Strål- och cytostatikabehandling av hjärntumörer

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Epidemiologi avseende primära hjärntumörer

- Totalt c:a 1300 fall per år i Sverige
- 3 % av alla cancerfall
- Åldersstandardiserad incidens 12 - 15 fall per 100.000/år

- Till detta kommer ett antal fall av cerebrala metastaser

Hjärntumörer, incidens i Sverige, 1990 - 2001.

Diagnos	Män	Kvinnor	Alla	Procent
Lågmaligna astrocytom	79	57	136	10,6%
Högmaligna astrocytom	203	156	359	28,1%
Ependymom	16	12	28	2,2%
Meningiom	114	275	389	30,5%
Malignt meningiom	4	6	10	0,8%
Neurinom	61	62	123	9,6%
Plexuspapillom	1	2	3	0,2%
Hemangioblastom, m.fl	16	14	30	2,3%
Kraniofaryngiom	6	6	12	0,9%
Pinealom	4	2	6	0,5%
Utan PAD	52	56	108	8,5%
Övriga	45	28	73	5,7%
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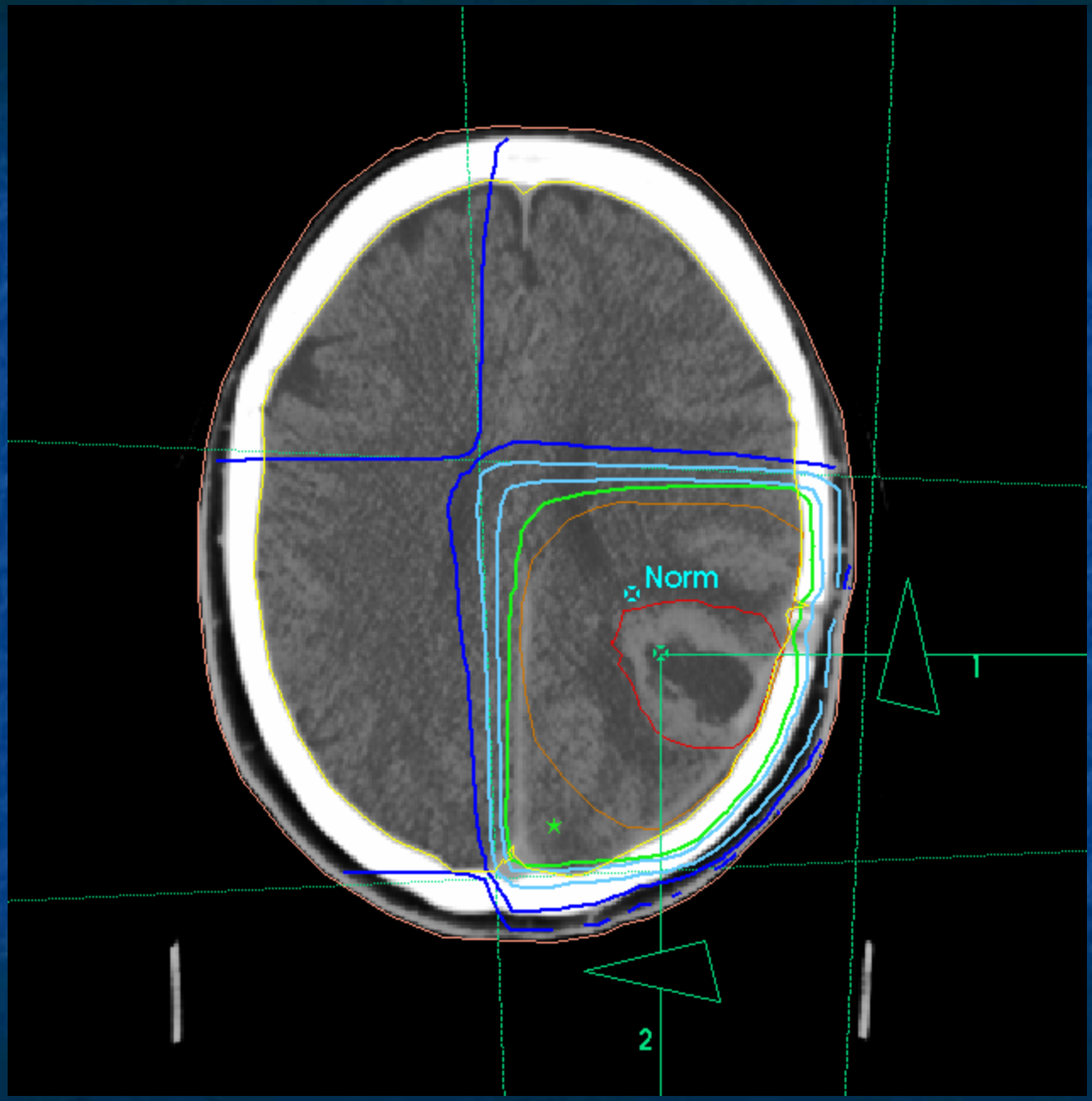
Totalt/år	601	676	1277	100 %

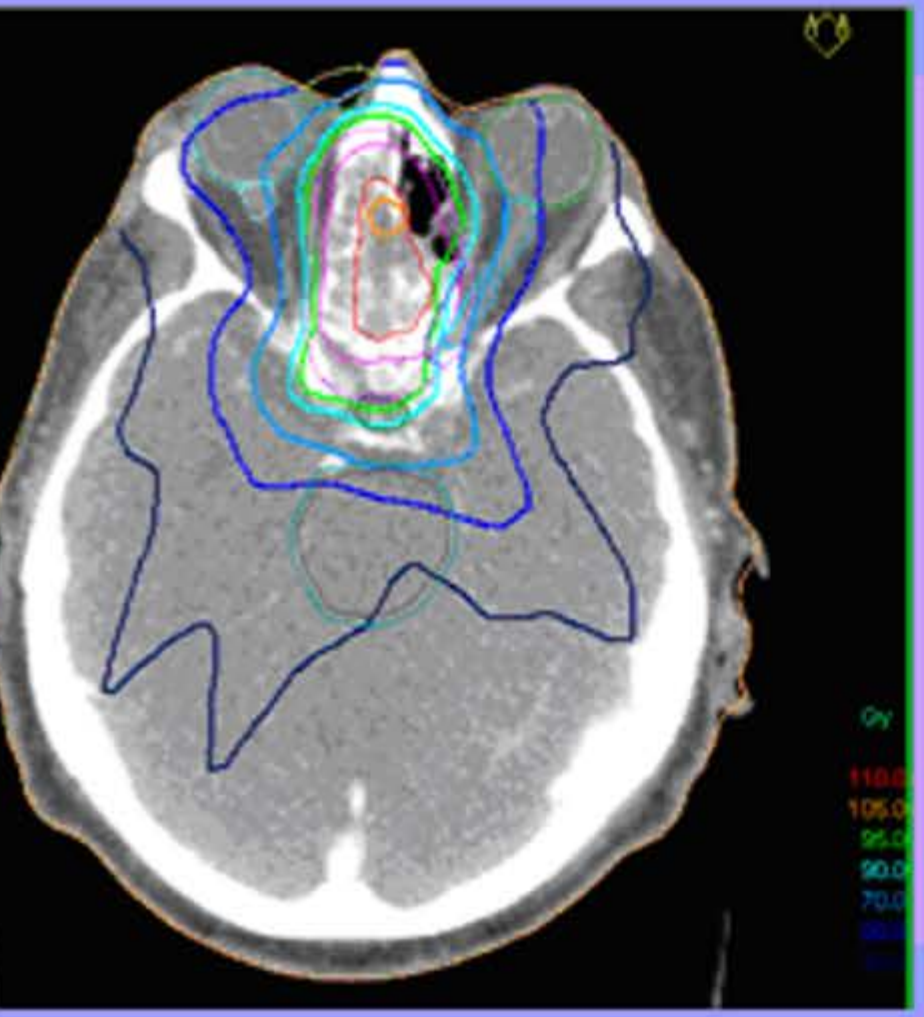
Terapi med joniserande strålning

- Fotoner
  - 3-D teknik
  - IMRT
  - VMAT
  - Gammakniv (”Född” på GWI på 60-talet)
- Elektroner
- Protoner (73 pat 1971; 1274 pat 2012 vid GWI / TSL i Uppsala
- (Neutroner; BNCT, Koljoner)

EB 2013

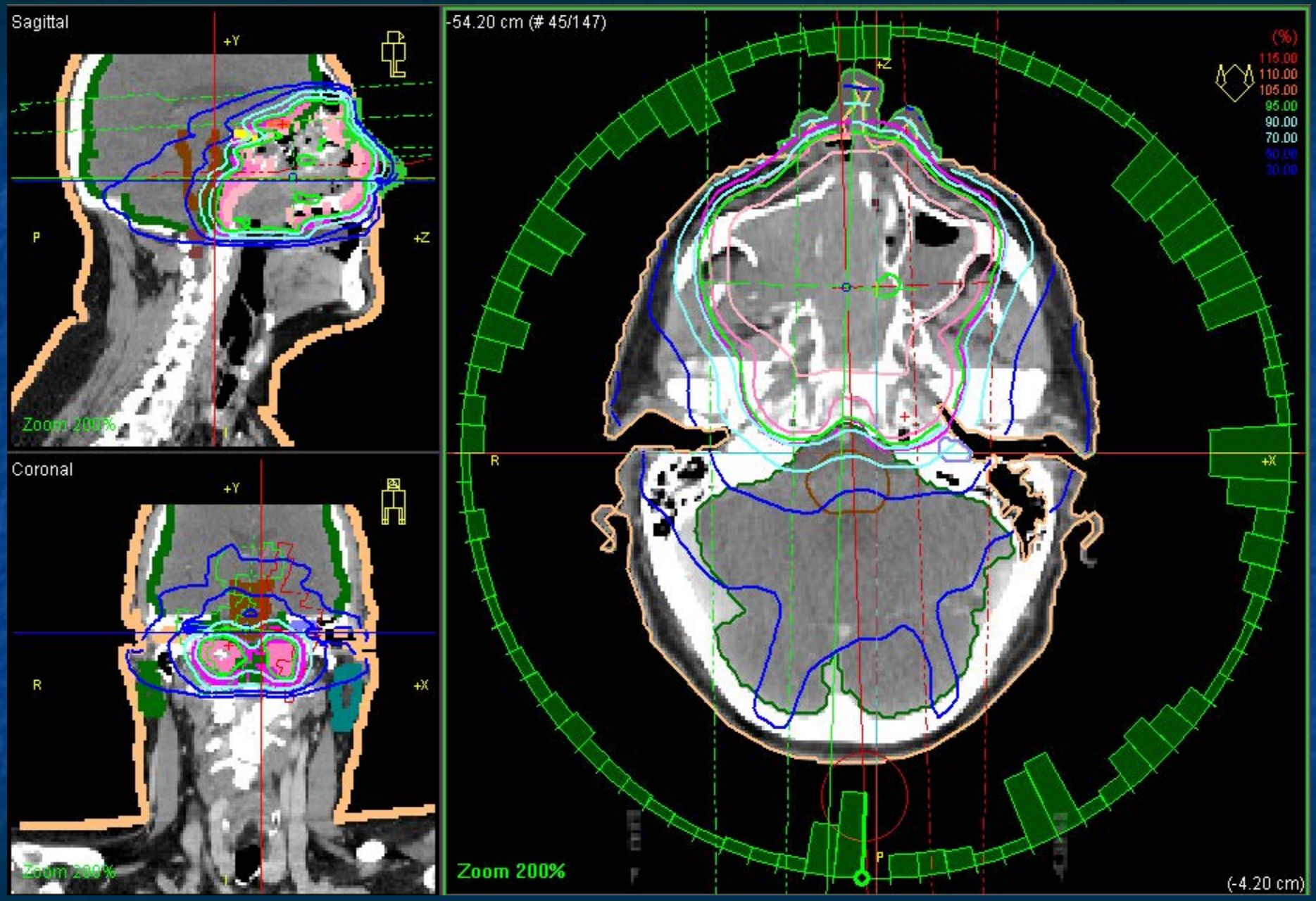

Norm
1
2

VMAT och IMRT



VMAT

IMRT


Sagittal
+Y
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Zoom 200%
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Coronal
+Y
R
+X
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I
-54.20 cm (# 45/147)
+Z
(%)
115.00
110.00
105.00
95.00
90.00
70.00
R
+X
P
Zoom 200%
(-4.20 cm)

Strålbehandling – kliniskt sammanhang

Kurativt syftande – Palliativ?

Preoperativ – Postoperativ – Per se?

Konkomitant behandling?

EB 2013

Huru veta vi att radioterapi av hjärnan hos patienter med malignt gliom har effekt?

EB 2007

Randomized Trials of +/- XRT

Author	N	Schema	Results
Shapiro (1976)	33	Post-op RT and BCNU vs BCNU	MST with BCNU alone 30 weeks compared to 44.4 wks for RT + BCNU (*P* =ns)
Andersen (1978)	108	Post-op RT best supportive care	Post-op RT significantly improves survival compared to best supportive care (*P* <.05)
Walker (1978)	303	Post-op BCNU,RT, BCNU+RT, or best supportive care	Patients receiving RT had significantly longer MST than patients receiving BCNU or best supportive care
Walker (1980)	467	Post-op, Me-CCNU RT, Me-CCNU+RT	Patients receiving RT had significantly longer survival than patients receiving Me-CCNU alone
Kristiansen (1981)	118	Post-op RT, RT + bleomycin, or supportive care	MST with RT alone 10.2 months compared to 5.2 months with supportiva care (*P* =significant)
Sandberg-W. (1991)	171	Post-op PCV +/-RT	MST with PCV alone 42 wks compared to 62 wks for PCV + RT (*P* =.028)

(EB 2007)

Strålbehandling - dosplanering

- Volym: GTV, CTV, PTV
- Fraktionsdos: 1,8 – 2,0
- Totaldos: 50 – 60 Gy
- Total behandlingstid: 5 dagar i veckan utan paus

Såå..... vid högmaligna gliom - strålbehandling..... Hur?

Fraktionsdos = 2 Gy

Veckodos = 10 Gy

Totaldos = 60 Gy

ev. Temodal: Neoadjuvant, concomitant, neo-adjuvant

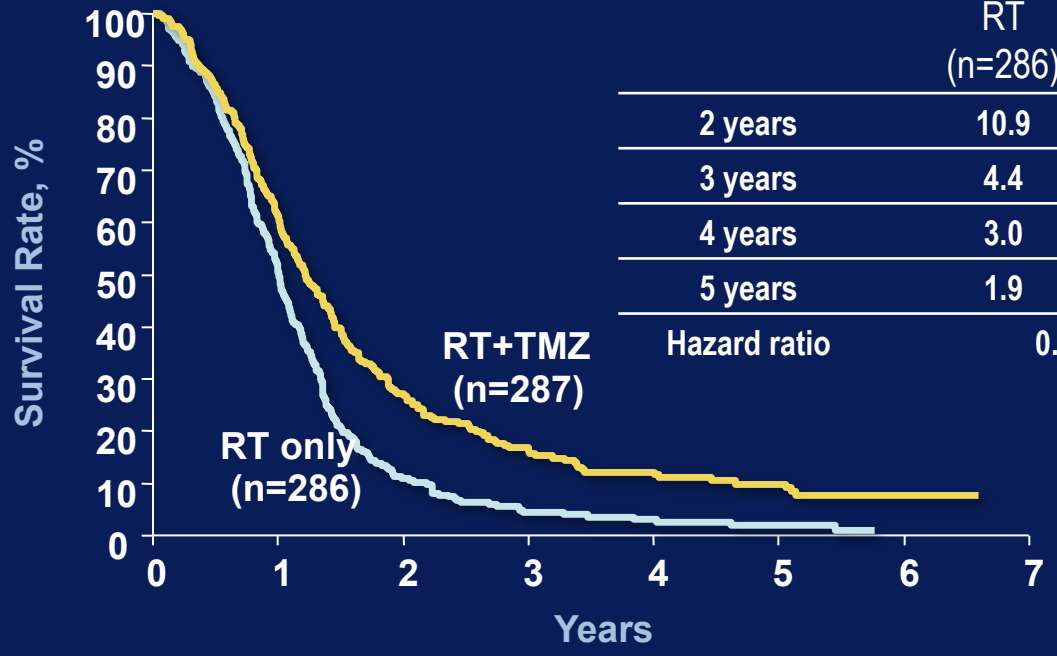
EB 2007

”A small step for dr Stupp - a big leap for patients with GBM”

1. Concomitant: Temozolomide 75 mg/m^2 daily during radiotherapy
2. Adjuvant: Temozolomide in 6 courses 200 mg/m^2 daily for 5 days and 23 days of a free interval

EB 2007

Adding Temozolomide to Radiation Significantly Improved Survival: 5-Year Follow-Up[1]



Overall Survival, %

	RT (n=286)	RT+TMZ (n=287)
2 years	10.9	27.2
3 years	4.4	16.0
4 years	3.0	12.1
5 years	1.9	9.8
Hazard ratio		0.63 [95% CI.,0.53−0.75] *P*<0.0001

RT = radiation therapy; TMZ = temozolomide.

1. Stupp R et al. *Lancet Oncol*. 2009;10:459–466.

”Låg-maligna” tumörer

Behandling:

- Vanligen 1,8 – 2,0 Gy till 50 – 56 Gy per se eller postop.
- Tabl. Temodal prövas ofta då re-operation

  och/eller re-bestrålning inte bedömes lämplig

  Vid Gliomatosis cerebri ges ofta Tabl. Temodal initialt

EB 2013

Blod-hjärn-barriären (”BBB”)

Mest använda cytostatika

- Temodal (temozolomid) p.o.
- Avastin (bevacizumb) i.v.
- PCV (kombination av procarbazin, CCNU och vincristin) p.o. o. i.v.

EB 2013

Strålreaktion

1. Akut
2. Intermediär
3. Sen

EB 2007

Strålreaktioner i CNS

EB 2007

Strålreaktioner i hjärnan

Akut strålreaktion

Vasogent ödem

Direkt stråleffekt på:

- endotel, astrocyter och oligodendrocyter
- kapillärer/arterioli i hjärnan och kärlen i blod-hjärnbarriären
- cerebrala ganglion

EB 2007

Strålreaktioner i hjärnan
Sen strålreaktion

Hjärnnekros - kan vara svår att skilja radiologiskt från återväxt av gliom

Plack med demyelinisering

Ischemisk infarkt

EB 2007

A short History of Proton Beam Therapy

1946 Wilson suggests high energy protons for radiotherapy

1954 First patient treated with protons at Berkeley

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

EB/2012

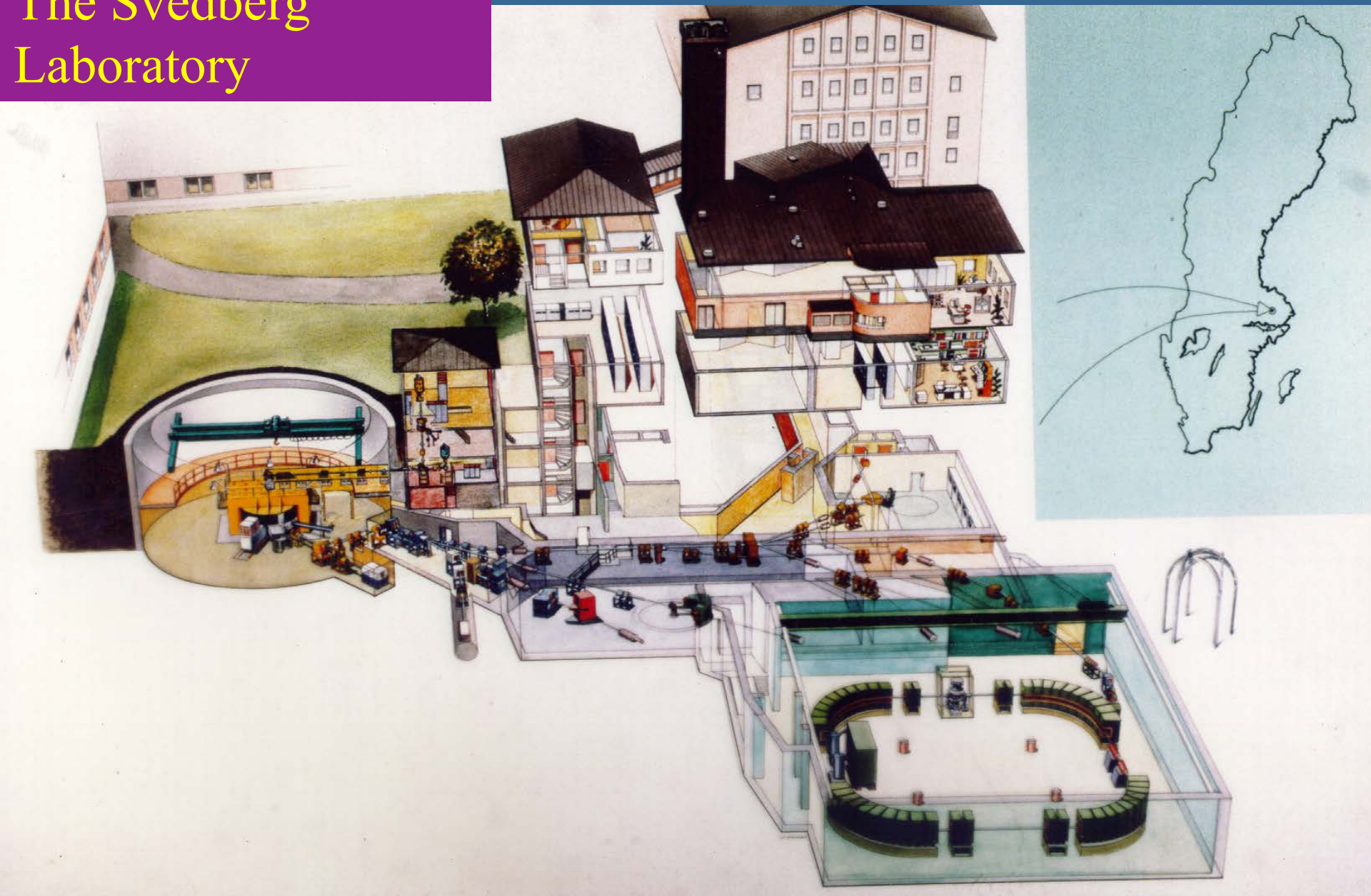
Något om p+-terapi vid The Svedberg Laboratoriet

