Radiotherapy of meningiomas with special reference to proton irradiation

Erik Blomquist et al.

Dept. of Oncology,
Uppsala University Hospital
”Akademiska Sjukhuset”
Uppsala, Sweden

A short History of Proton Beam Therapy

1946 Wilson suggests high energy protons for radiotherapy

1954 First patient treated with protons at Berkley

1957 First cancer in a patient treated with protons in Uppsala

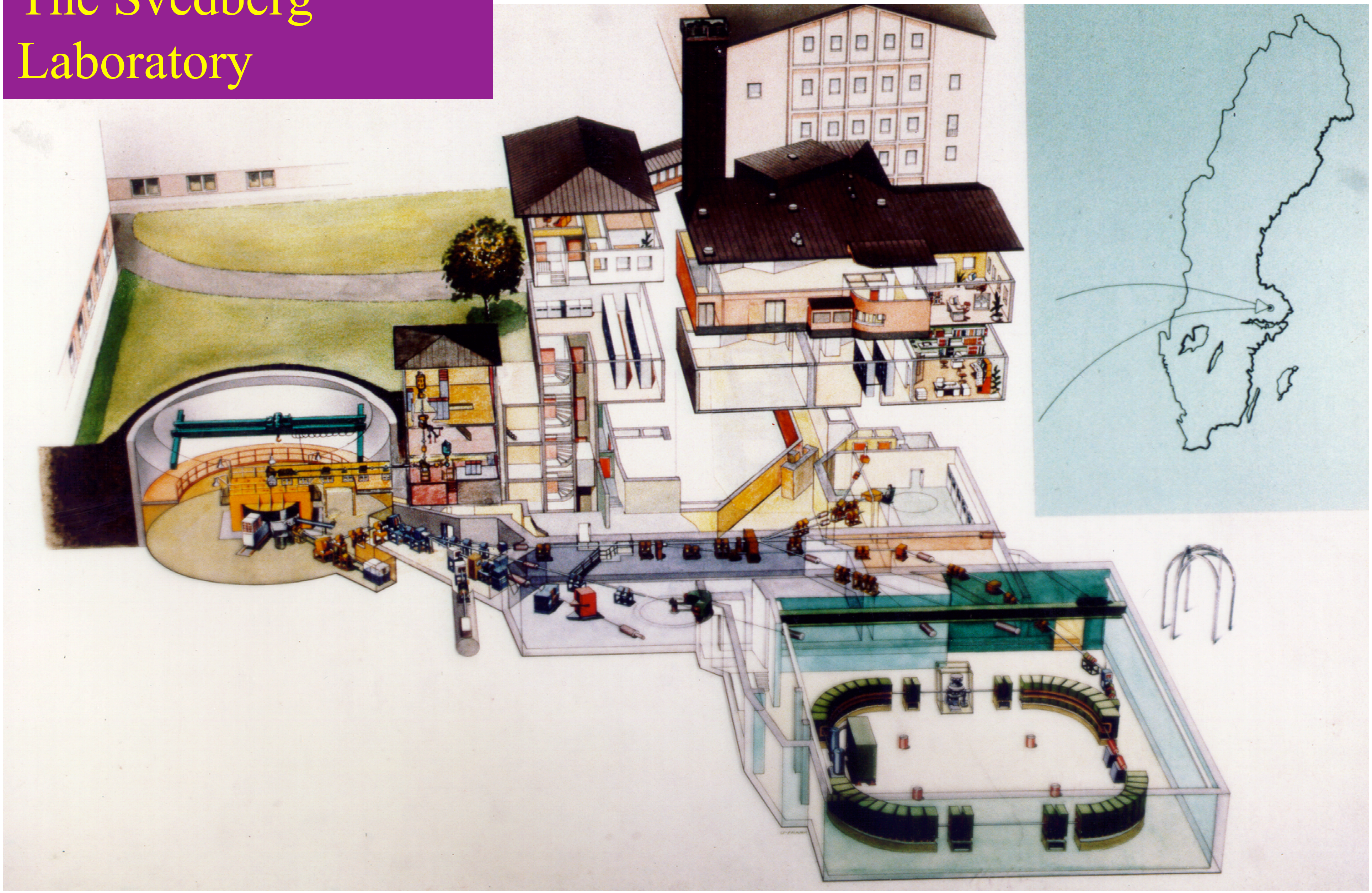
1961 First patient treated at the Harvard cyclotron

1989 Treatment restarted in Uppsala

1990 First hospital-based proton beam facility at Loma Linda, CA, USA

Proton beam treatments in Uppsala

The Svedberg Laboratory



Proton beam radiotherapy at TSL

4 fractions/month
Intracranial and subcranial targets
Tumors in the spine or with paraspinal location
Prostate cancers

Benign targets

- Just protons
  - AVM:s
  - Meningeomas
  - Pituitary tumors

Malignant targets

- Just protons
  - Metastases
  - Uveal and iris melanomas
- Protons as a boost
  - Malignant gliomas
  - Chordomas and chondrosarcomas
  - Head-and-neck cancers
  - Prostate cancers

EB/2004

Proton beam treatment of meningiomas

Team work

- Hospital physicists
- Radiotherapists, nurses
- Specialists in neurosurgery and neuroradiology

Meningioma theme

- Diagnosis – histopathology
- Symptoms and signs
- Etiology
- Imaging
- Therapy options
- Proton therapy dose planning
- Proton therapy results

Diagnosis

- Meningioma, benign WHO grade I

  The dominant part with many subtypes:

  Meningothelial, fibroblastic, transitional, angiomatous etc.

- Atypical meningioma WHO grade II

  4.7 - 7.2%

- Anaplastic meningioma WHO grade III

  1.0 - 2.8%

Meningioma development ”starter cell”

- Suggestions:
  - Arachnoidal cap cell
  - Earlier progenitor meningothelial cell

