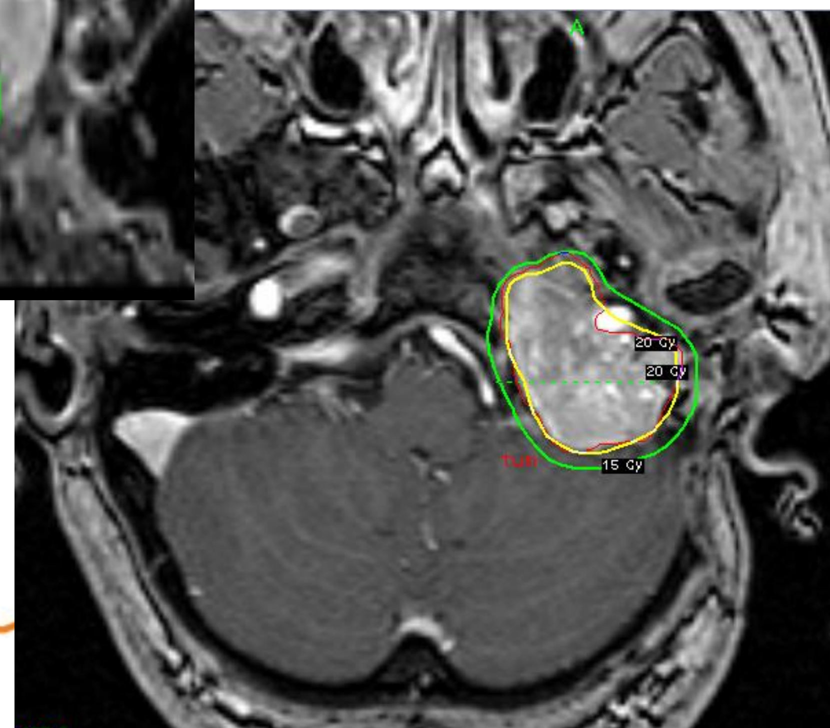
EDITORIAL

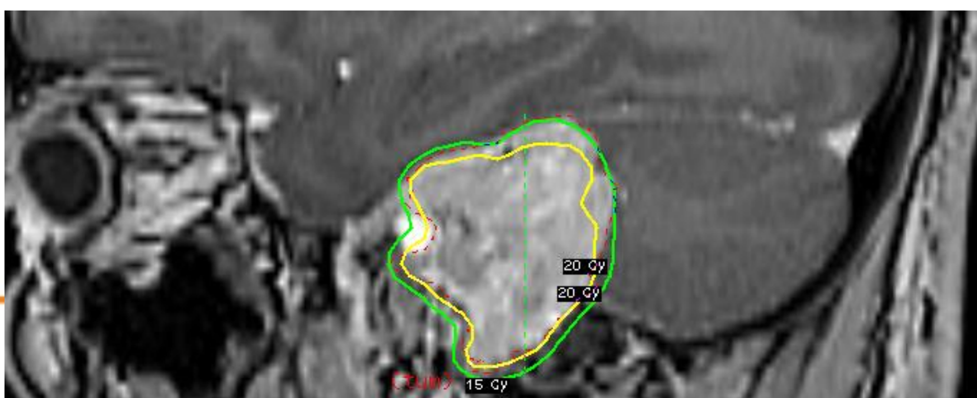
Contemporary management of jugular paragangliomas (glomus tumours): microsurgery and radiosurgery