- Nuvarande serie startade April 1989.
- Initialt 5 – 6 veckor om året o. 75 MeV
- Sedan 1 juli 2005 35 veckor om året o. 180 MeV
- 2012; 1274 patienter protonstrålbehandlade vid TSL
- 2015; Scandionkliniken startar

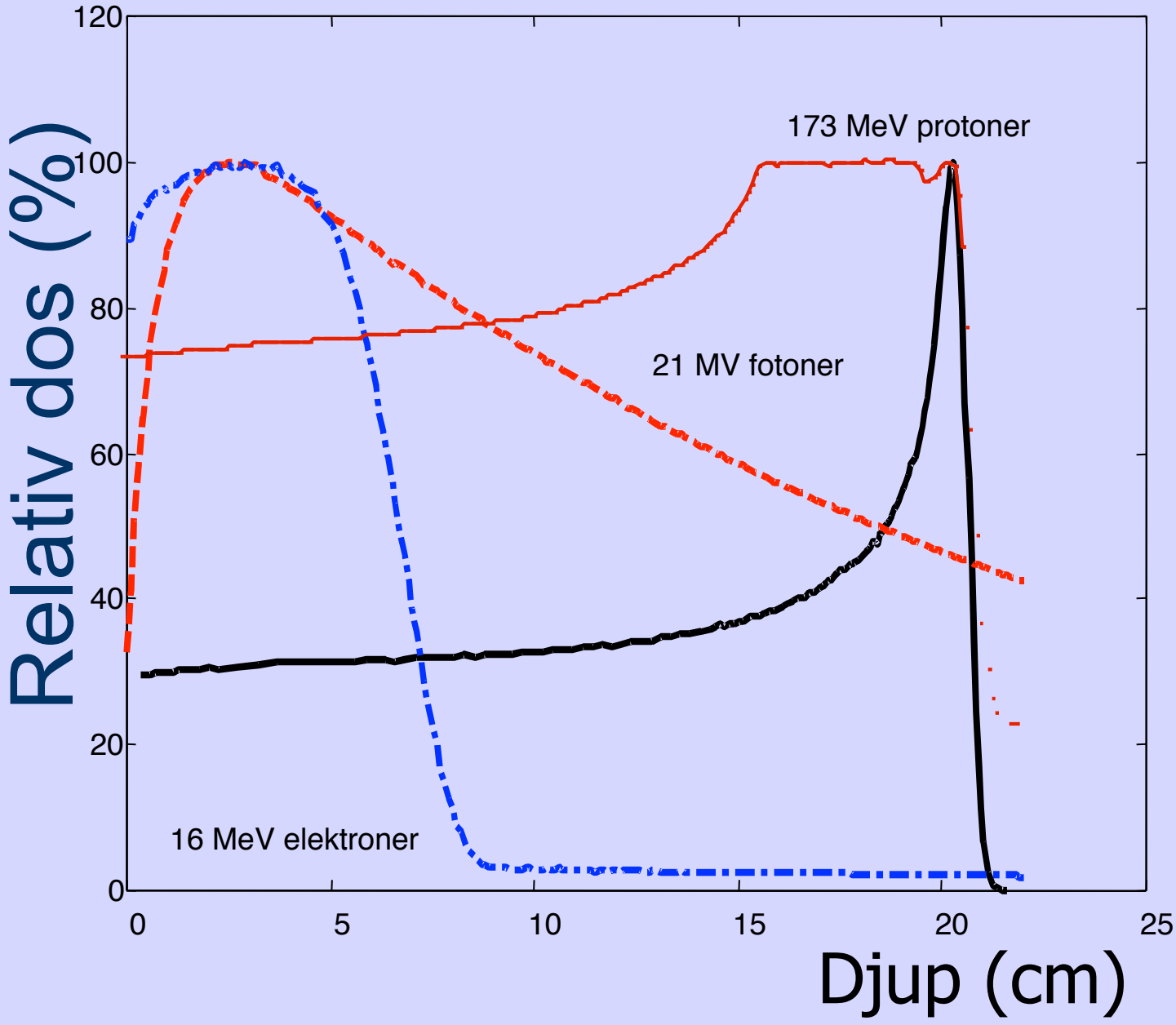
EB 2013

Proton beam treatments in Uppsala

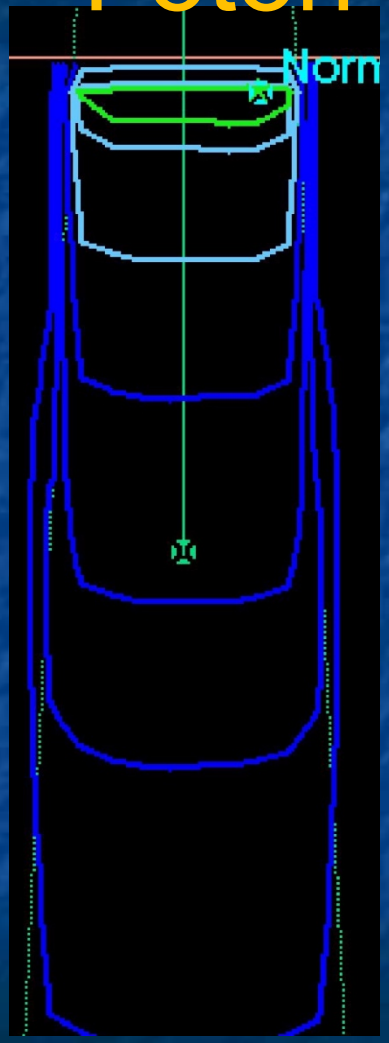
The Svedberg Laboratory



Strålfysikaliska skillnader

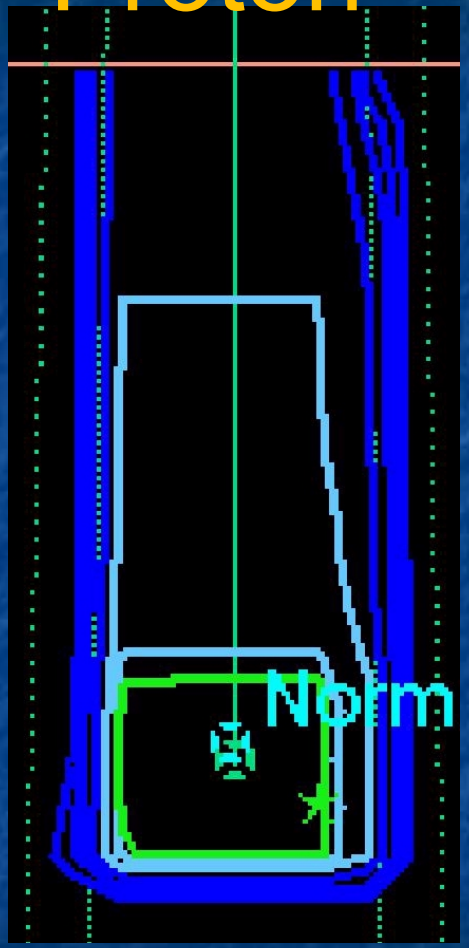


Foton



Elektron

Proton



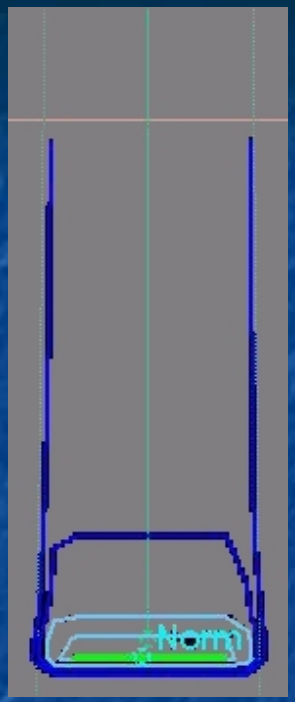
Cyclotrons

TSL Uppsala

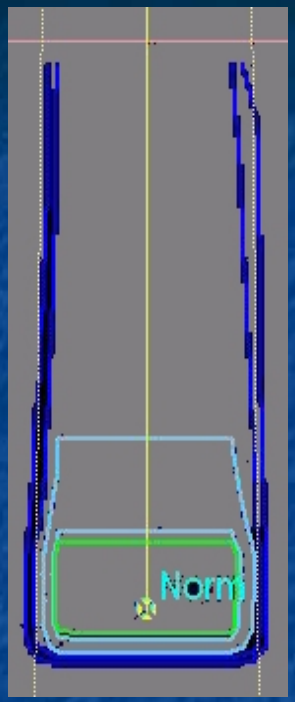
Continuous beam

Fixed energy

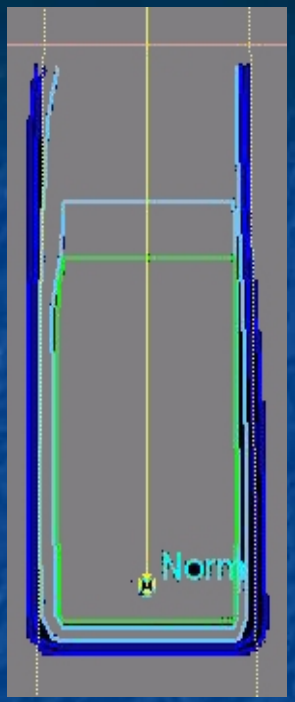
Range modulators



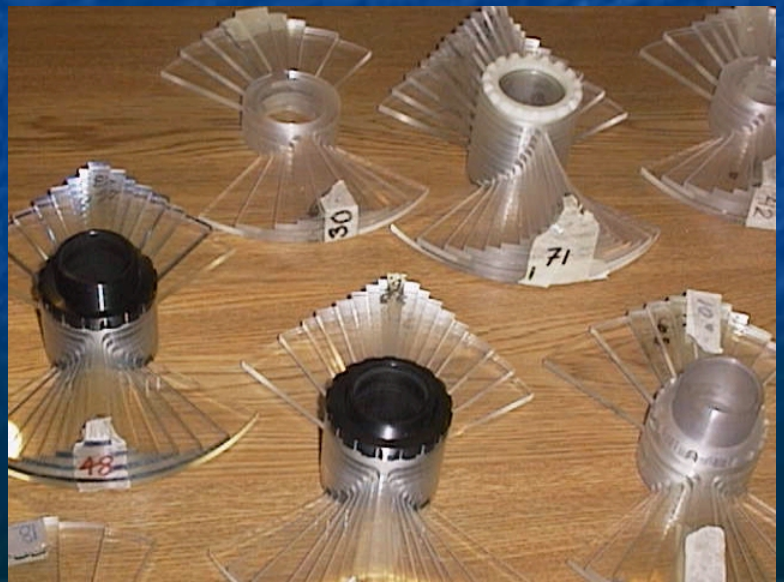
RM0



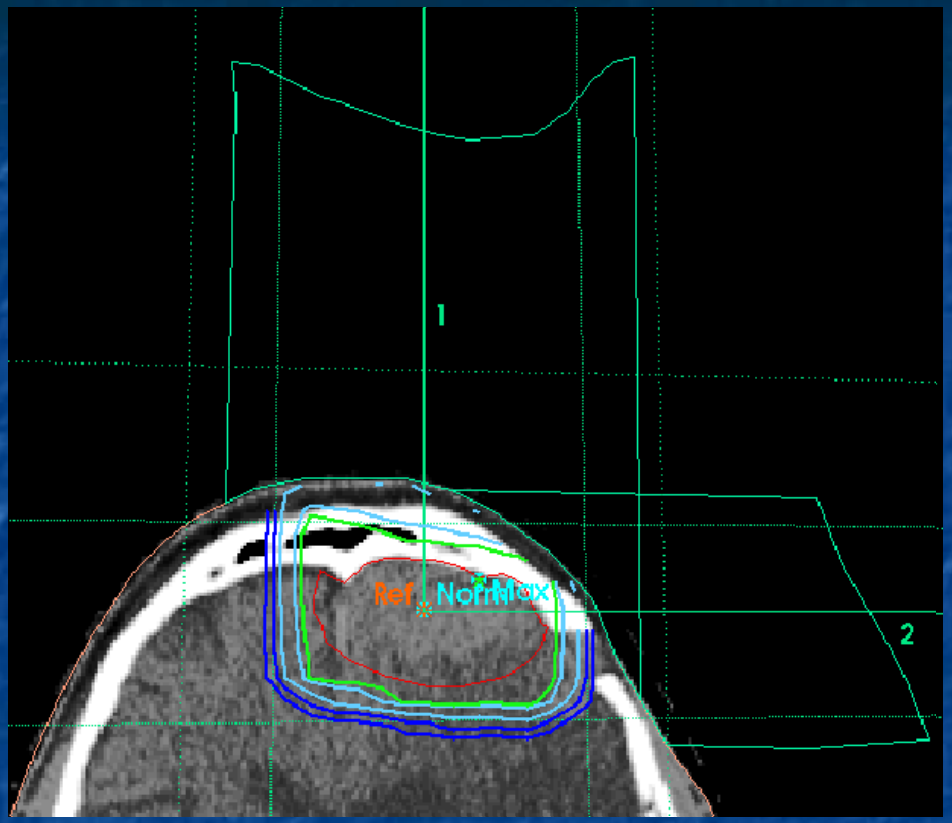
RM18



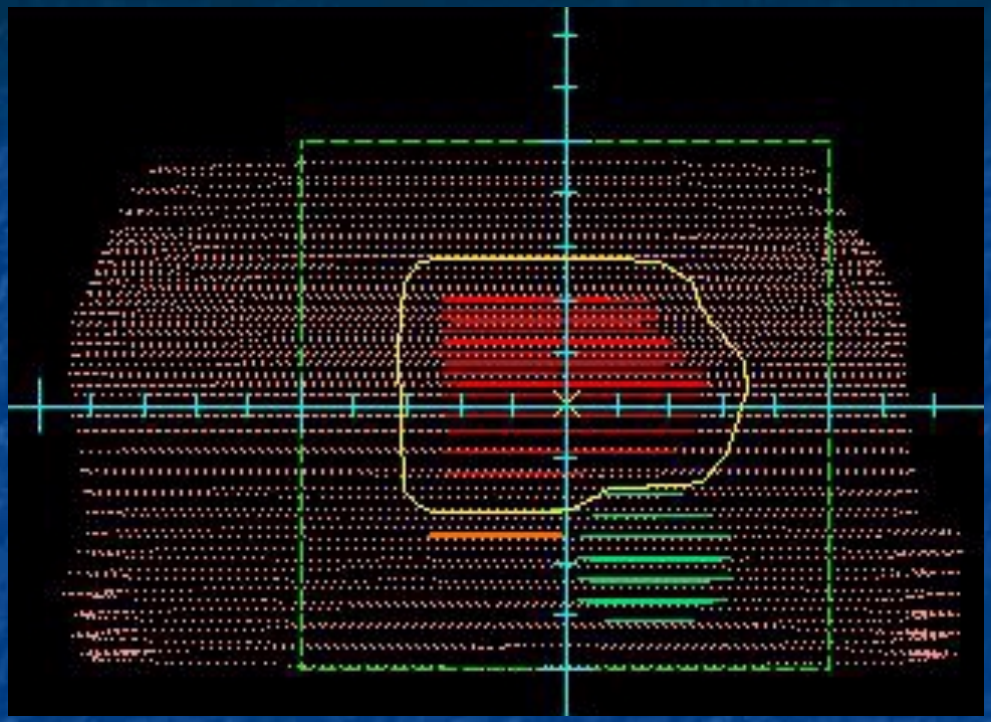
RM71

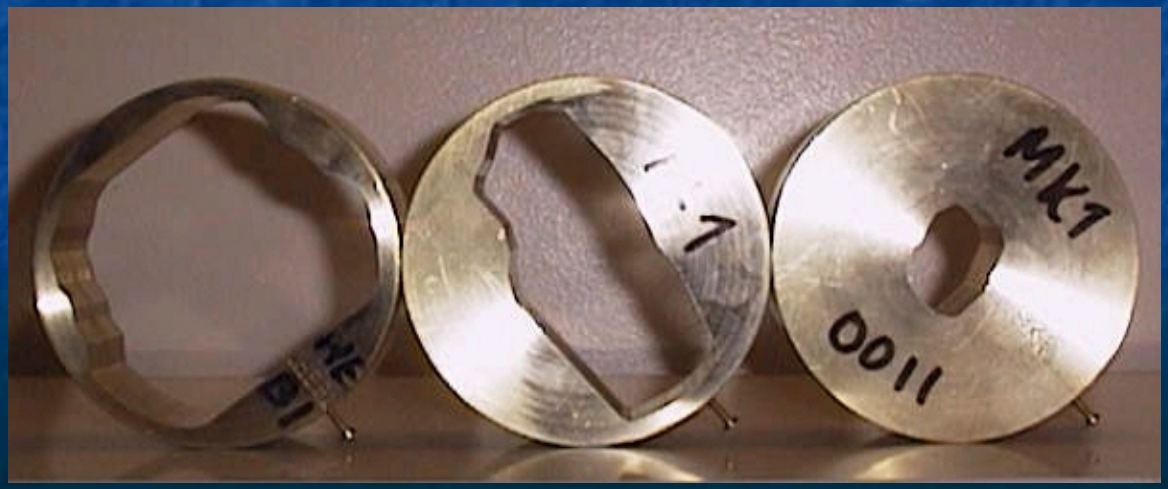


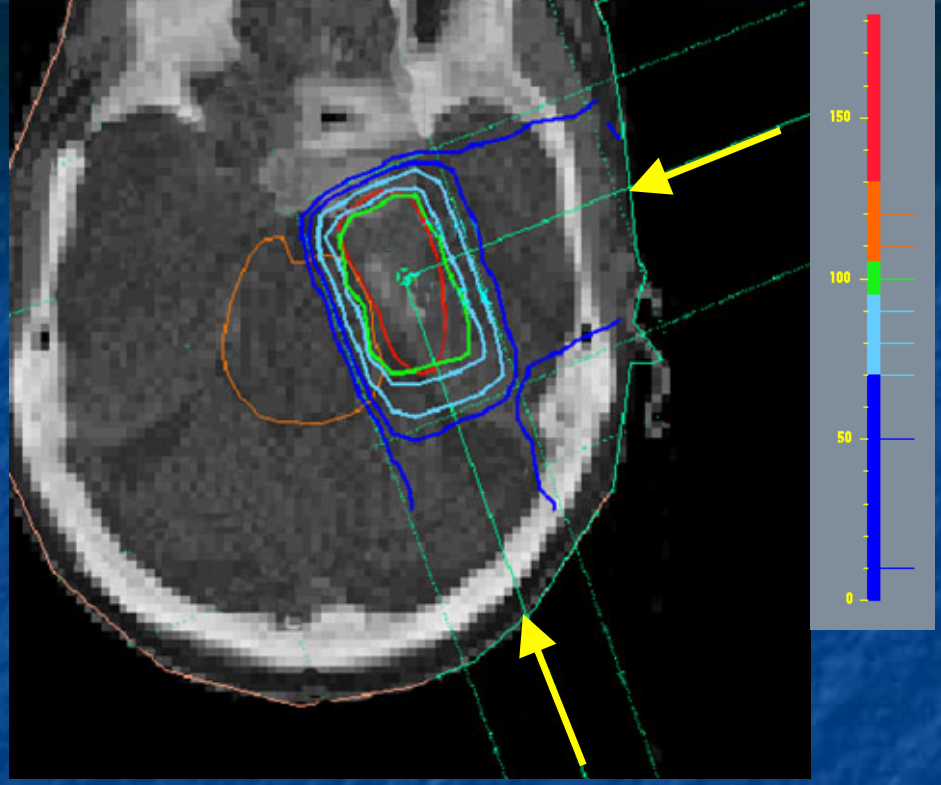
Range compensation filters

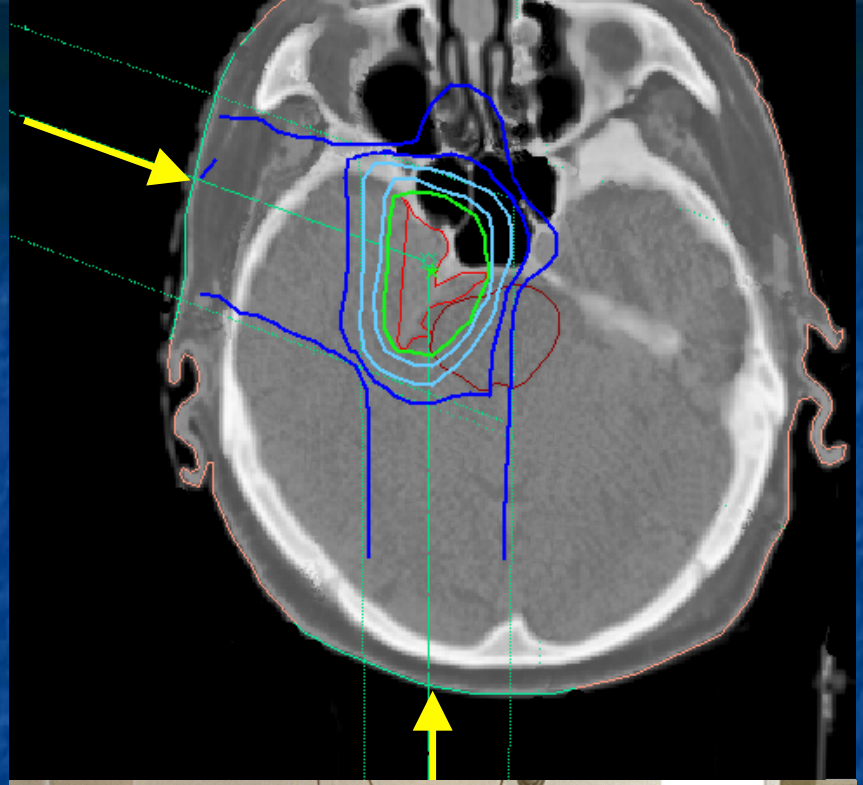


Collimators

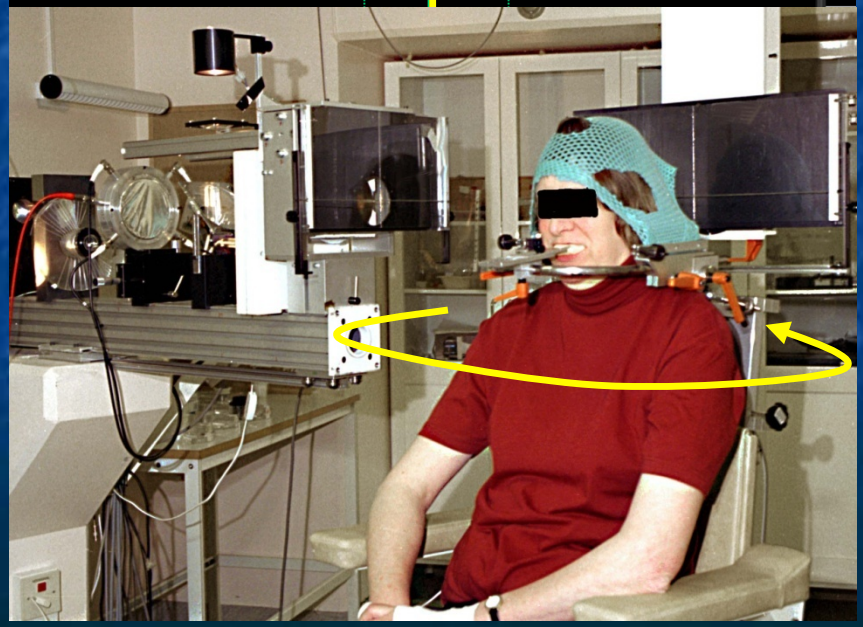




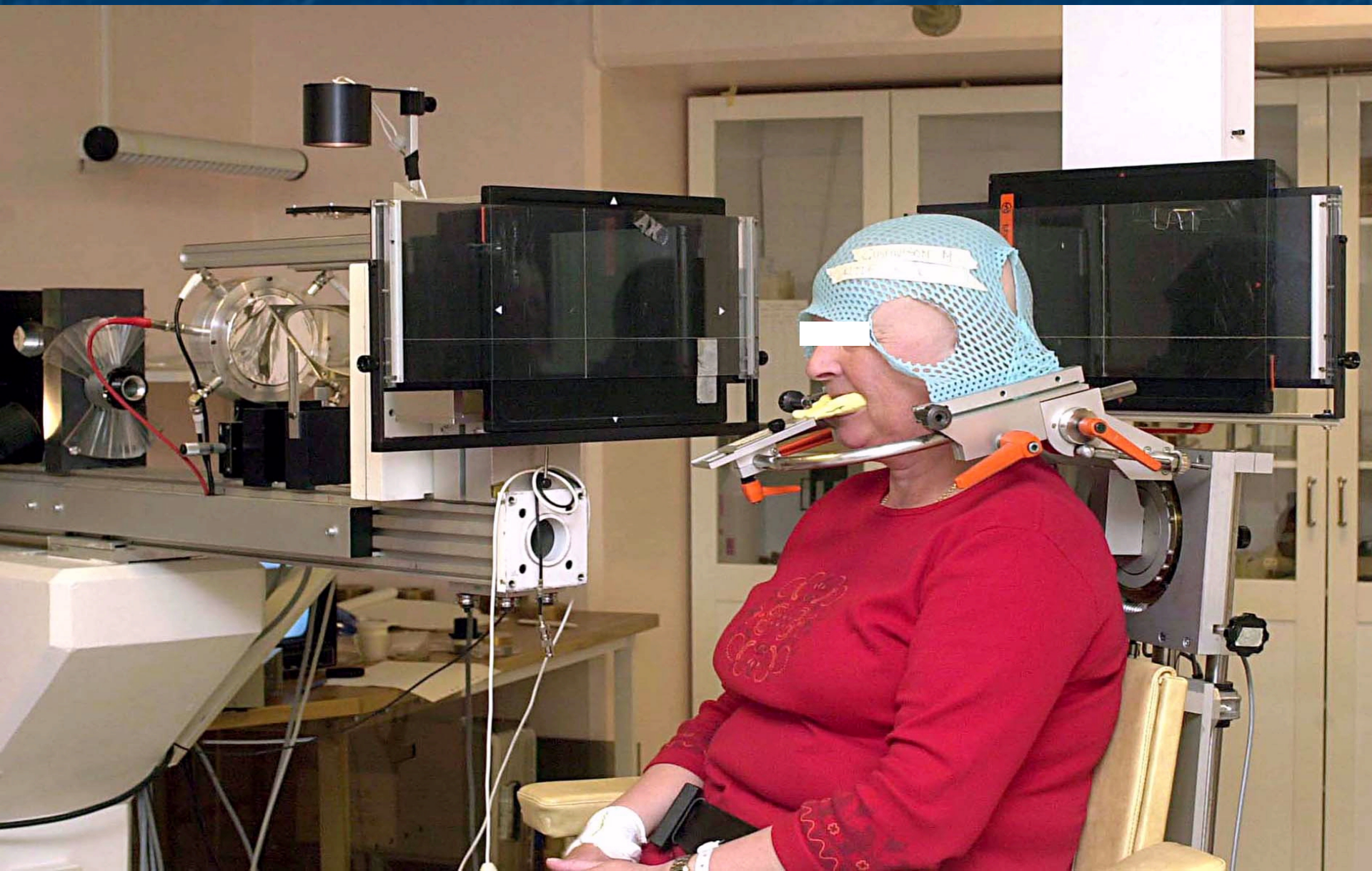




Examples of intracranialtargets (meningeomas) treated at TSL



Positioning och fixation



Proton beam radiotherapy at TSL

Now 35 weeks per year. (Recently: one week per month).
Intracranial and subcranial targets