Operative specimen

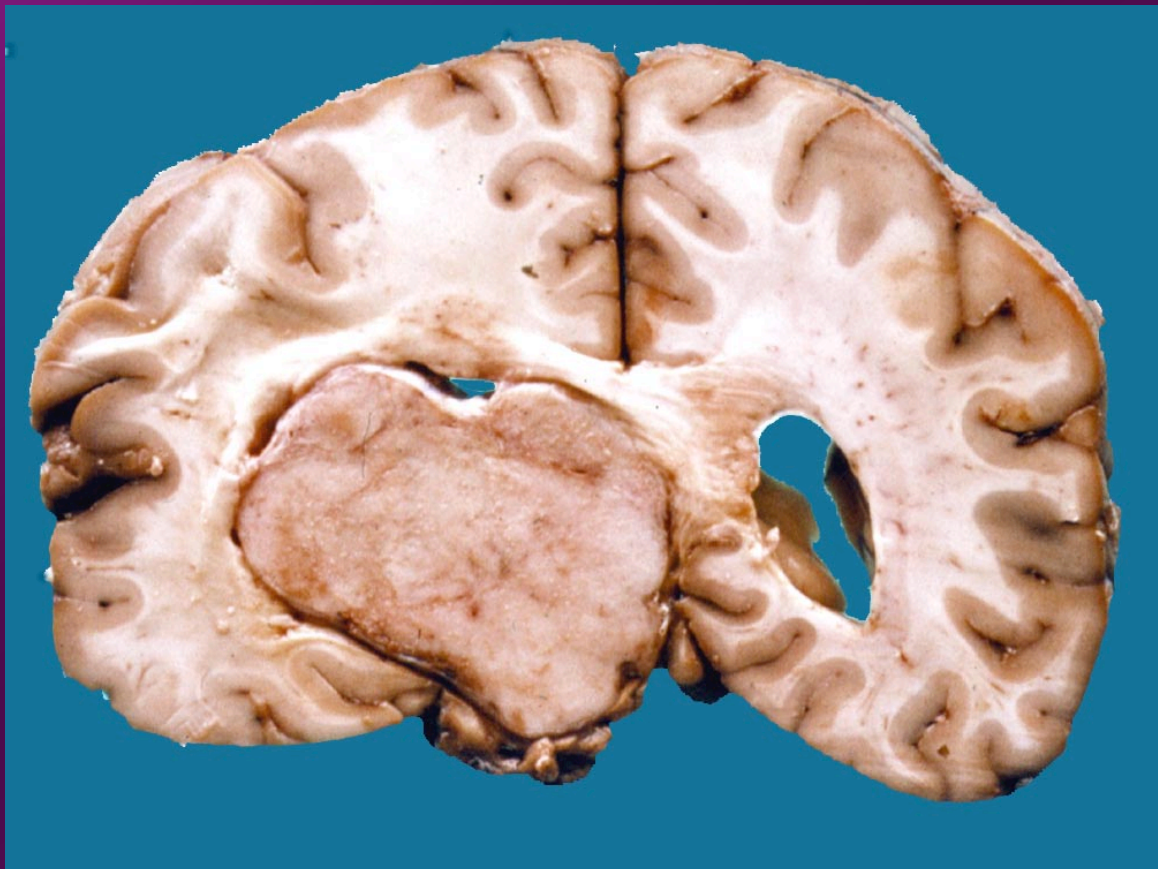
Courtesy of Prof. H. Kalimo

Bone invasion

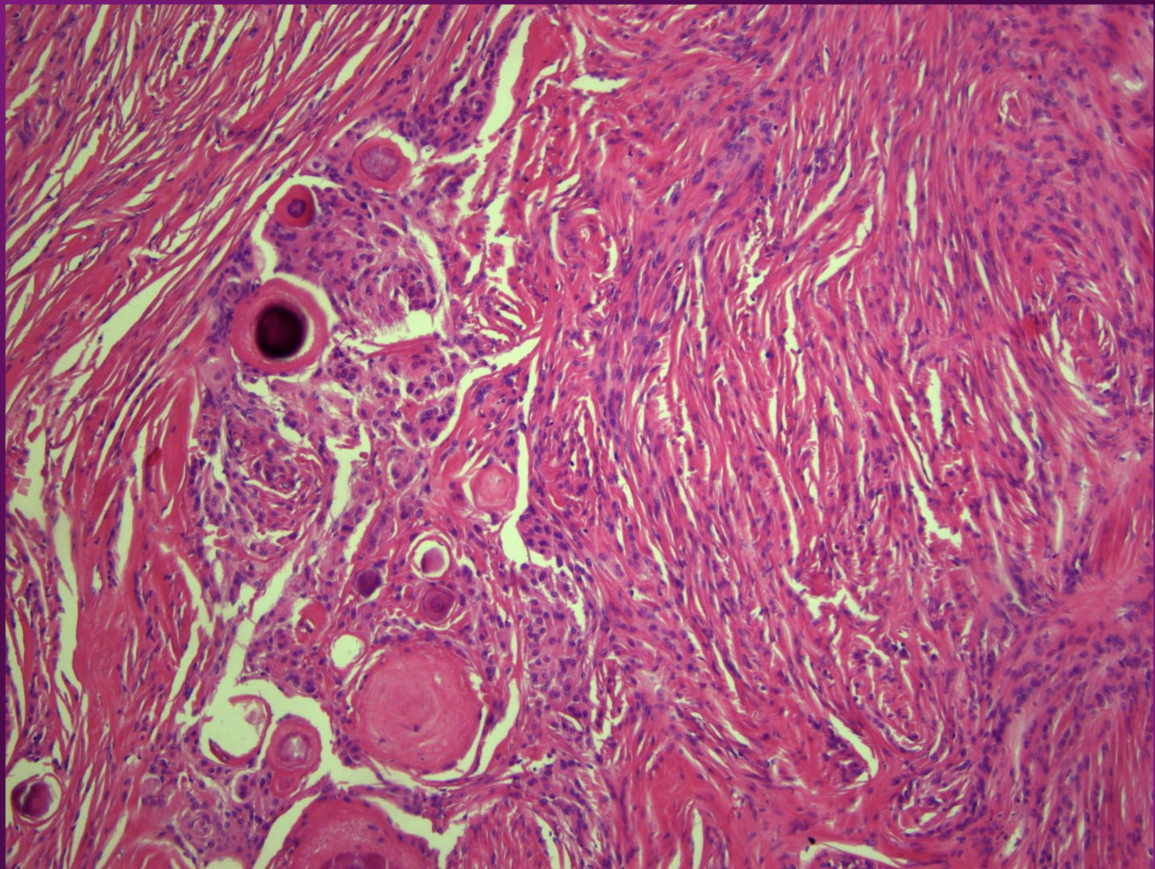
Courtesy of Prof. H. Kalimo

Interventricular growth

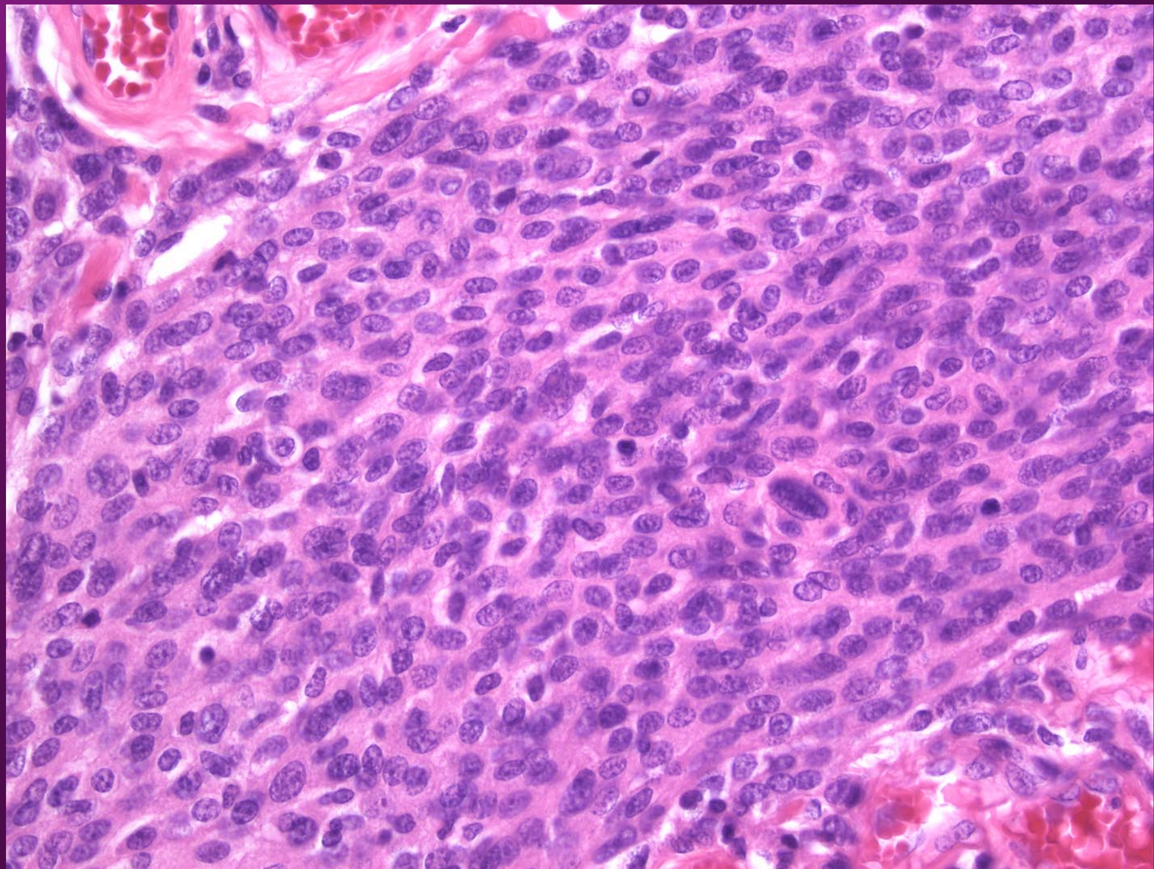
Courtesy of Prof. H. Kalimo



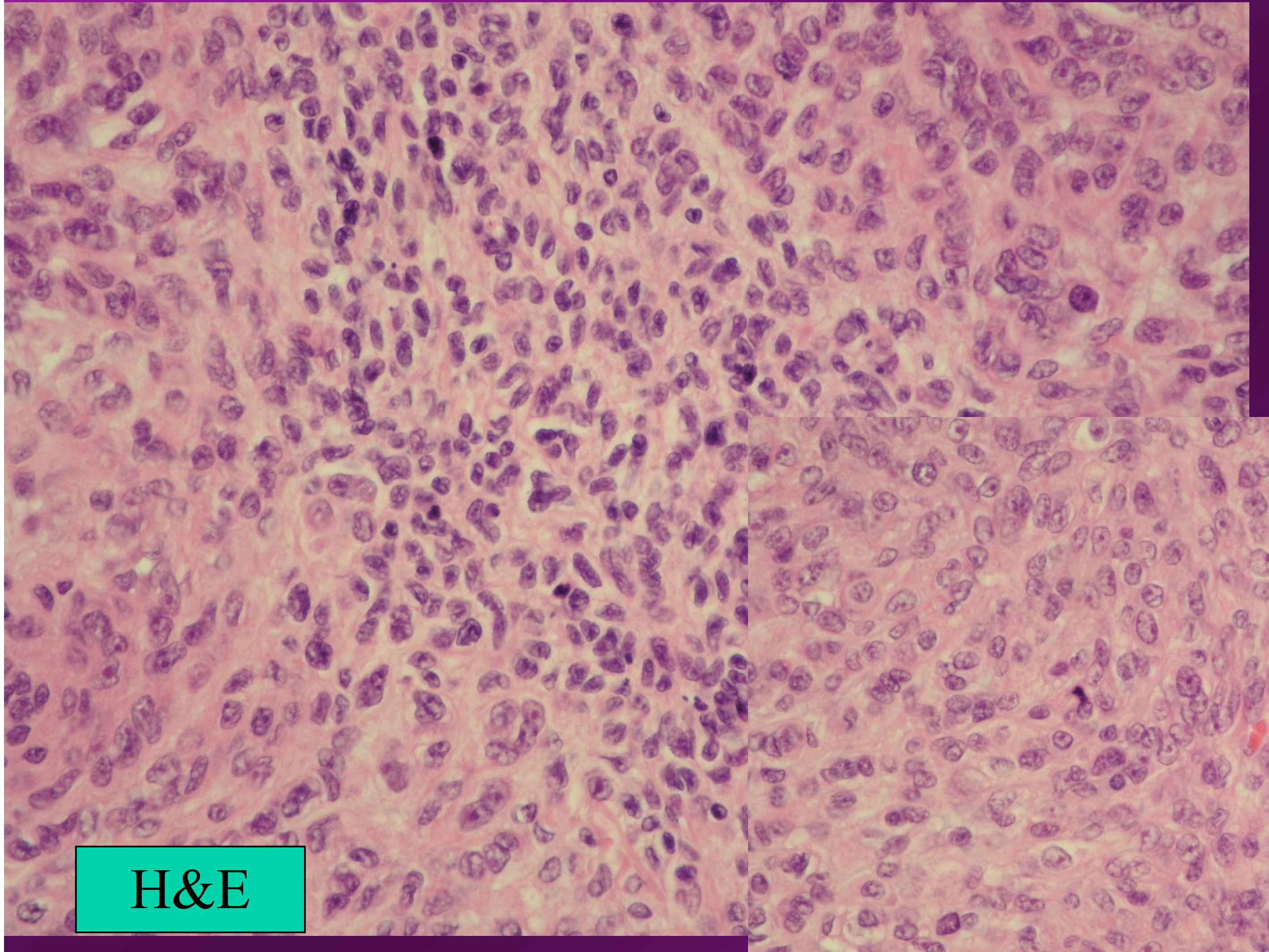
Benign meningioma

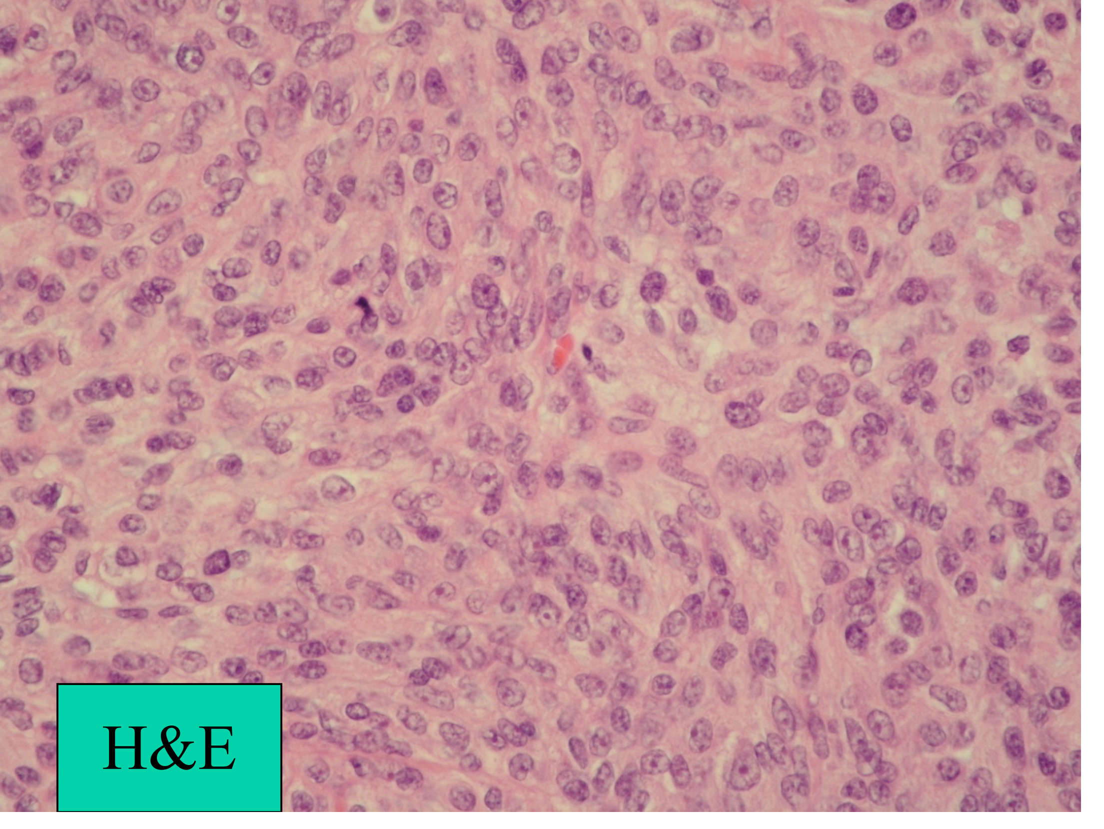


Atypical meningioma

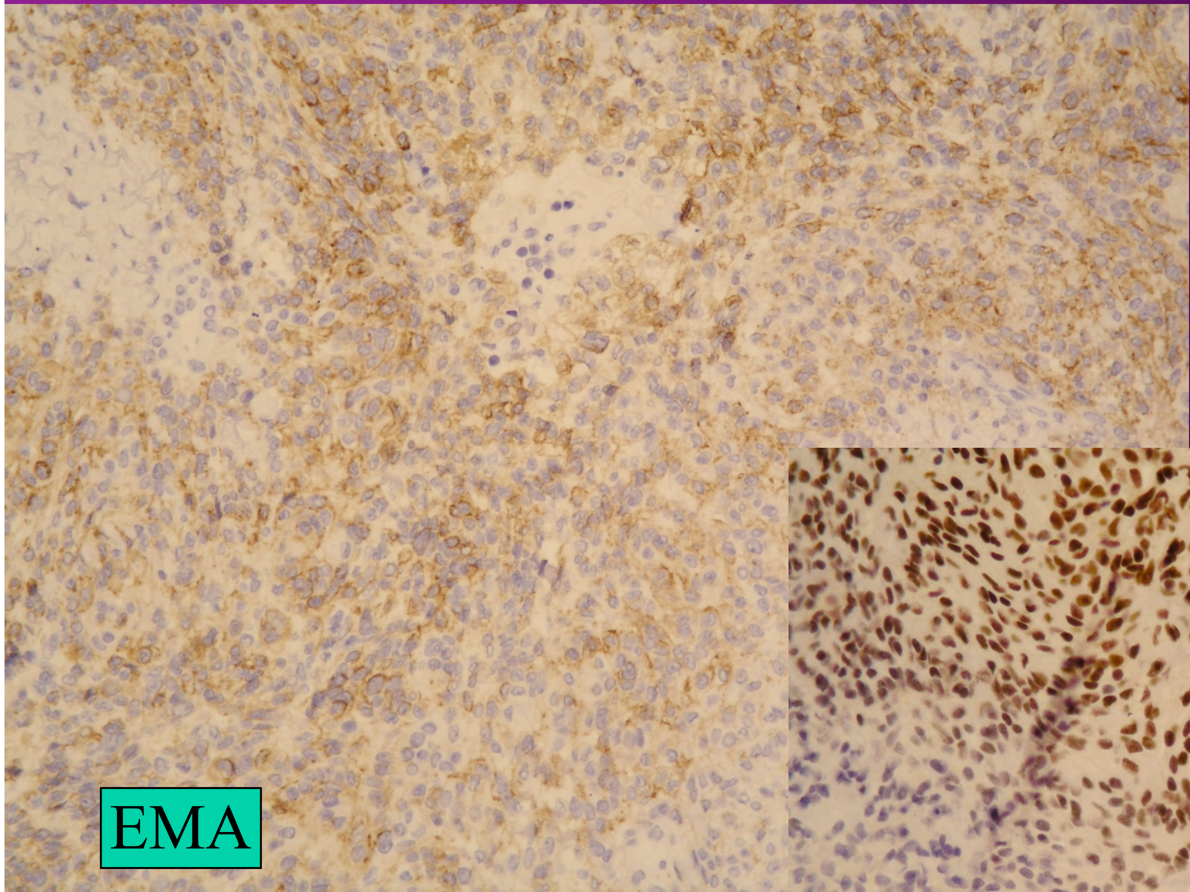


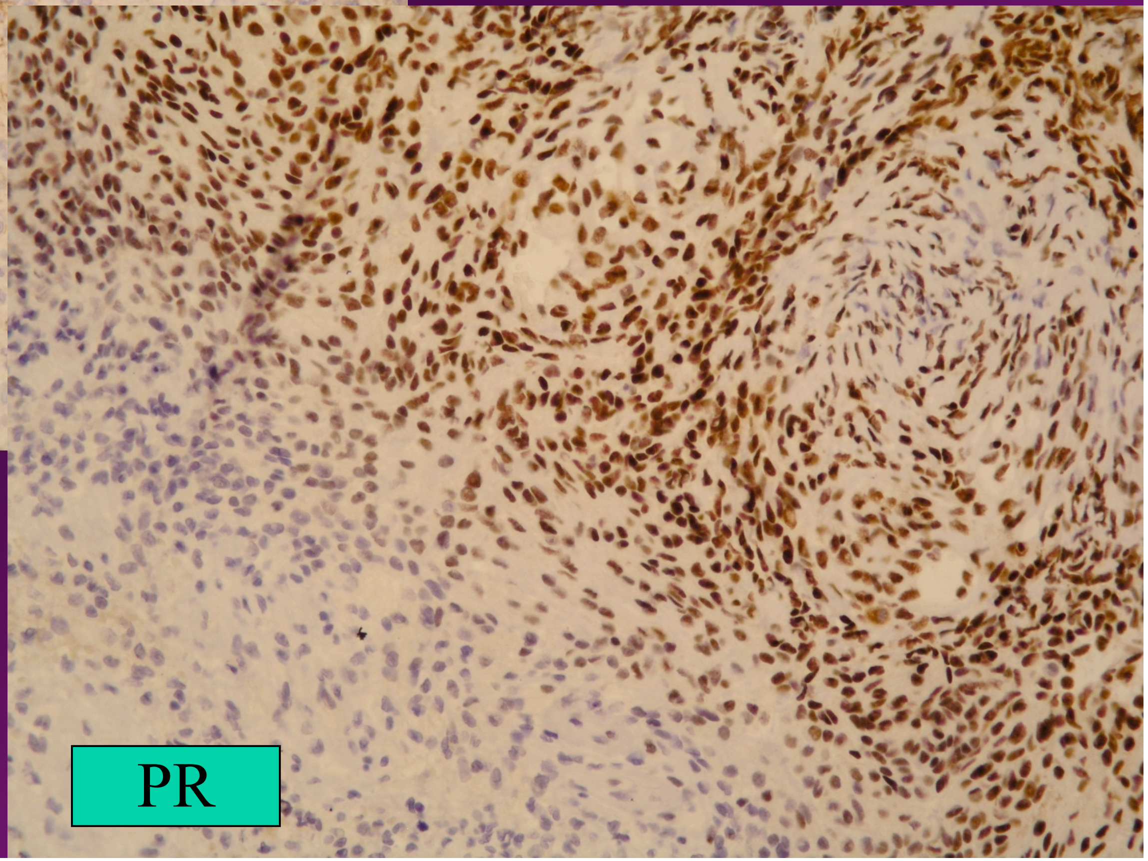
Anaplastic meningioma, WHO grade III



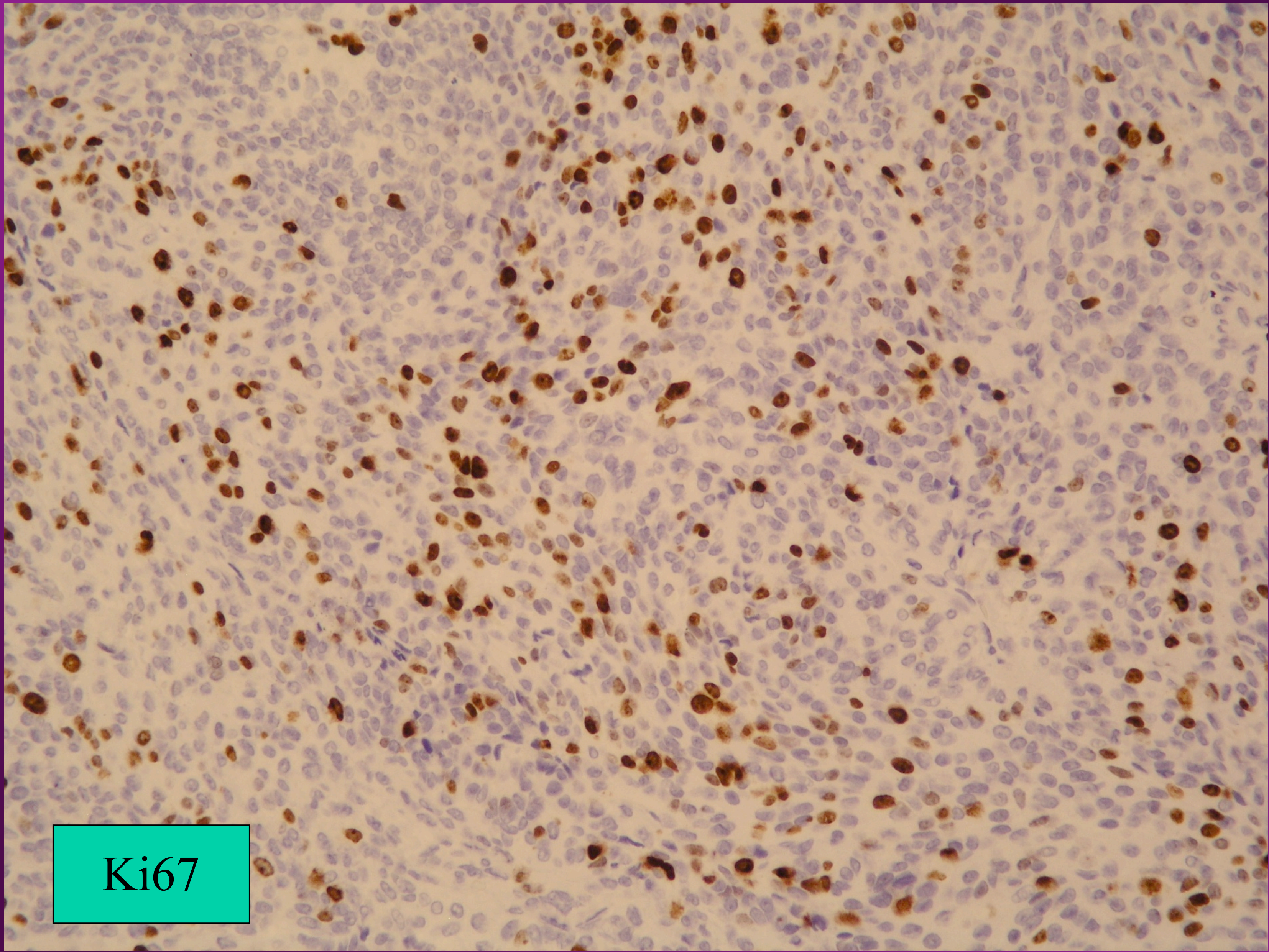


Anaplastic meningioma, WHO grade III





Anaplastic meningioma, WHO grade III



Brain tumors, statistics in Sweden, 1990 - 2001.

Diagnoses	Men	Women	All	Percent
Low malignant astrocytoma	79	57	136	10,6%
Highly malignant astrocytoma	203	156	359	28,1%
Ependymoma	16	12	28	2,2%
Meningioma	114	275	389	30,5%
Malignant meningioma	4	6	10	0,8%
Neurinoma	61	62	123	9,6%
Plexuspapilloma	1	2	3	0,2%
Hemangioblastom, and related	16	14	30	2,3%
Kraniofaryngioma	6	6	12	0,9%
Pinealoma	4	2	6	0,5%
Without histopathology	52	56	108	8,5%
Other	45	28	73	5,7%
Total/year	601	676	1277	100 %

Symptoms and signs 1

- Dependent by anatomic site
- Located supratentorially: 85 – 95%
- Presenting symptoms: headache (36%), change in mental status (21%) and paresis (22%)

Symptoms and signs 2

- Most common anatomical sites:

Convexity (35%): **Medial:** Headaches, seizures, motor and sensory deficits.

Parasagittal (22%): **Anterior**: Headaches, memory and behaviour changes. **Middle**: Motor and sensory deficits.

Posterior: Homonymous hemianopsia. **All:** Venous occlusions

Sphenoidal ridge (17%): **Medial**: Visual loss, cranial nerves III, IV and IV palsies. **Lateral**: Headaches, seizures, motor and sensory deficits.)

(Ref: Greenberg et al. Brain tumors. Oxford Univ Press 1999)

Etiology and more

- Female:male ratio 3:2 – 2:1
- Peak occurence at 50 – 70 years
- Irradiation followed by about two decades before appearance (800 – 2000 rad (sic!))
- Role of sex hormones?
- In children more aggressive forms
- Multiple forms

Molecular biology 1

- Neurofibromatosis type 2 (NF 2)
  Chromosome 22.12.2q LOH
- Progesteron- and estrogen-receptors
- Somatostatin receptors
- Radiation induced meningiomas may have losses on chromosome 1p11, 6q and 7p

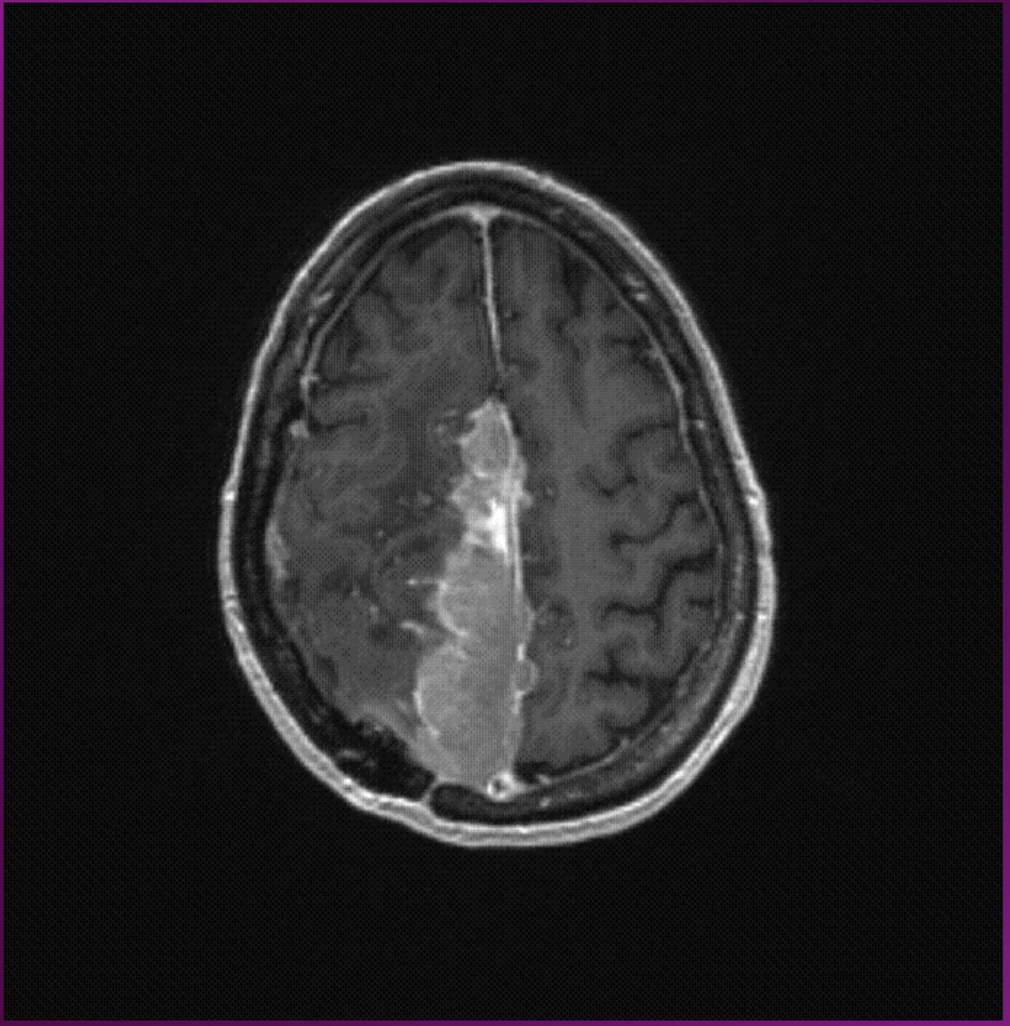
Molecular biology 2

- Cell cycle dysregulation
- Telomerase activation
- Genetic instability

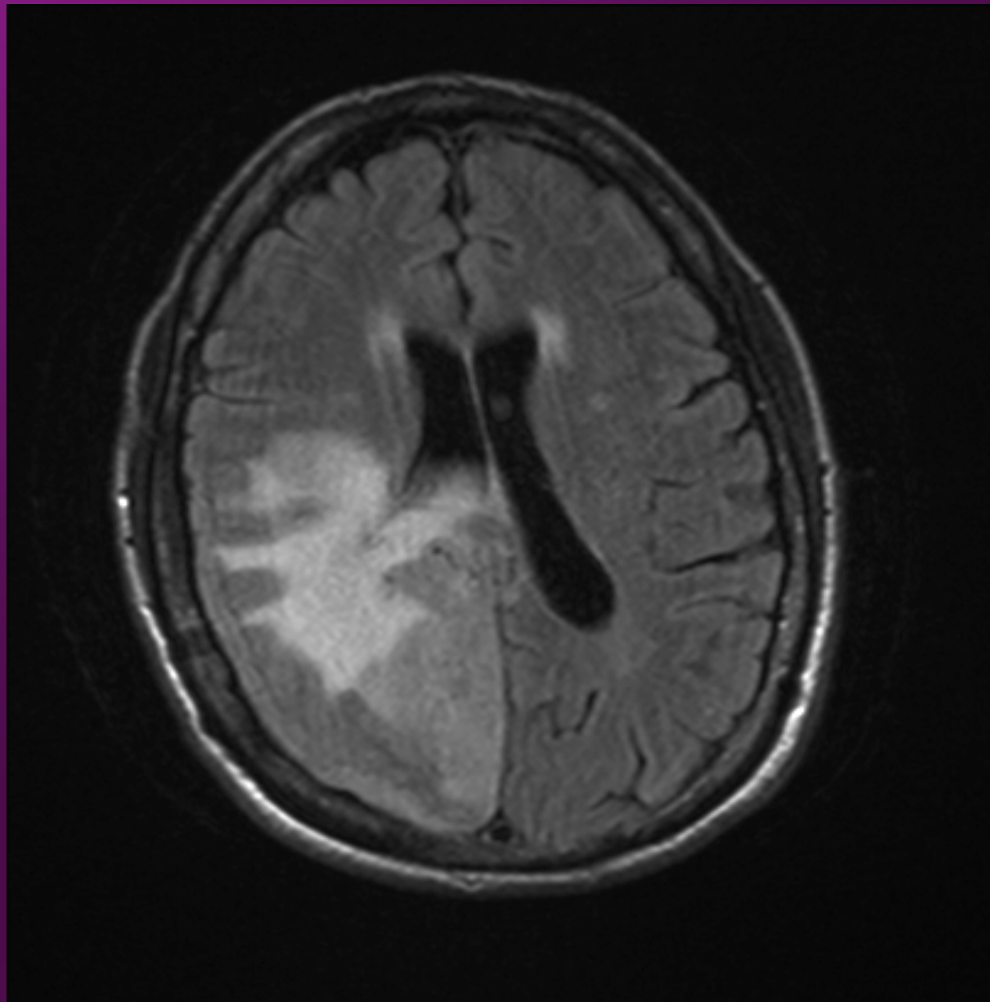
Imaging

- Isodense dural masses, may be calcified
- Contrast enhancemnt
- Compression of surrounding structures
- ”Dural tail”
- ”En plaque meningioma” – growing as a flat mass

Meningioma MRI T1



Meningioma MRI T2



Treatment options 1

- Surgery

  Total removal, partial resection, biopsy
- Radiotherapy

  Protons, photons (3-D conformal, IMRT, stereotactic techniques)
- Medical therapies?