Andras A. Kemeny

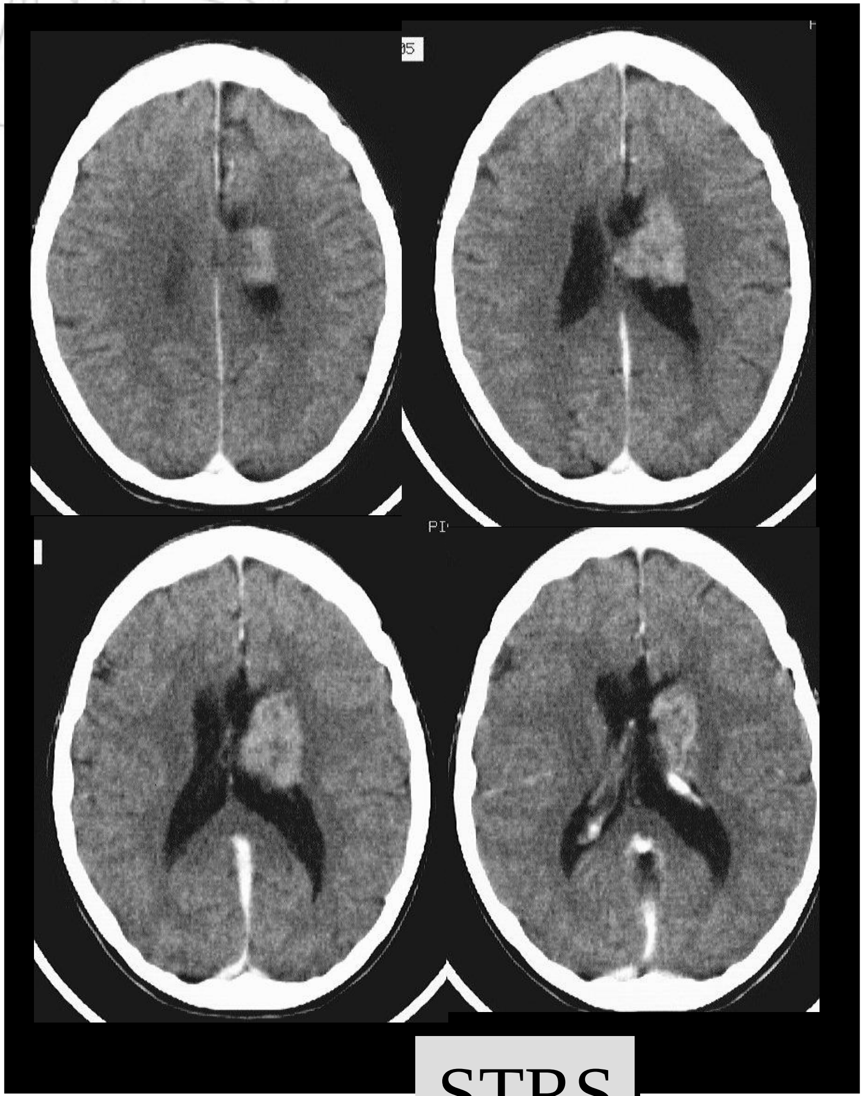
Acta Neurochir
DOI 10.1007/s00701-009-0266-9
Received: 3 March 2009 / Accepted: 3 March 2009