Tumors in the spine or with paraspinal location
Prostate cancers

Benign targets

Exclusively protons
- AVM:s
- Meningeomas
- Pituitary tumors

Malignant targets

Exclusively protons
- Metastases
- Uveal and iris melanomas

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

EB/2007

P+-terapi: Exempel

Meningiom (WHO grad I):

a. Hypofraktionering 4 x 6 Gy(RBE)
b. Hypofraktionering 10 x 3 Gy(RBE)
c. ”Konventionell” fraktionering:

   23 – 28 x 1,8 - 2 GY(RBE)

EB 2013

Glioblastomas; treatment

Doubtful effect on survival:

- Hyperfractionation
- Accelerated fractionation
- Higher total dose than 60 Gy in 2 Gy fractions
- Higher LET; fast neutrons, He-ions, Neon-ions,
- BNCT
- Oxygen mimicking drugs (mizonidazole)

EB 2007

A bright future for science and improvements for our patients

Tack för uppmärksamheten!

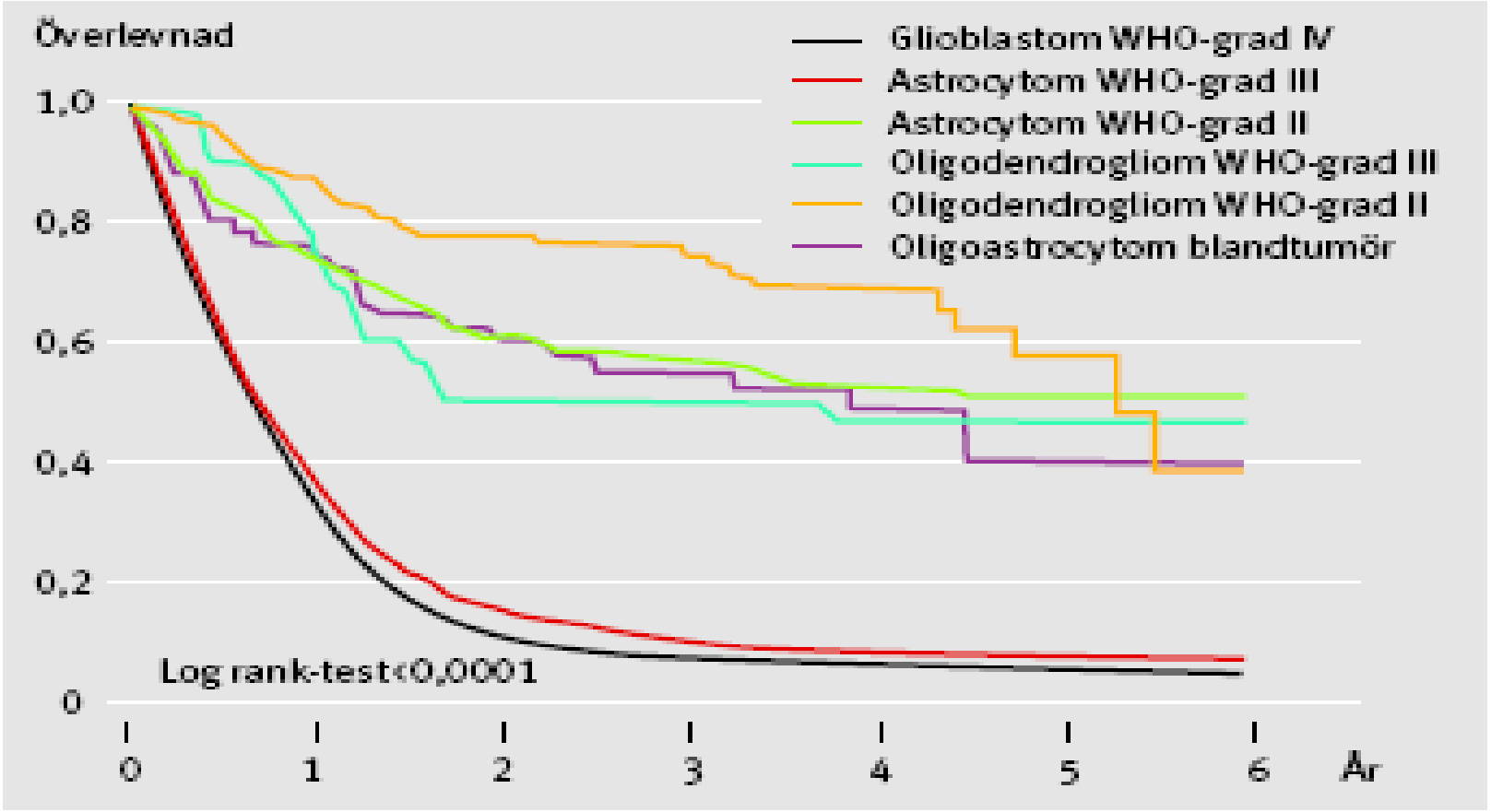
Högmaligna gliom
(glioblastom m. fl.)

Faktorer som påverkar prognos

- Ålder
- Allmän kondition (Karnofsky, WHO P.S.)
- Histopatologi - proliferationsindex
- Resektionens storlek

EB 2007

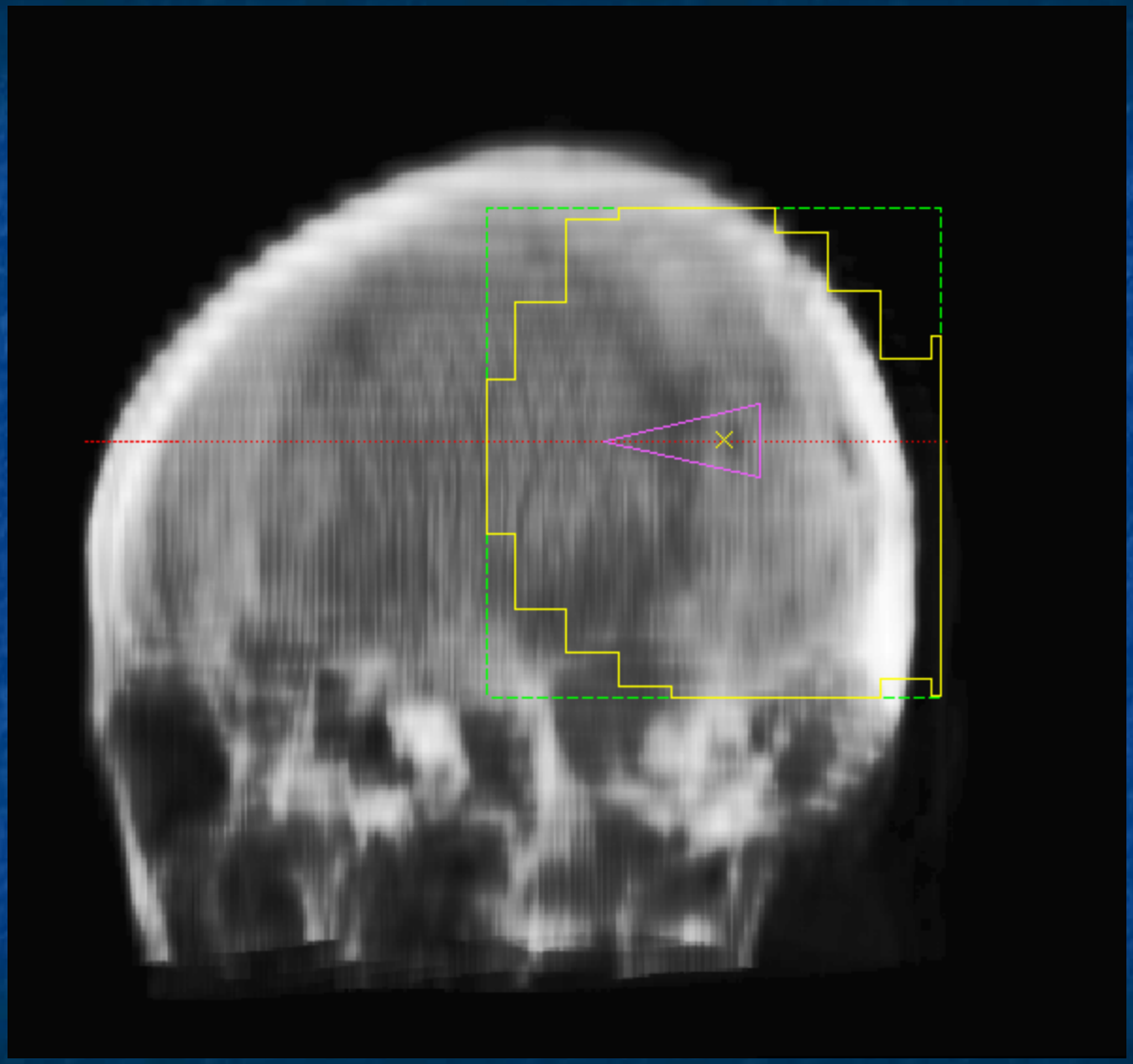
Overall survival of glioma patients in Sweden



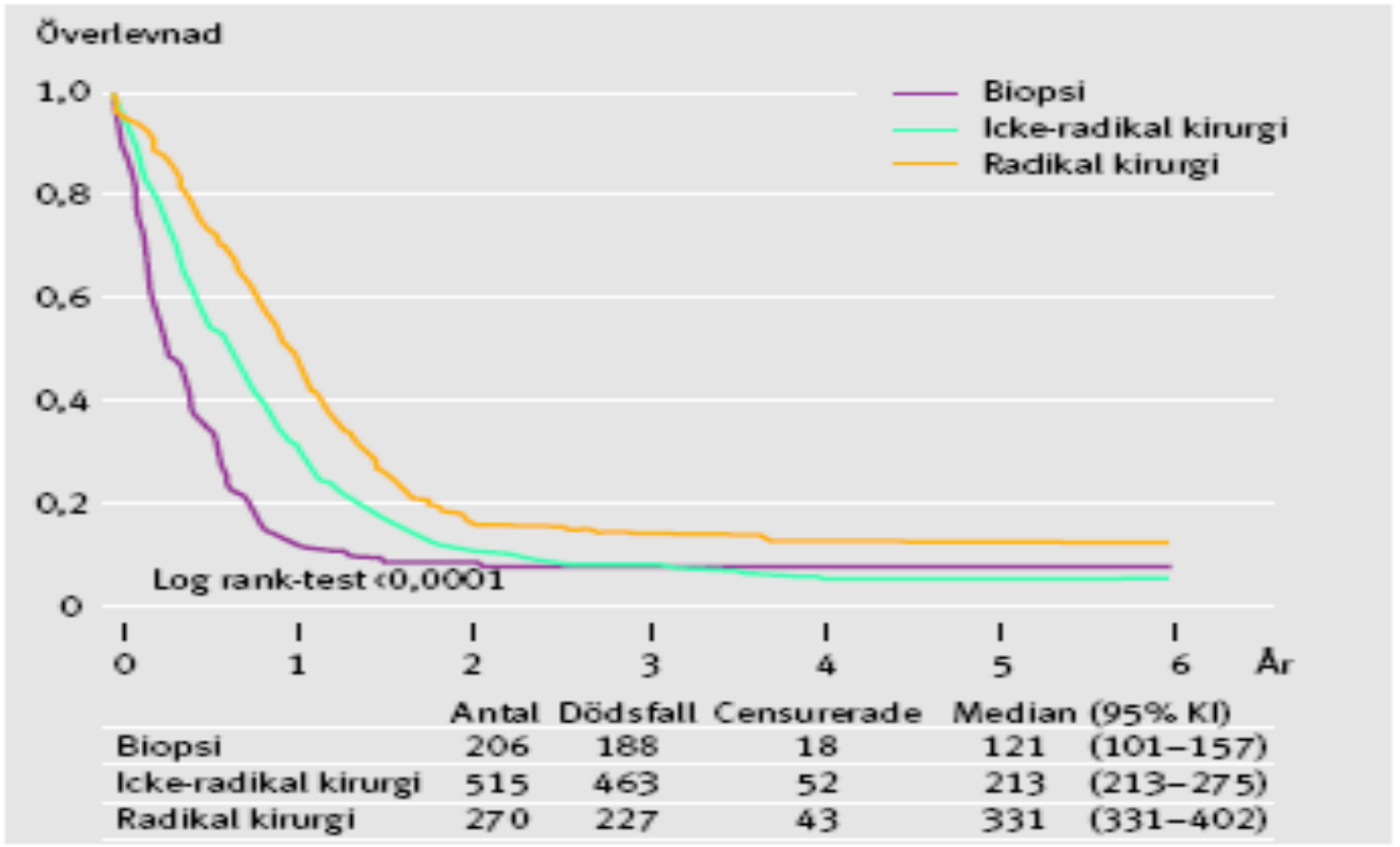
Figur 4. Överlevnad för alla rapporterade patienter med astrocytära tumörer, oligodendrogliom och oligoastrocytom.