  Interferons? Hydroxurea?

  Inhibition or targeting with signal transduction inhibiting molecules?

Surgical risk in skull base meningioma operations

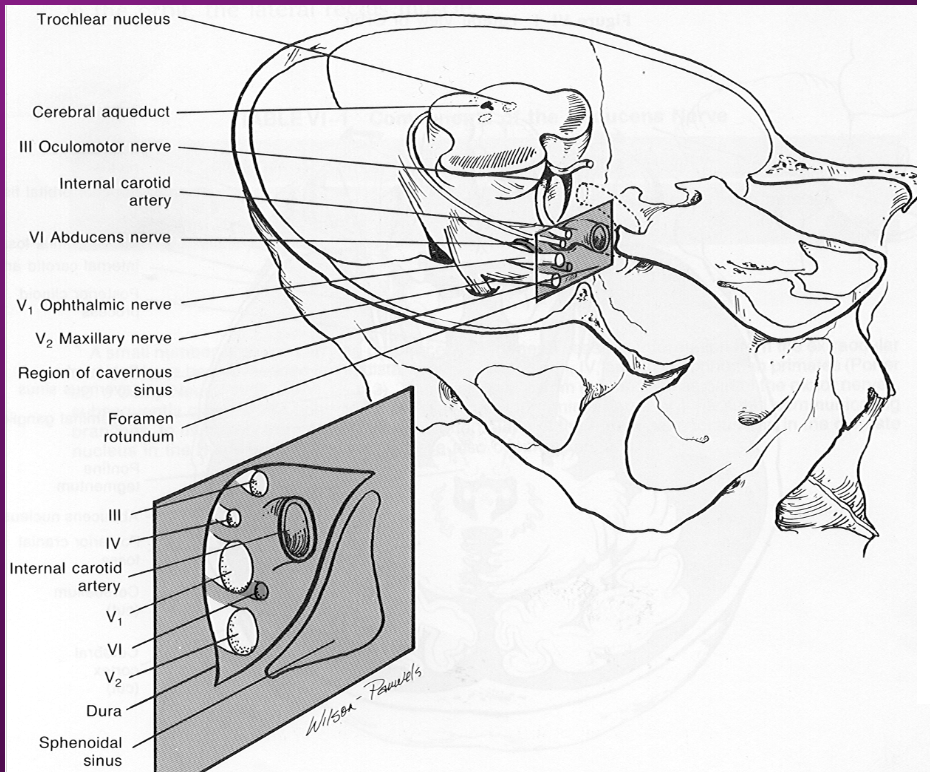
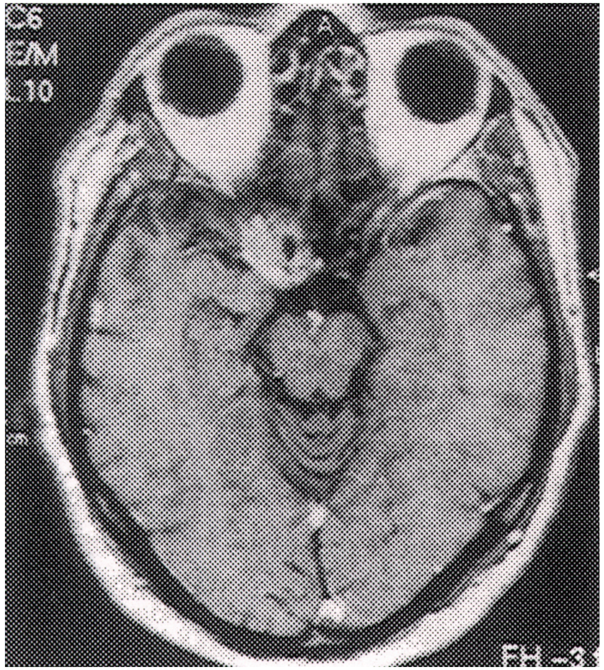


Figure VI–3 Region of Cavernous Sinus



Results of surgery alone

- Recurrence rate after ”total removal”:

Benign meningiomas: 7 – 20%

Atypical meningiomas: 29 – 38%

Anaplastic meningiomas: 50 – 78%

Ref: Pathology and Genetics. Tumors of the Nervous System. Kleinhues and Cavenee. IARC, 1997

Aim of radiotherapy

- A. In benign meningiomas – in case of a residual meningioma to prevent regrowth and the need for reoperation.

  B. To diminish symptoms
- In atypical meningioma – to ”cure”
- In anaplastic meningioma – advanced palliation

How does radiotherapy function in patients with benign meningiomas?

Suggestions:

1. Inhibition of division of cycling cells
   apoptosis induction
2. Parenchymal ”exhaustion”
3. Obliteration of small vessels

Radiotherapy

Photons

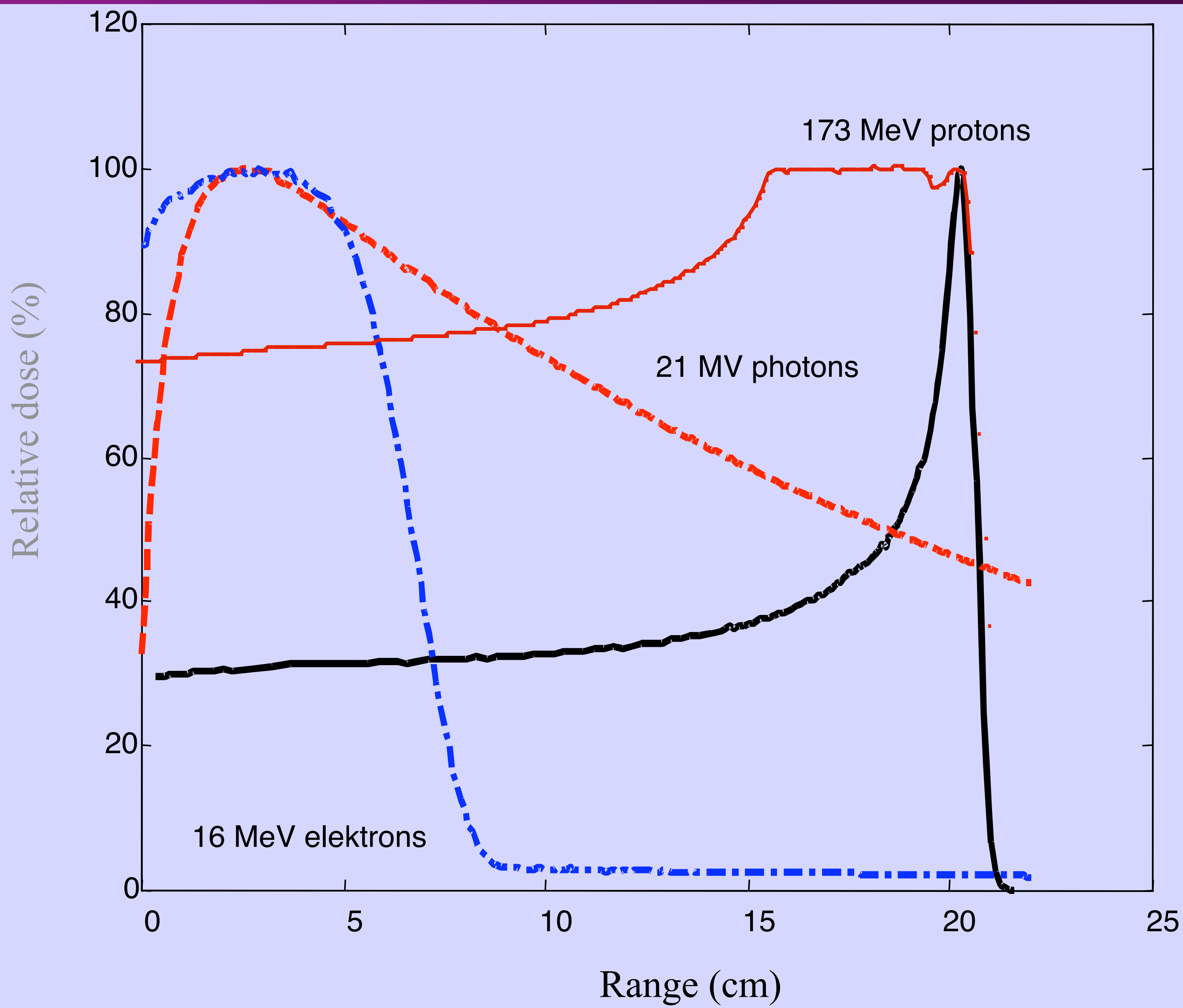
- Conventional 3-D, IMRT, stereotactic techniques, (gammaknife)

Protons

- Conventional fractionation
- Hypofractionation

Light ions?

Depth Dose Distributions



Important message

- Restriction of dose around the target

  CTV = GTV; PTV may need a few mm margin
- Lesser dose to surrounding normal tissue
- Hypofractionation possible

Radiotherapy with protons

- Conventional fractionation: 1.8 - 2.0 Gy x 25 – 30. Total doses: 50 - 56 (60) Gy
- Hypofractionation: 3 - 6 Gy x 4 – 8 mostly 5 – 6 Gy x 4. Total doses: 24 Gy to 32 Gy

Radiobiology

1. According to LQ- model:

   If $\alpha/\beta = 10$ Gy and $\gamma/\alpha = 0.6$ Gy/ day so

   6 Gy in 4 fractions during one week

   corresponds roughly to 2 Gy to 50 Gy.

2. According to CRE – model:

   6 Gy in 4 fractions during one week

   corresponds roughly to 2 Gy to 46 Gy

Dose and fractionation

From Shrieve et al in J Neurosurg (Suppl 3) 101: 390 – 395, 2004

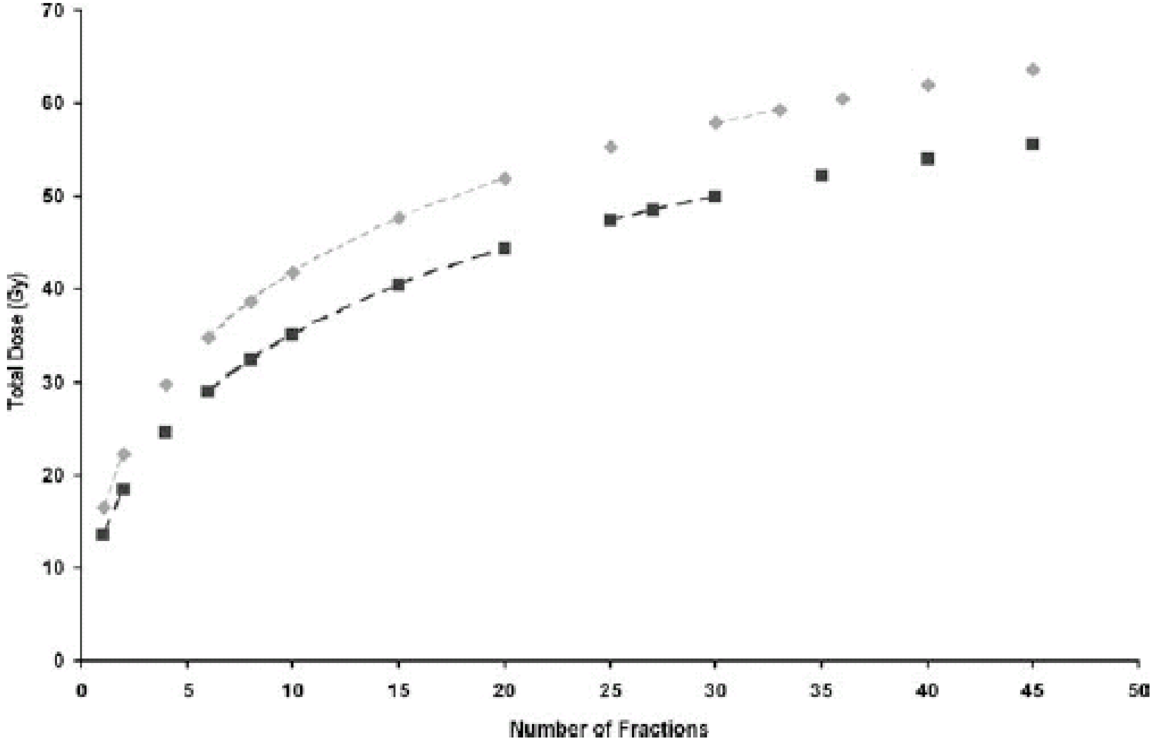


FIG. 1. Graph showing total doses of radiation associated with a predicted biologically equivalent effect on meningioma control for various numbers of equal daily fractions. Calculations were based on biological equivalency of 13.5 to 16.5 Gy for a single dose and 48.6 to 59.4 Gy in 30 fractions. Upper limit was calculated using an α/β of 3.85 Gy. The lower limit was calculated using an α/β of 2.70 Gy.

Dose and fractionation

From Shrieve et al in J Neurosurg (Suppl 3) 101: 390 – 395, 2004

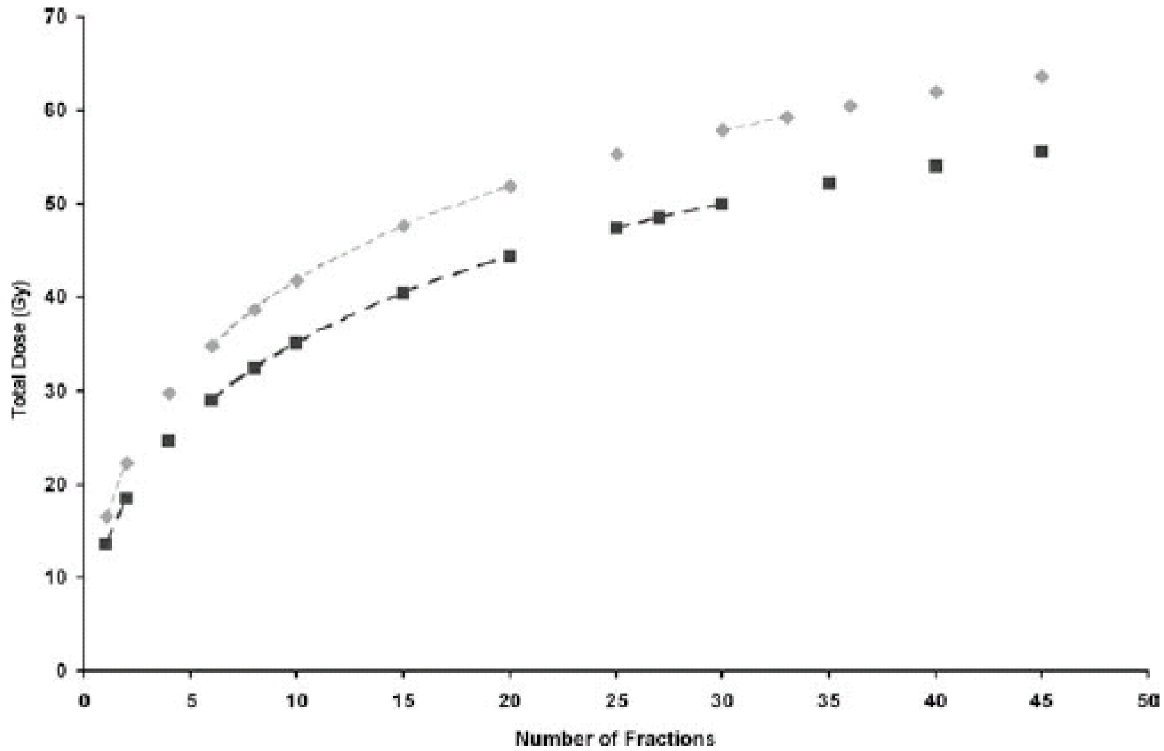
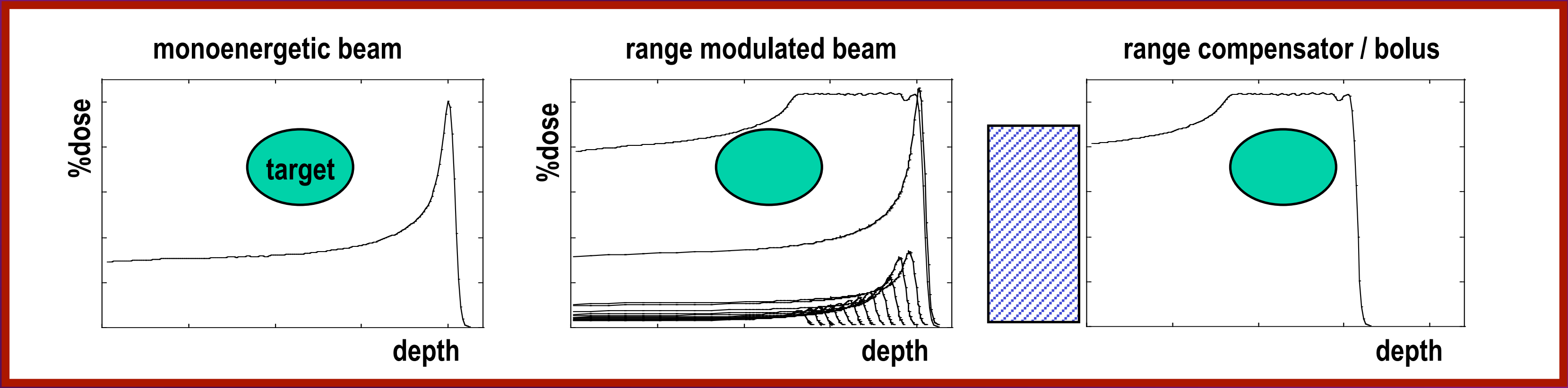
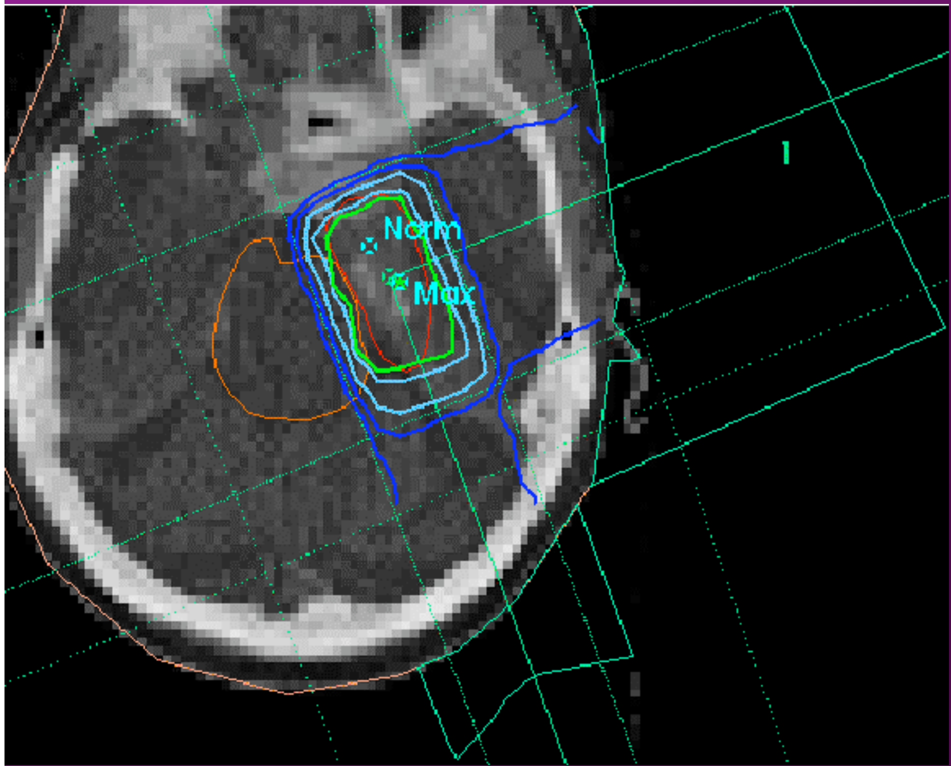


FIG. 4. Graph showing the range of total doses predicted to be associated with excellent control of meningioma *(dotted lines)* compared with the optic nerve tolerance for various equal daily doses *(solid line)*. The therapeutic range exceeds optic nerve tolerance until at least 20 fractions are used.

