ESTRO School

ESTRO Course Book

Multidisciplinary Management of Brain Tumours

4 - 6 October, 2015
Turin, Italy

NOTE TO THE PARTICIPANTS

The present slides are provided to you as a basis for taking notes during the course. In as many instances as practically possible, we have tried to indicate from which author these slides have been borrowed to illustrate this course.

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Faculty

Michael Brada

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The faculty of the teachers for this event has disclosed any potential conflict of interest that the teachers may have.

Programme

TIME	TITLE	SPEAKER
DAY 1	**SUNDAY 4-OCT- 2015**	
Introduction		
8:45	Introduction	Michael Brada
9:00	Modern imaging of CNS tumours	Ranj Bhangoo
10:00	What is new in brain tumour classification	Paola Cassoni
10:30	Coffee break / Expo	
11:00	Current surgical approaches	Ranj Bhangoo
Practical radiotherapy		
11:30	Radiotherapy –preparing the patient for treatment	Michael Brada
11:50	Radiotherapy – treatment techniques, wide field irradiation	Cristina Mantovani
12:10	Radiotherapy – treatment techniques, localised treatment	Michael Brada
12:30	Discussion	Michael Brada
13:00	Lunch / Expo	
14:00	Radiation tolerance of of the CNS	Damien Weber
14:30	Systemic therapy issues – current chemotherapy	Patrick Roth
15:00	Systemic therapy issues – novel therapies	Anthony Chalmers
15:30	Coffee break / Expo	
16:00	Debate/cases – proton therapy for CNS tumours	Damien Weber
17:00	Quality of life issues in neuro-oncology	Riccardo Soffietti

DAY 2	**MONDAY 5-OCT- 2015**	
Evidence based management of individual tumour types		
8:30	Management of grade II astrocytic tumours	Anthony Chalmers
9:00	Management of 1p;19q co-deleted tumours (oligodendrogliomas)	Patrick Roth
9:30	Management of grade III & IV astrocytomas	Anthony Chalmers
10:00	Coffee break / Expo	
10:30	Management of ependymoma of the brain and spinal cord	Damien Weber/Ranj Bhangoo
11:00	Management of cranial germ cell tumours	Umberto Ricardi
11:30	Management of CNS lymphoma	Patrick Roth
12:00	debate/cases – management of high grade glioma in the elderly	Anthony Chalmers
13:00	Lunch / Expo	
Evidence based management of individual tumour types – childhood tumours		
14:00	Management of high grade glioma and brain stem tumours	Darren Hargrave/ Umberto Ricardi
14:30	Management of medulloblastoma	Darren Hargrave/ Umberto Ricardi
15:00	Management of low grade gliomas	Darren Hargrave/ Umberto Ricardi
15:30	Coffee break / Expo	
16:00	Radiotherapy outlining / planning exercise	Cristina Mantovani/Michael Brada/Umberto Ricardi

DAY 3	TUESDAY 6-OCT- 2015	
Clinical trials and evidence based management		
8:45	Clinical trials in neuro-oncology	Anthony Chalmers/Darren Hargrave
9:45	Management of skull base tumours	Damien Weber
10:30	Coffee break / Expo	
11:00	Management of other benign intracranial tumours	Michael Brada
11:45	Management of brain metastases	Michael Brada
12:30	Debate	Michael Brada
13:00	Lunch / Expo	
14:00	Medical therapy and care of brain tumour patients	Patrick Roth
14:30	Debate – cranial reirradiation & Systemic therapy for brain metastases	Anthony Chalmers Michael Brada
15:30	Coffee break / Expo	
16:00	Radiotherapy outlining / planning exercise/case discussion	Cristina Mantovani/Michael Brada/Umberto Ricardi

Faculty

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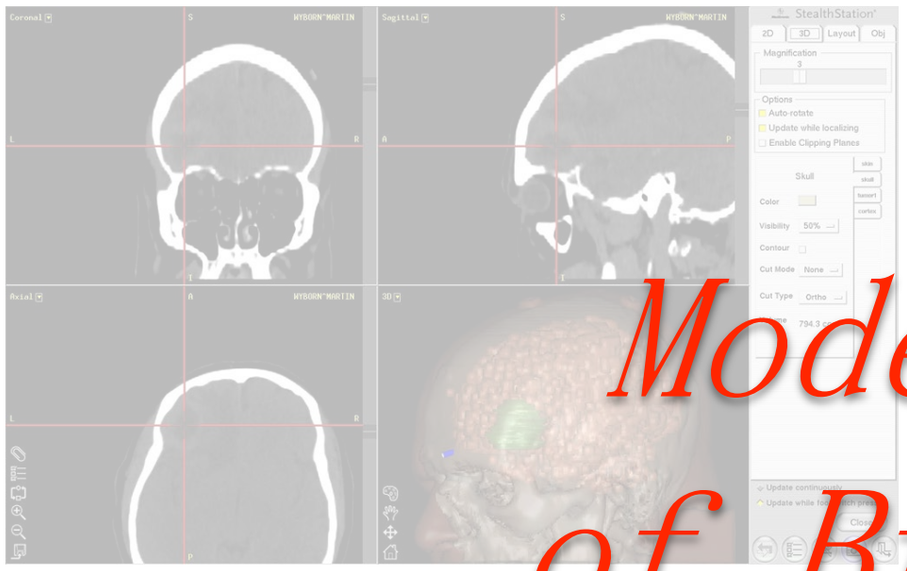
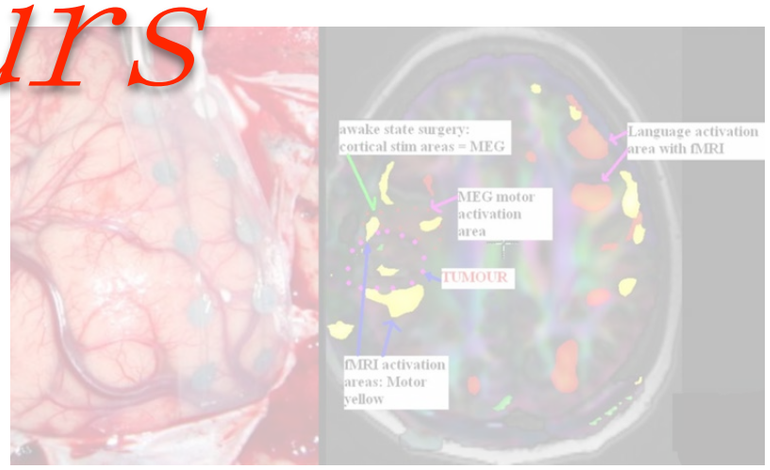


Modern Imaging of Brain Tumours



Ranj Bhangoo, *Christian Brogna*, *Francesco Vergani*

Department of Neurosurgery

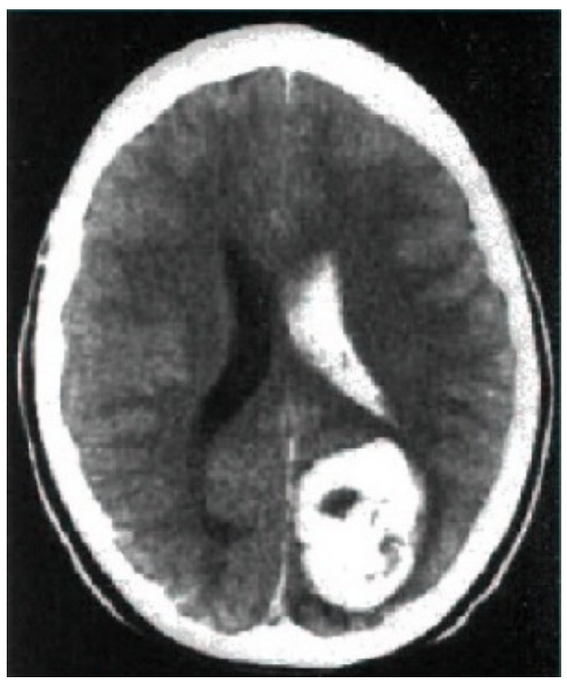
King's College Hospital - London

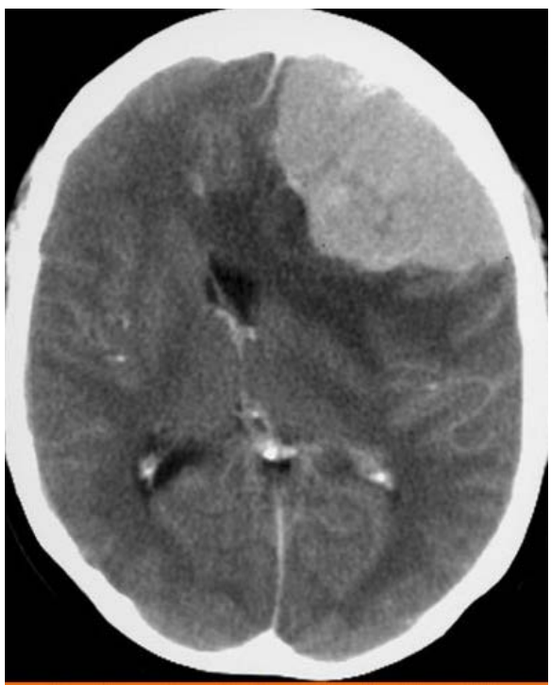
- **CT and routine MRI protocol**
- **Anatomic Imaging**
- **Metabolic Imaging**
- **Physiological Imaging**
- **Functional Imaging**
- **Pros and Cons Imaging followup**

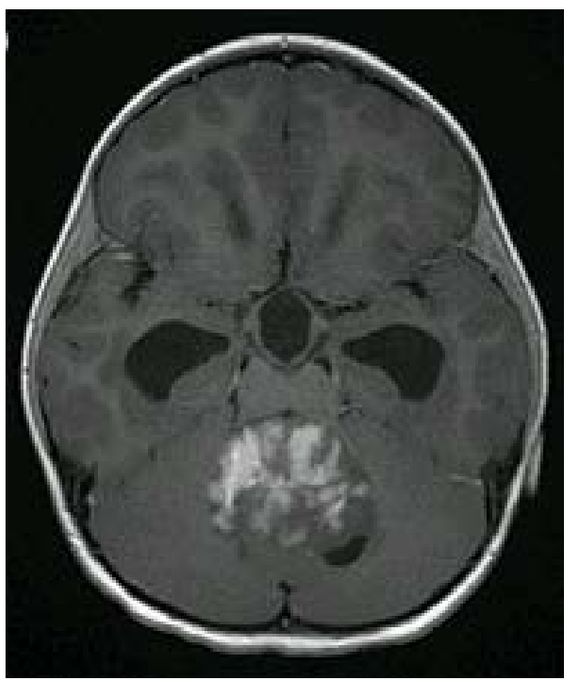
CT

- **CT:** acute symptomatology, first line assessment
  - to exclude: - intracranial hemorrhage
    - brain herniation
    - acute hydrocephalus

→ Urgent Neurosurgical Treatment







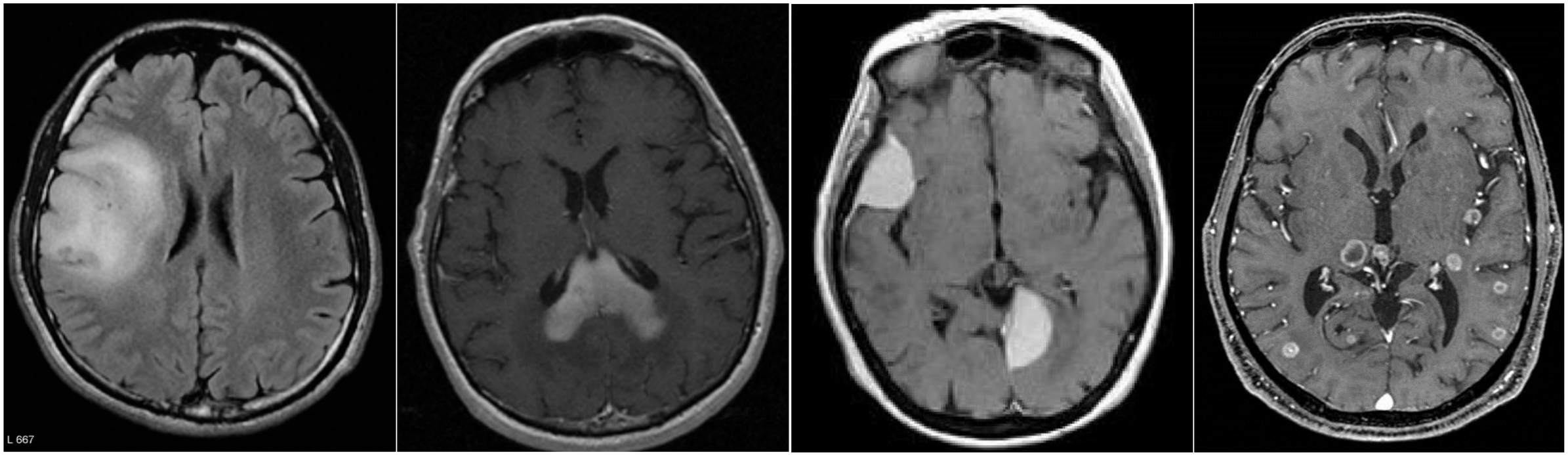
MRI ROUTINE PROTOCOL FOR BRAIN TUMOURS

- **MRI:** routine protocol

  - T1-weighted sequence before IV contrast medium
  - Axial T2 weighted
  - Axial T2 weighted FLAIR sequence (for lesions within the cortex or paraventricular - useful in low grade gliomas)
  - Axial Diffusion Weighted
  - Axial T2*-weighted sequence (sensitive to blood and calcifications)
  - Contrast enhanced T1 weighted sequences

MRI: ANATOMIC IMAGING

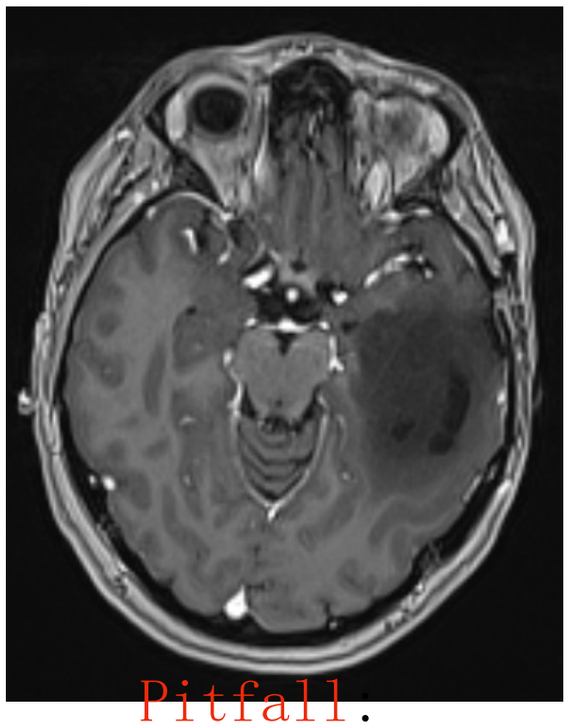
- Intraxial or extra-axial
  - Anatomical location



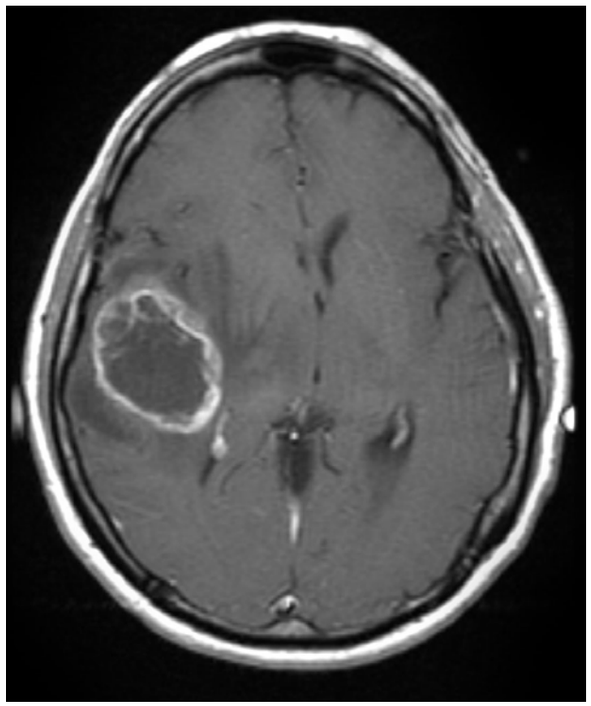
Oligodendroglioma | Lymphoma | Meningiomas | Multiple Mets

MRI: ANATOMIC IMAGING

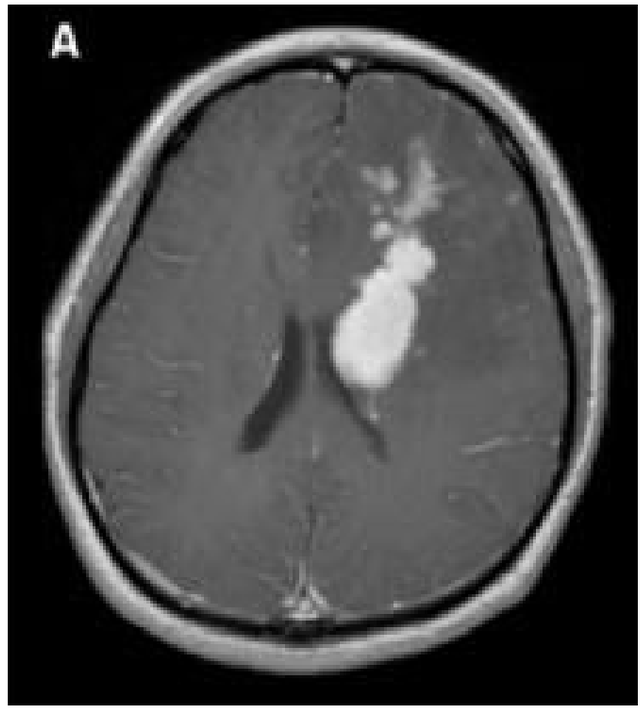
- Pattern of enhancement



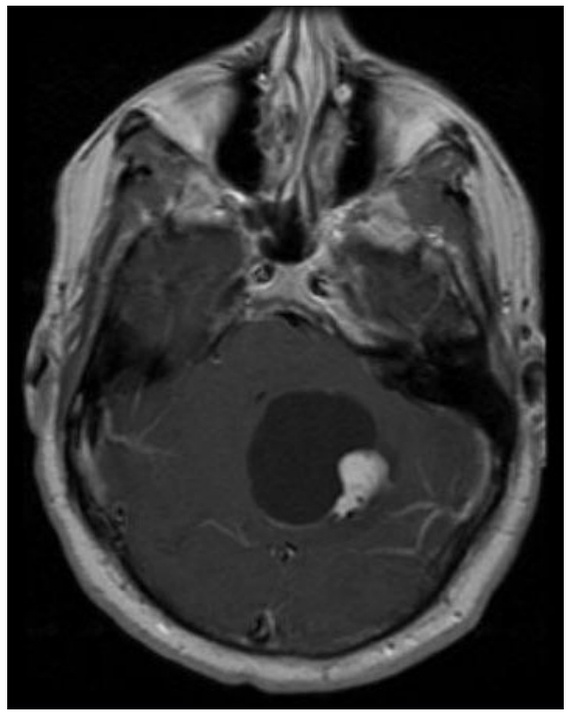
Pitfall:
Non enhancing astrocytoma grade III IDH1 negative, 1p 19q non codeleted



GBM



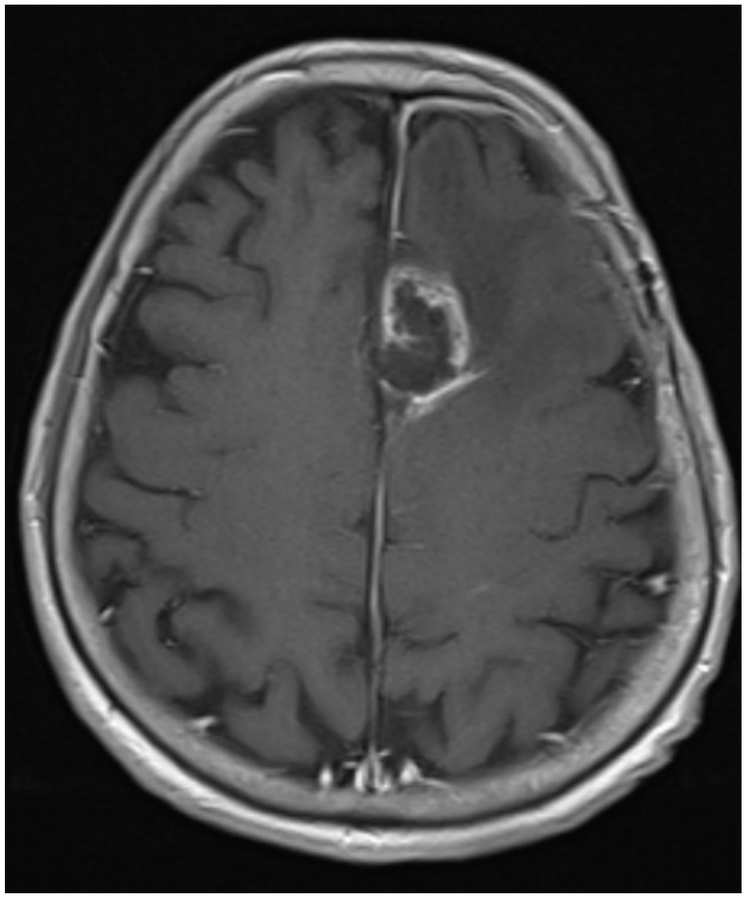
LYMPHOMA

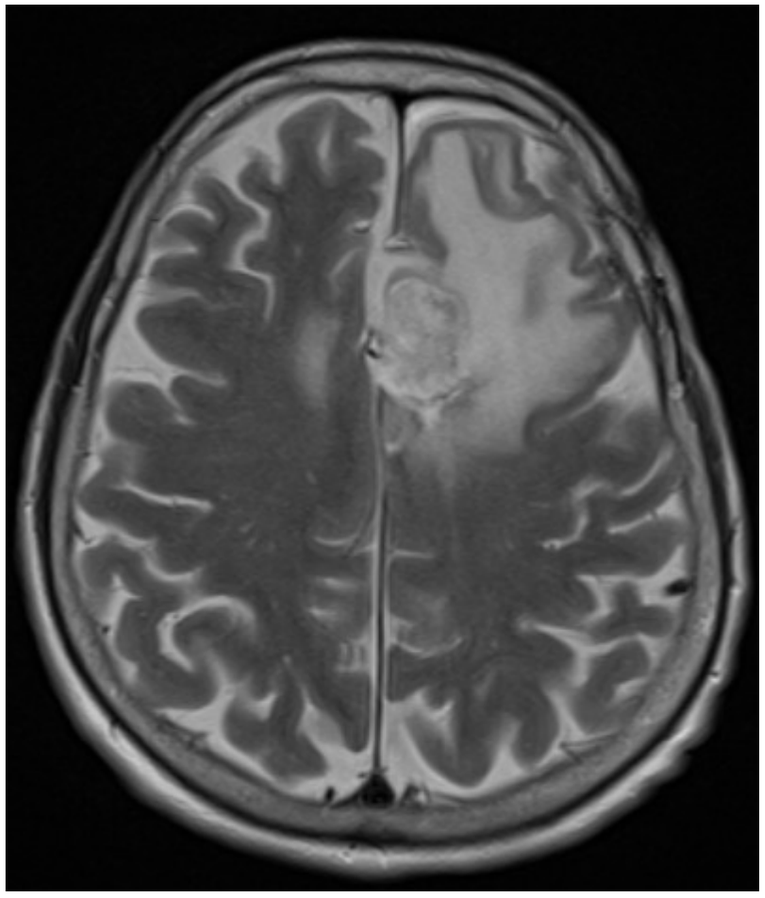


HEMANGIOBLASTOMA

MRI: ANATOMIC IMAGING
TUMOR MARGINS

Pitfall: the non enhancing signal alteration around a high grade brain tumor does not differentiate between brain edema and infiltrating tumor



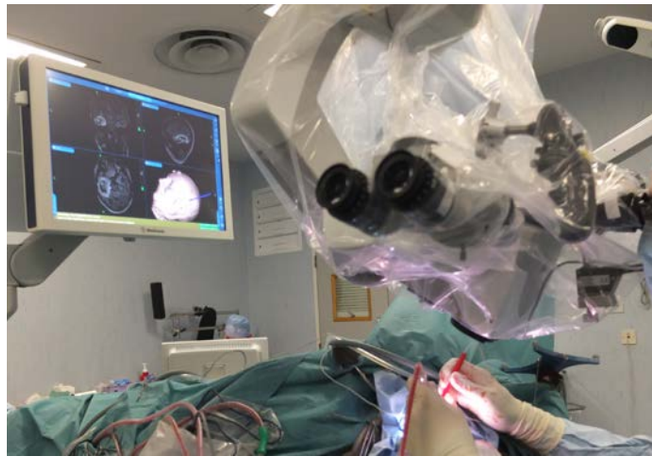


MRI: ANATOMIC IMAGING
TUMOR MIMICS

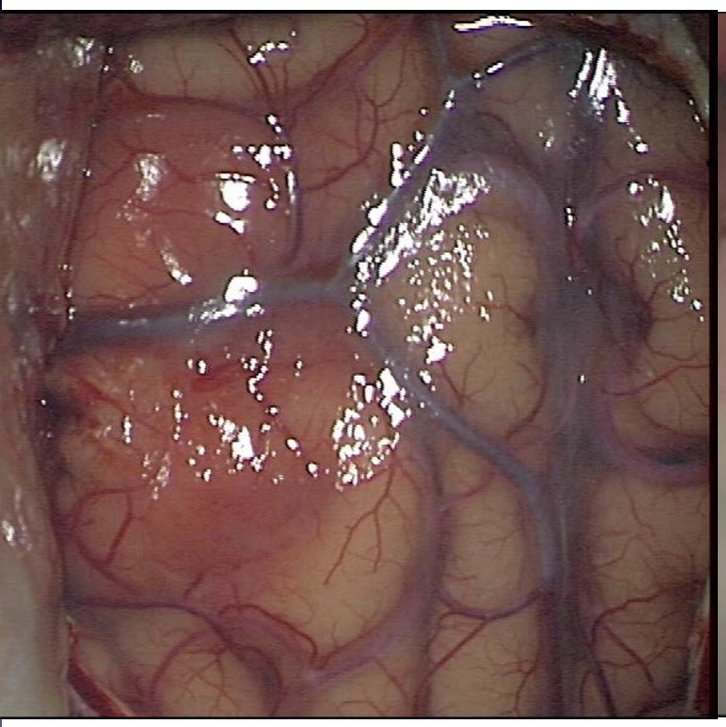
- Bacterial/fungal abscess
- Herpex simplex encephalitis
- Subacute infarction
- Tumefactive demyelination
- Sarcoidosis
- **Radiation Necrosis**

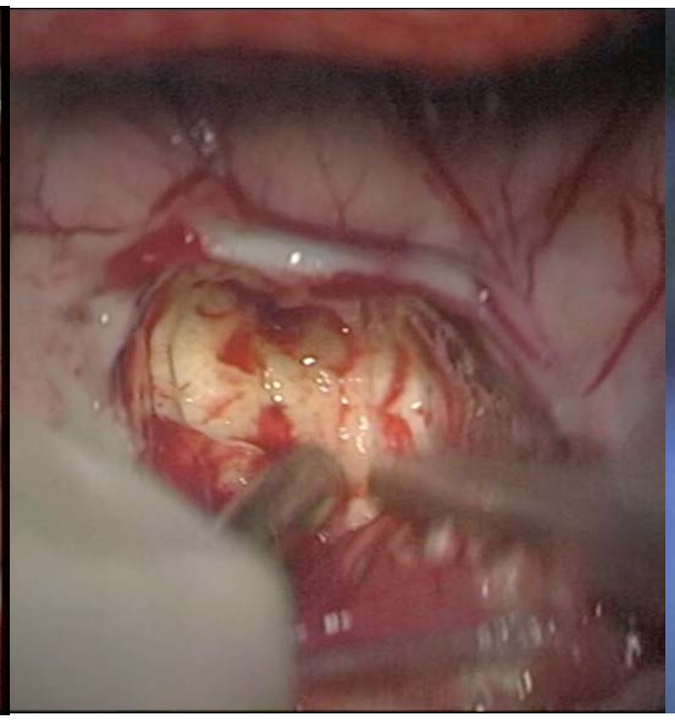
ANATOMIC IMAGING
EARLY POSTOP MRI

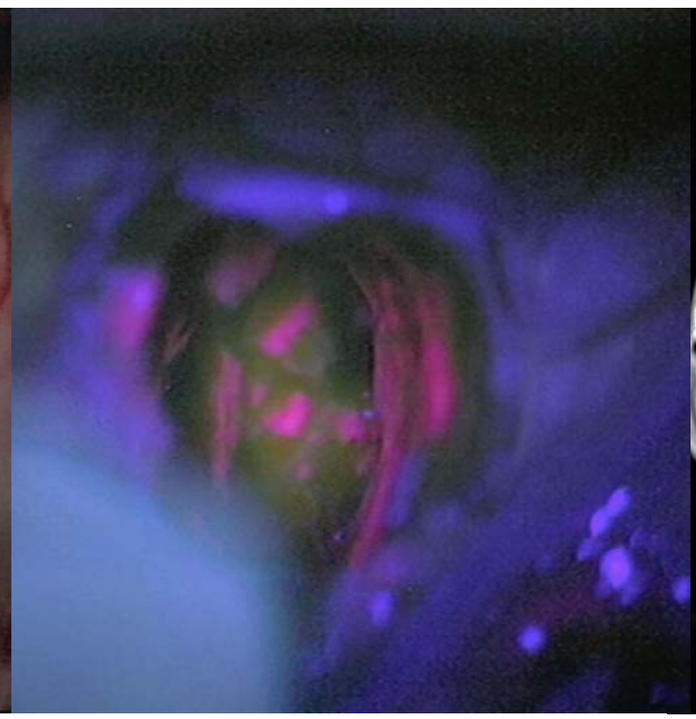
Enhancing granulation tissue begins to develop 3 days after surgery, persist for weeks to month, and mimics tutor

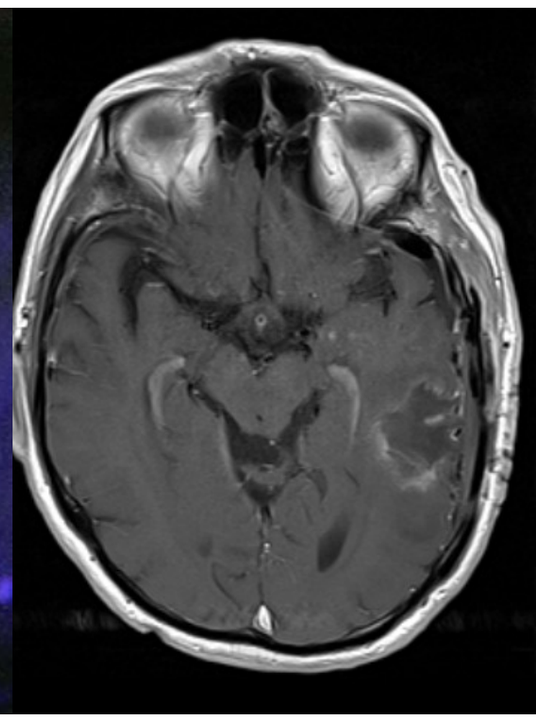


Post op imaging should be performed <u>within 48h of surgery</u>, the sooner the better





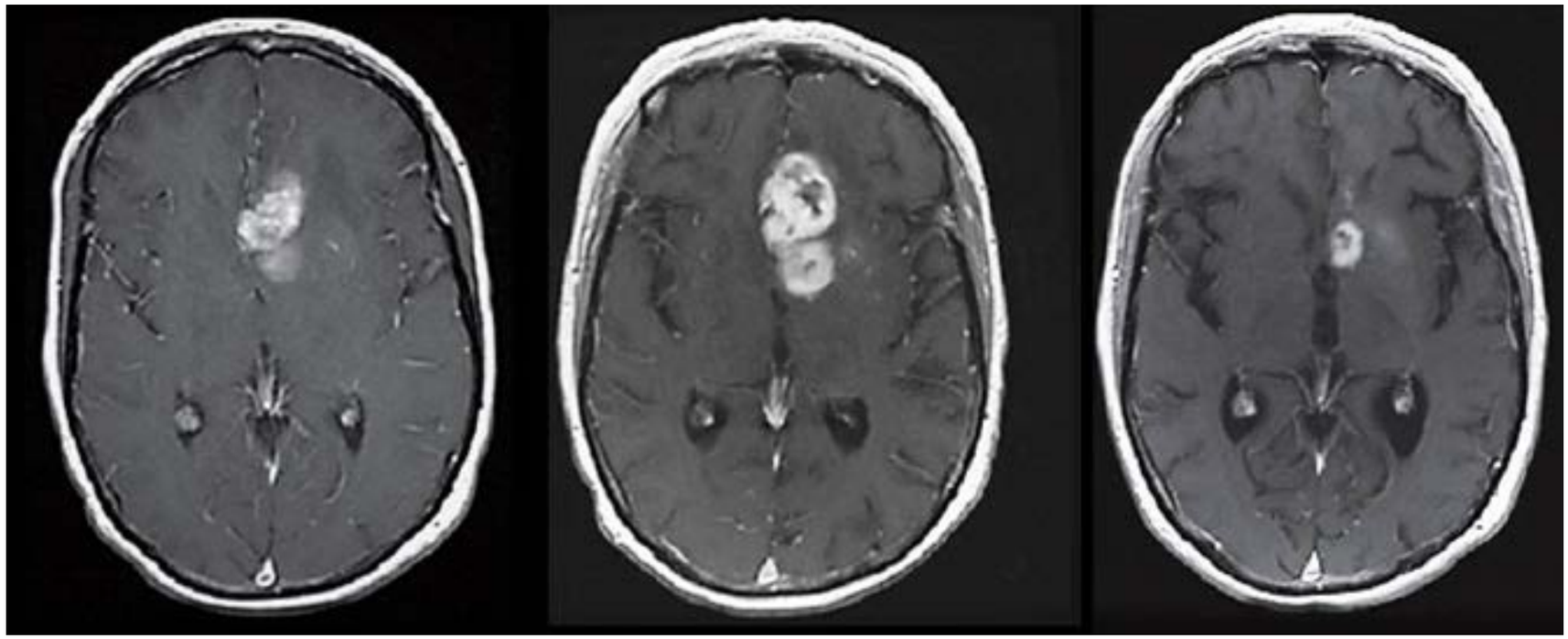




Pitfall: when comparing studies, the size and shape of a tumor can appear substantially different due to differences in the angle of imaging, slic thickness and gaps between slices

MRI: ANATOMIC IMAGING AND PSEUDO-PROGRESSION

PSEUDO-PROGRESSION is a self-limited type of treatment-related tissue injury that is common in the first 3-6 months after TMZ and radiation therapy, and mimics tumor progression, but then stabilises and decreases *(Brandsma D et al. Lancet oncol 2008)*

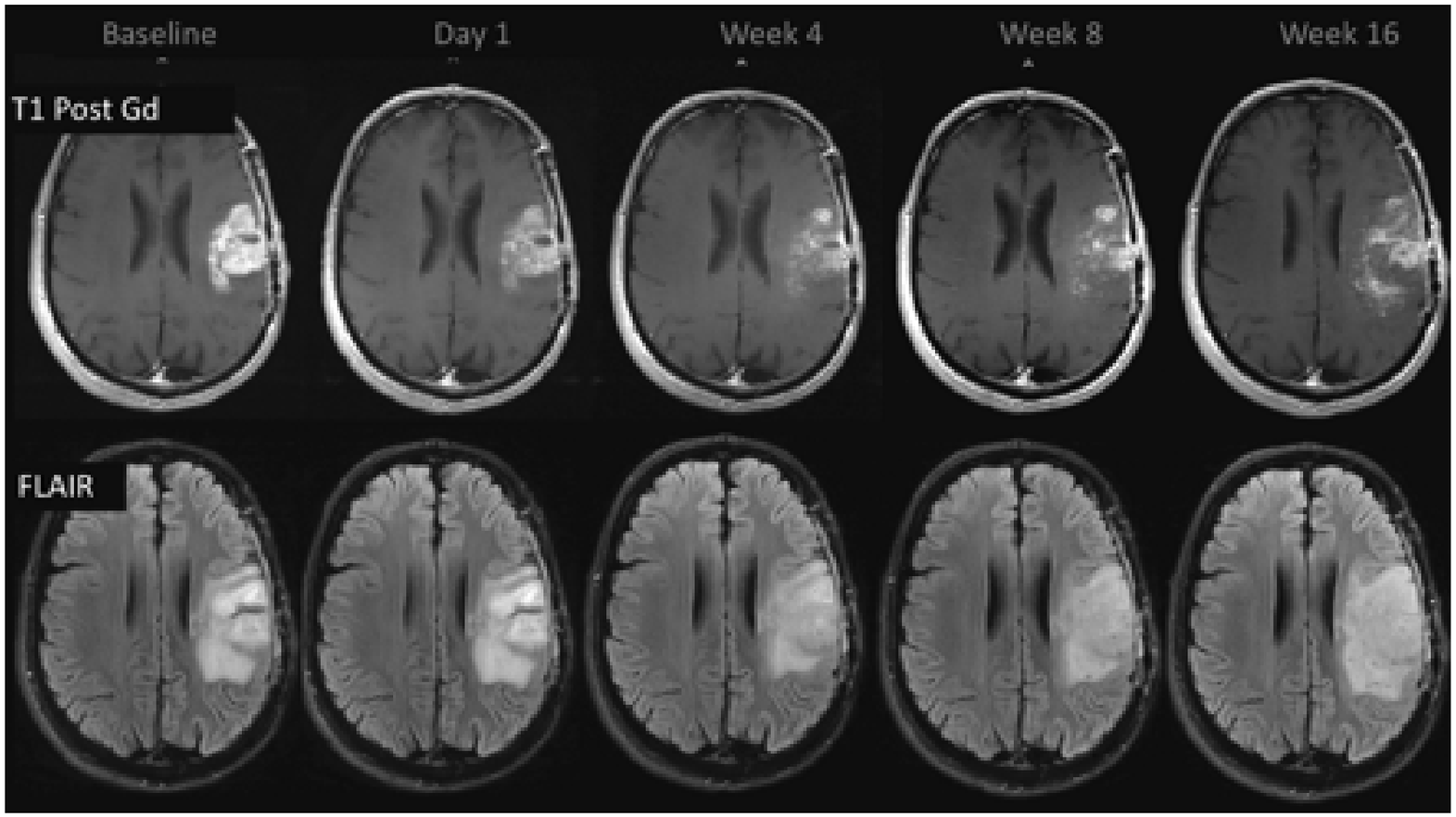


Before RT+TMZ Before adjuvant TMZ After 2 cycles adj TMZ

Differ from classic radiation necrosis, which can also mimics tumour progre
but is typically more severe and delayed in onset.

MRI: ANATOMIC IMAGING AND PSEUDO-RESPONSE

PSEUDO-RESPONSE: Angiogenetic inhibitors can cause a decrease in contrast enhancement due to reduction in blood-brain barrier permeability rather then true reduction in volume (*Clarke JL et al. Curr Neurol Neurosci Rep 2009)*

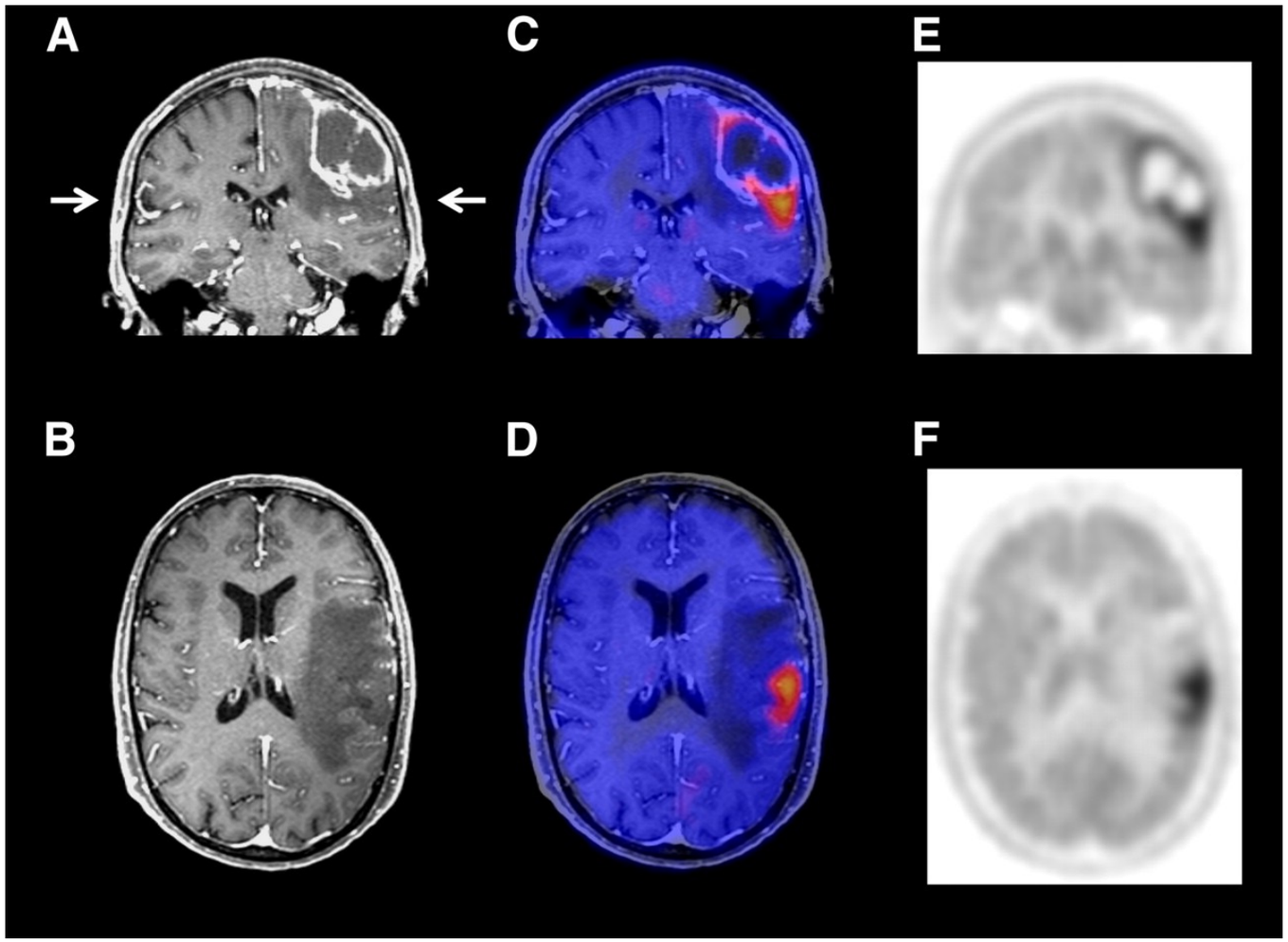


A 47-year-old man with GBM. A reduction of the enhancing portion of the lesion is observed 1 day after initiation of cediranib treatment. Four weeks later, besides a continuing reduction in the enhancing portion, an expansion is observed in the FLAIR images. Expansions in both the enhancing area and abnormal hyperintense areas consistent with tumor progression were observed subsequently (L.C. Hygino da Cruz Jr et al. AJNR 2011)

METABOLIC IMAGING

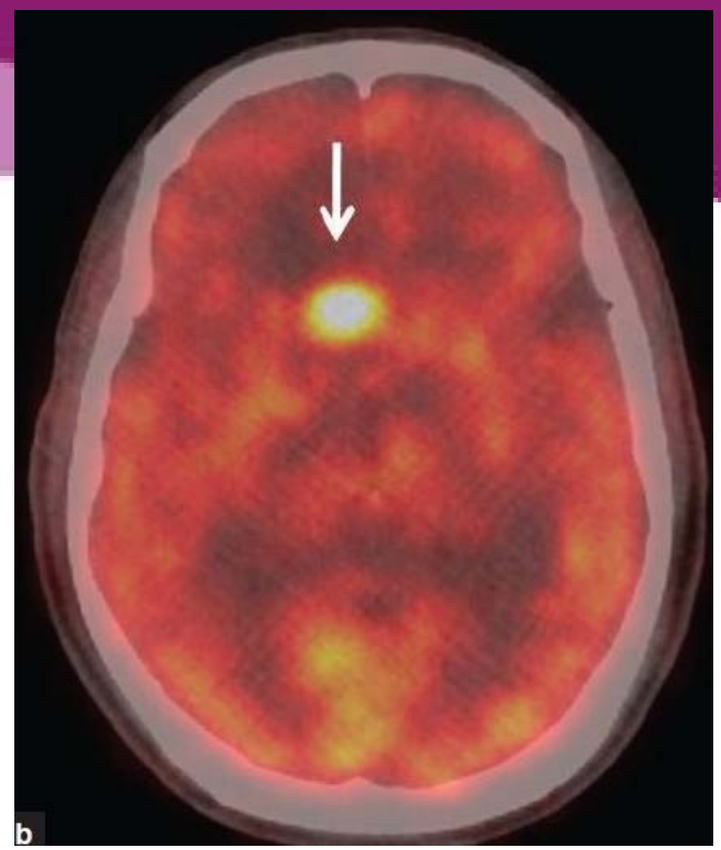
PET provides <u>metabolic in vivo measurement</u> of local tracer activity at a very high sensitivity

(Best if coupled with MRI scan)



- [(18)F]-FDG-PET
- [11C]Methionine (MET)
- [(18)F]-FLT-PET fluorothymidine

[(18)F]-FDG-PET



Pitfalls of [(18)F]-FDG-PET

- **LGG uptake is similar to normal white matter**
- **HGG uptake is similar to normal gray matter**

- **Cannot differentiate tumour vs inflammation vs acute stroke**
- **Radiation necrosis may be indistinguishable from recurrent tumour**

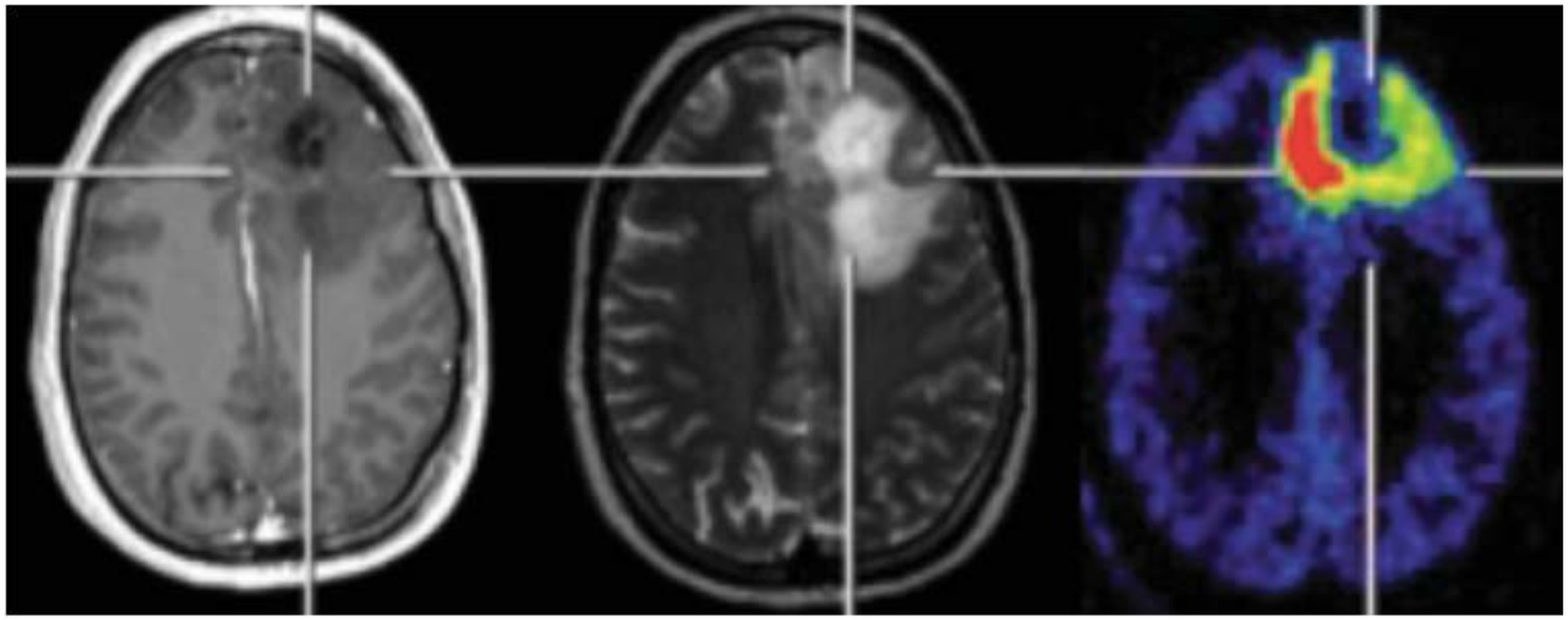
(Due to accumulation of [(18)F]-FDG in macrophages that may infiltrate the sites having received radiation therapy)

High pretreatment glucose metabolic rate is higher in responders to TMZ than non responders in patients with high grade glioma *(Brock CS. Br J Cancer 2000)*

METABOLIC IMAGING
PET [11C]Methionine (MET)

- **Marker for <u>ACTIVE TUMOR PROLIFERATION AND ANGIOGENESIS</u> (Correlates with Ki-67 expression, proliferating cell nuclear antigen expression and micro vessel density)**

- **<u>TRUE TUMOR EXTENSION?</u>** *[11C] MET uptake ratios compared with the background is favourable.*



GBM MARGINS IN PET-MET WELL BEYOND THE ENHANCING COMPONENT

METABOLIC IMAGING
PET [11C]Methionine (MET)

- **The highest uptake is observed in anaplastic oligodendrogliomas WHO grade III**
- **LGG are better detected by aminoacid tracers due to increased uptake in the absence of blood-brain barrier damage**
- **LGG: useful for differentiation from nonntumorous lesions, detection of recurrences, indication of progressing disease**
- **Can differentiate better between <u>Recurrent tumour and Radiation Necrosis</u> with high sensitivity and specificity <u>(~75%)</u>: necrosis and glioses after therapy show a reduction of ammoniated uptake in contrast to recurrent and residual tumour growth.**
- **<u>Deactivation of aminoacid transport is a early sign of response to chemotherapy</u> (Galldicks N et al Mol Imaging 2010). PET responders with a decrease of tumour brain/ratio of >10% had a significant longer TTP and OS than patient with increase tracer uptake after RT and CHT in GBM.**

PET [11C]Methionine (MET)

PITFALLS OF PET-MET

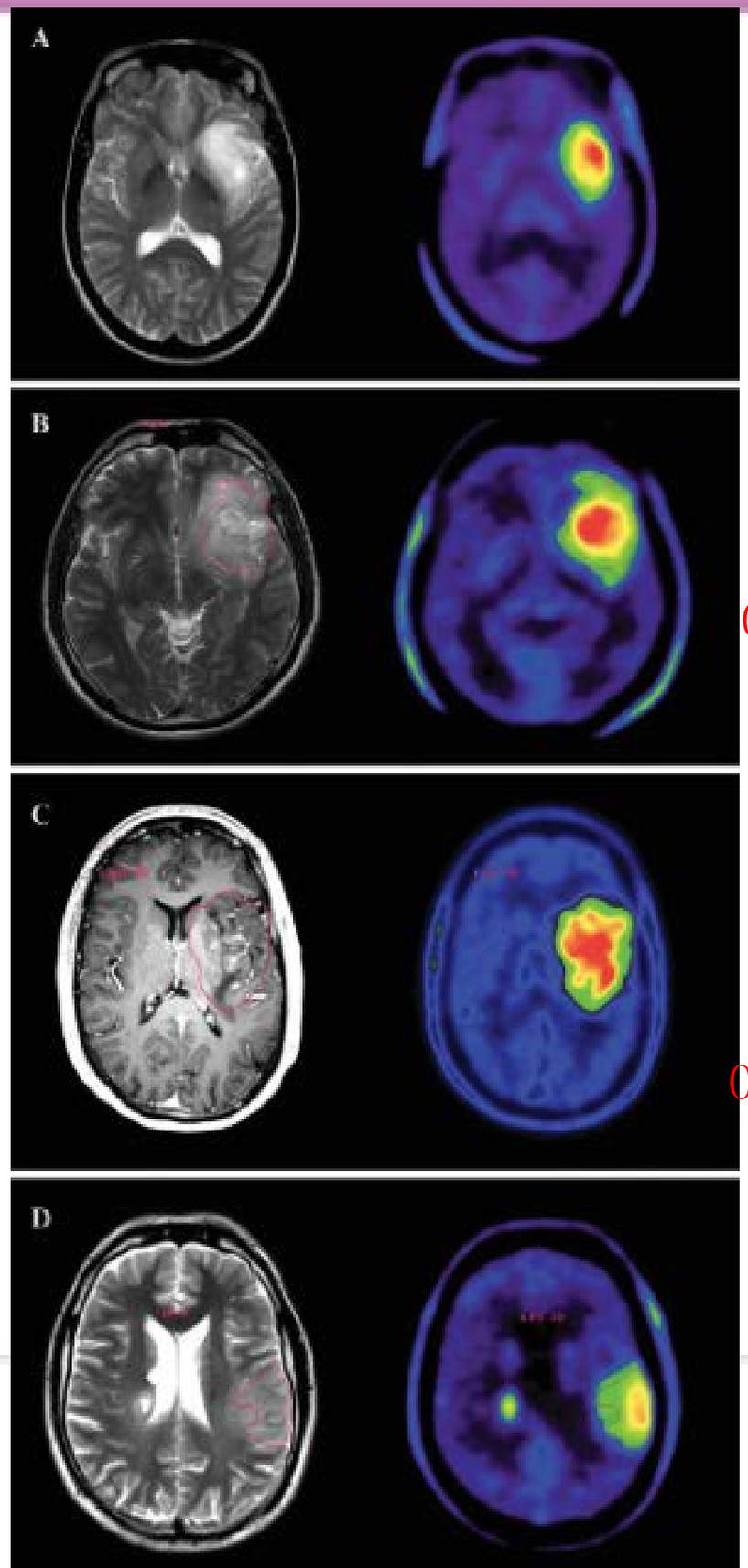
- **some low grade astrocytomas demonstrates only low tracer uptake**
- **acute inflammation or ischemic stroke might present with increased aminoacid uptake**
- **<u>NOT POSSIBLE TO PREDICT HISTOLOGICAL GRADE</u> which is paramount in treatment decision making**

IMAGING TUMOR PROLIFERATION

[(18)F]-FLT-PET *fluorothymidine*

- Uptake of FLT correlates with Thymidine kinase-1 activity expressed during DNA synthesis
- High correlation with Ki-67 expression (Yamamoto J Nucl Med 2012)
- Might be superior to MET for tumour grading
- The kinetics of FLT uptake are closely related to prognosis, early efficacy of treatment and to outcome (Wardak Clin Cancer Research 2011)

- **PITFALLS**:
  - less sensitivity than MET for low grade gliomas
  - **CANNOT PREDICT GRADE**



Astrocytoma Grade II

Oligodendroglioma Grade II

Anaplastic Oligodendroglioma Grade II

GBM Grade IV

PHYSIOLOGICAL IMAGING

- **DWI-MRI**
- **Dynamic Contrast-enhanced Perfusion MRI**
- **Spectroscopy**

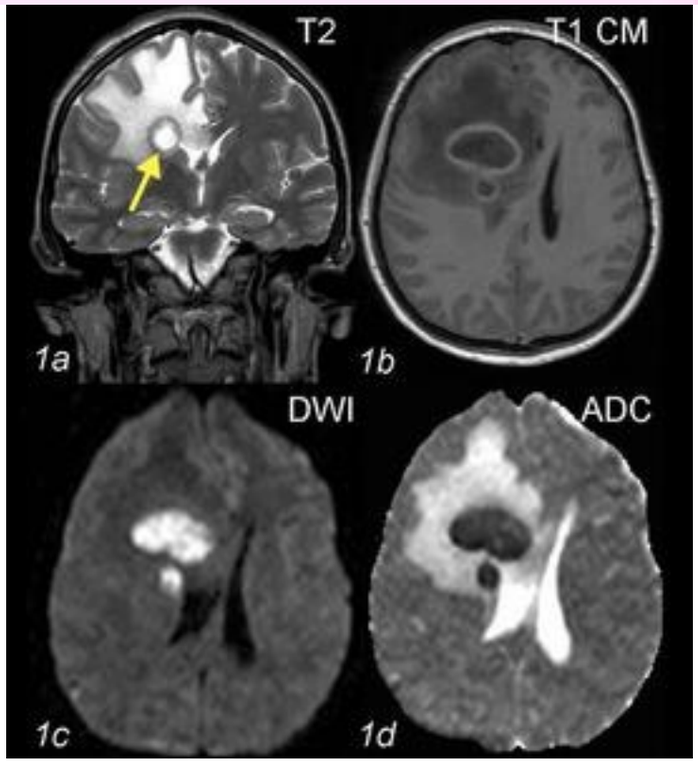
PHYSIOLOGICAL IMAGING
DWI MRI

- Differential diagnosis of cerebral abscess, epidermoid cyst, traumatic shearing injury, toxic and infectious encephalitis, immediate post brain injury

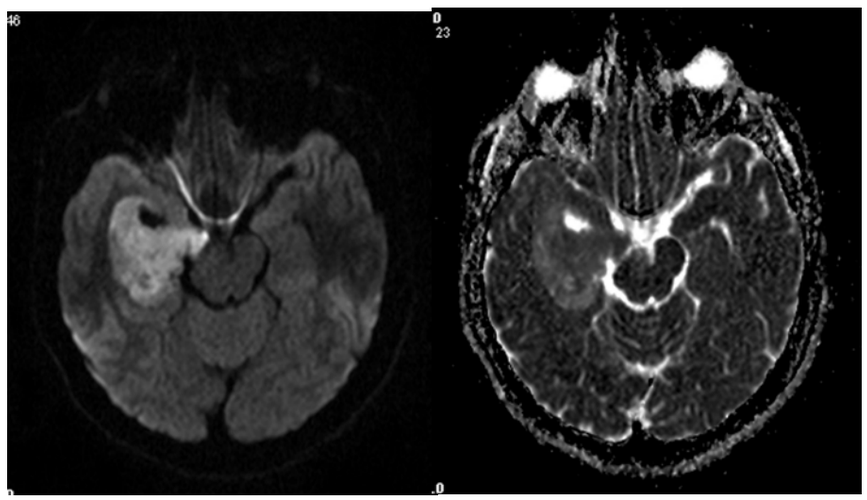
- Postoperative ischemia

- Accurate interpretation of new abnormal contrast enhancement developing soon after tumor resection

PITFALL: Para or ferromagnetic materials such as blood products or calcium within the brain can simulate pathology on DWI as well as perfusion MRI



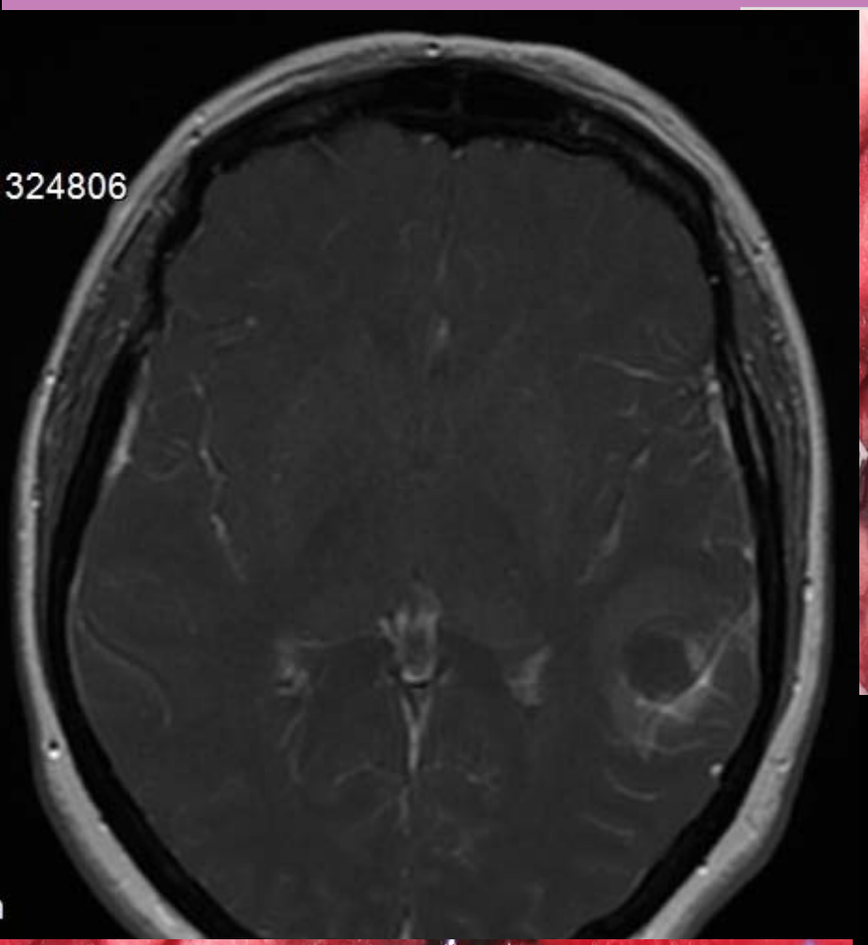
Brain abscess

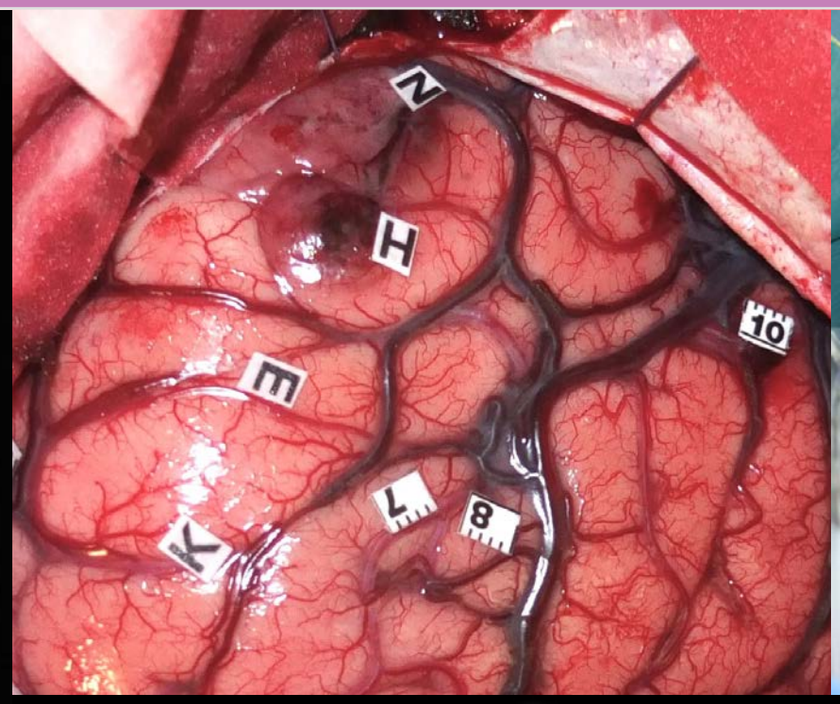


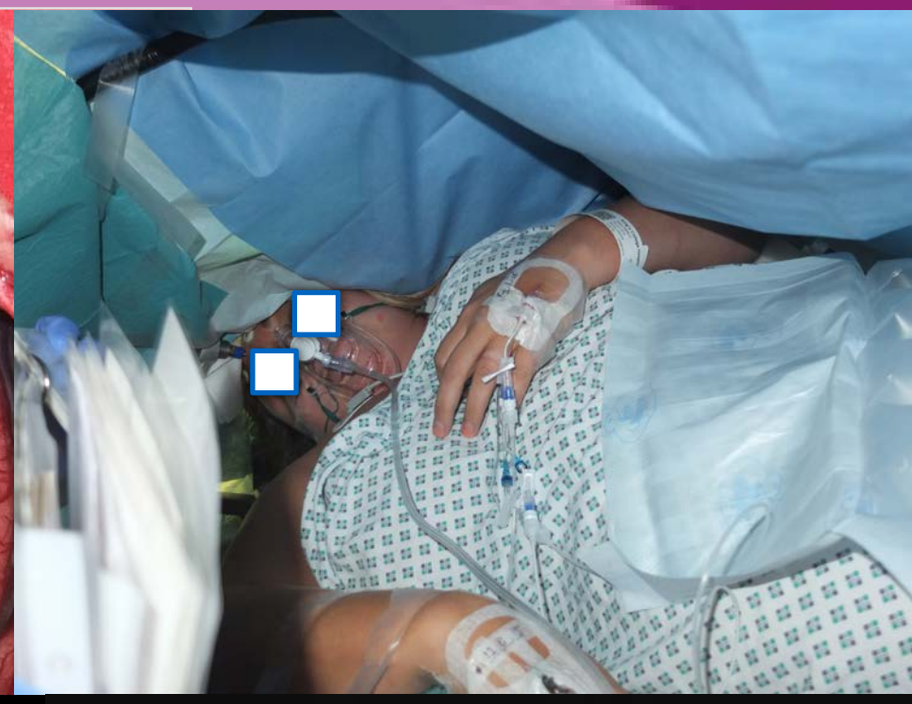
Epidermoid

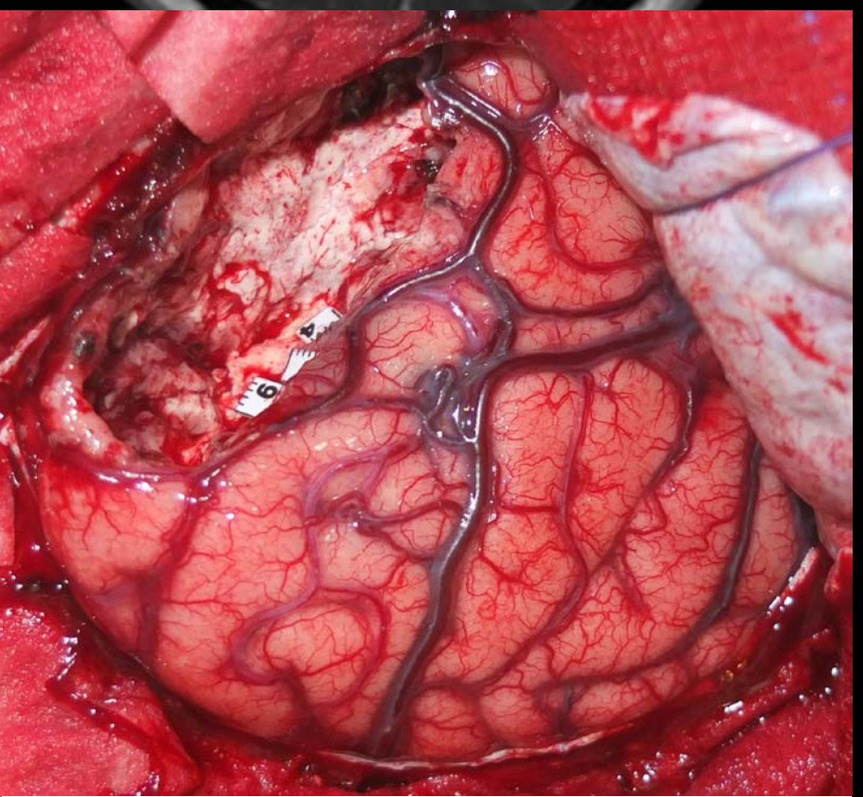
PHYSIOLOGICAL IMAGING

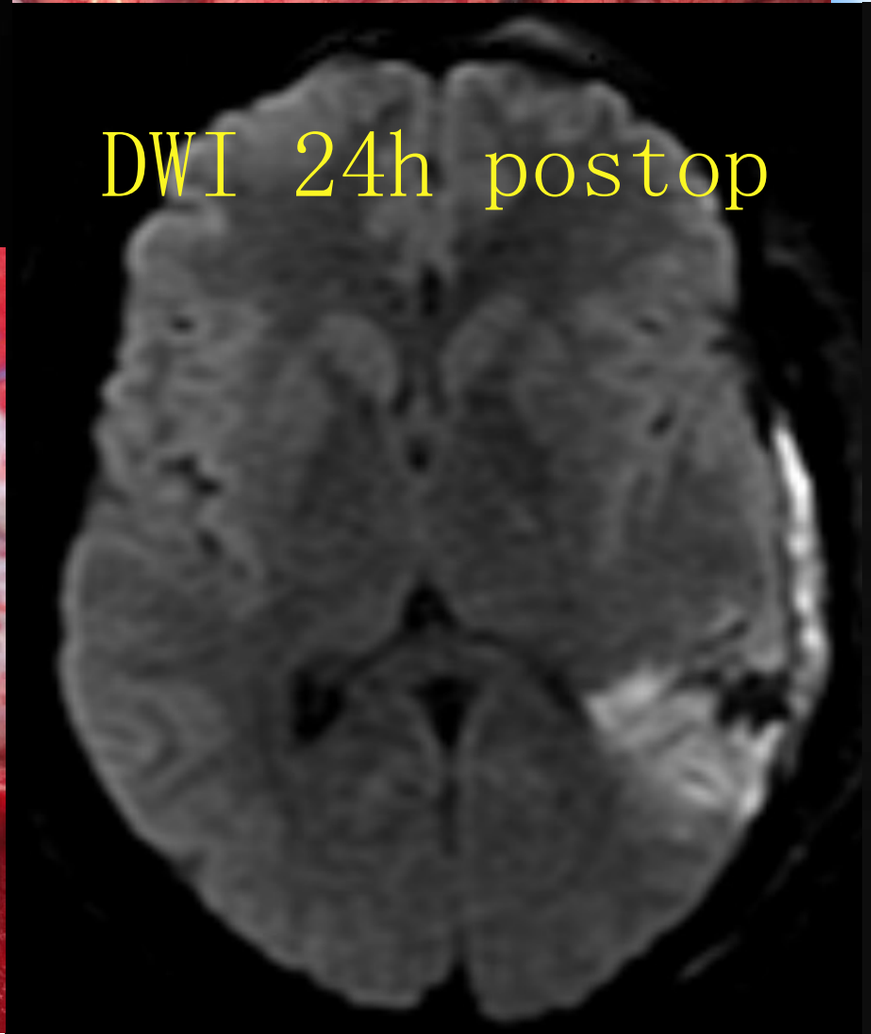
DWI- MRI

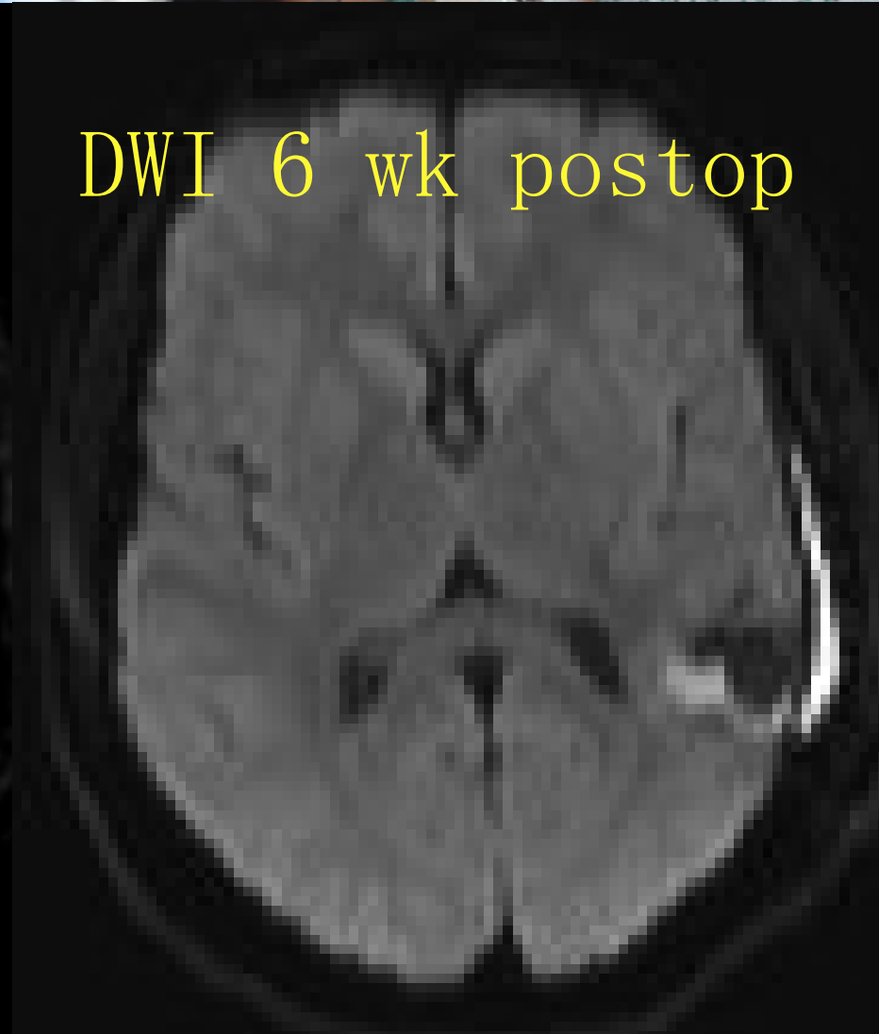








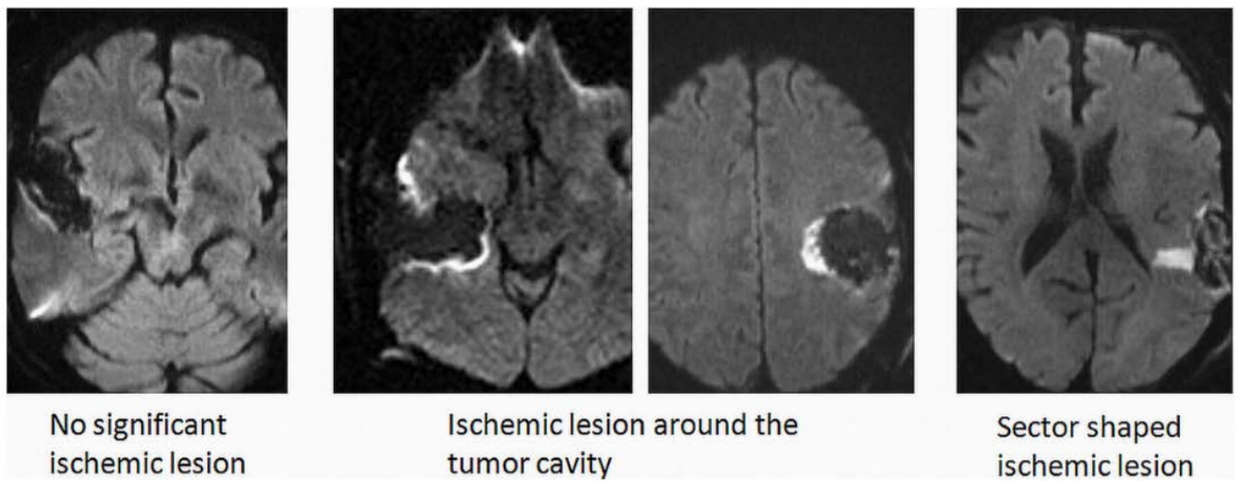




PHYSIOLOGICAL IMAGING
DWI- MRI

Surgically Acquired Deficits and Diffusion Weighted MRI Changes after Glioma Resection - A Matched Case-Control Study with Blinded Neuroradiological Assessment

Asgeir S. Jakola[1,2,3]*, Erik M. Berntsen[4,5], Pål Christensen[4], Sasha Gulati[1], Geirmund Unsgård[1,3,6], Kjell A. Kvistad[4,5], Ole Solheim[1,2,3]



No significant ischemic lesion

Ischemic lesion around the tumor cavity

Sector shaped ischemic lesion

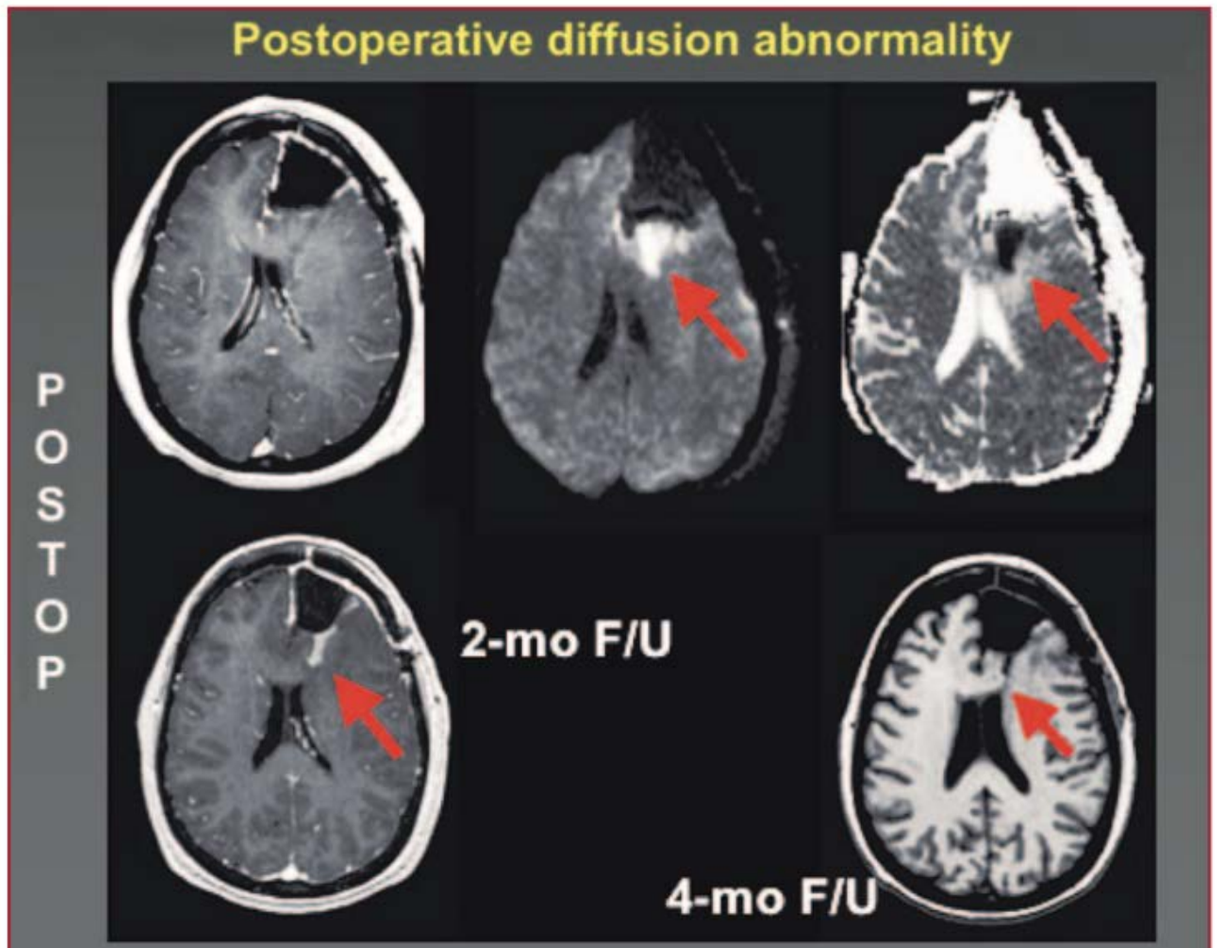


FIGURE 7. *DWI obtained 2 and 4 months postoperatively to identify areas of ischemia (bright signal DWI, dark signal void apparent diffusion coefficient) that enhances briefly postoperatively.*

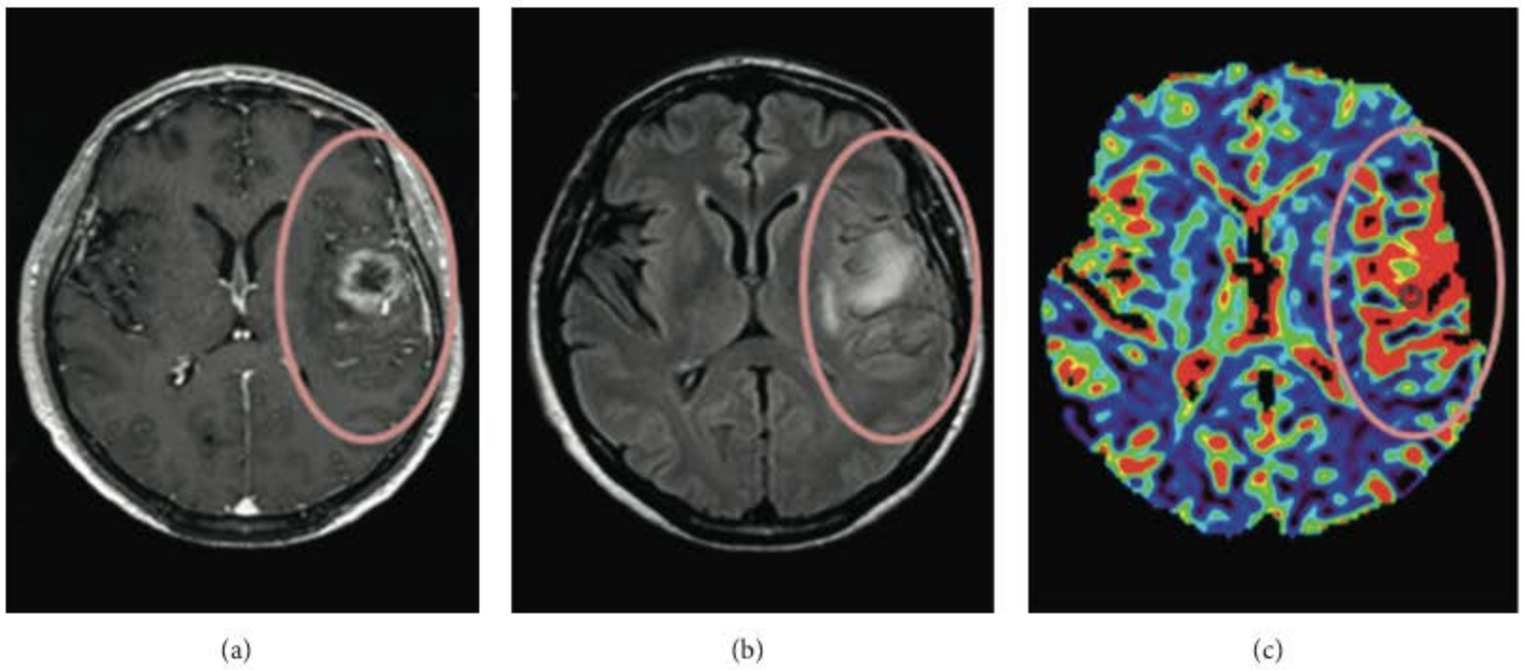
M. Berger et al. Neurosurgery 2000

PHYSIOLOGICAL IMAGING
PERFUSION MRI

- Provides hemodynamic information and estimates the cerebral blood volume that reflect the underlying microvasculature
- Exploit signal changes that accompany the passage of a paramagnetic contrast agent thorugh the cerebrovascular system
- Useful if patients receive antiangiogenetic cancer therapies to monitor its efficacy
- Maps of cerebral blood volume can serve as an additional targets for brain tumour biopsies
- May help in differentiating radiation necrosis and recurrent tumour
- May help differentiating tumor infiltrated edema (high grade gliomas) and vasogenic edema (in case of metastases)

PITFALL:

NO CORRELATION
WITH TUMOR GRADING



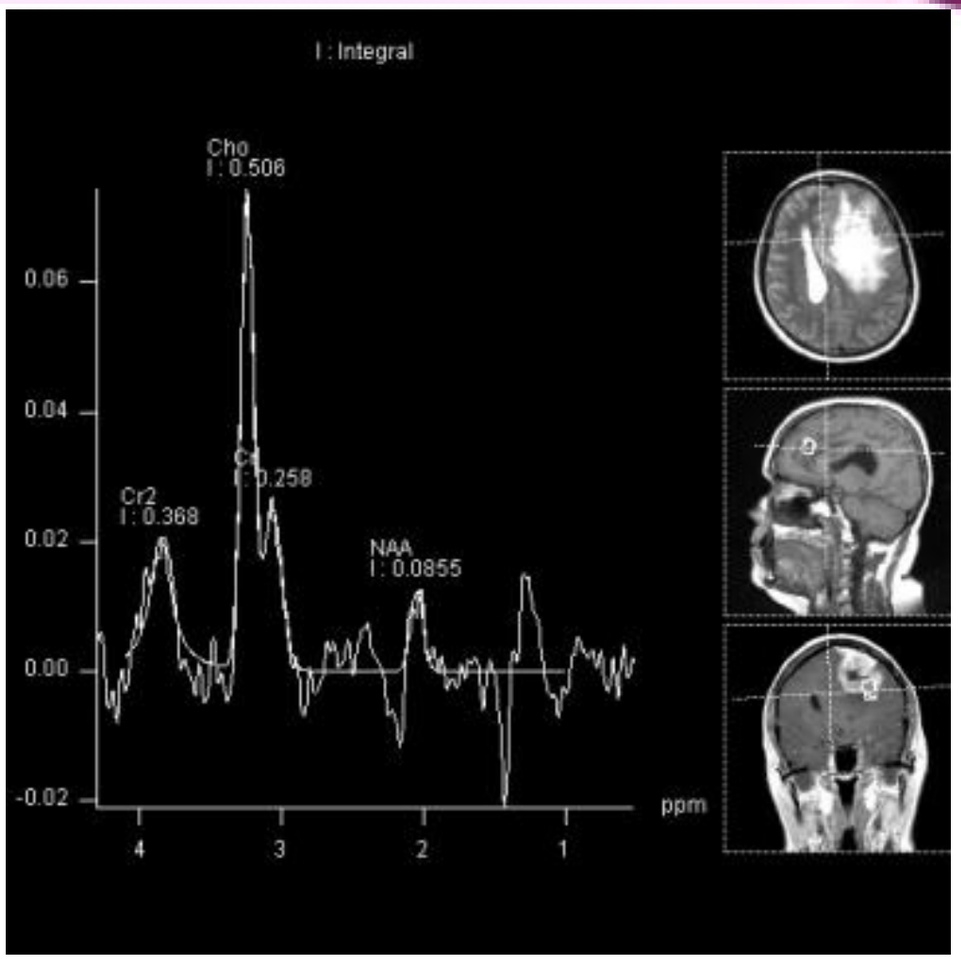
(a) (b) (c)

FIGURE 2: Axial coregistered contrast-enhanced axial T1-weighted image (a), FLAIR image (b), and CBV map (c) from a patient affected by glioma grade IV. In the CBV map (c) warmer colors indicate higher CBV values suggesting higher perfusion and neovascularization. Comparison of CBV map (c) and contrast-enhanced axial T1-weighted image highlights a mismatch area (surrounded by the circle) corresponding to the extension of the high perfusion area outside the contrast-enhancement: this indicates a more extensive neovascularization than that shown by conventional MRI (a, b).

Di Stefano et al. 2014

PHYSIOLOGICAL IMAGING
MRI SPECTROSCOPY

- **NAA**: marker of neural integrity
- **Choline**: membrane turnover
- Creatine: energetic
- **Myoinositol**: astrocytic marker
- **Lipid**: tissue destruction/necrosis marker
- Lactate: hypoxia marker
- Glutamine and Glutamate: excitatory markers

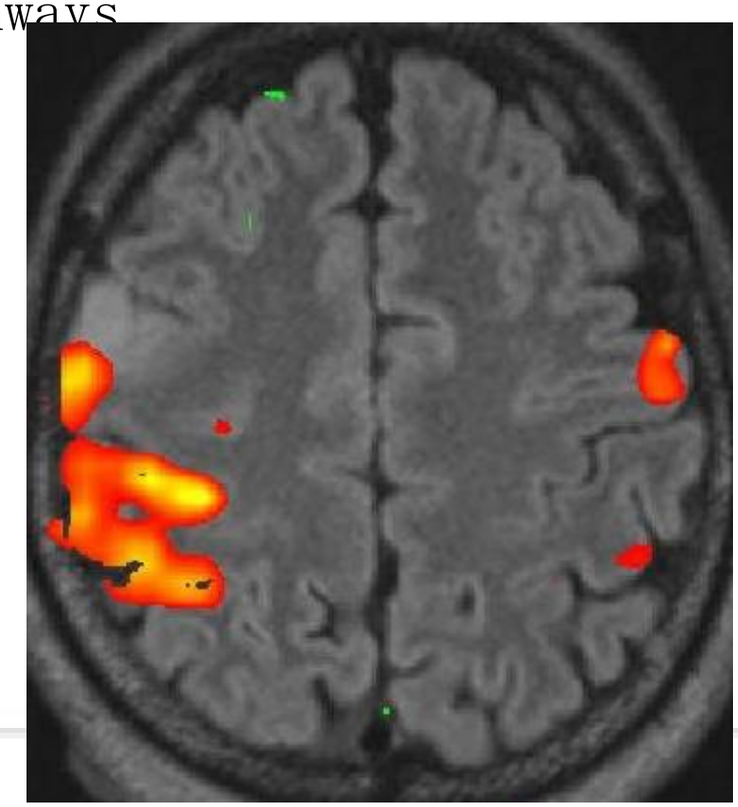


High choline correlate with high tumor proliferative index

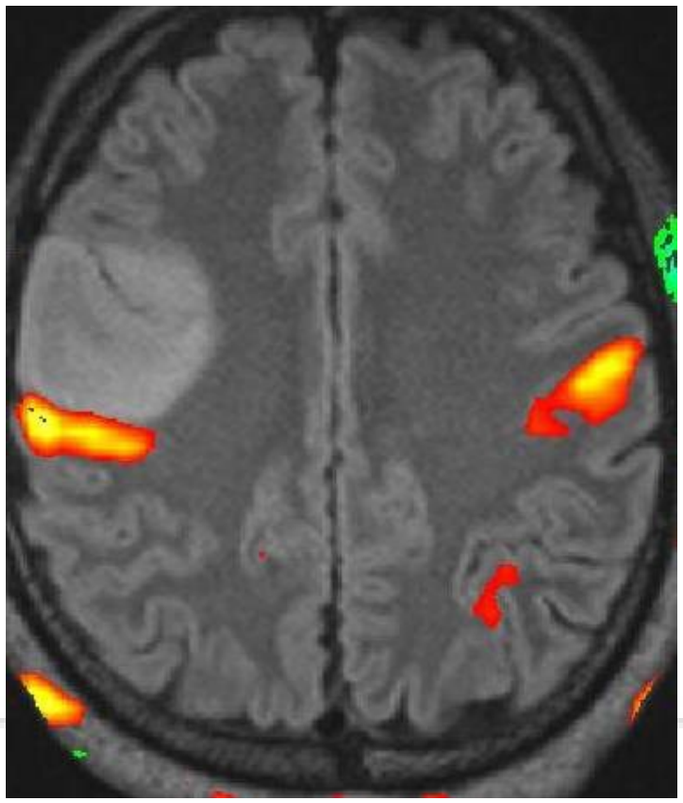
Pitfalls: - min 1 cm3 voxel size
- not suitable for posterior fossa lesions and lesions
- common aspecific spectral findings

PHYSIOLOGICAL IMAGING
FUNCTIONAL IMAGING - fMRI

- **Pitfalls:**
  - Does not monitor the neural response but a “surrogate” hemodynamic response
  - Cannot distinguish essential hubs -> need for intraoperative monitoring
  - Low localisation accuracy
  - **Neurovascular uncoupling** (tumor infiltration zone, neovascularity) with reduced fMRI signal in perilesional cortex
  - More accurate for motor mapping than for speech
  - Not giving any functional information about subcortical white matter pathways

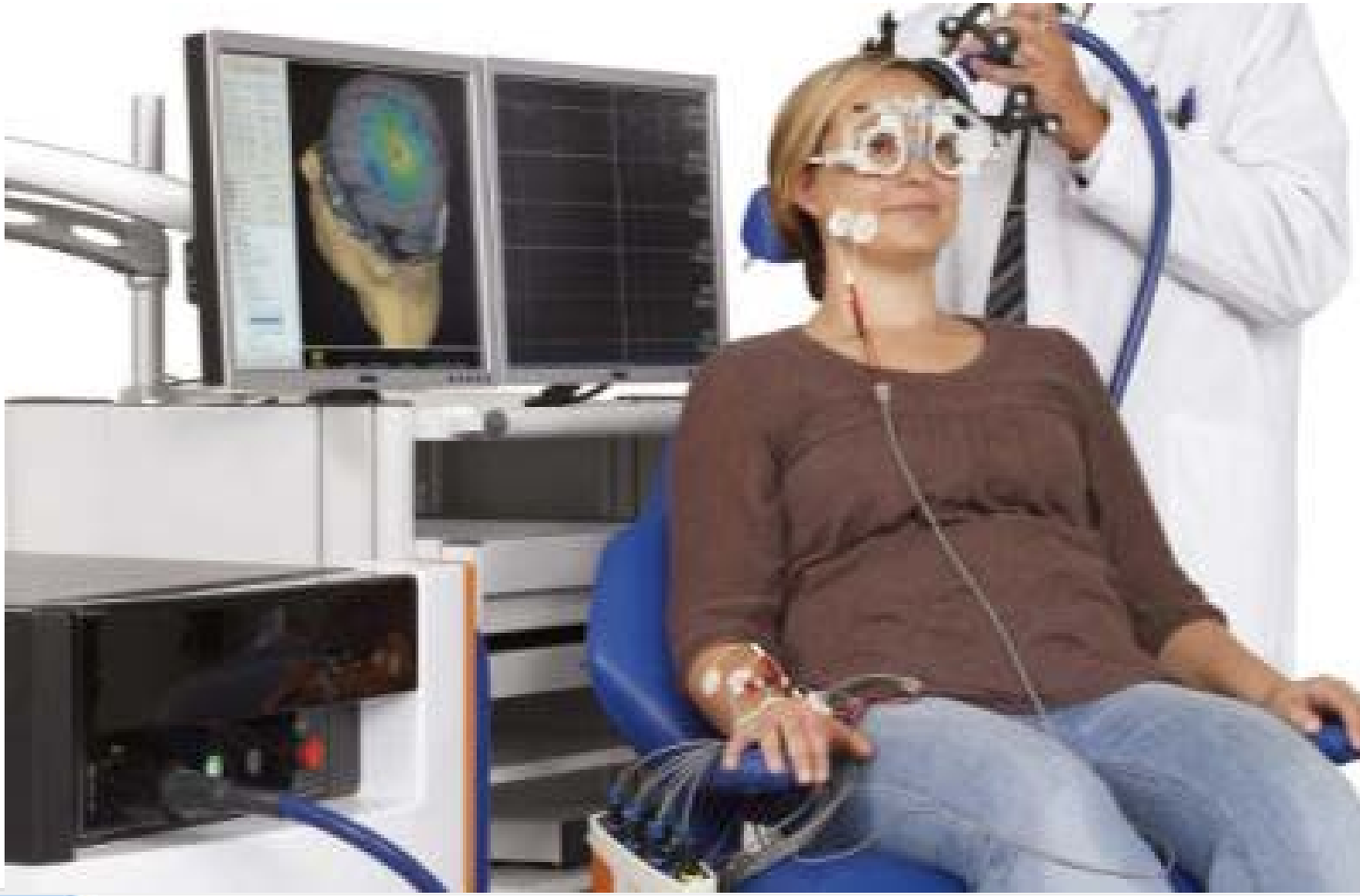


Finger Tapping

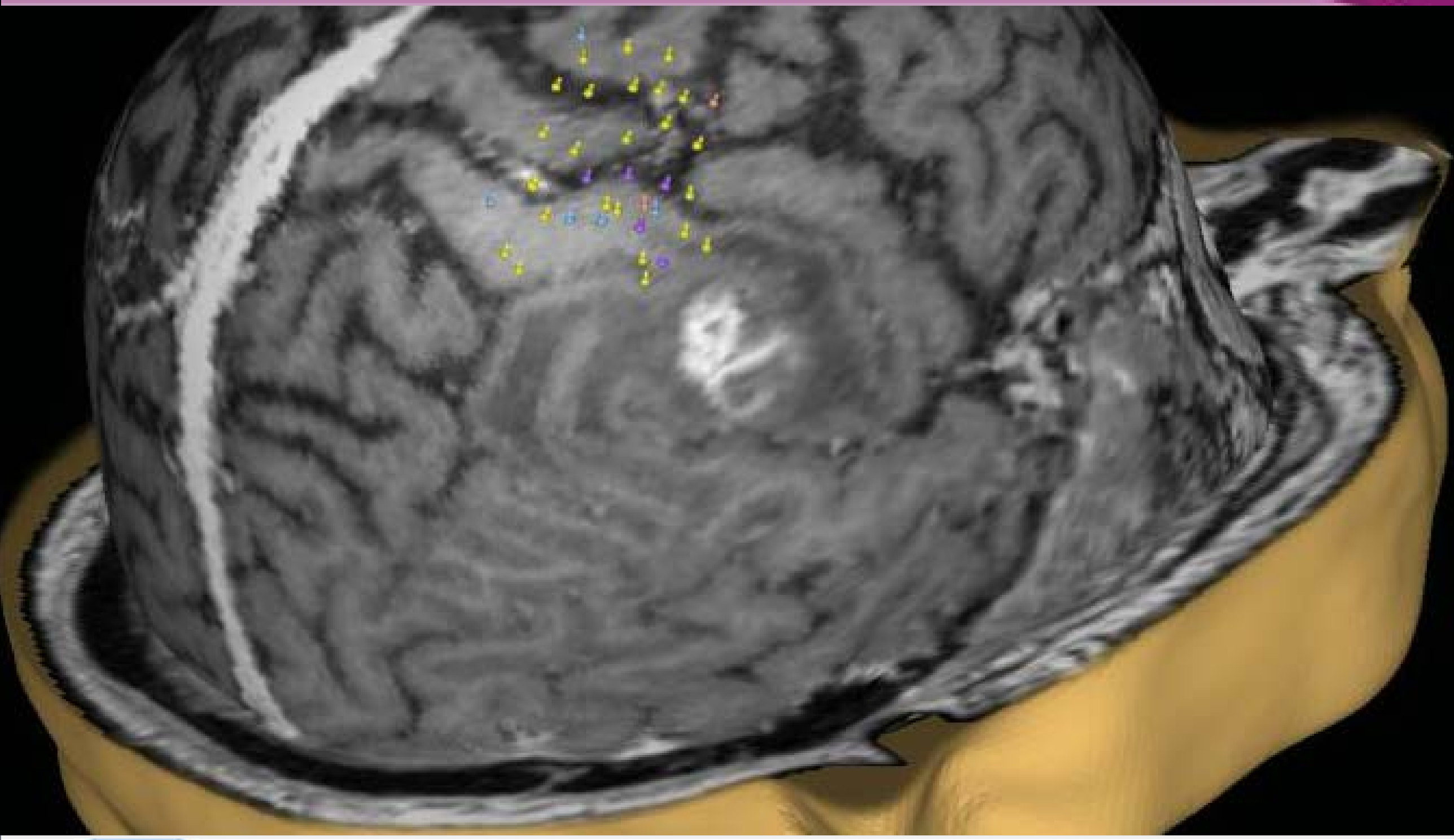


Semantic speech

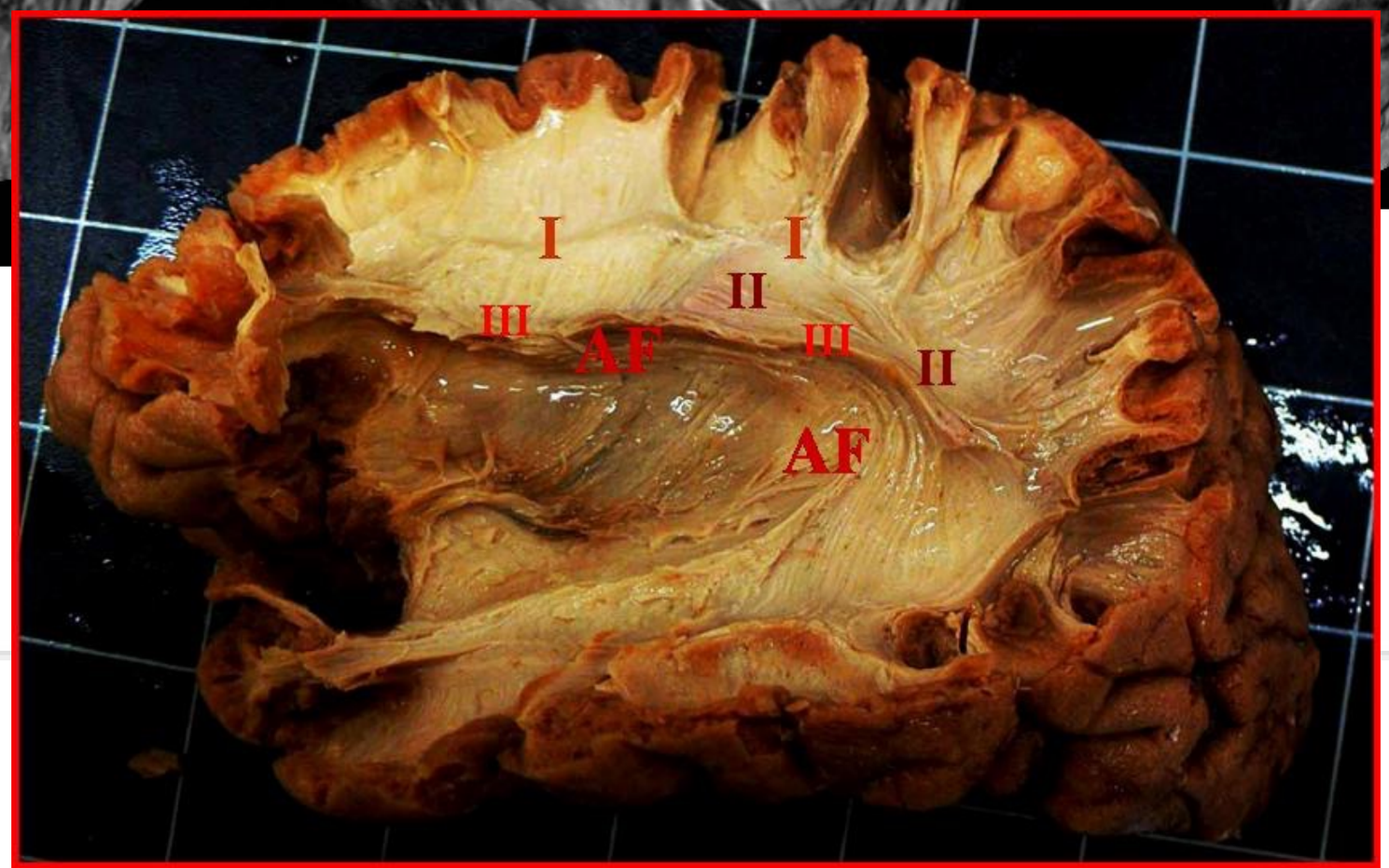
Trans-Cranial Magnetic Stimulation



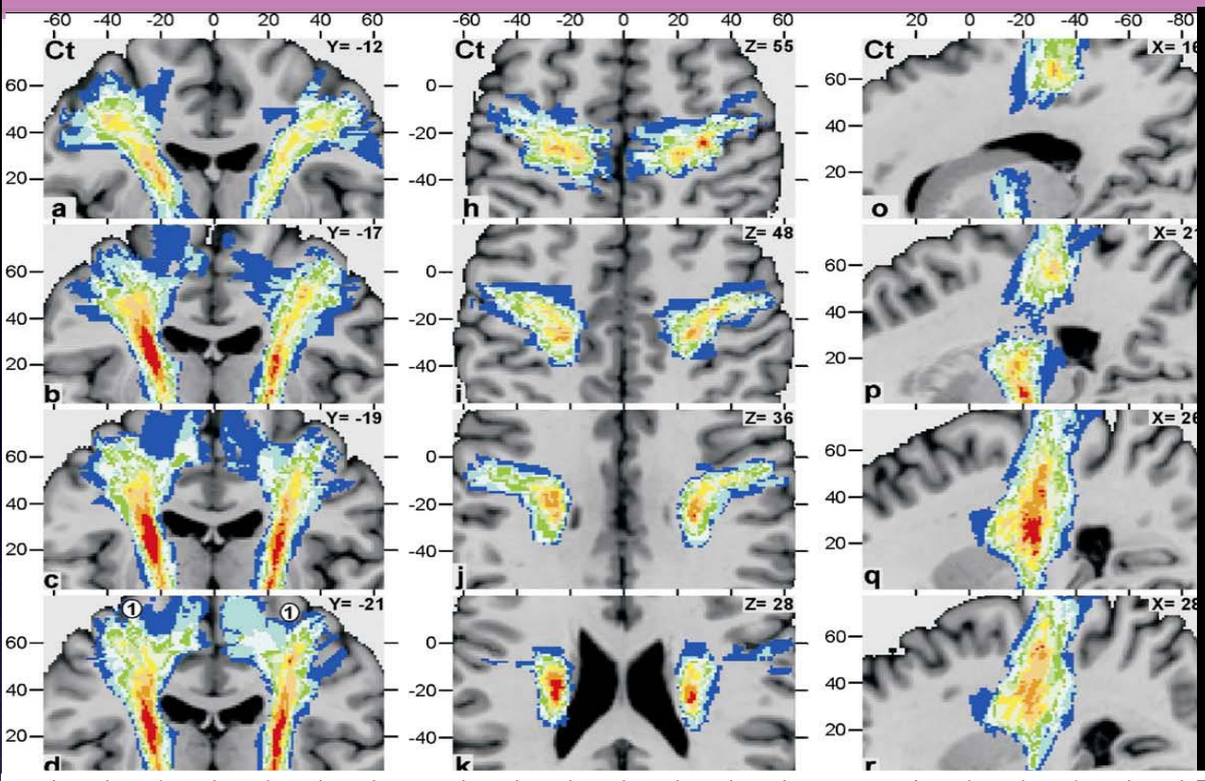
Trans-Cranial Magnetic Stimulation

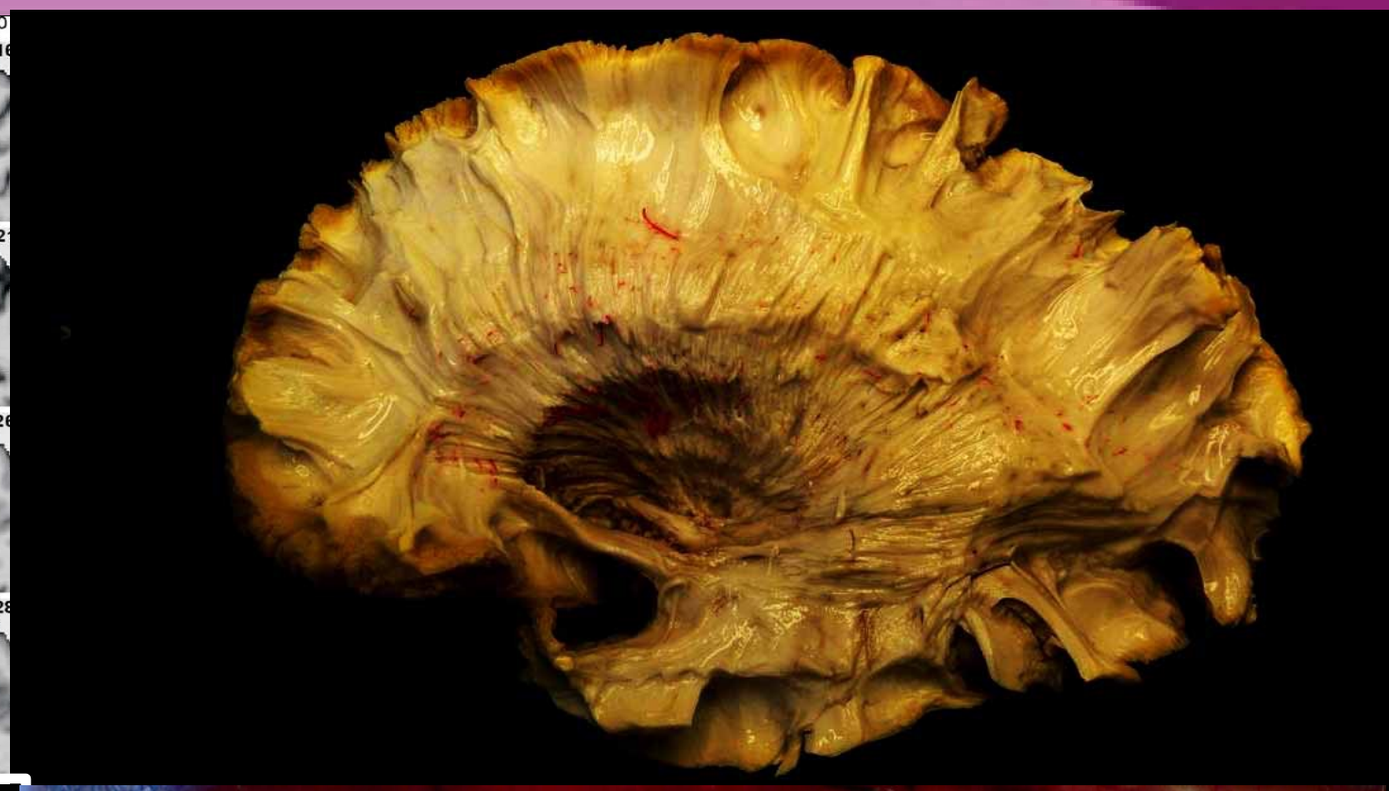


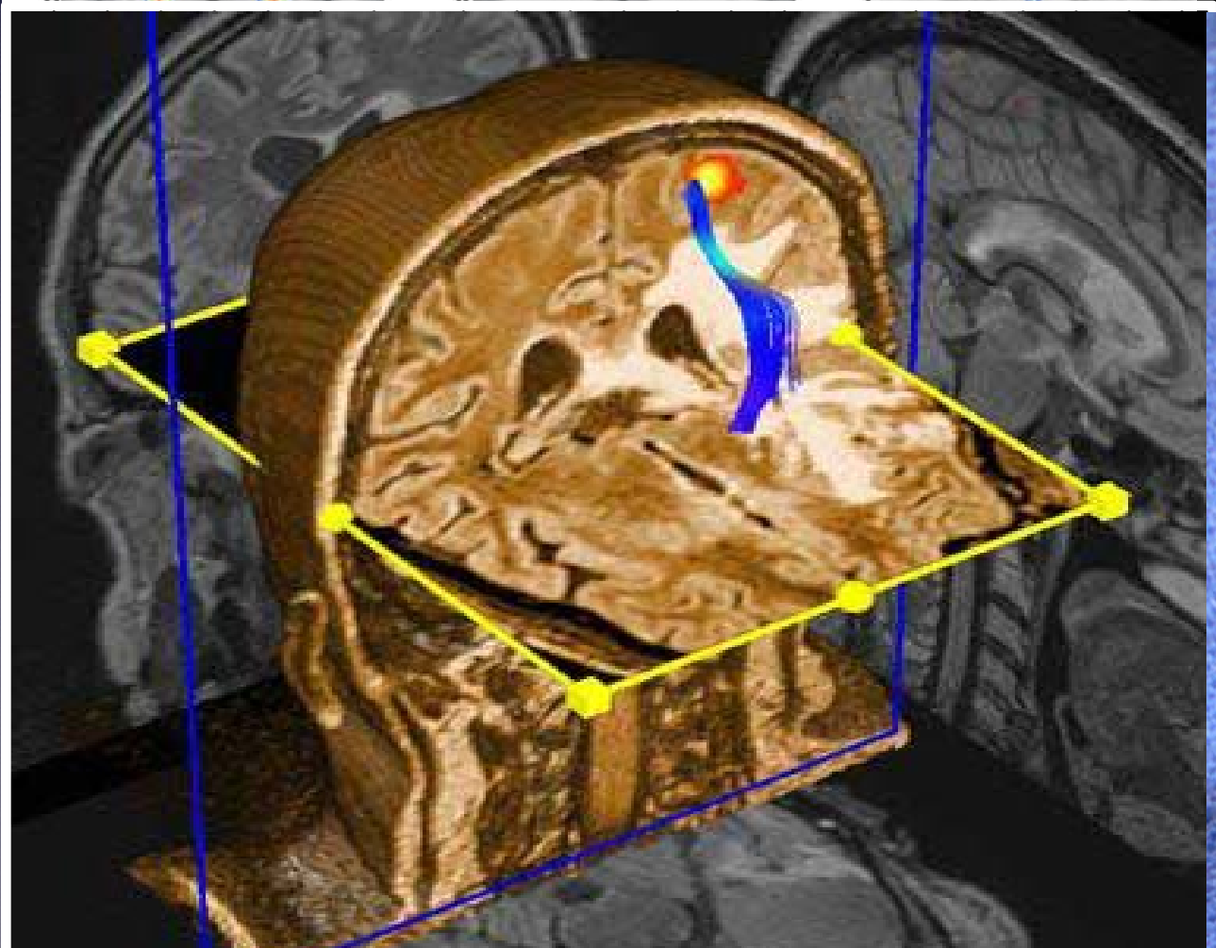
WHITE MATTER TRACTS

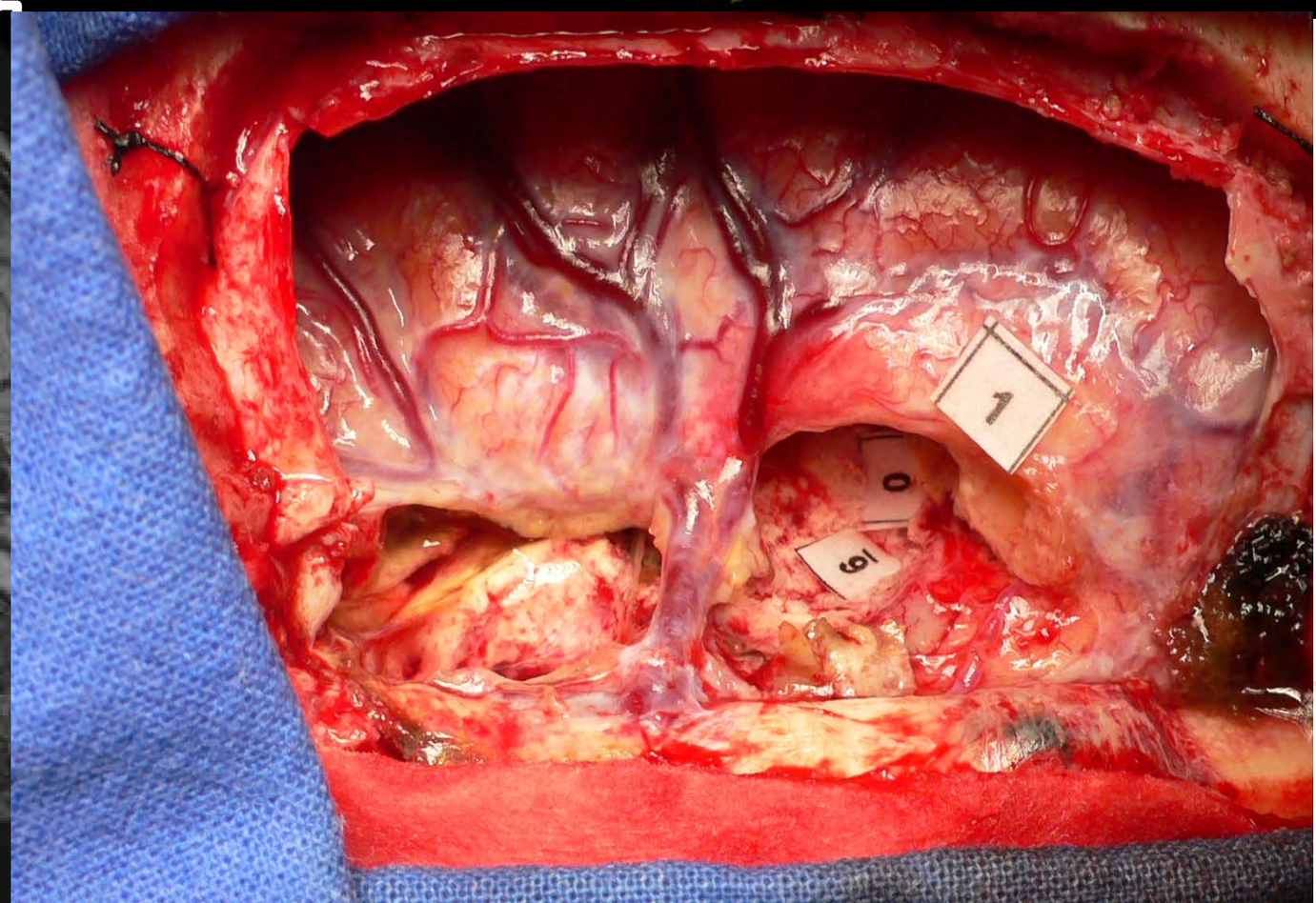


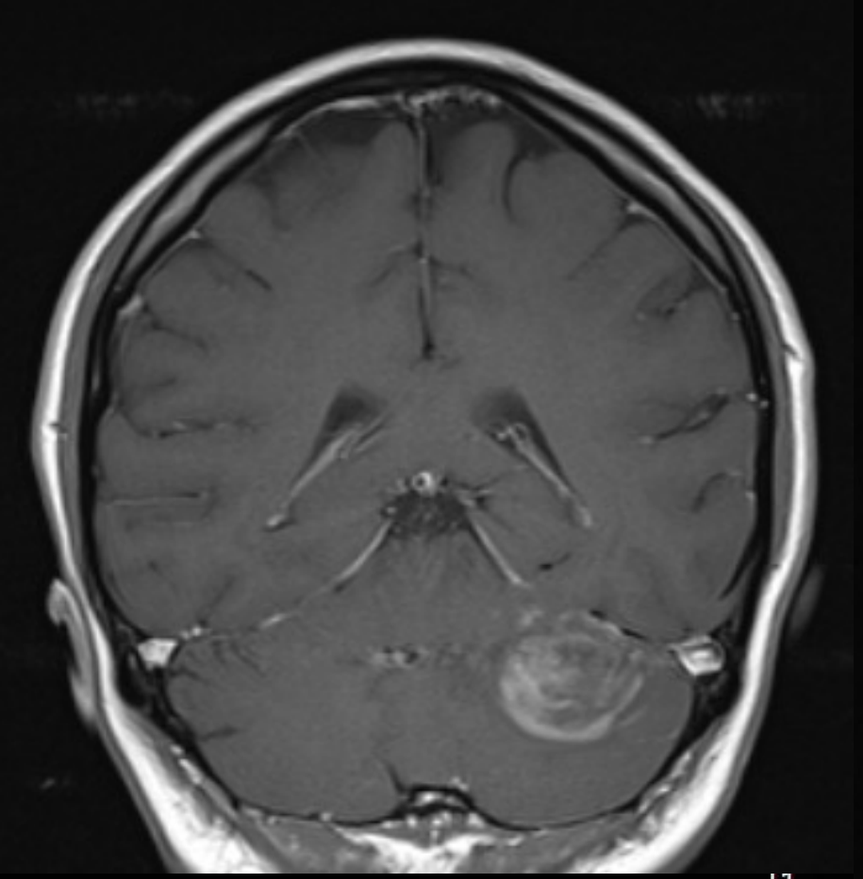
WHITE MATTER TRACTS - fMRI+DTI

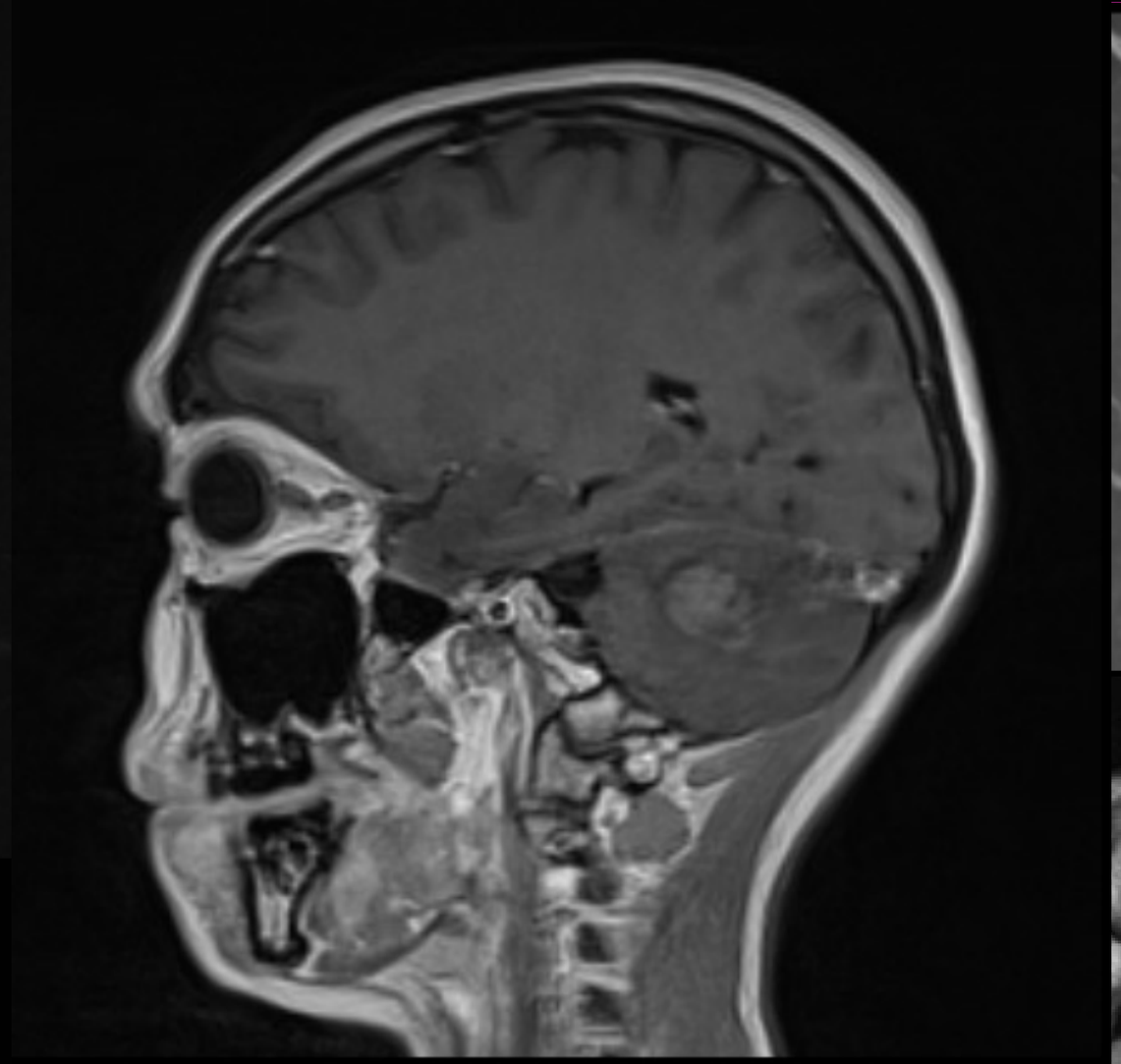


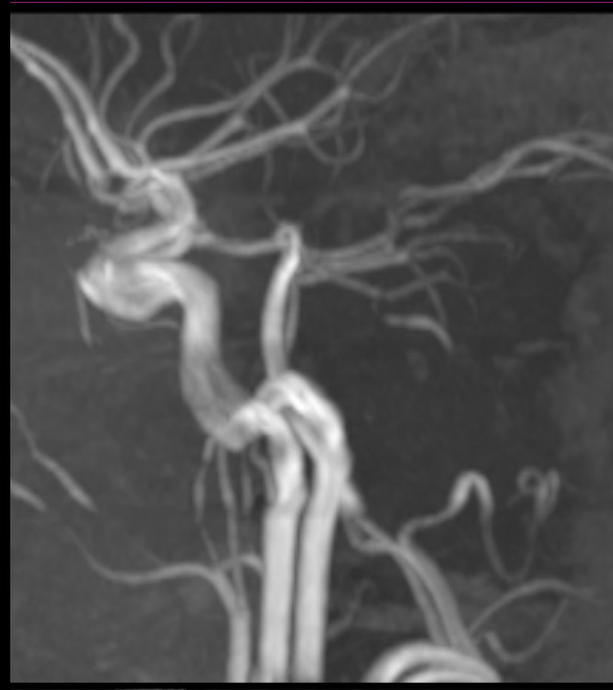


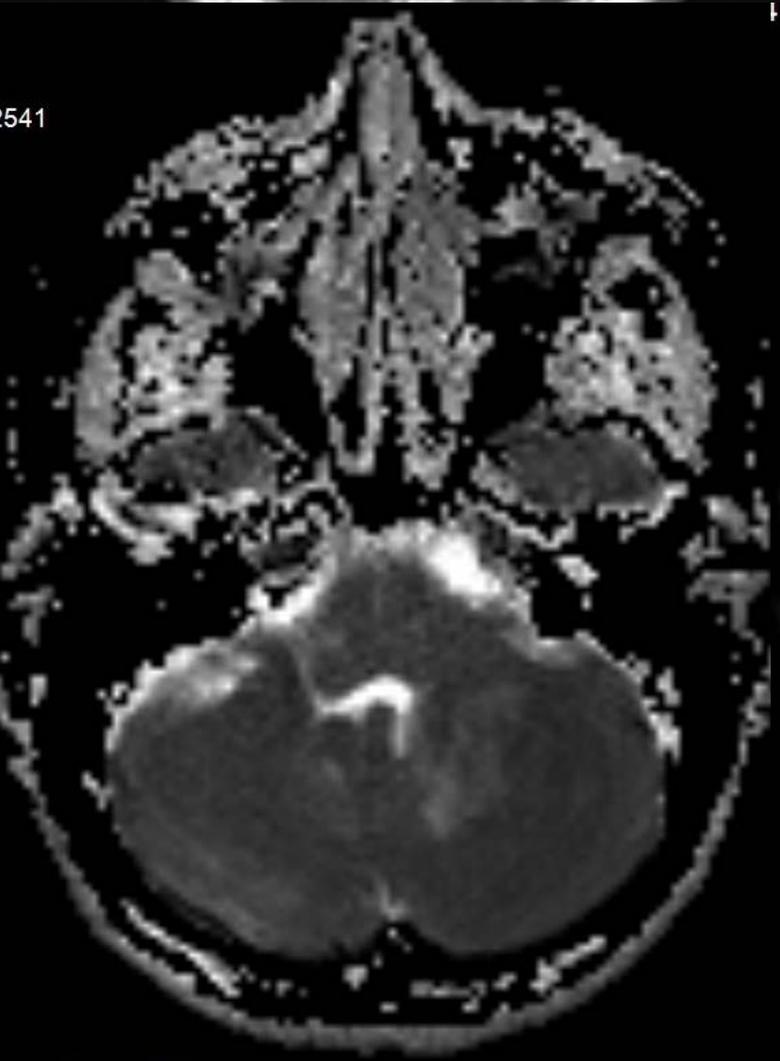


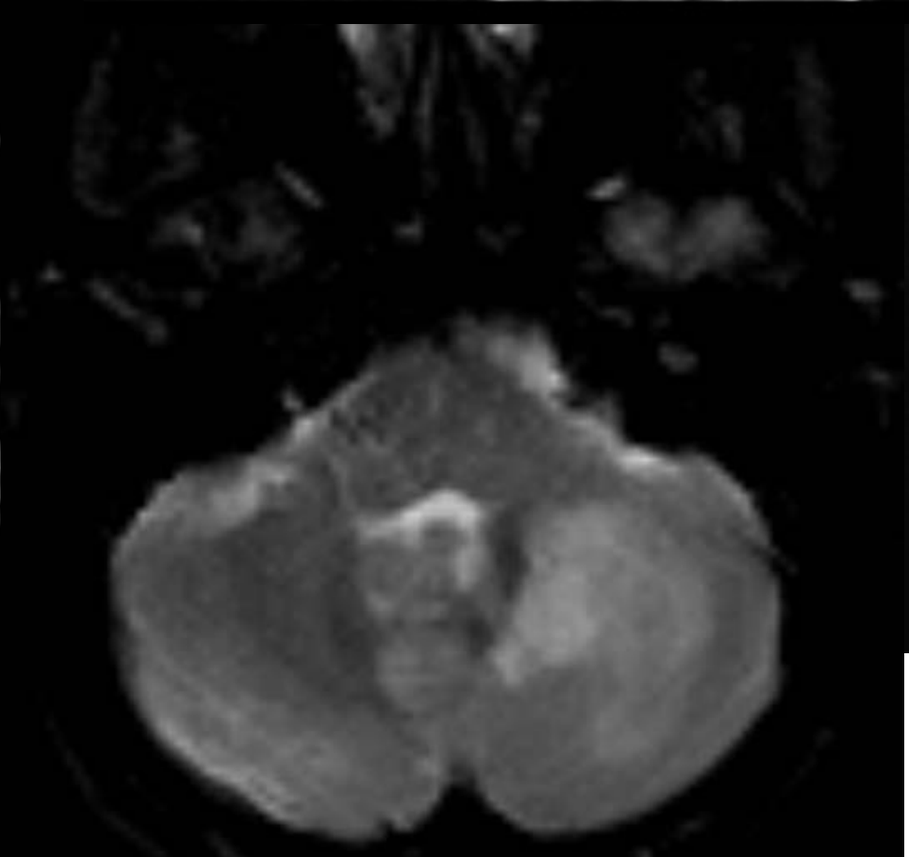


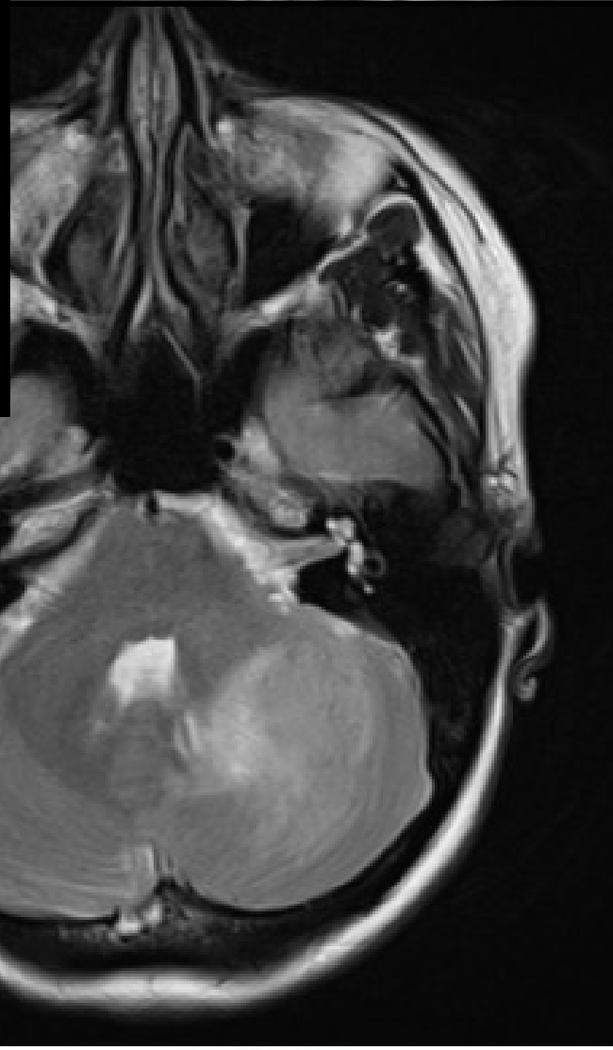













ESTRO
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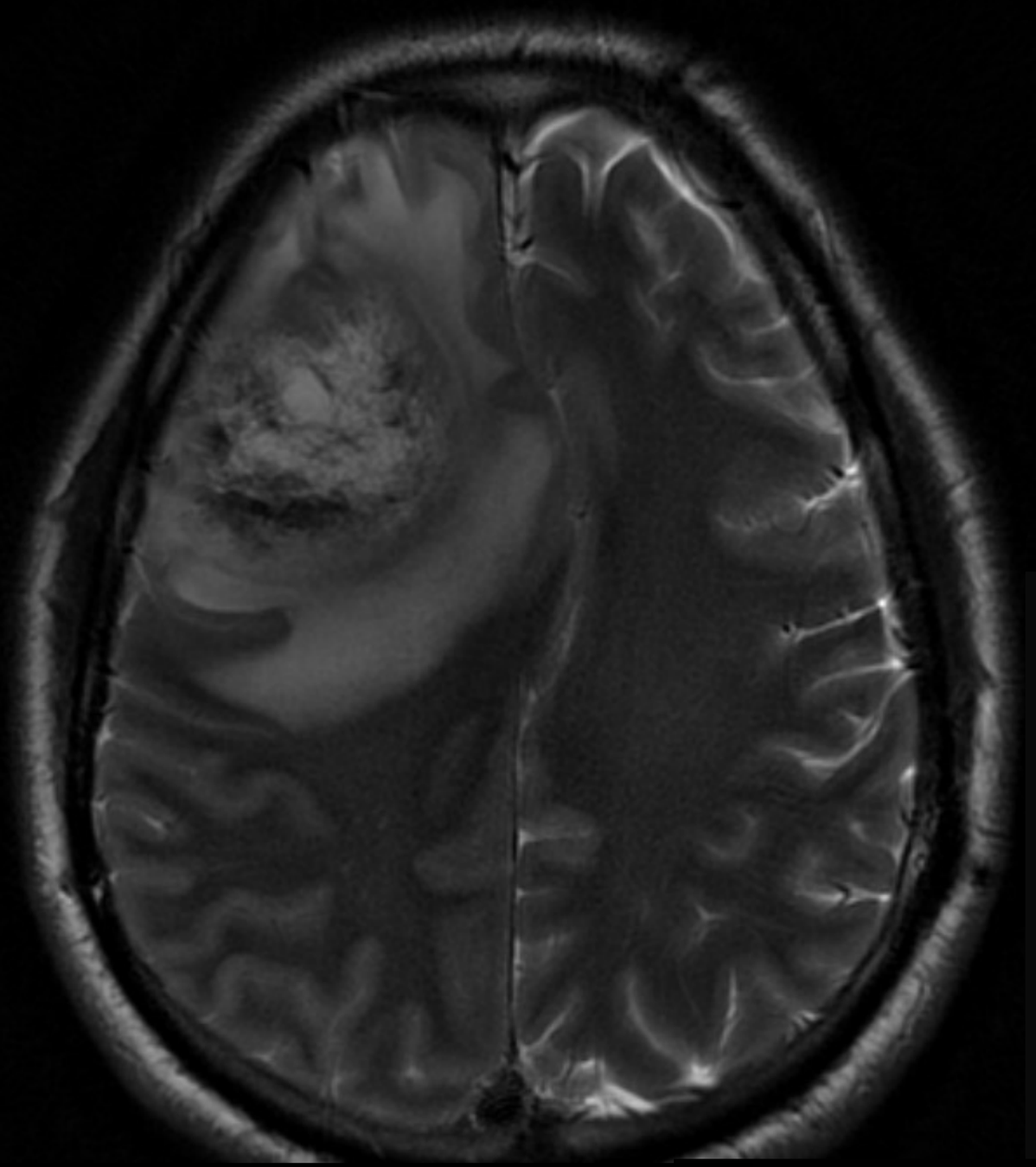

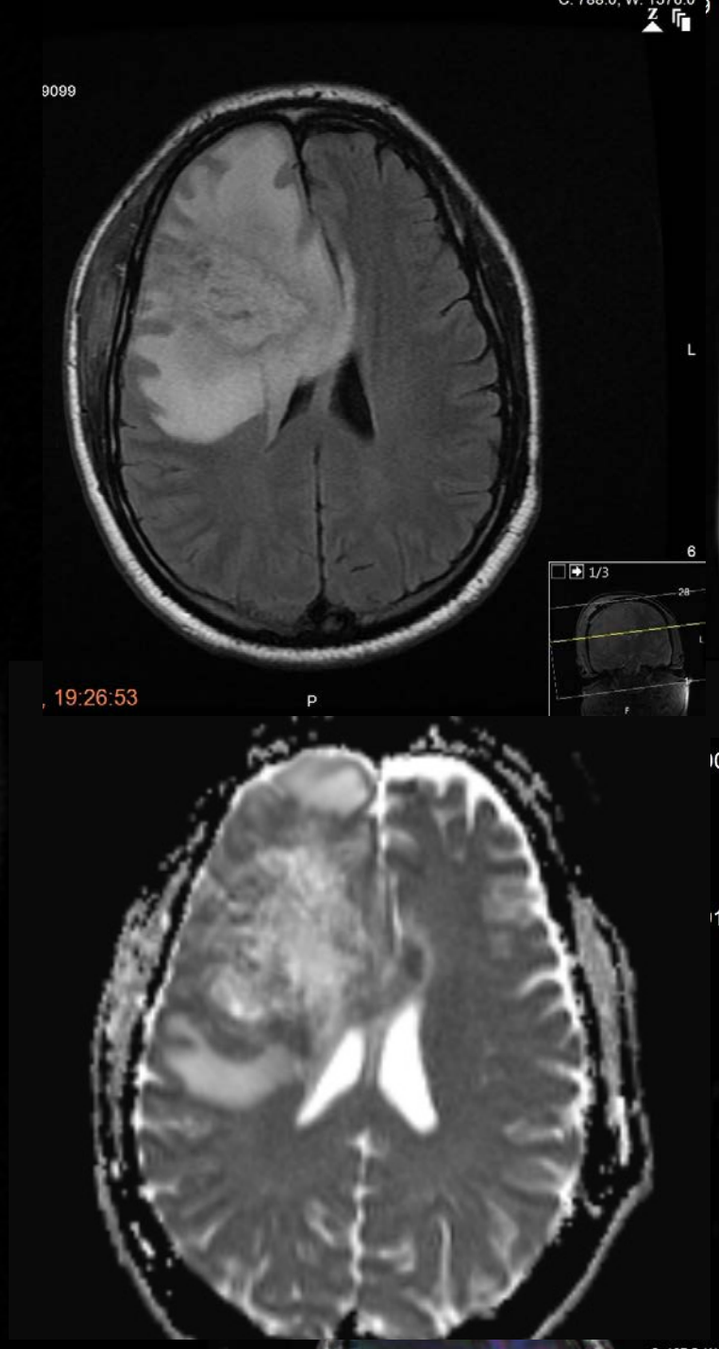
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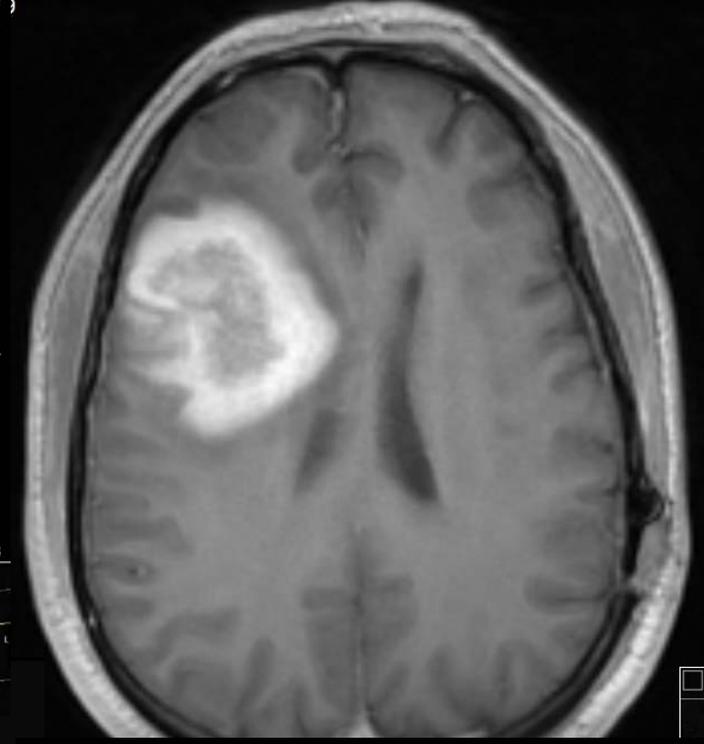

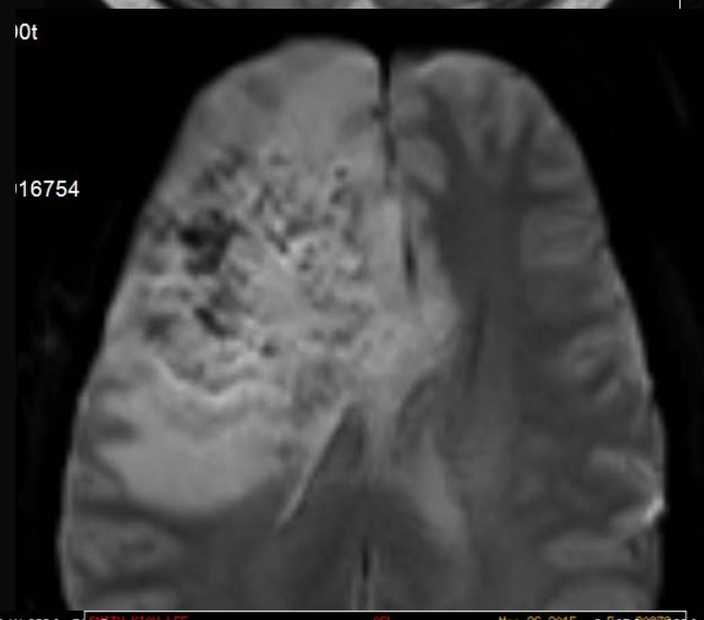
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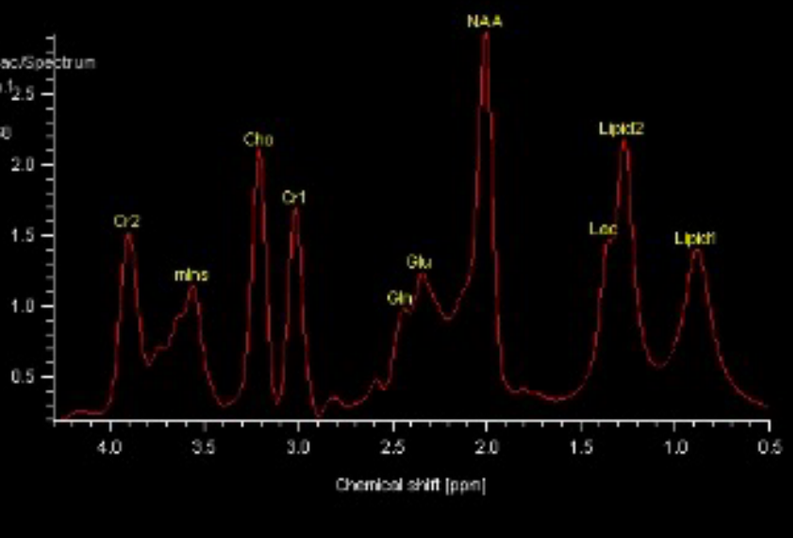
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mIns
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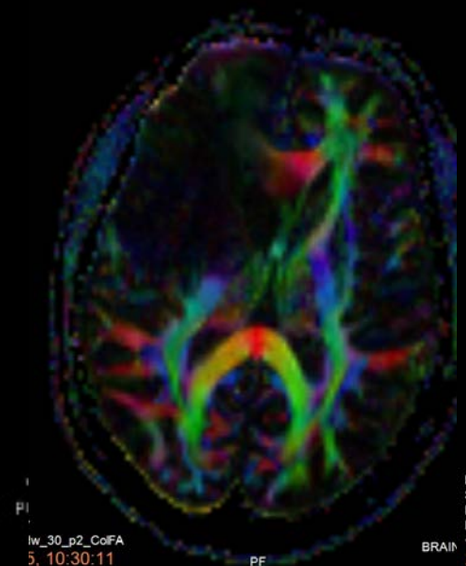
Chemical shift [ppm]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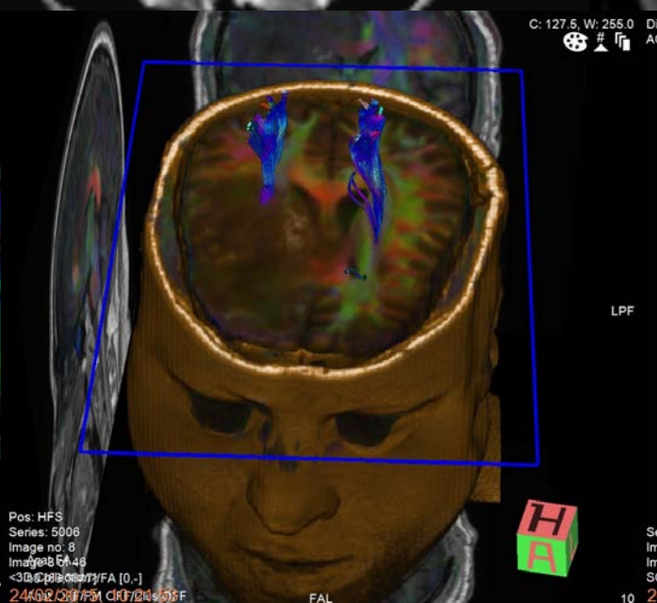
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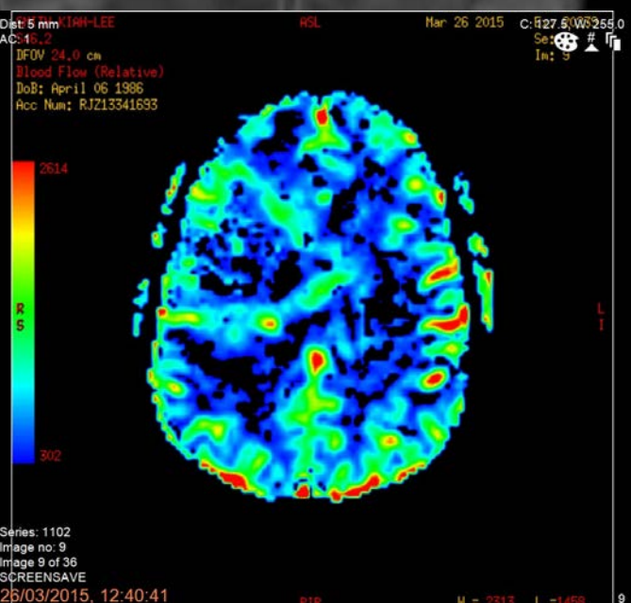
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Image 9 of 36
SCREENSAVE
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MODERN IMAGING OF BRAIN TUMOURS
TAKE HOME MESSAGE

- **Modern imaging offers a series of extraordinary complementary tools in diagnosis, treatment and follow up of brain tumours**

- **Unfortunately most of them still need to be validated**

- **Functional imaging and DTI in a clinical setting do not substitute cortical and subcortical intraoperative mapping**

- **<u>Despite advancement in multimodality imaging, definitive diagnosis of brain tumours still requires histopathology and molecular analysis in the vast majority of cases.</u>**

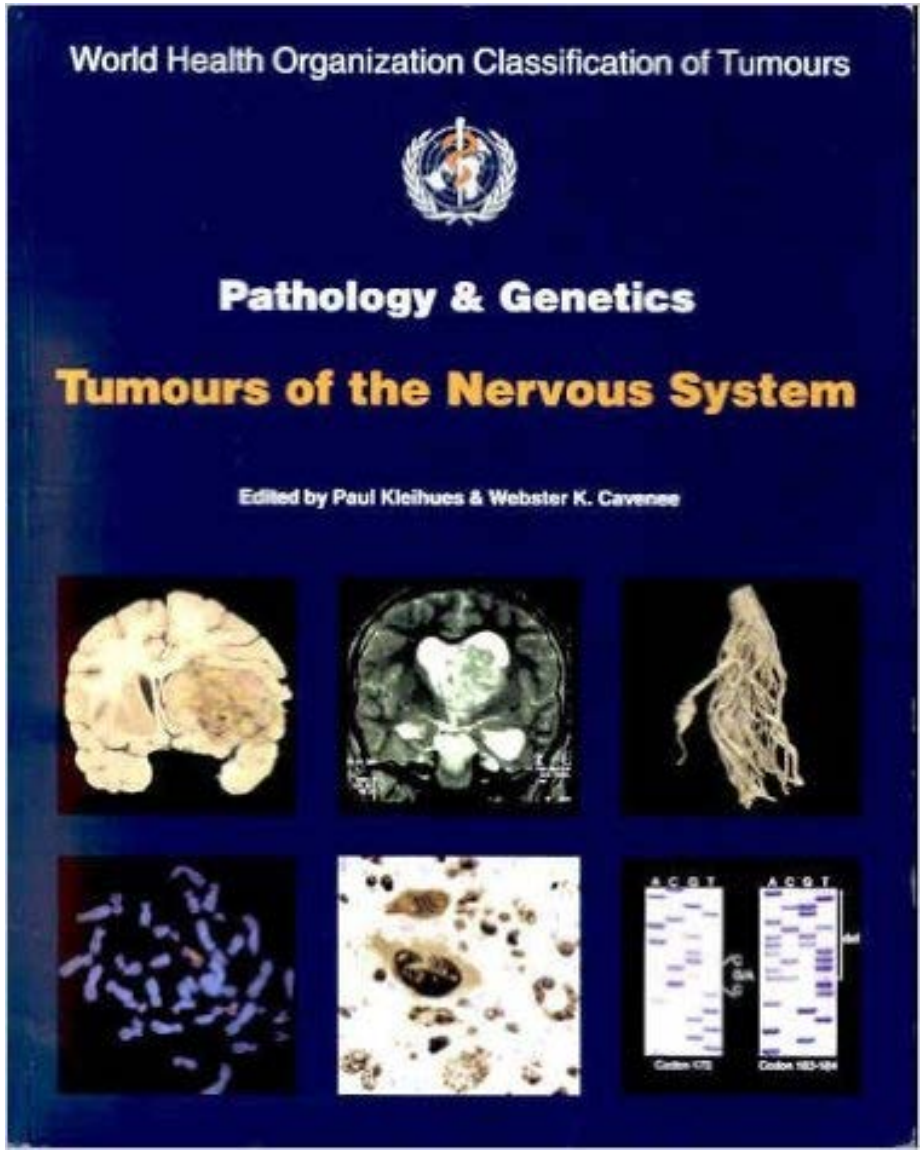
Thank You!