Femårsöverlevnad i procent

- Högmaligna astrocytom 4
- Lågmaligna astrocytom 43
- Oligodendrogliom 47
- Meningiom 80
- Neurinom 90



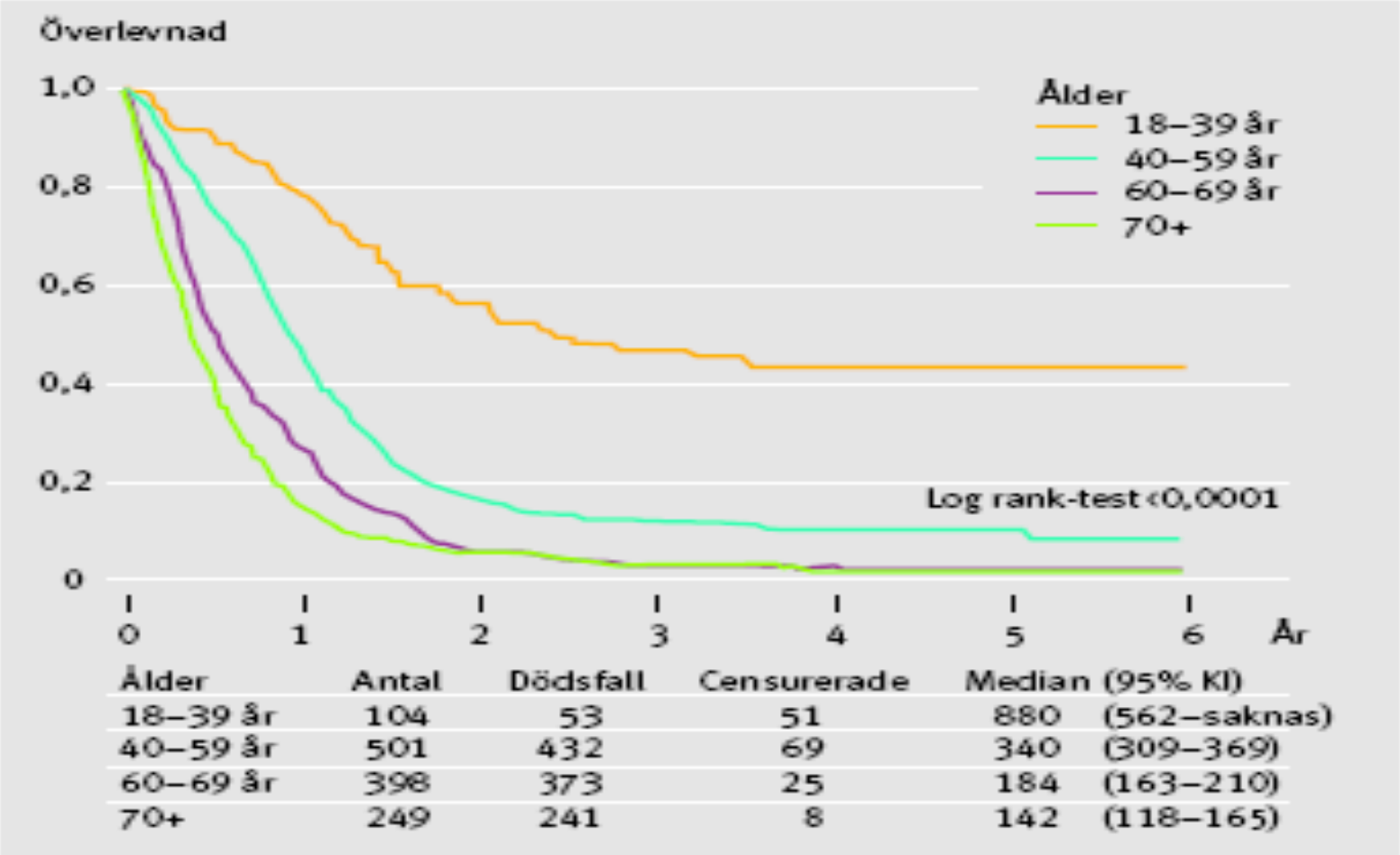
Survival after type of surgery in glioma patients



	Antal	Dödsfall	Censurerade	Median	(95% KI)
Biopsi	206	188	18	121	(101–157)
Icke-radikal kirurgi	515	463	52	213	(213–275)
Radikal kirurgi	270	227	43	331	(331–402)

Figur 5. Överlevnad för alla patienter med högmaligna gliom, uppdelade i typ av kirurgi.

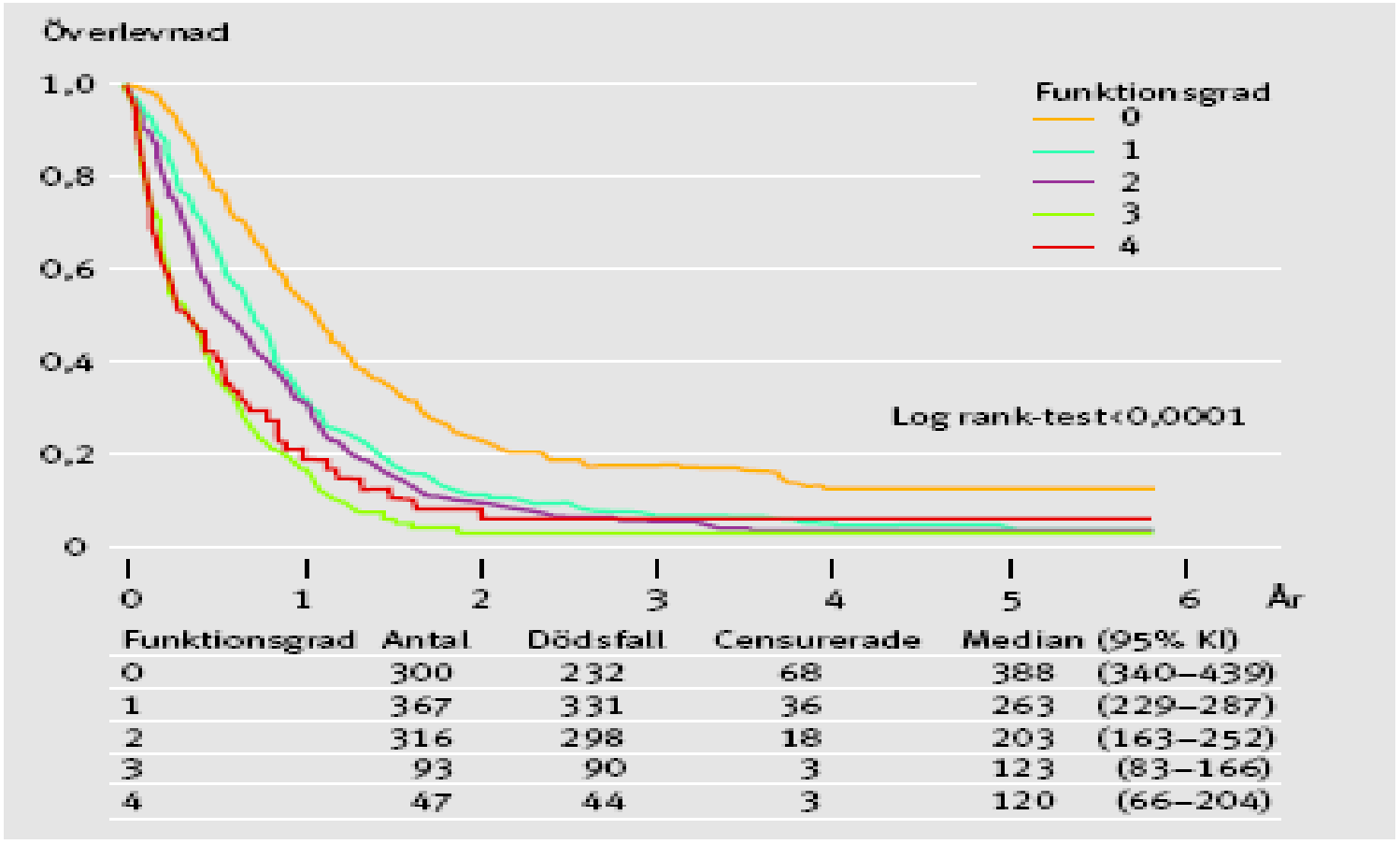
Survival of patients with highly malignant gliomas related to age



Ålder	Antal	Dödsfall	Censurerade	Median (95% KI)
18–39 år	104	53	51	880 (562–saknas)
40–59 år	501	432	69	340 (309–369)
60–69 år	398	373	25	184 (163–210)
70+	249	241	8	142 (118–165)

Figur 8. Överlevnad för alla patienter med högmaligna gliom, uppdelade i åldersgrupper.

Survival of patients with highly malignant gliomas related to initial performance



Funktionsgrad	Antal	Dödsfall	Censurerade	Median (95% KI)
0	300	232	68	388 (340–439)
1	367	331	36	263 (229–287)
2	316	298	18	203 (163–252)
3	93	90	3	123 (83–166)
4	47	44	3	120 (66–204)

Figur 9. Överlevnad för alla patienter med högmaligna gliom uppdelade efter funktionsgrad enligt WHO.

Kirurgi vid fall av hjärntumör

- Makroskopiskt radikal resektion
- Partiell resektion
- Biopsi

EB 2007

Högmaligna gliom

Glioblastom ("gamla sanningar"):

- Alla behandlingar är palliativa
- Strålbehandling postop. kan ge förlängd överlevnad
- Medelöverlevnad 9 – 12 månader (Op + SB)
- Färre än 10 % överlever längre än 2 år
- "Nyhet": Temozolomid samtidigt med SB kan förstärka strålbehandlingseffekten hos vissa patienter

EB 2007

Vård och omvårdnad

”Hela familjens sjukdom”

Vård hemma så länge det är praktiskt möjligt
Bevara livskvalitet - en ständig utmaning!

Resurser: Kurator, psykosocialt team, biståndshandläggare, distriktssköterska, personlig assistent, sjukgymnast, sjukhuskyrkan, palliativt team, hospice

EB 2008

Behandlingsmodaliteter

Kirurgi

Strålbehandling

Kemoterapi

Nuklearmedicin

Signaltransduktionshämmare

EB 2008

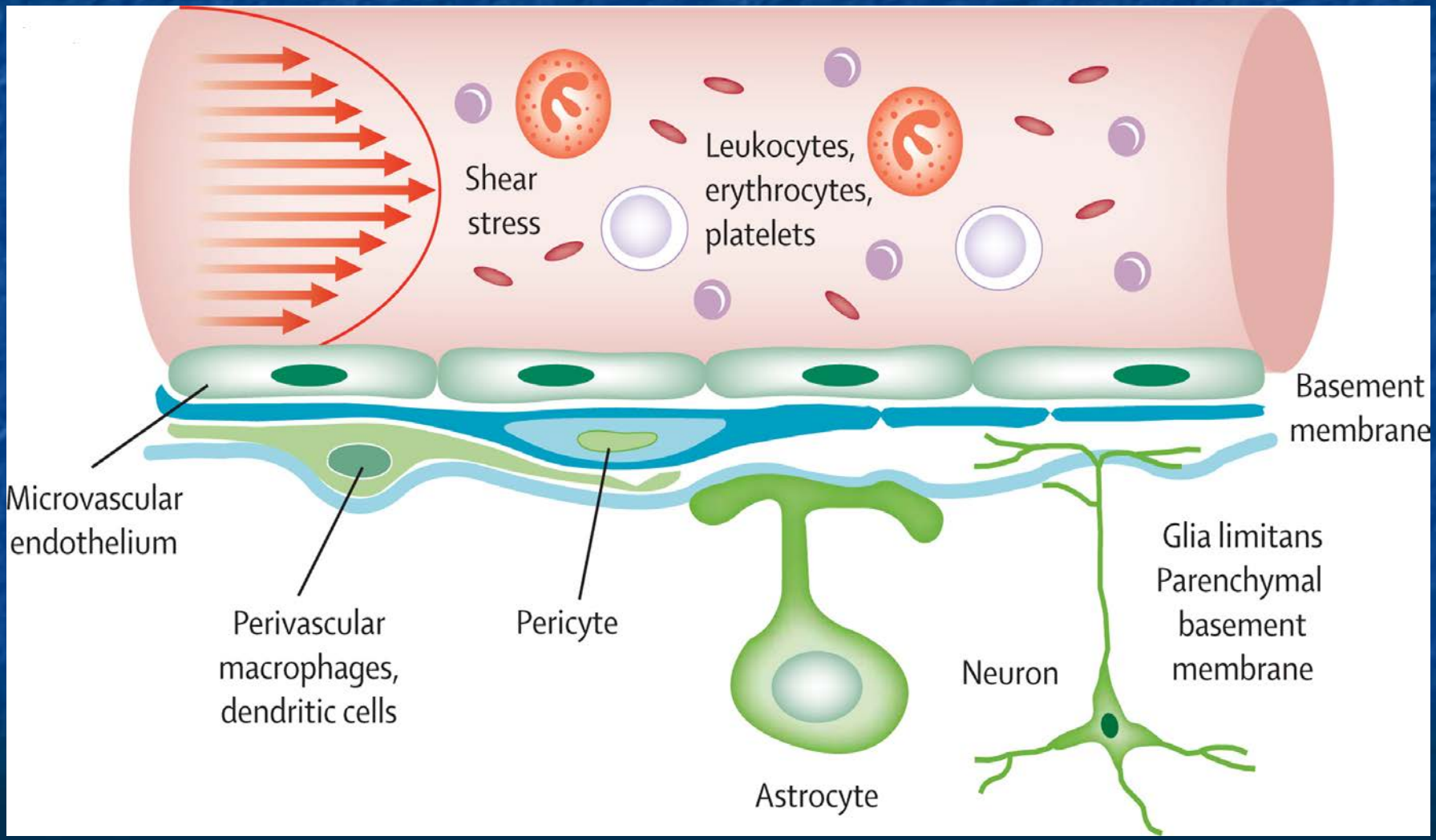
Blod-hjärn-barriären (”BBB”)

Blod-hjärnbarriären reglerar transport av näring, metaboliter och läkemedel till och från hjärnan. Den utgörs av endotelcellerna i hjärnans små blodkärl, kapillärerna. Trots att de bara utgör 0.1 % av hjärnans vikt är de i en människa 644 km långa med en yta på 20 m^2. Mellan endotelcellerna finns s k tight junctions som gör att alla läkemedel som ska passera in till eller ut ur hjärnan måste passera genom cellerna.

Endast de senaste 10 – 15 åren har man vetat att det finns aktiva transportörer som fungerar som ”dörrvakter” för läkemedelstransport in till hjärnan.

EB 2008

BBB (Lancet Neurology)



Dagens teman

1. Neuroonkologi
2. Omhändertagande på Onkologikliniken
3. Epidemiologi
4. Något om patofysiologi
5. Diagnostik och behandling

Neuroonkologi

- Ronder
  - Hypofys
  - CNS-tumör
  - Kärl (”Vaskrond”)
- Vårdprogram – Nationellt och regionalt
- RCC
  - Hjärntumör
  - Hypofys

EB 2008

Chemotherapy 1

Mode of utilisation:

Curative

Palliative

EB 2007

Chemotherapy 2

Mode of administration:

Neo-adjuvant

Concomitant

Adjuvant

EB 2007

Andra strålbehandlingsmodaliteter

- BNCT – borneutroninfångningsterapi
- Högenergetiska neutroner
- Stereotaktisk behandling med LINAC eller ”Larsson - Leksells gammakniv”
- Nuklearmedicinsk terapi

- EB 2007

Chemotherapy 3

Mode of administration:

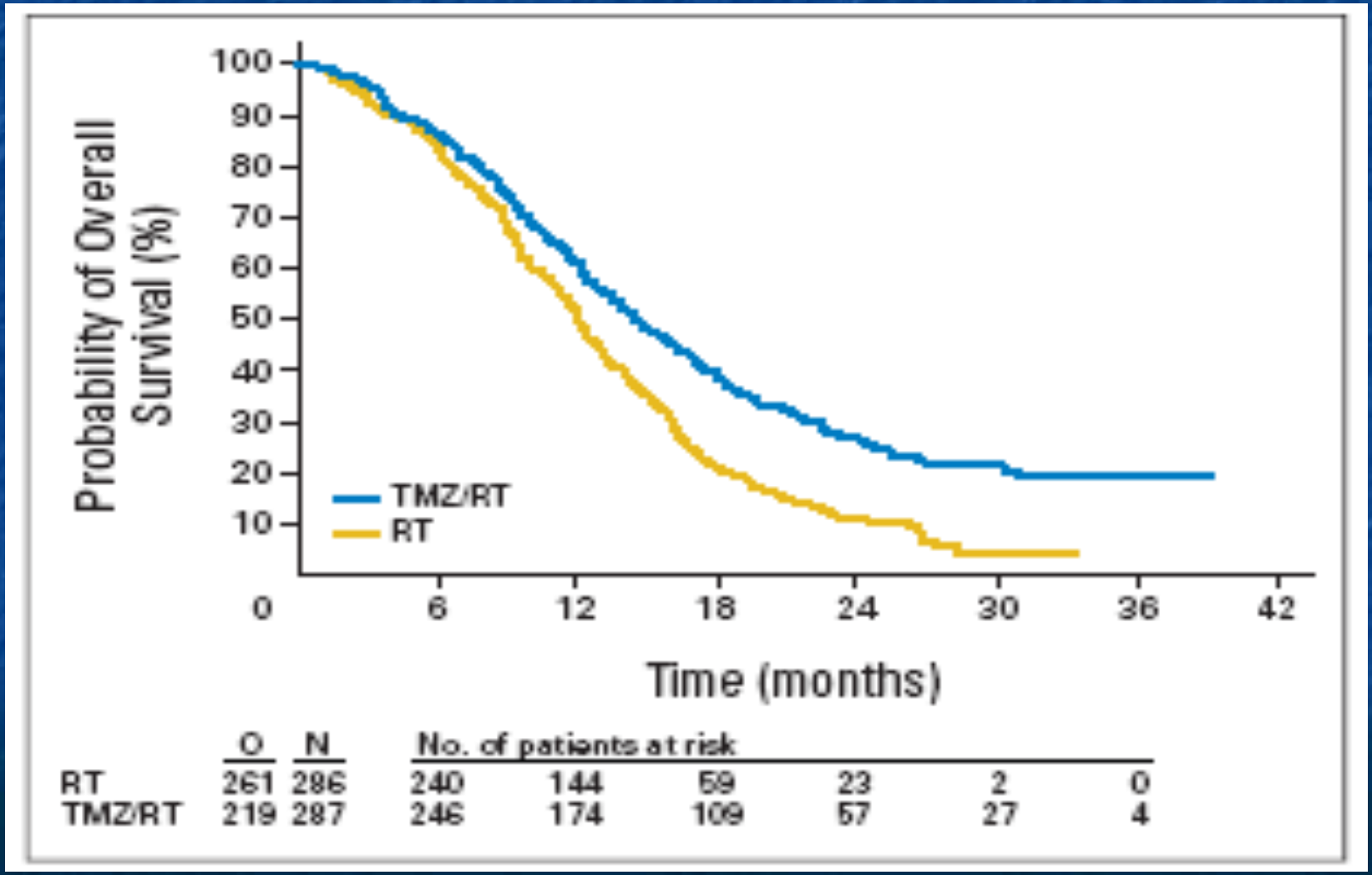
A. Neo-adjuvant: Temozolomide in trials

B. Concomitant: Temozolomide 75 mg/m^2 daily during radiotherapy

C. Adjuvant: Temozolomide in 6 courses 200 mg/m^2 daily for 5 days and 23 days of a free interval

EB 2007

Survival according to Stupp



Stupp et al. in NEJM, 2005

Methods

Patients with newly diagnosed, histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) or radiotherapy plus continuousdaily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). The primary end point was overall survival.

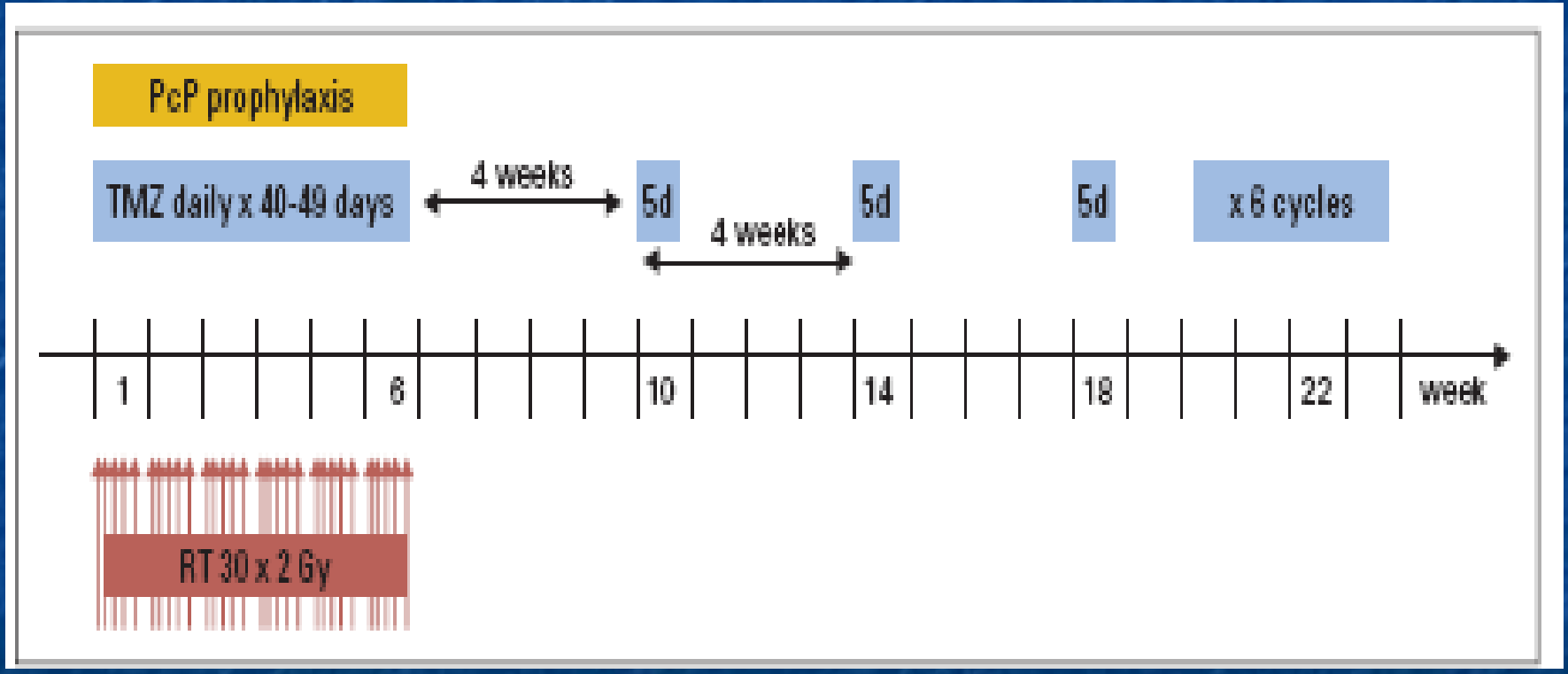
Results

A total of 573 patients from 85 centers underwent randomization. The median age was 56 years, and 84 percent of patients had undergone debulking surgery. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. The two-year survival rate was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapyalone. Concomitant treatment with radiotherapy plus temozolomide resulted in grade 3 or 4 hematologic toxic effects in 7 percent of patients.

Conclusions

The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity.