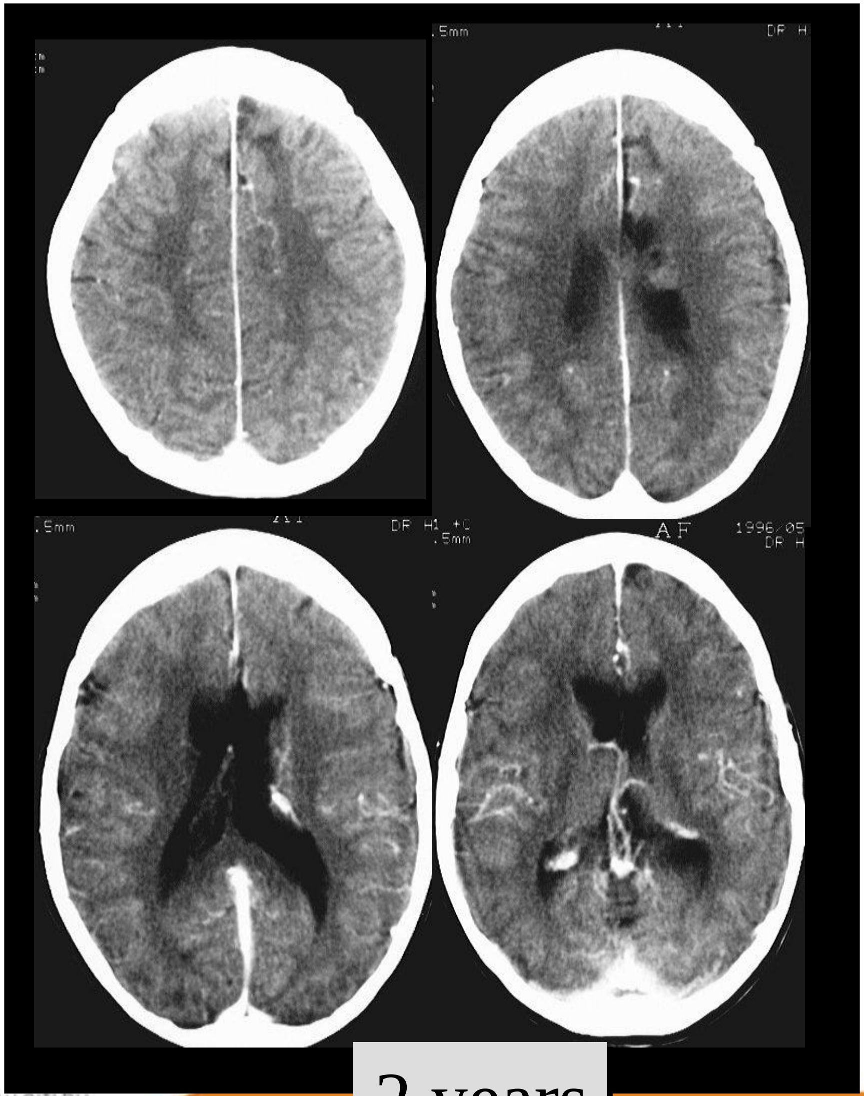




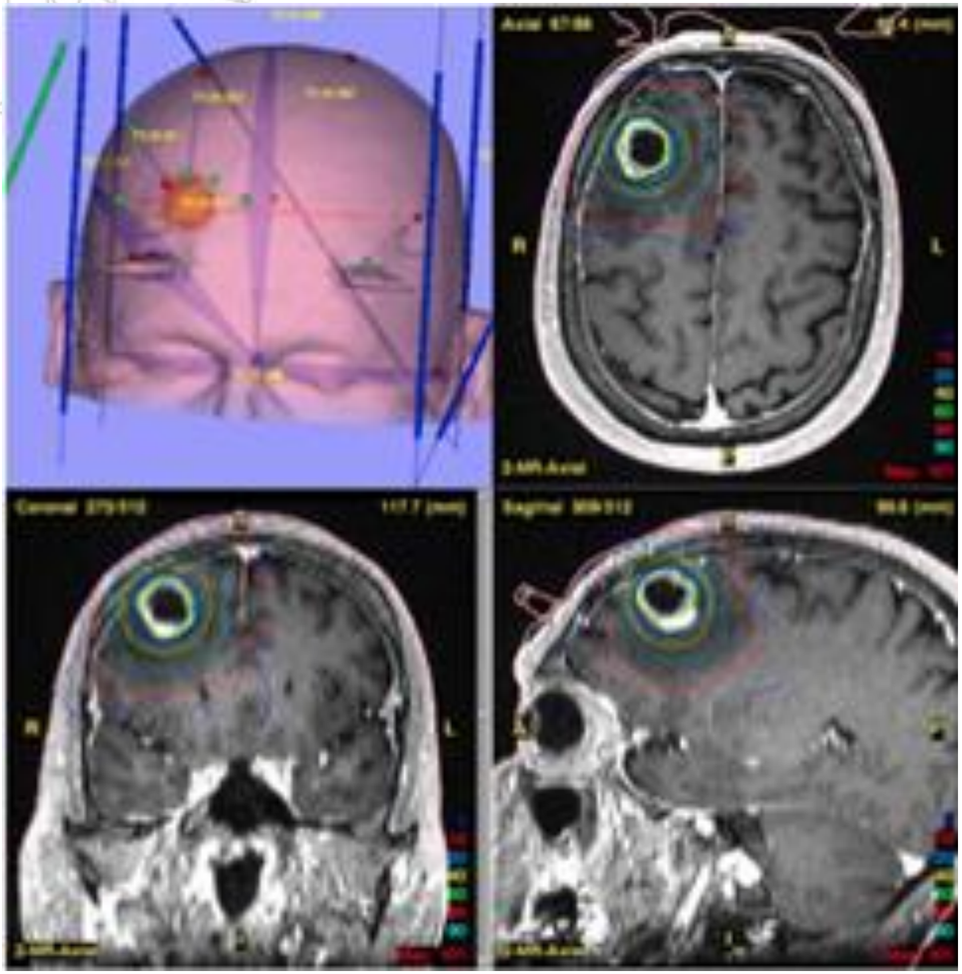


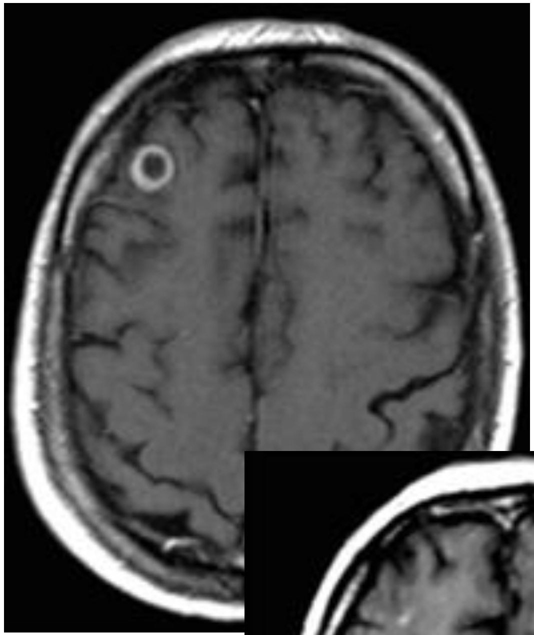
Central neurocytoma