What is new in brain tumor classification

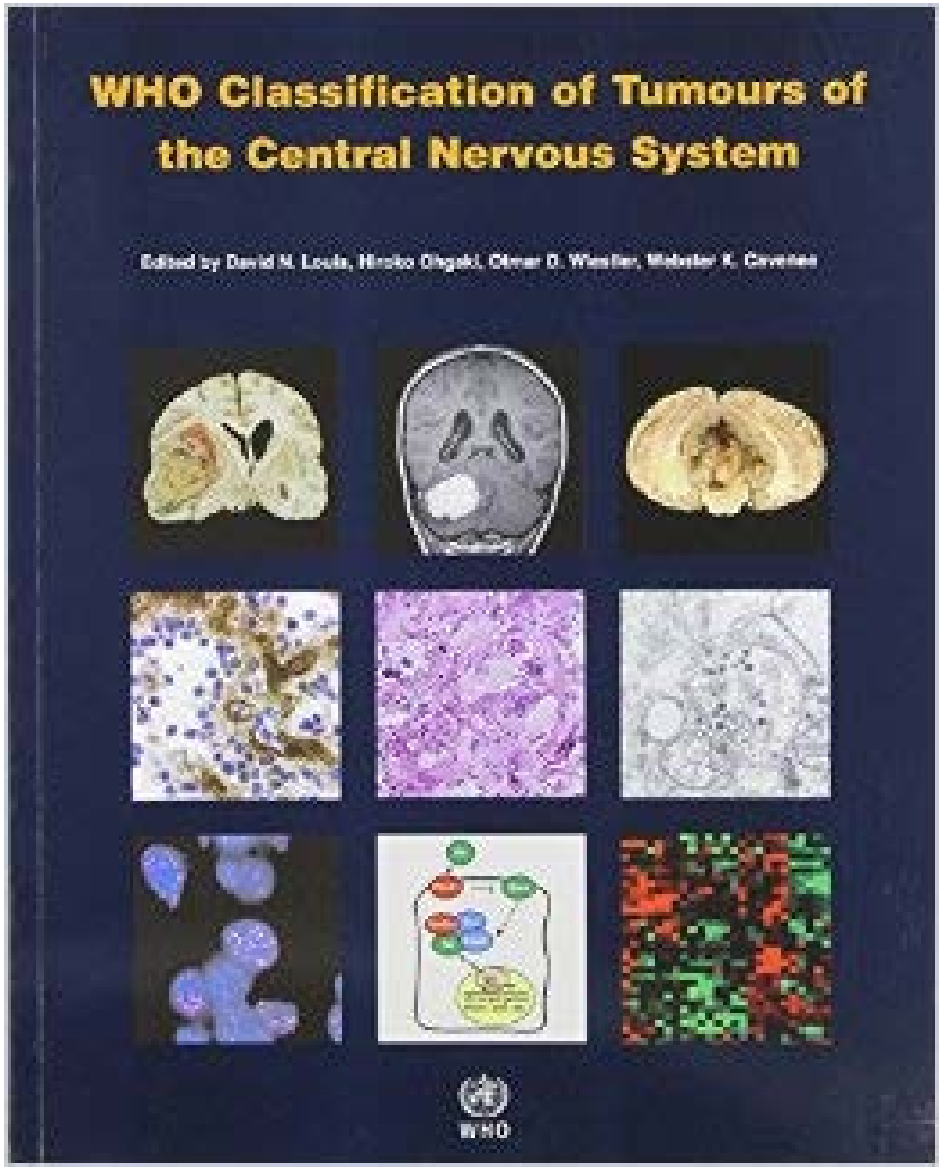
Paola Cassoni

Dept of Medical Sciences
University of Turin

2000


World Health Organization Classification of Tumours
Pathology & Genetics
Tumours of the Nervous System
Edited by Paul Kleihues & Webster K. Cavenee

2007

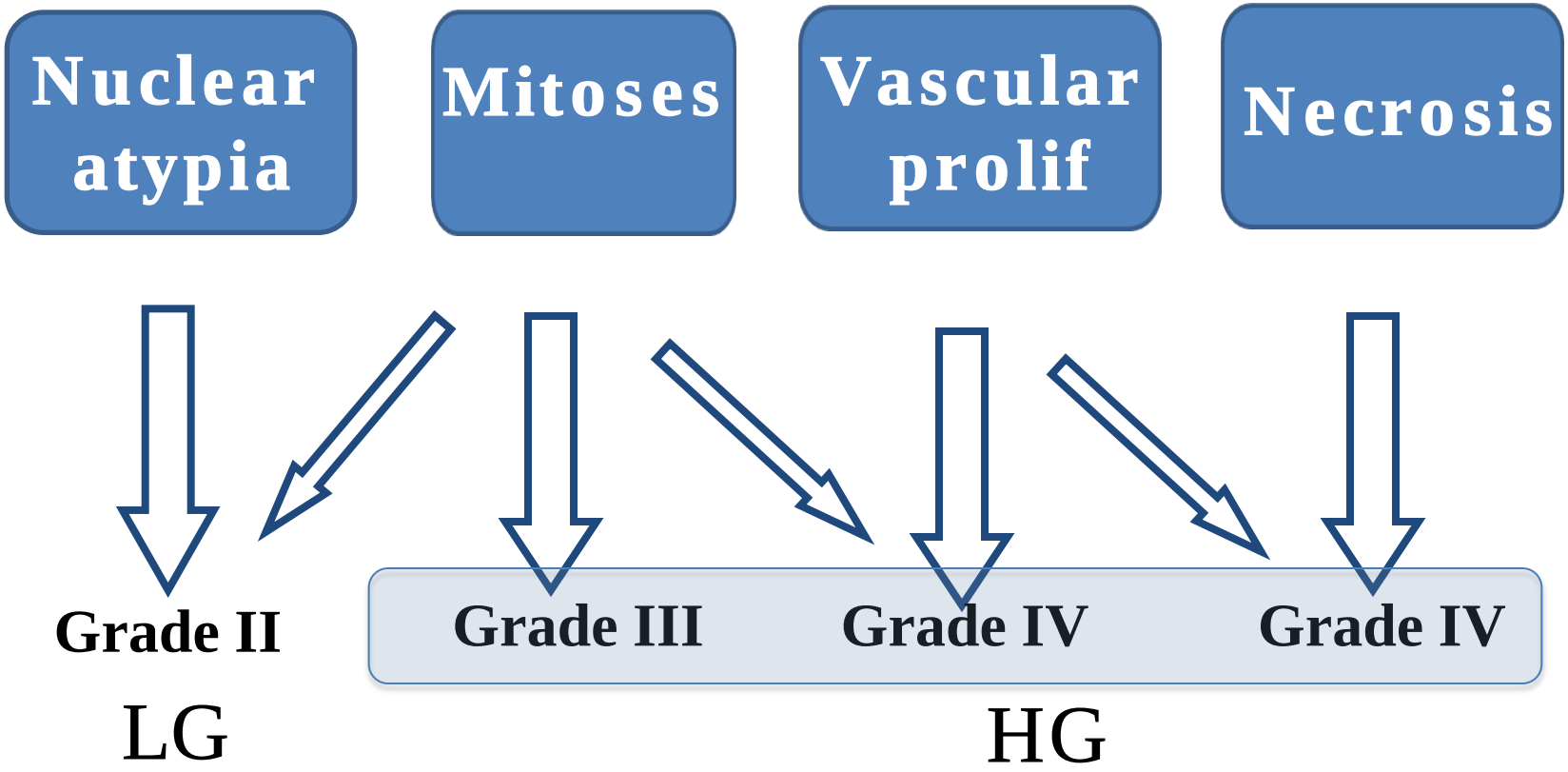

WHO Classification of Tumours of the Central Nervous System
WHO

Brain tumor diagnosis: a challenge step by step

- Histology and beyond
- The molecular background
- Handling Histo-molecular criteria
- Constructing an integrated diagnostic report

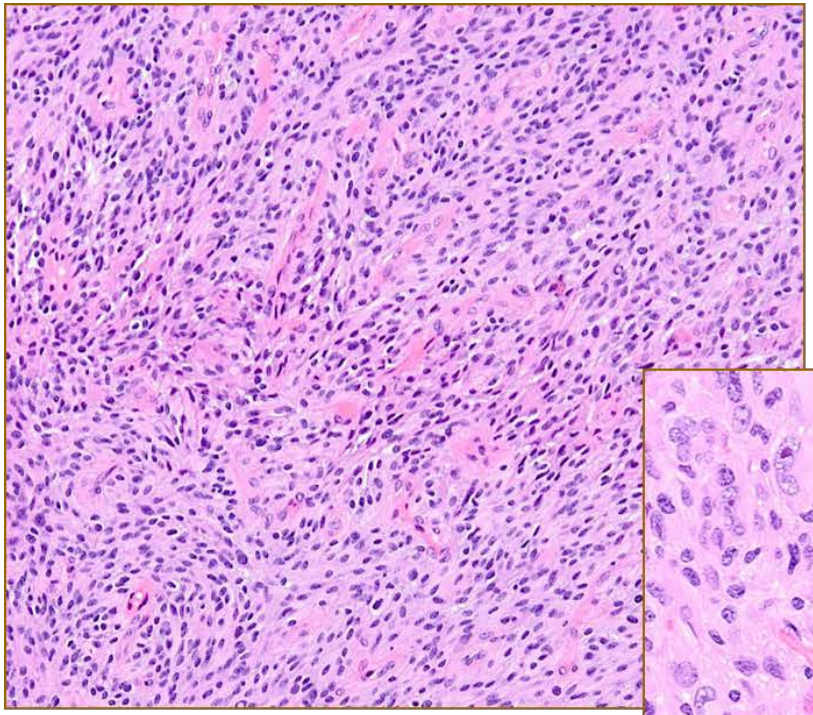
Histological Parameters for *Grading*

Increased cellularity **AND:**

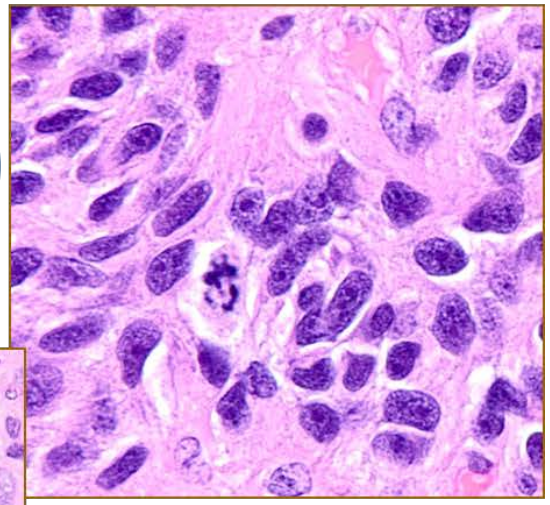


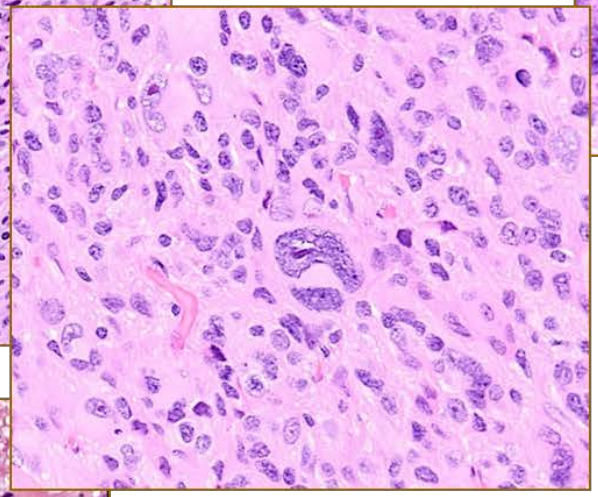
Histology and beyond

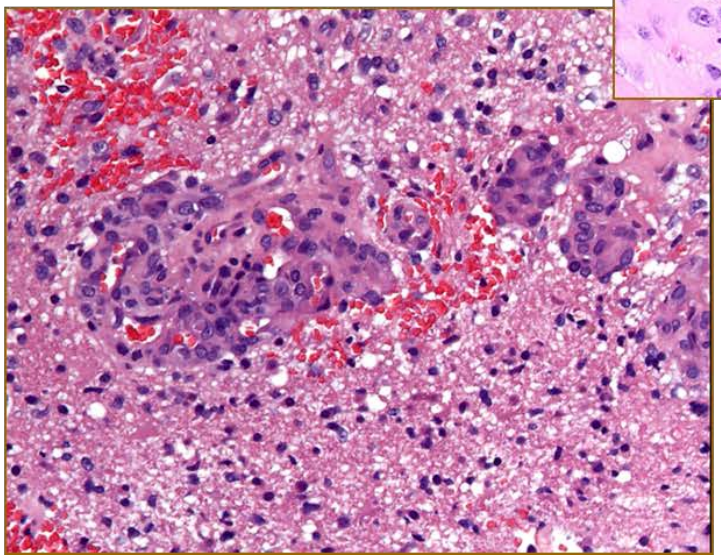
Criteria to look at for grading

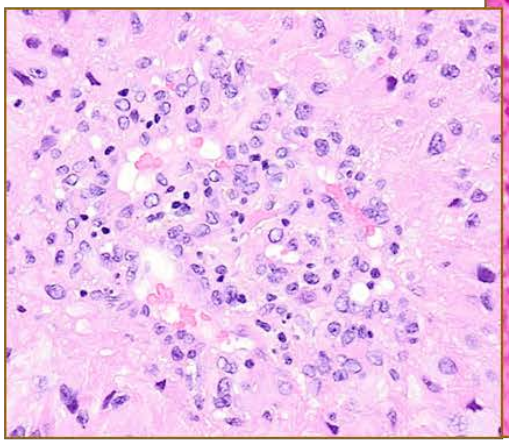


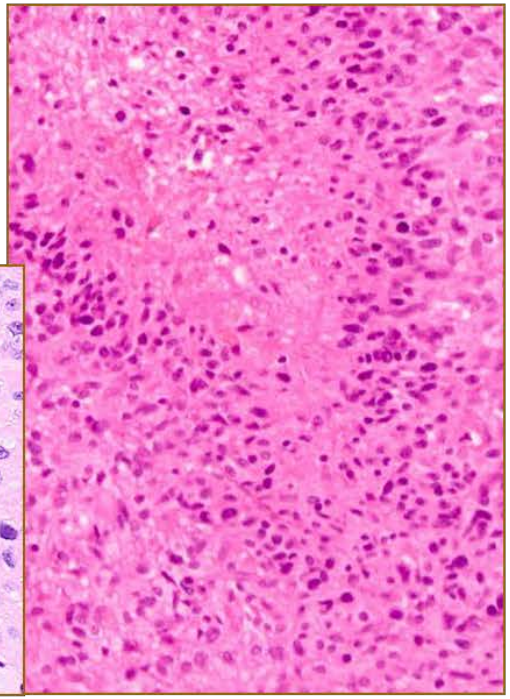
Still TRUE





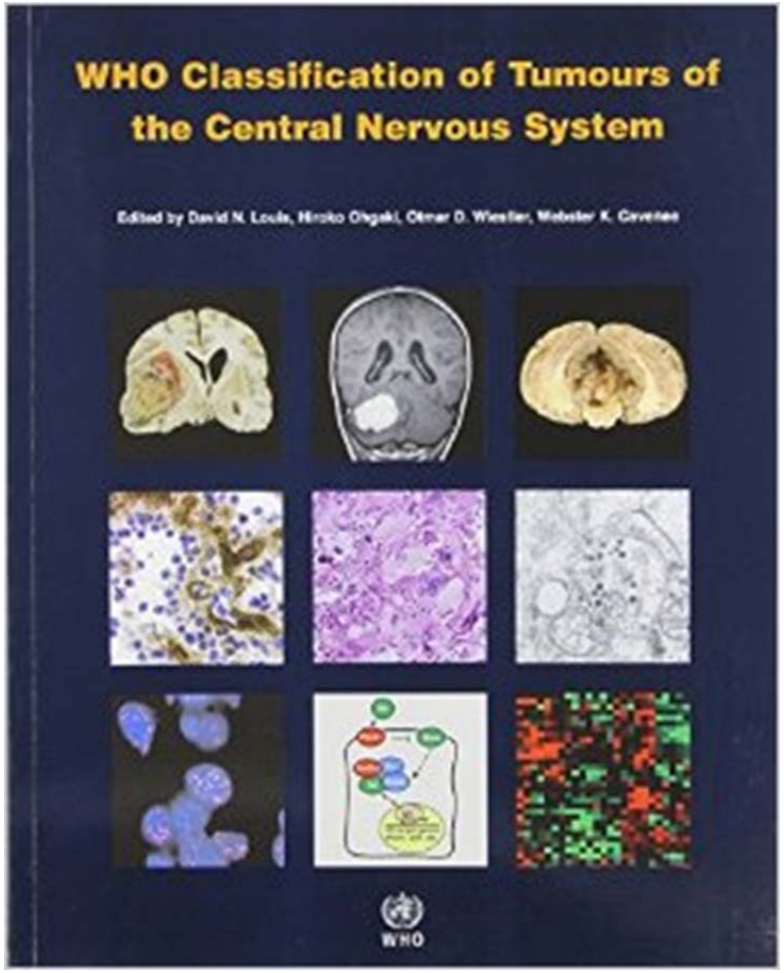






Histology and beyond

Histological Parameters for *Histotyping*



Acta Neuropathol (2007) 114:97–109
DOI 10.1007/s00401-007-0243-4

REVIEW

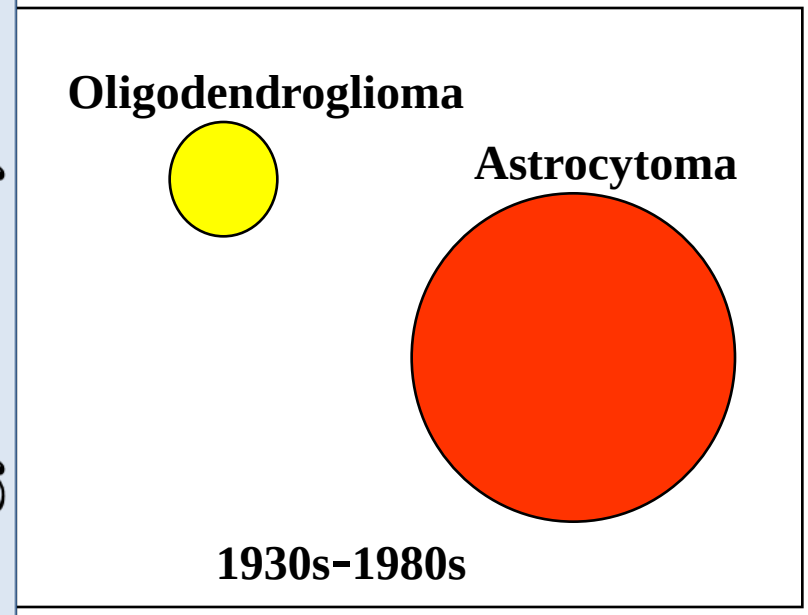
The 2007 WHO Classification of Tumours of the Central Nervous System

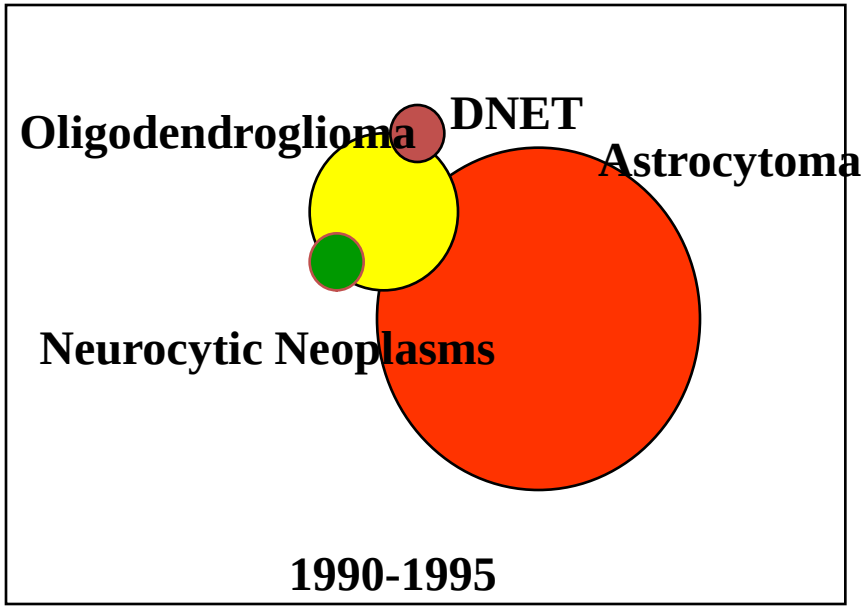
David N. Louis · Hiroko Ohgaki · Otmar D. Wiestler · Webster K. Cavenee · Peter C. Burger · Anne Jouvet · Bernd W. Scheithauer · Paul Kleihues

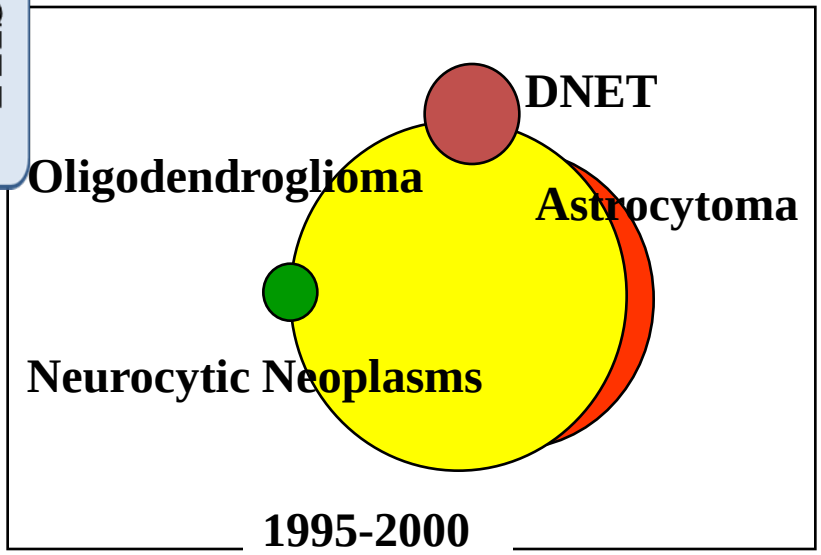
- **Eight** new ***entities*** (including 2 glio-neuronal tumors)

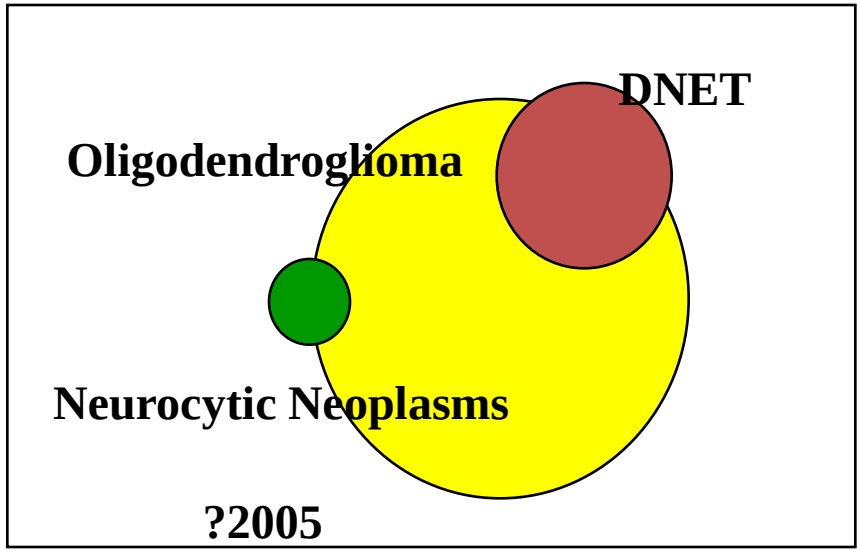
- **Many** new ***variants*** (i.e. anaplastic medulloblastoma) and ***patterns*** (i.e. small cell GBM, GBMO)

Histology and beyond



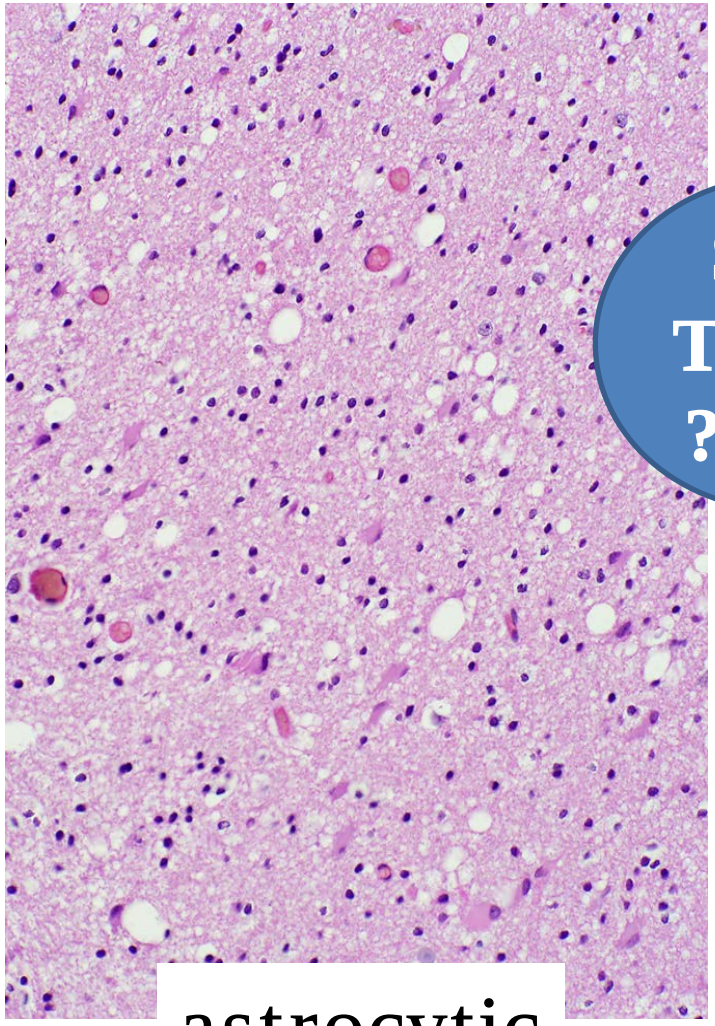






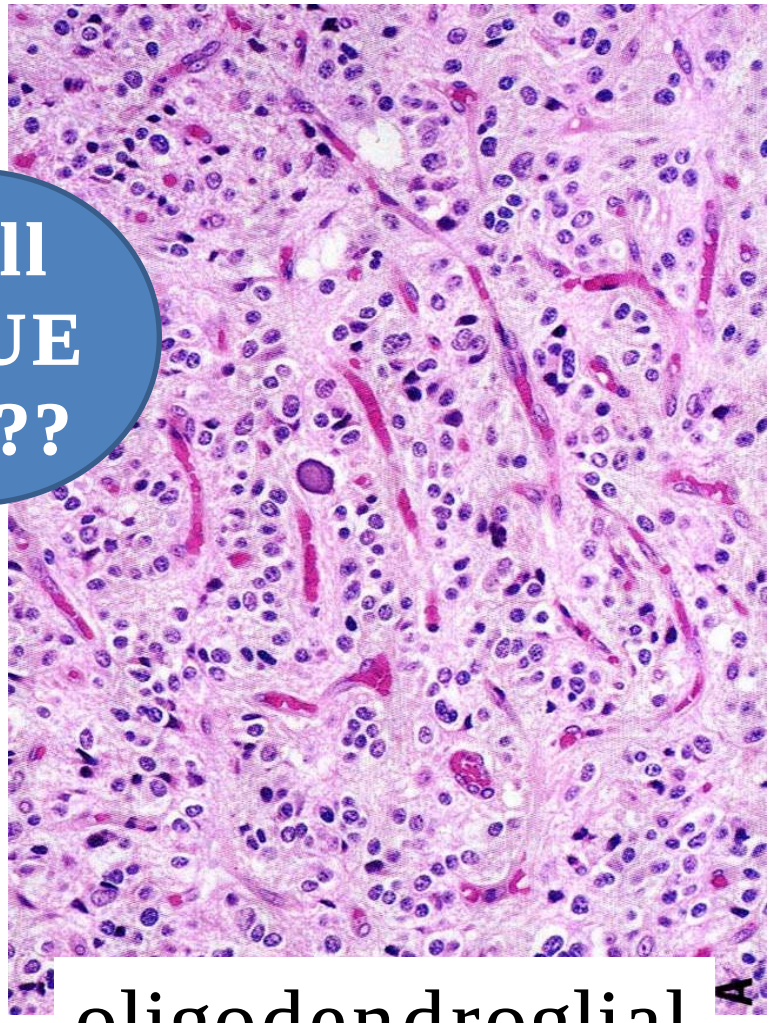
Burger PC: What is an oligodendroglioma? Brain Pathol; April 2002

Histology and beyond



astrocytic

Still TRUE ?????



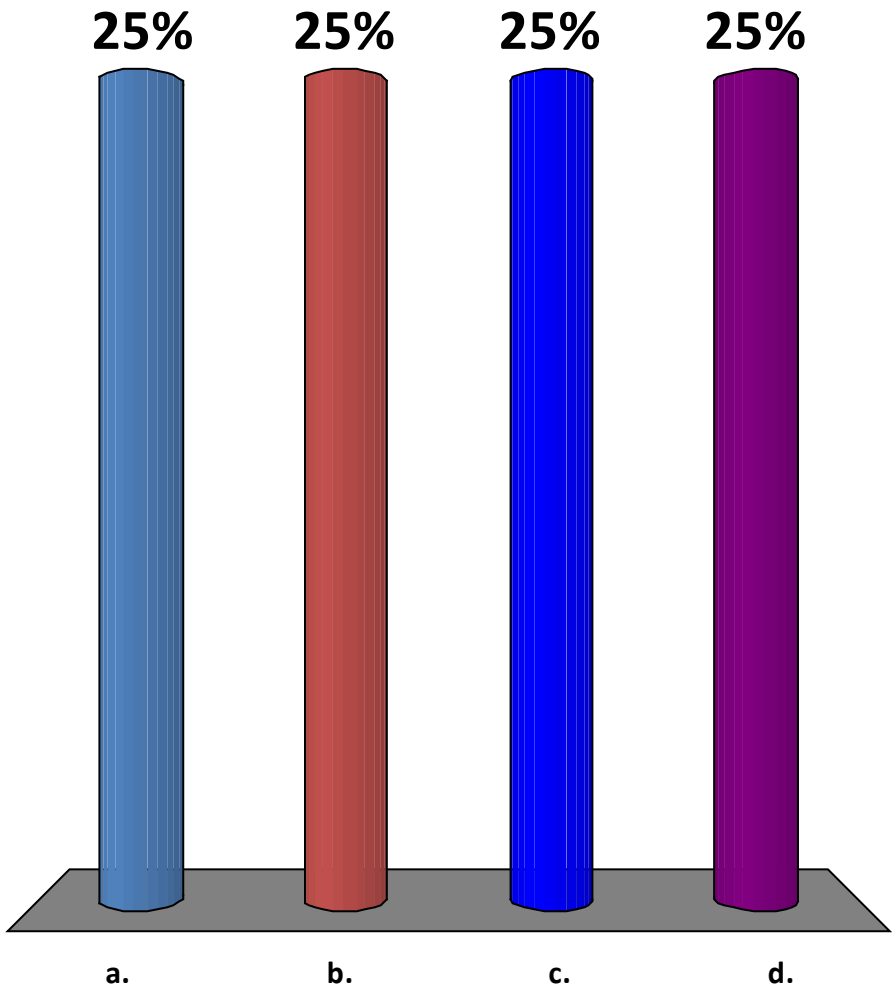
oligodendroglial

Alterations of Chromosome Arms 1p and 19q as Predictors of Survival in Oligodendrogliomas, Astrocytomas, and Mixed Oligoastrocytomas

By Justin S. Smith, Arie Perry, Thomas J. Borell, Hyun K. Lee, Judith O'Fallon, Sandra M. Hosek, David Kimmel, Allan Yates, Peter C. Burger, Bernd W. Scheithauer, and Robert B. Jenkins

A grade IV glioma is histologically diagnosed in presence of:

a. Mitoses
b. Necrosis
c. Vascular proliferation
d. b and c



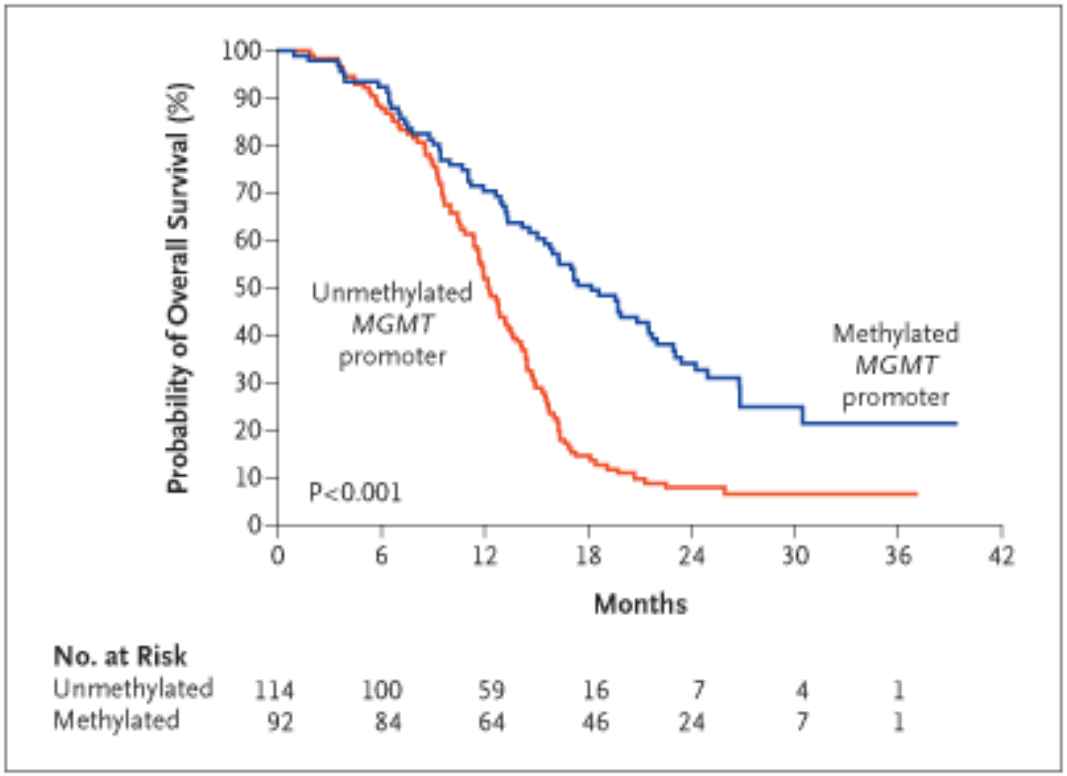
Brain tumor diagnosis: a challenge step by step

- Histology and beyond
- The molecular background
- Handling Histo-molecular criteria
- Constructing an integrated diagnostic report

The molecular background

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

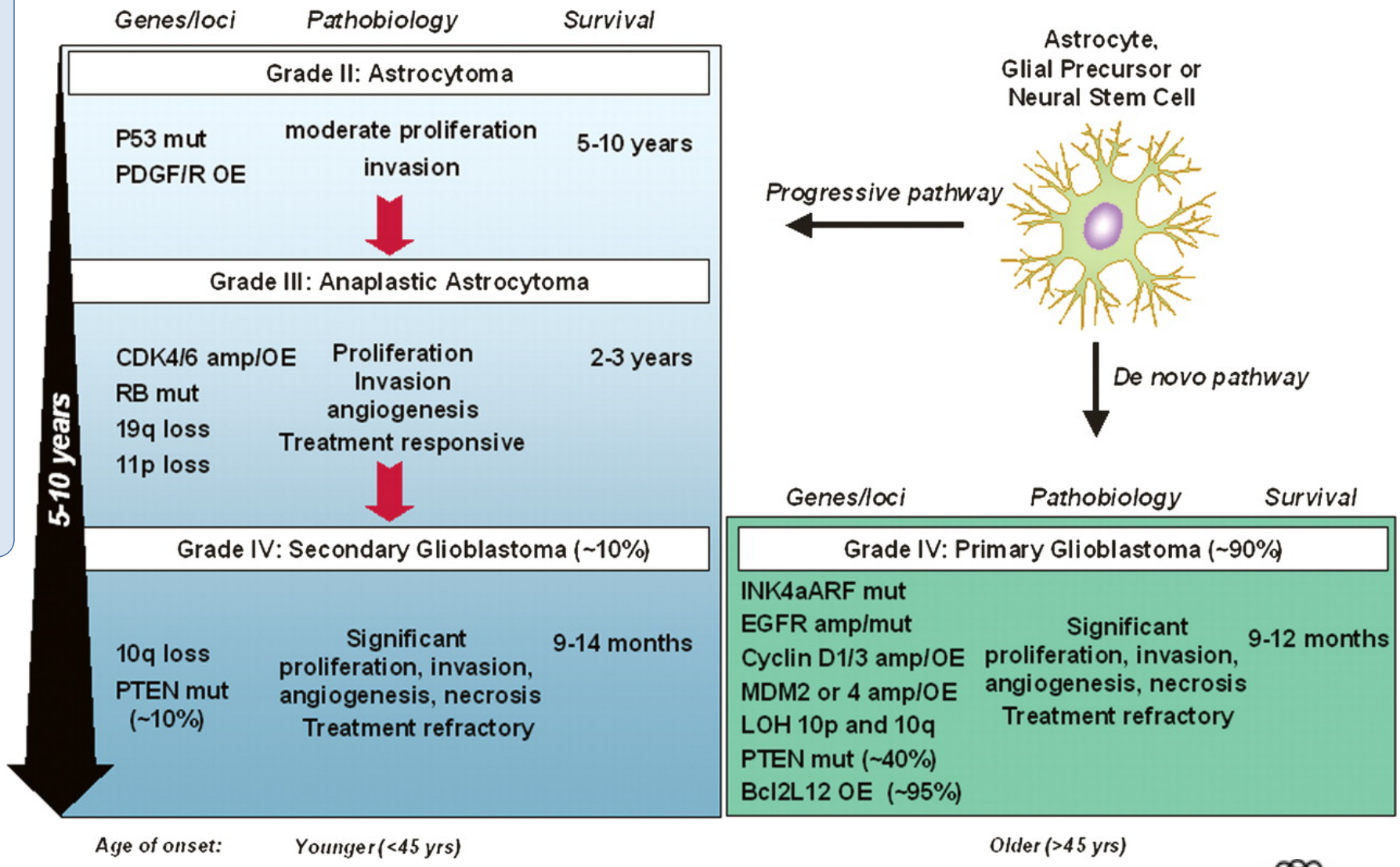
Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.



N Engl J Med 2005;352:997-1003.

The molecular background

Chromosomal and genetic aberrations involved in the genesis of glioblastoma



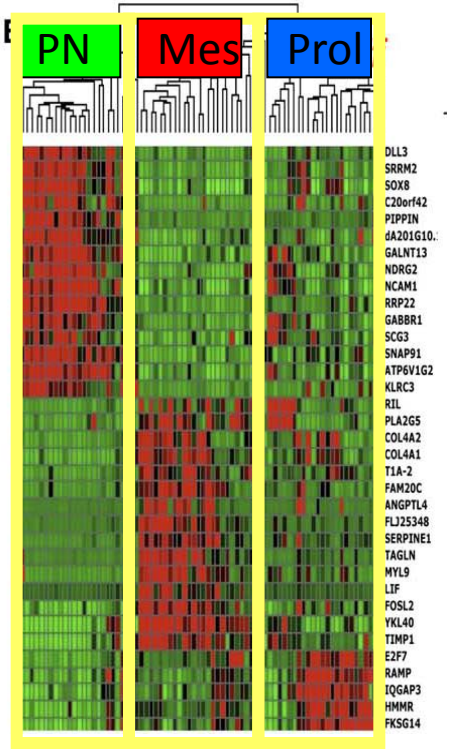
Furnari F. B. et.al. Genes Dev. 2007;21:2683-2710

The molecular background

Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis

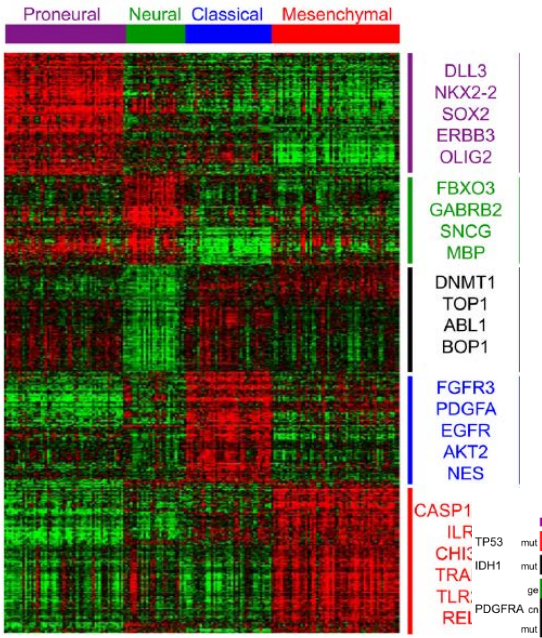
CANCER CELL 9, 157–173, MARCH 2006 ©

76 AIII+GBM



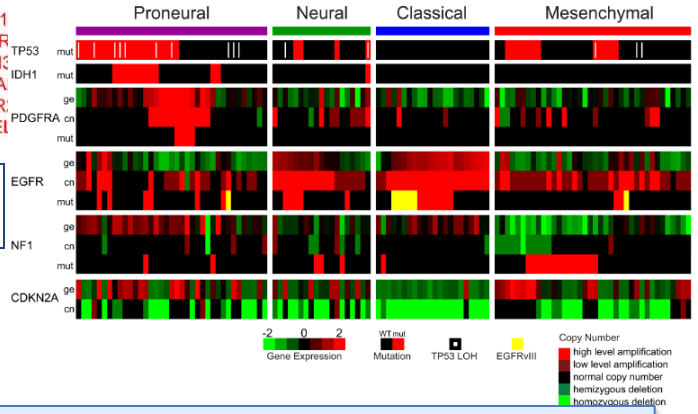
An integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR and NF1

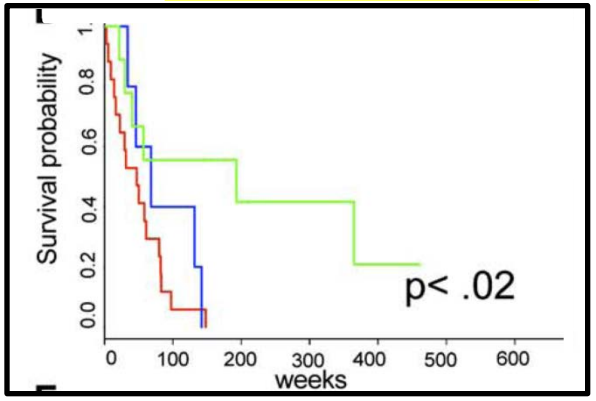
Cancer Cell. 2010 January 19; 17(1): 98.



Gene	Proneural (n=37)	Neural (n=19)	Classical (n=22)	Mesenchymal (n=38)	Total #Mut
TP53	**20 (54%)**	4 (21%)	**0 (0%)**	12 (32%)	36
PTEN	6 (16%)	4 (21%)	5 (23%)	12 (32%)	27
NF1	2 (5%)	3 (16%)	1 (5%)	**14 (37%)**	20
EGFR	6 (16%)	5 (26%)	7 (32%)	2 (5%)	20
IDH1	**11 (30%)***	1 (5%)	0 (0%)	0 (0%)	12
PIK3R1	7 (19%)	2 (11%)	1 (5%)	0 (0%)	10
RB1	1 (3%)	1 (5%)	0 (0%)	5 (13%)	7
ERBB2	2 (5%)	3 (16%)	1 (5%)	1 (3%)	7
EGFRvIII	1 (3%)	0 (0%)	5 (23%)	1 (3%)	7
PIK3CA	3 (8%)	1 (5%)	1 (5%)	1 (3%)	6
PDGFRA	4 (11%)	0 (0%)	0 (0%)	0 (0%)	4

173 GMB





III and IV astrocytic grades have specific, prognostic molecular signatures

The molecular background

Classical	Proneural	Mesenchymal	Neural
Cr 7 Ampl Cr 10 loss p16 deletion	IDH1 mut p53 mut PDGFRA mut	NF1 del YKL-40 expr Met expr	Neuron markers expression
	grade III/IV	Grade IV	
	No necrosis	Necrosis Inflammation	
	Younger (<40y)	older	
	better OS	poor OS	

Secondary GBM

same histology and grade BUT different prognosis

Verhaak R. et al 2010 and Phillips et al. 2006

The molecular background

Mutant Metabolic Enzymes Are at the Origin of Gliomas

Hai Yan,[1,2,3] Darell D. Bigner,[1,2,3] Victor Velculescu,[4] and D. Williams Parsons[4]

[1]The Pediatric Brain Tumor Foundation Institute, [2]The Preston Robert Tisch Brain Tumor Center, [3]Department of Pathology, Duke University Medical Center, Durham, North Carolina; and [4]The Ludwig Center for Cancer Genetics and Therapeutics at Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland

The NEW ENGLAND JOURNAL of MEDICINE

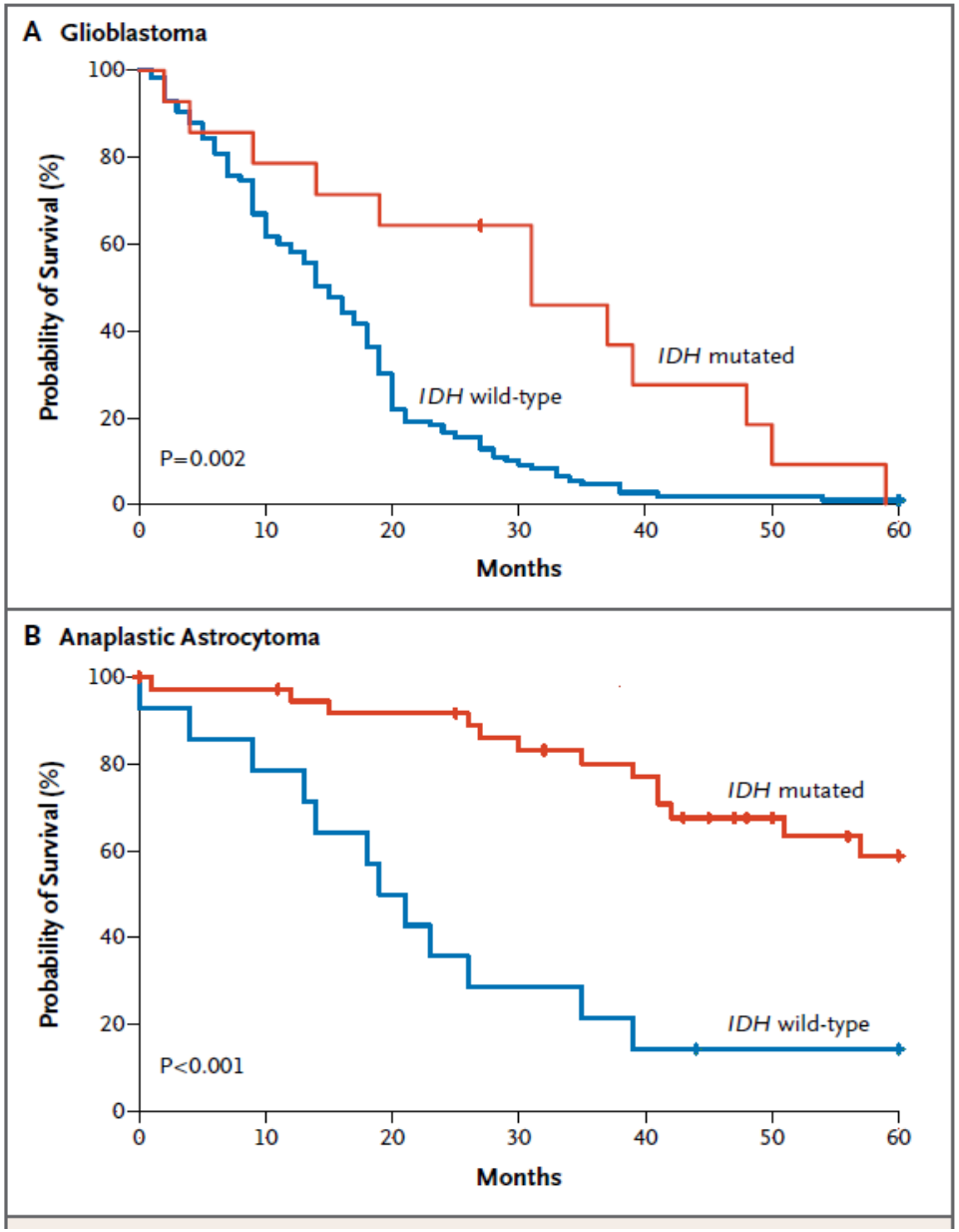
ORIGINAL ARTICLE

IDH1 and *IDH2* Mutations in Gliomas

Hai Yan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinic-Haberle, Ph.D., Siân Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

2009

The molecular background



Before

Grade II

Low Grade

vs

Grade III **Grade IV**

High Grades

After

Grade II **Grade III**

Lower Grades

vs

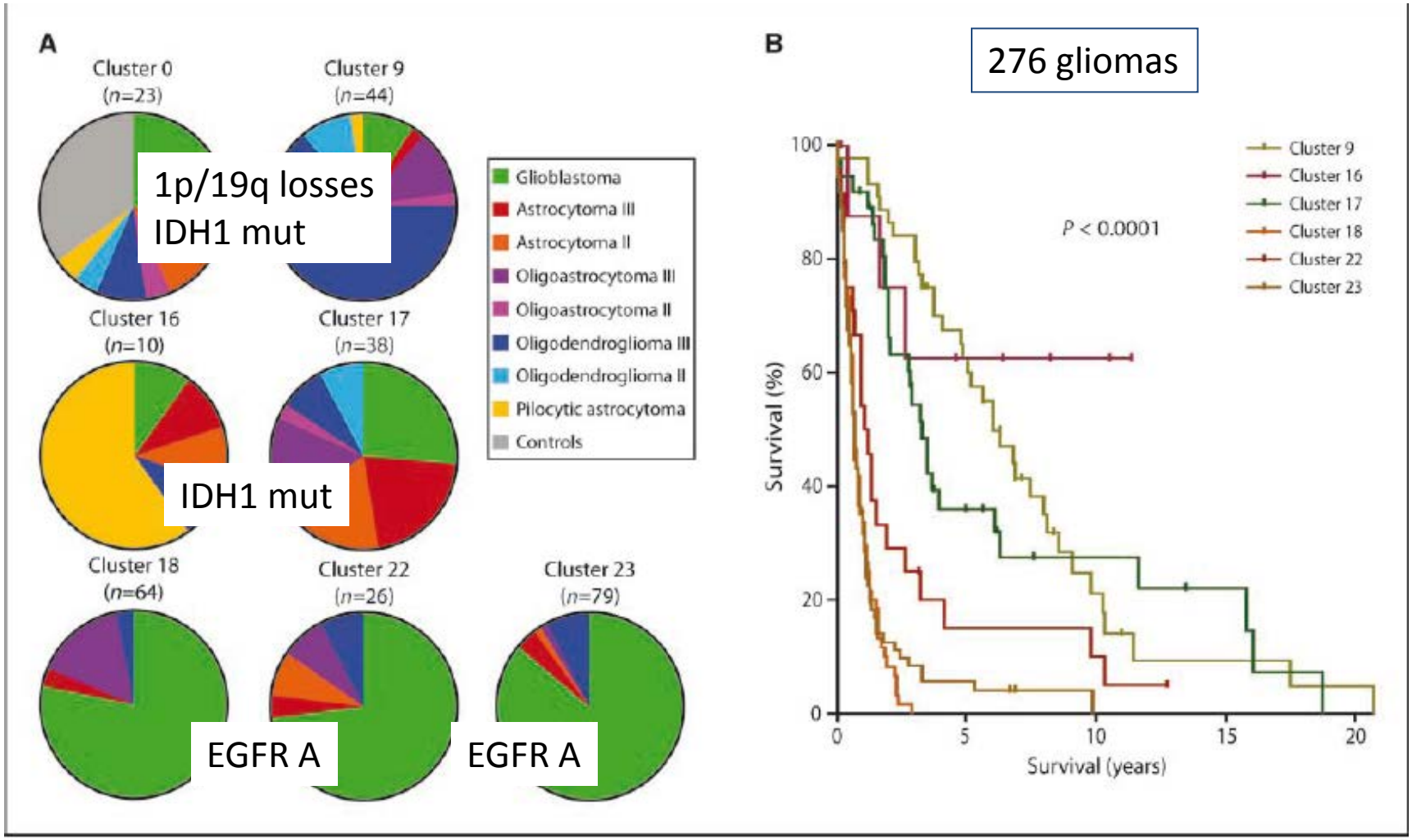
Grade IV

The molecular background

Intrinsic Gene Expression Profiles of Gliomas Are a Better Predictor of Survival than Histology

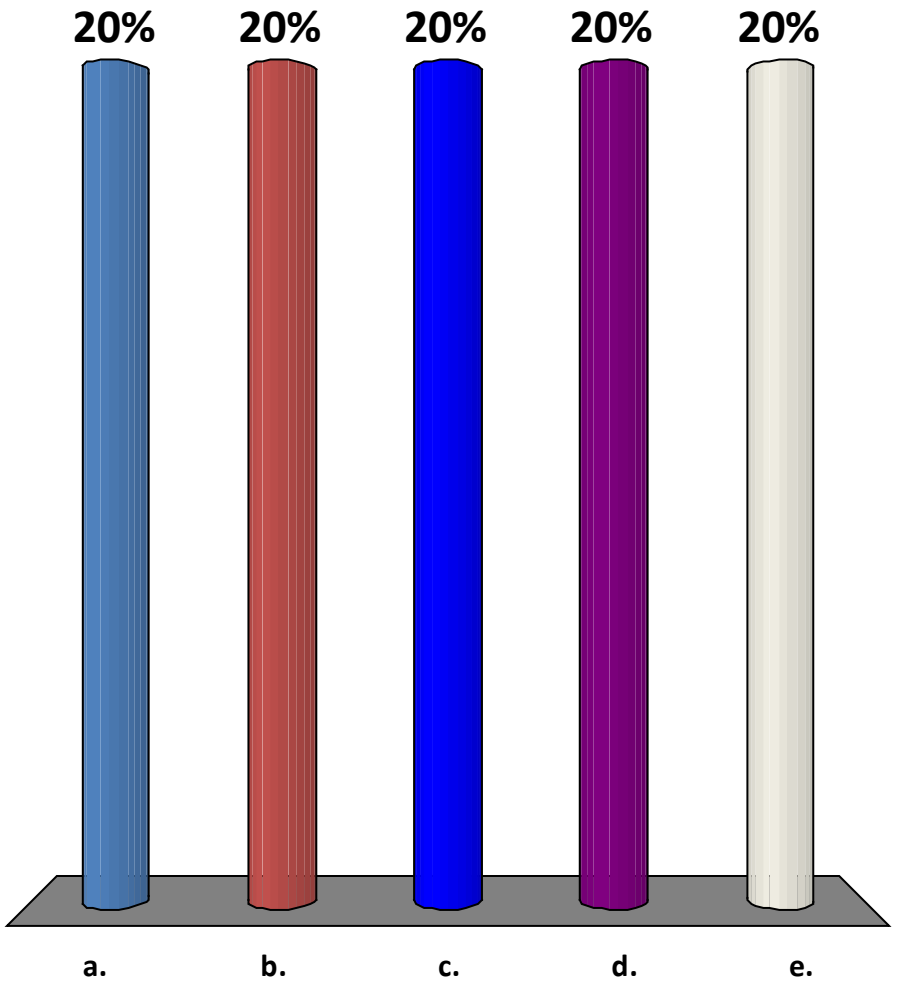
Lonneke A.M. Gravendeel, Mathilde C.M. Kouwenhoven, Olivier Gevaert, et al.

Cancer Res 2009;69:9065-9072. Published OnlineFirst November 17, 2009.



Neuropathology report should:

a. Low grades versus grade III and IV
b. Lower grades together with grade III, versus grade IV
c. Potentially aggressive as grade III if specific molecular characteristics are present
d. b and c
e. a and c



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Handling Histo-molecular criteria

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 25, 2015 VOL. 372 NO. 26

Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas

The Cancer Genome Atlas Research Network*

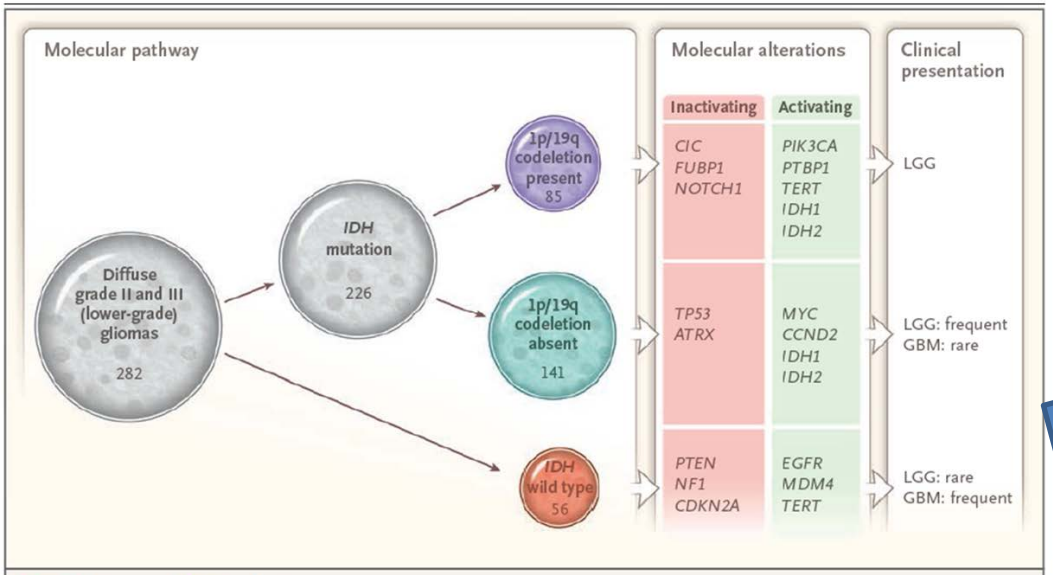


Figure 4. Summary of Major Findings.
Shown is a schematic representation that summarizes the major molecular findings and conclusions of our study: consensus clustering yielded three robust groups that were strongly correlated with *IDH* mutation and 1p/19q codeletion status and had stereotypical and subtype-specific molecular alterations and distinct clinical presentations. GBM denotes glioblastoma, and LGG lower-grade glioma.

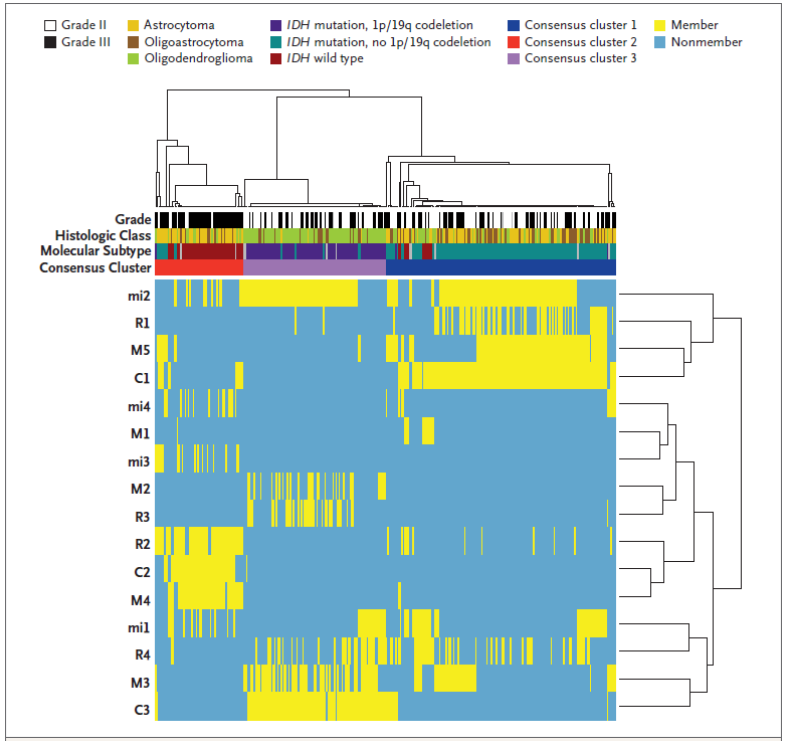
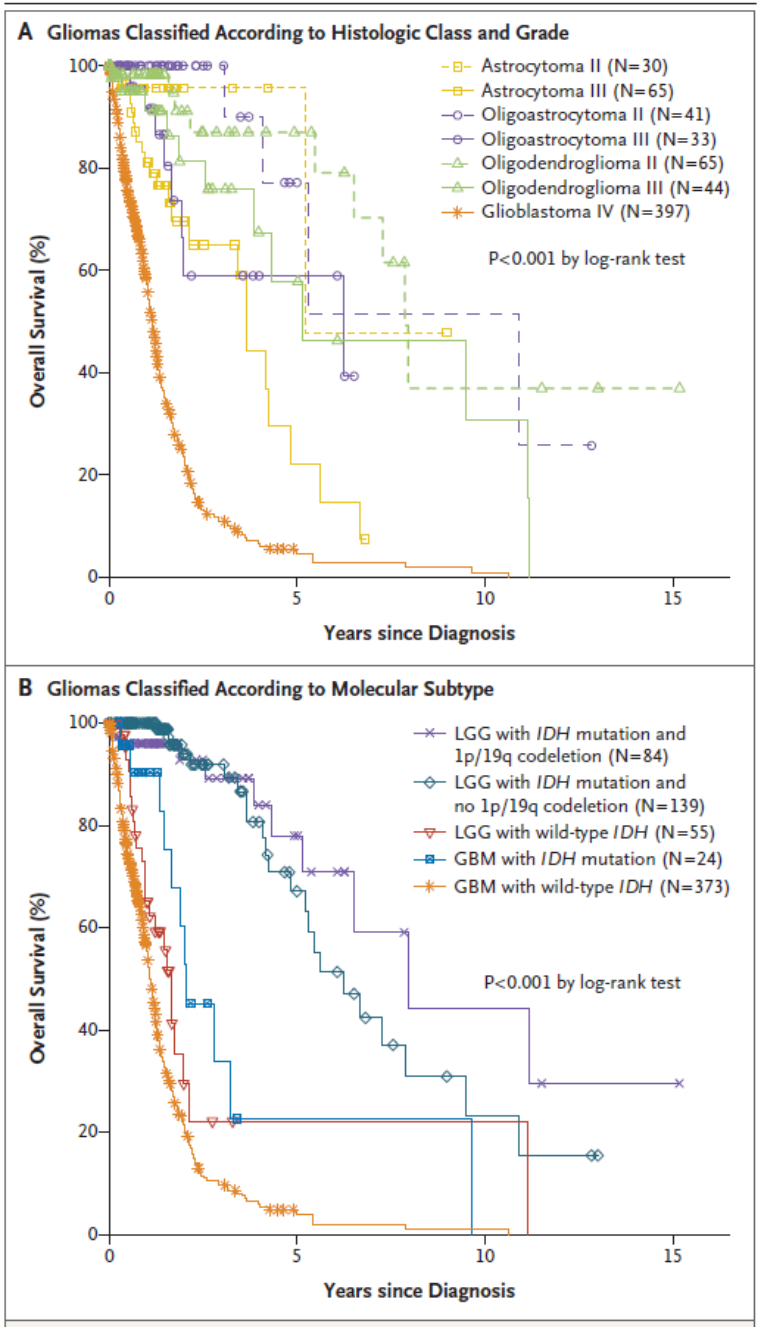


Figure 1. Cluster of Clusters (CoC) Analysis.
The results of multiplatform analyses point to biologic subtypes defined by *IDH* mutation and 1p/19q codeletion status. CoC analysis uses the cluster assignments derived from individual molecular platforms to stratify tumors, thereby integrating data from analysis of messenger RNA (mRNA) (designated by R on the y axis), microRNA (mi), DNA methylation (M), and copy number (C). For each sample, membership in a particular cluster is indicated by a yellow tick, and nonmembership is indicated by a blue tick. CoC analysis resulted in a strong three-class solution, and a comparison of tracks for CoC consensus cluster with tracks for histologic and molecular class shows a stronger correlation with molecular class.



Lower-grade gliomas with an **IDH mutation and 1p/19q codeletion** were of the **oligodendroglioma** histologic class and were associated with **favorable outcomes**.

Tumors with **wild-type IDH** were **molecularly and clinically distinct from subtypes with mutated IDH**, with most showing a striking resemblance to **primary glioblastoma** on all analytic platforms

It may transpire that **distinct therapeutic strategies** are required for effective disease control in molecular subtypes of lower-grade glioma.

Neuro-Oncology Advance Access published May 25, 2015

Neuro-Oncology

Neuro-Oncology 2015; **0**, 1–8, doi:10.1093/neuonc/nov082

Telomere maintenance and the etiology of adult glioma

Kyle M. Walsh, John K. Wiencke, Daniel H. Lachance, Joseph L. Wiemels, Annette M. Molinaro, Jeanette E. Eckel-Passow, Robert B. Jenkins, and Margaret R. Wrensch

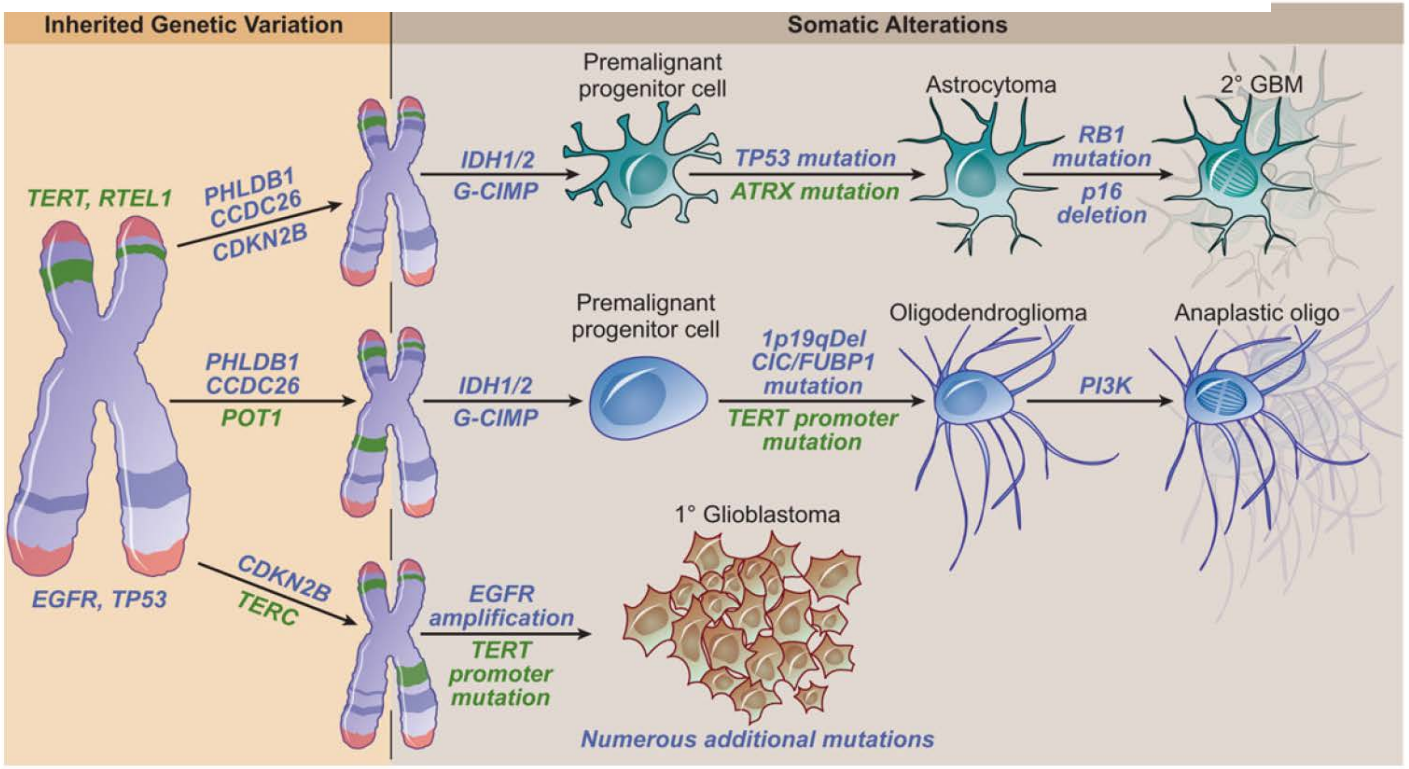
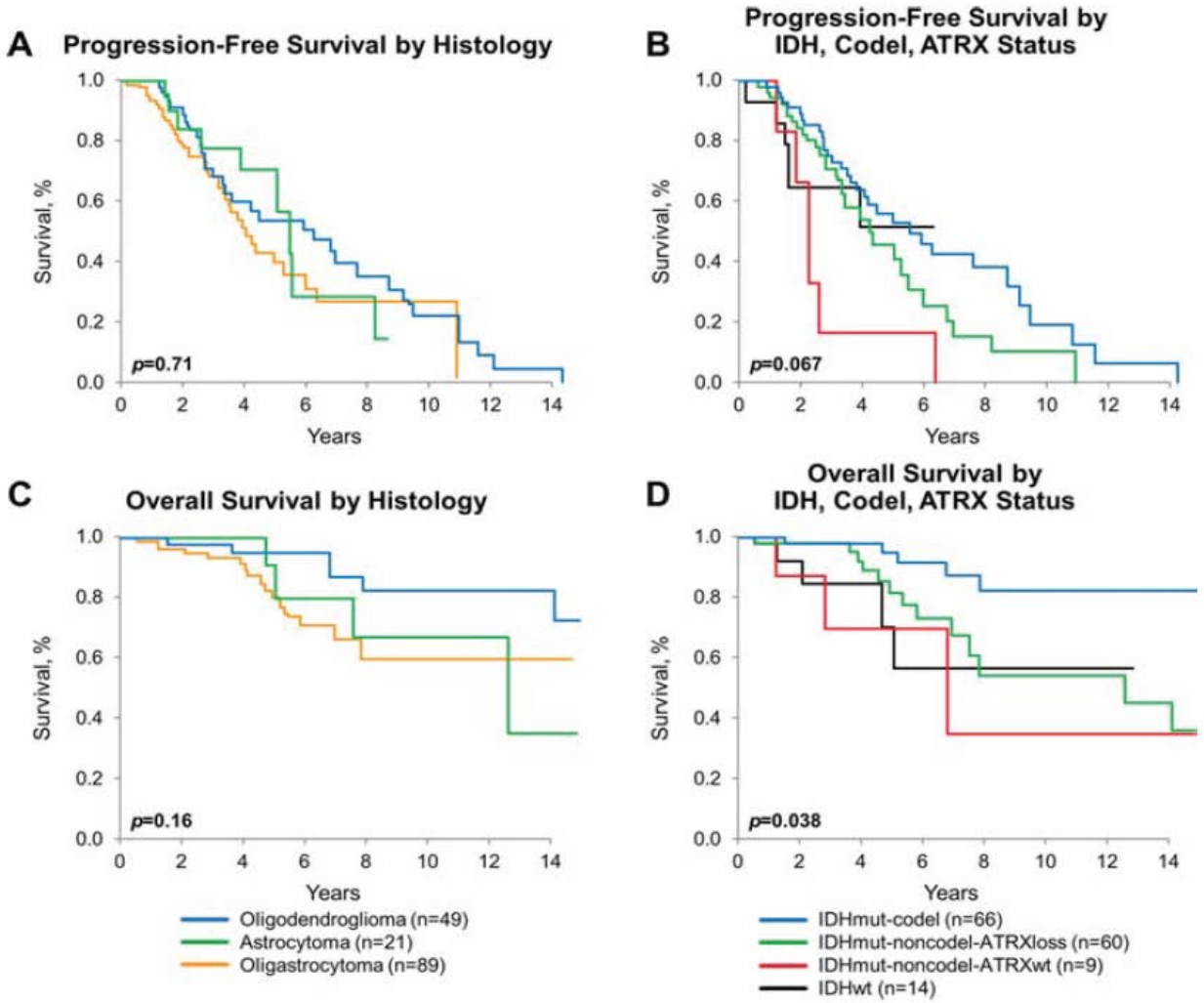


Fig. 1. Hypothesized pathways of glioma development, highlighting heritable and somatic genetic variants. From left to right: gene regions that contribute inherited risk for all histopathologic classifications of glioma. Gene regions that contribute inherited risk for specific histopathologic classifications of glioma. Somatic (ie, acquired) genetic changes that are believed to be early events in the development of glioma. Additional somatic events important for malignant progression. Gene names appearing in green font harbor glioma risk alleles associated with telomere lengthening. (Figure created with assistance from Xavier Studio.)



Conclusions: For WHO grade II diffuse glioma, molecular classification using 1p/19qcodel, IDHmut, and ATRX loss more accurately predicts outcome and should be incorporated in the neuropathologic evaluation.

Brain tumor diagnosis: a challenge step by step

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International Society of Neuropathology-Haarlem Consensus Guidelines for Nervous System Tumor Classification and Grading

David N. Louis[1]; Arie Perry[2]; Peter Burger[3]; David W. Ellison[4]; Guido Reifenberger[5,6]; Andreas von Deimling[6,7]; Kenneth Aldape[8]; Daniel Brat[9]; V. Peter Collins[10]; Charles Eberhart[3]; Dominique Figarella-Branger[11]; Gregory N. Fuller[12]; Felice Giangaspero[13,14]; Caterina Giannini[15]; Cynthia Hawkins[16]; Paul Kleihues[17]; Andrey Korshunov[6,18]; Johan M. Kros[19]; M. Beatriz Lopes[20]; Ho-Keung Ng[21]; Hiroko Ohgaki[22]; Werner Paulus[23]; Torsten Pietsch[24]; Marc Rosenblum[25]; Elisabeth Rushing[26]; Figen Soylemezoglu[27]; Otmar Wiestler[28]; Pieter Wesseling[29,30]

Table 5. Example: integrated diagnoses for WHO grade II adult diffuse gliomas.[#]

Molecular information	Histologic classification: Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p/19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*	*Diffuse glioma* (oligodendroglioma phenotype), 1p/19q non-deleted, ATRX loss of expression*	*Diffuse astrocytoma, ATRX loss of expression*
IDH-mut, 1p/19q-codel, ATRX intact	*Diffuse glioma (astrocytoma phenotype), 1p/19q-codeleted*	*Oligodendroglioma, 1p/19q-codeleted*	*Oligodendroglioma, 1p/19q-codeleted*
IDH wild type	*Diffuse astrocytoma, IDH wild type**	*Diffuse glioma* (oligodendroglioma phenotype), IDH wild type**	*Diffuse astrocytoma, IDH wild type**
Testing not performed	*Diffuse astrocytoma, NOS*	*Oligodendroglioma, NOS*	*"Diffuse glioma, NOS"*

This example shows how the integrated diagnostic terms for adult WHO grade II diffuse gliomas (names in italics in boxes) could involve a combination of histological and molecular data, although an NOS (not otherwise specified) diagnosis would be made in the absence of molecular information (bottom row). Highlighted in light gray are the common, narrowly histologically and molecularly defined, "classic" diffuse astrocytoma and oligodendroglioma. Note that in this suggested scheme, the term "oligoastrocytoma" does not appear in a diagnostic box, with the last column showing the alternative diagnoses for what has been inconsistently termed "oligoastrocytoma."

[#]A similar classification scheme would apply for WHO grade III, anaplastic gliomas.

doi:10.1

LETTER TO THE EDITOR

Letter in Response to David N. Louis *et al*, International Society of Neuropathology-Haarlem Consensus Guidelines for Nervous System Tumor Classification and Grading, Brain Pathology, doi: 10.1111/bpa.12171

Johannes Hainfellner

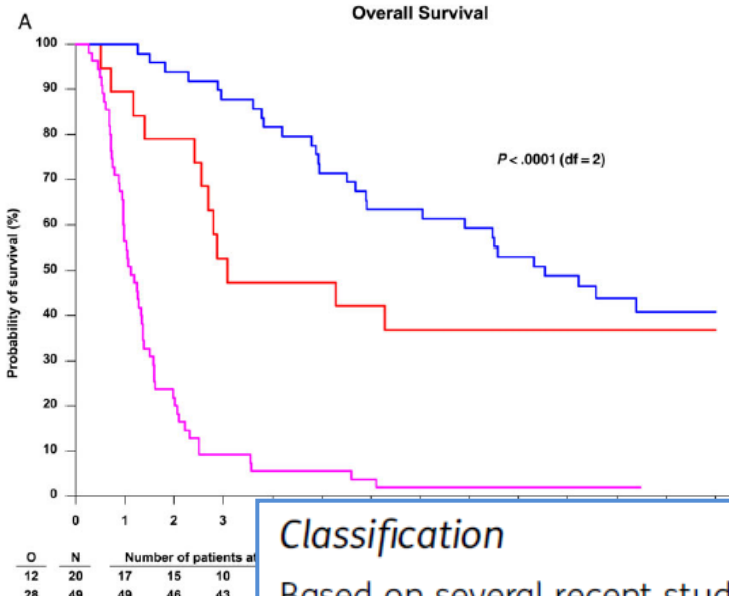
- The recommendation that tumor entities shall be defined as precisely and objectively as possible in order to optimize

- The recommendation that all tissue-based information (histological, molecular) shall be elements of an integrated

- The recommendation that molecular information should be incorporated in the definition of some diagnostic entities is relevant and is supported by already existing proof of concept

- The statement that the World Health Organization (WHO) grade reflects the natural history of a given tumor after surgery alone rather than the expected patient prognosis following current therapies is a plausible and pragmatic concept. It is good to have such a clarifying statement as contemporary reference in the literature.

Handling Histo-molecular criteria



Neuro-Oncology Advance Access published September 9, 2015

Neuro-Oncology

Neuro-Oncology 2015; **0**, 1–13, doi:10.1093/neuonc/nov182

Molecular classification of anaplastic oligodendroglioma using next-generation sequencing: a report of the prospective randomized EORTC Brain Tumor Group 26951 phase III trial

Hendrikus J. Dubbink†, Peggy N. Atmodimedjo†, Johan M. Kros, Pim J. French, Marc Sanson, Ahmed Idbaih, Pieter Wesseling, Roelien Enting, Wim Spliet, Cees Tijssen, Winand N. M. Dinjens, Thierry Gorlia, and Martin J. van den Bent

Classification

Based on several recent studies [17,18,20–22,24] for the molecular

Table 4. Review pathology diagnosis in the 3 molecularly defined glioma groups

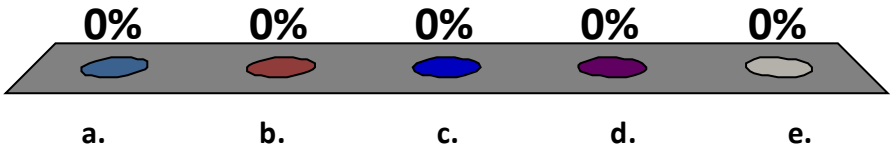
	Molecularly Defined Glial Subtype				Total ($N = 133$)	P
	No Type ($N = 9$) *N* (%)	Type I ($N = 49$) *N* (%)	Type II ($N = 20$) *N* (%)	Type III ($N = 55$) *N* (%)	*N* (%)	
Central pathology review						
Astrocytoma	0 (0.0)	0 (0.0)	3 (15.0)	1 (1.8)	4 (3.0)	<.0001*
Oligodendroglioma	8 (88.9)	45 (91.8)	10 (50.0)	30 (54.5)	93 (69.9)	
GBM	0 (0.0)	1 (2.0)	7 (35.0)	24 (43.6)	32 (24.1)	
Missing	1 (11.1)	3 (6.1)	0 (0.0)	0 (0.0)	4 (3.0)	

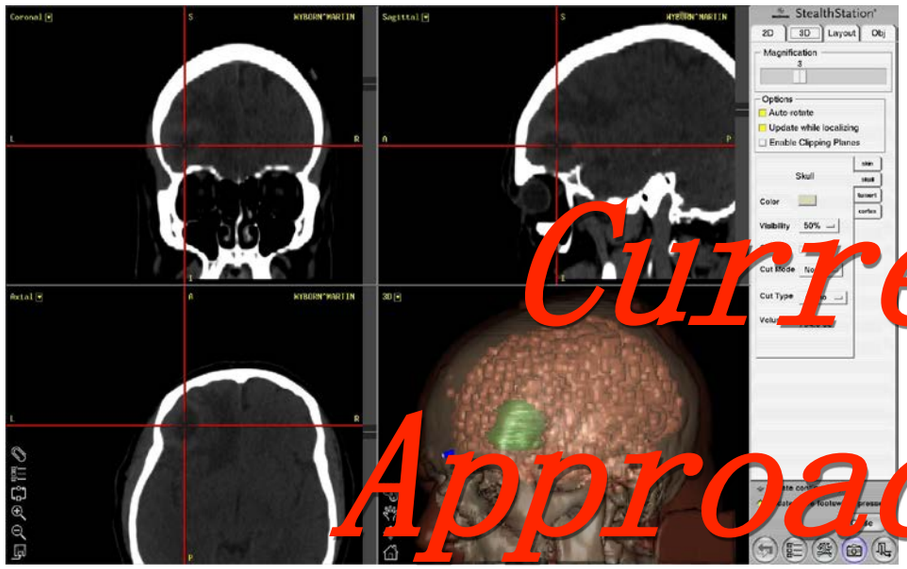
Abbreviation: GBM, glioblastoma multiforme. *Kappa 0.33 (0.22–0.45), overall concordance: 59% (71/121).

Fig. 1
by th

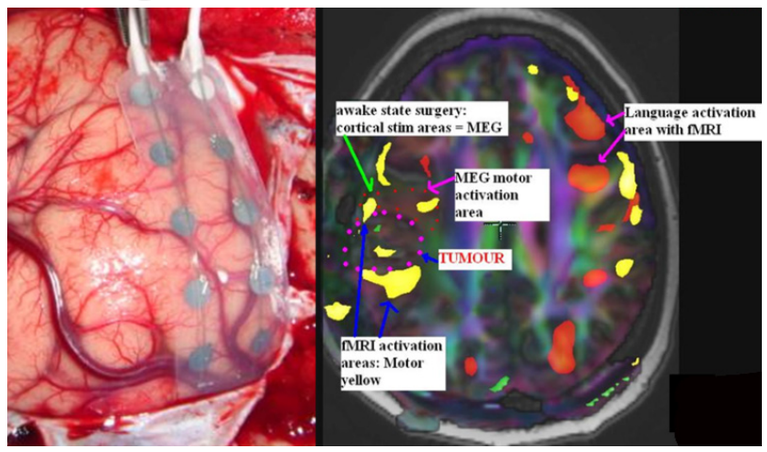
Neuropathology report should:

a. Include molecular characterization, only in GBM
b. Include molecular characterization, especially for lower grade gliomas
c. Avoid the use of mixed histological oligo-astrocytic categories
d. a and b
✓ e. b and c





Current Surgical Approaches for Brain Tumours



Ranj Bhangoo, *Francesco Vergani*, *Christian Brogna*

Neurosurgery Department

King's College Hospital - London

- Introduction
- Intra-operative mapping
- Fluorescence-guided tumour resection
- Intra-operative imaging
- Illustrative cases
- Future directions

Introduction

- Emerging intraoperative technologies and state-of-the-art microsurgical techniques, can facilitate extent of resection while minimizing the associated morbidity profile.

- What is the current role of surgery in the management of brain tumours?

Volumetric extent of resection studies in High-Grade Glioma

Study	Tumor grade(s)	Patients	Extent of resection (*n*)	Overall survival: Mean survival (months)	Overall survival: Univariate analysis *P* value	Overall survival: Multivariate analysis *P* value
Keles *et al.* [12]	IV	107	<25% (25)	8.0	NA	<0.0005
			25–49% (21)	14.2		
			50–74% (18)	15.7		
			75–99% (20)	22.1		
			100% (23)	23.3		
Pope *et al.* [21]	IV	110	<20%	27.4	NS	NS
			20–89%	11.1		
			90–99%	17.1		
			100%	22.1		
Lacroix *et al.* [15]	IV	416	<98%	8.8	<0.0001	<0.0001
			≥98%	13.0		
Keles *et al.* [13]	III	102	0–100%	41.0	NS	NS
Sanai *et al.* 2011 [32▪]	IV	500	>77%	12.5	<0.0001	0.004
			>79%	12.8		
			>89%	13.8		
			100%	16		

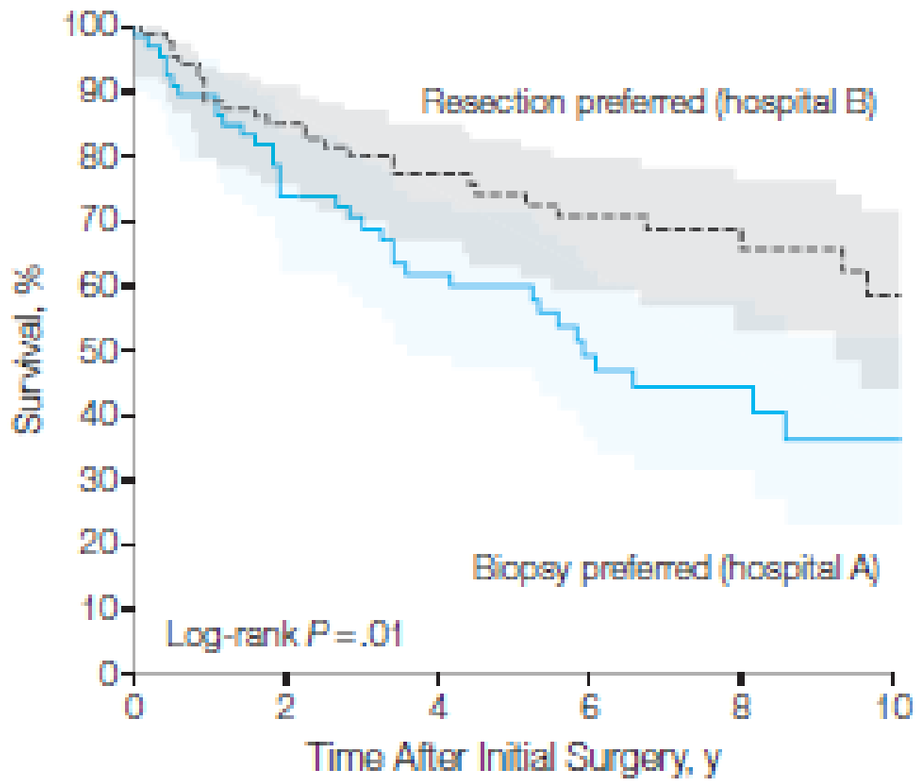
Volumetric extent of resection studies in Low-Grade Glioma

Study	Patients	Extent of resection (*n*)	5-Year overall survival		
			5-Year survival	Univariate analysis *P* value	Multivariate analysis *P* value
van Veelen *et al.* [44]	90	>75% (13)	62%	0.002	0.04
		<75% (59)	18%		
Claus *et al.* [42]	156	100% (56)	98.2%	0.05	<0.05
		<100% (100)	92.0%		
Smith *et al.* [43]	216	0–40% (21)	NA	NA	<0.001
		41–69% (39)	NA		
		70–89% (55)	NA		
		90–99% (26)	97.0%		
		100% (75)	98.0%		

ONLINE FIRST

Comparison of a Strategy Favoring Early Surgical Resection vs a Strategy Favoring Watchful Waiting in Low-Grade Gliomas

Survival Analysis Comparing Favored Surgical Strategies for Low-Grade Gliomas

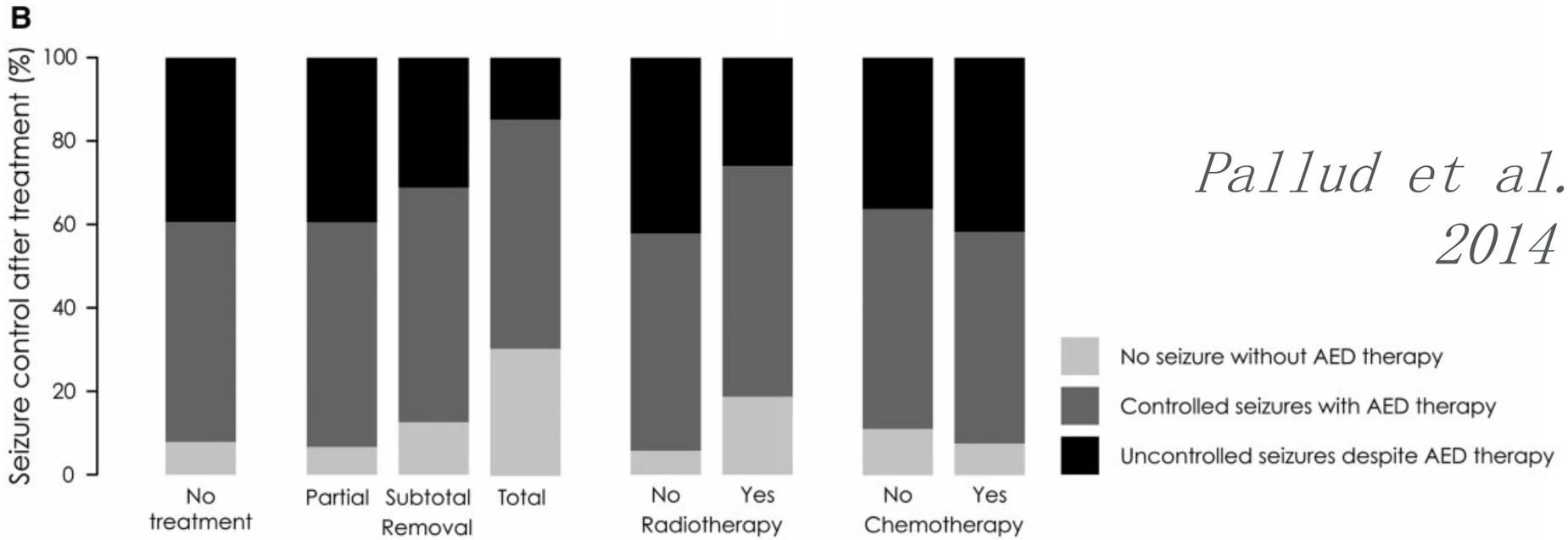


Jakola et al. JAMA, 2012

Low grade gliomas

BRAIN
A JOURNAL OF NEUROLOGY

Epileptic seizures in diffuse low-grade gliomas in adults



Pallud et al. Brain, 2014

Patient age (P≤ 0.001), subtotal (P = 0.007) and total (P≤ 0.001) resections were independent predictors of total epileptic seizure control after oncological treatment. Patients diagnosed with epileptic seizures andthose with complete and early surgical resections have better oncological outcomes.

Early and maximal surgical resection is thus required for diffuse low-grade gliomas, both for oncological and epileptological purposes.

Brain metastases

TABLE II Randomized trials of surgery plus radiation therapy as compared with radiation therapy alone

Reference	*Treatment*	*Patients (n)*	*Eligibility criteria*	*Steroids*	*Median survival (months)*	*Local recurrence (%)*	*Median functionally independent survival (months)*
Patchell *et al.* 1990 [5]	WBRT WBRT + surgery	23 25	KPS≥70, age≥18	All	3.5 9.2 $p<0.01$	52 20 $p<0.02$	1.8 8.8 $p<0.005$
Vecht *et al.* 1993 [8]	WBRT WBRT + surgery	31 32	WHO PS≤2, age≥18	Most	6 10 $p=0.04$	NR	3.5 7.5 $p=0.06$
Mintz *et al.* 1996 [6]	WBRT WBRT + surgery	43 41	KPS≥50, age<80	All	6.3 5.6 $p=0.24$	NR	NR

WBRT = whole-brain radiation therapy; KPS = Karnofsky performance status; WHO PS = World Health Organization performance status; NR = not reported.

trials comparing WBRT alone vs Surgery + WBRT (for single brain metastasis)

2 positive (Patchell and Vecht); 1 negative (Mintz)

Brain metastases

Cochrane review

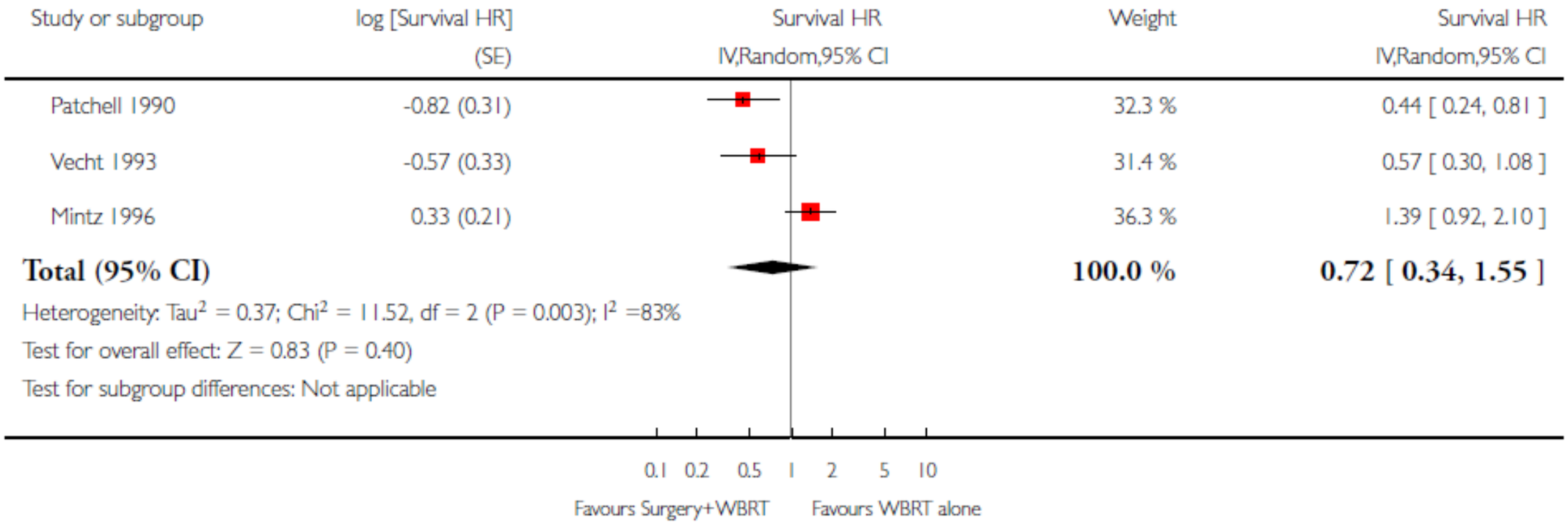
THE COCHRANE COLLABORATION®

Analysis 1.1. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 1 Survival.

Review: Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

Comparison: 1 Surgery + Radiotherapy vs Radiotherapy

Outcome: 1 Survival



Hart MG, et al. 2014 (revised edition)

Brain metastases

AUTHORS' CONCLUSIONS

Implications for practice

It is difficult to advise either patients or colleagues on the basis of evidence from such small studies. It is important to note that these results were obtained in a highly selected group of patients - under close follow-up and receiving further active therapy in many cases - who are not necessarily representative of the majority of those with single brain metastasis. In this group, the surgical approach did not improve OS. Surgery may reduce the number of deaths due to neurological cause, while one trial has suggested an increase in the duration of a patients FIS. Adverse events were similar in each group whilst QoL was not directly examined. Those most likely to benefit from surgery are of young age, have good neurological function, and controlled primary disease (Noordijk 1994). Careful attention to prognostic factors will see only those who have the most to gain from surgery, while those who are less well will avoid unnecessary risks and morbidity. It must not be forgotten that the overall outlook for patients at two years is dismally poor with either intervention and death is commonly due to systemic disease. Currently, the management for the majority of those with single brain metastasis will be WBRT alone, due to active systemic disease and other co-morbidity. Decisions of the most appropriate treatment for an individual patient should be made at an MDT meeting in line with NICE guidance (NICE 2006).

THE COCHRANE COLLABORATION®

Difficult to draw conclusions from small trials

OS no different in pooled analysis – possible improvement in FIS and reduction of neurological deaths

Pts likely to benefit: young age, good neurological function and controlled primary disease

Decision should be made in MDT

King's

ESTRO School

INTRA-OPERATIVE MAPPING

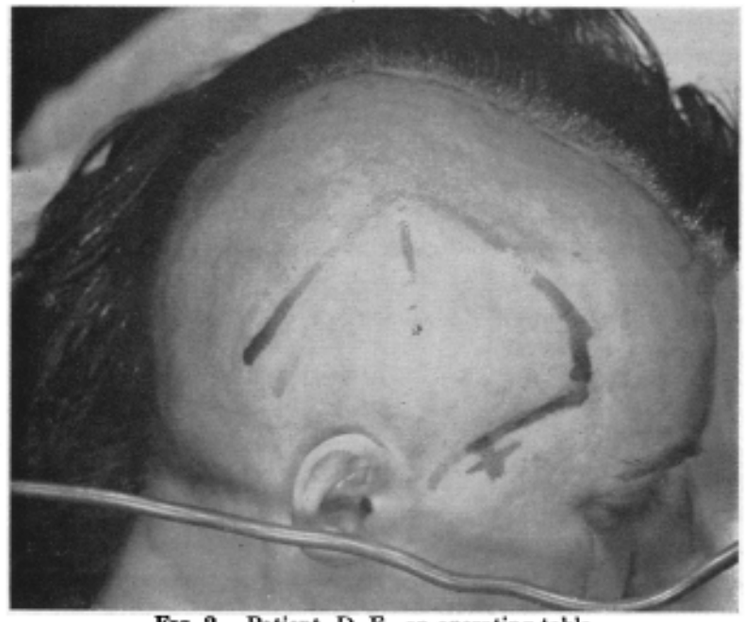


FIG. 2.—Patient, D. F., on operating table

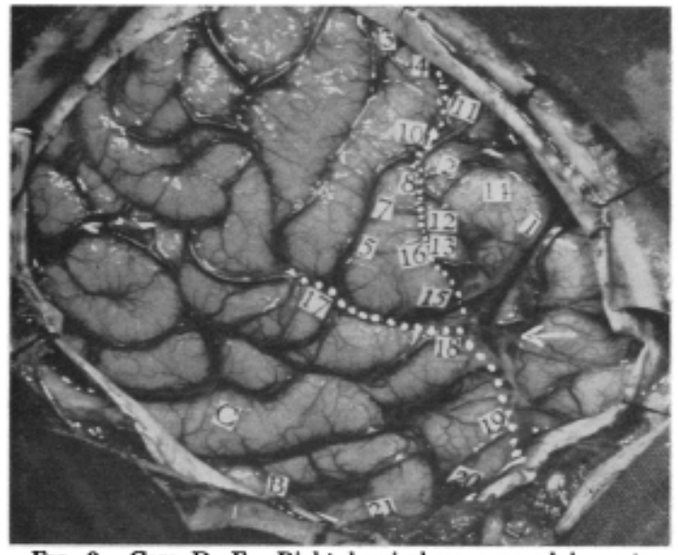


FIG. 3.—Case D. F. Right hemisphere exposed by osteoplastic craniotomy under local anesthesia. Arrow points to cortical abnormality which was more marked on the mesial surface. Numbered tickets indicate points at which electrical stimulation produced positive responses.

Wilder Penfield, 1958

Cortical and subcortical mapping strategies

- Stimulation done either awake or asleep
- Always done awake for Speech
- Stimulation either
    - Inhibitory – speech
    - Stimulatory – Motor Movement
- Continuous EcoG and SSEPS , MEPS running in background if patient asleep
- Continuous Movement and Speech if patient awake
- Can stimulate both Cortex and Sub- Cortical White Matter Tracts

Motor mapping

Monopolar stimulation

Monophasic pulse 50 Hz

Intensity: 1mA-

Continous EMG recording

Continuous EcoG and SSEPs . MEPs running in background if patient asleep

Subcortical stimulation to 5 mA

EEG Electrodes

inomed
we share competence

King's

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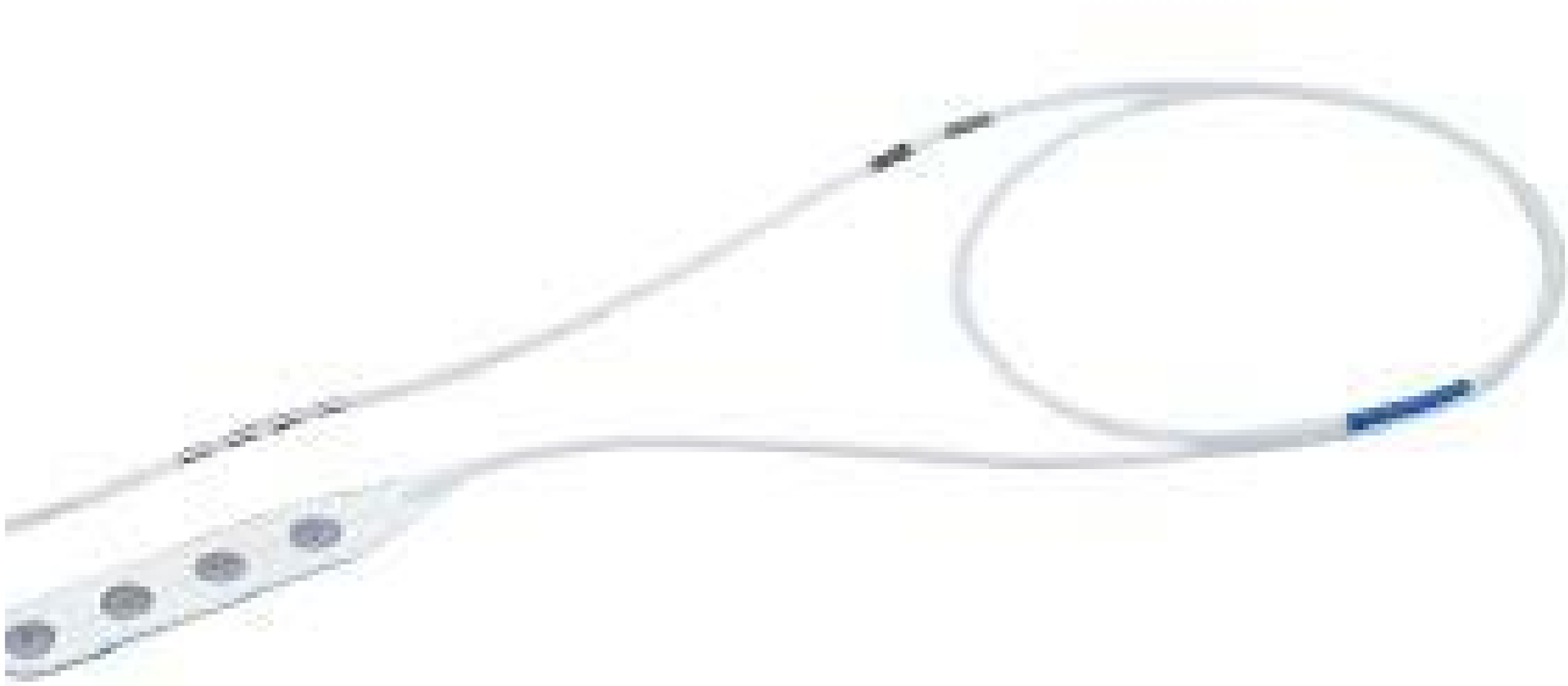
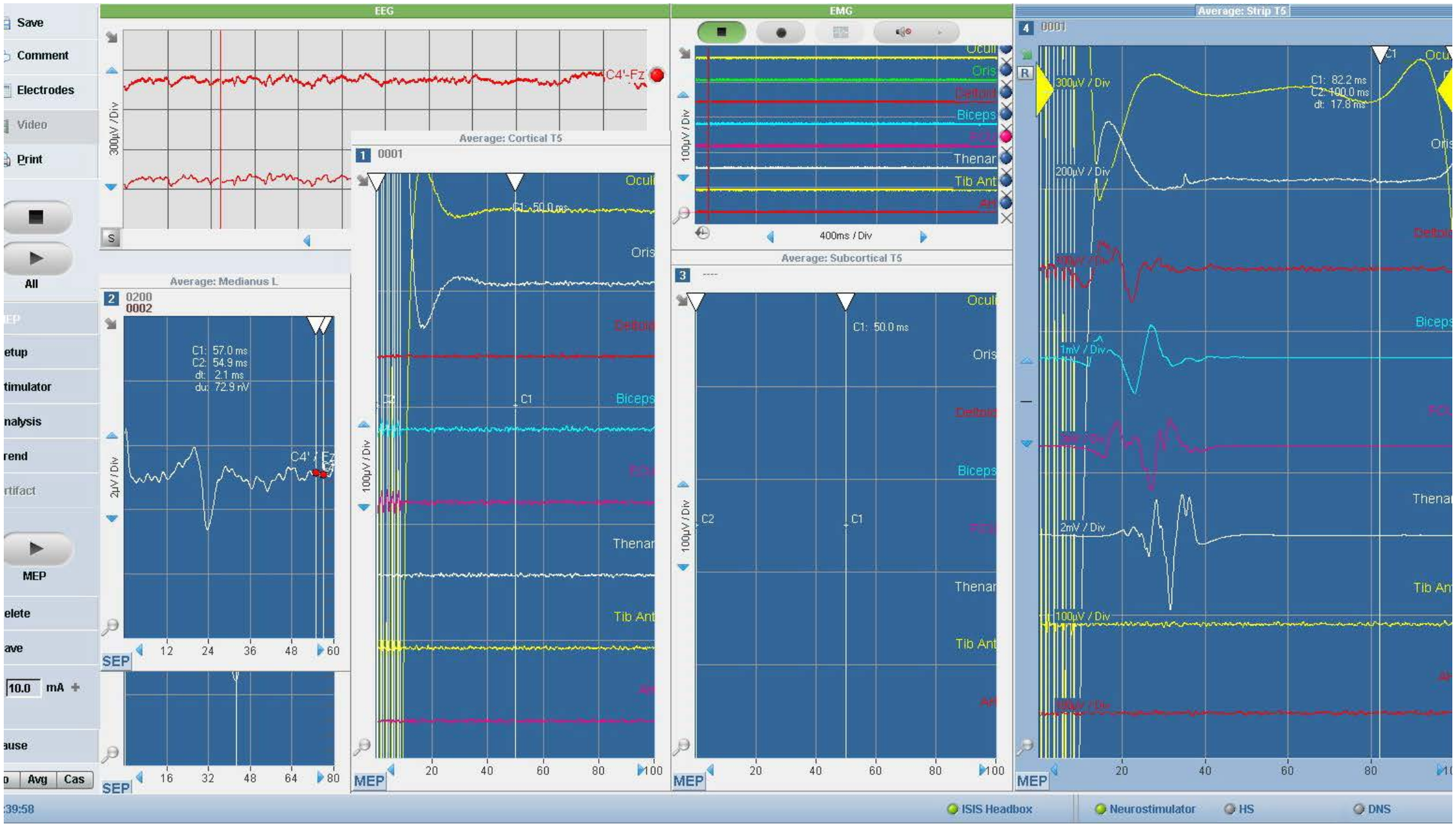
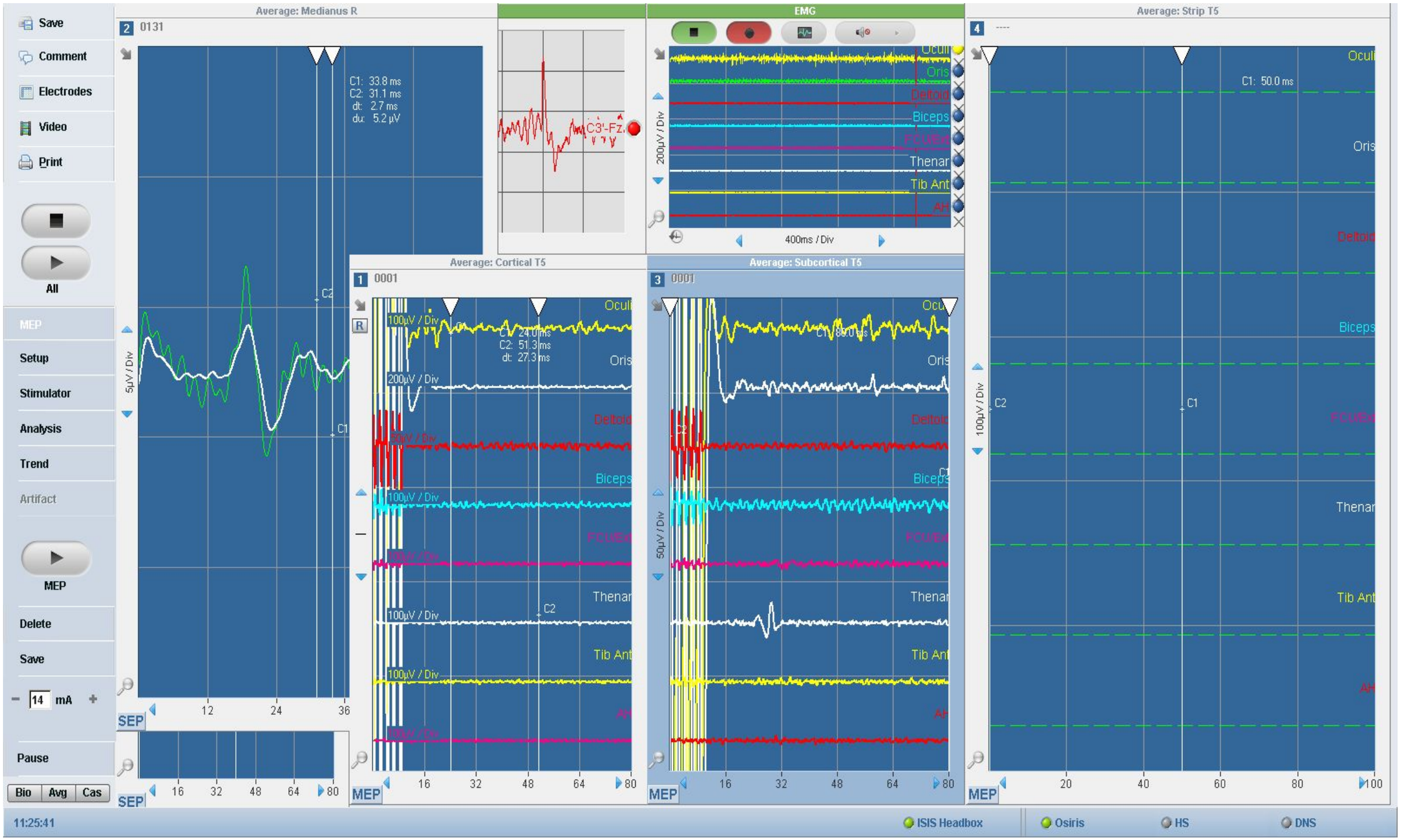
Cortical Strips - Ecog and Tonic Stimulation



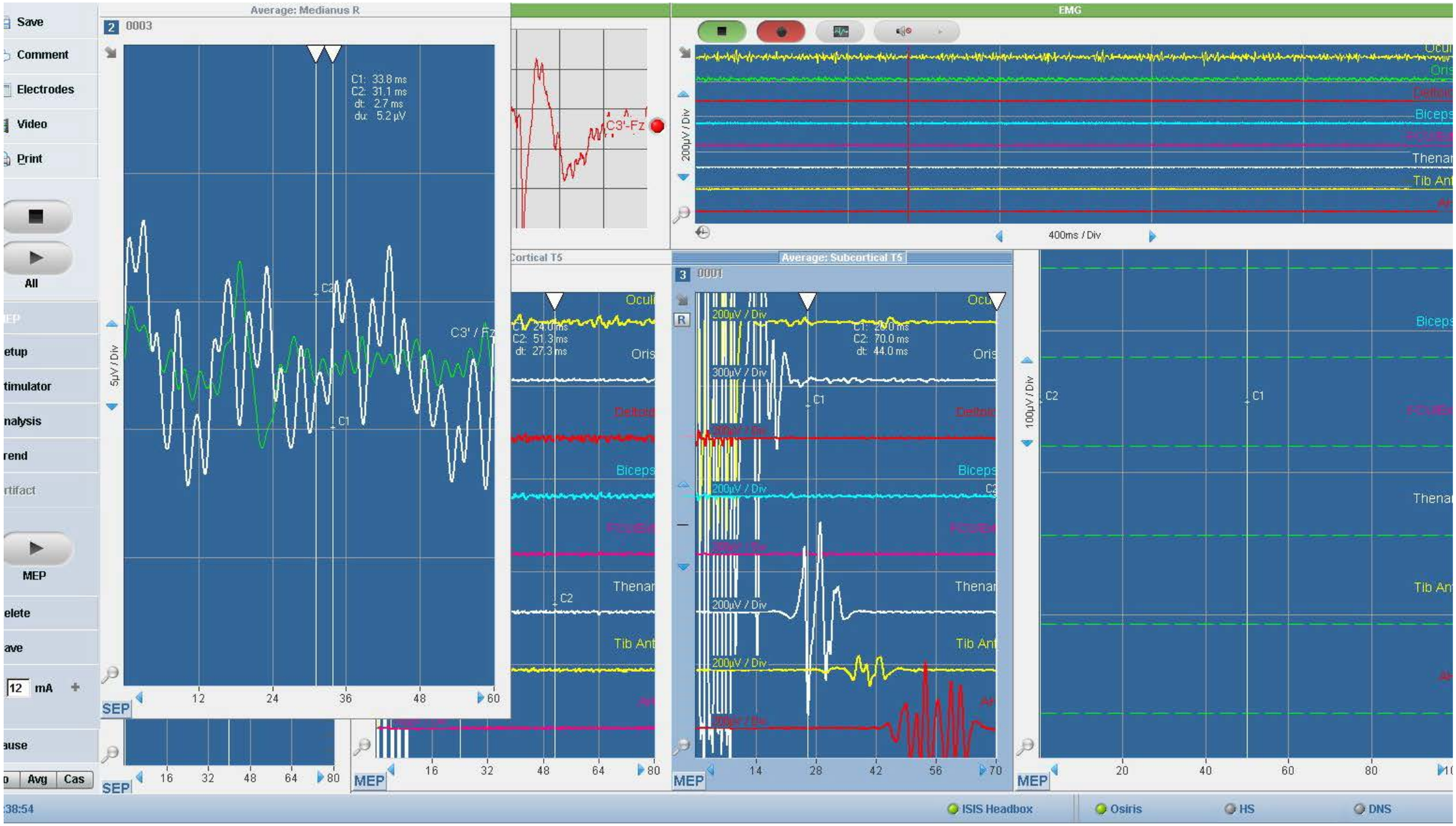
Cortical Strip over Upper Limb Representation



EMG Outputs - Subcortical

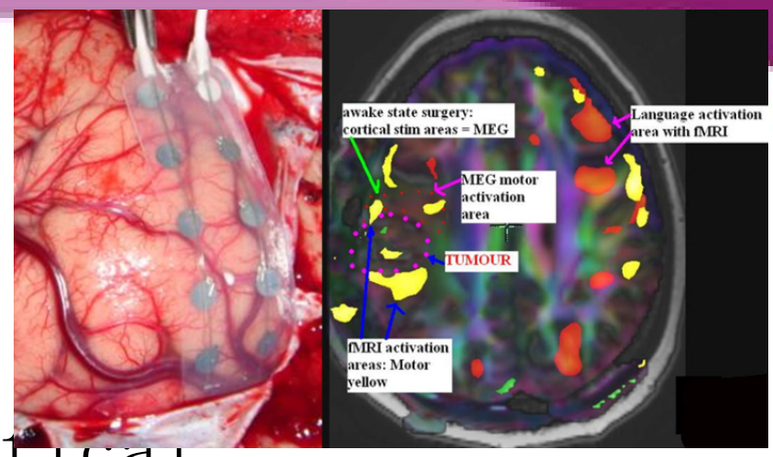


EMG Output - Subcortical



Cortical and subcortical motor mapping

Carrabba G, Fava E, Giussani C, et al. Cortical and subcortical motor mapping in rolandic and perirolandic glioma surgery: impact on postoperative morbidity and extent of resection. J Neurosurg Sci 2007; 51:45 – 51



- Stimulation mapping of cortical and subcortical motor pathways enables the surgeon to identify descending motor pathways during tumour removal.

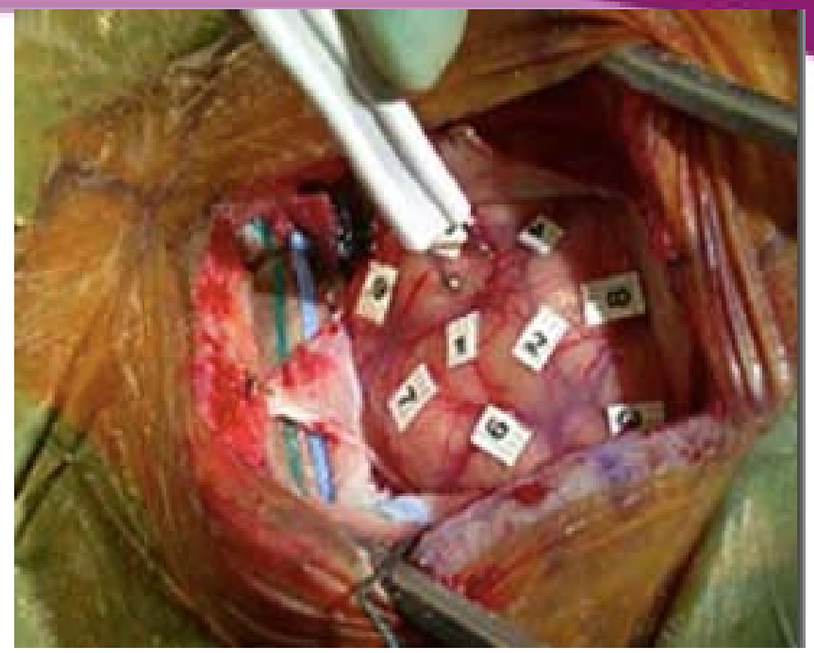
- New immediate postoperative motor deficits documented in 59.3% of patients in whom a subcortical motor tract was identified intra-operatively and in 10.9% of those in whom sub-cortical tracts were not observed.

- Permanent deficits observed in 6.5 and 3.5%, respectively

Language mapping

- Bipolar stimulation
- Cortical mapping started at low stimulus (1 mA)
- Constant-current generator delivers biphasic square wave pulses in 4-s trains at 60 Hz across 1 -mm bipolar electrodes separated by 5 mm
- Stimulation sites marked with sterile numbered tickets
- Throughout motor and language mapping, continuous ECoG used to monitor after discharge potentials

Language mapping



Counting task – “speech arrest”

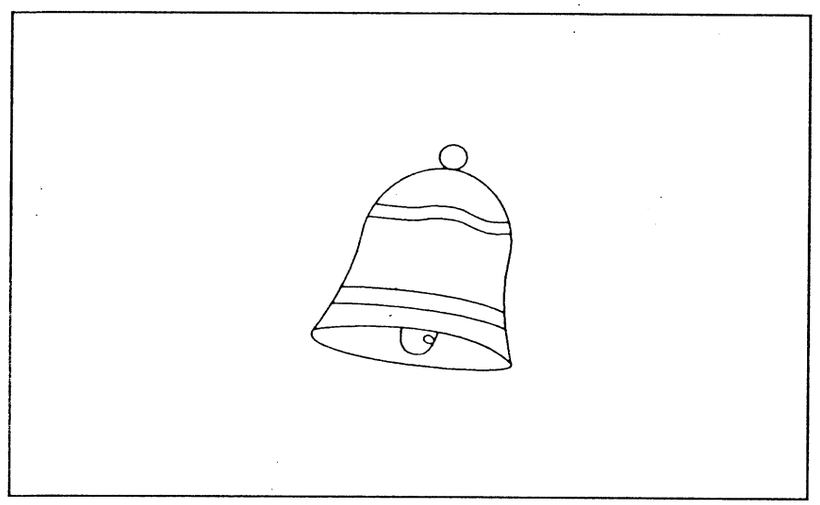
Denomination task :

- anomias
- semantic paraphasias
- phonological paraphasias

Spontaneous speech

Reading

CECI EST



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

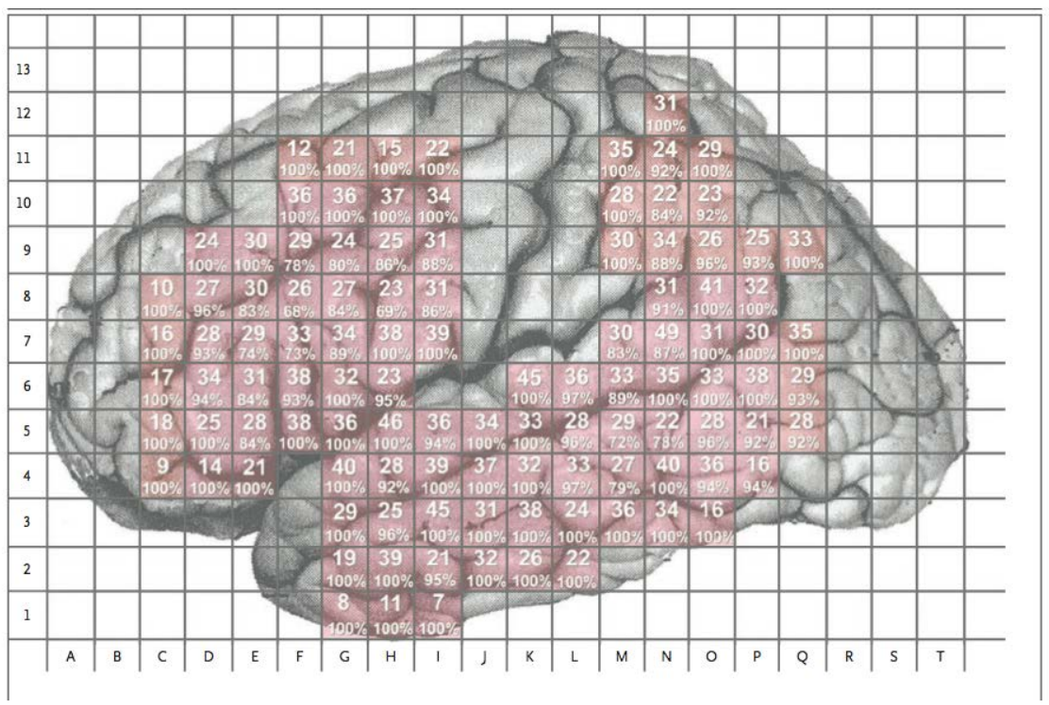
Functional Outcome after Language Mapping for Glioma Resection

Nader Sanai, M.D., Zaman Mirzadeh, Ph.D., and Mitchel S. Berger, M.D.

N ENGL J MED 358;1 WWW.NEJM.ORG JANUARY 3, 2008

250 pts

1.6% of patient with language deficits at 6 months



Negative sites for language of the dominant hemisphere

Intraoperative stimulation mapping – cinical relevance

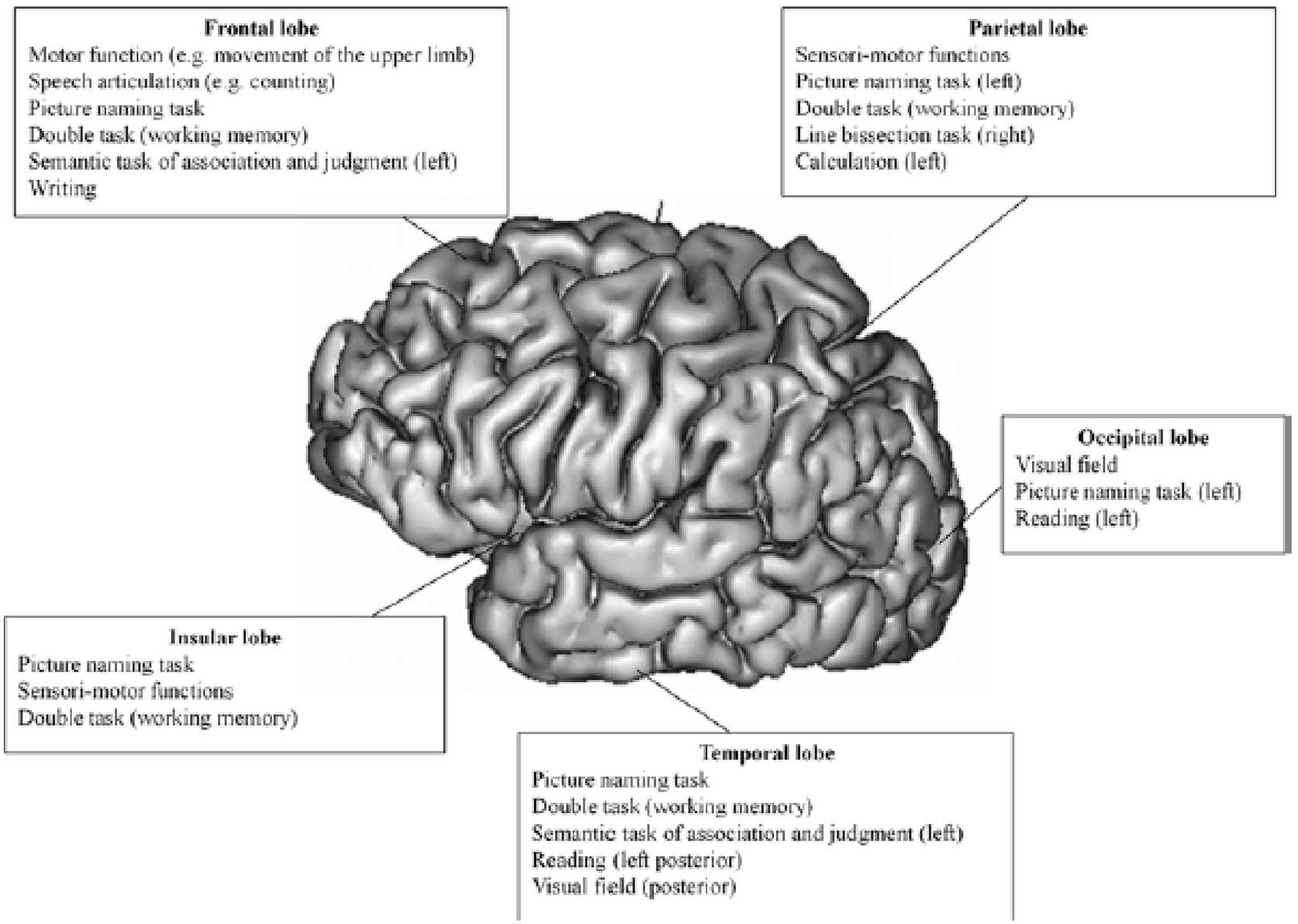
De Witt Hamer PC, Gil Robles S, Zwinderman AH, et al. Impact of & intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 2012; 10:2559 – 2565.

Meta-analysis including 8091 patients

Late Severe Neurological Deficits observed in 3.4% of ISM vs 8.2%

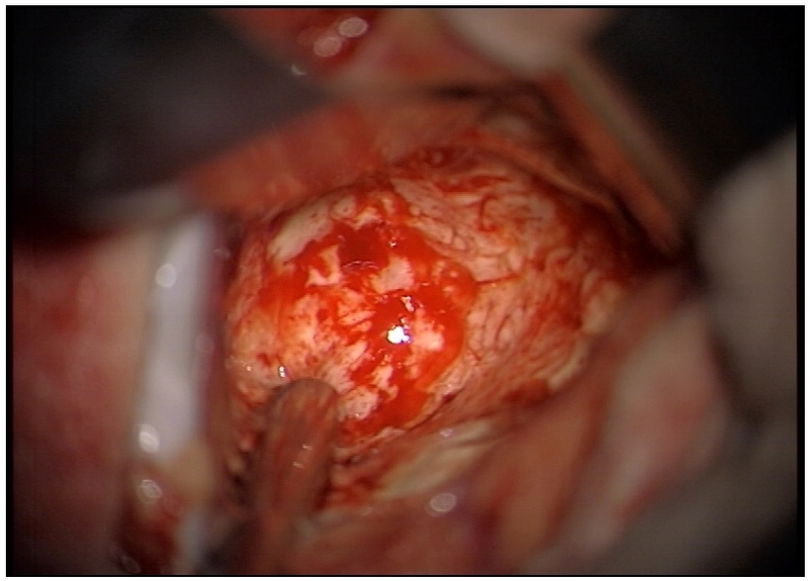
"Glioma resections using ISM are associated with fewer late severe neurologic deficits and more extensive resection, and they involve eloquent locations more frequently. This indicates that ISM should be universally implemented as standard of care for glioma surgery".

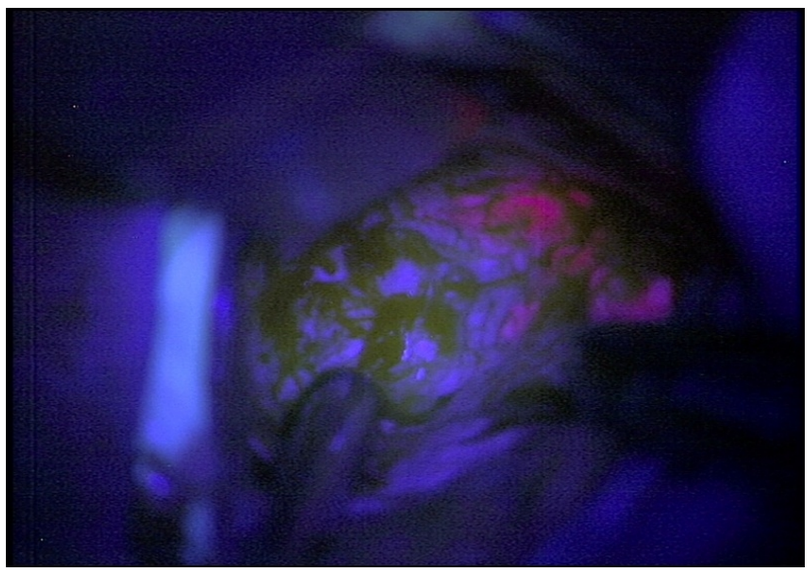
Beyond motor and language



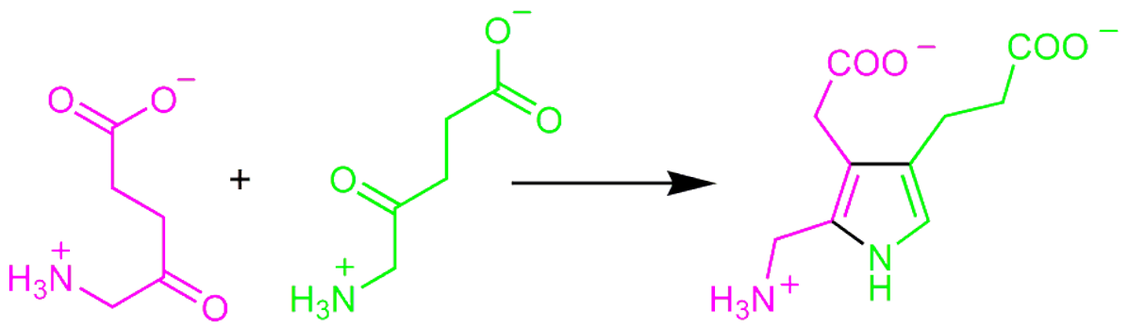
Fernandez-Coello et al. J Neurosurg, 2013

Fluorescence-guided resection



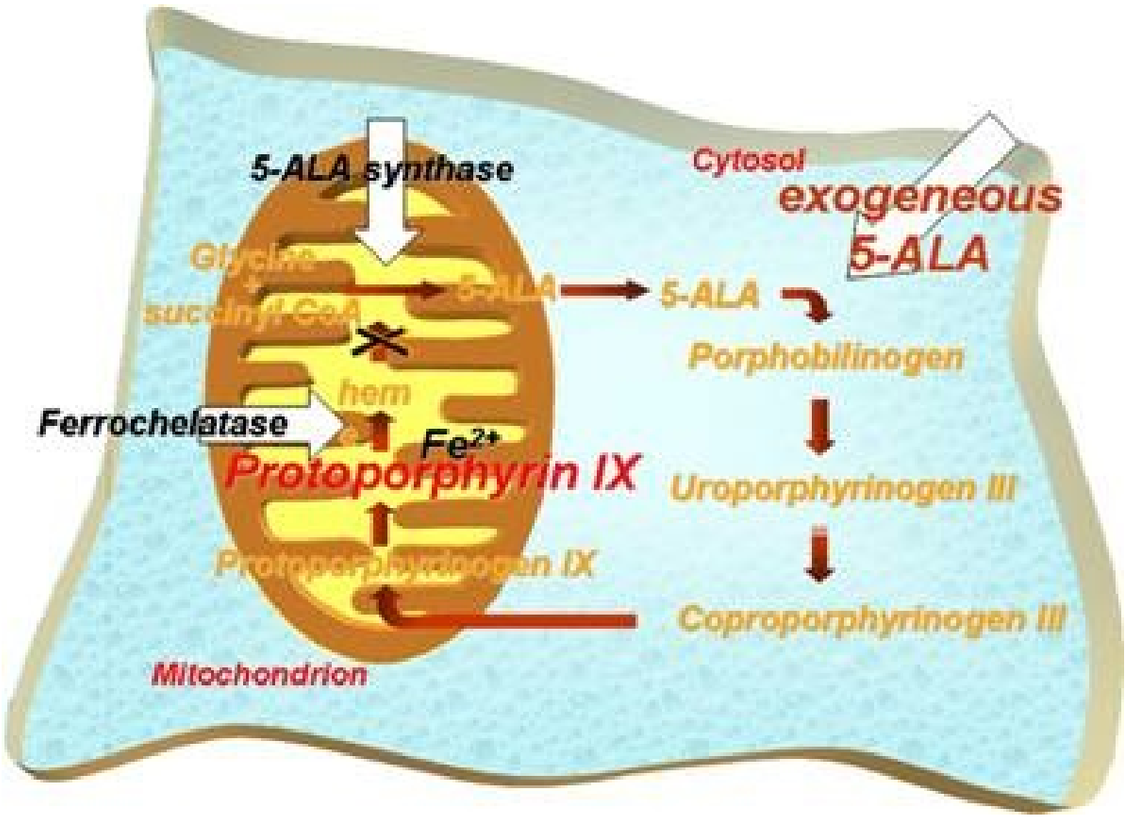


5-ALA



5-Aminolävulinat

Porphobilinogen

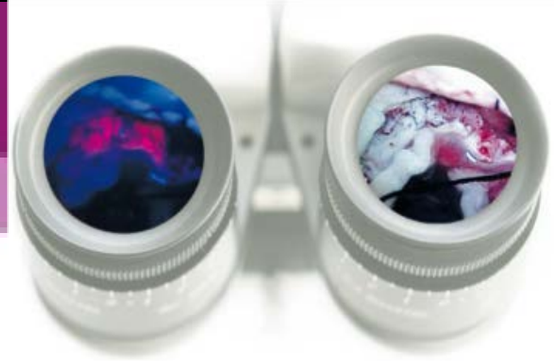


Porphyrin that cannot be metabolised in Tumour Cells

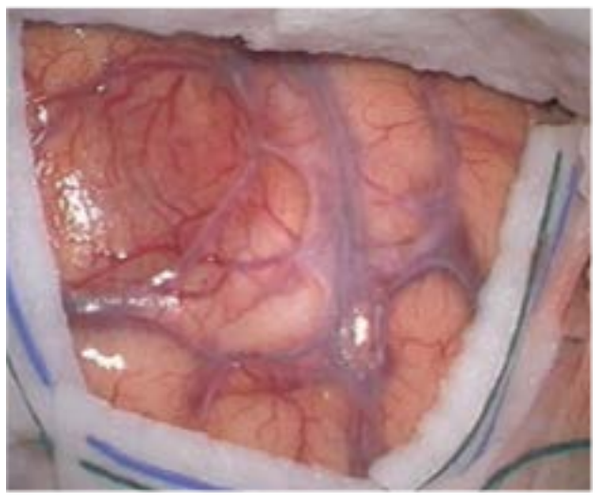
Fluoresces when exposed to 400nm Light

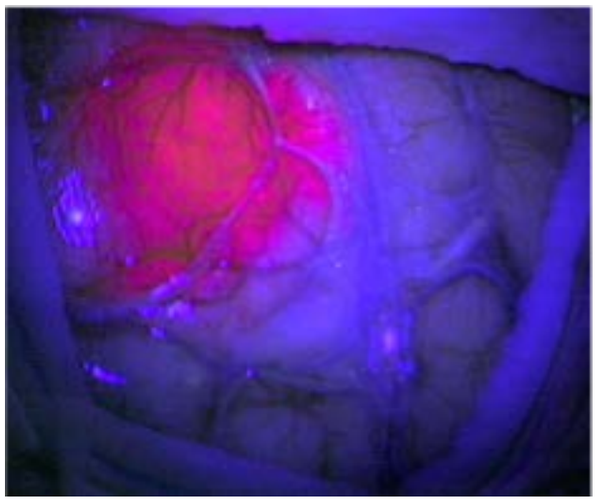
Given Orally 2-4 hour before Surgery

Intraoperative use of 5-ALA

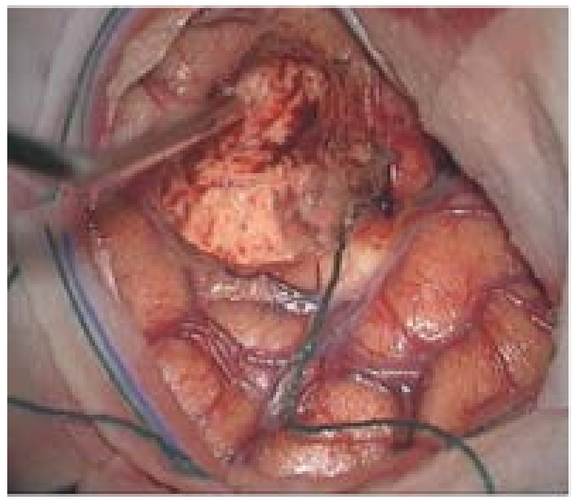


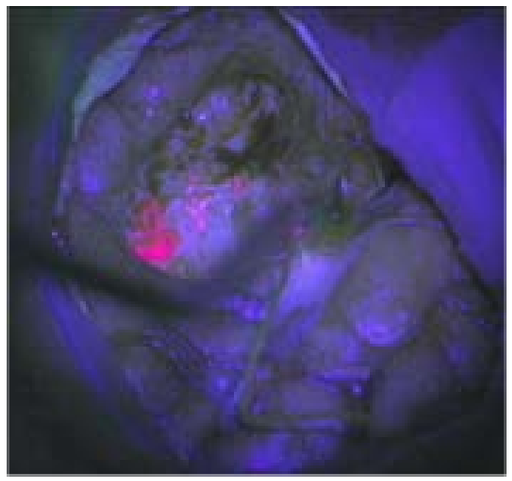
Tumour Identification

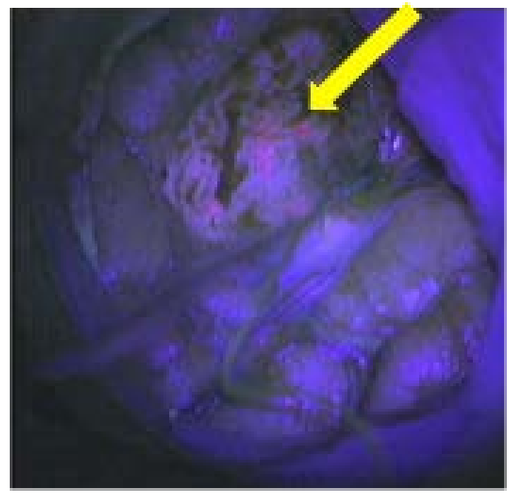




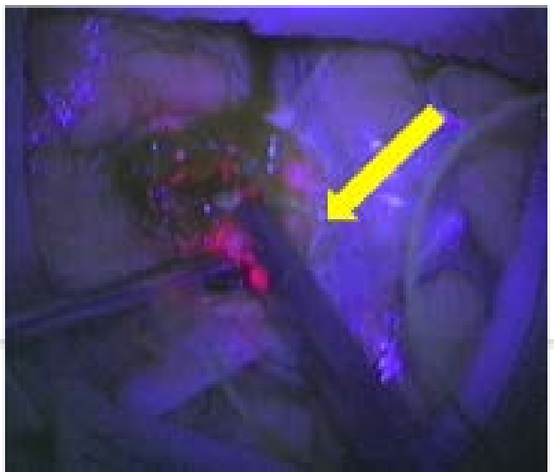
Residual tumour







Tumour sampling



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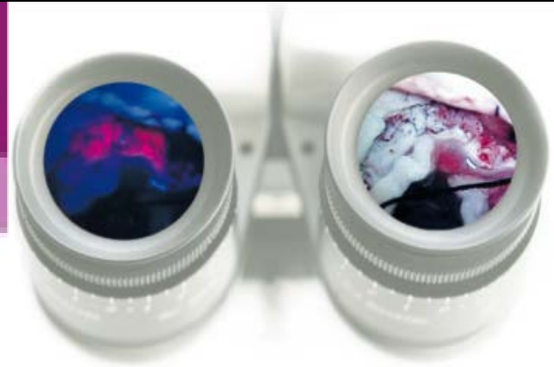
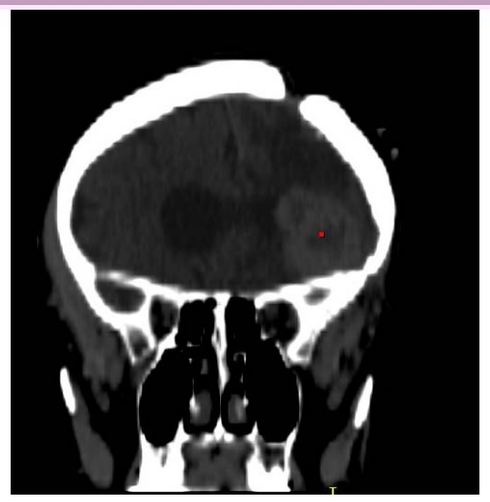
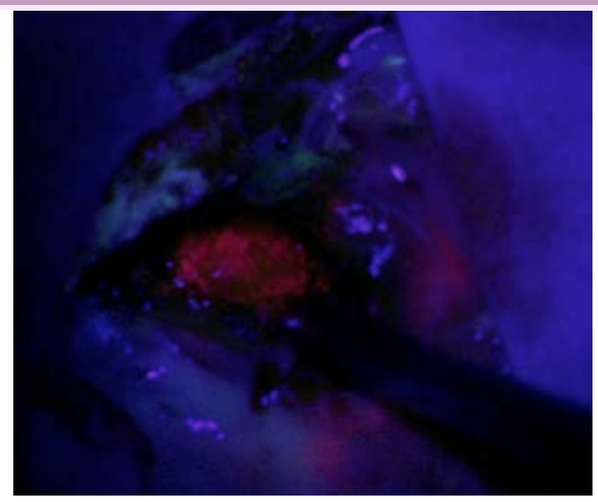
Fluorescence-guided surgery



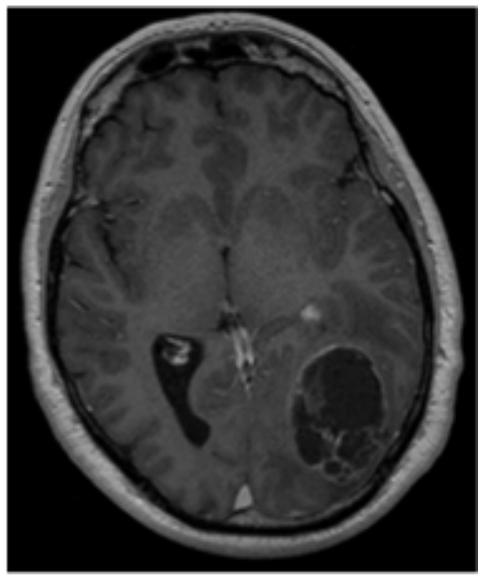
Fluorescent tumours…

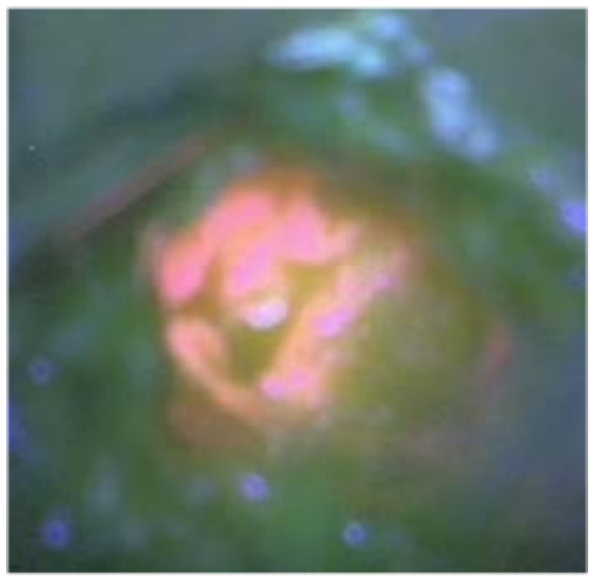
Malignant Meningioma



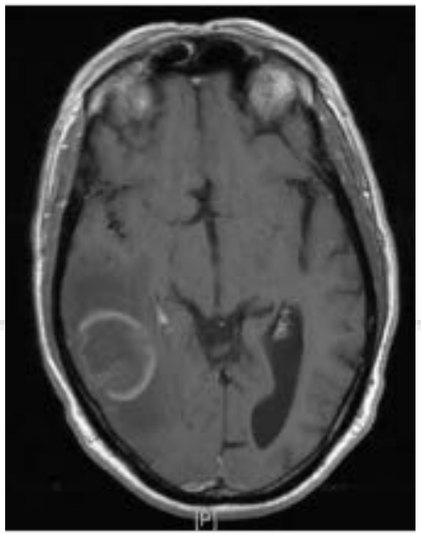


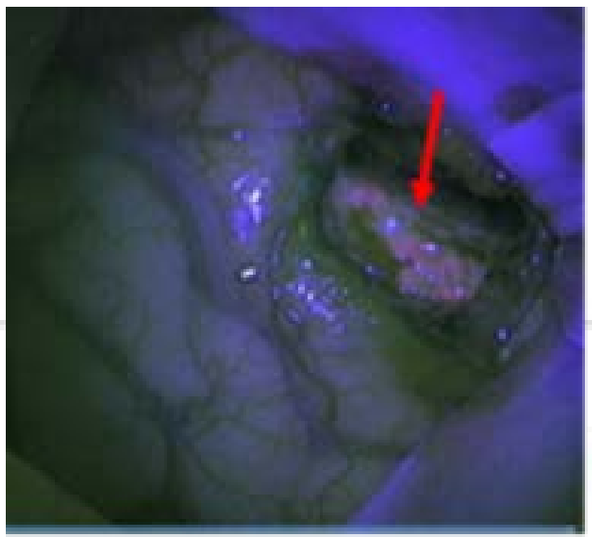
Ependymoma





Lymphoma





Lancet Oncol 2006; 7: 392–401

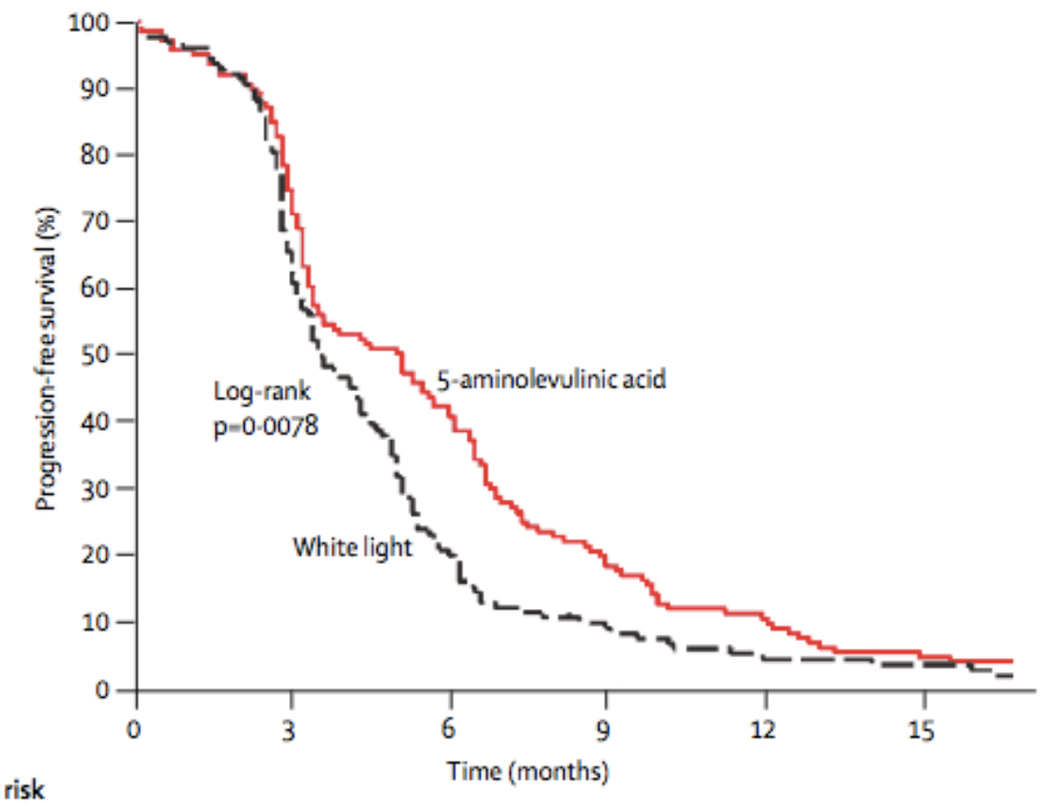
Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial

*Walter Stummer, Uwe Pichlmeier, Thomas Meinel, Otmar Dieter Wiestler, Friedhelm Zanella, Hans-Jürgen Reulen, for the ALA-Glioma Study Group**

322 pts

Complete resection in 65% vs 36%

(p<0.0001)



Numbers at risk

5-aminolevulinic acid	139	104	59	28	16	8
White light	131	85	28	13	7	5

OPEN ACCESS Freely available online May 2013 | Volume 8 | Issue 5 | e63682 PLOS ONE

Intraoperative Fluorescence-Guided Resection of High-Grade Malignant Gliomas Using 5-Aminolevulinic Acid–Induced Porphyrins: A Systematic Review and Meta-Analysis of Prospective Studies

Shiguang Zhao[1,2*], Jianing Wu[1,2], Chunlei Wang[1,2], Huailei Liu[1,2], Xingli Dong[3], Chen Shi[4], Changbin Shi[5], Yaohua Liu[1,2], Lei Teng[1,2], Dayong Han[1,2], Xiaofeng Chen[1,2], Guang Yang[1,2], Ligang Wang[1,2], Chen Shen[1,2], Huadong Li[1,2]

10 studies included for Systematic review

5 studies included for met analysis

Publication	5-ALA		Neuronavigation	
	sensitivity	specificity	sensitivity	specificity
Panciani et al. (2012)	91.1%	89.4%	57.8%	57.4%
Hefti et al. (2008)	87.0%	85.0%	66.0%	68.0%

Publication	No. of patients	Subgroup	Overall survival (mo)		PFS rate at 6 months	
			5-ALA	WL	5-ALA	WL
Stummer et al. (2011)	349	–	14.3	13.7	46.0%	28.3%
Eljamel et al. (2008)	27	–	12.3	5.6	–	–
Stummer et al. (2006)	270	older	14.1	11.5	41.0%	21.1%
		younger	18.0	17.5		

Level 2 evidence that 5-ALA-guided surgery is more effective than conventional neuronavigation-guided surgery in increasing diagnostic accuracy, extent of resection and PFS

See the corresponding editorial in this issue, pp 737–739.

J Neurosurg 115:740–748, 2011

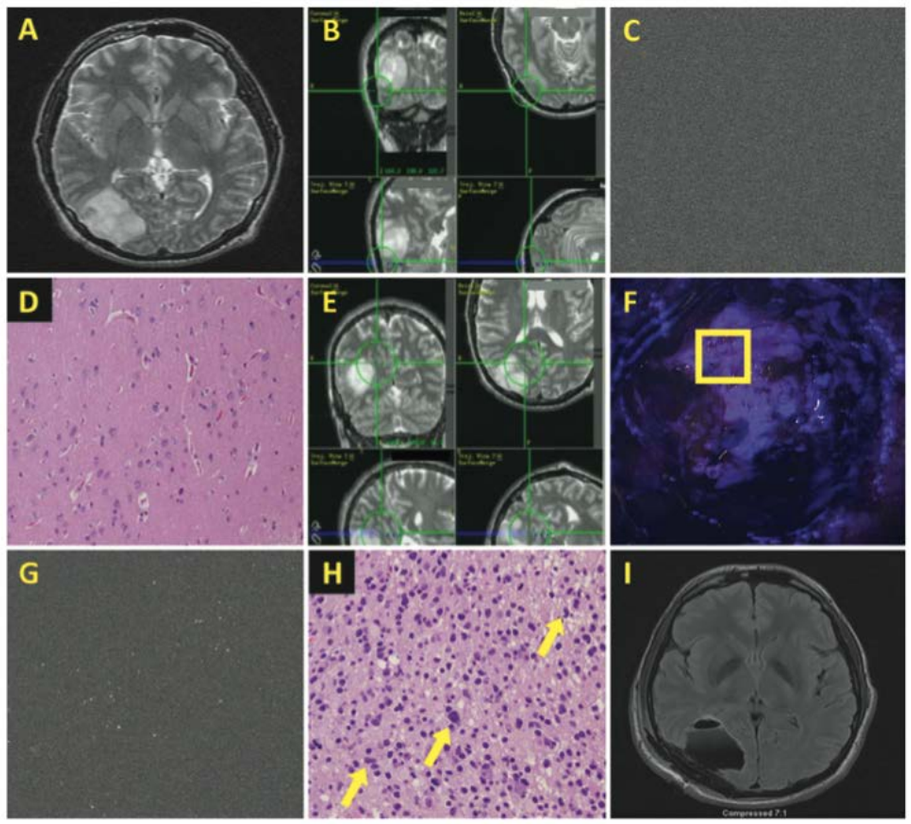
Intraoperative confocal microscopy in the visualization of 5-aminolevulinic acid fluorescence in low-grade gliomas

Clinical article

Nader Sanai, M.D., Laura A. Snyder, M.D., Norissa J. Honea, M.S.N., Stephen W. Coons, M.D., Jennifer M. Eschbacher, M.D., Kris A. Smith, M.D., and Robert F. Spetzler, M.D.

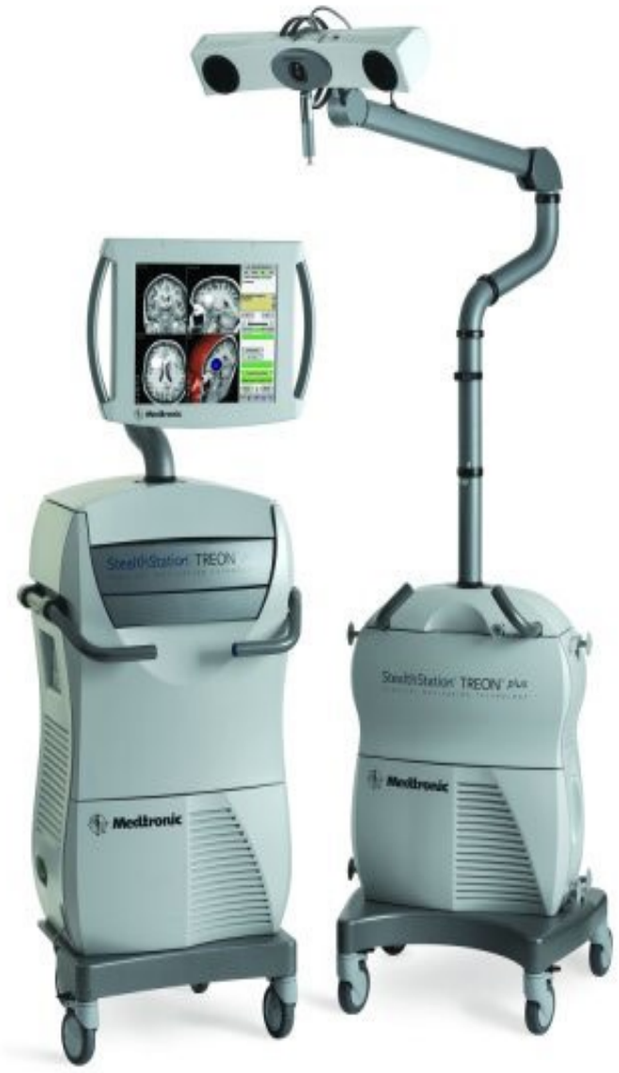
Barrow Brain Tumor Research Center, Barrow Neurological Institute, Phoenix, Arizona

10 LGG pts
Evaluation of tumour surface,
Midpoint tumour resection
and
Brain-tumour interface

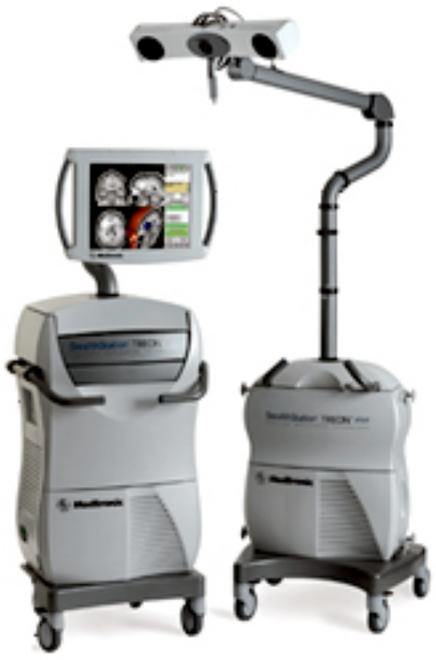


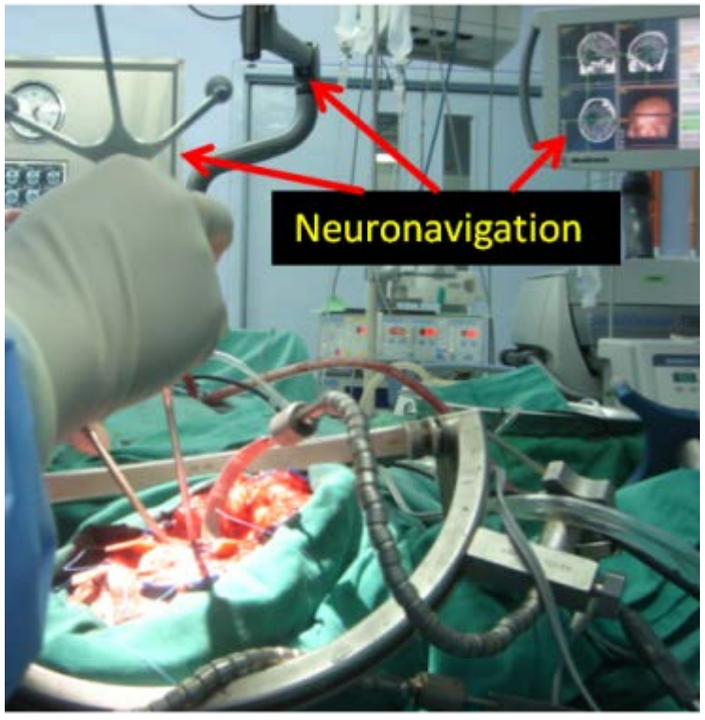
Intraoperative confocal microscopy can visualize cellular 5-ALA–induced tumor fluorescence within LGGs and at the brain-tumor interface.

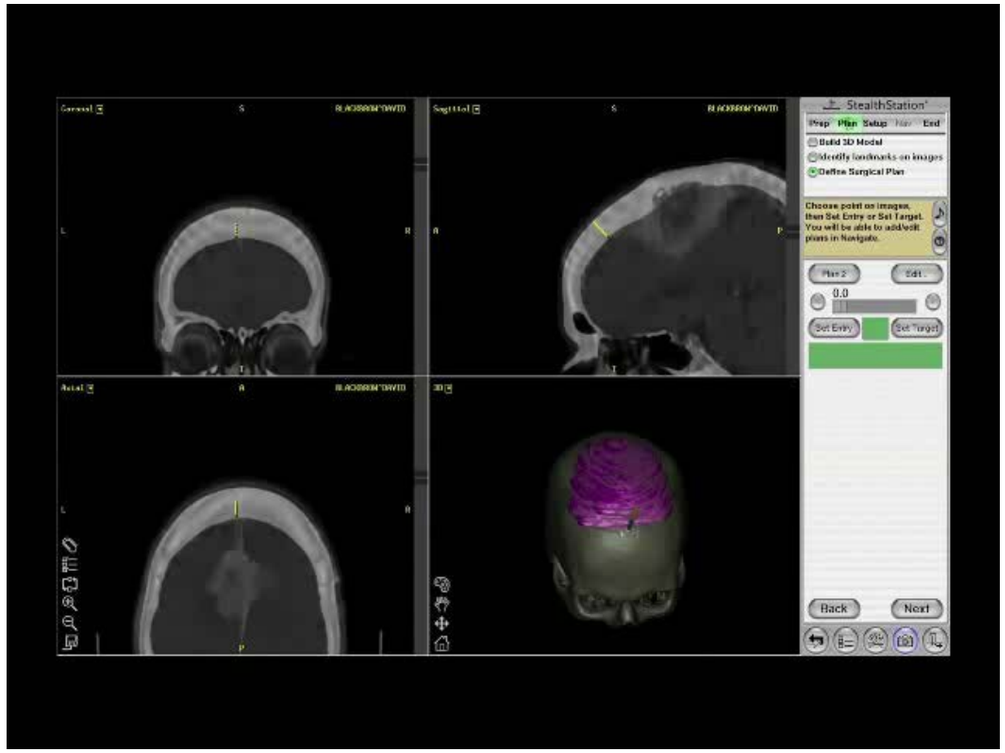
Intra-operative imaging

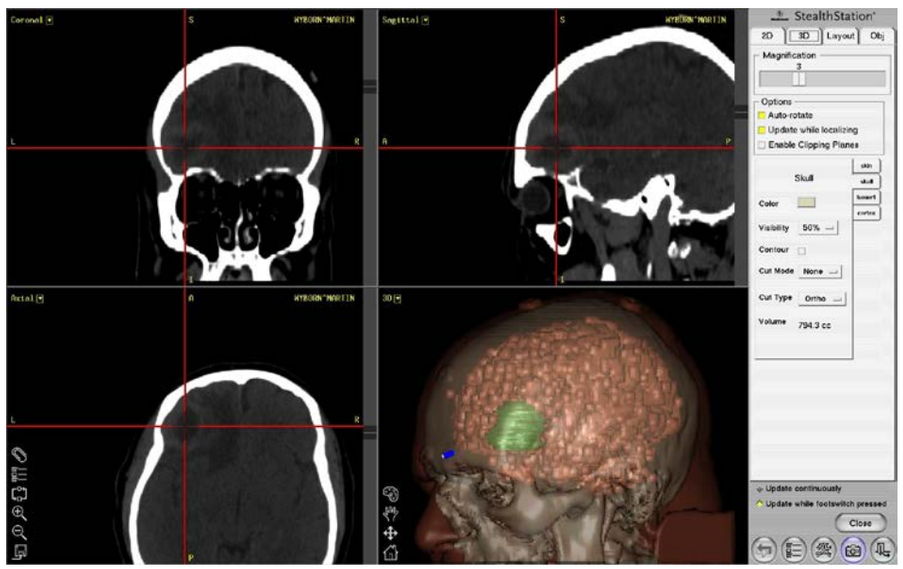


Intra-operative neuronavigation







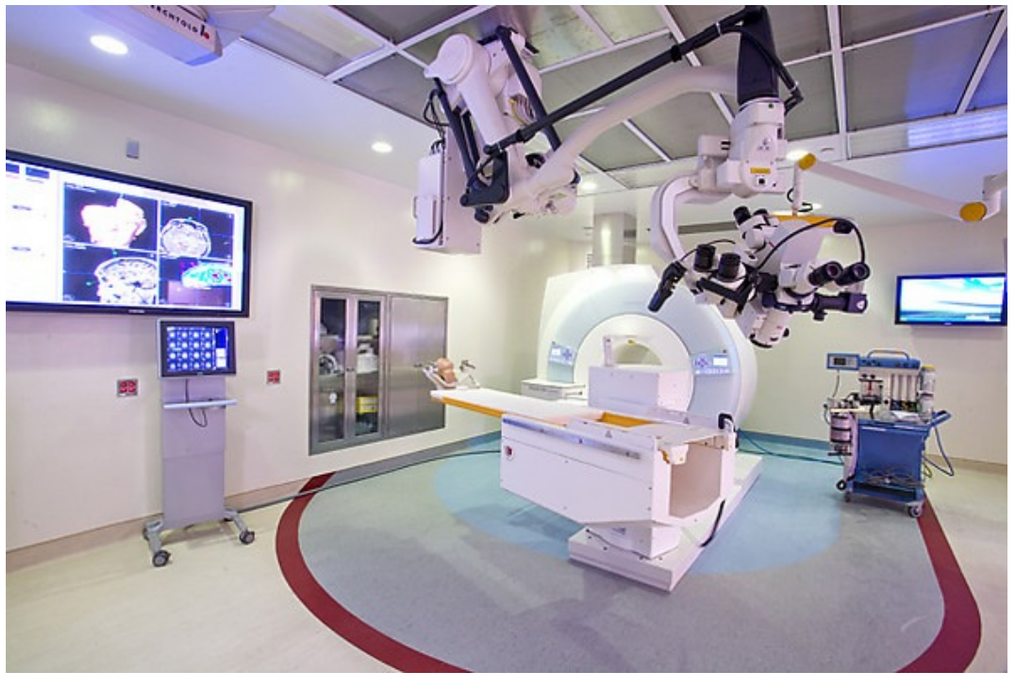


Tailored craniotomy

Help to access deep-seated lesions

Help in maximize the extent of resection (?)