Temozolomide - administration according to Stupp



Temozolomide: Overall Safety

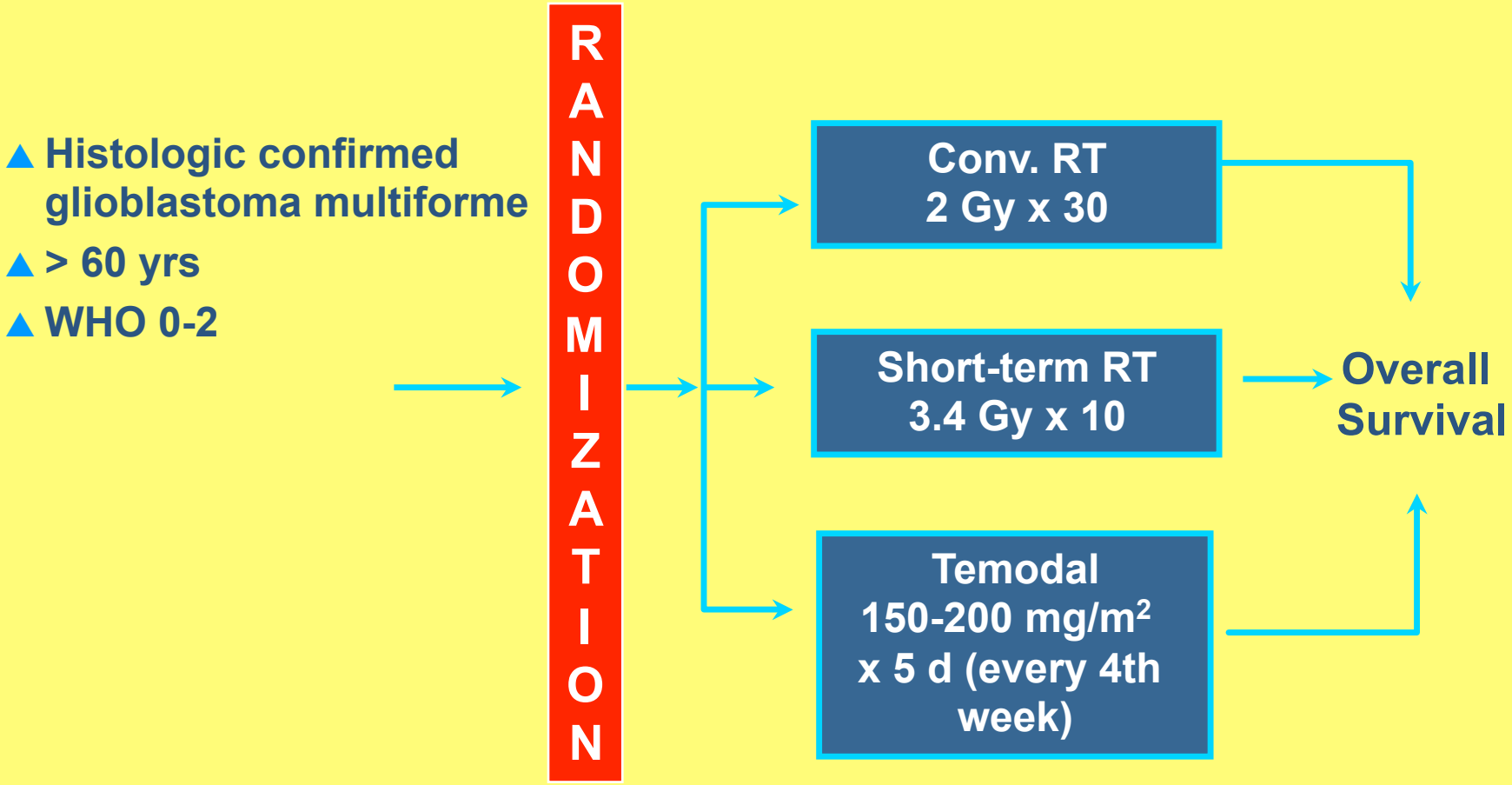
- Dose-limiting toxicity is myelotoxicity:
  - Thrombo- and leukocytopenia
  - Grade 3/4 events: 10%
- Most commonly reported adverse events:
  - Nausea/vomiting, constipation, fatigue and headache

Tolerability

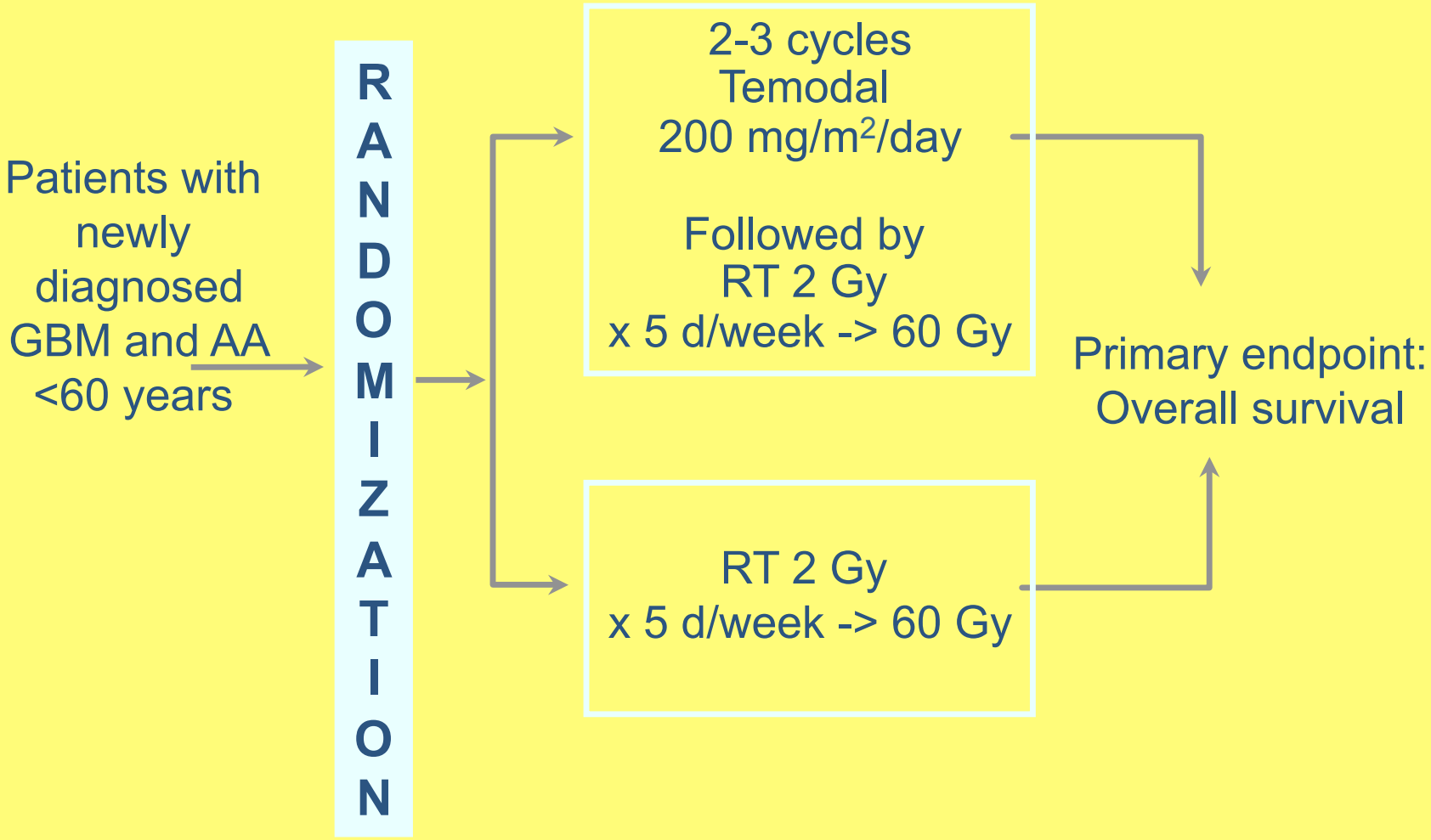
- Adverse events: myelosuppression (grade 3/4); GI episodes are mild and infrequent
- Discontinuation due to toxicity: 3%
- No CNS toxicity
- Compliance to treatment
  - Interval between cycles >32 days: 13% of cycles
  - Reduced dose: 14
  - Increased dose (200 mg/m^2): 4 patients

Newly diagnosed GBM in an elderly population

NCBTSG (n=480)



Neoadjuvant study



Chemotherapy 4

Palliation

First line:

Temozolomide: 150 - 200 mg/m^2
x 5 days and 23 days of a free interval

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Chemotherapy 5

Is there a role for second-line chemotherapy in palliation of patients with malignant glioma?

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Chemotherapy 6

If so, consider the following alternatives:

1. PCV - courses (procarbazine, CCNU, vincristine)
2. Gleevec + Hydroxurea (Clinical trial just finished)
3. Temozolomide given daily 75 - 100 mg/m^2 (”low dose”) during 21 out of 28 days and repeated

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Chemotherapy 7

PCV - courses (procarbazine, CCNU, vincristine) seems to be most effective in an adjuvant setting after radiotherapy in patients with anaplastic oligodendroglioma.

Initially promising data in palliative treatment of patients with glioblastoma seems difficult to verify.

However, in a few patients, a surprisingly growth inhibiting effect may occur.

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Arterio-Venous Malformations

Treatment alternatives:

- Surgery
- Embolisation
- Radiotherapy

  Proton beam, gammaknife, linear accelerator with a stereotactic equipment

Treatment of glioma patients

Where is nuclear medicine?

In diagnostics?

In treatment?

Glioma patients - Where is nuclear medicine?

- Diagnosis
  a. Location of primary tumor and possible spread in the CNS
  b. Improved analysis of the properties of the tumor cells and the surrounding normal tissue

- Treatment

  Adding to externally given irradiation dose on selected tumor cells

Cancer stam celler

1. CSC:s finns i leukemier och solida tumörer t.ex gliom
2. CSC:s står för mindre än 1 % av tumörcellerna
3. CSC:s och normala stamceller har flera gemensamma cellytemarkörer.
4. CSC:s kan ha störd funktion i signaltransduktion
5. CSC:s och normala stamceller har höga nivåer av ”drug efflux transporters”
6. Angreppspunkter vid behandling: Särskilda ytmarkörer signaltransduktionsproteiner, apoptosmekanismer

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Cancer stem cells

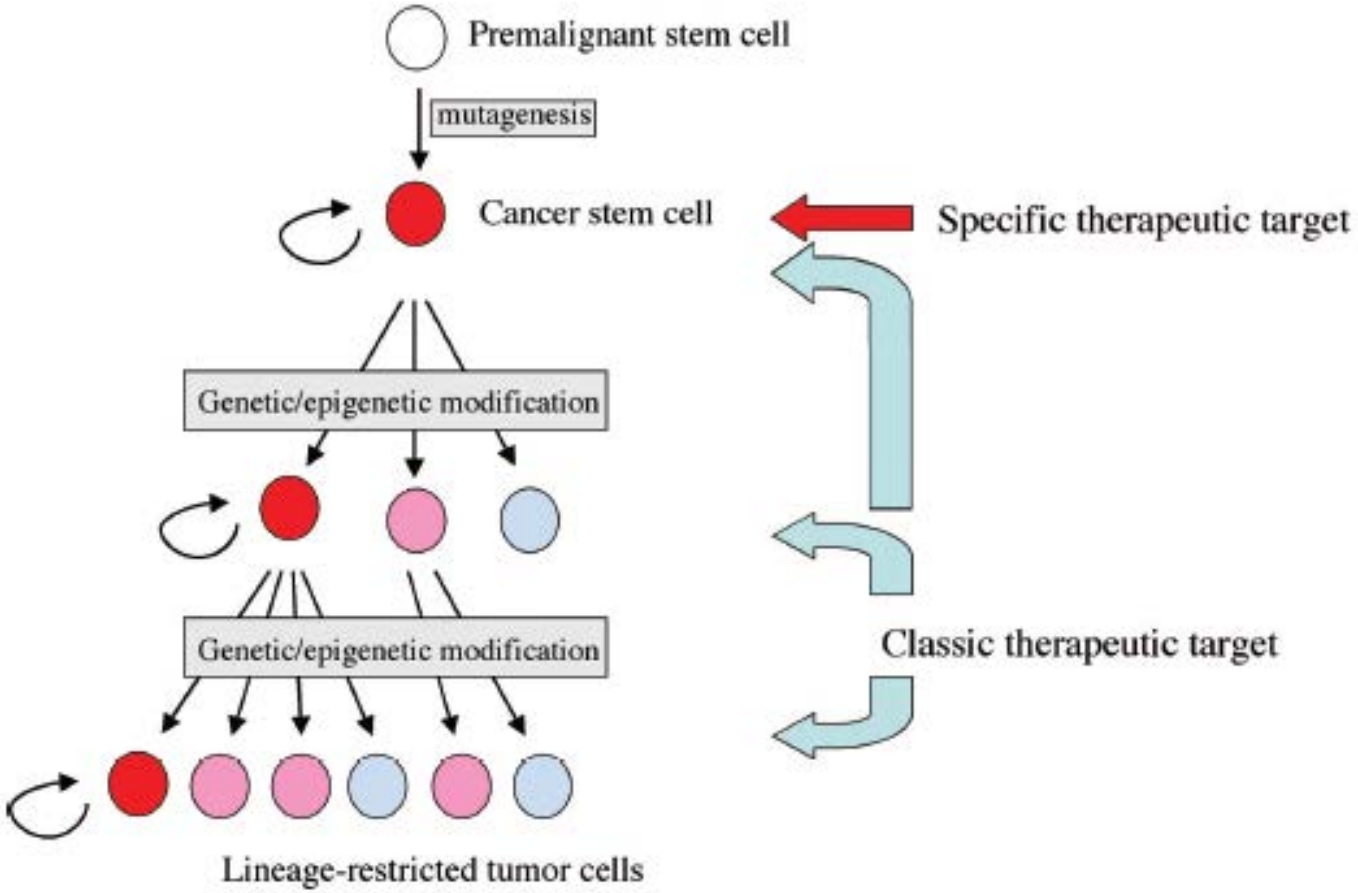

Figure 2. Clinical implication for cancer stem cell theory.

Epigenetics

Epigenetics is a term in biology used today to refer to features such as chromatin and DNA modifications that are stable over rounds of cell division but do not involve changes in the underlying DNA sequence of the organism.[1] These epigenetic changes play a role in the process of cellular differentiation, allowing cells to stably maintain different characteristics despite containing the same genomic material.

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Maligna gliom
”Egna forskningsprojekt”

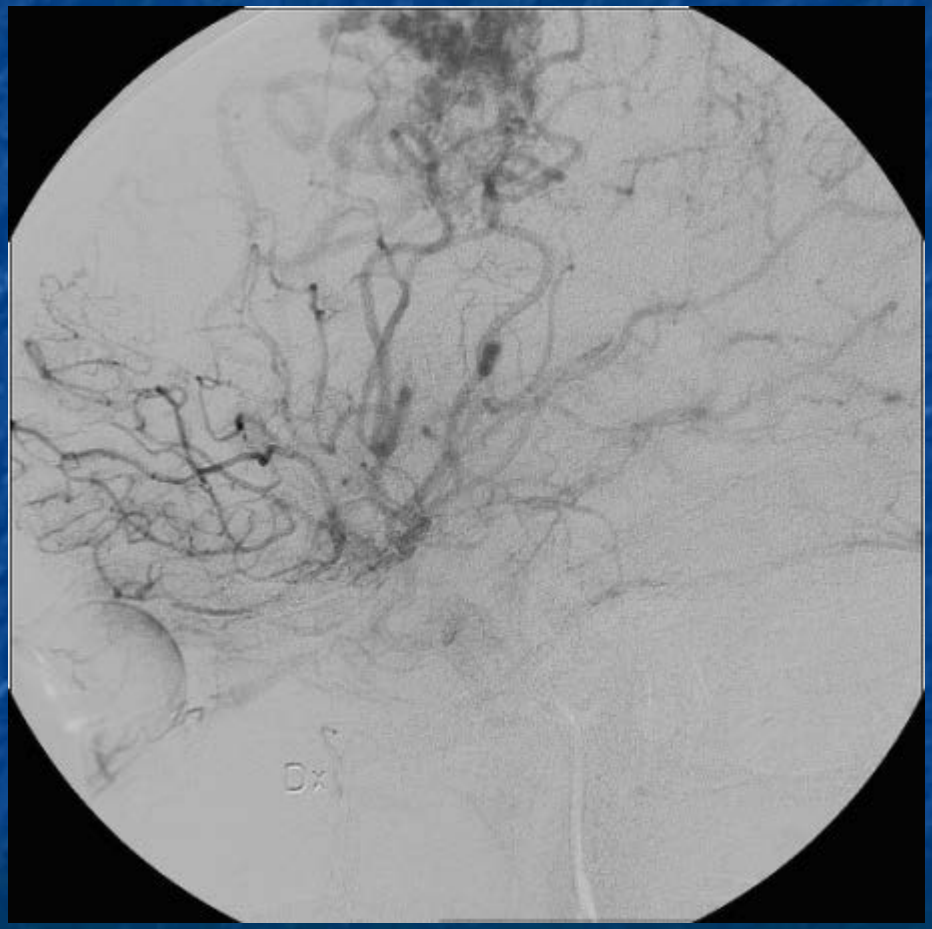
1. MR och MRS av hjärnan
2. Intraventrikulära inj. av EGF-affibody
3. Fortsatt p+-terapi av strålmål i hjärnan
4. Genomic microarrays /Teresita Diaz de Ståhl/Jan Dumanski
5. Uppföljning av behandlade patienter
6. Nationella behandlingsprotokoll

EB 2008

And now to something completely different!

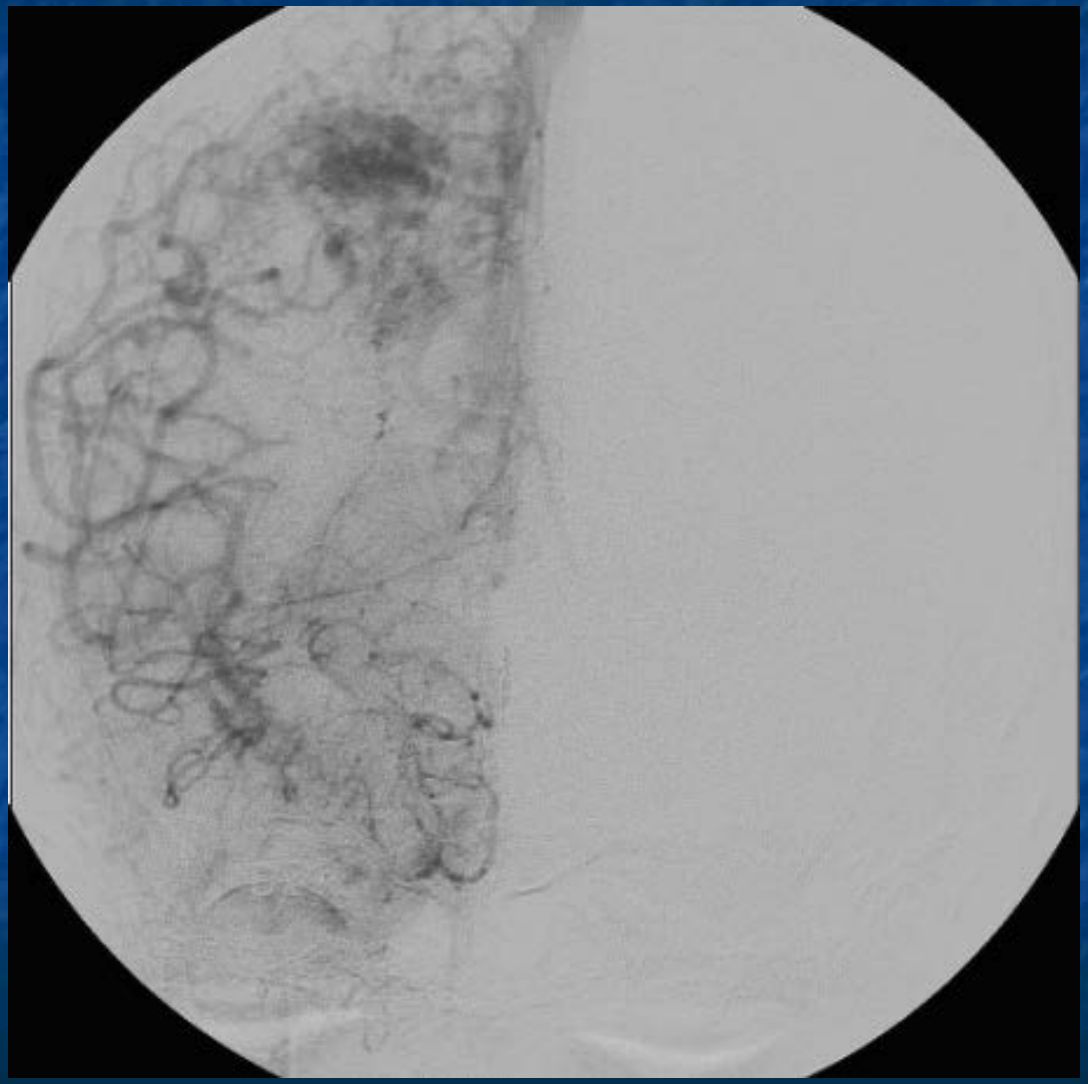
- Arterio-Venous Malformations (AVM)