Dose modulation

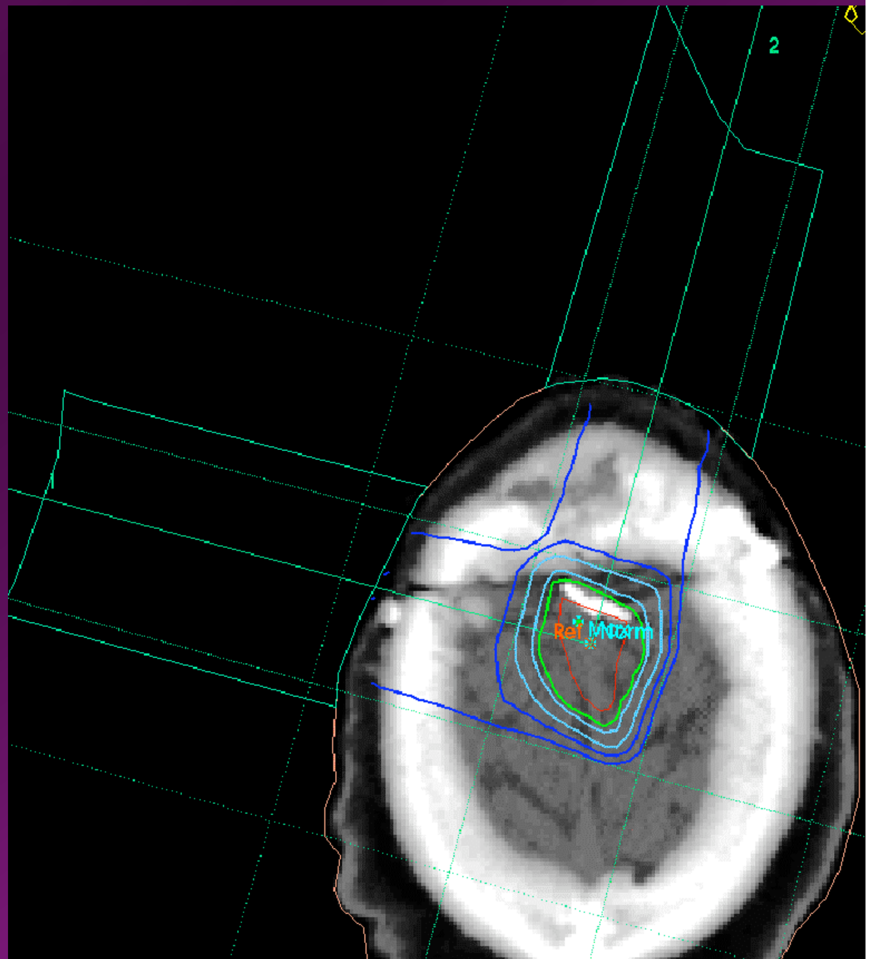


Dose plans



Meningeoma

2-field proton plan



Meningeoma

2-field proton plan

IMRT - solution

(Milker-Zabel, IJROBP 2007)

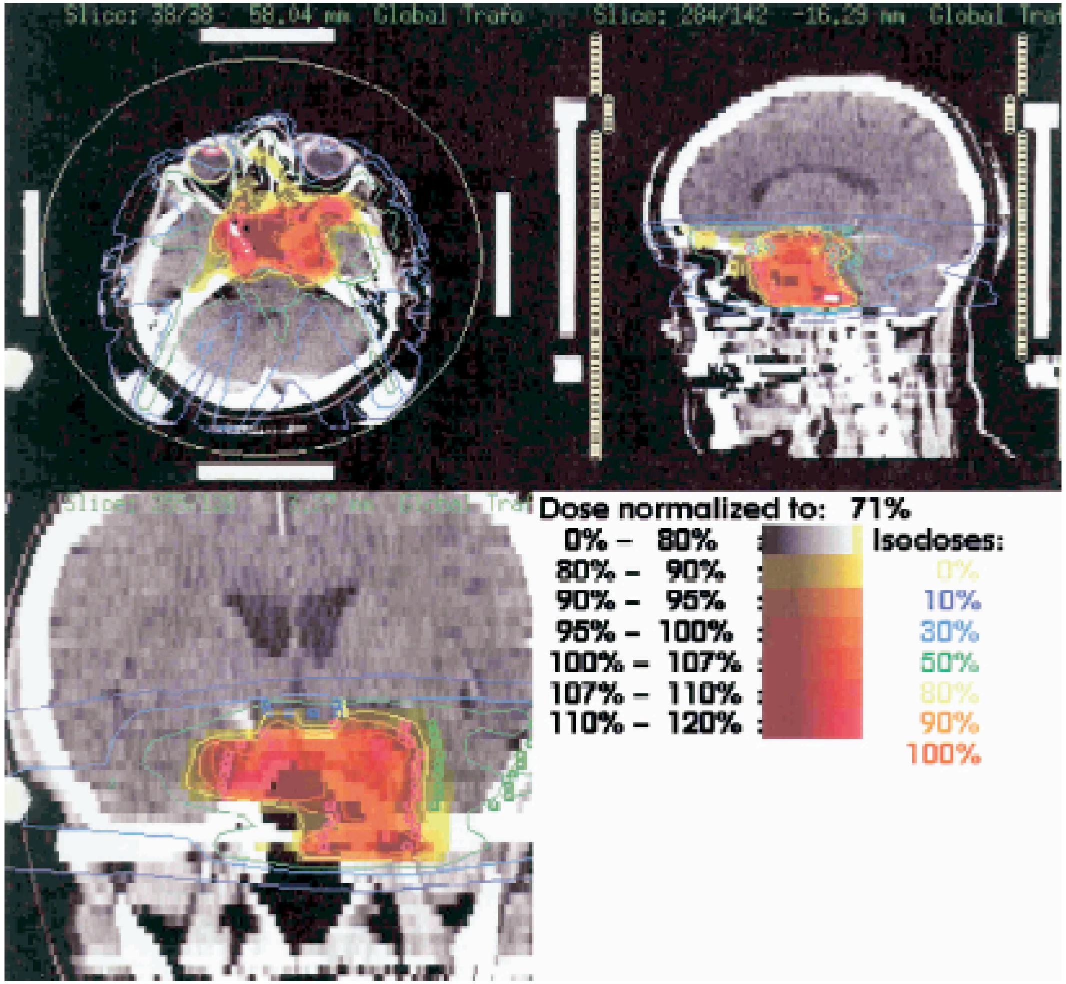


Fig. 1. Exemplary treatment plan of a patient with a World Health Organization Grade 1 meningioma of the left sphenoidal wing. Figure appears in color online.

Dose distribution photon-proton combination
Lopes et al, IJROBP, 2003

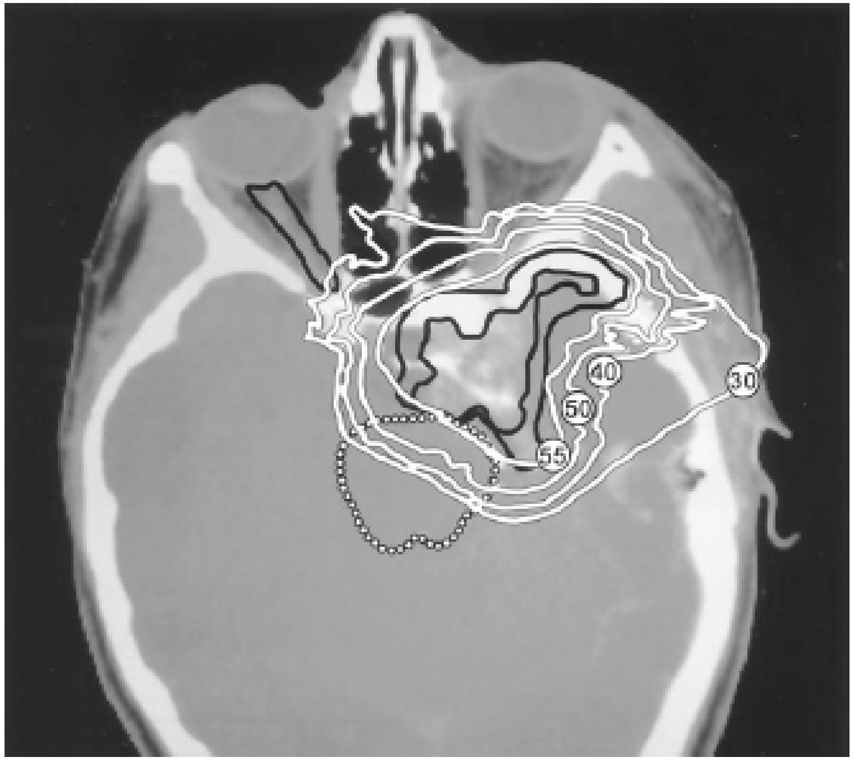
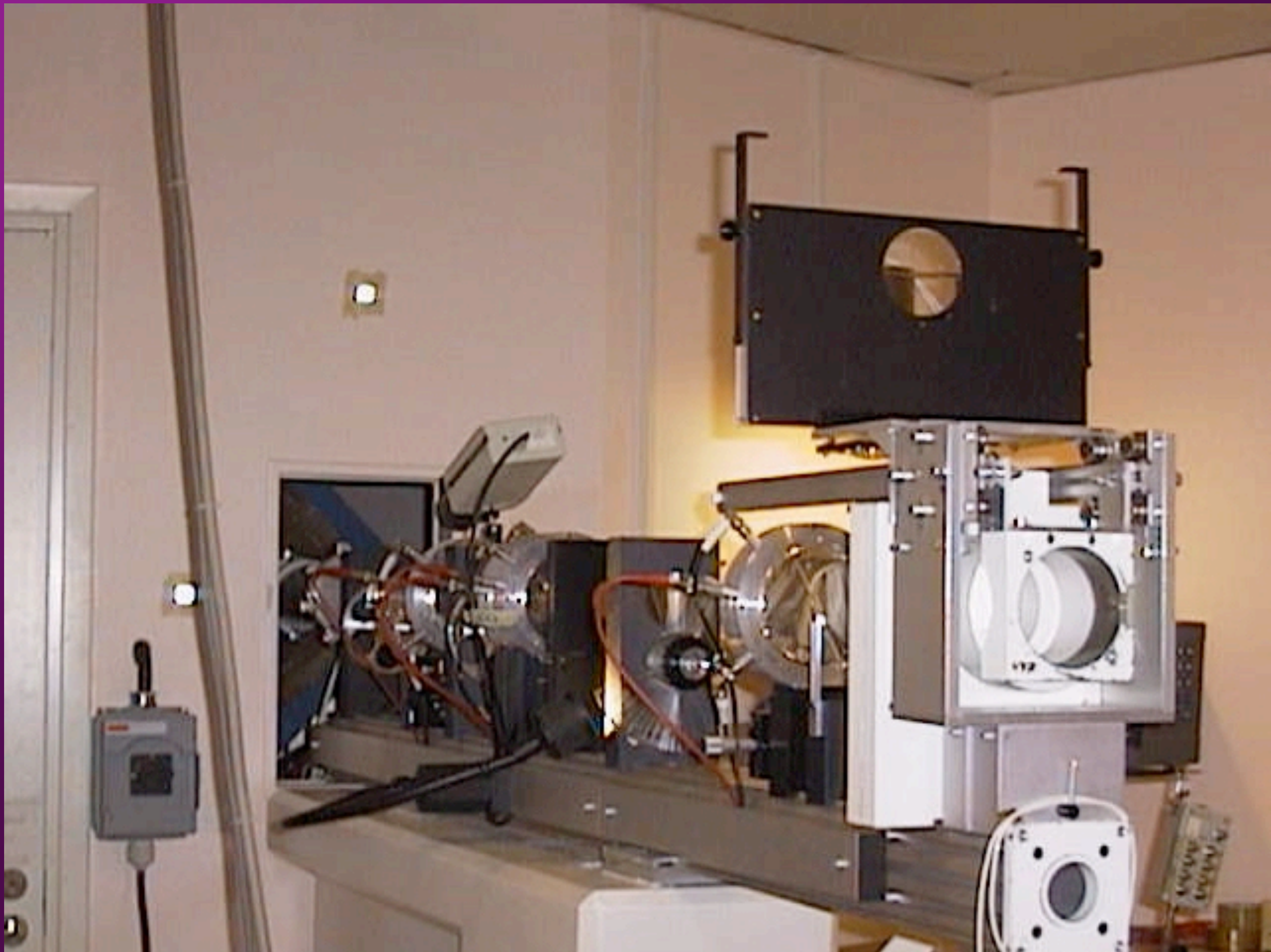


Fig. 1. Composite dose distribution to 55.8 CGE for the combined photon-proton technique. This plan incorporates 3 photon beams and 4 proton beams.

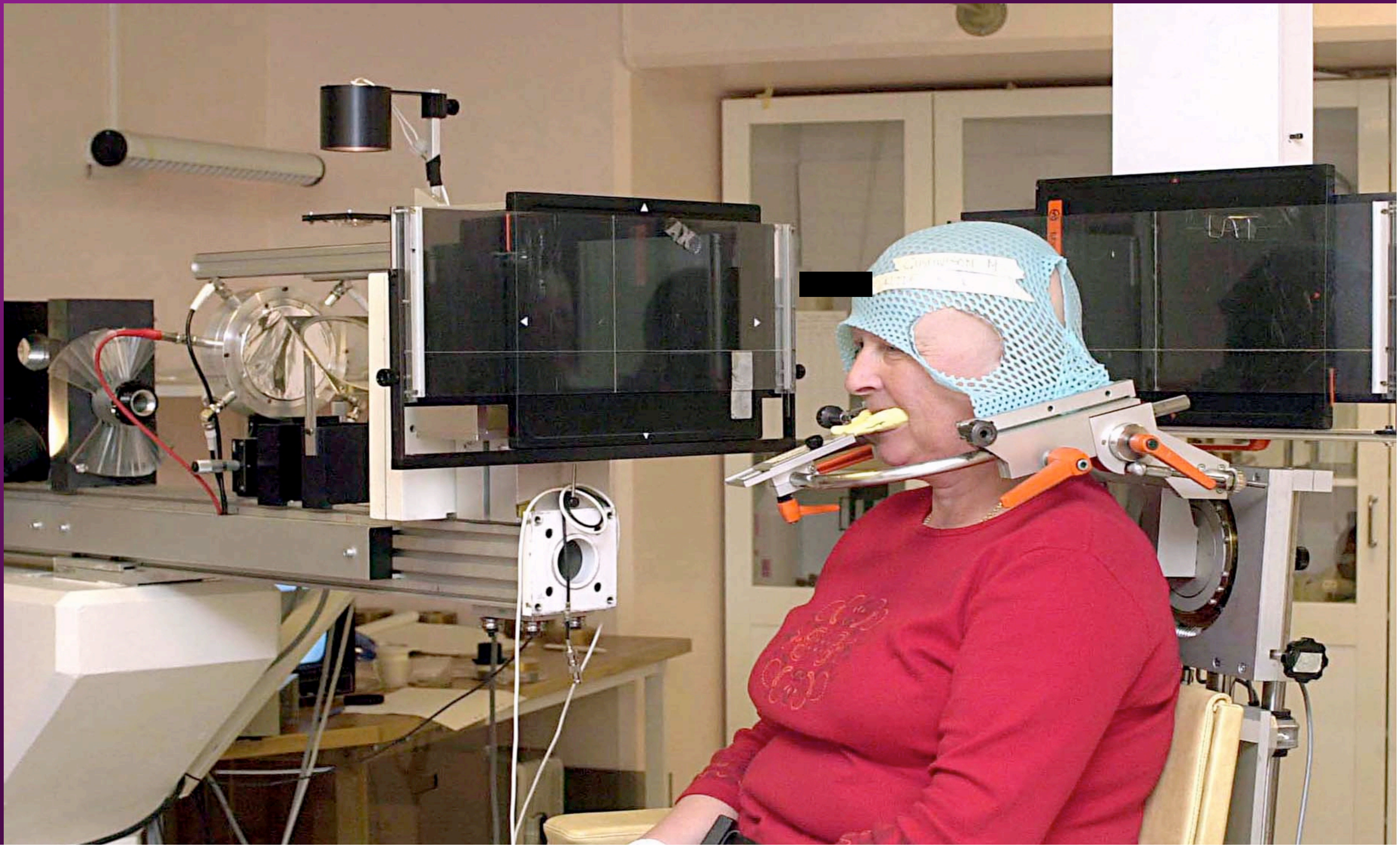
The Uppsala experience

- Seated patients
- Fixed beam
- Co-planar fields
- Restrictions in beam-time until June 2005
- Forced to find solutions with hypofractionation or boost in combination with photon techniques

The Optical Bench



Positioning and fixation

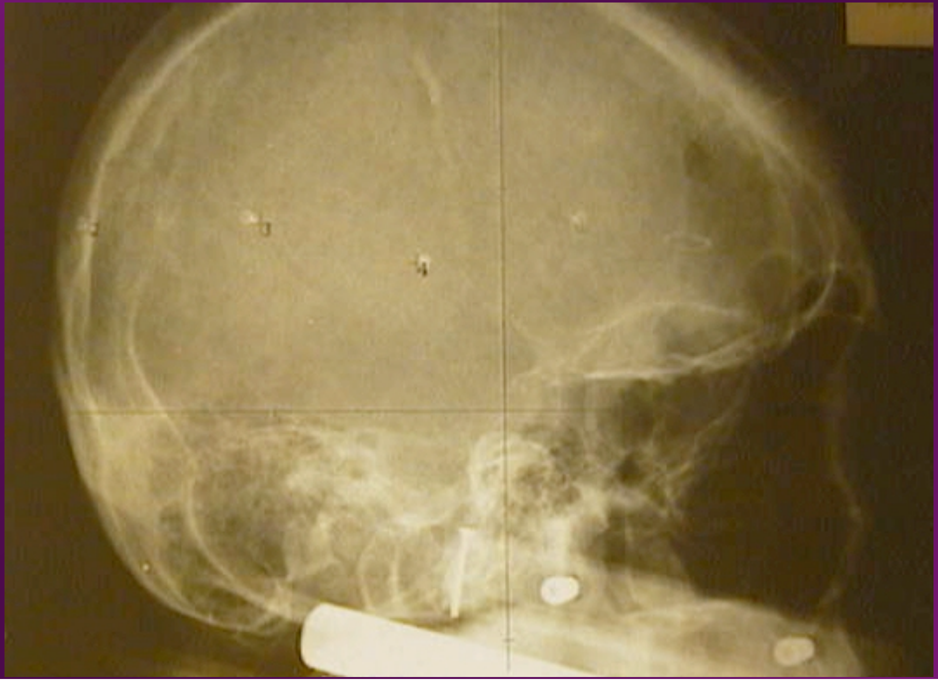


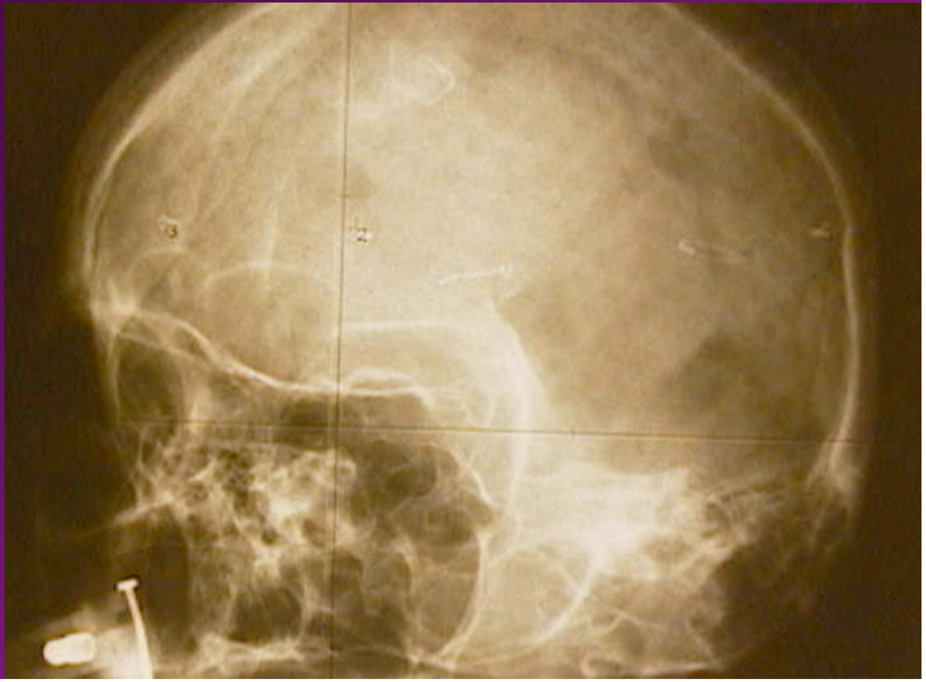
Positioning

* Fiduciual markers in the bone of the skull

* Isocentric position

* Two orthogonal x-ray images





Dose planning with protons

* Helax -TMS dose planning system
* Ray tracing and a semi-analytic pencil beam algoritm
* Same patient data as for planning with photons and elektrons