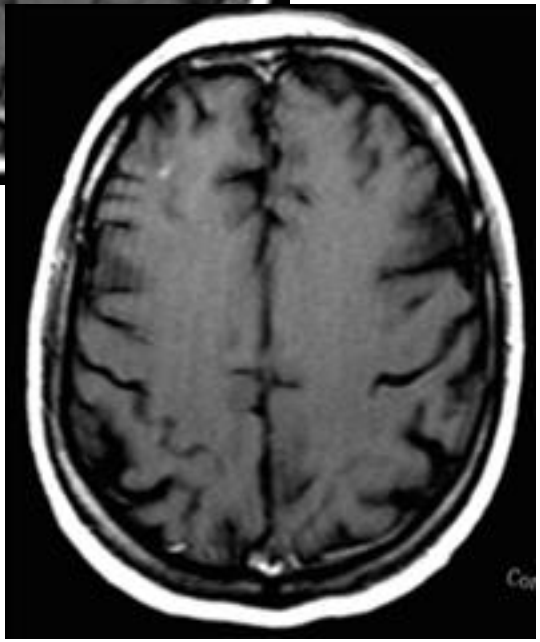




Metastasis: LINAC

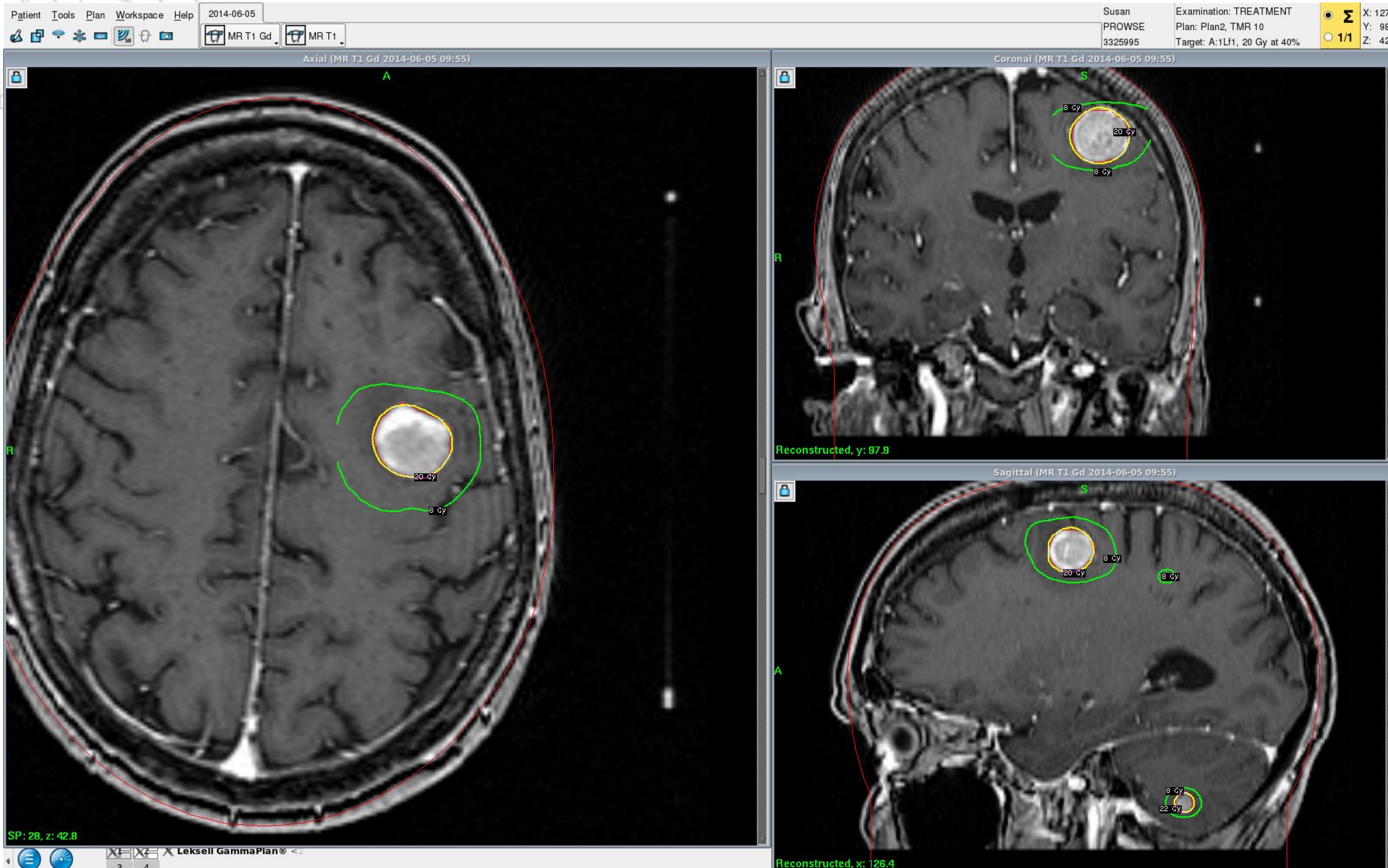






Bagó A., OKITI-OOI

Metastases: Gamma Knife



Kemény A., Sheffield, UK