Intra-operative MRI



Articles

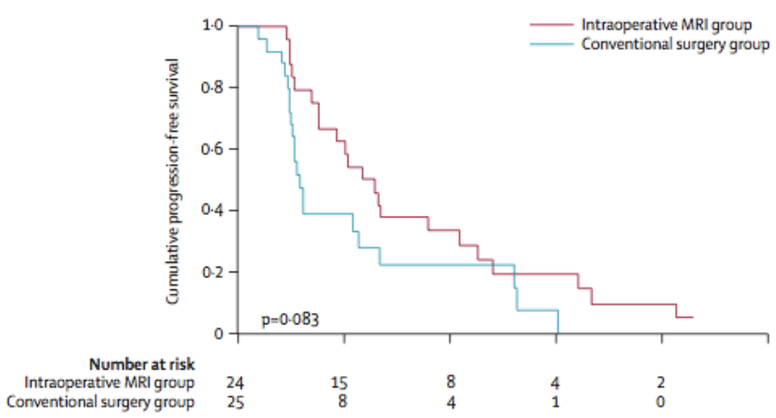
Lancet Oncol 2011; 12: 997–1003

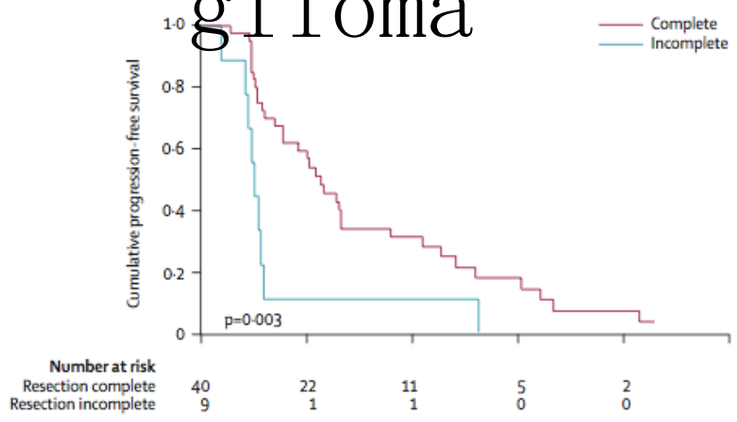
Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial

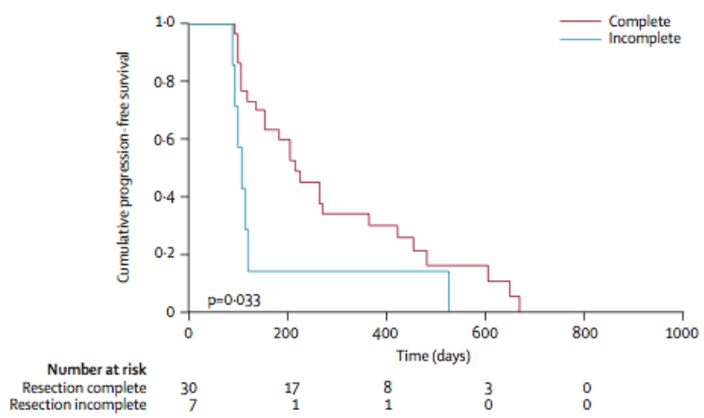
Christian Senft, Andrea Bink, Kea Franz, Hartmut Vatter, Thomas Gasser, Volker Seifert

Prospective randomized study

58 pts with enhancing glioma



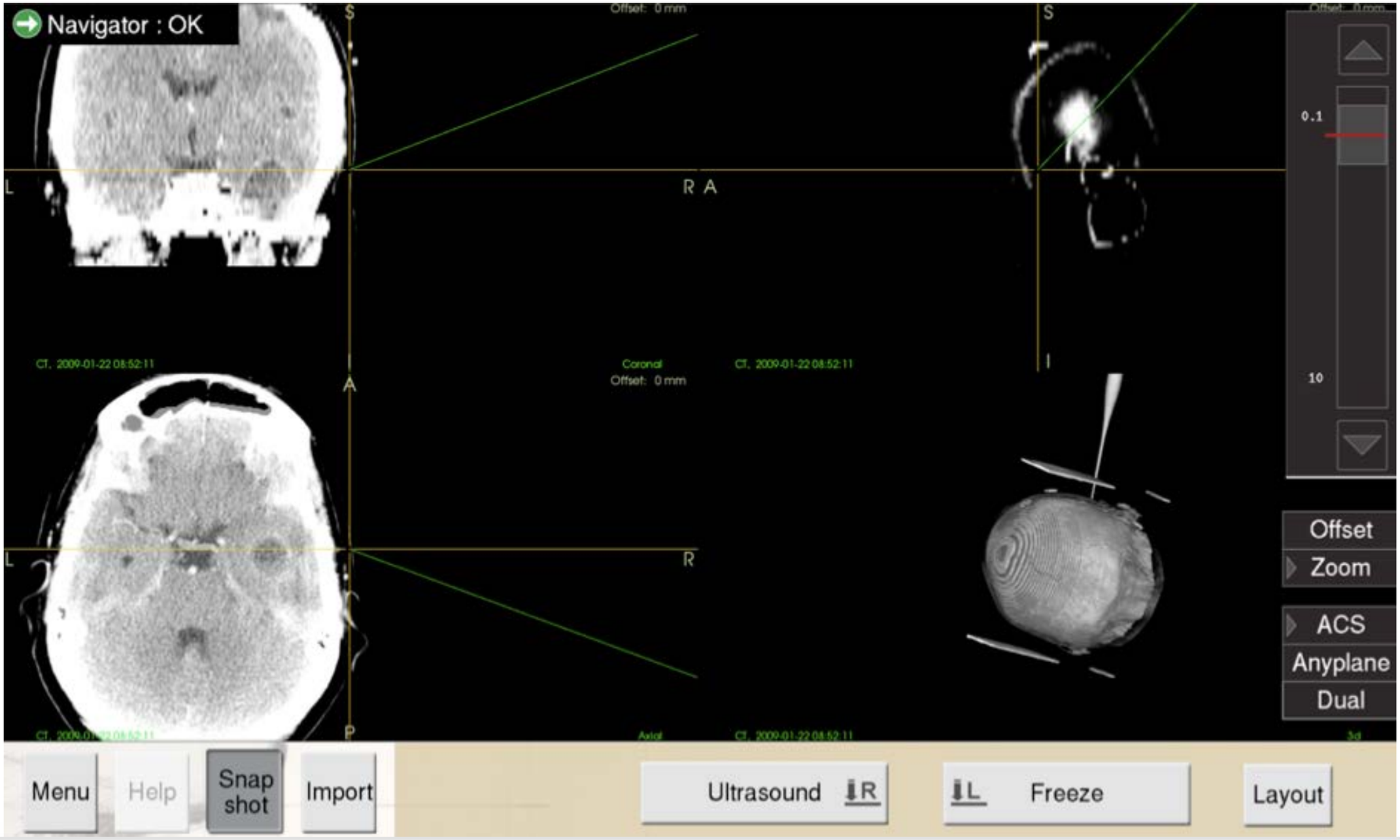




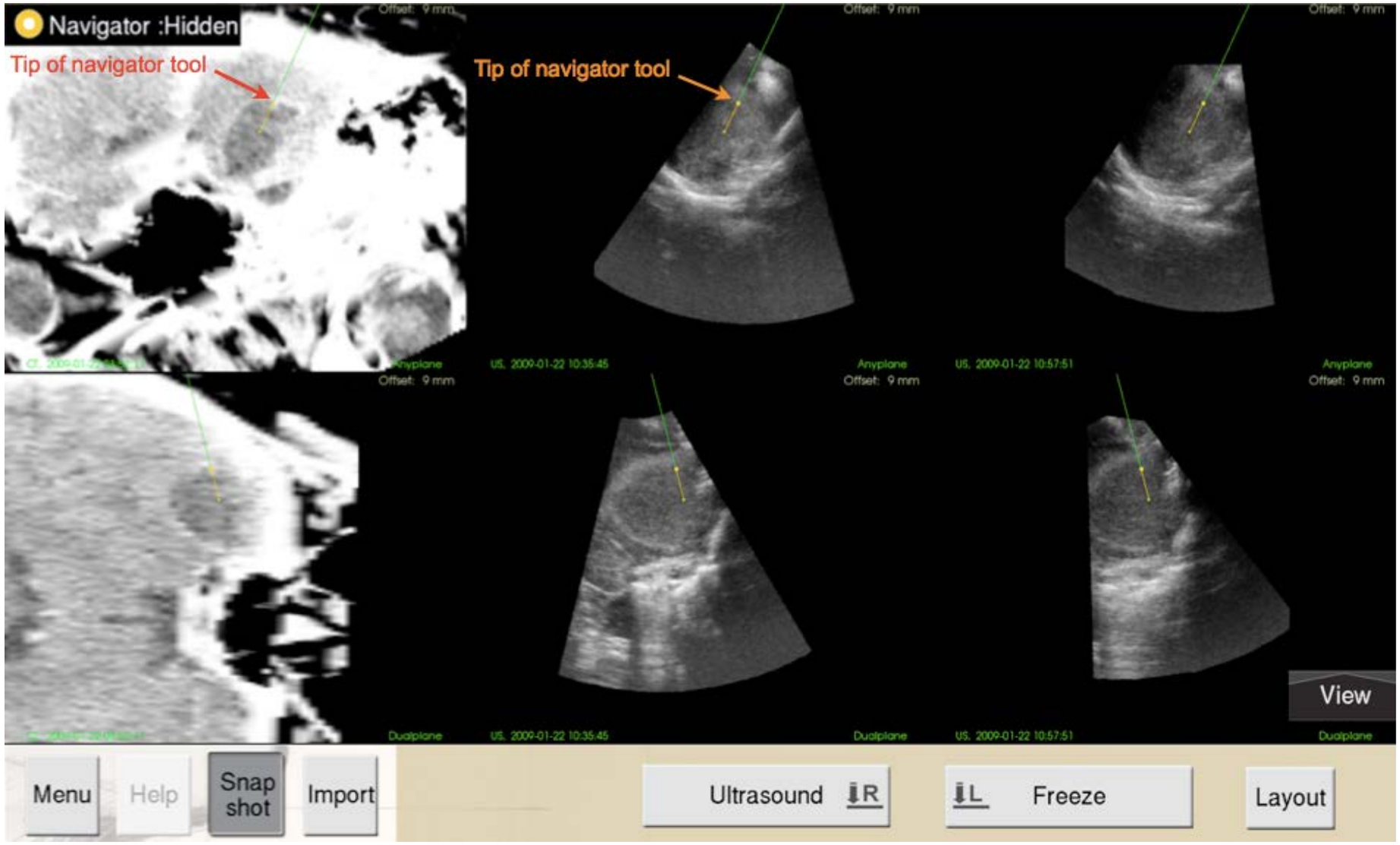
Greater extent of resection (96% vs 68%, p=0.023)

No difference in neurological outcome

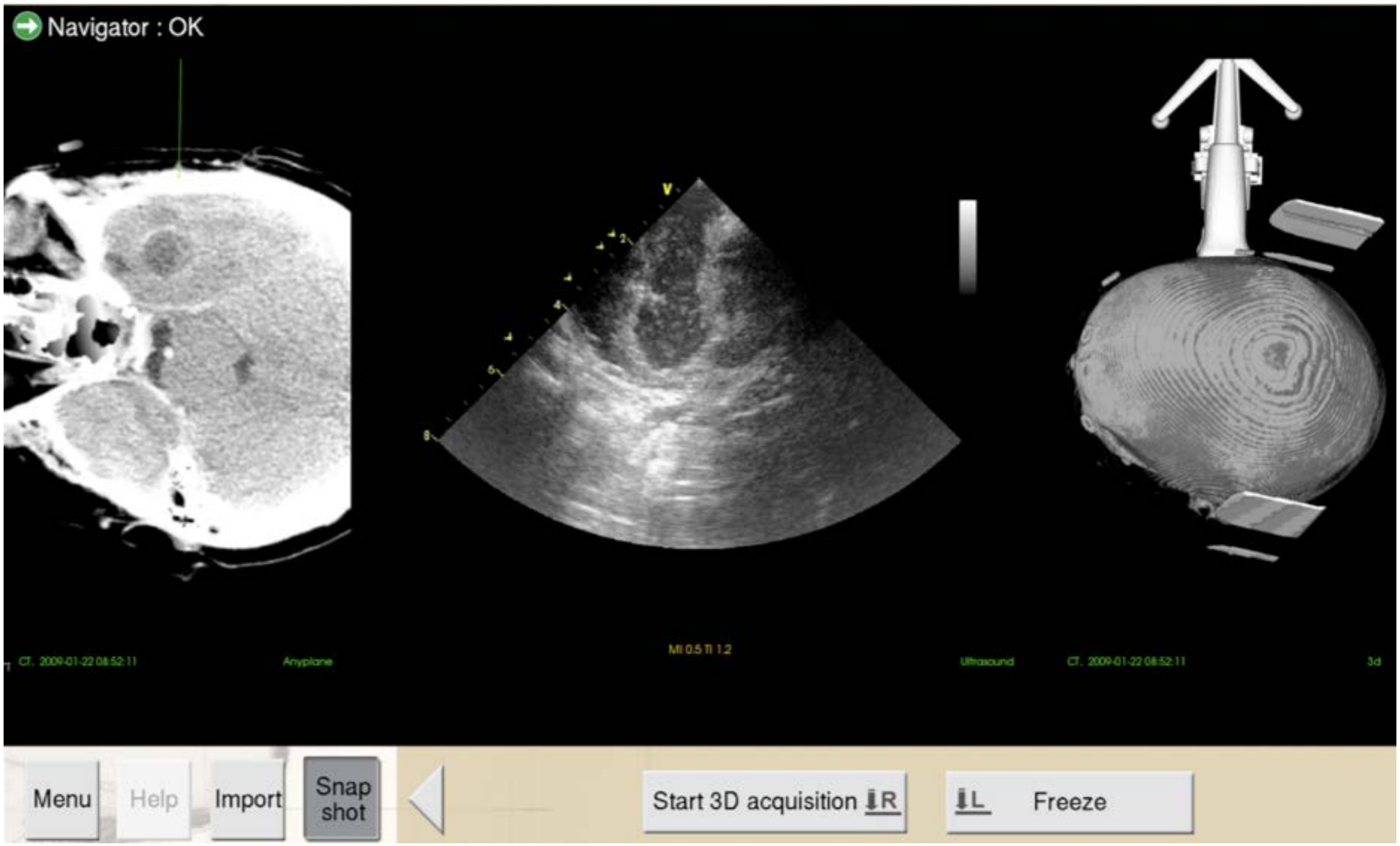
Pre-operative planning in ACS view



First and second US acquisition



Towards end of resection



Towards end of resection

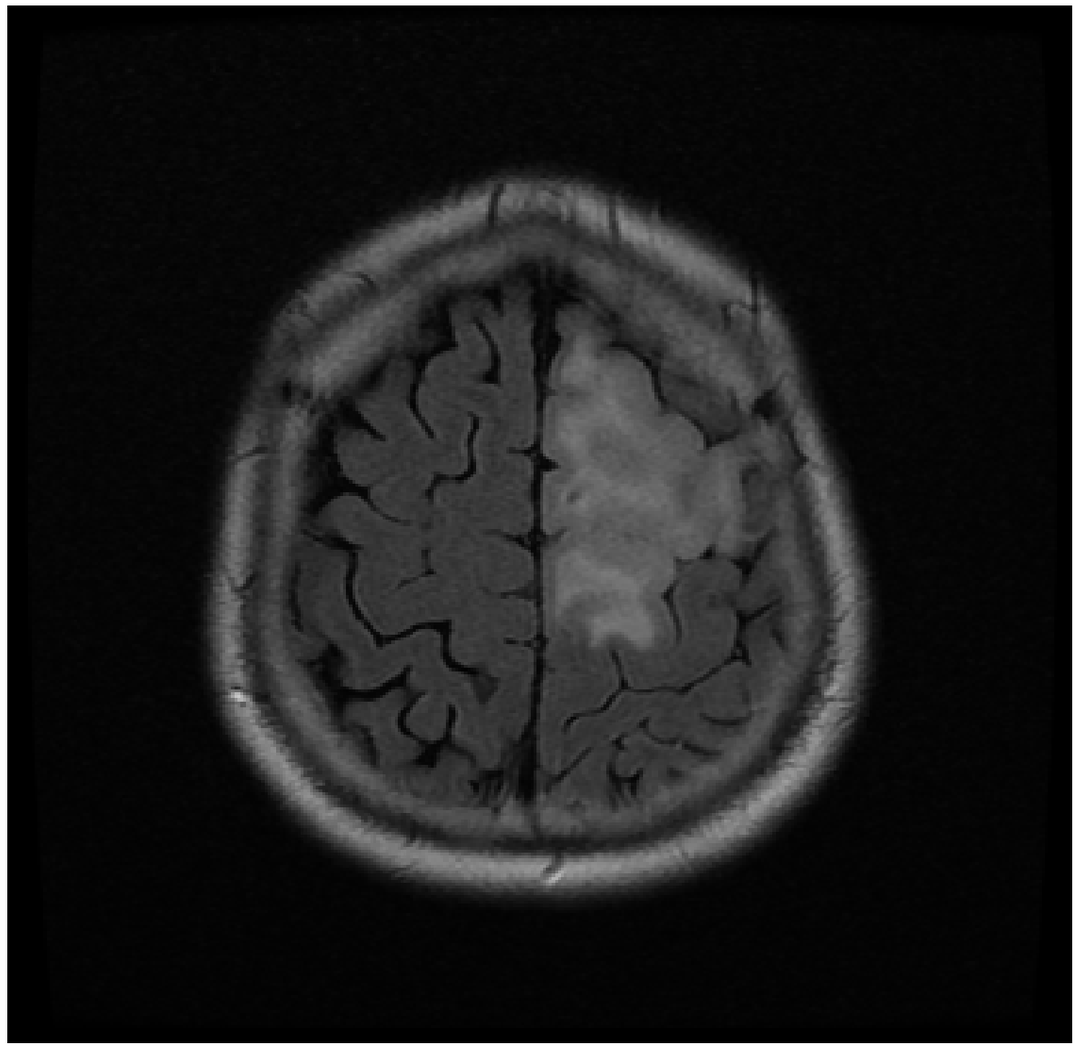
Illustrative cases

Illustrative case

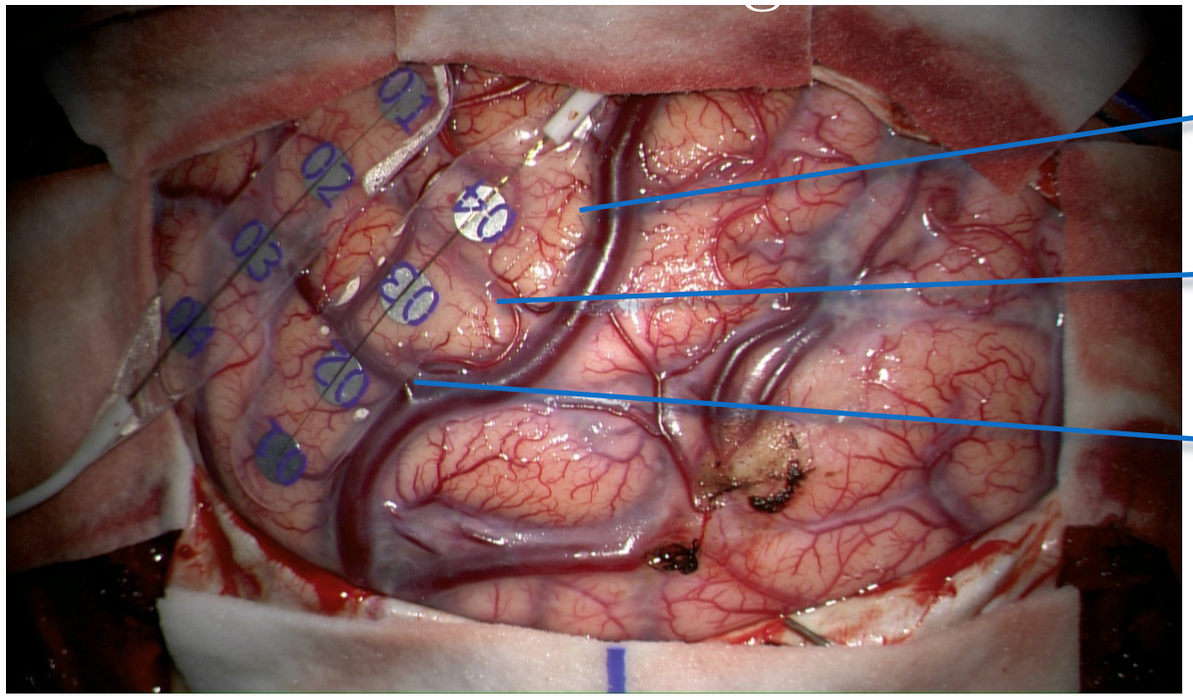
55, male

presented in October 2014 with generalised tonic clonic seizure.

CT and MRI showed left SMA tumour, suggestive of low grade glioma



Case I – intraop monitoring

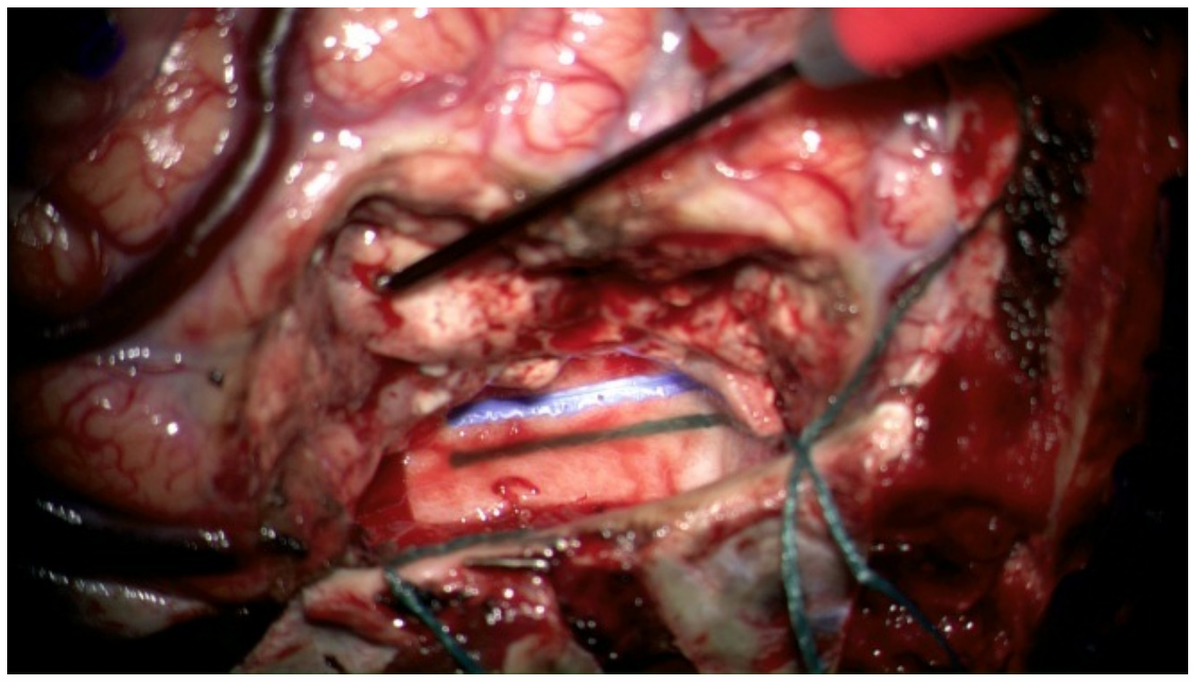


4: hand

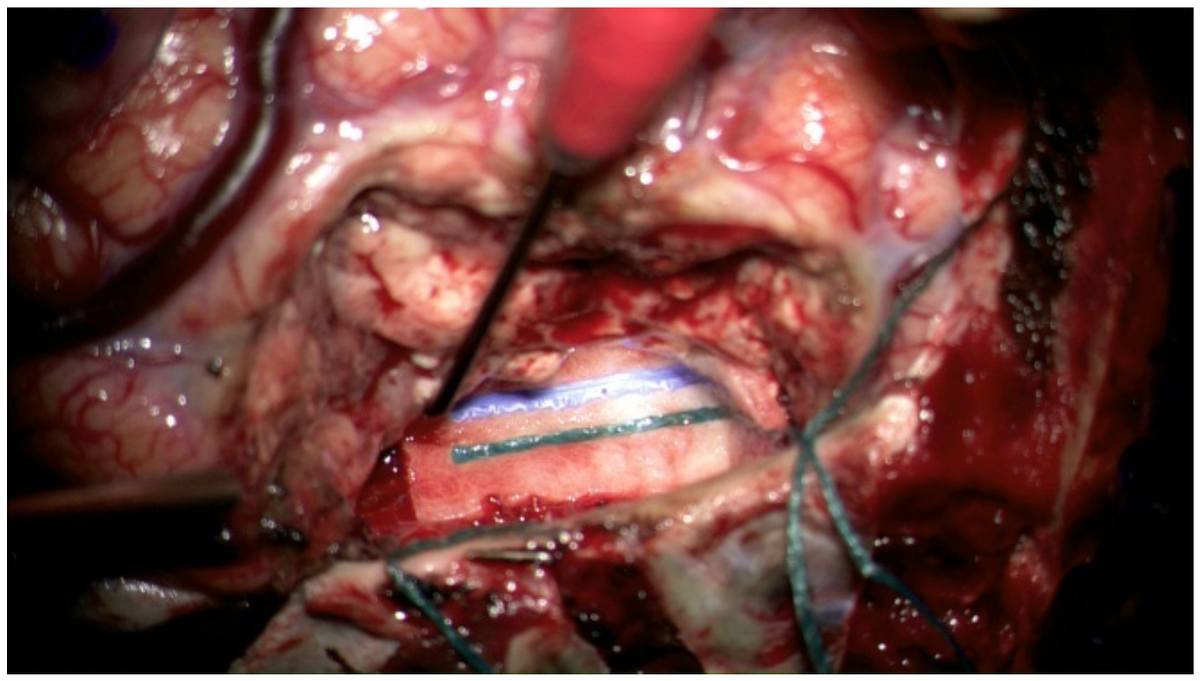
3: hand and forearm

2: hand

Spontaneous speech and object naming continuously assessed



face



hand

Case I - postop course

Pt developed transient SMA syndrome

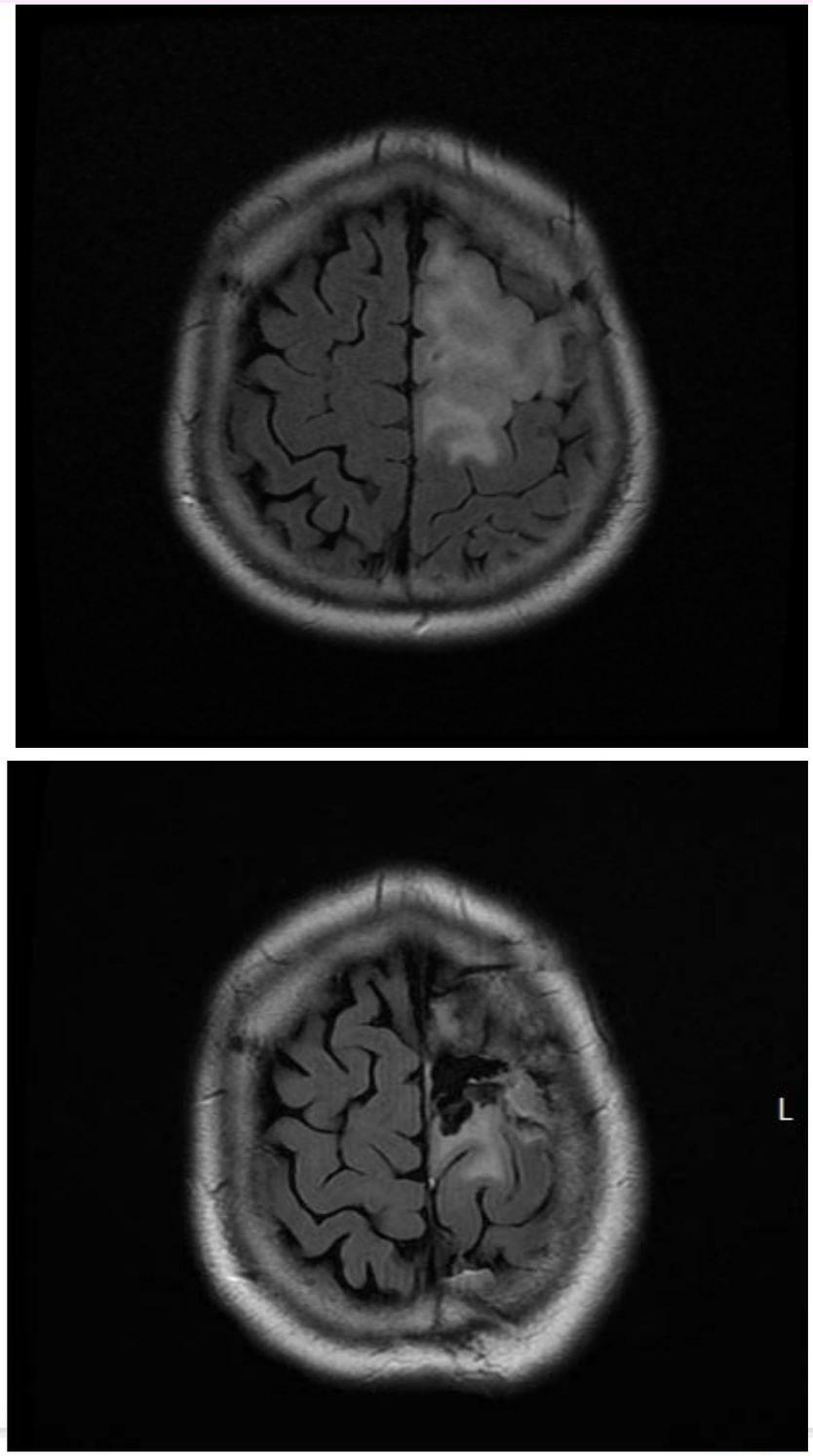
Akinesia recovered within 1 week

Language recovered within 3 weeks

Physiotherapist involved at an early stage in the postop recovery

Pt transferred to rehab unit

90% resection on postop MRI



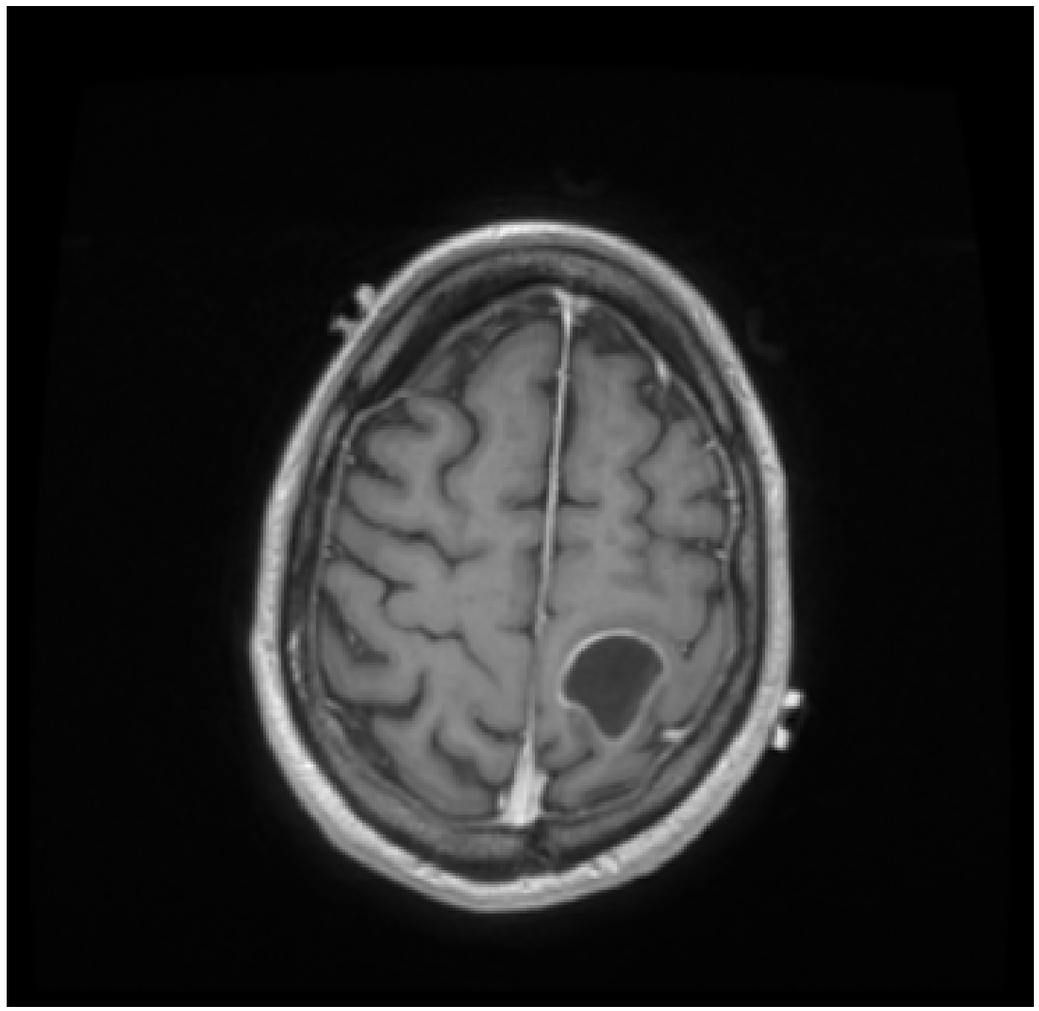
Illustrative case II

66, male

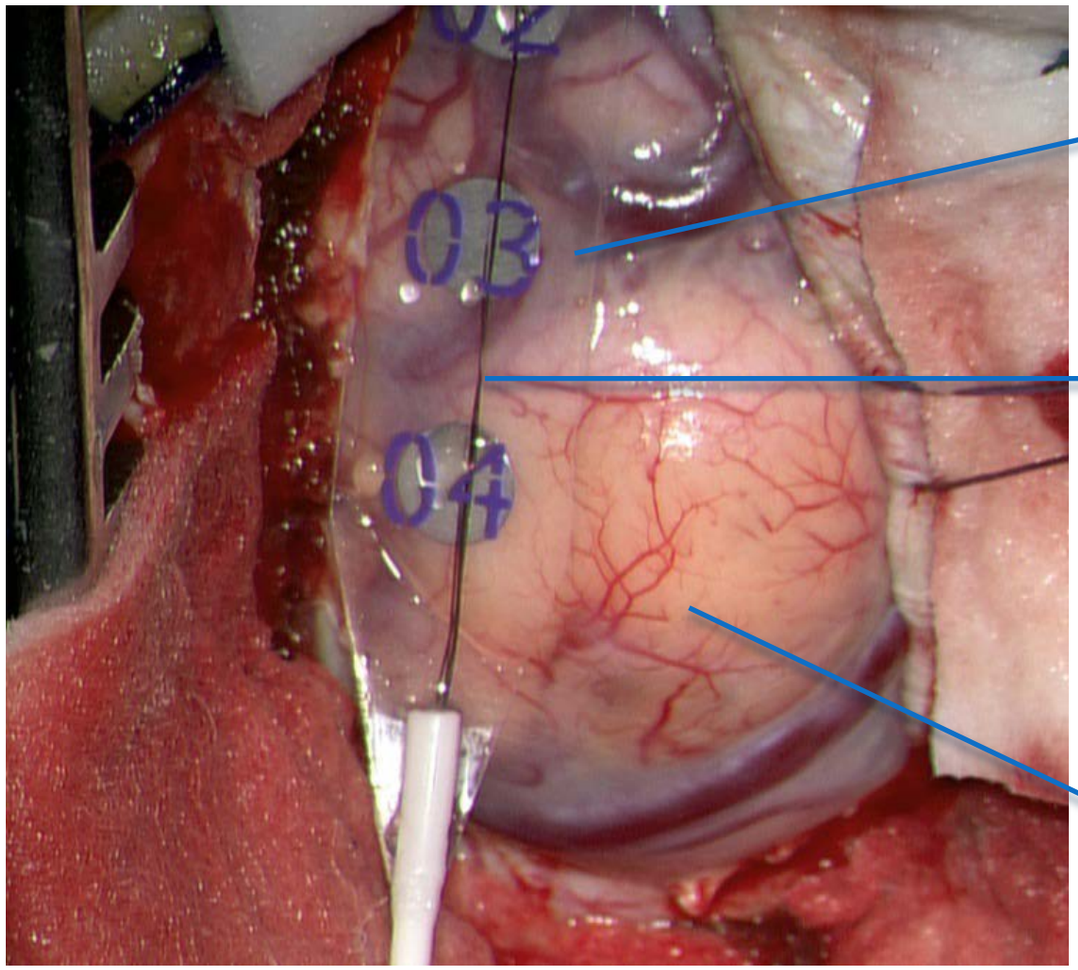
Numbness and mild right weakness, improved with steroids

Preop assessment: 4/5 right power

CT and MRI: SOL in left post-central gyrus; suggestive of high grade glioma



case II - cortical mapping

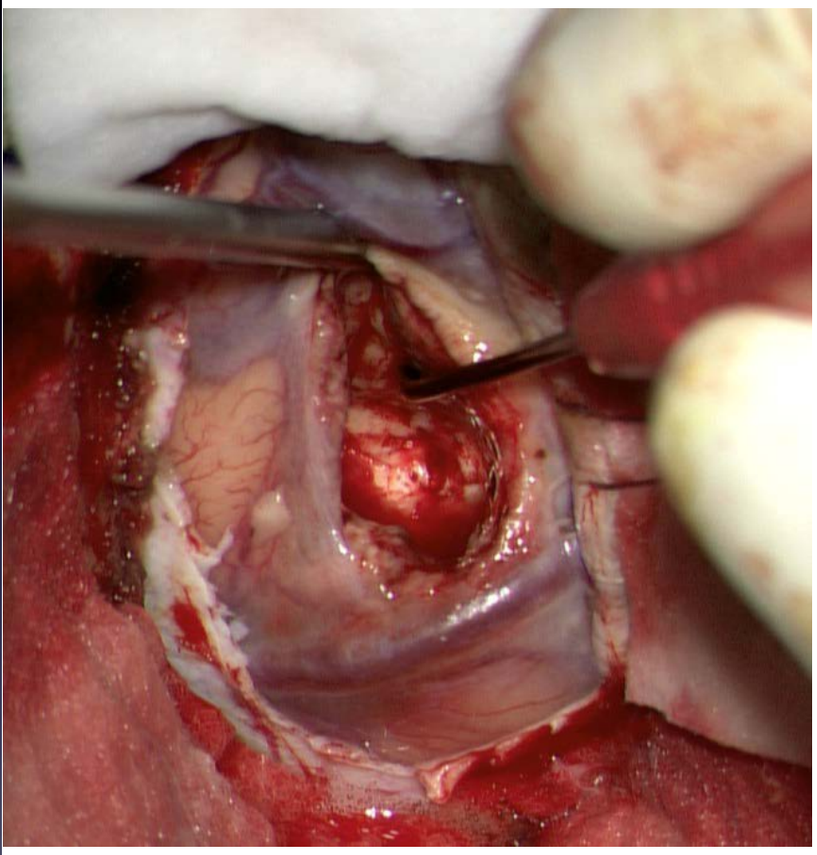


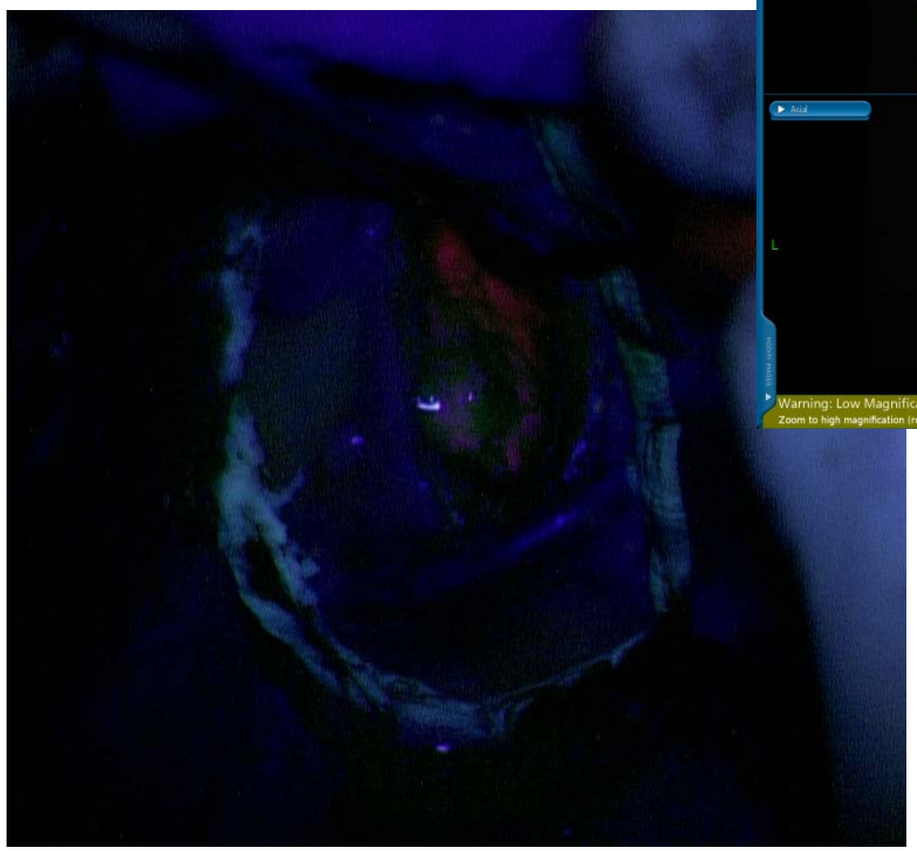
Hand and forearm response

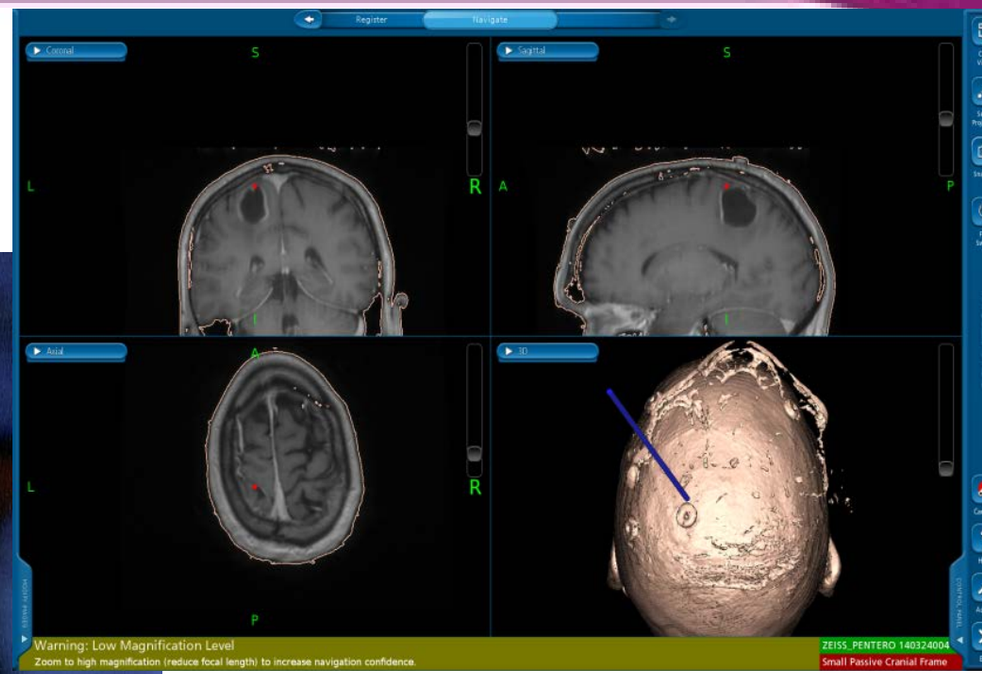
Central sulcus. SSEP run between 3 and 4 demonstrated “phase reversal”

Postcentral gyrus expanded by tumour. The corticotomy is performed at this level

case II - subcortical mapping







Subcortical stimulation under normal light (left) and with GLIOLAN (right). A positive motor response, corresponding to stimulation of the cortico-spinal tract, was elicited at this level. This represented the most anterior margin of resection

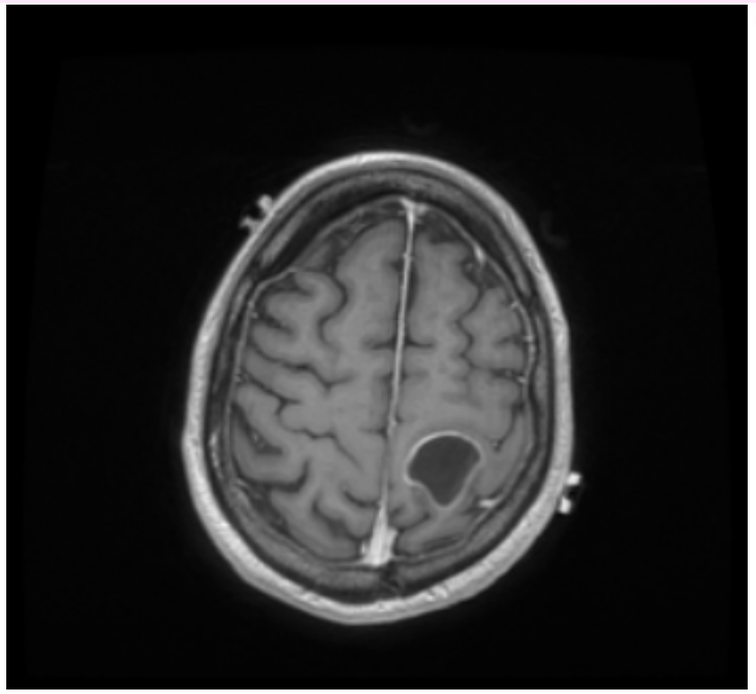
case II - postop course

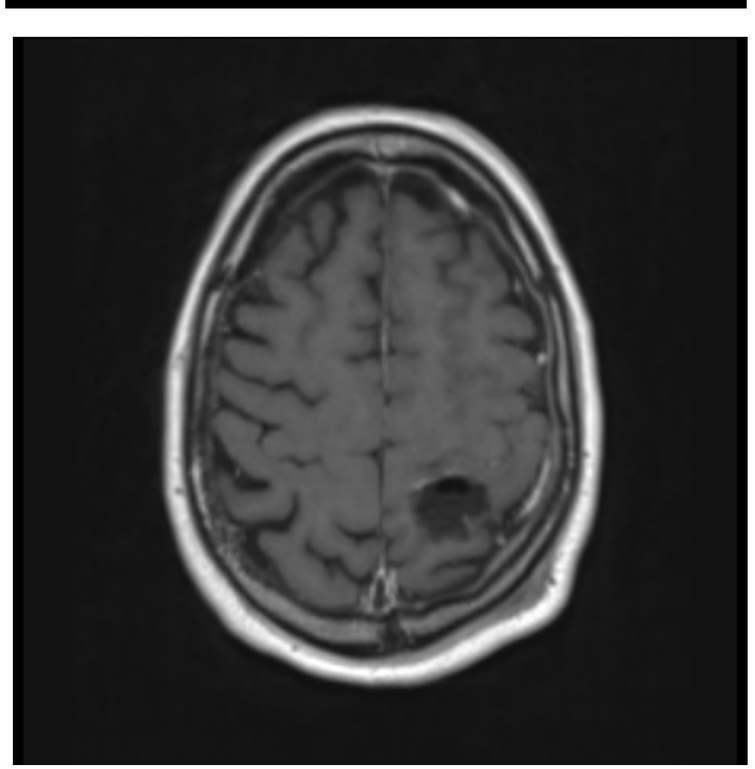
Transient worsening of prep weakness

Physiotherapy treatment from day 1 postop

Discharged to rehab unit, full recovery in 3 weeks

95% resection on postop MRI





Illustrative case

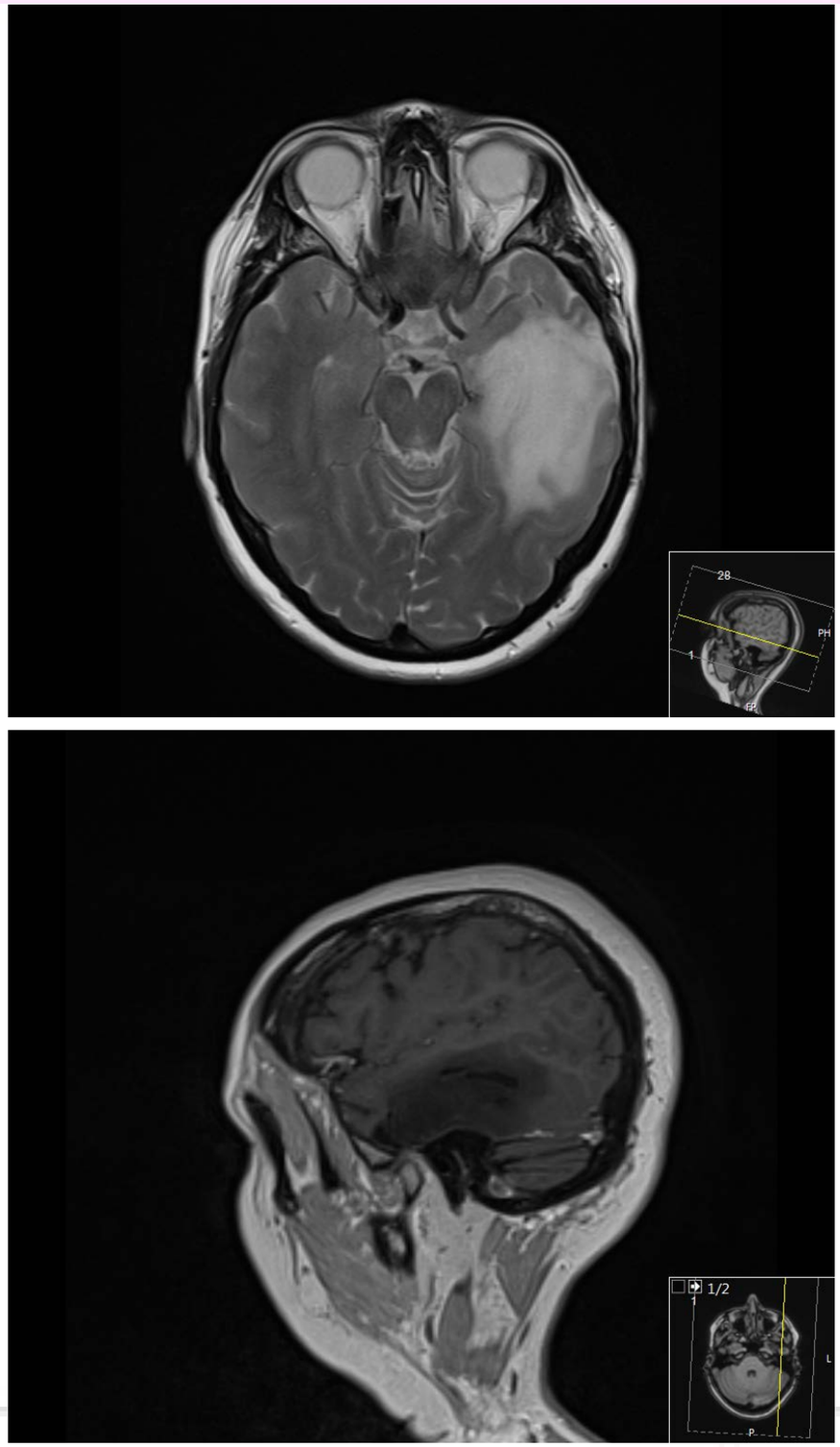
III

43 yrs female

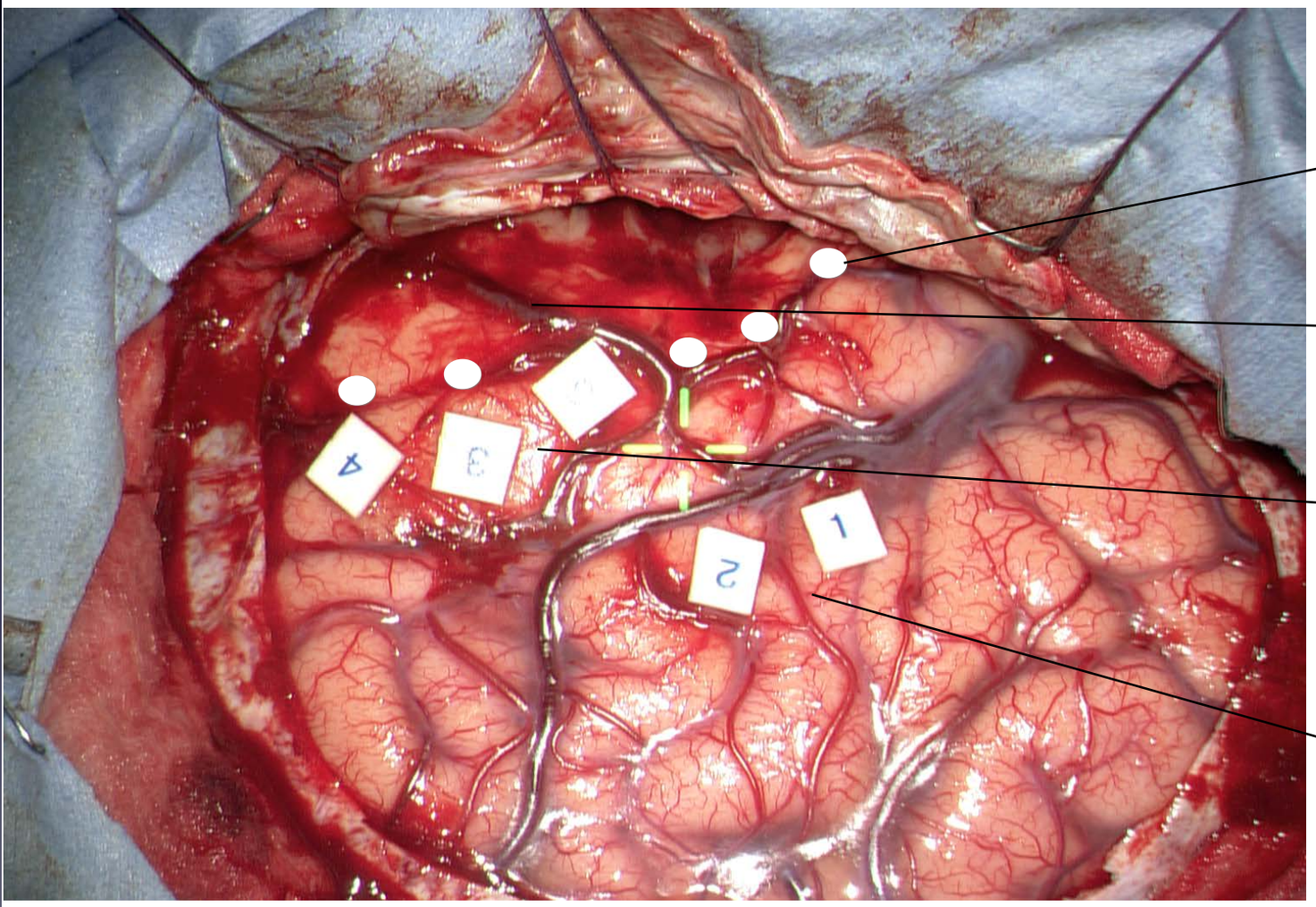
Previous debulking of WHO grade II olygoastrocytoma in 2011

Slow progression/recurrence over the years

Complex temporal seizures well controlled with levetiracetam



Case III - cortical mapping



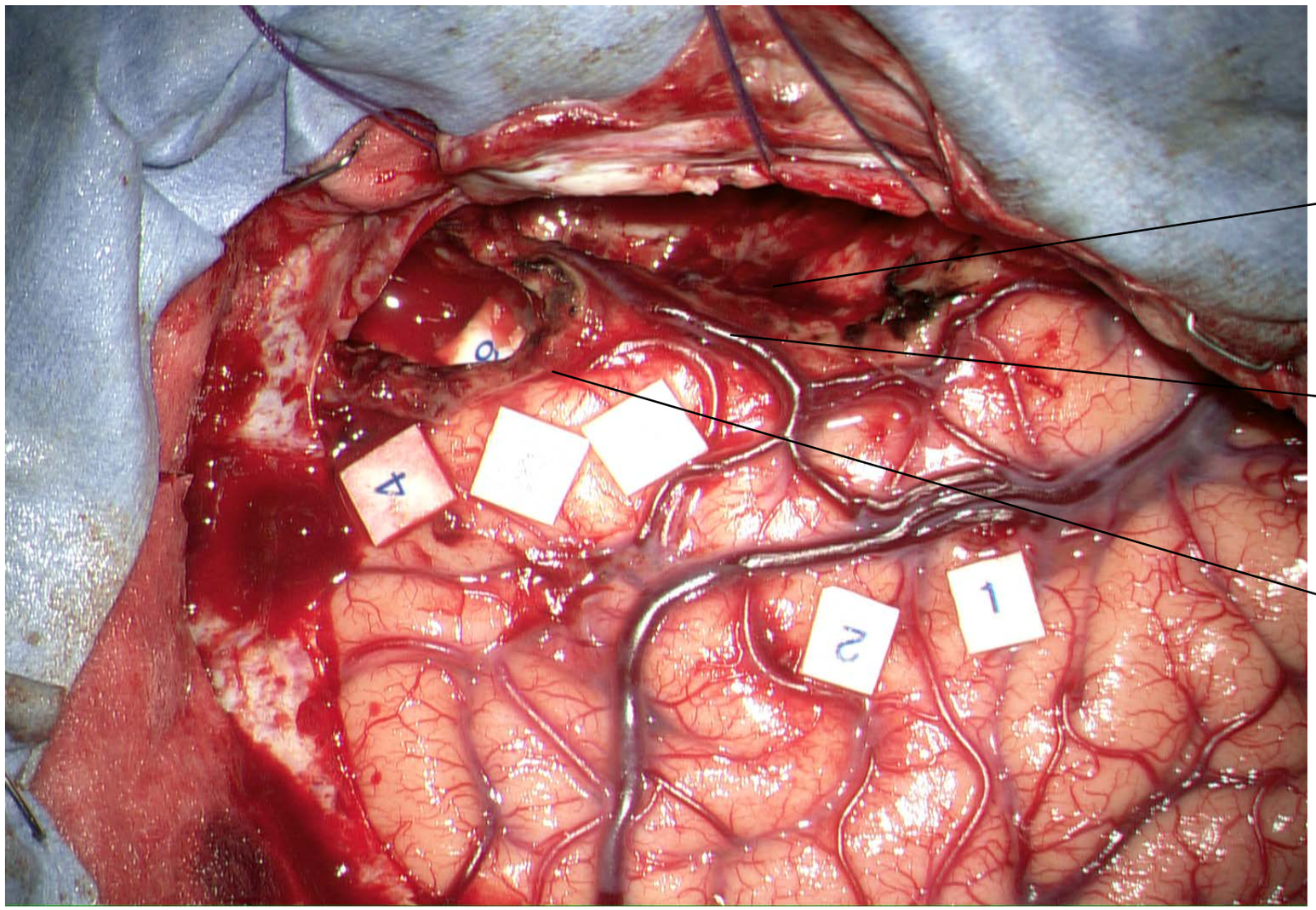
Tumour boundaries

Vein of Labbe'

3,4 &5: anomias and phonological paraphasias

1&2: speech arrest

Case III - subcortical mapping



Resection cavity

Labbe' vein

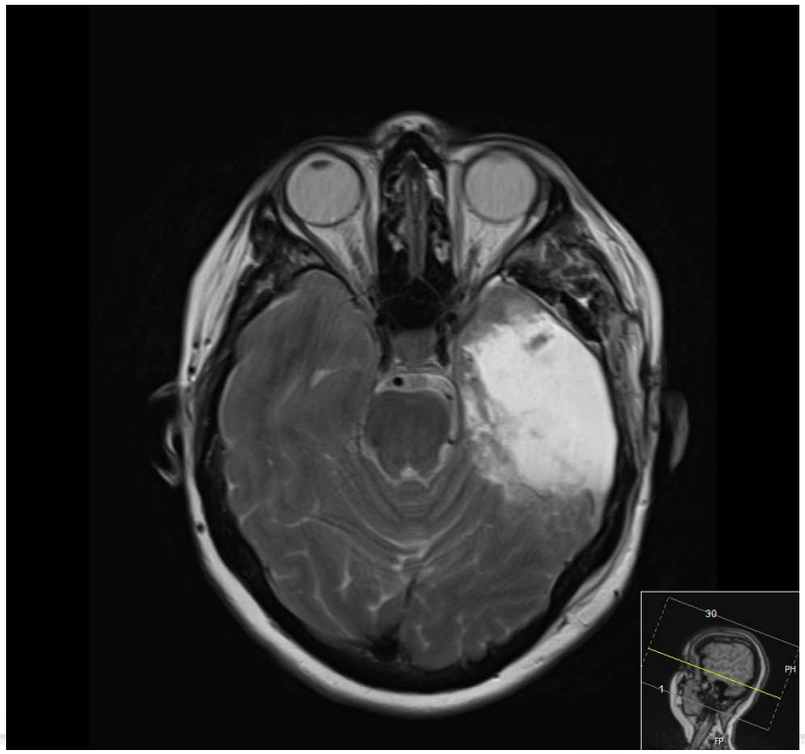
6: site inducing positive visual phenomena

Case III - postop course

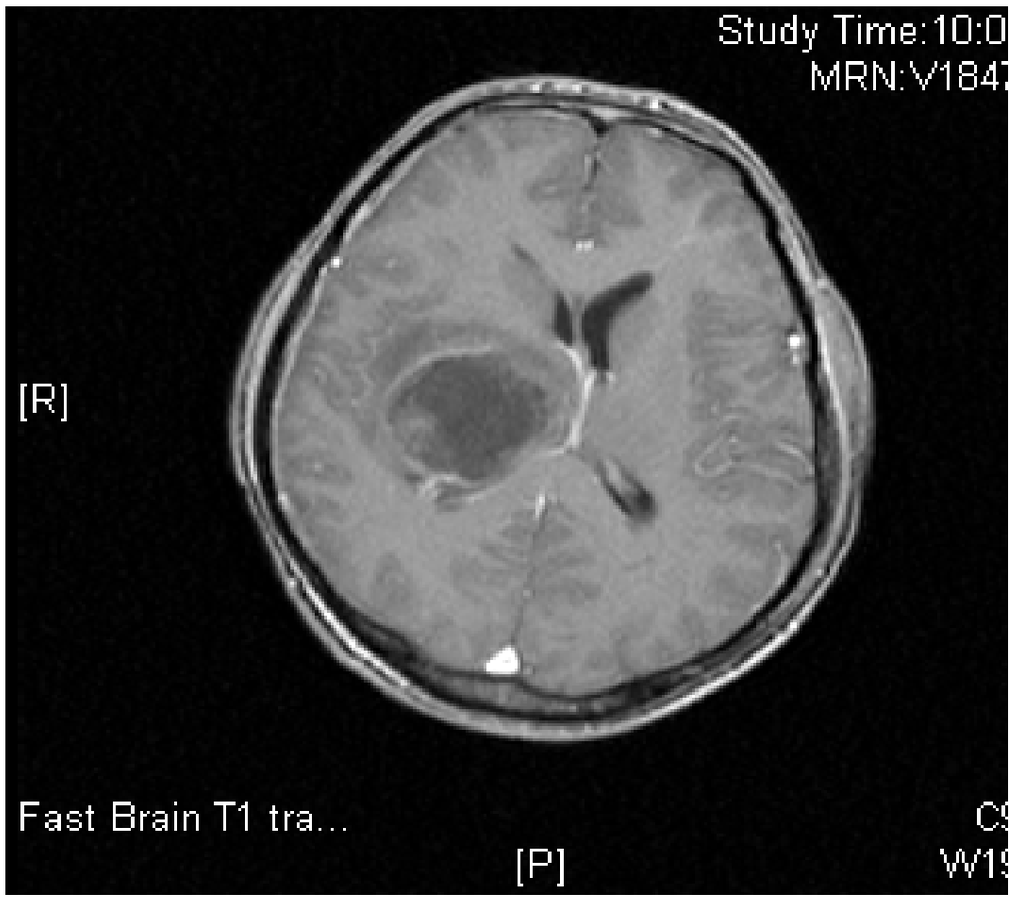
No language deficits

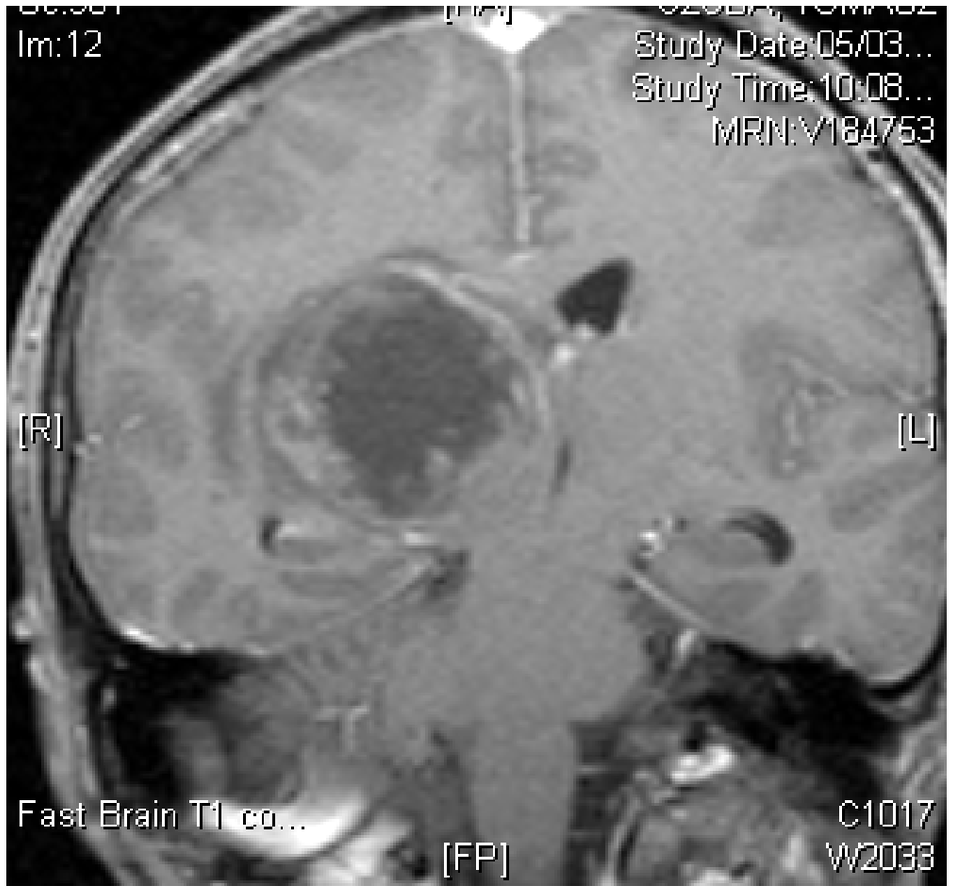
80% tumour resection

Pt awaiting discharge

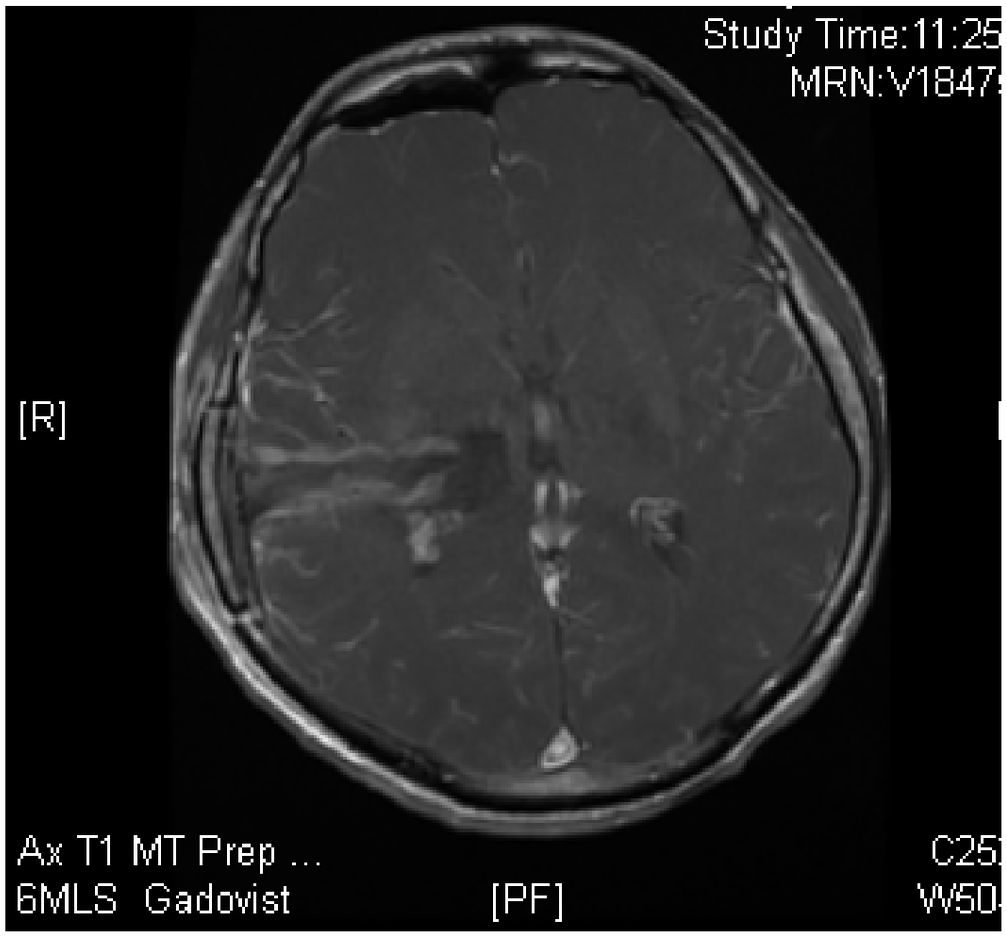


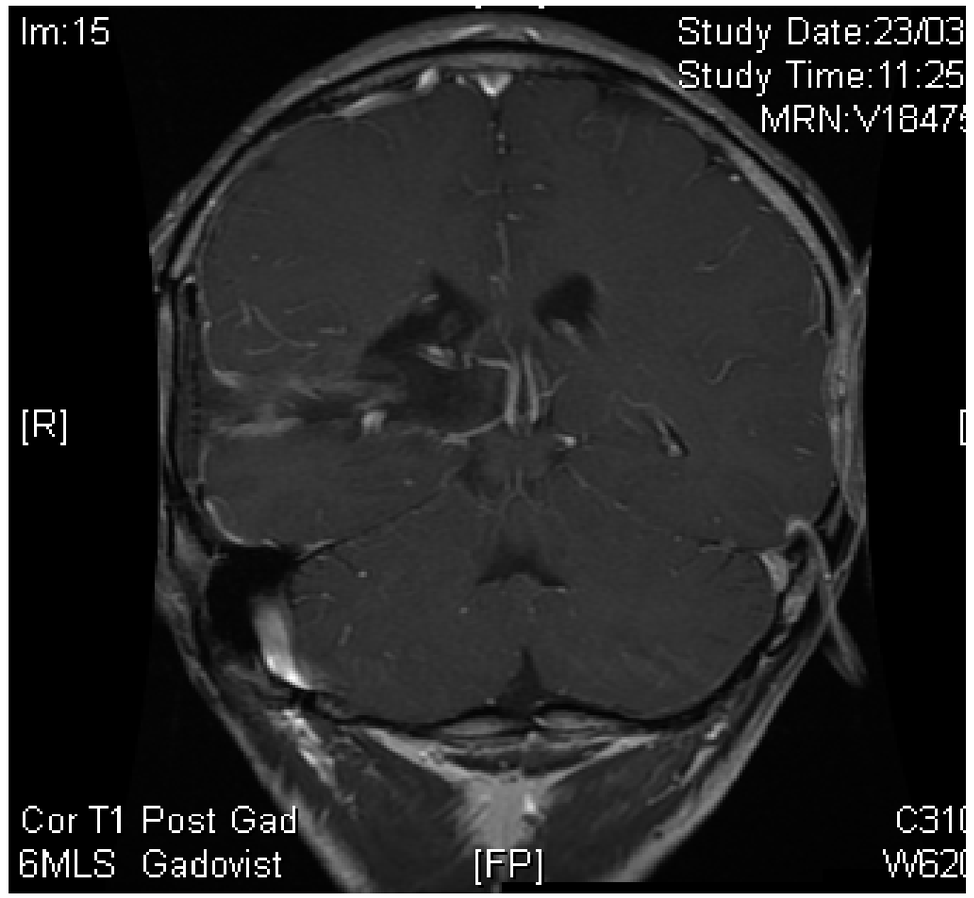
30 year old male - Left Hemiparesis



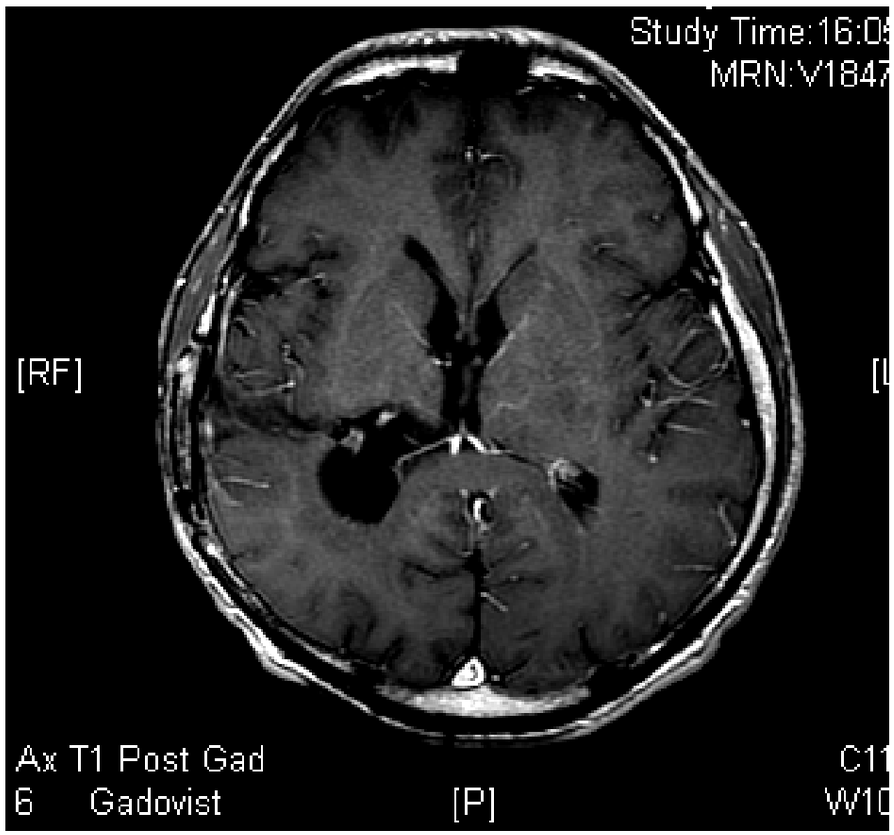


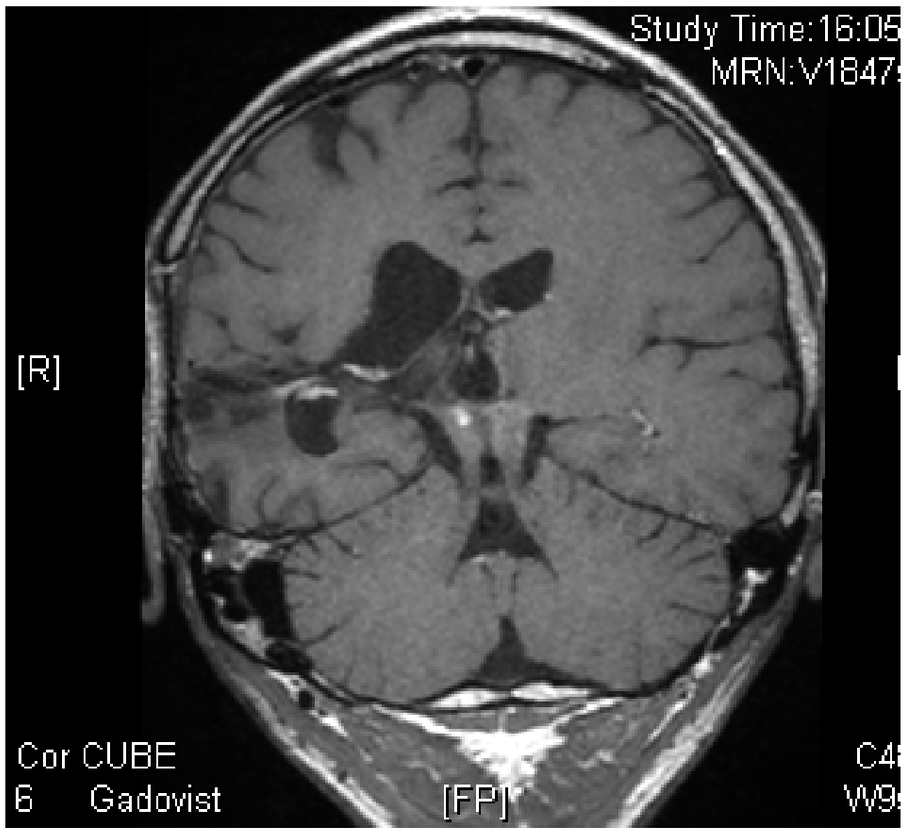
Immediate Post -Op Scan



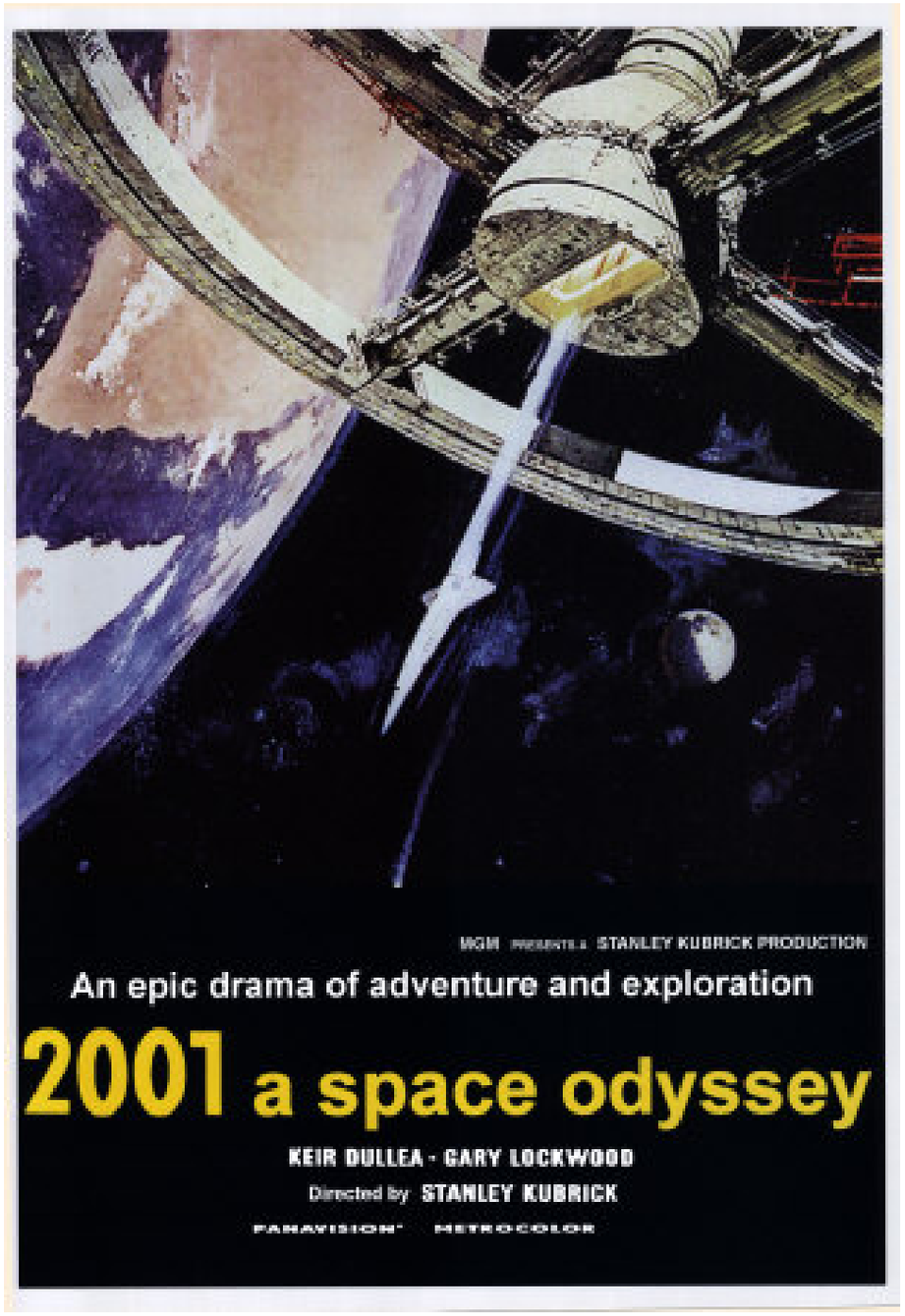


3 Years Later

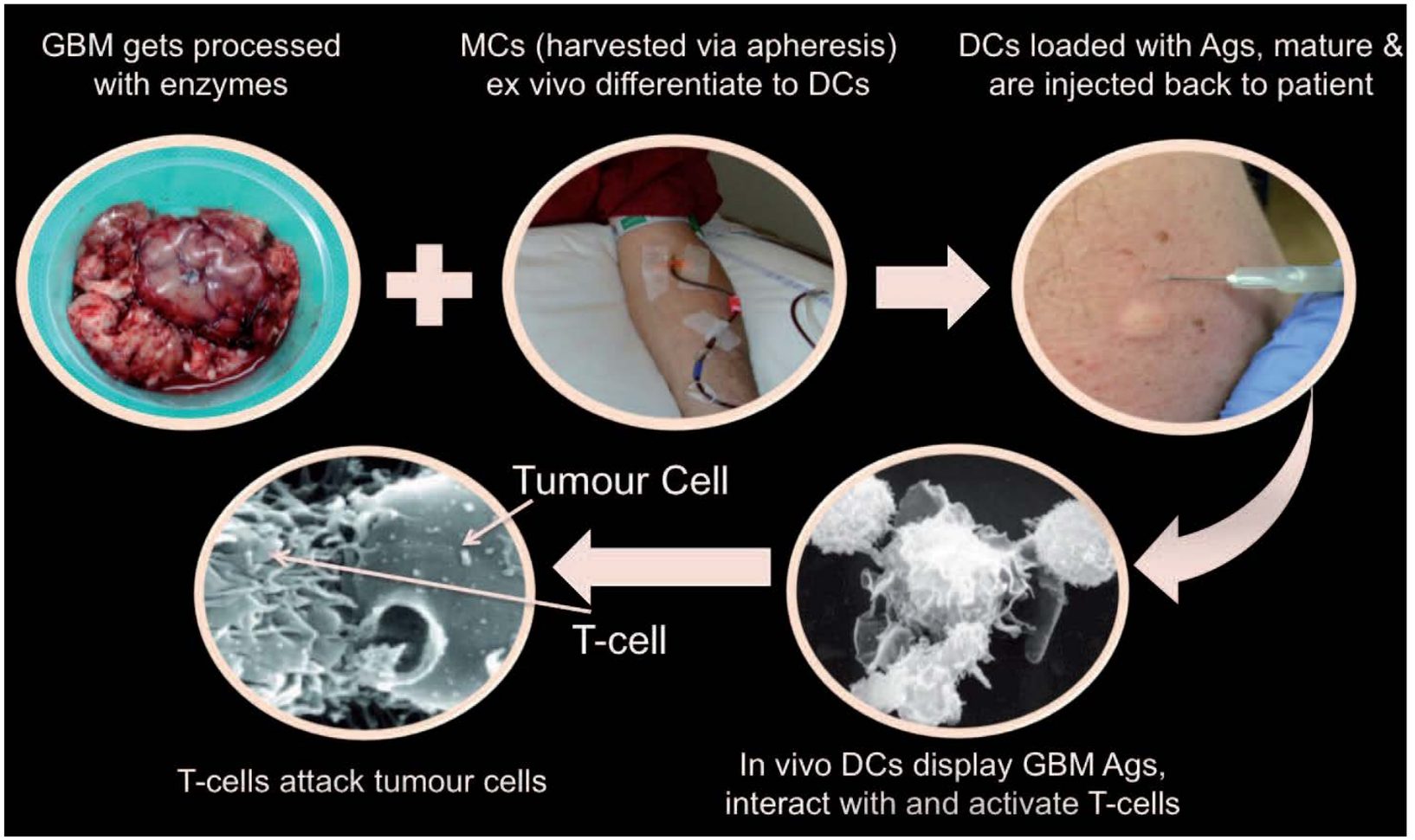




Future directions

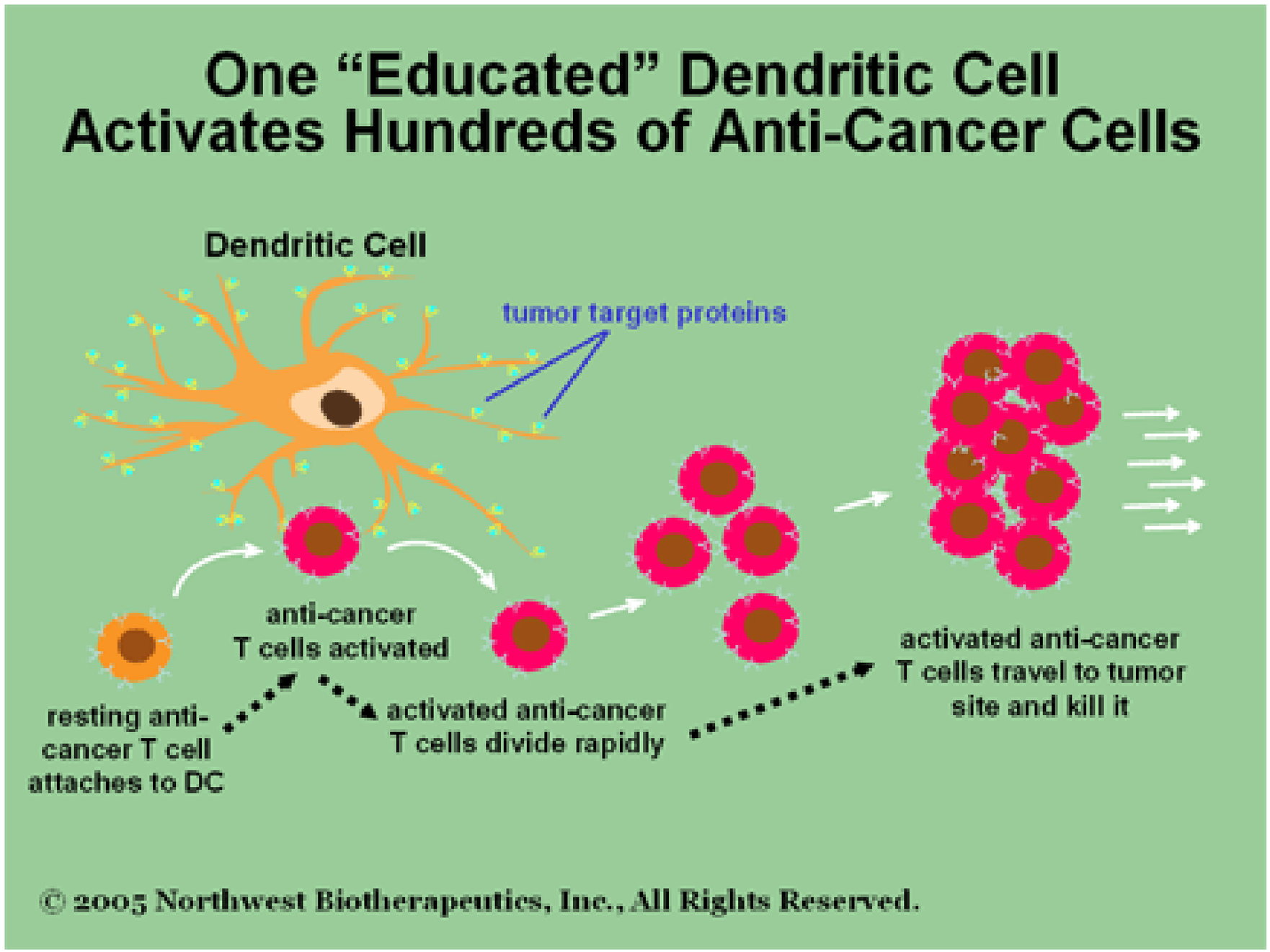


Dendritic-cell immunotherapy (DC-VAX)



Schematic illustration of the biology underlying DC-based vaccination against GBM. Key: Ags, Antigens; DCs, dendritic cells; GBM, glioblastoma multiforme; MCs, monocytes.

DC-Vax Production



British Journal of Neurosurgery, 2014; Early Online: 1–9

ISSN: 0268-8697 print / ISSN 1360-046X online
DOI: 10.3109/02688697.2014.994473

informa
healthcare

REVIEW ARTICLE

Active dendritic cell immunotherapy for glioblastoma: Current status and challenges

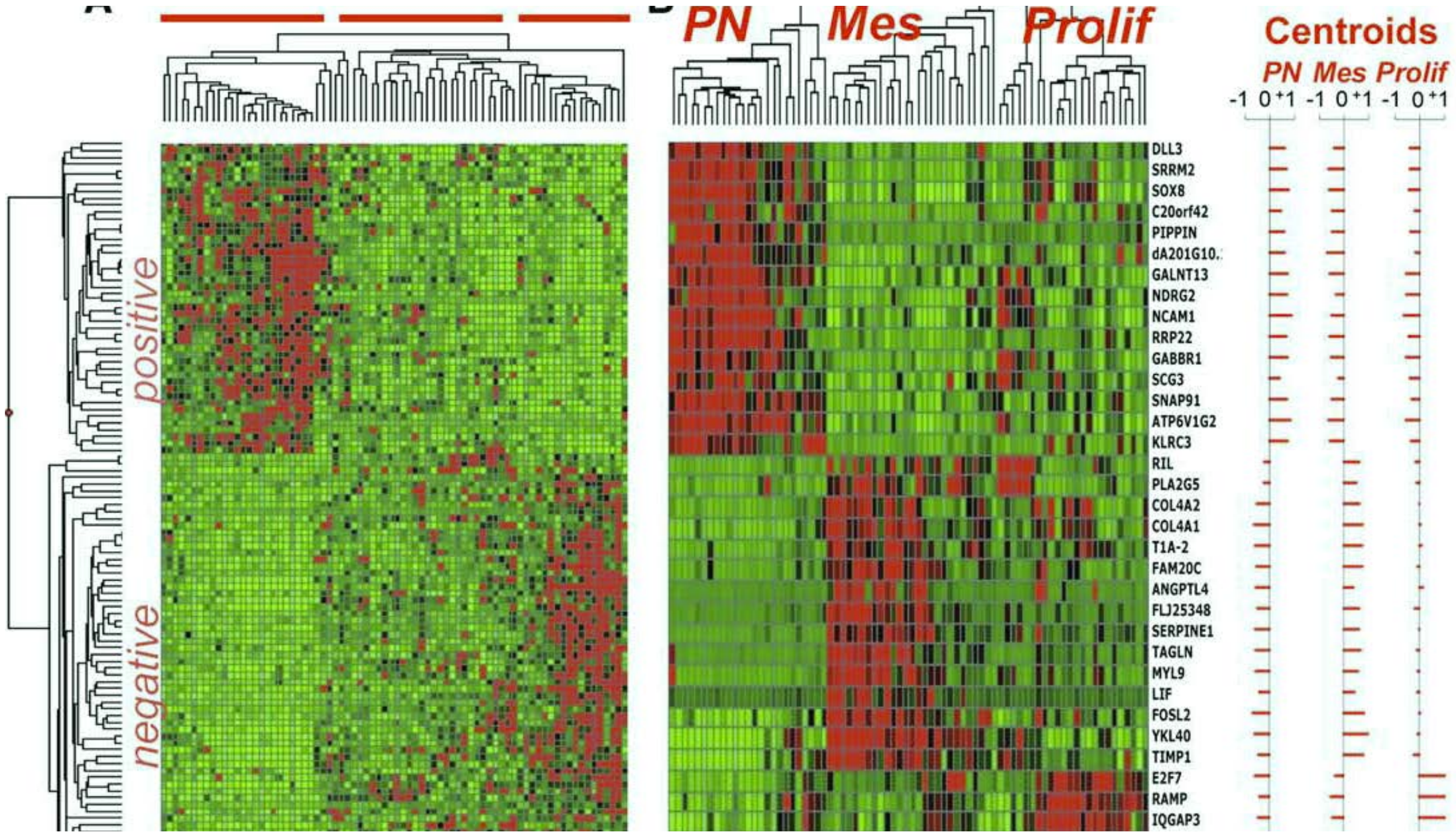
Stavros Polyzoidis[1], Juel Tuazon[2], Lucy Brazil[3], Ronald Beaney[3], Safa Taha Al-Sarraj[4], Lawrence Doey[4], Jamie Logan[5], Victoria Hurwitz[5], Jozef Jarosz[6], Ranjeev Bhangoo[1], Richard Gullan[1], Aleksandar Mijovic[7], Mark Richardson[8], Farzin Farzaneh[9] & Keyoumars Ashkan[1]

Median overall survival ranged between 16.0 and 38.4 months for ND-GBM and between 9.6 and 35.9 months for Rec-GBM.

Vaccine-related side effects were in general mild (grade I and II), with serious adverse events (grade III, IV and V) reported only rarely.

DC immunotherapy appears to have the potential to increase the overall survival in patients with HGG, with an acceptable side effect profile. The findings will require confirmation by the ongoing and future phase III trials.

Use the Genomics



King's

ESTRO School

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 25, 2015 VOL. 372 NO. 26

Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas

The Cancer Genome Atlas Research Network*

CONCLUSIONS

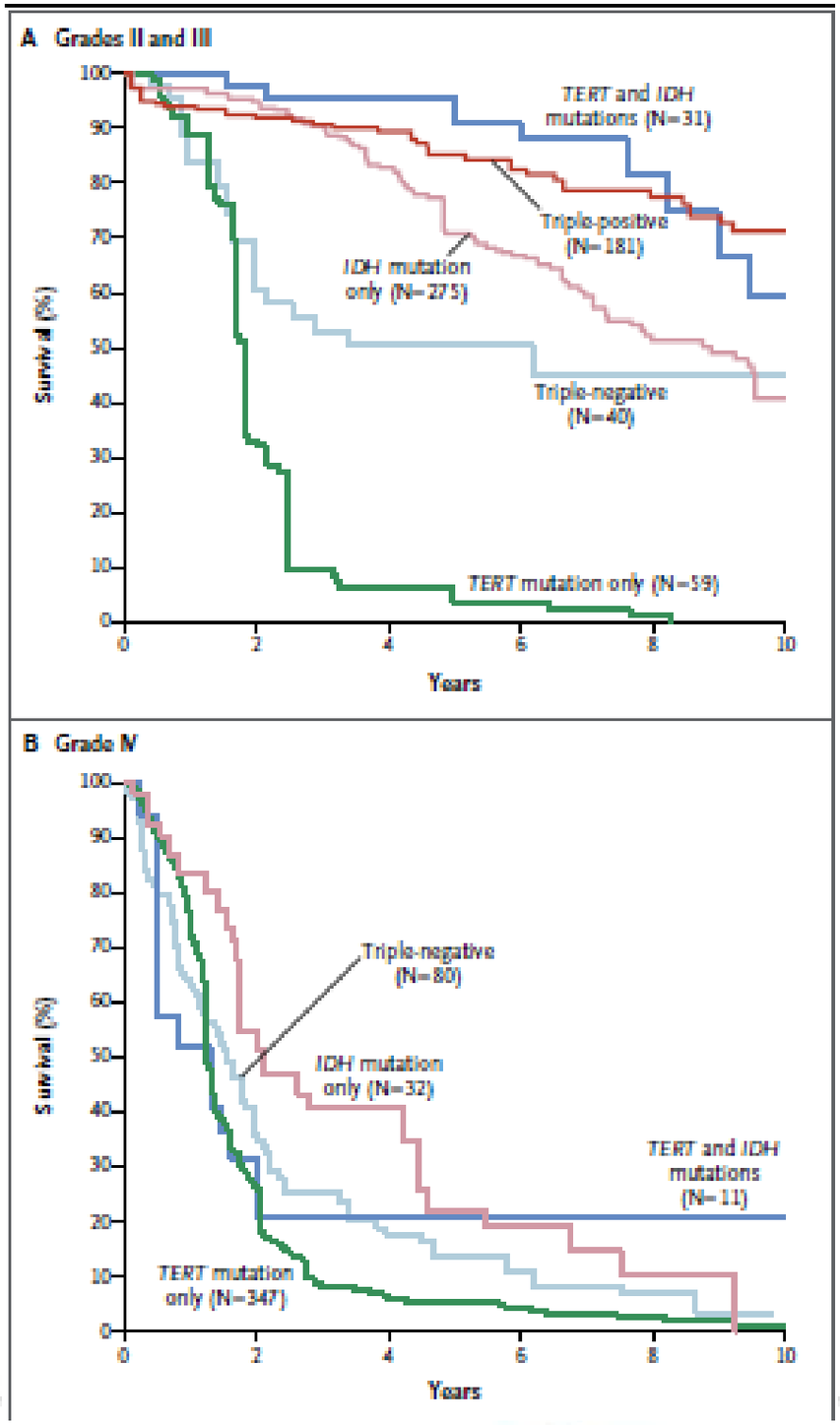
The integration of genomewide data from multiple platforms delineated three molecular classes of lower-grade gliomas that were more concordant with *IDH*, 1p/19q, and *TP53* status than with histologic class. Lower-grade gliomas with an *IDH* mutation either had 1p/19q codeletion or carried a *TP53* mutation. Most lower-grade gliomas without an *IDH* mutation were molecularly and clinically similar to glioblastoma. (Funded by the National Institutes of Health.)

ORIGINAL ARTICLE

Glioma Groups Based on 1p/19q, *IDH*, and *TERT* Promoter Mutations in Tumors

Gliomas were classified into five principal groups on the basis of three tumor markers. The groups had different ages at onset, survival, and associations with germline variants, which implies that they are characterized by distinct mechanisms of pathogenesis.

Eckel-Passow et al. NEJM, 2015

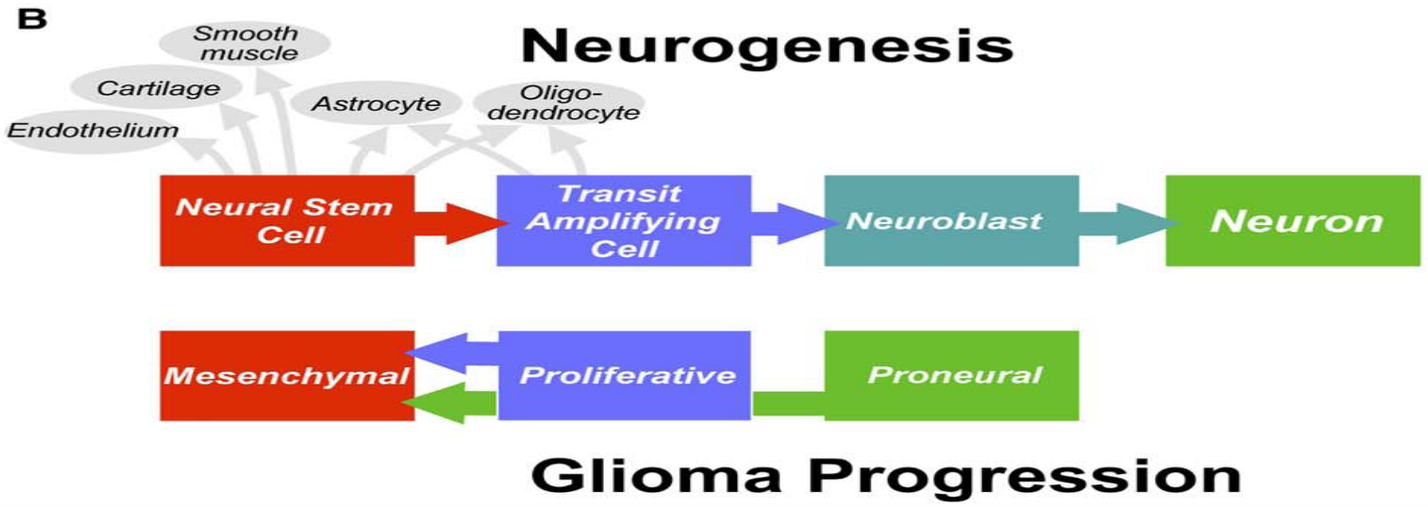


Genetics

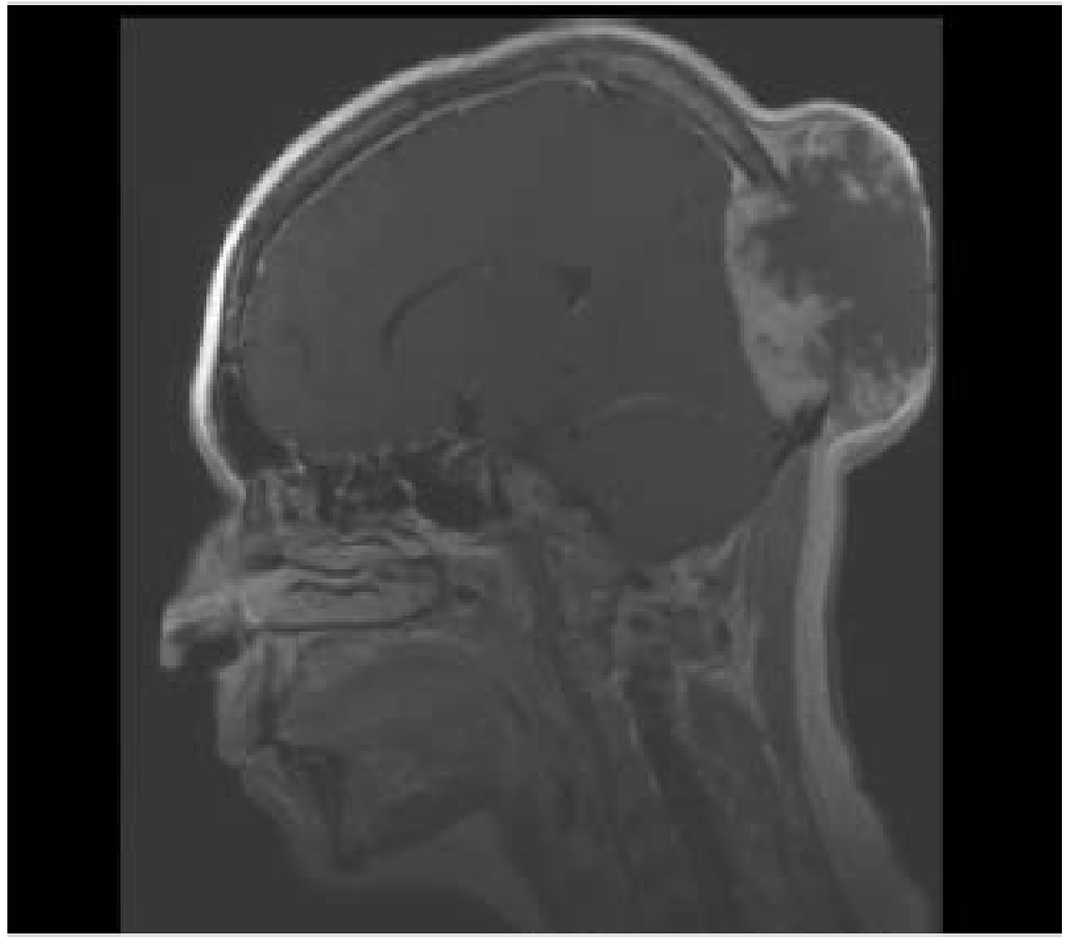
A

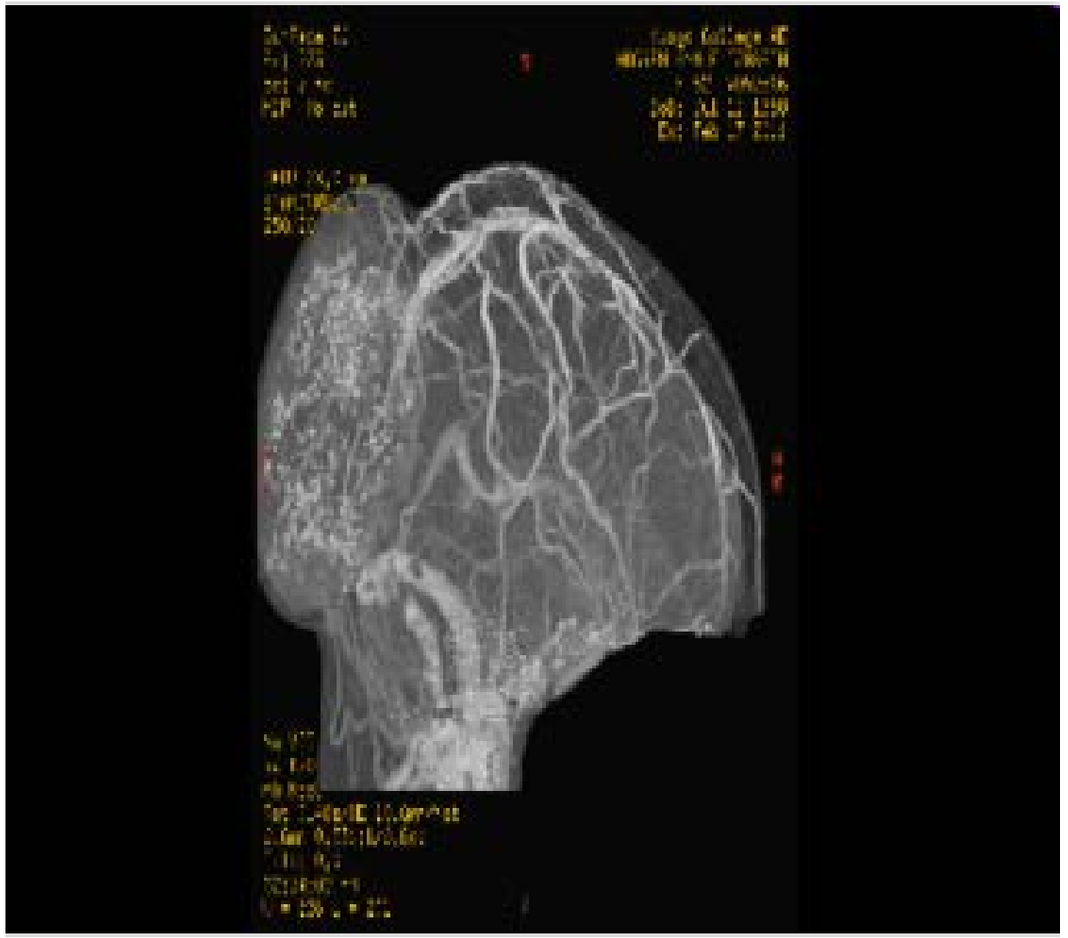
	Proneural	Proliferative	Mesenchymal
Histological grade	WHO grade III or WHO grade IV with or without necrosis	WHO grade IV with necrosis	WHO grade IV with necrosis
Cellular morphology	Astrocytic or Oligodendroglial	Astrocytic	Astrocytic
Evolution of signature	Arises in 1° tumor, may persist or convert to *Mes*	Arises in 1° tumor, may persist or convert to *Mes*	Arises in 1° tumor or by conversion from other subtype
Patient age	Younger (~40 yrs.)	Older (~50 yrs.)	Older (~50 yrs.)
Prognosis	Longer survival	Short survival	Short survival
Histological Markers	Olig2, DLL3, BCAN	PCNA, TOP2A	CHI3L1/YKL40, CD44, VEGF
Tissue similarities	Adult and Fetal Brain	HSC, lymphoblast	Bone, cartilage, smooth musc, endothelium, dendritic cells
Biological process	Neurogenesis	Proliferation	Angiogenesis
Analogous forebrain cell	Neuroblast	Neural Stem Cell and/or Transit Amplifying Cell	Neural Stem Cell
Chromosome gain/loss	None	Gain of 7 & Loss of 10 or 10q	Gain of 7 & Loss of 10
PTEN locus	PTEN intact	PTEN loss	PTEN loss
EGFR locus	EGFR normal	EGFR amplified or normal	EGFR amplified or normal
Signaling	Notch activation	Akt activation	Akt activation

B



Planning ahead - Radiosurgery / Reconstructive Surgery

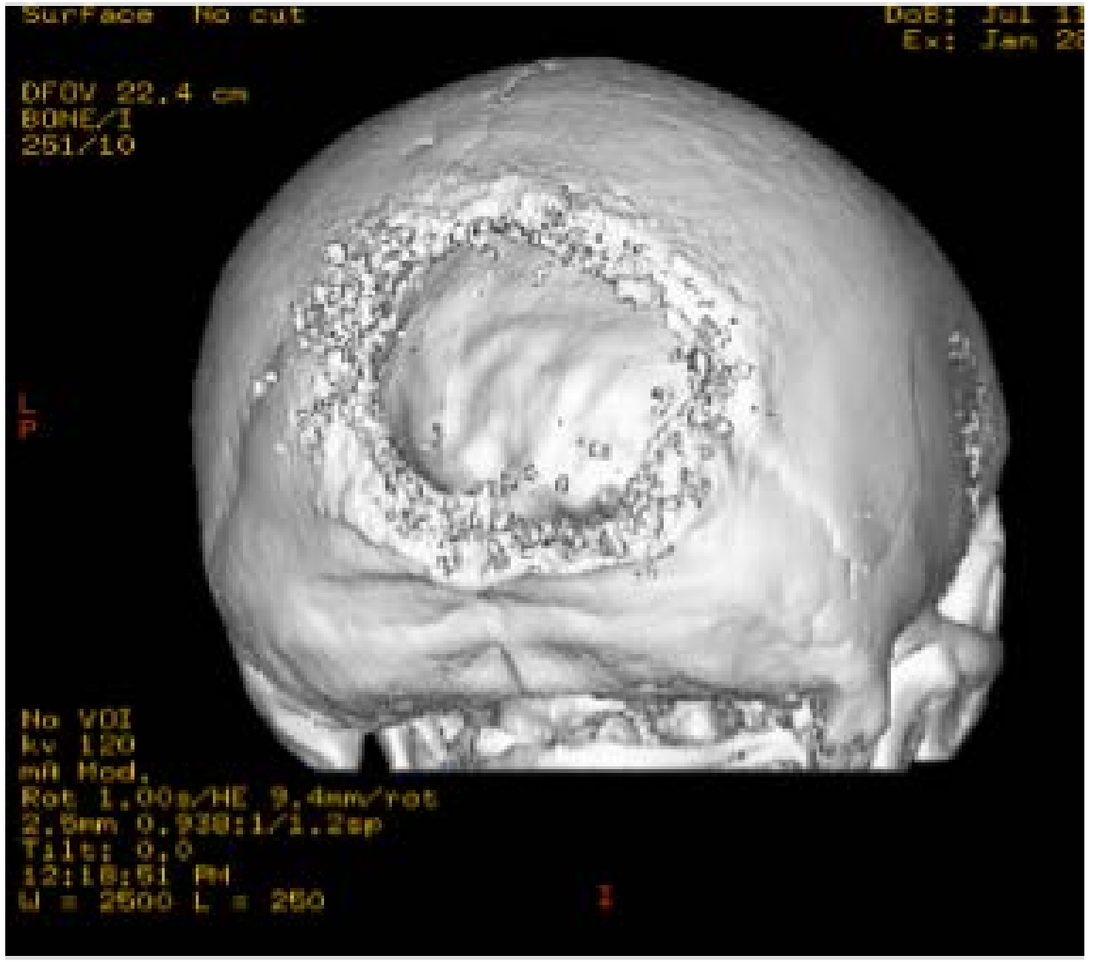




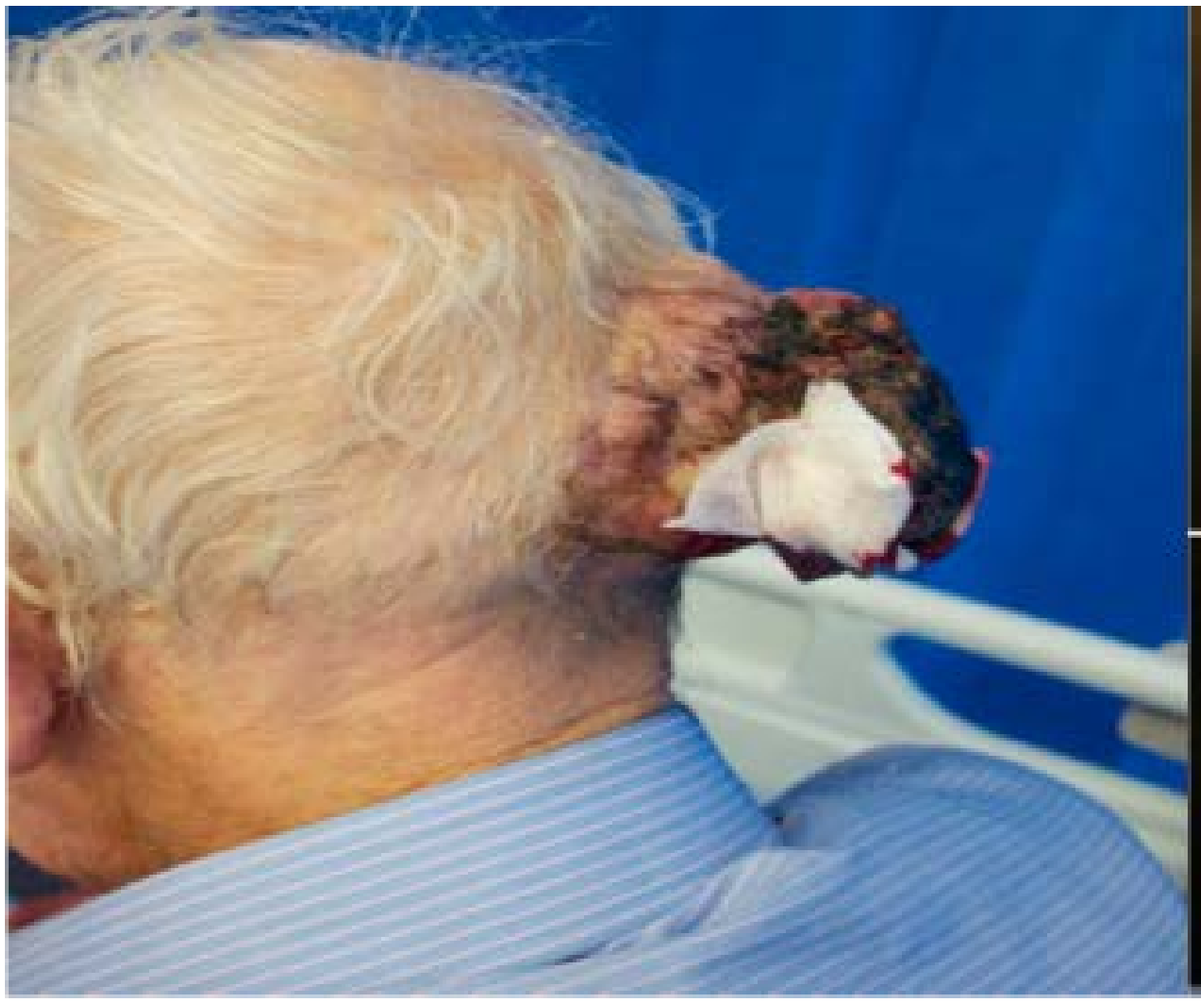
Planning ahead - Radiosurgery / Reconstructive Surgery

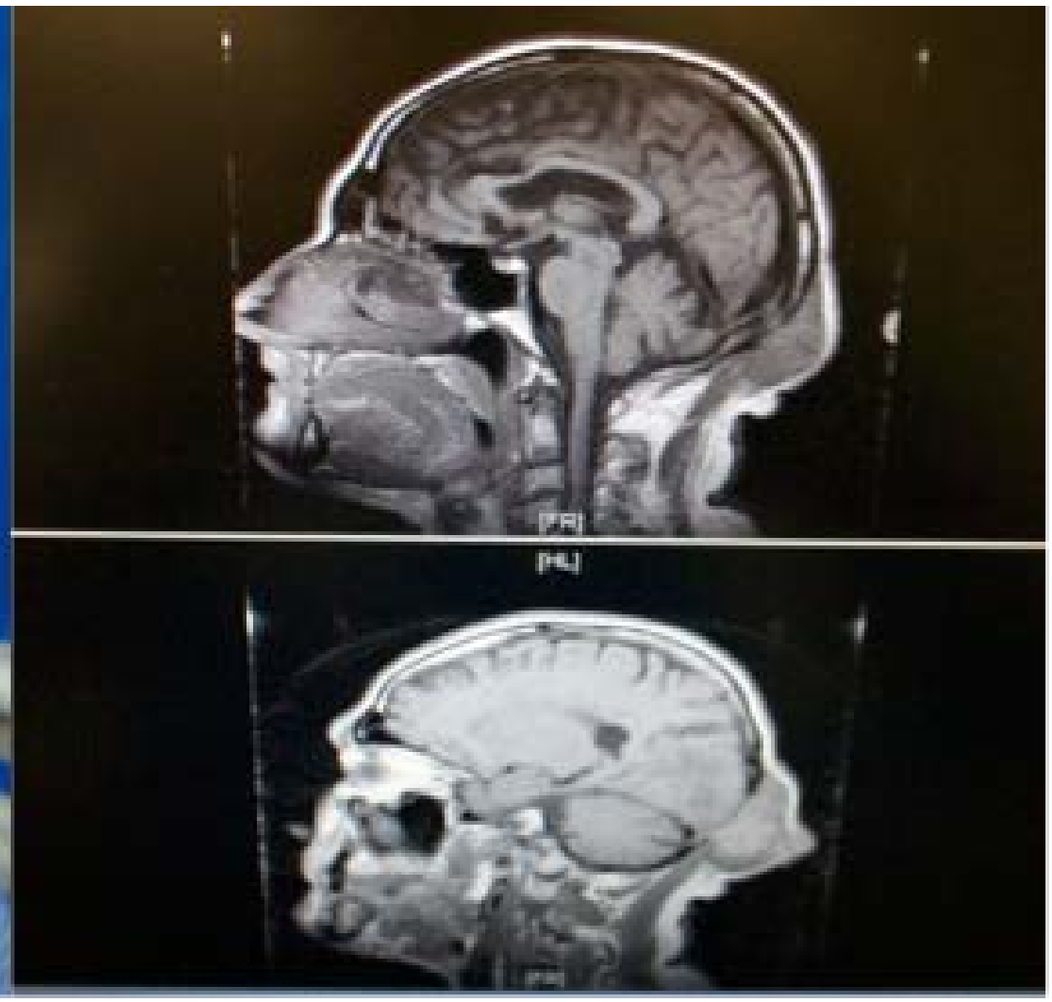
- Underwent planned Craniectomy with optimal debulking and Simultaneous Cranioplasty

- Followed Cyberknife© radiosurgery to intra-sinus remnant

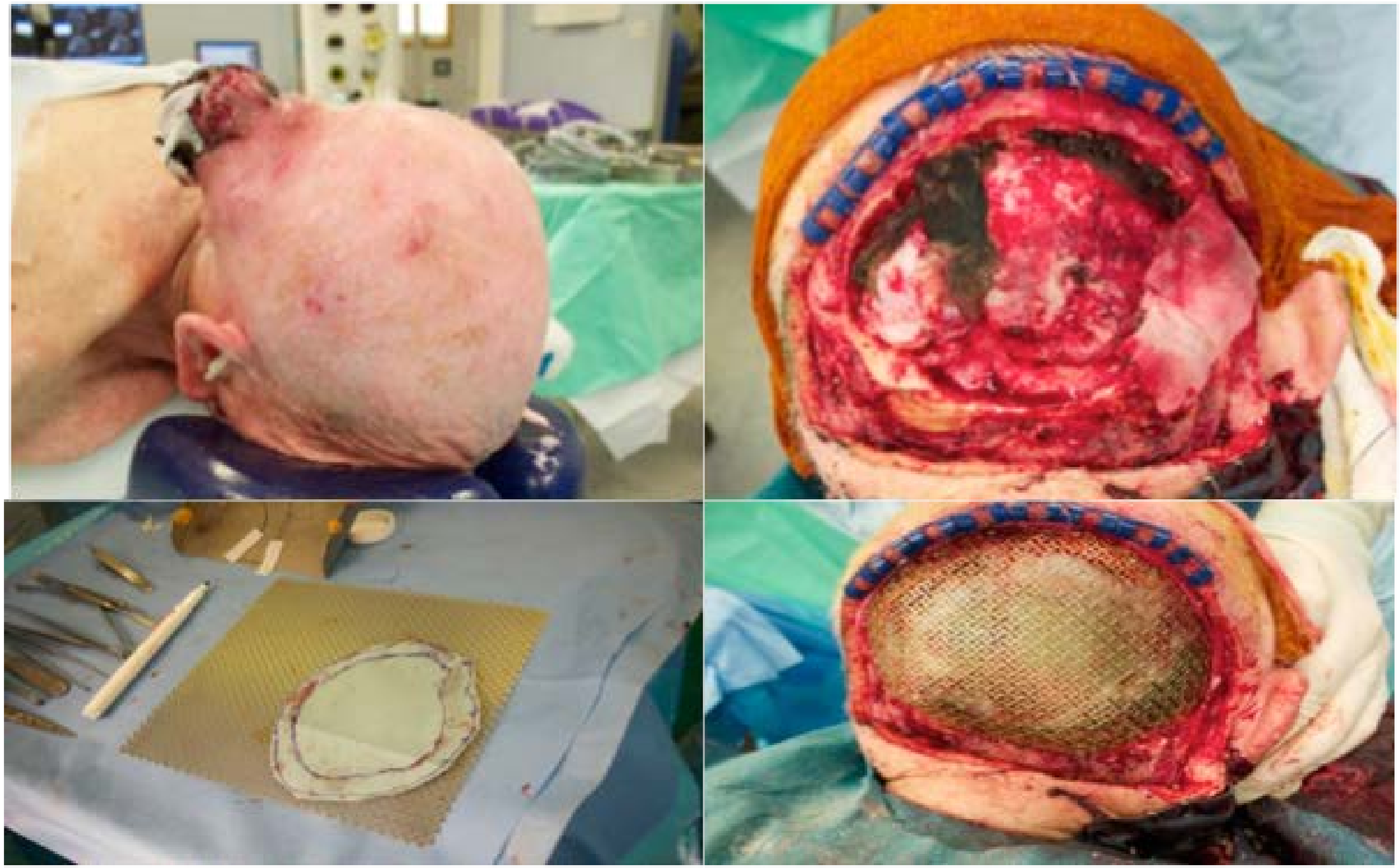


Immediate Mesh Cranioplasty

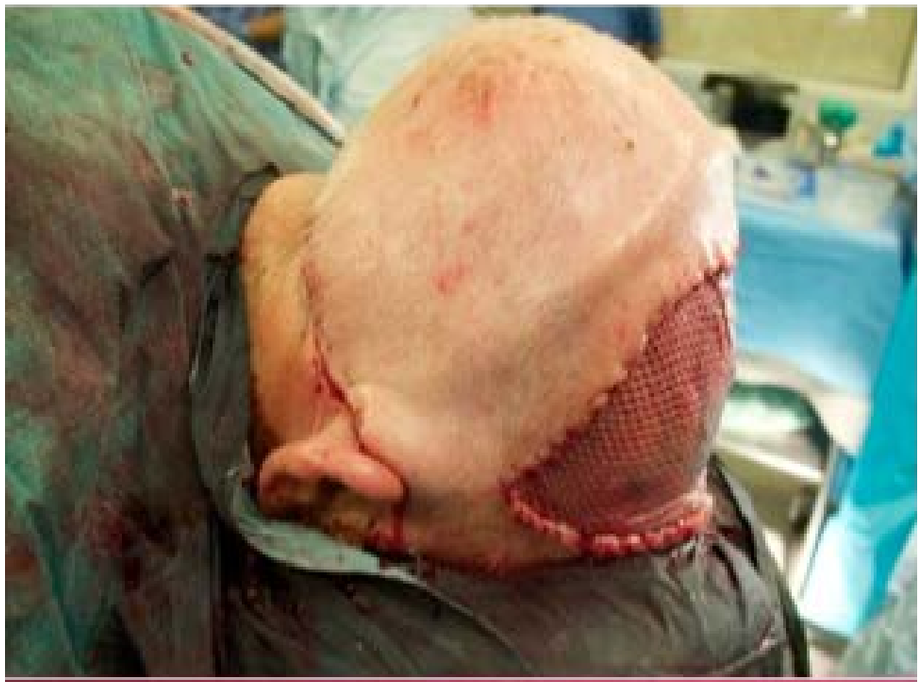


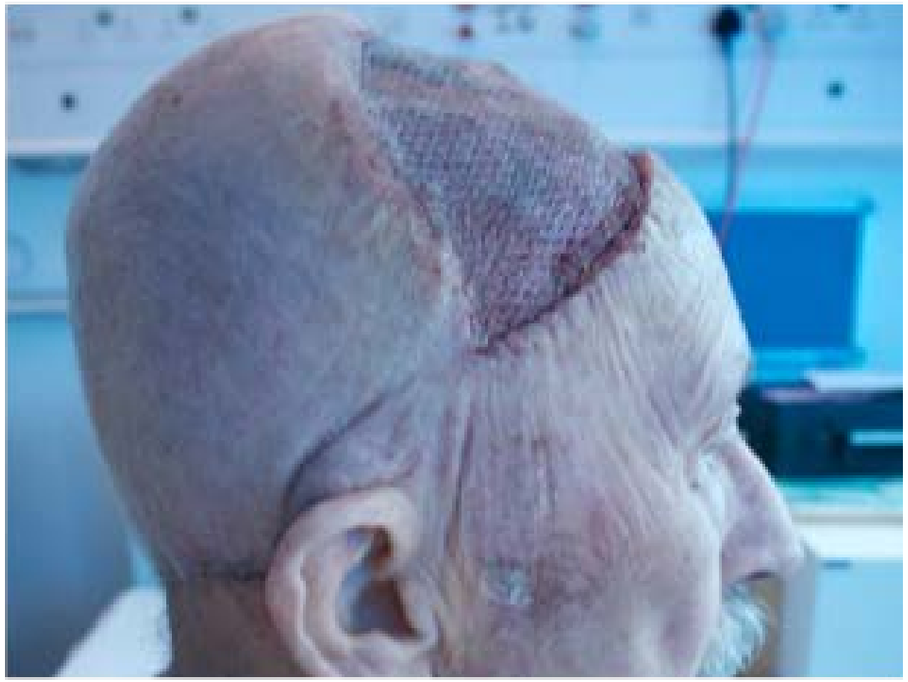


Planning ahead - Radiosurgery / Reconstructive Surgery



Planning ahead - Radiosurgery / Reconstructive Surgery



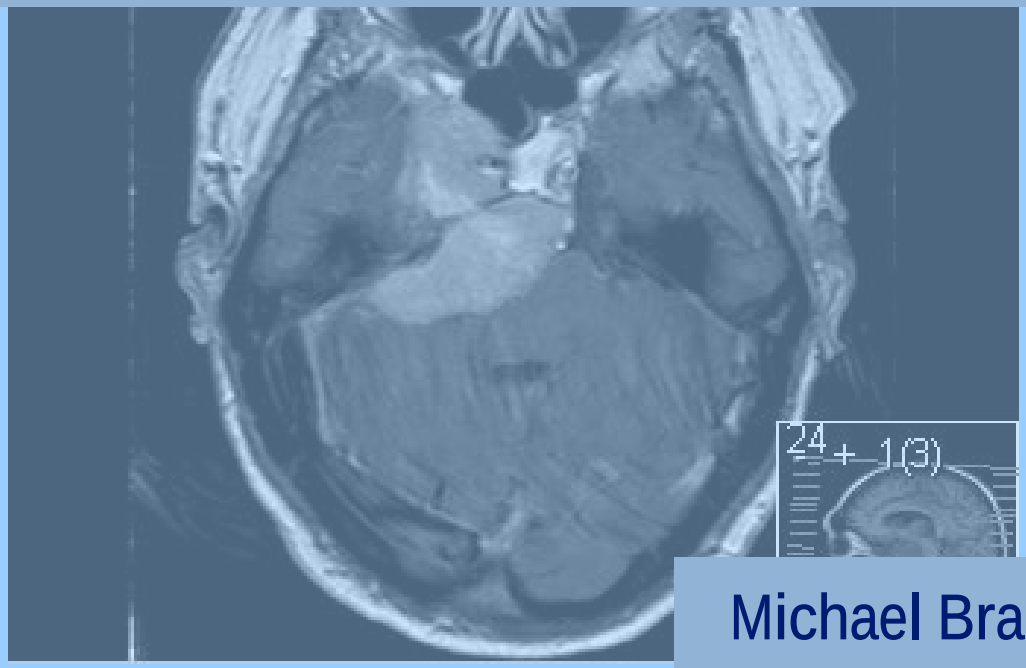


Take-home Message

- Neurosurgical intervention remains the first step in effective glioma management.
- With intraoperative mapping techniques, aggressive microsurgical resection can be safely pursued even when tumours occupy essential functional pathways.
- With the development of tumour-specific fluorophores, such as 5- aminolevulinic acid, real-time microscopic visualization of tumour infiltration can be surgically targeted prior to adjuvant therapy.

Cranial radiotherapy

preparing the patient for treatment

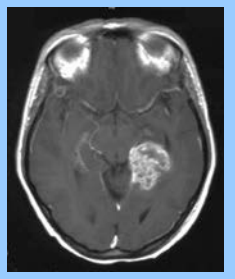


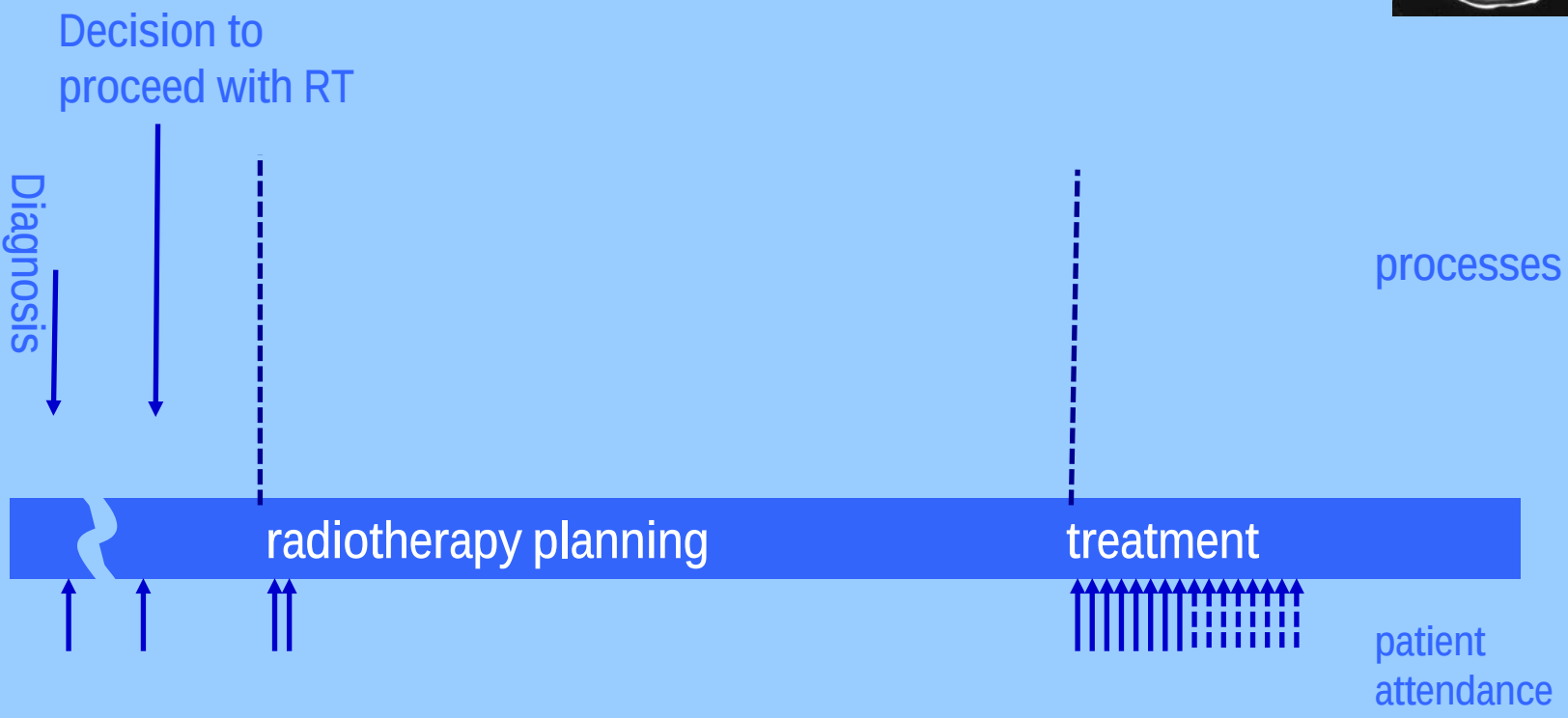
Michael Brada

ESTRO BT course

Torino October 2015

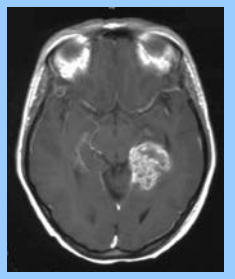
Deconstructing cranial radiotherapy

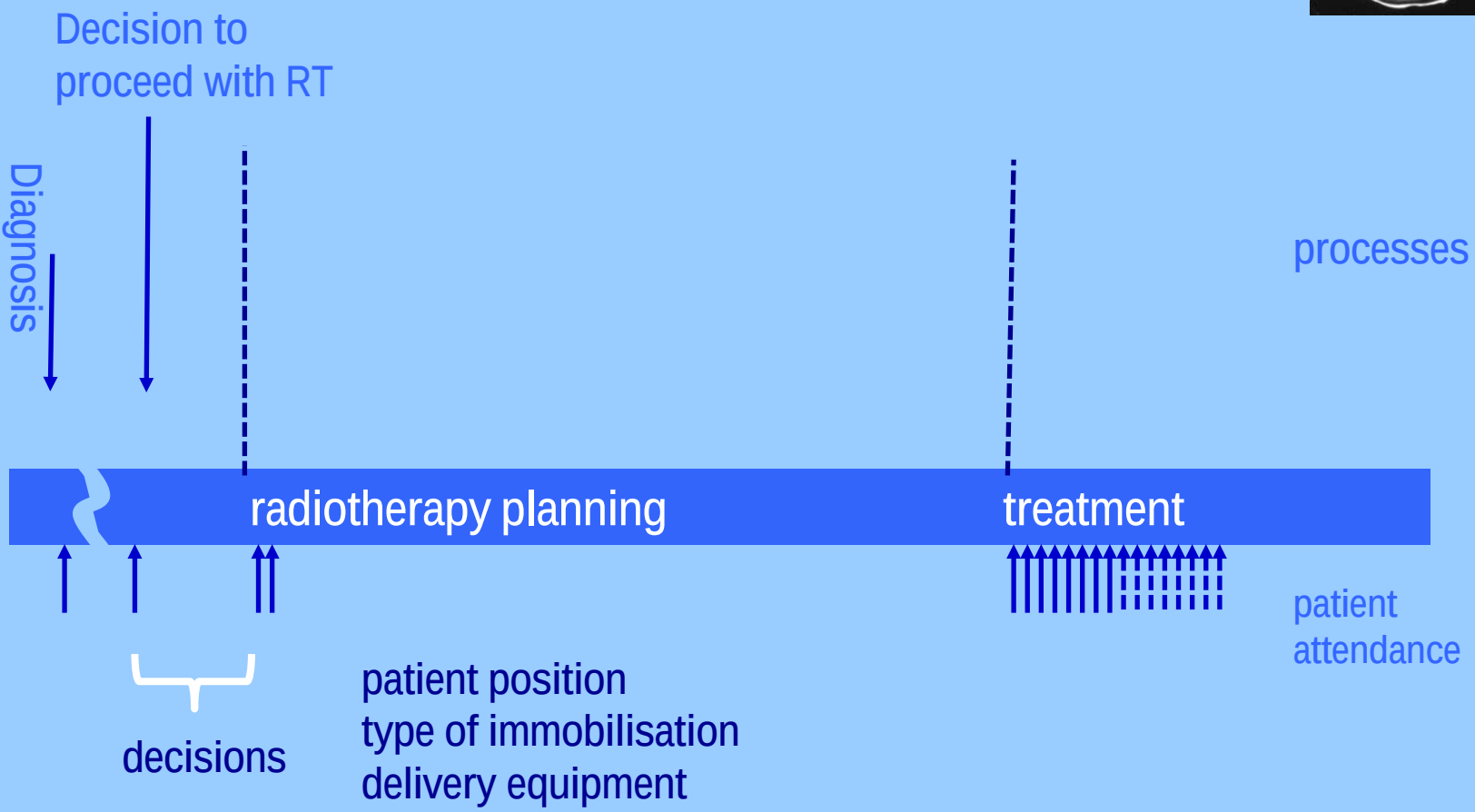




Preparation for radiotherapy

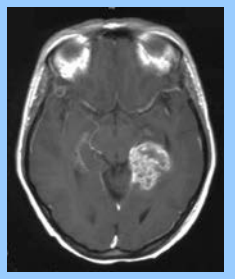
Deconstructing cranial radiotherapy

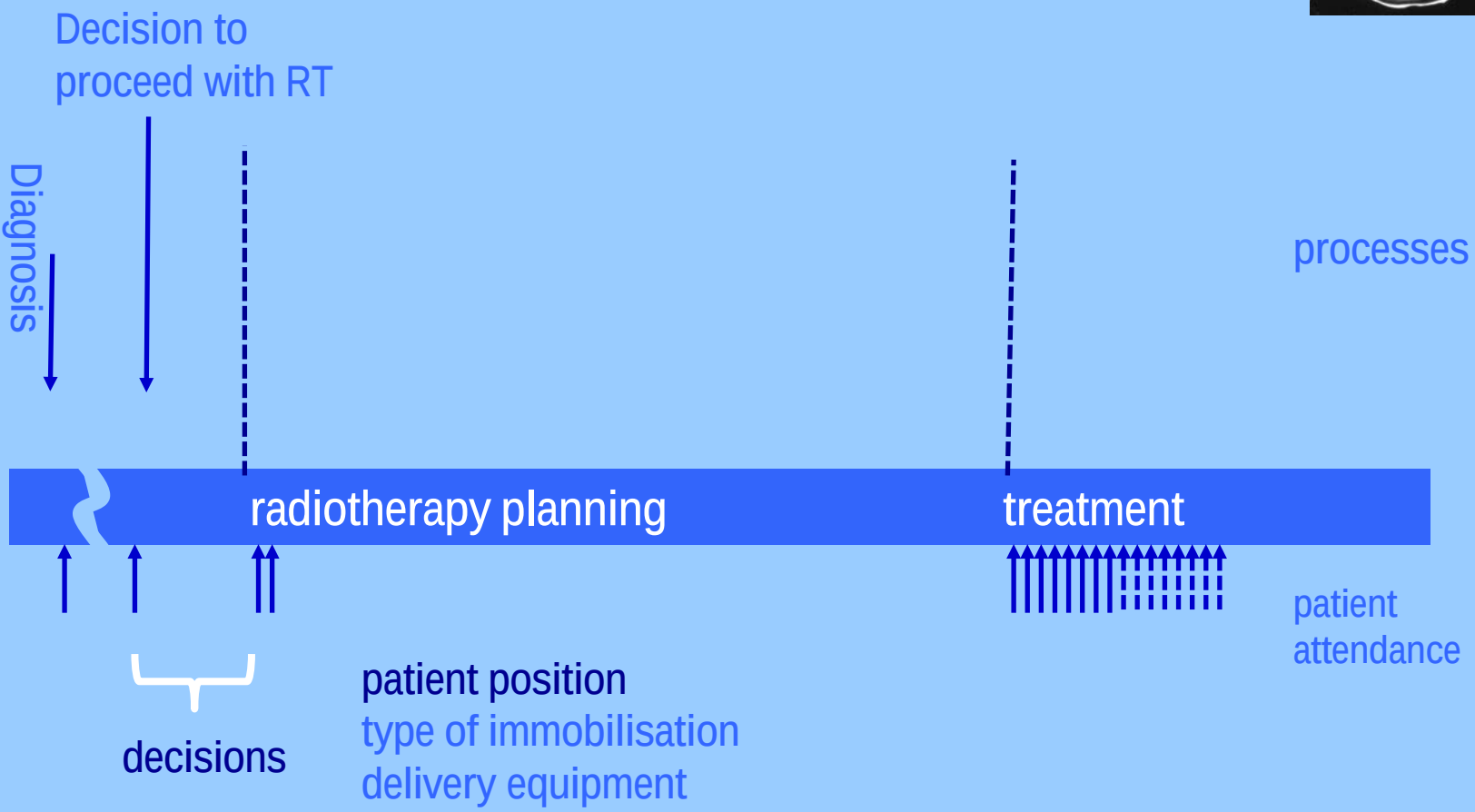




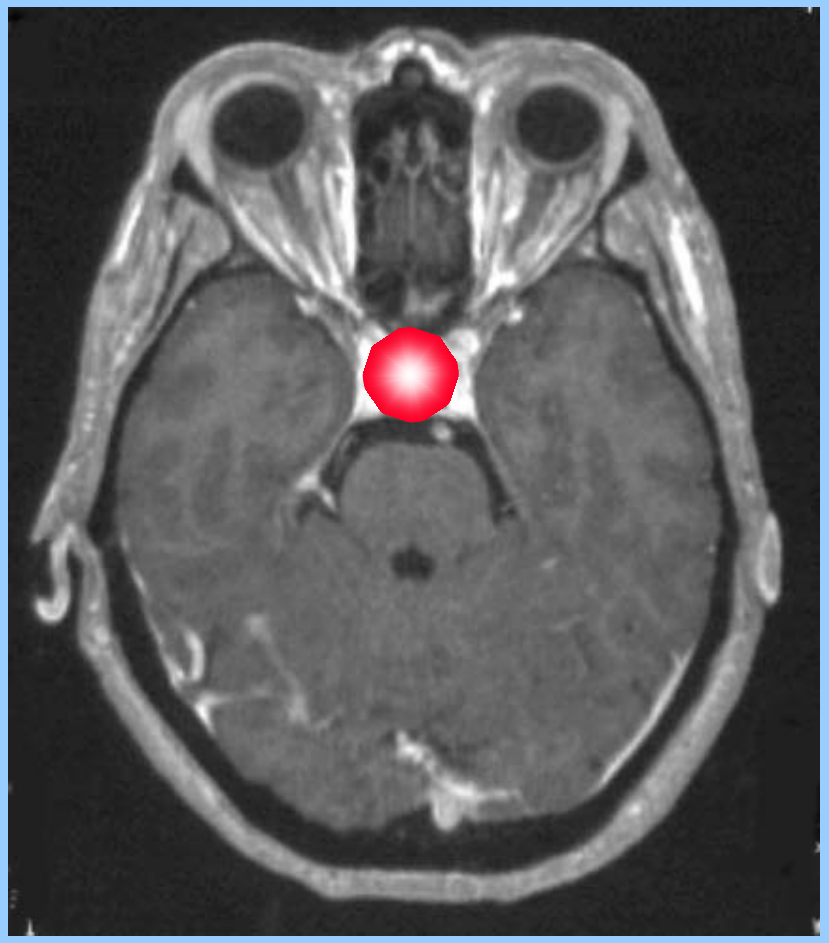
Preparation for radiotherapy

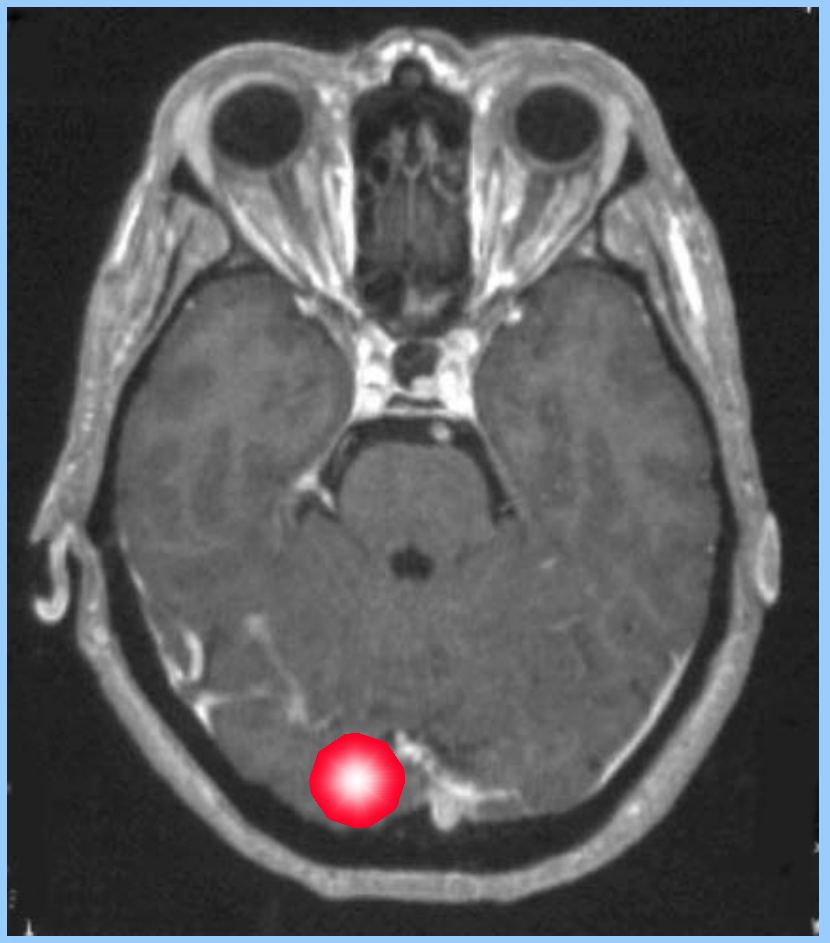
Deconstructing cranial radiotherapy





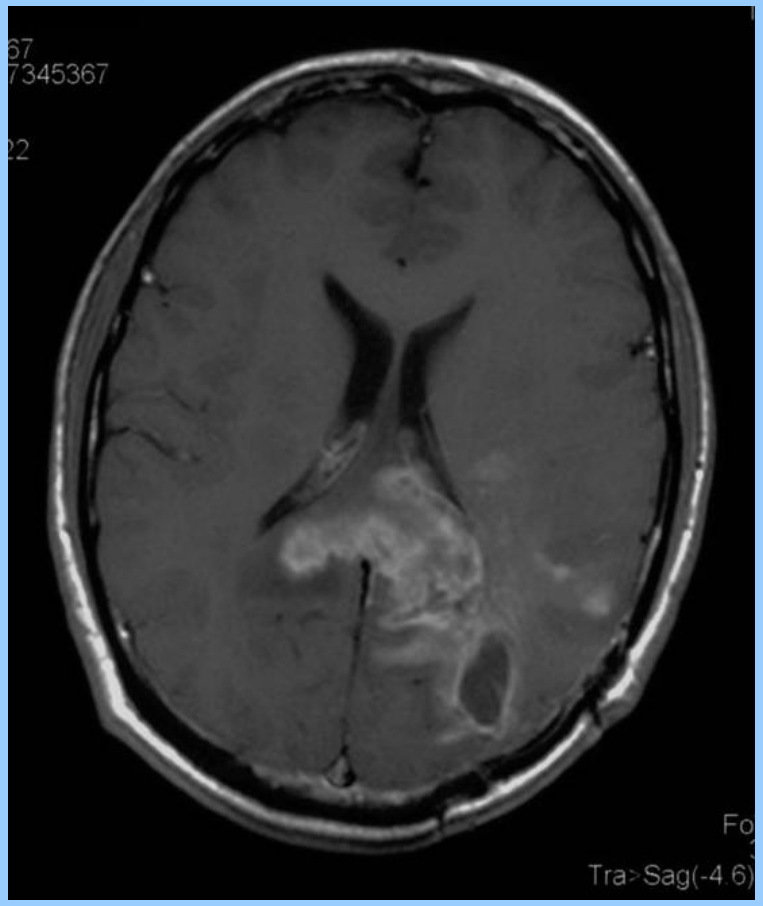
Preparation for radiotherapy

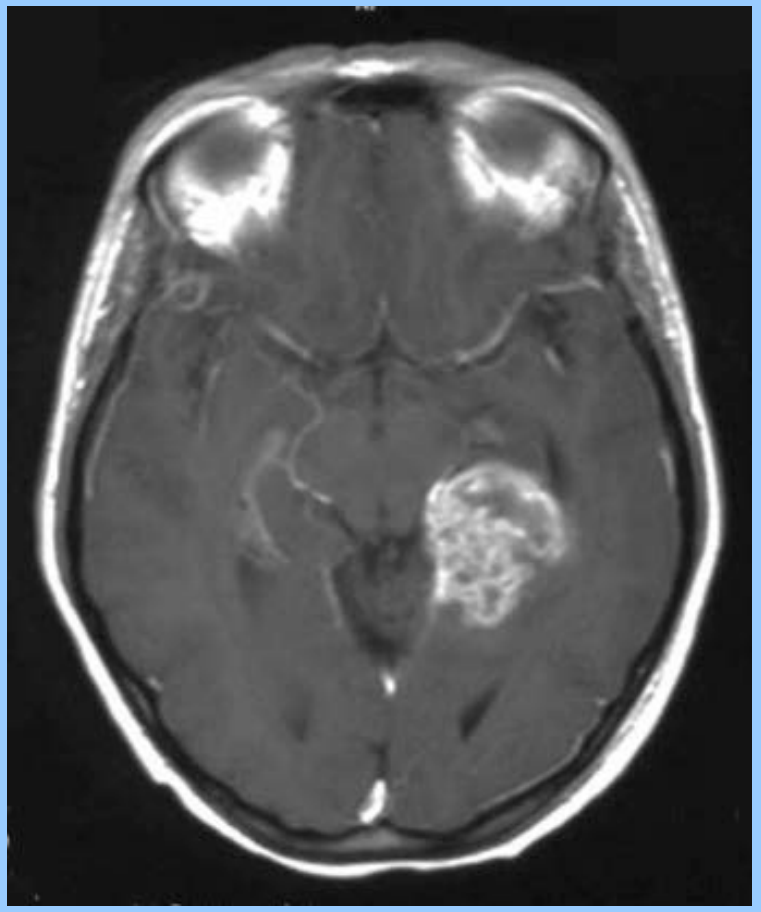




supine/prone/lateral
neck - straight/flexed/extended
knees

Patient position

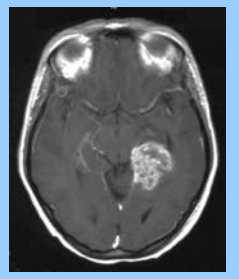


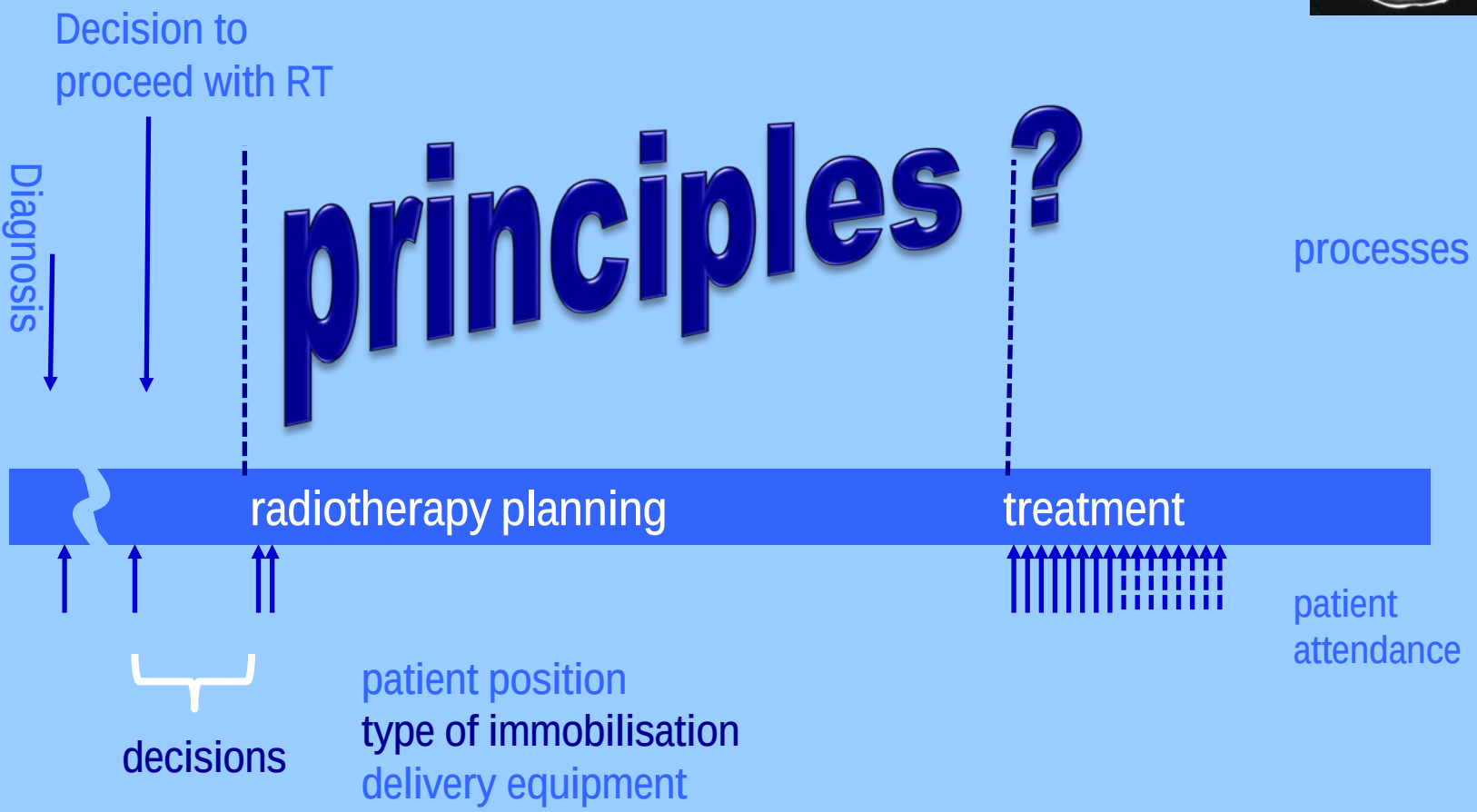


supine/prone/lateral
neck - straight/flexed/extended
knees

Patient position

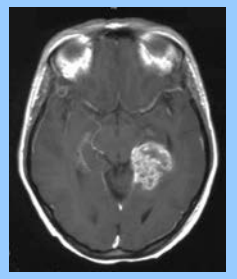
Deconstructing cranial radiotherapy





Preparation for radiotherapy

Deconstructing cranial radiotherapy



Decision to proceed with RT

Diagnosis

immobilisation systems

- shell
  - posicast
  - thermoplastic
- shell +
  - mouthbite
  - neck & shoulders
- frame
  - relocatable
  - fixed