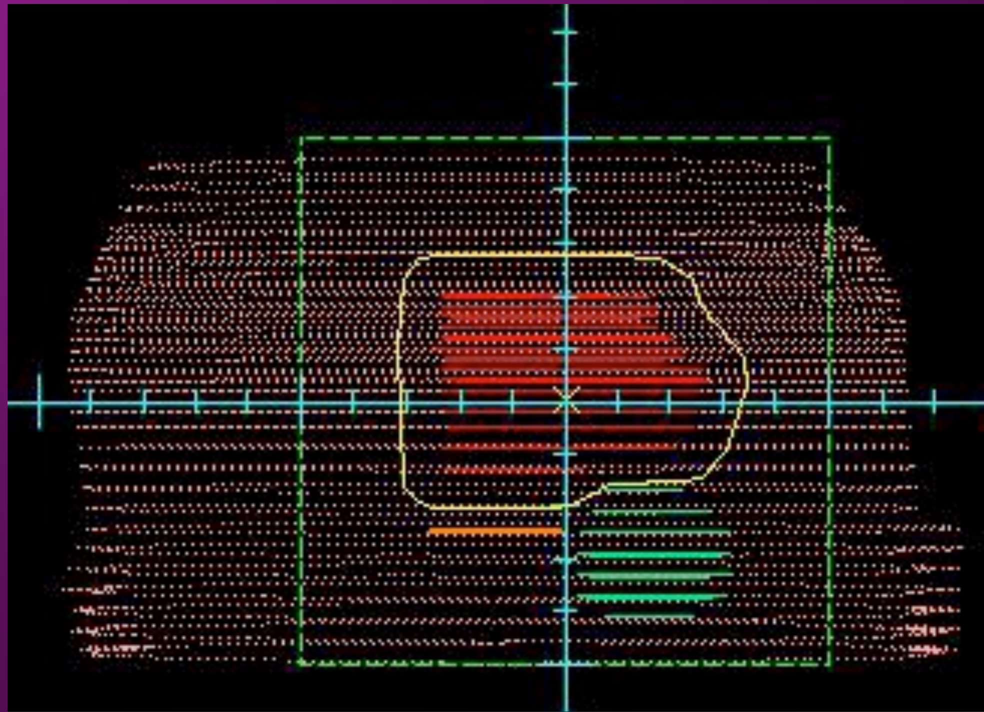
Dose planning with protons

- A comparison with ”conventional photons”

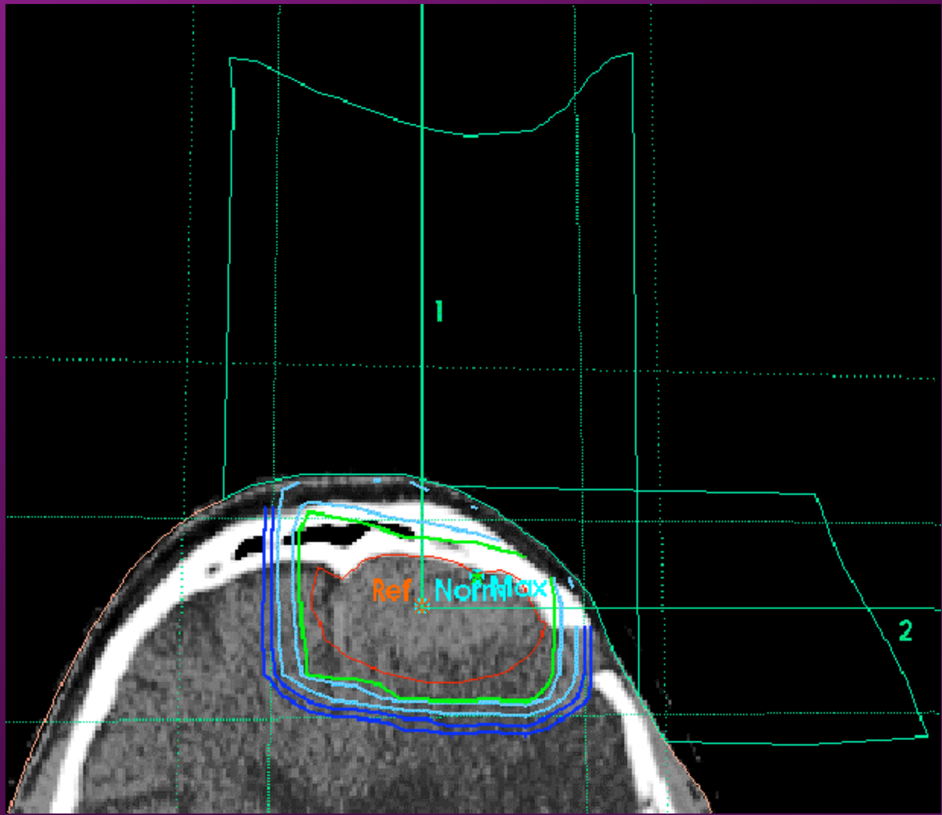
* All fields must have:

  - an individually made collimator
  - a range modulator
  - a range compensation filter

Collimators



Range compensation filters



Evaluation of results

- Change in volume over time
- Progression or shrinkage measured in mm?
- Relief of symptoms or upcoming of new symptoms
- Avoidance of reoperation
- Progression-free survival
- Survival

Results

- No phase III study exists (?)
- Many authors claim shrinkage of meningioma after certain time intervals
- Long term follow-up is necessary – 10 years or more!
- Prolongation of survival after successfull treatment?

Results 2

- Local control rate SRS 75 – 100% at 5 – 10 years
- External Beam Radiation Therapy – 10 year recurre nce-free survival = 100% (!). Debus 2002
- Optic nerve sheath meningiomas – only EBRT – overall disease control is 95 % (!)
- Recurrent meningiomas 78 % 8-year PFS in patients with surgery and EBRT vs 11 % surgery alone (Miralbell 1992)

Proton therapy of m eningeoma patients 1994 - 2003

81 patients

M/F 19/62

Mean age: 54.1 y Range: 22 - 85 y

Dose: Fractional dose: 5 – 6 Gy Total dose: 20 – 24 Gy

Results: 76 patients without progressive disease

Complications:

1 progressive disease

3 reoperations: development of a cyst, patients own wish, growth outside primary target

1 partial temporal lobe necrosis: mainly not in the treatment field

Suggested publications

Stereotactic irradiation of Skull Base Meningiomas with High Energy Protons

O. Gudjonsson, E. Blomquist, G. Nyberg, L. Pellettieri, A. Montelius, E, Grusell, C. Dahlgren, U. Isacsson, A. Lilja och B. Glimelius.

Acta Neurochir (Wien) 141: 933 – 940, 1999.

Evaluation of the effect of high-energy proton irradiation treatment on meningiomas by means of 11-C-L-methionine PET.

O. Gudjonsson, E. Blomquist, A. Lilja, H. Ericsson, M. Bergström and G. Nyberg.

European Journal of Nuclear Medicine 27(12): 1793 – 1799, 2000

Suggested publications

The potential of proton beam radiationtherapy in intracranial and ocular tumours.

Blomquist E, Bjelkengren G, Glimelius B.

Acta Oncol. 2005;44(8):862-70. Review.

Thank You for Your attention!

A short History of Proton Beam Therapy

1946 Wilson suggests high energy protons for radiotherapy

1954 First patient treated with protons at Berkley

1957 First cancer in a patient treated with protons in Uppsala

1961 First patient treated at the Harvard cyclotron

1989 Treatment restarted in Uppsala

1990 First hospital-based proton beam facility at Loma Linda, CA, USA

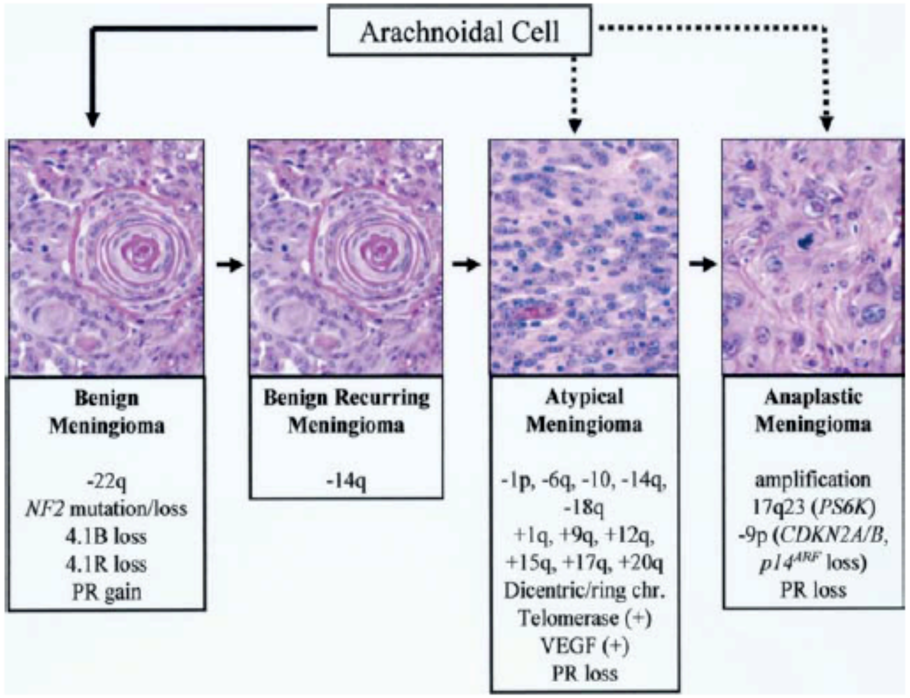


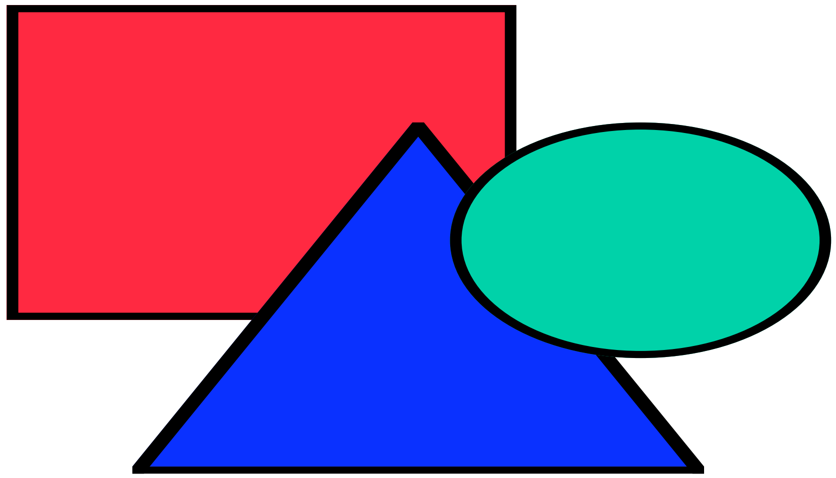
Figure 10. Current molecular model of meningioma tumorigenesis and malignant progression. The cell of origin is suspected to be either the arachnoidal cap cell or an earlier meningothelial progenitor cell. Progression from benign to atypical to anaplastic has been well documented, though direct transformation from a precursor cell to a more aggressive form of meningioma (dotted lines) is probably more common. Genetic alterations thought to be involved at each step are listed.

(*pl6*^{INK4a}), *p14*^{ARF}, and *CDKN2B* (*p15*^{INK4b}) tumor suppressor genes on 9p21 are associated with

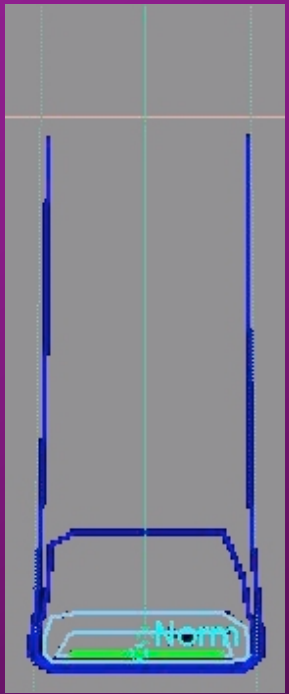
motility, growth, proliferation, and differentiation. For example, as a mechanism of bypassing cellular

”Stereotactic fractionated therapy”

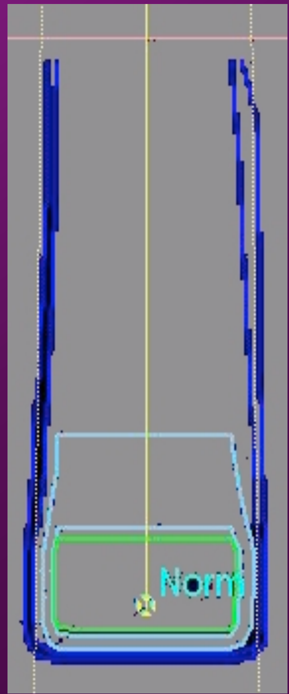
(Candish et al., IJROBP 2005)



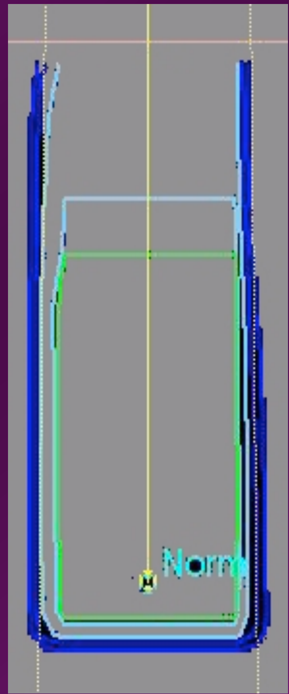
Range modulators



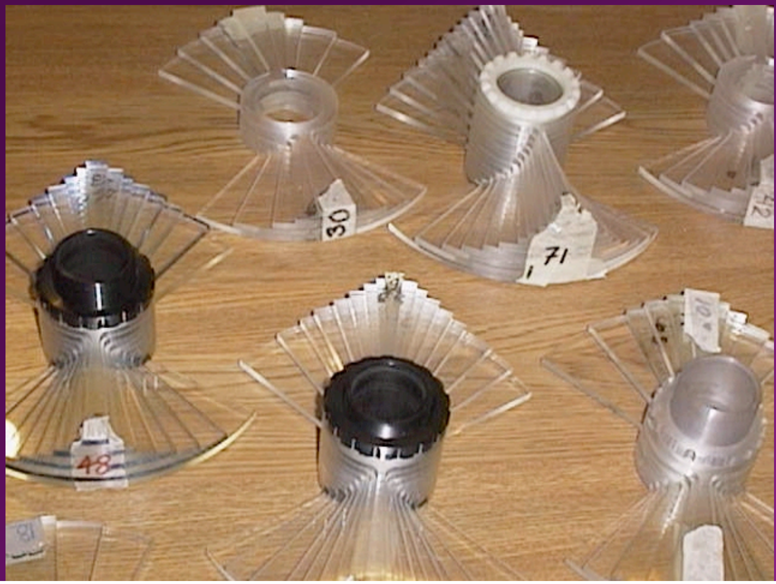
RM0



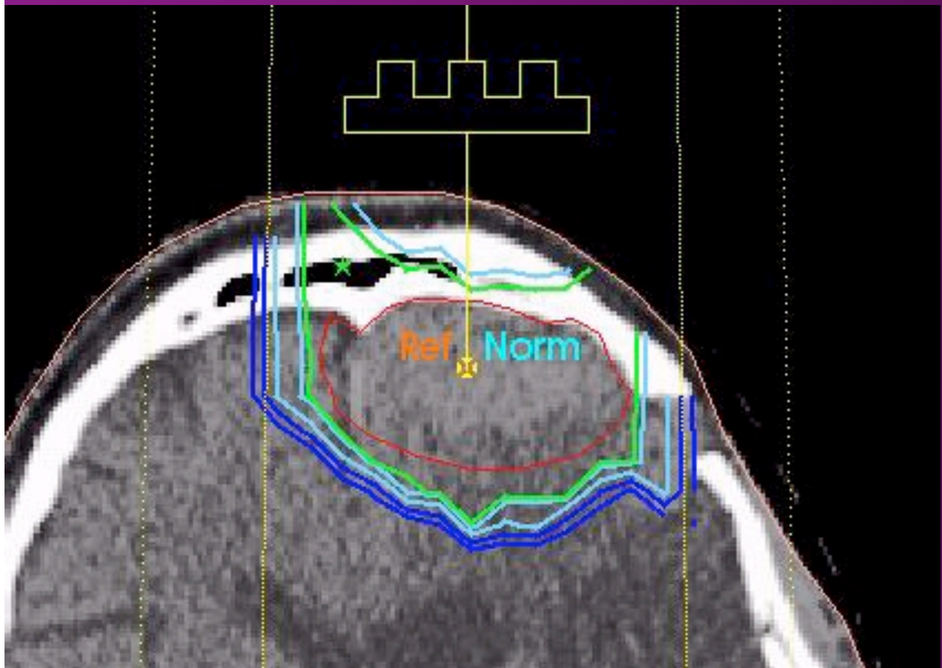
RM18

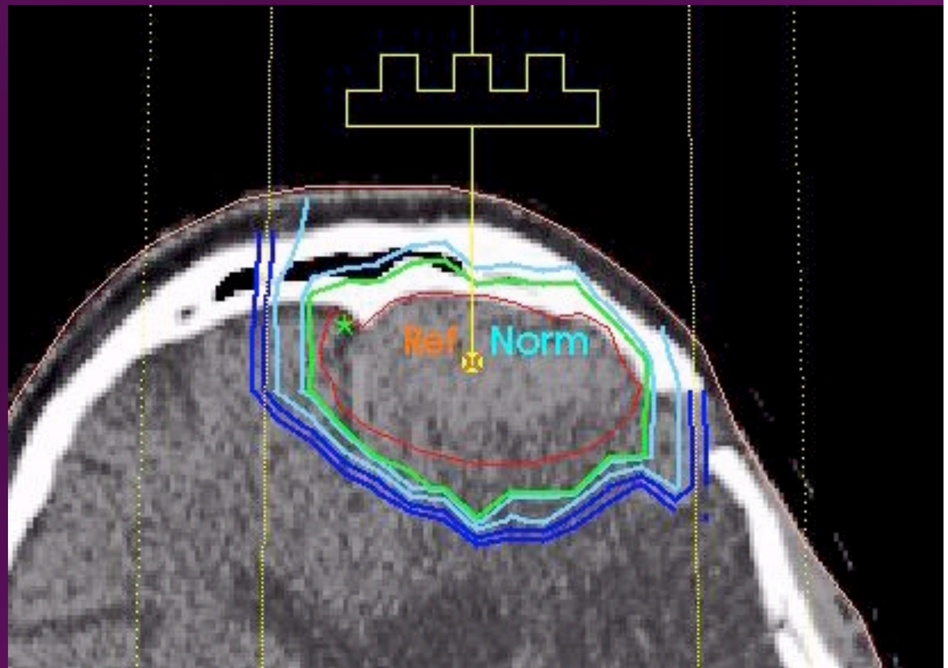


RM71



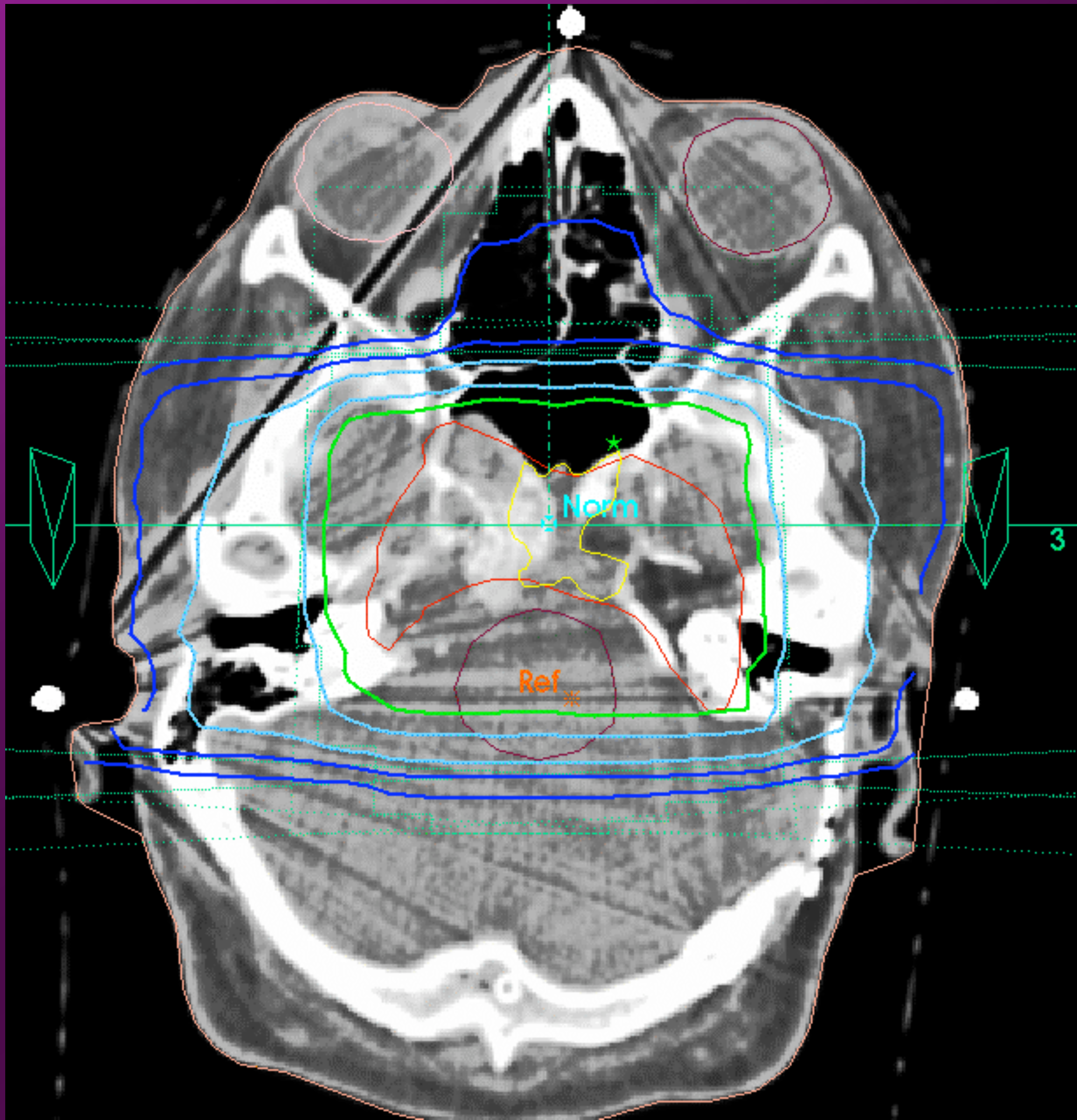
Automatically defined range compensators