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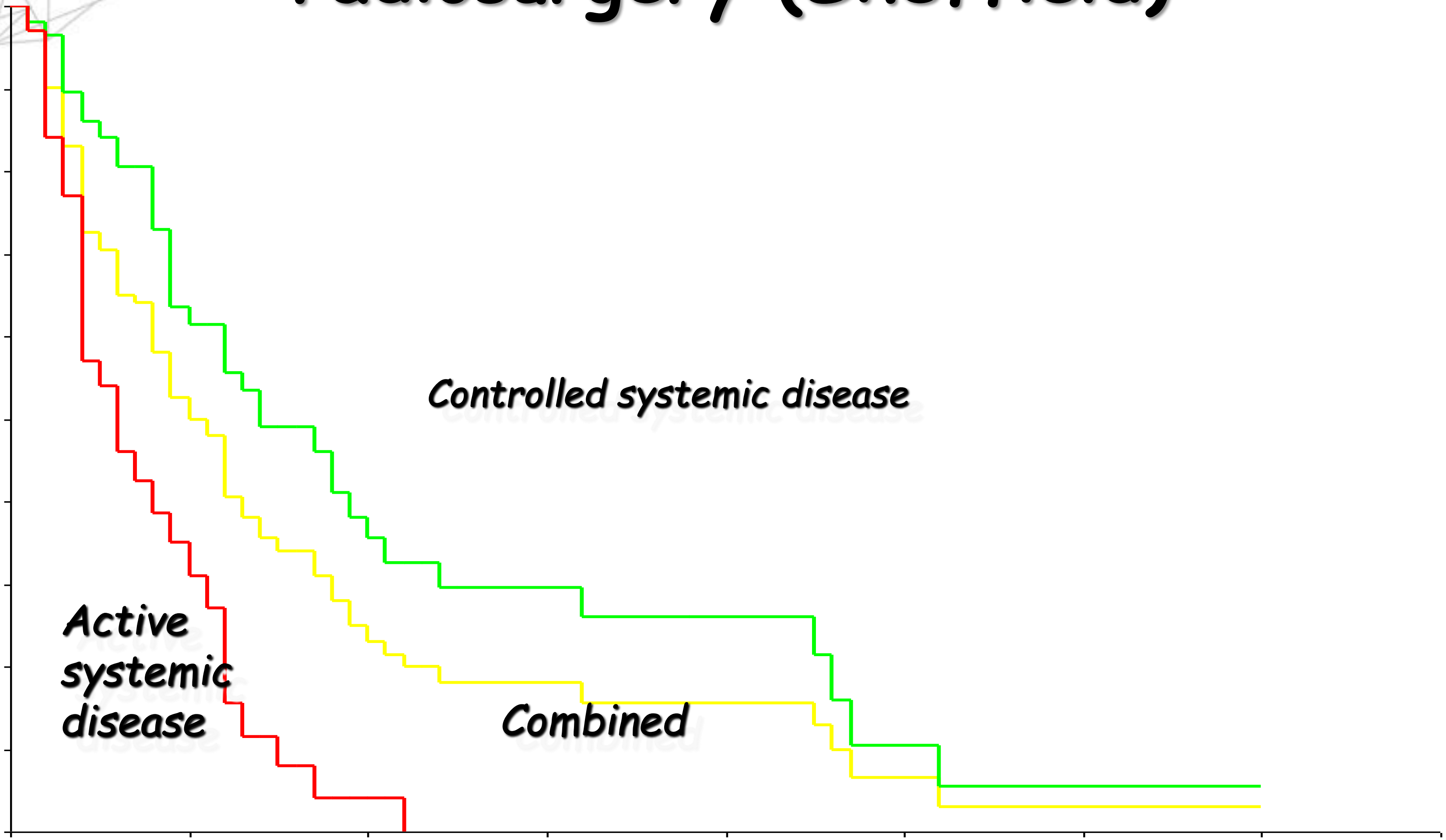
Metastasis: overall survival after radiosurgery (Sheffield)