processes

radiotherapy planning

treatment

patient attendance

decisions

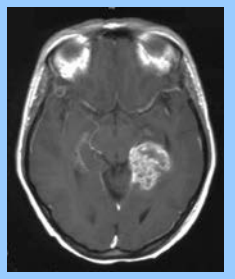
ition

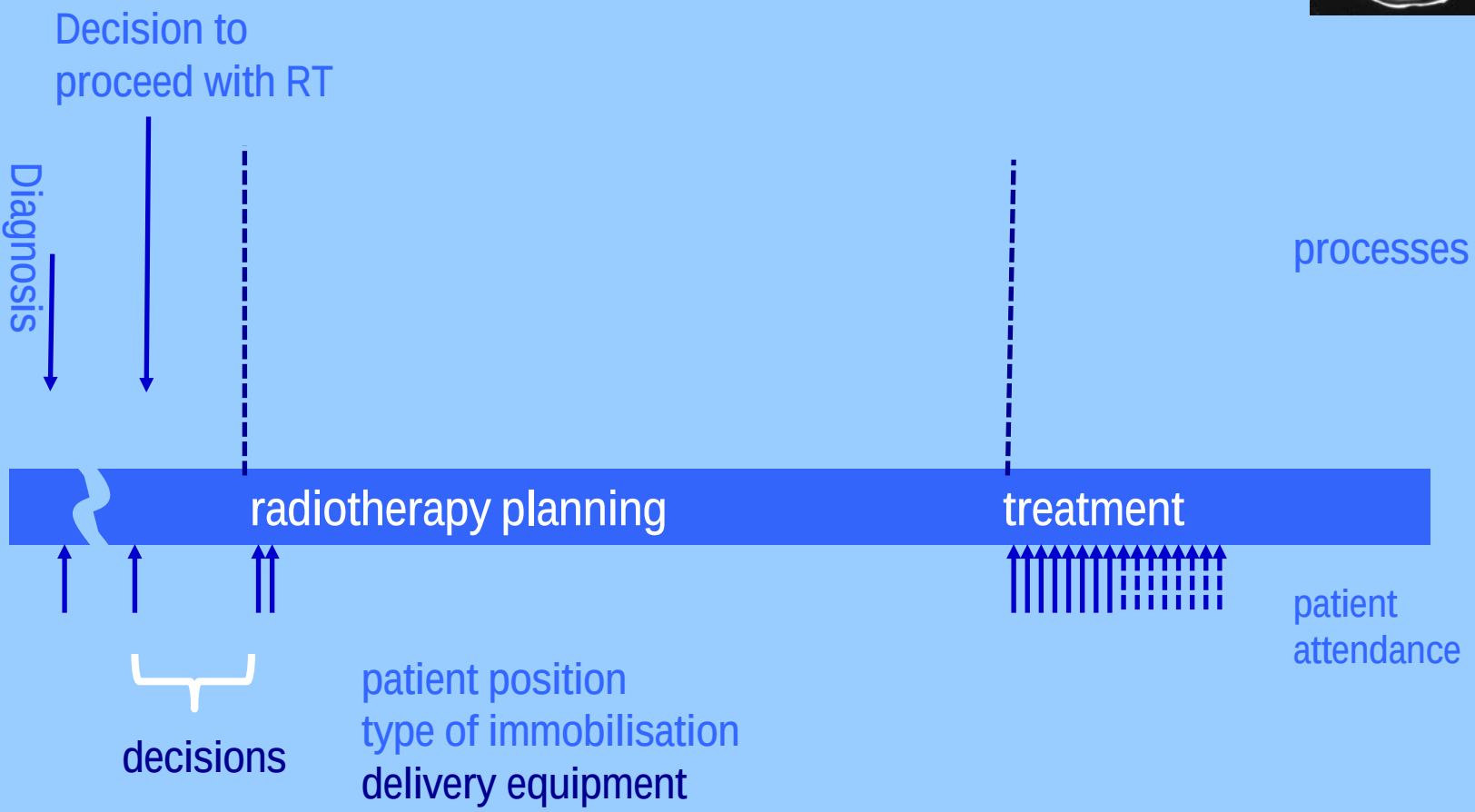
type of immobilisation

delivery equipment

Preparation for radiotherapy

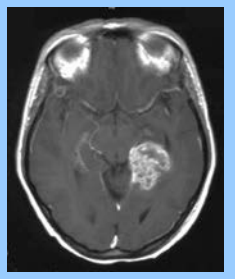
Deconstructing cranial radiotherapy

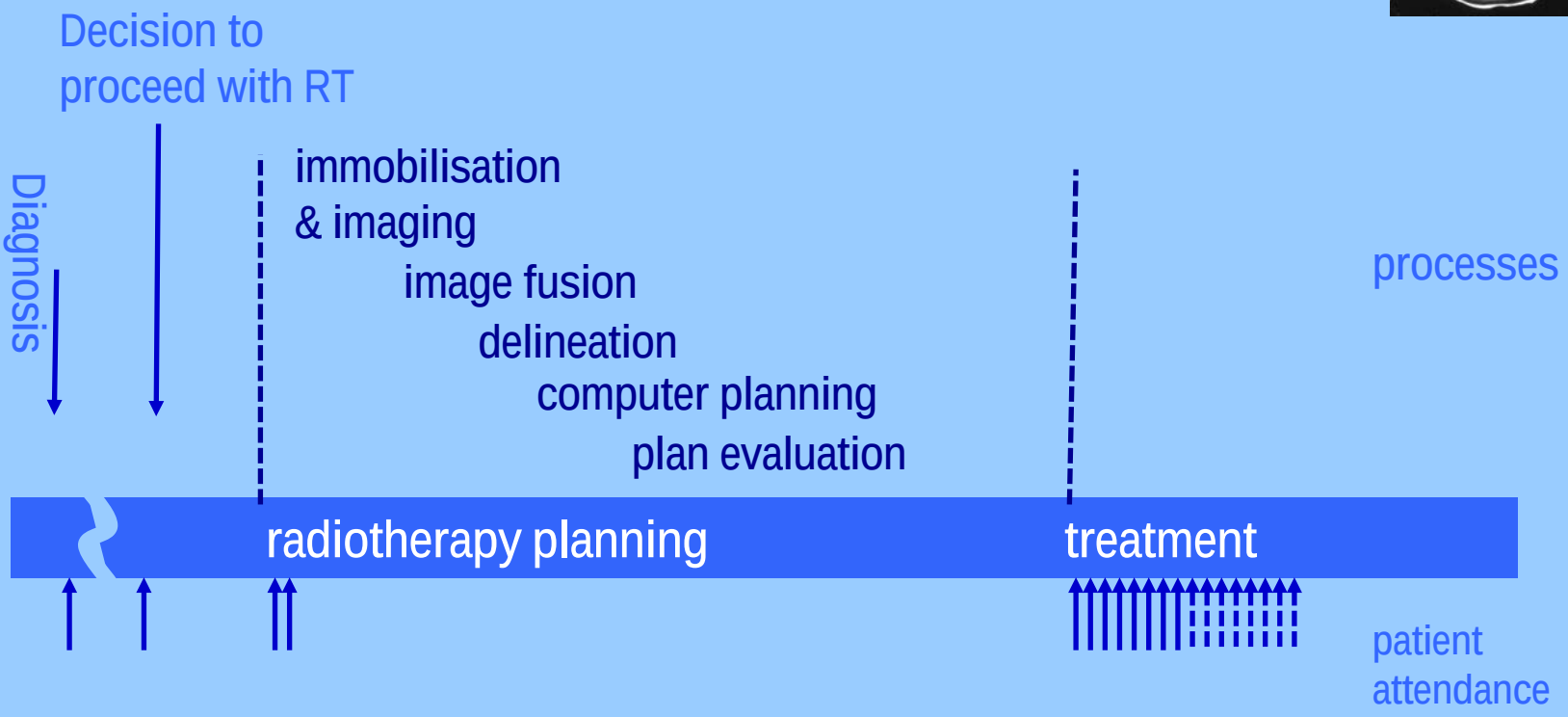




Preparation for radiotherapy

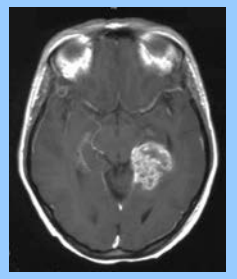
Deconstructing cranial radiotherapy

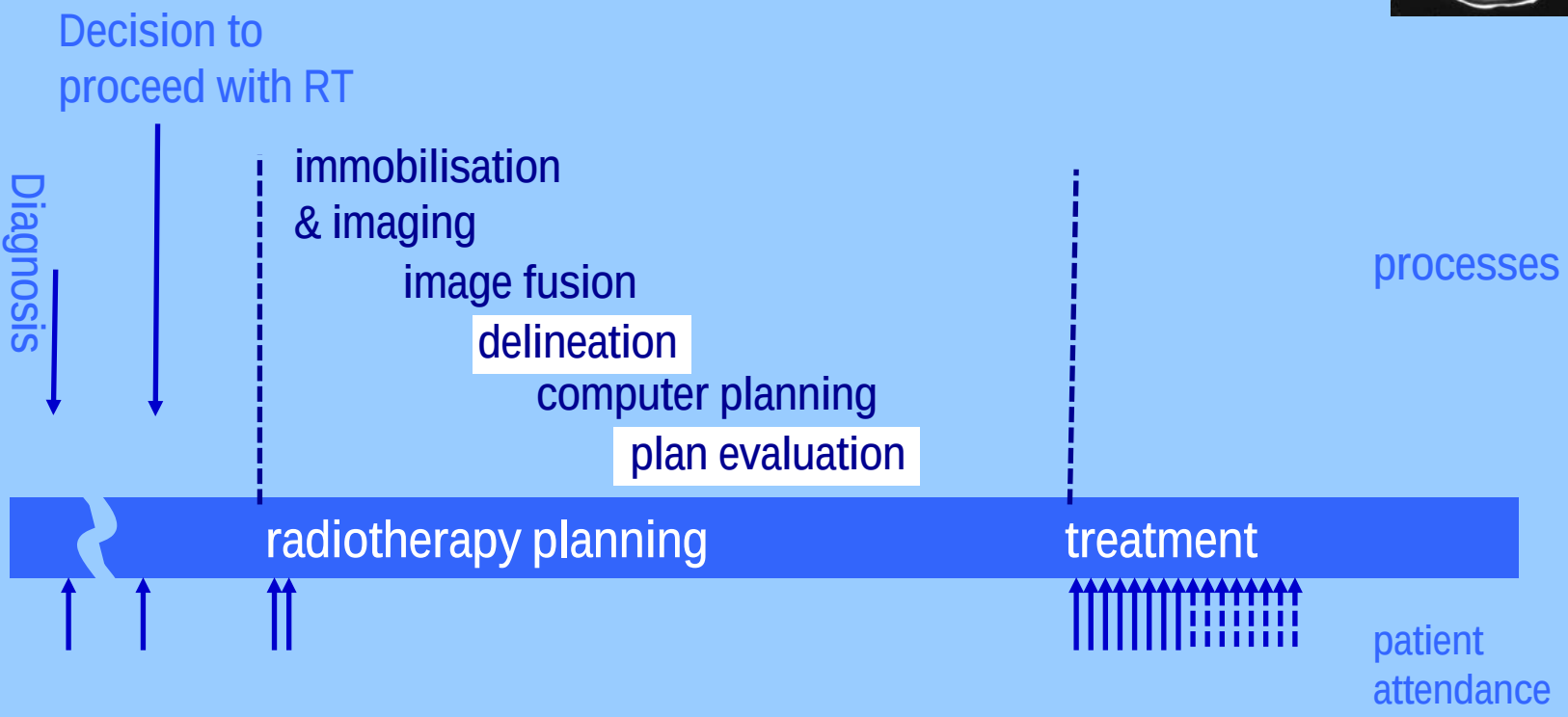




Preparation for radiotherapy

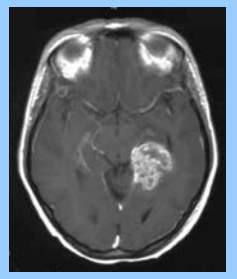
Deconstructing cranial radiotherapy

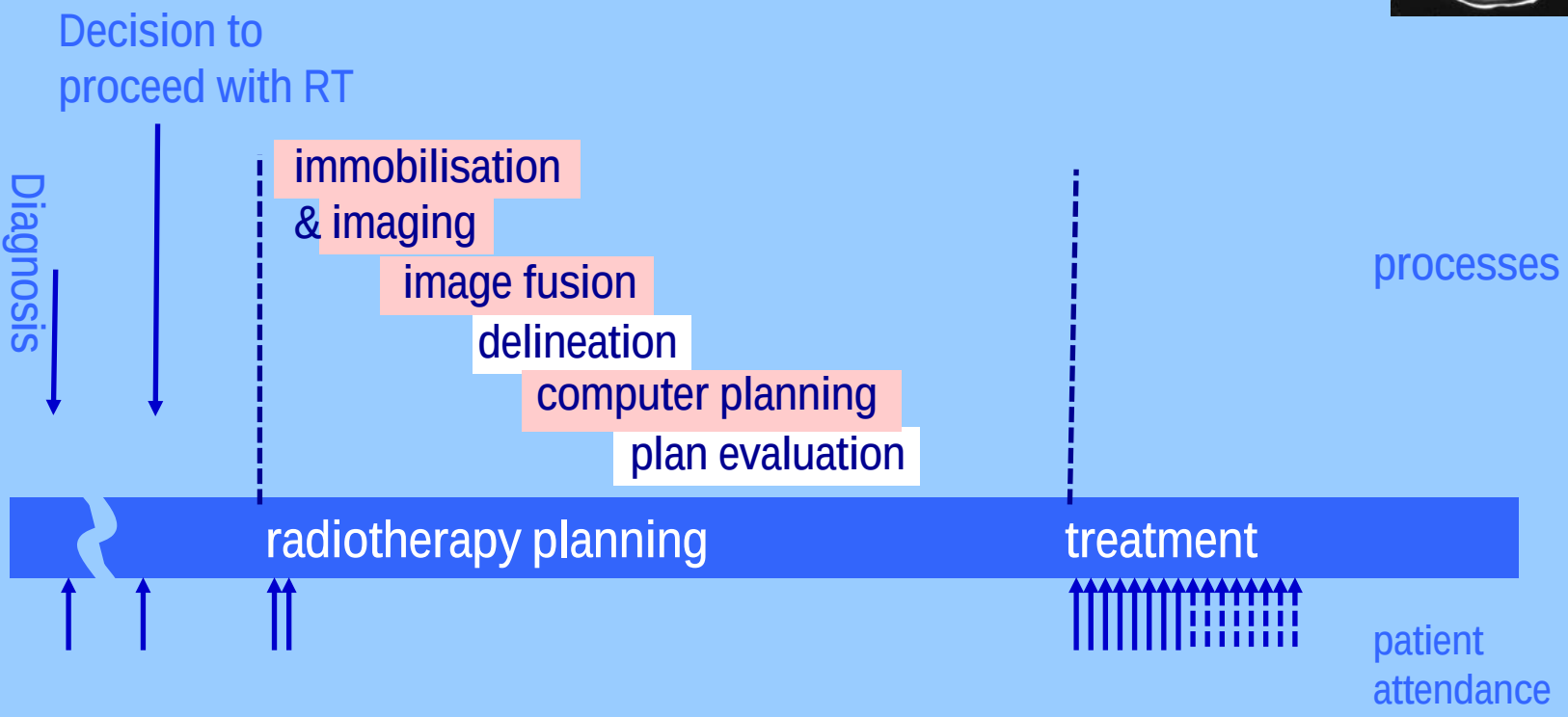




Preparation for radiotherapy

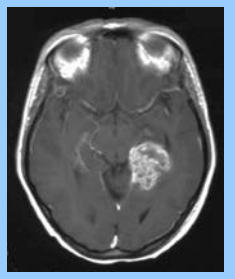
Deconstructing cranial radiotherapy





Preparation for radiotherapy

Deconstructing cranial radiotherapy



Decision to proceed with RT

Diagnosis

immobilisation systems

- shell
  - posicast
  - thermoplastic
- shell + mouthbite
  - neck & shoulders
- frame
  - relocatable
  - fixed

immobilisation & imaging

image fusion

computer planning

plan evaluation

radiotherapy planning

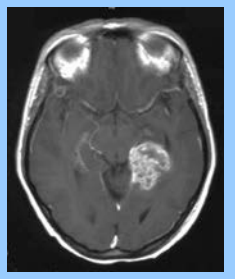
treatment

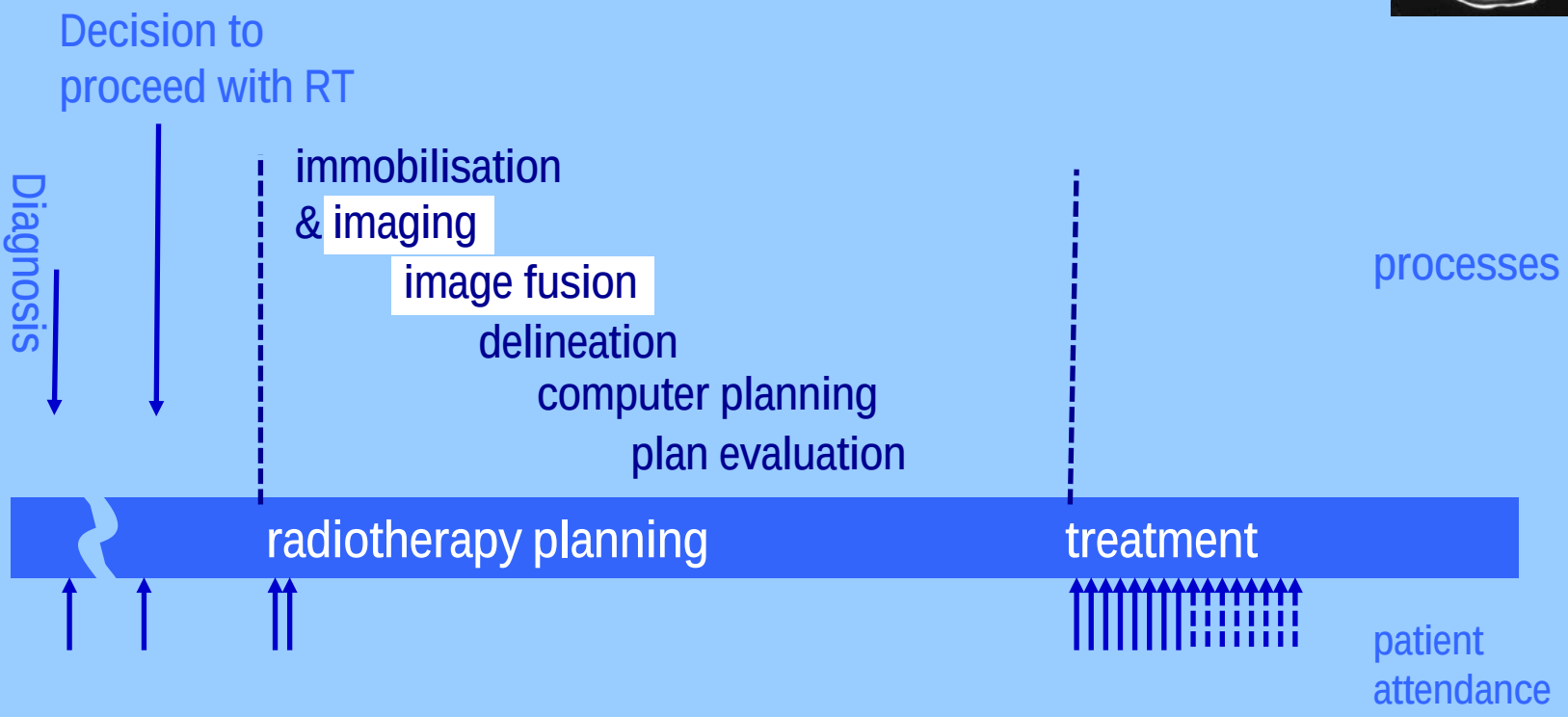
processes

patient attendance

Preparation for radiotherapy

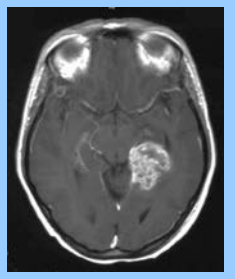
Deconstructing cranial radiotherapy





Preparation for radiotherapy

Deconstructing cranial radiotherapy



Decision to
proceed with RT

Diagnosis

delineation

- target
  - GTV
  - CTV

image fusion

delineation

computer planning

plan evaluation

processes

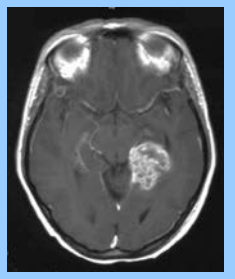
radiotherapy planning

treatment

patient
attendance

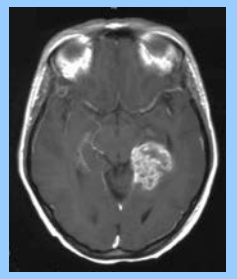
Preparation for radiotherapy

Deconstructing cranial radiotherapy



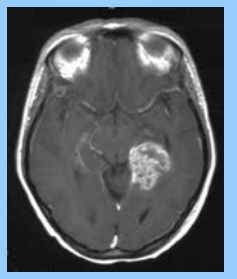
Preparation for radiotherapy

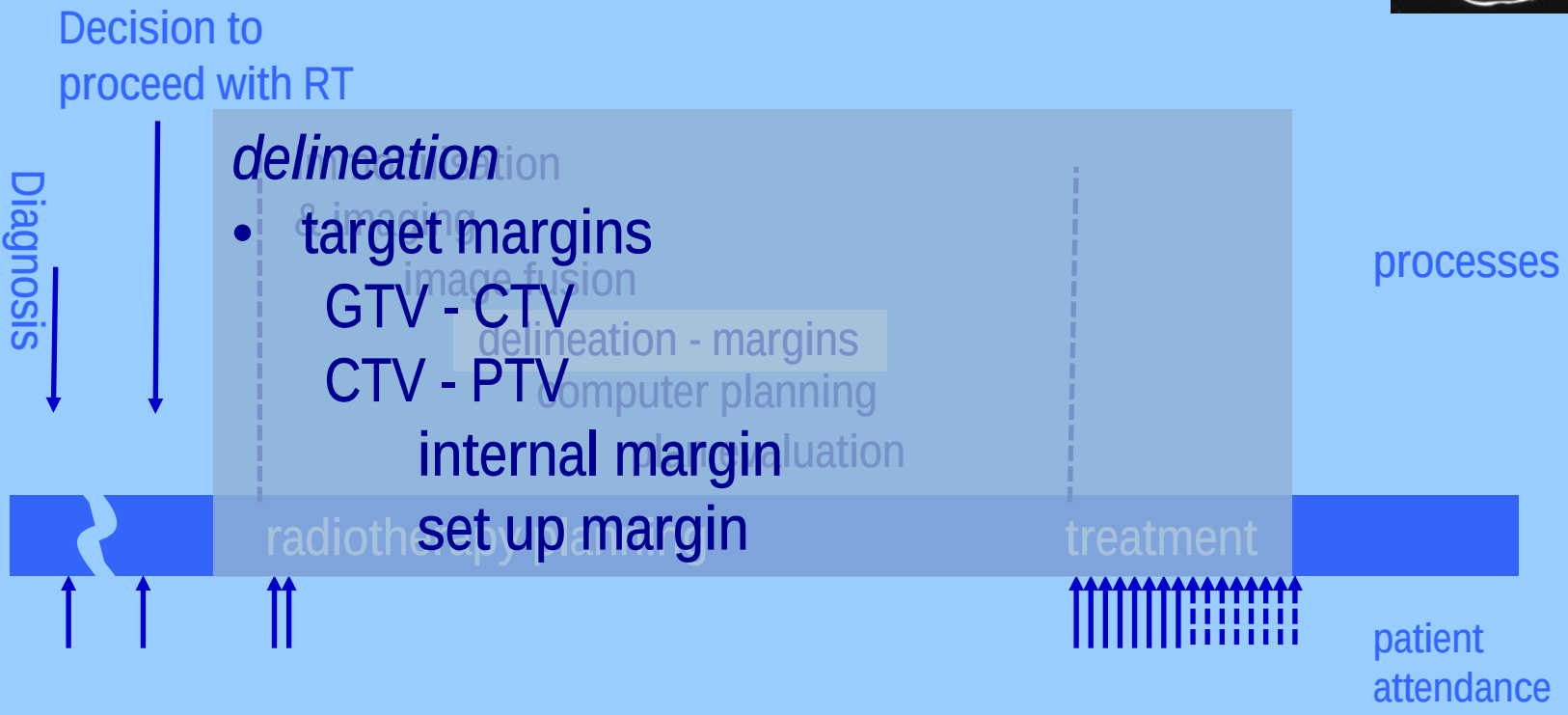
Deconstructing cranial radiotherapy



Preparation for radiotherapy

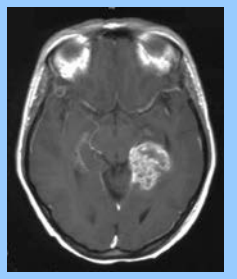
Deconstructing cranial radiotherapy





Preparation for radiotherapy

Deconstructing cranial radiotherapy



Preparation for radiotherapy

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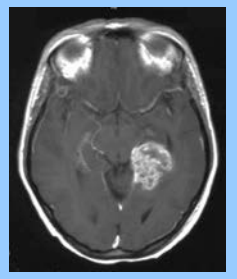
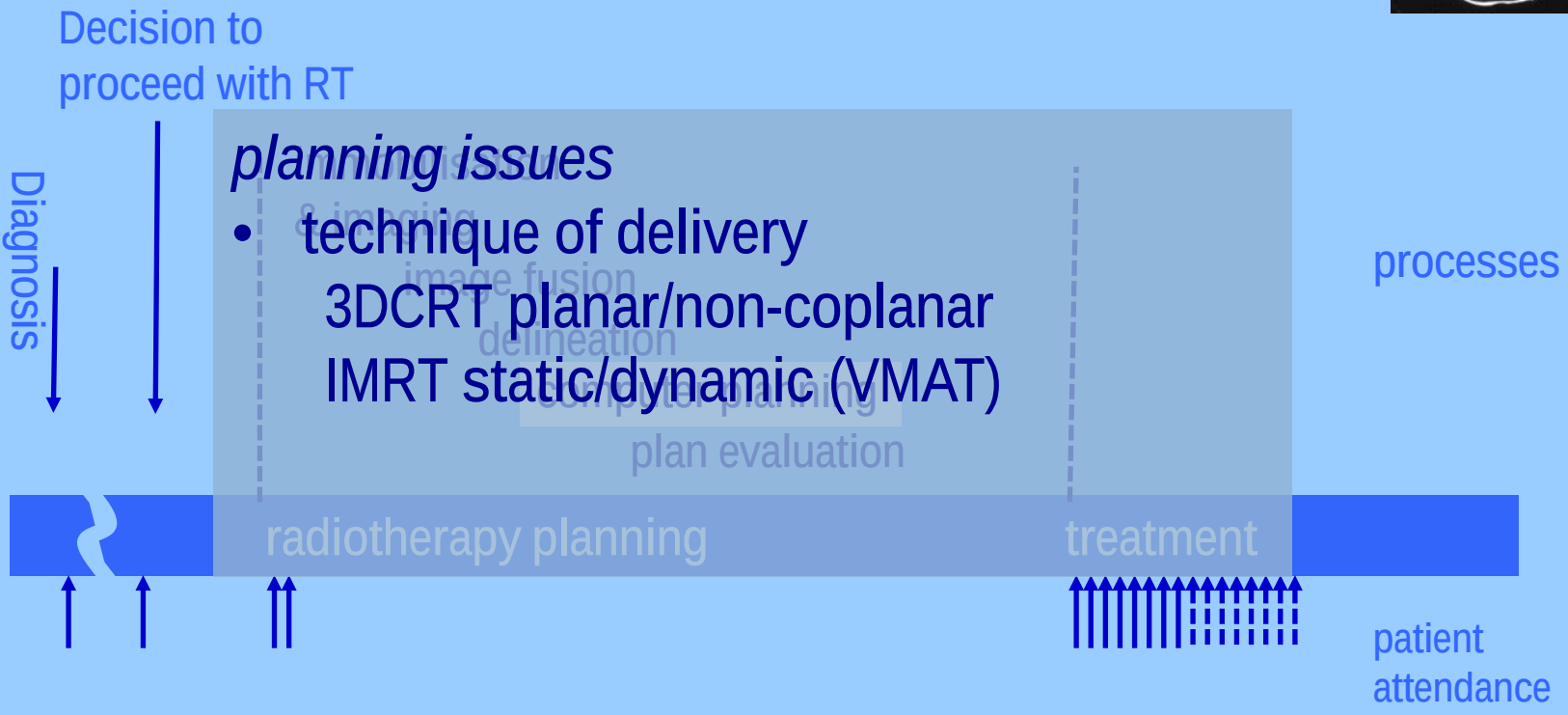
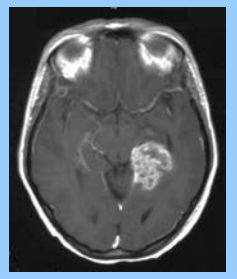
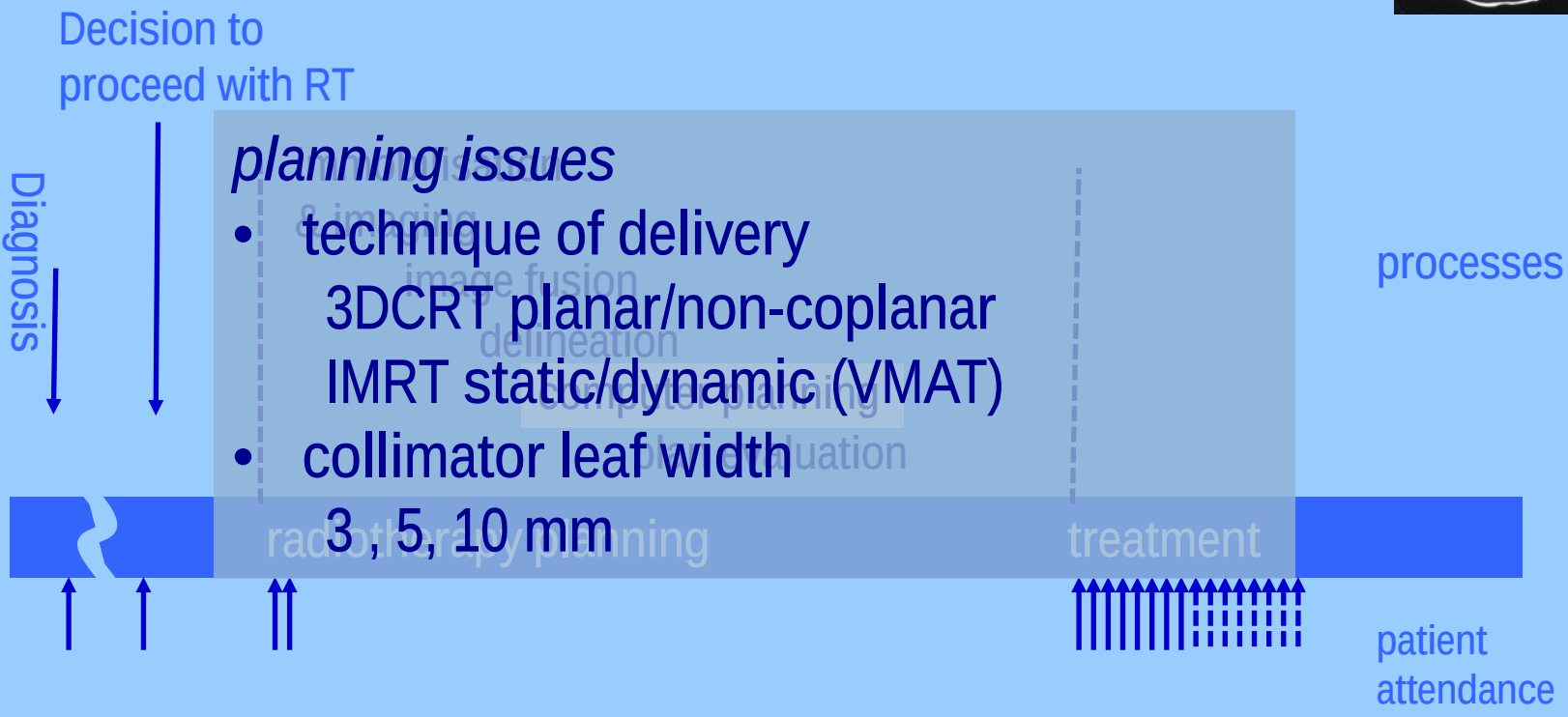




Preparation for radiotherapy

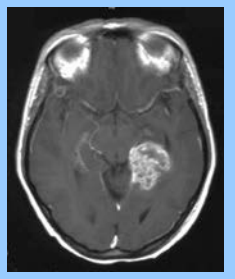
Deconstructing cranial radiotherapy

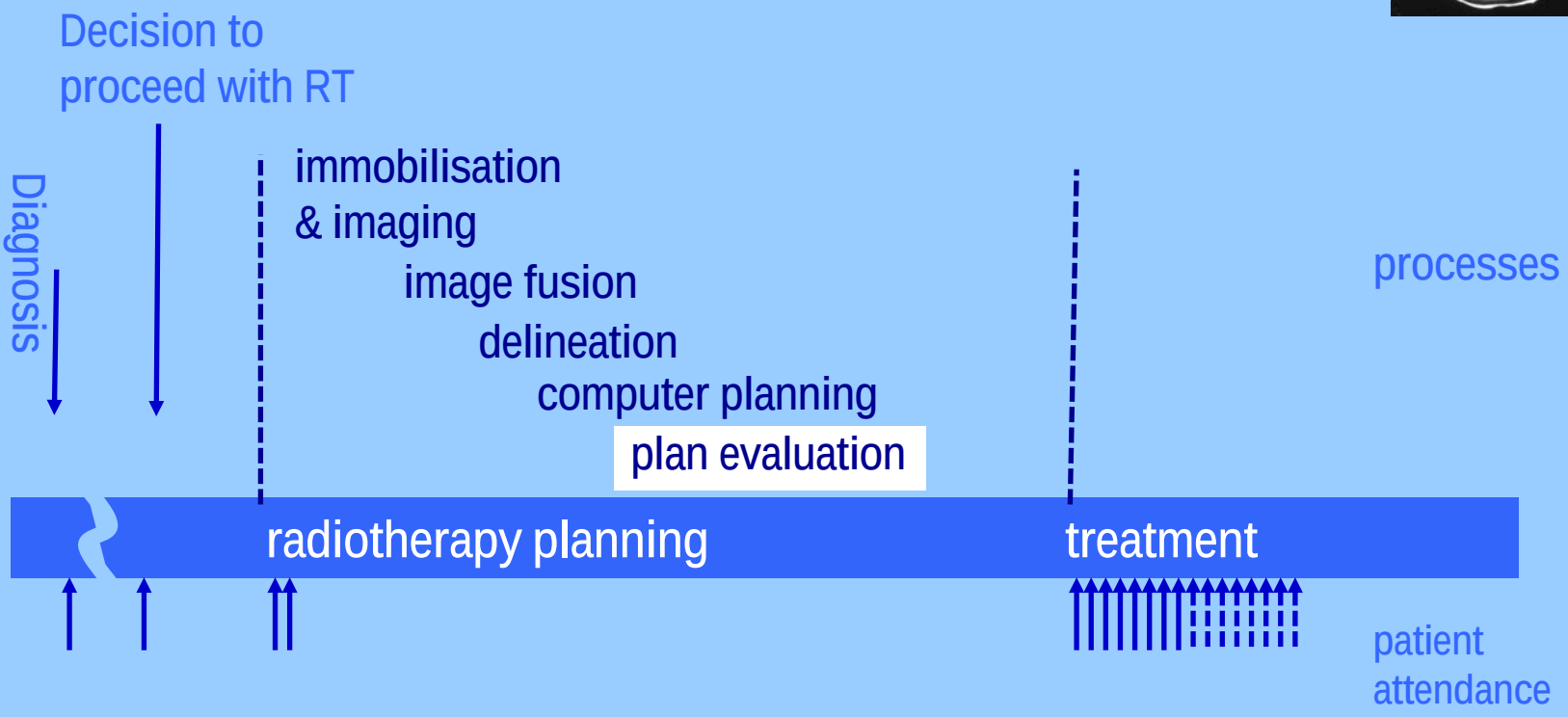




Preparation for radiotherapy

Deconstructing cranial radiotherapy

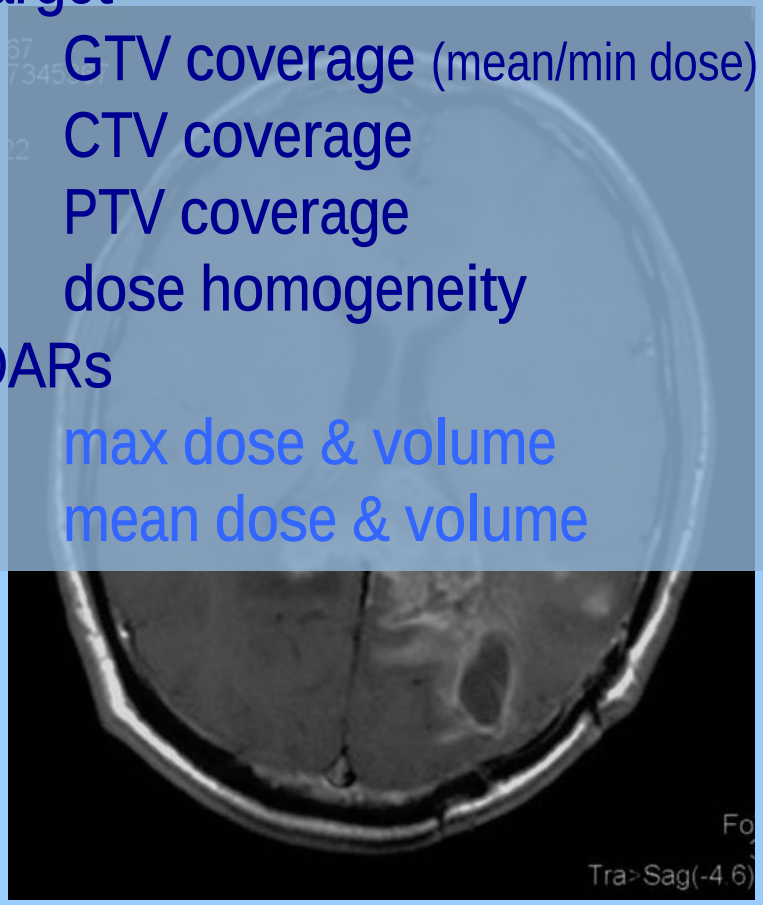


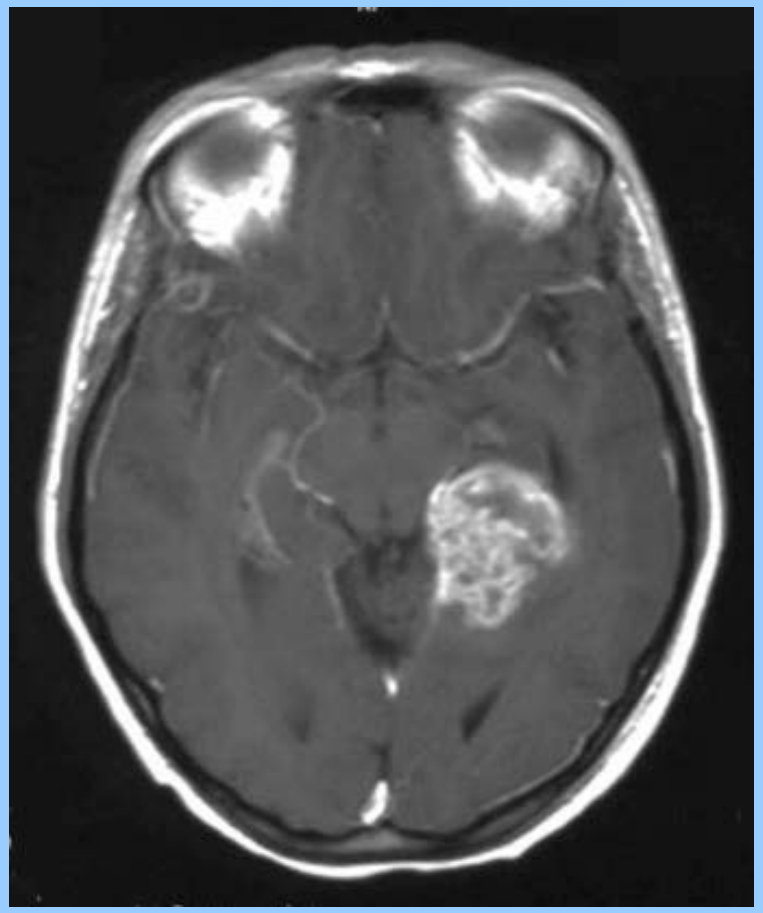


Preparation for radiotherapy

target
- GTV coverage (mean/min dose)
- CTV coverage
- PTV coverage
- dose homogeneity

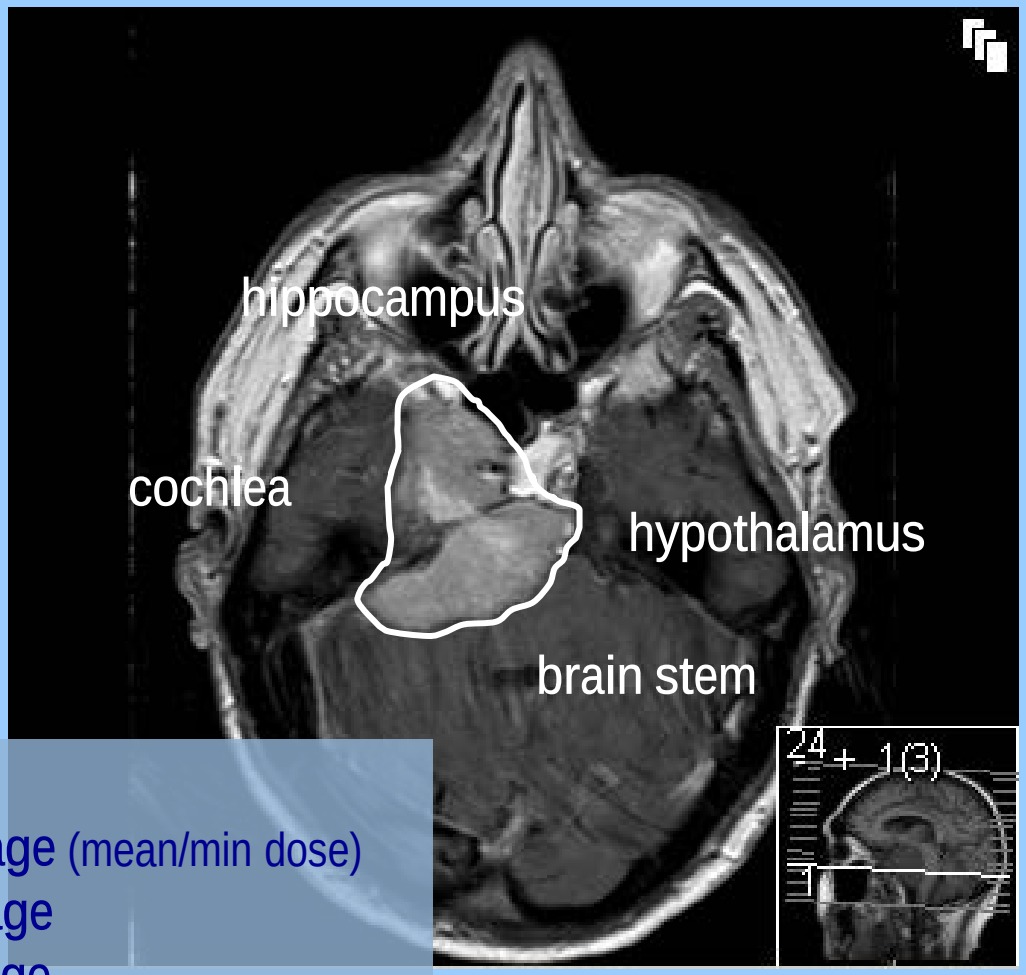
OARs
- max dose & volume
- mean dose & volume





What is important in evaluating plans for these tumours?

Principles of plan evaluation



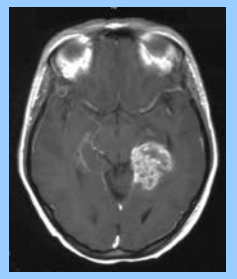
target
- GTV coverage (mean/min dose)
- CTV coverage
- PTV coverage
- dose homogeneity

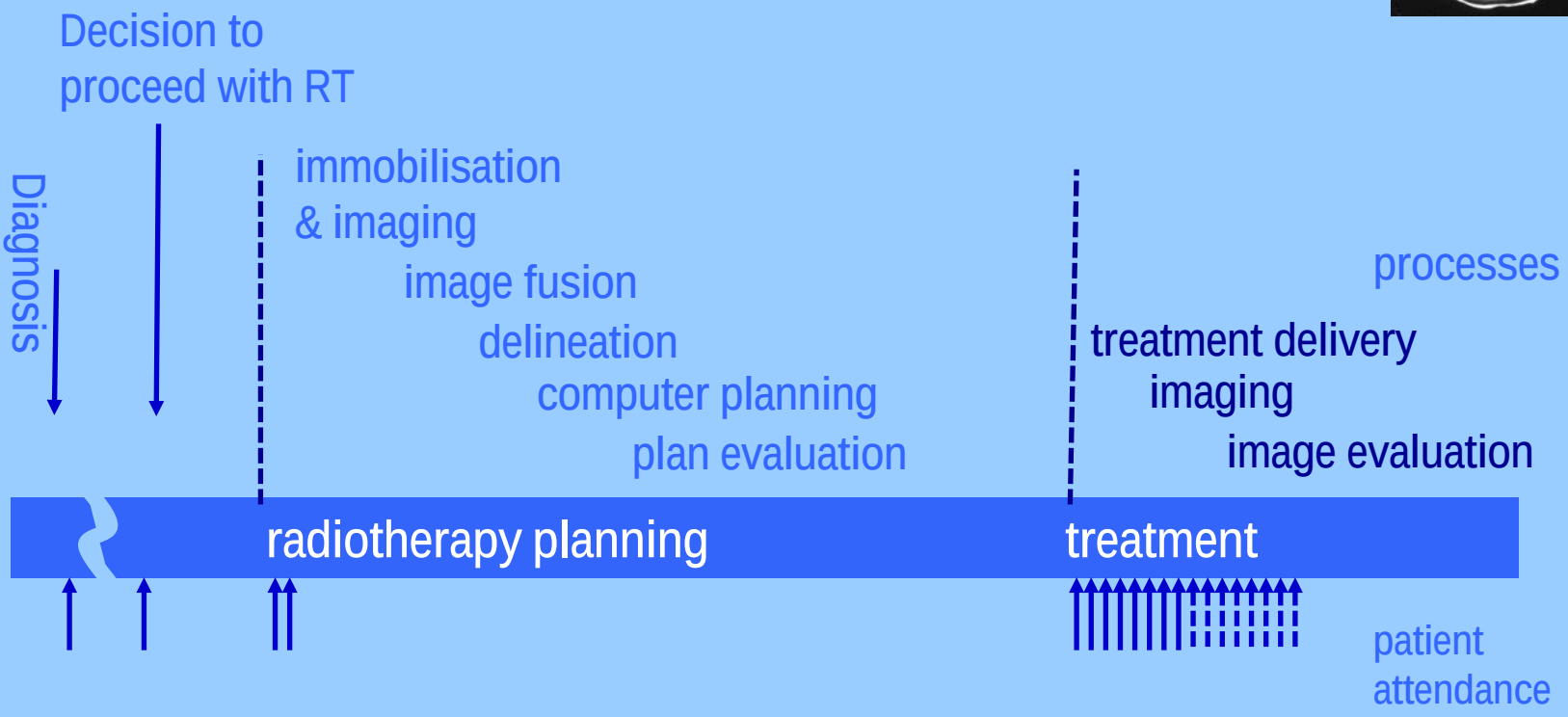
OARs
- max dose & volume
- mean dose & volume

What is important in evaluating plans for this tumour?

Principles of plan evaluation

Deconstructing cranial radiotherapy

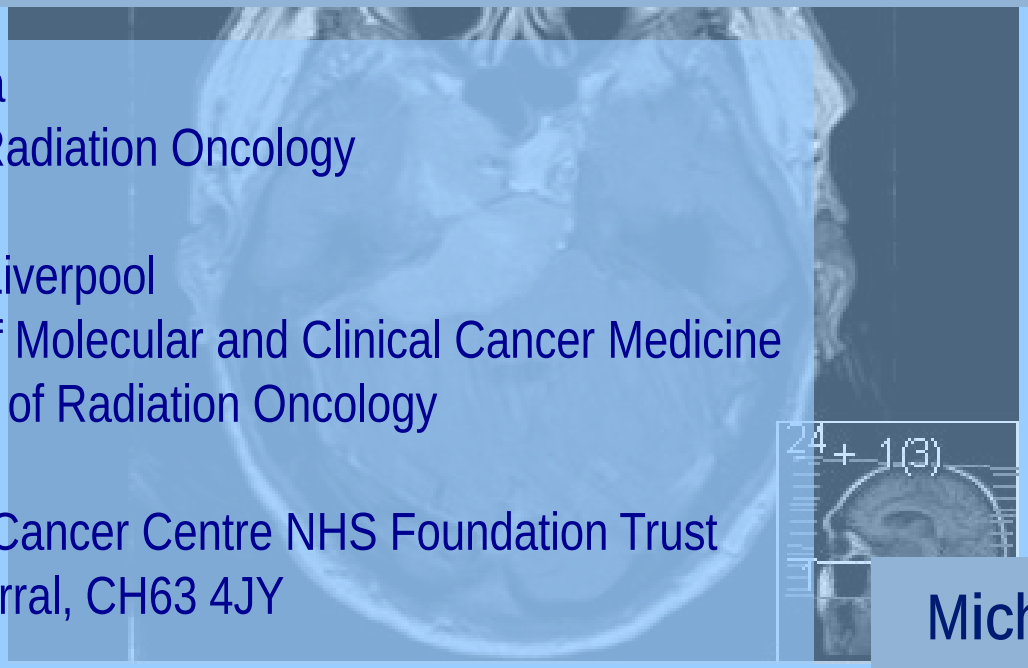




Preparation for radiotherapy

Cranial radiotherapy

preparing the patient for treatment



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ESTRO BT course
Torino October 2015

Radiotherapy treatment techniques:

wide field irradiation

CS axis and WBRT

Cristina Mantovani

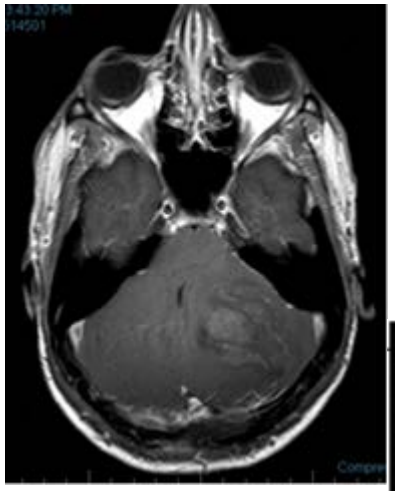
University of Torino

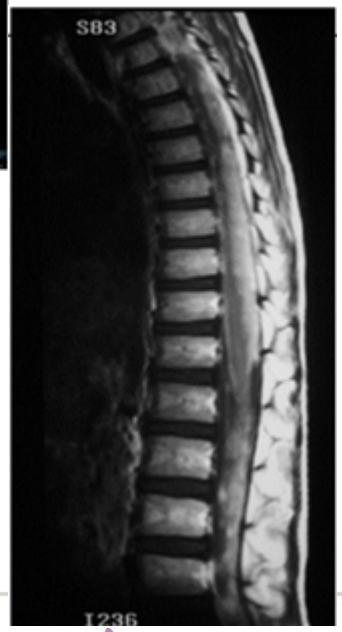
Department of Oncology

ESTRO School

Cranio-spinal irradiation (CSI)

"Irradiation of the entire CSF compartment from the top the skull to the end of the thecal sac in primary CNS tumours that have a propensity to spread via the CSF pathway"





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Radiotherapy technique

- Cranio-spinal irradiation

  - ✓ Clinical target volume = whole brain + spinal cord with overlying meninges

A complex technique….

- Carrie M-SFOP 98 1998-2001
  - 14/48 patients found on pre-RT review to have major targeting errors
    - 9 for eye blocks
    - 5 for spinal field width
    - (Carrie, Int J Rad Onc Biol Phys 2005)
- Packer A9961 1996-2000
  - 421 eligible patients
  - 21% with RT deviations
    - (Packer, JCO 2006)
- QARC ACNS0331 April 2004-August 2005
  - Modifications requested in 40% of the first 53 cases

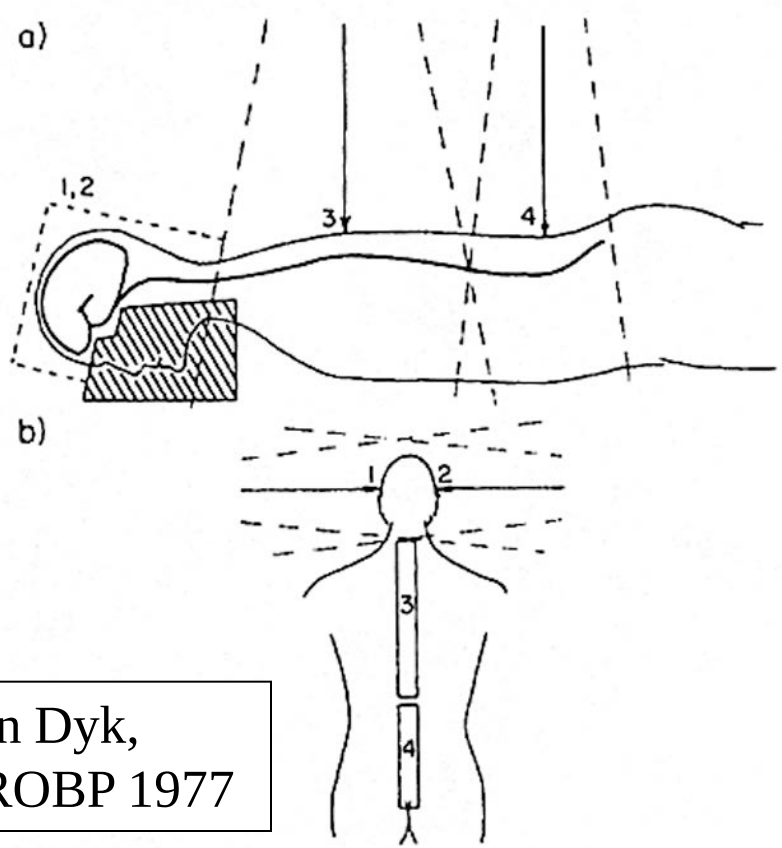
That has to be done properly….

- Targeting deviations correlate with outcome

  (Hardy 1978, Jereb 1982... Carrie 1992, Miralbell 1997, Taylor 2004, Oyharcabal-Bourden 2005)

- Dose reductions to 23.4 and 18 Gy make optimal coverage even more critical

A standard CSI technique



Van Dyk, IJROBP 1977

Patient prone in a head rest with neck extended

Junction of non-coplanar fields over the cervical spine

Extended SSD or second posterior field to cover whole length of spine/second junction over the spinal cord

CSI in 2015: new/improved tools

- Better imaging for target volume definition
  - CT simulation
  - MRI and CT-MRI co-registration
- CT-based treatment planning
- Improved delivery techniques

CSI

- Target volume definition

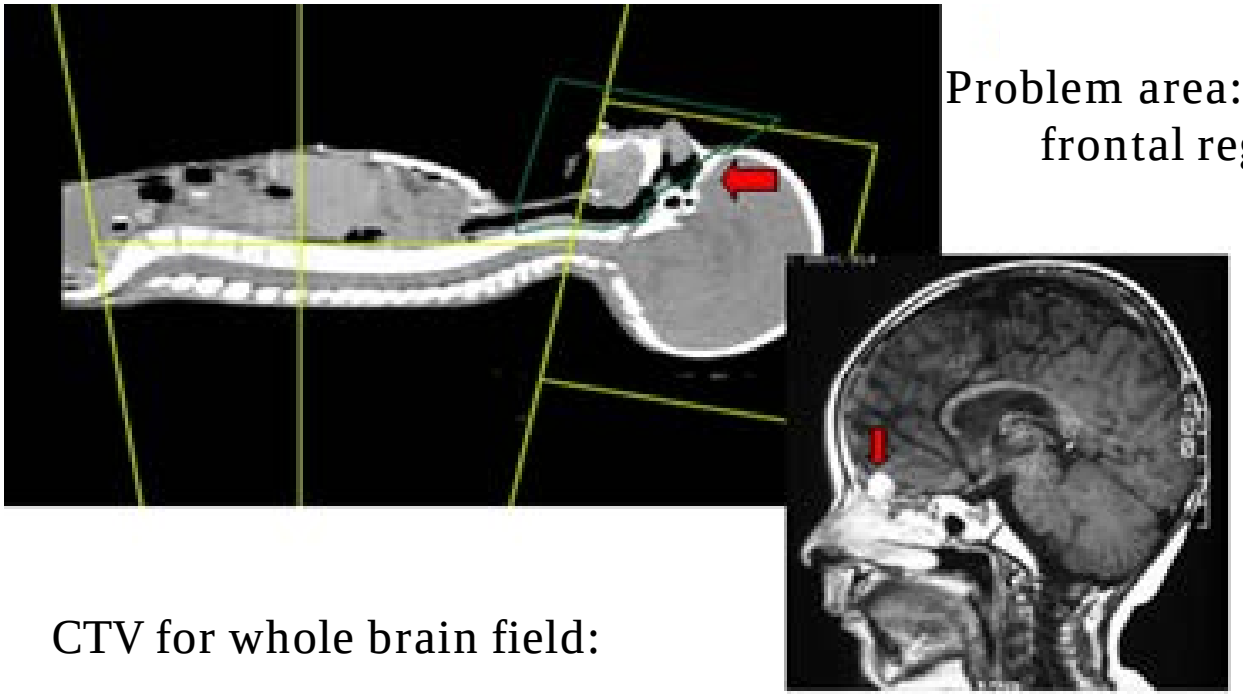
Target volume definition

Target definition: is necessary to outline the cranio-spinal axis → whole brain, spinal cord and thecal sac

The whole brain should include the entire frontal lobe and cribriform plate region

Target volume definition

Frontal region/cribriform plate

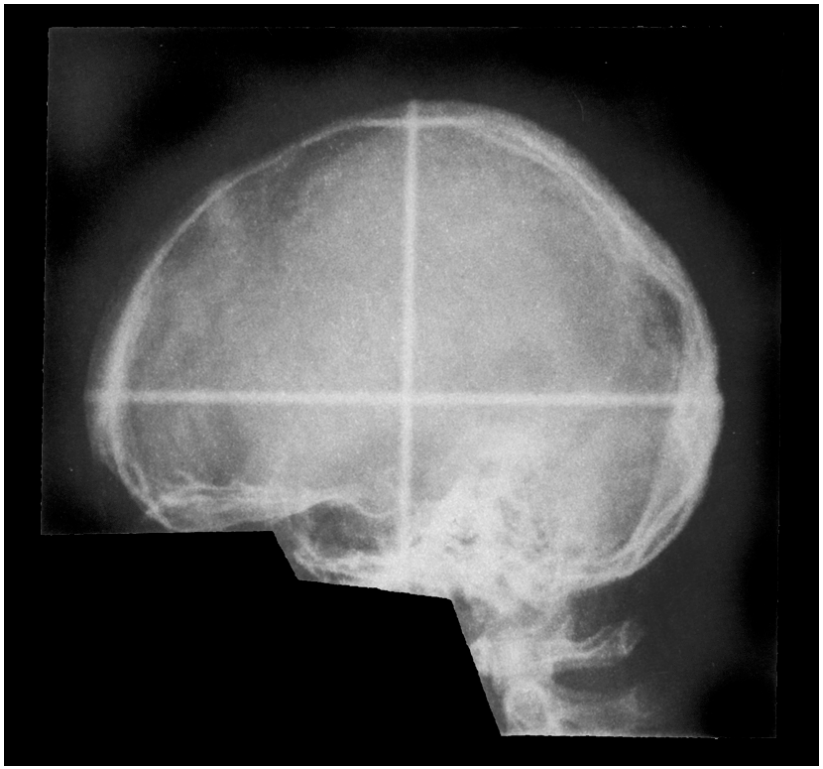


Problem area:
frontal region/cribriform plate

CTV for whole brain field:

« ...shall extend anteriorly to include the entire frontal region and cribriform plate region. The volume shall cover the superior orbital tissue (but not the posterior globe as in leukemia protocols)»

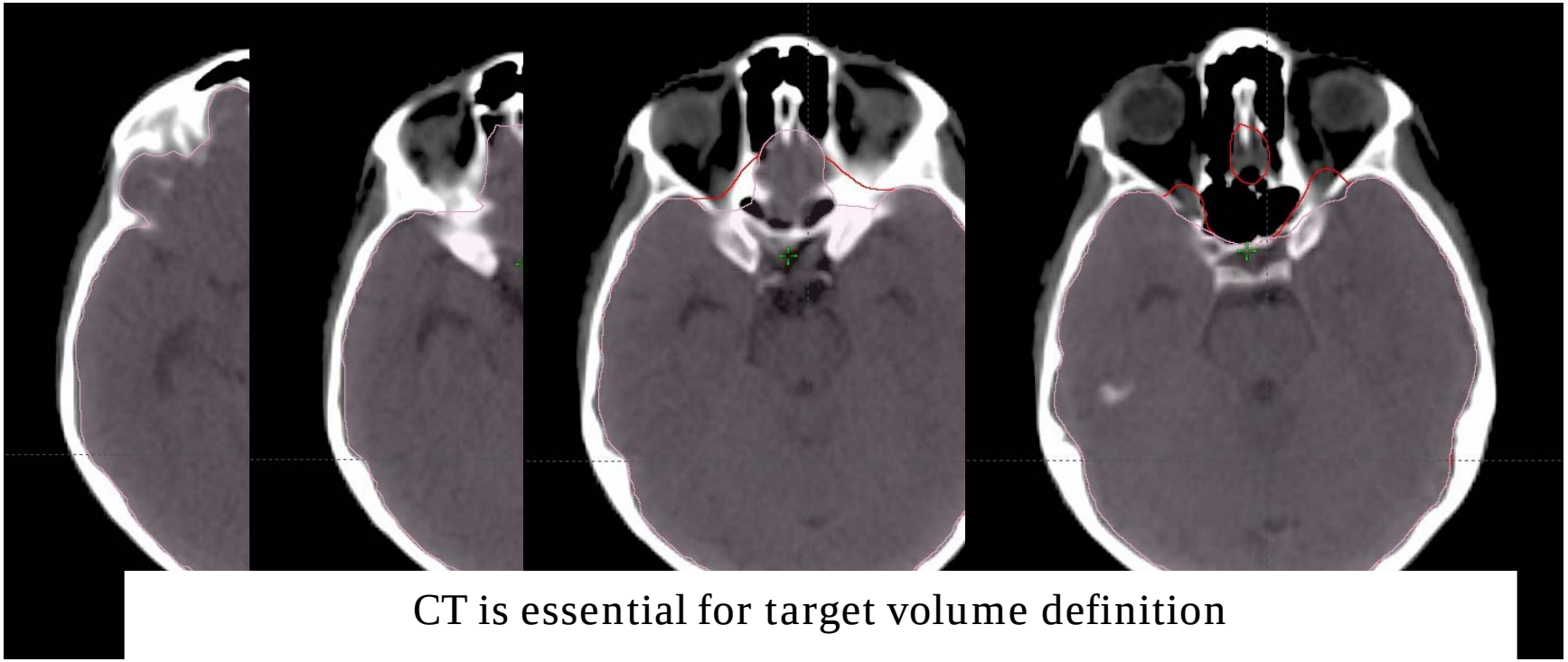
Coverage of the target volume: cribriform plate



- Lateral radiographs are not adequate for target volume delineation
- 5 radiologists and 5 radiation oncologists:
  - Correct within 2mm in only 39% of cases
  - Mislocations
    - 2-5mm in 34%
    - 5-10mm in 20%
    - >10mm in 7%

Gripp IJROBP 2004

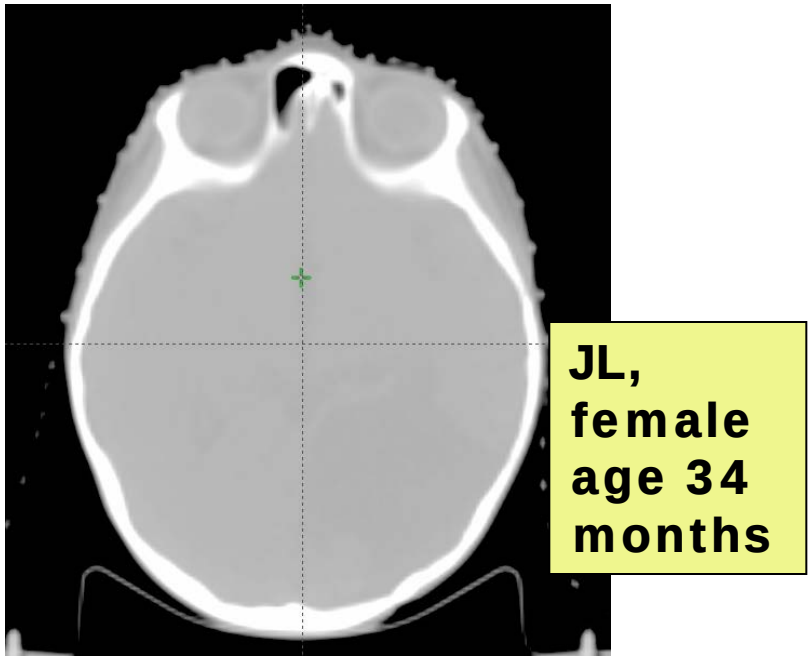
Coverage of the target volume: cribriform plate



CT is essential for target volume definition

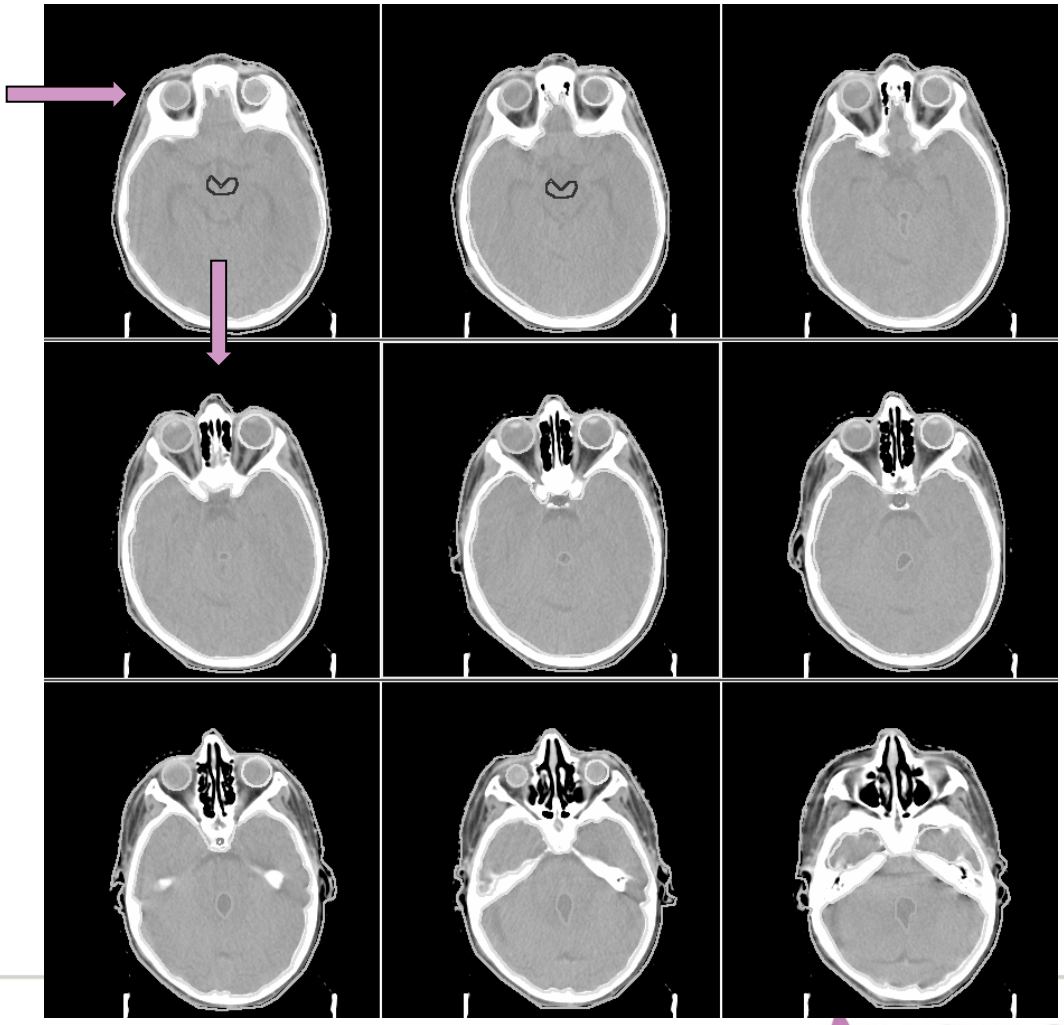
In most children, it is impossible to shield the eyes **and** cover the target volume

Especially in very young children....



Coverage of the target volume: cribriform plate

- To include the cribriform fossa in the CTV and allowing an additional appropriate margin to the PTV, the PTV frequently includes the lenses.
- We consider it necessary to frequently deliver a higher dose to the lens (accepting an increased probability of later cataract development) than not adequately cover the cribriform plate.
- SFOP group suggested that the edge of the shielding block/ MLCs is **at least 5 mm below the cribriform fossa** as this field edge definition is not associated with an increase risk of frontal recurrence



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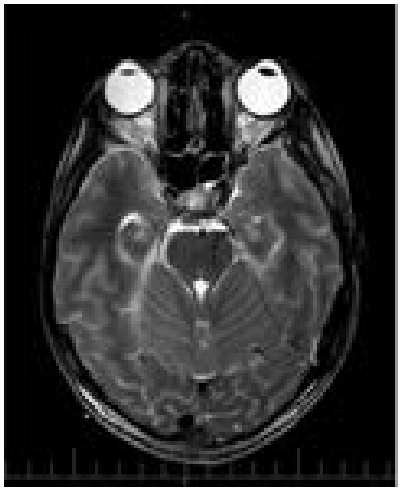
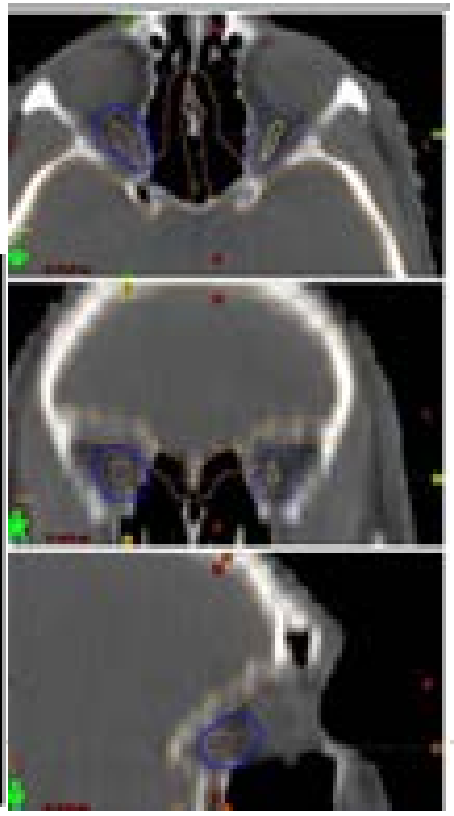
A new problem: the optic nerves



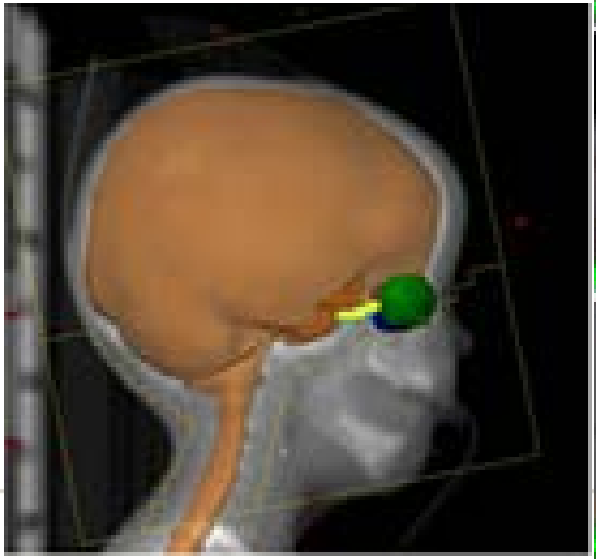
Subarachnoid space ends at the lamina cribrosa



Dose to optic nerve PTV (V95%):

-3DCRT 99% (95%-100%)

-Tomotherapy 81% (49.9%-96%)



Optic nerves need to be contoured

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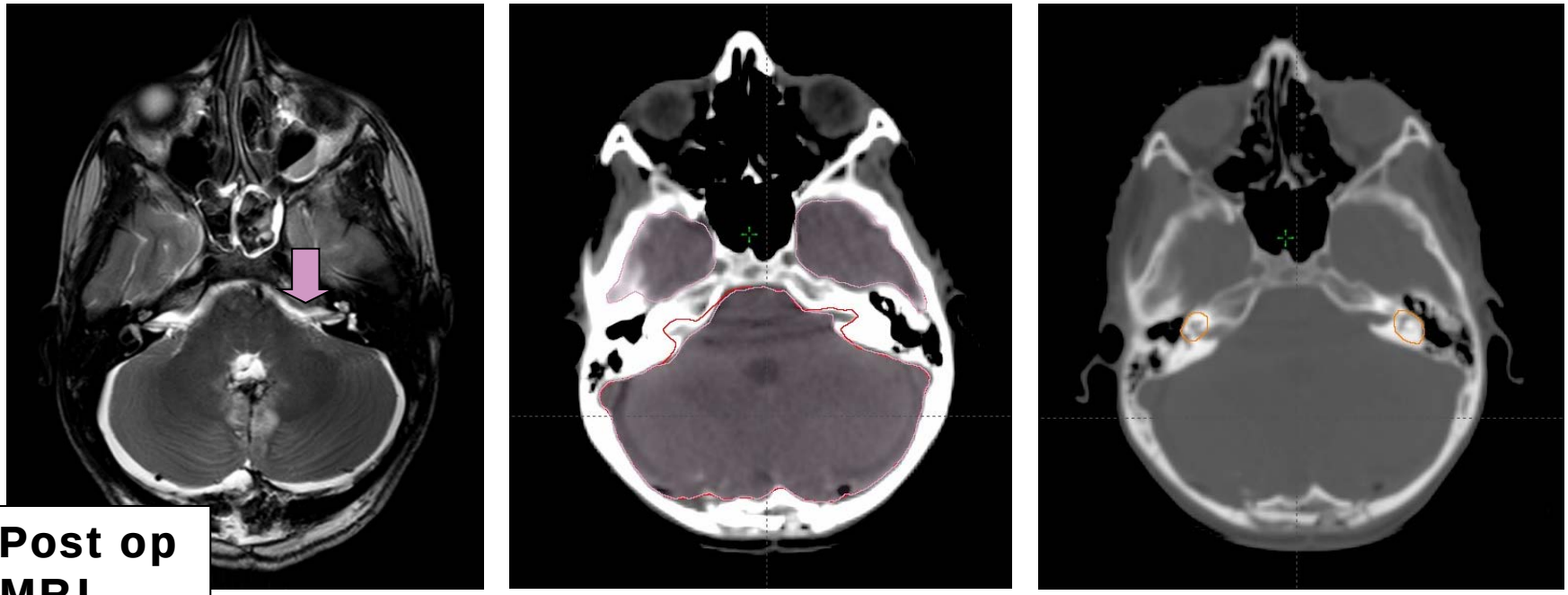
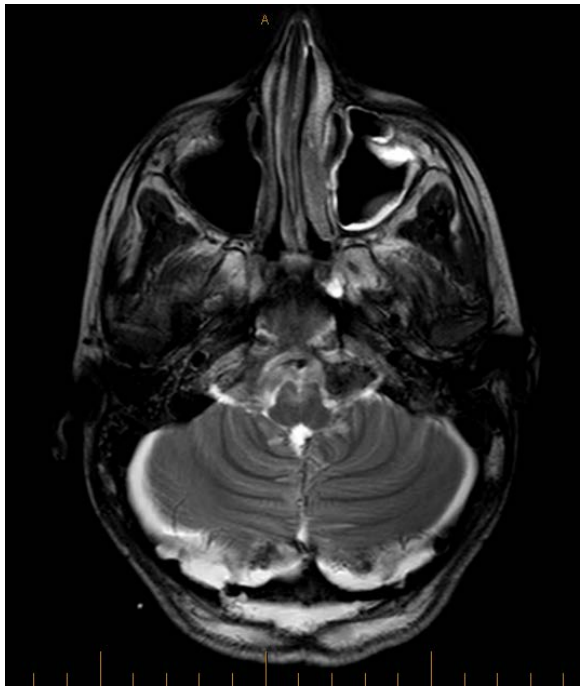
Another new problem… extension of subarachnoid space around cranial nerves

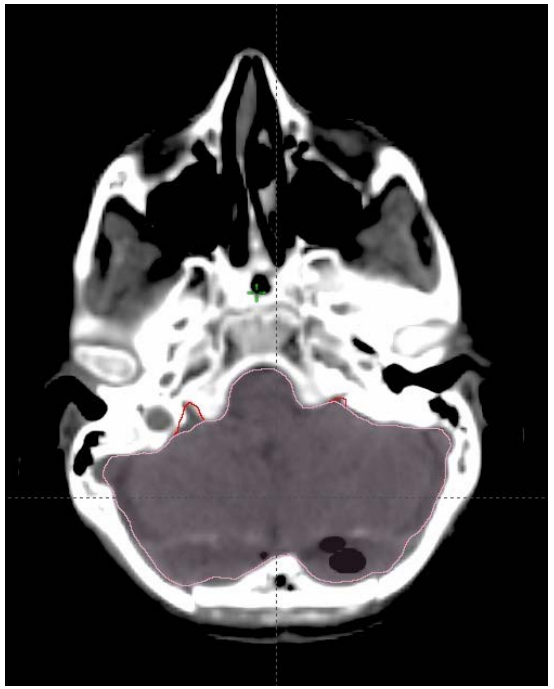


Use T2-weighted MRI for contouring

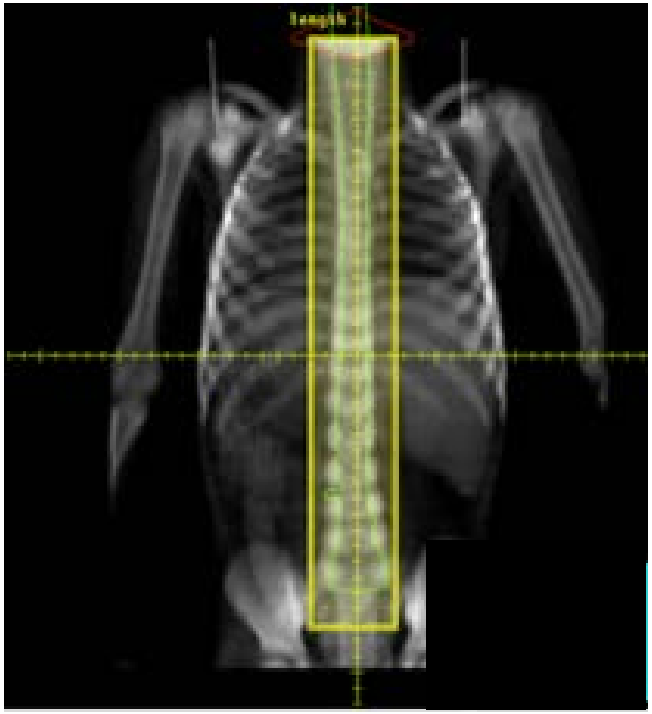
Difficult or impossible to spare cochlea

The lower cranial nerves too…





Coverage of the target volume: the spine



ACNS0331:
«...laterally on both sides to cover the recesses of the entire vertebral bodies, with at least 1 cm margin on either side

Lower limit: 2 cm below the termination of the subdural space..... At least to the inferior border of the 2° sacral segment (S2-S3 interspace)

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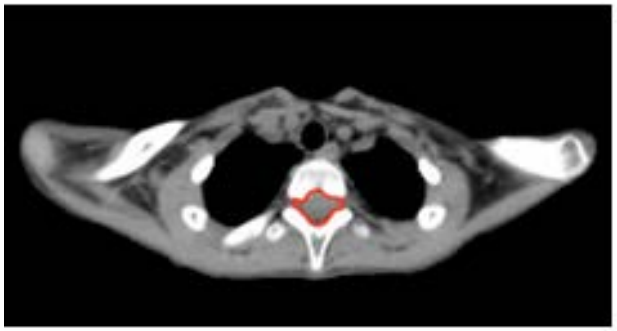
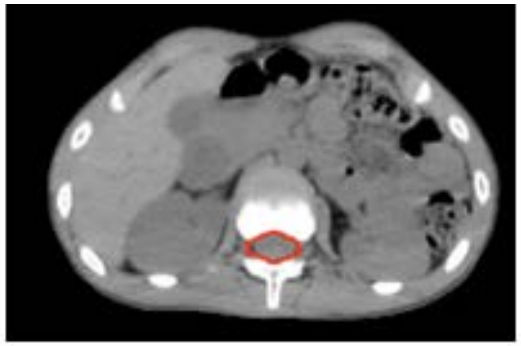
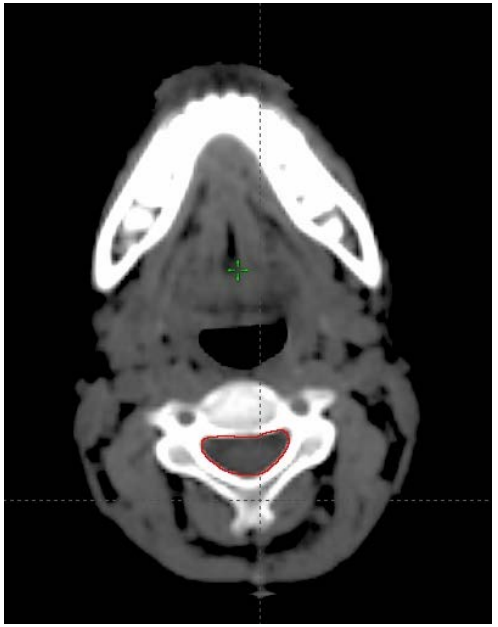
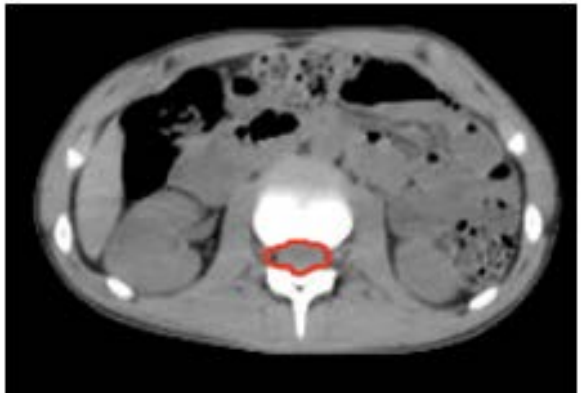
Coverage of the target volume: the spine

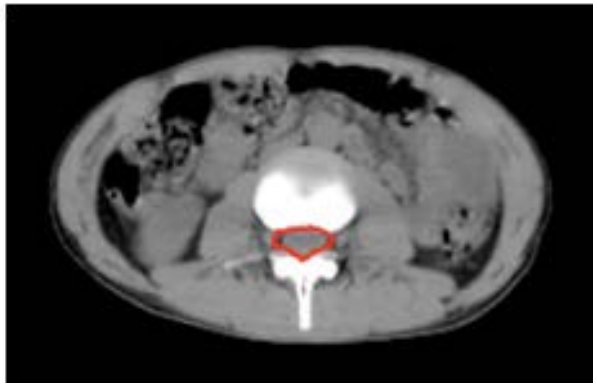
Now spine is contoured slice by slice





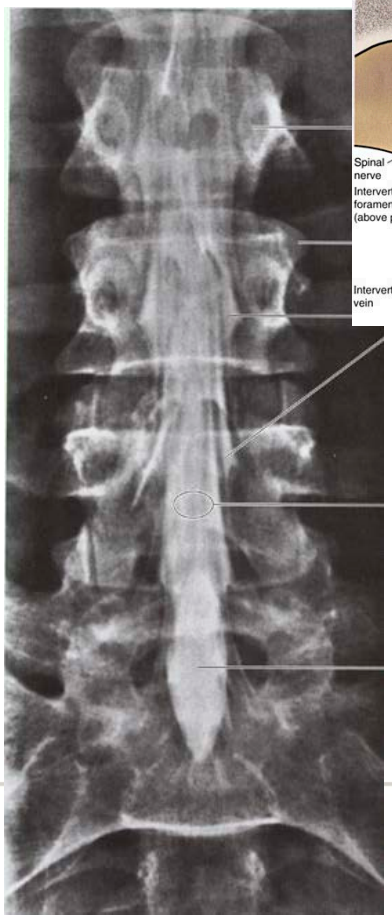


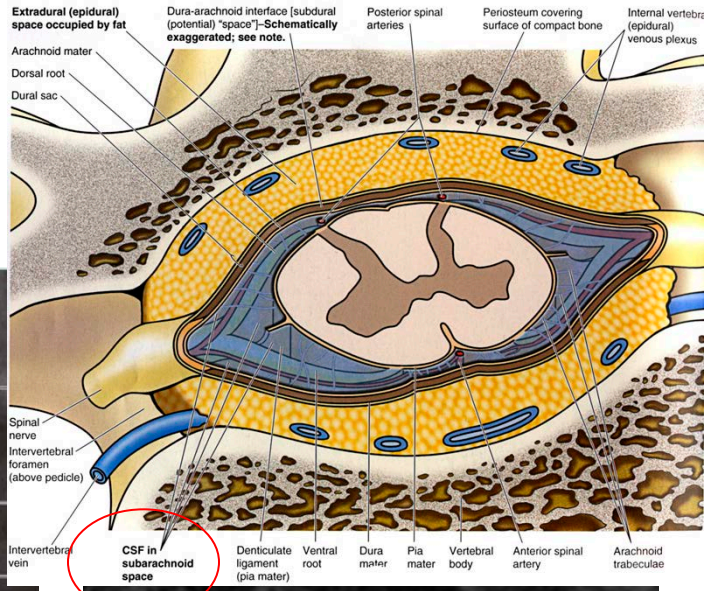


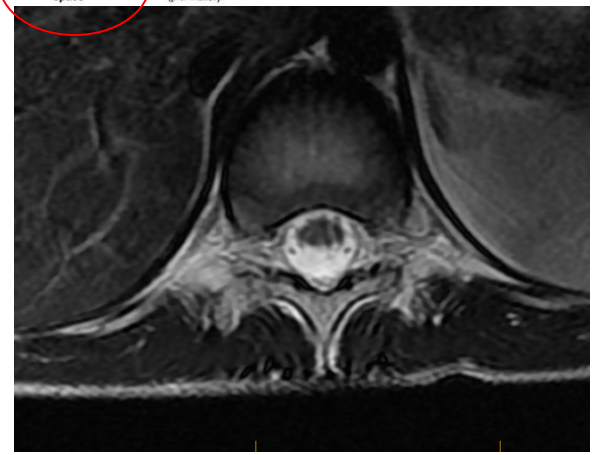


Coverage of the spine: lateral borders

- Dural root sleeves extend to envelop the spinal ganglia
- Lateral aspect of the spinal ganglia have been related to the pedicles as seen on conventional radiographs/ simulation films
- Lateral limit well seen on axial T2- weighted images

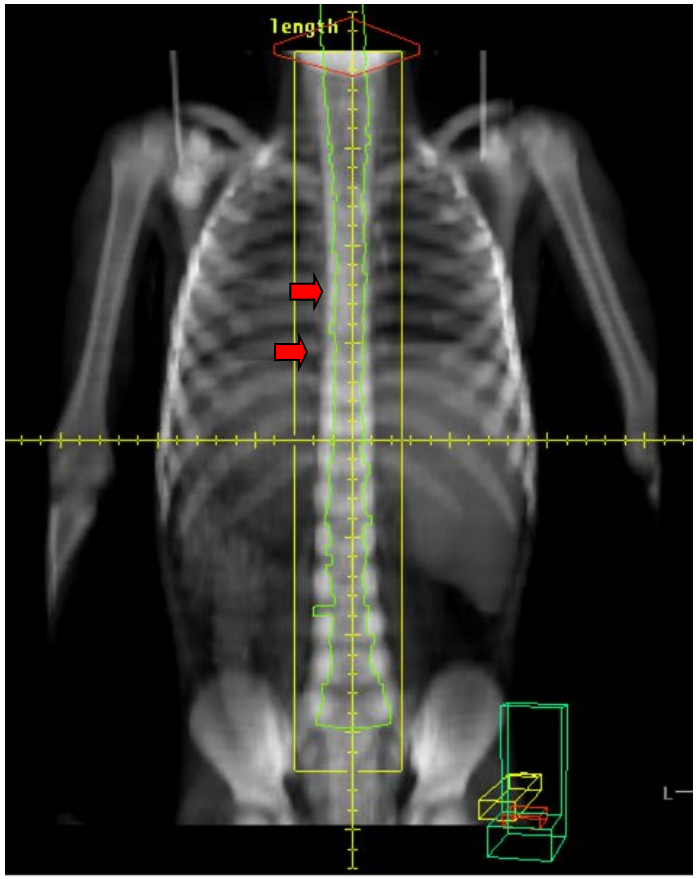




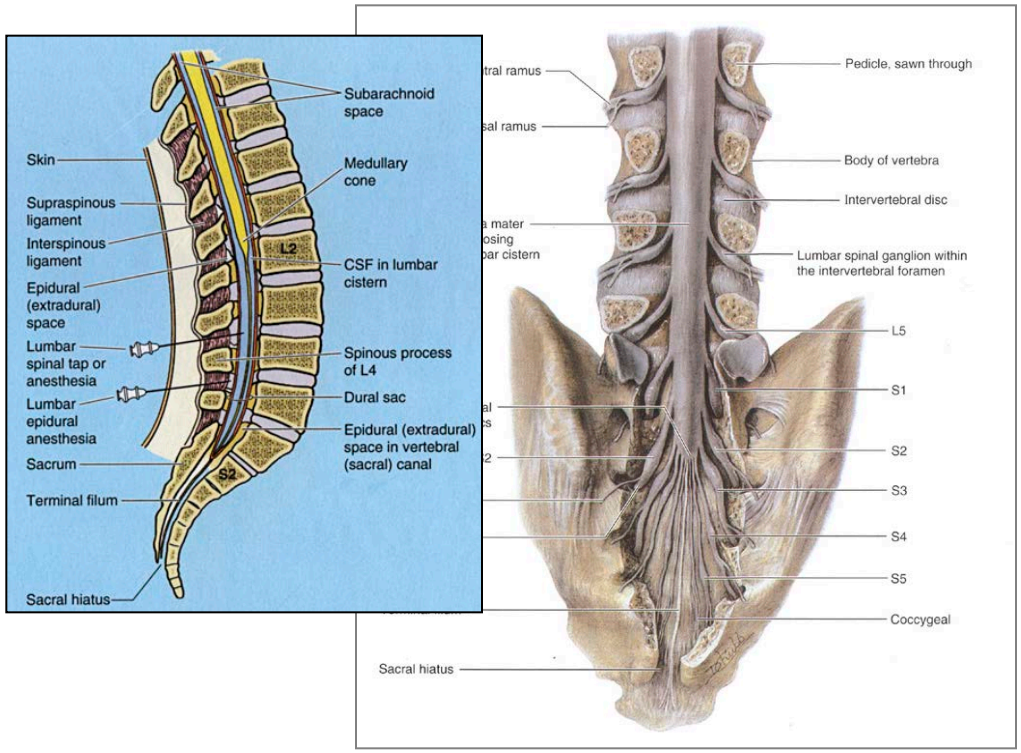


Why is this important?

- Use of optimal imaging/CT simulation/ 3D planning/field shaping allows ↓ width of the spine field
  - Reduces dose to the heart and lungs, other OARs
  - Reduces integral dose



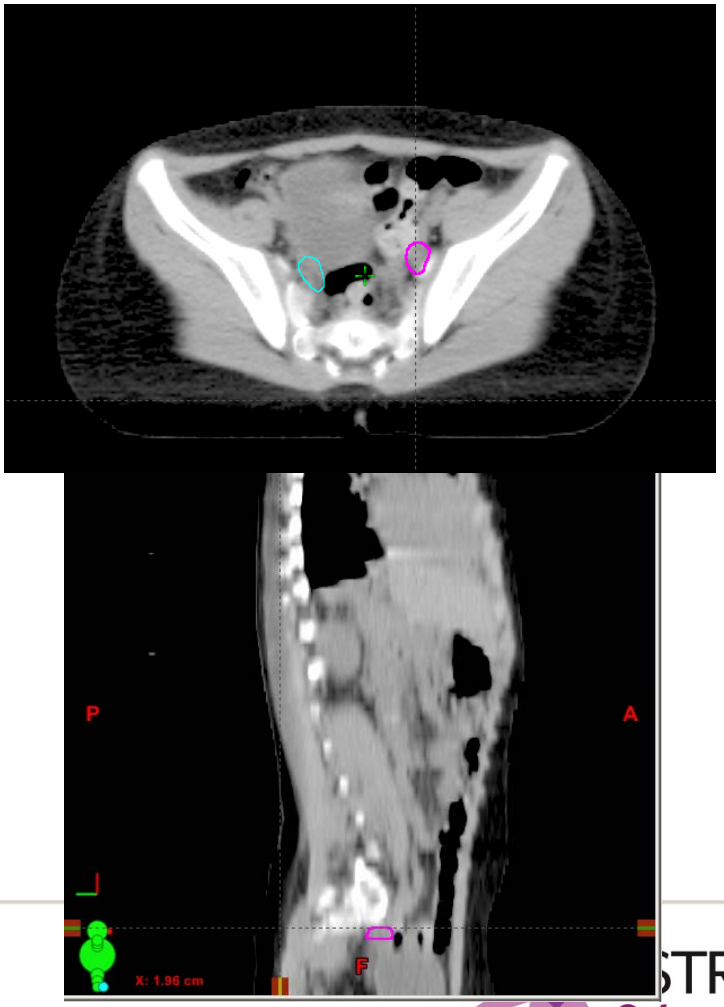
Coverage of the spine: caudal extent of thecal sac



- Dural sac "generally" ends at S1/2
- But:
  - ~50% by bottom S1
  - >90% by bottom S2
  - <10% above L5/S1

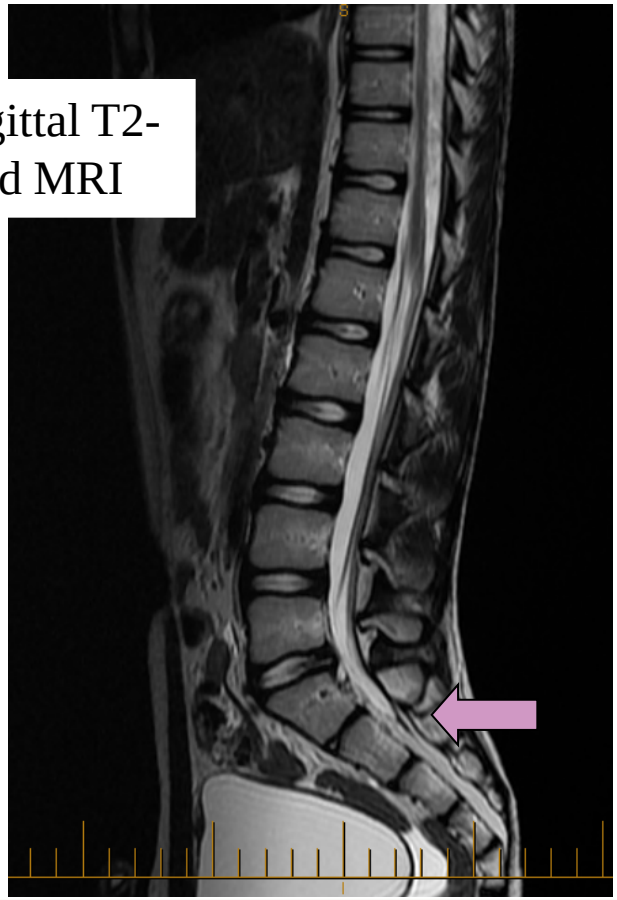
Why is this important?

- Accurate determination of the caudal limit of the thecal sac
  - Reduces risk of geographic miss/ recurrence
  - Minimizes dose to OARs, especially the ovaries



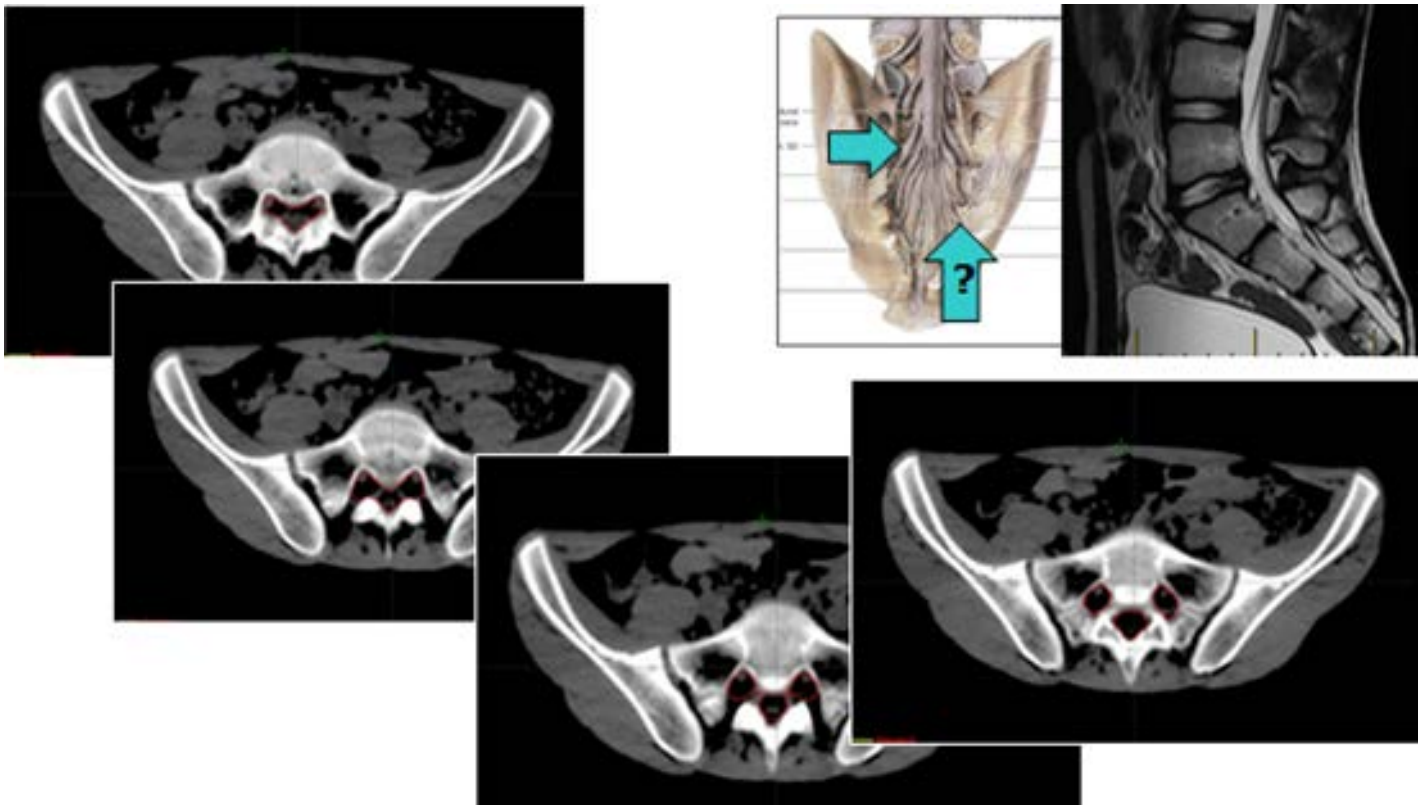
Coverage of the spine: caudal extent of thecal sac

Mid-sagittal T2-weighted MRI



oMRI is **essential** for accurate determination of the caudal extent of the thecal sac

Contouring the distal thecal sac



Bottom line…

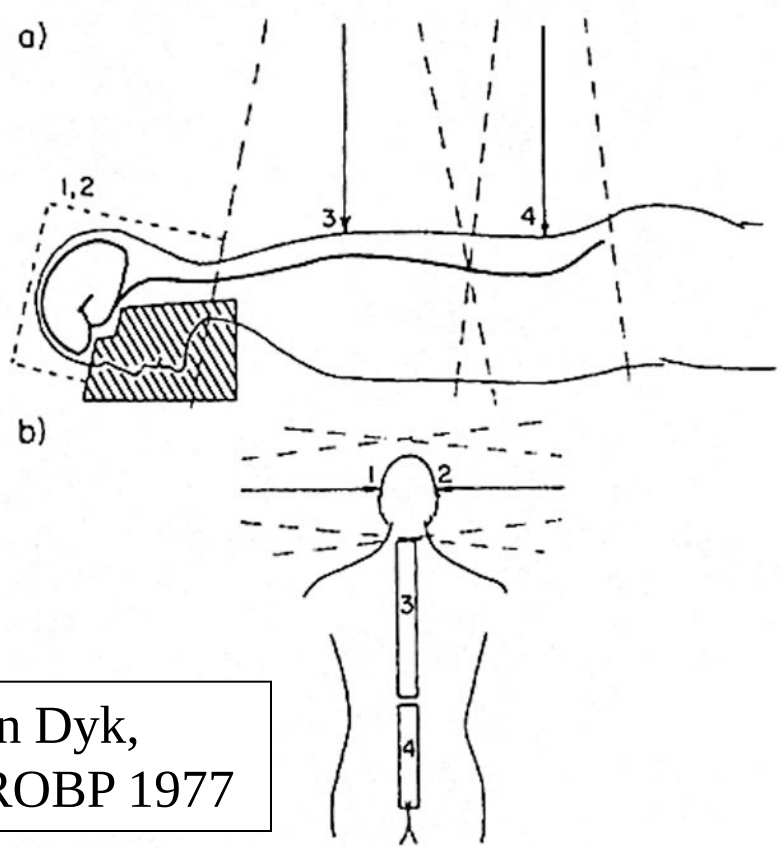
- Contouring for CSI is time consuming but absolutely critical
    - Optimal definition of target volumes
    - Maximum sparing of normal tissues

- Context of new techniques, lower doses

Radiotherapy technique: CSI

CSI: technical issues

A standard CSI technique



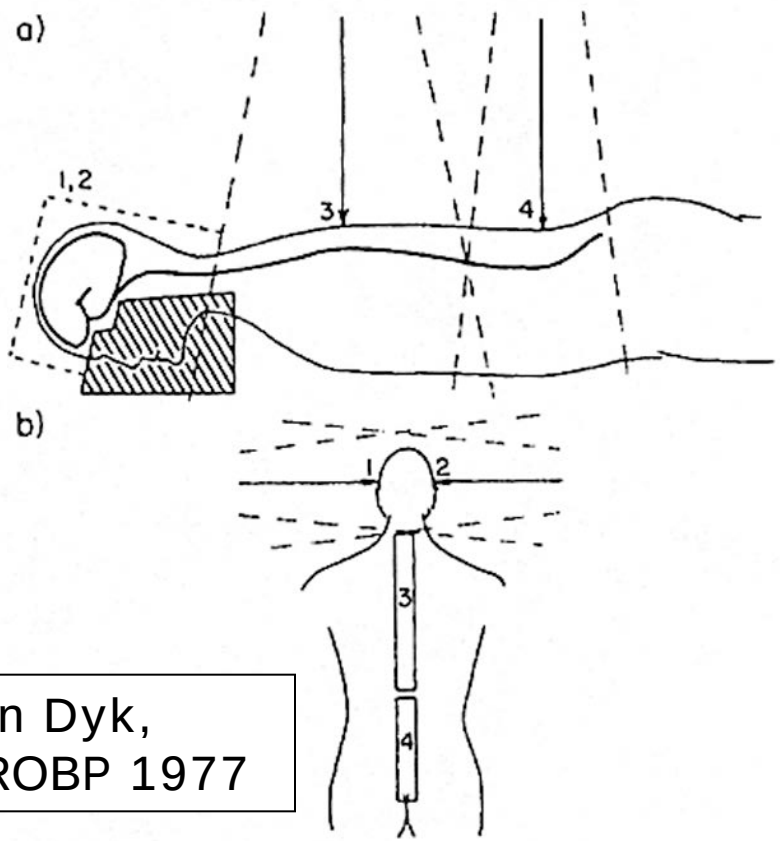
Van Dyk, IJROBP 1977

Patient prone in a head rest with neck extended

Junction of non-coplanar fields over the cervical spine

Extended SSD or second posterior field to cover whole length of spine/second junction over the spinal cord

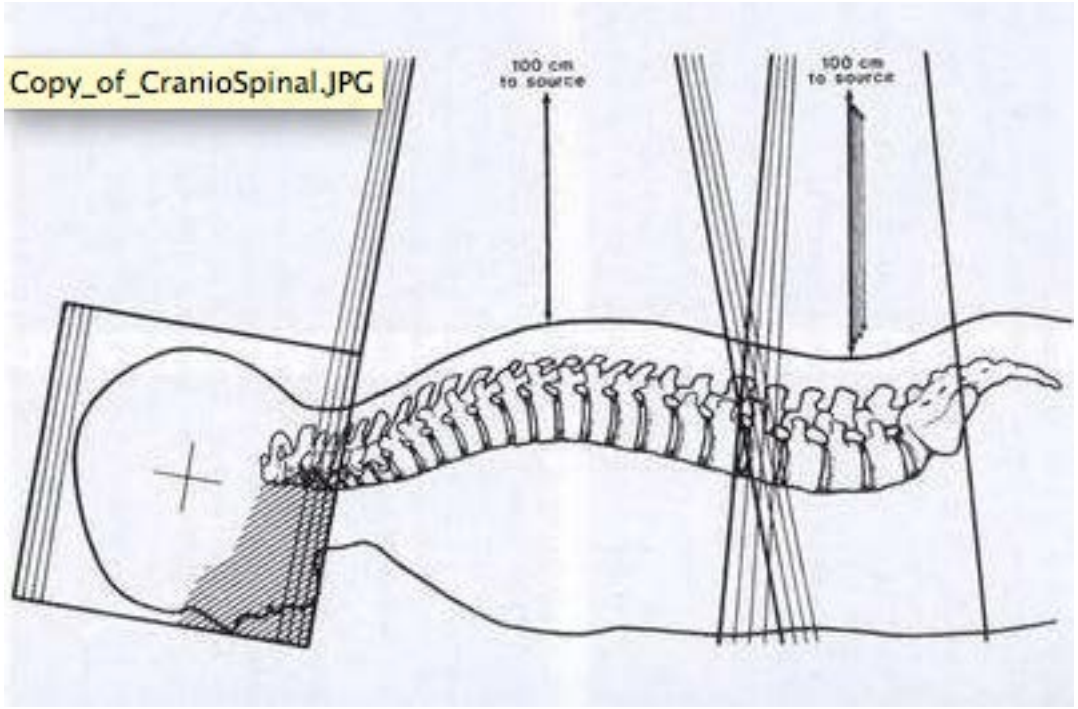
Conventional technique



Van Dyk, IJROBP 1977

- Reproducibility of positioning/margins required to account for set-up errors
- Safety of anaesthesia for infants treated in the prone position
- Time taken for simulation and for each daily treatment
- Dose inhomogeneities in the target volume, especially at the junctions and along the length of the spinal axis

Just some of the issues…



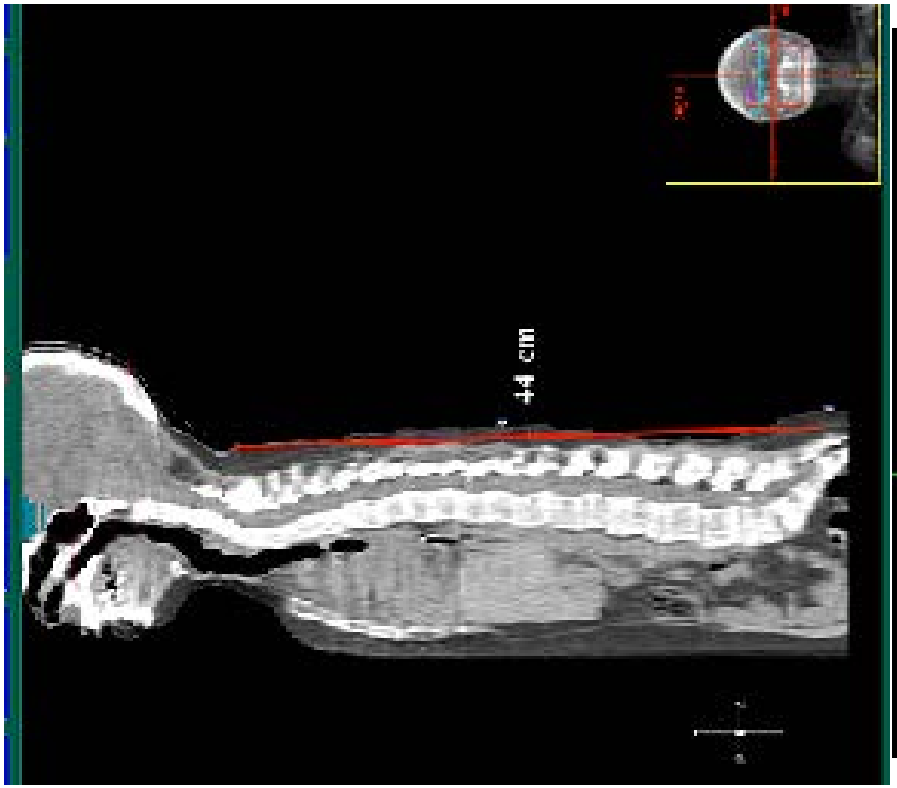
Just some of the issues…

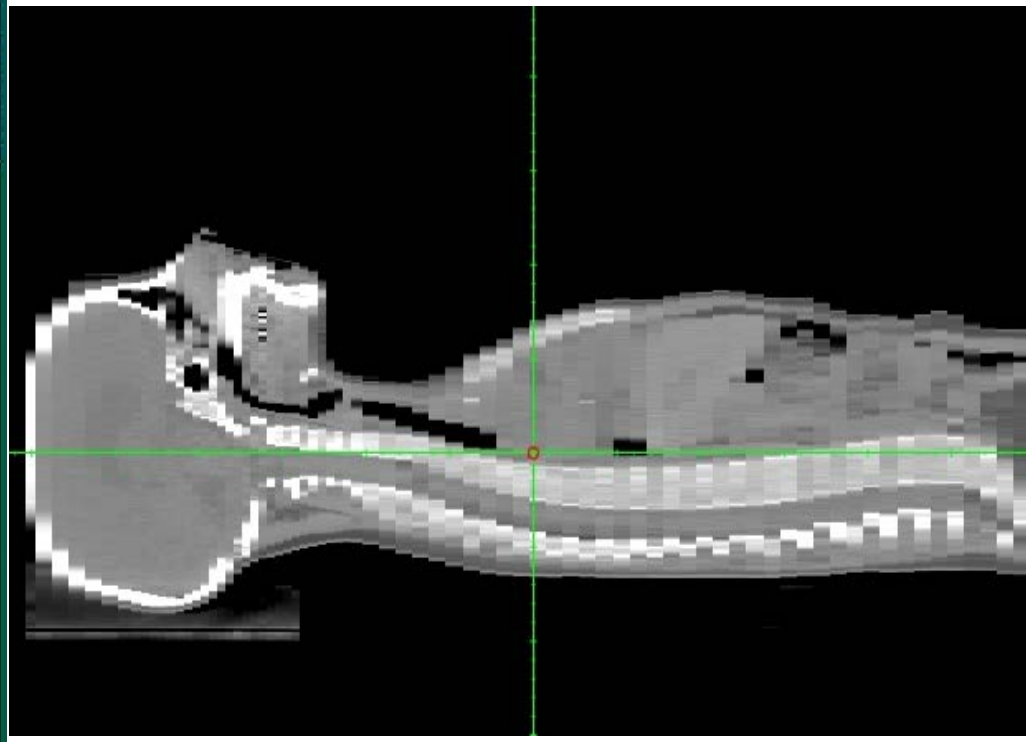
- Placement of centre of brain fields
- Posterior angulation of lateral fields to spare contralateral lens
- MLC *vs* custom blocks for shielding
- High *vs* low junction in the cervical region
- Use of couch rotation or match line wedge for junction in the cervical region
- Use of a gap/feathering of junction in the cervical region
- Second field *vs* extended SSD for spinal axis

Evolution of CSI technique

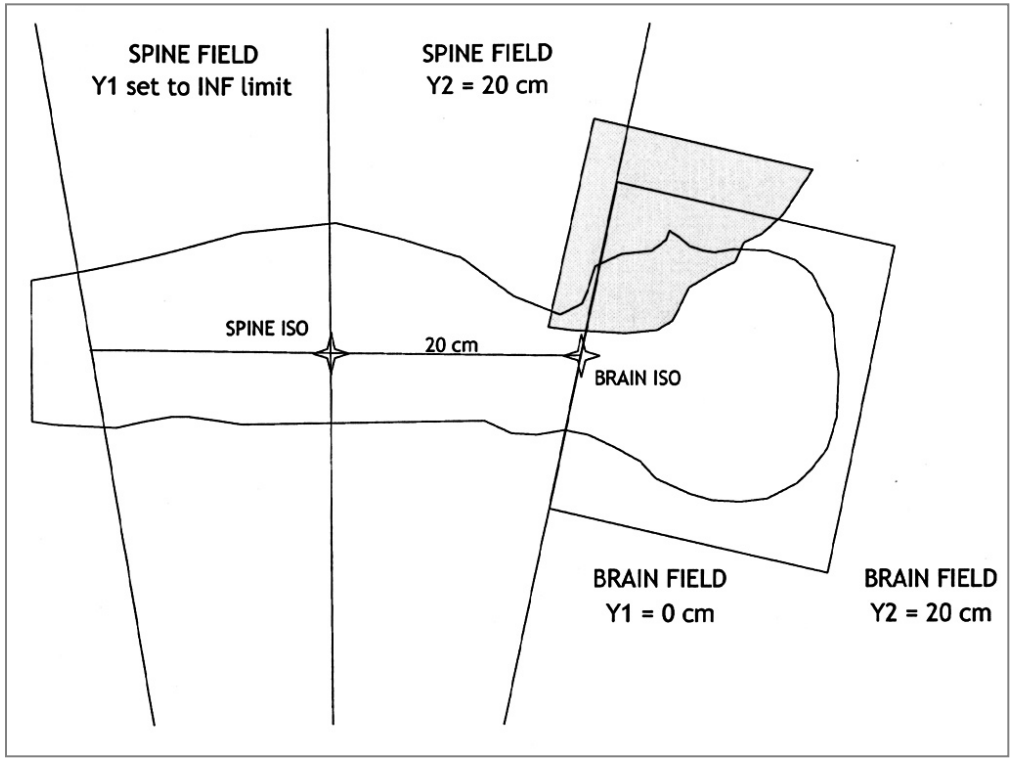
- Supine position
- CT simulation
- Simplification of beam geometry
- Better junction planning
- New delivery options (e.g., Tomotherapy, VMAT)

From prone to supine….





McGill technique



- Supine position, neck extended
- Isocentre of brain fields at junction with spine field
- Isocentre of (upper) spine field at fixed distance from centre of brain field/fixed collimator angle of 11° for brain fields

Parker and Freeman, Radiotherapy and Oncology 2006; 78:217-222

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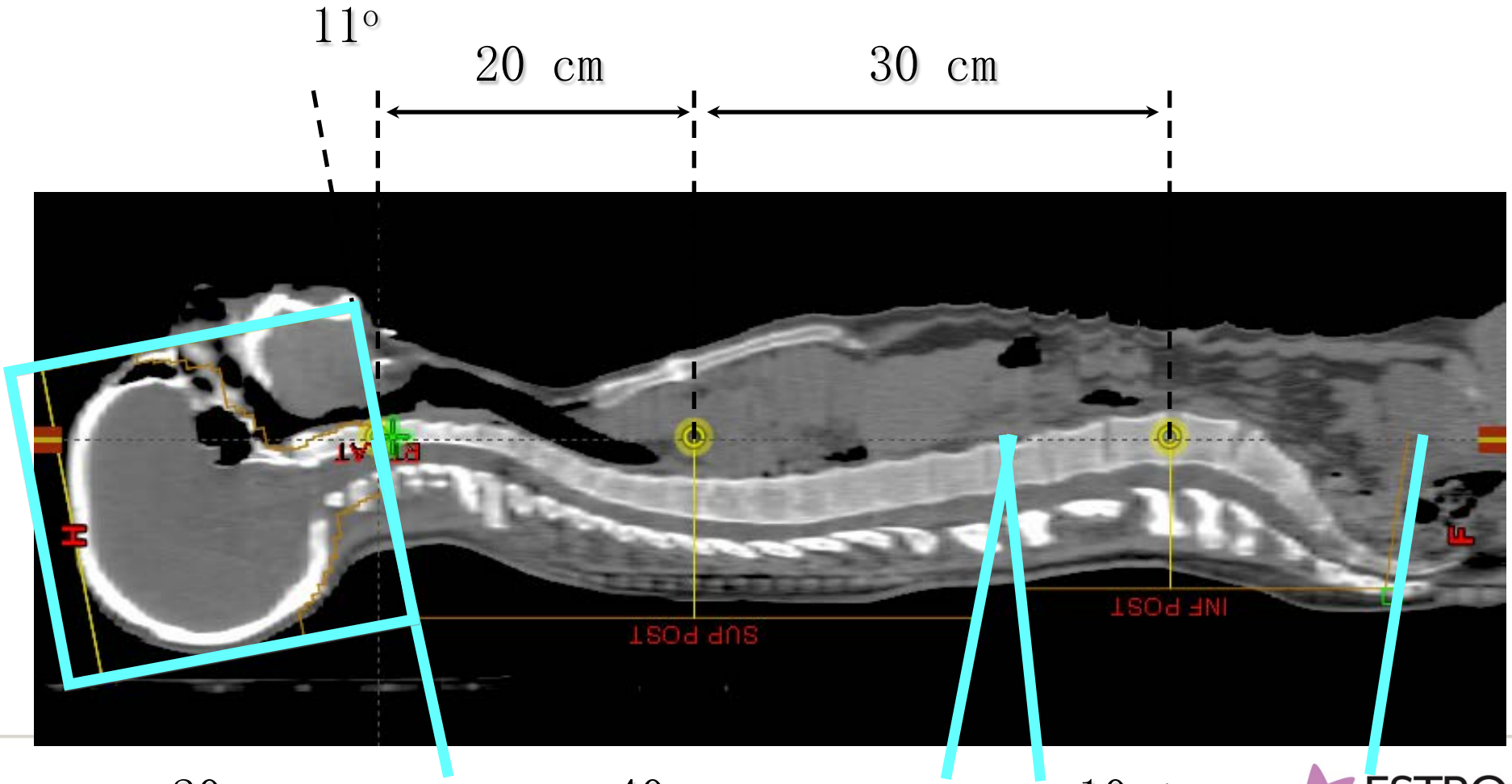
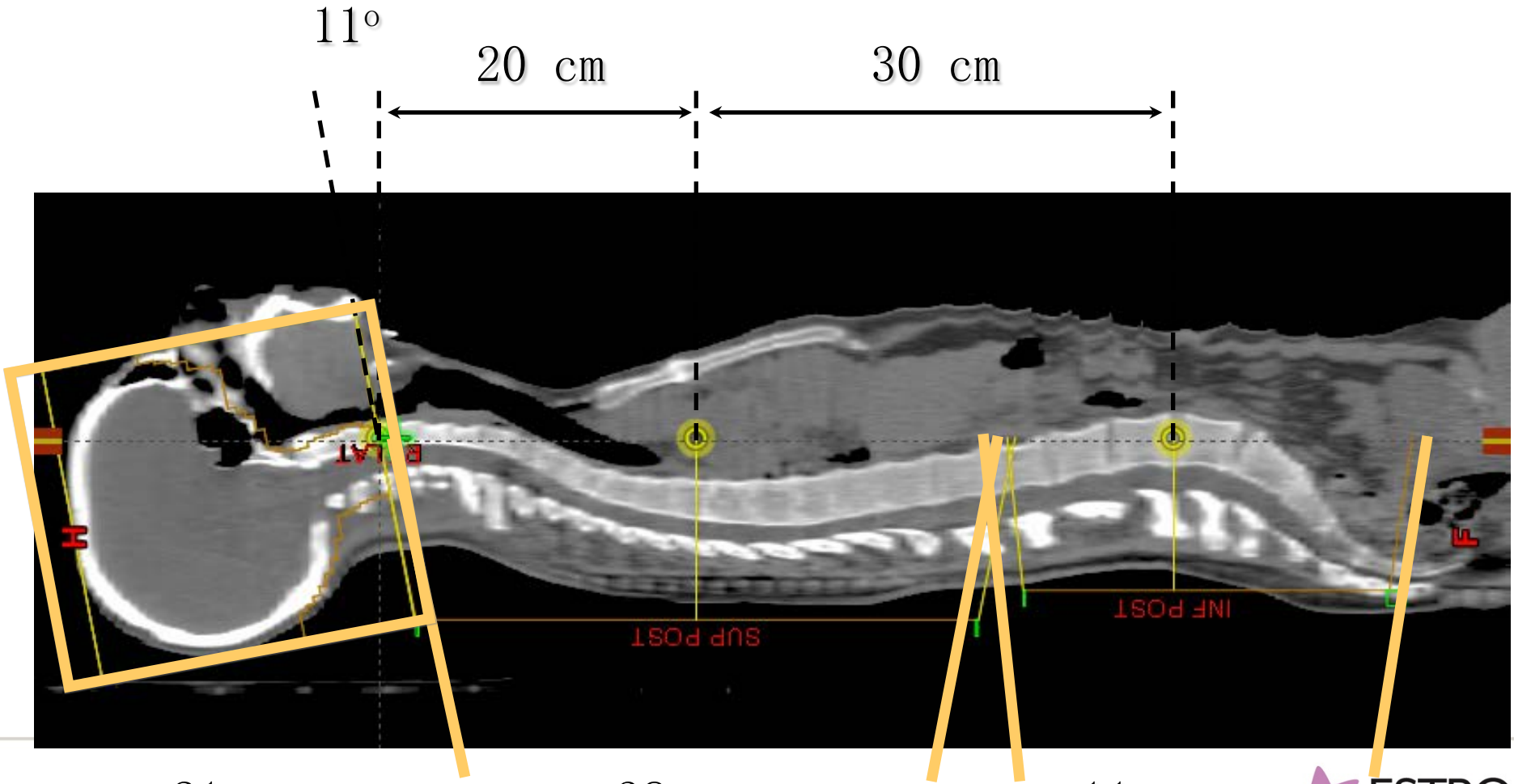
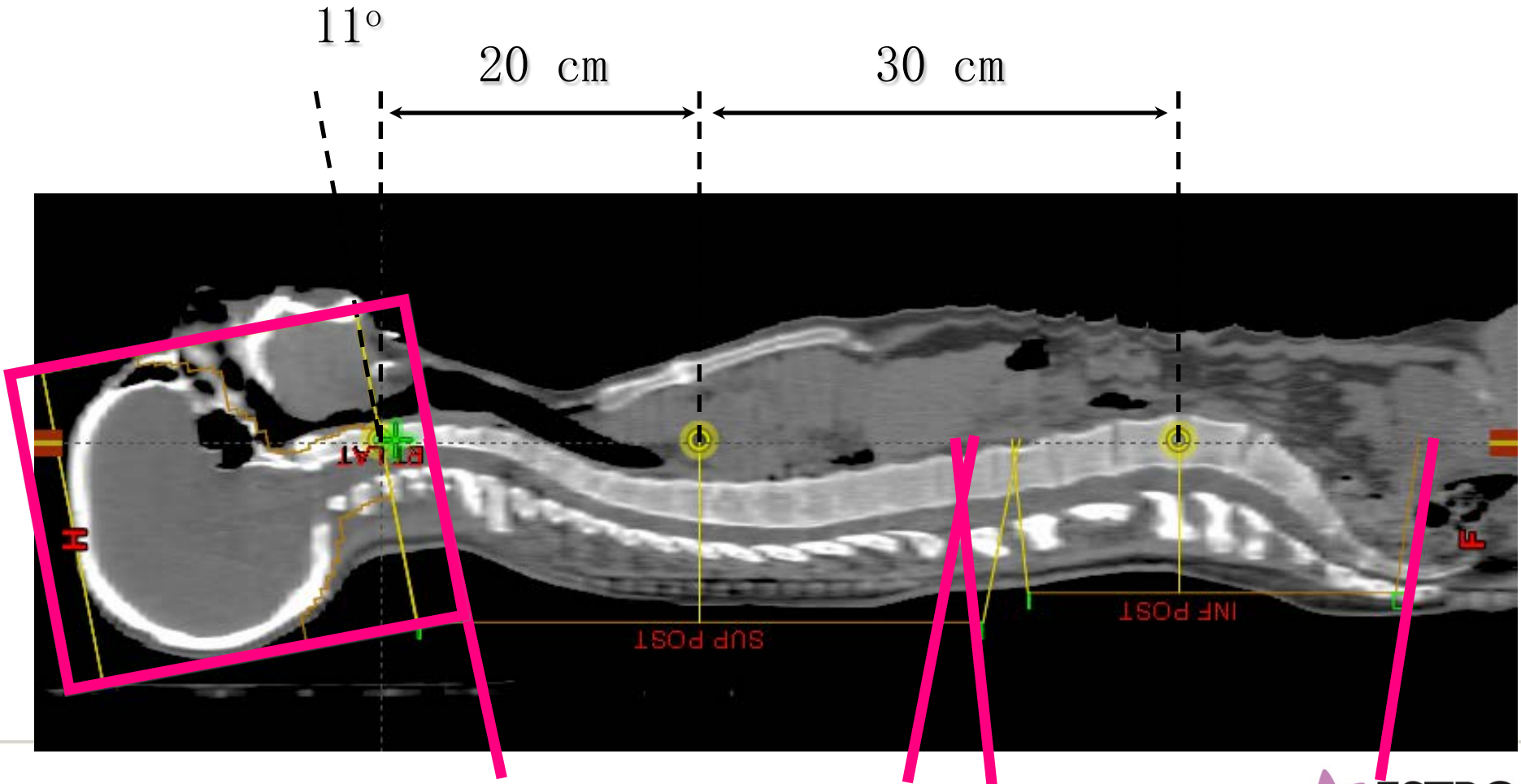
McGill technique: junctions



McGill technique: junctions



McGill technique: junctions



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Comparison with other CT-based techniques

- Advantages of McGill technique
  - **Supine position** → greater comfort, reproducibility, safety if anaesthesia required
  - Clean junction/**no couch rotation**
  - **Fixed distance longitudinal couch movements** only
  - MLC compensation for spinal axis, **automated delivery**
- Fulfills requirement for a technique "as simple and practical as possible" (Van Dyk, 1978)!

Other options for CSI

Rationale: to reduce long term complications of treatment

Long-term complications of radiotherapy

Due to radiotherapy to the brain
- Neuro-cognitive deficits/effects on social interactions
- Hypopituitarism
- Alopecia
- Cataracts
- Hearing loss

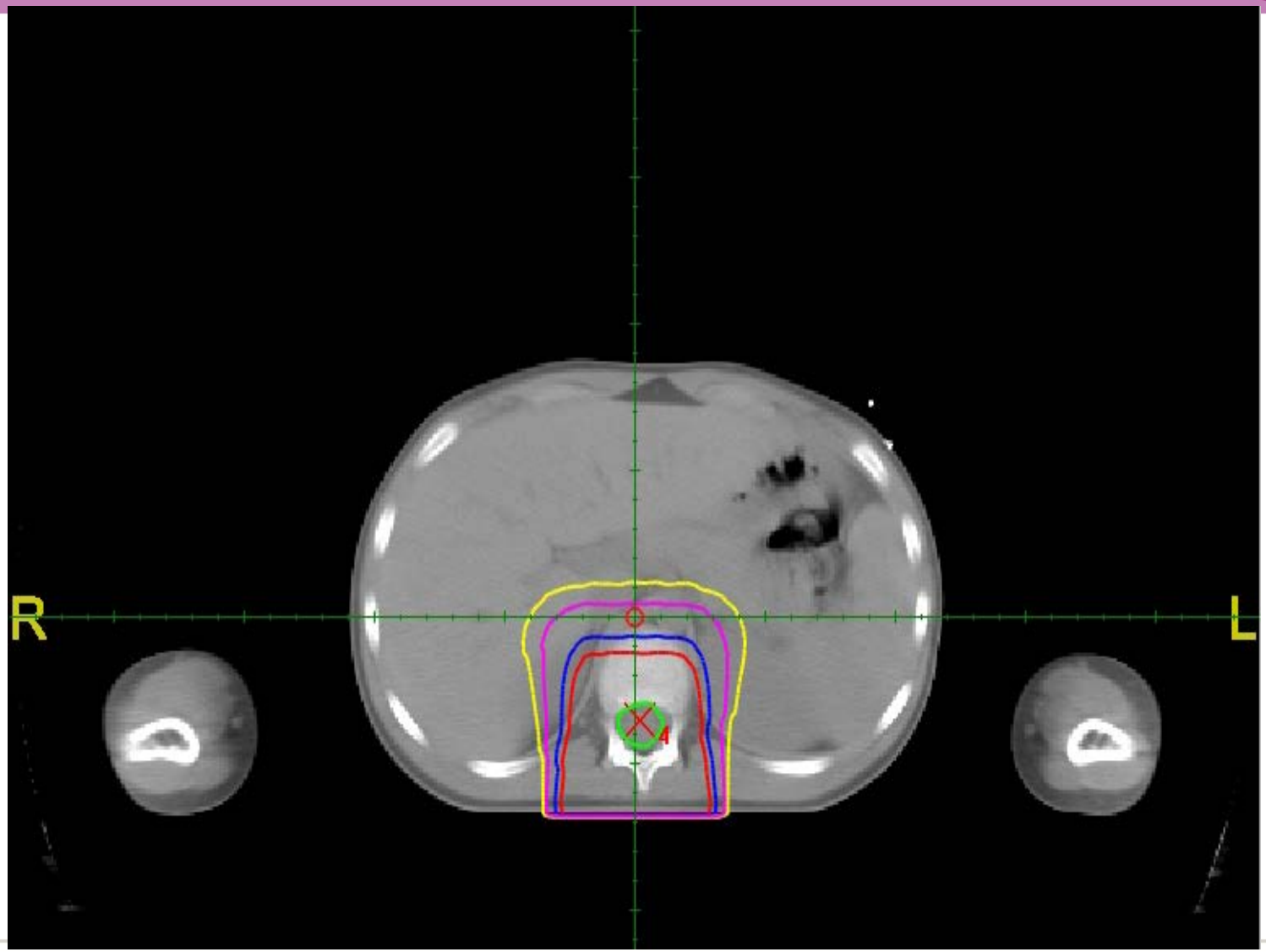
Due to radiotherapy to the spine
- Short stature
- Primary hypothyroidism
- Impaired lung function
- Effects on the heart
- Primary ovarian failure

Both
- Second cancers...

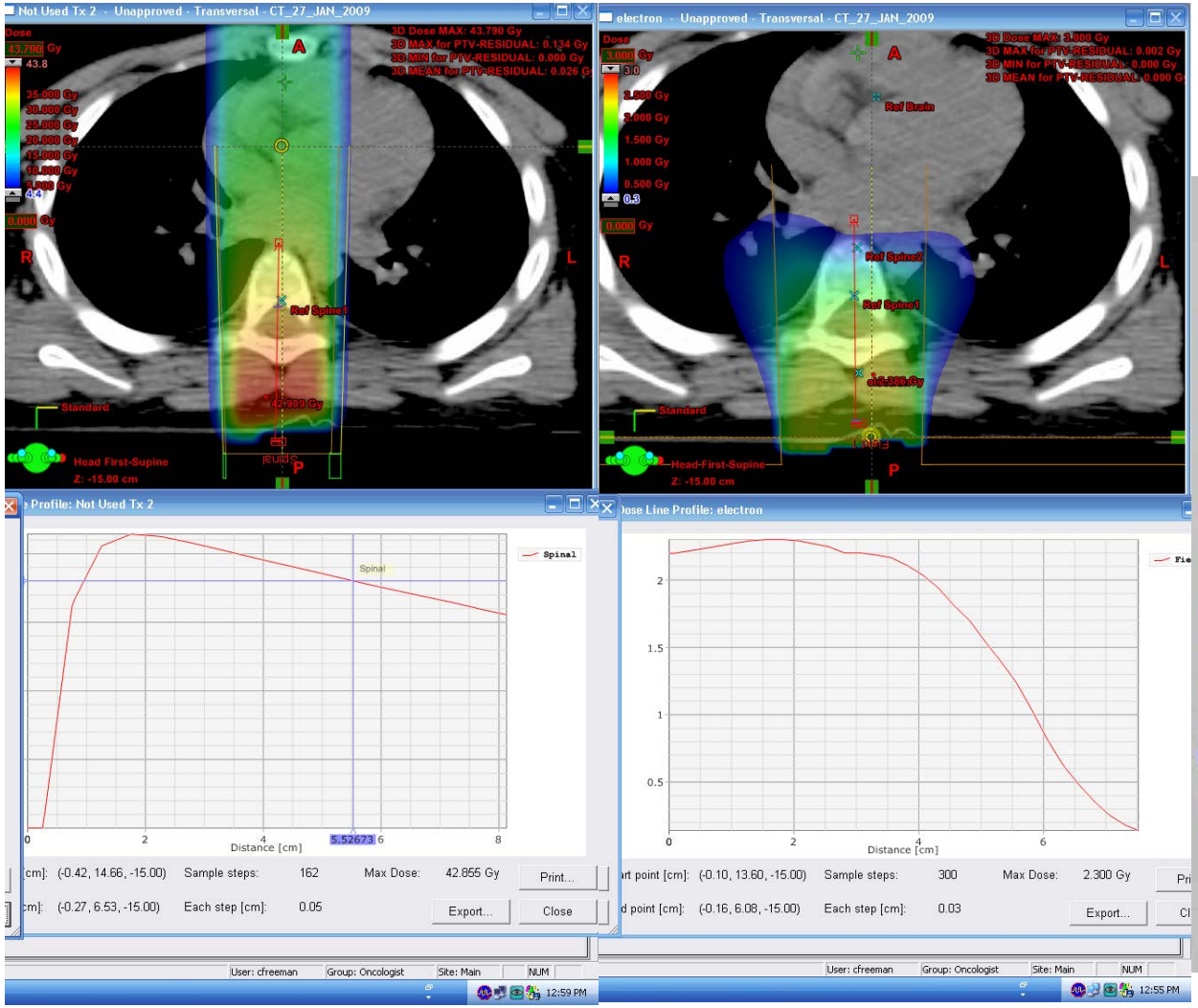
Other options for CSI

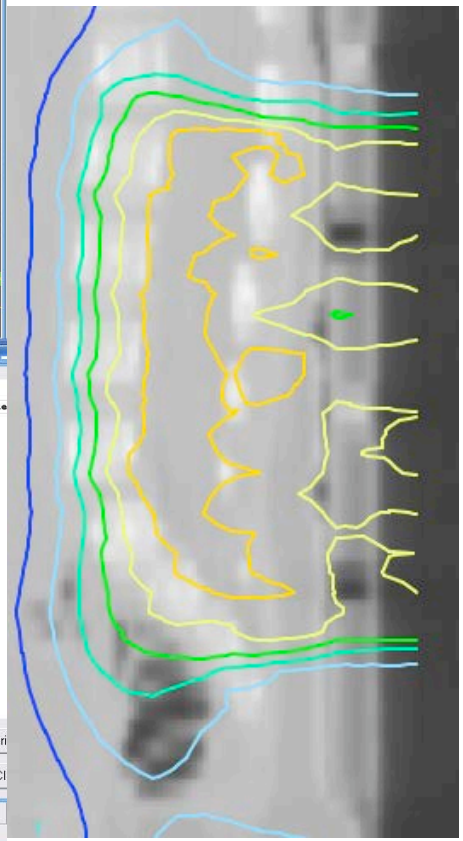
- Electrons for the spinal axis
- IMRT (tomotherapy, VMAT)
- Proton therapy

Electrons for spinal irradiation



Electrons for the spinal axis

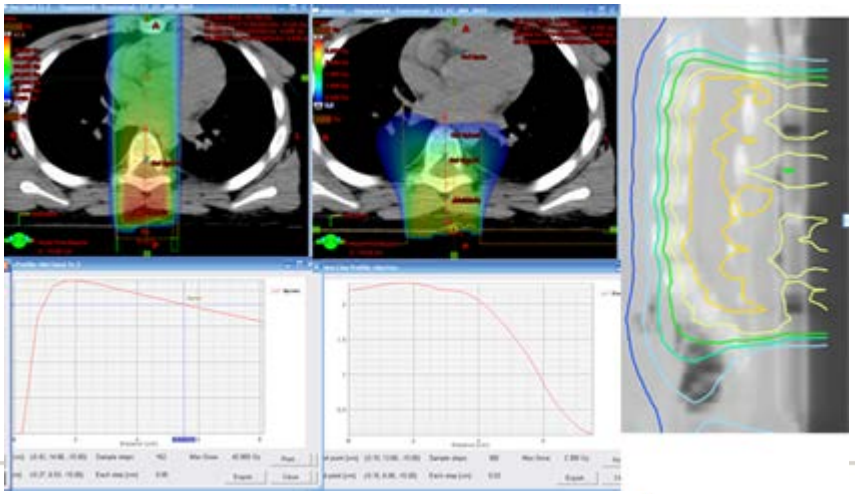




Electrons for the spinal axis

Problems:

- Limitations on length of field (20-25 cm)
- Dosimetry at junctions
- Possible variations in dose to CTV because of attenuation by bone
- Dose gradient in vertebrae
- Increased dose to lungs
- Use of energies < 22 MEV are associated with an excess of failures (Carrie, 1992)
- Use with care !



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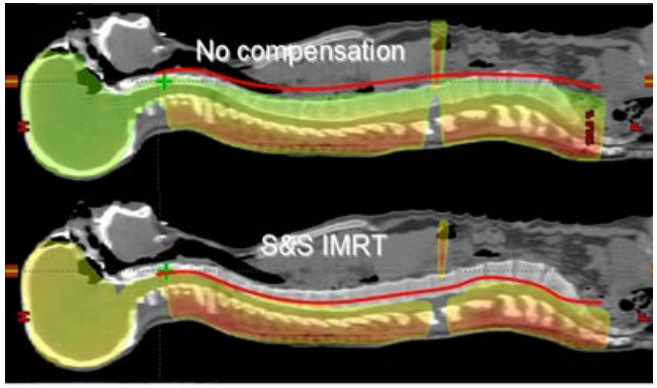
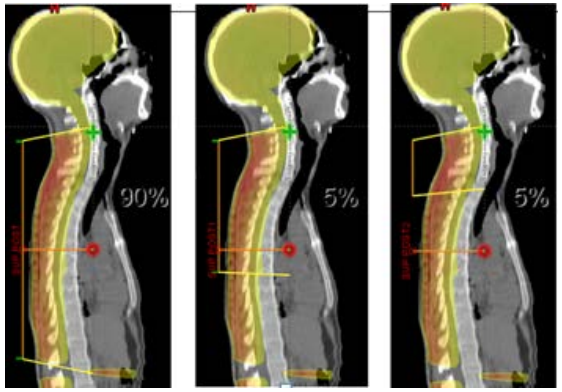
IMRT for the spinal axis

- IMRT reduces high dose exposure to all OARs: Thyroid,lungs,heart,liver,kidneys,ovaries

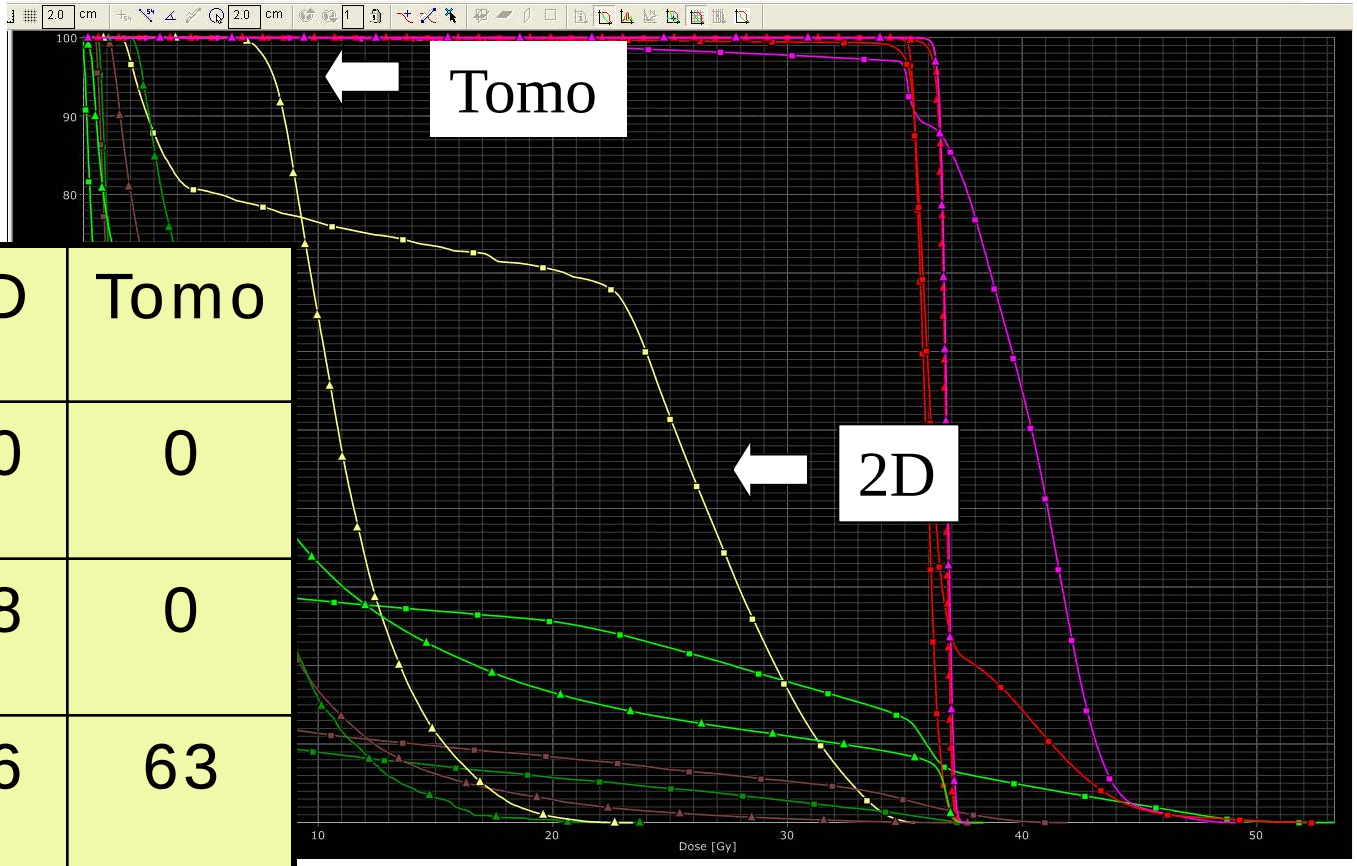
..... At the expense of increased low dose exposure





Dose to the heart

	2D	3D	Tomo
V30Gy	17	10	0
V20Gy	70	58	0
V10Gy	76	66	63
V5Gy	82	73	100



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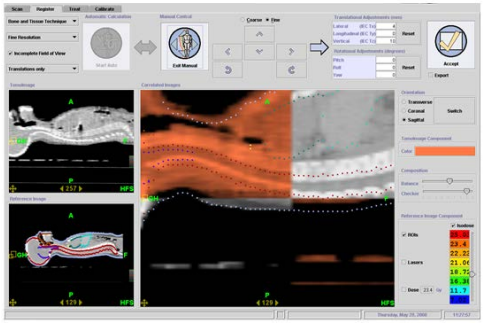
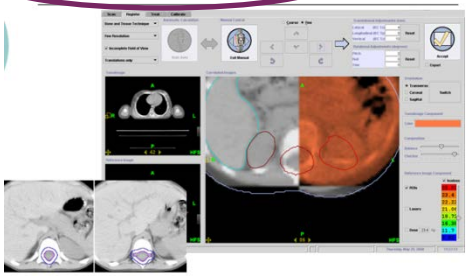
New technical approaches

- Tomotherapy for CSI with IGRT
- VMAT planning using a conventional LINAC with IGRT

Improved reproducibility



Reduced PTV margin



No junctions or field matching

No junctions or field matching

- Less dose posterior to the target
- No overlap/less dose anterior to the target
- Bath dose (?)

A Little to a Lot or a Lot to a Little?

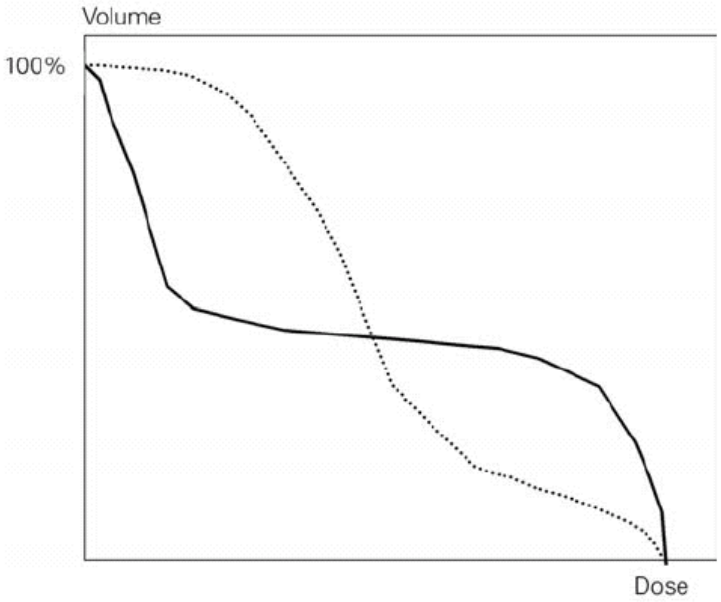
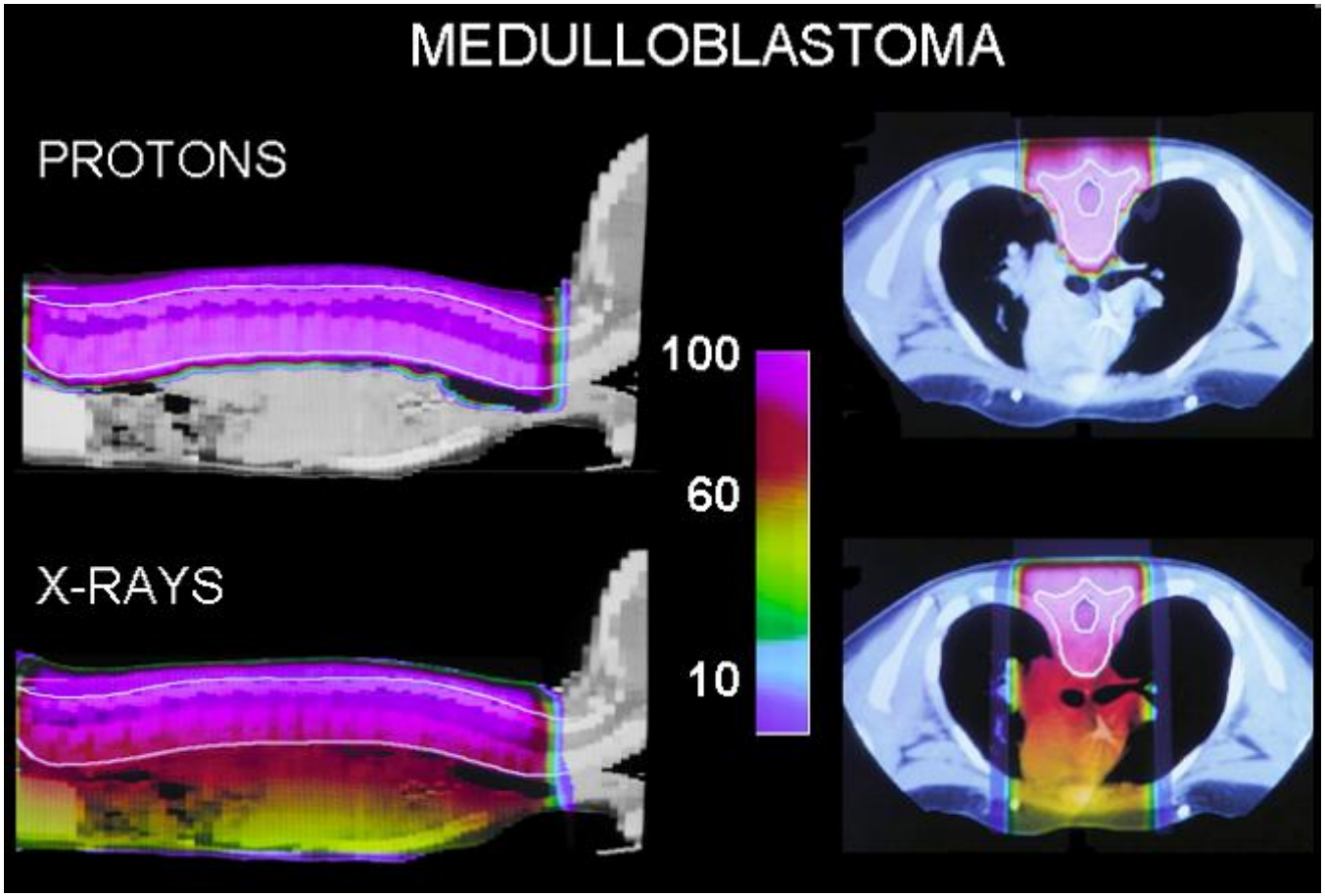


Figure 1. Schematic cumulative dose-volume histogram.

Abbildung 1. Schematische Beschreibung des Problems am Dosis-Volumen-Histogramm.

Protons



Thanks to Nancy Tarbell MD

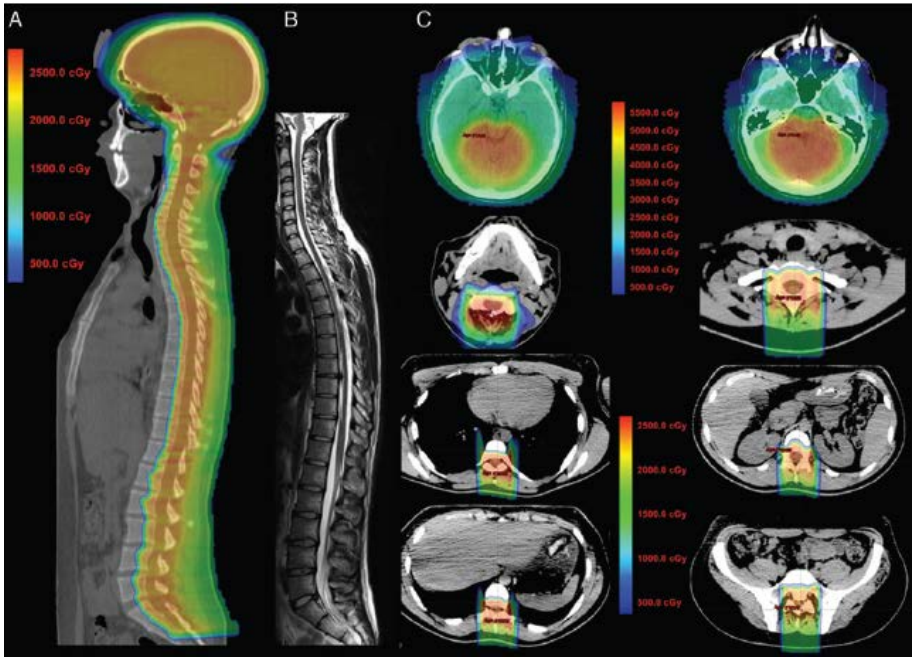
Proton therapy

Attractive for...

•Dose escalation

•Potentially reducing adverse effect of treatment

•Focal treatment and large volumes (i.e. CSI)



Caution for....
-Deviations (organ motion, set-up errors, density changes..)
-Metal implants
-High weighted spots
-Beam arrangements

Barney CL et al., Neuro-oncology, 2014

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CSI: concluding remarks

- CSI is a complex treatment that for optimal results must be done properly, using modern technology including CT simulation with additional information provided by MRI for target volume definition
- Newer techniques address many of the technical issues that were associated with older techniques, as well as being much simpler to plan and treat
- Reduced dose to OARs is possible using IMRT + IGRT
- The future: protons for all?

CSI: concluding remarks

POINT/COUNTERPOINT

Pediatric medulloblastoma: Is proton beam the only ethically appropriate radiation treatment?

Anthony Zietman, MD, FASTRO, *Editor-in Chief IJROBP*

International Journal of Radiation Oncology biology • physics
www.redjournal.org

PRO

- Fewer acute toxicity

- Substantial reduced risk of radiation related secondary neoplasm

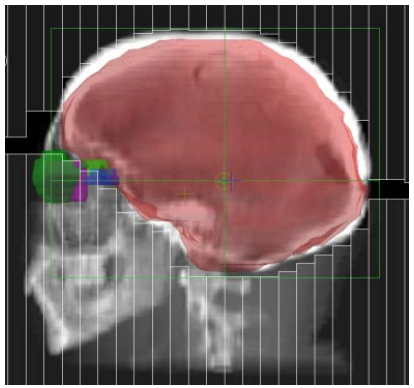
CON

- No sufficient clinical data to argue that proton therapy is the only acceptable treatment

- Future study is required to better characterize the long-term clinical benefit of proton therapy

Radiotherapy: treatment techniques wide field irradiation

Whole Brain Radiation Therapy



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WBI

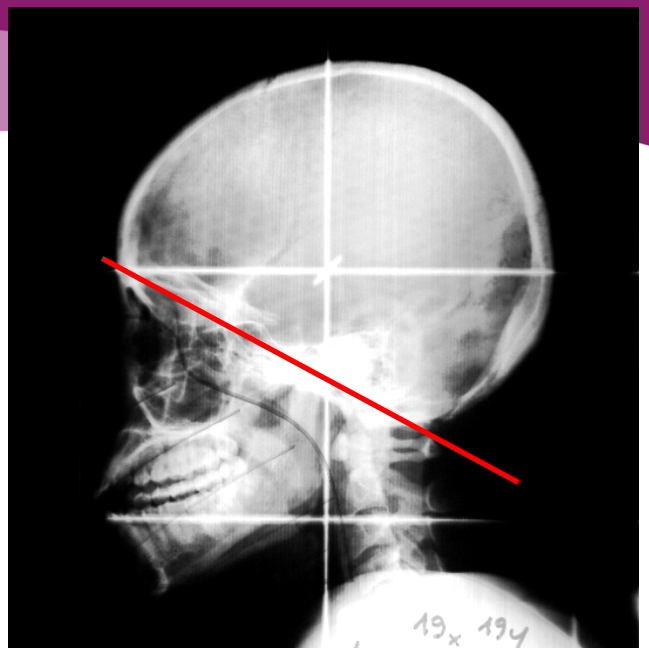
- WBI: technical aspects

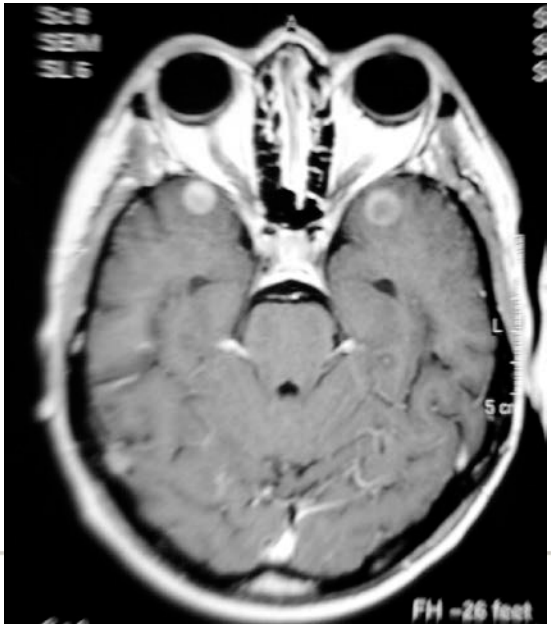
Good RT technique also for palliation

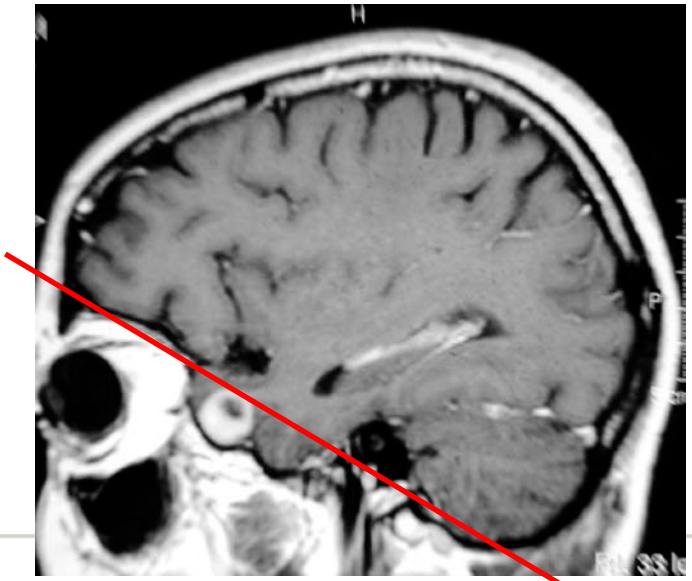
Technical considerations:

Modern conventional CNS RT:

- conformal
- conventional fraction size







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PHYSICS CONTRIBUTION

THE ROLE OF CT SIMULATION IN WHOLE-BRAIN IRRADIATION

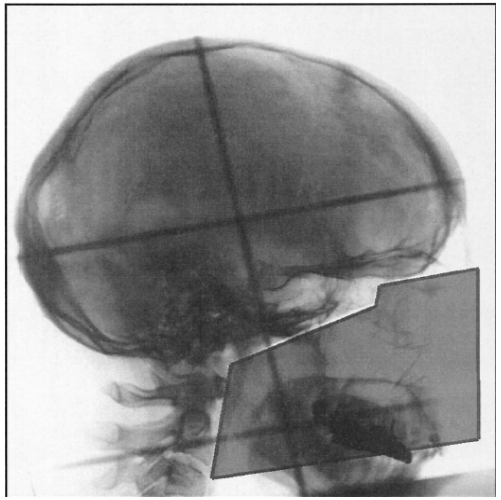
STEPHAN GRIPP, M.D., ROLF DOEKER, M.D., MICHAEL GLAG, M.D., PETRA VOGELSANG, BURCKHARDT BANNACH, M.S., THORSTEN DOLL, M.S., KLAUS MUSKALLA, PH.D., AND GERD SCHMITT, M.D.

Klinik für Strahlentherapie und Radiogische Onkologie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

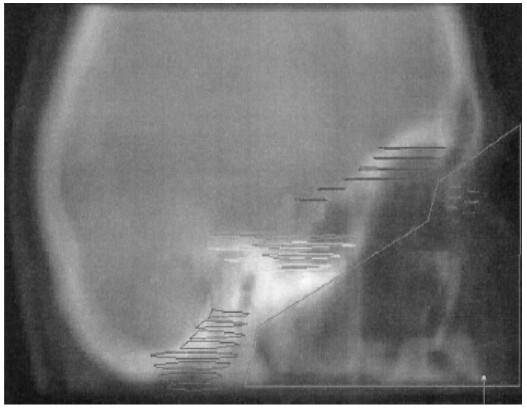
To evaluate the potential benefits of CT simulation in WBI comparing field-shaping based on 3D CT simulation to conventional 2D simulation.

- CT head scans were obtained from 20 patients.
- Conventional 2D planning was obtained by drawing the block contours on digitally reconstructed radiographs (DRR) as in conventional simulation
- 3D-planning was obtained by contouring target volume on the CT slices.

- To assess the adequacy of margins, the minimal distance from the field edge to the contoured organ was measured for both planning situations at six sites (the subfrontal region (midline), both ocular lenses, both temporal lobes, and the medulla)



Portal design in WBI by conventional simulation



3D block shaping in 3D-planning

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Klinik für Strahlentherapie und Radiogische Onkologie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

RESULTS

In conventional planning using DRR

- major geographic mismatches (>3 mm) occurred in the subfrontal region
- minor mismatches (-3 to 0 mm) predominantly occurred in the contralateral lens (21%), ipsilateral lens (10%), and subfrontal region (9%)
- close margins (0–5 mm) were most frequently noted at the contralateral lens (49%), ipsilateral lens (35%), and the subfrontal region (28%)

In 3D planning

- mismatches were not found
- close margins were inevitable at the ipsilateral lens (5%), subfrontal region (30%), and contralateral lens (70%)

PHYSICS CONTRIBUTION

THE ROLE OF CT SIMULATION IN WHOLE-BRAIN IRRADIATION

STEPHAN GRIPP, M.D., ROLF DOEKER, M.D., MICHAEL GLAG, M.D., PETRA VOGELSANG, BURCKHARDT BANNACH, M.S., THORSTEN DOLL, M.S., KLAUS MUSKALLA, PH.D., AND GERD SCHMITT, M.D.

Klinik für Strahlentherapie und Radiogische Onkologie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

CT simulation in WBI is significantly superior to conventional simulation with respect to complete coverage of the target volume and protection of the eye lenses

Neurocognitive effects of WBRT

Dementia after WBI

Risk factors

- Treatment volume
- Fraction size >2 Gy
- Total dose: less important than fraction size
- Concurrent chemotherapy: possible
- Age: elderly patients (> 60 yrs) at higher risk

Neurocognitive effects of WBRT

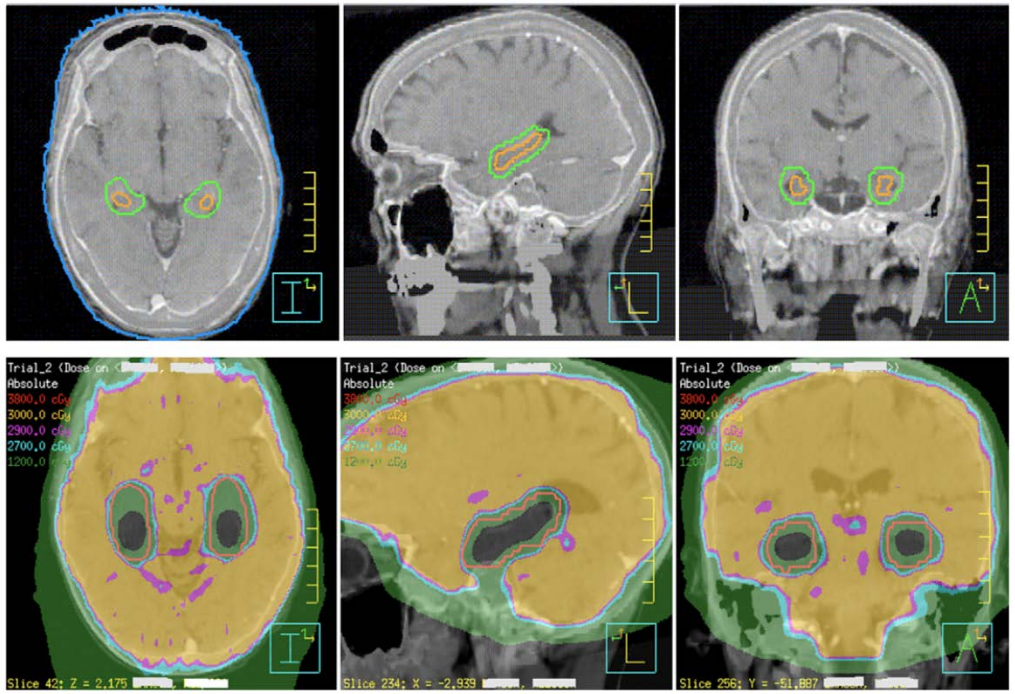
A European Organisation for Research and Treatment of Cancer Phase III Trial of Adjuvant Whole-Brain Radiotherapy Versus Observation in Patients With One to Three Brain Metastases From Solid Tumors After Surgical Resection or Radiosurgery: Quality-of-Life Results

- HRQOL was assessed at baseline, at 8 weeks, and then every 3 months for 3 years (EORTC Quality of Life Questionnaire C30 and Brain Cancer Module).

- The following six primary HRQOL scales were considered: global health status; physical, cognitive, role, and emotional functioning and fatigue.

- Overall, patients in the observation only arm reported better HRQOL scores than did patients who received WBRT.
- The differences were statistically significant mostly during the early follow-up period (for global health status at 9 months, physical functioning at 8 weeks, cognitive functioning at 12 months and fatigue at 8 weeks).