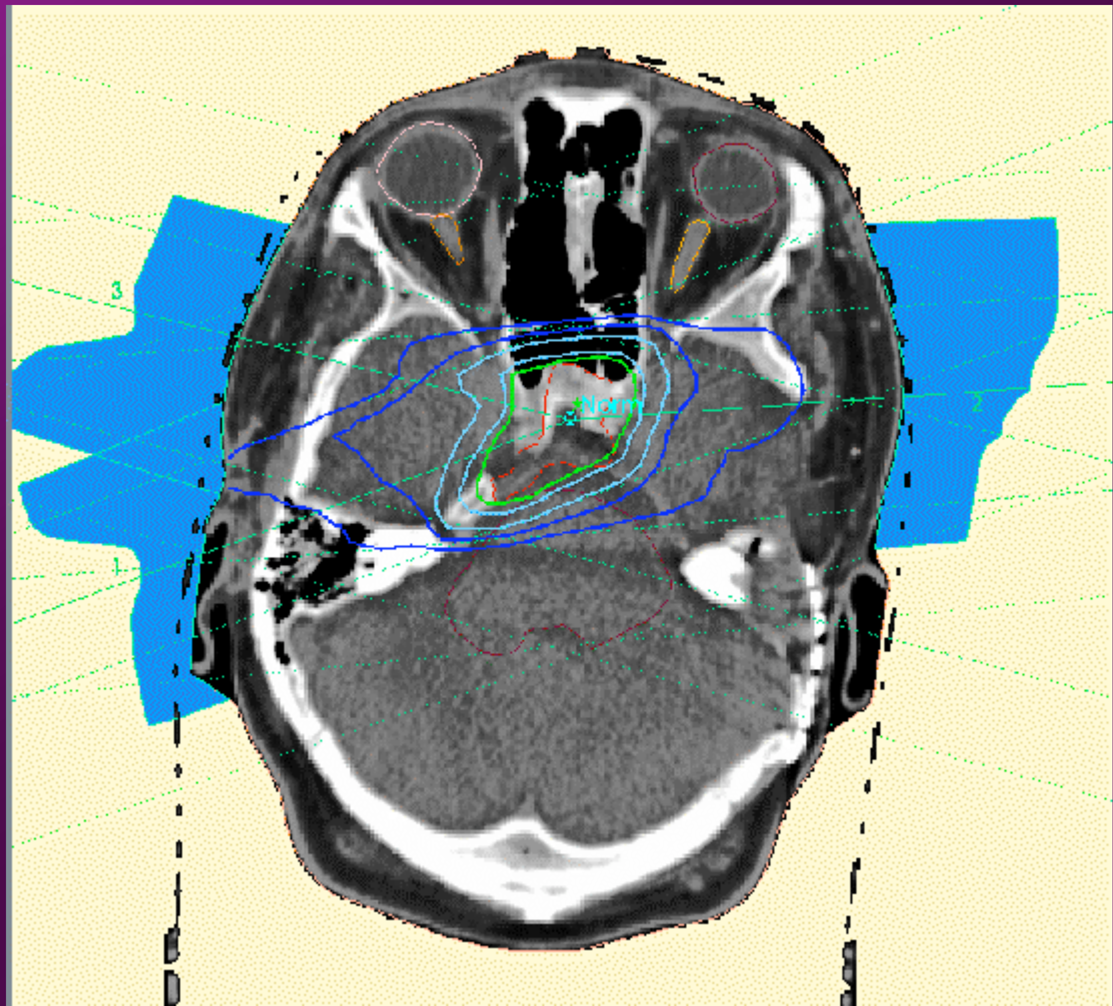




Fixed range modulator

Variabel range modulator


Norm
Ref
3


3
1
2
Norm

Proton beam radiotherapy at TSL

4 fractions/month
Intracranial and subcranial targets
Tumors in the spine or with paraspinal location
Prostate cancers

Benign targets

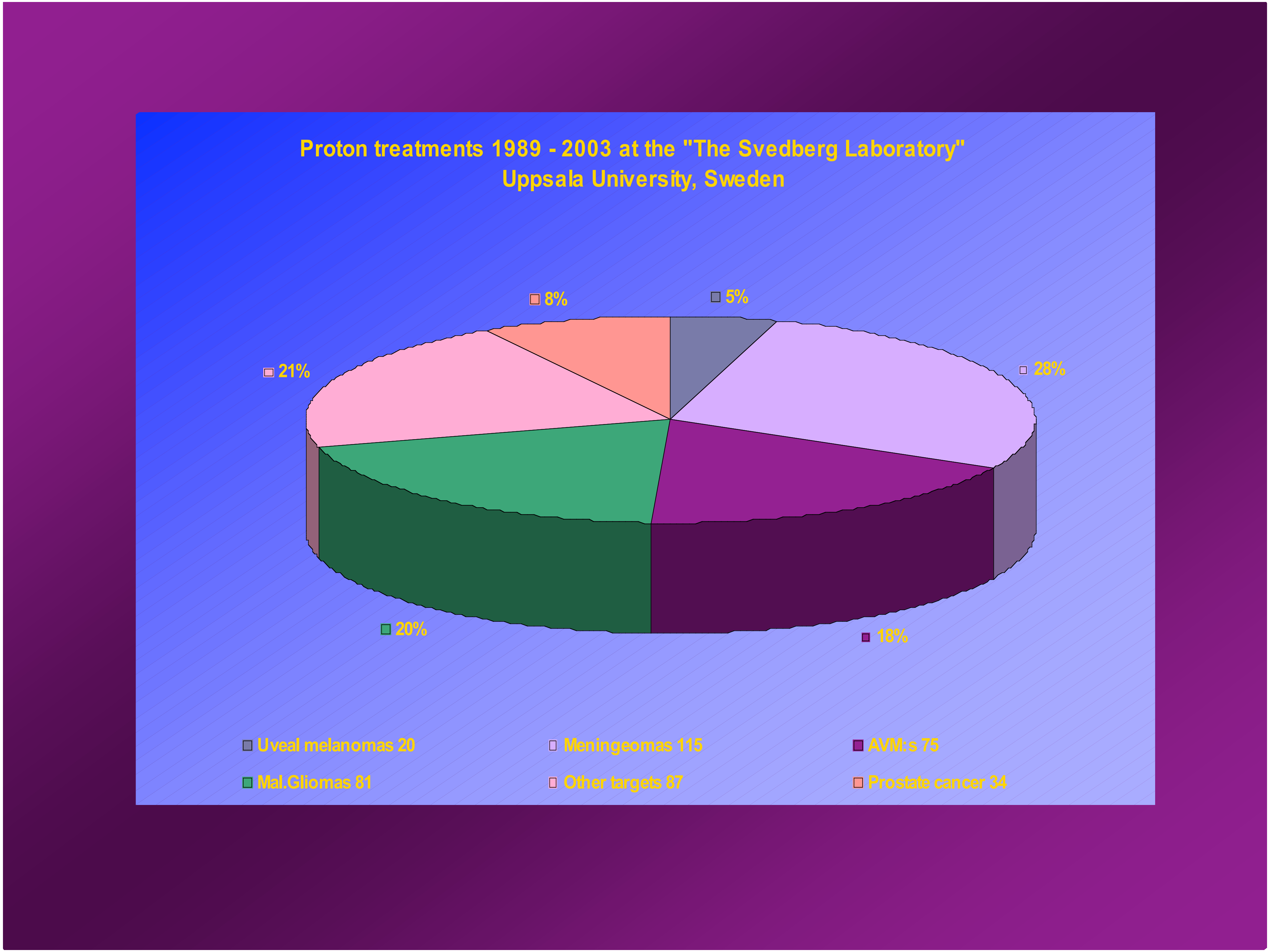
- Just protons
  - AVM:s
  - Meningeomas
  - Pituitary tumors

Malignant targets

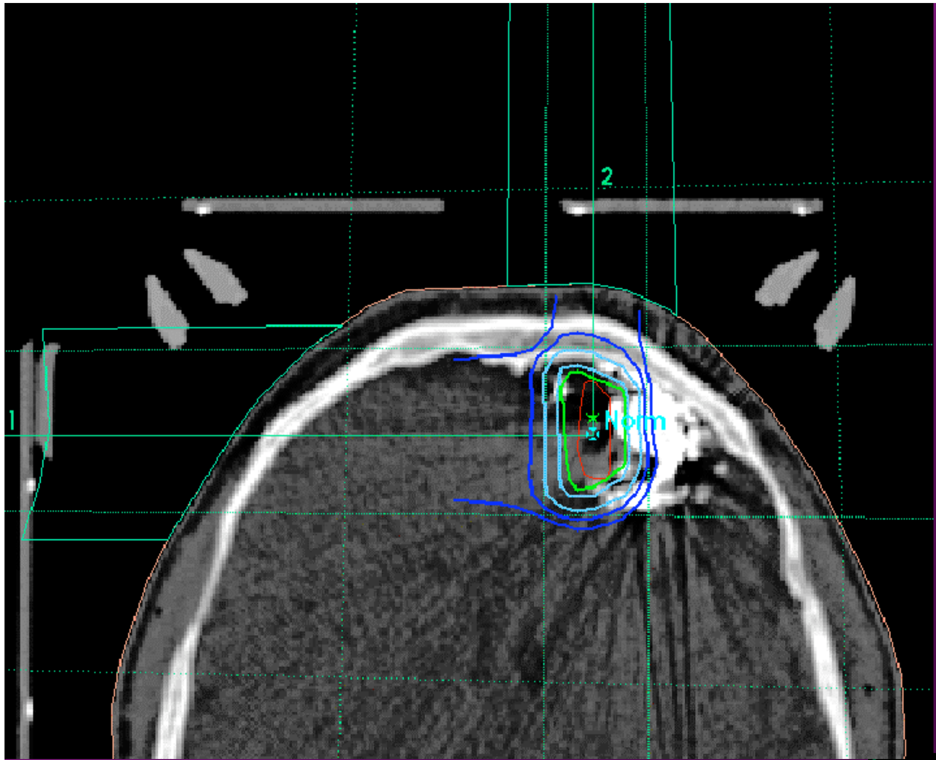
- Just protons
  - Metastases
  - Uveal and iris melanomas

- Protons as a boost
  - Malignant gliomas
  - Chordomas and chondrosarcomas
  - Head-and-neck cancers
  - Prostate cancers

EB/2004



Proton treatments 1989 - 2003 at the "The Svedberg Laboratory"
Uppsala University, Sweden
5%
28%
18%
20%
21%
8%
Uveal melanomas 20
Meningeomas 115
AVM:s 75
Mal.Gliomas 81
Other targets 87
Prostate cancer 34

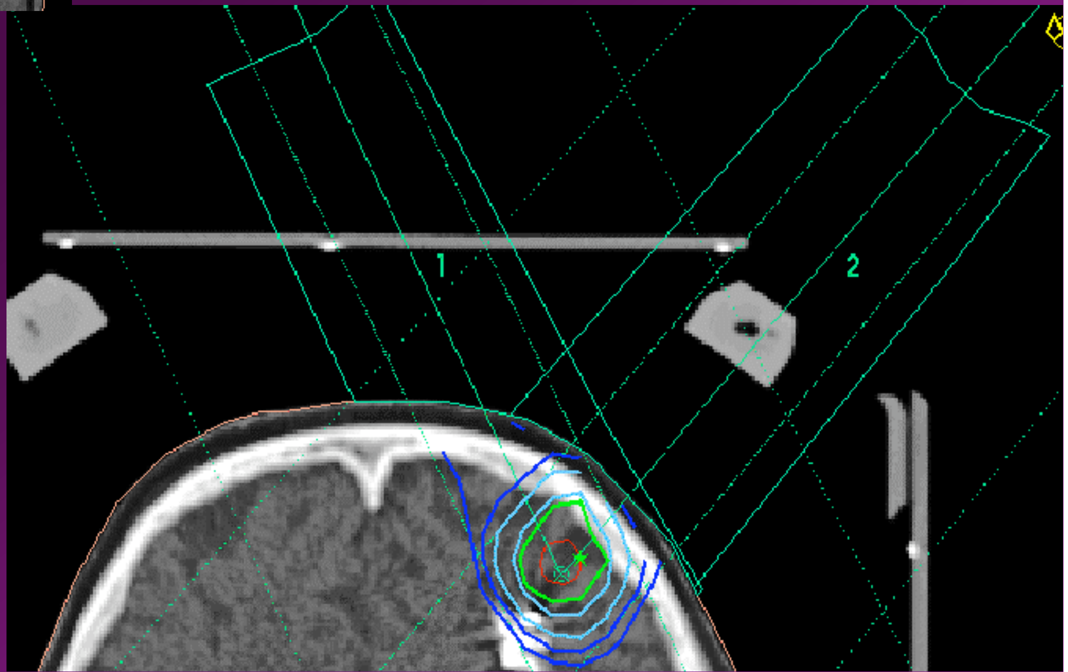


AVM (arterio venous malformation)

2-field proton plan

AVM (arterio venous malformation)

2-field proton plan



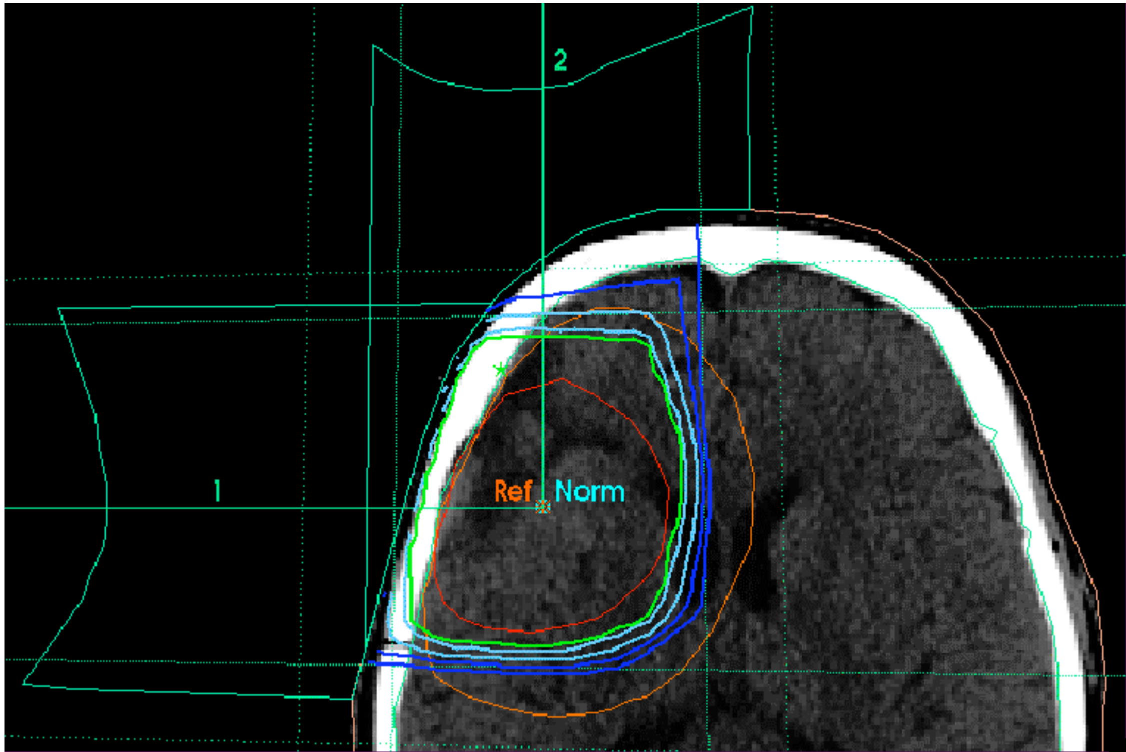
Arteriovenous malformations
(AVM:s)

First 60 patients

M/F 25/35

Mean: 43.2 y

Range: 9 – 69 y



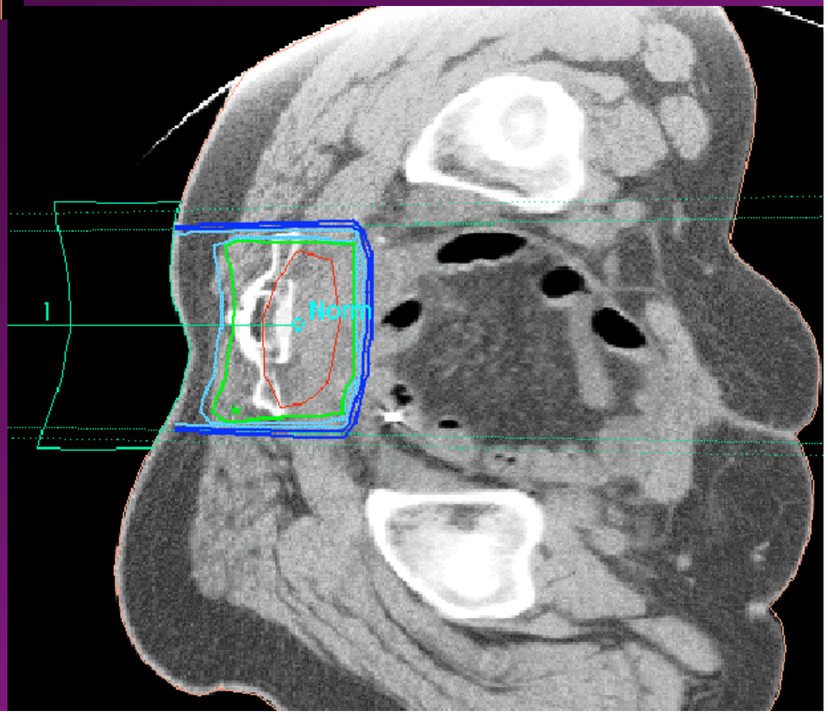
Glioma

2-field proton plan

boost therapy

Rectal cancer
(Lokal recurrence)

1-field proton plan



Malignant gliomas I

First 37 patients: M/F 15/22

Mean: 52.3 y   Range: 28 – 74 y

20 Astrocytoma grade IV

Escalation of photons + protons:

Photons: Fraction: 2 Gy   Total: 50 - 60 Gy

Protons: Fraction: 4 – 6 Gy   Total: 16 - 24 Gy

Target volumes: 13 – 146 cm^3

Mean survival: 15.6 mo

Malignant gliomas II

Next 39 patients: M/F 17/22

Mean: 49.5 y Range: 16 – 68 y

Dose: Photons 2 Gy to 60 Gy Protons: 6 Gy to 24 Gy

Diagnoses:

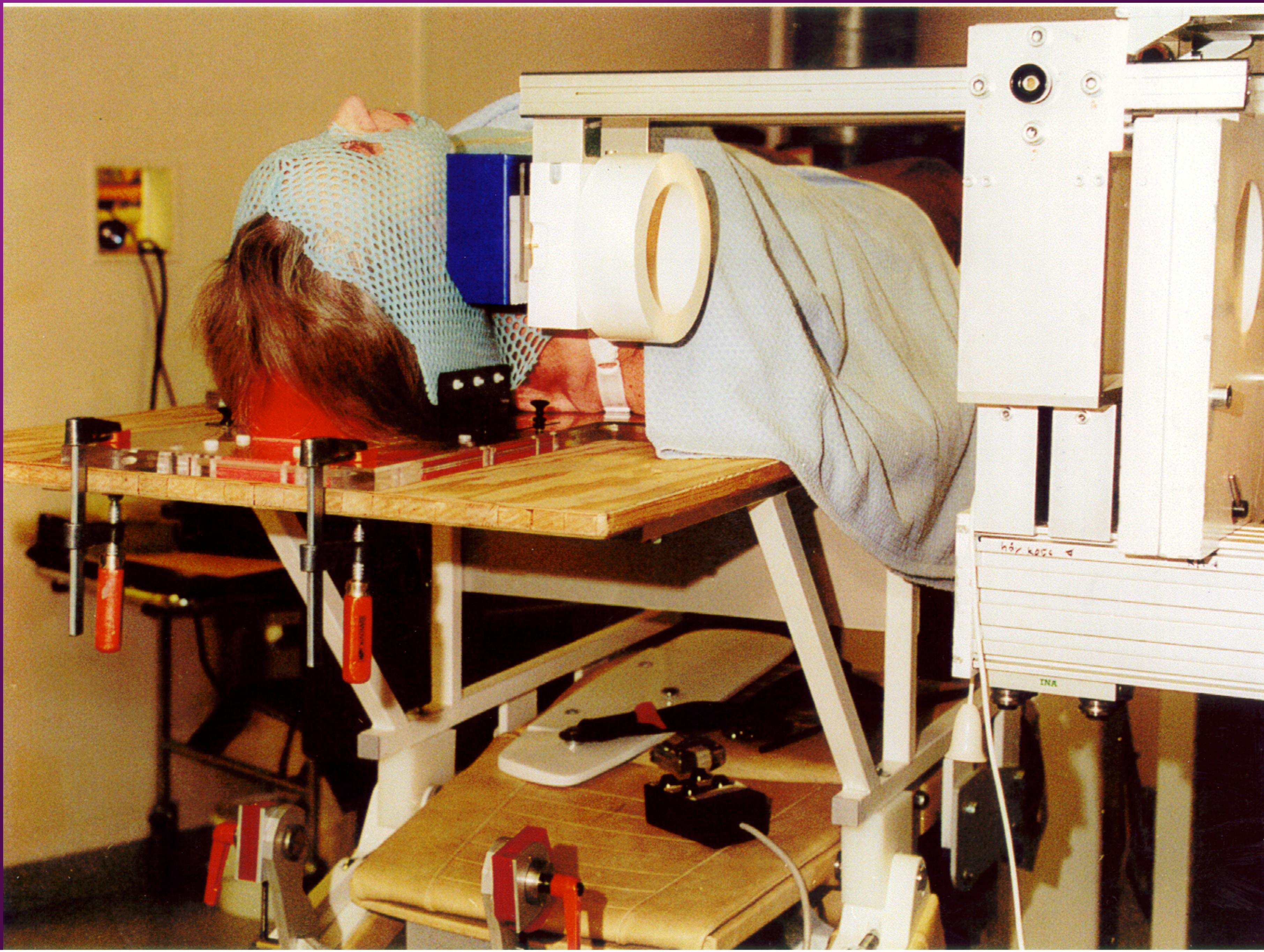
23 Astrocytoma grade IV

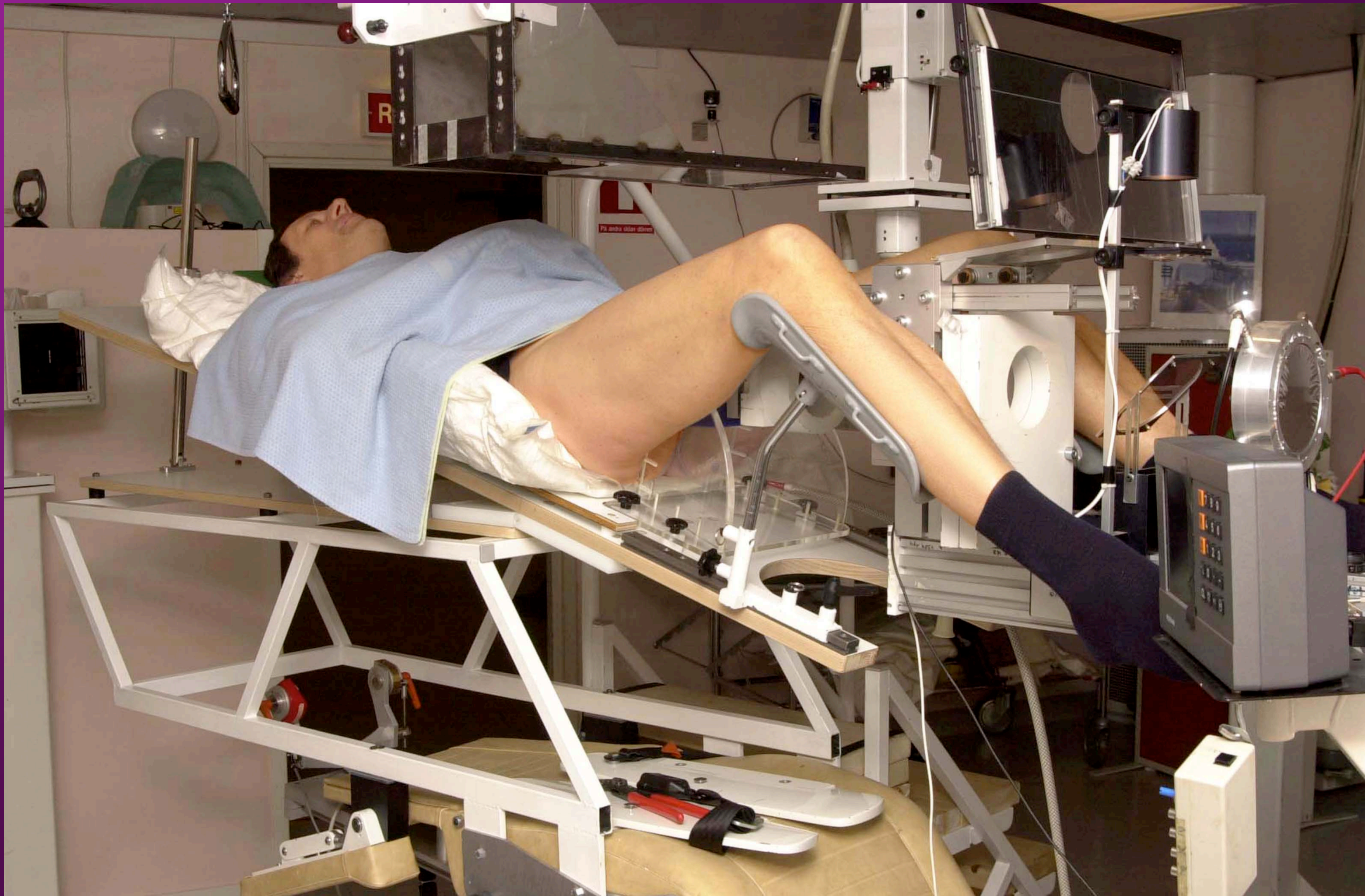
9 Astrocytoma grade III

Target volumes: 29 – 301 cm^3

Mean survival: 13.7 mo

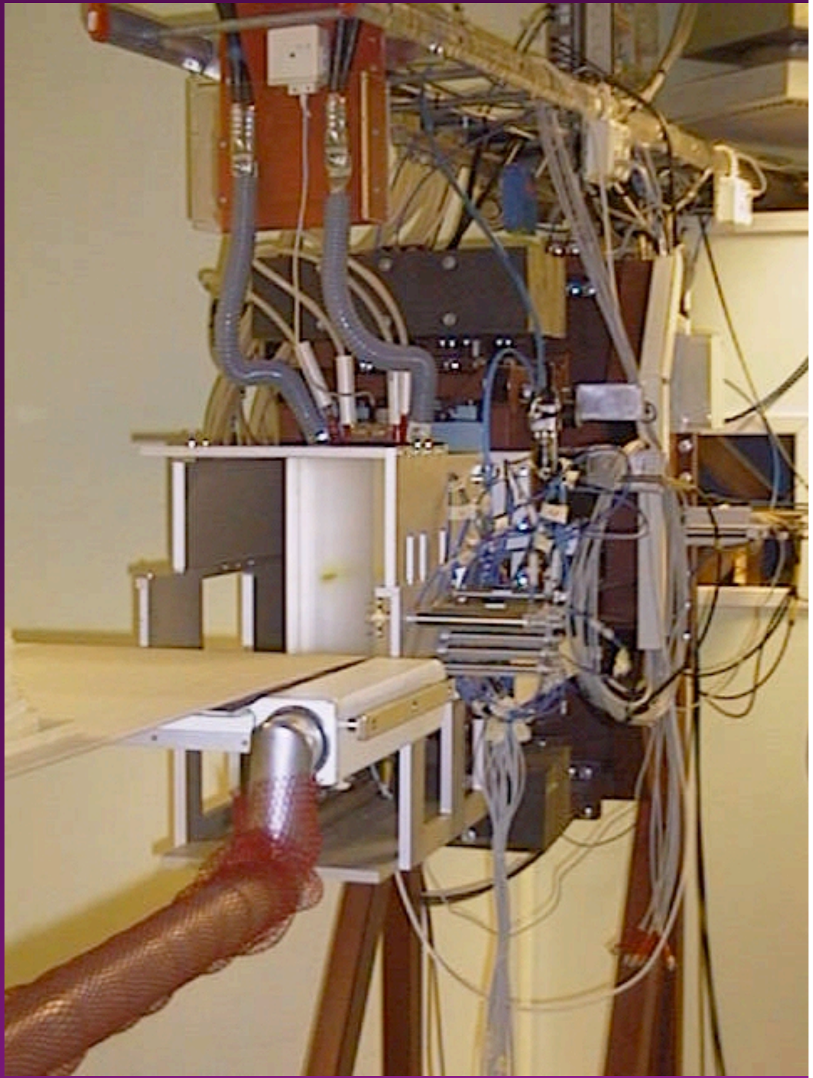
EB/2003

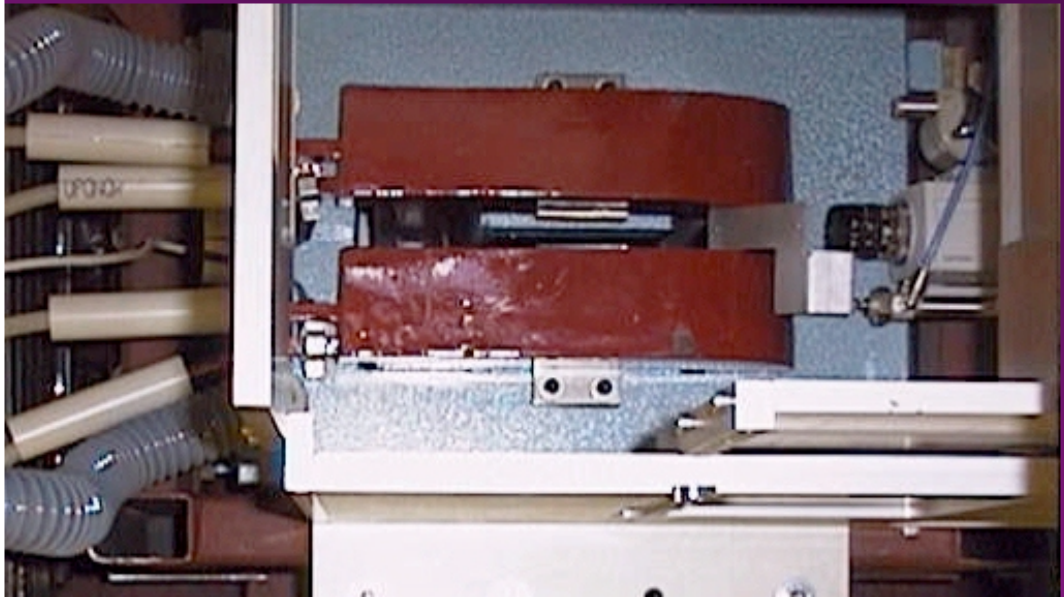




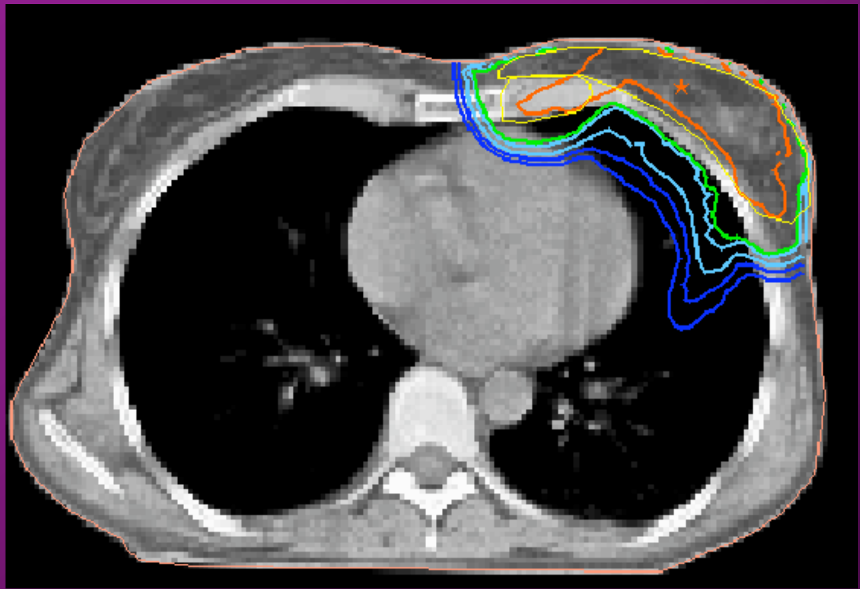
A scanning Proton Beam

* FWHM 5 mm
* Magnetic scanning of the beam
* Field sizes 30 x 30 cm
* Variable range modulation
* IMRT with protons

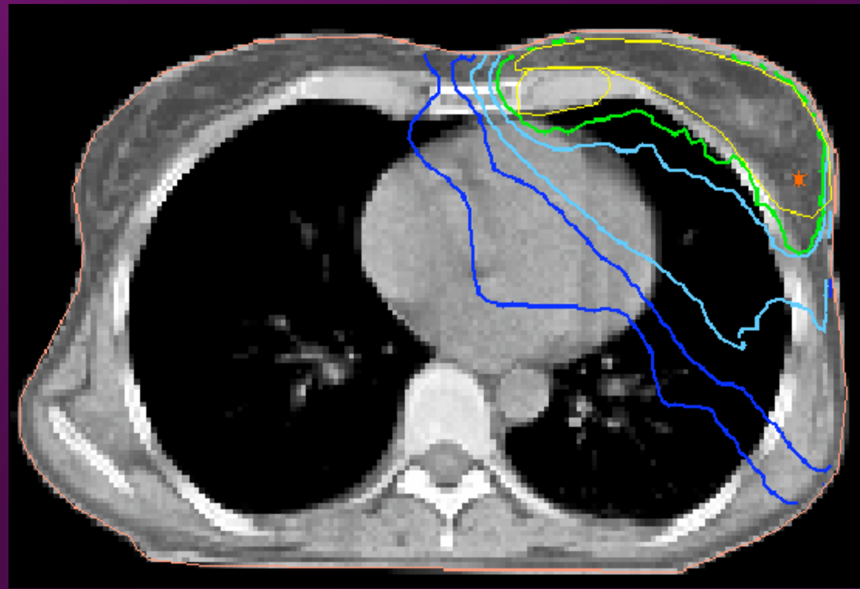




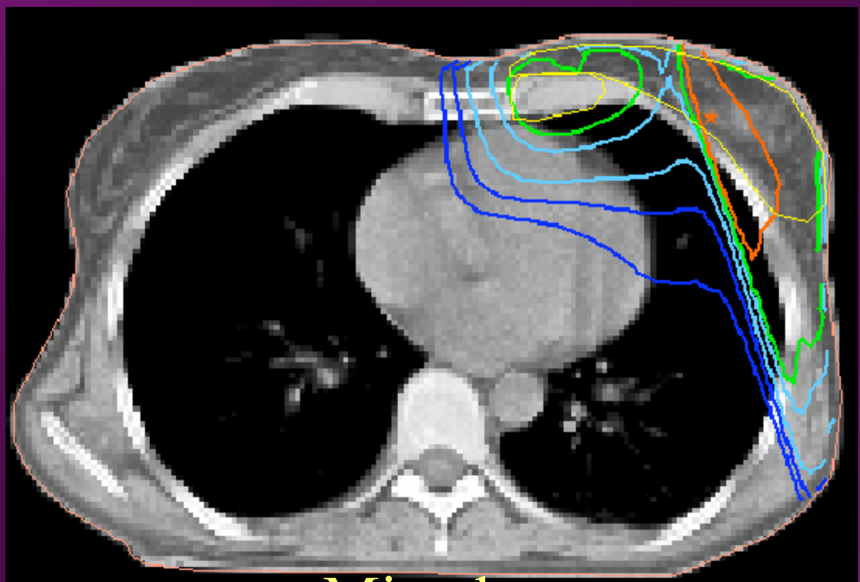
Patient with breast cancer and engaged axillary lymph nodes