AVM before proton beam therapy side view



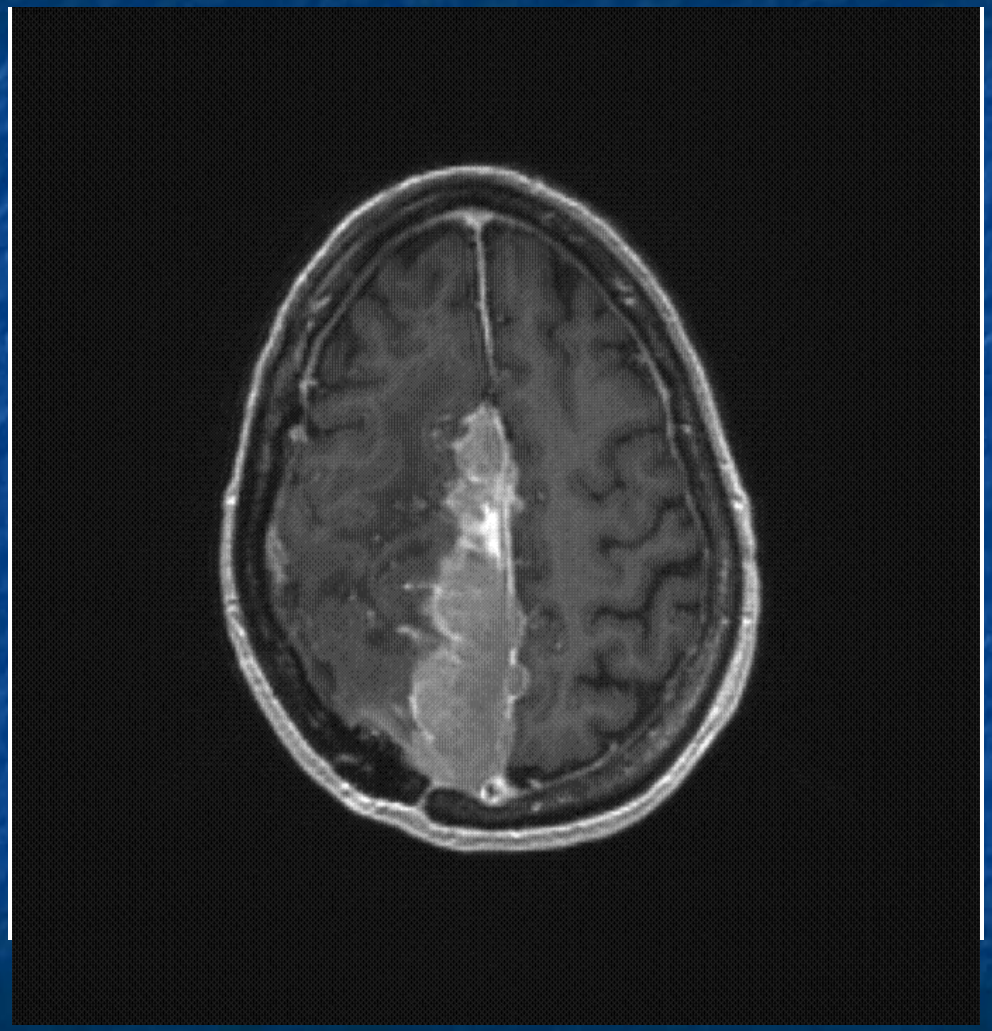
AVM after proton beam therapy side view

AVM before proton beam therapy frontal view

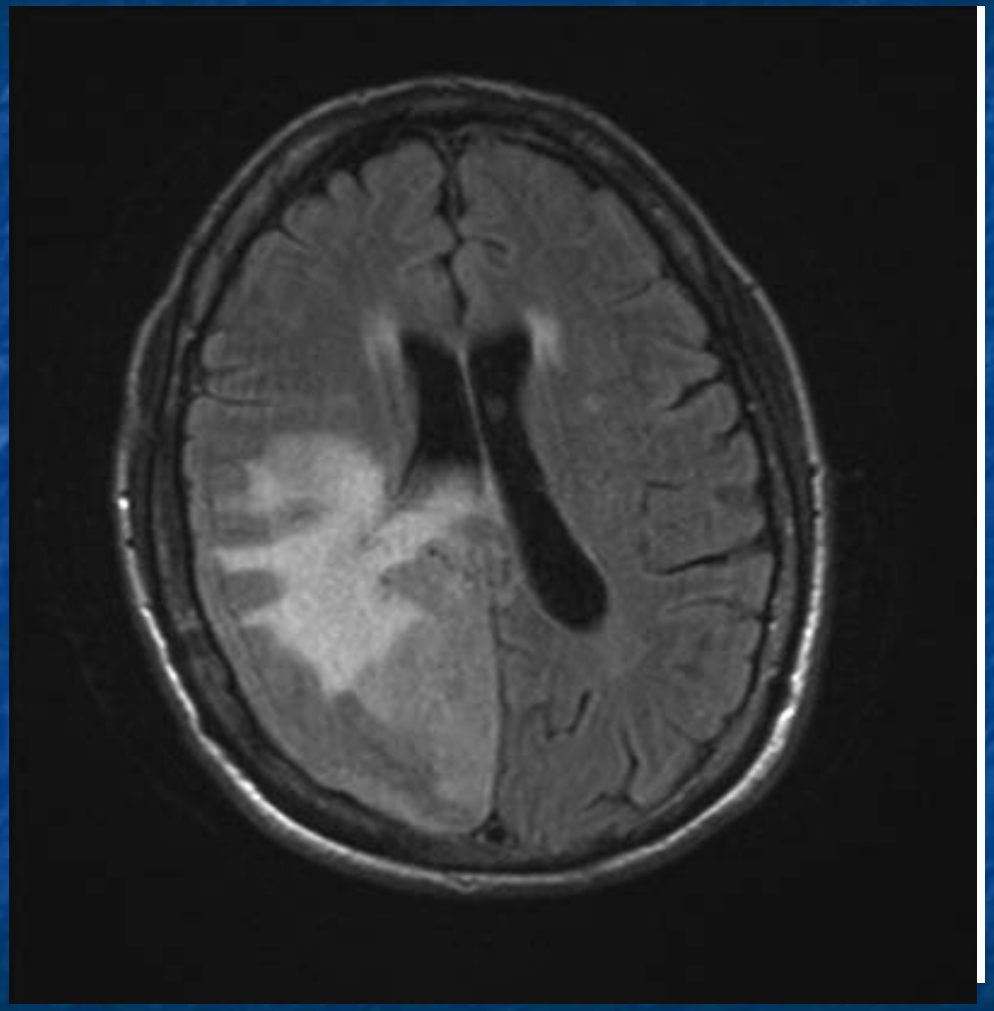


AVM after proton beam therapy frontal view

Meningioma



Meningioma



Glioma invasion

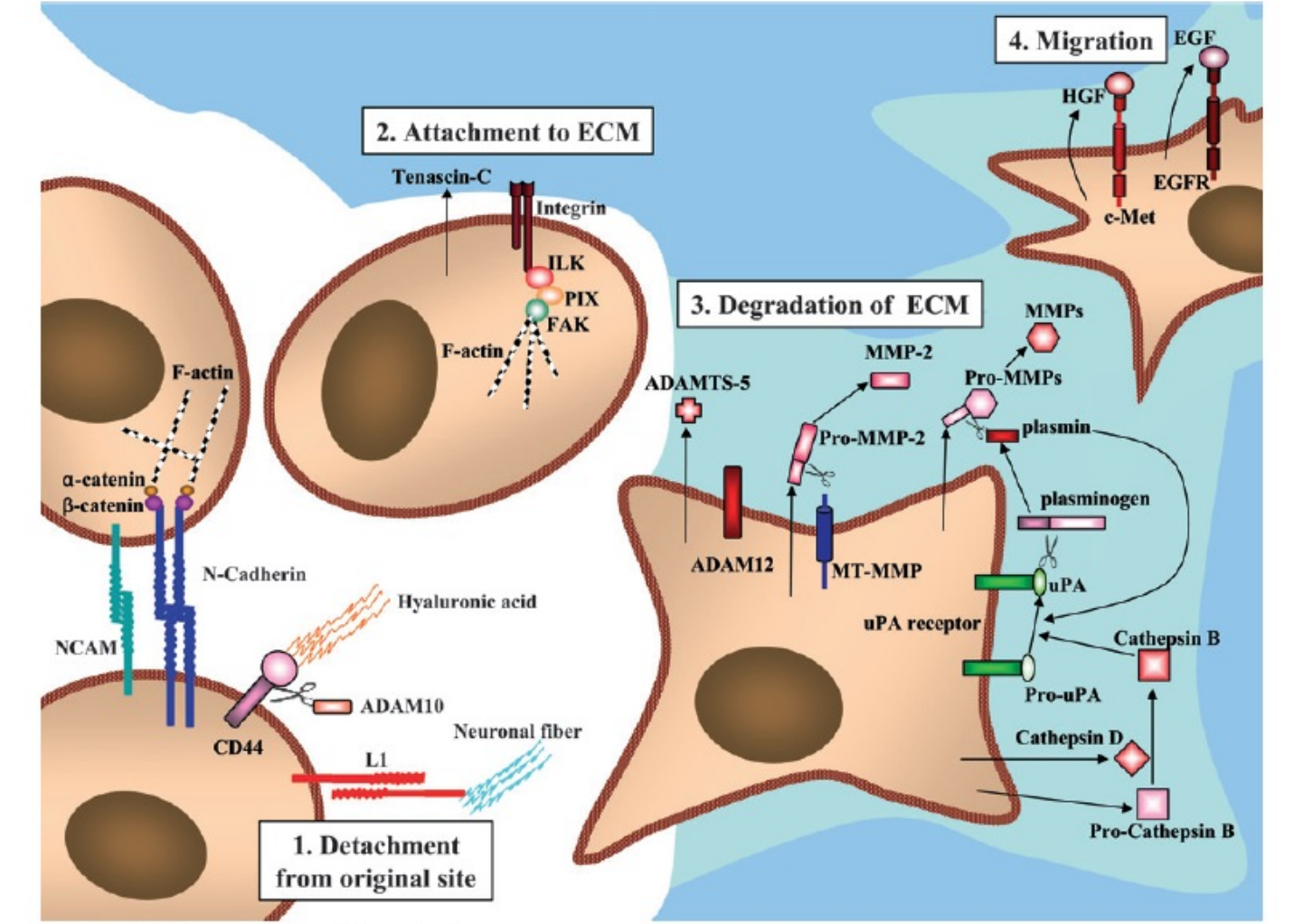
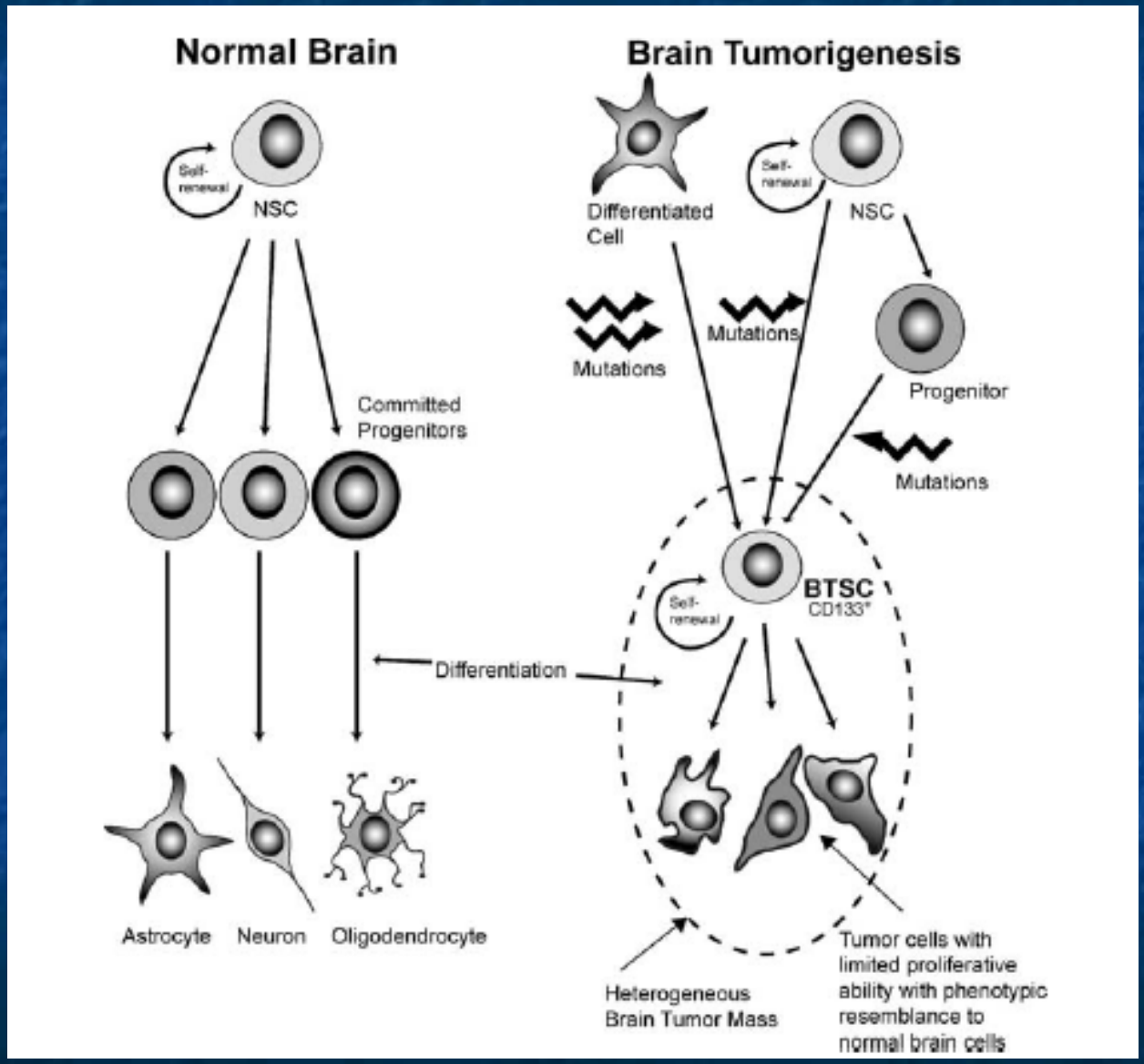


Figure 3. Putative mechanism of glioma invasion

Glioma stem cells



Radiotherapy of glioblastomas
Concomitant with temozolomide

- Epigenetic inactivation of the DNA repair enzyme methylguanine methyltransferase (MGMT) seems to be the strongest predictive marker for outcome in patients treated with alkylating agent chemotherapy. Patients whose tumors do not have MGMT promoter methylation are less likely to benefit from the addition of temozolomide chemotherapy and require alternative treatment strategies. Epigenetic inactivation of the DNA repair enzyme methylguanine methyltransferase (MGMT) seems to be the strongest predictive marker for outcome in patients treated with alkylating agent chemotherapy. Patients whose tumors do not have MGMT promoter methylation are less likely to benefit from the addition of temozolomide chemotherapy and require alternative treatment strategies

- Its key mode of action appears to be methylation at N(7) and O(6)-positions of guanine. The level of expression and activity of the DNA repair enzyme O(6)-methylguanine DNA methyltransferase is thought to be a major predictor of response to TMZ

MGMT promoter status and survival after radiotherapy

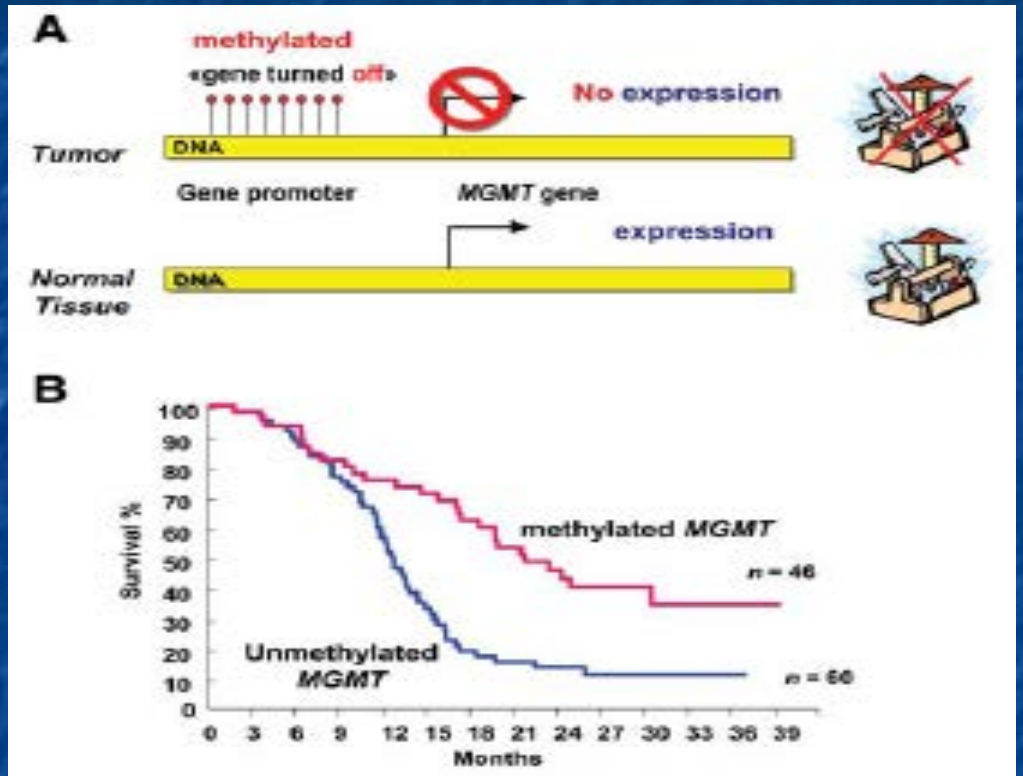


Figure 3. Inactivation of the methylguanine methyltransferase (*MGMT*) gene and benefit from temozolomide (TMZ). (**A**): Epigenetic silencing of the *MGMT* gene by promoter methylation. (**B**): The survival of patients treated with TMZ plus radiotherapy according to *MGMT* promoter status. Adapted from Hegi ME, Diserens AC, Gorlia T et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997–1003, Copyright © 2005 Massachusetts Medical Society.

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Three interesting publications

Trog et al. in Amino Acids, 2006: Non-sufficient cell cycle control as possible clue for the resistance of human malignant glioma cells to clinically relevant treatment conditions.

Bao et al. in Nature vol. 444, s. 756 – 760, dec 2006: Glioma stem cells promote radioresistance by preferential reaction of DNA damage response.

Pan et al. in Future Oncol vol. 2(6), s. 723 -731, 2006: Implications of cancer stem cells in the treatment of cancer.