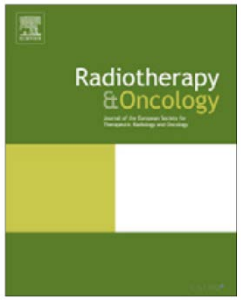
Hippocampal avoidance and WBI



Review

Why avoid the hippocampus? A comprehensive review

Vinai Gondi [a,*], Wolfgang A. Tomé [a,b], Minesh P. Mehta [a]



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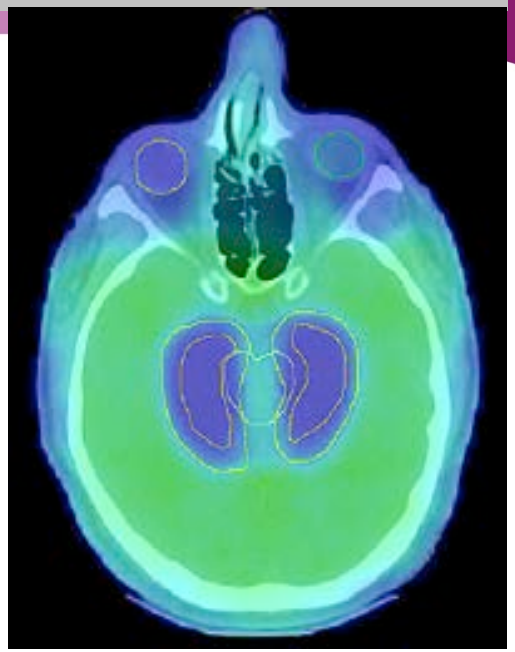
Hippocampal avoidance



Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 4, pp. 1244–1252, 2010

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2010.01.039

PHYSICS CONTRIBUTION

HIPPOCAMPAL-SPARING WHOLE-BRAIN RADIOTHERAPY: A "HOW-TO" TECHNIQUE USING HELICAL TOMOTHERAPY AND LINEAR ACCELERATOR–BASED INTENSITY-MODULATED RADIOTHERAPY

Vinai Gondi, M.D.,* Ranjini Tolakanahalli, M.S.,† Minesh P. Mehta, M.D.,* Dinesh Tewatia, M.S.,*† Howard Rowley, M.D.,‡ John S. Kuo, M.D., Ph.D.,*§ Deepak Khuntia, M.D.,* and Wolfgang A. Tomé, Ph.D.*†

Departments of *Human Oncology, †Medical Physics, ‡Neuroradiology, and §Neurological Surgery, University of Wisconsin Comprehensive Cancer Center, Madison, WI

Radiotherapy and Oncology 95 (2010) 327–331

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Whole brain radiotherapy

Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: Safety profile for RTOG 0933

Vinai Gondi [a,*], Wolfgang A. Tome [a,b], James Marsh [e], Aaron Struck [a], Amol Ghia [a], Julius V. Turian [e], Søren M. Bentzen [a,c], John S. Kuo [a,d], Deepak Khuntia [a], Minesh P. Mehta [a]

[a] Department of Human Oncology; [b] Department of Medical Physics; [c] Department of Biostatistics and Medical Informatics; and [d] Department of Neurological Surgery, University of Wisconsin Comprehensive Cancer Center, Madison, WI, USA; [e] Department of Radiation Oncology, Rush University Medical Center, Chicago, IL, USA

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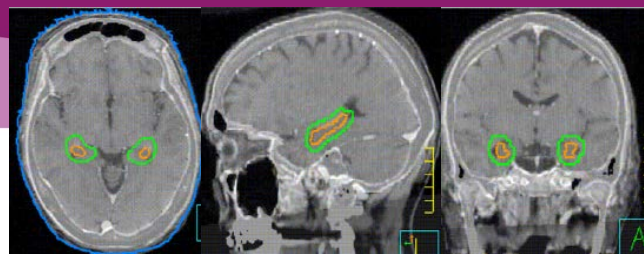
WBI with hippocampal sparing Remarks



- Hippocampus plays a fundamental role in immediate or long-term memory and the spatial learning and is rarely involved by metastasis
- Sparing hippocampi during WBI becomes possible with volumetric modulated arc therapy (VMAT) or with helical tomotherapy
- The delineation of the structures should be performed after co-registration of gadolinium-enhanced T1-weighted MR-images with the planning CT
- The D40 to both hippocampi should not be greater than 7.3 Gy
- Preliminary informations of a possibile neurocognitive sparing effect (delayed recall as assessed by HTVL-R)

Hippocampal avoidance and WBI

6.8 Compliance Criteria and Critical Structure Constraints (12/5/11)

Treatment Component	Parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
MRI/CT Fusion and Contouring	MRI-CT fusion	No corrections to MRI/CT fusion requested	No corrections to MRI/CT fusion requested	Corrections to MRI/CT fusion requested
	Hippocampal Contouring	≤ 2 mm deviation using the Hausdorff distance*	> 2, ≤ 7 mm deviation using the Hausdorff distance*	> 7 mm deviation using the Hausdorff distance*
HA-WBRT IMRT Planning	PTV	D2% ≤ 37.5 Gy D98% ≥ 25 Gy	D2% > 37.5 Gy, ≤ 40 Gy D98% < 25 Gy	V30 < 90% D2% > 40 Gy
	Hippocampus	D100% ≤ 9 Gy Maximum dose ≤ 16 Gy	D100% ≤ 10 Gy Maximum dose ≤ 17 Gy	D100% > 10 Gy Maximum dose > 17 Gy
	Optic Nerves and Chiasm	Maximum dose ≤ 37.5 Gy	Maximum dose ≤ 37.5 Gy	Maximum dose > 37.5 Gy
Unscheduled Break Days		0 break days	1-3 break days	> 3 break days

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Hippocampal avoidance and WBI

Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial

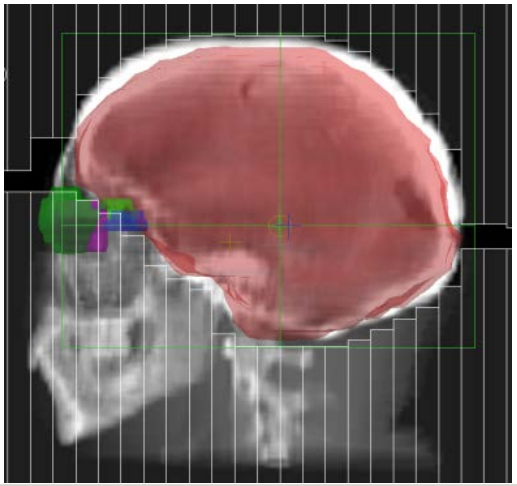
Vinai Gondi, Stephanie L. Pugh, Wolfgang A. Tome, Chip Caine, Ben Corn, Andrew Kanner, Howard Rowley, Vijayananda Kundapur, Albert DeNittis, Jeffrey N. Greenspoon, Andre A. Konski, Glenn S. Bauman, Sunjay Shah, Wenyin Shi, Merideth Wendland, Lisa Kachnic, and Minesh P. Mehta

- Eligible adult patients with brain metastases received HA-WBRT (30 Gy/10 fr).
- Standardized cognitive function and quality-of-life (QOL) assessments were performed at baseline and 2, 4, and 6 months.
- The primary end point was the Hopkins Verbal Learning Test–Revised Delayed Recall (HVLT-R DR) at 4 months.

- 42/113 pts were analyzable at 4 months. Mean relative decline in HVLT-R DR from baseline to 4 months was 7%, significantly lower in comparison with the historical control ($p < .001$).
- No decline in QOL scores was observed.

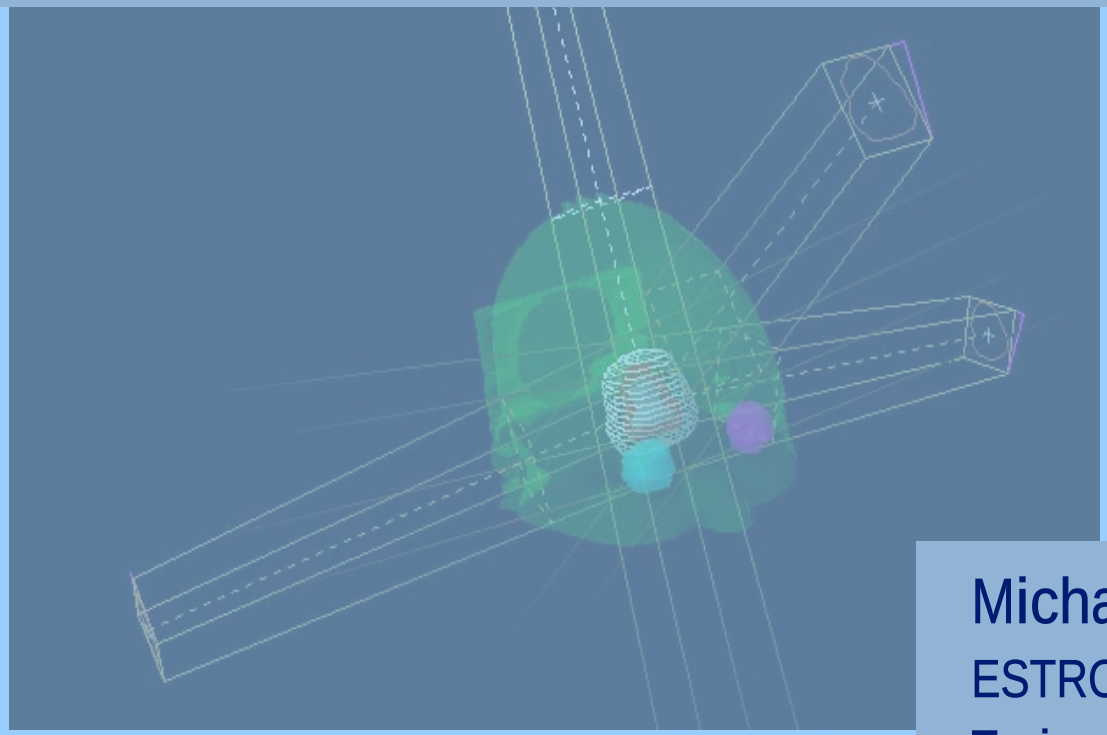
Whole Brain Radiation Therapy:

A simple technique still quite useful in the clinical arena



Localised radiotherapy techniques

for intracranial tumours



Michael Brada

ESTRO BT course

Torino October 2015

terminology

evaluation

Localised radiotherapy for intracranial tumours

3D conformal radiotherapy

IMRT

stereotactic radiotherapy

stereotactic radiosurgery

volumetric arcing IMRT (VMAT/RapidArc)

tomotherapy

image guided radiotherapy

particle therapy

Techniques of local radiation delivery

Attributes of modern local RT delivery

refinements of conformal radiotherapy

precision

conformality

- photons
- protons

time factor (4D RT)

- intrafraction patient and tumour motion
- interfraction changes in tumour & normal tissue

quality assurance

- imaging closer to treatment delivery (IGRT)

Classification of radiotherapy technologies

Attributes of modern local RT delivery

refinements of conformal radiotherapy

precision

- accurate tumour localisation
- precise dose targeting
  - immobilisation
  - image guidance

conformality

- photons
- protons

time factor (4D RT)

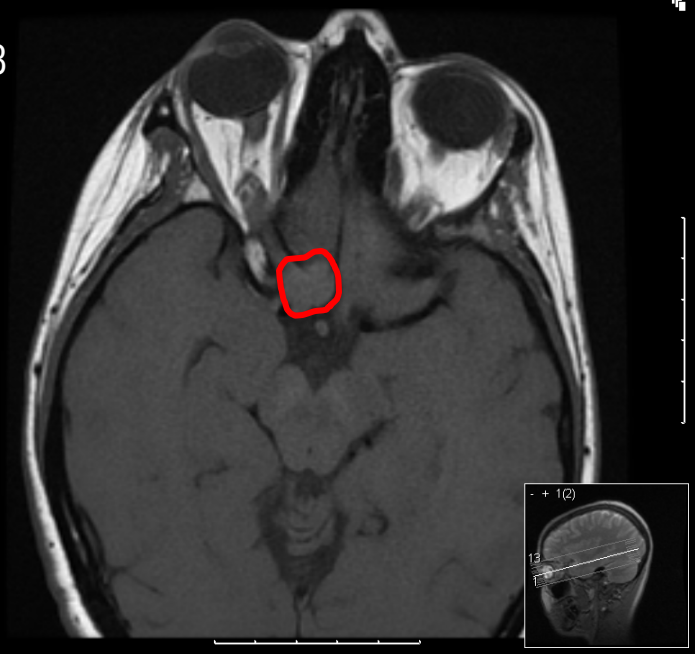
- intrafraction patient and tumour motion
- interfraction changes in tumour & normal tissue

quality assurance

- imaging closer to treatment delivery (IGRT)

Classification of radiotherapy technologies

12.8.08



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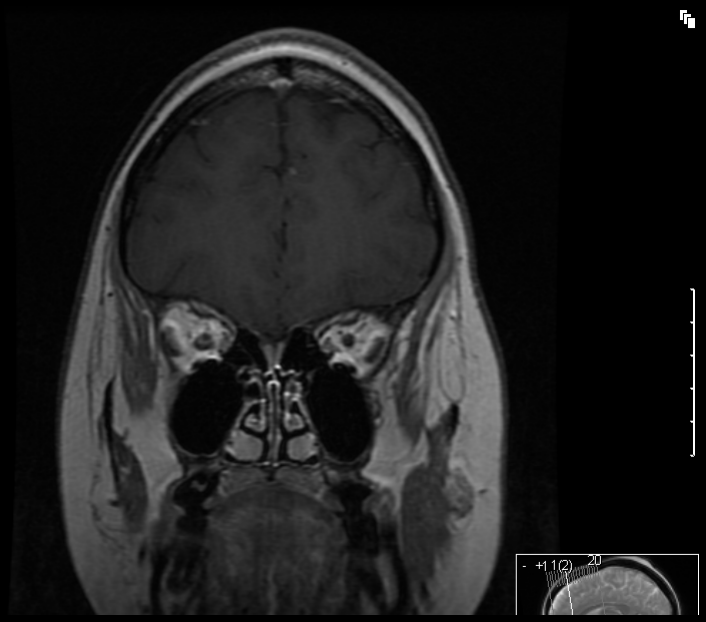

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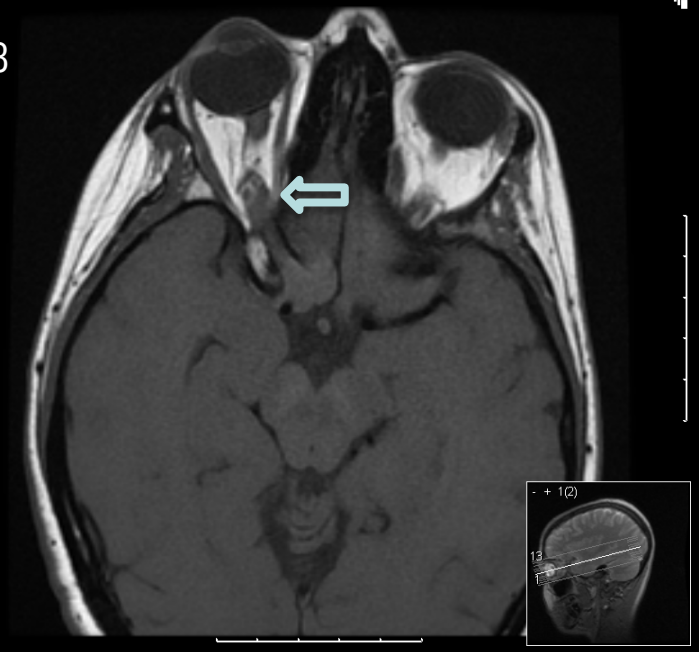

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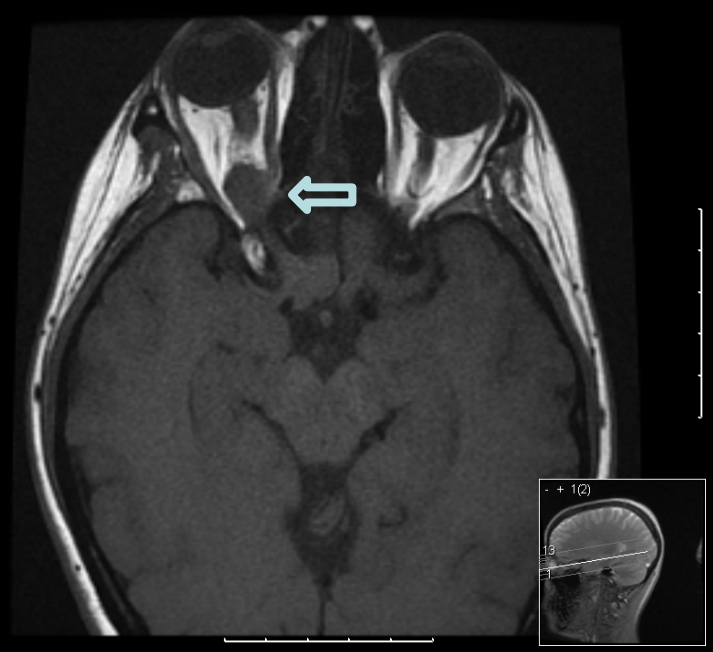

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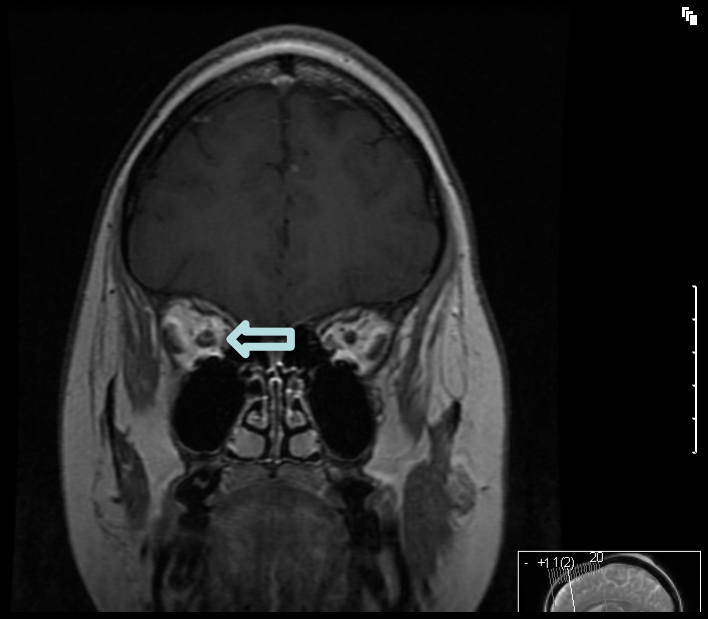

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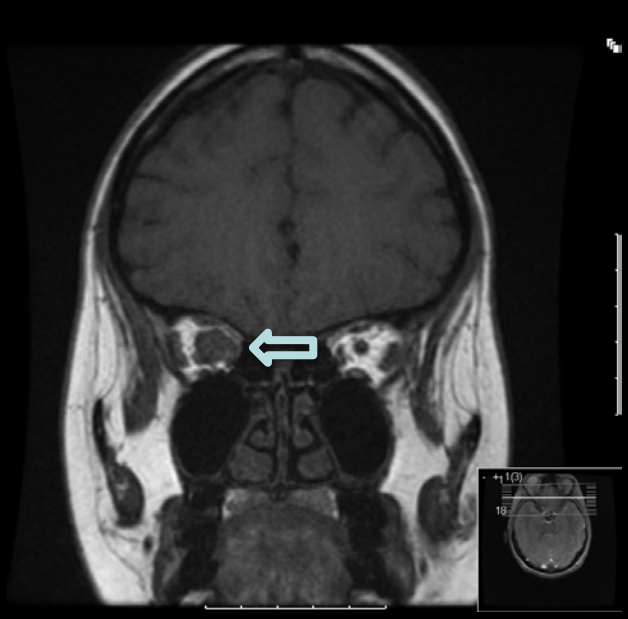


Attributes of modern local RT delivery

refinements of conformal radiotherapy

precision

- accurate tumour localisation
- precise dose targeting
  - immobilisation
  - image guidance

conformality

- photons
- protons

time factor (4D RT)

- intrafraction patient and tumour motion
- interfraction changes in tumour & normal tissue

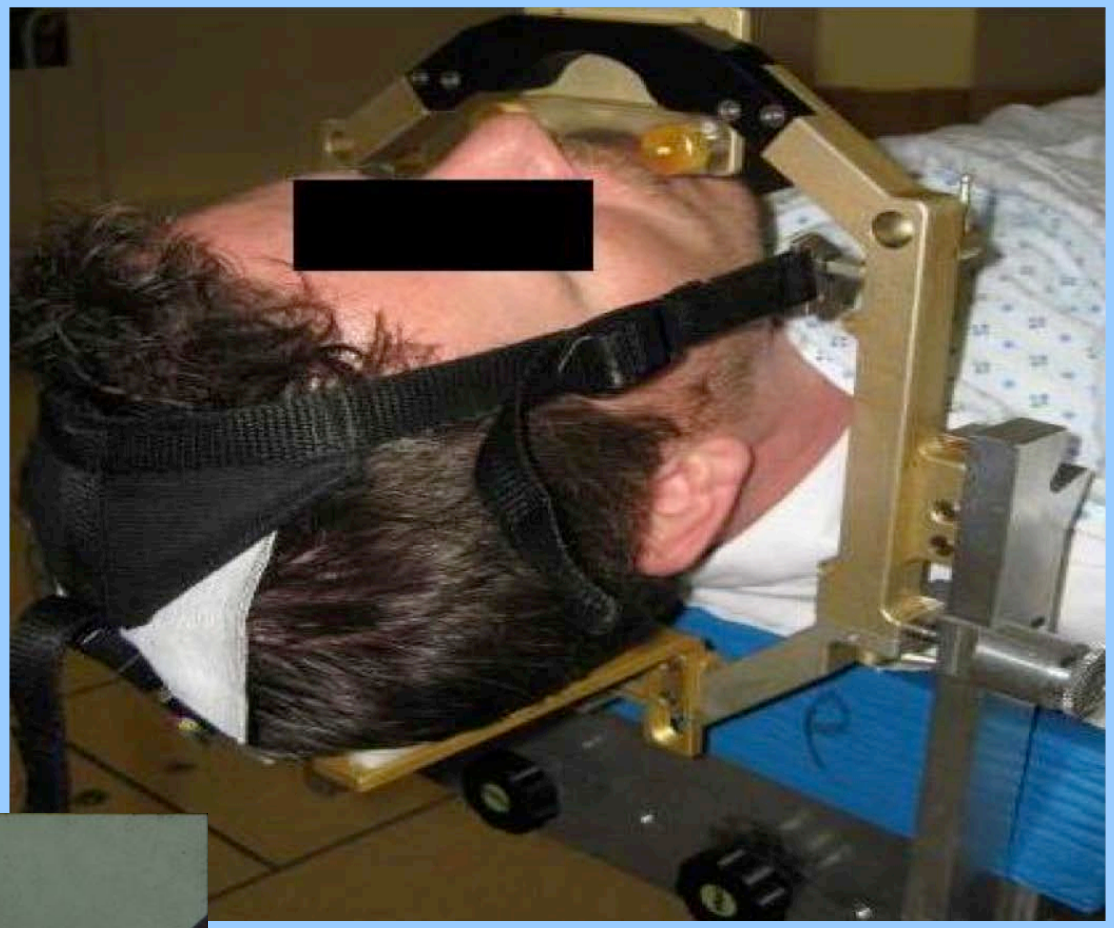
quality assurance

- imaging closer to treatment delivery (IGRT)

Classification of radiotherapy technologies

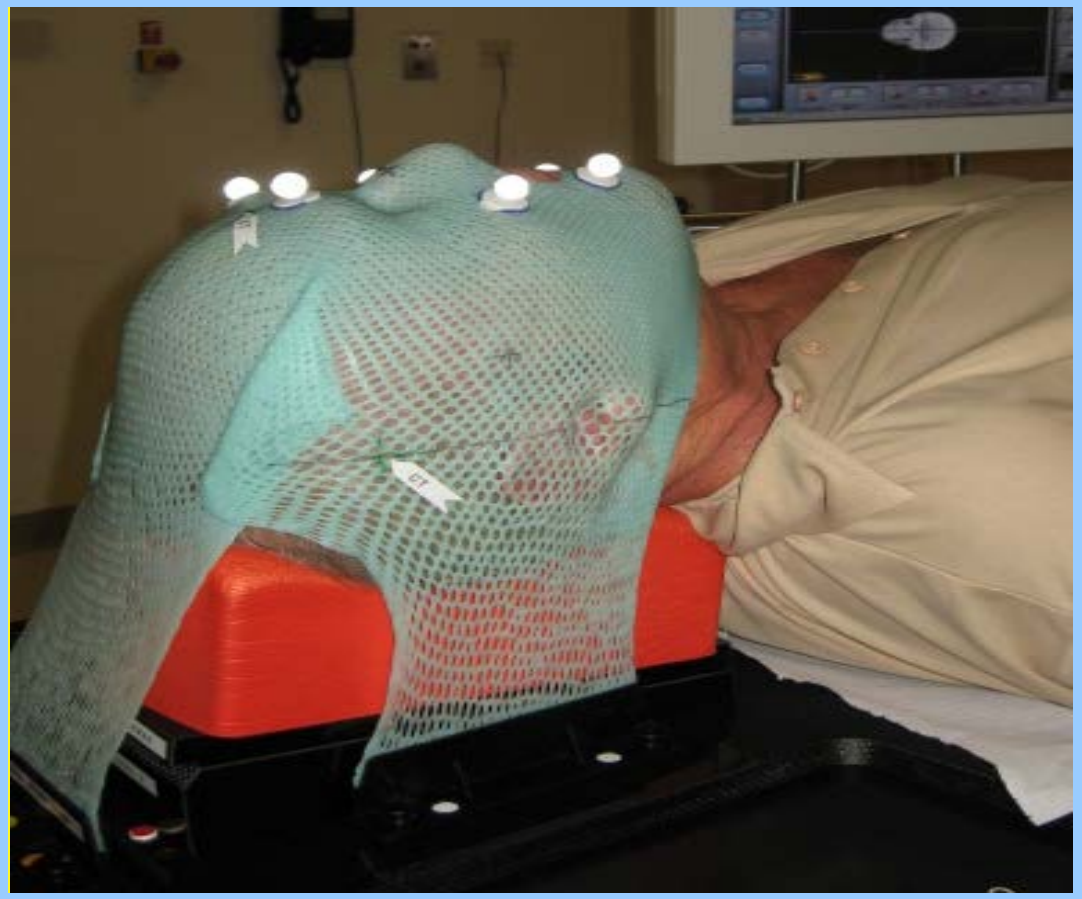
Frame system

GTC relocatable frame



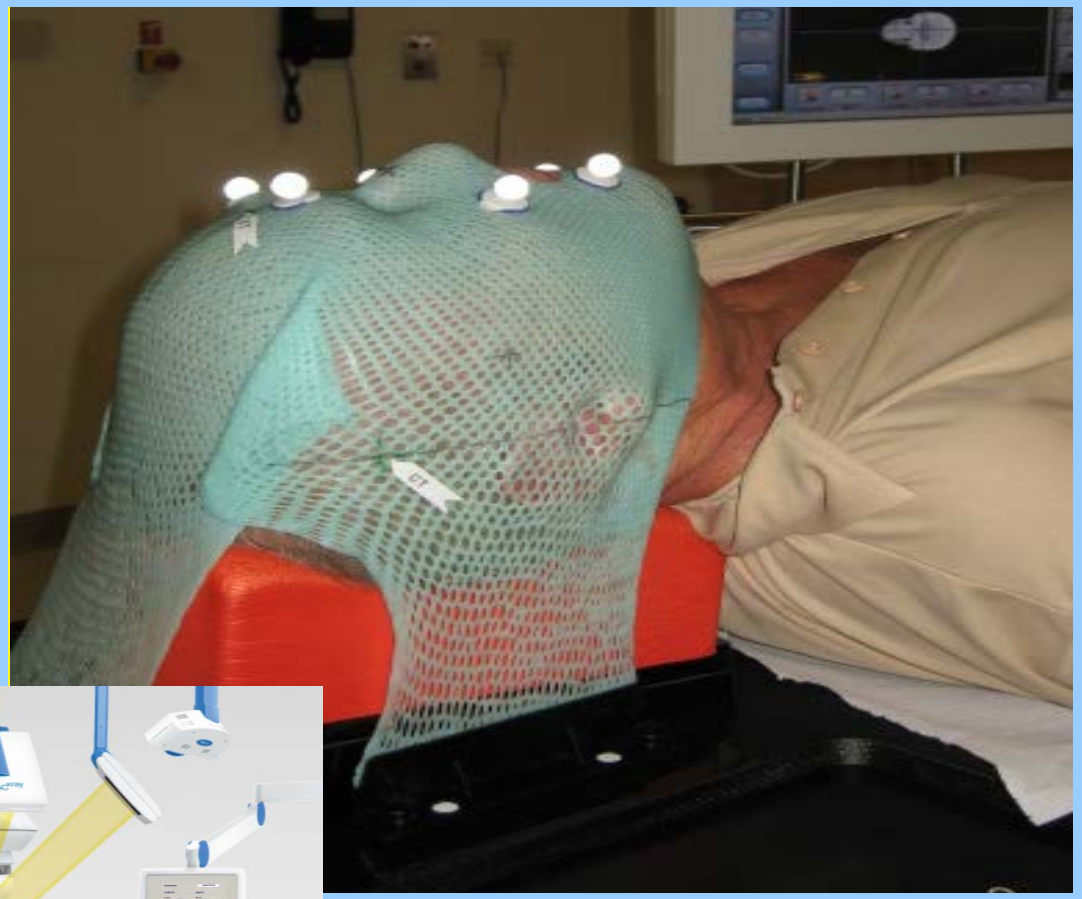
Methods of immobilization

Mask system



Methods of immobilization

Mask system
with on line correction



Methods of immobilization

CTV-PTV margins 3mm

Specialized mouthbite (dentist)
Expensive
4 visits for planning (incl. CT verification)
Relocation accuracy < 2 mm

CTV-PTV margins 4mm

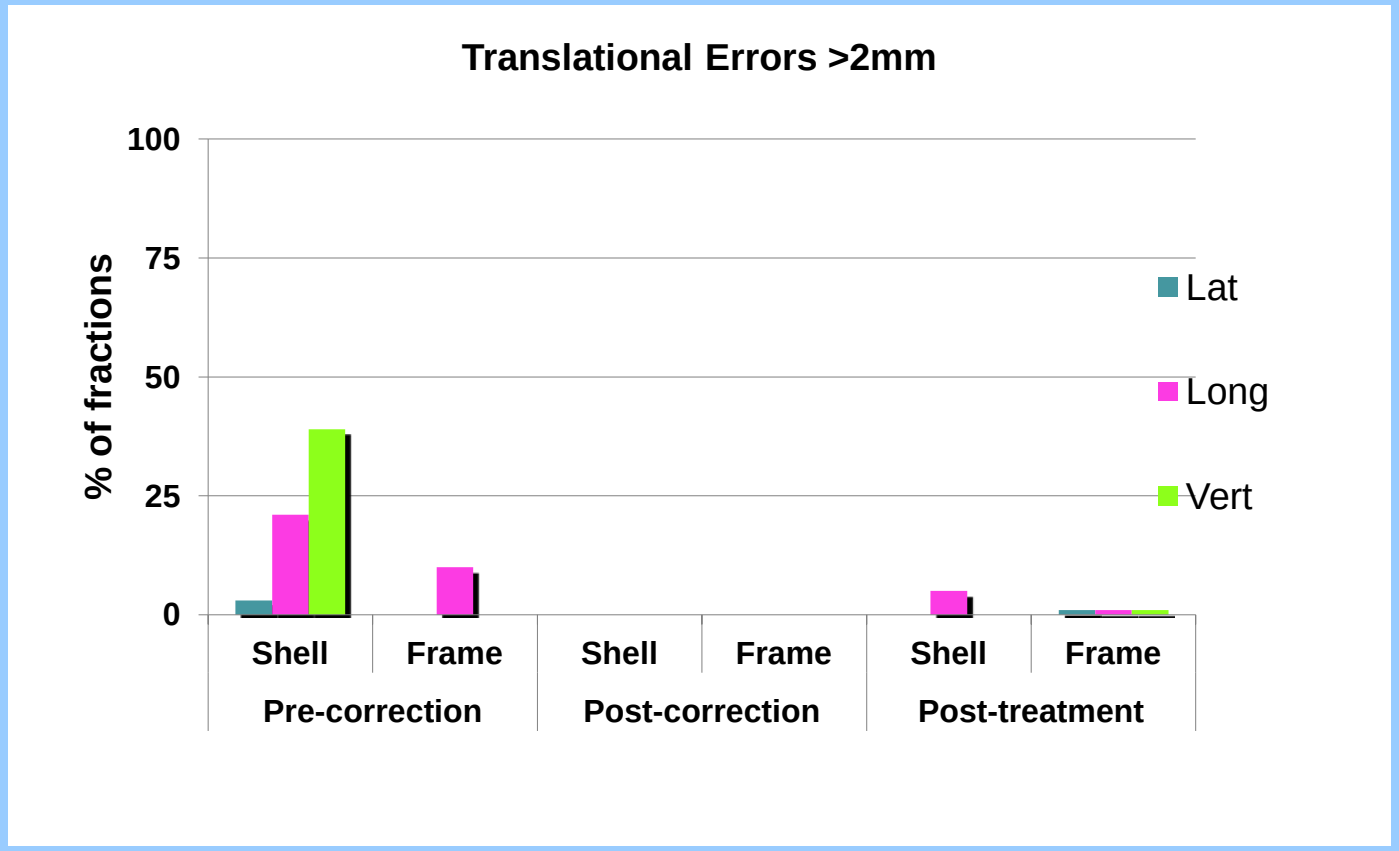
No specialist equipment
Inexpensive
3 visits for planning
Relocation accuracy 3-5 mm

Comparison of immobilisation techniques

The ExacTrac kV stereoscopic image verification system

Comparison of immobilisation techniques

IGRT with ExacTrac kV stereoscopic image verification system



Comparison of immobilisation techniques

Rosenfelder et al 2013, Clin Oncol 25 (1); 66–73

IGRT with ExacTrac kV stereoscopic image verification system

SETUP MARGIN (mm)		Lateral	Longitudinal	Vertical
Pre-correction	Frame	1.3	1.0	1.0
	Shell	1.0	4.5	4.0
Post-correction	Frame	0.4	0.6	0.4
	Shell	0.4	0.6	0.7

Comparison of immobilisation techniques

Rosenfelder et al 2013, Clin Oncol 25 (1); 66–73

Attributes of modern local RT delivery

refinements of conformal radiotherapy

precision

conformality

- photons
- protons

time factor (4D RT)

- intrafraction
- interfraction

quality assurance

- imaging closer to treatment delivery (IGRT)

multiple conformal fixed fields
multiple isocentres (gamma knife/Linac)
multiple small beams (Cyberknife)
IMRT
- static
- arcing (VMAT/RapidArc/Tomotherapy)

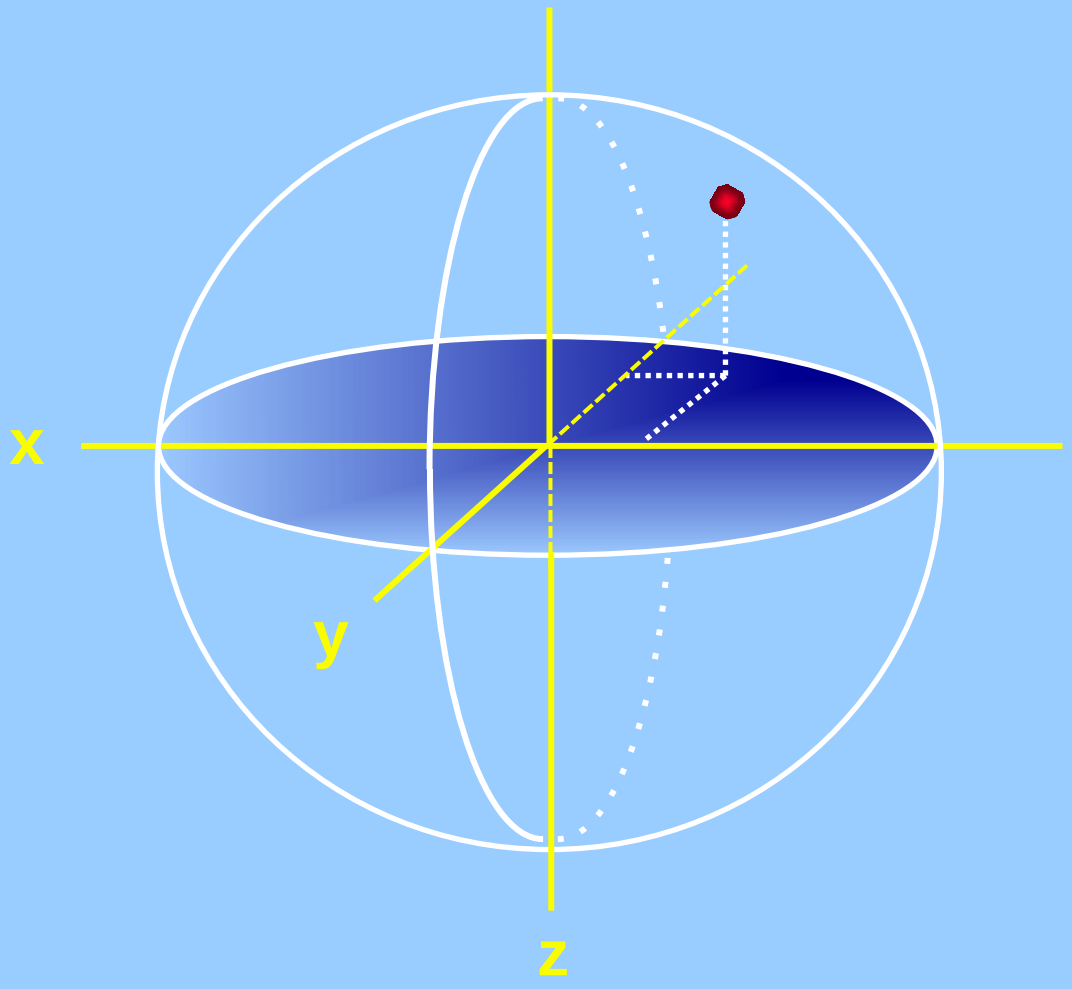
Classification of radiotherapy technologies

Stereotaxy

stereotactic radiotherapy is dead

Classification of radiotherapy technologies

Stereotaxy



Classification of radiotherapy technologies

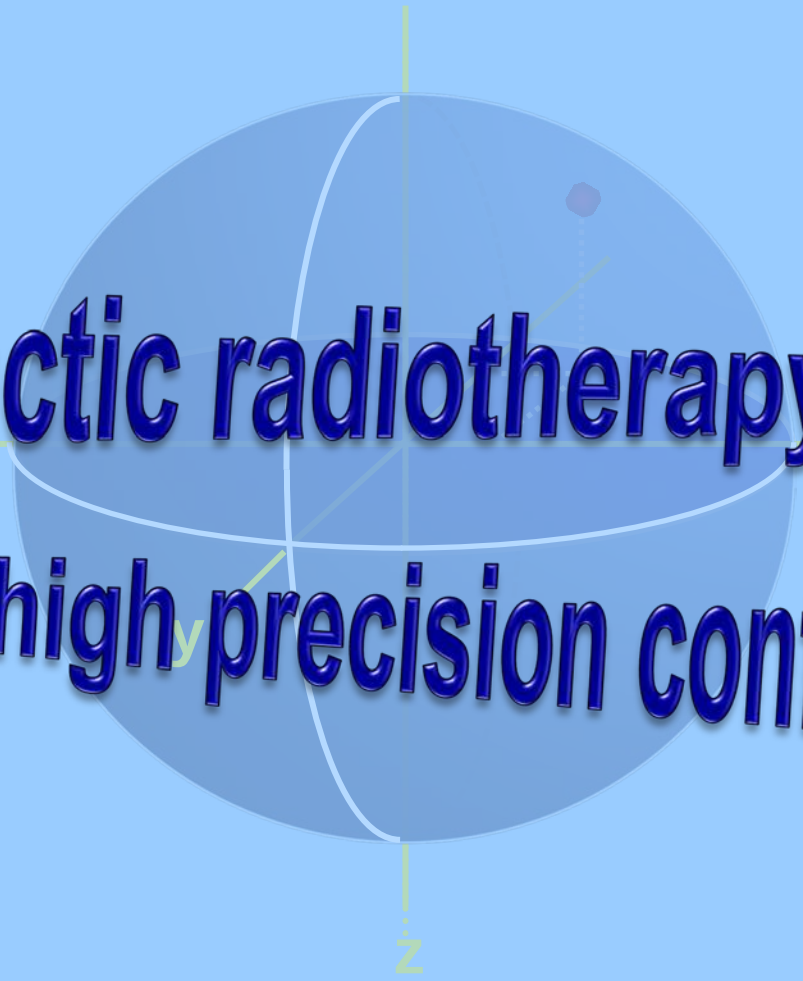
Stereotactic radiotherapy attributes

- Precision
- Conformality
- Dose
- Fractionation

High precision localised radiotherapy

Deconstructing stereotactic radiotherapy

Stereotaxy



stereotactic radiotherapy is dead

long live high precision conformal RT

Classification of radiotherapy technologies

Attributes of modern local RT delivery

refinements of conformal radiotherapy

- precision
- conformality
  - photons
  - protons
- time factor (4D RT)
  - intrafraction patient and tumour motion
  - interfraction changes in tumour & normal tissue
- quality assurance
  - imaging closer to treatment delivery (IGRT)

Classification of radiotherapy technologies

Attributes of modern local RT delivery

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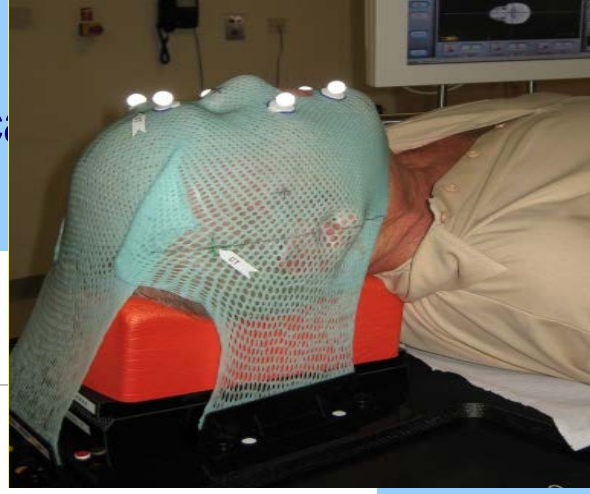
- interfraction changes in tumour & normal tissue

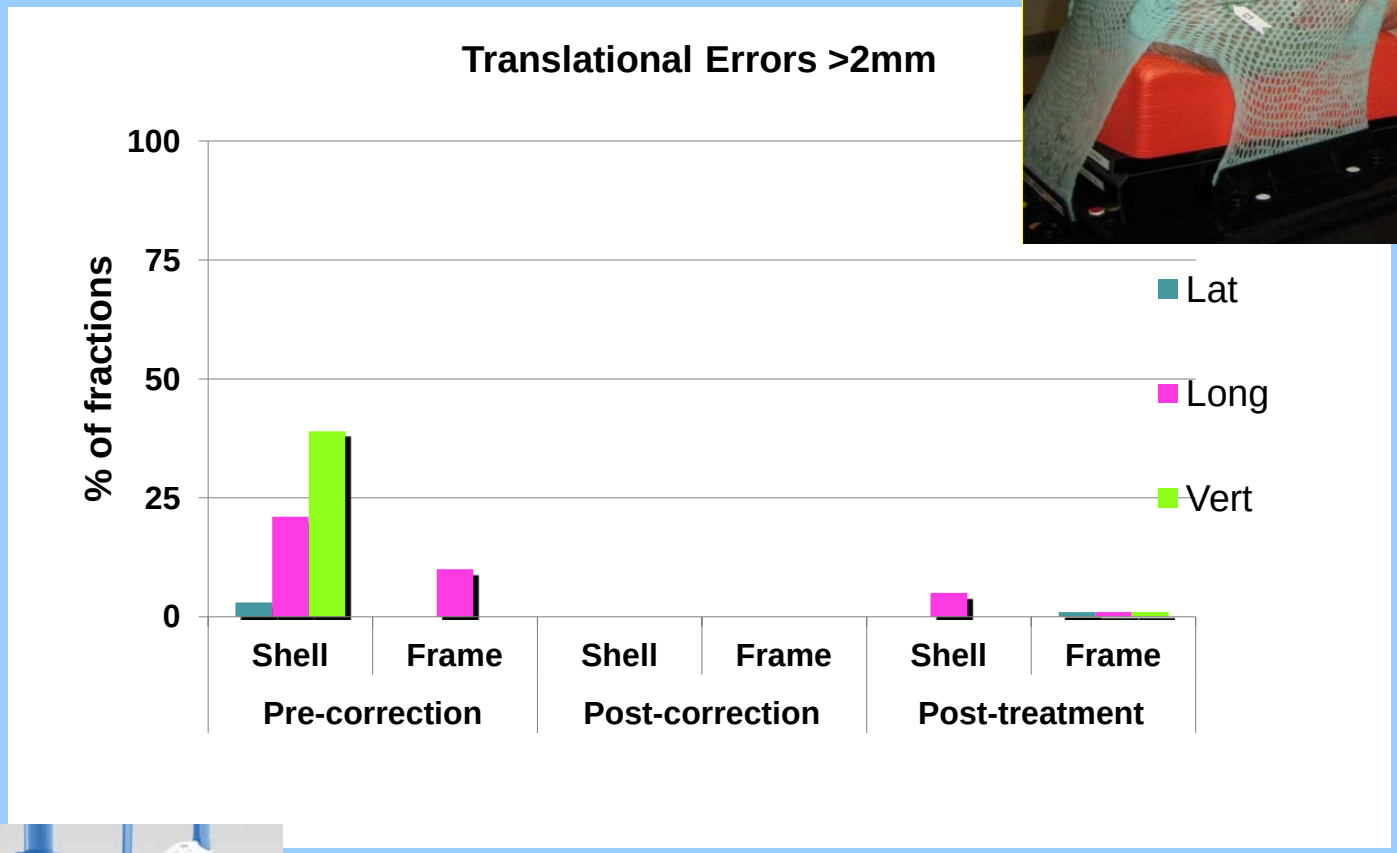
quality assurance

- imaging closer to treatment delivery (IGRT)

Classification of radiotherapy technologies

IGRT with ExacTrac kV stereoscopic image verific

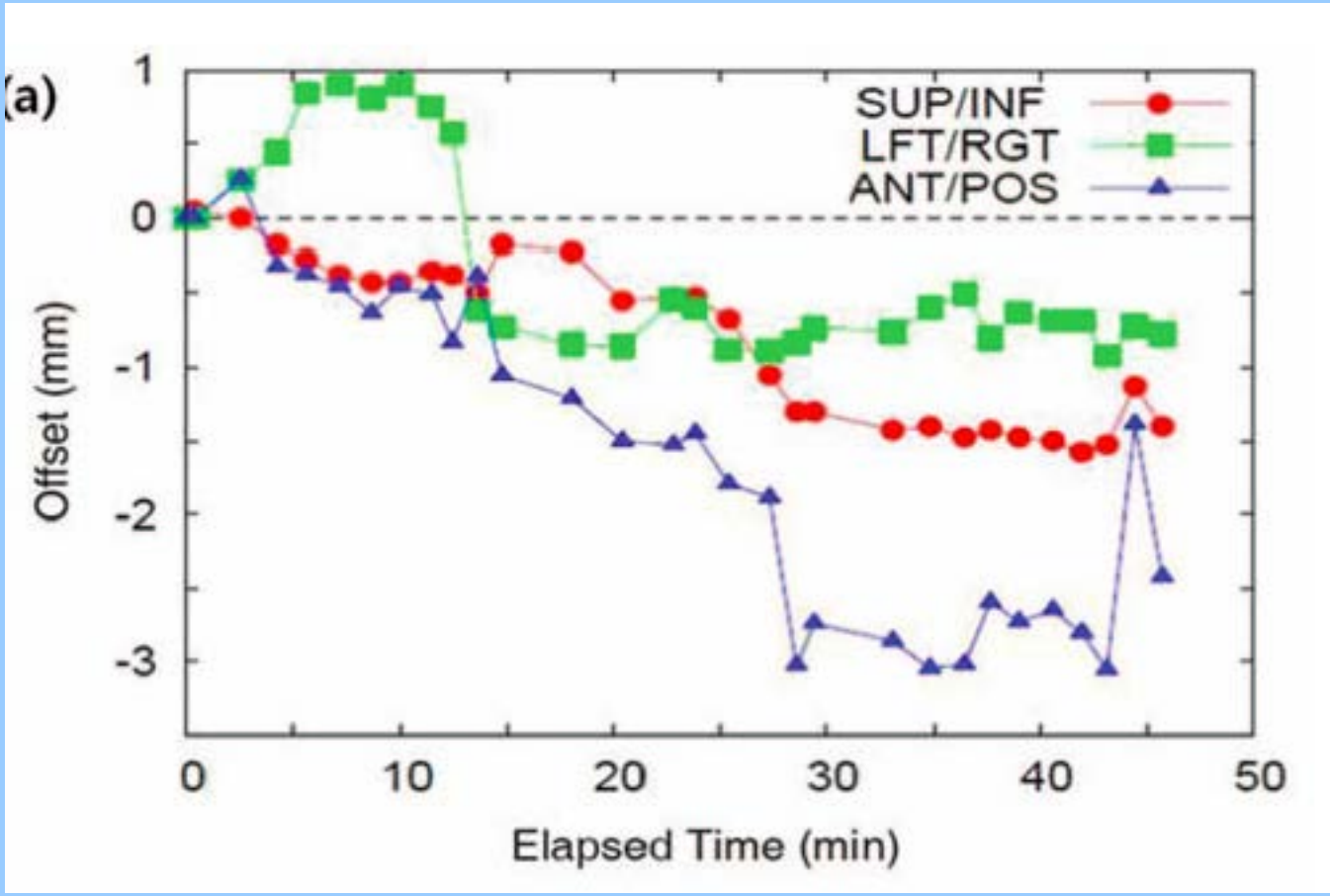




Clin Oncol 25 (1); 66–73

Interfraction motion

example of intrafraction movement

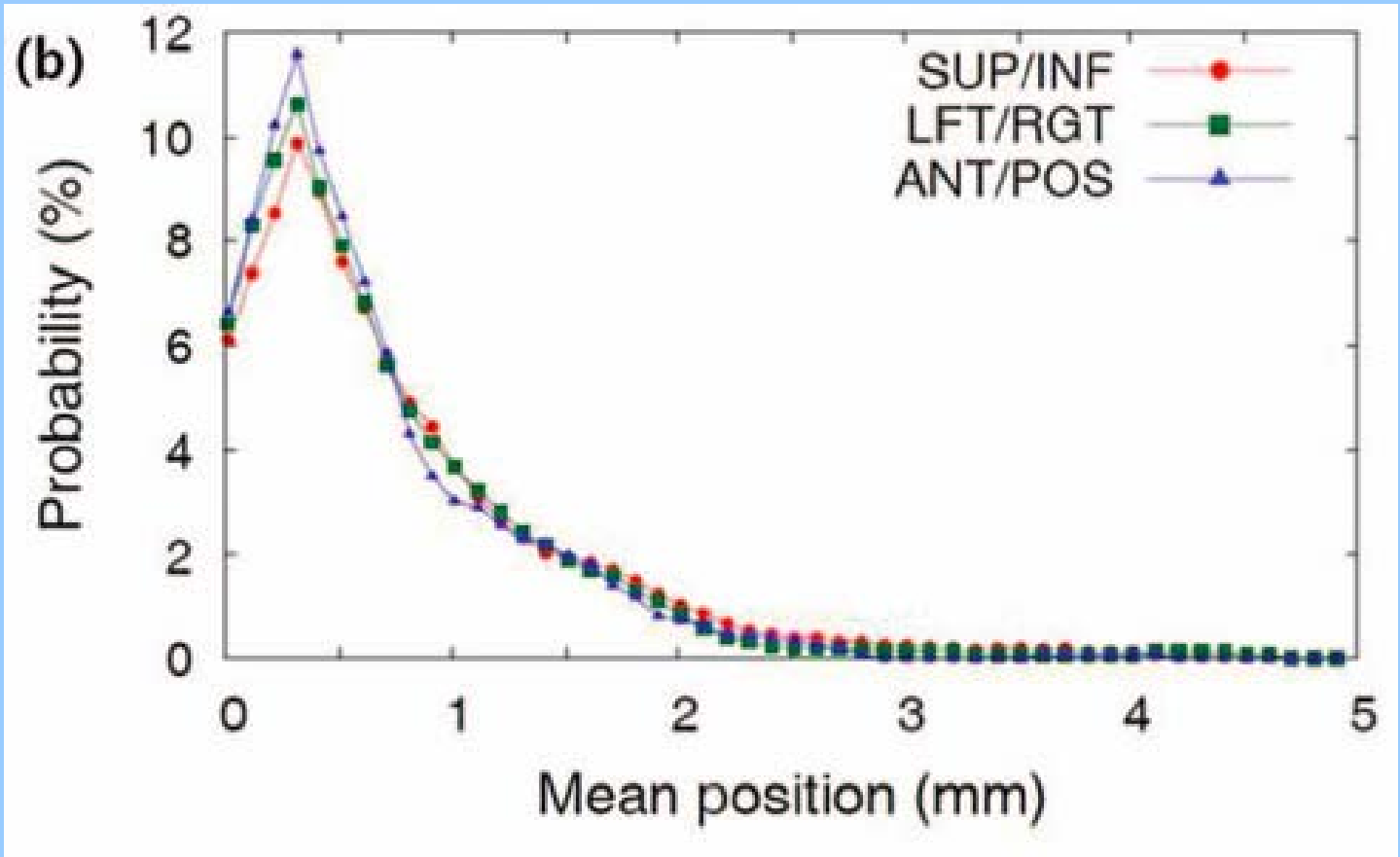


Intrafraction motion in CK radiosurgery

Ki Mun Kang et al 2013, Medical Physics 40, 051716

statistical distribution of mean position

(262 radiosurgery fractions)



Intrafraction motion in CK radiosurgery

Ki Mun Kang et al 2013, Medical Physics 40, 051716

Attributes of modern local RT delivery

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- precision
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  - photons
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- time factor (4D RT)
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- quality assurance
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Classification of radiotherapy technologies

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  - intrafraction patient and tumour motion
  - interfraction changes in tumour & normal tissue
- quality assurance
  - imaging closer to treatment delivery (IGRT)

Classification of radiotherapy technologies

IGRT - adaptive radiotherapy
adjusting for interfraction motion

change in tumour position	change in tumour shape & volume

IGRT - adaptive radiotherapy
adjusting for interfraction motion

change in tumour position

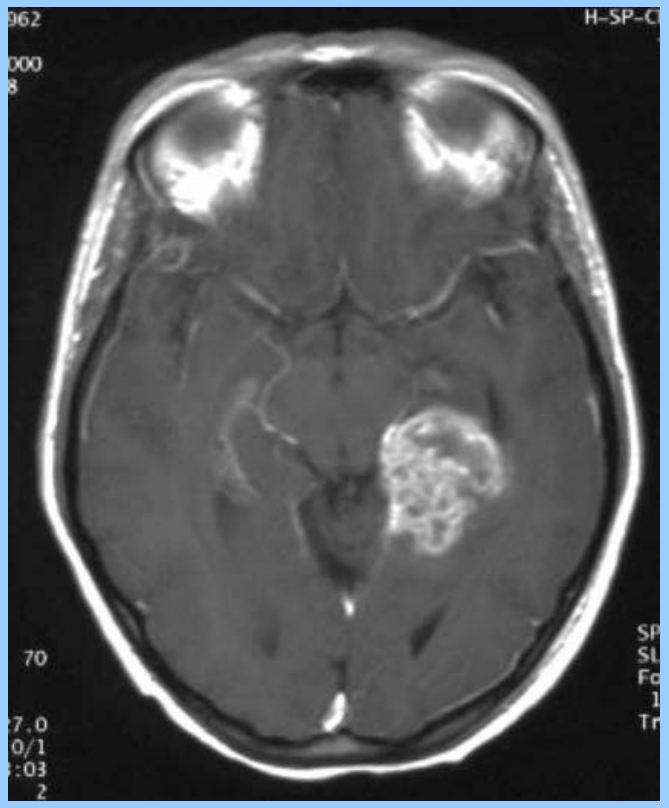
change in tumour shape & volume

IGRT - adaptive radiotherapy
adjusting for interfraction motion

change in tumour position

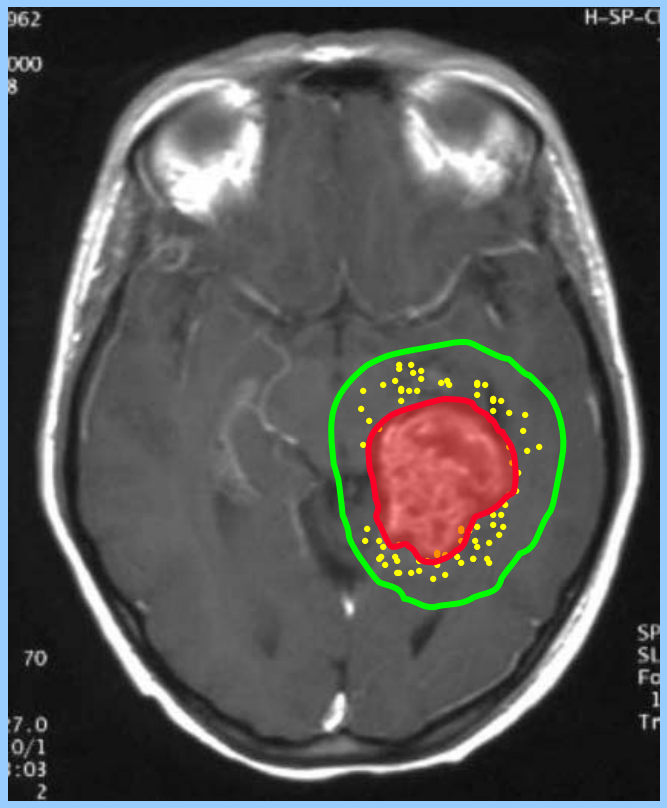
change in tumour shape & volume

IGRT - adaptive radiotherapy
adjusting for interfraction change in size and shape



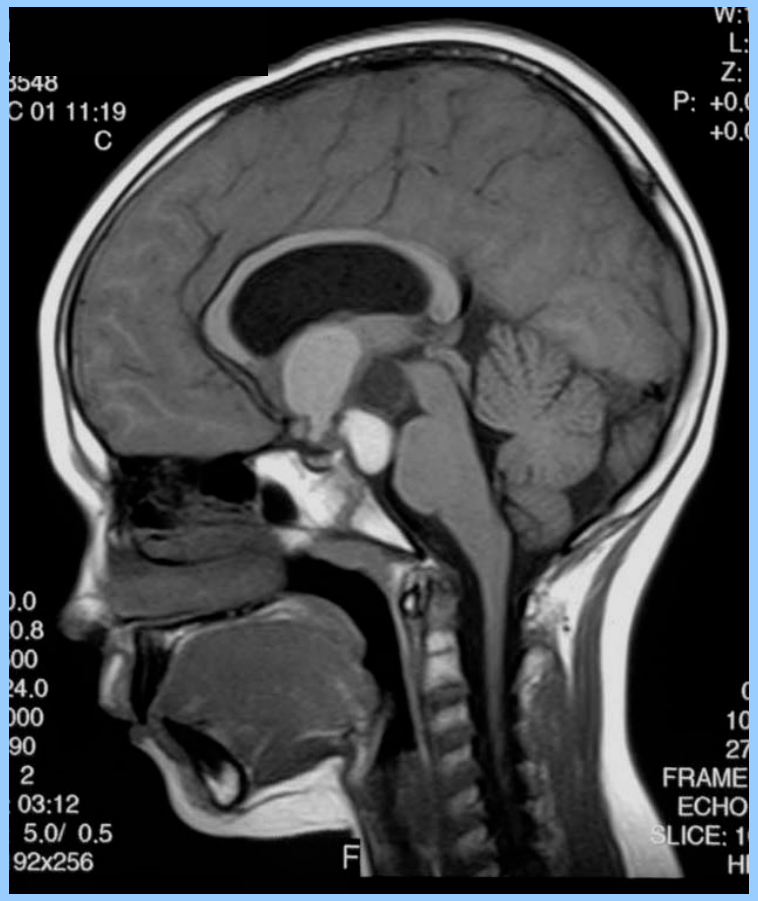
High grade glioma

IGRT - adaptive radiotherapy
adjusting for interfraction change in size and shape



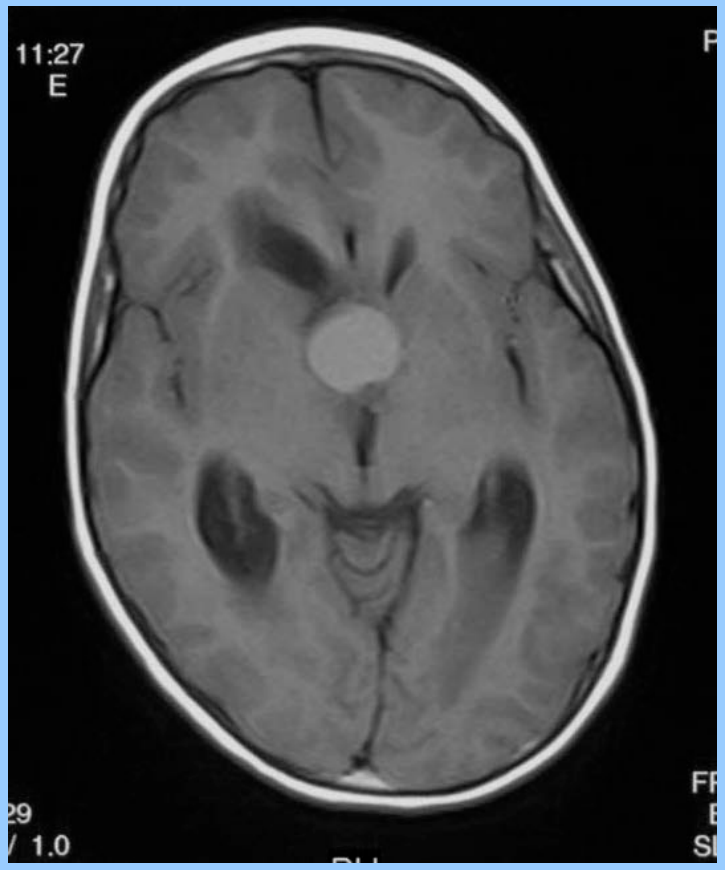
High grade glioma

IGRT - adaptive radiotherapy
adjusting for interfraction change in size and shape



Craniopharyngioma

IGRT - adaptive radiotherapy
adjusting for interfraction change in size and shape



Craniopharyngioma

terminology | evaluation

Localised radiotherapy for CNS tumours

Conformal radiotherapy techniques

multiple conformal fixed fields
multiple isocentres (gamma knife/Linac)
multiple small beams (Cyberknife)
IMRT
- static
- arcing (VMAT/RapidArc/Tomotherapy)

protons

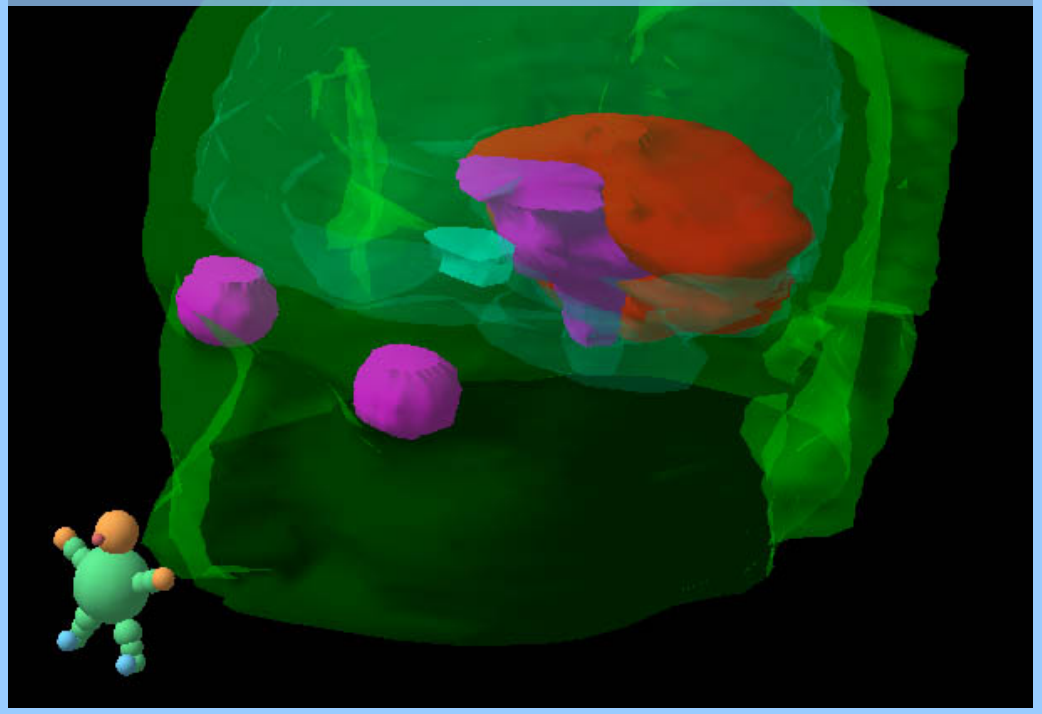
aim

standard radiotherapy paradigm

Localised radiotherapy for CNS tumours

Localised radiation delivery

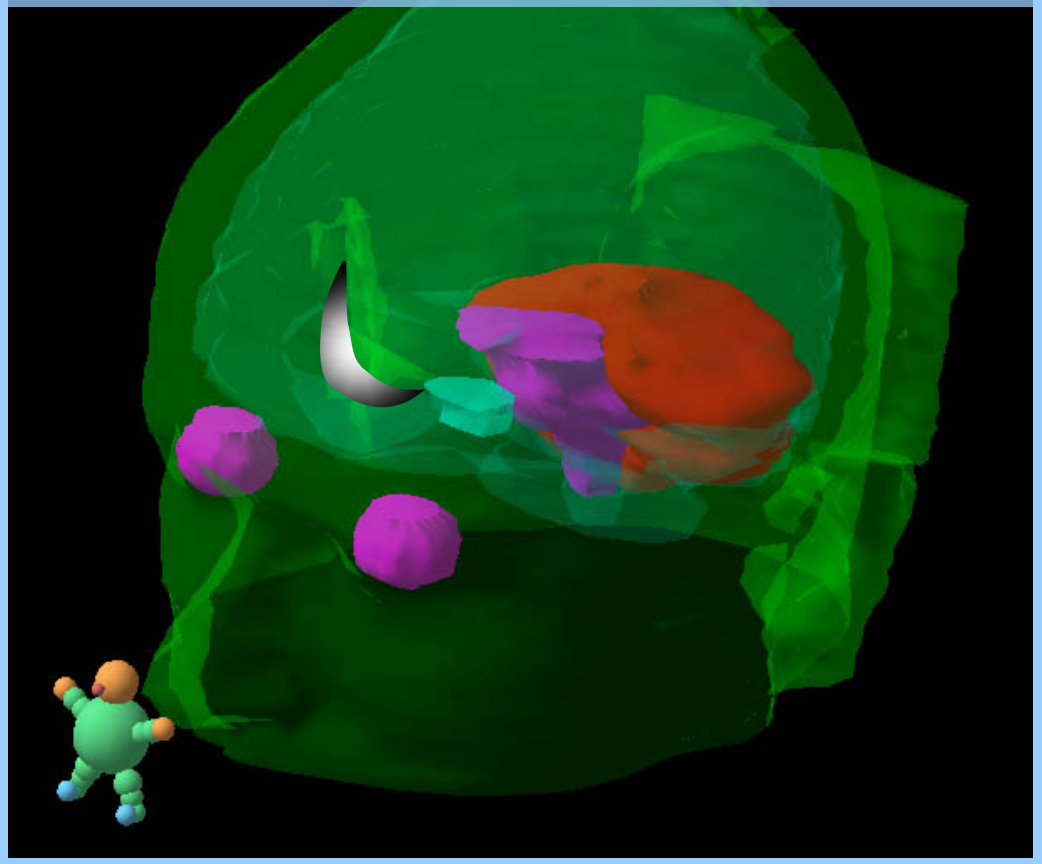
- physical endpoints
- standards for comparison
- clinical relevance



Evaluation of local radiotherapy techniques

Physical endpoints – target dose

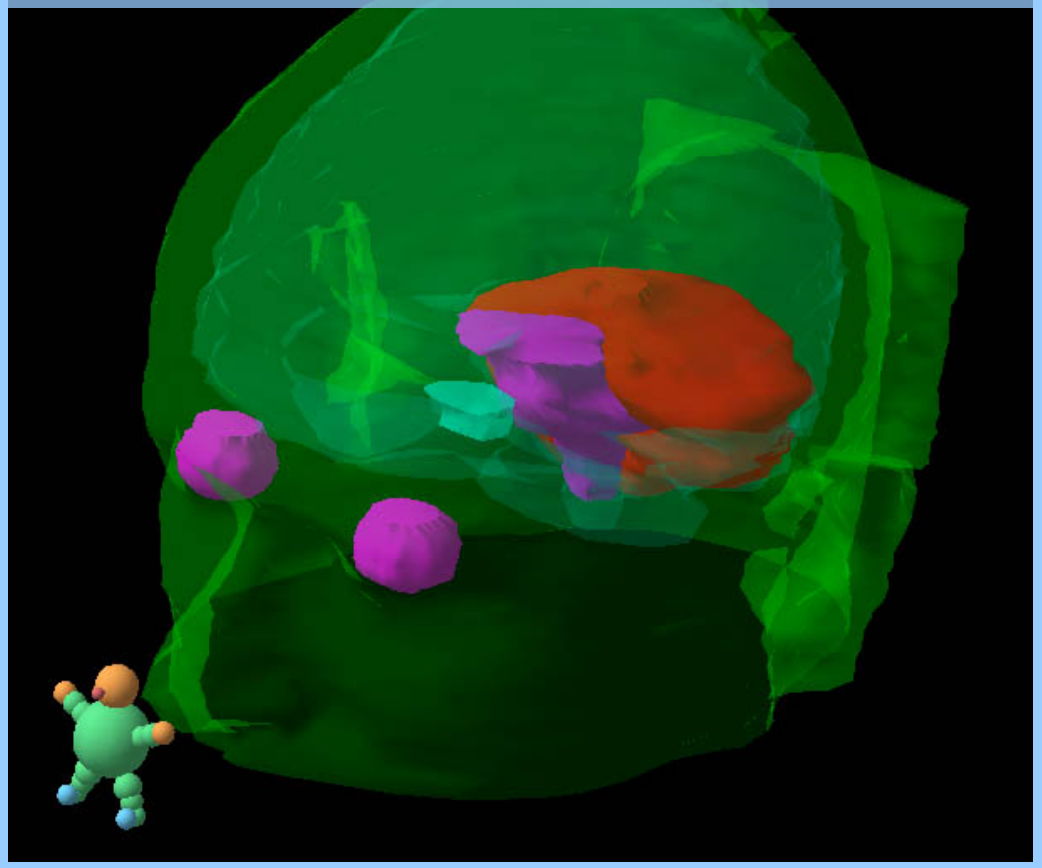
optimise target dose



Evaluation of local radiotherapy techniques

Physical endpoints – normal tissue avoidance

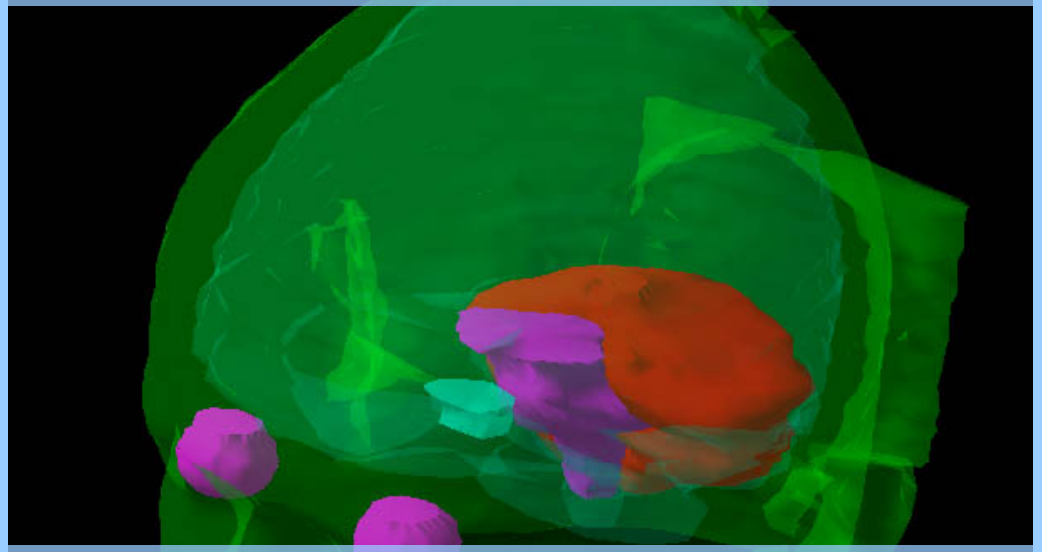
reduce normal tissue volume & dose



Evaluation of local radiotherapy techniques

Physical endpoints – normal tissue avoidance

reduce normal tissue volume & dose



all normal tissue

central nervous system

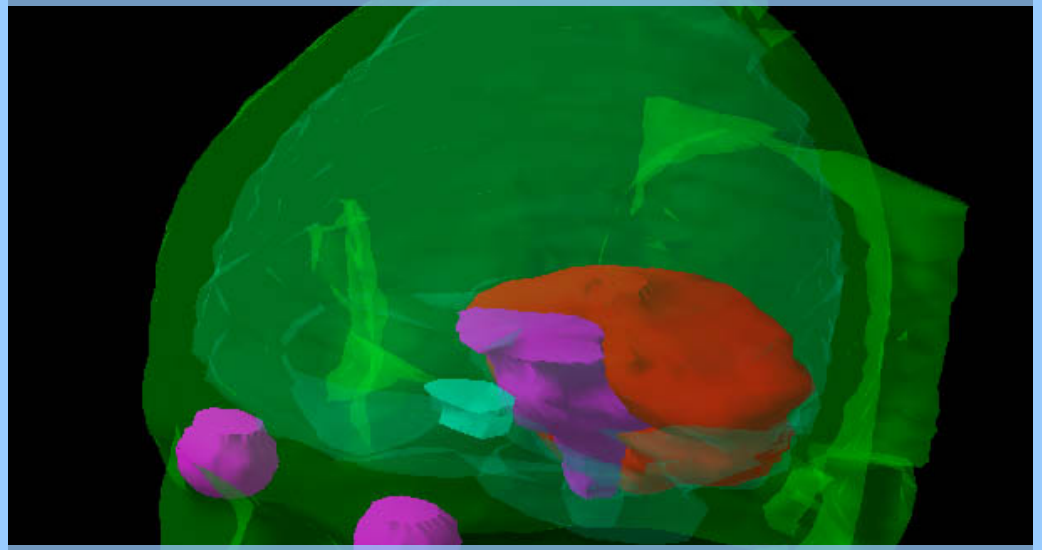
critical structures (OARs)

Evaluation of local radiotherapy techniques

OAR – organ at risk

Physical endpoints – normal tissue avoidance

reduce normal tissue volume & dose



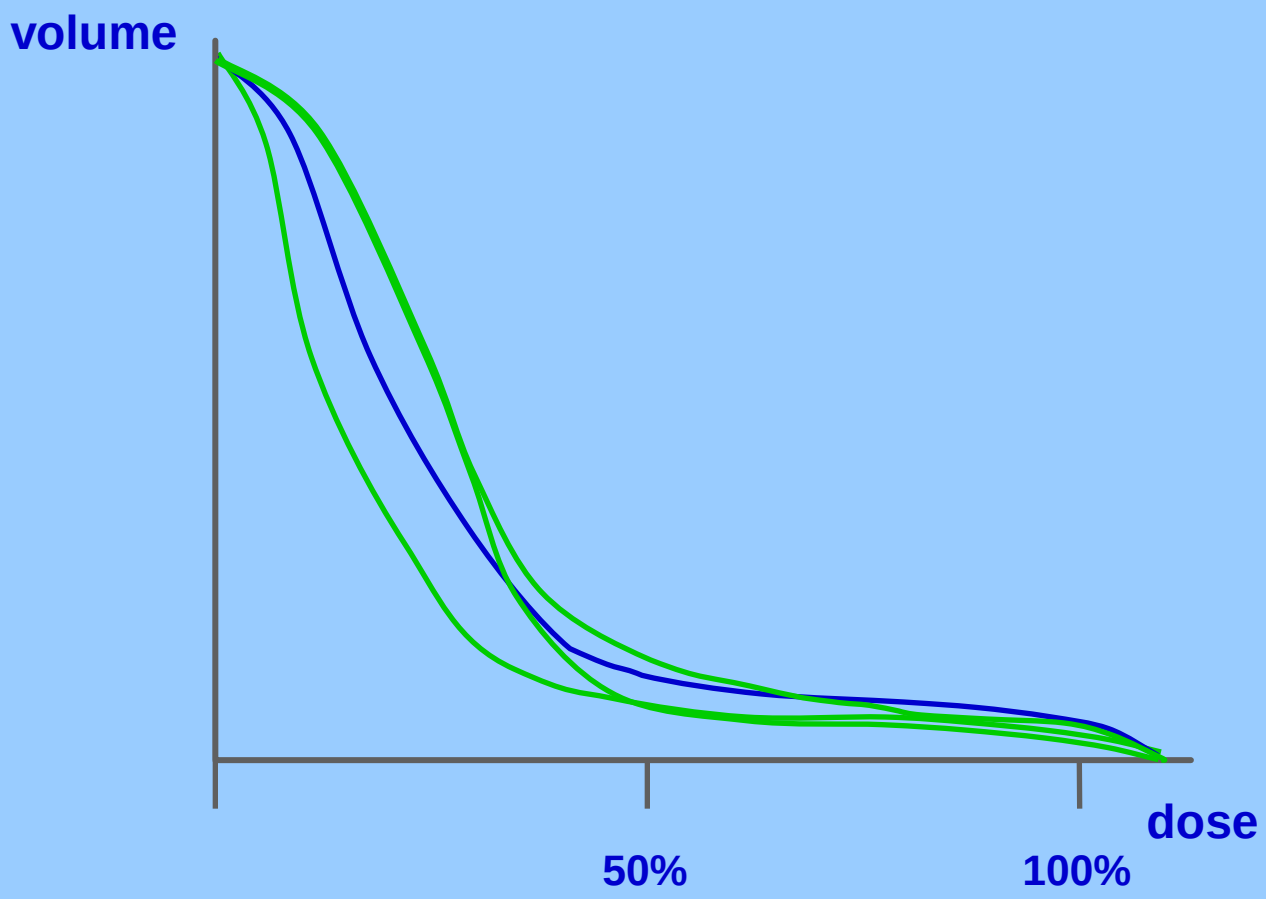
all normal tissue

central nervous system

critical structures (OARs)

Evaluation of local radiotherapy techniques

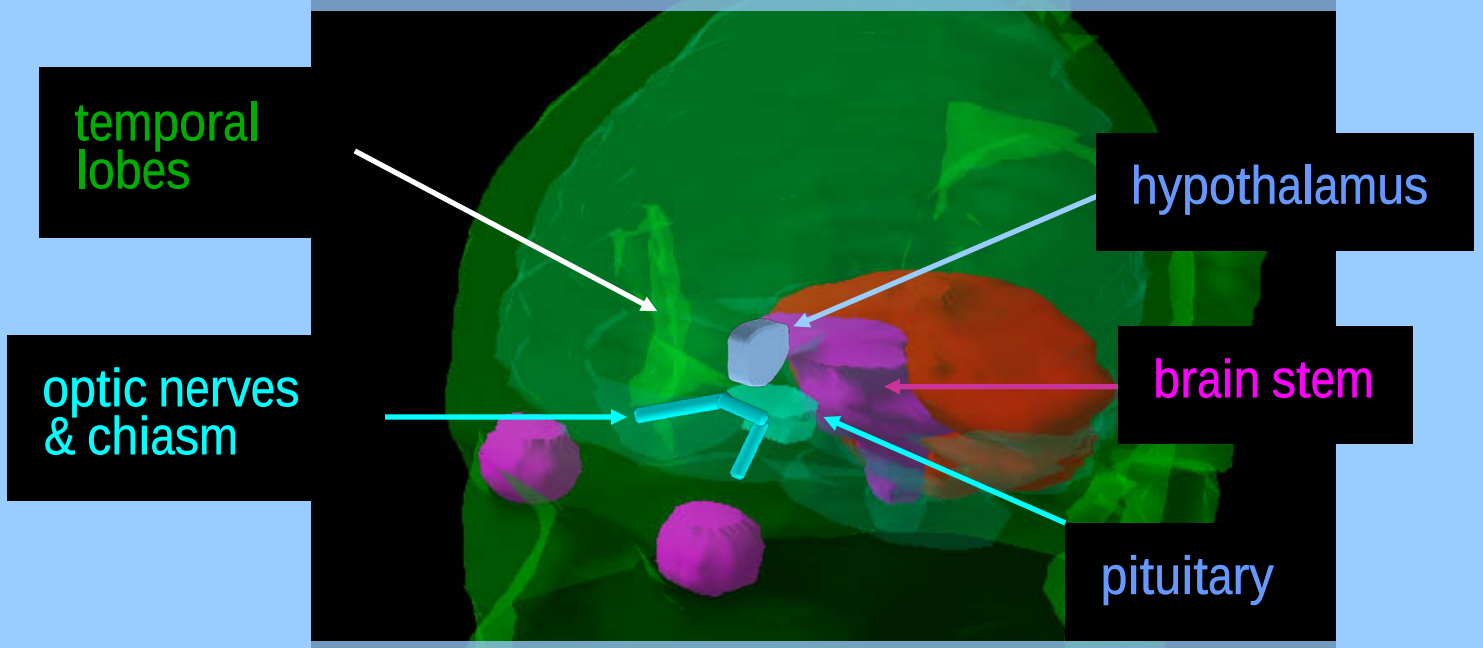
Physical endpoints central nervous system DVH



Evaluation of local radiotherapy techniques

Avoidance in the treatment of skull base tumours

reduce normal tissue volume & dose



central nervous system

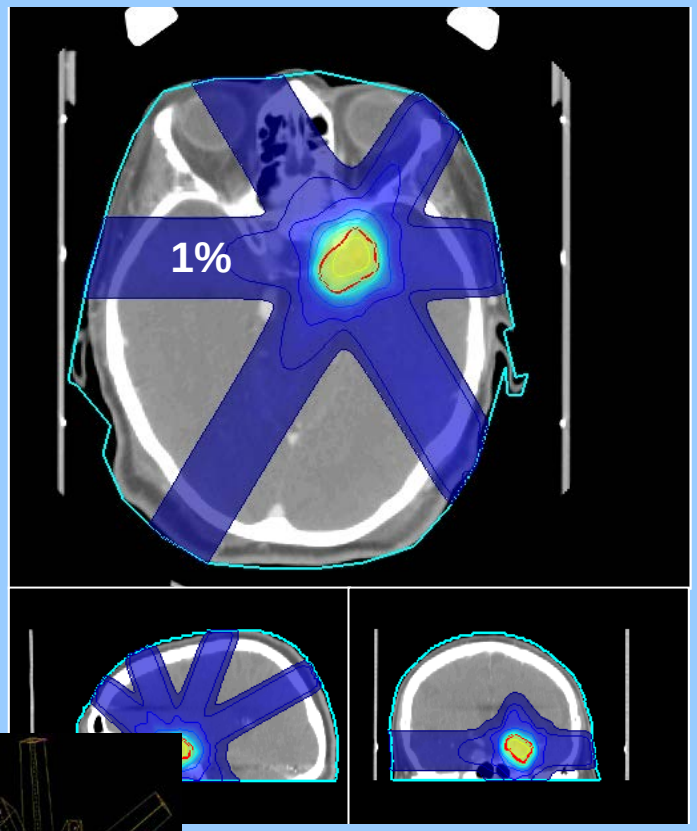
critical structures (OARs)

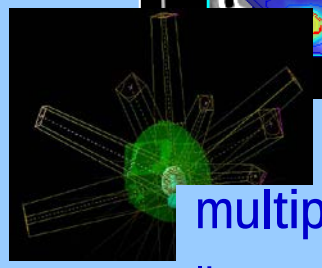
Evaluation of local radiotherapy techniques

Conformal radiotherapy techniques

multiple conformal fixed fields
multiple isocentres (gamma knife/Linac)
multiple small beams (Cyberknife)
IMRT
- static
- arcing (VMAT/RapidArc/Tomotherapy)

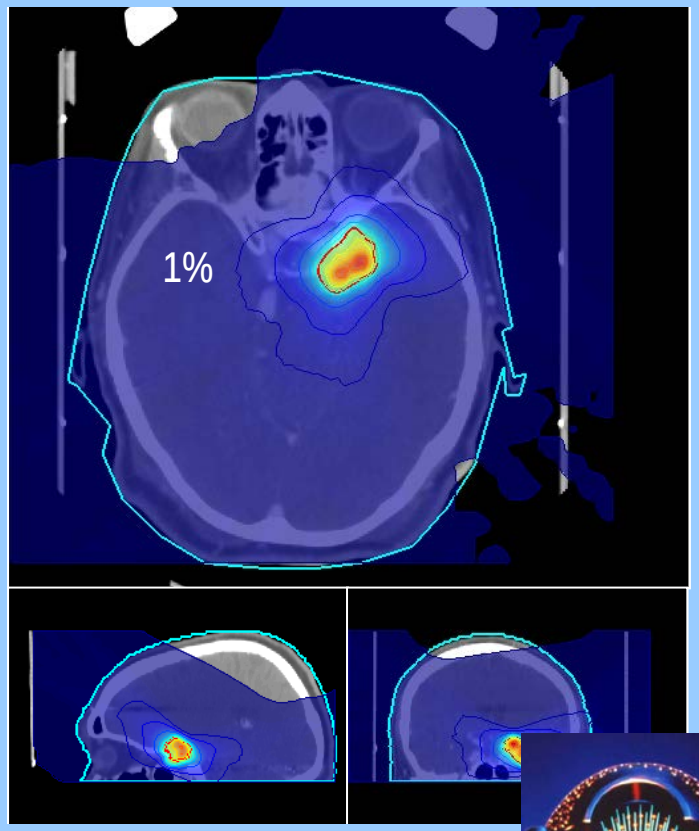
protons

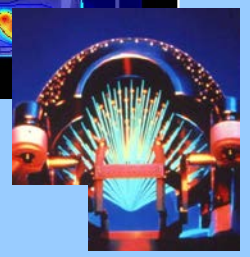




multiple conformal fileds

linear accelerator





multiple isocentres

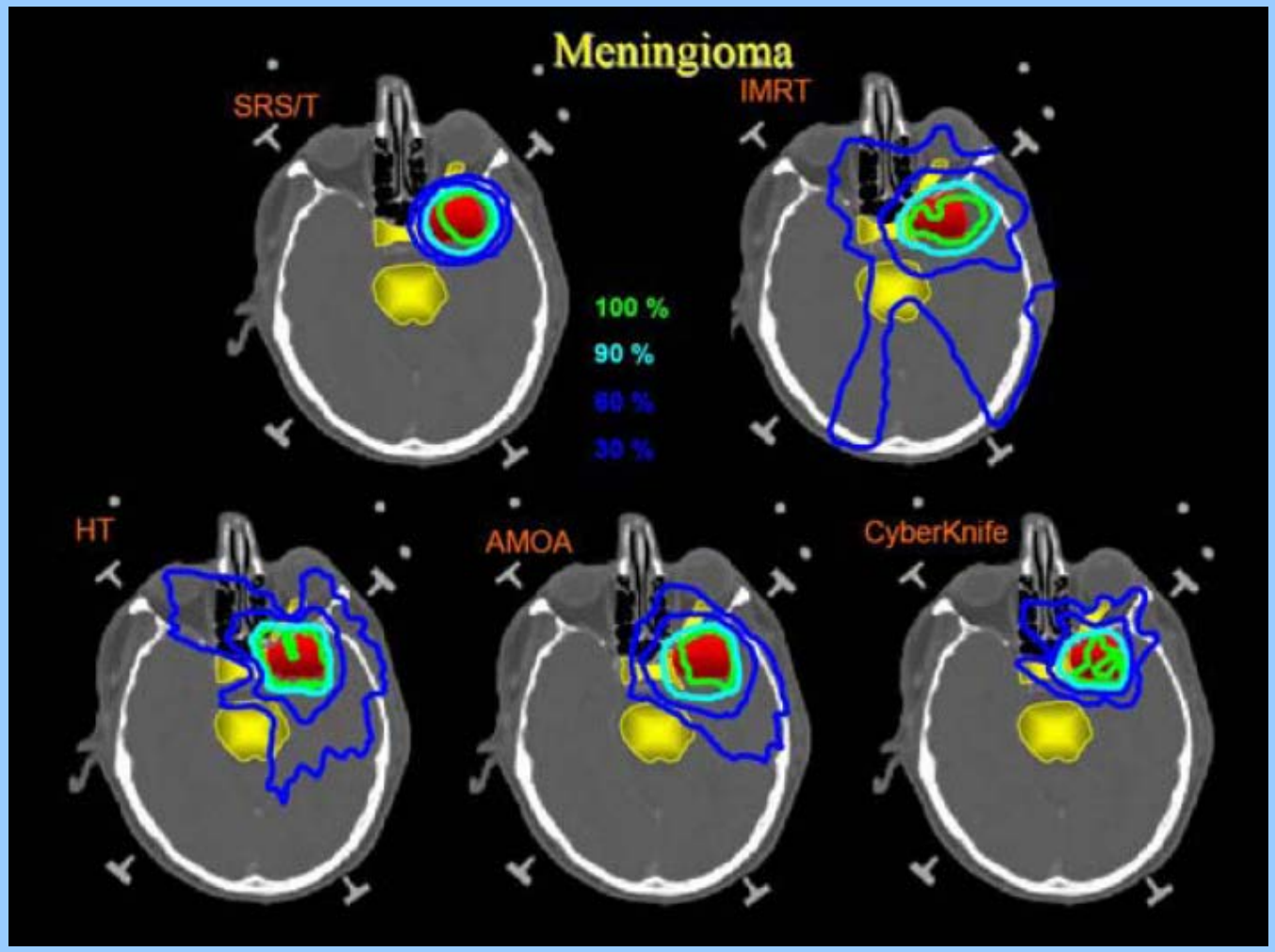
gamma knife

Comparison of conformal fixed field & multiple isocentre techniques

Conformal radiotherapy techniques

multiple conformal fixed fields
multiple isocentres (gamma knife/Linac)
multiple small beams (Cyberknife)
IMRT
- static
- arcing (VMAT/RapidArc/Tomotherapy)

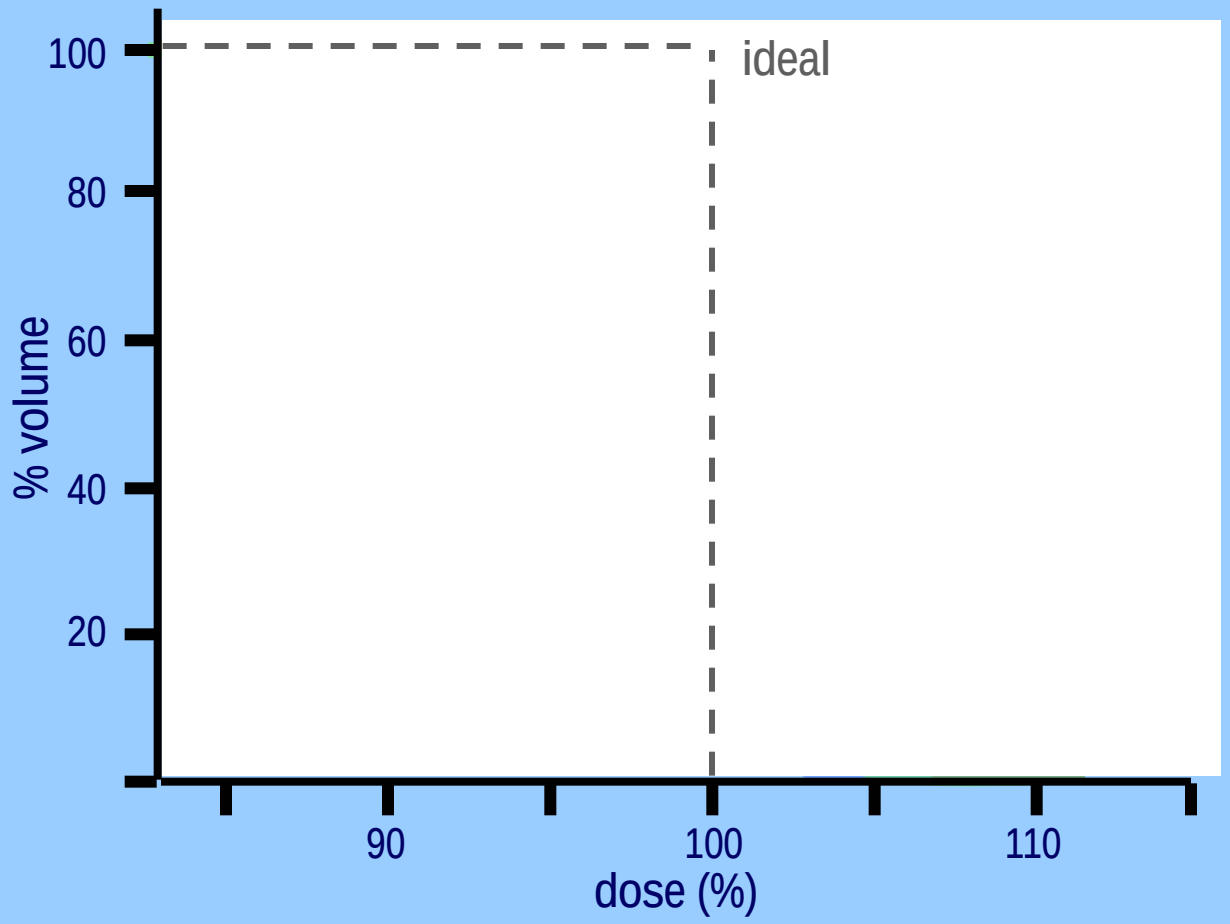
protons



Comparison of conformal radiotherapy techniques

Cozzi et al 2006

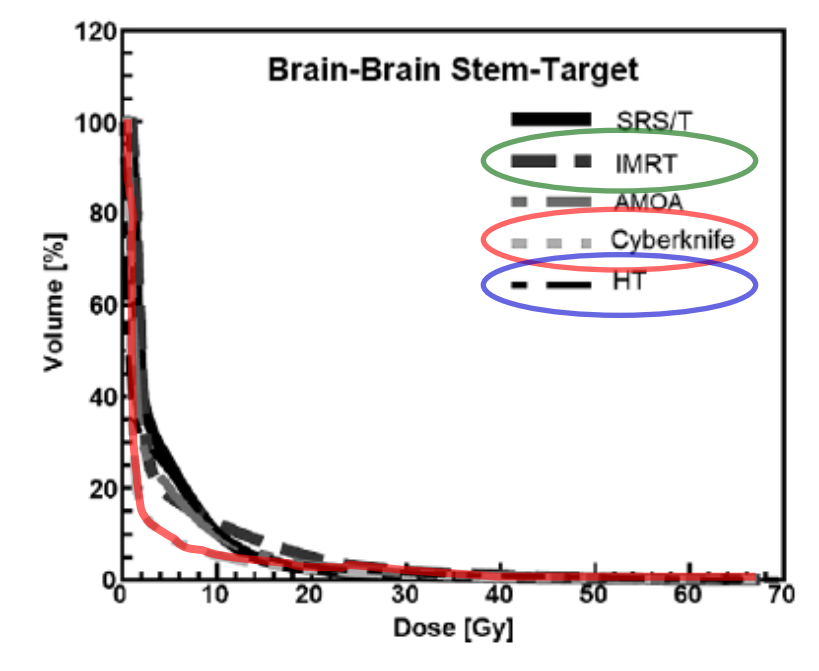
Planning Target Volume (PTV) dose distribution

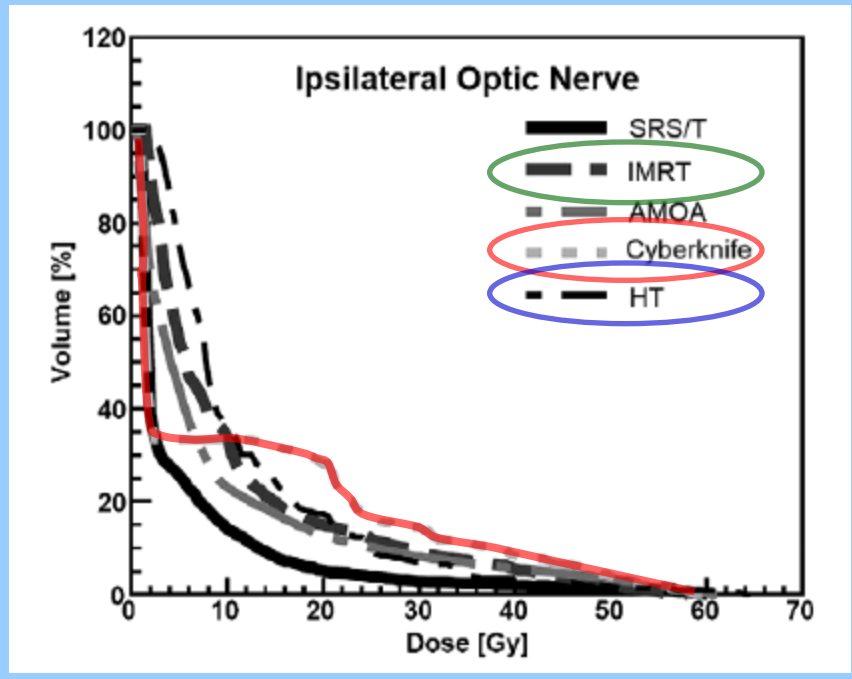


Comparison of conformal radiotherapy techniques

Cozzi et al 2006

Organs at risk DVH





Comparison of conformal radiotherapy techniques

Cozzi et al 2006

Conformal radiotherapy techniques

multiple conformal fixed fields
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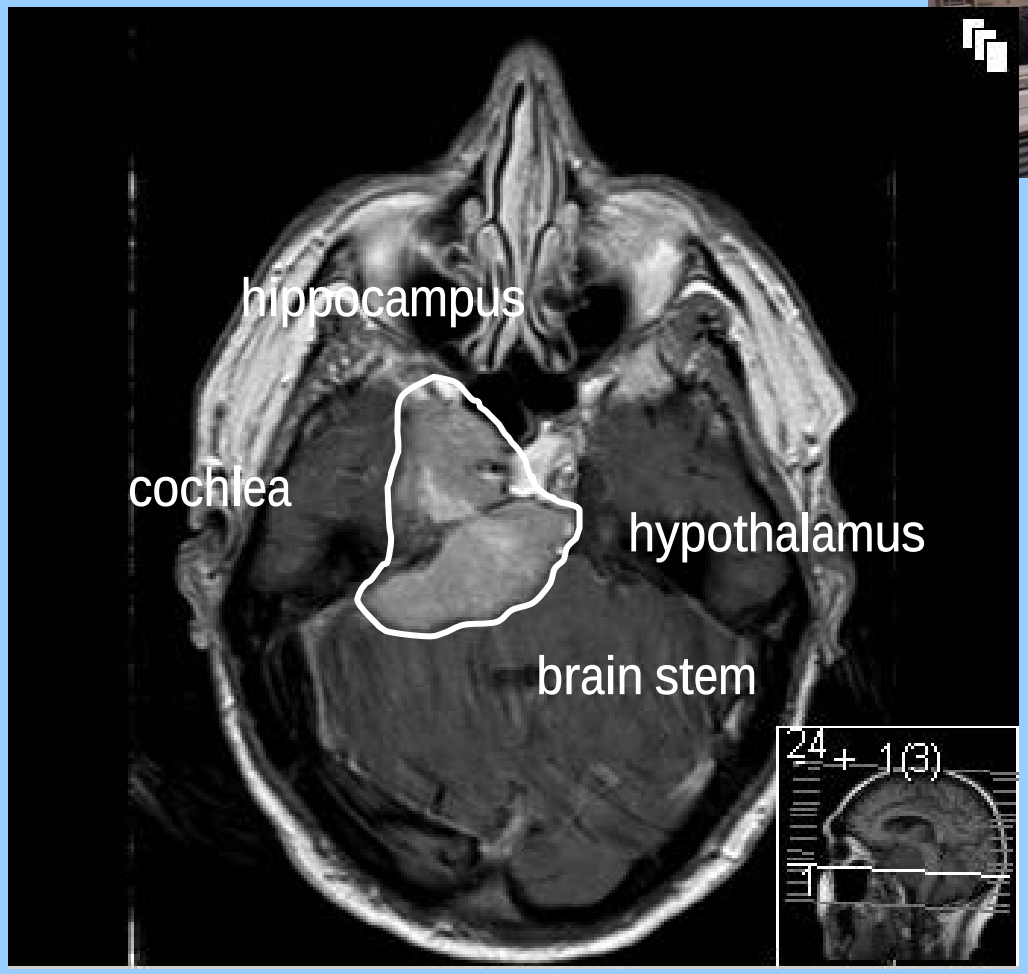
multiple small beams (Cyberknife)
IMRT
- static
- arcing (VMAT/RapidArc/Tomotherapy)

protons

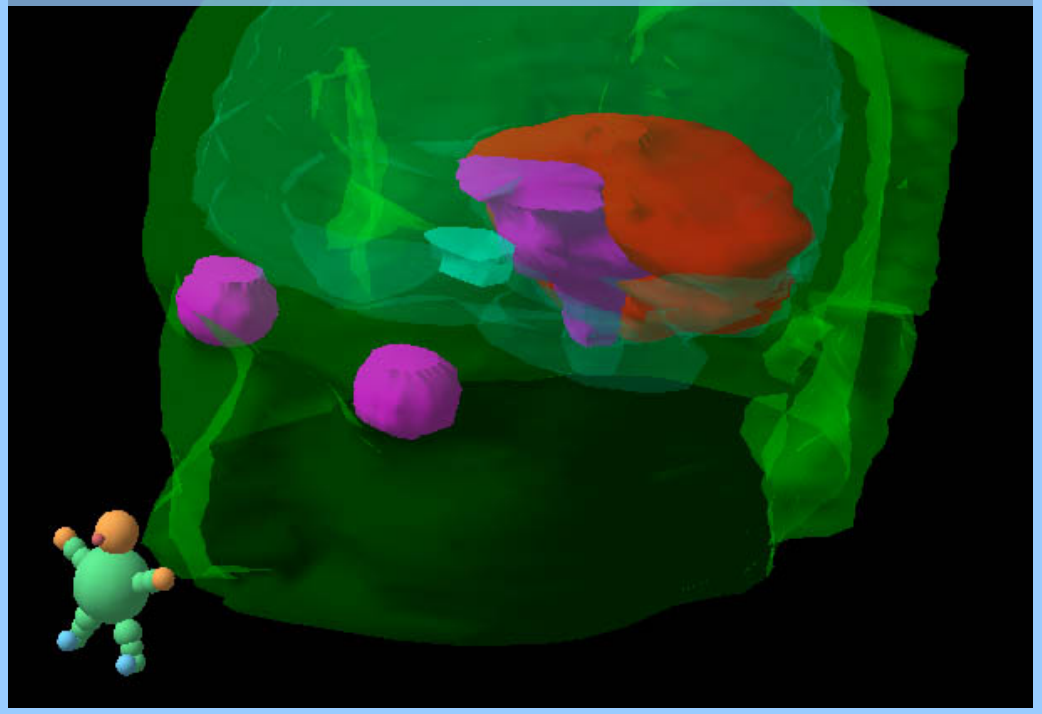
Avoidance of critical structures



IMRT for meningioma

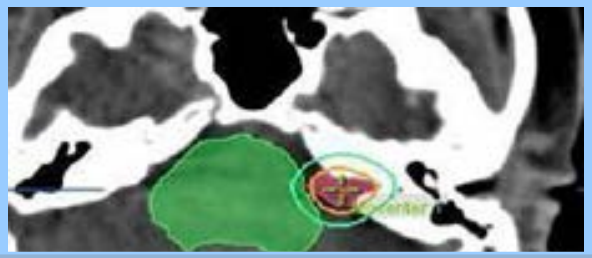
Localised radiation delivery

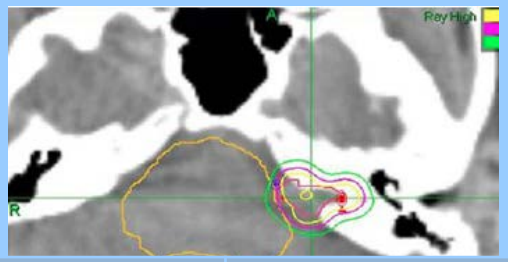
- physical endpoints
- standards for comparison
- clinical relevance



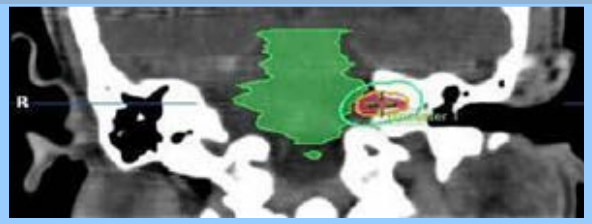
Evaluation of local radiotherapy techniques

Acoustic neuromas

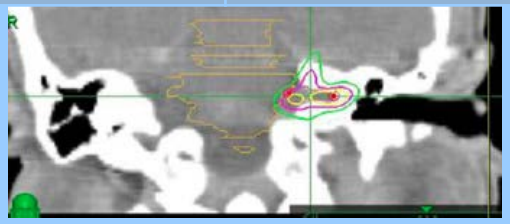




	Linac	CK
conformity index	no difference	
maximum brain stem dose	no difference	
mean cochlear dose	higher	lower
mean mesial temporal dose	higher	lower



Linac

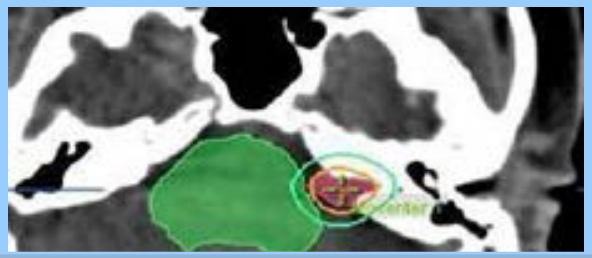


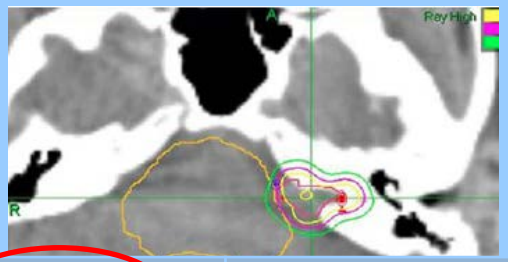
Cyberknife

Comparison of conformal radiotherapy techniques

Dutta et al 2011 J Neurooncology

Acoustic neuromas - standards for comparison

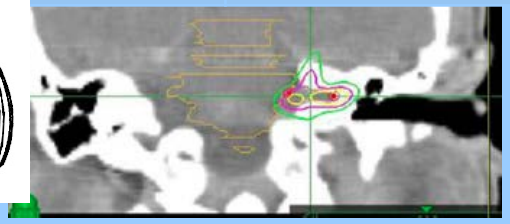




	Linac	CK
conformity index	no difference	
maximum	no difference	
mean co	gher	lower
mean me	gher	lower

single isocentre
multiple non-coplanar arcs

Linac

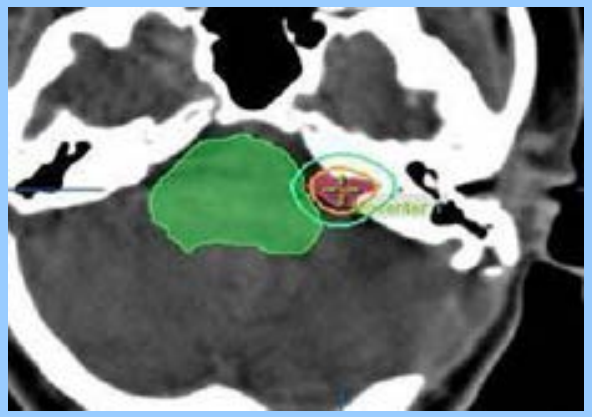


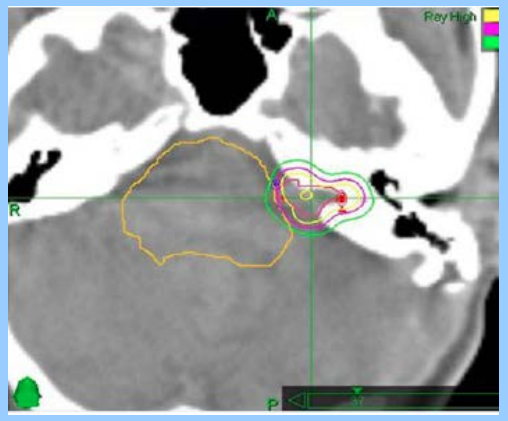
Cyberknife

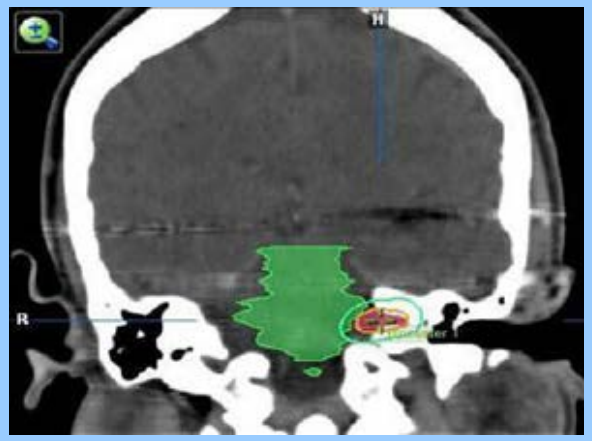
Comparison of conformal radiotherapy techniques

Dutta et al 2011 J Neurooncology

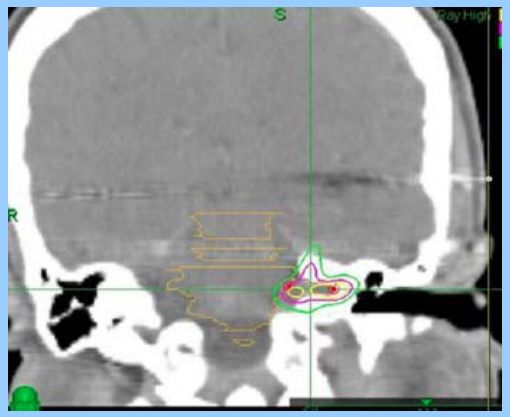
Acoustic neuromas







Linac



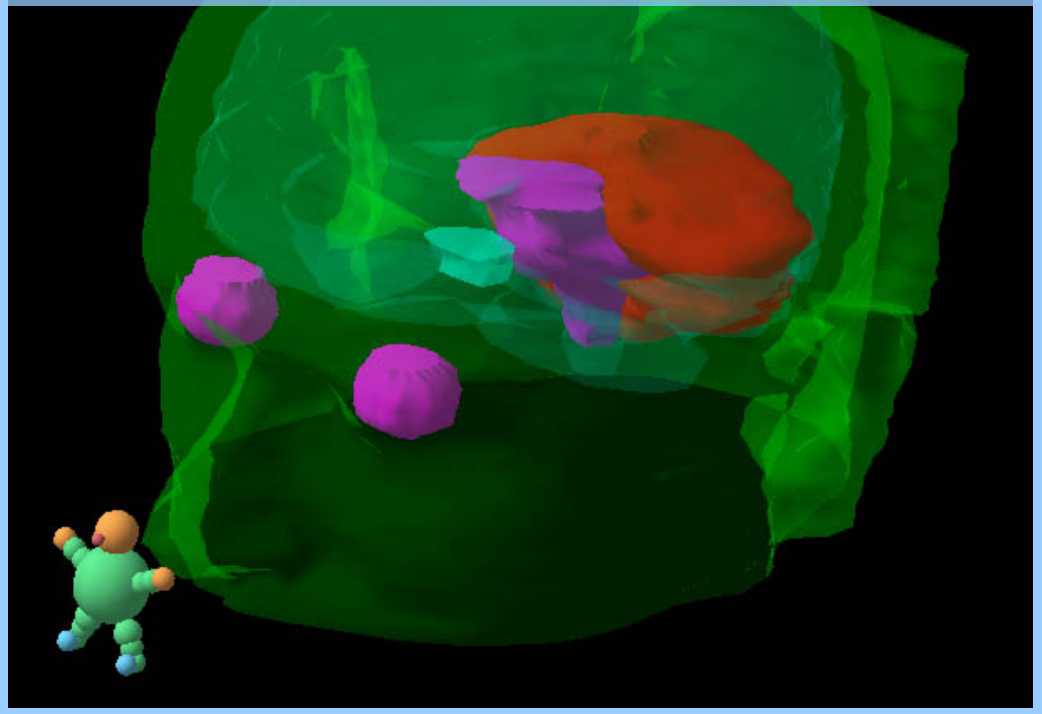
Cyberknife

Comparison of conformal radiotherapy techniques

Dutta et al 2011 J Neurooncology

Localised radiation delivery

- physical endpoints
- standards for comparison
- clinical relevance



Evaluation of local radiotherapy techniques

Clinical relevance of complex techniques

standard radiotherapy paradigm

clinical relevance of

increased tumour dose

Evaluation of local radiotherapy techniques

Clinical relevance of complex techniques

standard radiotherapy paradigm

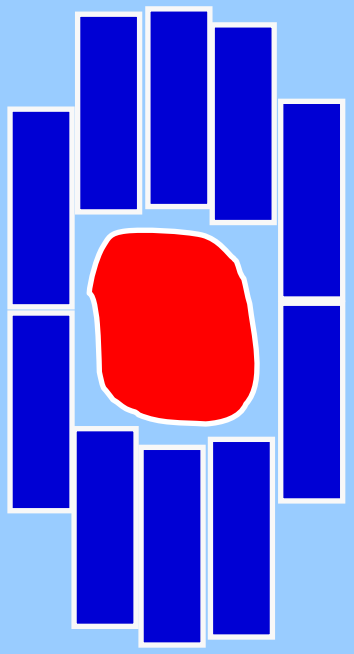
clinical relevance of

increased tumour dose

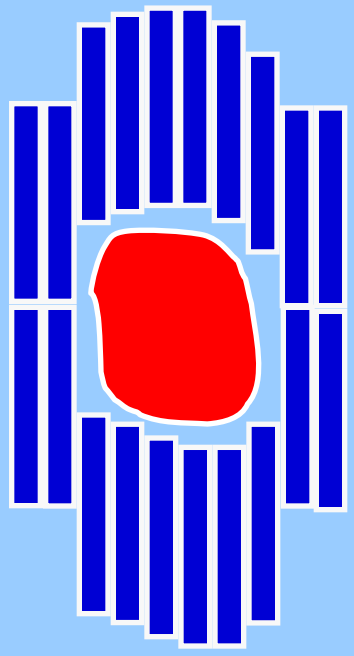
reduced normal tissue/OAR dose

Evaluation of local radiotherapy techniques

conformal treatment delivery – 3DCRT or IMRT



5 mm



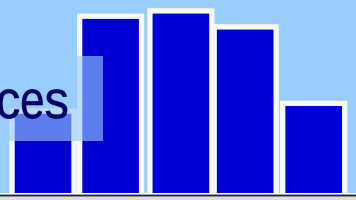
2.5 mm

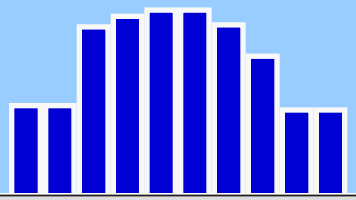
multi-leaf collimator leaf size

Collimation

PTV coverage 5mm vs 2.5 mm MLC

differences



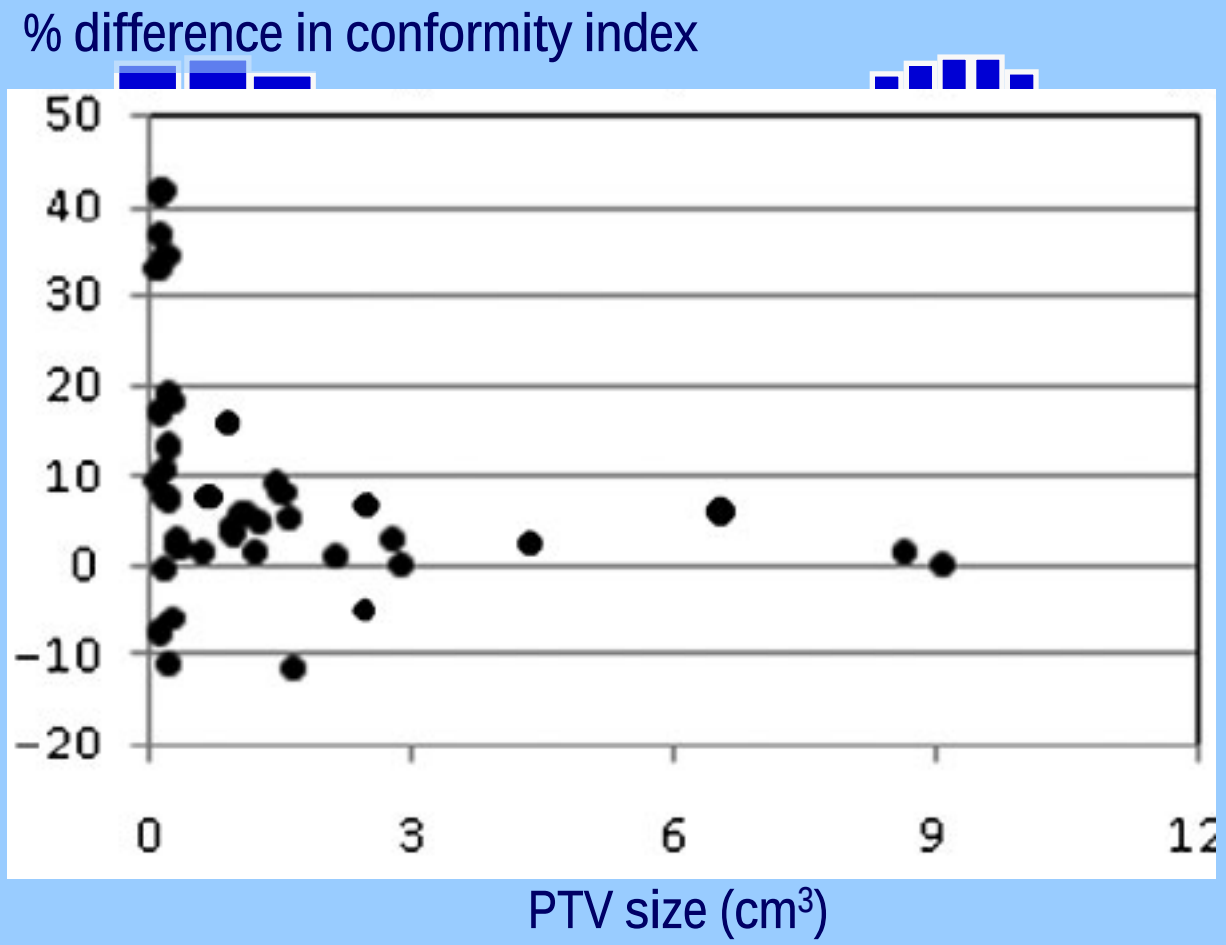


Category		$^{a}D_{min}$ (Gy)	$^{b}D_{mean}$ (Gy)	$^{b}D_{max}$ (Gy)	^{b}Conformity index
Collimation optimisation					
Overall (n=68)		−0.09±0.28 (−0.05, −0.3%) 0.010	−0.07±0.27 (−0.08, −0.4%) 0.007	0.15±0.38 (0.05, 0.2%) 0.004	0.15±0.34 (0.05, 3.0%) <0.001
	PTV				
I (n=34)	<1 cm^3	−0.13±0.34 (−0.09, −0.4%) 0.022	−0.16±0.25 (−0.15, −0.7%) <0.001	0.26±0.48 (0.23, 0.9%) 0.004	0.26±0.45 (0.15, 14.2%) <0.001
II (n=25)	≥1 cm^3 <5 cm^3	−0.09±0.18 (−0.06, −0.3%) 0.010	−0.00±0.30 (−0.06, −0.3%) 0.294	0.11±0.21 (0.05, 0.2%) 0.028	0.05±0.09 (0.03, 2.7%) 0.007
III (n=9)	≥5 cm^3	0.10±0.19 (0.14, 0.8%) 0.192	0.09±0.17 (0.05, 0.3%) 0.086	−0.12±0.09 (−0.13, −0.8%) 0.015	0.01±0.04 (0.01, 0.8%) 0.635

Collimation

Tanyi et al 2011

PTV coverage 5mm vs 2.5 mm MLC (DVH)



Collimation

Tanyi et al 2011

technique of high precision conformal radiotherapy

	precision imaging/immobilisation/image guidance	dose distribution	
		target	normal tissues
linac fixed field	++	++	+
linac IMRT/arcing IMRT	++	++	+
GK multiple isocentres	++	+	+
cyberknife	++	+/-	+

Comparison of conformal radiotherapy techniques

Attributes of modern local RT delivery

refinements of conformal radiotherapy

precision

conformality

- photons
- protons

time factor (4D RT)

- intrafraction patient and tumour motion
- interfraction changes in tumour & normal tissues

quality assurance

- imaging closer to treatment delivery (IGRT)

accurate tumour localisation

precise dose targeting

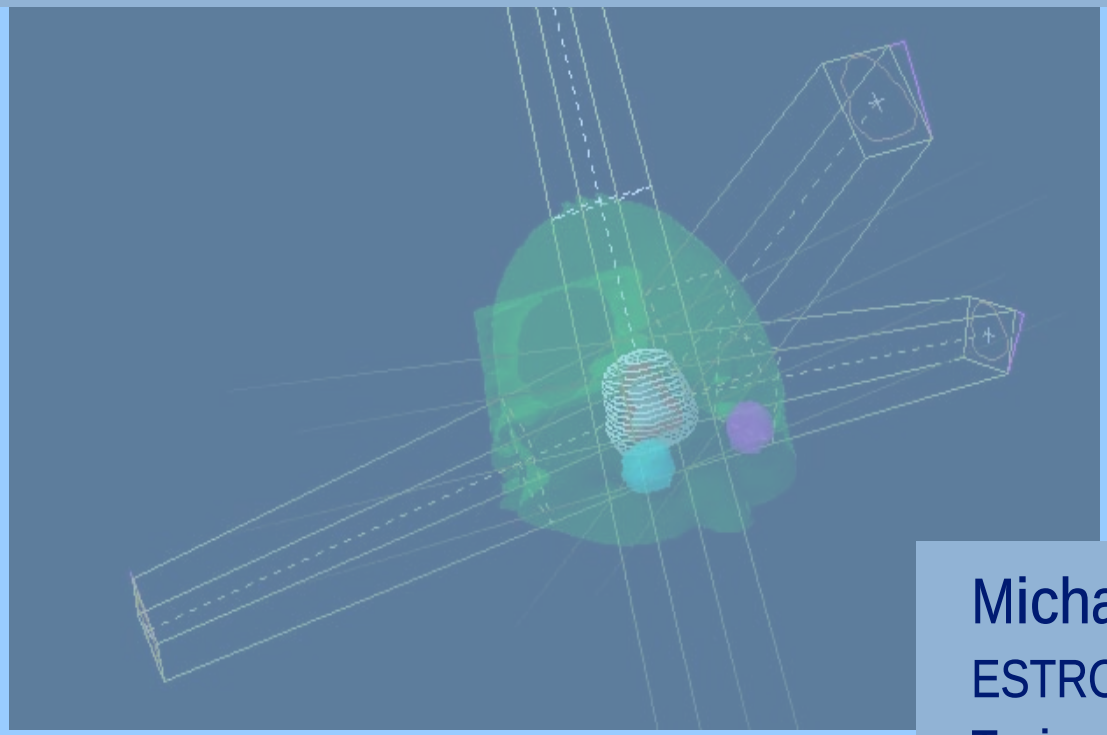
- immobilisation
- image guidance

technical and clinical skill

Classification of radiotherapy technologies

Localised radiotherapy techniques

for intracranial tumours



Michael Brada

ESTRO BT course

Torino October 2015

Radiation tolerance of the CNS: acute and late effects

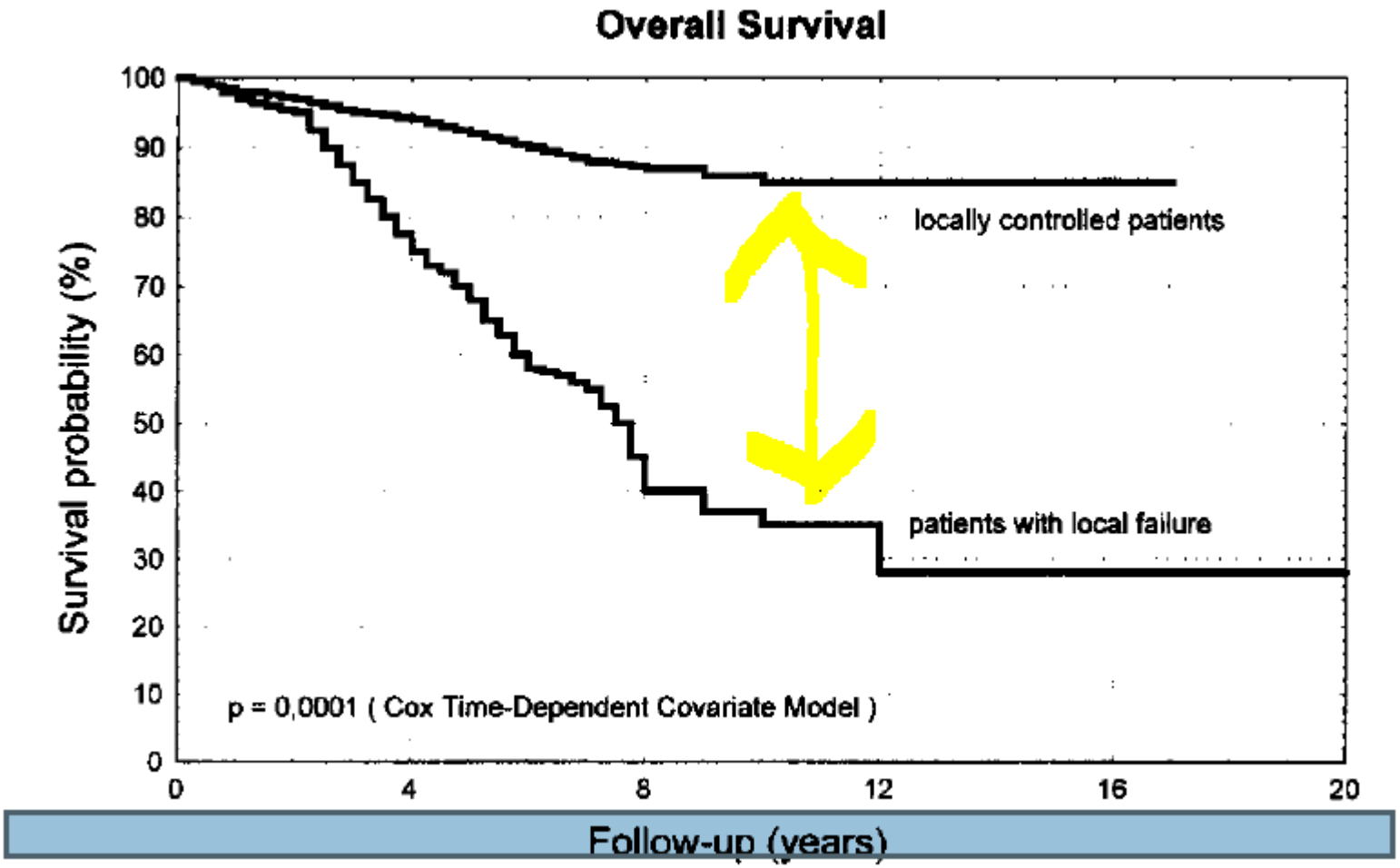
Prof. Dr.med. Damien Charles Weber

Center for Proton Therapy

Paul Scherrer Institute

Why high-dose delivered to the brain?

Int. J. Radiation Oncology Biol. Phys., Vol. 39, No. 5, pp. 967–975, 1997



BRAINSTEM TOLERANCE TO CONFORMAL RADIOTHERAPY OF SKULL BASE TUMORS

J. Debus, M.D., Ph.D.,† E. B. Hug, M.D.,* N. J. Liebsch, M.D., Ph.D.,* D. O'Farrel, M.S.,* D. Finkelstein, Ph.D.,* J. Efird, M.S.,* and J. E. Munzenrider, M.D.*

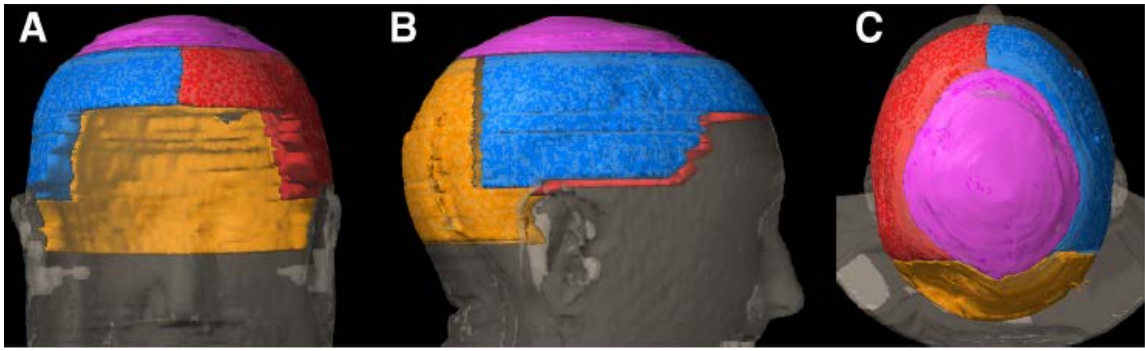
Acute toxicity

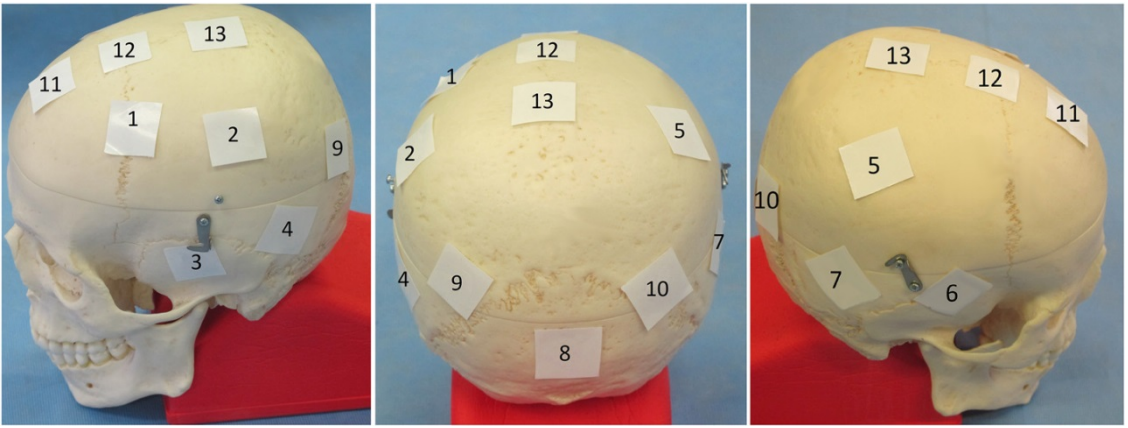
- Fatigue
- Alopecia
- Skin erythema
- Headache
- Nausea/vomitting

Alopecia

- Hair follicles located 5 mm below the scalp
- Follicle-avoidance RT

Hair-sparing whole brain radiotherapy with volumetric arc therapy in patients treated for brain metastases: dosimetric and clinical results of a phase II trial





De Puysseleyr *et al. Radiation Oncology* 2014, **9**:170
http://www.ro-journal.com/content/9/1/170

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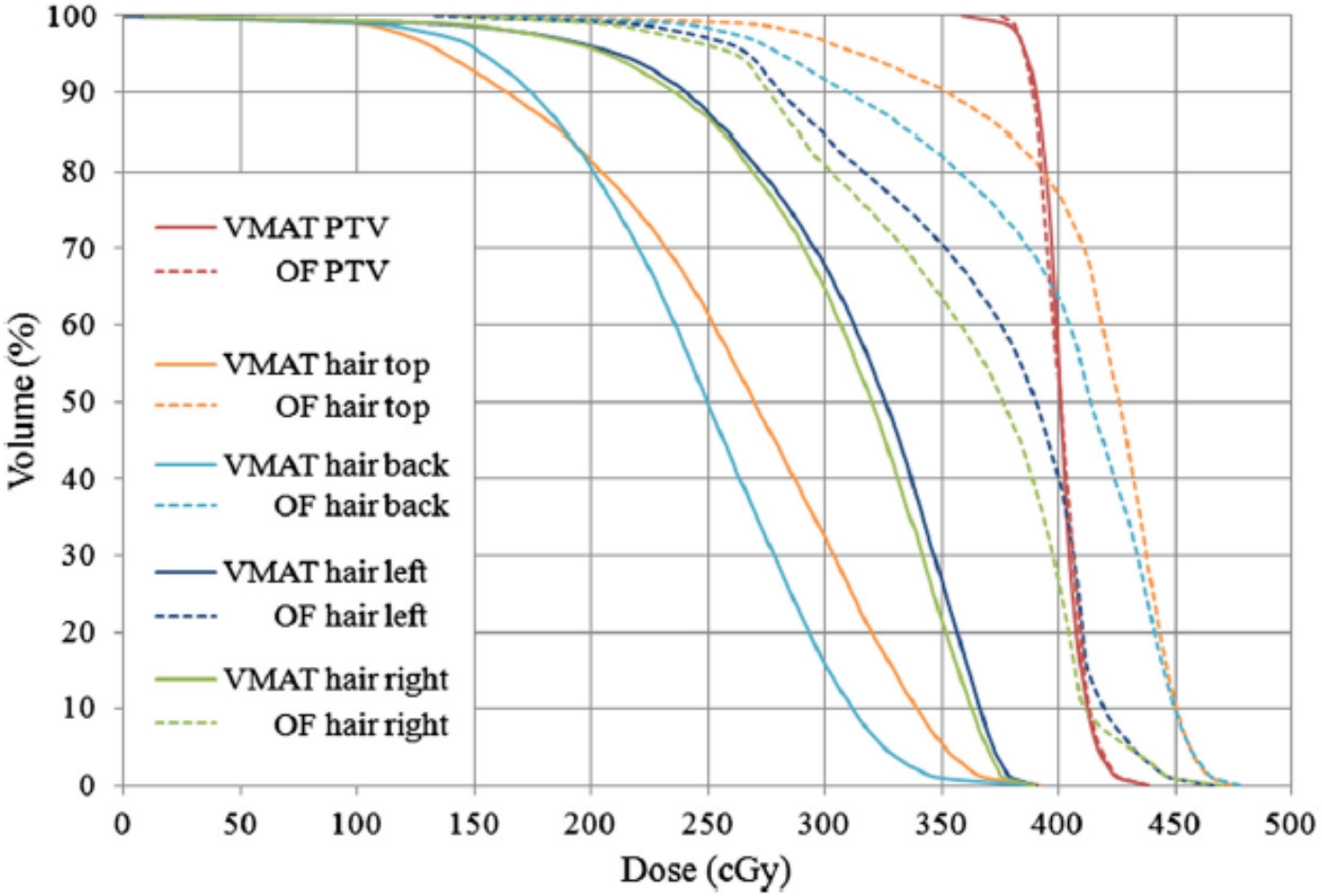
Alopecia

Reduction of **20% - 42%** dose reduction of follicule voulme (vertex-frontal-occipital)



De Puysseleyr *et al. Radiation Oncology* 2014, **9**:170
http://www.ro-journal.com/content/9/1/170

ESTRO School

Alopecia

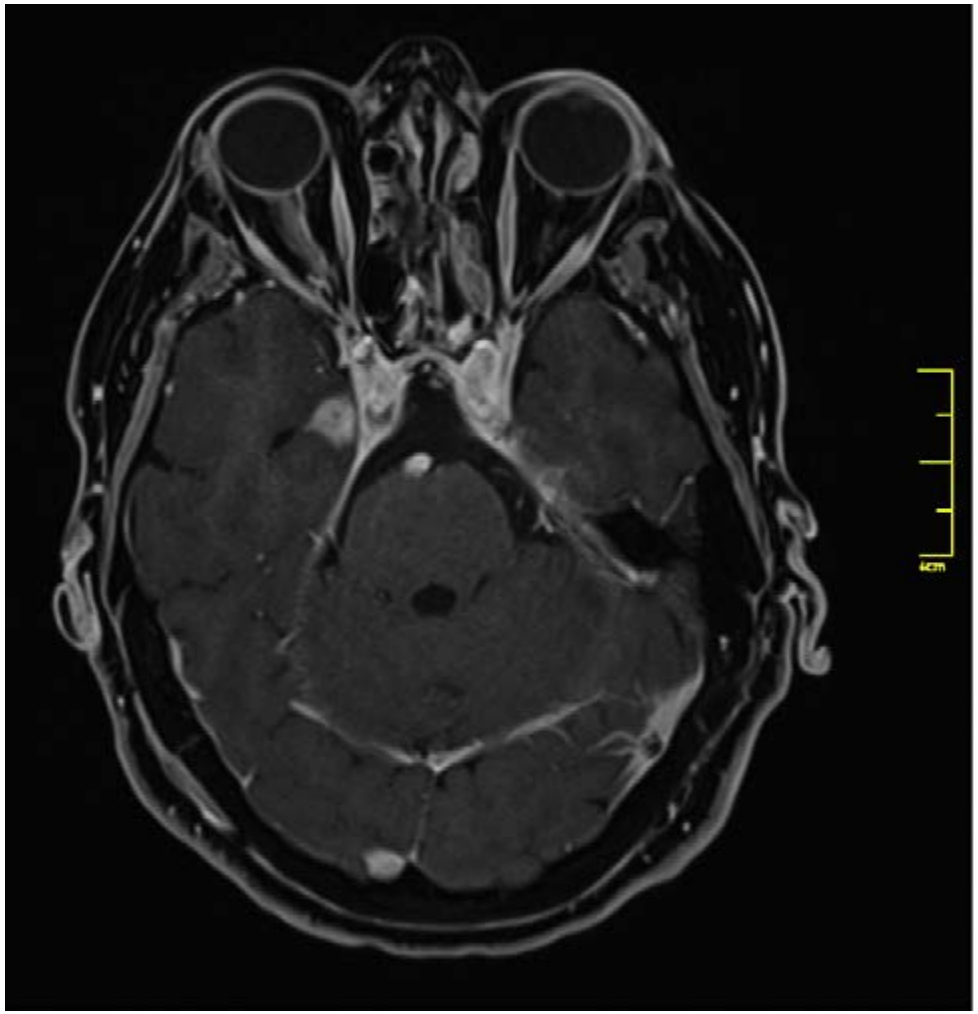
Patient planning results of the phase II trial for the different hair follicle subvolumes for 5 fractions (prescription dose 20 Gy)

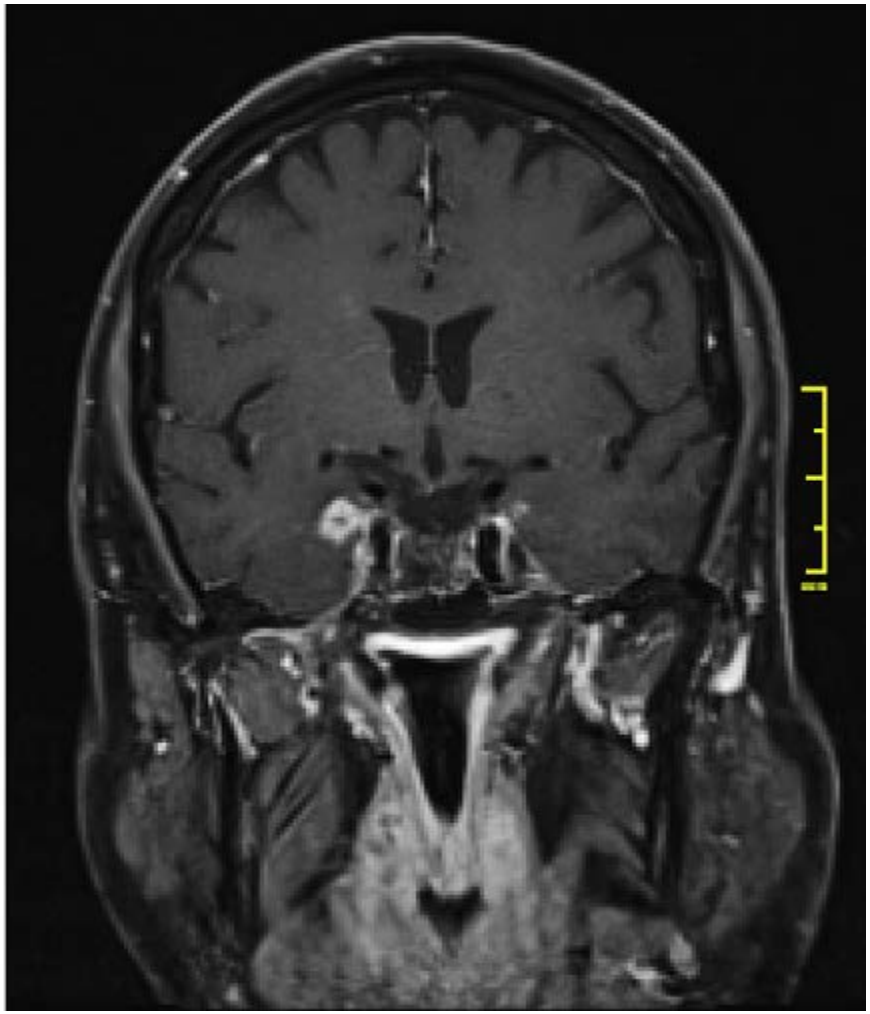
Hair follicle subvolume	Mean SALT score	Mean D50 ± SD (Gy)	% of prescribed dose	Mean V5 ± SD (%)	Mean V10 ± SD (%)	Mean V15 ± SD (%)	Mean V20 ± SD (%)
Total	75 ± 13	12.6 ± 0.9	62.9	92.2 ± 4.2	66.8 ± 6.4	31.1 ± 9.3	0.4 ± 0.8
Left	96 ± 0.05	15.7 ± 0.8	78.4	86.1 ± 1.5	79.8 ± 8.5	51.6 ± 8.5	0 ± 0
Right	96 ± 0.05	16.0 ±	80.0	.6 ± 7.3	78.9 ± 4.5	50.5 ± 7.1	0 ± 0
Back	60 ± 18.7	10.5 ±	.3	.9 .8	10.6	12.8 ± 9.2	0 ± 0
Top	65 ± 18.3	11.3 ±	56.3	76.6 ± 11.3	± 18.4	21.8 ± 16.8	0.6 ± 2

Futility

De Puysseleyr *et al. Radiation Oncology* 2014, **9**:170
http://www.ro-journal.com/content/9/1/170

Late toxicity After Radiotherapy….





Type of Late Toxicity (CNS)

- Brain necrosis
- Brainstem damage
- Pituitary dysfunction
- Cochlear toxicity
- Optic apparatus
- Hippocampal toxicity

Factors affecting toxicity (General)

I.	Host	Age Comorbid conditions Host response to radiation Smoking KPS	
II	Organ	Pre-radiation organ condition (Poor PFTs; LFTs; COPD) Regional variation of radiosensitivity with the organ Impact of other organs Hierarchal organization of the organ: Serial: dose effect: spinal cord Parallel: volume effect: lung, liver Both: kidney	
III	Natural history of tumor		
IV	Treatment	A—Radiation Dose (max, min, mean) Fractionation (fractional dose): BED Dose rate Overall treatment time Treatment energy Volume (V dose: absolute or relative)	
IV	Treatment	B—Nonradiation Chemotherapy (drug type, dose, schedule) Radiation modifiers (type, dose, schedule) Surgery (interval)	
V	End points ACUTE	Type: Clinical Radiographical: anatomical, functional Biochemical (blood test, functional test) Degree of severity Degree of frequency Impact on quality of life (QOL)	LATE
VI	Issues on reporting of toxicity		

Reports of Radiotherapy and Oncology
Vol.1 No.1 Spring 2013

Brain Toxicity

Vol.1	No.1	Spring 2013

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Brain	Symptomatic necrosis	<3 <5		<60 <65	
Brainstem	Necrosis or cranial neuropathy	<5 <5	D100 <54 Gy D1–10 cc ≤59 Gy	<64 Point	
Spinal cord	Grade ≥2 myelopathy	<1		50	
Optic nerve & chiasm	Optic neuropathy	<3 3–7		<55 55–60	<50

Reports of Radiotherapy and Oncology

Brain Toxicity QUANTEC

Dose	Incidence radio-necrosis*
> 60 Gy	< 3%
> 72 Gy	5%
90 Gy	10%

Normal fractionation and a/b ratio of 3

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	Whole organ	Permanent cranial neuropathy or necrosis	Dmax <54	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	D1–10 cc‖ ≤59	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
	Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neuropathy	Dmax <55	<3	Given the small size, 3D CRT is often whole organ‡‡
	Whole organ	3D-CRT	Optic neuropathy	Dmax 55–60	3–7	
	Whole organ	3D-CRT	Optic neuropathy	Dmax >60	>7-20	
	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	
	Partial organ	SRS (single fraction)	Myelopathy	Dmax = 13	1	Partial cord cross-section irradiated
	Partial organ	SRS (hypofraction)	Myelopathy	Dmax = 20	1	3 fractions, partial cord cross-section irradiated
Cochlea	Whole organ	3D-CRT	Sensory neural hearing loss	Mean dose ≤45	<30	Mean dose to cochlear, hearing at 4 kHz
	Whole organ	SRS (single fraction)	Sensory neural hearing loss	Prescription dose ≤14	<25	Serviceable hearing

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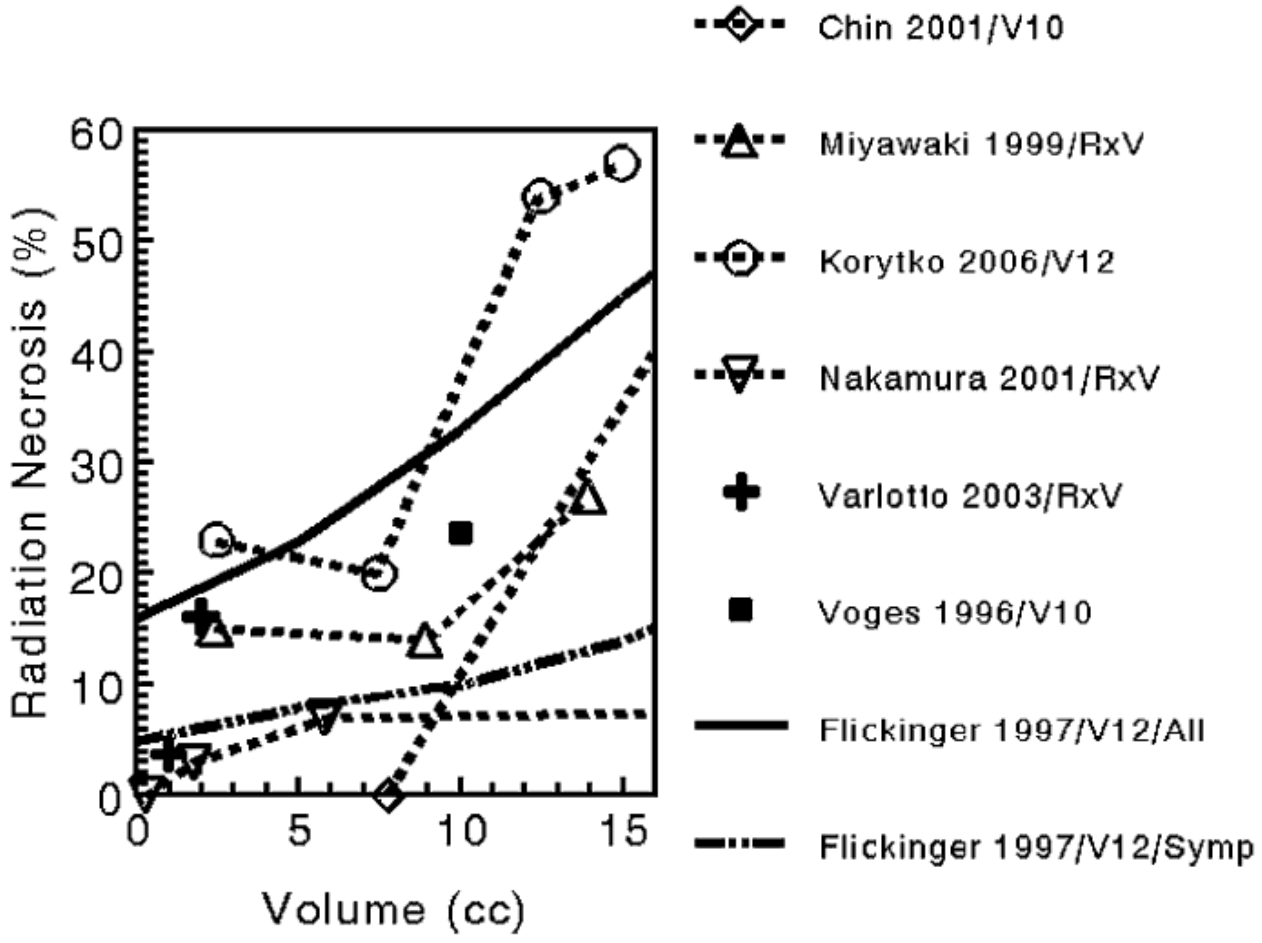
Brain Toxicity QUANTEC

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S20–S27, 2010



QUANTEC: ORGAN SPECIFIC PAPER Central Nervous System: Brain

RADIATION DOSE–VOLUME EFFECTS IN THE BRAIN

Yaacov Richard Lawrence, M.R.C.P.,* X. Allen Li, Ph.D.,† Issam el Naqa, Ph.D.,‡

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Brain necrosis Introduction

- **Coagulation necrosis**
- **Vascular Thickening**
- **Peri-vascular fibrosis**
- **Infiltartion of chr inflammatory cells**

Therory

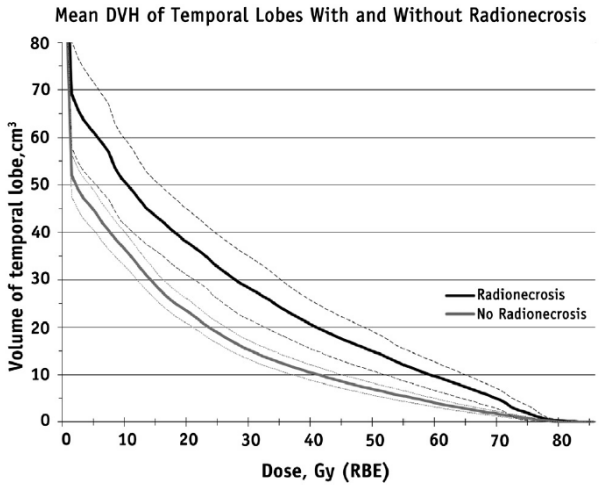
1. **Vascular hypothesis**: lesions of small to medium vessels, necrosis is secondary to ischemia.
2. **Glial hypothesis**: irradiation damage glial cells (oligodendrocytic +++) leading to white matter cavitation and demylenisation
3. **Immunologic hypothesis**: radiation necrosis and vascular change in response to Ag release from damaged glial cells

Brain necrosis (0)

Mental status	Seizures	Motor function
Gr. 1: Mild subjective memory loss or transient alteration of mental status	–	–
Gr. 2: Moderate subjective memory loss or mental disorder status alteration substantially affecting function	Transient seizure	Substantially affects function: <50% decrease of baseline capabilities
Gr. 3: Severe memory loss affecting function <50% of time	Seizure disorder controlled by medical therapy	Substantially affects function: >50% decrease of baseline capabilities
Gr. 4: Coma	Seizure disorder not controlled by medical therapy	Paralysis

Modified RTOG-EORTC late morbidity scoring system.

Brain necrosis (1)



Necrosis @ 3 year	**12.4%**
Necrosis @ 3 year (grade 2 and higher)	5.7%

Dose–Volume Relationships Associated With Temporal Lobe Radiation Necrosis After Skull Base Proton Beam Therapy

Mark W. McDonald, MD,*,† Okechukwu R. Linton, MD, MBA,* and Cynthia S.J. Calley, MA‡

Mean dose–volume information to area of radiation necrosis by grade of radiation necrosis

	Grade 1/asymptomatic	Grade 2 or higher	*P* value
Volume, cm^3	2.15	3.66	.51
Minimum dose	54.0	50.2	.58
Maximum dose	75.0	82.9	<.01
Mean dose	68.6	73.0	.02
Epicenter dose	70.9	76.7	<.01

Dose is given in Gy (relative biological effectiveness).

Dose–volume levels associated with 3-year risk of any-grade temporal lobe radiation necrosis

Risk level	aV40	aV50	aV60	aV70
10%	16.5	9.0	5.1	1.2
15%	16.5	9.6	5.5	1.7
20%	16.6	10.1	5.8	2.0
30%	16.7	10.8	6.3	2.5
40%	16.7	11.4	6.8	3.1
50%	16.8	12.2	7.2	3.9

Abbreviations: aV = absolute volume of temporal lobes exposed to dose in Gy (RBE); RBE = relative biological effectiveness. Volume is expressed in cubic centimeters (cm^3).

Int J Radiation Oncol Biol Phys, Vol. 91, No. 2, pp. 261–267, 2015

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Brain necrosis (2)

Number of patients	N=96
Tumor	**CS & Chordoma**
Dose	PRT RTOG 85-26 66.6 vs. 72 Gy RBE
Unilater(bilateral) BN	80% (20%)
BN @ 5 years	13.2%

Int. J. Radiation Oncology Biol. Phys., Vol. 41, No. 1, pp. 59–68, 1998

	Grade (clinical symptoms)			
Patient	Headache	Motor function	Seizures	Mental status
1	–	2	2	2
2	–	–	3	2
3	1	–	–	–
4	–	–	3	–
5	–	–	3	3
6	–	–	3	3
7	–	–	–	3
9	–	–	–	3
10	3	–	–	–

Characteristic	*n*
Age	
≤50	64
>50	32
Gender	
Male	51
Female	45
T-site	
Occipital bone	41
Sphenoid bone	26
Temporal bone	28
Nasopharynx	1
Histology	
Chondroid chordoma	17
Nonchondroid chordoma	32
Intermediate-grade *chondrosarcoma*	28
Low-grade *chondrosarcoma*	19
Type of presentation	
Primary tumor	75
Persistent and or recurrent tumor	21
Number of surgical procedures	
1 Surgery	64
>1 Surgery	32
Type of surgical procedure	
Craniotomy	58
Noncraniotomy	38
Primary target volume	
<70 cc	83
≥70 cc	13
Prescribed dose (CGE) to the target volume	
66.6	44
72	52

Patient	Clinical symptoms	Status*
1	Partial improvement after surgical resection; persistent loss of memory	A.P.R.
2	Complete recovery after surgical resection	A.C.R.
3	Improved after surgical resection; local recurrence; dead local disease	D.D.
4	Complete control of seizures	A.C.R.
5	Deteriorated mental condition	A.C.R.
6	Complete control of seizures; persistent memory impairement	A.P.R.
7	Increasing memory loss	A.S.E.
8	Initially asymptomatic; local recurrence; cerebral infarction	A.D.
9	Increasing memory loss	A.S.E.
10	Complete control of seizures	A.C.R.