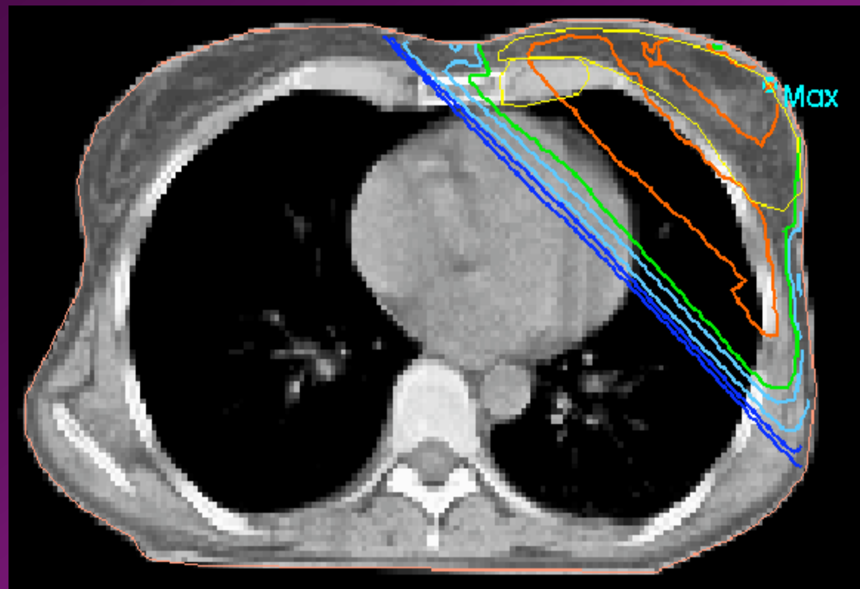
Protons



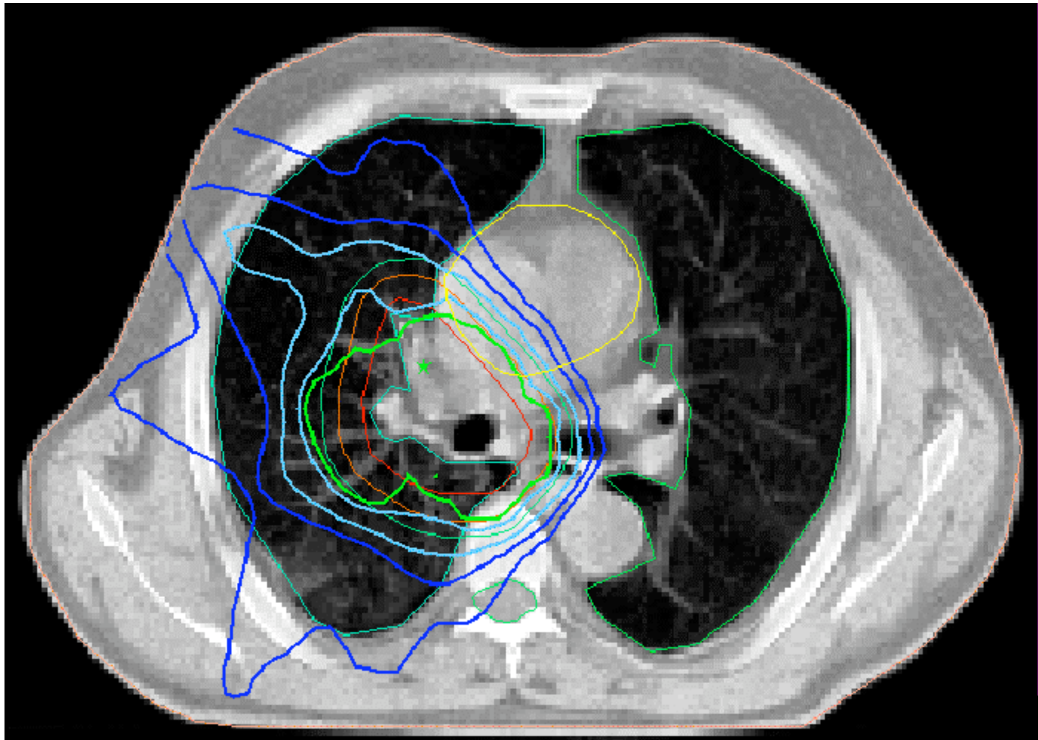
IMRT



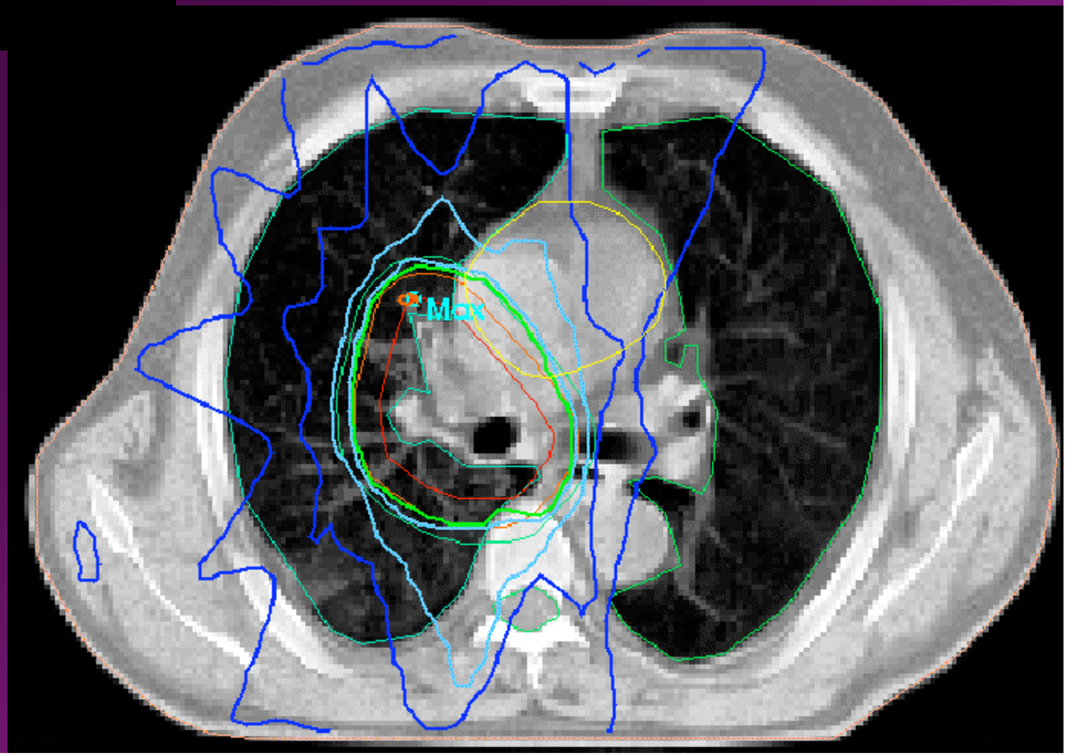
Mixed



Tangential

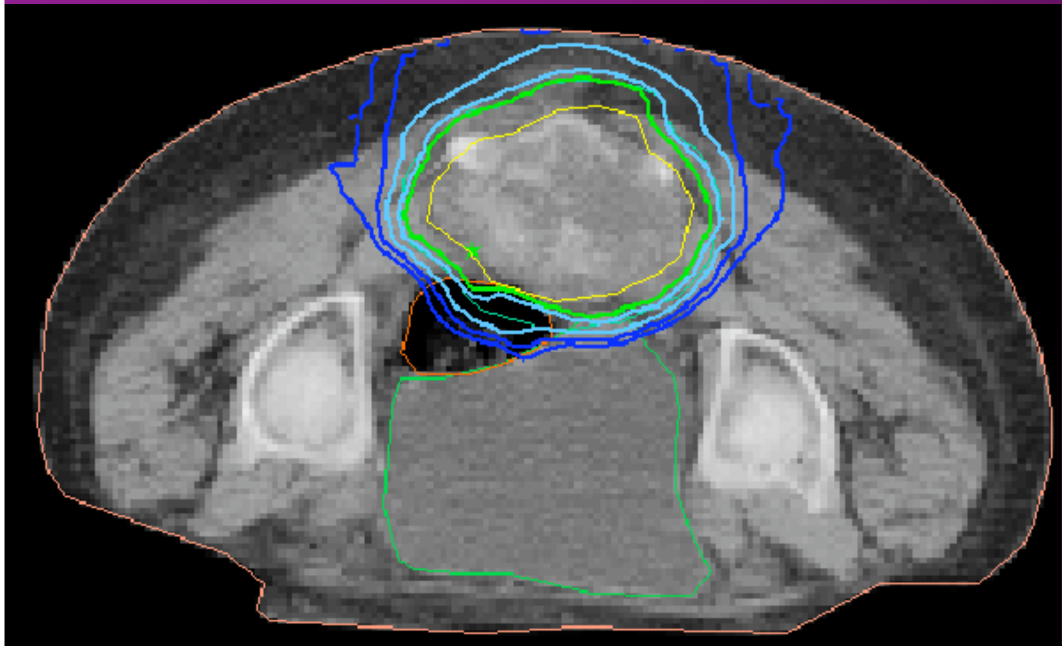


3-field proton plan

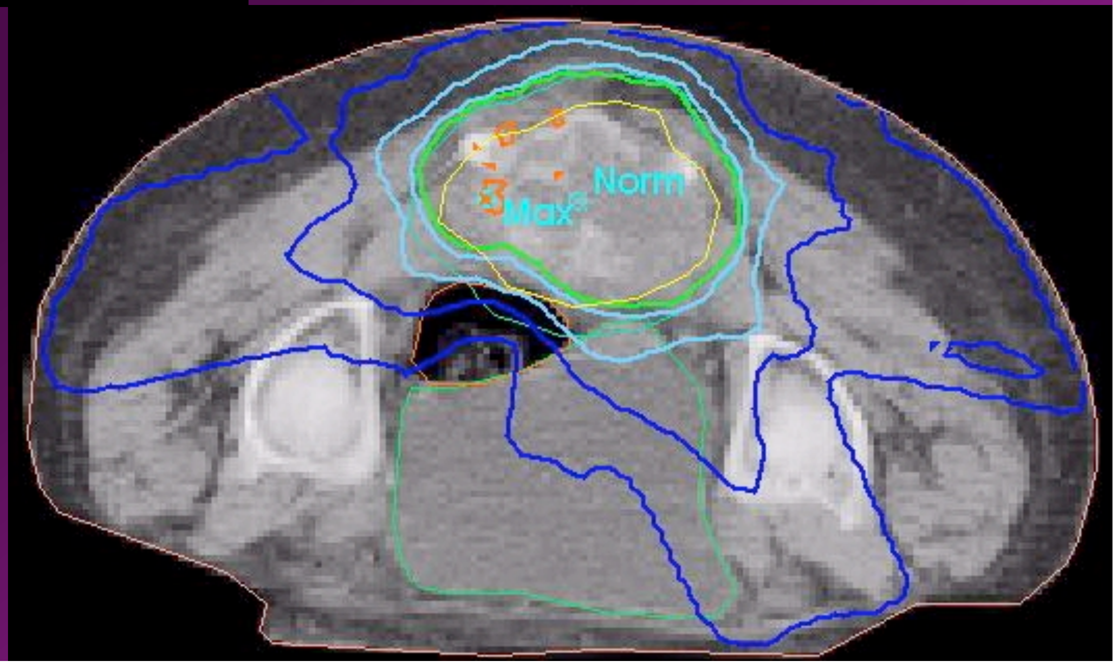


7-field IMRT plan

Comparing dose plans



3-field proton plan



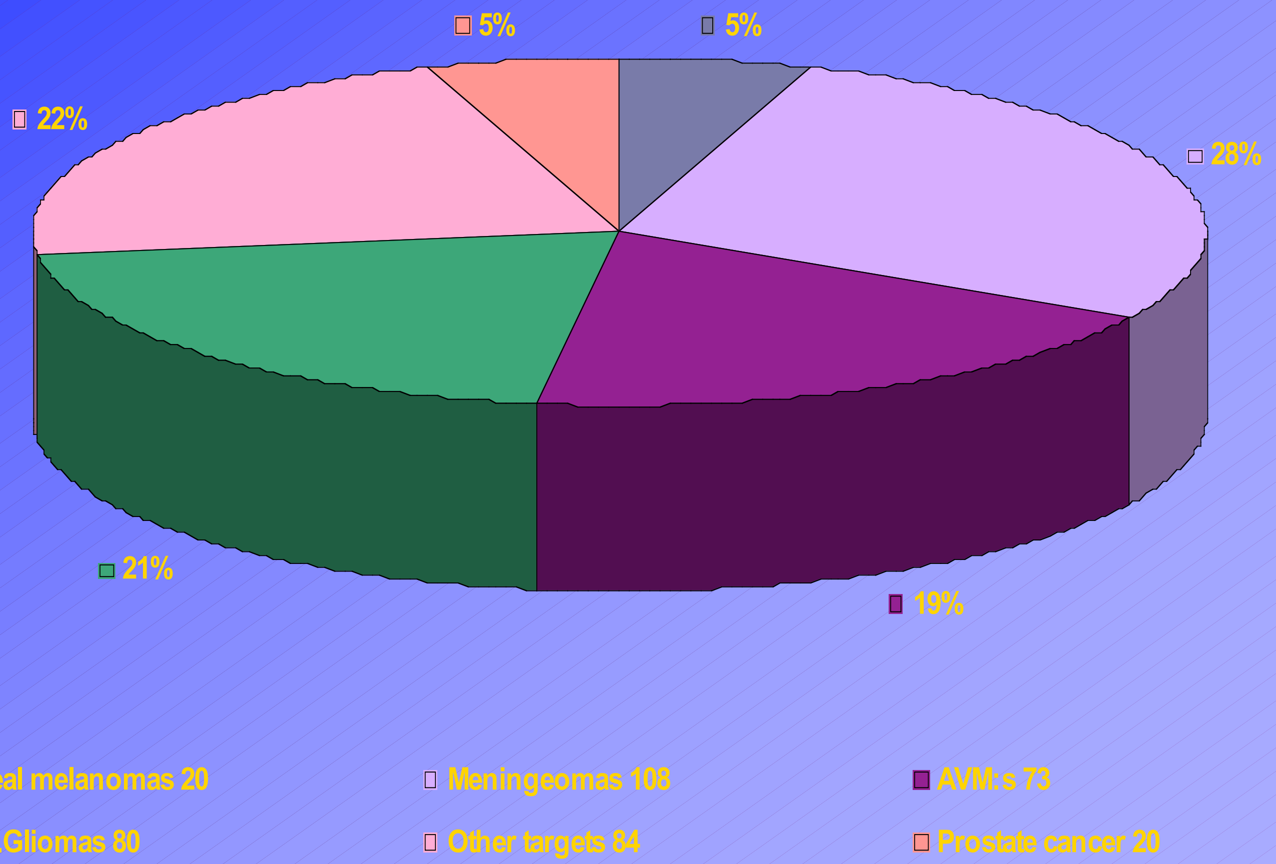
7-field IMRT plan

Välkomna till Uppsala!

Welcome to Uppsala!

Herzlich willkommen in Uppsala!

Proton treatments April 1989 - June 2003 at the "The Svedberg Laboratory", Uppsala University, Sweden



Important messages

- Opens up for hypofractionation
- Diminsh ”radiation load” on surrounding normal tissue.
- If hypofractionation – shortening of overall time for treatment

Radiobiology

1. According to LQ- model:

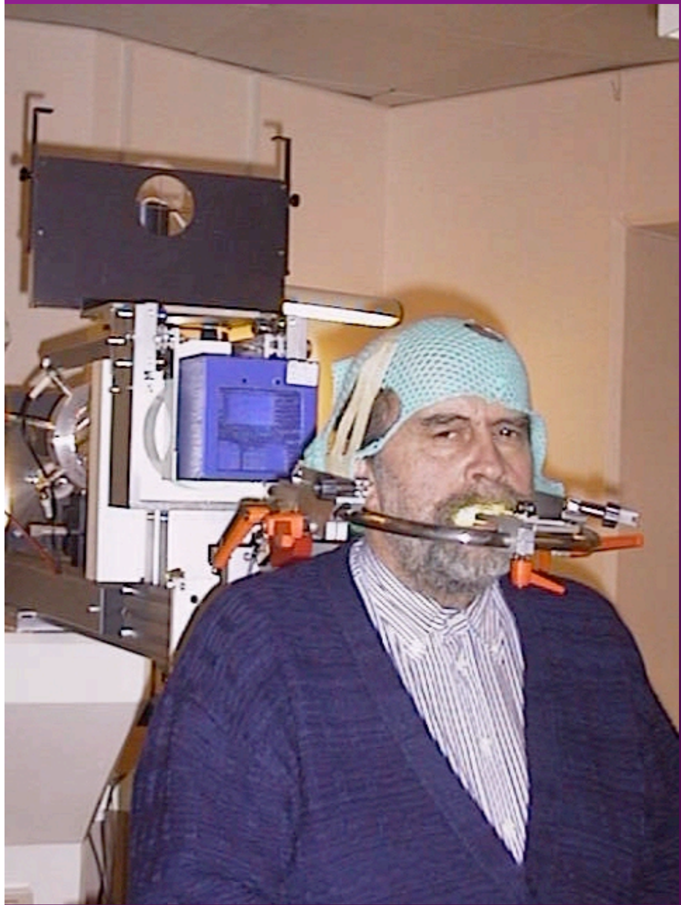
   If $\alpha/\beta = 10$ Gy and $\gamma/\alpha = 0.6$ Gy/ day so

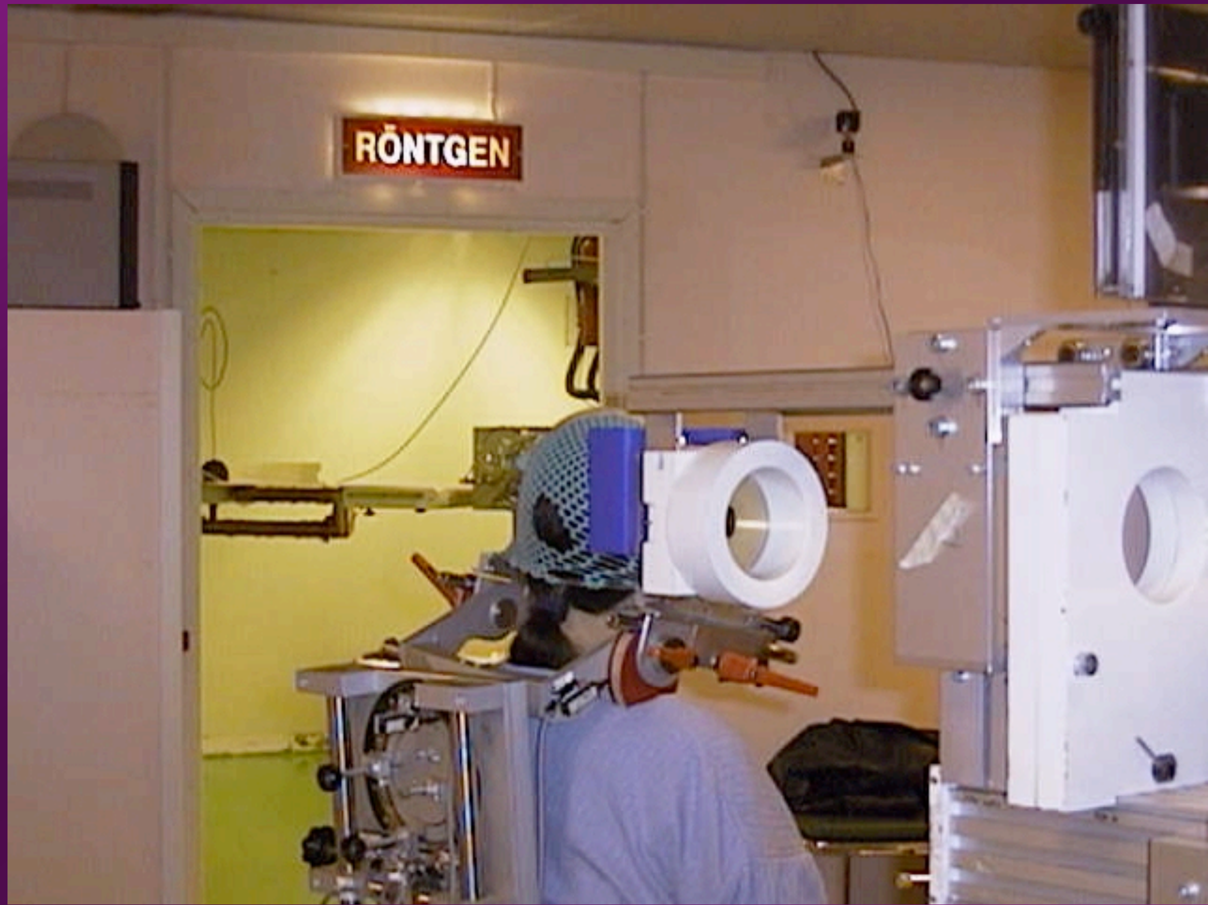
   6 Gy in 4 fractions during one week corresponds roughly to 2 Gy to 50 Gy.

2. According to CRE – model:

   6 Gy in 4 fractions during one week

   corresponds roughly to 2 Gy to 46 Gy





Patients positioned for treatment

Target definition. Noel et al. IJROBP 2005

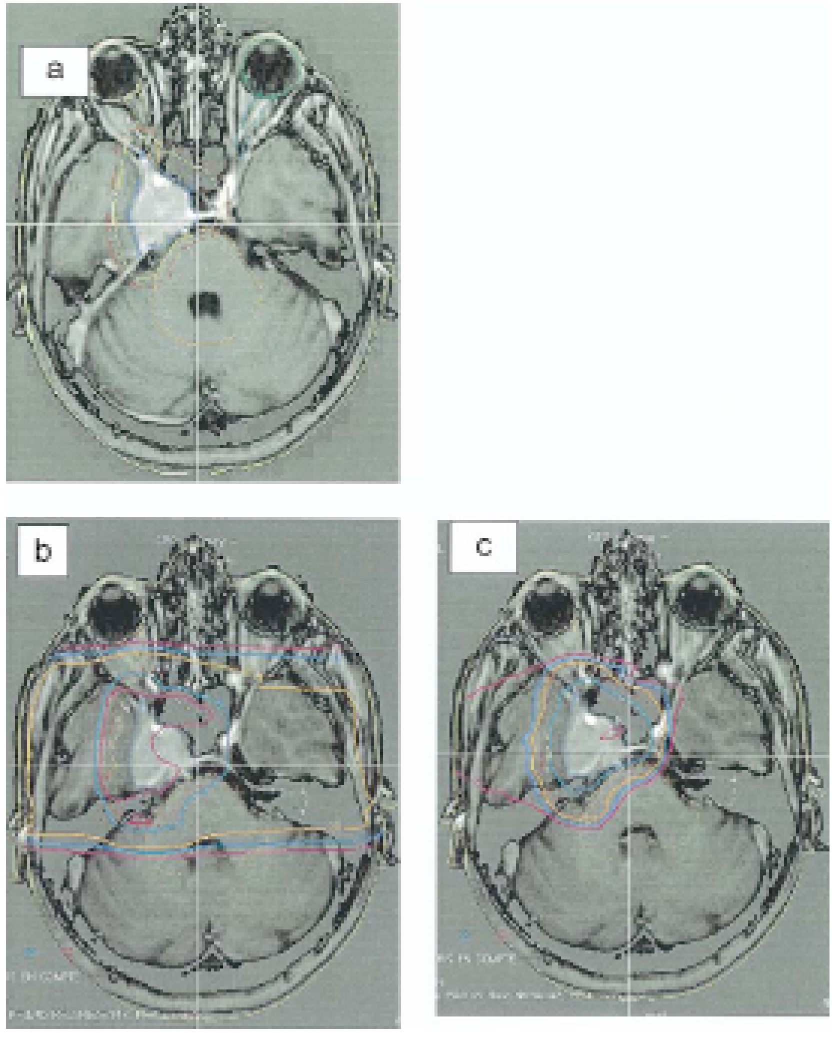


Fig. 5. (a) Delineation of sinus cavernous meningioma. Dose distribution with (b) photons and (c) protons.