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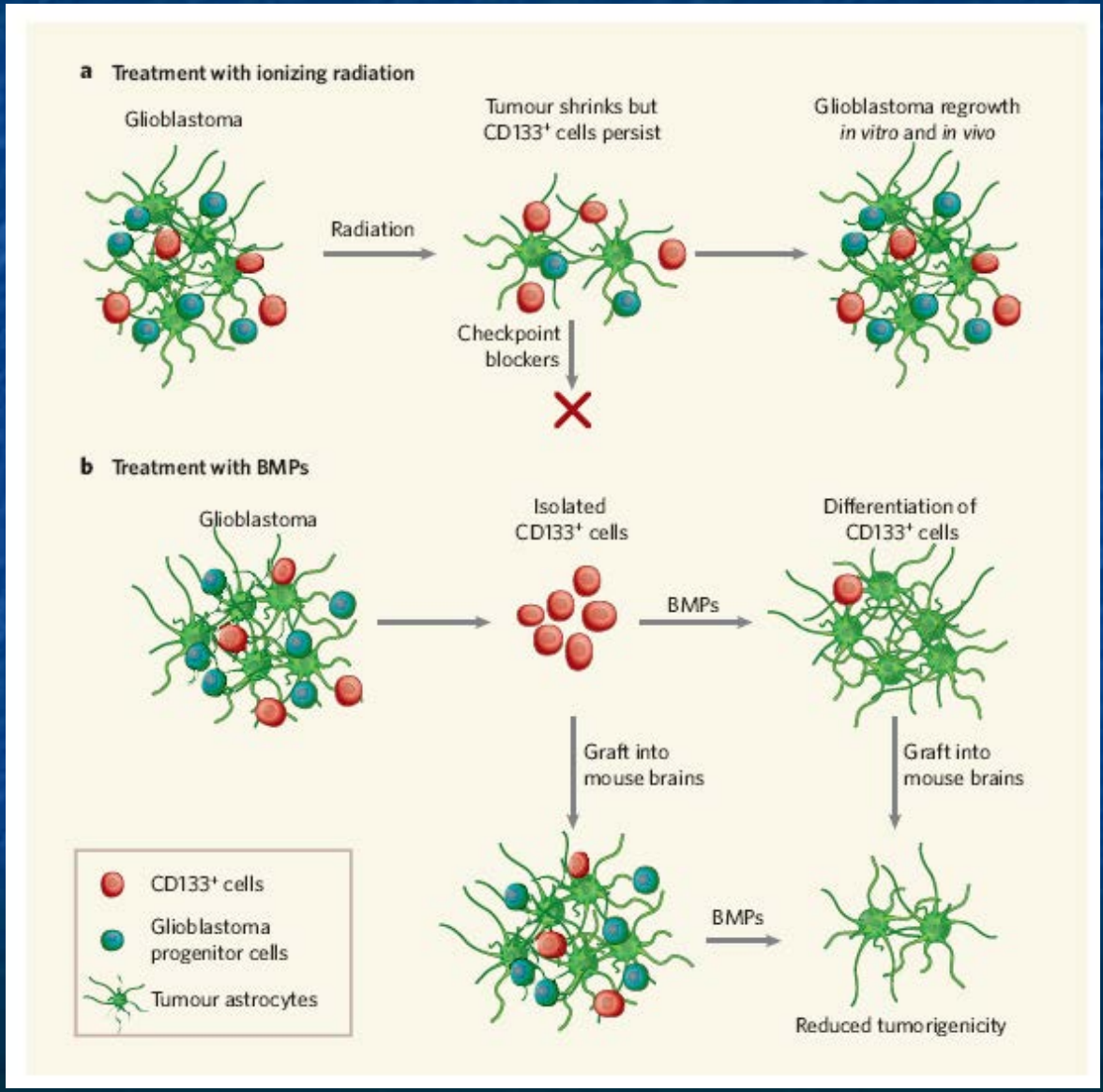
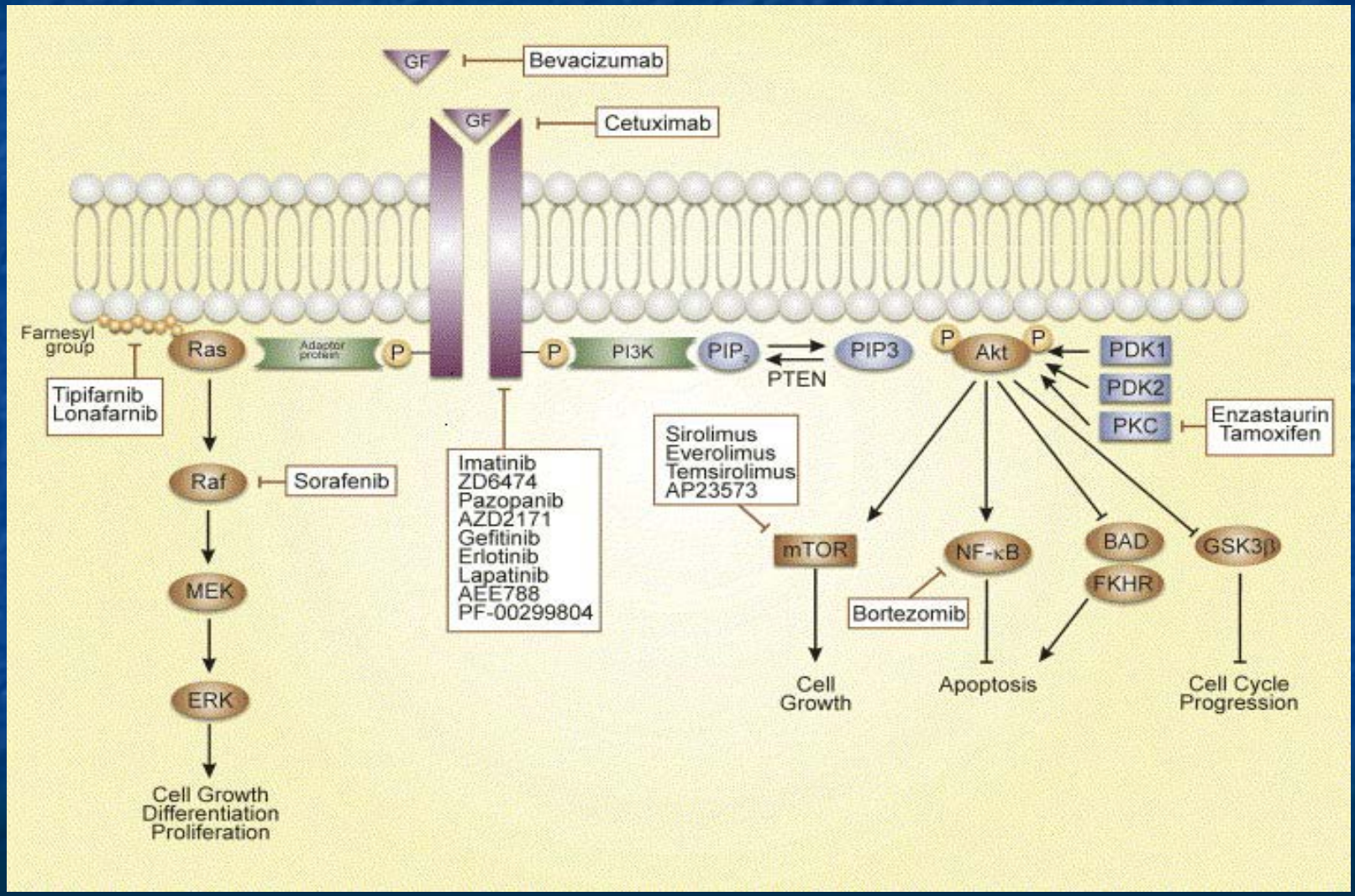
Questions for the future

- Do all brain tumors contain cancer stem cells?
- What are the differences and similarities between cancer stem cells from different tumors?
- Does malignant progression of low grade to high grade gliomas directly involve brain tumor stem cells?
- Is CD-133 the best marker for the prospective isolation of cancerstem cells?
- Can we attack brain tumor stem cells without attacking normal neural stem cells?
- Would this matter?
- These questions and many others highlight the early state of this fieldand the great amount of work needed before putting thediscovery of cancer stem cells to productive use.

Glioma stem cells



Treatment approach in gliomas



BBB

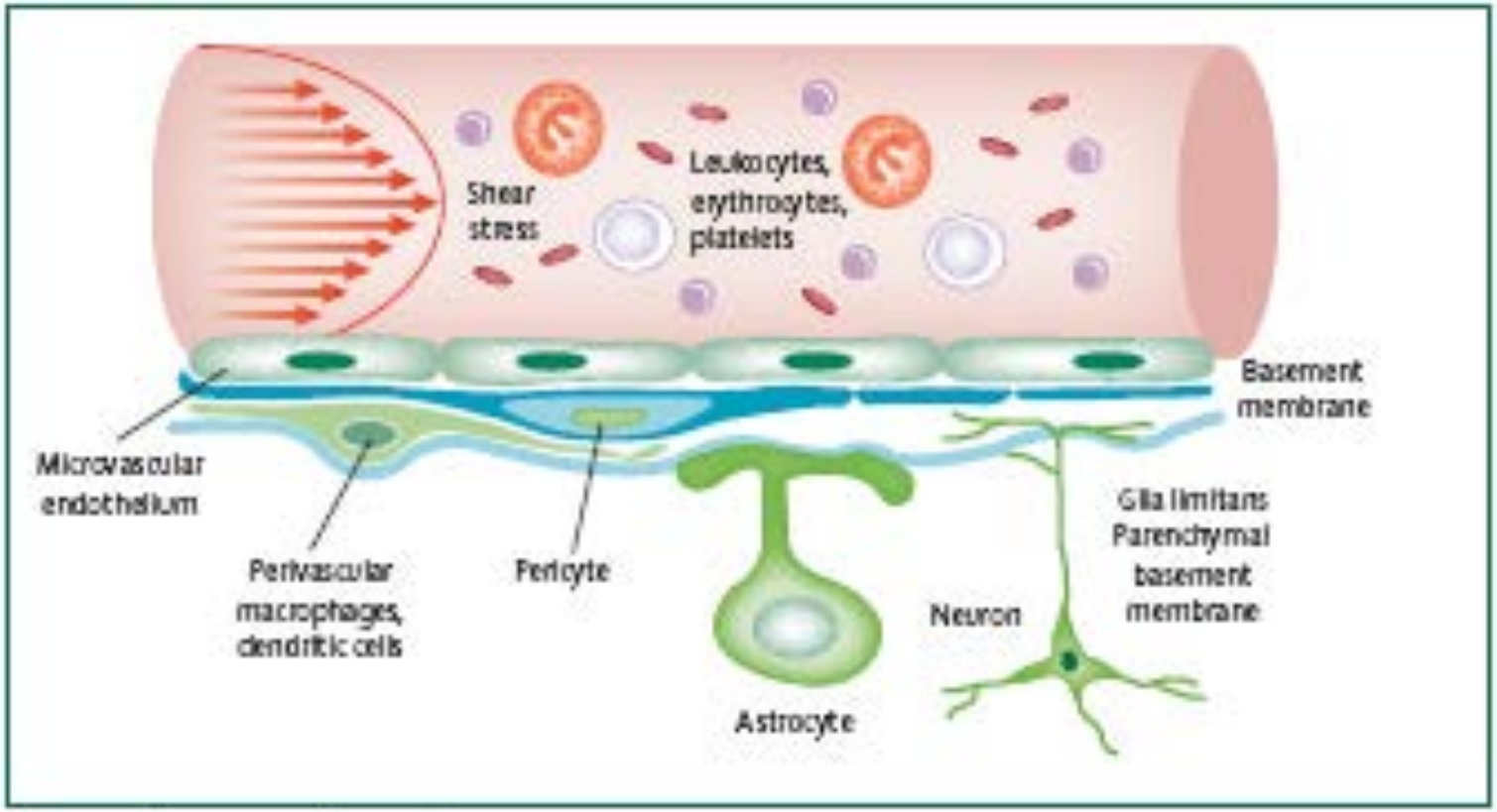


Figure 1: The neurovascular unit (NVU)

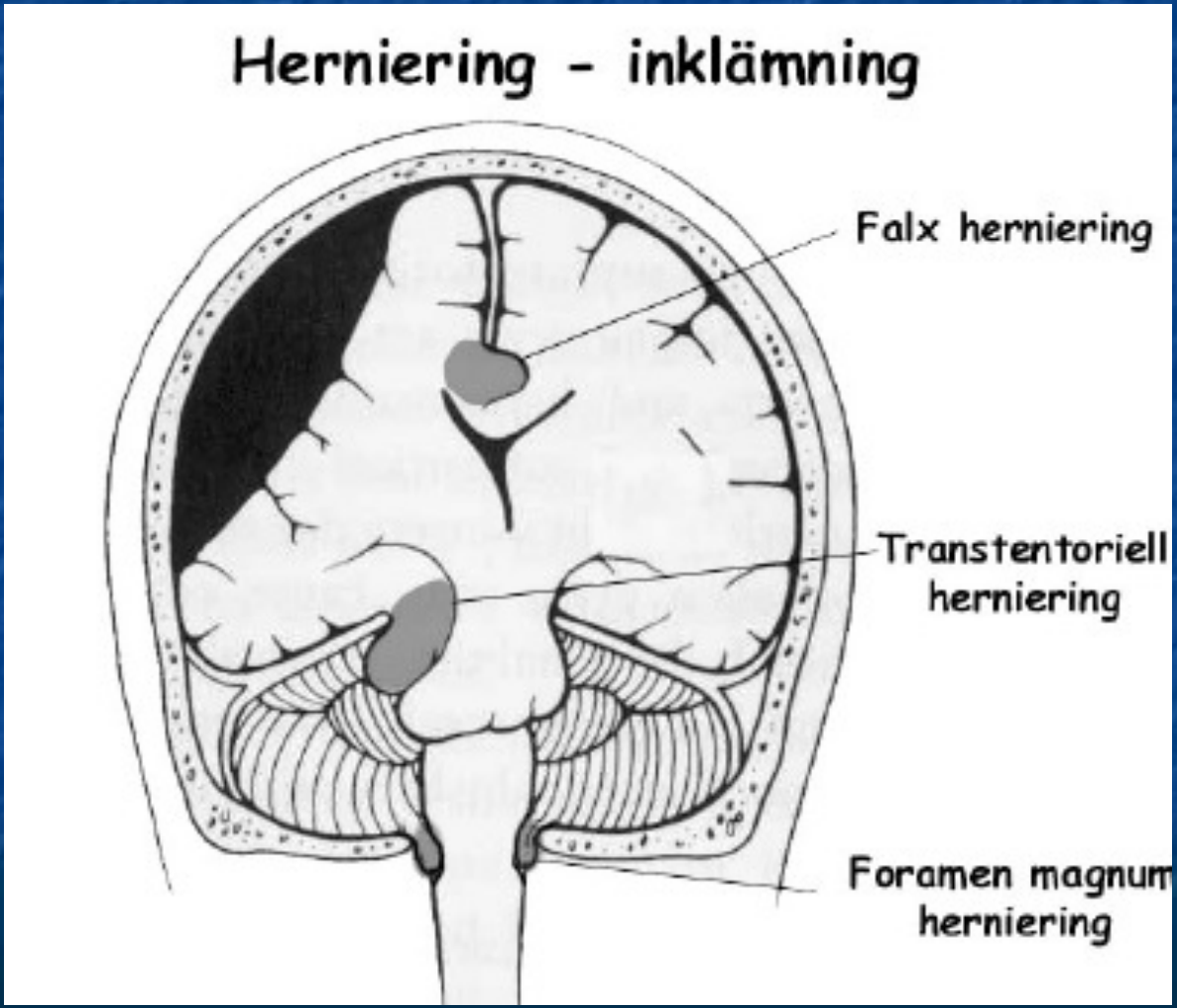
The NVU is a complex cellular system that includes circulating blood components, highly specialised endothelial cells, a high concentration of pericytes embedded in the endothelial cell basement membrane, perivascular antigen-presenting cells, astrocytic endfeet, and associated parenchymal basement membrane and neurons. Although the endothelial cells form the BBB, the continuous communication between the brain endothelium and the other cellular elements of the NVU are prerequisites for barrier function.

En föreläsning på svengelska

Inget för puristerna

The brain is located in a enclosed volume

Herniation


Herniering - inklämning
Falx herniering
Transtentoriell herniering
Foramen magnum herniering

En bild säger mer än tusen ord?

- CT
- MRT - MRS
- PET
- Angiografi
- Ultraljudsledd navigation

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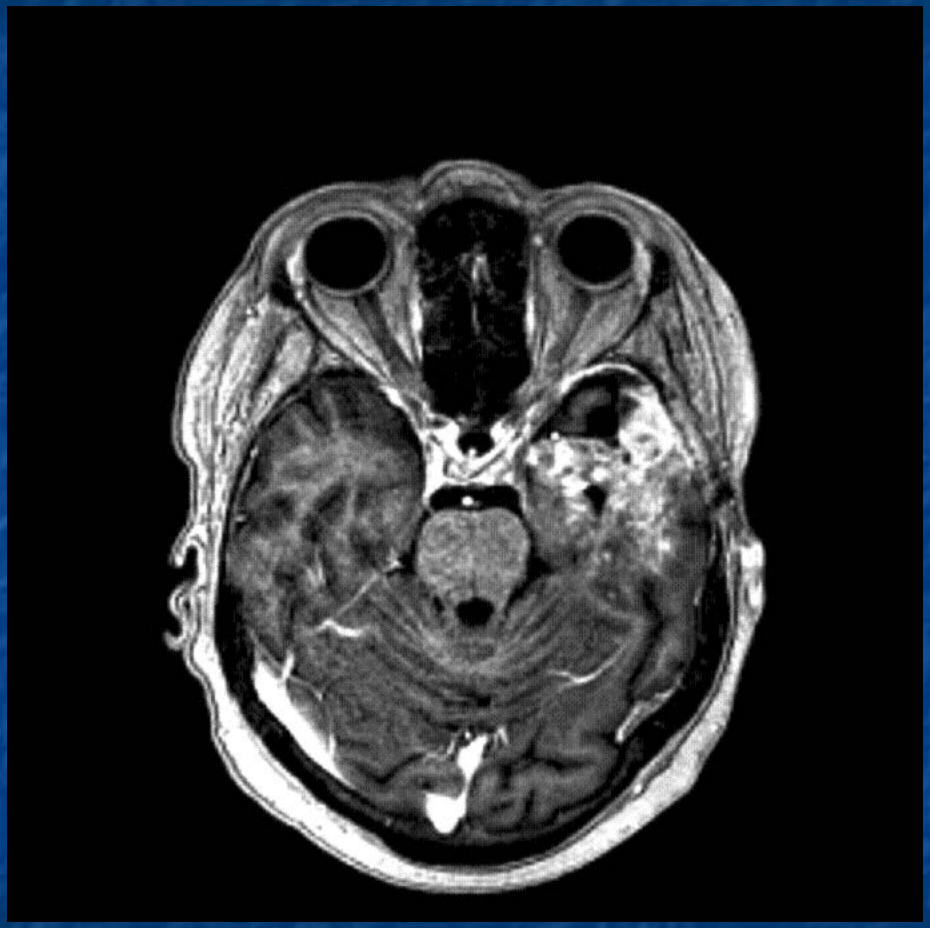
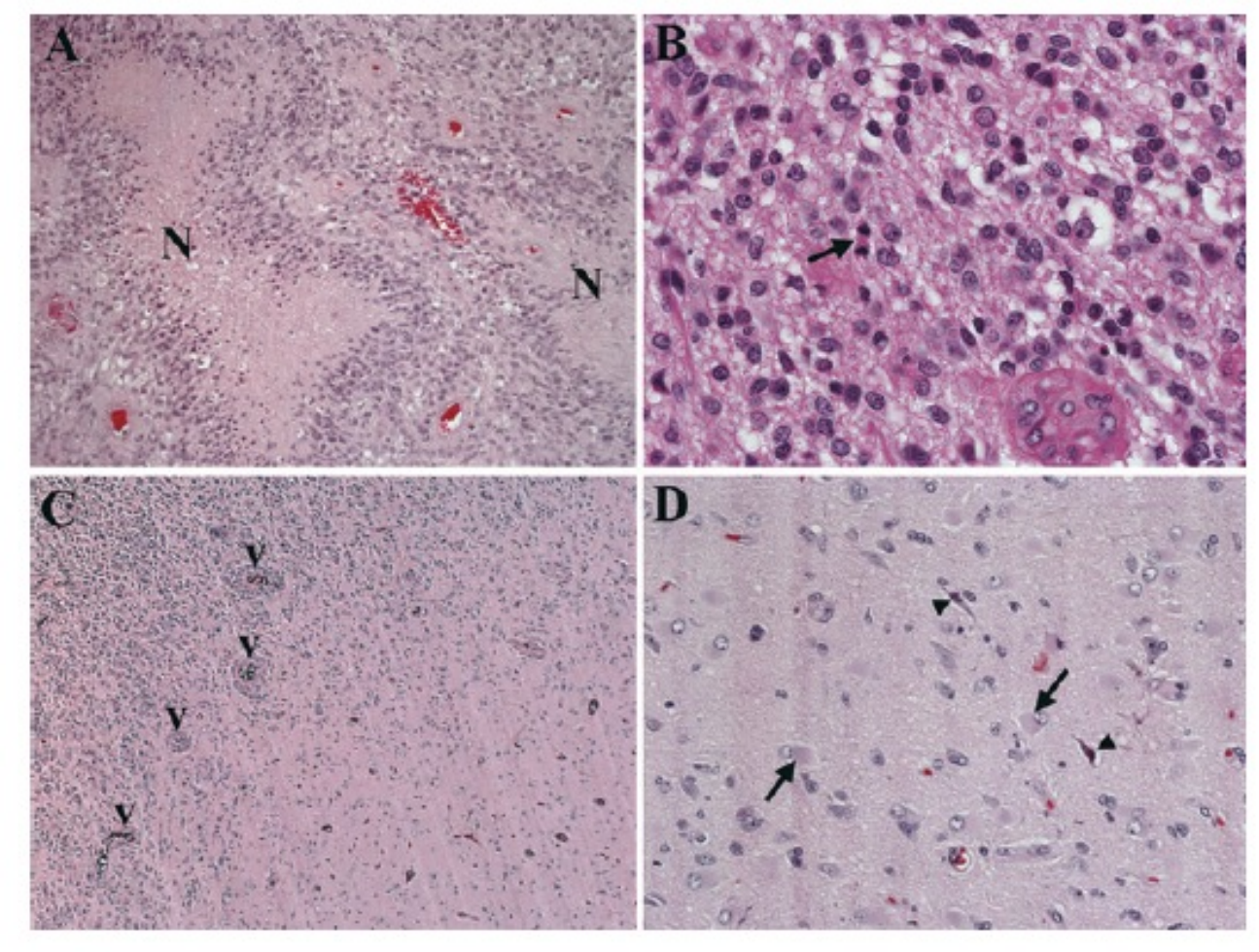
Glioblastoma