WBRT vs SRS: Overall survival

ORIGINAL CONTRIBUTION

JAMA. 2006;295:2483-2491

Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases

A Randomized Controlled Trial

Hidefumi Aoyama, MD, PhD
Hiroki Shirato, MD, PhD
Masao Tago, MD, PhD
Keiichi Nakagawa, MD, PhD

Context In patients with brain metastases, it is unclear whether adding up-front whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) has beneficial effects on mortality or neurologic function compared with SRS alone.

Objective To determine if WBRT combined with SRS results in improvements in survival, brain tumor control, functional preservation rate, and frequency of neurologic death.

- 1-4 metastases
- SRS+WBRT: 7.5, SRS: 8 months of median survival
- 1-year recurrence: 47 vs 76%

➢ **„Compared with SRS alone, the use of WBRT plus SRS did not improve survival for patients with 1 to 4 brain metastases, but intracranial relapse occurred considerably more frequently in those who did not receive WBRT. Consequently, salvage treatment is frequently required when up-front WBRT is not used.”**

WBRT vs SRS: Cognitive function

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuckle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers

Lancet Oncol 2009; 10: 1037–44

- 1-3 metastases, terminated early
- SRS+WBRT: 52%, SRS: 24% the risk of cognitive decline after 4 months

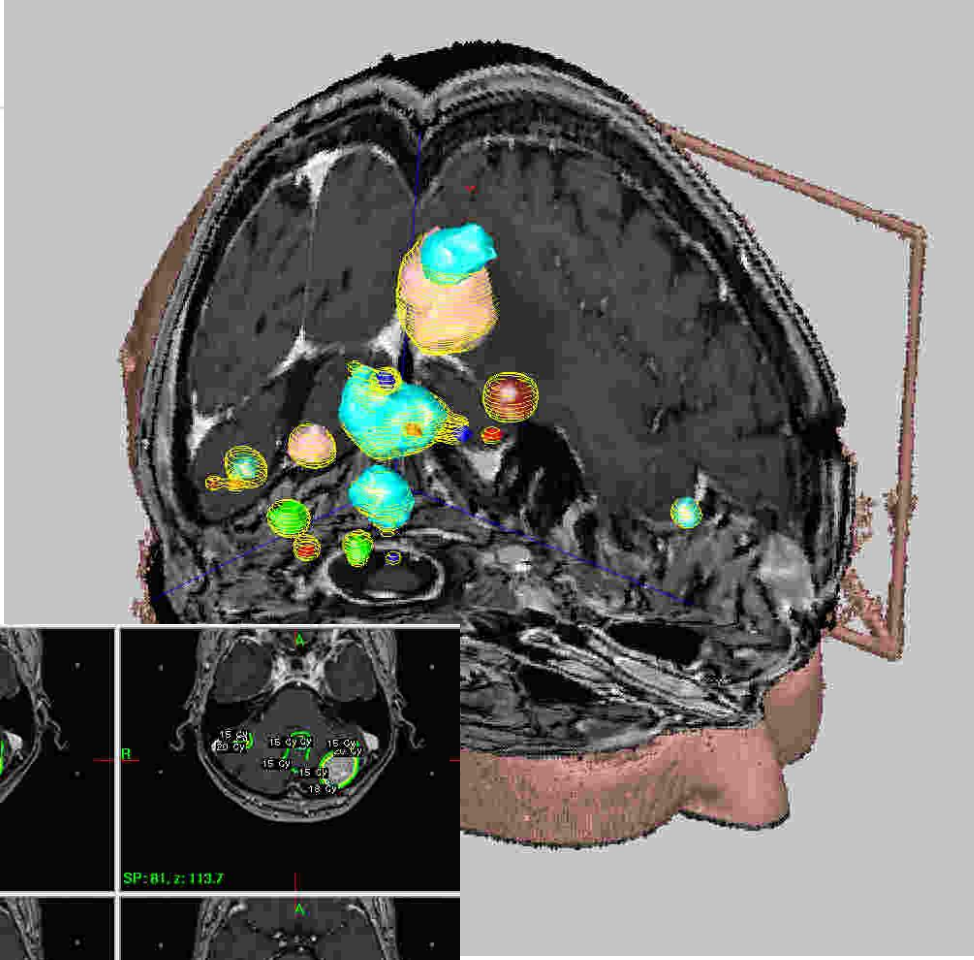
➢ **„Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients with newly diagnosed brain metastases."**