TEMPORAL LOBE (TL) DAMAGE FOLLOWING SURGERY AND HIGH-DOSE PHOTON AND PROTON IRRADIATION IN 96 PATIENTS AFFECTED BY CHORDOMAS AND CHONDROSARCOMAS OF THE BASE OF THE SKULL

RICCARDO SANTONI, M.D.,* NORBERT LIEBSCH, M.D., PH.D.,* DIANNE M. FINKELSTEIN, PH.D.,†

Int. J. Radiation Oncology Biol. Phys., Vol. 41, No. 1, pp. 59–68, 1998

Variable	Patients with damage (%)	*p* value
Age		
≤50	3 of 64 (5%)	
>50	7 of 32 (22%)	0.191
Gender		
Males	9 of 51 (18%)	
Females	1 of 45 (2%)	0.0155
Tumor site		
OR	4 of 41 (10%)	
Type of presentation		
Primary t.	7 of 75 (9%)	
Recurrent t.	3 of 21 (14%)	0.513
Tumor volume		
≥70 cc	4 of 13 (31%)	
<70 cc	6 of 83 (7%)	0.391
Intracranial arteries involvement*		
Absent	4 of 43 (9%)	
1 artery	2 of 35 (11%)	0.689
>1 artery	4 of 18 (11%)	
Number of surgical procedures		
1	5 of 64 (8%)	
>1	5 of 32 (16%)	0.189
Type of surgery		
at least 1 craniotomy	6 of 58 (10%)	
Noncraniotomy	4 of 38 (10%)	0.980
Prescribed dose†		
66.6 CGE	3 of 44 (7%)	
72 CGE	7 of 52 (13%)	0.304

Gender

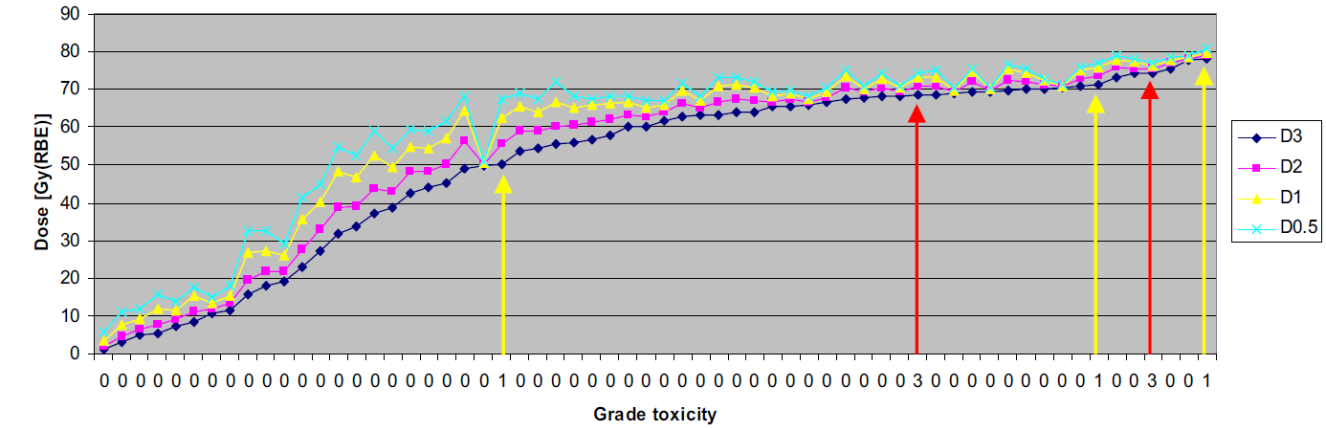
Males	9 of 51 (18%)	
Females	1 of 45 (2%)	0.0155

TEMPORAL LOBE (TL) DAMAGE FOLLOWING SURGERY AND HIGH-DOSE PHOTON AND PROTON IRRADIATION IN 96 PATIENTS AFFECTED BY CHORDOMAS AND CHONDROSARCOMAS OF THE BASE OF THE SKULL

RICCARDO SANTONI, M.D.,* NORBERT LIEBSCH, M.D., PH.D.,* DIANNE M. FINKELSTEIN, PH.D.,†

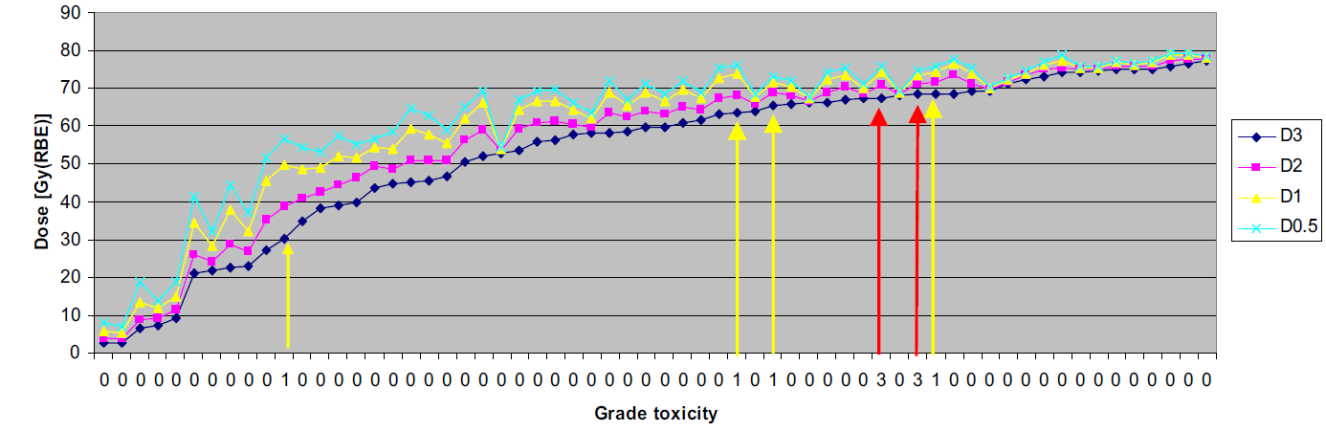
Brain necrosis

Number of patients	N=62
Tumor	**CS & Chordoma**
Dose	Median 71.7 GyRBE
Unilater(bilateral) BN	40% (60%)
BN crude	11.3%



c)

Left temporal lobe toxicity



No clear association with DVH metrics

74 Gy CGE to 2 cm³

Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, pp. 1432–1440, 2012

Temporal Lobe Toxicity Analysis After Proton Radiation Therapy for Skull Base Tumors

Berrin Pehlivan, M.D., Carmen Ares, M.D., Antony J. Lomax, Ph.D.,

Brainstem tolerance

Int. J. Radiation Oncology Biol. Phys., Vol. 39, No. 5, pp. 967–975, 1997

Number of patients	**N=367**
Tumor	**CS & Chordoma**
Dose	Median 67.8 Gy RBE (63.0 vs. 79.2)
Constraints	64/53 GyCGE
Toxicity-free BS Survival @ 5-10 years	**94-88%**

Statistics of dosimetric values	Prescribed dose targetvol.	Maximum dose brainstem	Median dose brainstem	Volume ≥50 CGE brainstem	Volume ≥55 CGE brainstem	Volume ≥60 CGE brainstem
Average	69.75 CGE	62.21 CGE	36.44 CGE	6.74 cc	3.70 cc	1.17 cc
Median	68.50 CGE	63.00 CGE	38.00 CGE	6.30 cc	3.10 cc	0.90 cc
Minimum	61.20 CGE	4.00 CGE	3.00 CGE	0.00 cc	0.00 cc	0.00 cc
Maximum	79.20 CGE	70.00 CGE	55.00 CGE	31.00 cc	19.30 cc	6.60 cc
Standard deviation	3.03 CGE	5.54 CGE	10.90 CGE	3.70 cc	3.06 cc	1.24 cc

RTOG grade	0	I	II	III	IV	V
No. of patients at "peak" toxicity	331	3 ≥I°	3 ≥II°	4 ≥III°	4 ≥IV°	3 ≥V°
Crude cumulative toxicity %		4.9%	4.0%	3.2%	2.0%	0.9%
No. of patients with residual grade at latest follow-up	332	6 ≥I°	2 ≥II°	2 ≥III°	3 ≥IV°	3 ≥V°
Crude cumulative toxicity %		4.6%	2.9%	2.3%	1.7%	0.9%

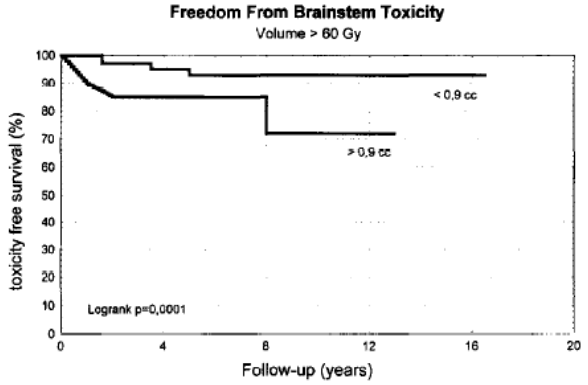
BRAINSTEM TOLERANCE TO CONFORMAL RADIOTHERAPY OF SKULL BASE TUMORS

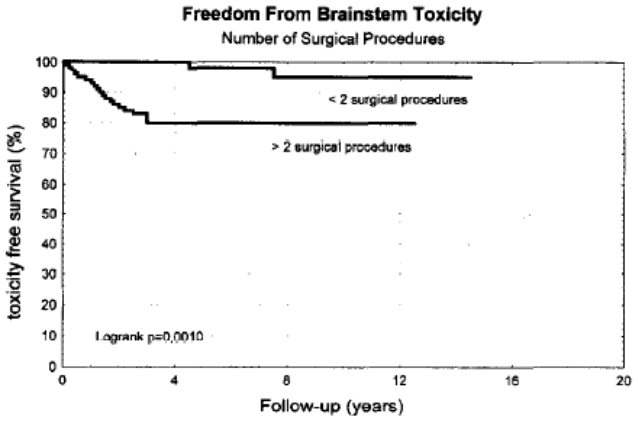
J. Debus, M.D., Ph.D.,† E. B. Hug, M.D.,* N. J. Liebsch, M.D., Ph.D.,* D. O'Farrel, M.S.,* D. Finkelstein, Ph.D.,* J. Efird, M.S.,* and J. E. Munzenrider, M.D.*

Brainstem tolerance

Int. J. Radiation Oncology Biol. Phys., Vol. 39, No. 5, pp. 967–975, 1997

Variable	Significance in univariate analysis	Significance in multivariate analysis	"Threshold"	Actuarial risk ratio
Prescribed tumor dose	0.3	0.5	70 CGE	1.1
Maximum dose at brainstem	0.001	0.09	64 CGE	1.3
Volume of brainstem receiving ≥50 CGE	0.001	0.1	≥5.9 cc	1.3
Volume of brainstem receiving ≥55 CGE	0.001	0.08	≥2.7 cc	1.5
Volume of brainstem receiving ≥60 CGE	0.0001	0.001	≥0.9 cc	11.4
History of smoking	0.08	0.2	yes/no	1.4
Diabetes	0.04	0.01	yes/no	5.7
High blood pressure	0.1	0.3	yes/no	1.4
Surgical procedures at the base of skull	0.0006	0.001	≥2	2.6





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Pituitary

St Jude Lifetime Cohort study.

Number of patients	**748**
FU period	**27.3 years (range, 10.8-47.7)**
Prevalence GHD	**46.5%**
Prevalence LH/FSHD	**10.8%**
Prevalence TSHD	**7.5%**
Prevalence ACTHD	**4%**
Treatment of GHD	**0.3%**
Treatment LH/FSHD	**21.5%**

JOURNAL OF CLINICAL ONCOLOGY

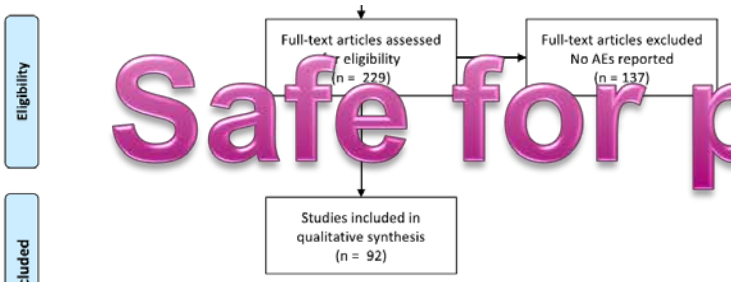
J Clin Oncol. 2015 Feb 10;33(5):492-500. doi: 10.1200/JCO.2014.56.7933. Epub 2015 Jan 5.

Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study.

Chemaitilly W[1], Li Z[2], Huang S[2], Ness KK[2], Clark KL[2], Green DM[2], Barnes N[2], Armstrong GT[2], Krasin MJ[2], Srivastava DK[2], Pui CH[2], Merchant TE[2], Kun LE[2], Gajjar A[2], Hudson MM[2], Robison LL[2], Sklar CA[2].

Pituitary

Growth Hormone & IGF Research 25 (2015) 149–157



Safe for pituitary tumors

Study	41'000 patients/9 studies (pituitary-hypothalamic tumors)
NFPA	**10y TPFS 70% vs. 74% (NS)**
Craniopharyngioma	**TP not affected by GHR** (Significant factor: residual tumor, RT)
NFPA	**GH not predictor of tumor progression** after ajusting for gender, resction, age, invasion cav. Sinus)
Secondary tumors in patients with RT +/- GHR (match pait analysis)	**No difference observed**

Pituitary

Table 6. SAEs Related to Growth or Recurrence of Preexisting Intracranial Tumors Including Pituitary Adenomas[a]

Intracranial Tumor	GH-Treated	Untreated	*P* Value
Pituitary adenomas	24/965 (2.5%)	12/273 (4.4%)	.21
Craniopharyngiomas	8/211 (3.8%)	2/36 (5.6%)	.82
Other intracranial tumors[b]	4/133 (3.0%)	1/30 (3.3%)	.90

Prospective Safety Surveillance of GH-Deficient Adults: Comparison of GH-Treated vs Untreated Patients

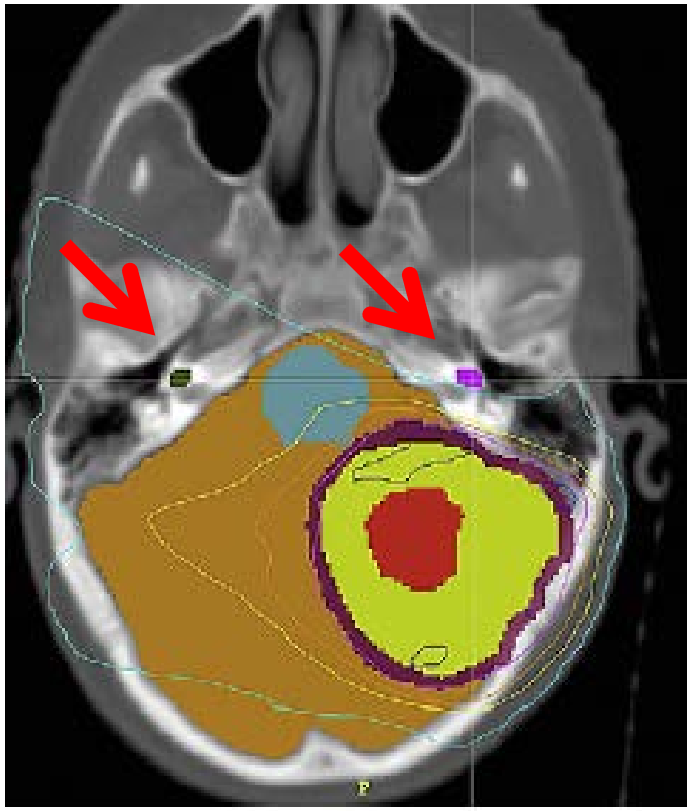
Mark L. Hartman, Rong Xu, Brenda J. Crowe, Leslie L. Robison,

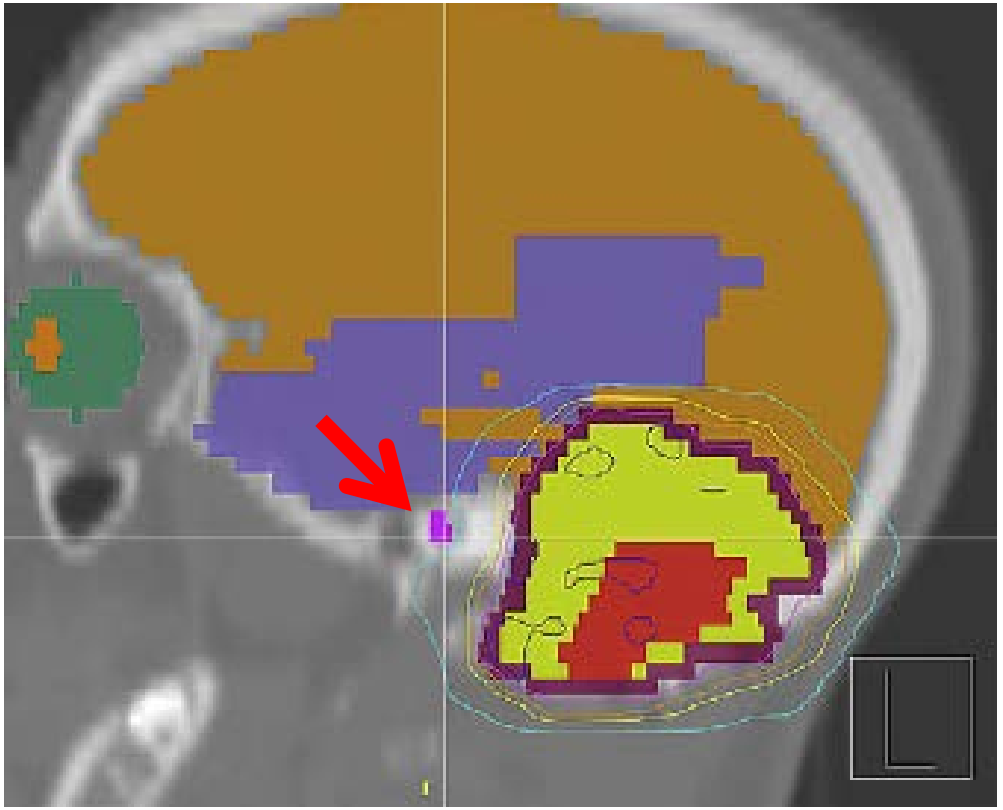
J Clin Endocrinol Metab, March 2013, 98(3):980–988

Table 5. Summary of Number of SAEs Related to Benign Extracranial Tumors or Cysts (Either New Tumors or Progression of Preexisting Tumors)[a]

	GH-Treated (n = 1988)	Untreated (n = 442)
Tumor type, n (%)		
Uterine leiomyoma	3 (0.15)	0
Ovarian cyst or adenoma	3 (0.15)	0
Hemangioma	2 (0.10)	0
Histiocytosis	0	1 (0.23)
Colon adenoma	1 (0.05)	0
Lipoma	1 (0.05)	0
Synovial cyst	1 (0.05)	0
Total benign tumors and cysts, n (%)	11 (0.55)	1 (0.23)

Hearing Loss





Hearing Loss

Grade POG	Decription
0	Normal
1	20 to 40 dB loss at >4 KHz
2	>40 dB loss at 4 KHz
3	>40 dB loss at >2 KHz
4	40 dB loss at <2 KHz

https://www.childrensoncologygroup.org/index.php/sensory/hearingproblems

Hearing Loss

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S20–S27, 2010

Dose	Rate
Mean dose < 45 Gy	< 30% of non-serviceable hearing
< 14 Gy Single fraction (SRS)	< 25% of non-serviceable hearing

POG ototoxicity	Frequence	%	% accumulated
0 - 2	34	82.9%	82.9%
3 - 4	7	17.1%	100%
Total	41	100%	

Variable	Coefficient	Standard error	*p*-value	Odds ratio
Median < 42.04 Gy	−2.191	1.180	0.043	0.112
Cisplatin dose < 375 mg/m^2	−2.825	1.035	0.006	0.059

N=42 MB patientd Treated with CDDP and IMRT

Ototoxicity evaluation in medulloblastoma patients treated with involved field boost using intensity-modulated radiation therapy (IMRT): a retrospective review

Wilson Albieri Vieira[1,2*], Eduardo Weltman[1,2], Michael Jenwei Chen[1], Nasjla Saba da Silva[3],

Vieira *et al. Radiation Oncology* 2014, **9**:158
http://www.ro-journal.com/content/9/1/158

RADIATION ONCOLOGY

ESTRO School

Hearing Loss

Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 5, pp. 1445–1450, 2010

Study (Ref)	*n*	Tumor	Estimated cisplatin dose (mg/m^2)	Estimated cochlear RT dose (Gy)	Median audiogram follow-up (mo)	No. of patients with ototoxicity
Fouladi *et al.* (8)	97	MB	300	49 (median)	19	22/97 (22.7%) Grade 3–4 ototoxicity
Huang *et al.* (4)	15	MB	300	36.7 (mean)	18	13% Grade 3–4 ototoxicity
Polkinghom *et al.* (12)	16	MB	Not stated	53% of prescription boost dose (mean)	12	13% Grade 3–4 ototoxicity
Kwong *et al.* (13)	132	NP	100–185 (52/132 pts received cisplatin)	59.5–76.5	24	24.2% persistent hearing loss
Chen *et al.* (14)	22	NP	200–500	48.5 (median)	29	At 4 KHz, 61% for >48 Gy and 24% for ≤48 Gy
Oh *et al.* (15)	30	NP	229 (mean)	64.4–69.6	24 (minimum)	29.2% of ears with hearing loss
Chan *et al.* (16)	140	NP	160–240 (median for concurrent and sequential chemo/RT)	48.9 (median)	24	55% at high frequency and 7.9% at low frequency
Zuur *et al.* (17)	146	HN	263 (intra-arterial)	13 (median)	7.5 weeks	23% of ears considered for hearing aids
Current study	44	MB	300	35.3 standard-risk, 43.0 high-risk (median)	41	25% Grade 3–4 ototoxicity (18.2% of ears)

Grade 3-4 POG toxicity: **25%**

No patient had grdae 3-4 tox if mean dose **< 43 Gy**

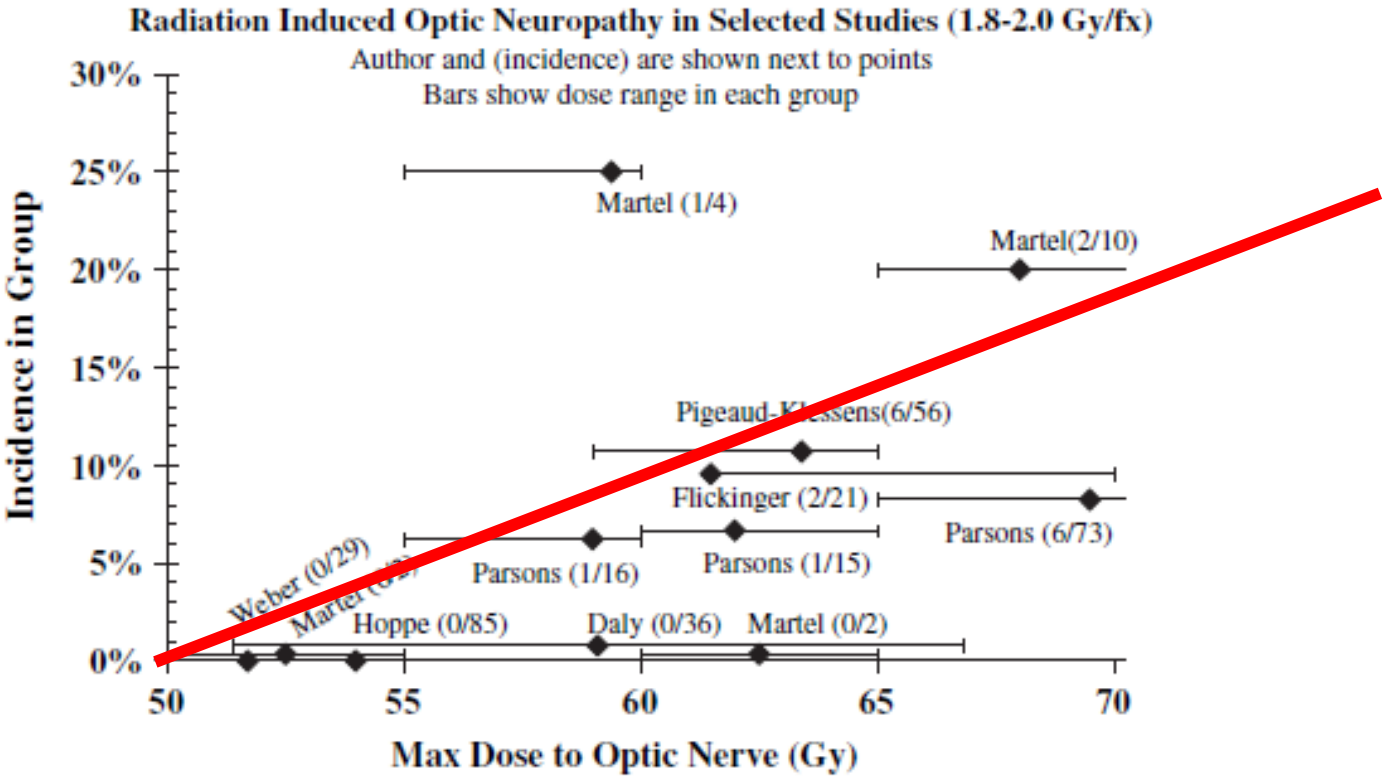
OTOTOXICITY AFTER INTENSITY-MODULATED RADIATION THERAPY AND CISPLATIN-BASED CHEMOTHERAPY IN CHILDREN WITH MEDULLOBLASTOMA

ARNOLD C. PAULINO, M.D.,*†‡ MARK LOBO, M.D.,‡ BIN S. TEH, M.D.,*‡

Visual toxicity

RADIATION DOSE–VOLUME EFFECTS OF OPTIC NERVES AND CHIASM

CHARLES MAYO, PH.D.,* MARY K. MARTEL, PH.D.,† LAWRENCE B. MARKS, M.D.,‡



Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S20–S27, 2010

ESTRO School

Visual toxicity

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Brain stem	Whole organ	Whole organ	Permanent cranial neuropathy or necrosis	Dmax <54	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	D1–10 cc‖ ≤59	<5	
	Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
	Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neuropathy	Dmax <55	<3	Given the small size, 3D CRT is often whole organ‡‡
	Whole organ	3D-CRT	Optic neuropathy	Dmax 55–60	3–7	
	Whole organ	3D-CRT	Optic neuropathy	Dmax >60	>7-20	
	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	
	Partial organ	SRS (single fraction)	Myelopathy	Dmax = 13	1	Partial cord cross-section irradiated
	Partial organ	SRS (hypofraction)	Myelopathy	Dmax = 20	1	3 fractions, partial cord cross-section irradiated
Cochlea	Whole organ	3D-CRT	Sensory neural hearing loss	Mean dose ≤45	<30	Mean dose to cochlear, hearing at 4 kHz
	Whole organ	SRS (single fraction)	Sensory neural hearing loss	Prescription dose ≤14	<25	Serviceable hearing

Visual toxicity

OAR	CGE									
	D_{max}		D_{90}		D_{50}		D_{10}		D_{Min}	
	(median)	(range)	(median)	(range)	(median)	(range)	(median)	(range)	(median)	(range)
ON[a]	53.1	29.4–80	32	0.4–65.7	43.5	11.8–75	49.5	23.3–77.1	25	0.3–55
Chiasm	48.2	22.9–65.2	37.1	13.2–60	41.6	13.9–61	44.7	21.2–63.9	33.2	10–58.7
Lens	22.5	2.1–39	5.3	0.9–28.2	9.7	1.5–29.4	20.6	2.1–31.2	4.7	0.9–26.2
Retina	55.7	22.9–80.9	15.7	1.8–33.4	21.4	8.2–52.4	50	20–67.7	7.9	0.3–22.9
MLG[b]	29.3	4.4–54.1	8.1	2.7–13.5	19	3.2–34.7	27.1	4.1–50	6.2	2.4–10
Brainstem	52.8	28.2–64.11	19.7	0.6–46.1	24.1	2.4–49.1	34.4	17.1–55	12.9	0–37.8
TL (Brain)[c]	70.5	54.1–89.7	3.8	0–22.1	14.7	0.9–50	47.4	24.7–73.5	2.4	0–14.8
FL (Brain)[d]	78.7	67.1–86.1	2.4	0.1–18.1	26.8	0.7–41.9	58.4	25–69	1.3	0–7.1

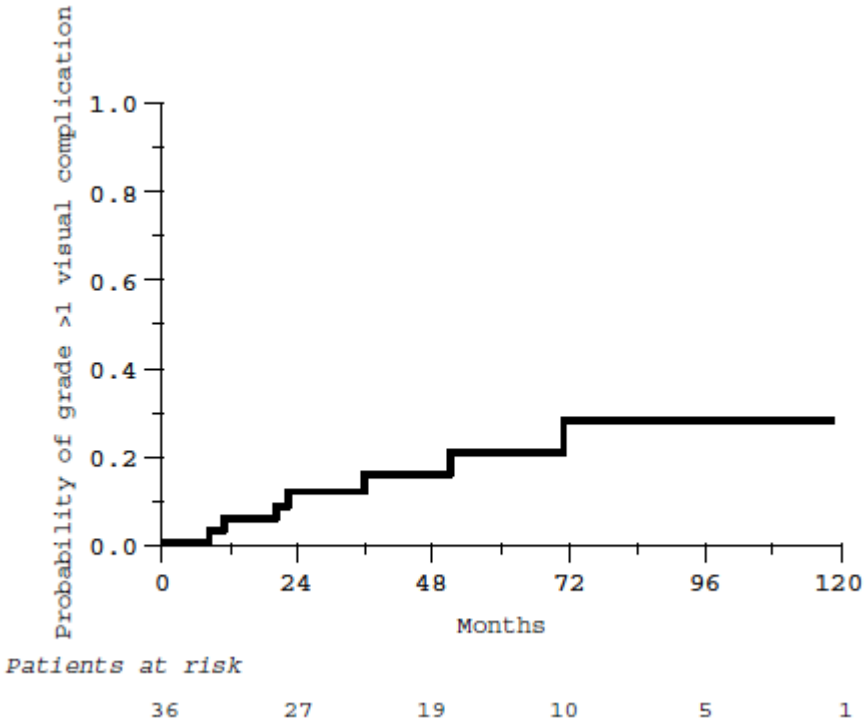
[a] Optic nerve.
[b] Major lacrimal gland.
[c] Temporal lobe.
[d] Frontal lobe.

Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons

Damien C. Weber[a,b,*], Annie W. Chan[a], Simmons Lessell[c], James F. McIntyre[a],

Radiotherapy and Oncology 81 (2006) 243–249
www.thegreenjournal.com

Visual toxicity



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ESTRO School

Visual toxicity

Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons

Damien C. Weber[a,b,*], Annie W. Chan[a], Simmons Lessell[c], James F. McIntyre[a],

Results of univariate analysis[a] of possible variables contributing to late visual/ocular toxicity in 36 advanced nasal cavity and paranasal sinuses cancer patients treated with AFR

Variables	Visual/ocular late toxicity Mean ± SD	No visual/ocular late toxicity Mean ± SD	*P* value
GTV dose (CGE)	73.6 ± 1	70.2 ± 0.9	0.02
Age (years)	44.5 ± 3.9	56.3 ± 3.1	0.02
D_{oc90} (CGE)[b]	41.7 ± 2.9	32.8 ± 2.6	0.03
D_{oc50} (CGE)	45 ± 2.6	36.2 ± 2.6	0.03
D_{on10} (CGE)	56.1 ± 2.8	48.4 ± 2.1	0.04
D_{on50} (CGE)	50.2 ± 3.7	40.7 ± 3	0.06
D_{onMax} (CGE)	58.3 ± 2.7	51.8 ± 1.8	0.06
D_{oc10} (CGE)	47.8 ± 2.7	41.4 ± 2.3	0.08
CTV dose (CGE)	56.7 ± 0.8	55 ± 0.6	0.1
Dose photon (Gy)	40.9 ± 3	34.4 ± 2.3	0.1
Follow-up (months)	68.9 ± 10.2	49.1 ± 6.2	0.1
Treatment duration (days)	40.7 ± 1.9	37.1 ± 1.2	0.1
GTV volume (cc)	79.7 ± 14.1	99.8 ± 14.3	0.3
CTV volume (cc)	278.4 ± 41.5	303.8 ± 27.4	0.6

[a] Student *T*-test.

[b] $D_{oc/on90}$, dose received by 90% of optic chiasm/optic nerve.

Radiotherapy and Oncology 81 (2006) 243–249
www.thegreenjournal.com

Visual toxicity

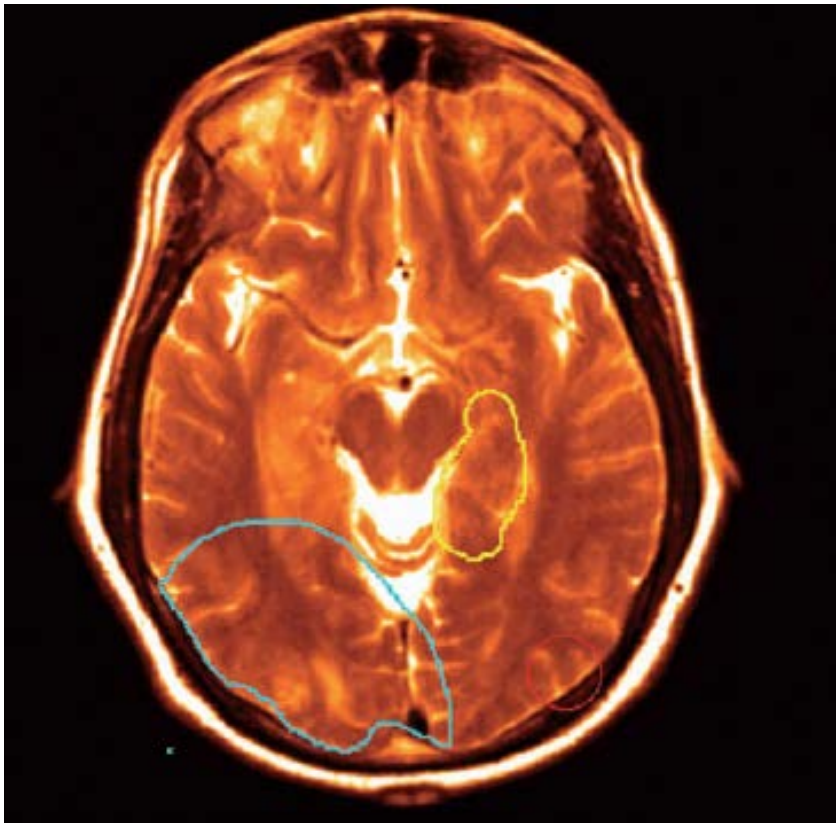
RT technique	Eye (Gy)			Chiasm (Gy)			Optic nerve (Gy)		
	Dmax	Dm	D_{05}	Dmax	Dm	D_{05}	Dmax	Dm	D_{05}
Conventional									
Median	60	—	—	53	—	—	—	—	—
Range	32–65	—	—	48–58	—	—	—	—	—
CT based, no DVH									
Median	56	—	—	52	—	—	56	—	—
Range	18–63	—	—	27–61	—	—	36–63	—	—
3D-CRT									
Median	48	8	29	51	52	46	52	32	51
Range	8–74	3–43	5–68	34–59	19–49	32–55	36–79	21–70	34–78
IMRT									
Median	47	16	3	53	40	48	53	37	51
Range	14–72	3–41	7–67	4–105	5–51	6–53	4–105	6–81	11–100

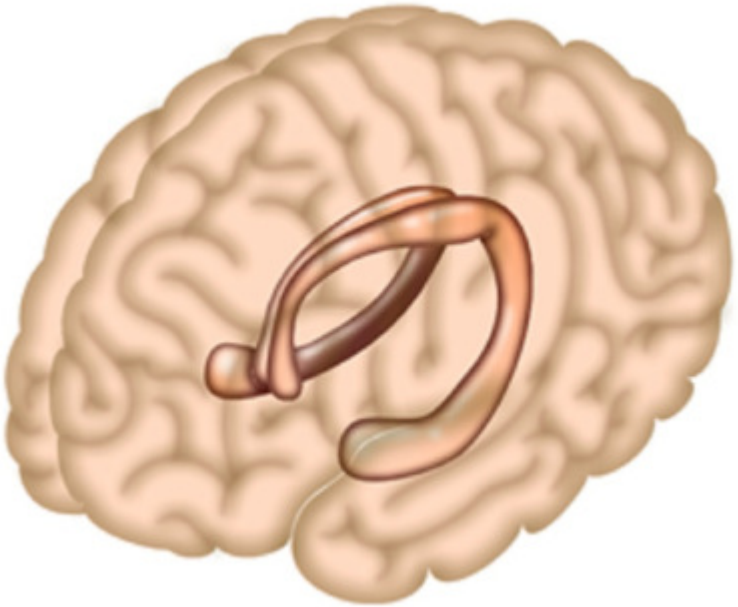
4.5% of grade 1-4 visual toxicity

TREATMENT OF NASAL CAVITY AND PARANASAL SINUS CANCER WITH MODERN RADIOTHERAPY TECHNIQUES IN THE POSTOPERATIVE SETTING—THE MSKCC EXPERIENCE

BRADFORD S. HOPPE, M.D.,* LAUREN D. STEGMAN, M.D., PH.D.,* MICHAEL J. ZELEFSKY, M.D.,*

Memory loss

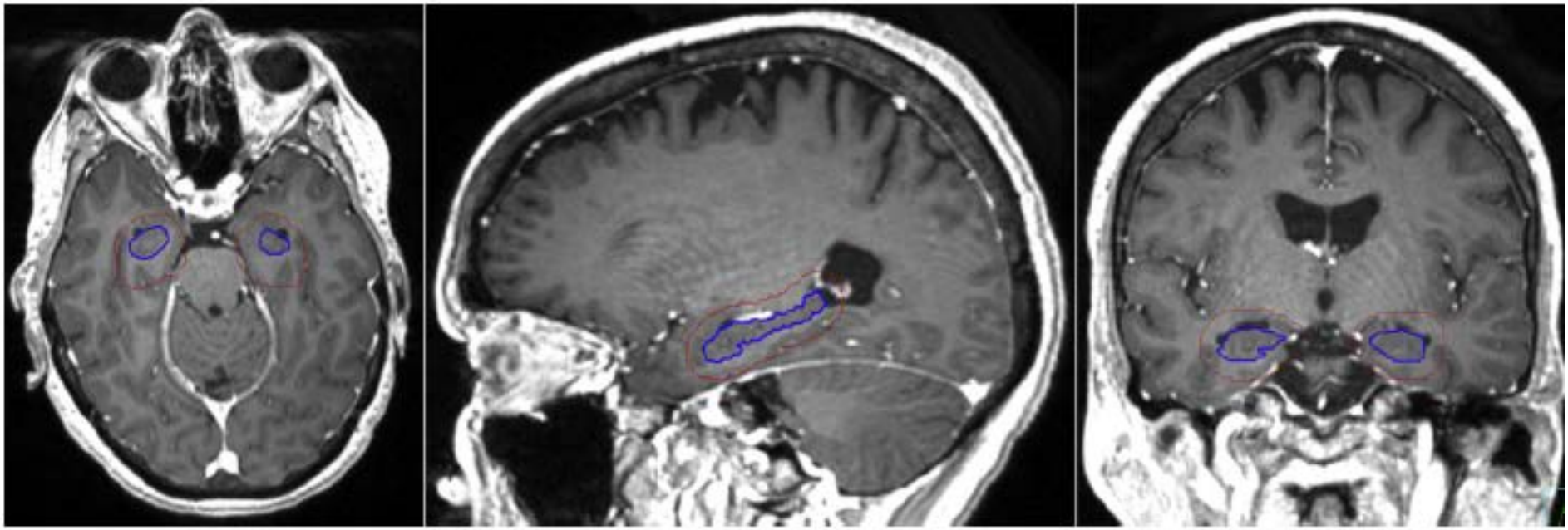




Memory loss

HC volume, cm^3	HA region, cm^3	Whole brain volume, cm^3	Percentage of whole brain volume occupied by HA region
5.5	37.9	1370.7	2.7

Abbreviations: HA region = hippocampal avoidance region; HC volume = hippocampus volume; WBRT = whole brain radiation therapy.



Memory loss

Neurocognitive Function Test	Measure
Estimated premorbid function	
NART	Estimated premorbid intelligence
Intelligence	
WAIS Full Scale Intelligence Quotient	Adult intelligence
Language	
Boston Naming Test	Visual confrontation naming
Token Test	Language comprehension
Visual perception	
Judgment of Line Orientation	Visuospatial orientation
Facial Recognition Test	Discrimination of unfamiliar faces
Hooper Visual Organization Test	Visual integration
Memory	
Wechsler Memory Scale-III Word Lists (immediate and delayed recall)	Verbal memory
WMS-III Faces (immediate and delayed recall)	Visual memory
WMS-III Spatial Span and Letter-Number Sequencing	Working memory
Executive function	
Trail Making Test	Mental flexibility
Processing speed	
Wechsler Adult Intelligence Scale Digit Symbol and Symbol Search Tests	Cognitive and mental-motor speed
Stroop Test	Elemental cognitive processing speed

Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. e487–e493, 2012

Hippocampal Dosimetry Predicts Neurocognitive Function Impairment After Fractionated Stereotactic Radiotherapy for Benign or Low-Grade Adult Brain Tumors

Vinai Gondi, M.D.,* Bruce P. Hermann, Ph.D.,† Minesh P. Mehta, M.D., FASTRO,¶

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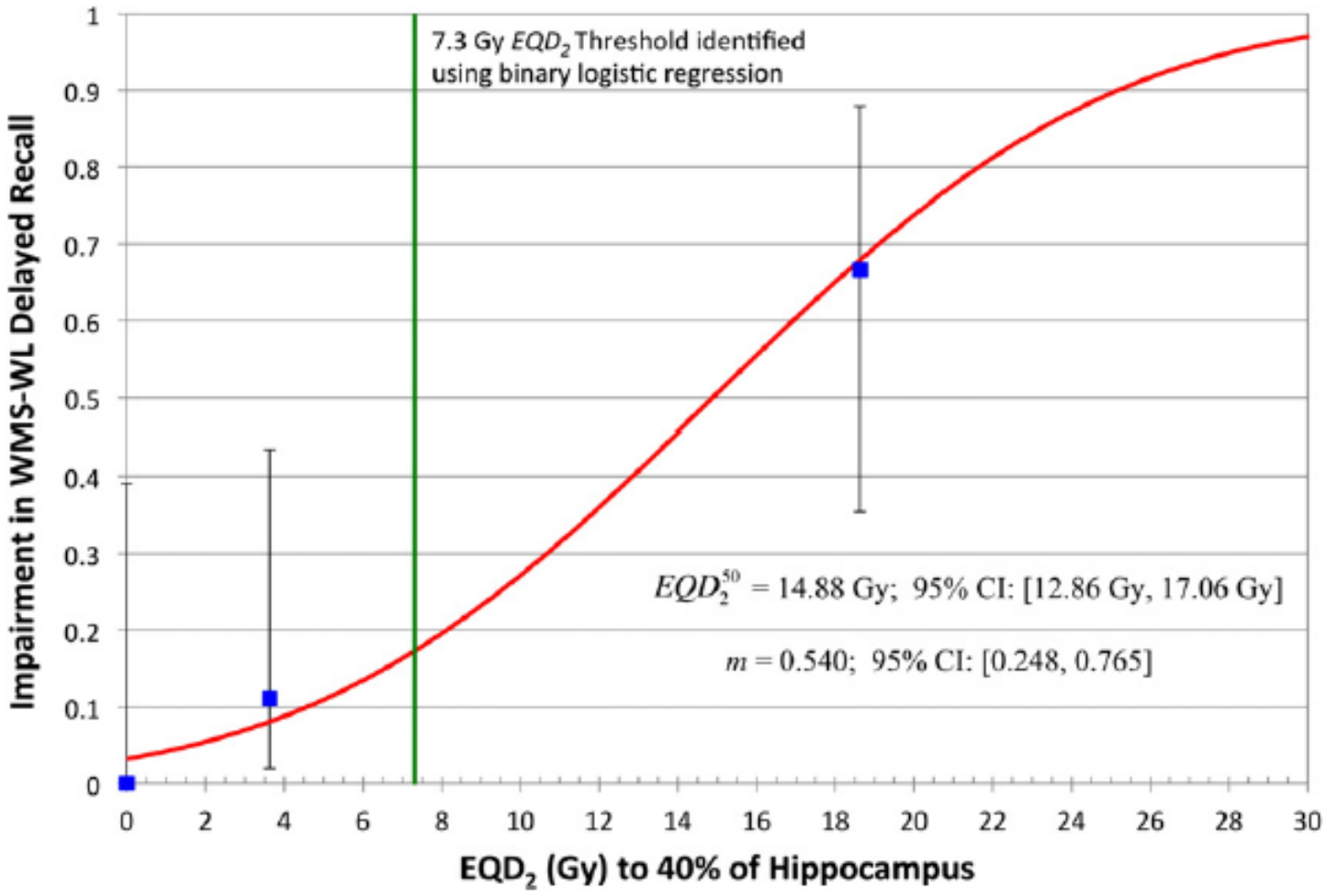
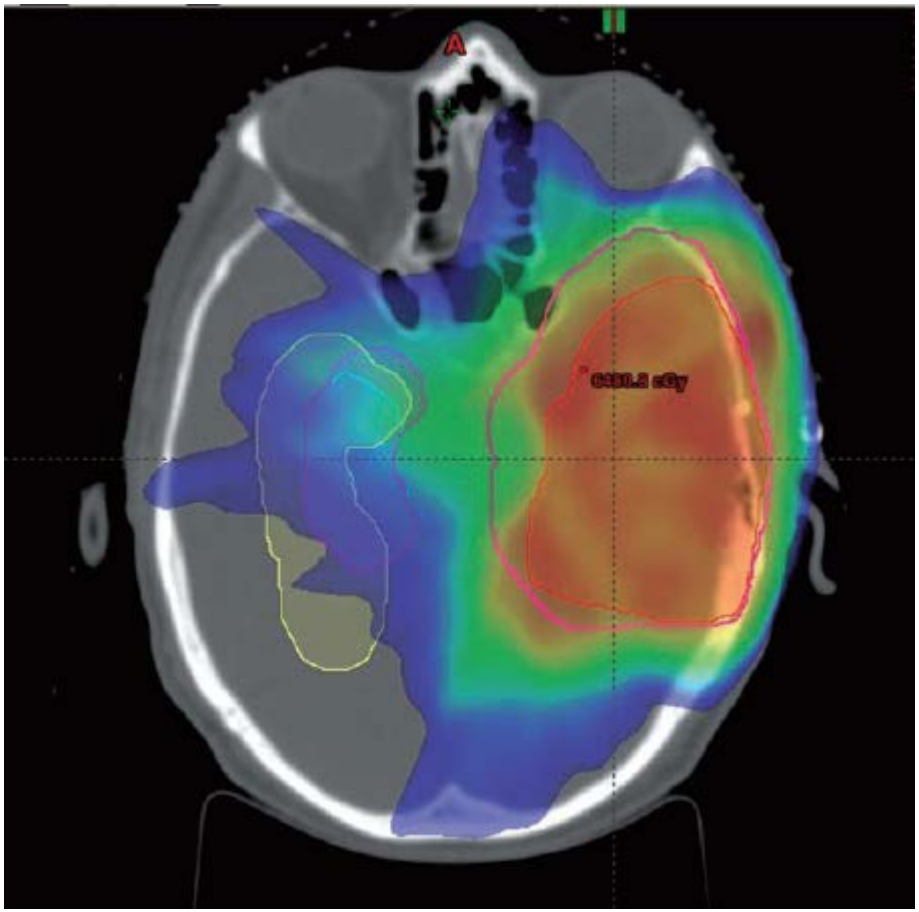
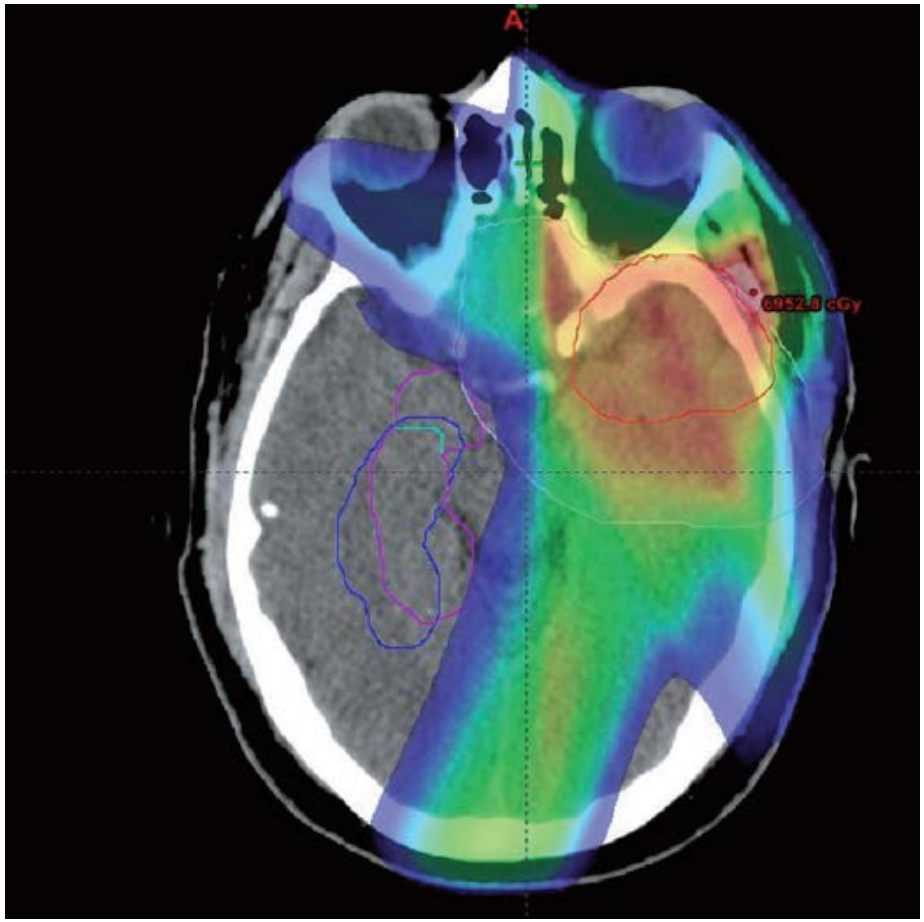
Memory Loss



Int J Radiation Oncol Biol Phys, Vol. 83, No. 4, pp. e487–e493, 2012

Memory loss





Memory loss

Int J Radiation Oncol Biol Phys, Vol. 91, No. 4, pp. 781–786, 2015

	Distribution of de novo CNS metastasis				Distribution of CNS metastasis on progression			
	HM		Rest of the brain		HM		Rest of the brain	
	HC	HC + <5 mm	5-15 mm	>15 mm	HC	HC + <5 mm	5-15 mm	>15 mm
Total no. of deposits	2	1	23	333	0	1	6	141

Abbreviations: CNS = central nervous system; HC + <5 mm = HA region; HC = hippocampus.

For de novo patients, the mean number of deposits outside the HA region was 5.1 (standard deviation 7.2). On progression of CNS disease, mean number of deposits outside the HA region was 7.7 (standard deviation 10.0).

5% of patients had BM in HR (CI95% 0-10%)

Baseline characteristics of the study group (N=70)

Characteristic	Patients who experienced brain metastases, n (%)
Median age, y (range)	63 (41-82)
Age ≥65 y	32 (46)
Male	39 (56)
De novo extensive stage disease	58 (83)
Liver metastases	12 (17)
De novo brain metastasis	59 (84)*
Post-PCI brain metastasis	8 (11)*

Risk of Hippocampal Metastases in Small Cell Lung Cancer Patients at Presentation and After Cranial Irradiation: A Safety Profile Study

Conclusions (late toxicity)

1. CNS toxicity is dose dependant and volume dependant
2. Metrics/dose constraints are based on studies with varying parameters (target volume, sample size, radiation modality, brain region, etc...)
3. Brain necrosis after (very) high-dose RT frequent: 10-15% @ 5 years
4. Is usually symptomatic and requires therapy
5. Risk factors: Gender?, DVH metrics
6. Pituitary dysfunction: very common for GHD but not treated in the majority of cases
7. GH replacement for cancer patient: no evidence of tumor recurrence
8. Constraints mean dose to cochlea to < 43-45 Gy
9. Constraint dose to 60 and 55-56 Gy to the ON and OC, respectively.
10. Correlation between hippocampal irradiation and neuro-cognitive toxicity
11. Hippocampal avoidance in young patients with LGG or benigh tumors?


THANK
YOU


?
?
?

SYSTEMIC THERAPY ISSUES

ESTRO teaching course
Management of brain tumours

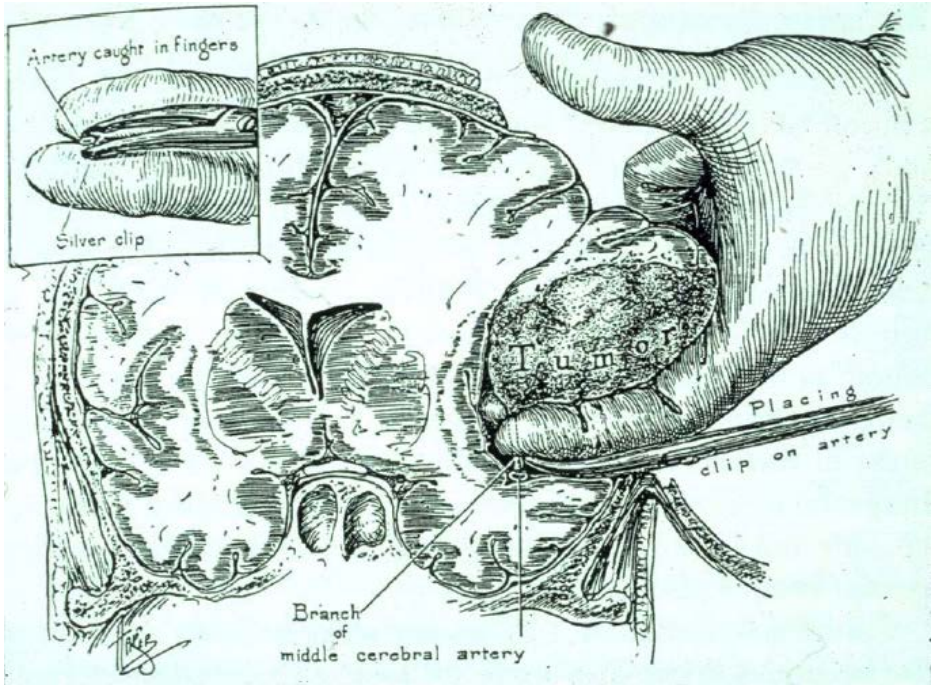
Patrick Roth

Department of Neurology and Brain Tumor Center
University Hospital Zurich

ESTRO School

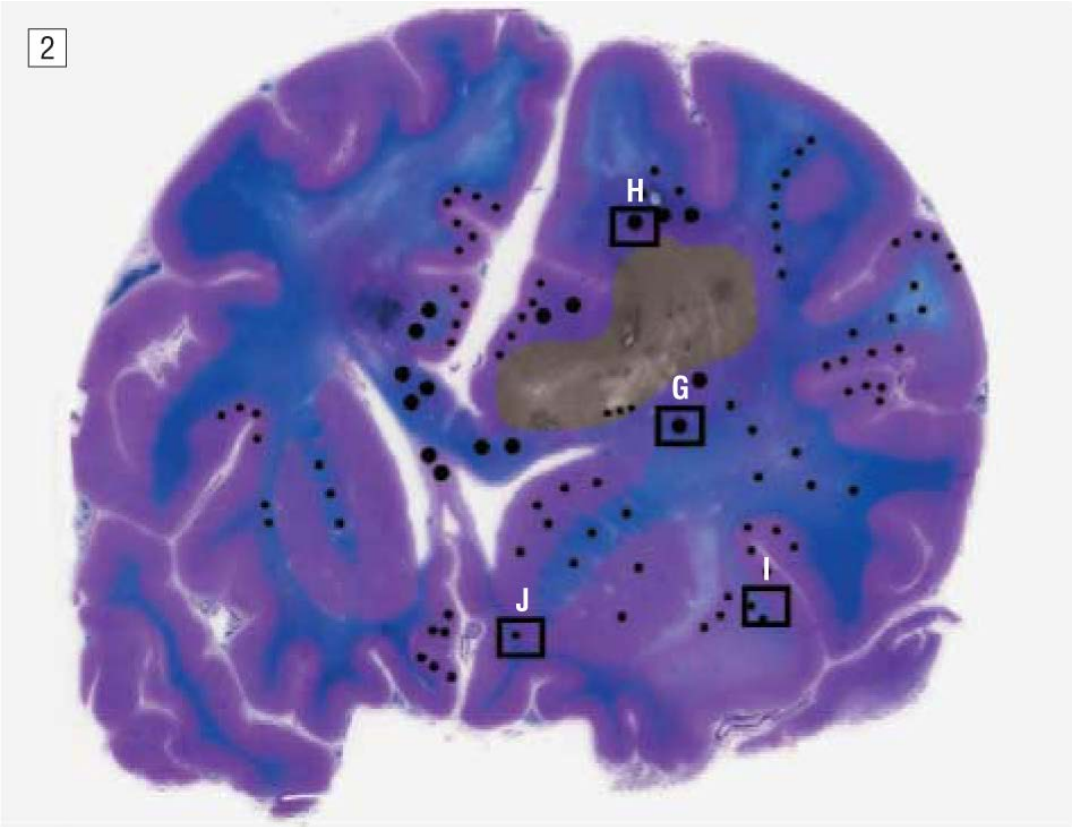
« On the treatment of brain masses »

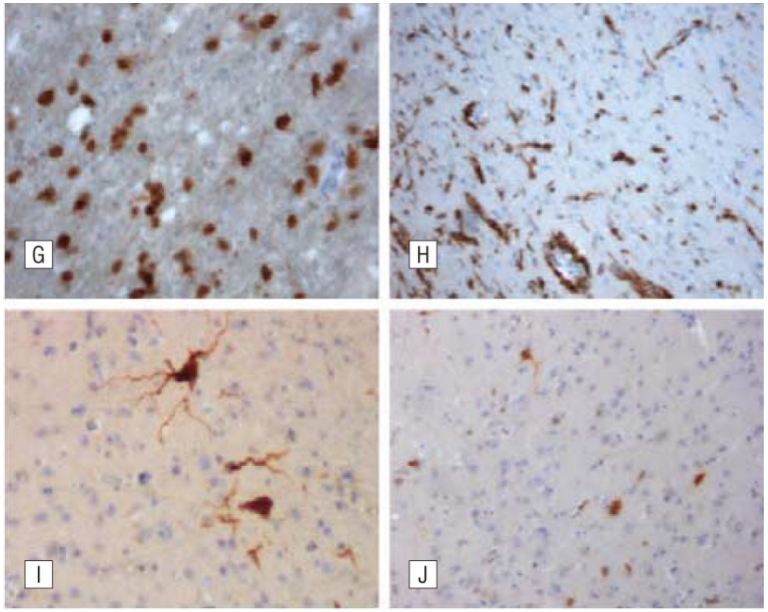
„The art of surgery has been used with varying luck on brain neoplasms. Hygenic life style, preservation of strength and phlebotomy to minimize blood flow to the head are our only aids.“



Dr. Anna Fischer-Dückelmann, 1905

Why systemic therapy?





anti-IDH1 R132H

Sahm et al, Arch Neurol 2012

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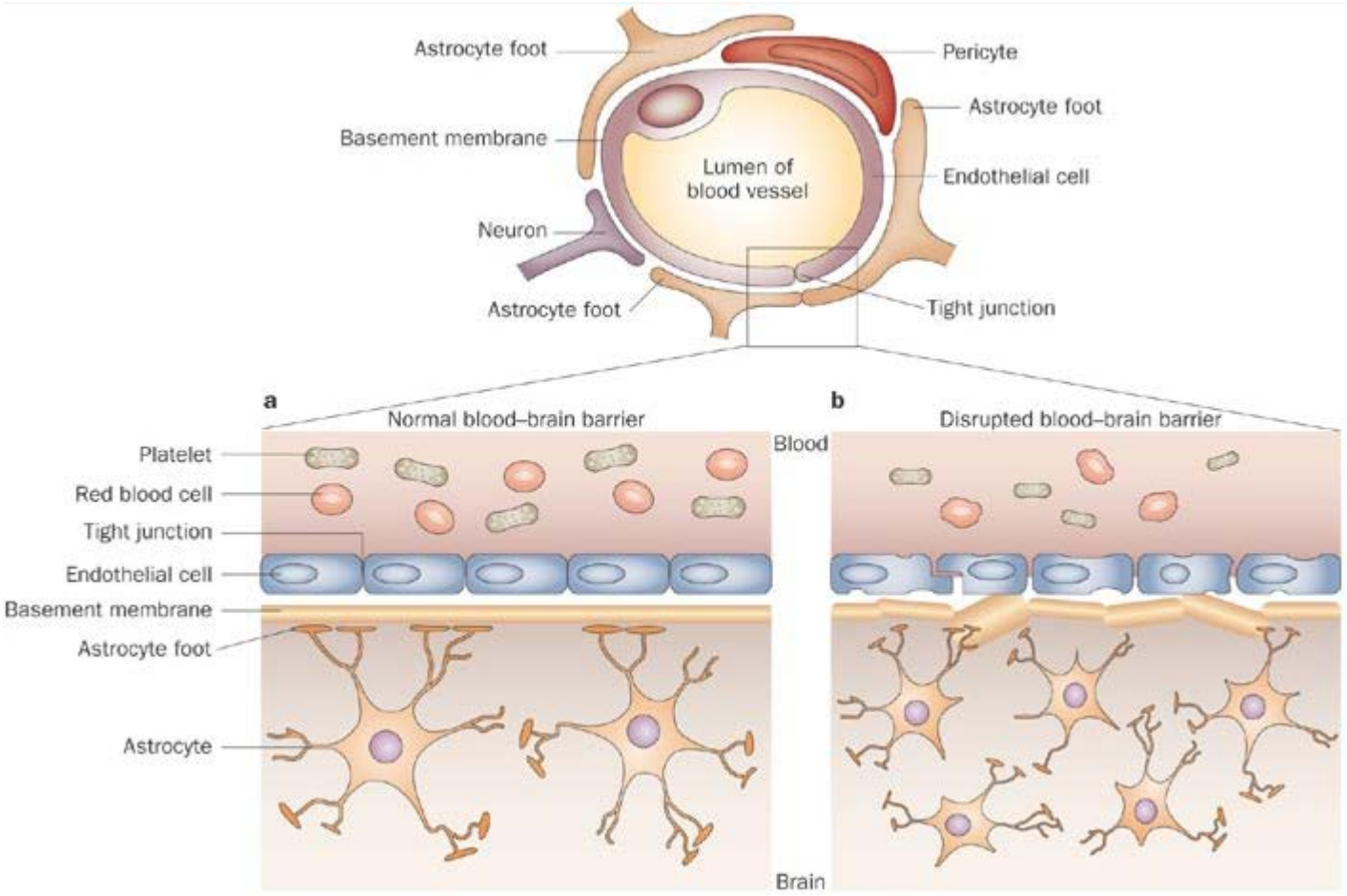
Systemic therapy: blood-brain barrier



Tumor-derived mediators of BBB disruption:

- VEGF
- Nitric oxide (NO)
- Leukotrienes
- Prostaglandins

Gerstner et al. Nat Rev Clin Oncol 2009

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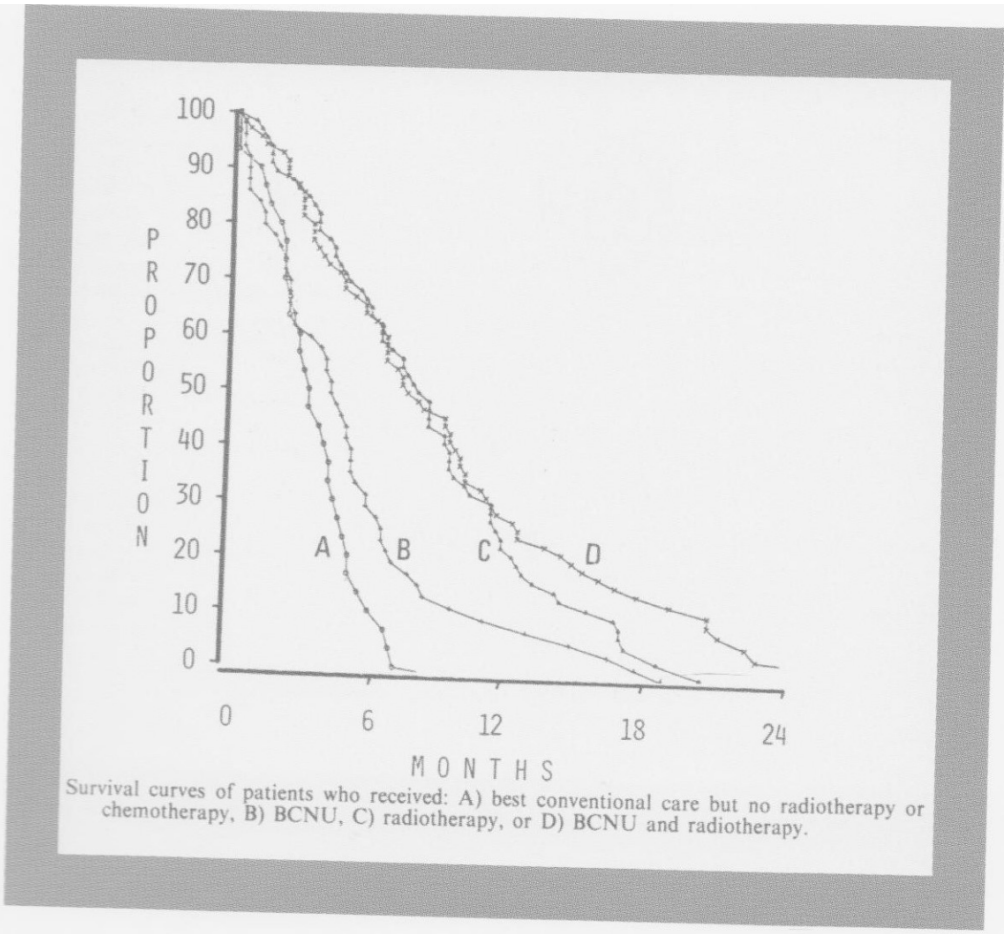
Chemotherapy and the BBB

Drug	CSF penetration
Nitrosoureas (ACNU,BCNU; CCNU, Fotemustine)	++
Procarbazine	++
Thiotepa	+
Dacarbazine Temozolomide	(+) ++
Cyclophosphamide, Ifosfamide	+/-
AraC	++
Methotrexate	-/+
5-FU	(++)
Anthracyclins Liposomal doxorubicine	- ++
VM26	-/+
Etoposide	-/+
Vincaalkaloids, Taxanes	-
Topotecan	++
Cisplatin, Carboplatin	-

Müller et al., Malignant brain tumors 1995

Systemic therapy for glioma: the early days



Survival curves of patients who received: A) best conventional care but no radiotherapy or chemotherapy, B) BCNU, C) radiotherapy, or D) BCNU and radiotherapy.

J Neurosurg 49:333–343, 1978

Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas

A cooperative clinical trial

MICHAEL D. WALKER, M.D., EBEN ALEXANDER, JR., M.D., WILLIAM E. HUNT, M.D., COLLIN S. MACCARTY, M.D., M. STEPHEN MAHALEY, JR., M.D., JOHN MEALEY, JR., M.D., HORACE A. NORRELL, M.D., GUY OWENS, M.D., JOSEPH RANSOHOFF, M.D., CHARLES B. WILSON, M.D., EDMUND A. GEHAN, PH.D., AND THOMAS A. STRIKE, PH.D.

The Brain Tumor Study Group and the National Cancer Institute, National Institutes of Health, Bethesda, Maryland

A controlled, prospective, randomized study evaluated the use of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and/or radiotherapy in the treatment of patients who were operated on and had histological confirmation of anaplastic glioma. A total of 303 patients were randomized into this study, of whom 222 (73%) were within the Valid Study Group (VSG), having met the protocol criteria of neuropathology, corticosteroid control, and therapeutic approach. Patients were divided into four random groups, and received BCNU (80 mg/sq m/day on 3 successive days every 6 to 8 weeks), and/or radiotherapy (5000 to 6000 rads to the whole brain through bilateral opposing ports), or best conventional care but no chemotherapy or radiotherapy. Analysis was performed on all patients who received any amount of therapy (VSG) and on the Adequately Treated Group (ATG), who had received 5000 or more rads radiotherapy, two or more courses of chemotherapy, and had a minimum survival of 8 or more weeks (the interval that would have been required to have received either the radiotherapy or chemotherapy). Median survival of patients in the VSG was, best conventional care: 14 weeks (ATG: 17.0 weeks); BCNU: 18.5 weeks (ATG: 25.0 weeks); radiotherapy: 35 weeks (ATG: 37.5 weeks); and BCNU plus radiotherapy: 34.5 weeks (ATG: 40.5 weeks). All therapeutic modalities showed some statistical superiority compared to best conventional care. There was no significant difference between the four groups in relation to age distribution, sex, location of tumor, diagnosis, tumor characteristics, signs or symptoms, or the amount of corticosteroid used. An analysis of prognostic factors indicates that the initial performance status (Karnofsky rating), age, the use of only a surgical biopsy, parietal location, the presence of seizures, or the involvement of cranial nerves II, III, IV, and VI are all of significance. Toxicity included acceptable, reversible thrombocytopenia and leukopenia.

KEY WORDS · brain tumor · glioblastoma · chemotherapy · radiotherapy · BCNU · prognostic factors

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Temozolomide to the rescue

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

2005

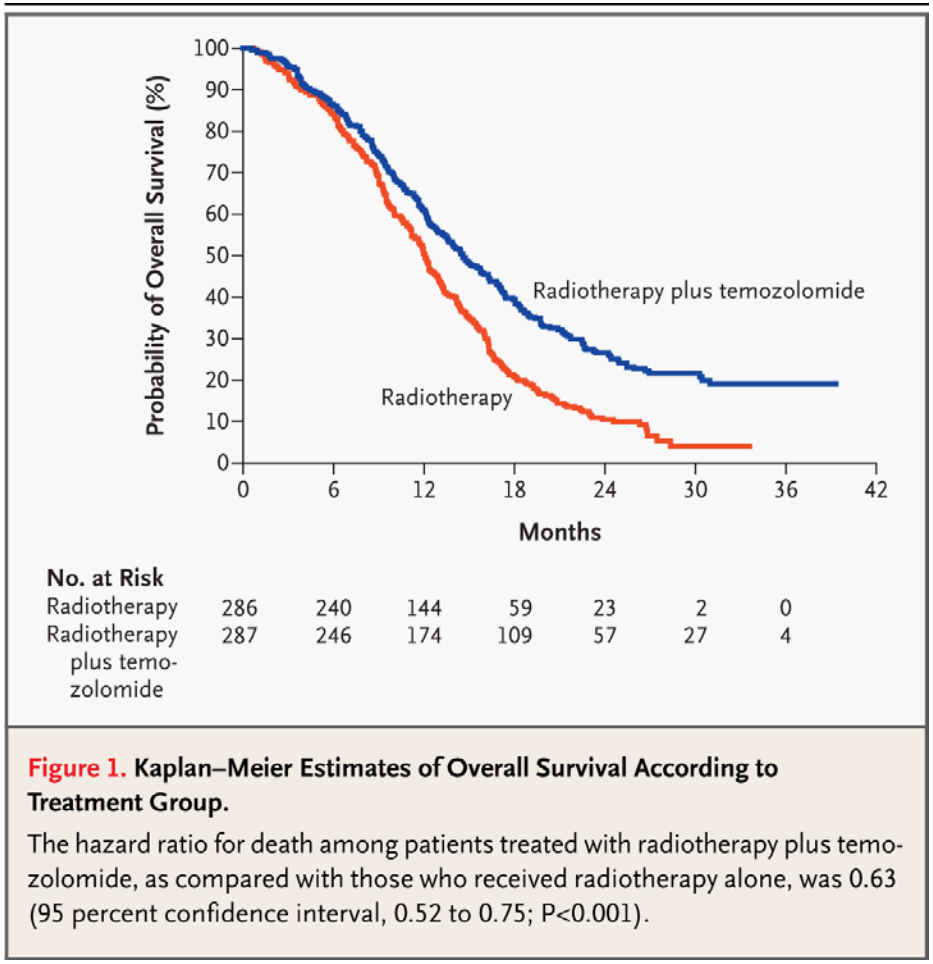

Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

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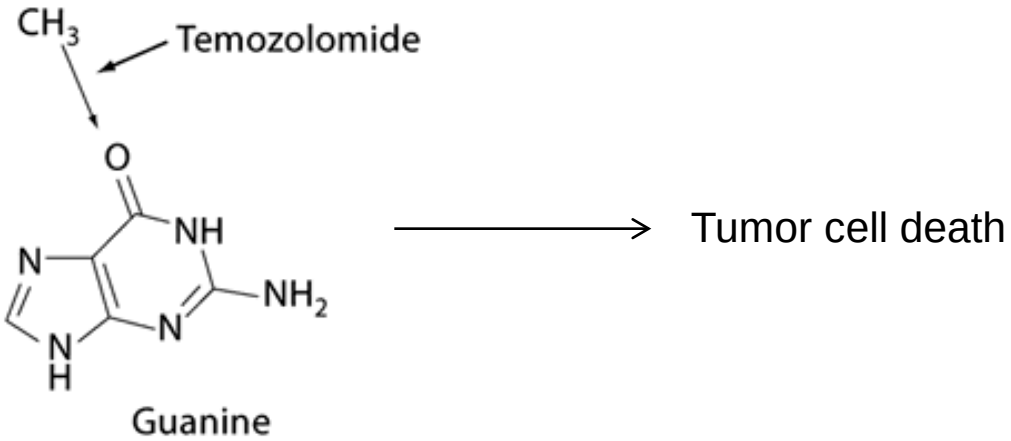
Temozolomide

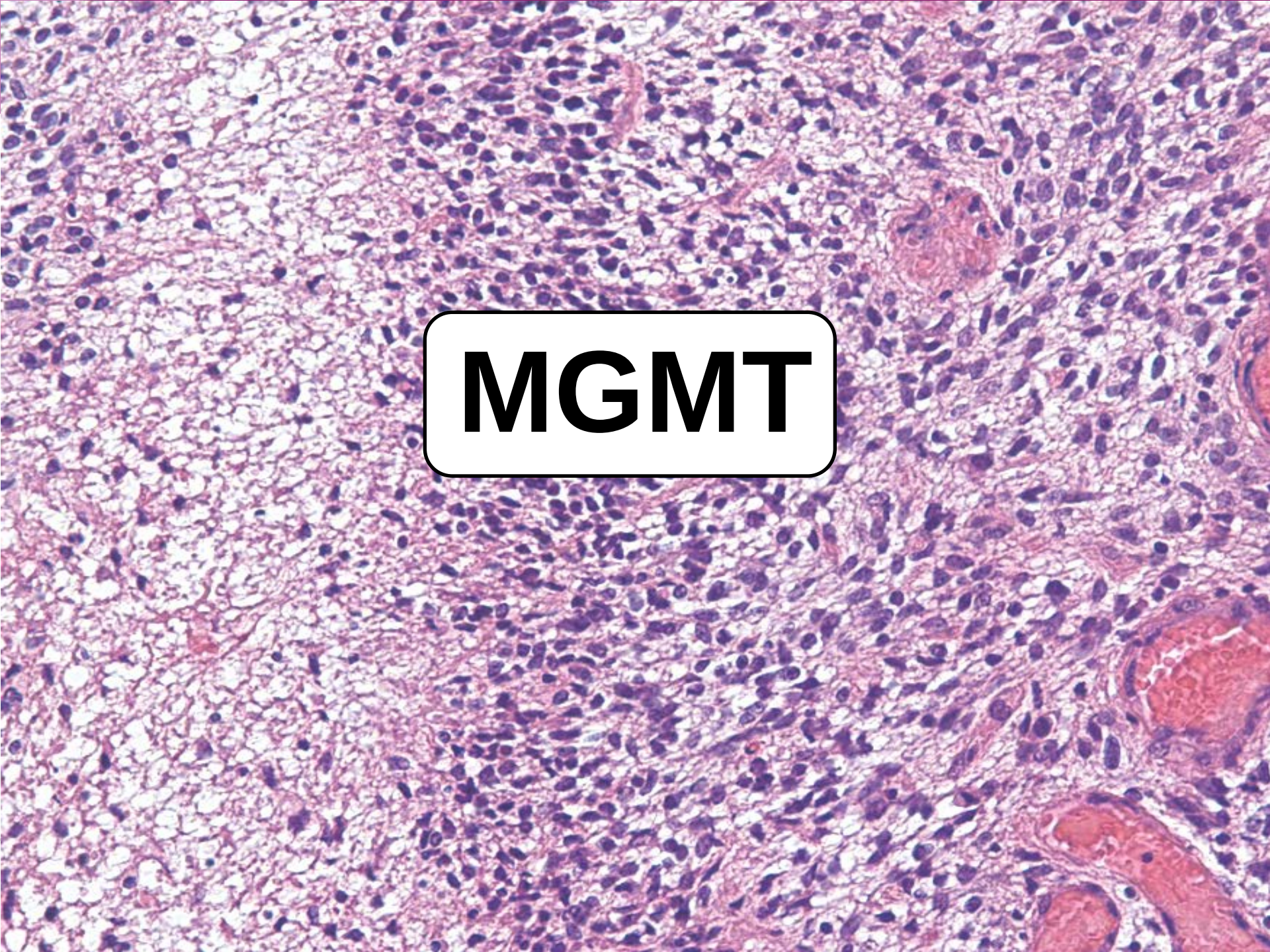
- Imidazotetrazine derivative of dacarbazine
- Conversion in the systemic circulation at physiological pH to the active compound, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC)
- Good BBB penetration
- Oral application (note: there is also an i.v. formulation)
- Methylation of O6 guanine:



Toxicity

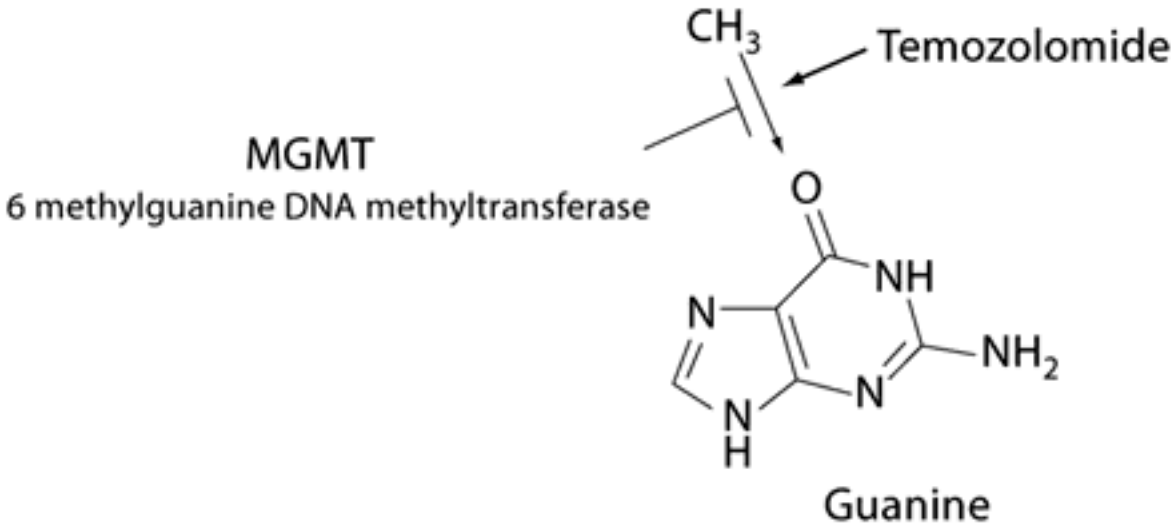
Table 4. Grade 3 or 4 Hematologic Toxic Effects in Patients Treated with Temozolomide.

Toxic Effect	Concomitant Temozolomide Therapy (N=284)	Adjuvant Temozolomide Therapy (N=223)	Entire Study Period* (N=284)
	number of patients (percent)		
Leukopenia	7 (2)	11 (5)	20 (7)
Neutropenia	12 (4)	9 (4)	21 (7)
Thrombocytopenia	9 (3)	24 (11)	33 (12)
Anemia	1 (<1)	2 (1)	4 (1)
Any	19 (7)	32 (14)	46 (16)

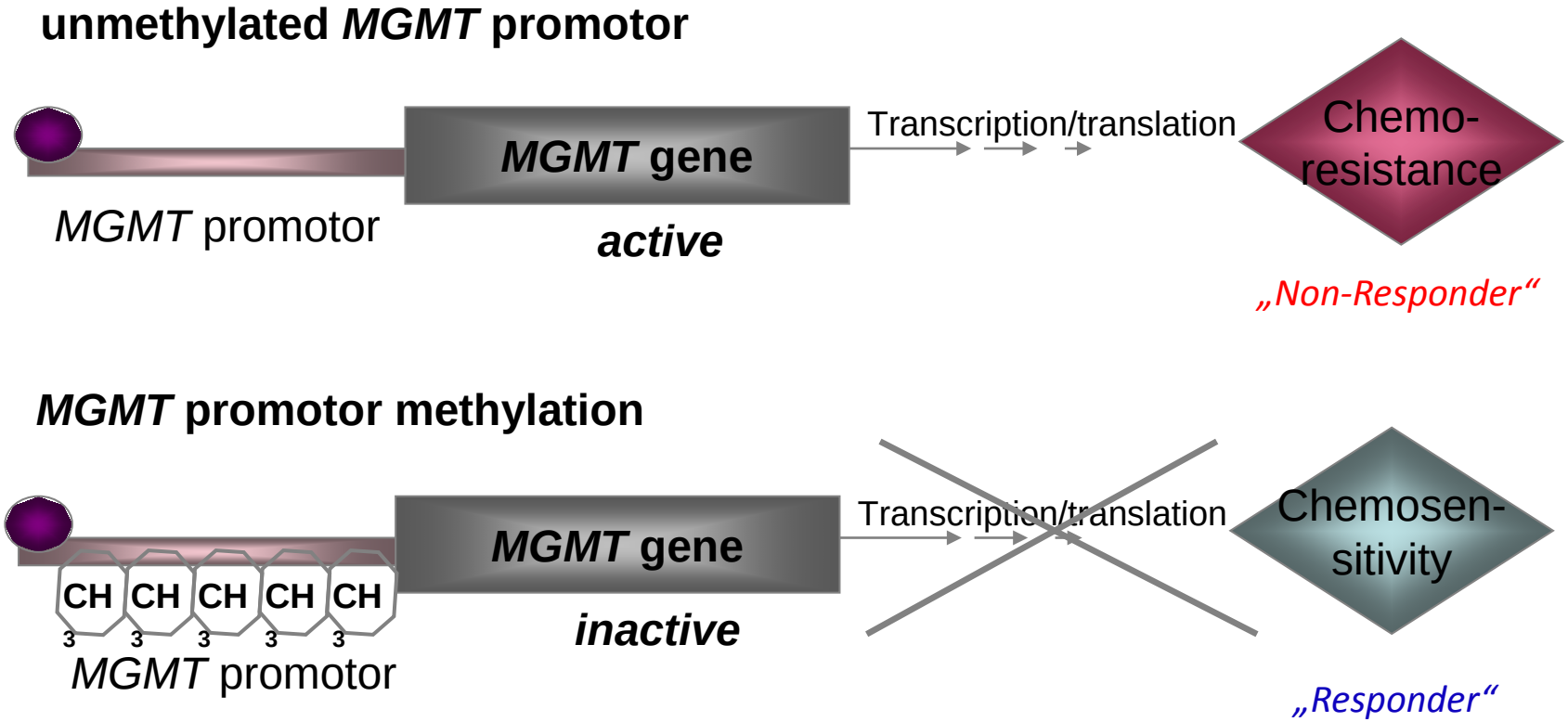

MGMT

What is MGMT?

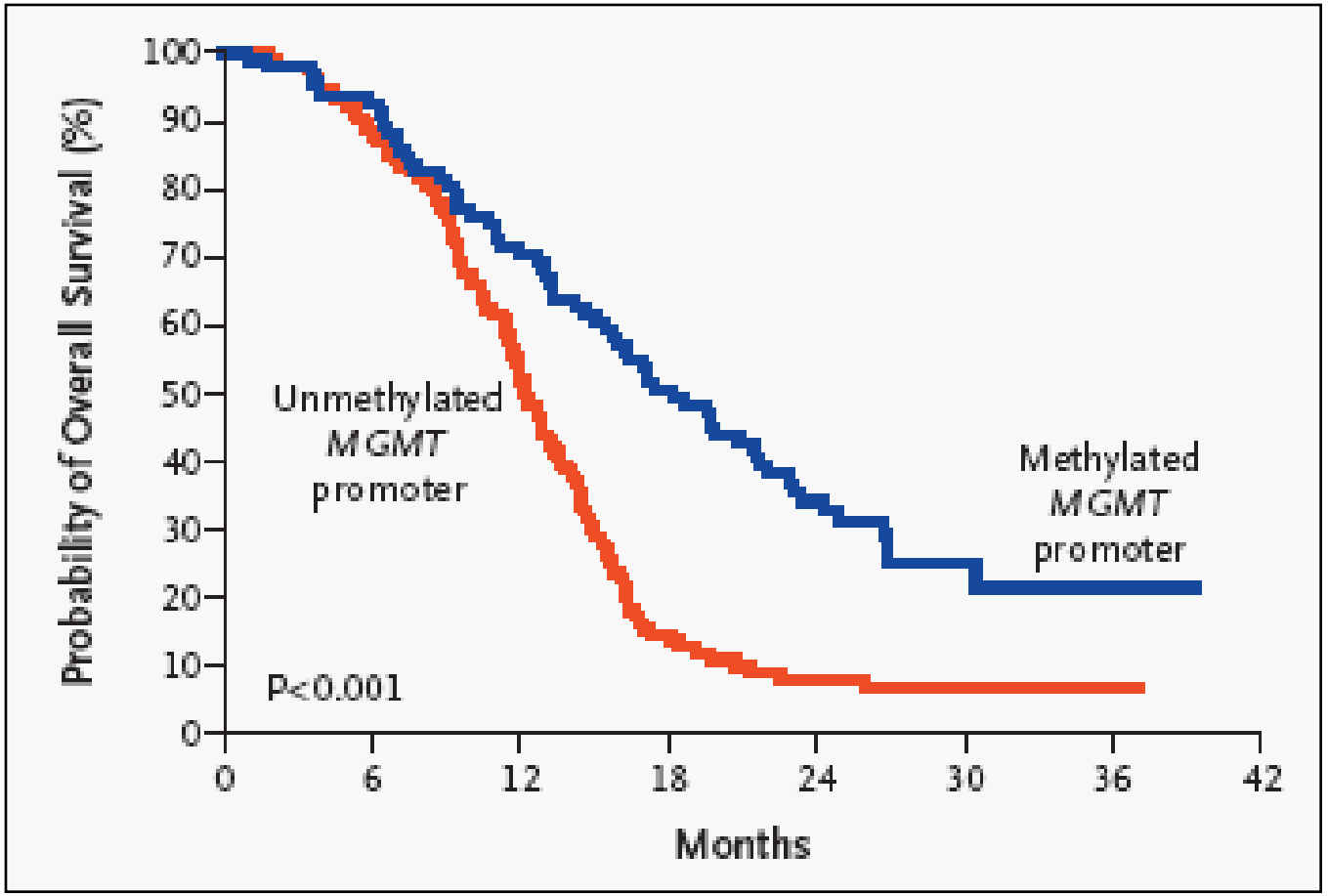
- O6-Methylguanin-Methyltransferase (= MGMT)
- DNA repair protein
- MGMT removes methyl group from O6 position of guanine („protects tumor cell DNA from damage by chemo- and radiotherapy“)



Inactivation of MGMT gene by promoter methylation

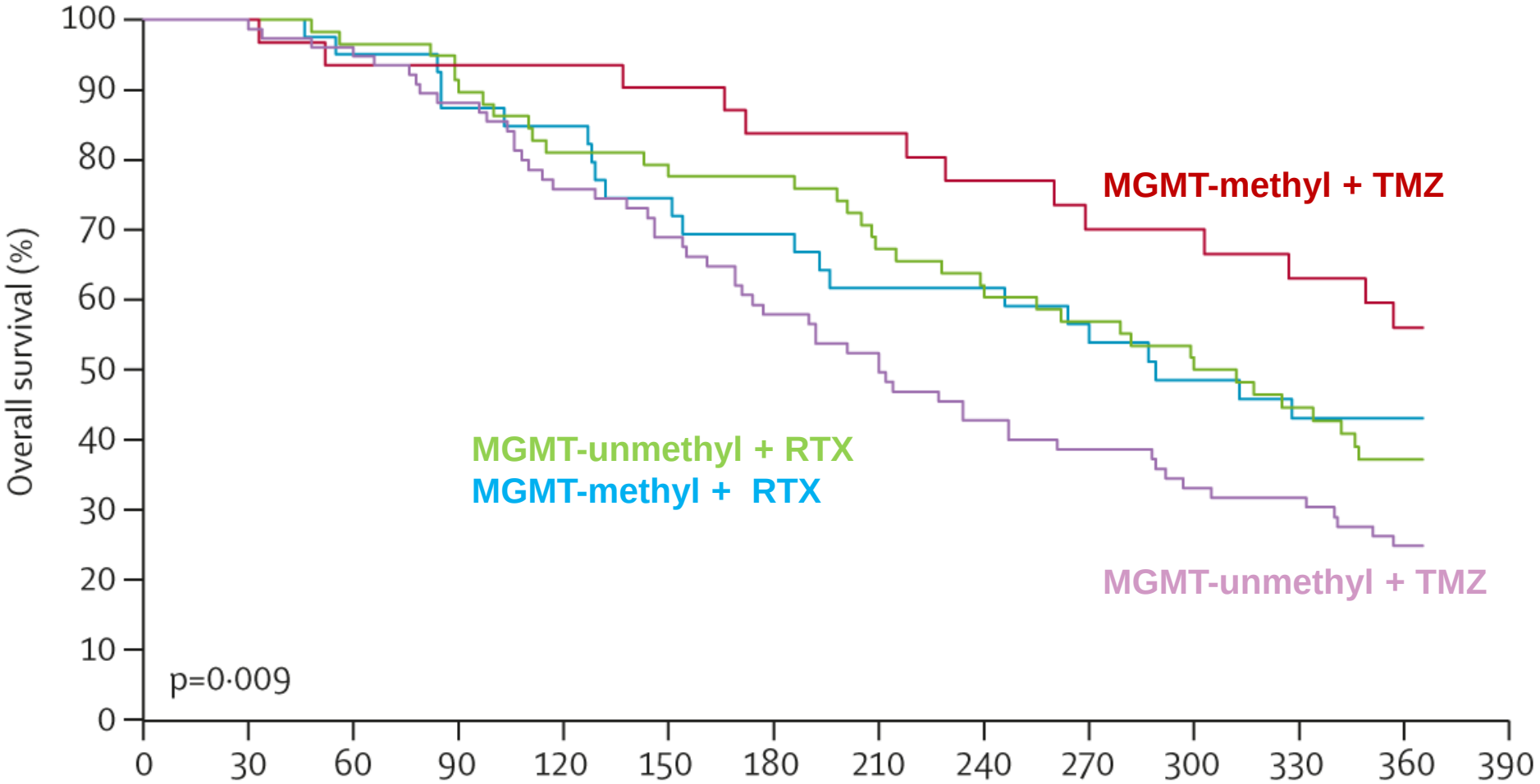


Prognostic effect



Hegi et al, NEJM 2005

Predictive effect in elderly GBM



Wick et al, Lancet Oncol 2012

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Beware! Before you start testing….

… you need a reliable MGMT test!

Essential properties of clinical biomarkers

Clinical performance

= the prognostic or predictive value of a given candidate biomarker

Analytical performance

= the reliability of the results yielded by a particular assessment or test

Problem: results may vary between tests and investigators

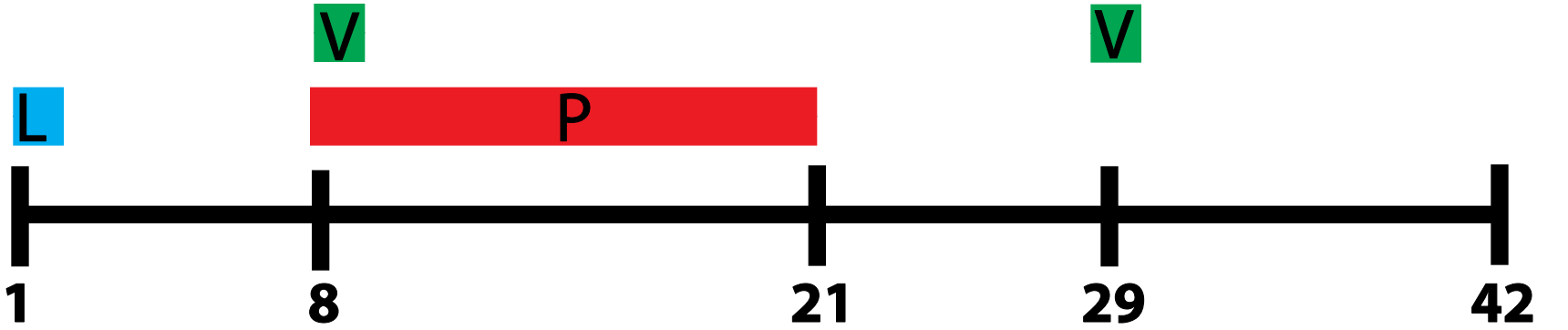
PCV

- Established in 1980s
- Used in 1p/19q co-deleted tumors
- Combination not used in other tumor entities
- Differing schedules
  - PCV +/- radiation therapy
  - PCV before/after radiation therapy
  - Dose intensity

What is PCV?

Procarbazine	Lomustine (CCNU)	Vincristine
p.o.	p.o.	i.v.
Alkylating agent Breaking of DNA strands	Alkylating nitrosourea compound Breaking of DNA strands	Vinca alkoid Mitotic inhibitor – inhibiting the assembly of microtubule structures
Good penetration trough blood-brain-barrier	Good penetration trough blood-brain-barrier	Moderate to low penetration trough blood-brain-barrier
Molecular weight: 258 Da	Molecular weight: 233 Da	Molecular weight: 923 Da
Dose limiting side effects: Hematotoxicity High (>90%) emetogenic	Dose limiting side effects: Hematotoxicity	Dose limiting side effects: Peripheral neuropathy

What is PCV?



L Lomustine 110 mg/m2 p.o.

P Procarbazine 60mg/m2 daily p.o.

V Vincristine 1,4 mg/m2 (max 2mg) i.v

PCV toxicities EORTC 26951 vs RTOG 9402

Toxicities (Grade 3/4)	EORTC 26951	RTOG 9402
Hematologic, any	46%	56%
Neutropenia	32%	42%
Thrombocytopenia	21%	37%
Anemia	7%	5%
Peripheral neuropathy	2%	8%
Nausea/vomiting	6%	8%
Toxicity leading to treatment stop	38%	20%

Systemic treatment of brain mets

Basic considerations

There is no specific chemotherapy (or any specific medical treatment) for brain mets

Most brain mets derive from chemo-resistant primary tumors

The best chemotherapy for the primary tumor is also the best choice for brain metastases

Brain mets have (probably) no blood-brain barrier (BBB)

Drugs that cross the BBB may be helpful for the prevention of metastasis to the brain and/or for the treatment of „micrometastases“

Good old chemotherapy

Chemotherapeutic drugs used to treat brain mets in NSCLC patients

- **Cisplatin / Carboplatin**
- **Vinorelbine**
- **Paclitaxel / Docetaxel**
- **Gemcitabine**
- **Pemetrexed**

Treatment of brain mets

- **Cerebral response rates of about 40% have been reported for NSCLC patients with BM following treatment with platinum and pemetrexed**
- **These results are not inferior to the local response rates typically seen with WBRT**

Barlesi et al. Ann Oncol 2011
Bailon et al. Neuro Oncol 2012

Chemotherapeutic drugs: BBB crossing

Drug levels in brain metastases and neighboring tissues, measured at time of resection or at autopsy

Drug	Tumor level: necrotic lesion	Tumor level: viable lesion	Neighboring normal brain level
Etoposide (63)	5.9 µg/g	3.4 µg/g	1.4 µg/g adjacent, 0.1 µg/g 2 cm distance
Cisplatin (64)			
20 to 25 mg/m^2	Not reported	1.29 µg/g	0.25 to 0.65 µg/g, 2 to 5 cm
60 to 100 mg/m^2		2.97 µg/g	0.7 to 1.11 µg/g, 2 to 5 cm
Vinorelbine (65)	Not reported	68 ng/g	22 ng/g adjacent, 5 ng/g >4 cm
Mitoxantrone (66)	15 to 322 ng/g	25 to 29 ng/g	Not reported

=> but: drug levels in brain mets lower than in extracranial mets

Deeken and Löscher, Clin Cancer Res 2007

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WBRT + Temozolomide

WBRT +/- temozolomide:

- Patients with NSCLC and ≥ 1 newly diagnosed brain metastasis
- Poor accrual
- WBRT alone: median OS: 5.7 months
- WBRT + temozolomide: median OS 4.4

Daily low-dose temozolomide:

- Patients with advanced NSCLC; many of them with brain mets
- “minimal activity as salvage therapy in patients with advanced NSCLC”

Chua et al. Clin Lung Cancer 2014
Kouroussis et al. Oncology 2009

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Targeted therapy

…the ultimate solution?

Targeted therapy

- **Bevacizumab**

  => probably no need to cross the BBB

- **EGFR inhibitors (erlotinib, gefitinib…)**

  => only in patients with sensitizing EGFR mutation

- **ALK inhibitors (crizotinib, ceritinib…)**

  => only in patients with EML4-ALK translocation

Bevacizumab

- Only low risk for CNS hemorrhage in patients with NSCLC and brain mets who are treated with bevacizumab
- Potentially strong anti-edema activity
- Bevacizumab alone or in combination with chemotherapy in patients with brain mets from NSCLC:
  - Median PFS: 7.8 months
  - Median OS: 14.1 months
- WBRT + bevacizumab in patients with brain mets (REBECA):
  - Safe, but clinical benefit remains unclear

Socinski et al. J Clin Oncol 2009
De Braganca et al. J Neurooncol 2010
Lévy et al. Ann Oncol 2014

EGFR inhibitors

- Activating EGFR mutations particularly commmon in adenocarcinomas of the lung
- EGFR mutations may be overrepresented in brain mets of lung cancer patients
- Clinical activity of EGFR inhibitors in patients with activating EGFR mutations has been shown in several large trials
- Modest BBB penetration of EGFR inhibitors

Lynch et al. N Engl J Med 2004
Paez et al. Science 2004
Matsumoto et al. Int J Cancer 2006
Park et al. Lung Cancer 2012
Maemondo et al. N Engl J Med 2010
Rosell et al. Lancet Oncol 2012

CNS response rates in NSCLC patients treated with EGFR-TKI

EGFR mutation status	Therapy	Response rate (%)
Unselected	EGFR-TKI	60%
		43%
		10%
		32%
		33%
		70%
	EGFR-TKI + WBRT	81%
		71%
EGFR mutation	EGFR-TKI	83%
		82%
		89%
		75%
	EGFR-TKI + WBRT	84%

Berger et al. Lung Cancer 2013

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Addition of EGFR inhibitors to WBRT does (probably) not prolong survival

WBRT + gefitinib or temozolomide

- Gefitinib: median OS **6.3** months
- Temozolomide: median OS **4.9** months
- Fatigue as major side effect

WBRT and SRS + erlotinib or temozolomide in patients with ≤ 3 brain mets

- WBRT and SRS: median OS **13.4** months
- Addition of temozolomide: median OS **6.3** months
- Addition of erlotinib: median OS **6.1** months
- Increased toxicity in the gefitinib and temozolomide arm

Pesce et al. Eur J Cancer 2012
Sperduto et al. Int J Radiat Oncol Biol Phys 2013

ALK fusion genes

- Found in around 5% of NSCLC
- Encountered more frequently in never smokers, the adenocarcinoma subtype, and in younger patients
- NSCLC patients with ALK rearrangement have improved OS after radiotherapy for brain metastases compared with EGFR or KRAS mutations

  => Subsequent receipt of targeted therapy is associated with additional improvement in OS
- Crizotinib first approved ALK inhibitor

Shaw et al. J Clin Oncol 2009
Mak et al. Neuro Oncol 2015
Shaw et al. New Engl J Med 2013

Brain mets: a particular challenge?

Cancer Biology & Therapy 13:14, 1376–1383; December 2012; © 2012 Landes Bioscience

Isolated central nervous system progression on Crizotinib

An Achilles heel of non-small cell lung cancer with EML4-ALK translocation?

Stephen G. Chun,* Kevin S. Choe,† Puneeth Iyengar,† John S. Yordy† and Robert D. Timmerman†

=> Crizotinib: very limited CNS penetrance (< 1%)

- Novel ALK inhibitors: ceritinib and alectinib which are both active against ALK-positive NSCLC
- Ceritinib concentration in the CNS may reach approximately 13% of systemic levels in preclinical models

Shaw et al. New Engl J Med 2014
Gadgeel et al. Lancet Oncol 2014
Kim et al. ASCO 2014

ASCEND-1: ceritinib in patients with brain mets

Endpoint[a]	ALKi-pretreated patients with brain metastases n = 98	ALKi-naïve patients with brain metastases n = 26	All NSCLC patients with brain metastases n = 124
ORR, n (%)[95% CI]	49 (50.0)[39.7, 60.3]	18 (69.2)[48.2, 85.7]	67 (54.0)[44.9, 63.0]
DOR, median (months) [95% CI]	6.9[4.8, 8.5]	NE[b][5.5, NE]	7.0[5.5, 9.7]
PFS, median (months) [95% CI]	6.7[4.9, 8.5]	8.3[4.6, NE]	6.9[5.4, 8.4]

=> Promising treatment for patients with brain mets?

Shaw et al. ESMO 2014

ESTRO School

Conclusions

- Systemic therapies can improve outcome in brain tumor patients
- Blood brain barrier can be a limiting factor
- Insufficient understanding of tumor biology as one limiting factor
- Emerging targeted agents with putative activity in brain tumors
- Predictive factors may help to tailor systemic therapies
- Need for more research

Systemic treatment for gliomas: Novel therapies

Anthony Chalmers

ESTRO Brain Tumour Course

October 2015

Vol 455|23 October 2008|doi:10.1038/nature07385 nature

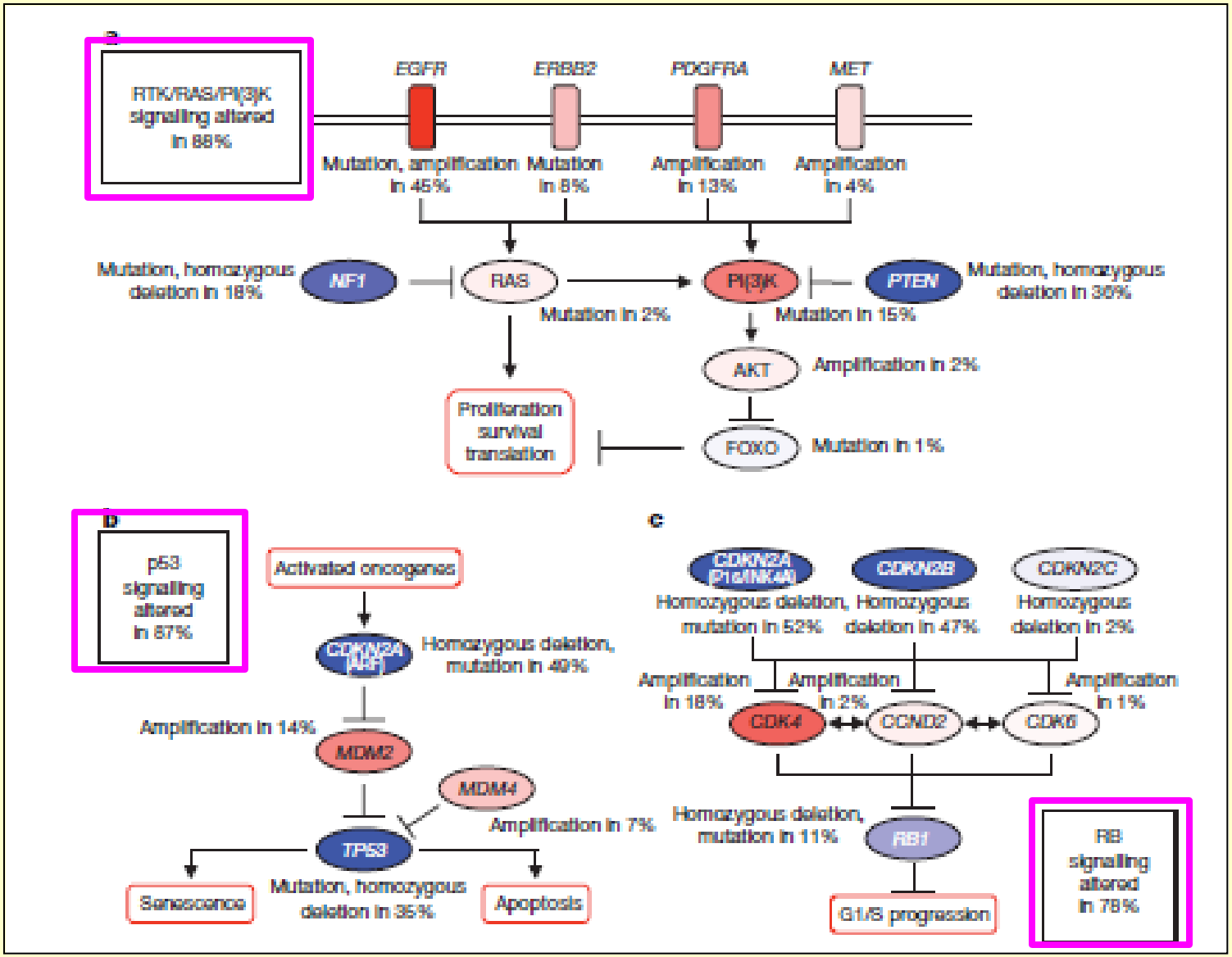
ARTICLES

Comprehensive genomic characterization defines human glioblastoma genes and core pathways

The Cancer Genome Atlas Research Network*

Human cancer cells typically harbour multiple chromosomal aberrations, nucleotide substitutions and epigenetic modifications that drive malignant transformation. The Cancer Genome Atlas (TCGA) pilot project aims to assess the value of large-scale multi-dimensional analysis of these molecular characteristics in human cancer and to provide the data rapidly to the research community. Here we report the interim integrative analysis of DNA copy number, gene expression and DNA methylation aberrations in 206 glioblastomas—the most common type of primary adult brain cancer—and nucleotide sequence aberrations in 91 of the 206 glioblastomas. This analysis provides new insights into the roles of *ERBB2*, *NF1* and *TP53*, uncovers frequent mutations of the phosphatidylinositol-3-OH kinase regulatory subunit gene *PIK3R1*, and provides a network view of the pathways altered in the development of glioblastoma. Furthermore, integration of mutation, DNA methylation and clinical treatment data reveals a link between *MGMT* promoter methylation and a hypermutator phenotype consequent to mismatch repair deficiency in treated glioblastomas, an observation with potential clinical implications. Together, these findings establish the feasibility and power of TCGA, demonstrating that it can rapidly expand knowledge of the molecular basis of cancer.

CGARN glioblastoma study, Nature 2008

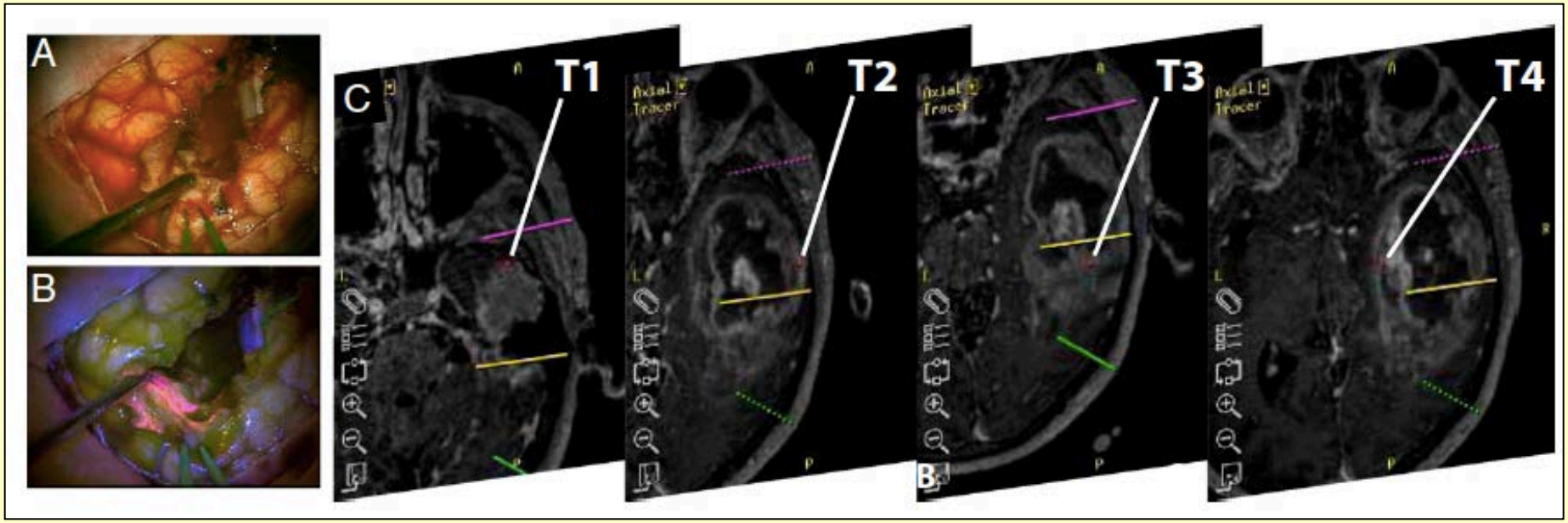


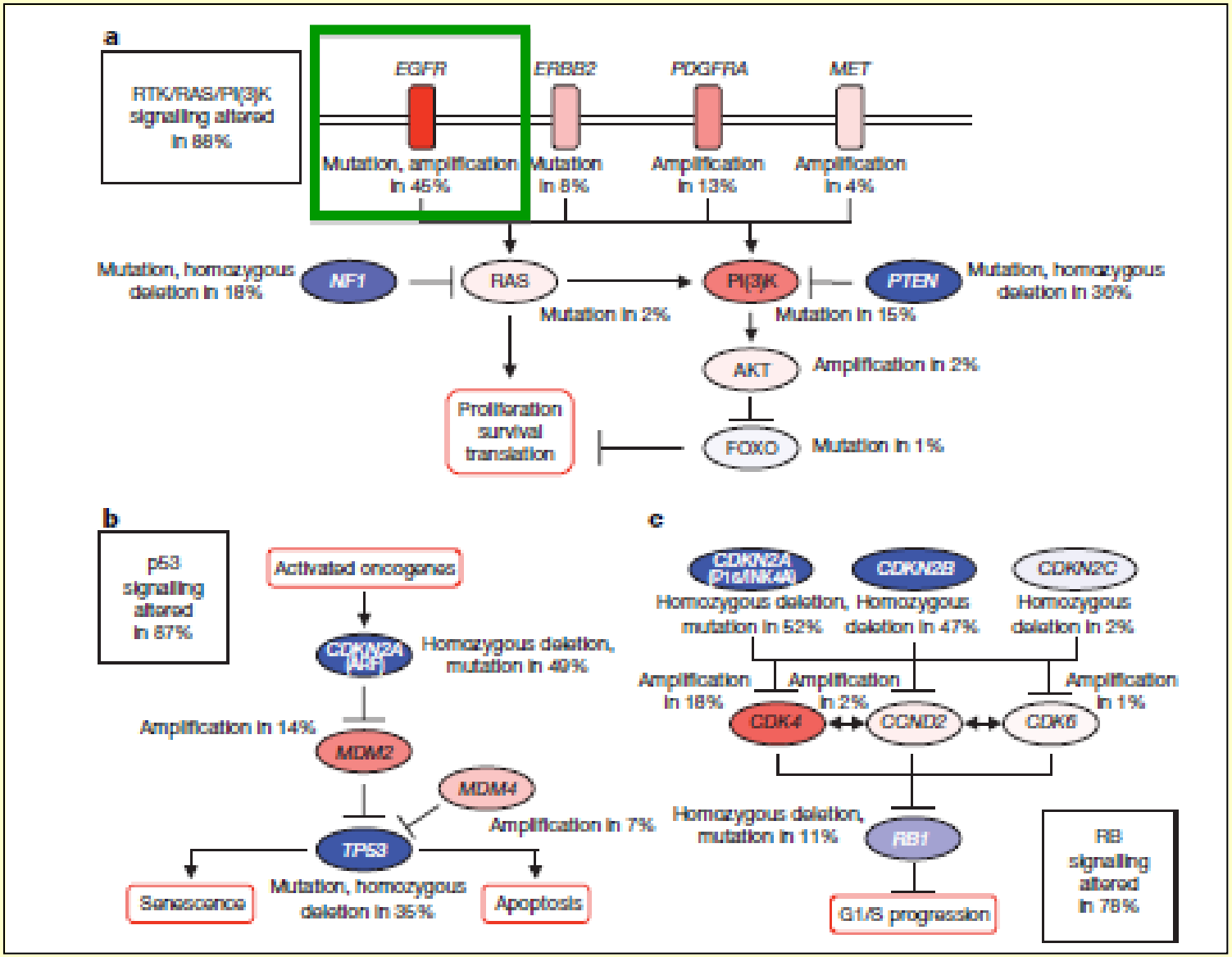
CGARN glioblastoma study, Nature 2008

Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics

Andrea Sottoriva[a,b,c,1], Inmaculada Spiteri[b,1], Sara G. M. Piccirillo[d], Anestis Touloumis[b,e], V. Peter Collins[f], John C. Marioni[e], Christina Curtis[c], Colin Watts[d,g,2], and Simon Tavaré[a,b,h,2]

[a]Department of Oncology, University of Cambridge, Cambridge CB2 2XZ, United Kingdom; [b]Cancer Research UK, Cambridge Research Institute, Li Ka Shing Centre, Cambridge CB2 0RE, United Kingdom; [c]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033; [d]Department of Clinical Neurosciences, Cambridge Centre for Brain Repair, University of Cambridge, Cambridge CB2 0PY, United Kingdom; [e]European Molecular Biology Laboratory-European Bioinformatics Institute, Wellcome Trust Genome Campus, Cambridge CB10 1SD, United Kingdom; [f]Division of Molecular Histopathology, Department of Pathology, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom; [g]Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QQ, United Kingdom; and [h]Department of Biological Sciences, University of Southern California, Los Angeles, CA 90089



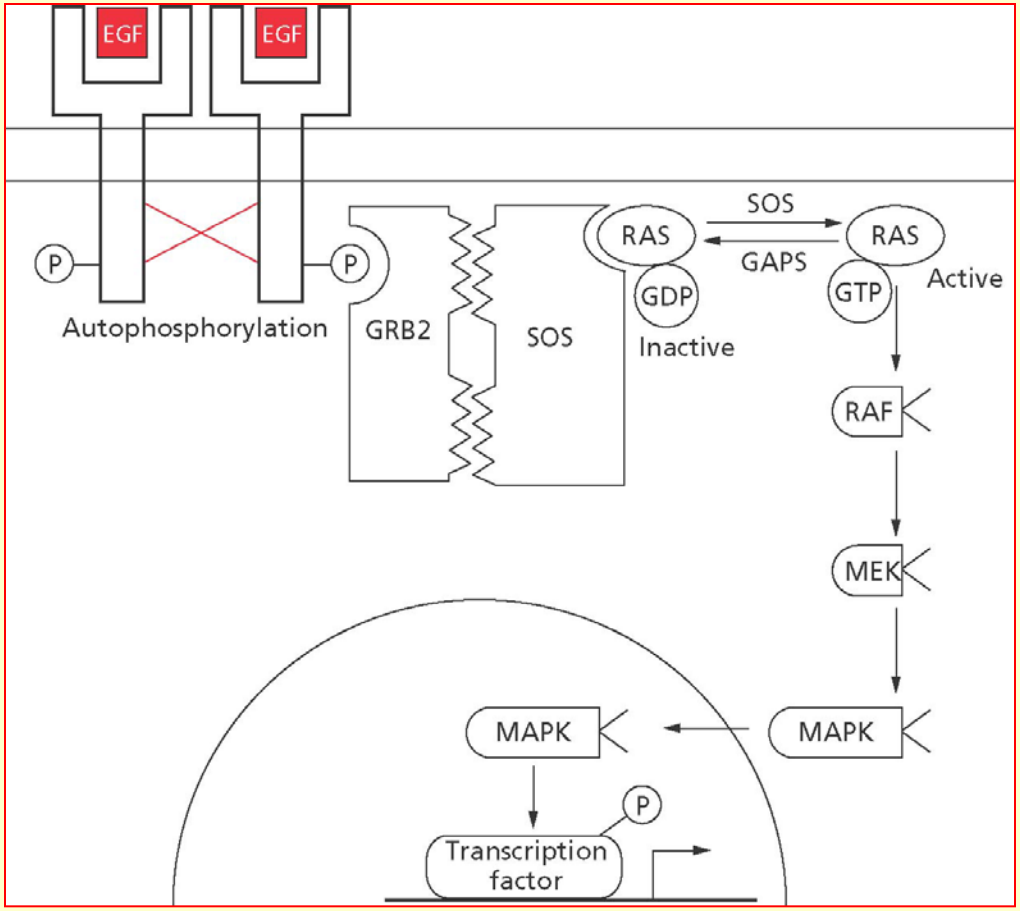


CGARN glioblastoma study, Nature 2008

EGFR

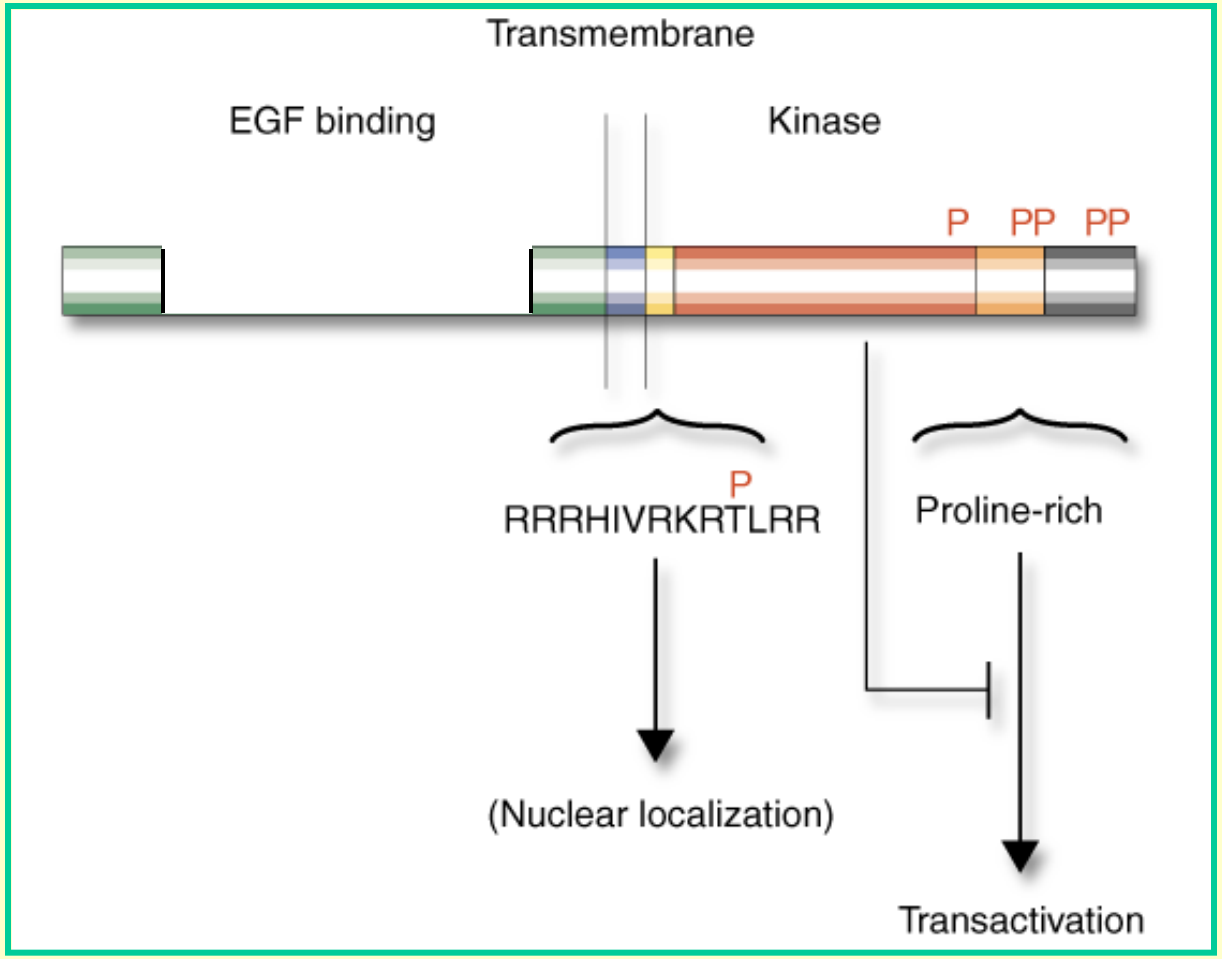
- Growth factor receptor

  erbB encodes the EGFR receptor
- oncogenic mutations generate EGFR that is activated even in the absence of EGF
- amplification of *erbB* gene(s) increases membrane expression of EGFR



Over-activity of RAS - MAPK pathway induces over-expression of genes promoting proliferation and the malignant phenotype

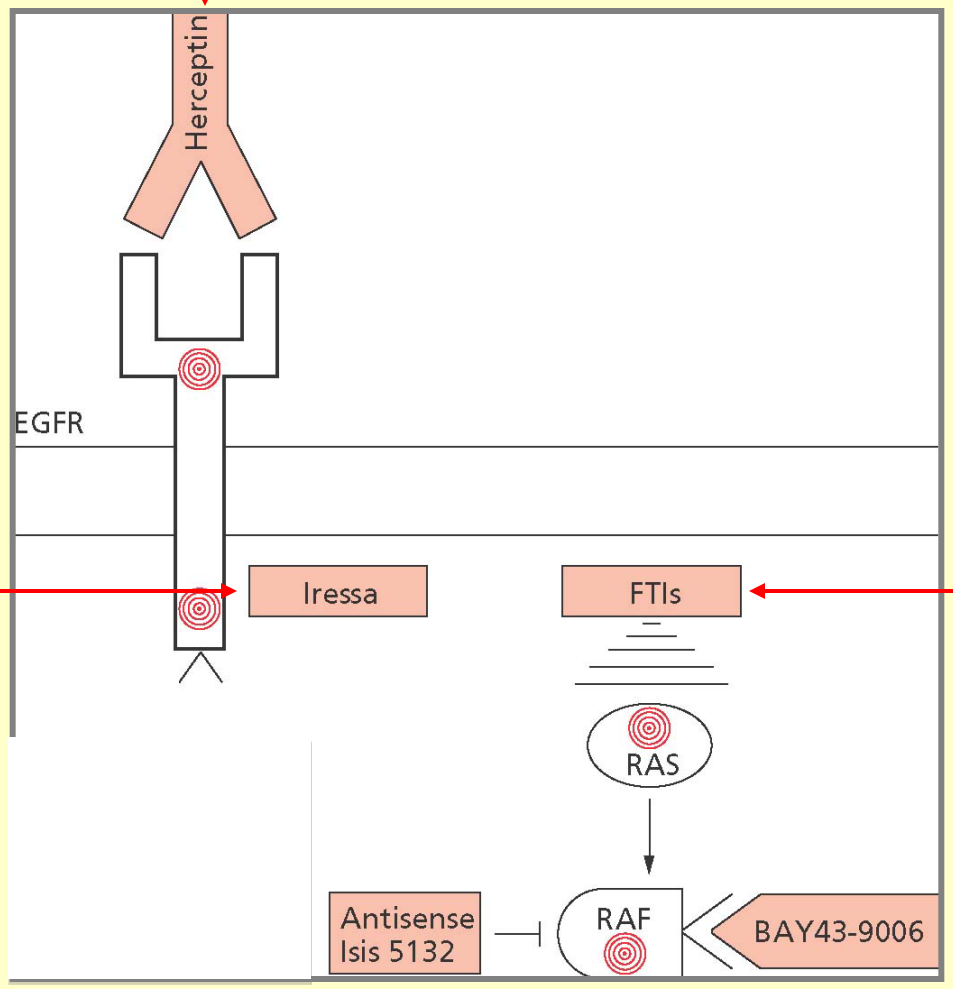
commonest mutation is deletion of exons 2 - 7:



- mutant protein (EGFRvIII) cannot bind ligand but is **constitutively activated**
- common in high grade gliomas (25-30%)

Targeting the EGFR pathway

monoclonal antibodies



tyrosine kinase inhibitors

farnesyl transferase inhibitors

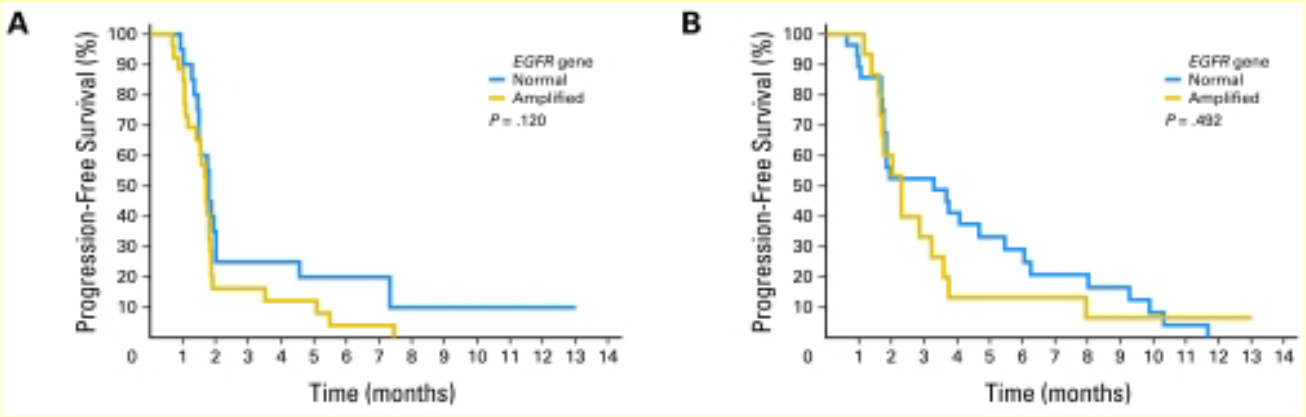
Raf kinase inhibitors

antisense strategies

EGFR inhibitors show efficacy *in vitro* but are ineffective in patients

Erlotinib

TMZ



Randomised phase II study in recurrent GBM:

PFS-6

Erlotinib 11%

TMZ 24%

Van den Bent et. al., J Clin Oncol, 27(8); 2009

Phase II study of erlotinib with radiotherapy and temozolomide in newly diagnosed GBM:

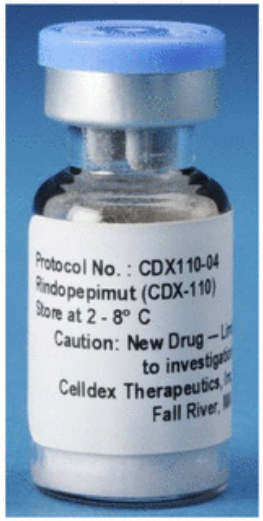
- No improvement in outcome compared to historical controls
- Worse toxicity

Perreboormtet. al., J Neurooncol, 2010

New EGFR targeting strategies showing more promise

Rindopepimut: A Phase 3 Immunotherapy Targeting EGFR*vIII*-expressing Glioblastoma

- Rindopepimut is the only vaccine in development targeting EGFR*vIII* (*v3*)
- EGFR*vIII*
  - Highly tumor specific, expressed only in tumors not normal tissues
  - Target has been validated, gaining importance as a tumor marker
  - Historical poor prognosis for *vIII* patients, historical median survival ~13-15 months, few survive two years
  - ~30% of GB express EGFR*vIII* (~4,000 EGFR*vIII* patients in US and ~8,800 in EU annually)
- Strong proprietary patent position
- Fast track U.S. granted
- Orphan Drug Status in US and EU (7 yrs. & 10 yrs.)



3

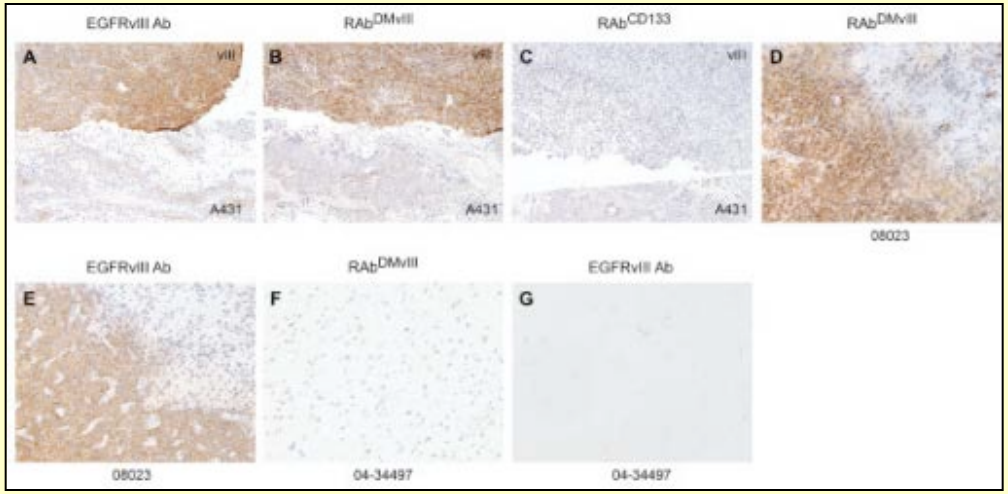
Celldex therapeutics

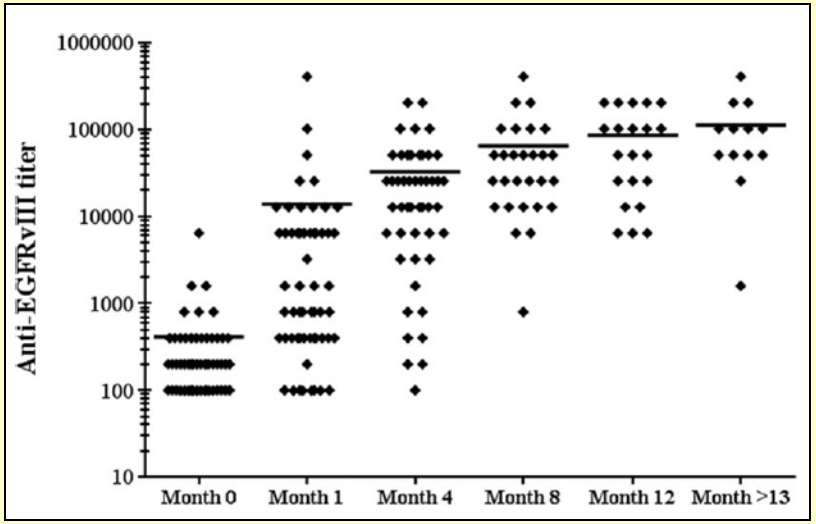
Neuro-Oncology

Neuro-Oncology 17(6), 854–861, 2015
doi:10.1093/neuonc/nou348
Advance Access date 13 January 2015

A phase II, multicenter trial of rindopepimut (CDX-110) in newly diagnosed glioblastoma: the ACT III study

James Schuster†, Rose K. Lai†, Lawrence D. Recht, David A. Reardon, Nina A. Paleologos, Morris D. Groves, Maciej M. Mrugala, Randy Jensen, Joachim M. Baehring, Andrew Sloan, Gary E. Archer, Darell D. Bigner, Scott Cruickshank, Jennifer A. Green, Tibor Keler, Thomas A. Davis, Amy B. Heimberger, and John H. Sampson





- EGFRvIII mutation detected in 26% of patients
- Anti-EGFRvIII antibody titre increased >4x in 85% of patients

Neuro-Oncology

Neuro-Oncology 17(6), 854–861, 2015
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A phase II, multicenter trial of rindopepimut (CDX-110) in newly diagnosed glioblastoma: the ACT III study

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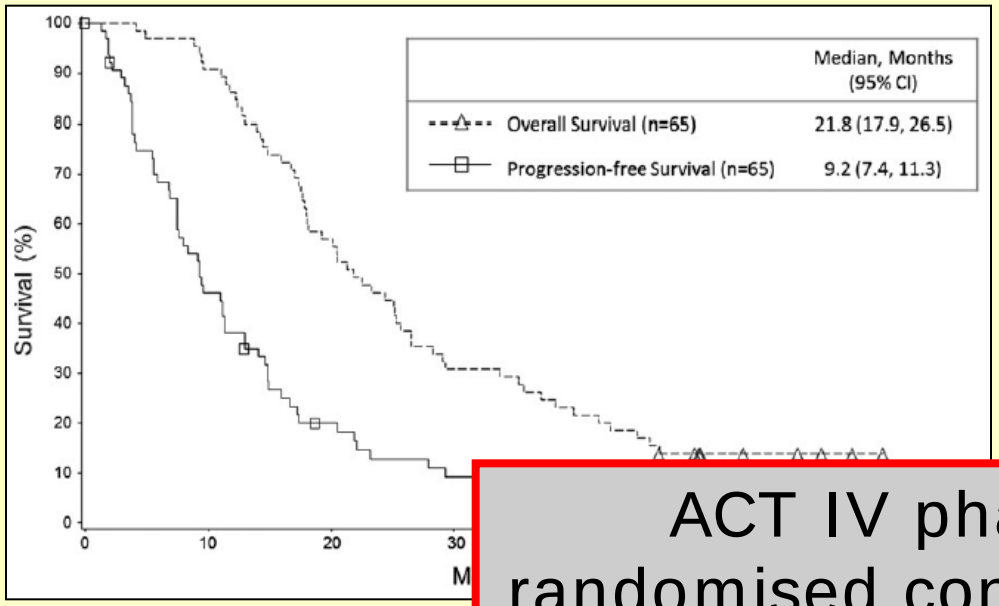
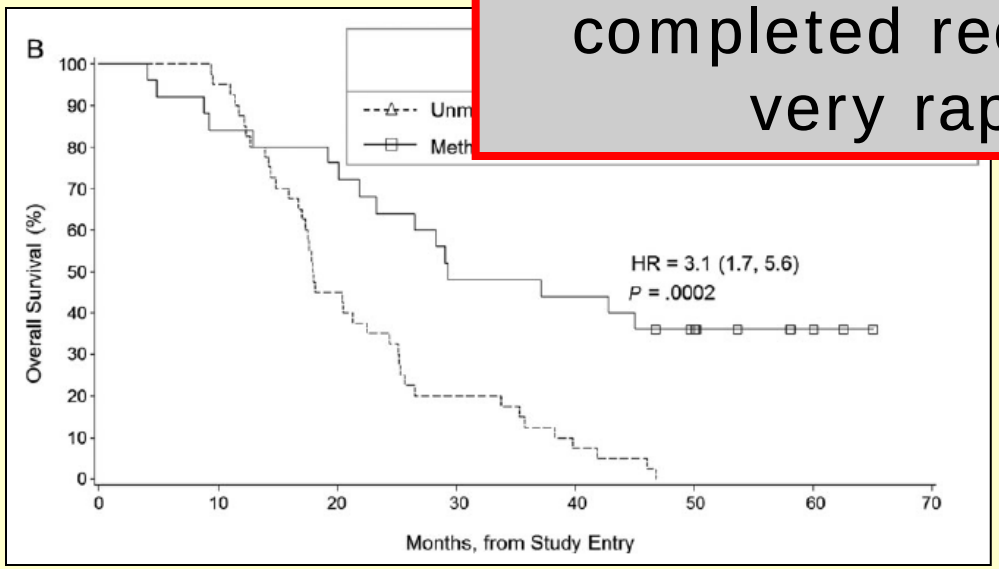


ACT IV phase III randomised controlled trial completed recruitment very rapidly



- 62% of EGFRvIII patients MGMT unmethylated

A phase 1 study evaluating ABT-414 in combination with temozolomide (TMZ) for subjects with recurrent or unresectable glioblastoma (GBM).

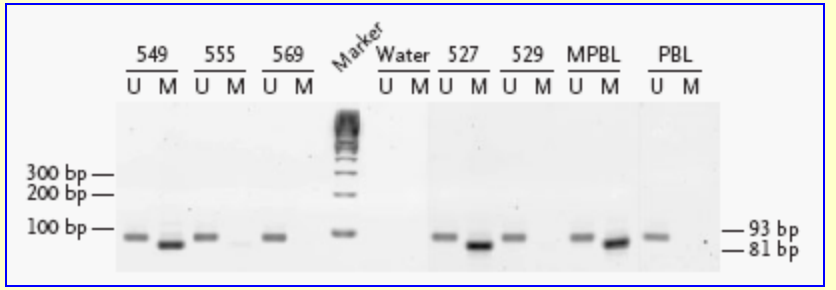
2014 ASCO Annual Meeting

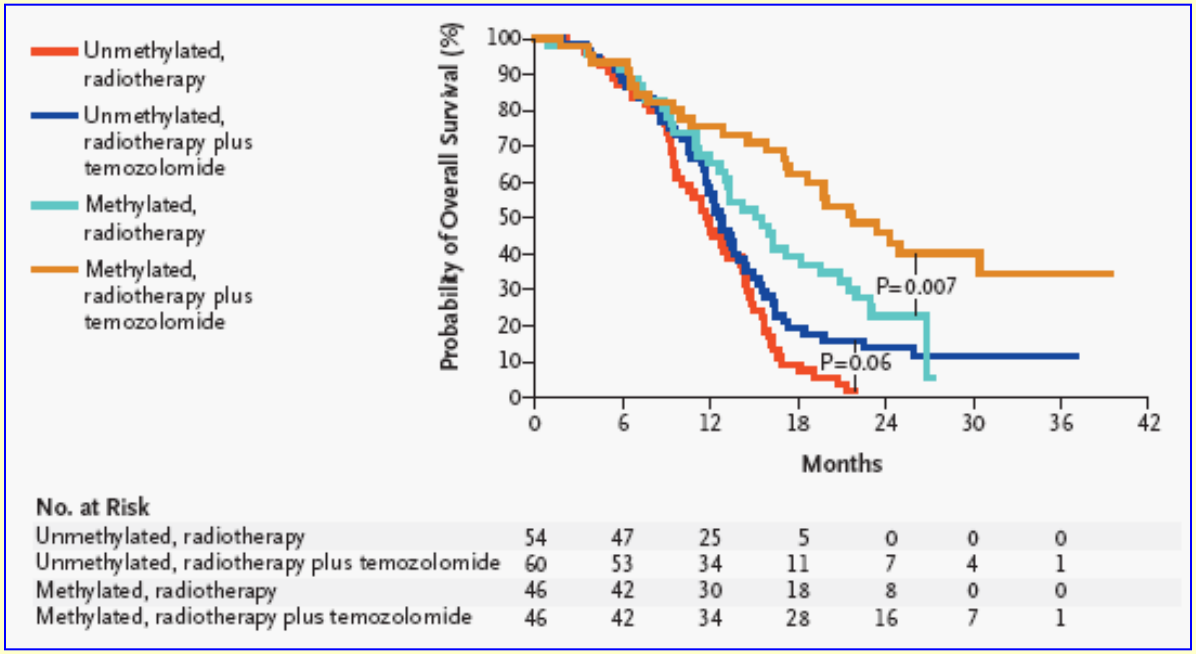
- Antibody targeting EGFR or mutant EGFRvIII conjugated to a cytotoxic anti-microtubule agent
- Preclinical activity against GBM tumor models - either amplified wild type EGFR or EGFRvIII
- Preliminary safety data demonstrate unique toxicity - corneal epithelial microcysts
- Preliminary responses in 3/9 pts with TMZ refractory GBM; 1 CR
- Phase 2 studies of ABT-414 in GBM underway:
  - **With TMZ in recurrent GBM (EGFR amplified or EGFRvIII mutated)**
  - **With RT-TMZ in first line GBM (EGFR amplified or EGFRvIII mutated)**

ORIGINAL ARTICLE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

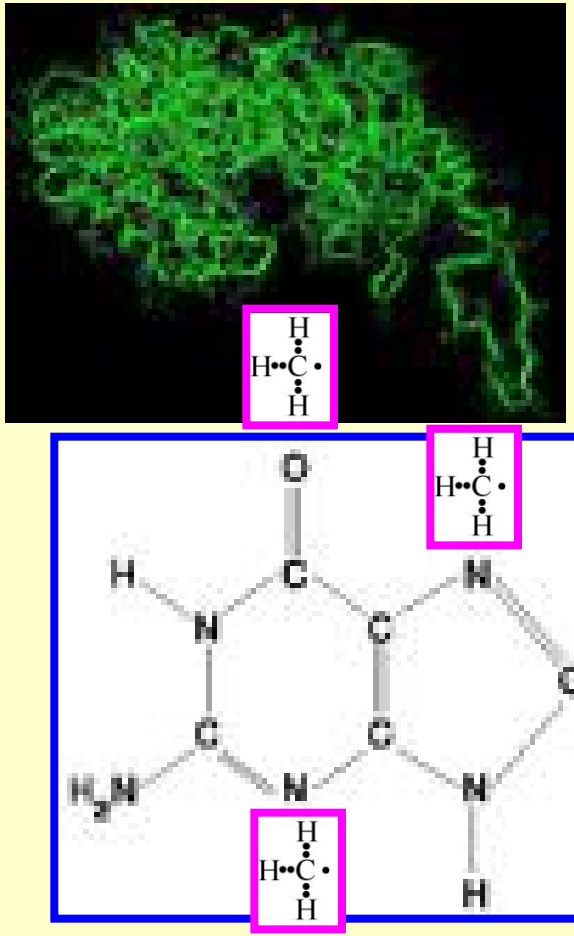
Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc.,





- Is MGMT a prognostic or predictive biomarker?
- Can we target MGMT to overcome TMZ resistance?

MGMT



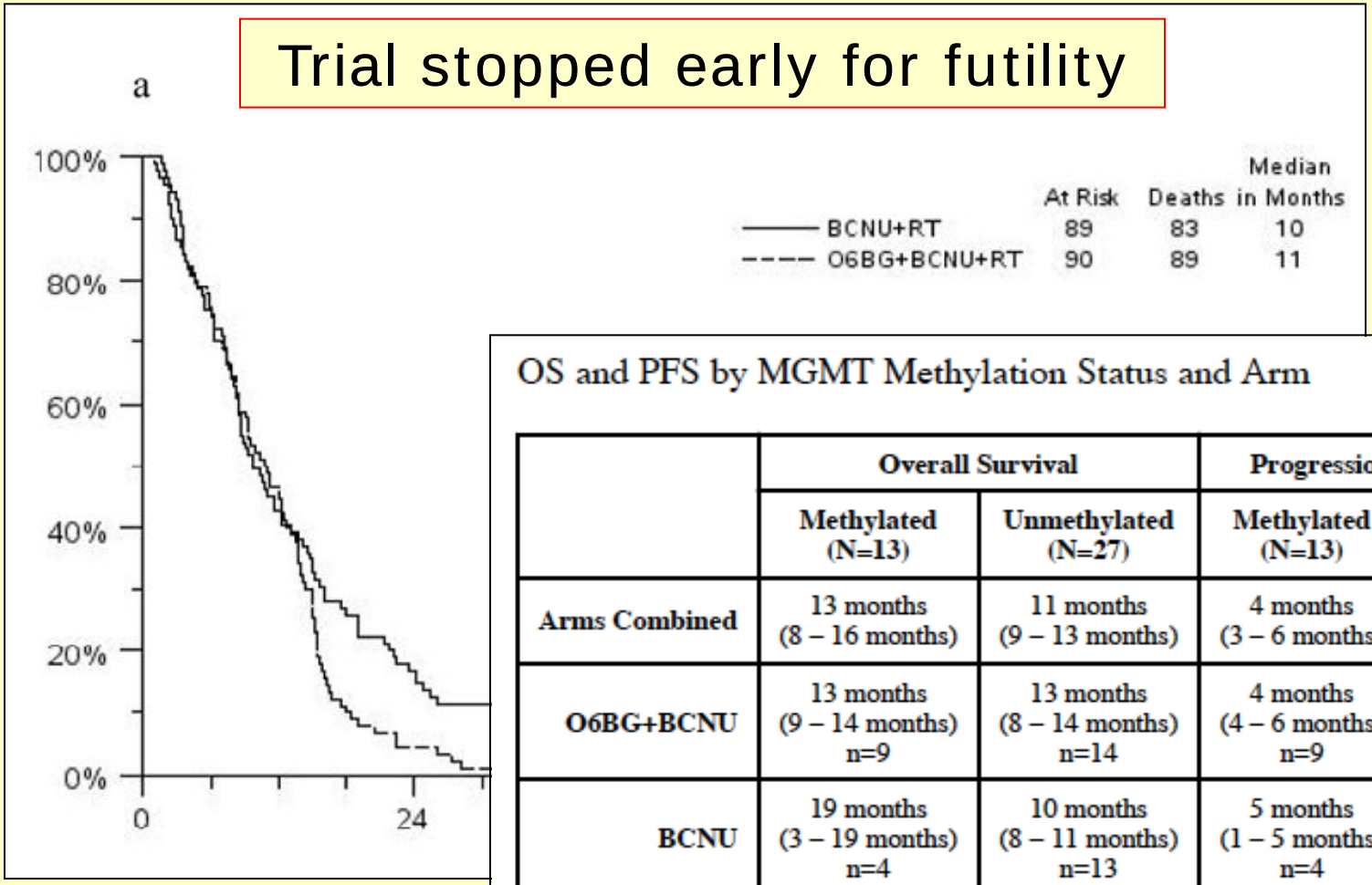
O^6-benzylguanine

guanine

Int J Clin Oncol. 2015 August ; 20(4): 650–658. doi:10.1007/s10147-014-0769-0.

A phase III study of radiation therapy (RT) and O⁶-benzylguanine, (O⁶-BG) plus BCNU versus RT and BCNU alone and methylation status in newly-diagnosed glioblastoma (GBM) and gliosarcoma: Southwest Oncology Group (SWOG) Study S0001

Trial stopped early for futility



OS and PFS by MGMT Methylation Status and Arm

	Overall Survival		Progression-Free Survival	
	Methylated (N=13)	Unmethylated (N=27)	Methylated (N=13)	Unmethylated (N=27)
Arms Combined	13 months (8 – 16 months)	11 months (9 – 13 months)	4 months (3 – 6 months)	3 months (3 – 5 months)
O6BG+BCNU	13 months (9 – 14 months) n=9	13 months (8 – 14 months) n=14	4 months (4 – 6 months) n=9	3 months (3 – 4 months) n=14
BCNU	19 months (3 – 19 months) n=4	10 months (8 – 11 months) n=13	5 months (1 – 5 months) n=4	4 months (3 – 8 months) n=13

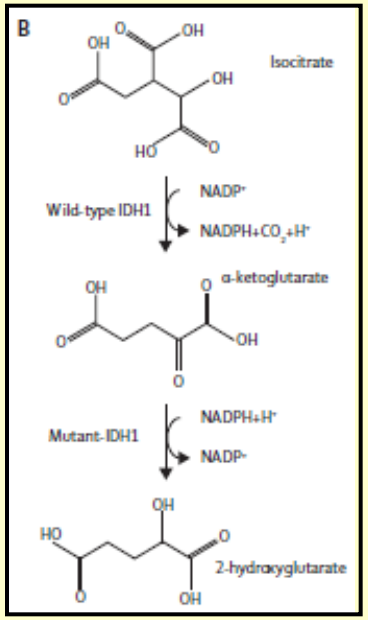
	O^6BG+BCNU+RT (n=90)							BCNU+RT (n=82)						
	Grade							Grade						
ADVERSE EVENT	Unk	0	1	2	3	4	5	Unk	0	1	2	3	4	5
ADR	0	90	0	0	0	0	0	0	81	0	0	0	0	1
Cardiovascular	0	67	10	10	3	0	0	0	63	4	10	4	1	0
Clotting	0	89	0	0	1	0	0	0	82	0	0	0	0	0
Dermatologic	0	38	24	27	1	0	0	0	33	30	16	3	0	0
Ear	0	85	2	2	1	0	0	0	72	9	1	0	0	0
Endocrine	0	85	0	5	0	0	0	0	78	1	3	0	0	0
Eye	0	70	6	14	0	0	0	0	71	3	7	1	0	0
Flu-like Symptoms	0	27	23	31	8	1	0	0	23	26	28	5	0	0
Gastrointestinal	0	28	32	28	2	0	0	0	27	31	20	3	1	0
Hematologic	0	2	4	7	34	43	0	0	2	12	24	30	14	0
Hemorrhage	0	79	7	3	1	0	0	0	79	2	0	1	0	0
Immunological	0	87	1	2	0	0	0	0	81	1	0	0	0	0
Infection	0	57	2	5	17	7	2	0	69	0	4	6	1	2
Liver	0	44	34	7	3	2	0	0	61	12	7	2	0	0
Lung	0	57	10	13	8	1	1	1	61	4	8	5	2	1
Metabolic	0	57	21	4	6	2	0	0	64	13	2	2	1	0
Musculoskeletal	0	79	3	7	0	1	0	0	76	2	2	2	0	0
Neurologic	0	42	11	24	12	1	0	2	40	6	17	14	3	0
Pain	0	36	23	24	7	0	0	1	38	19	16	7	1	0
Renal/Bladder	0	74	10	4	1	0	1	0	76	4	1	0	1	0
Sexual/Reproductive Function	0	87	0	1	2	0	0	0	81	0	1	0	0	0
MAXIMUM GRADE ANY ADVERSE EVENT														
Number	0	0	0	9	33	45	3	0	0	1	24	35	18	4

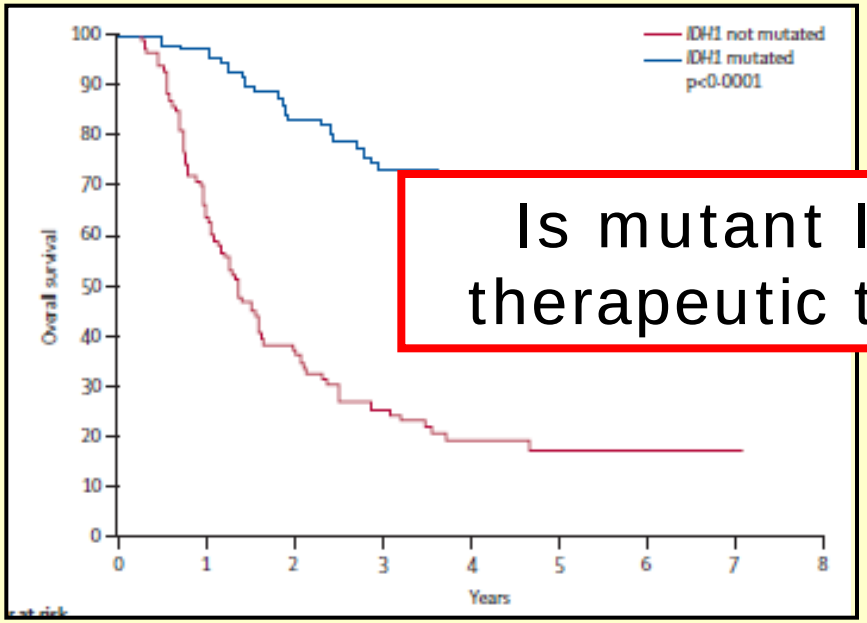
Mutations in IDH1 and IDH2

Table 1. Reported rates of *IDH1/IDH2* mutation according to glioma grade

		Tumor grade I	Tumor grade II	Tumor grade III	Primary GBM (IV)	Secondary GBM	All grades
IDH1	*n*[a]	253	1,034	1,118	1,392	123	3,920
	Mutated (%)	1 (0.4)	738 (71)	719 (64)	80 (6)	94 (76)	1,632 (42)
	(literature range, %)	(0.0–0.7)	(58–86)	(25–79)	(3–16)	(73–88)	(36–71)
IDH2	*n*[a]	21	542	667	193	13	1,436
	Mutated (%)	0 (0.0)	13 (2.4)	27 (4.0)	0 (0.0)	0 (0.0)	40 (2.8)
	(literature range, %)		(2.1–3.6)	(3.8–5.7)			ND

[a]Number of tumors analyzed in the literature [1–10].
Abbreviations: GBM, glioblastoma; IDH, isocitrate dehydrogenase; ND, not determined.





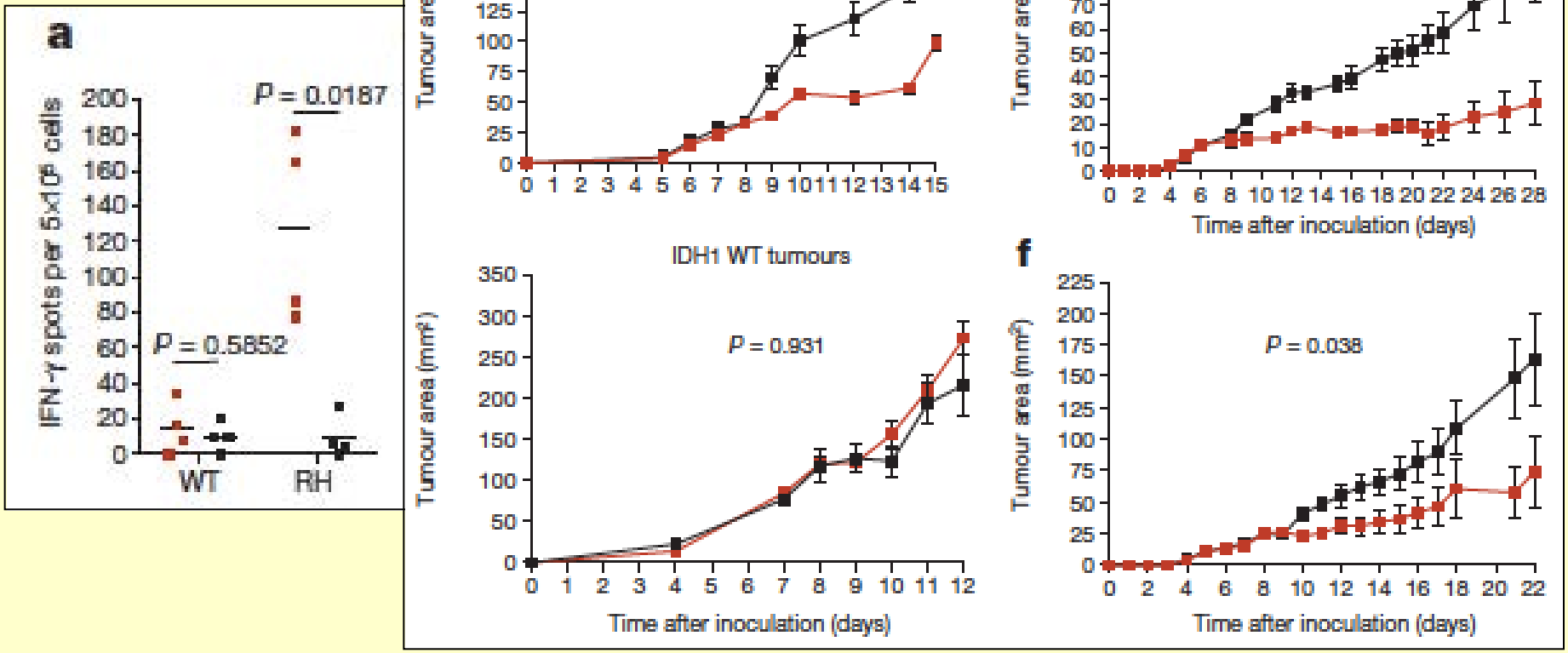
Is mutant IDH a therapeutic target?

LETTER

doi:10.1038/nature13387

A vaccine targeting mutant IDH1 induces antitumour immunity

Theresa Schumacher[1,2*], Lukas Bunse[1,2*], Stefan Pusch[3,4], Felix Sahm[3,4], Benedikt Wiestler[1,5], Jasmin Quandt[6], Oliver Menn[1], Matthias Osswald[1,5], Iris Oezen[1,2], Martina Ott[1,2], Melanie Keil[1,2], Jörg Balß[2,4], Katharina Rauschenbach[1,2], Agnieszka K. Grabowska[7], Isabel Vogler[8], Jan Diekmann[9], Nico Trautwein[10], Stefan B. Eichmüller[6], Jürgen Okun[11], Stefan Stevanović[10], Angelika B. Riemer[7], Ugur Sahin[9], Manuel A. Friese[12], Philipp Beckhove[6], Andreas von Deimling[3,4], Wolfgang Wick[1,5] & Michael Platten[1,2]

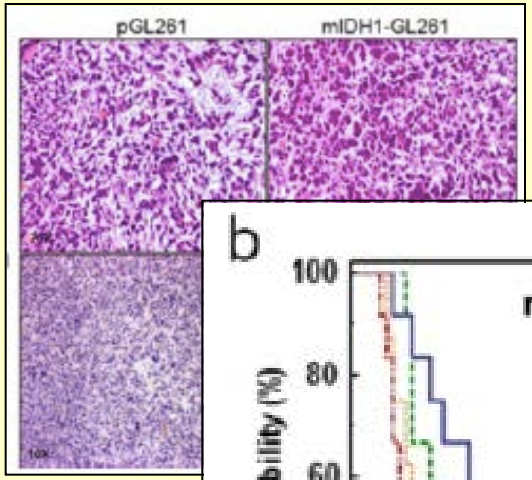


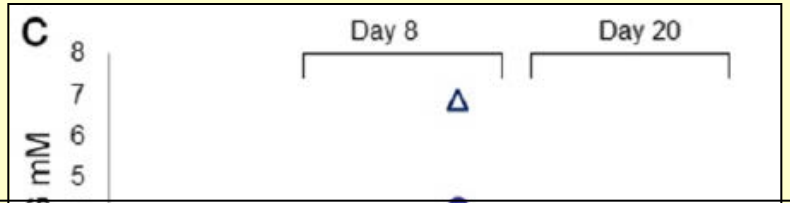
Pellegatta *et al. Acta Neuropathologica Communications* (2015) 3:4
DOI 10.1186/s40478-014-0180-0

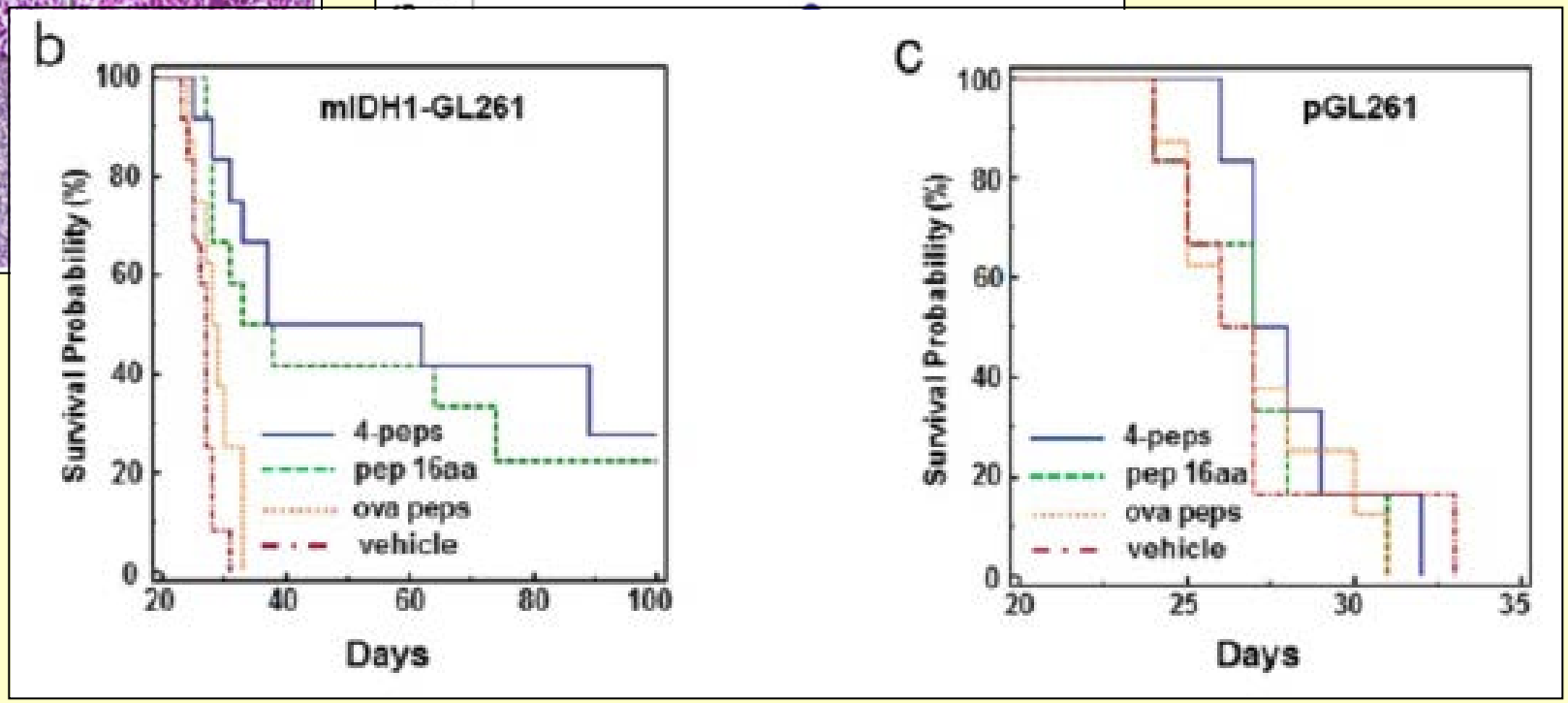
ACTA NEUROPATHOLOGICA COMMUNICATIONS

RESEARCH Open Access

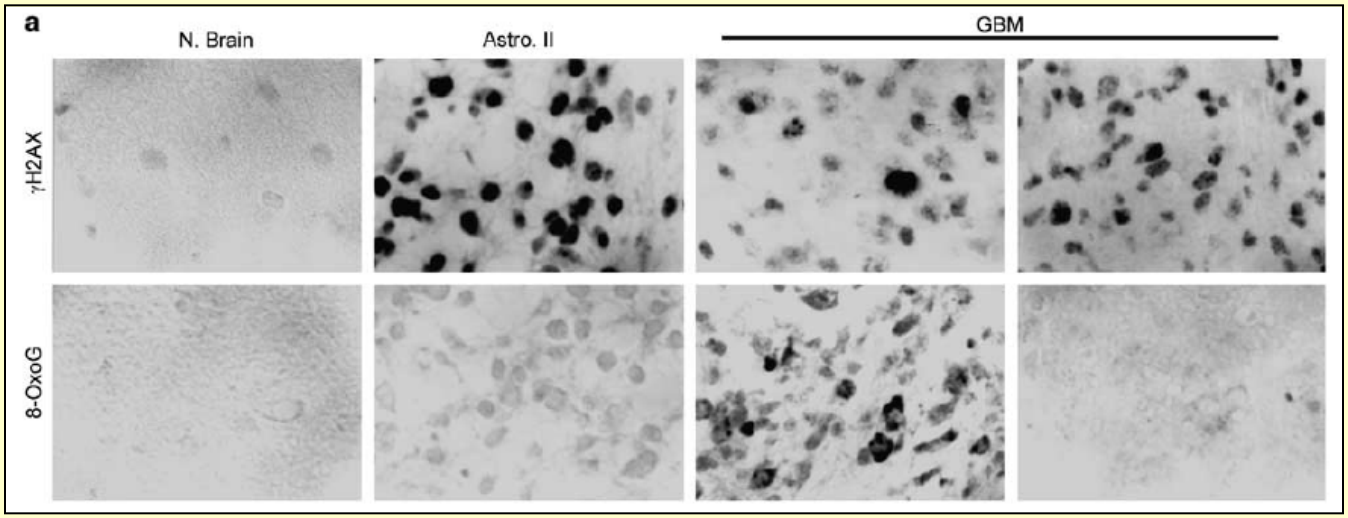
Effective immuno-targeting of the IDH1 mutation R132H in a murine model of intracranial glioma

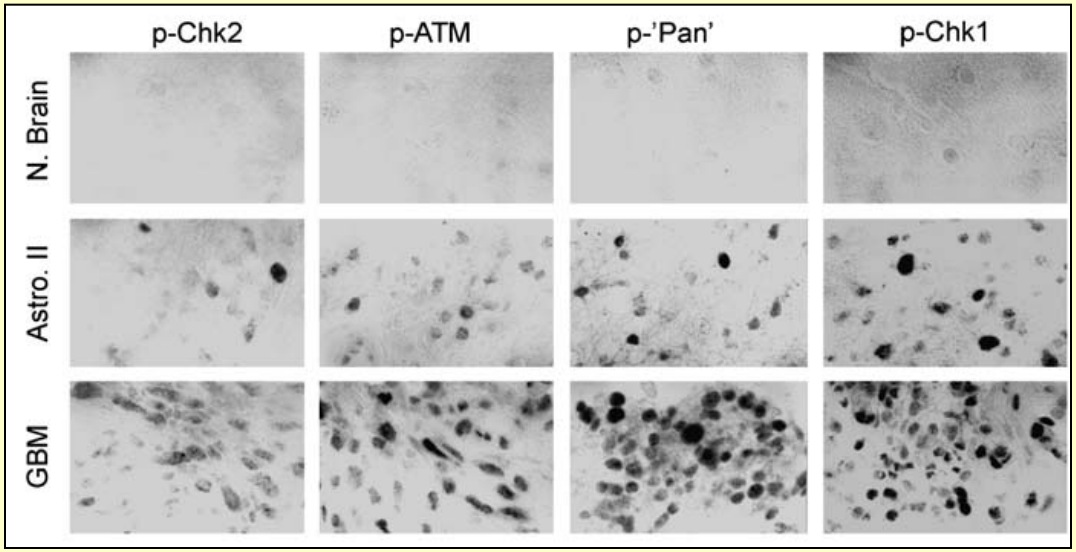






DNA damage levels and DNA damage response elements are upregulated in GBM





Bartkova *et al*, Oncogene 2010

nature Vol 444 | 7 December 2006 | doi:10.1038/nature05236

LETTERS

Glioma stem cells promote radioresistance by preferential activation of the DNA damage response

Shideng Bao[1,2], Qiulian Wu[1,2], Roger E. McLendon[2,3], Yueling Hao[1,2], Qing Shi[1,2], Anita B. Hjelmeland[1,2], Mark W. Dewhirst[4], Darell D. Bigner[2,3] & Jeremy N. Rich[1,2,5,6]

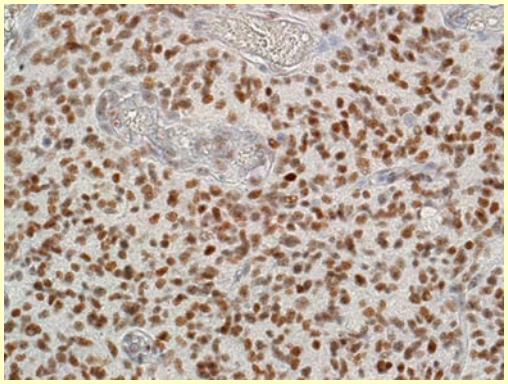
Cell Death and Differentiation (2014) 21, 258–269

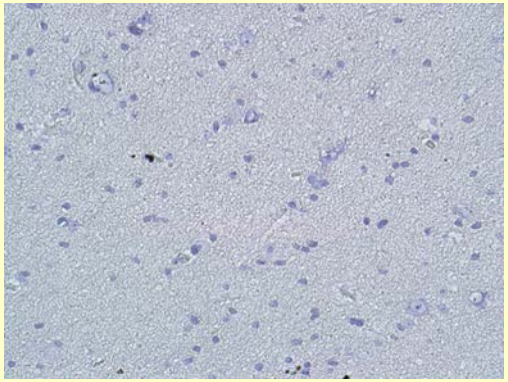
www.nature.com/cdd

Therapeutic targeting of constitutive PARP activation compromises stem cell phenotype and survival of glioblastoma-initiating cells

M Venere[1,6], P Hamerlik[2,3,6], Q Wu[1], RD Rasmussen[2], LA Song[1], A Vasanji[4], N Tenley[4], WA Flavahan[1], AB Hjelmeland[1,5], J Bartek[*,2,3] and JN Rich[*,1,5]

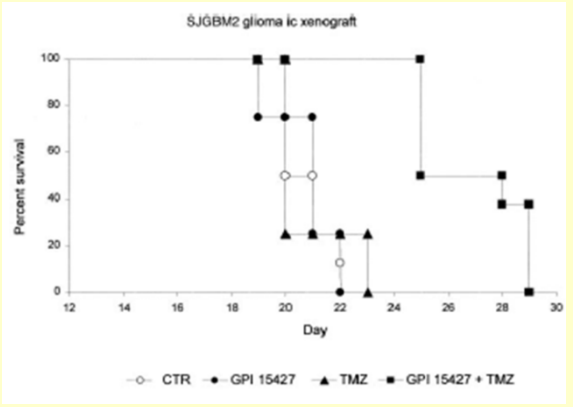
PARP-1 is overexpressed in GBM and is not expressed in normal brain

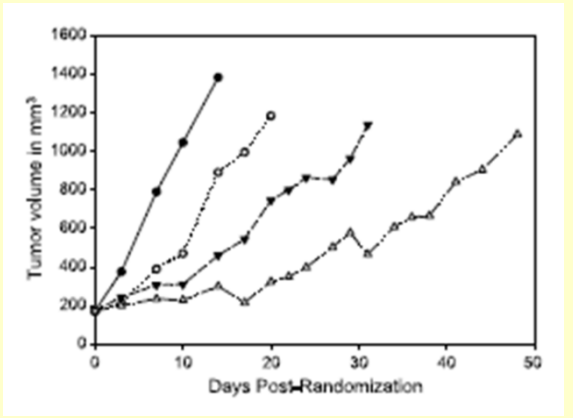


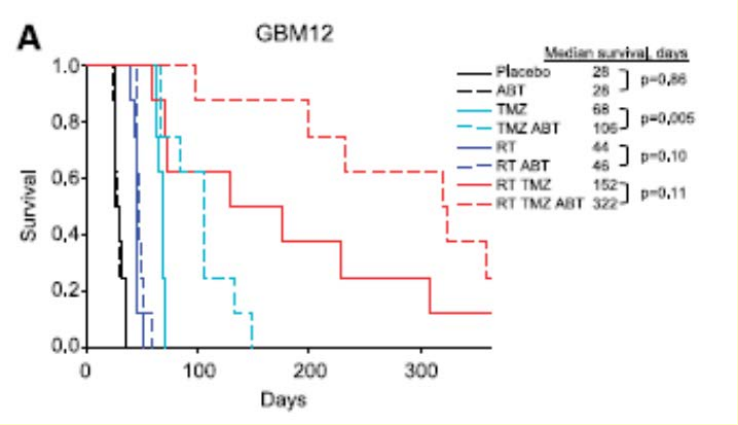


More tomorrow…..