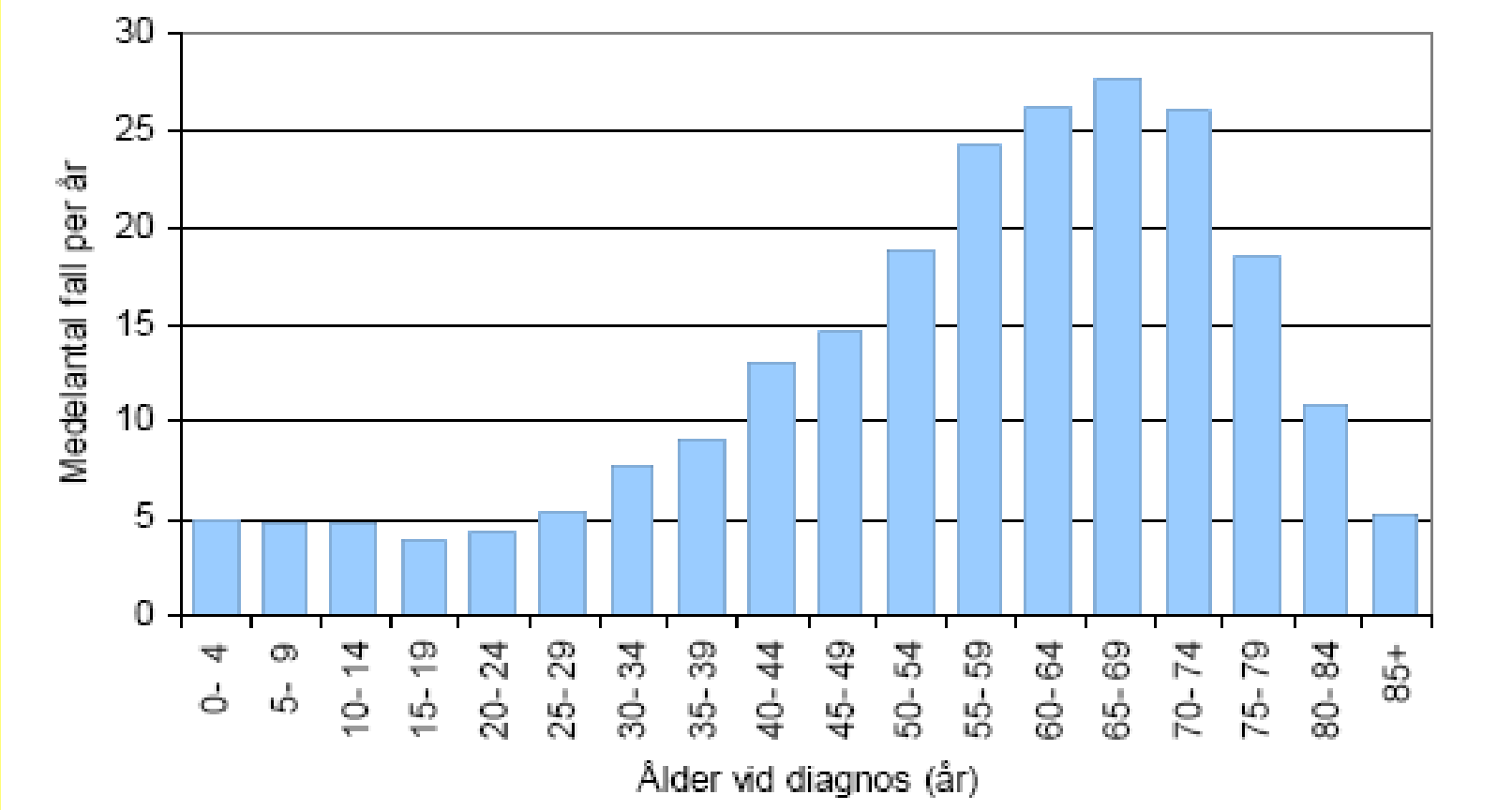
Glioblastoma



Glioblastoma histopathology



Hjärntumörer; ålder vid diagnos



High grade gliomas; treatment

- Radiotherapy

  Fractional dose: 2 Gy

  Weekly dose: 10 Gy

  Total dose: 60 Gy
- Treatment volume : GTV + 2 – 3 cm
- Radiotherapy with concomitant temozolomide

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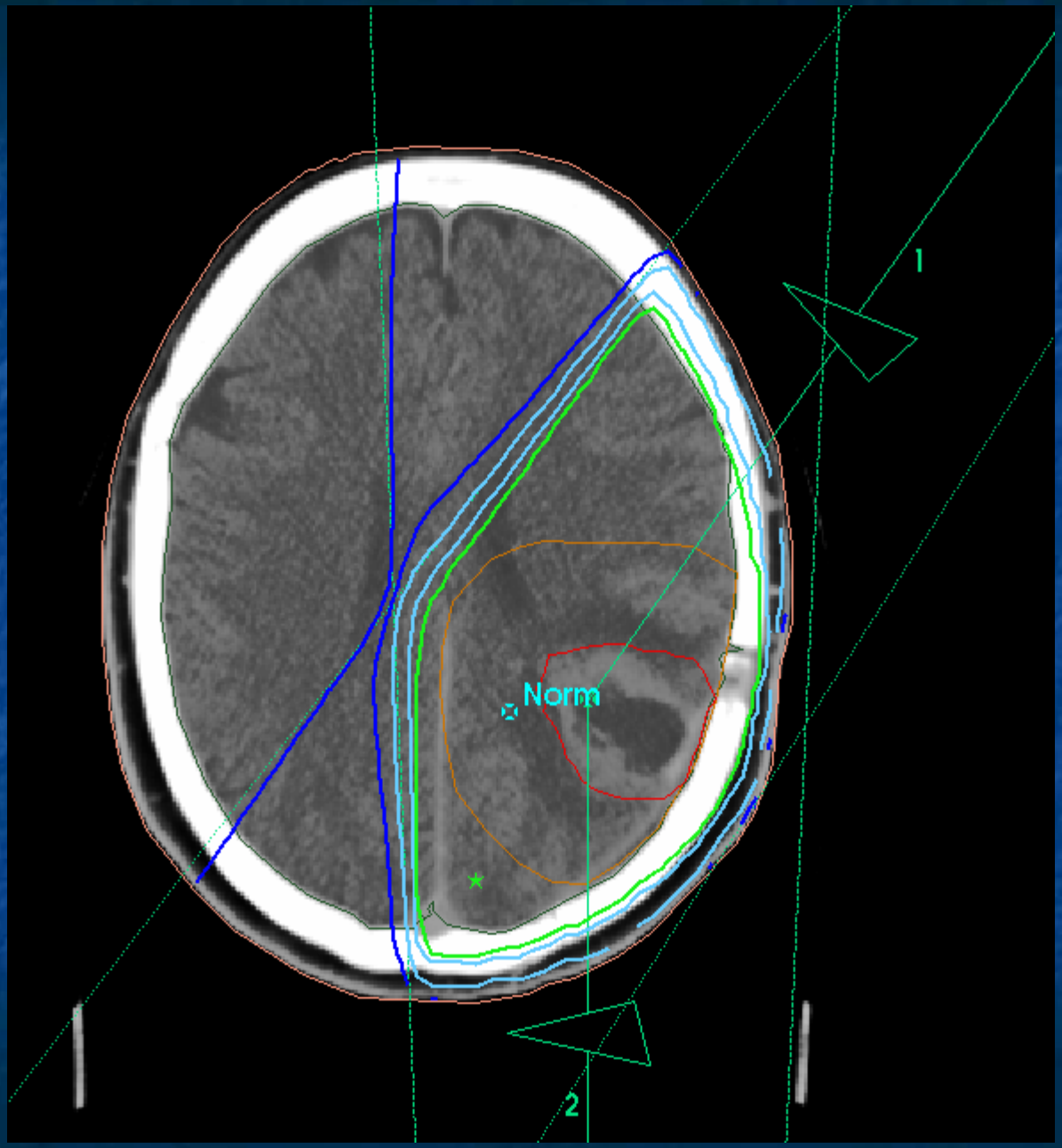
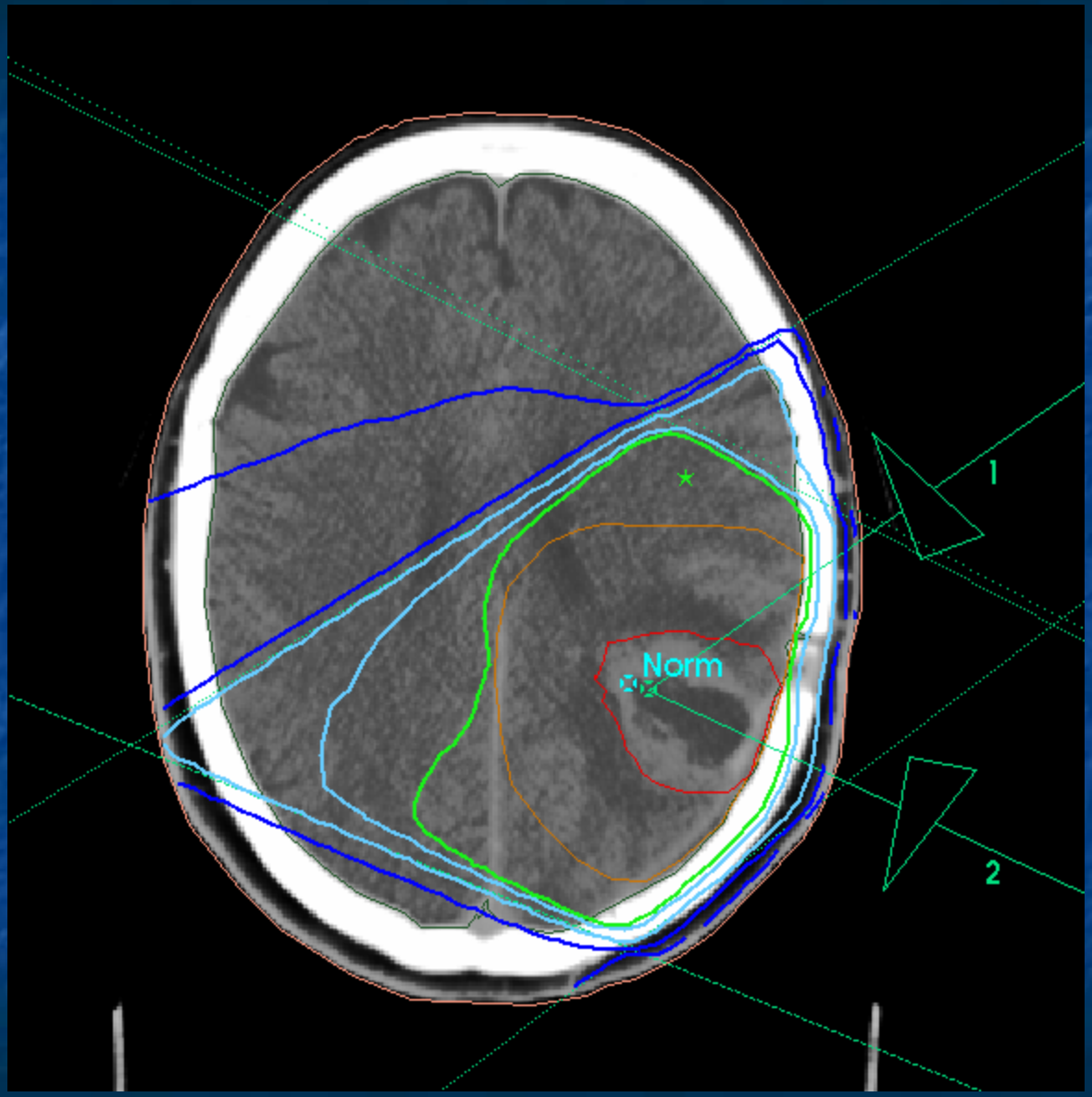

1
Norm
2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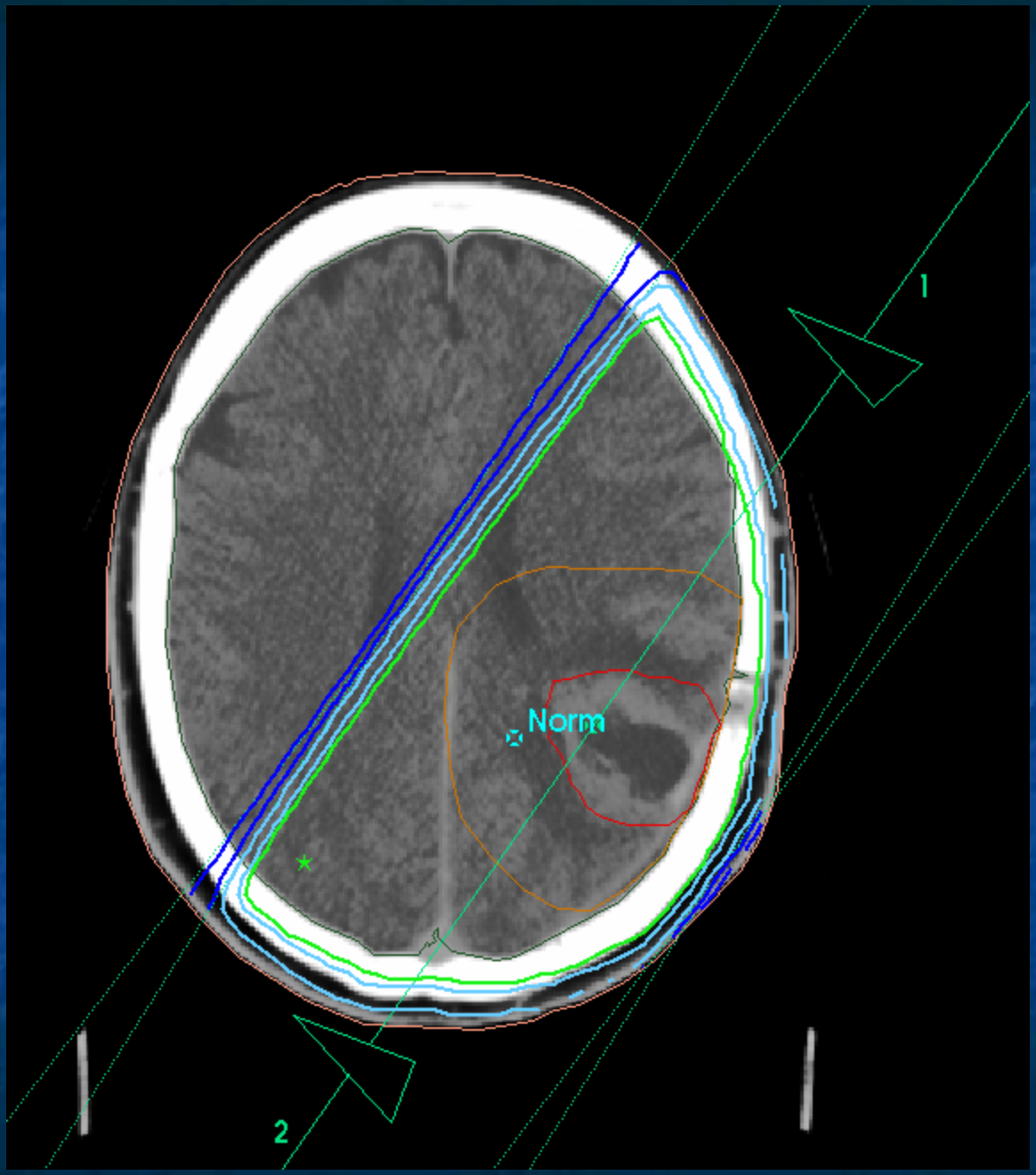

1
Norm
2

Såå igen..... vid högmaligna gliom - strålbehandling..... Hur?

Volymen?

GTV

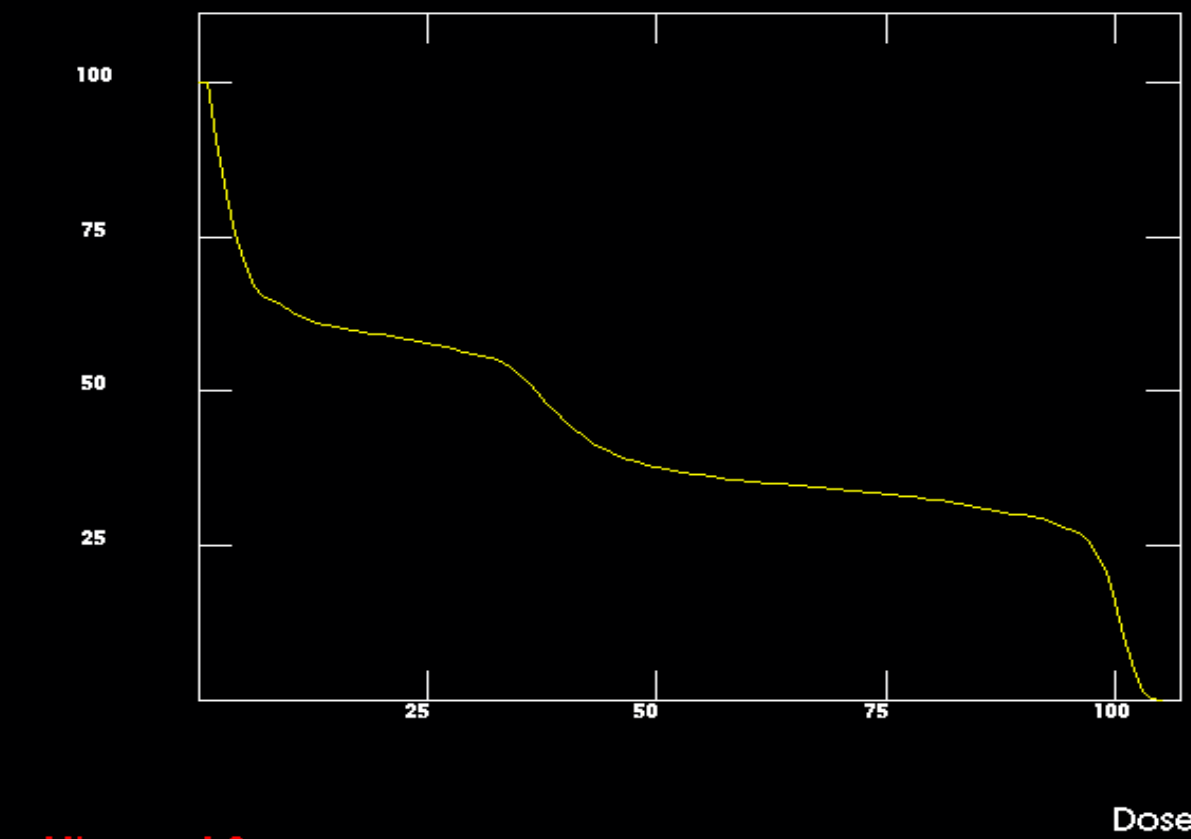
CTV

PTV

DVH-VOI id 4 hjarna

Volume (ccm): 1254.

Calc. pnts 25164 / 25953



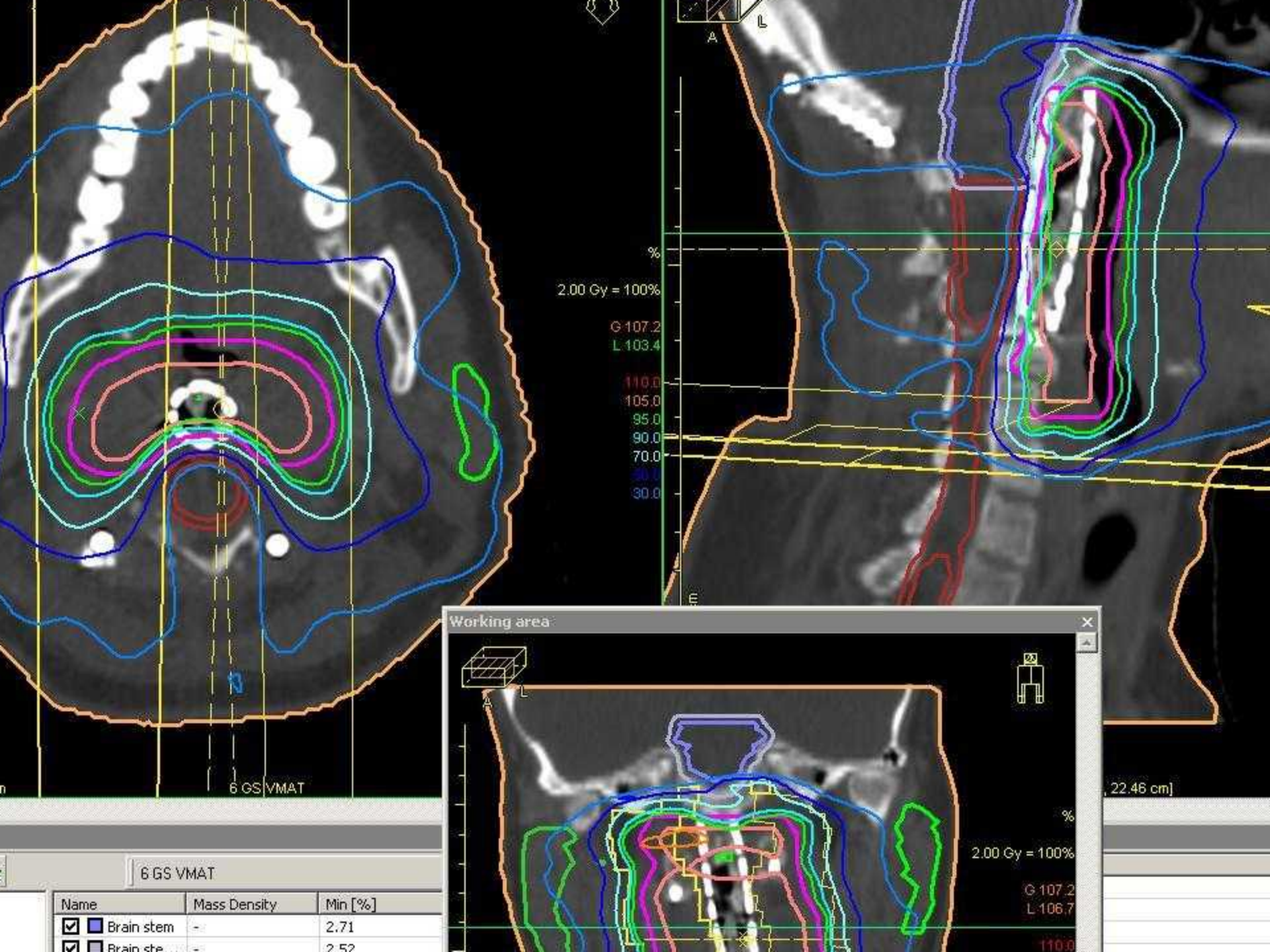
Min 1.0

Max 104.5

Median 36.9

Mean 45.1

Stand.dev 40.7


%
2.00 Gy = 100%
G 107.2
L 103.4
110.0
105.0
95.0
90.0
70.0
30.0
6 GS VMAT
Working area
%
2.00 Gy = 100%
G 107.2
L 106.7
110.0
6 GS VMAT
Name
Mass Density
Min [%]
Brain stem
2.71