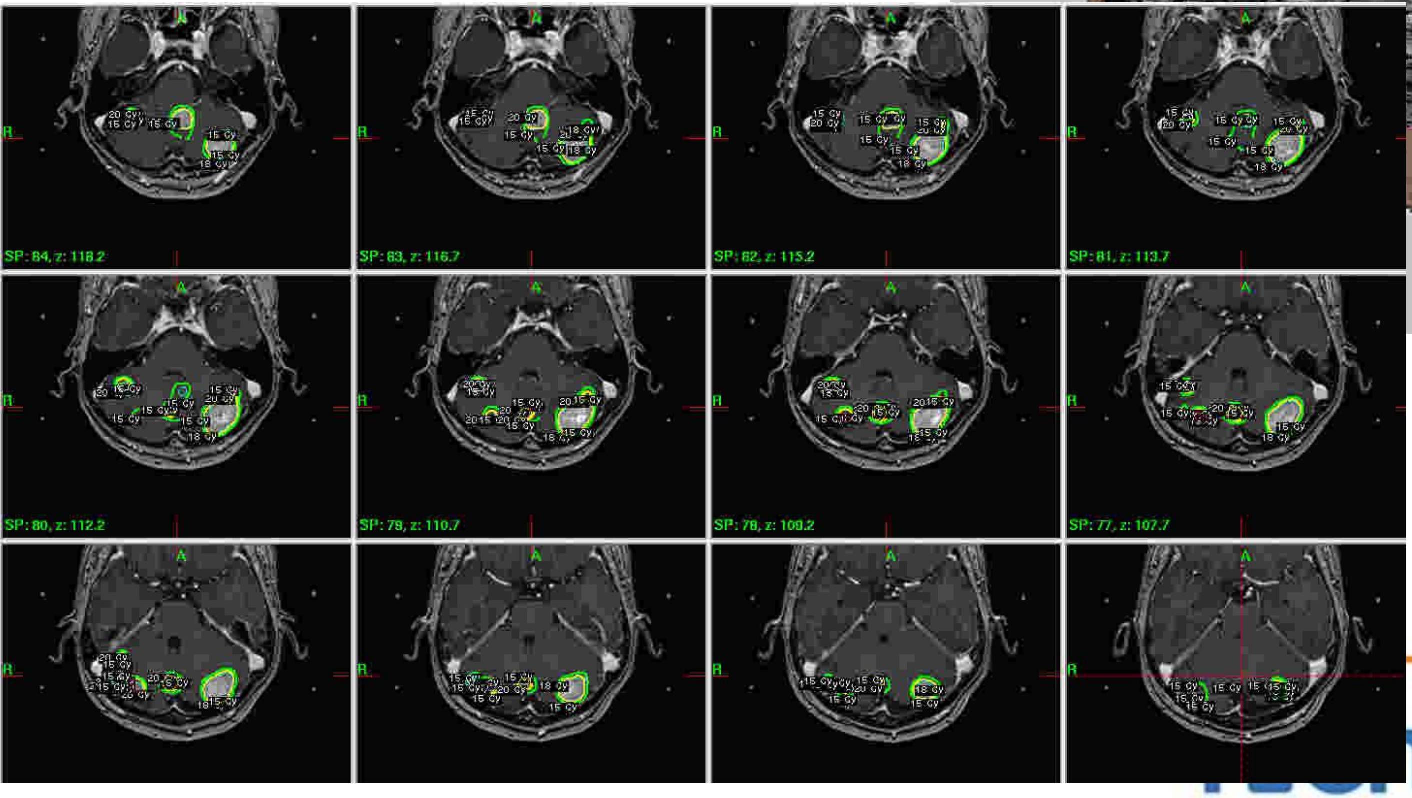
The practice of our onkoteam

	SCLC	NSCLC
KOMPLETT REZEKCIÓ	WBRT	OBS (MR)
INKOMPLETT REZEKCIÓ, INVAZIVITÁS, NAGY TU, SULCALIS KÖTŐDÉS	WBRT	WBRT/SRS boost
DURALIS, LEPTOMENINGEALIS INFILTRÁCIÓ	WBRT	WBRT +/- FBRT
HÁTSÓ SCALA	WBRT	WBRT

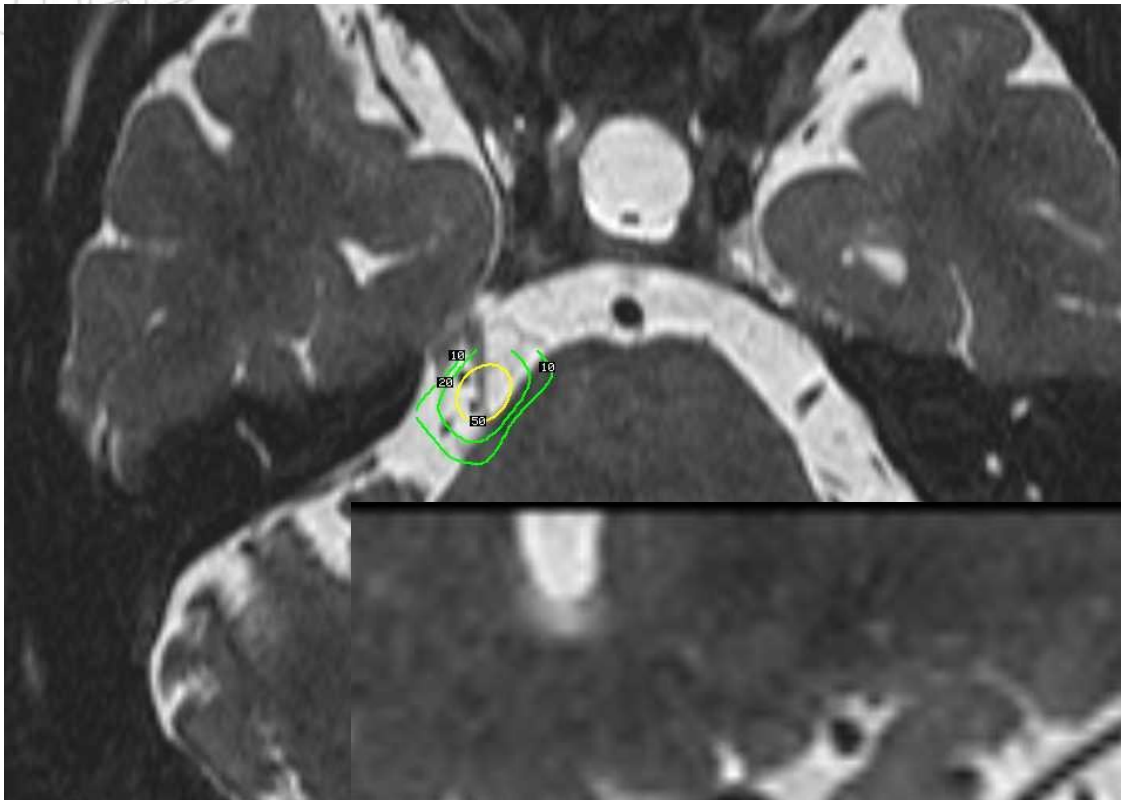
Metastasis

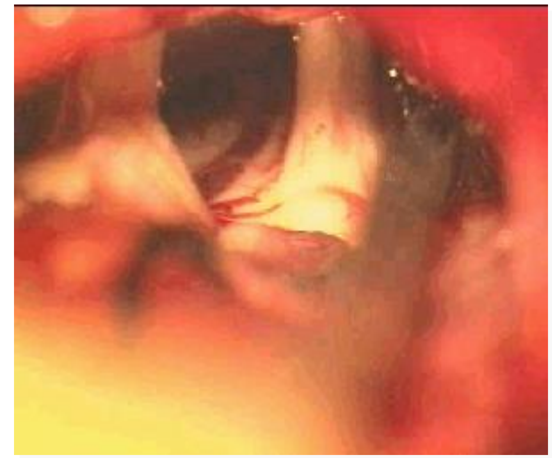
Does number matter?





Funkcional neurosurgery: Trigeminal neuralgia





Thank you for your attention!