PARP inhibitors increase sensitivity of GBM xenografts to TMZ and IR







Summary

- GBM exhibit multiple genetic abnormalities
- Inter- and intra-patient heterogeneity
- Targeting single pathways ineffective to date
- Tumour specificity essential
- Immunological/vaccine therapies have potential
- DNA damage response also a potential target

QUALITY OF LIFE ISSUES IN NEURO-ONCOLOGY

Riccardo Soffietti

Department of Neuro-Oncology
University of Turin and City of Health and Science Hospital,
Turin, Italy

ESTRO Teaching Course on Management of Brain Tumors

Turin, October 4-6, 2015

CONFLICT OF INTEREST

- I have received grants and honoraria for Lectures and Advisory Boards from MSD, Roche, Merck Serono, Celldex Therapeutics, Novartis and Mundipharma.

OUTLINE

- Instruments to evaluate Quality of Life (QoL).
- Quality of Life in glioma trials.
- Quality of Life in brain metastasis trials
- The issue of cognitive dysfunctions in brain metastases
- Conclusions

Table 1. Patient reported outcome measures used in neuro-oncology

Patient-reported outcome measure	Domain and items included
EORTCQLQ30	Thirty-one items total, consisting of 6 individual items, and others grouped as global QOL (2 items); physical (5 items), social (2 items), emotional (4 items), cognitive (2 items), role (2 items), fatigue (3 items), nausea (2 items), pain (2 items)
EORTC BN-20	Twenty items total, which are grouped as future uncertainty (4 items), visual disorder (3 items), motor dysfunction (3 items) communication disorder (3 items) and 7 individual items including headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control
FACT-BR	Fifty items total (27 general, and 23 brain tumor specific). Can generate a brain symptom index based on 15 items.
MDASI-BT	Twenty-eight items total (22 symptoms and 6 interference items). Can generate a global symptom burden score, mean symptom severity score, and mean interference score. Domains representing 6 factor groupings (general, gastrointestinal, constitutional, neurologic deficit, cognitive, and affective) and 3 interference items each representing activity and mood-related interference

EORTCQLQ30 Europe Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30, *EORTC BN-20* Europe Organisation for Research and Treatment of Cancer Brain Module 20, *FACT-BR* Functional Assessment of Cancer Therapy-Brain, *MDASI-BT* M.D. Anderson Symptom Inventory-Brain Tumor,

Armstrong and Gilbert, Curr Treat Options Oncol, 2014

MEASURING HRQoL AND COGNITIVE FUNCTIONS IN BRAIN TUMORS PATIENTS: CRITICAL ISSUES

- Timing
- Compliance ⟹ missing data
- Post-progression assessment
- Usefulness as early indicators of disease progression

Health-related quality of life in patients with glioblastoma: a randomised controlled trial

Martin J B Taphoorn, Roger Stupp, Corneel Coens, David Osoba, Rolf Kortmann, Martin J van den Bent, Warren Mason, René O Mirimanoff, Brigitta G Baumert, Elizabeth Eisenhauer, Peter Forsyth, Andrew Bottomley, for the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour Group, EORTC Radiotherapy Group, and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)

Summary

Background A randomised controlled trial of radiotherapy alone versus radiotherapy with concomitant and adjuvant temozolomide for patients with glioblastoma showed that survival was higher for patients assigned combination treatment compared with those assigned standard radiotherapy alone. This paper reports the health-related quality of life (HRQOL) of the patients in this trial.

Methods 573 patients with newly diagnosed glioblastoma were randomly allocated either radiotherapy alone or radiotherapy and temozolomide. The primary endpoint was survival, and HRQOL was a secondary endpoint. We assessed HRQOL at baseline and at every 3 months during treatment until progression using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core-30 (QLQ-C30) and the EORTC brain cancer module (EORTC BN-20). We calculated changes from baseline score for seven predefined HRQOL measures (fatigue, overall health, social function, emotional function, future uncertainty, insomnia, and communication deficit) and differences between groups for these measures at every time point. The significance of, and proportions of patients with, improved HRQOL scores—defined as a change of 10 points or more—were recorded. This trial is registered on the US National Cancer Institute website http://www.cancer.gov/search/NewClinicalTrials, NCT00006353.

Findings Baseline questionnaires were available for 490 (86%) patients. Baseline HRQOL scores did not differ between groups. At first follow-up, groups differed only in social functioning, favouring the radiotherapy-only group (mean score 79·0 [SD 3·2] for patients assigned radiotherapy *vs* 67·4 [2·7] for those assigned radiotherapy and temozolomide; difference between groups 11·6 points [95% CI 3·5–19·7], p=0·0052). Over subsequent assessments, HRQOL was much the same between treatment groups.

Interpretation Addition of temozolomide during and after radiotherapy for patients with newly diagnosed glioblastoma significantly improved survival without a negative effect on HRQOL.

Lancet Oncol 2005; 6: 937–44

Published online: November 17, 2005
DOI:10.1016/S1470-2045(05)70432-0

See Reflection and Reaction page 913

Medical Centre Haaglanden, The Hague, The Netherlands (M J B Taphoorn MD); University Medical Centre, Utrecht, The Netherlands (M J B Taphoorn); University Hospital Centre Vaudois, Lausanne, Switzerland (R Stupp MD, R O Mirimanoff MD); EORTC Data Centre, Quality of Life Unit, Brussels, Belgium (C Coens MSC, A Bottomley PhD); QOL Consulting, Vancouver, Canada (D Osoba MD); University Clinic Leipzig, Leipzig, Germany (R Kortmann MD); Daniel den Hoed Cancer Centre and Erasmus University Hospital, Rotterdam, The Netherlands (M J van den Bent MD); Princess Margaret Hospital, Ontario,

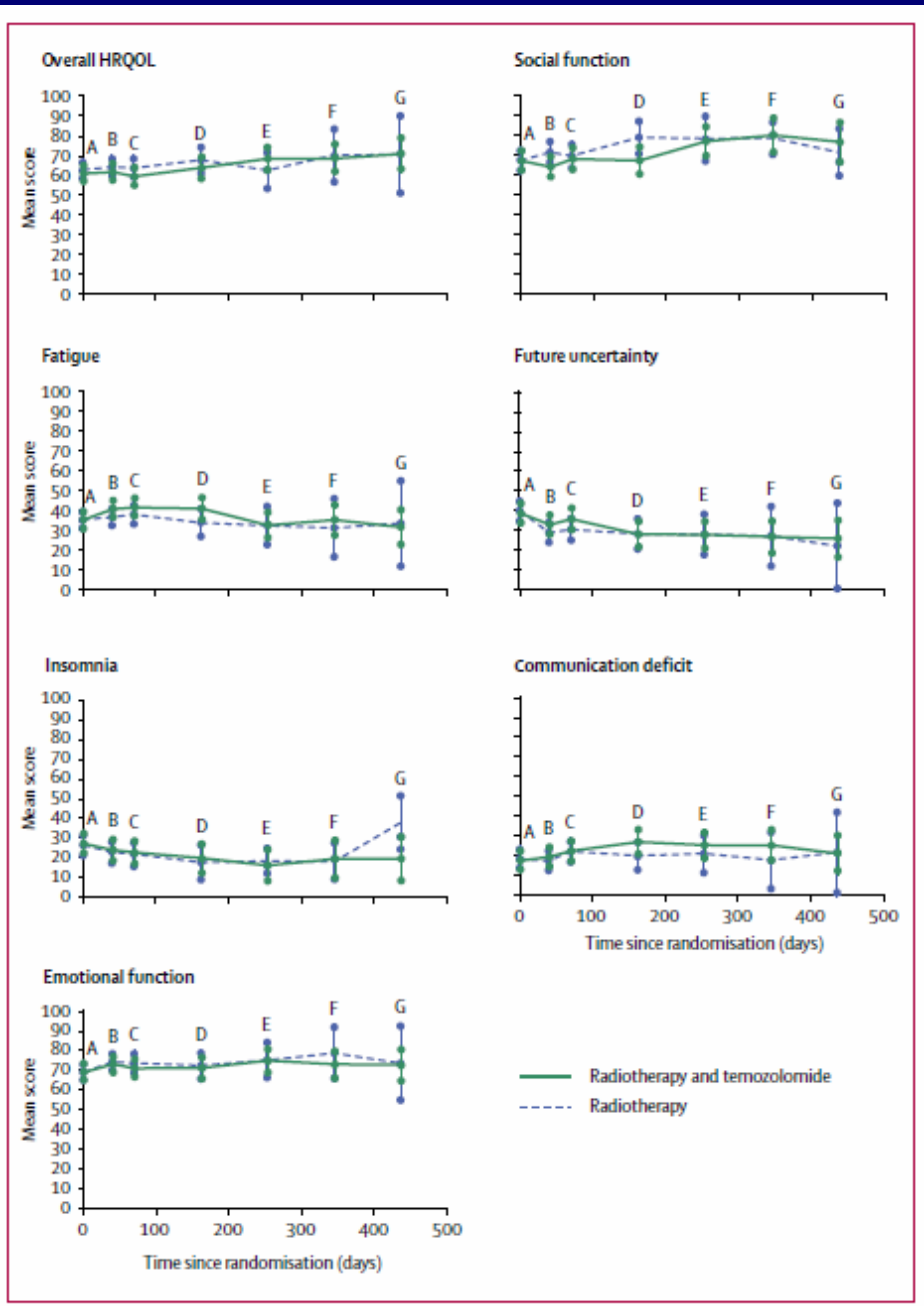


Figure 2: **Changes over time in mean HRQOL**
Data are mean (99% CI). A=baseline. B=during radiotherapy. C=after radiotherapy. D=first follow-up. E=second follow-up. F=third follow-up. G=fourth follow-up.

Taphoorn et al, Lancet Oncol 2005

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Net Clinical Benefit Analysis of Radiation Therapy Oncology Group 0525: A Phase III Trial Comparing Conventional Adjuvant Temozolomide With Dose-Intensive Temozolomide in Patients With Newly Diagnosed Glioblastoma

Terri S. Armstrong, Jeffrey S. Wefel, Meihua Wang, Mark R. Gilbert, Minhee Won, Andrew Bottomley, Tito R. Mendoza, Corneel Coens, Maria Werner-Wasik, David G. Brachman, Ali K. Choucair, and Minesh Mehta

See accompanying article on page 4085

Terri S. Armstrong, University of Texas Health Science Center-School of Nursing; Terri S. Armstrong, Jeffrey S. Wefel, Mark R. Gilbert, Tito R. Mendoza, MD Anderson Cancer Center, Houston, TX; Meihua Wang, Minhee Won, Radiation Therapy Oncology Group Statistical Center; Maria Werner-Wasik, Thomas Jefferson University Hospital, Philadelphia, PA; Andrew Bottomley, Corneel Coens, European Organisation for Research and Treatment of Cancer, Brussels, Belgium; David G. Brachman, Arizona Oncology Services Foundation and Barrow Neurological Institute, Phoenix, AZ; Ali K. Choucair, Mayo Clinic, Jacksonville, FL; Minesh Mehta, University of Maryland, Baltimore, MD.

Published online ahead of print at www.jco.org on October 7, 2013.

Supported by Grants No. NCI U10CA 21661, U10CA37422, and ABC[2] and by Merck Pharmaceuticals.

T.S.A. and J.S.W. authors contributed equally to this work.

Presented at the 47th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2011 (poster presentation) and at the 16th Annual Scientific Meeting of the Society of Neuro-Oncology, Garden Grove, CA, November 17-20, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

ABSTRACT

Purpose
Radiation Therapy Oncology Group trial 0525 tested whether dose-intensifying temozolomide versus standard chemoradiotherapy improves overall survival (OS) or progression-free survival (PFS) in newly diagnosed glioblastoma. Tests of neurocognitive function (NCF) and symptoms (using the MD Anderson Symptom Inventory–Brain Tumor module; MDASI-BT) and of quality of life (European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ] –C30/BN20) examined the net clinical benefit (NCB) of therapy.

Patients and Methods
NCF tests (Hopkins Verbal Learning Test–Revised, Trail Making Test, and Controlled Oral Word Association), MDASI-BT, and EORTC QLQ-C30/BN20 were completed in a subset of patients. Multivariate Cox proportional hazard regression modeling determined the prognostic value of baseline and early change from baseline to cycle 1 for OS and PFS. Two-sample proportional test statistic was used to evaluate differences between treatments (dose-dense *v* standard-dose) on NCB measures from baseline to cycle 4 in stable patients.

Results
Overall, 182 patients participated in the study. Baseline NCF tests and the physical functioning quality of life scale were associated with OS and PFS. Baseline to cycle 1 in all NCB components were associated with OS and PFS. There was greater deterioration in the dose-dense arm from baseline to cycle 4 in the Global Health and Motor Function subscales (EORTC QLQ-C30/BN20) as well as in overall symptom burden, overall symptom interference, and activity-related symptom interference subscales (MDASI-BT). There were no between-arm differences in NCF.

Conclusion
Longitudinal collection of NCB measures is feasible in cooperative group studies and provides an added dimension to standard outcome measures. Greater adverse symptom burden and functional interference, as well as decreased global health and motor function were observed in patients randomly assigned to the dose-dense arm. Baseline and early change in NCB measures were associated with decreased rates of survival.

J Clin Oncol 31:4076-4084. © 2013 by American Society of Clinical Oncology

VOLUME 33 · NUMBER 19 · JULY 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Health-Related Quality of Life in a Randomized Phase III Study of Bevacizumab, Temozolomide, and Radiotherapy in Newly Diagnosed Glioblastoma

Martin J.B. Taphoorn, Roger Henriksson, Andrew Bottomley, Timothy Cloughesy, Wolfgang Wick, Warren P. Mason, Frank Saran, Ryo Nishikawa, Magalie Hilton, Christina Theodore-Oklota, Arliene Ravelo, and Olivier L. Chinot

Author affiliations appear at the end of this article.

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Written on behalf of the AVAglio investigators.

Sponsored by F. Hoffmann-La Roche, Basel, Switzerland. The sponsor was involved in trial design, coordination of data collection, data analysis and interpretation, the writing of the manuscript, and the provision of bevacizumab. After data lock for the final overall survival analysis, the sponsor, investigators, and authors had full data access.

Presented in part at the American Society of Clinical Oncology Annual Meeting, Chicago, IL, May 31-June 4, 2013, the European Society for Medical Oncology Congress, Amsterdam, the Netherlands, September 27-October 1, 2013, and the Scientific Meeting and Education Day of the Society for Neuro-Oncology, San Francisco, CA, November 21-24, 2013.

The views expressed in this manuscript reflect those of the authors and do not necessarily reflect the official views of the authors' institutions.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are

ABSTRACT

Purpose

As glioblastoma progresses, patients experience a decline in health-related quality of life (HRQoL). Delaying this decline is an important treatment goal. In newly diagnosed glioblastoma, progression-free survival was prolonged when bevacizumab was added to radiotherapy plus temozolomide (RT/TMZ) versus placebo plus RT/TMZ (phase III AVAglio study; hazard ratio, 0.64; 95% CI, 0.55 to 0.74; $P < .001$). To ensure that addition of bevacizumab to standard-of-care therapy was not associated with HRQoL detriment, HRQoL assessment was a secondary objective.

Patients and Methods

Patients completed European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BN20 at each tumor assessment (Appendix Table A1, online only). Raw scores were converted to a 100-point scale and mean changes from baseline scores were evaluated (stable: < 10-point change; clinically relevant deterioration/improvement: ≥ 10-point change). Deterioration-free survival was the time to deterioration/progression/death; time to deterioration was the time to deterioration/death.

Results

Most evaluable patients who had not progressed (> 74%) completed all HRQoL assessments for at least 1 year of treatment, and almost all completed at least one HRQoL assessment at baseline (98.3% and 97.6%, bevacizumab and placebo arms, respectively). Mean changes from baseline did not reach a clinically relevant difference between arms for most items. HRQoL declined at progression in both arms. The addition of bevacizumab to RT/TMZ resulted in statistically longer ($P < .001$) deterioration-free survival across all items. Time to deterioration was not statistically longer in the placebo plus RT/TMZ arm (*v* bevacizumab) for any HRQoL item.

Conclusion

The addition of bevacizumab to standard-of-care treatment for newly diagnosed glioblastoma had no impact on HRQoL during the progression-free period.

J Clin Oncol 33:2166-2175. © 2015 by American Society of Clinical Oncology

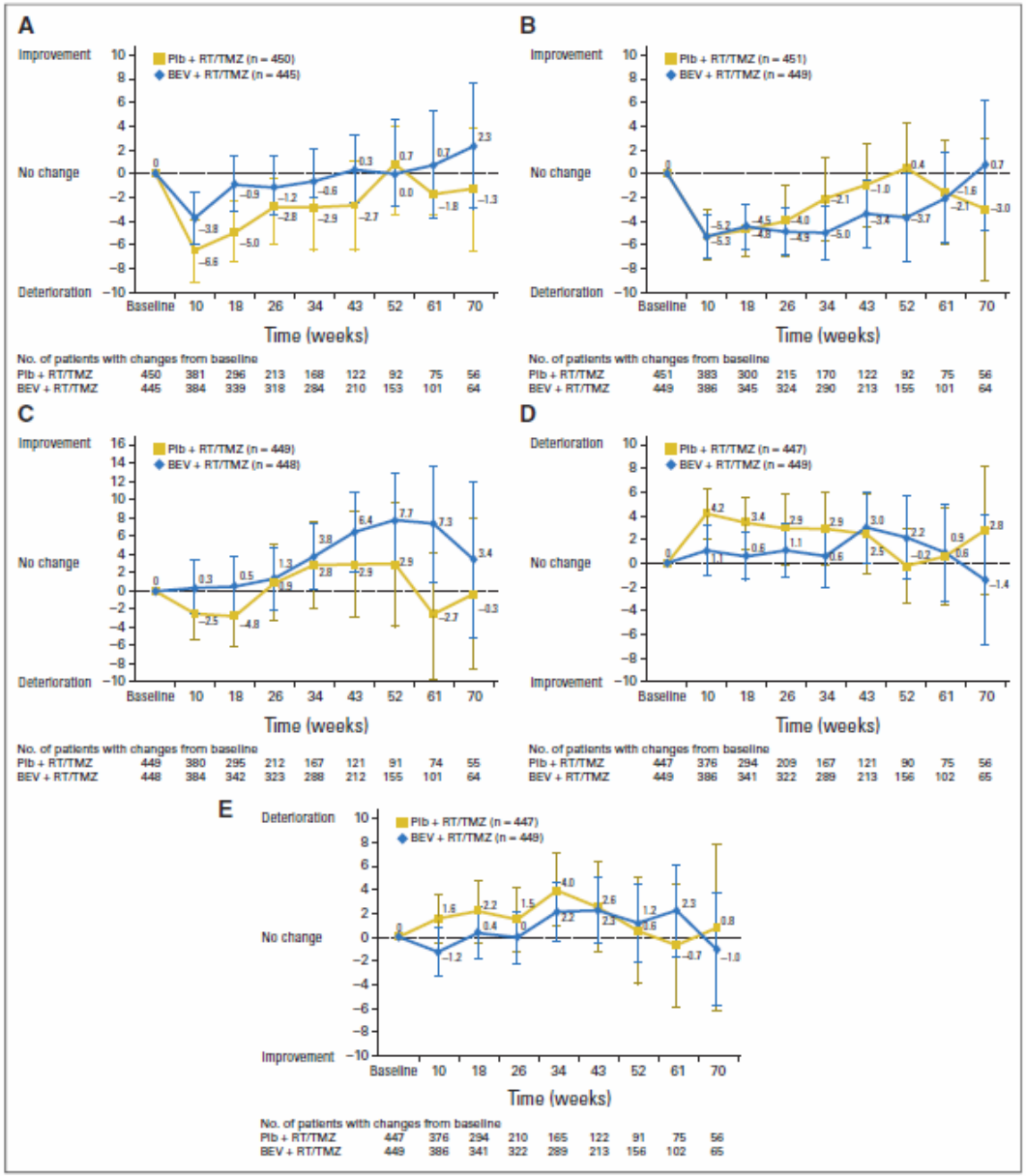

Fig 2. Mean (and standard deviation) changes from baseline for five European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 and Brain Cancer Module 20 scales by trial treatment (remaining scales are shown in the Data Supplement). (A) Global health status; (B) physical functioning; (C) social functioning; (D) motor dysfunction; (E) communication deficit. The dotted line represents a clinically relevant change from baseline. BEV, bevacizumab; Plb, placebo; RT/TMZ, radiotherapy/temozolomide.

Taphoorn et al, JCO 2015

J Neurooncol (2014) 116:161–168
DOI 10.1007/s11060-013-1278-0

CLINICAL STUDY

Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors

Esther J. J. Habets · Martin J. B. Taphoorn · Sylvie Nederend · Martin Klein · Daniel Delgadillo · Khê Hoang-Xuan · Andrew Bottomley · Anouk Allgeier · Tatjana Seute · Anja M. M. Gijtenbeek · Jan de Gans · Roelien H. Enting · Cees C. Tijssen · Martin J. van den Bent · Jaap C. Reijneveld

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.56.9079

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Health-Related Quality of Life in Stable, Long-Term Survivors of Low-Grade Glioma

Florien W. Boele, Linda Douw, Jaap C. Reijneveld, Rianne Robben, Martin J.B. Taphoorn, Neil K. Aaronson, Jan J. Heimans, and Martin Klein

Florien W. Boele, Linda Douw, Jaap C. Reijneveld, Rianne Robben, Jan J. Heimans, and Martin Klein, VU University Medical Center; Neil K. Aaronson, Netherlands Cancer Institute, Amsterdam; and Martin J.B. Taphoorn, Medical Center Haaglanden, the Hague, the Netherlands.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Florien W. Boele, MSc, Department of Medical Psychology, D-345, VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, the Netherlands; e-mail: f.boele@vumc.nl.

0732-183X/15/3399-1/$20.00

DOI: 10.1200/JCO.2014.56.9079

ABSTRACT

Purpose
Patients with low-grade glioma (LGG) often experience long periods of stable disease, emphasizing the importance of maintaining good health-related quality of life (HRQOL). We assessed the changes in HRQOL in long-term survivors of WHO grade I or II astrocytoma, oligodendroglioma, or oligoastrocytoma with clinically and radiologically stable disease.

Patients and Methods
Patients completed self-report measures of generic HRQOL (Short Form-36 [SF-36]) and disease-specific HRQOL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Brain Cancer Module). Assessments took place at midterm and long-term follow-up, on average 6 and 12 years after histologic diagnosis and initial treatment, respectively. Comparisons between patients with LGG and individually matched healthy controls were made, and change within the patients with LGG was calculated, as was minimal detectable change.

Results
Although no statistically significant differences between patients with LGG and healthy matched controls were found at midterm follow-up, patients with LGG had worse physical role functioning ($P = .004$) and general health perceptions ($P = .004$) than controls at long-term follow-up. Within patients with stable LGG (n = 65), physical HRQOL (the SF-36 physical component summary and the physical functioning subscale) was significantly worse at long-term than at midterm follow-up (both $P < .001$). Although 48% of patients improved or remained stable on all HRQOL scales, 38.5% of patients experienced detectable decline on one or more scales.

Conclusion
Although HRQOL remains mostly preserved in the majority of patients with LGG, a subset of patients experience detectable decline on one or more HRQOL scales despite long-term stable disease. For this subgroup, further research is recommended to better aid patients in dealing with the consequences of LGG.

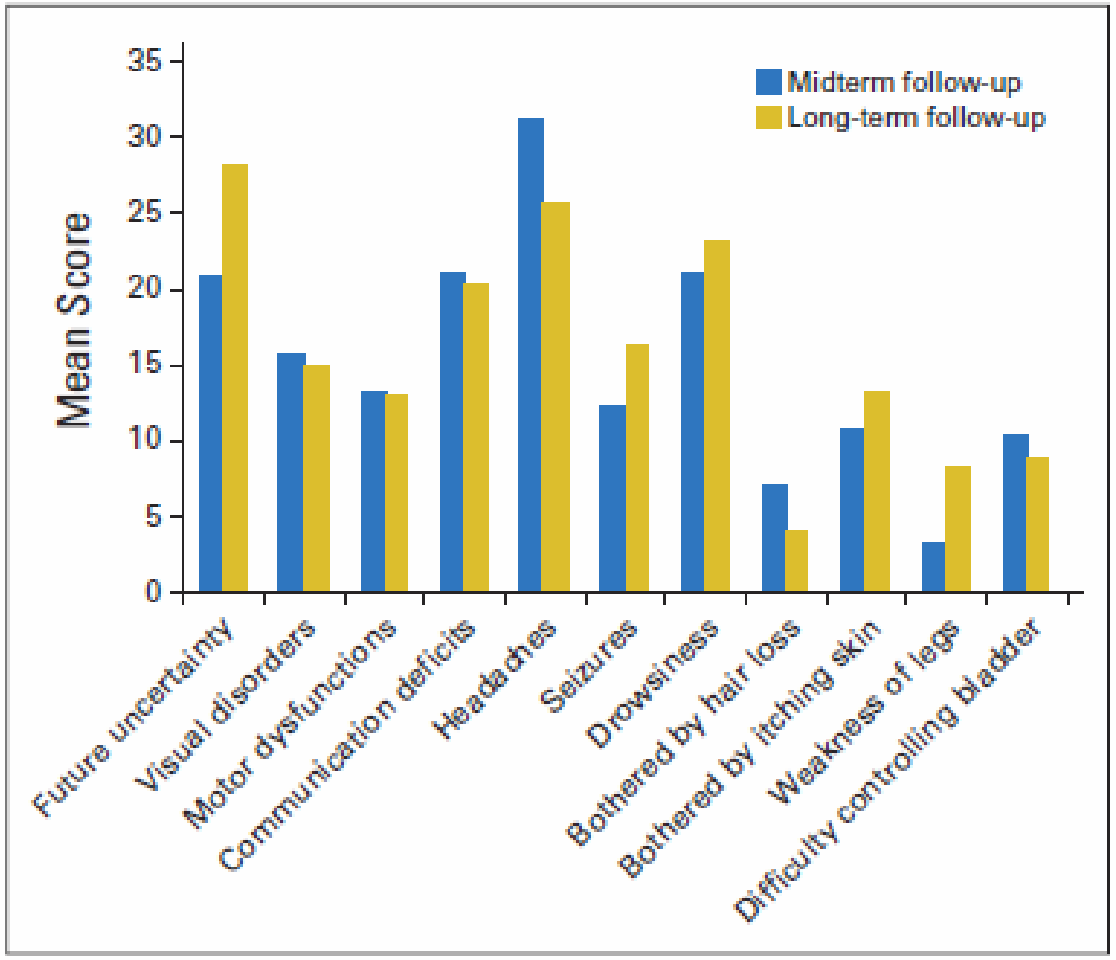


Fig 1. Disease-specific health-related quality of life at first (midterm) and second (long-term) assessment. Higher scores indicate more symptoms being present.

Boele et al, JCO 2015

NEURO-ONCOLOGY

Quality of life in low-grade glioma patients receiving temozolomide

Raymond Liu, Karla Solheim, Mei-Yin Polley, Kathleen R. Lamborn, Margaretta Page, Anne Fedoroff, Jane Rabbitt, Nicholas Butowski, Michael Prados, and Susan M. Chang

Department of Medicine, Division of Hematology, Oncology (R.L.), Medical School (K.S.), Department of Neurological Surgery, Neuro-Oncology (M.-Y.P., K.R.L., M.P., A.F., J.R., N.B., M.P., S.M.C.), University of California, San Francisco, San Francisco, CA, USA

WBRT MAY NEGATIVELY IMPACT HEALTH-RELATED QUALI TY OF LIFE (HRQL) IN BRAIN METASTASIS

- Increasing interest for HRQL as an endpoint for treatment comparisons in many cancer types, especially in advanced stages (*Bottomley et al, Eur J Cancer 2005*)
- After PCI for SCLC significant, but reversible, short-term (3 months) negative impact on selected HRQL scales, such as fatigue, hair loss, or cognitive functioning (*Slotman et al, JCO 2009*).
- After PCI for NSCLC significant decline in memory at 1 year (*Sun et al, JCO 2011*)
- No data available so far regarding the impact of adjuvant WBRT on HRQL of patients with brain metastases.

EORTC 22952-26001

Quality of Life results of an EORTC phase III randomized trial of adjuvant Whole Brain Radiotherapy versus Observation after Radio surgery or Surgical Resection of 1-3 Cerebral Metastases of solid tumors

HRQOL results

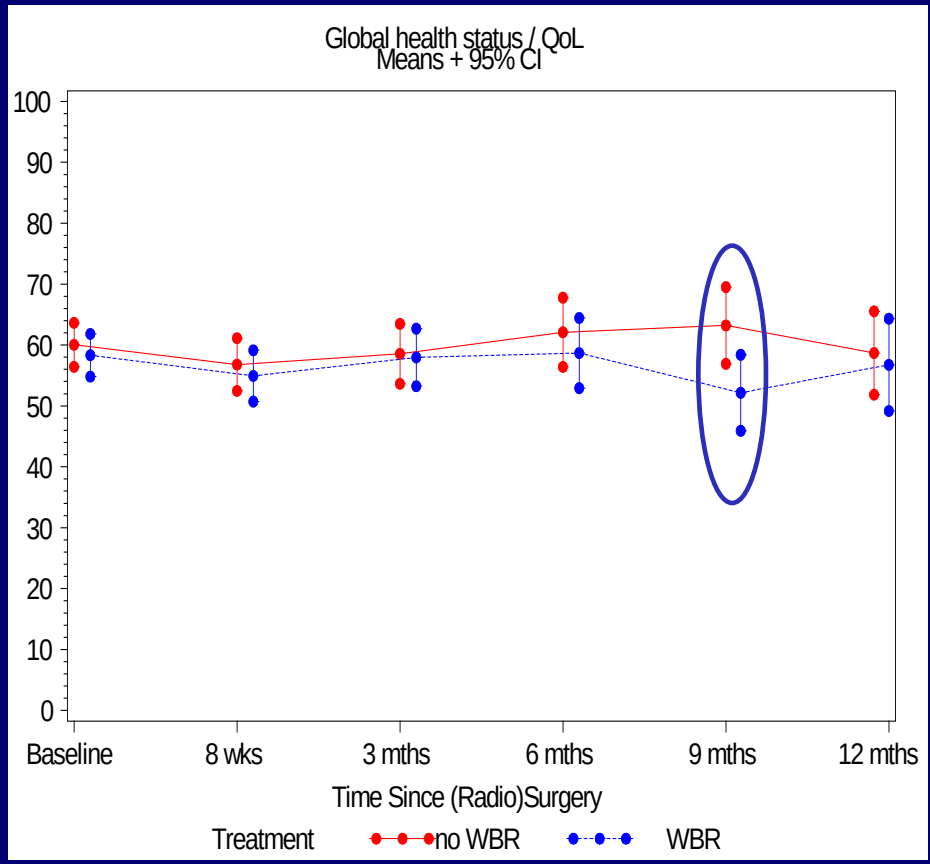
R. Soffietti[1], M. Kocher[2], M. U. Abacioglu[3], S. Villa[4], F. Fauchon[5], B. G. Baumert[6], L. Fariselli[7], R. P. Mueller[2], G. Tridello[8], A. Bottomley[8]

1.Azienda Ospedaliera San Giovanni Battista, Neurology, Universita di Torino, Torino, Italy – 2.University of Cologne, Radiation Oncology, Koeln, Germany – 3.Marmara University Hospital, Radiation Oncology, Istanbul, Turkey – 4.Hospital Germans Trias i Pujol, ICO, Radiation Oncology, Barcelona, Spain – 5.Centre Haute Energie, Nice, France – 6.Radiation-Oncology (MAASTRO), Maastricht University Medical Centre (MUMC), GROW (School for Oncology), Maastricht, Netherlands – 7.Fondazione Istituto Neurologico “Carlo Besta”, Milano – 8.EORTC Headquarters, Brussels, Belgium

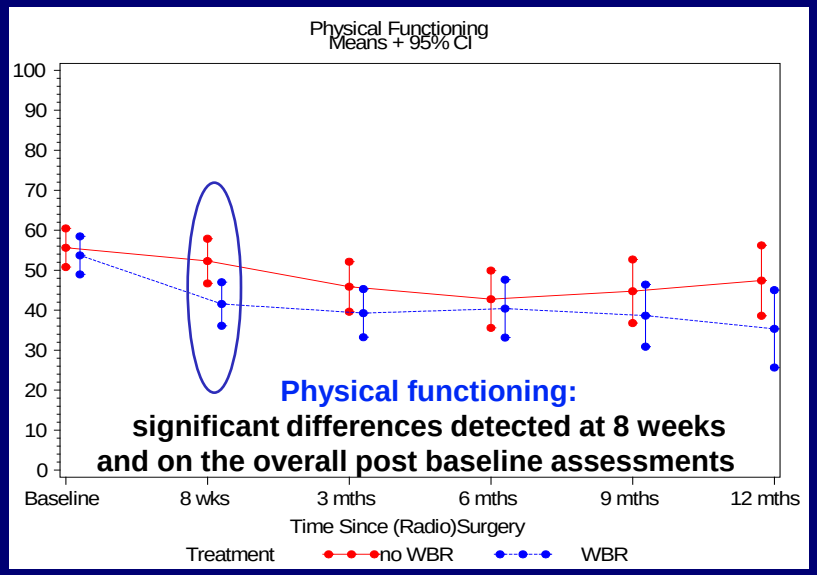
J Clin Oncol. 2013 Jan 1;31(1):65-72

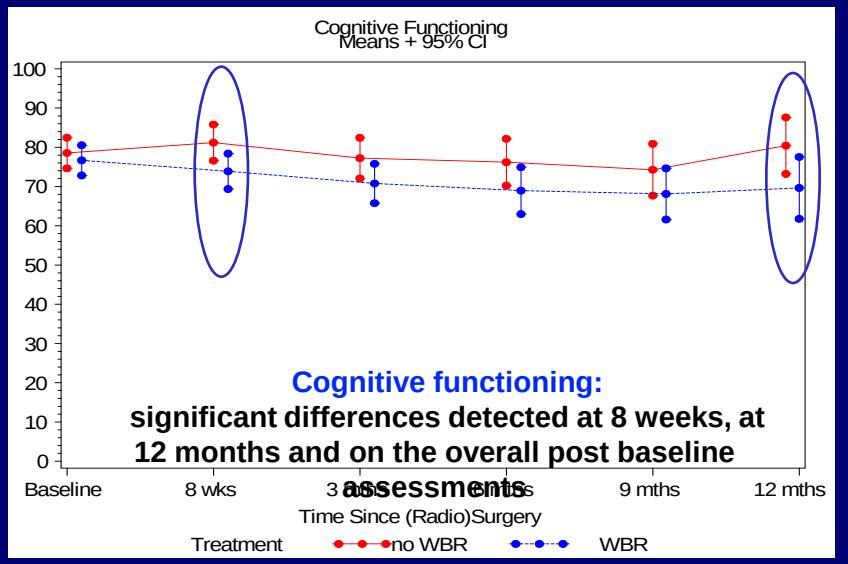
Results: Global health status / QoL

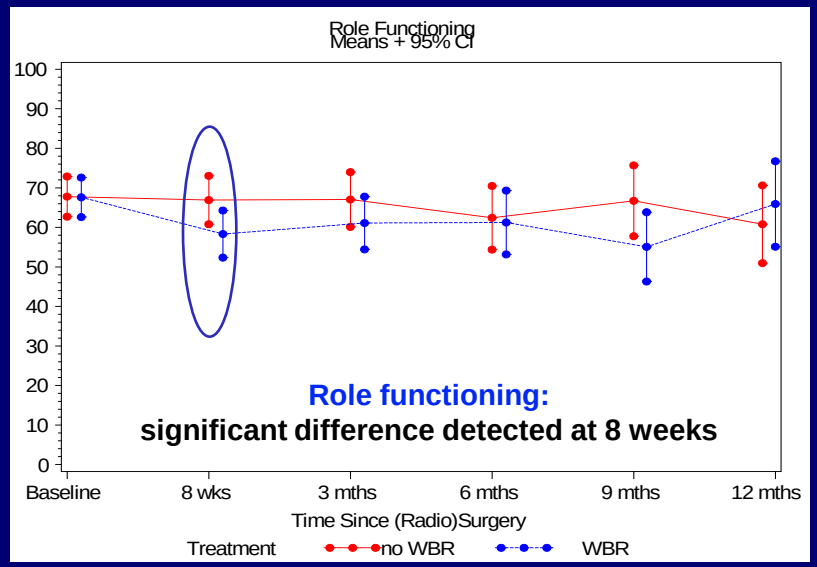
Timepoint	WBI Estimate (Std.Err.)	No WBI Estimate (Std.Err.)	Treatment difference p-value
Baseline	**58.3 (1.8)**	**60.0 (1.8)**	**0.5**
8 wks	**54.9 (2.1)**	**56.8 (2.2)**	**0.5**
3 mths	**58.0 (2.4)**	**58.6 (2.5)**	**0.9**
6 mths	**58.7 (2.9)**	**62.1 (2.9)**	**0.4**
9 mths	**52.2 (3.2)**	**63.2 (3.2)**	**0.01**
12 mths	**56.8 (3.9)**	**58.7 (3.5)**	**0.7**
Overall post baseline			**0.1**

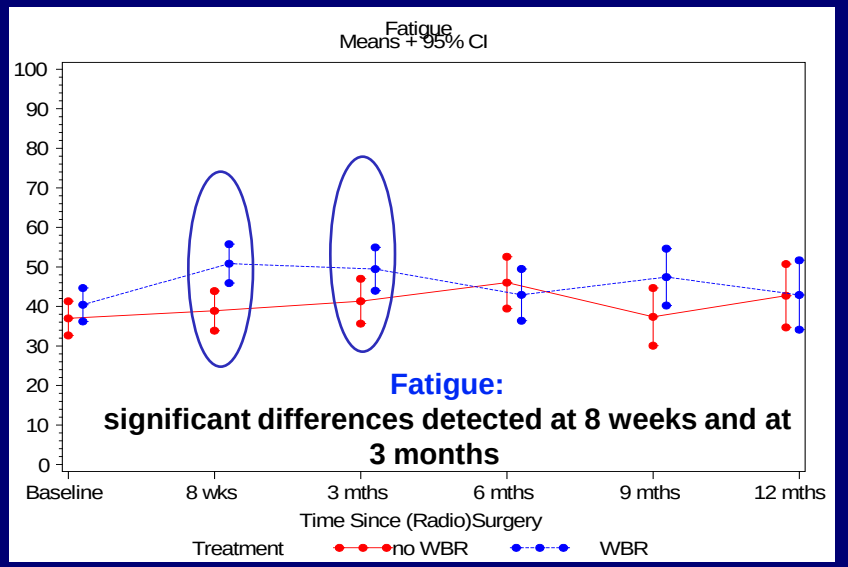


Results: secondary QoL endpoints









Emotional functioning: no differences were detected

NEUROCOGNITIVE FUNCTIONING IN ADULT WHO GRADE II GLIOMAS : IMPACT OF OLD AND NEW TREATMENT MODALITIES

- Surgery : conventional vs awake surgery
- Radiotherapy : large fields vs conformal techniques
- Chemotherapy
- Antiepileptics

Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up

Linda Douw, Martin Klein, Selene S A A Fagel, Josje van den Heuvel, Martin J B Taphoorn, Neil K Aaronson, Tjeerd J Postma, W Peter Vandertop, Jacob J Mooij, Rudolf H Boerman, Guus N Beute, Jasper D Sluimer, Ben J Slotman, Jaap C Reijneveld, Jan J Heimans

Lancet Neurol 2009; 8: 810–18

Published Online August 10, 2009 DOI:10.1016/S1474-4422(09)70204-2

See Reflection and Reaction page 779

Department of Neurology (L Douw MSc, M J B Taphoorn MD, T J Postma MD, J C Reijneveld MD, J J Heimans MD), Department of Medical Psychology (M Klein PhD, S S A A Fagel MSc, J van den Heuvel MSc), Department of Radiology (J D Sluimer MD), Department of Radiation Oncology (B J Slotman MD), and Department of Neurosurgery (W P Vandertop MD), VU University Medical Center, Amsterdam, Netherlands; Department of Neurology, University Medical Center Utrecht, Utrecht, Netherlands (M J B Taphoorn); Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Amsterdam, Netherlands (N K Aaronson PhD); Department of Neurosurgery, University Medical Center Groningen, Netherlands (J J Mooij); Department of Neurology,

Summary

Background Our previous study on cognitive functioning among 195 patients with low-grade glioma (LGG) a mean of 6 years after diagnosis suggested that the tumour itself, rather than the radiotherapy used to treat it, has the most deleterious effect on cognitive functioning; only high fraction dose radiotherapy (>2 Gy) resulted in significant added cognitive deterioration. The present study assesses the radiological and cognitive abnormalities in survivors of LGG at a mean of 12 years after first diagnosis.

Methods Patients who have had stable disease since the first assessment were invited for follow-up cognitive assessment (letter–digit substitution test, concept shifting test, Stroop colour–word test, visual verbal learning test, memory comparison test, and categoric word fluency). Compound scores in six cognitive domains (attention, executive functioning, verbal memory, working memory, psychomotor functioning, and information processing speed) were calculated to detect differences between patients who had radiotherapy and patients who did not have radiotherapy. White-matter hyperintensities and global cortical atrophy were rated on MRI scans.

Findings 65 patients completed neuropsychological follow-up at a mean of 12 years (range 6–28 years). 32 (49%) patients had received radiotherapy (three had fraction doses >2 Gy). The patients who had radiotherapy had more deficits that affected attentional functioning at the second follow-up, regardless of fraction dose, than those who did not have radiotherapy (–1·6 [SD 2·4] *vs* –0·1 [1·3], p=0·003; mean difference 1·4, 95% CI 0·5–2·4). The patients who had radiotherapy also did worse in measures of executive functioning (–2·0 [3·7] *vs* –0·5 [1·2], p=0·03; mean difference 1·5, 0·2–2·9) and information processing speed (–2·0 [3·7] *vs* –0·6 [1·5], p=0·05; mean difference 0·8, 0·009–1·6]) between the two assessments. Furthermore, attentional functioning deteriorated significantly between the first and second assessments in patients who had radiotherapy (p=0·25). In total, 17 (53%) patients who had radiotherapy developed cognitive disabilities deficits in at least five of 18 neuropsychological test parameters compared with four (27%) patients who were radiotherapy naive. White-matter hyperintensities and global cortical atrophy were associated with worse cognitive functioning in several domains.

Interpretation Long-term survivors of LGG who did not have radiotherapy had stable radiological and cognitive status. By contrast, patients with low-grade glioma who received radiotherapy showed a progressive decline in attentional functioning, even those who received fraction doses that are regarded as safe (≤2 Gy). These cognitive deficits are associated with radiological abnormalities. Our results suggest that the risk of long-term cognitive and radiological compromise that is associated with radiotherapy should be considered when treatment is planned.

Funding Kaptein Fonds; Schering Plough.

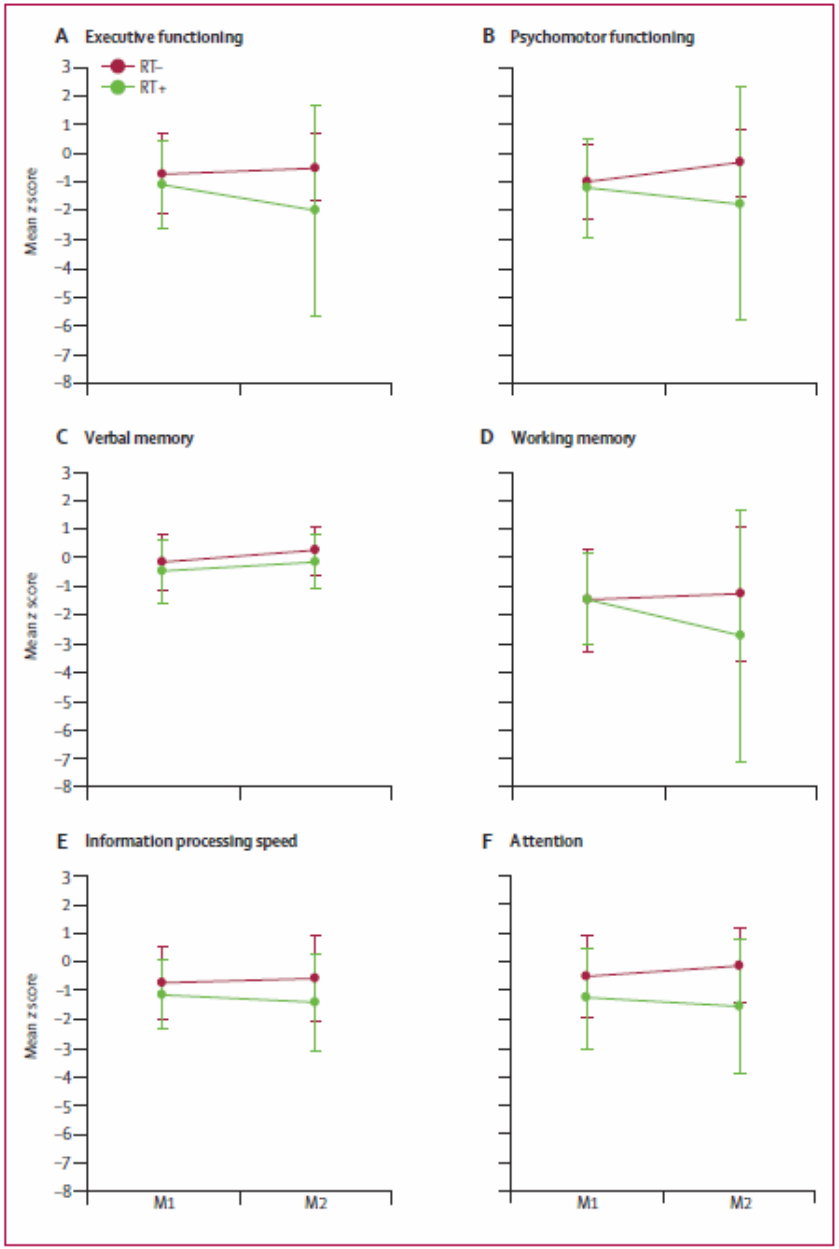


Figure 3: Changes in cognitive functioning in six cognitive domains between the first and second assessments in patients who did or did not have radiotherapy

RT+=patients who had radiotherapy. RT–=patients who did not have radiotherapy. M1=first assessment. M2=second assessment. Bars are SD.

Douw et al, Lancet Neurol 2009

IMPACT OF WBRT ON COGNITIVE FUNCTIONS : GENERAL CONCEPTS IN BRAIN METASTASIS

- A radiation-induced dementia with ataxia and urinary incontinence has been reported in up to 30% of patients by 1 year from receiving unconventional large size fractions of WBRT (6-8.5 Gy) (*De Angelis et al, Neurology, 1989*).

- When using more conventional size fractions (up to 3 or 4 Gy per fraction) the incidence of cognitive deficits in long-term survivors is unknown.

- Long-term survivors frequently develop overtime changes on MRI, such as cortical atrophy, hyperintensity of the white matter in T_2/FLAIR images and hydrocephalus, but the clinical concomitants are poorly known.

WHAT HAVE WE LEARNED FROM CLINICAL TRIALS : EARLY DECLINE AFTER WBRT FOR BRAIN METASTASIS

- Two phase III trials in patients with 1-3 brain metastases comparing SRS + WBRT with SRS alone.
- A significant decline in learning and memory function at 4 months in patients receiving WBRT (*Chang et al, Lancet Oncol 2009*).
- A significant decline at 3 months in immediate recall, delayed recall and verbal fluency (*Brown et al 2015, Irradiance trial, ASCO 2015*).
- Unknown whether this early decline is associated with long-term and/or permanent decline

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 5, pp. 1388–1395, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.03.048

CLINICAL INVESTIGATION **Brain**

NEUROCOGNITIVE FUNCTION OF PATIENTS WITH BRAIN METASTASIS WHO RECEIVED EITHER WHOLE BRAIN RADIOTHERAPY PLUS STEREOTACTIC RADIOSURGERY OR RADIOSURGERY ALONE

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Purpose: To determine how the omission of whole brain radiotherapy (WBRT) affects the neurocognitive function of patients with one to four brain metastases who have been treated with stereotactic radiosurgery (SRS).

Methods and Materials: In a prospective randomized trial between WBRT+SRS and SRS alone for patients with one to four brain metastases, we assessed the neurocognitive function using the Mini-Mental State Examination (MMSE). Of the 132 enrolled patients, MMSE scores were available for 110.

Results: In the baseline MMSE analyses, statistically significant differences were observed for total tumor volume, extent of tumor edema, age, and Karnofsky performance status. Of the 92 patients who underwent the follow-up MMSE, 39 had a baseline MMSE score of ≤27 (17 in the WBRT+SRS group and 22 in the SRS-alone group). Improvements of ≥3 points in the MMSEs of 9 WBRT+SRS patients and 11 SRS-alone patients ($p = 0.85$) were observed. Of the 82 patients with a baseline MMSE score of ≥27 or whose baseline MMSE score was ≤26 but had improved to ≥27 after the initial brain treatment, the 12-, 24-, and 36-month actuarial free rate of the 3-point drop in the MMSE was 76.1%, 68.5%, and 14.7% in the WBRT+SRS group and 59.3%, 51.9%, and 51.9% in the SRS-alone group, respectively. The average duration until deterioration was 16.5 months in the WBRT+SRS group and 7.6 months in the SRS-alone group ($p = 0.05$).

Conclusion: The results of the present study have revealed that, for most brain metastatic patients, control of the brain tumor is the most important factor for stabilizing neurocognitive function. However, the long-term adverse effects of WBRT on neurocognitive function might not be negligible. © 2007 Elsevier Inc.

Brain metastasis, Radiosurgery, Whole brain radiotherapy, Neurocognitive function, Leukoencephalopathy.

NEW APPROACHES TO MINIMIZE COGNITIVE DECLINE FOLLOWING WBRT ("GENTLER WBRT")

- Use of "protective" drugs (memantine) (RTOG 0614)
- Hippocampus avoidance with intensity modulated radiotherapy (RTOG 0933)
- Anti-inflammatory compounds
- Identification of subgroups of patients at higher risk of developing cognitive deficits

Gondi and Mehta, Curr Opin Neurol 2010;
Steeg et al, Nat Rev Cancer 2011

RATIONALE FOR NEUROPROTECTIVE DRUGS IN ASSOCIATION WITH WBRT

- The pathogenesis of the radiation-induced damage could be similar to that of the small vessel disease of vascular dementia: injury of the endothelium → accelerated atherosclerosis → chronic ischemia

↓

To investigate compounds with efficacy in vascular dementia

- Memantine is a non-competitive, low affinity antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is activated by glutamate, and has the potential to block the excessive NMDA stimulation following ischemia.

Neuro-Oncology 15(10):1429–1437, 2013.
doi:10.1093/neuonc/not114
Advance Access publication August 16, 2013

NEURO-ONCOLOGY

Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial

Paul D. Brown, Stephanie Pugh, Nadia N. Laack, Jeffrey S. Wefel, Deepak Khuntia, Christina Meyers, Ali Choucair, Sherry Fox, John H. Suh, David Roberge, Vivek Kavadi, Soren M. Bentzen, Minesh P. Mehta, and Deborah Watkins-Bruner for the Radiation Therapy Oncology Group (RTOG)

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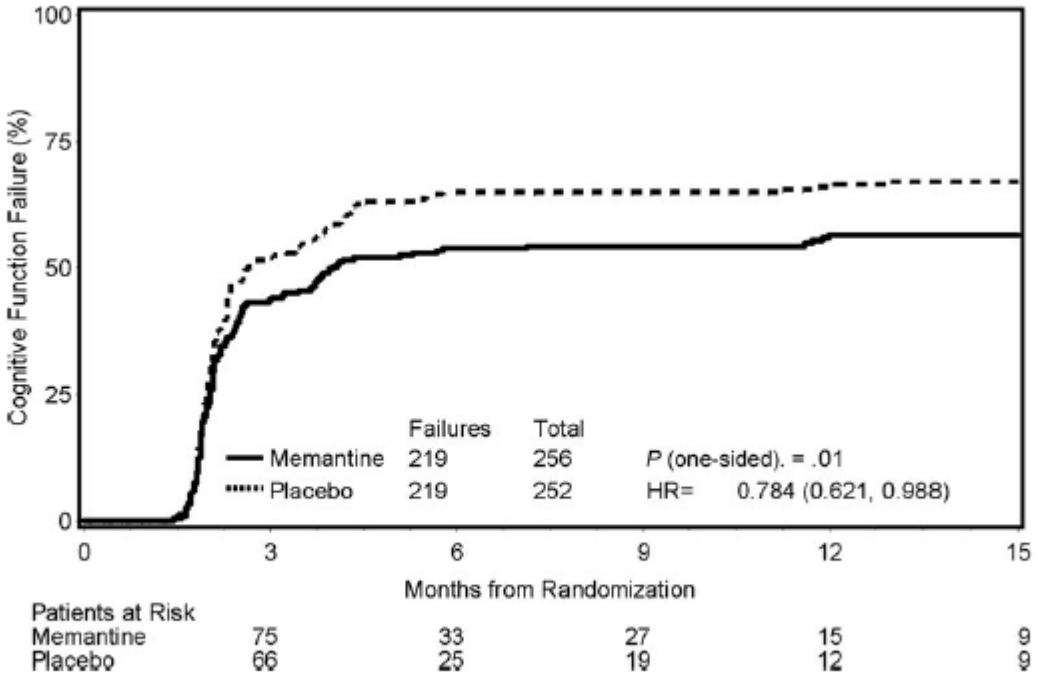


Fig. 2. Cumulative incidence of cognitive function failure according to treatment arm.

Brown et al, Neuro Oncol, 2013

RATIONALE FOR HIPPOCAMPAL AVOIDANCE IN ASSOCIATION WITH WBRT

- Hippocampus has a central role in learning and memory functions, especially in the episodic memory (process of forming new memories of events or facts).

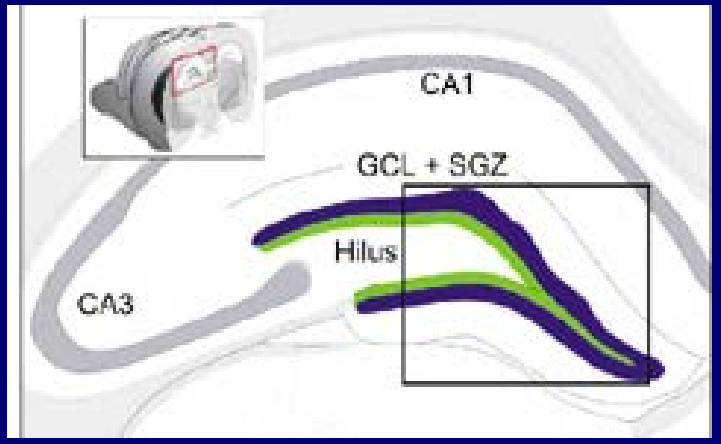
- Neuronal stem cells in the subgranular zone of the hippocampus are responsible for maintaining neurogenesis, which is critical for preserving memory functions.

- Irradiation of the hippocampus in patients receiving radiation therapy for nasopharingeal, maxillary, pituitary and skull base tumors is associated with impairment in the learning and memory domain.

Gondi et al, JCO 2010; Gibson and Monje, Curr Opin Oncol 2012

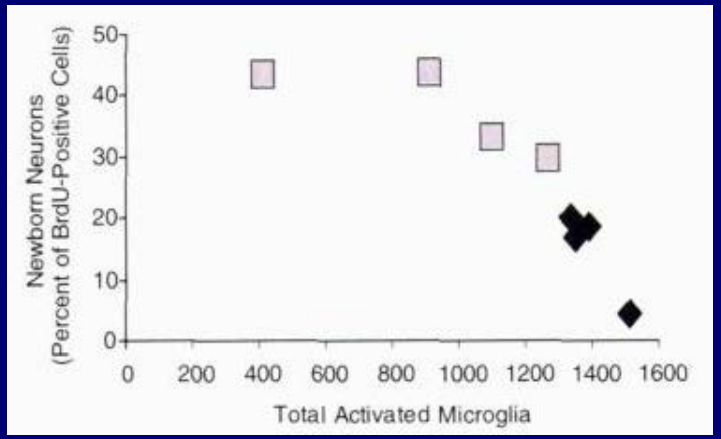
Hippocampal Injury from Cranial RT

- Preclinical evidence
  - 97% reduction in hippocampal neurogenesis 2 months after cranial RT
  - Up-regulation of microglial differentiation and activation



Blue: GCL,

Green: SGZ



Black: Cranial RT

White: Control

Monje et al, Nat Med 2002; Gondi et al, JCO 2010.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial

Vinai Gondi, Stephanie L. Pugh, Wolfgang A. Tome, Chip Caine, Ben Corn, Andrew Kanner, Howard Rowley, Vijayananda Kundapur, Albert DeNittis, Jeffrey N. Greenspoon, Andre A. Konski, Glenn S. Bauman, Sunjay Shah, Wenyin Shi, Merideth Wendland, Lisa Kachnic, and Minesh P. Mehta

See accompanying editorial doi: 10.1200/JCO.2014.58.4367

Author affiliations appear at the end of this article.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Clinical trial information: NCT01227954.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

ABSTRACT

Purpose
Hippocampal neural stem-cell injury during whole-brain radiotherapy (WBRT) may play a role in memory decline. Intensity-modulated radiotherapy can be used to avoid conformally the hippocampal neural stem-cell compartment during WBRT (HA-WBRT). RTOG 0933 was a single-arm phase II study of HA-WBRT for brain metastases with prespecified comparison with a historical control of patients treated with WBRT without hippocampal avoidance.

Patients and Methods
Eligible adult patients with brain metastases received HA-WBRT to 30 Gy in 10 fractions. Standardized cognitive function and quality-of-life (QOL) assessments were performed at baseline and 2, 4, and 6 months. The primary end point was the Hopkins Verbal Learning Test–Revised Delayed Recall (HVLT-R DR) at 4 months. The historical control demonstrated a 30% mean relative decline in HVLT-R DR from baseline to 4 months. To detect a mean relative decline $\leq$ 15% in HVLT-R DR after HA-WBRT, 51 analyzable patients were required to ensure 80% statistical power with $\alpha = 0.05$.

Results
Of 113 patients accrued from March 2011 through November 2012, 42 patients were analyzable at 4 months. Mean relative decline in HVLT-R DR from baseline to 4 months was 7.0% (95% CI, −4.7% to 18.7%), significantly lower in comparison with the historical control ($P < .001$). No decline in QOL scores was observed. Two grade 3 toxicities and no grade 4 to 5 toxicities were reported. Median survival was 6.8 months.

Conclusion
Conformal avoidance of the hippocampus during WBRT is associated with preservation of memory and QOL as compared with historical series.

J Clin Oncol 32.

MRG-CC 101 TRIAL IN BRAIN METASTASES

- Phase III trial comparing WBRT (30x10) + memantine vs WBRT (30x10) + memantine + hippocampal avoidance
- Primary endpoint : time to cognitive deterioration.

RATIONALE FOR NON-STEROIDAL ANTI-INFLAMMATORY THERAPY

- The radiation-induced blockade of hippocampal neurogenesis is not attributable to a direct depletion of stem cell populations, but instead of an inflammatory perturbation of the normal microenvironment that support neurogenesis

↓

Microglia activation and increase of proinflammatory cytokines

↓

Inhibition of neuronal differentiation of stem cells

- The inflammatory cascade can be mitigated in rodent models by nonsteroidal anti-inflammatory drugs (pioglitazone, fenofibrate, angiotensin type 1 receptor antagonists) or other proneurogenic strategies (aerobic exercise).

Monje et al, Science 2003; Ramanan et al, Int J Radiat Oncol Biol Phys 2009

HOW TO TREAT RADIATION-ASSOCIATED NEUROCOGNITIVE SYMPTOMS ?

- Modafinil and fluoxetine as psychostimulants.
- Animal studies have shown that irradiation of the brain adversely affects cholinergic neurons → rationale fro the use of cholinergic neurotransmitter modulators.
- Donepezil is a drug that reversibly inhibits acethylcholine esterase, thus enhancing the cholinergic transmission.
- Donepezil increases cerebral perfusion in brain regions critical to cognitive processing.

Howard et al, N Engl J Med, 2012

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Donepezil for Irradiated Brain Tumor Survivors: A Phase III Randomized Placebo-Controlled Clinical Trial

Stephen R. Rapp, L. Doug Case, Ann Peiffer, Michelle M. Naughton, Michael D. Chan, Volker W. Stieber, Dennis F. Moore Jr, Steven C. Falchuk, James V. Piephoff, William J. Edenfield, Jeffrey K. Giguere, Monica E. Loghin, and Edward G. Shaw

See accompanying editorial on page 1633

Stephen R. Rapp, L. Doug Case, Ann Peiffer, Michelle M. Naughton, Michael D. Chan, and Edward G. Shaw, Wake Forest School of Medicine and Wake Forest Community Clinical Oncology Program Research Base; Volker W. Stieber, Novant Health System, Winston-Salem, NC; Dennis F. Moore Jr, Wichita Community Clinical Oncology Program, Wichita, KS; Steven C. Falchuk, Christiana Care Health Services, Newark, DE; James V. Piephoff, Mercy Hospital, St Louis, MO; William J. Edenfield and Jeffrey K. Giguere, Cancer Center of Carolinas, Greenville, SC; and Monica E. Loghin, University of Texas MD Anderson Cancer Center, Houston, TX.

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Supported by Grant No. 5R01NR009675 from the National Institute of Nursing Research, National Institutes of Health; by Grant No. 2U10CA081851 from the National Cancer Institute Division of Cancer Prevention to the Wake Forest Community Clinical Oncology Program Research Base; and by Eisai.

Presented in part at 49th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 31-June 4, 2013.

ABSTRACT

Purpose
Neurotoxic effects of brain irradiation include cognitive impairment in 50% to 90% of patients. Prior studies have suggested that donepezil, a neurotransmitter modulator, may improve cognitive function.

Patients and Methods
A total of 198 adult brain tumor survivors ≥ 6 months after partial- or whole-brain irradiation were randomly assigned to receive a single daily dose (5 mg for 6 weeks, 10 mg for 18 weeks) of donepezil or placebo. A cognitive test battery assessing memory, attention, language, visuomotor, verbal fluency, and executive functions was administered before random assignment and at 12 and 24 weeks. A cognitive composite score (primary outcome) and individual cognitive domains were evaluated.

Results
Of this mostly middle-age, married, non-Hispanic white sample, 66% had primary brain tumors, 27% had brain metastases, and 8% underwent prophylactic cranial irradiation. After 24 weeks of treatment, the composite scores did not differ significantly between groups ($P = .48$); however, significant differences favoring donepezil were observed for memory (recognition, $P = .027$; discrimination, $P = .007$) and motor speed and dexterity ($P = .016$). Significant interactions between pretreatment cognitive function and treatment were found for cognitive composite ($P = .01$), immediate recall ($P = .05$), delayed recall ($P = .004$), attention ($P = .01$), visuomotor skills ($P = .02$), and motor speed and dexterity ($P < .001$), with the benefits of donepezil greater for those who were more cognitively impaired before study treatment.

Conclusion
Treatment with donepezil did not significantly improve the overall composite score, but it did result in modest improvements in several cognitive functions, especially among patients with greater pretreatment impairments.

J Clin Oncol 33:1653-1659.

NEW APPROACHES TO AVOID COGNITIVE DECLINE FOLLOWING WBRT

- Stereotactic radiosurgery to the resection cavity
- Targeted agents to treat asymptomatic small brain metastases

RISK OF RADIONECROSIS FOLLOWING SRS TO THE RESECTION CAVITY

- The reference value is 2.6% following WBRT (*EORTC study, Kocher et al, JCO 2011*).
- The values following SRS range between 9% and 17.5% in recent papers (*Minniti et al, J Neurooncol 2013; Brennan et al, Cell 2014; Ling et al, Neurosurgery 2015*).
- More often the reported values are based on both biopsy and MRI : thus, the distinction between true radiation necrosis and pseudoprogression is unknown.

RISK OF RADIONECROSIS FOLLOWING SRS TO THE RESECTION CAVITY

- Not always the clinical relevance of the so called “radionecrosis” is detailed.
- Some papers do not mention toxicity or simply state that “no toxicity was observed”.
- The actuarial risk could increase over time: 7% at 1 year ; 16% at 2 years (*Minniti at al, J Neurooncol 2013*).

RISKS OF NEUROLOGICAL COMPLICATIONS OTHER THAN RADIONECROSIS FOLLOWING SRS TO THE RESECTION CAVITY

- Seizures, headache and hemorrhage as acute complications in individual patients (*Minniti et al, J Neurooncol 2013*).
- Increased T2 signal changes on MRI around the resection cavity (radiation-related edema) in 10.8% of patients (*Mathieu et al, Neurosurgery 2008*).
- A steroid dependency can occur, and both frequency and duration have not been recorded.
- Overall, the incidence of both radionecrosis and other neurological complications is underestimated.

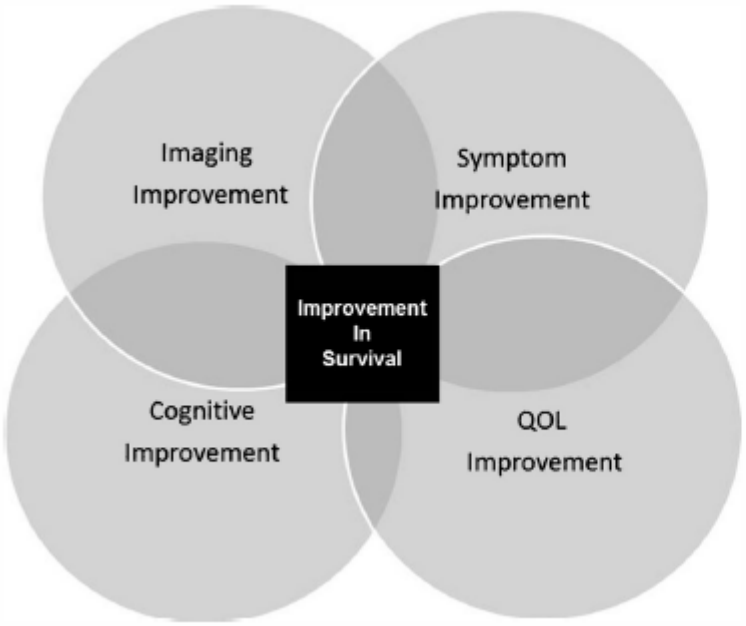
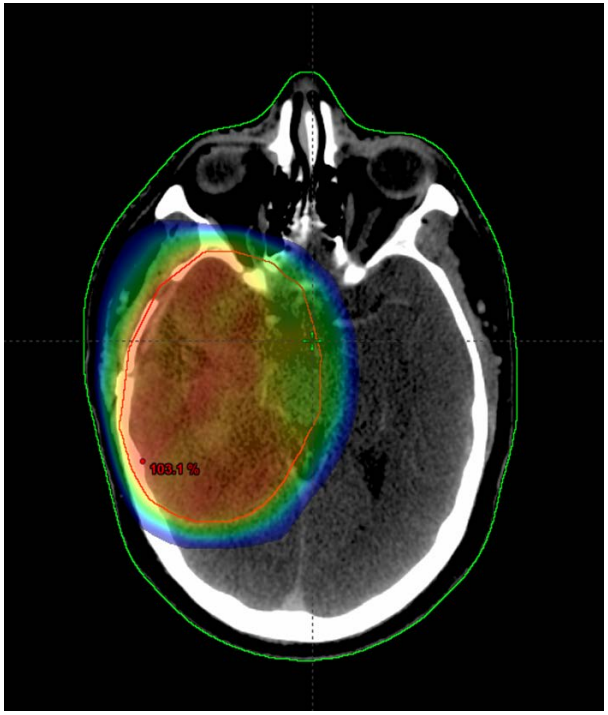
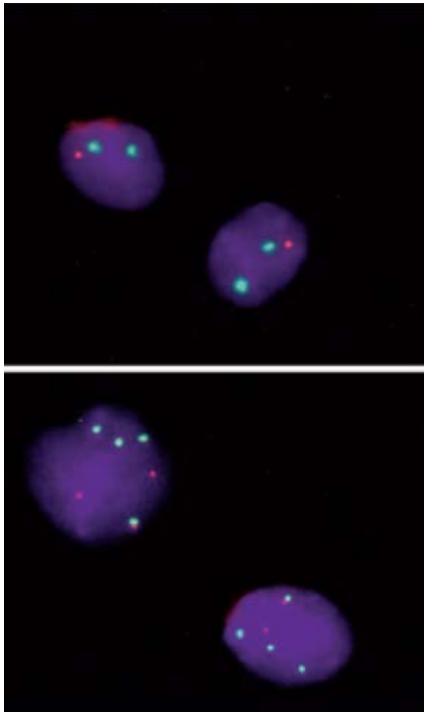
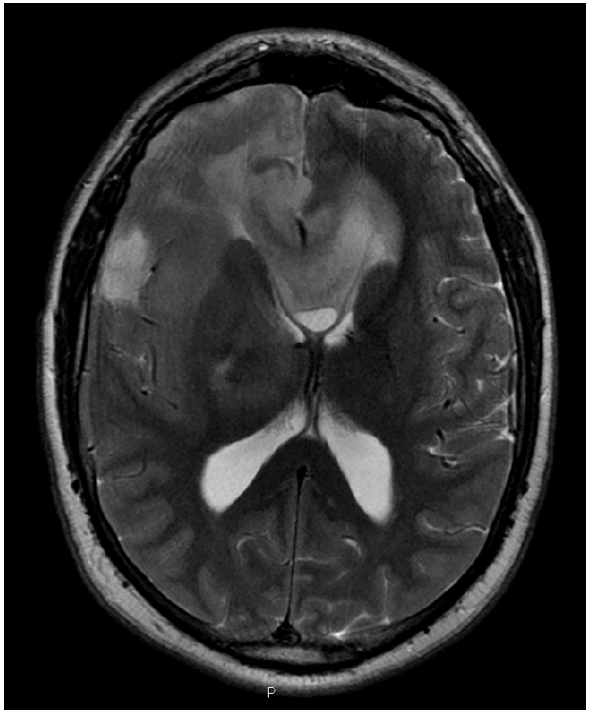


Figure 1. Net clinical benefit components used in RTOG0525 and RTOG0825.

Armstrong and Gilbert, Curr Treat Options Oncol, 2014



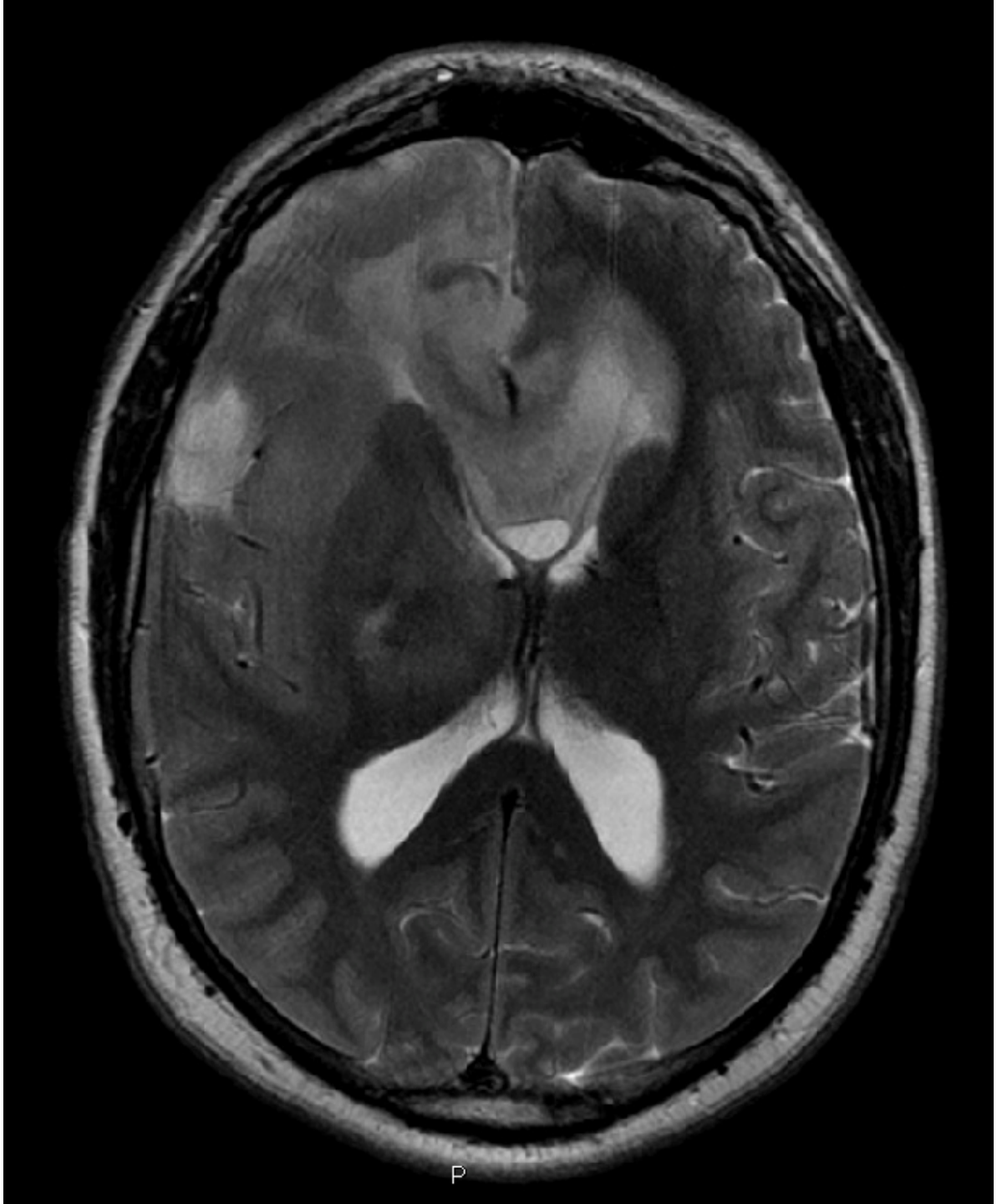



Management of low grade astrocytoma

Anthony Chalmers

Chair of Clinical Oncology

University of Glasgow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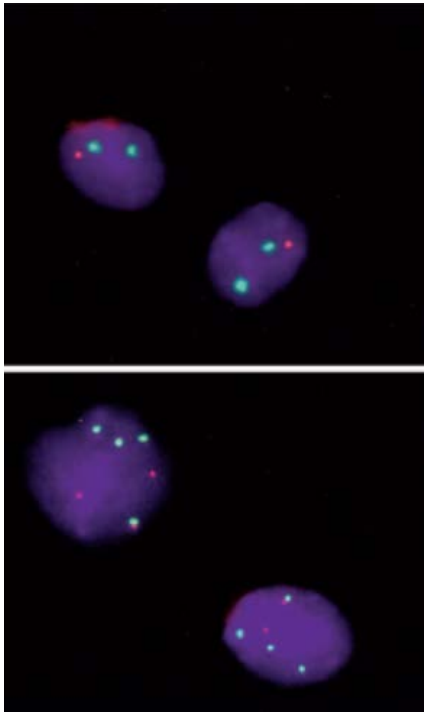


Patients with grade 2 astrocytomas require treatment if:

A. Age <40

B. Incomplete neurosurgical resection

C. Presented with seizures

D. Tumour ≥6 cm diameter

E. WHO performance status ≥2

Prognostic Factors for Survival in Adult Patients With Cerebral Low-Grade Glioma

By Francesco Pignatti, Martin van den Bent, Desmond Curran, Channa Debruyne, Richard Sylvester, Patrick Therasse, Denes Áfra, Philippe Cornu, Michel Bolla, Charles Vecht, and Abul B.M.F. Karim for the European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group and Radiotherapy Cooperative Group

Table 4. Prognostic Factors for Survival in Adults Patients with Cerebral LGG: Multivariate Model Construction and Validation

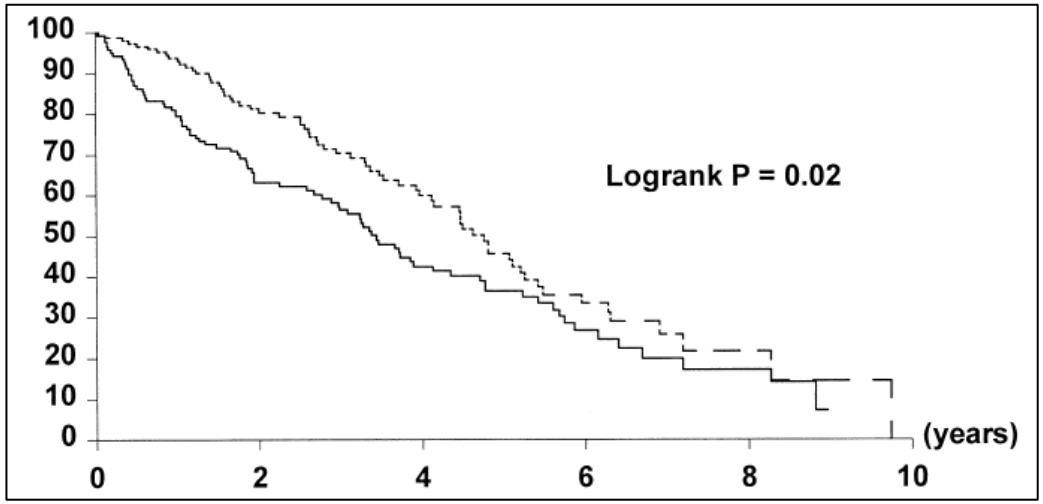
	Construction Set (n = 281)			Validation Set (n = 253)		
Prognostic Factor (reference level)	HR	95% CI	*P*	HR	95% CI	*P*
Age at randomization						
< 40 years	1			1		
≥ 40 years	1.26	1.06-1.48	.0077	1.43	1.17-1.74	.0005
Largest diameter of the tumor						
< 6 cm	1			1		
≥ 6 cm	1.39	1.16-1.66	.0003	1.23	1.02-1.50	.0350
Tumor crossing midline						
No	1			1		
Yes	1.37	1.15-1.63	.0005	1.43	1.11-1.84	.0051
Histology type						
Oligo/mixed	1			1		
Astrocytoma	1.30	1.08-1.56	.0050	1.46	1.18-1.82	.0006
Neurologic deficit						
Absent	1			1		
Present	1.35	1.13-1.62	.0013	1.29	1.02-1.63	.0310

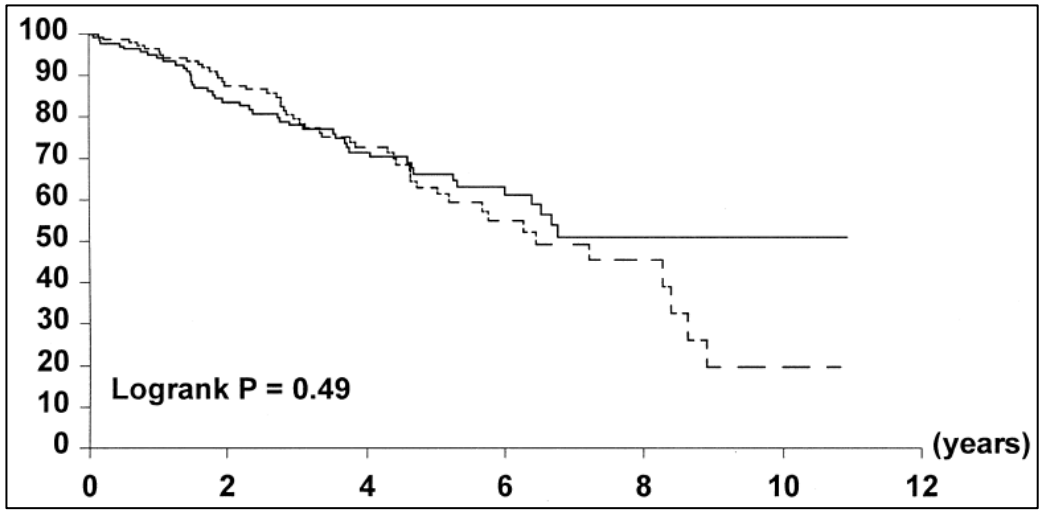
Consructed on 322 patients
Validated on 288 patients

J Clin Oncol 20:2076-2084. © 2002

CLINICAL INVESTIGATION Brain

RANDOMIZED TRIAL ON THE EFFICACY OF RADIOTHERAPY FOR CEREBRAL LOW-GRADE GLIOMA IN THE ADULT: EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER STUDY 22845 WITH THE MEDICAL RESEARCH COUNCIL STUDY BRO4: AN INTERIM ANALYSIS





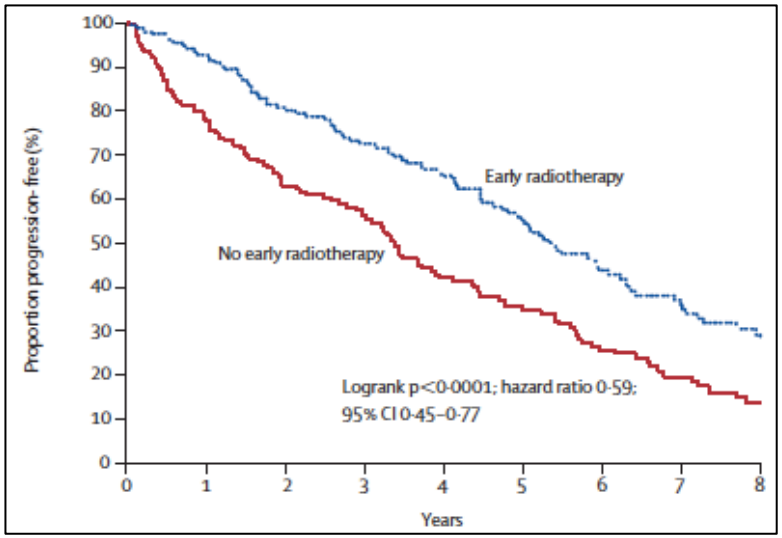
Immediate v. delayed radiotherapy

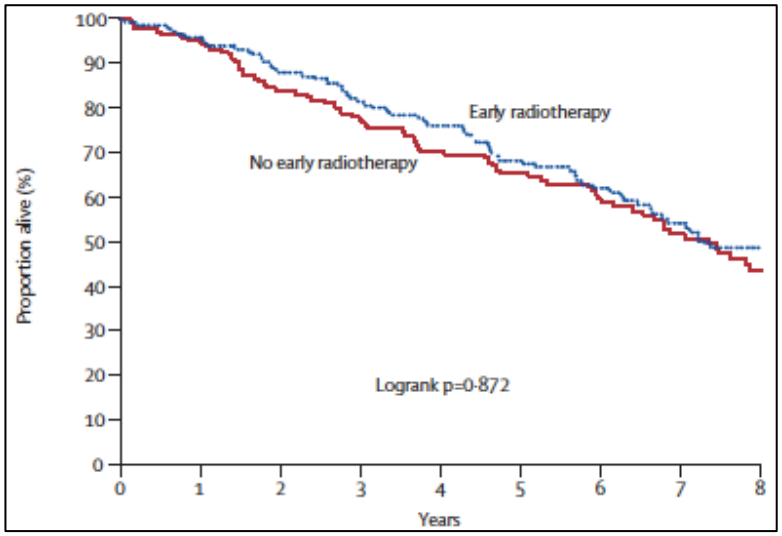
54 Gy in 30f

Karim *et al*, IJROBP 2002

Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial

M J van den Bent, D Afra, O de Witte, M Ben Hassel, S Schraub, K Hoang-Xuan, P-O Malmström, L Collette, M Piérart, R Mirimanoff, A B M F Karim, for the EORTC Radiotherapy and Brain Tumor Groups and the UK Medical Research Council





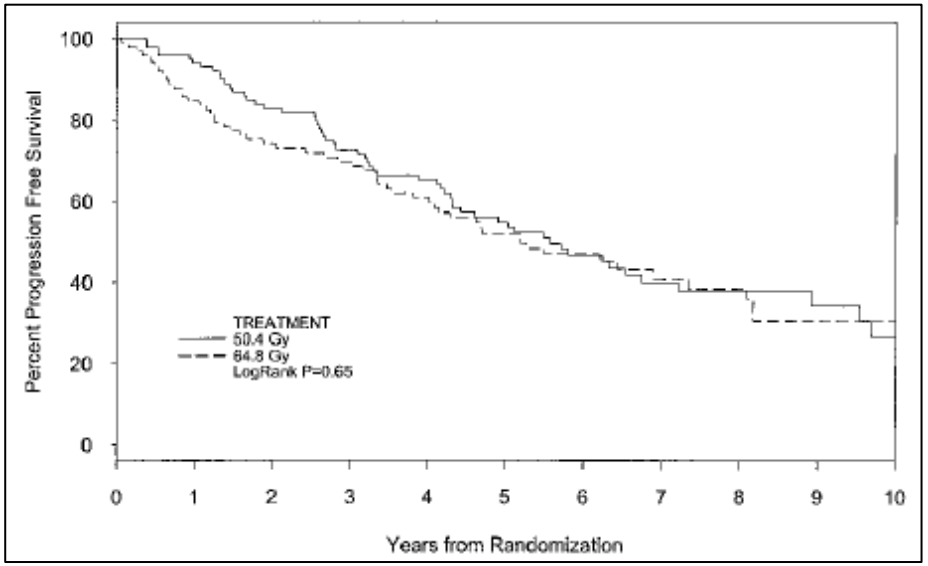
Immediate v. delayed radiotherapy

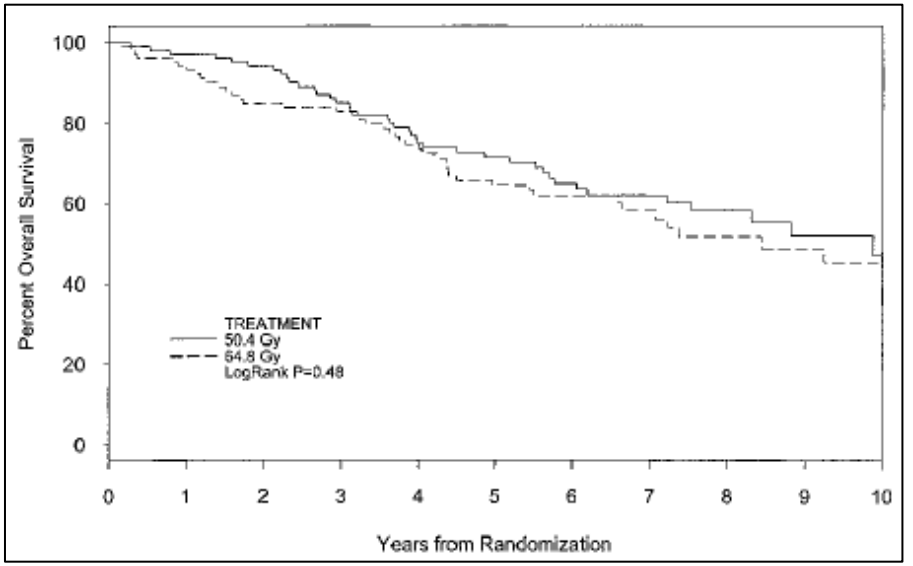
54 Gy in 30f

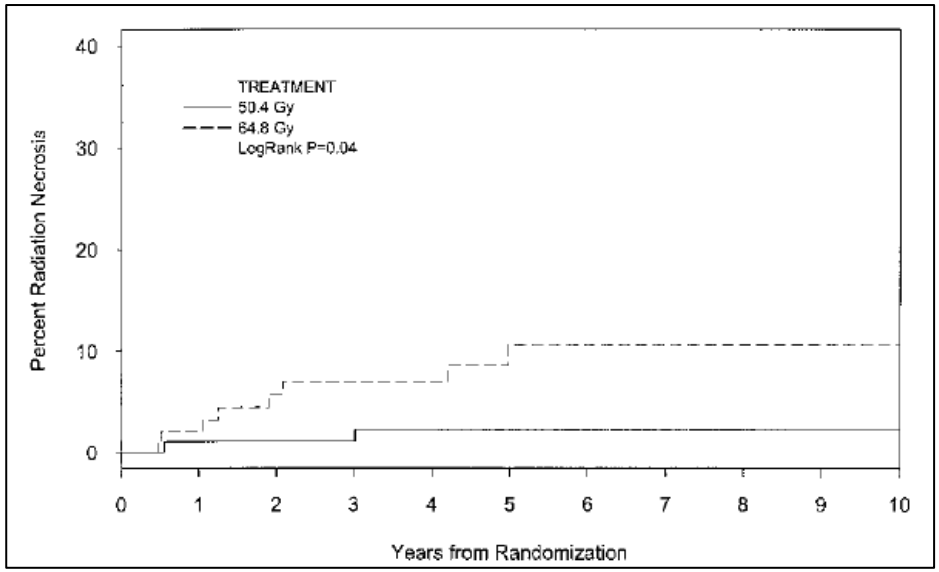
Van den Bent *et al*, Lancet 2005

50.4 Gy in 28f v. 64.8 Gy in 36f; 203 patients with low grade glioma

Shaw *et al*, JCO 2002







Radiation necrosis
Grade ≥3

J Neurosurg 78:909–914, 1993

A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas: a Southwest Oncology Group study

HARMON J. EYRE, M.D., JOHN J. CROWLEY, PH.D., JEANNETTE J. TOWNSEND, M.D., JAMES R. ELTRINGHAM, M.D., ROBERT A. MORANTZ, M.D., SUSAN F. SCHULMAN, B.A., JOSEPH M. QUAGLIANA, M.D., AND MUHYI AL-SARRAF, M.D.

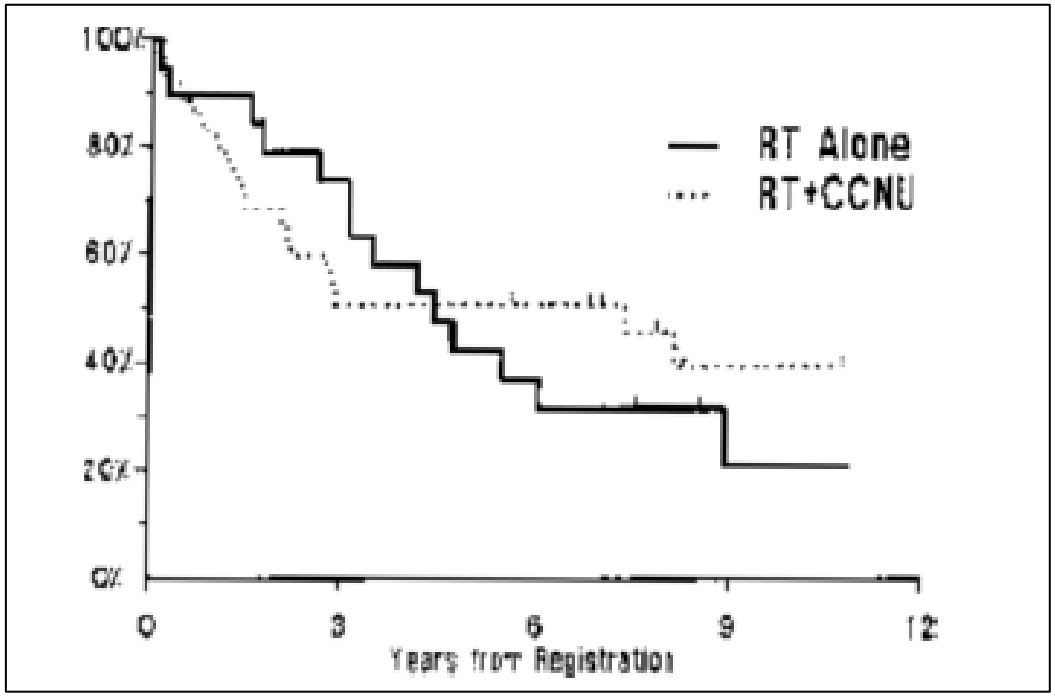


TABLE 2

*Response rate by treatment arm in 54 patients**

Response	Radiotherapy		Radiotherapy + CCNU	
	No.	Percent	No.	Percent
complete remission	11	58	7	20
partial remission	4	21	12	34
stable/no change	3	16	11	32
increasing disease	1	5	5	14
total cases	19		35	

VOLUME 30 · NUMBER 25 · SEPTEMBER 1 2012

JOURNAL OF CLINICAL ONCOLOGY

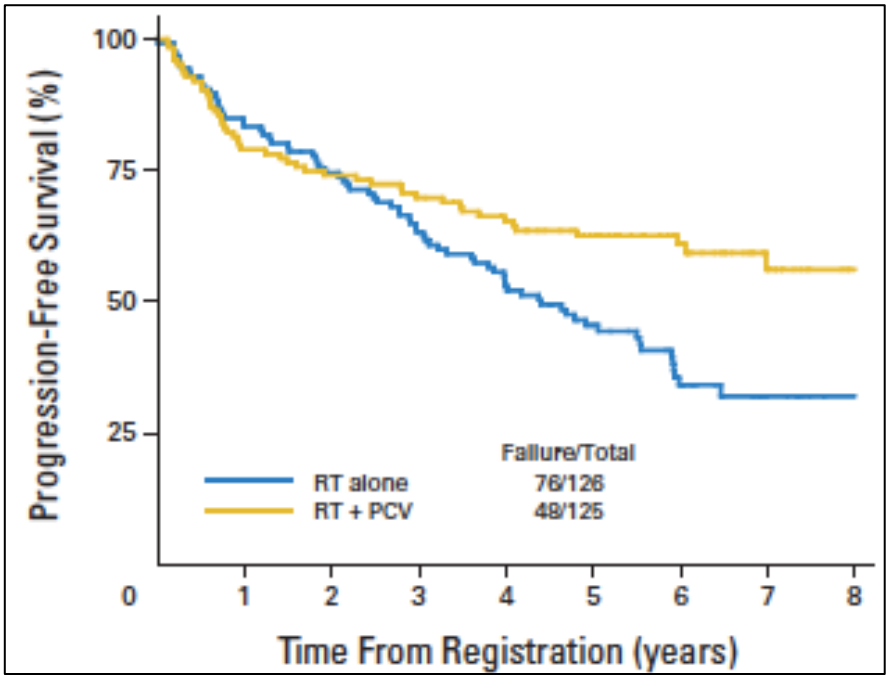
ORIGINAL REPORT

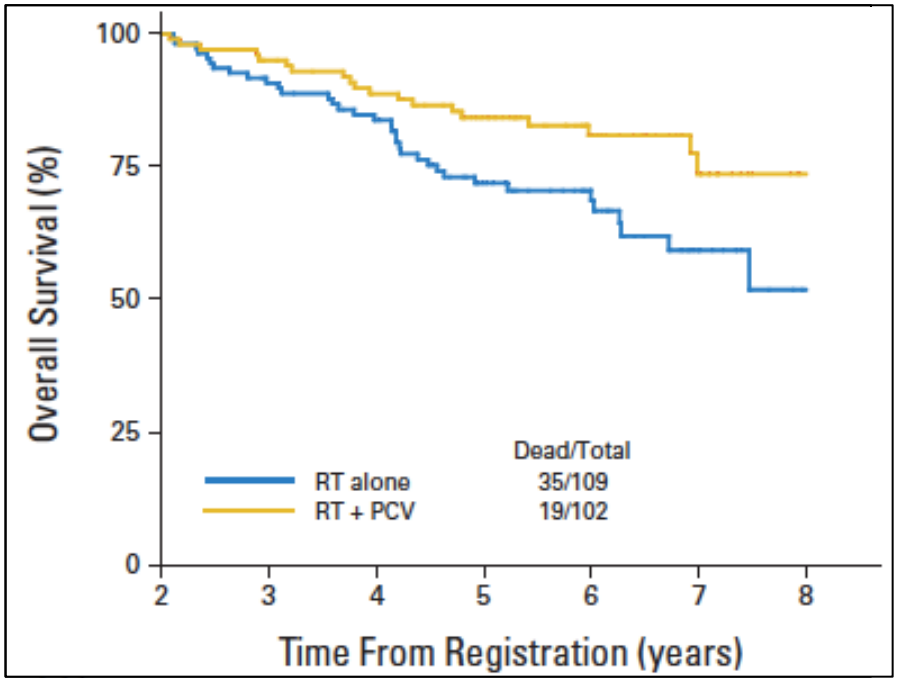
Randomized Trial of Radiation Therapy Plus Procarbazine, Lomustine, and Vincristine Chemotherapy for Supratentorial Adult Low-Grade Glioma: Initial Results of RTOG 9802

Edward G. Shaw, Meihua Wang, Stephen W. Coons, David G. Brachman, Jan C. Buckner, Keith J. Stelzer, Geoffrey R. Barger, Paul D. Brown, Mark R. Gilbert, and Minesh P. Mehta

Table 1. Patient Characteristics

Characteristic	RT Arm No.	RT Arm %	RT + PCV Arm No.	RT + PCV Arm %
Age, years				
Median	40		41	
Range	22-79		18-82	
Median tumor size, cm	5.0		4.7	
KPS 90-100		74		75
Gross total resection		9		11
Histology				
Astrocytoma		23		29
Oligodendroglioma		45		40
Mixed astrocytoma/oligodendroglioma		32		31
Enhancement: yes		60		65





So how should we be treating grade 2 gliomas WITHOUT 1p19q codeletion?

For patients with grade 2 astrocytoma WITHOUT 1p19q codeletion who DO require treatment, I would recommend:

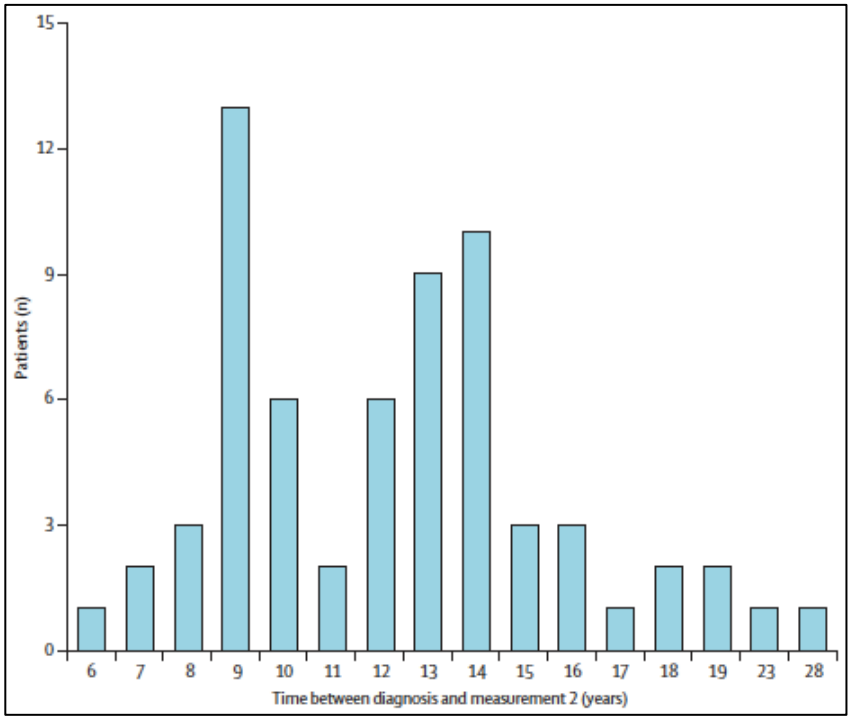
A. Radiotherapy alone
B. Radiotherapy with concomitant TMZ
C. Radiotherapy with concomitant and adjuvant TMZ
D. Radiotherapy with adjuvant PCV
E. PCV followed by radiotherapy

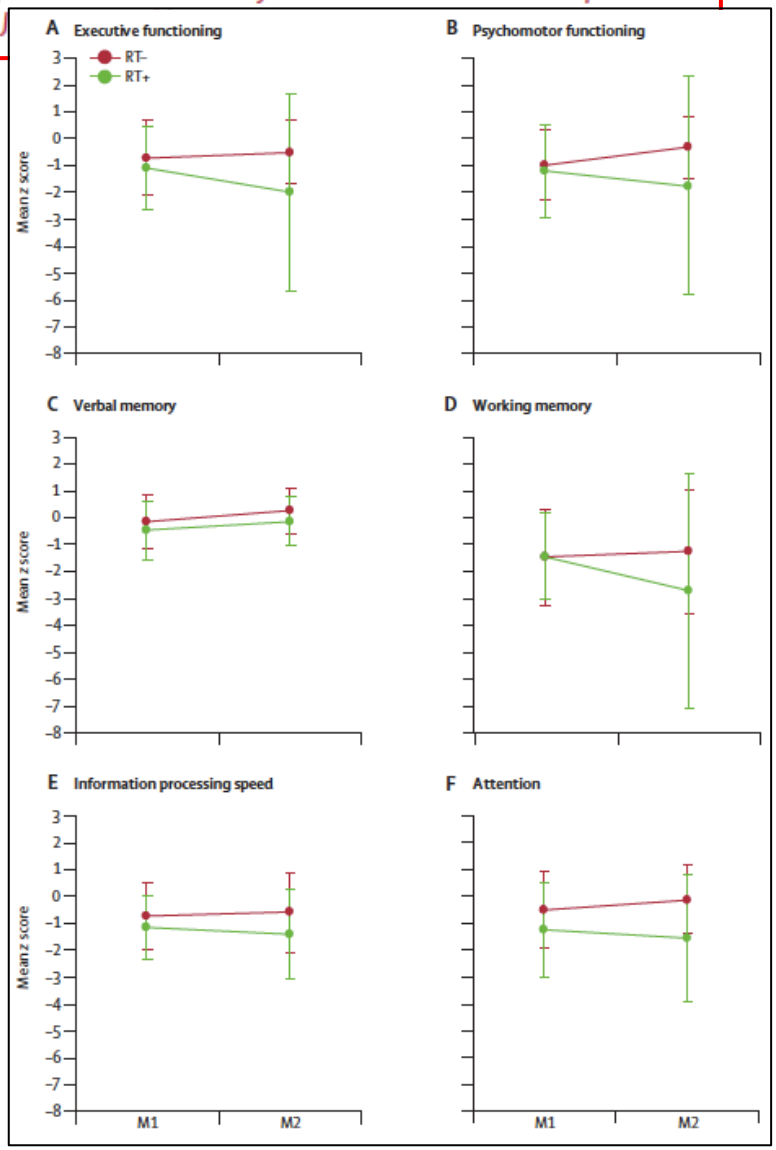
For patients with grade 2 astrocytoma WITHOUT 1p19q codeletion who require radiotherapy, I would recommend:

A. 45 Gy in 25 fractions
B. 50.4 Gy in 28 fractions
C. 54 Gy in 28 fractions
D. 60 Gy in 30 fractions

Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up

Linda Douw, Martin Klein, Selene S A A Fagel, Josje van den Heuvel, Martin J B Taphoorn, Neil K Aaronson, Tjeerd J Postma, W Peter Vandertop, Jacob J Mooij, Rudolf H Boerman, Guus N Beute, Jasper D Sluimer, Ben J Slotman, J





VOLUME 33 · NUMBER 9 · MARCH 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Health-Related Quality of Life in Stable, Long-Term Survivors of Low-Grade Glioma

Florien W. Boele, Linda Douw, Jaap C. Reijneveld, Rianne Robben, Martin J.B. Taphoorn, Neil K. Aaronson, Jan J. Heimans, and Martin Klein

Table 4. Demographic and Clinical Characteristics of the Patients in Whom Meaningful Change Was Either Present or Absent

	Patients With Stable HRQOL (n = 14)		Patients With Declining HRQOL Only (n = 25)		Patients With Improving HRQOL Only (n = 17)		Patients With Both Declining and Improving HRQOL (n = 9)	
Characteristic	No.	%	No.	%	No.	%	No.	%
Surgery (resection)	9	64.3	16	64	12	70.6	4	44.4
Radiotherapy (yes)	6	42.9	14	56	7	41.2	5	55.6

Need more and better studies on impact of radiotherapy on QoL and neurocognitive function

European Journal of Neurology 2010, **17:** 1124–1133 doi:10.1111/j.1468-1331.2010.03151.x

EFNS GUIDELINES/CME ARTICLE

Guidelines on management of low-grade gliomas: report of an EFNS–EANO* Task Force

R. Soffietti[a], B.G. Baumert[b], L. Bello[c], A. von Deimling[d], H. Duffau[e], M. Frénay[f], W. Grisold[g], R. Grant[h], F. Graus[i], K. Hoang-Xuan[j], M. Klein[k], B. Melin[l], J. Rees[m], T. Siegal[n], A. Smits[o], R. Stupp[p] and W. Wick[q]

- For patients with unfavorable prognostic factors (older age, incomplete or no resection, existing neurological symptoms), an adjuvant treatment is indicated at any time (Level B), and this is more commonly RT (good practice point).
- A total RT dose of 50.4–54 Gy in fractions of 1.8 Gy represents the current standard of care (Level A). Modern RT techniques (conformal dose delivery or intensity modulated techniques) should preferably be used (Level B).
- Younger patients (< 40 years of age) with (nearly) complete resection and tumors with an oligodendroglial component have a more favorable prognosis and can be observed after surgery (Level B), but close follow-up is needed (good practice point).

- Chemotherapy is an option for patients with recurrence after surgery and radiation therapy (Level B).
- Chemotherapy is an option as initial treatment for patients with large residual tumors after surgery or unresectable tumors to delay the risk of late neurotoxicity from large-field RT, especially when 1p/19q loss is present (Level B).

Management of 1p/19q co-deleted tumors

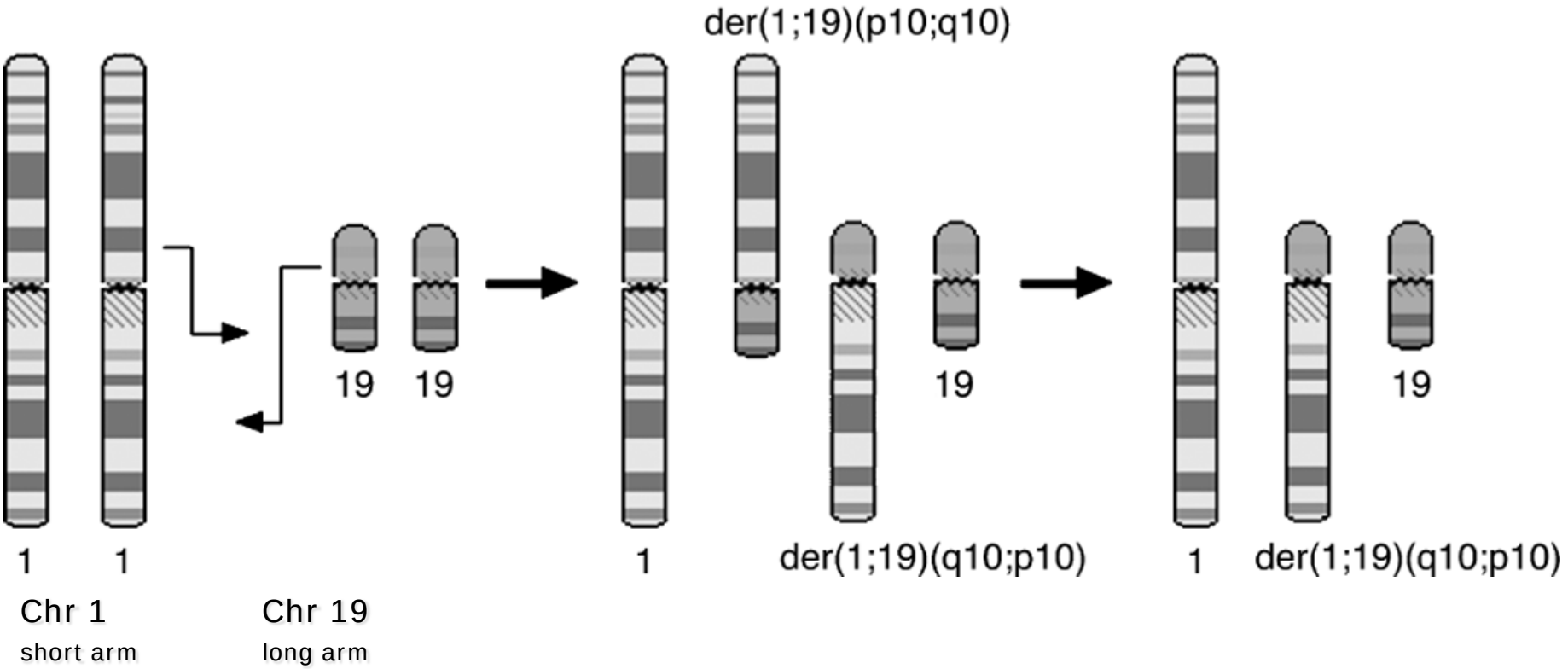
ESTRO teaching course
Management of brain tumours

Patrick Roth

Department of Neurology and Brain Tumor Center
University Hospital Zurich

1p/19q deletion

1p 19q deletion due to early unbalanced translocation t(1;19)(q10;p10)



Griffin et al. J Neuropathol Exp Neurol 2006

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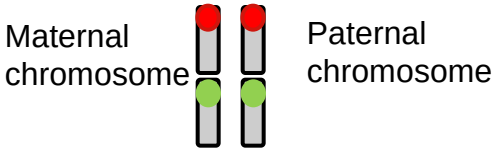
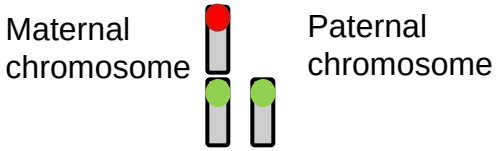
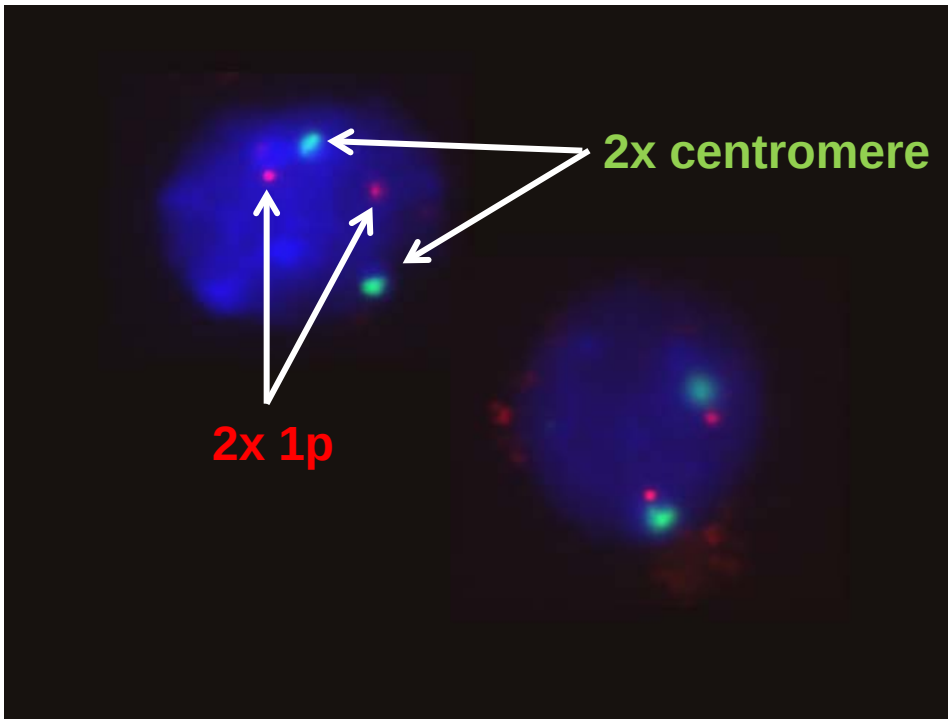
FISH (fluorescent in situ hybridization)

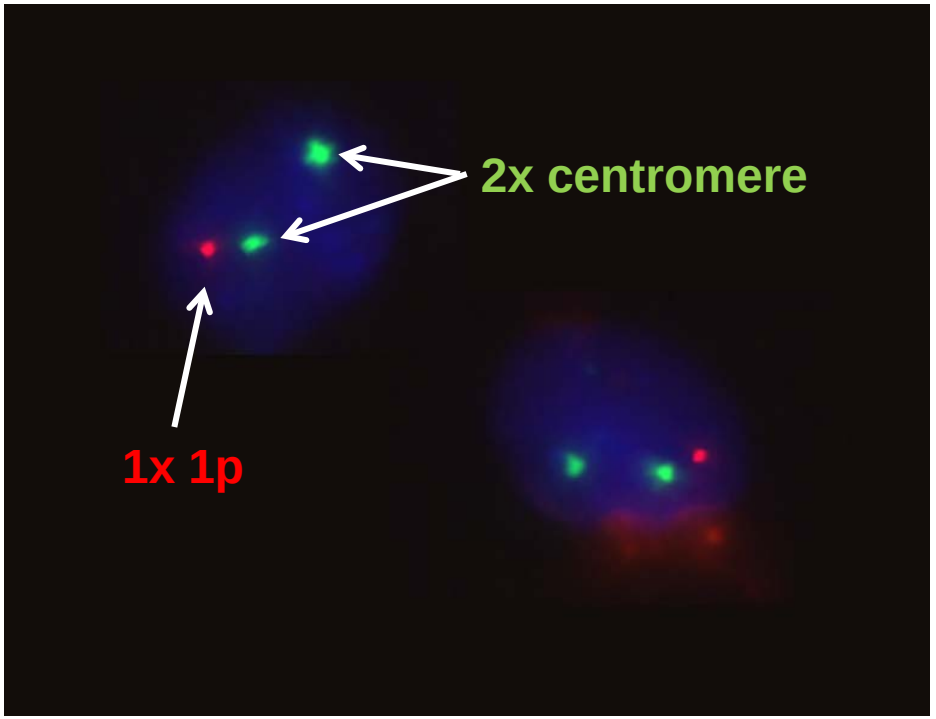




1p non-deleted



1p deletion



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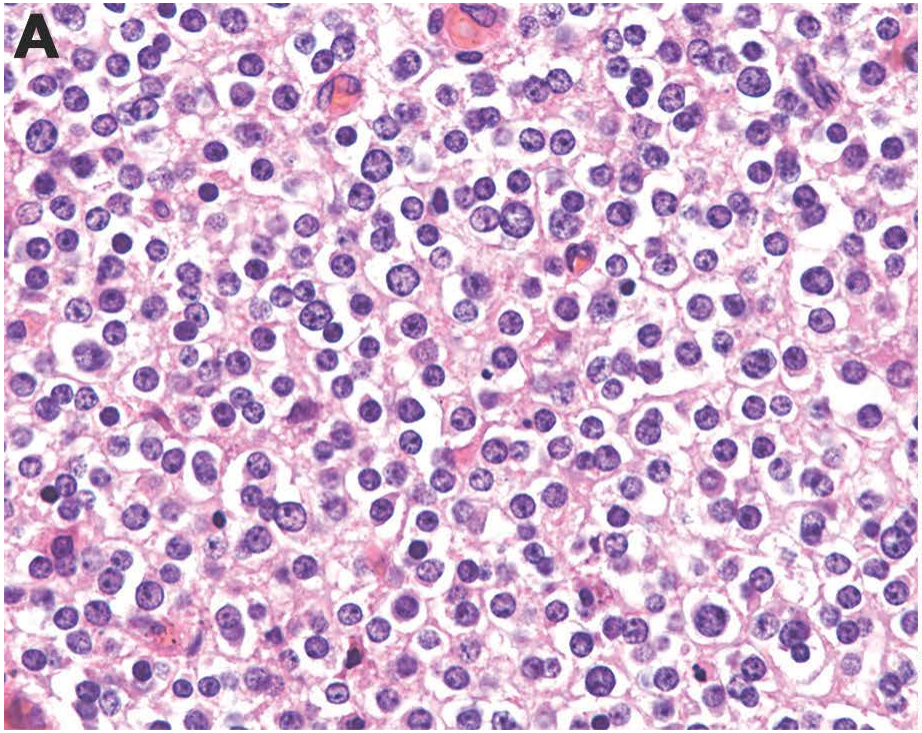
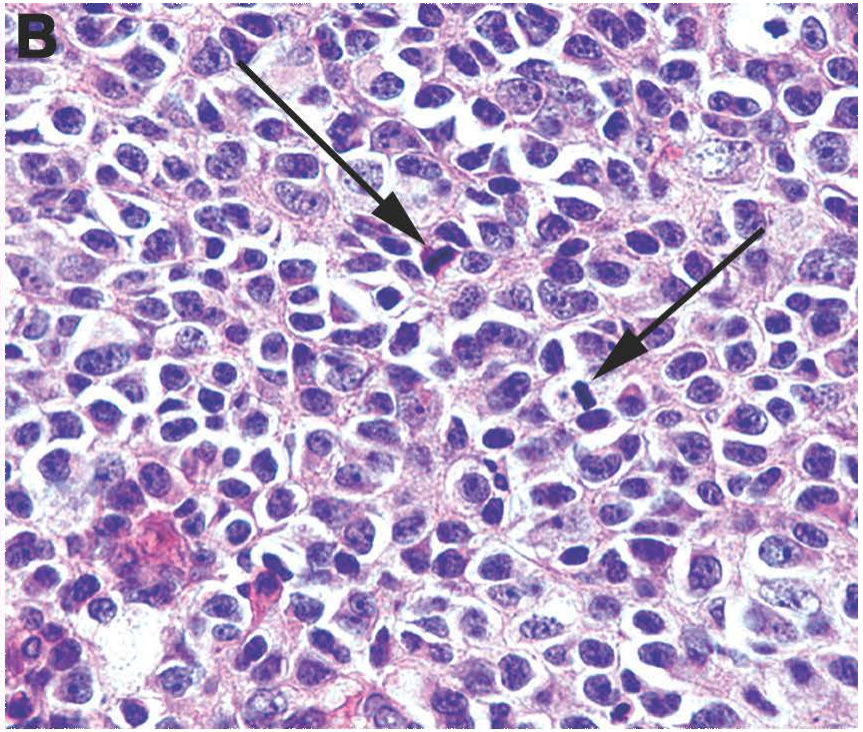
Where do we find 1p/19q co-deletion?



Oligodendroglioma (grade II)



Anaplastic oligodendroglioma (grade III)

1p/19q and IDH status

Table 1. Summary of Genetic and Clinical Characteristics of Brain Tumors in the Study.*

Tumor Classification†	No. of Tumors Analyzed	Median Age of Patient‡	Male Sex	Median Survival	Tumors with *IDH* Mutations			Median Age of Patient		Tumors with Other Alterations§				
					IDH1	*IDH2*	Combined	Mutated *IDH*	Wild-Type *IDH*	*TP53*	1p and 19q	*PTEN*	*EGFR*	*CDKN2A* or *CDKN2B*
		yr	%	mo	no.		%	yr				%		
Astrocytic tumors														
Pilocytic astrocytoma (grade I)	21	5	48	ND	0	0	0	ND	5	0	NA	0	0	NA
Subependymal giant-cell astrocytoma (grade I)	2	16	100	ND	0	NA	0	ND	ND	NA	NA	NA	NA	NA
Diffuse astrocytoma (grade II)	30	34	53	132	25	2	90	35	5	74	0	0	0	0
Pleomorphic xanthoastrocytoma (grade II)	7	11	14	44	1	NA	14	20	11	NA	NA	NA	0	NA
Anaplastic astrocytoma (grade III)	52	38	67	51	36	2	73	34	56	65	10	9	2	9
Secondary glioblastoma (grade IV)¶	13	33	70	16	11	0	85	32	62	62	NA	0	0	20
Primary adult glioblastoma (grade IV)	123	59	60	15	6	0	5	32	59	23	4	23	38	42
Primary pediatric glioblastoma (grade IV)	15	5	60	8	0	0	0	ND	5	33	NA	NA	NA	20
Oligodendroglial tumors														
Oligodendroglioma (grade II)	51	37	63	135	41	2	84	37	13.5	16	60	0	0	4
Anaplastic oligodendroglioma (grade III)	36	45	64	84	31	3	94	45	ND	10	84	0	0	14
Oligoastrocytic tumors														
Oligoastrocytoma (grade II)	3	38	67	ND	3	NA	100	38	ND	33	NA	0	0	0
Anaplastic oligoastrocytoma (grade III)	7	30	57	ND	7	NA	100	30	ND	71	50	0	0	0
Ependymoma (grade II)	30	5.5	45	ND	0	0	0	ND	5.5	0	NA	0	NA	NA
Medulloblastoma (grade IV)	55	7	65	27	0	0	0	ND	7	NA	NA	NA	NA	NA

* Of the indicated tumors, 6 secondary and 60 primary glioblastomas were previously described in Parsons et al.[16] Copy-number changes in *EGFR*, *CDKN2A*, and *CDKN2B* were determined by quantitative real-time polymerase chain reaction. For such assays, copy-number levels of more than 6 or less than 0.3 were considered amplifications or losses, respectively. NA denotes not analyzed, and ND not determined because of limited sample size and status of data censoring.
† Tumors were graded according to histopathological and clinical criteria established by the World Health Organization.
‡ Patient age refers to age at which the study sample was obtained.
§ Alterations included mutations in *TP53* and *PTEN*, loss of heterozygosity in 1p and 19q, amplification in *EGFR*, and deletion in *CDKN2A* or *CDKN2B*.
¶ Secondary glioblastoma designates a tumor that was resected more than 1 year after a previous diagnosis of a lower-grade glioma (grade II or grade III).

Yan et al, NEJM 2009

1p/19q deletion and response to chemotherapy

Specific Genetic Predictors of Chemotherapeutic Response and Survival in Patients With Anaplastic Oligodendrogliomas

J. Gregory Cairncross, Keisuke Ueki, Magdelena C. Zlatescu, David K. Lisle, Dianne M. Finkelstein, Robert R. Hammond, Jonathan S. Silver, Paul C. Stark, David R. Macdonald, Yasushi Ino, David A. Ramsay, David N. Louis

Table 2. Univariate genetic predictors of response and risk of death in patients with anaplastic oligodendrogliomas*

	Chemotherapeutic response		Risk of death		
Variable	Response rate, No./total No. (%)	*P*	RR	*P*	95% CI
Chromosome 1p					
Allelic loss	24/24 (100)	**<.001**	0.059	**<.0001**	0.018–0.199
Intact	3/12 (25)				
Chromosome 19q					
Allelic loss	23/28 (82)	.126	0.250	**.0116**	0.085–0.734
Intact	3/6 (50)				
Chromosomes 1p and 19q					
Allelic loss of both	22/22 (100)	**<.001**	0.121	**<.0001**	0.044–0.331
No allelic loss of both	4/13 (31)				
Chromosome 10q					
Allelic loss	5/8 (63)	.126	1.817	.2549	0.650–5.081
Intact	23/26 (88)				
CDKN2A gene					
Deleted	5/8 (63)	.363	4.901	**.0009**	1.924–12.487
Intact	24/30 (80)				
TP53 gene					
Mutant	3/6 (50)	.123	2.586	.0724	0.917–7.293
Wild-type	28/34 (82)				

*Risk of death was calculated as RR (relative risk) and was determined for all Cox models. Corresponding *P* values are shown with significant values in boldface type. All *P* values are two-sided. CI = confidence interval.

J Nat Cancer Inst 1998

1p/19q co-deletion: what is the therapeutic impact?

Two trials – one result:

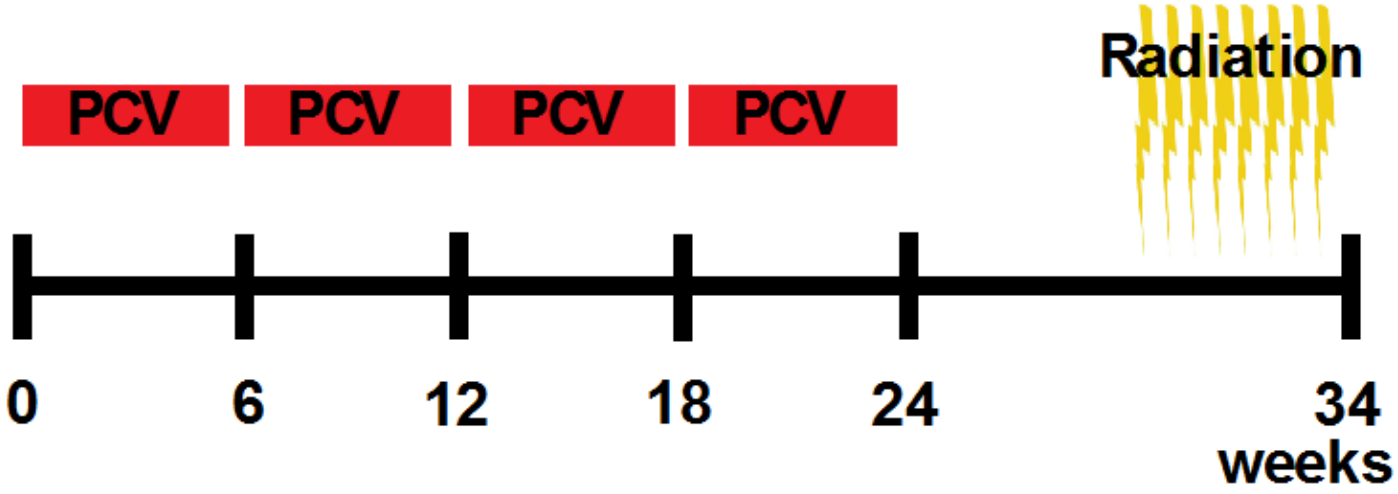
Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC Brain Tumor Group Study 26951.

van den Bent et al., J Clin Oncol 2013

Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402.

Cairncross et al., J Clin Oncol 2013

RTOG 9402



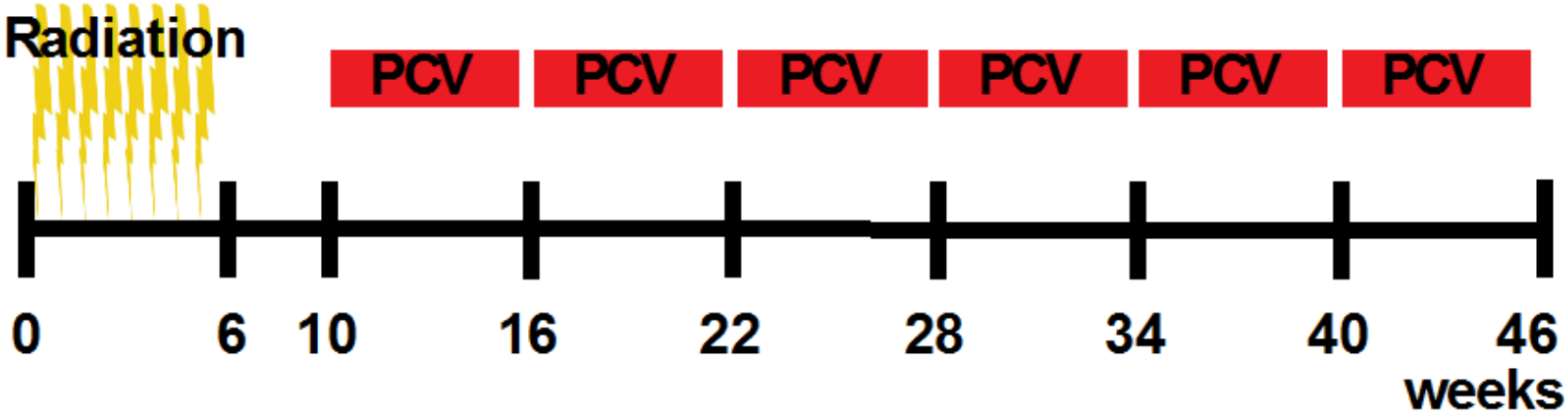
AO or AOA, age >=18, KPS >=60

Intensive PCV followed by immediate involved-field RT (experimental arm) or RT alone (control arm).

RT: 59.4 Gy in 33 fractions (1.8 Gy each), 5 days a week. Patients randomly assigned to PCV plus RT began RT within 6 weeks of the last chemotherapy dose.

Cairncross et al., JCO 2013

EORTC 26951



AO or AOA, age 16-70, ECOG 0-2

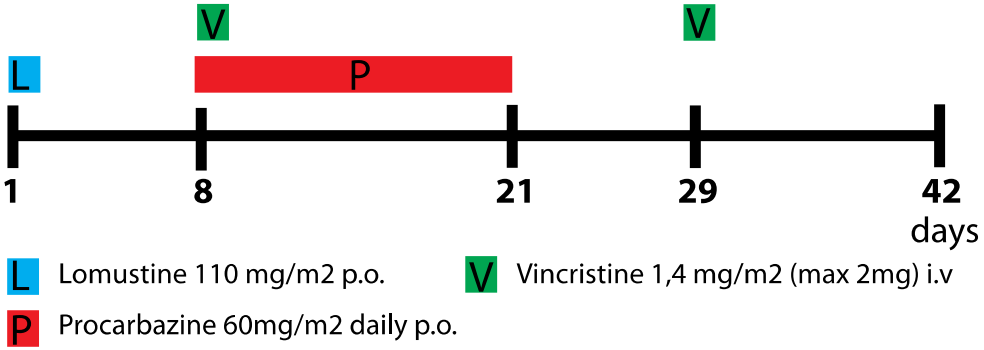
RT was to begin within 6 weeks from surgery and consisted of a dose of 45 Gy to be delivered to the planning target volume (PTV-1). Thereafter, a boost of 14.4 Gy (up to a cumulative dose of 59.4 Gy) was delivered to PTV-2

PCV chemotherapy consisted of up to six cycles of standard PCV chemotherapy and had to start within 4 weeks after the end of RT.

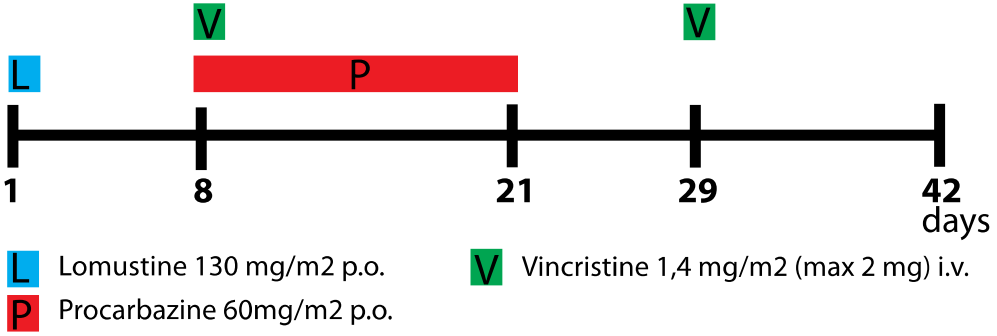
Van den Bent et al., JCO 2013

PCV regimens EORTC 26951 vs RTOG 9402

EORTC 26951
Standard PCV



RTOG 9402
Intensive PCV



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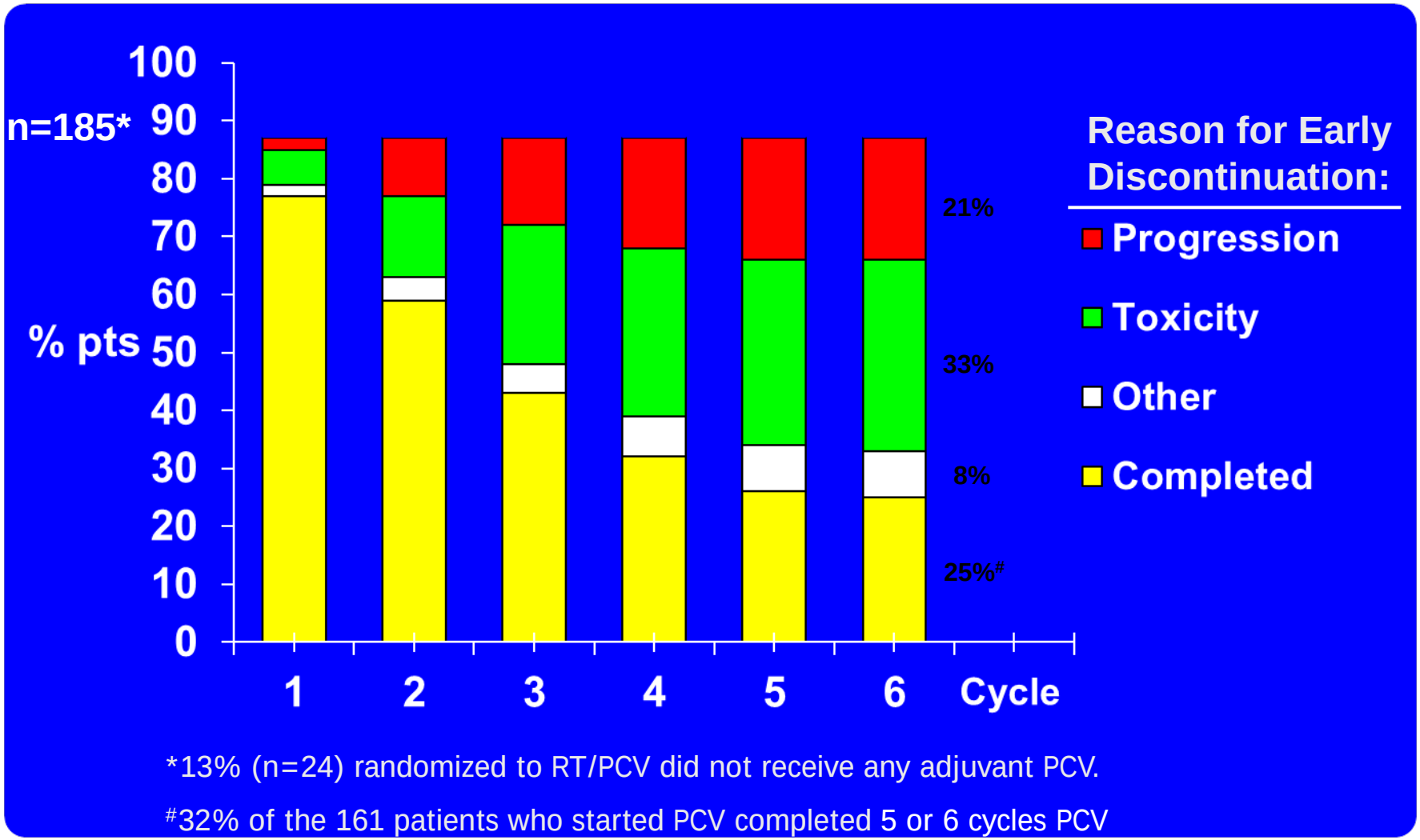
PCV toxicities EORTC 26951 vs RTOG 9402

Toxicities (Grade 3/4)	EORTC 26951	RTOG 9402
Hematologic, any	46%	56%
Neutropenia	32%	42%
Thrombocytopenia	21%	37%
Anemia	7%	5%
Peripheral neuropathy	2%	8%
Nausea/vomiting	6%	8%
Toxicity leading to abbreviation of therapy	38%	20%

Reasons for discontinuation of PCV in EORTC 26951



*13% (n=24) randomized to RT/PCV did not receive any adjuvant PCV.

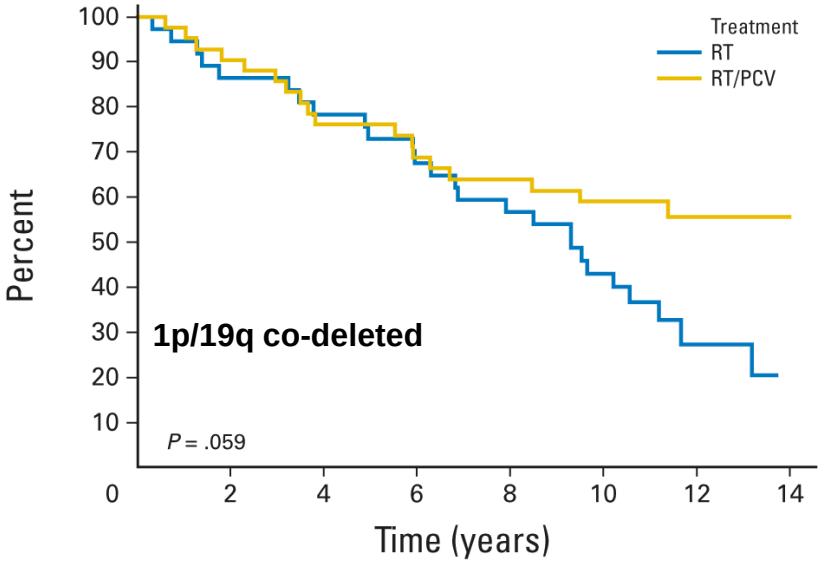
#32% of the 161 patients who started PCV completed 5 or 6 cycles PCV

van den Bent, ASCO 2012

OS in patients with 1p/19q co-deleted tumors

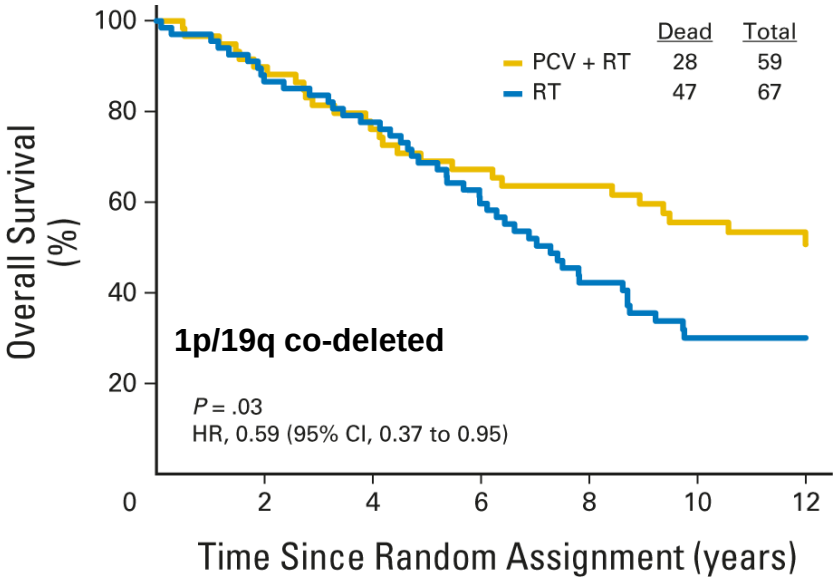
Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

Martin J. van den Bent, Alba A. Brandes, Martin J.B. Taphoorn, Johan M. Kros, Mathilde C.M. Kouwenhoven, Jean-Yves Delattre, Hans J.J.A. Bernsen, Marc Frenay, Cees C. Tijssen, Wolfgang Grisold, László Sipos, Roelien H. Enting, Pim J. French, Winand N.M. Dinjens, Charles J. Vecht, Anouk Allgeier, Denis Lacombe, Thierry Gorlia, and Khê Hoang-Xuan



Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402

Gregory Cairncross, Meihua Wang, Edward Shaw, Robert Jenkins, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperriere, Walter Curran, and Minesh Mehta



=> RT plus PCV as standard of care (?)

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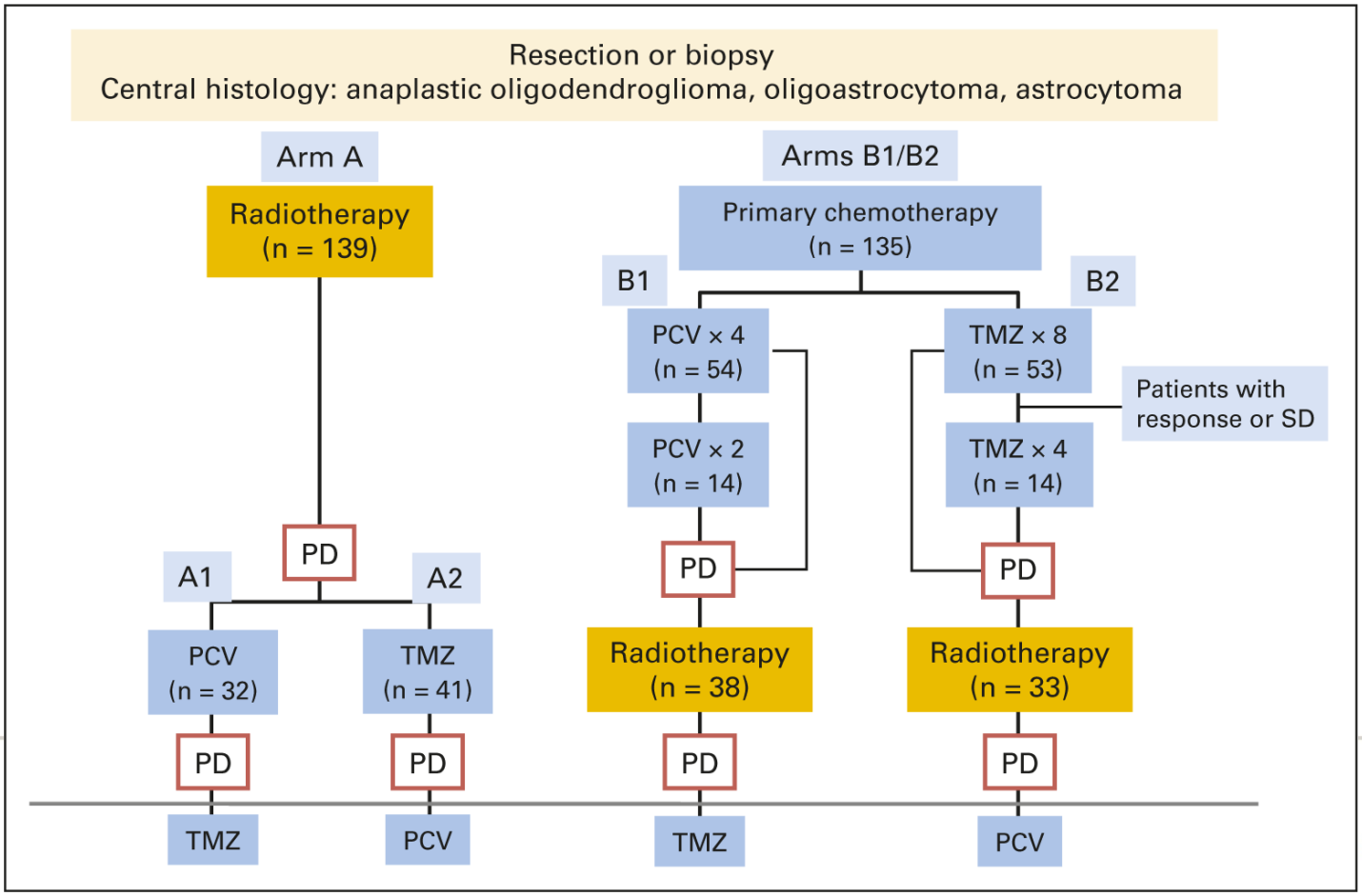
Can we avoid RT and use chemotherapy alone?

NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide

Wolfgang Wick, Christian Hartmann, Corinna Engel, Mandy Stoffels, Jörg Felsberg, Florian Stockhammer, Michael C. Sabel, Susanne Koeppen, Ralf Ketter, Richard Meyermann, Marion Rapp, Christof Meisner, Rolf D. Kortmann, Torsten Pietsch, Otmar D. Wiestler, Ulrike Ernemann, Michael Bamberg, Guido Reifenberger, Andreas von Deimling, and Michael Weller

See accompanying editorial on page 5861 and article on page 5881



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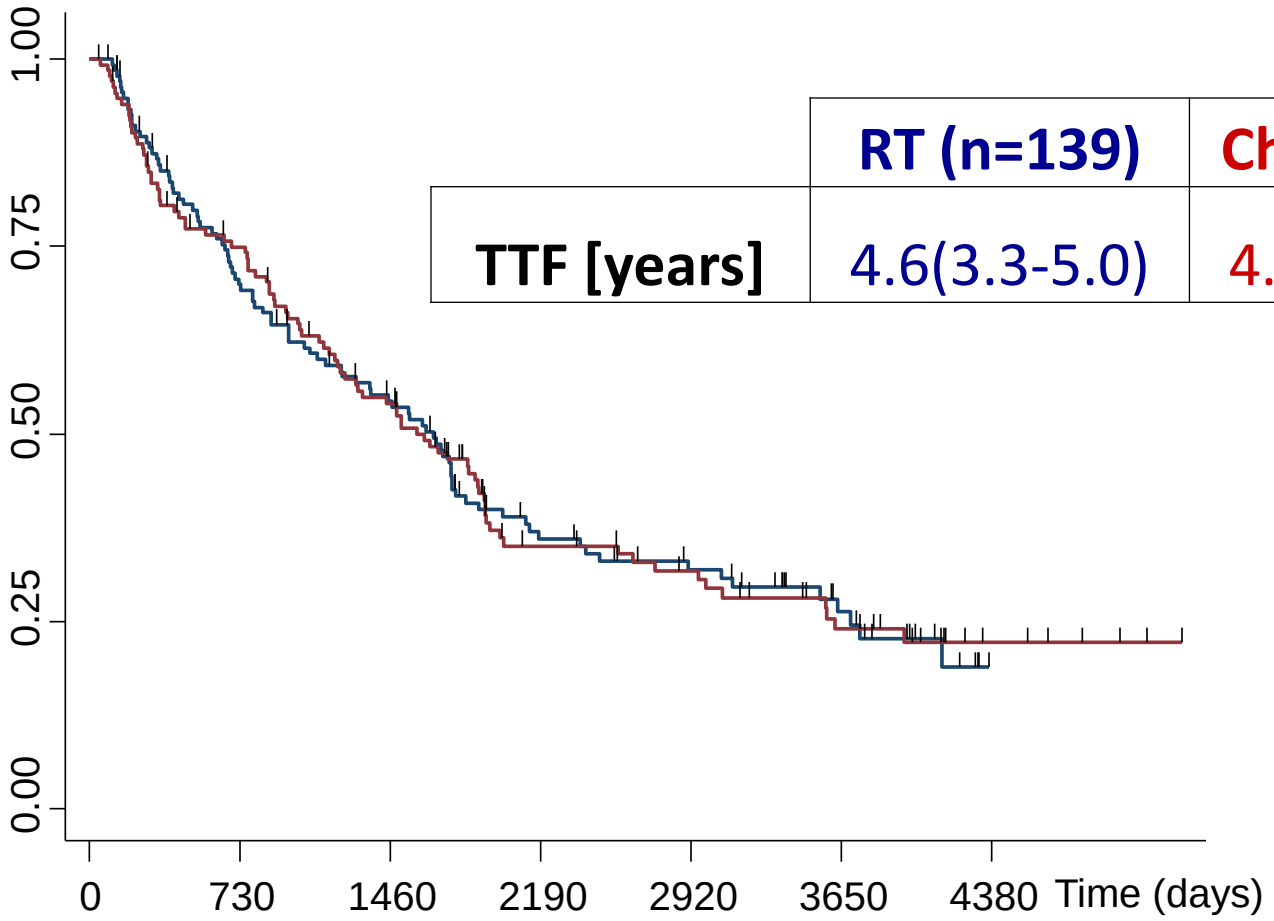
Time to treatment failure – by therapy



	RT (n=139)	ChT (n=135)
TTF [years]	4.6(3.3-5.0)	4.4(3.3-5.2)

Number at risk

RT	139	92	68	37	28	15	0
ChT	135	95	66	33	27	17	6

Wick et al., ASCO 2015

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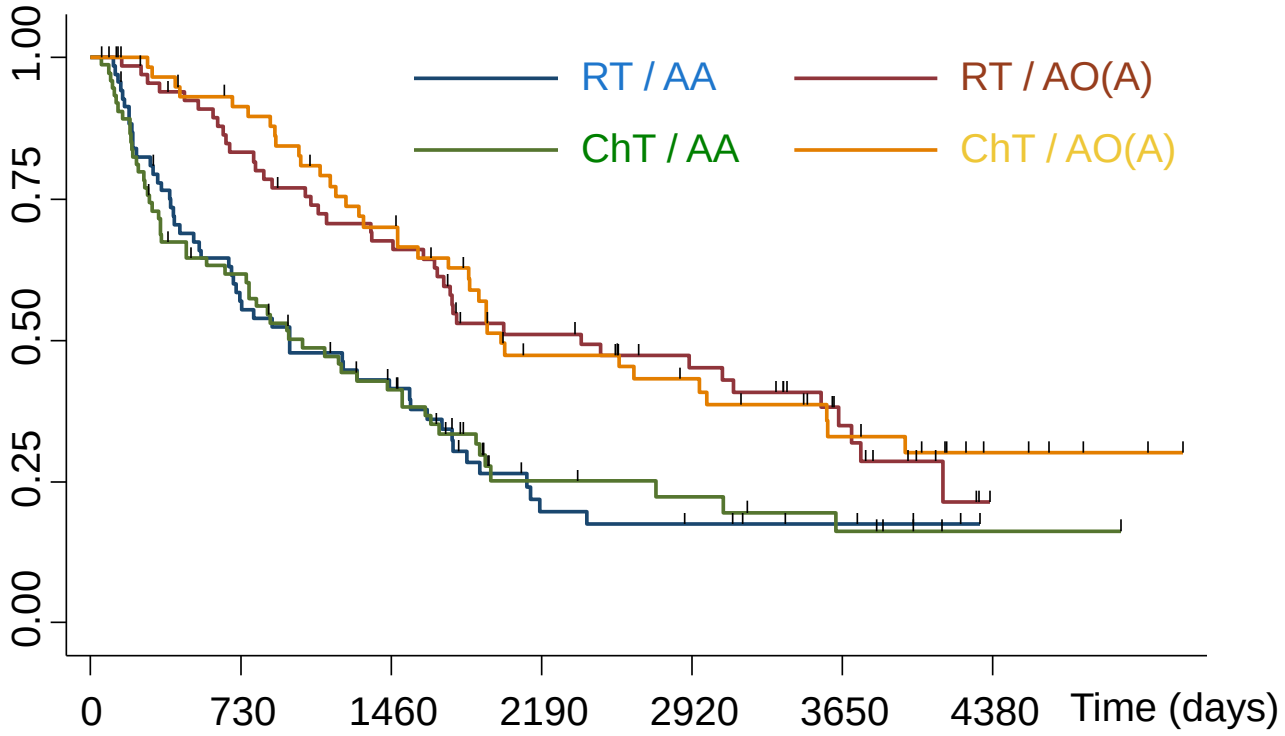
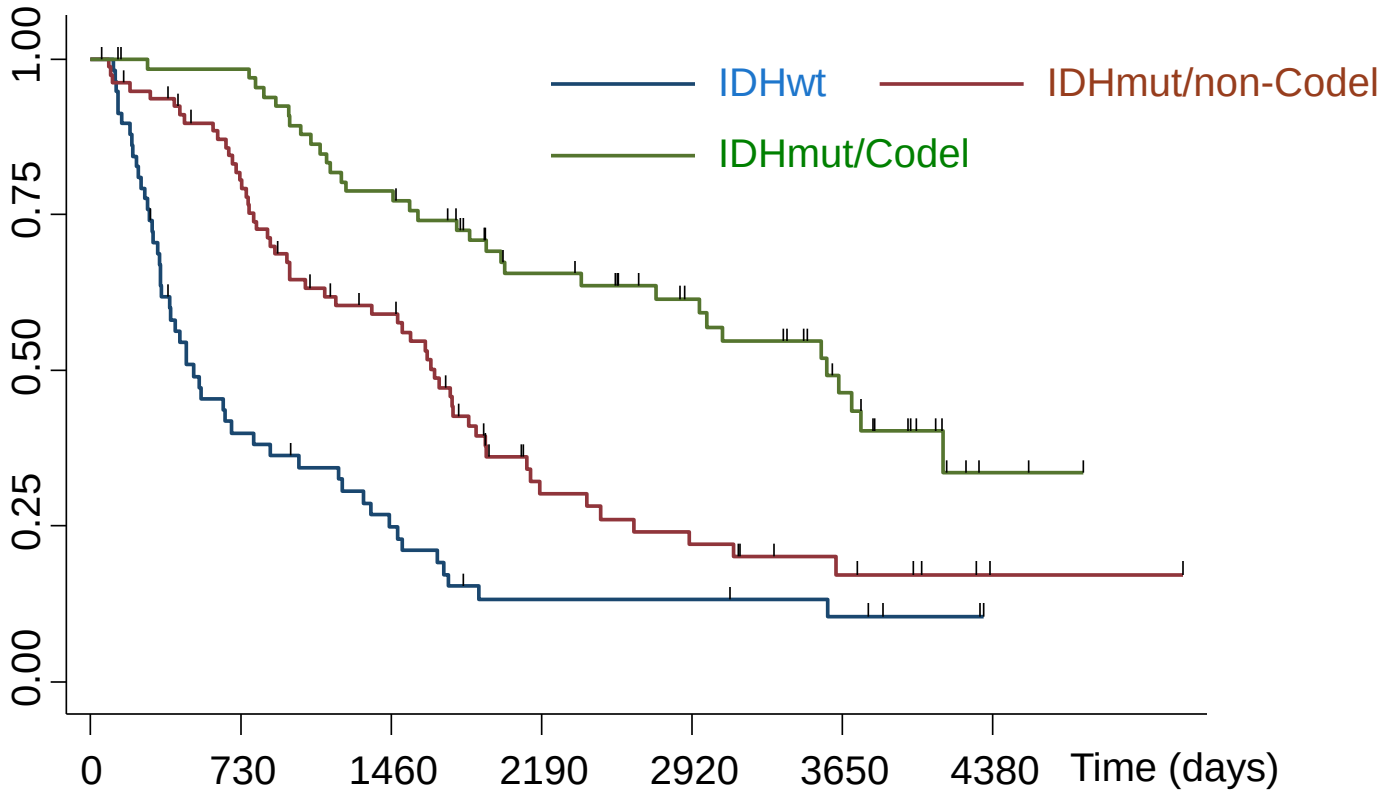
Time to treatment failure – by therapy/histology



Number at risk

RT / AA	70	38	25	9	7	4	0
RT / AO(A)	69	54	43	28	21	11	0
ChT / AA	74	43	27	10	8	5	1
ChT / AO(A)	61	52	39	23	19	12	5

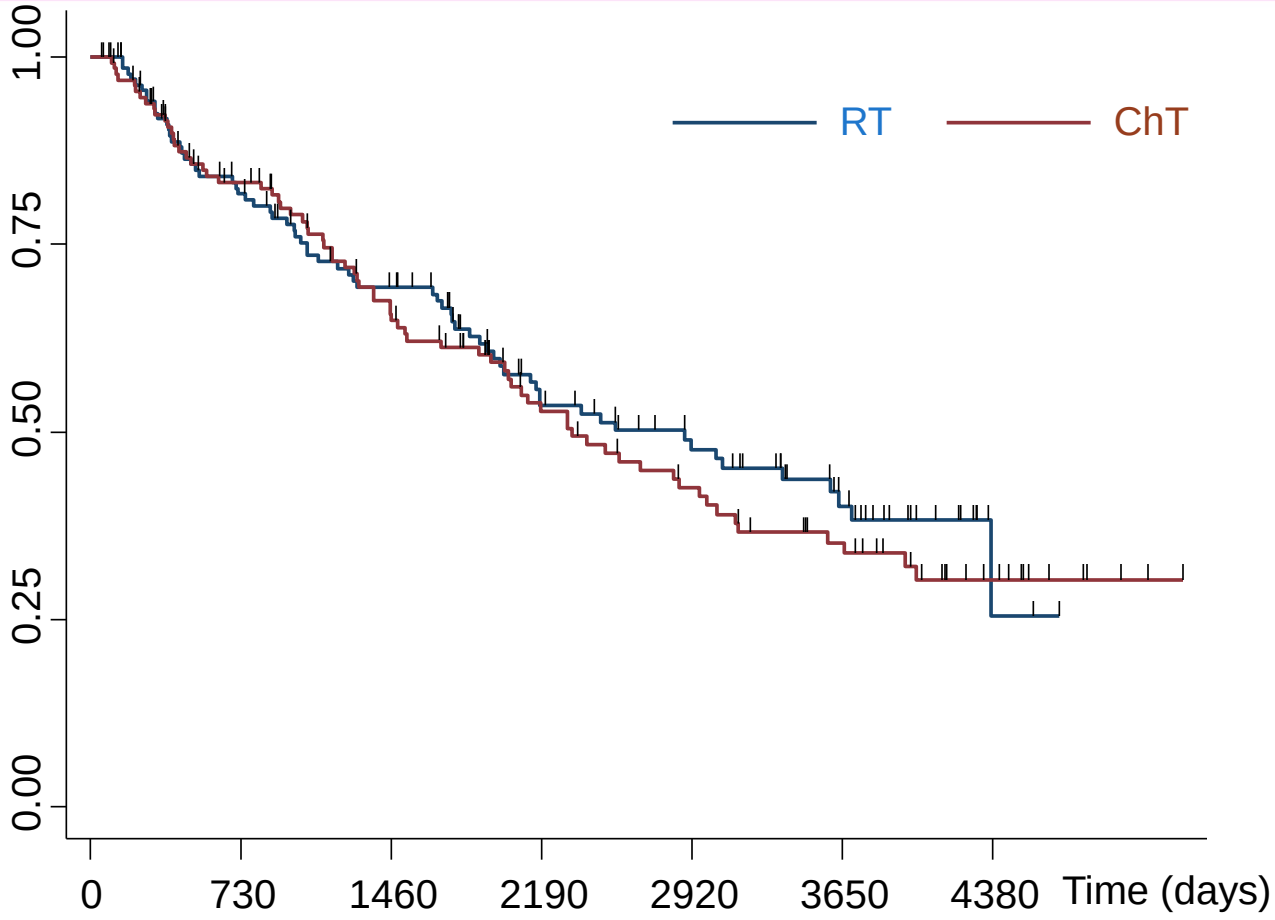
Time to treatment failure – by molecular diagnosis



Number at risk

IDHwt	58	22	13	6	6	4	0
IDHmut	81	61	41	15	11	6	1
Codel	68	65	52	36	27	16	2

Overall survival – by therapy



Number at risk

RT	139	103	81	51	38	22	2
ChT	135	100	74	48	36	25	11

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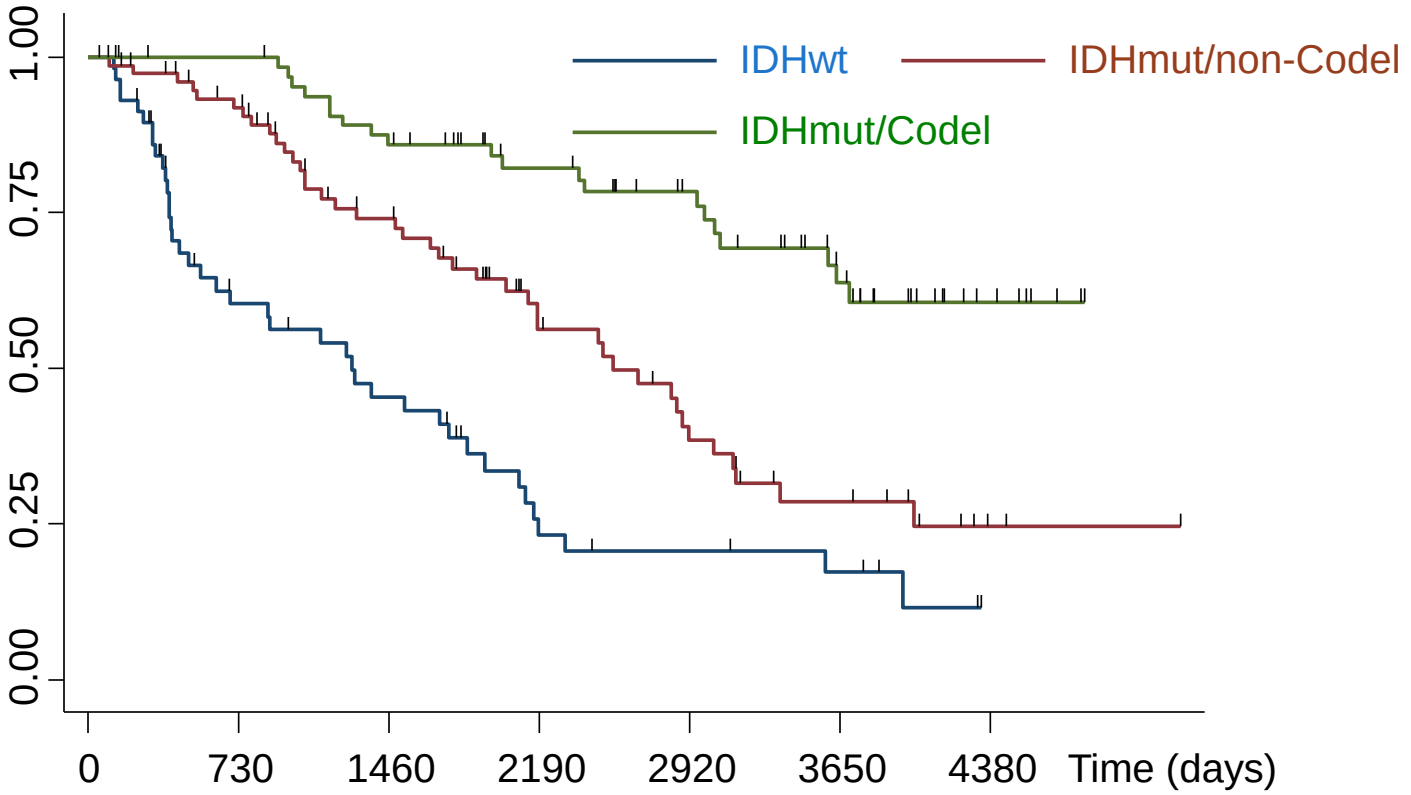
Overall survival – by molecular diagnosis



Number at risk

IDHwt	58	29	21	9	7	5	0
IDHmut	81	67	47	27	17	10	2
Codel	68	65	55	44	35	22	7

Efficacy outcomes – by molecular diagnosis/therapy

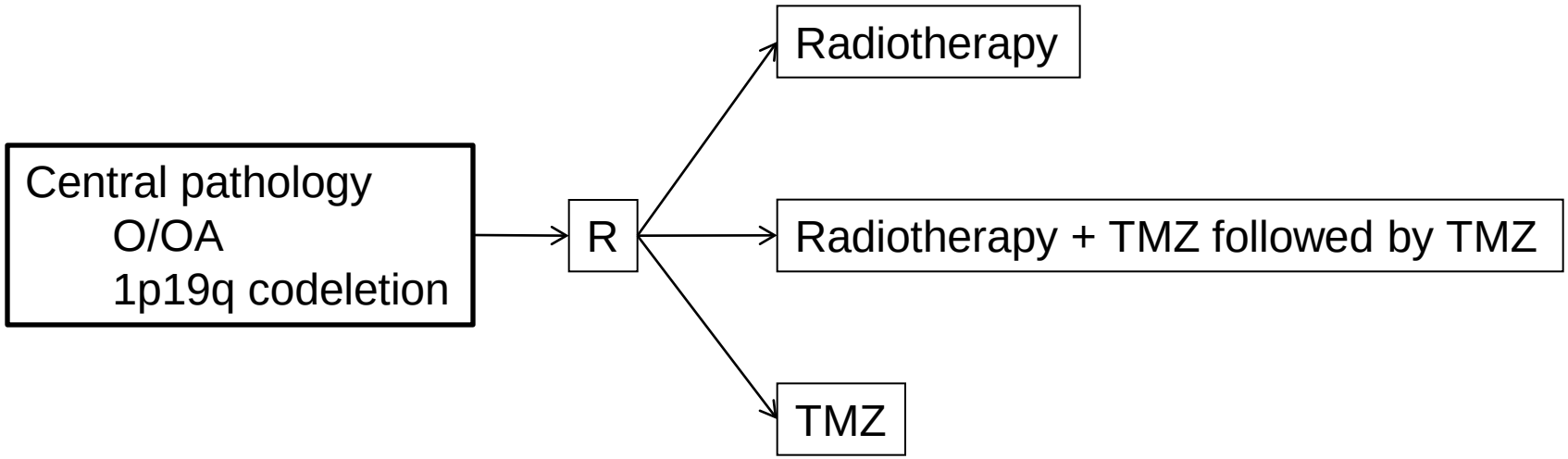
	RT (A)	ChT (B/C)	RT (A)	ChT (B/C)	RT (A)	ChT (B/C)
	IDHwt		IDHmut			
	(n=28)	(n=30)	Non-Codel (n=40)	Non-Codel (n=43)	Codel (n=35)	Codel (n=31)
PFS [years]	0.8 (0.4-1.2)	0.8 (0.7-1.4)	3.0 (1.6-4.6)	2.1 (1.5-3.1)	8.7 (3.9-11.1)	7.5 (4.0-9.4)
TTF [years]	1.5 (0.9-3.3	1.2 (0.8-3.2)	4 (2.6-6)	4.5 (2.6-5.3)	10.1 (6.5-nr)	8.1 (5.0-nr)
OS [years]	4.7 (1.9-5.9)	3.1 (1.1-5.7)	7 (4.8-9.2)	7.3 (4.7-8.6)	nr (10-nr)	nr (6.6-nr)

Efficacy outcomes – across trial

	RTOG 9402[2]		EORTC 26951[1]		NOA-04	
	RT	PCV+RT	RT	RT+PCV	RT	CT
PFS, IDHwt/1p/19q intact	1.0	1.2	0.6	0.8	0.8	0.8
OS, IDHwt/1p/19q intact	2.7	2.6	1.8	2.1	4.7	3.1
PFS, 1p/19q codel	2.9	8.4	4.2	13.1	8.7	7.5
OS, 1p/19q codel	7.3	14.7	9.3	Not reached	Not reached	Not reached

1. van den Bent et al. J Clin Oncol 2013
2. Cairncross et al. J Clin Oncol 2013

CODEL trial: initial design



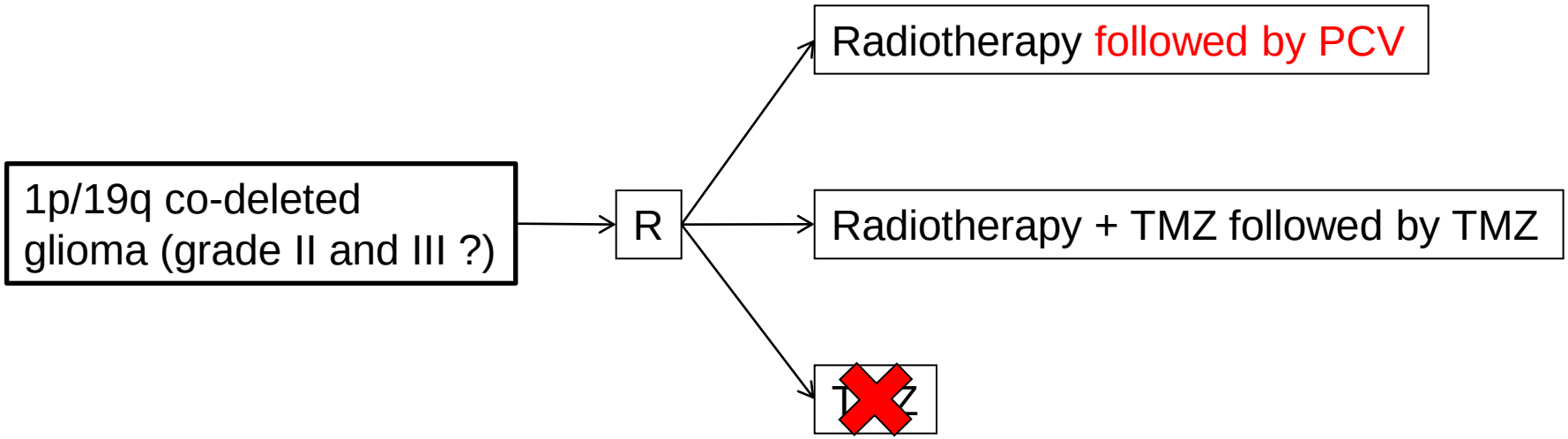
Estimated Enrollment: 520

Study Start Date: October 2009

Estimated Primary Completion Date: December 2018

CODEL trial: updated design

Proposed design of revitalized CODEL trial



Estimated Enrollment: 520

Study Start Date: October 2009

Estimated Primary Completion Date: December 2018

Conclusions: anaplastic gliomas

1p/19q co-deleted tumors:

- The combination of RT and PCV may be regarded as standard of care for newly diagnosed anaplastic oligodendroglial tumors with 1p/19q co-deletion
- RT -> PCV and PCV -> RT are both feasible options
- Temozolomide instead of PCV? => no final answer so far

Non-1p/19q co-deleted tumors:

- RT as current standard for newly diagnosed cases
- Role of temozolomide to be defined in **CATNON** trial

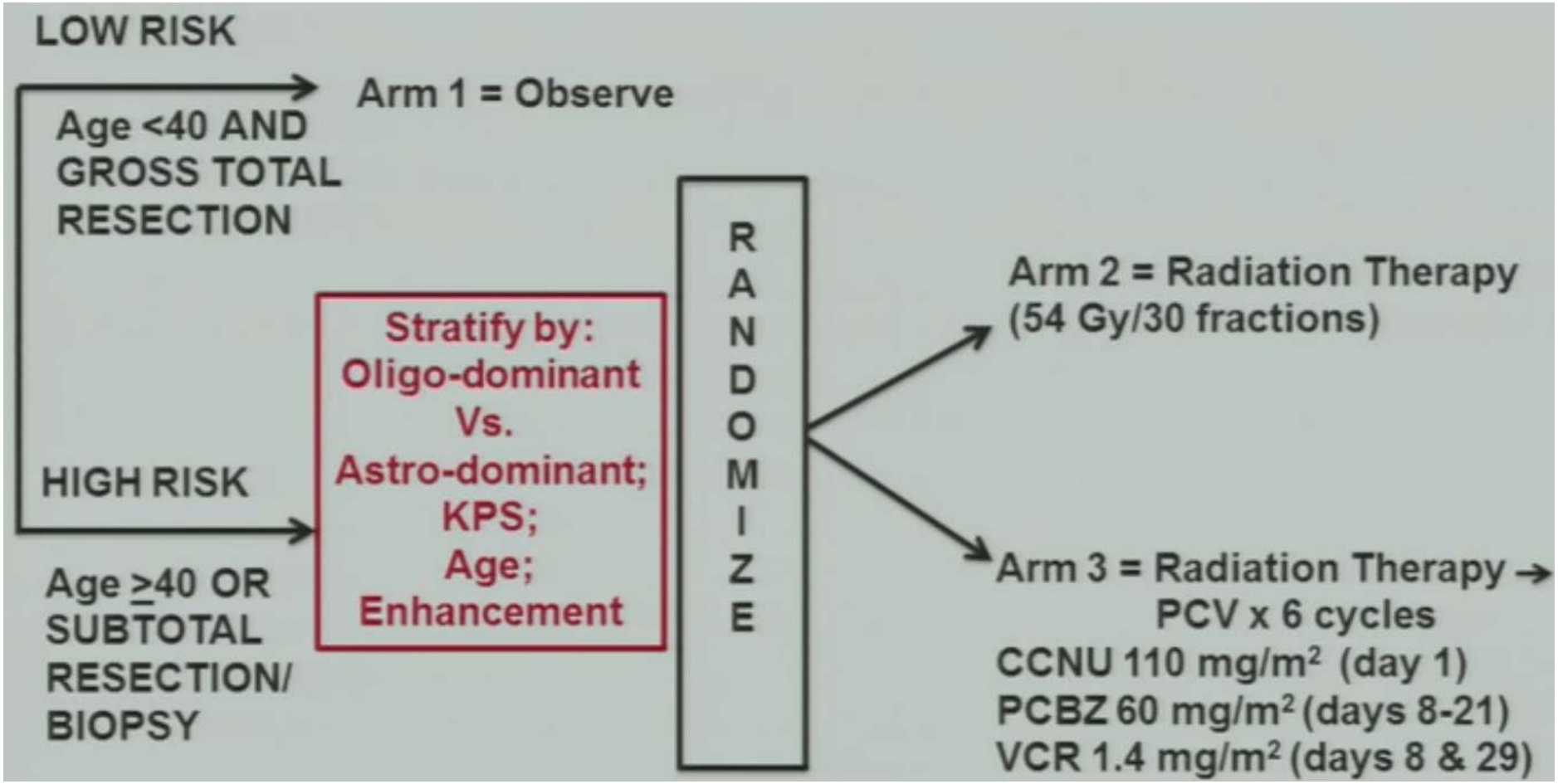
And in patients with low-grade gliomas…?

Feasible options:

- Watch and wait
- Surgery
- Radiotherapy
- Chemotherapy
- Combined radiochemotherapy

And in patients with low-grade gliomas…?

RTOG 9802



Buckner, ASCO 2014

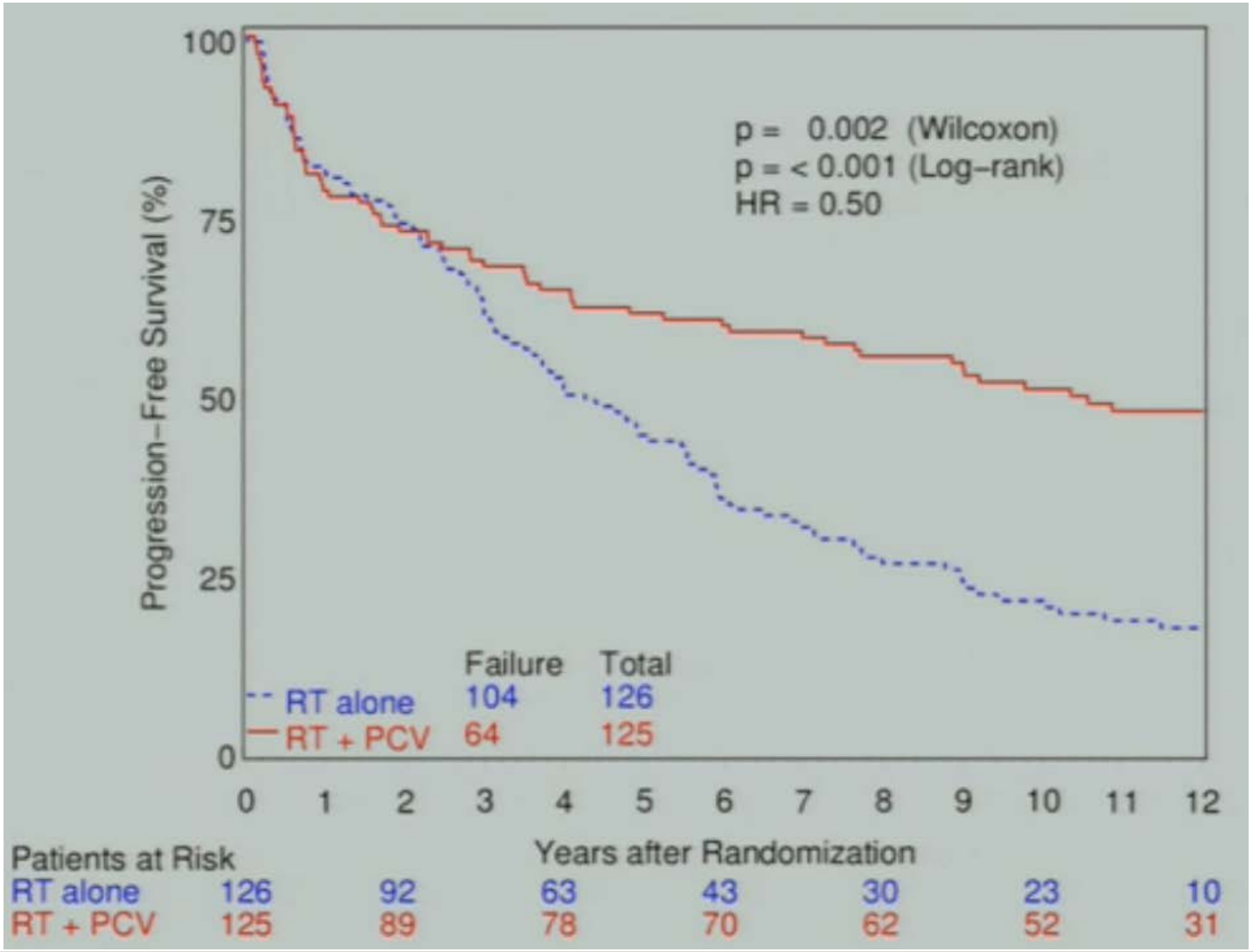
RTOG 9802: histology

Pretreatment Patient Characteristics Surgery and Histology

	RT Alone (n=126)	RT+PCV (n=125)
Extent of surgery		
Biopsy	59 (47%)	60 (48%)
Partial resection	56 (44%)	51 (41%)
Total resection	11 (9%)	14 (11%)
Histology		
Astrocytoma	29 (23%)	36 (29%)
Oligodendroglioma	57 (45%)	50 (40%)
Oligoastrocytoma, astro dominant	19 (15%)	19 (15%)
Oligoastrocytoma, astro=oligo	5 (4%)	1 (1%)
Oligoastrocytoma, oligo dominant	16 (13%)	19 (15%)

Buckner, ASCO 2014

RTOG 9802: PFS long-term follow-up



Buckner, ASCO 2014

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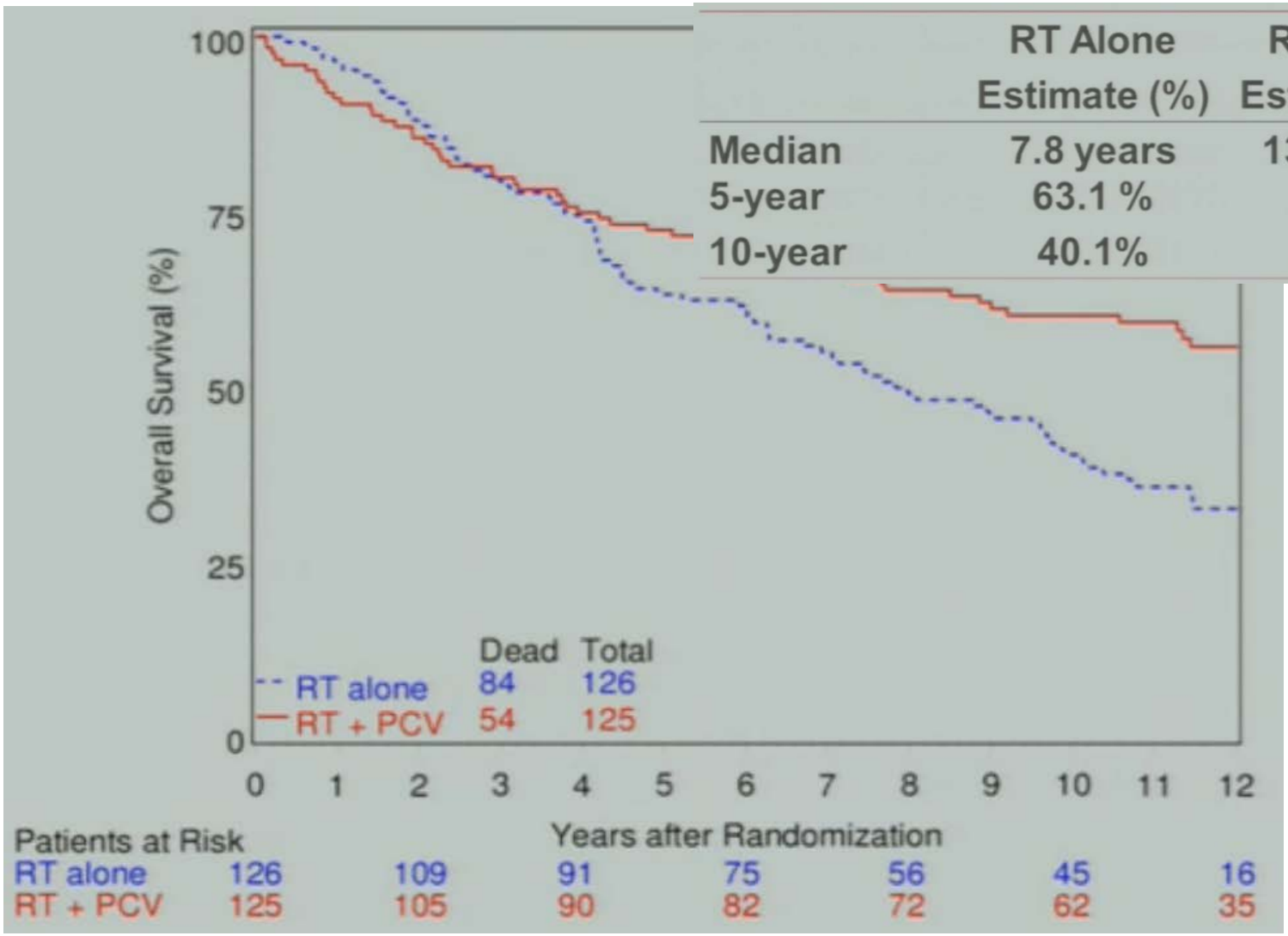
RTOG 9802: OS long-term follow-up



	RT Alone Estimate (%)	RT + PCV Estimate (%)
Median	7.8 years	13.3 years
5-year	63.1 %	72.3%
10-year	40.1%	60.1%

Buckner, ASCO 2014

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RTOG 9802: Prognostic factors

Cox Proportional Hazards Model for Overall Survival (n=251)

Variable (**Bolded** value has **unfavorable** outcome)	p-value	Hazard Ratio (95%CI)
Assigned treatment (RT+PCV vs. **RT alone**)	0.001	0.56 (0.40, 0.79)
Histology (**Mixed Oligoastrocytoma** vs Oligodendroglioma)	<.001	2.06 (1.38, 3.09)
(**Astrocytoma** vs Oligodendroglioma)	<.001	2.54 (1.66, 3.87)
Gender (**Male** vs. Female)	0.018	1.53 (1.07, 2.17)

Model derived from stepwise selection.

Variable(s) not included in final model: surgery (dropped out during the stepwise selection process)

Buckner, ASCO 2014

Conclusions

- Long-term data from **EORTC 26951** and **RTOG 9402** suggest RT + PCV as standard of care for patients with anaplastic glioma and 1p/19q co-deletion
- **NOA-04** data do not support an attempt to achieve comparable outcomes with monochemotherapy in patients with 1p/19q co-deleted tumors
- **RTOG 9802** long-term data suggest a benefit from RT/PCV compared to RT alone in the entire cohort of grade II tumors
- PFS and OS gain in the RTOG 9802 dataset is most prominent in patients with oligodendroglial (= **1p/19q co-deleted**?) tumors
- Whether **PCV** can be replaced by **temozolomide** remains unclear

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Management of high grade glioma

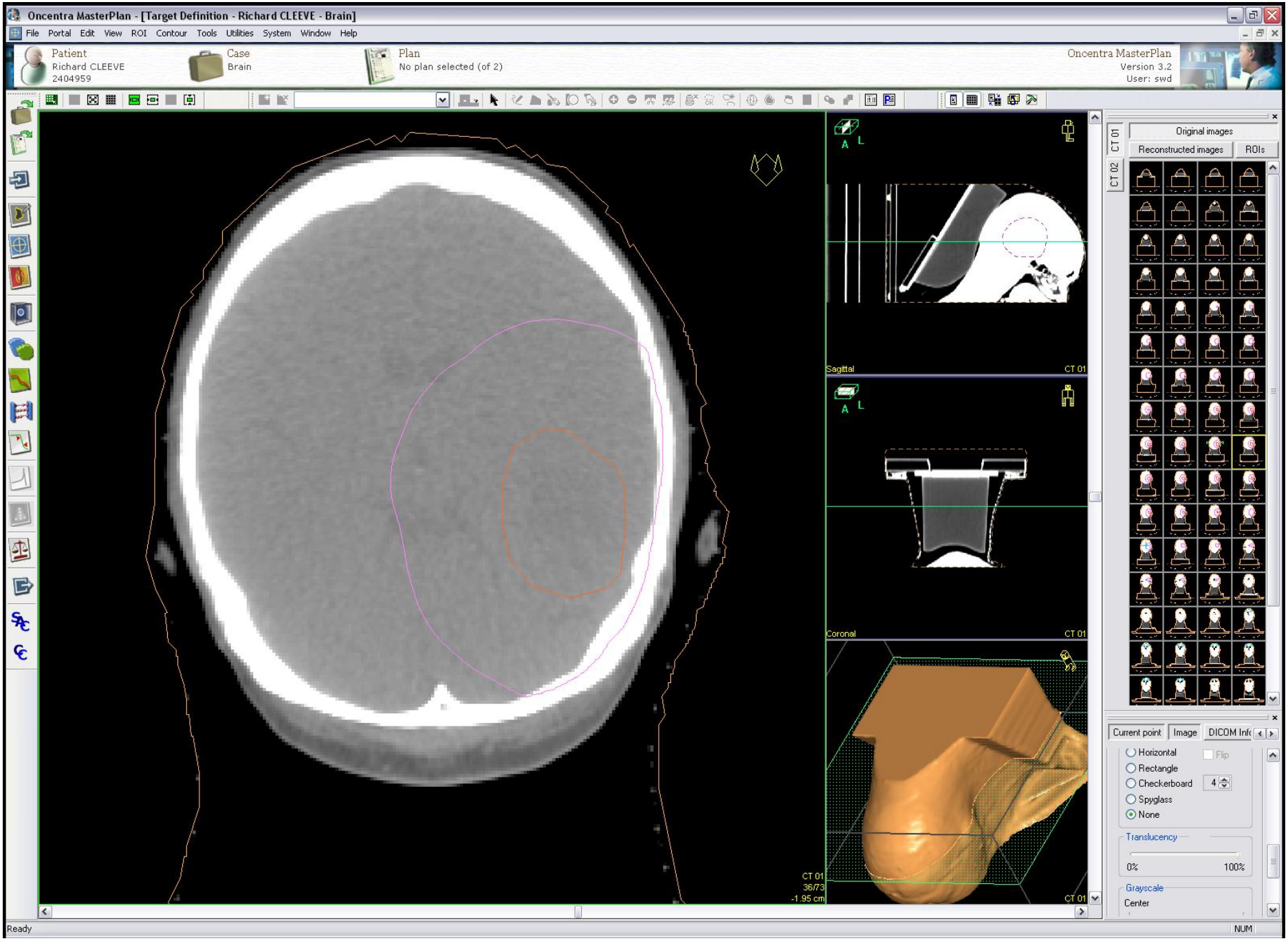
Anthony Chalmers

ESTRO Brain Tumour Course

2015

Prognostic factors

- tumour grade
- age
- performance status
- molecular markers:
  - 1p19q co-deletion; MGMT promoter methylation; IDH1 mutation
- extent of surgical resection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File Portal Edit View ROI Contour Tools Utilities System Window Help
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Richard CLEEVE
2404959
Case
Brain
Plan
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Oncentra MasterPlan
Version 3.2
User: swd
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-1.95 cm
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Original images
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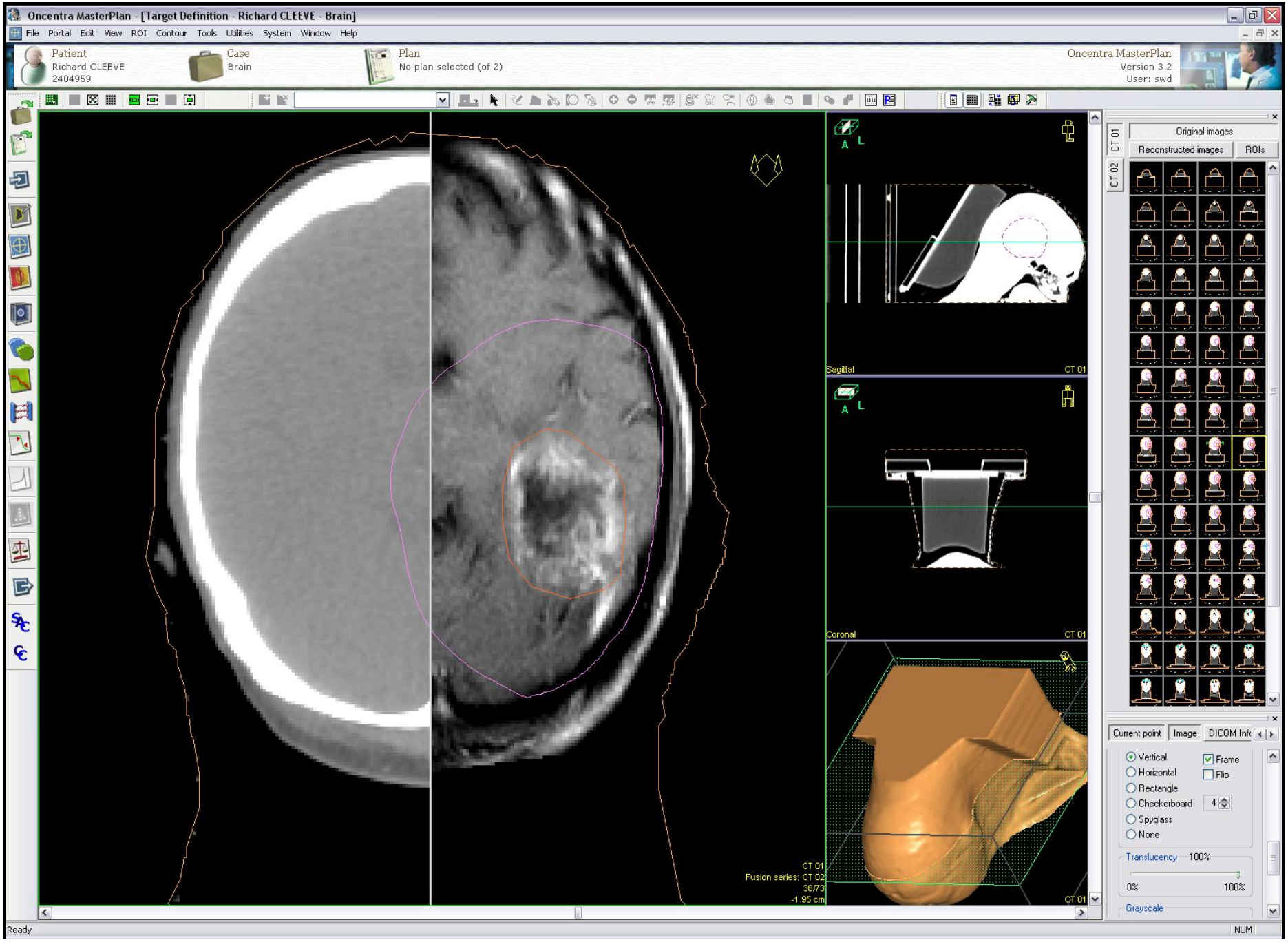
Oncentra MasterPlan - [Target Definition - Richard CLEEVE - Brain]
File Portal Edit View ROI Contour Tools Utilities System Window Help
Patient
Richard CLEEVE
2404959
Case
Brain
Plan
No plan selected (of 2)
Oncentra MasterPlan
Version 3.2
User: swd
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Coronal
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-1.95 cm
CT 01
CT 02
Original images
Reconstructed images
ROIs
Current point
Image
DICOM Info
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Horizontal
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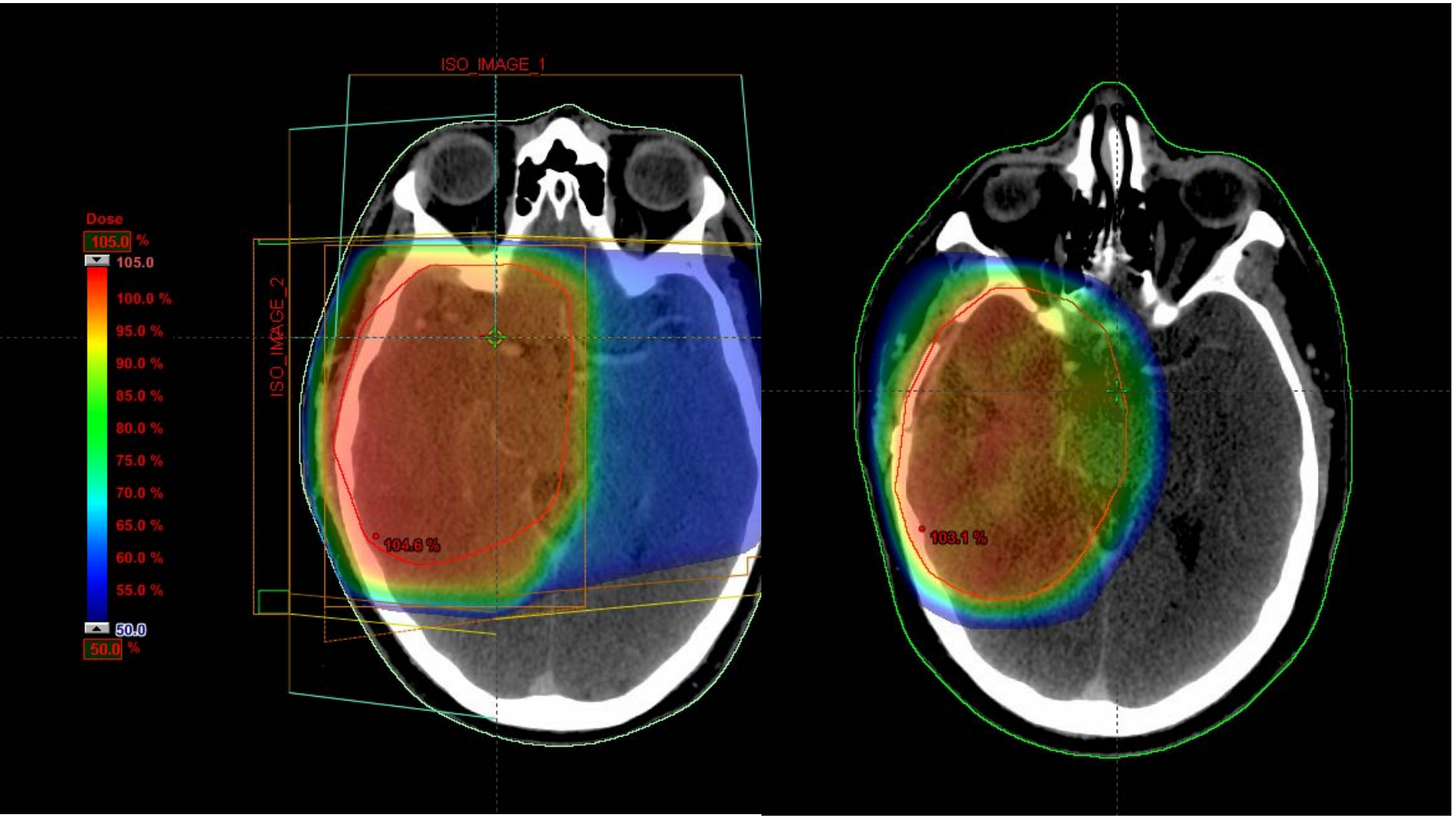
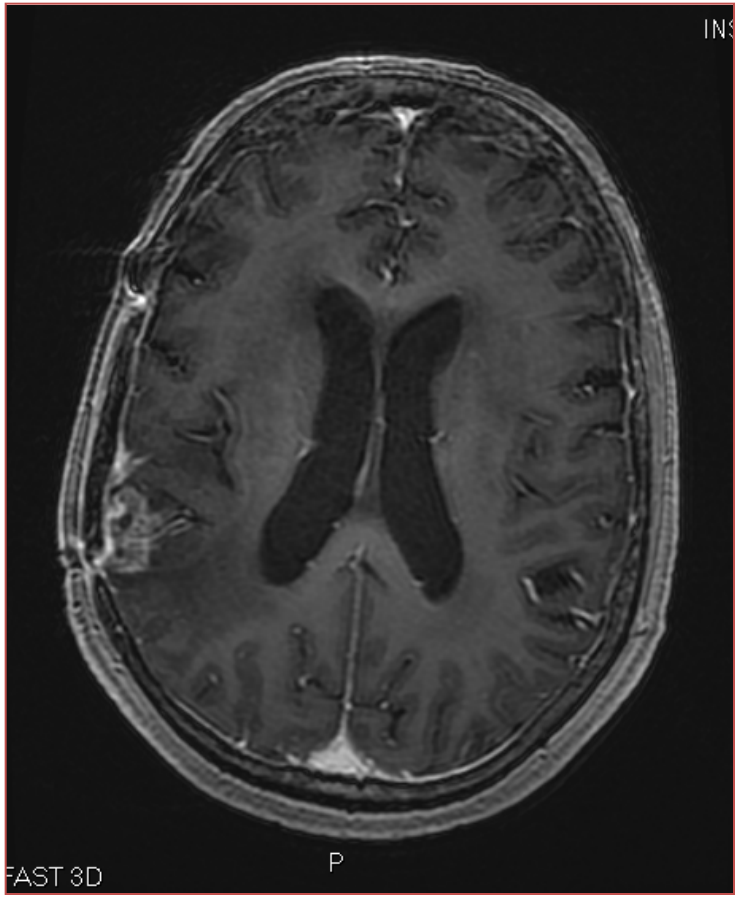
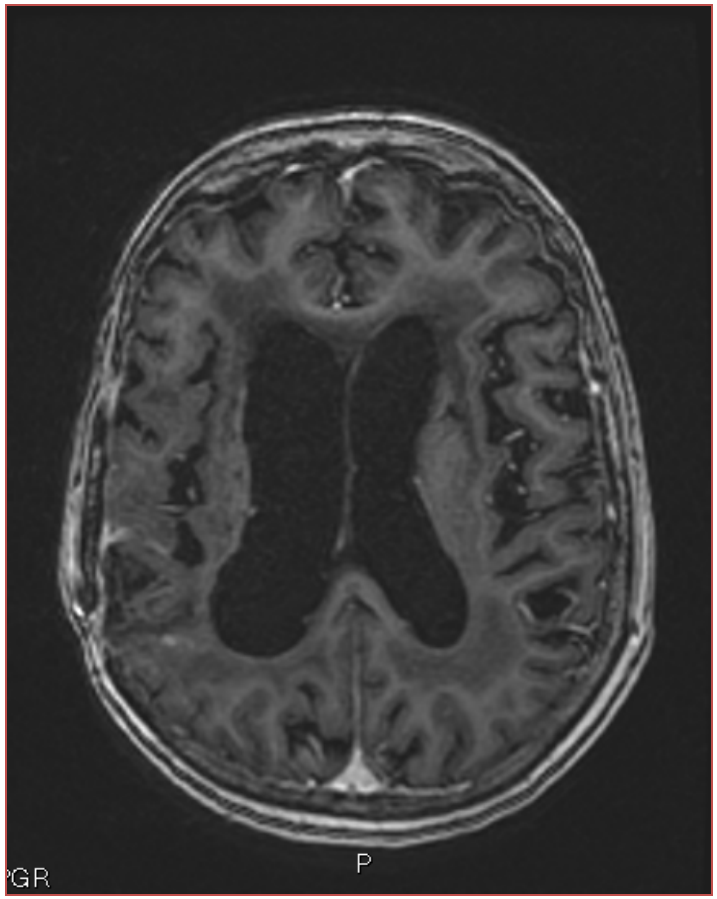
Conformal RT

IMRT



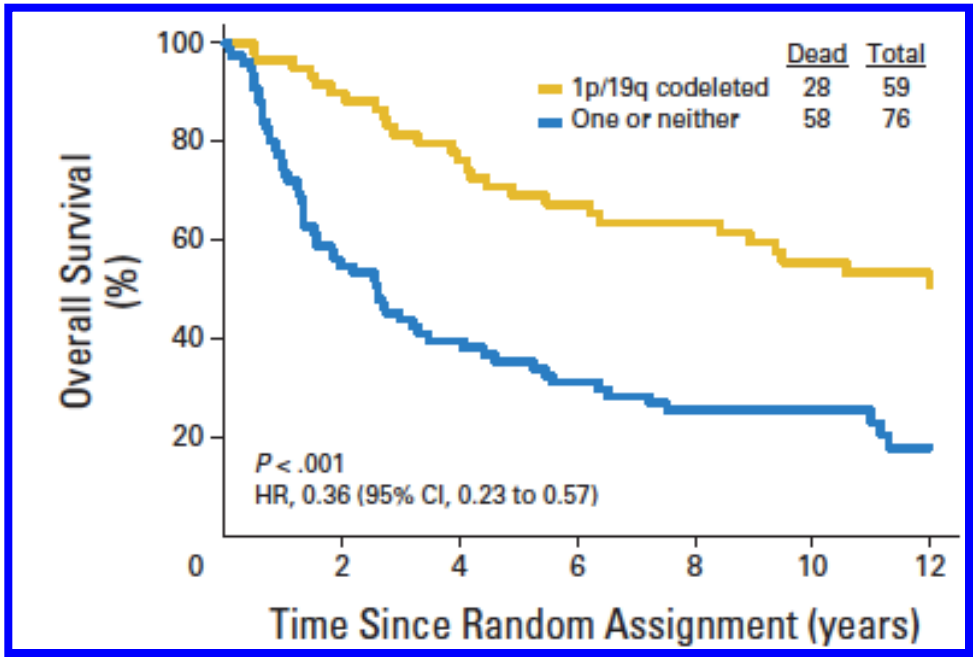


Pre-radiation



18 months
post-radiation

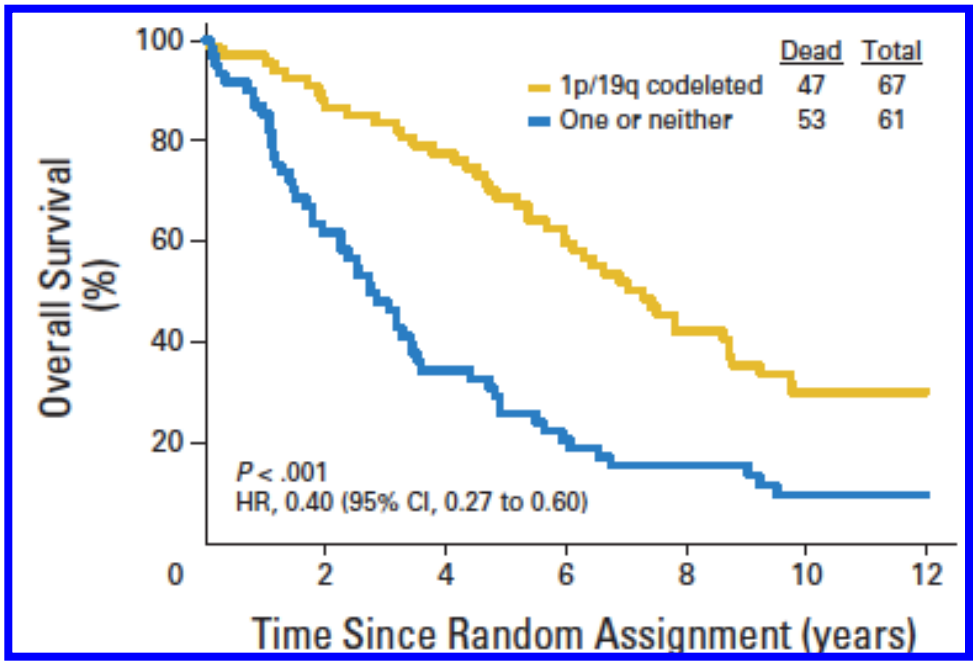
PCV - RT



1p19q codeleted

1p19q intact

RT

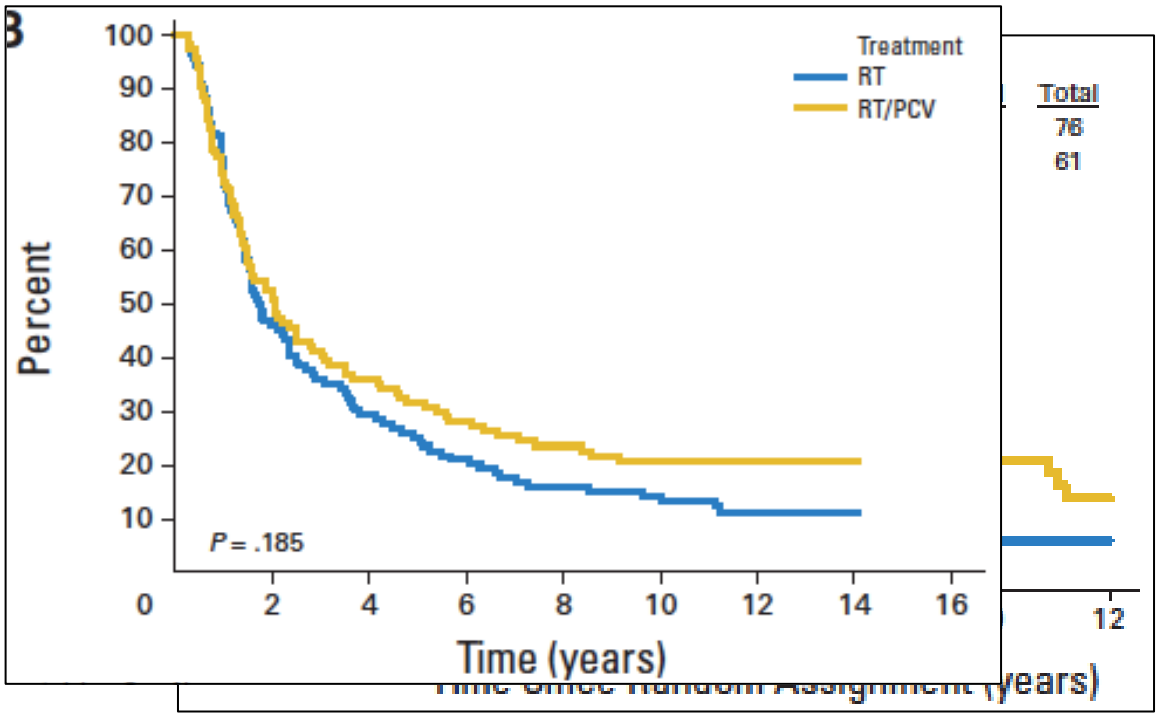


1p19q codeleted

1p19q intact

Grade 3 glioma

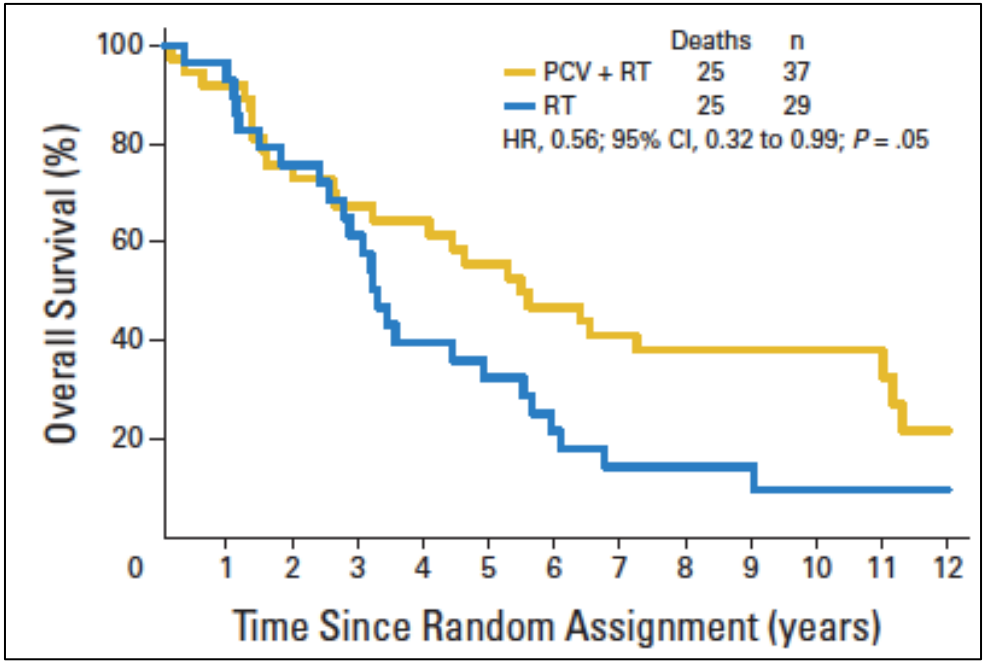
Cairncross, J Clin Onc 2014



All patients without 1p19q codeletion

HR = 0.85
p = 0.39

HR = 0.83
p = 0.185



IDH1 mutated patients without 1p19q codeletion

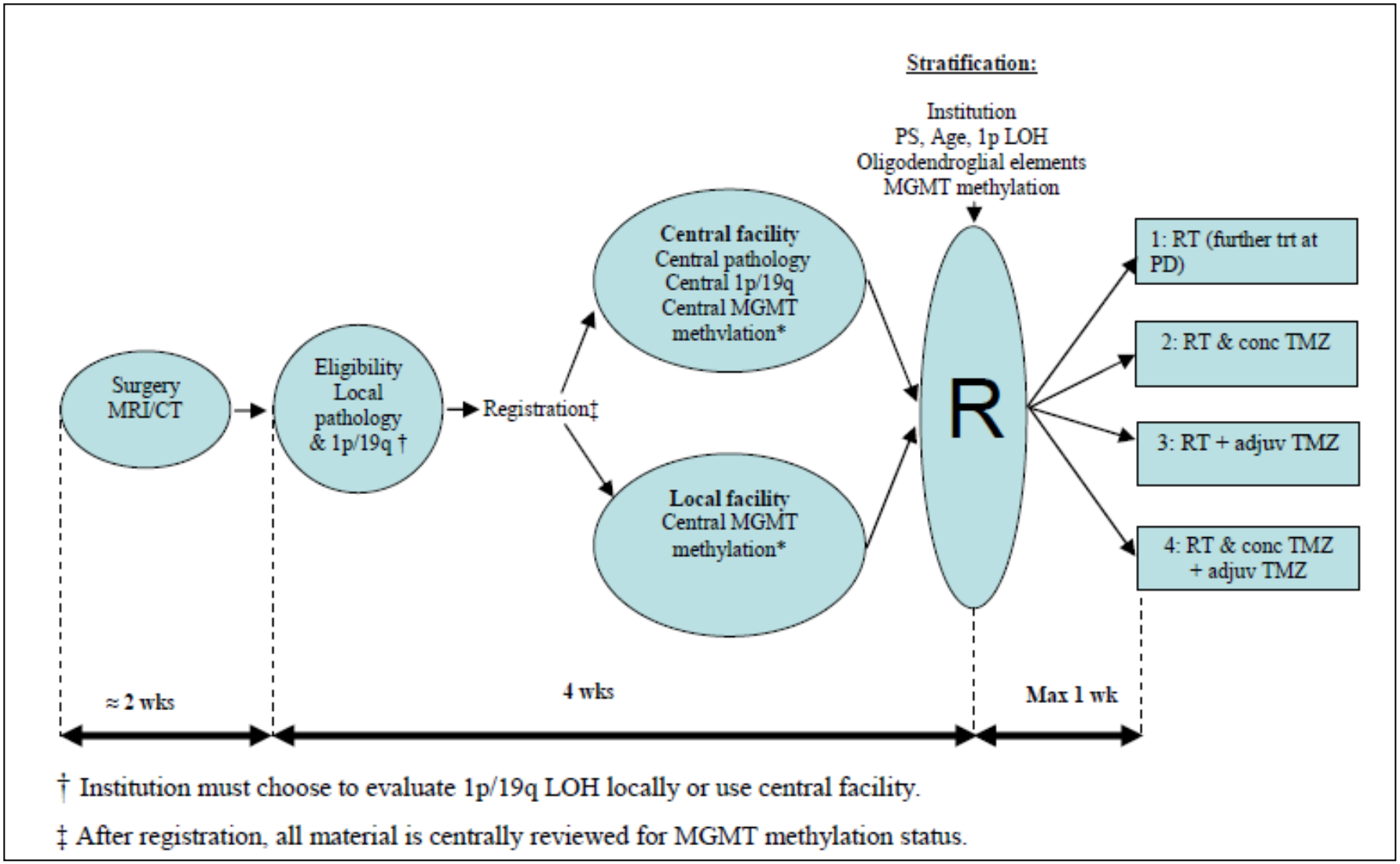
HR = 0.56
p = 0.05

The treatment I would recommend for a patient with grade 3 glioma without 1p19q codeletion is:

A. Radiotherapy alone
B. PCV followed by radiotherapy
C. Radiotherapy followed by PCV
D. Radiotherapy with concomitant TMZ
E. Radiotherapy with concomitant and adjuvant TMZ

CATNON

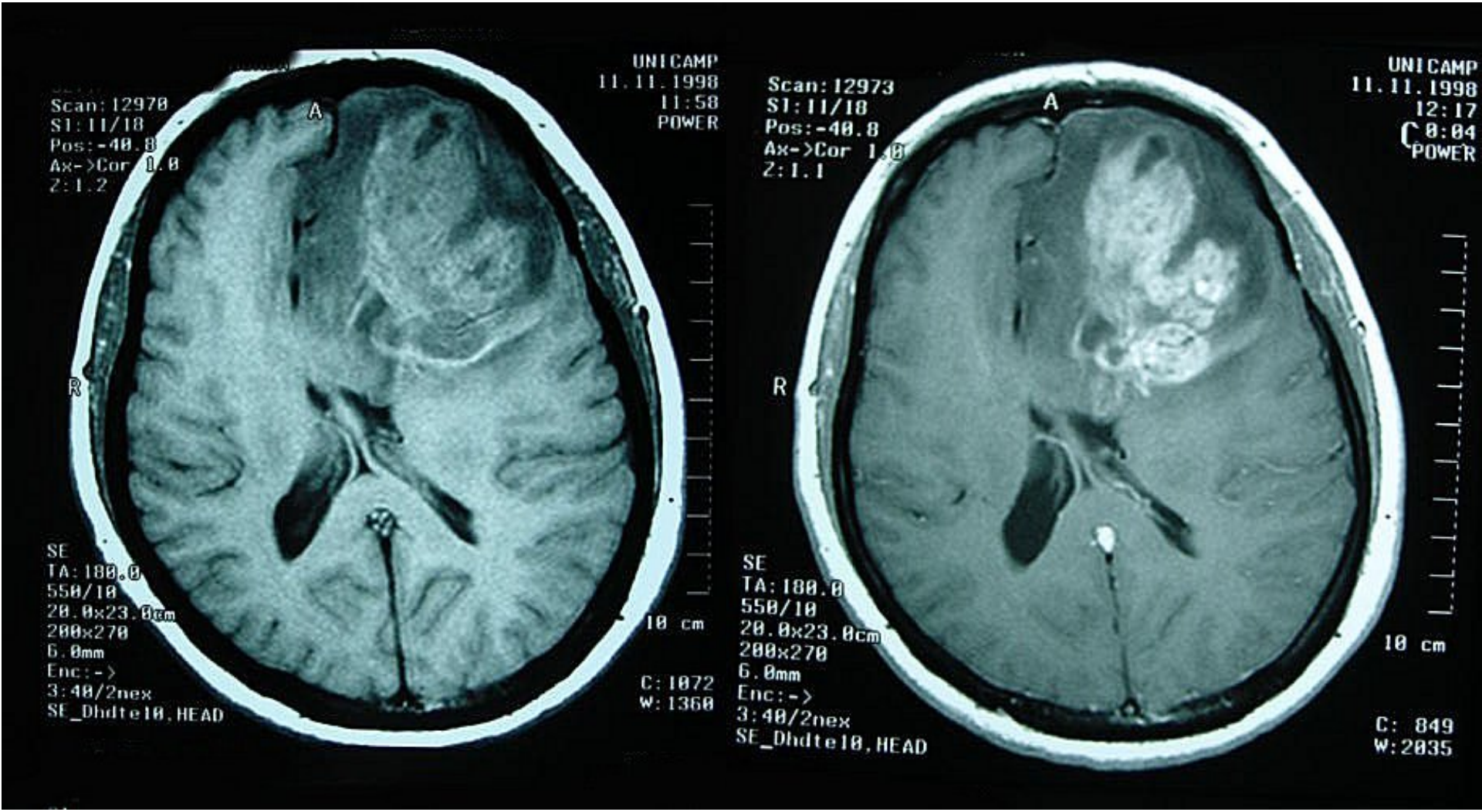
grade 3 gliomas WITHOUT co-deletion of 1p19q

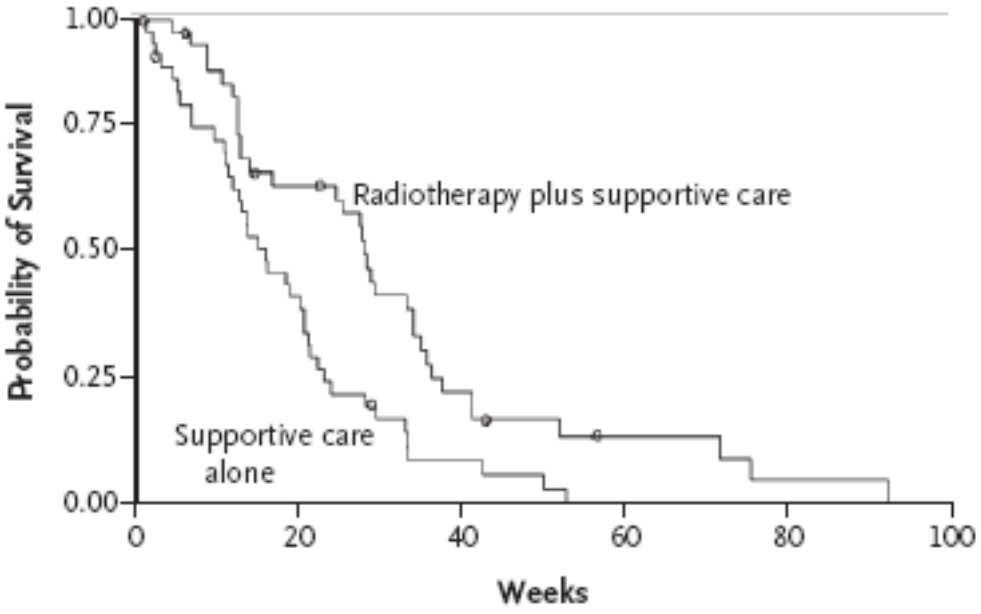


† Institution must choose to evaluate 1p/19q LOH locally or use central facility.

‡ After registration, all material is centrally reviewed for MGMT methylation status.

Glioblastoma





No. at Risk					
Supportive care alone	42	17	3	0	0
Radiotherapy plus supportive care	39	24	8	3	1

Figure 2. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients who received radiotherapy plus supportive care as compared with those who received supportive care alone was 0.47 (95% CI, 0.29 to 0.76; P=0.002).

Glioblastoma patients aged > 70 yrs

Debate later…

Keime-Guibert NEJM 2007

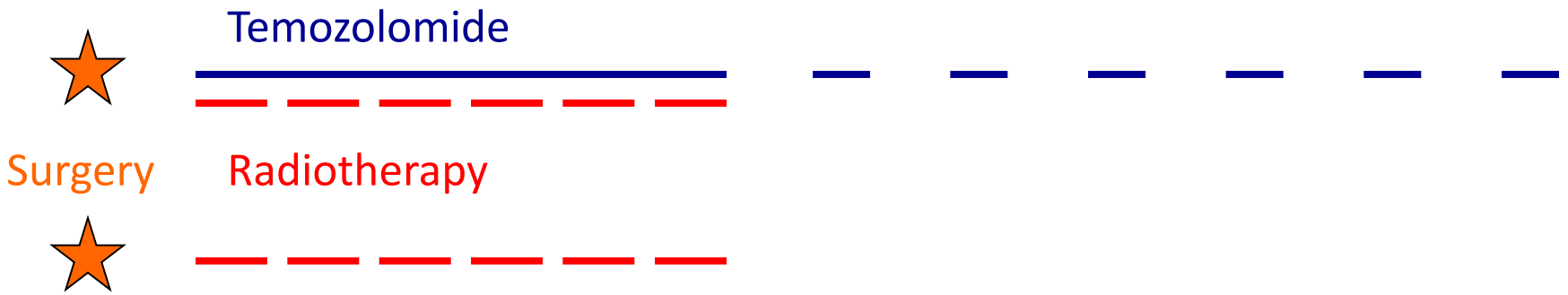
Survival of GBM patients did not improve between 1978 and 2005....

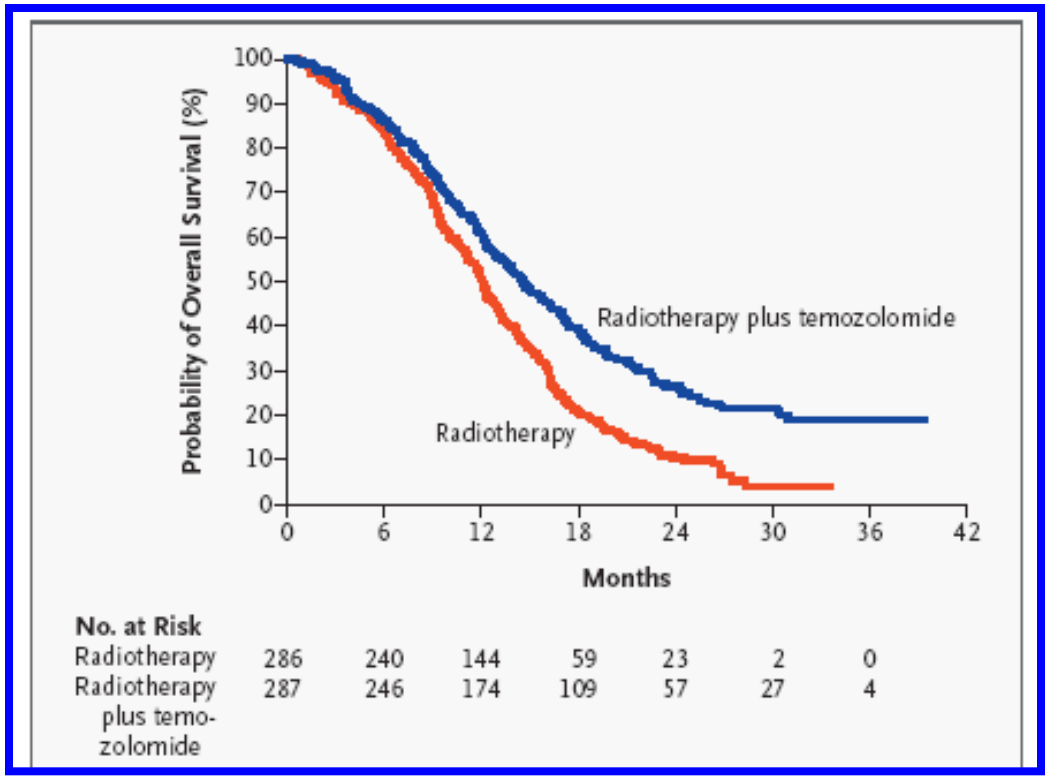
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*





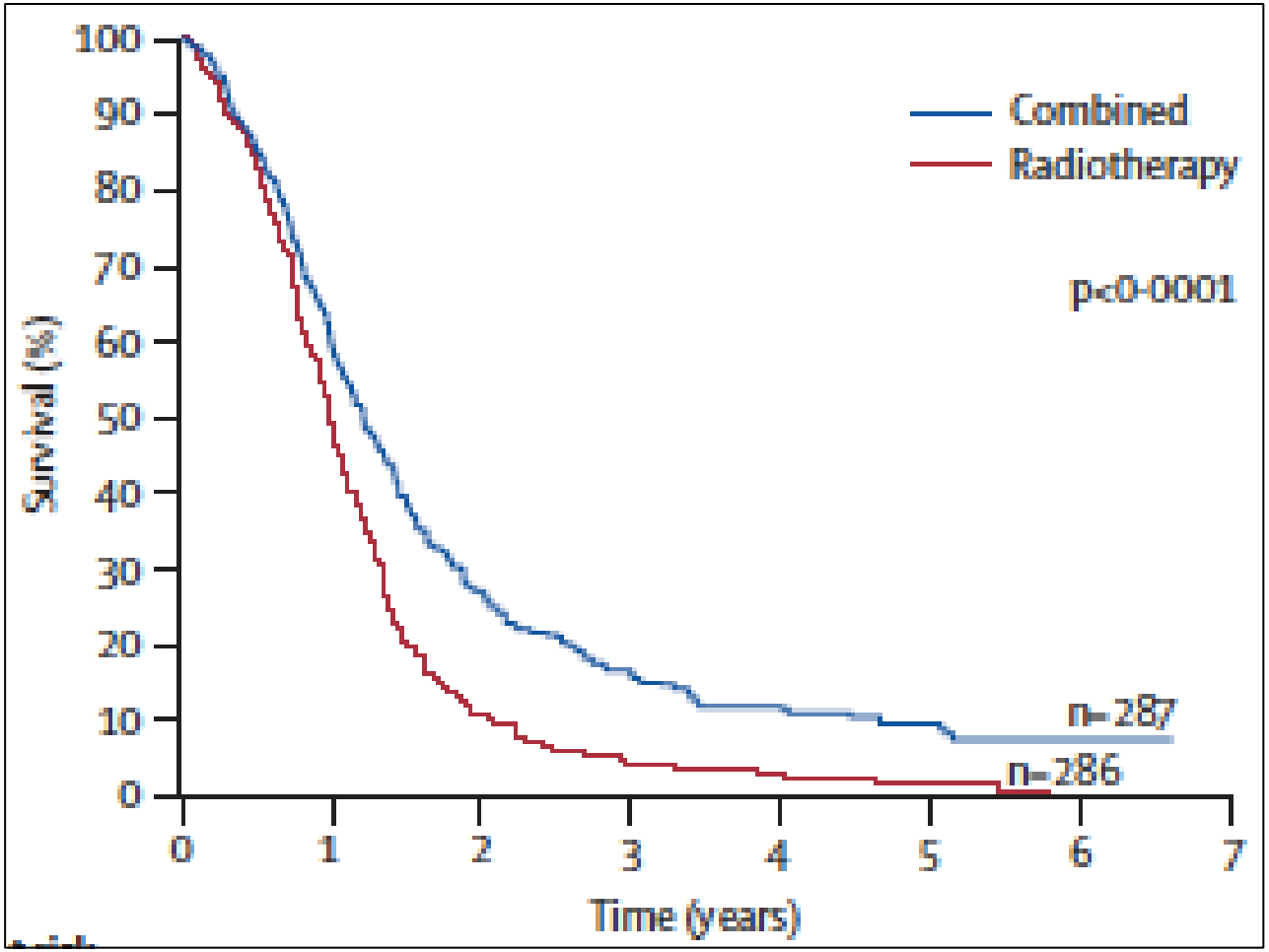
Glioblastoma patients aged < 70 yrs

Stupp NEJM 2005

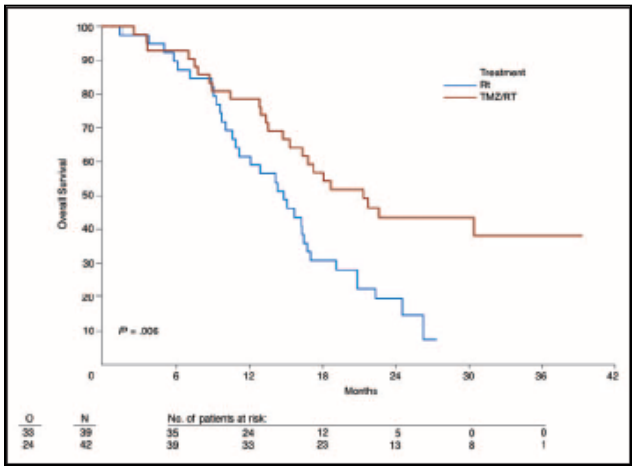
‘Stupp’ regime

- radiotherapy to enhancing tumour or resection cavity plus 2-3 cm margin
- daily temozolomide 75 mg/m^2 during radiotherapy
- standard radiotherapy dose (60 Gy 30#)
- 6 cycles of adjuvant temozolomide (5/28 days)
  - 1st cycle 150 mg/m^2
  - escalate to 200 mg/m^2 if tolerated
  - about 50% of patients completed 6 cycles

Mature data

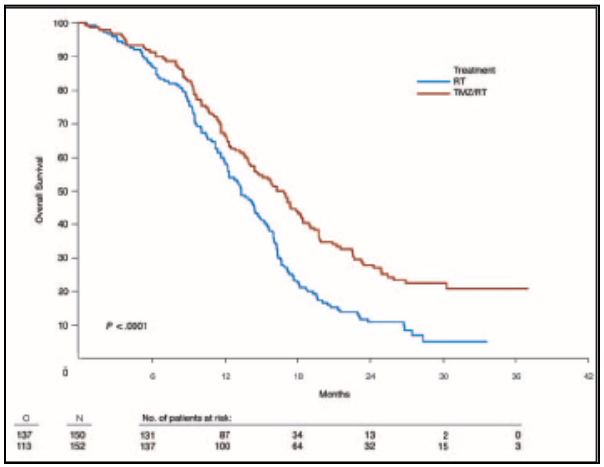

100
90
80
70
60
50
40
30
20
10
0
Survival (%)
0
1
2
3
4
5
6
7
Time (years)
Combined
Radiotherapy
p<0·0001
n=287
n=286

who benefits from TMZ-RT?



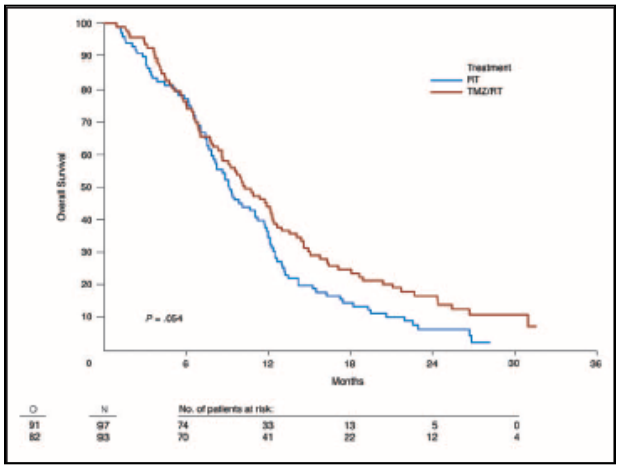
RPA III

p=0.006



RPA IV

p=0.0001



RPA V

p=0.054

48 year old patient with MGMT unmethylated GBM, >90% resection, PS=1 post-op. Completes RT-TMZ. She attends for 1st cycle adjuvant TMZ; PS now 2: fatigue, poor short term memory. Your recommendation is:

A. Commence adjuvant TMZ as protocol

B. Defer adjuvant TMZ until PS = 1 or better

C. Commence adjuvant TMZ but reconsider after cycle 1

D. Decision to proceed with adjuvant TMZ depends on result of MRI scan after RT/TMZ

E. Advise patient no benefit from adjuvant TMZ

61 year old science journalist from Los Angeles. MGMT methylated multifocal GBM, biopsy only. PS=1 post-op. Completes 1st cycle adjuvant TMZ with marked fatigue and ongoing mild cognitive deficit. Patient and wife seek your advice on (a) whether to go ahead with planned 5 week holiday to Italy for 30th wedding anniversary, visiting relatives, and (b) whether to continue with adjuvant TMZ. You advise:

A. Cancel trip to Italy and continue adjuvant TMZ

B. Travel to Italy, continue TMZ while away and on return

C. Travel to Italy, take a break from TMZ, continue on return

D. Decision to proceed with adjuvant TMZ depends on result of MRI scan

E. Advise patient that benefit from adjuvant TMZ is insufficient to justify fatigue and other toxicities

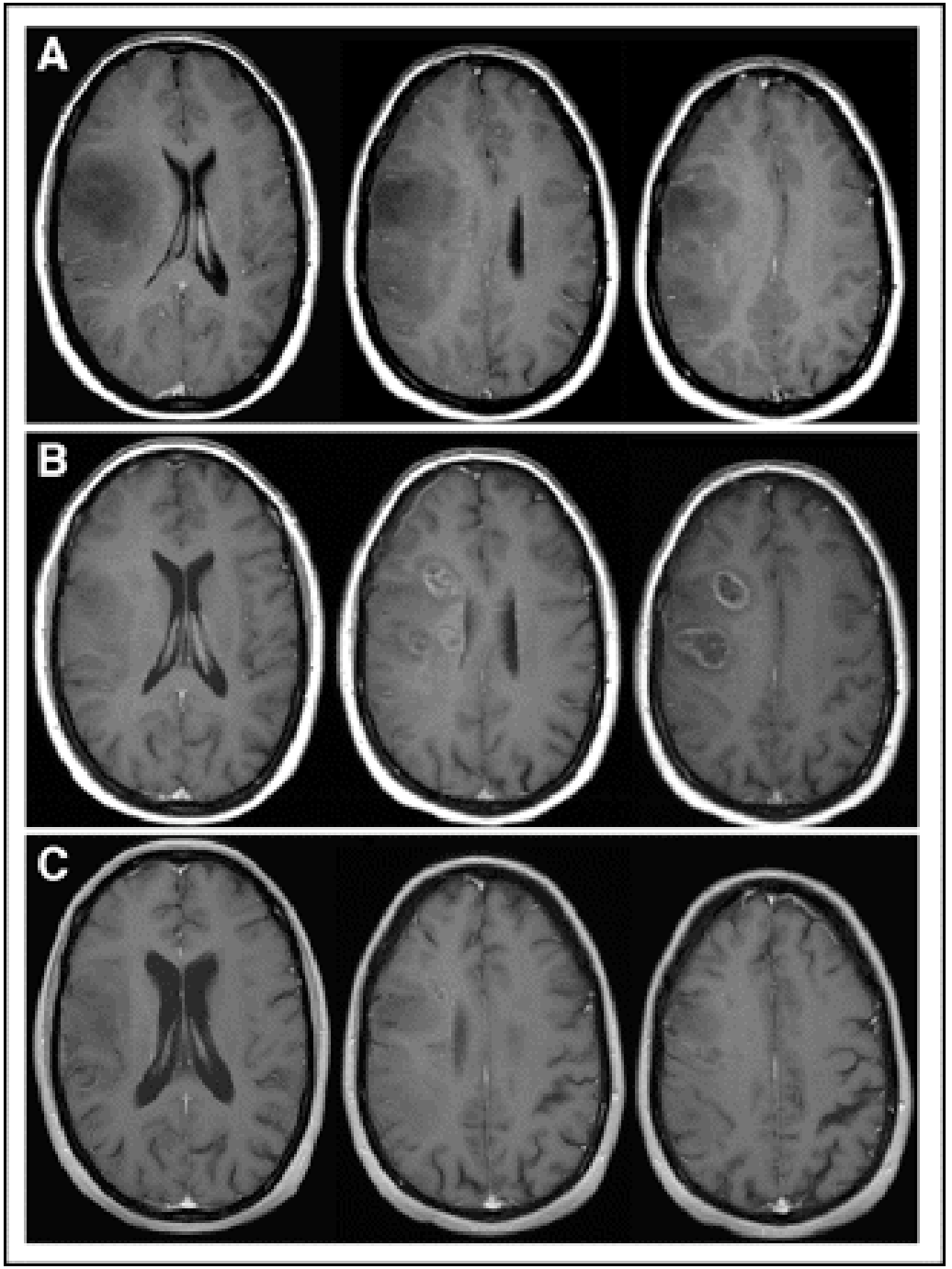
Chemoradiation for GBM

- continuous temozolomide associated with **lymphopenia**
  - exacerbated by prior and concomitant steroid treatment
  - prophylactic co-trimoxazole or pentamidine recommended if lymphocyte count <0.5
- adjuvant temozolomide associated with **neutropenia, thrombocytopenia and fatigue**
- occasional patients experience pancytopenia during concomitant treatment
- no increase in **late neurotoxicity** documented to date
- **'pseudoprogression'** on post-RT imaging
  - may reflect treatment related inflammation or necrosis
  - no validated imaging methods for discriminating progression from pseudoprogression

Post-op, pre-CRT

1 month post-CRT

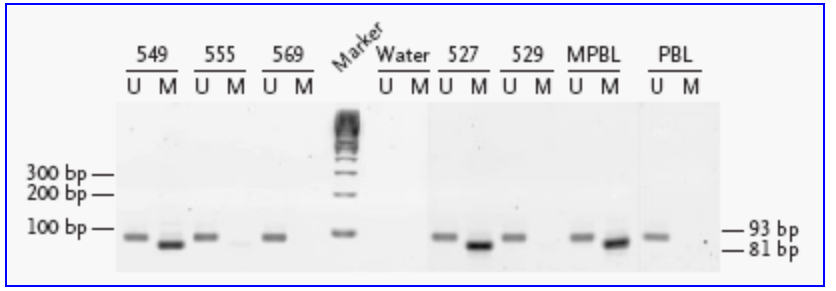
6 months post-CRT

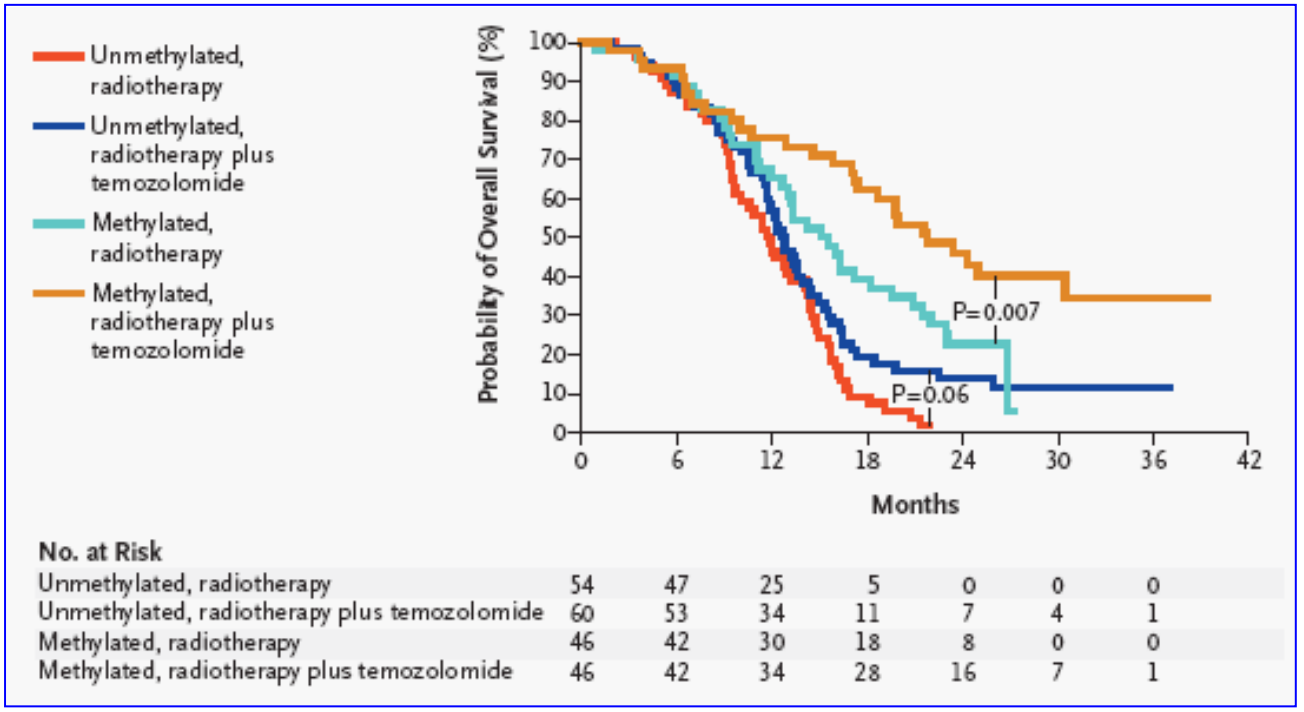


ORIGINAL ARTICLE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc.,





No. at Risk

Unmethylated, radiotherapy	54	47	25	5	0	0	0
Unmethylated, radiotherapy plus temozolomide	60	53	34	11	7	4	1
Methylated, radiotherapy	46	42	30	18	8	0	0
Methylated, radiotherapy plus temozolomide	46	42	34	28	16	7	1

- Can we overcome TMZ resistance by increasing dose intensity?

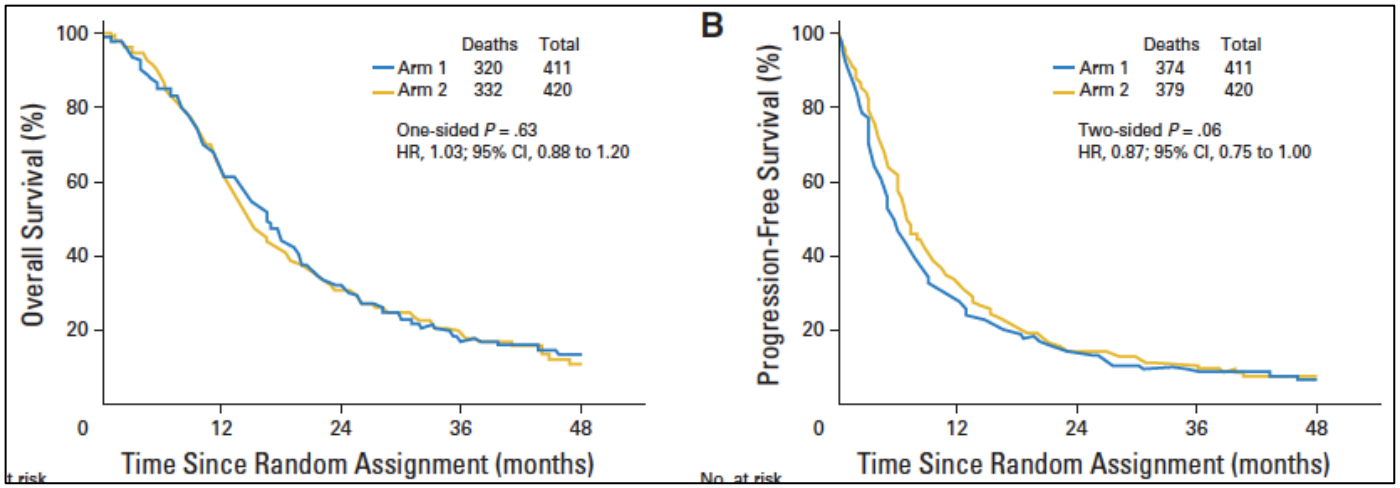
VOLUME 31 · NUMBER 32 · NOVEMBER 10 2013

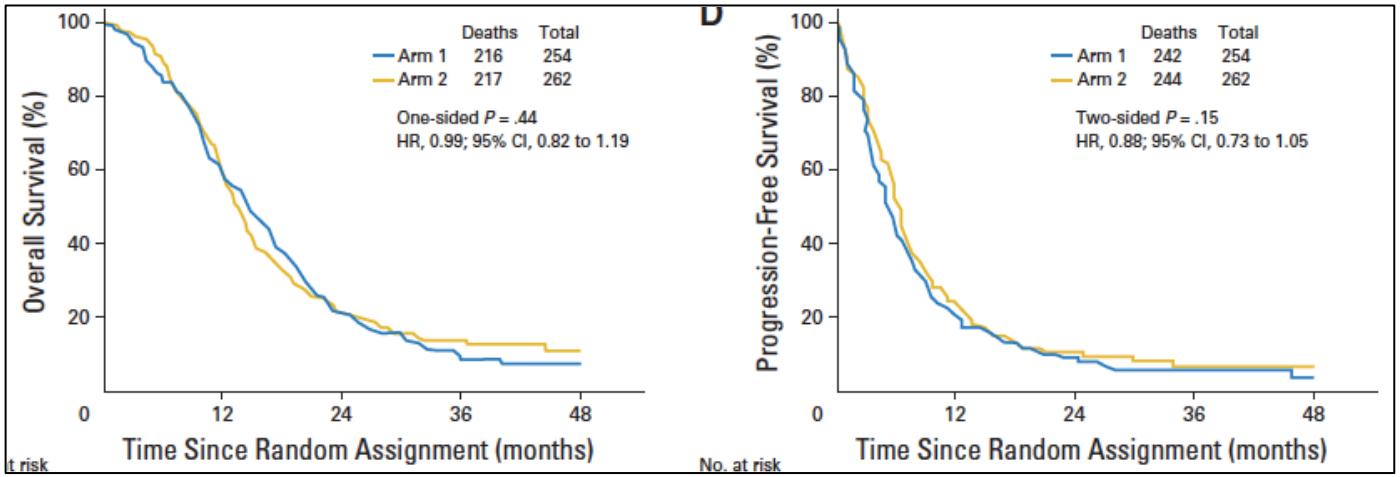
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Dose-Dense Temozolomide for Newly Diagnosed Glioblastoma: A Randomized Phase III Clinical Trial

Mark R. Gilbert, Meihua Wang, Kenneth D. Aldape, Roger Stupp, Monika E. Hegi, Kurt A. Jaeckle, Terri S. Armstrong, Jeffrey S. Wefel, Minhee Won, Deborah T. Blumenthal, Anita Mahajan, Christopher J. Schultz, Sara Erridge, Brigitta Baumert, Kristen I. Hopkins, Tzahala Tzuk-Shina, Paul D. Brown, Arnab Chakravarti, Walter J. Curran Jr, and Minesh P. Mehta





MGMT unmethylated

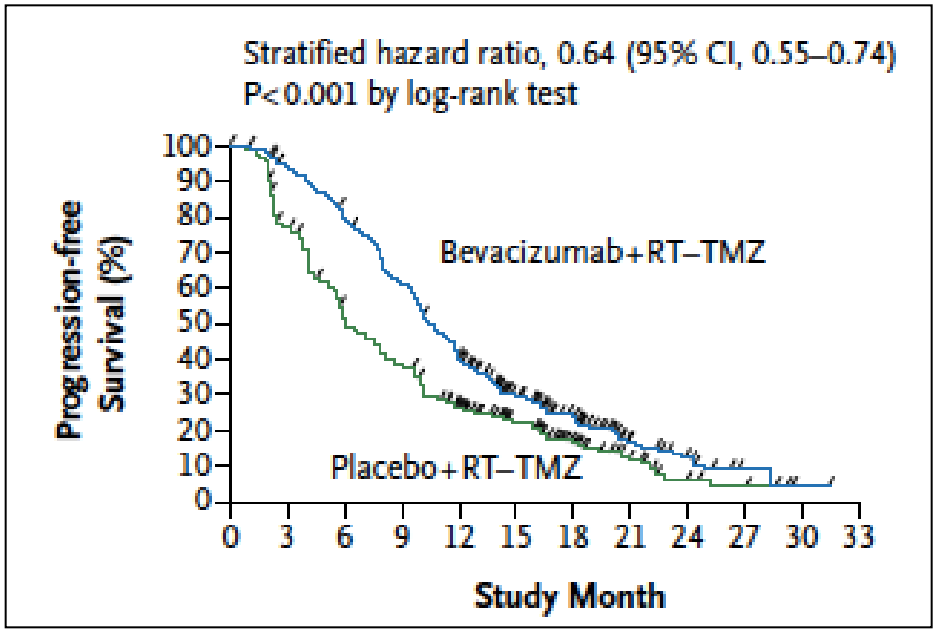
The NEW ENGLAND JOURNAL of MEDICINE

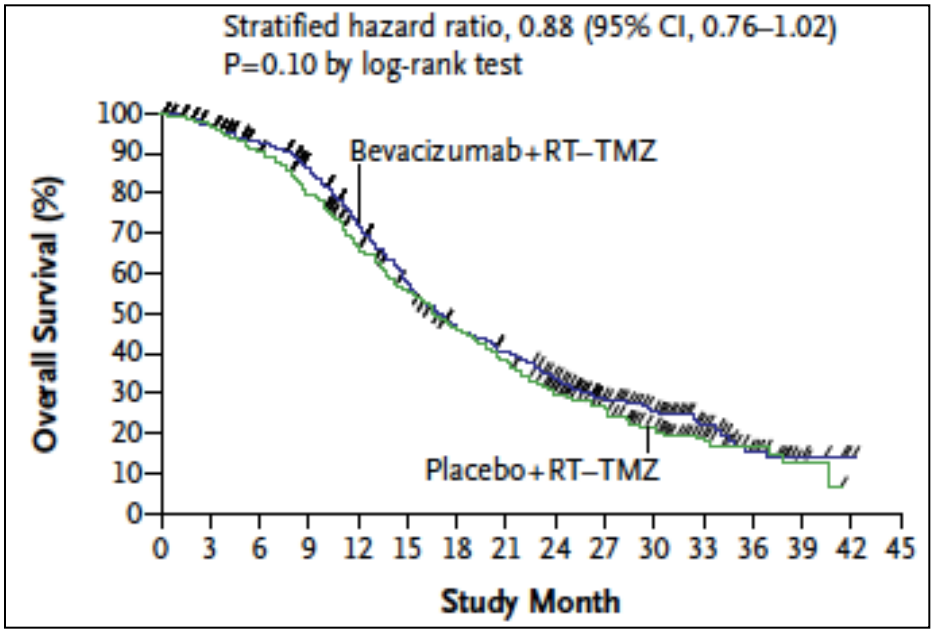
ORIGINAL ARTICLE

Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma

Olivier L. Chinot, M.D., Wolfgang Wick, M.D., Warren Mason, M.D., Roger Henriksson, M.D., Frank Saran, M.D., Ryo Nishikawa, M.D., Antoine F. Carpentier, M.D., Ph.D., Khe Hoang-Xuan, M.D., Ph.D., Petr Kavan, M.D., Ph.D., Dana Cernea, Ph.D., Alba A. Brandes, M.D., Magalie Hilton, M.Sc., Lauren Abrey, M.D., and Timothy Cloughesy, M.D.

AVAGLIO trial





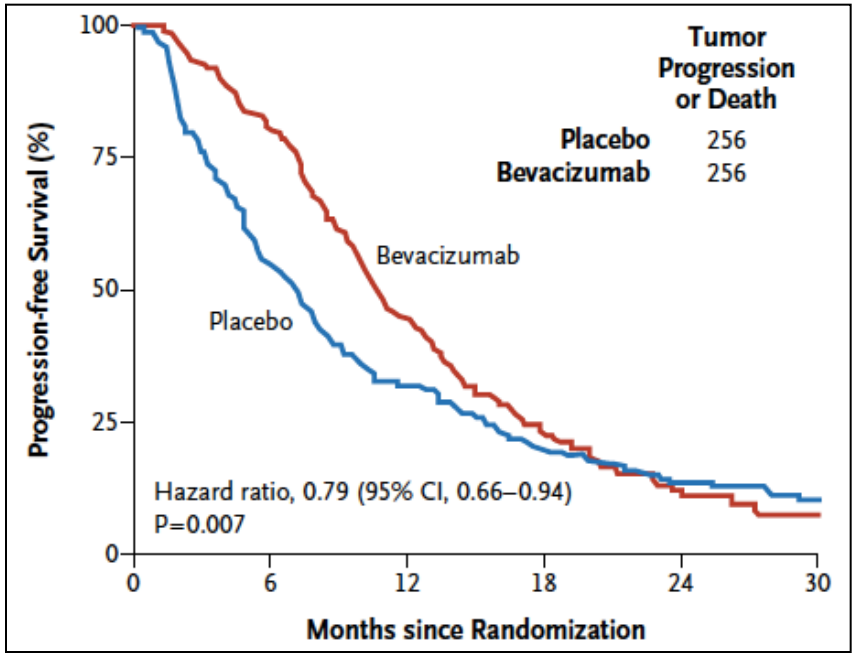
The NEW ENGLAND JOURNAL of MEDICINE

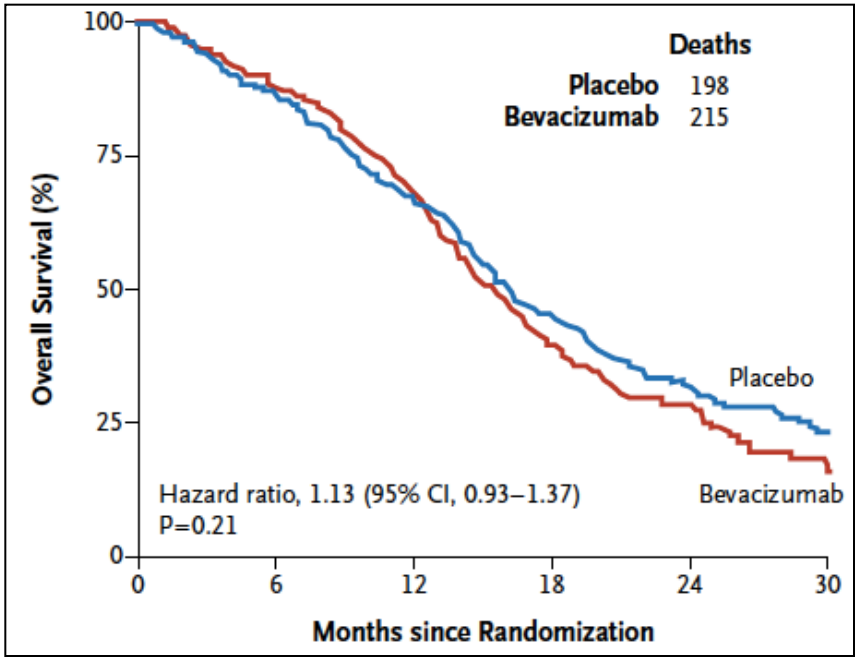
ESTABLISHED IN 1812 FEBRUARY 20, 2014 VOL. 370 NO. 8

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

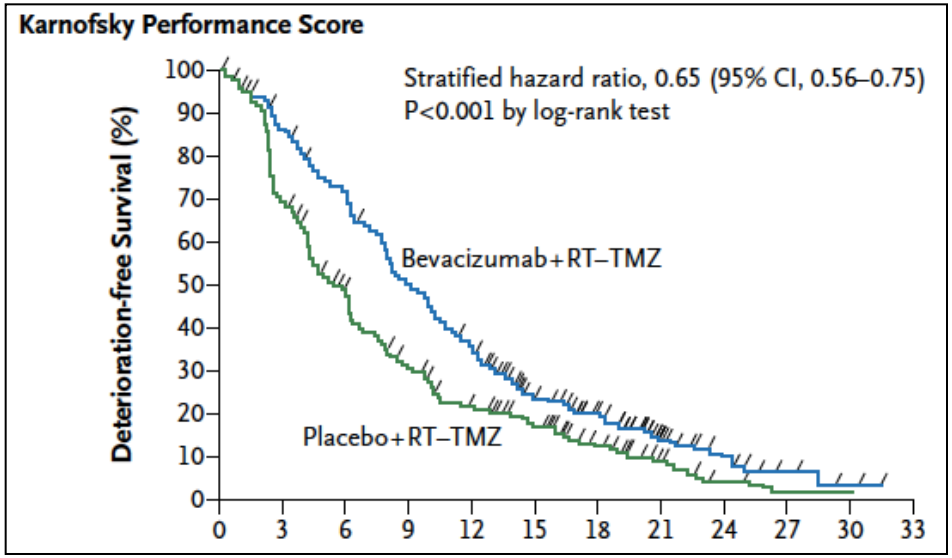
Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.A., Robert Jeraj, Ph.D., Paul D. Brown, M.D., Kurt A. Jaeckle, M.D., David Schiff, M.D., Volker W. Stieber, M.D., David G. Brachman, M.D., Maria Werner-Wasik, M.D., Ivo W. Tremont-Lukats, M.D., Erik P. Sulman, M.D., Kenneth D. Aldape, M.D., Walter J. Curran, Jr., M.D., and Minesh P. Mehta, M.D.

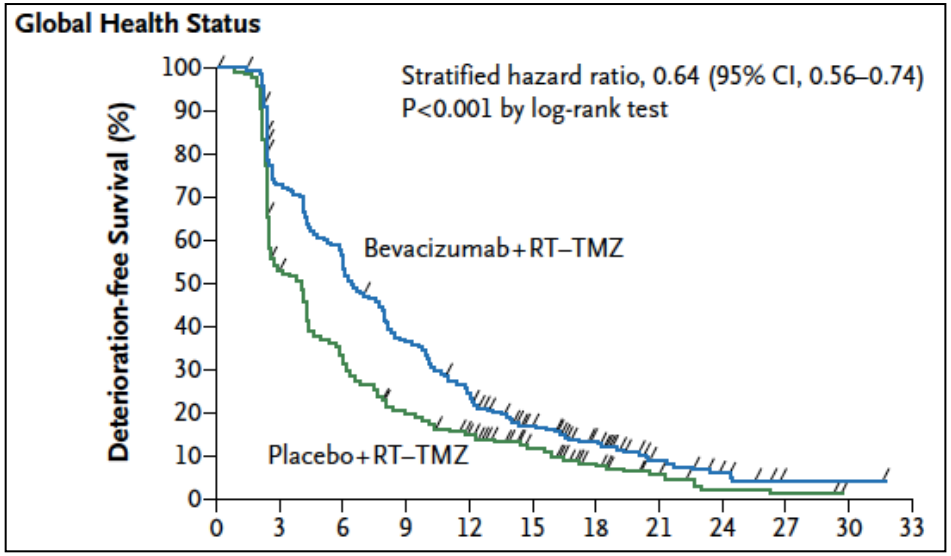
RTOG 0825





Does bevacizumab maintain QoL?





NET CLINICAL BENEFITS

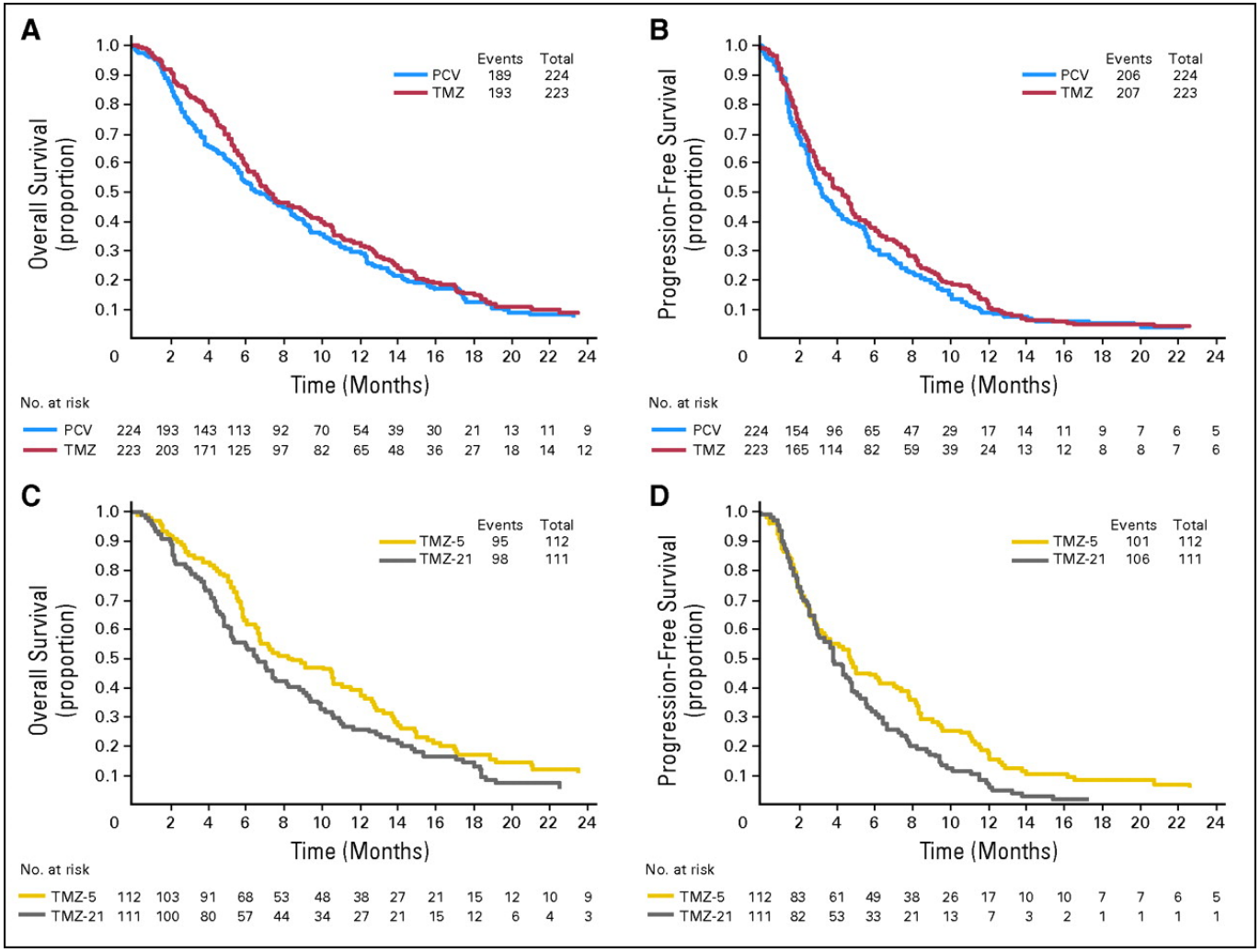
In the NCB substudy, we found greater deterioration over time in the bevacizumab group than in the placebo group on the basis of the between-group difference in the composite scores on the neurocognitive-function test battery (P=0.05), as well as the scores for the Con-

Longitudinal evaluation also revealed greater deterioration in the bevacizumab group on the basis of the MDASI-BT composite symptom score (P=0.02), composite symptom-interference score (P<0.001), and the scores for activity-related

During the maintenance phase, serious adverse events were more prevalent in the bevacizumab group than in the placebo group, including hypertension (4.2% vs. 0.9%), thromboembolic disease (7.7% vs. 4.7%), wound dehiscence (1.5% vs. 0.9%), fatigue (13.1% vs. 9.0%), visceral perforation (1.2% vs. 0.4%), and serious hemorrhage (1.5% vs. 0.9%).

Recurrent GBM:

BR12 trial: PCV v TMZ (5/28) v TMZ (21/28)

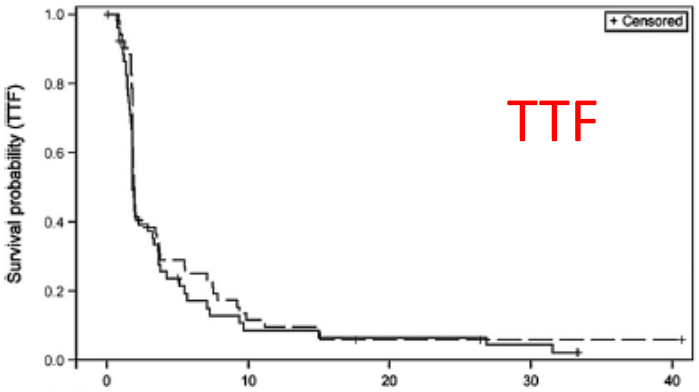


Michael Brada et al. JCO 2010;28:4601-4608

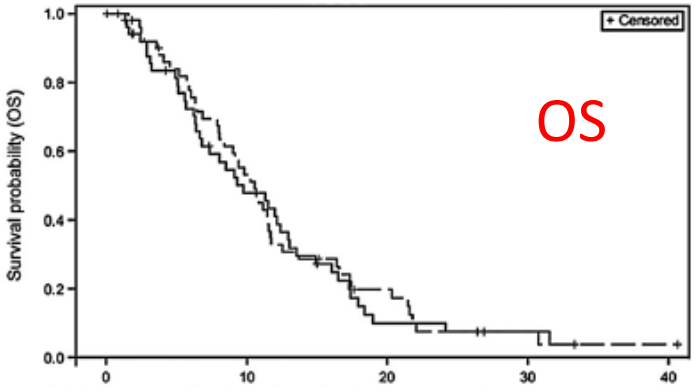
Personalized Medicine and Imaging

Clinical Cancer Research

MGMT Promoter Methylation Is a Strong Prognostic Biomarker for Benefit from Dose-Intensified Temozolomide Rechallenge in Progressive Glioblastoma: The DIRECTOR Trial

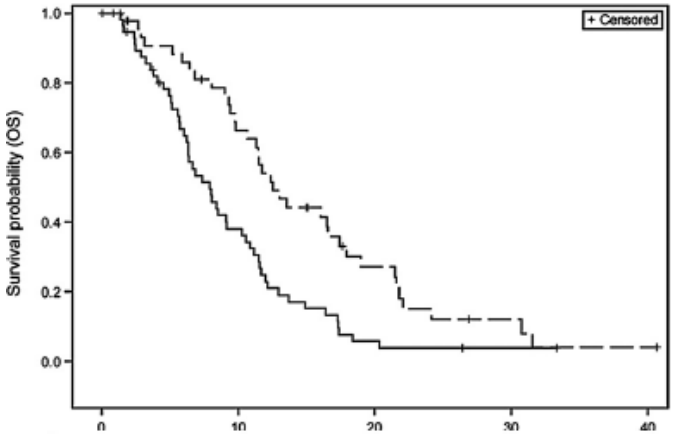


TTF



OS

TMZ 7/14 days
v. 21/28 days



Improved survival
in MGMT
methylated

Relapsed GBM after RT-TMZ

- **No established standard**
  - re-resection +/- carmustine wafers?
  - PCV?
  - various studies of chemo + bevacizumab
    - High response rates but no clear survival benefit
  - cediranib (VEGFR inhibitor) +/- CCNU:
    - no benefit
  - other studies of EGFR TK inhibitors
    - erlotinib associated with *reduced* PFS (van den Bent JCO 2009)
  - TMZ rechallenge +/- altered temozolomide scheduling?

Opportunity to test novel agents

VOLUME 25 · NUMBER 30 · OCTOBER 20 2007

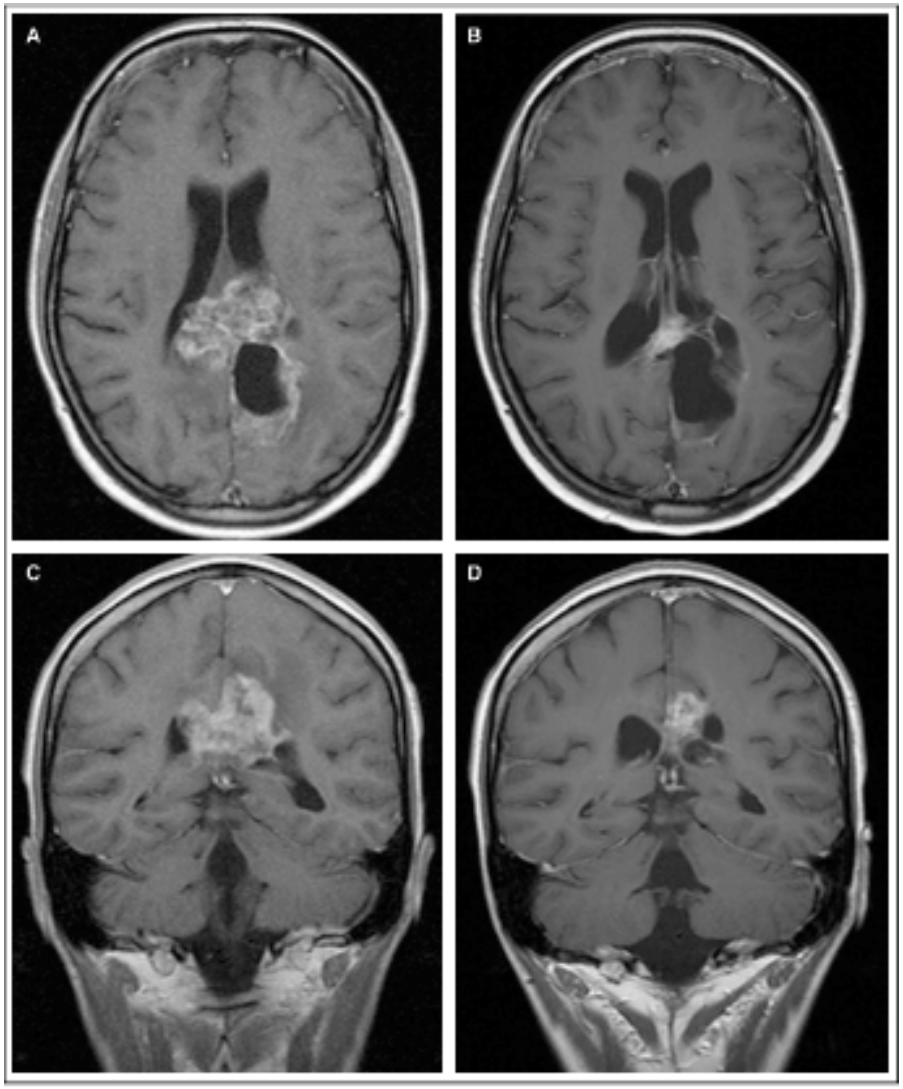
JOURNAL OF CLINICAL ONCOLOGY

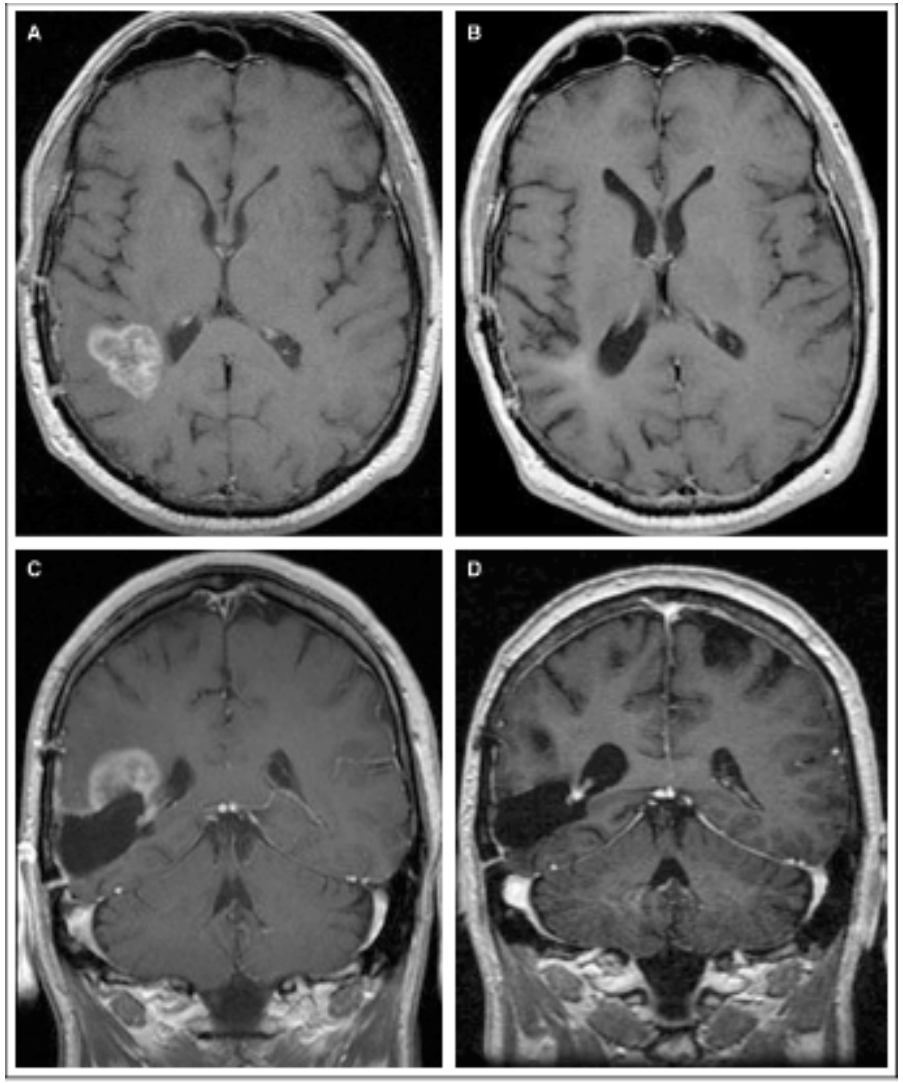
ORIGINAL REPORT

Bevacizumab Plus Irinotecan in Recurrent Glioblastoma Multiforme

James J. Vredenburgh, Annick Desjardins, James E. Herndon II, Jennifer Marcello, David A. Reardon, Jennifer A. Quinn, Jeremy N. Rich, Sith Sathornsumetee, Sridharan Gururangan, John Sampson, Melissa Wagner, Leighann Bailey, Darell D. Bigner, Allan H. Friedman, and Henry S. Friedman

- 35 patients, median 2 progressions
- Median time from diagnosis 14 months
- 57% RR
- 6 month PFS 46%
- 11 patients discontinued because of toxicity





Response v. pseudoresponse?

42 year old patient with MGMT methylated GBM, >90% resection, RT-TMZ. Recurrent, inoperable disease 14 months after completing adjuvant TMZ; PS=1. I would recommend:

A. TMZ rechallenge, 5/28 day schedule
B. TMZ rechallenge, 21/28 day schedule
C. PCV
D. TMZ + bevacizumab
E. Bevacizumab + irinotecan

61 year old patient with MGMT unmethylated GBM, >90% resection, RT-TMZ. Recurrent, inoperable disease 5 months after completing adjuvant TMZ; PS=1. I would recommend:

A. TMZ rechallenge, 5/28 day schedule
B. PCV
C. TMZ + bevacizumab
D. Bevacizumab + irinotecan
E. Best supportive care

Management of ependymoma of the brain and spinal cord

Prof. Damien Charles Weber

Prof. Ranjeev Bhangoo

Intracranial EP

Introduction (1)

- Originate from **ependymal cells** lining the ventricules and central canal
- Classified according to the **WHO** classification (i.e. grade 1*-2-3)
- **30%** of change of grading after centreal review UKCCR/SIOP (50%/50%)
- Can arise anywhere in the CNS but show a preference for the **posterior fossa (Children+++)**
- In older patients, ependymoma often arise within the brain parenchyma

Introduction (2)

Posterior fossa ependymoma

- 69% occur in children
- 3rd most common pediatric brain tumor
- 50% occur before the age of 5 years
- 58% presents in IV ventricule
- 5-6% of all intracranial tumors

Differential diagnosis of ventricule tumors

- **Ependymoma**
- Subependymoma
- MB
- Astrocytoma
- Epidermoid
- Choroid Plexus tumors

Introduction (3)

Treatment

- Goal: Gross total resection
- Recurrence frequent

Aduvant therapy

- RT beneficial
- Chemotherapy: no proven benefit

Outcome

	n	Event-free survival (%)		Overall survival (%)		"Radiotherapy-free" survival
		3-year	5-year	3-year	5-year	
Pediatric Oncology Group[3,22]	48	46*	27	58*	40·5	0
Children's Cancer Group[6]	15	26	18	NA	NA	NA
SFOP[2]	73	40*	22	68*	52	22
CCG-9921	74	50*	32	65	59	40
St Jude[4]	48	69·5	55†	NA	NA	0
This study	89	48	42	79·3	63	42

NA=not available. *Estimated on the basis of exponential survival using the quoted 5-year rates. †Projected survival, assuming exponential survival rates. The German Paediatric brain tumour studies are not included as they only include anaplastic (grade III) tumours on Hirntumor Säuglinge und Kleinkinder (HIT-SKK) protocols.

- Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study

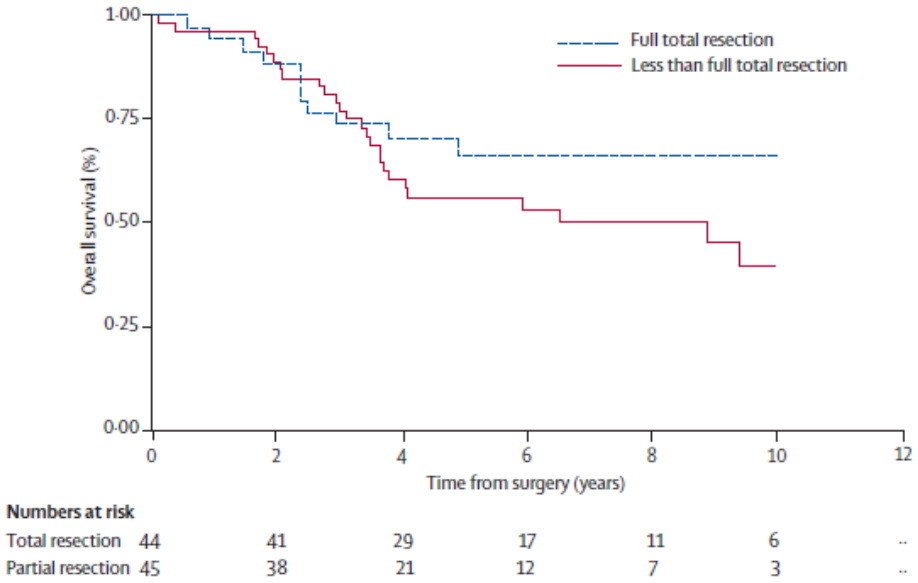
Lancet Oncol 2007; 8: 696–705

EP Prognostic factors

	N	HR for death (95% CI)	p
Age <1 year at diagnosis	14	1·4 (0·9-2·2)	0·18
Female sex	31	1·1 (0·5-2·1)	0·13
Infratentorial ependymoma	76	3·1 (0·8-12·5)	0·12
WHO III histology	30	1·6 (0·8-3·2)	0·15
Partial resection (judged by neurosurgeon)	45	1·8 (0·9-3·6)	0·07
Partial resection (judged by radiological review)	55	1·5 (0·7-3·0)	0·28
Dose intensity <0·8	32	1·6 (1·0-2·7)	0·04

- Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study

Lancet Oncol 2007; 8: 696–705



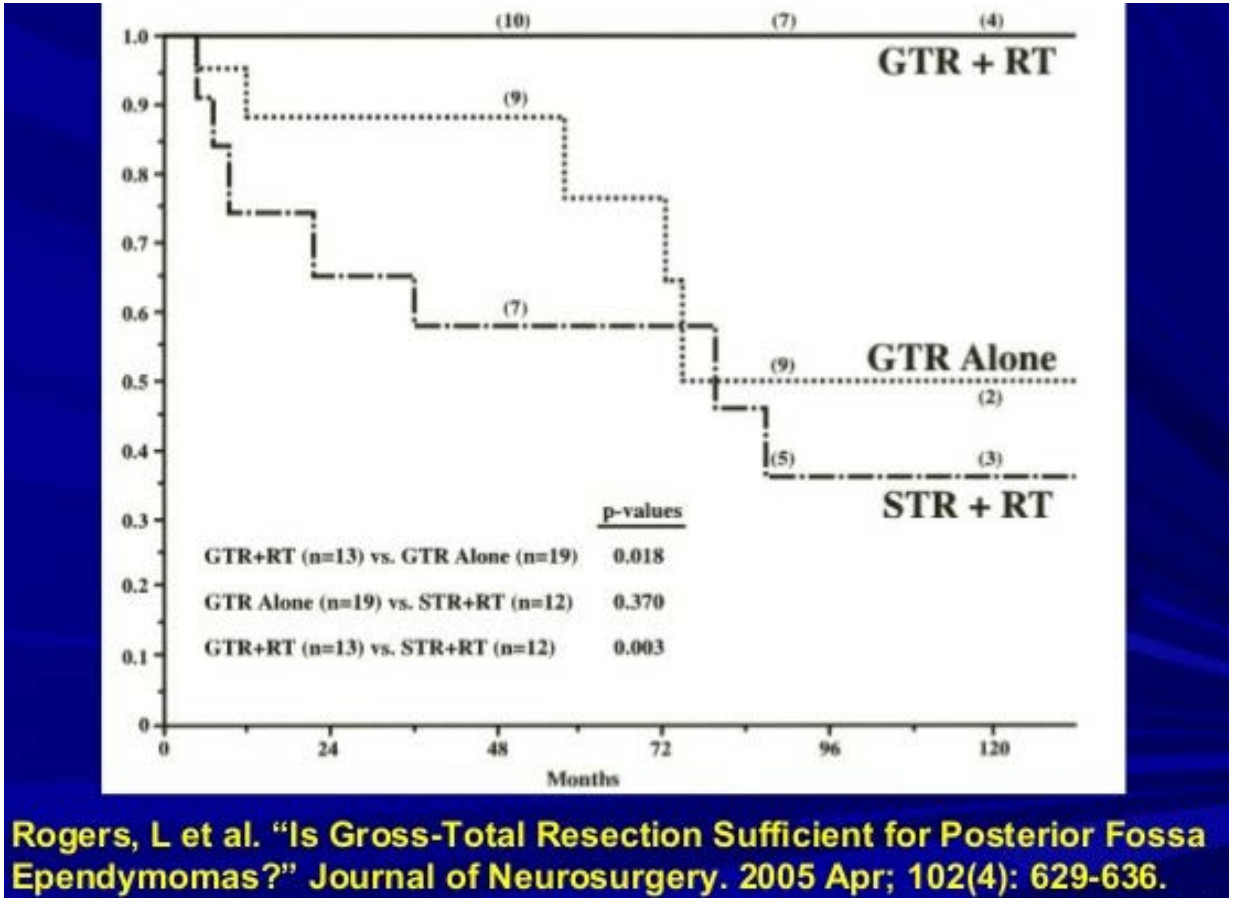
ESTRO School

Prognostic factors

Characteristics of treatment in patients with posterior fossa ependymomas

Characteristic	No. of Patients (%)
total no. of patients	45 (100)
method of treatment	
GTR w/o radiotherapy	19 (42)
GTR plus radiotherapy	13 (29)
STR w/o radiotherapy	1 (2)
STR plus radiotherapy	12 (27)
extent of postop radiotherapy (25 patients)	
local only	19 (76)
craniospinal w/ local boost	6 (24)
final posterior fossa/tumor bed radiation dose (Gy)	
median	54.0
range	44.0–59.4

Rogers, L et al. "Is Gross-Total Resection Sufficient for Posterior Fossa Ependymomas?" Journal of Neurosurgery. 2005 Apr; 102(4): 629-636.



Rogers, L et al. "Is Gross-Total Resection Sufficient for Posterior Fossa Ependymomas?" Journal of Neurosurgery. 2005 Apr; 102(4): 629-636.

EP and chemotherapy

- Direct evaluation of the response of EP to several chemotherapy agents has **failed** to demonstrate significant chemosensitivity
- However, given the concern of radiation-related neurotoxicity in (very) young children, **several trials of postoperative chemotherapy** have been undertaken
- Response rate to single agents is **11%**, with < **5% complete responses**, **CDDP** being the most active agent in phase II studies

EP and chemotherapy

Table 1 Response rate to single agents in recurrent ependymoma (*CR* complete response, *PR* partial response)

Agent	CR+PR/patients	CR	Reference
Cisplatin	11/33	6	[2–5]
Carboplatin	4/31		[6, 7]
AZQ	2/29	2	[18–22]
Ifosfamide	1/20		[11, 12]
Idarubicin	0/13		[27]
thio-TEPA	0/12		[13, 14]
Dibromodulcitol	0/12		[23]
PCNU	1/11	1	[8, 9]
Etoposide	2/9	1	[16, 17]
Iproplatin	0/7		[7]
Topotecan	0/4		[15]
Procarbazine	0/3		[24–26]
Cyclophosphamide	1/2		[10]
Interferon-β	0/2		[29]
Interferon-α	1/1		[28]
Paclitaxel	0/1		[30]
Vincristine	0/1		[24]
Cytarabine	0/1		[24]
Total	21/192 (11%)	9 (4.6%)	

Child's Nerv Syst (1999) 15:563–570

E. Bouffet
N. Foreman

Chemotherapy for intracranial ependymomas

EP and chemotherapy

Number of patients	N=19
Age	3-14 years (median, 7.5 years)
Regimen	carboplatin, 560 mg/m2, with vincristine, 1.5 mg/m2, weekly for 3 weeks, alternating at 4-week intervals with ifosfamide, 1.8 g/m2, and etoposide, 100 mg/m2, for 5 consecutive days for a total of 4 cycles
5 years PFS	**74%**
Prognostic factors	The extent of surgical resection was not a significant prognostic factor in this study
PD with non-R0	**20%**

Cancer. 1997 Jul 15;80(2):341-7.

Adjuvant chemotherapy for the treatment of intracranial ependymoma of childhood.

Needle MN[1], Goldwein JW, Grass J, Cnaan A, Bergman I, Molloy P, Sutton L, Zhao H, Garvin JH Jr, Phillips PC

EP and chemotherapy

	Results
Number of M0 patients	N=80
FFRT	42% (95% CI 32–53)
Median FU	6 years (range 1·5–11·3)
OS-5 years	63·4% ((95% CI 51·2–73·4)

Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study

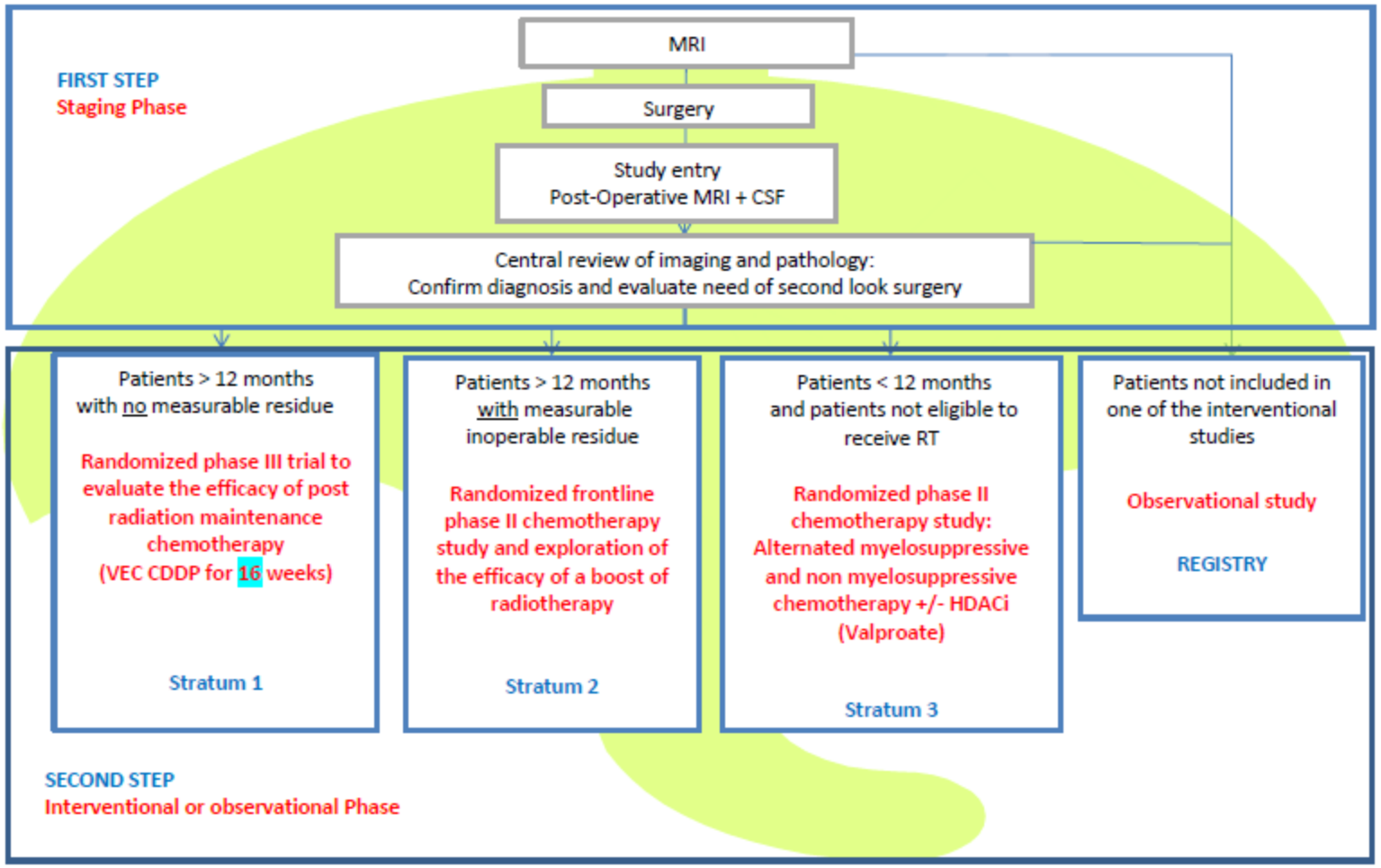
Richard G Grundy, Sophie A Wilne, Claire L Weston, Kath Robinson, Linda S Lashford, James Ironside, Tim Cox, W Kling Chong, Richard H A Campbell, Cliff C Bailey, Rao Gattamaneni, Sue Picton, Nicky Thorpe, Conor Mallucci, Martin W English, Jonathan A G Punt, David A Walker, David W Ellison, David Machin, for the Children's Cancer and Leukaemia Group (formerly UKCCSG) Brain Tumour Committee

Current stratgey

SIOP EPENDYMOMA II

An international clinical program for the diagnosis and treatment of children, adolescents and young adults with ependymoma

INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY



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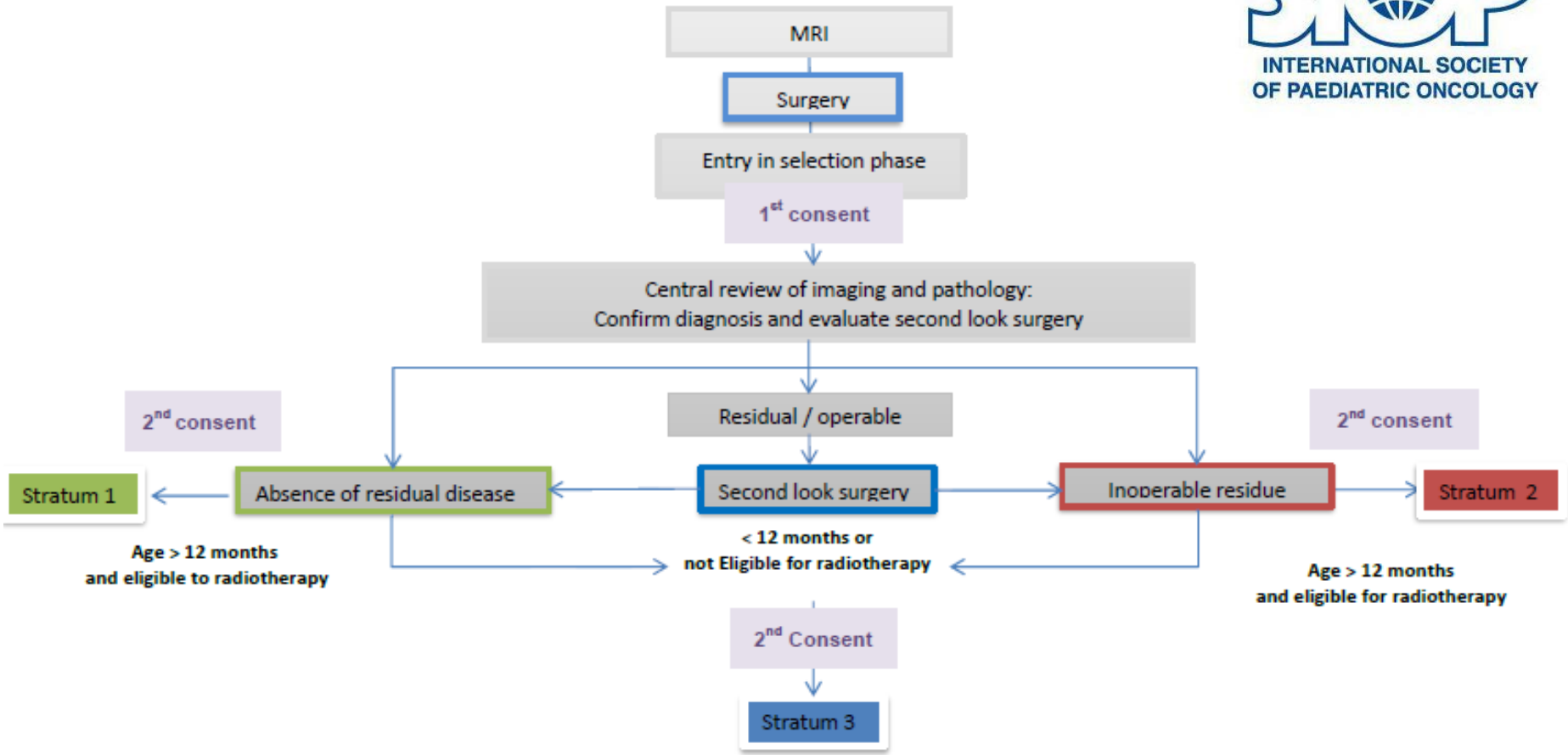
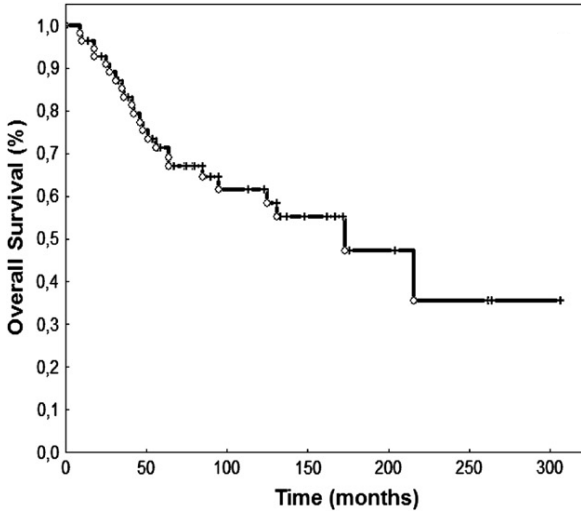
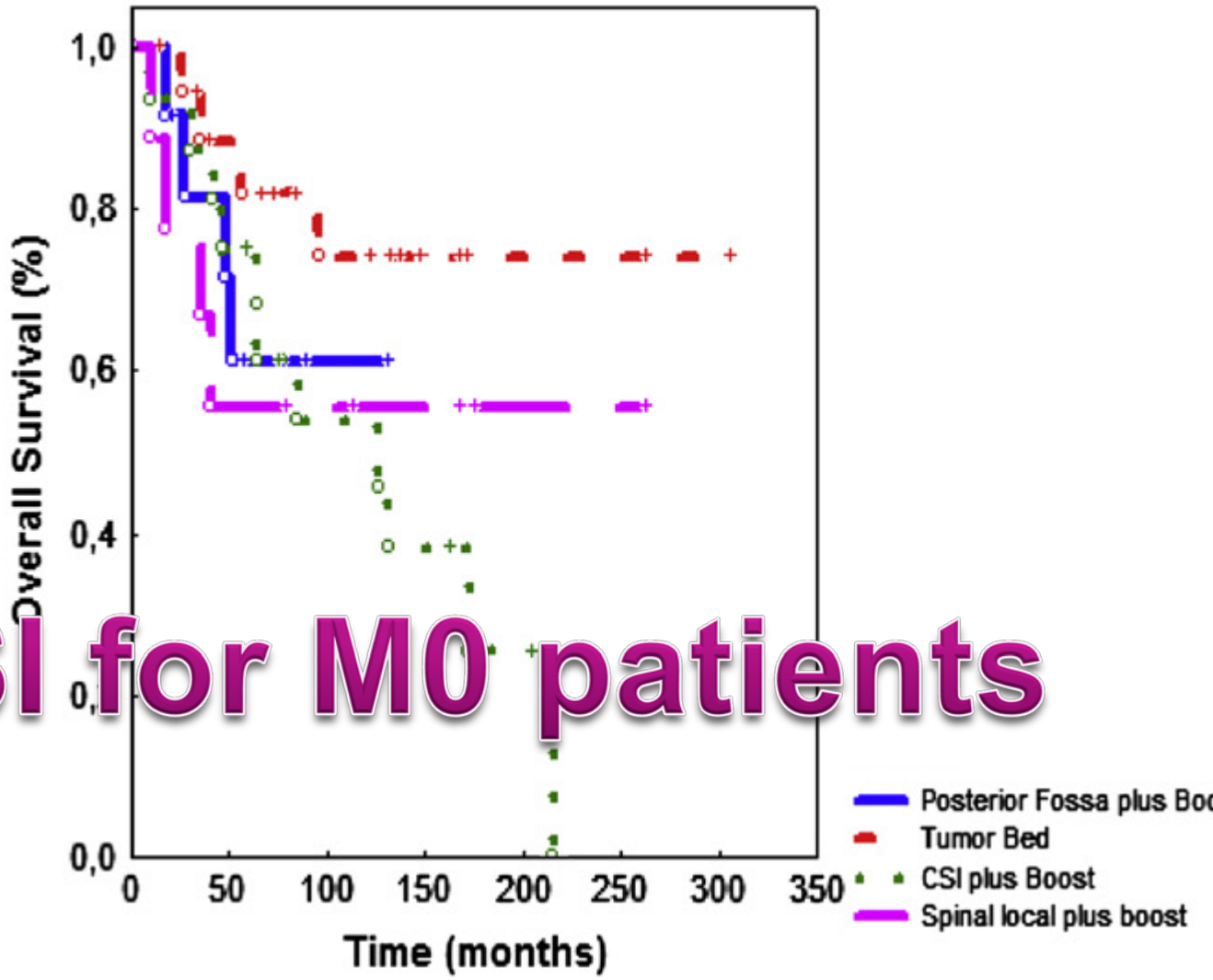
Current strategy



RT and EP (treatment volume)





No CSI for M0 patients

INFLUENCE OF RADIOTHERAPY TREATMENT CONCEPT ON THE OUTCOME OF PATIENTS WITH LOCALIZED EPENDYMOMAS

STEPHANIE E. COMBS, M.D.,* VERENA KELTER,* THOMAS WELZEL, M.D.,* WOLFGANG BEHNISCH, M.D.,†

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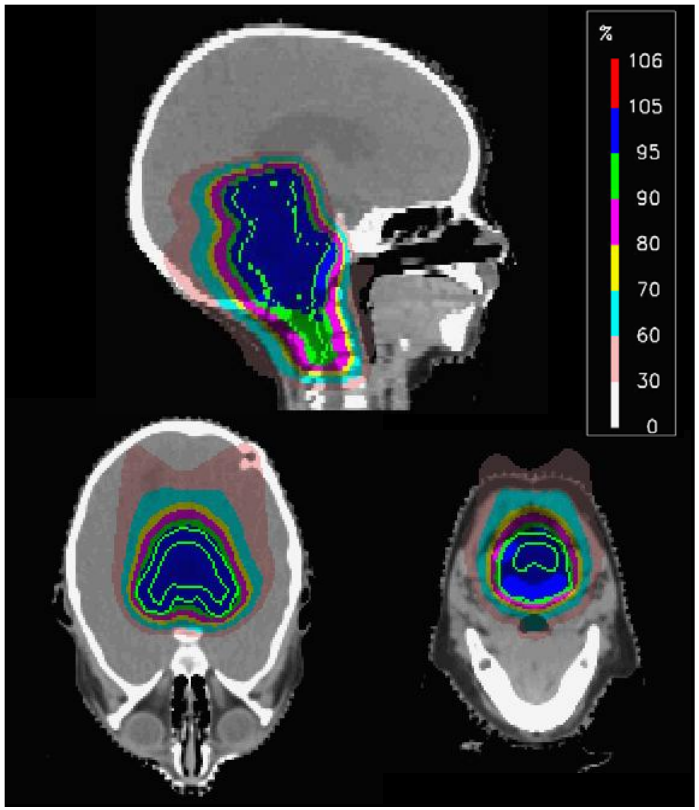
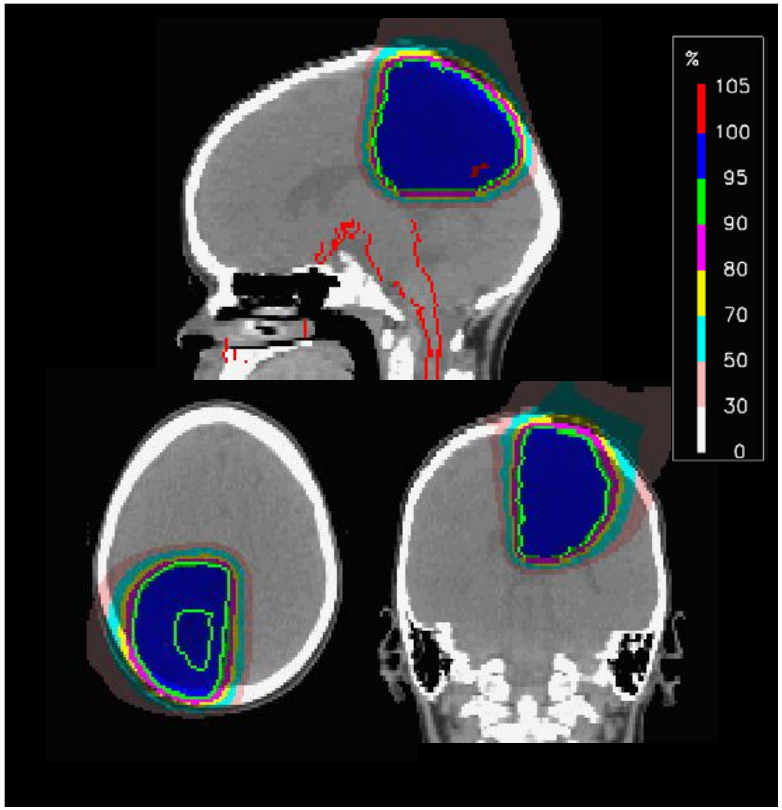
Example: 14 months old boy posterior fossa anaplastic ependymoma



Example: 4 years old boy supratentorial anaplastic ependymoma



Prescription dose 59.4 Gy(RBE) at 1.8 Gy(RBE)/fraction

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RT and EP (dose)

Conformal RT

59.4 Gy (children < 18 months or with risk factors (*): 54 Gy)

Daily fraction 1.8 Gy, 5 fractions/week

(*) multiple surgeries (more than 2) or poor neurological status.

RT and treatment duration

Treatment era	Craniospinal RT	Whole brain RT	Local RT	Total
1965–1975	1	1	2	4
1976–1985	8	7	0	15
1986–1997	5	1	9	15
Total	14	9	11	34

Reason for RT delay
Low blood counts
Patient compliance
Low blood counts
Planned split course
Low blood counts
Low blood counts
Patient compliance
Low blood counts
Low blood counts
Low blood counts
Low blood counts
Low blood counts, infection

Variable	<50 Days Frequency (%)	≥50 Days Frequency (%)	*p*-Value
Gender			NS
Male	17/22 (77.3)	9/12 (75.0)	
Female	5/22 (22.7)	3/12 (25.0)	
Age			NS
≤3 years	5/22 (22.7)	2/12 (16.7)	
>3 years	17/22 (77.3)	10/12 (83.3)	
Location			NS
Infratentorial	15/22 (68.2)	8/12 (66.7)	
Supratentorial	7/22 (31.8)	4/12 (33.3)	
Grade			NS
Low-grade	18/22 (81.8)	7/12 (58.3)	
High-grade	4/22 (18.2)	5/12 (41.7)	
Surgery			NS
GTR	9/22 (40.9)	3/12 (25.0)	
STR or Bx	13/22 (59.1)	9/12 (75.0)	
RT Volume			<0.01
Craniospinal	5/22 (22.7)	9/12 (75.0)	
WBRT or Local	17/22 (77.3)	3/12 (25.0)	
RT Dose			NS
4500–5399 cGy	10/22 (45.5)	6/12 (50.0)	
5400–6600 cGy	12/22 (54.5)	6/12 (50.0)	
Chemotherapy			NS
Yes	3/22 (13.6)	2/12 (16.7)	
No	19/22 (86.4)	10/12 (83.3)	

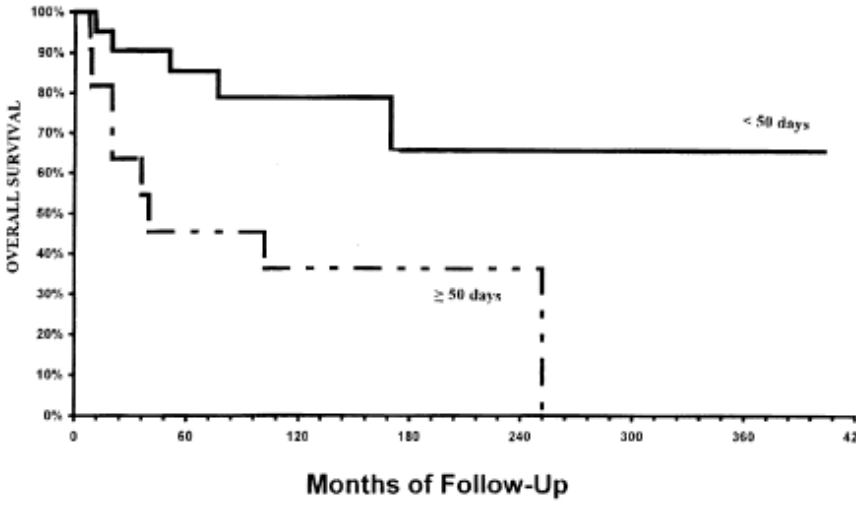
Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 3, pp. 585–589, 2000

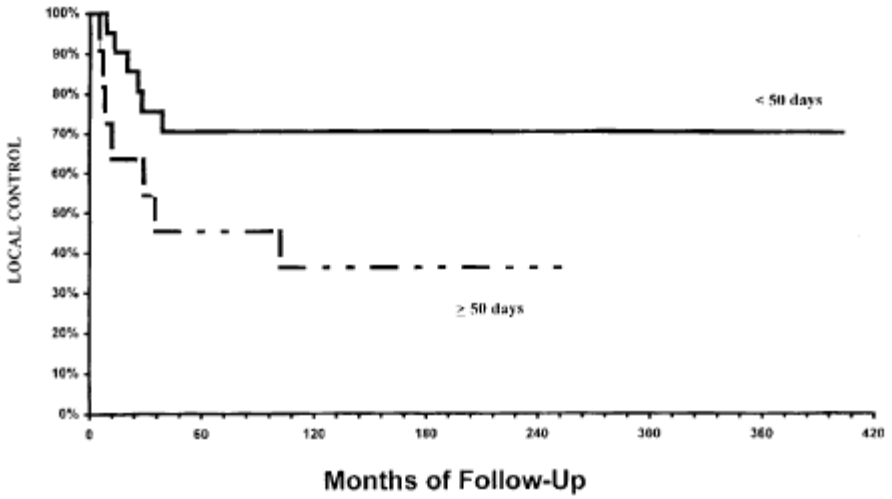
THE SIGNIFICANCE OF RADIOTHERAPY TREATMENT DURATION IN INTRACRANIAL EPENDYMOMA

ARNOLD C. PAULINO, M.D.,*† AND B-CHEN WEN, M.D.*

RT and treatment duration

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 3, pp. 585–589, 2000

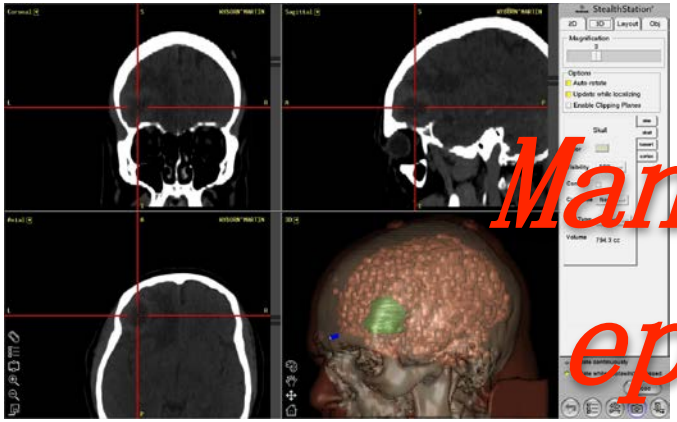




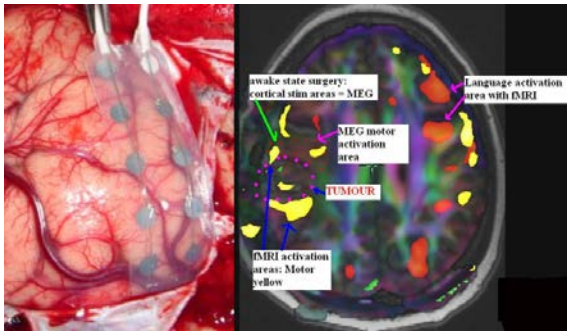
THE SIGNIFICANCE OF RADIOTHERAPY TREATMENT DURATION IN INTRACRANIAL EPENDYMOMA

ARNOLD C. PAULINO, M.D.,*† AND B-CHEN WEN, M.D.*

Spinal ependymoma



Management of ependymomas



Ranj Bhangoo, Francesco Vergani, Christian Brogna
Department of Neurosurgery
King's College Hospital - London

Adult intracranial ependymomas

- 2% adult intracranial tumours
- Data often from small series
- Controversy regarding treatment
- Role of chemotherapy/radiotherapy

Myxopapillary

- Commonly occurs in young adults in cauda equina
- Slow growing WHO Grade I
- ? Well Controlled after Surgery

WHO Grade I - Subependymoma

Slow growing noninvasive tumor

Are less cellular masses usually attached to the ventricle wall (cerebrospinal fluid filled cavity in the brain).

More common in adults and older men

Associated with long-term survival

Surgery can be potentially curative

WHO Grade II - Ependymoma (conventional)

Most common brain tumor in young children

Most common type of spinal glioma in adults

Often develop in the ventricles when intracranial

Several variants exist making diagnosis challenging:

- Cellular ependymoma
- Papillary ependymoma
- Clear cell ependymoma
- Tanycytic ependymoma

Can potentially recur as a higher grade tumor even after treatment

WHO Grade III Anaplastic Ependymoma

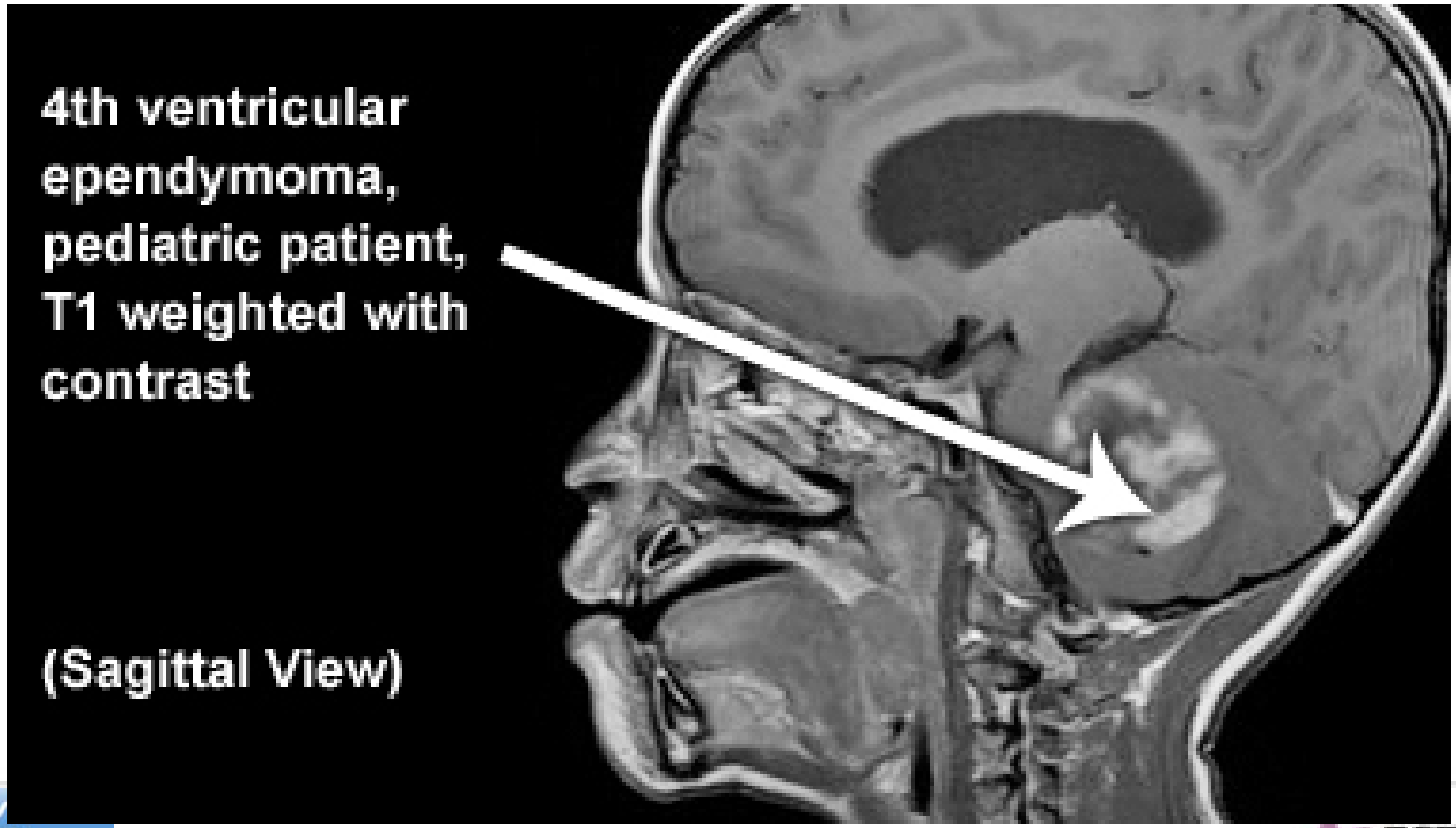
Show evidence of increased tumor cell growth compared to conventional ependymoma

Show evidence of new blood vessel formation to support active growth

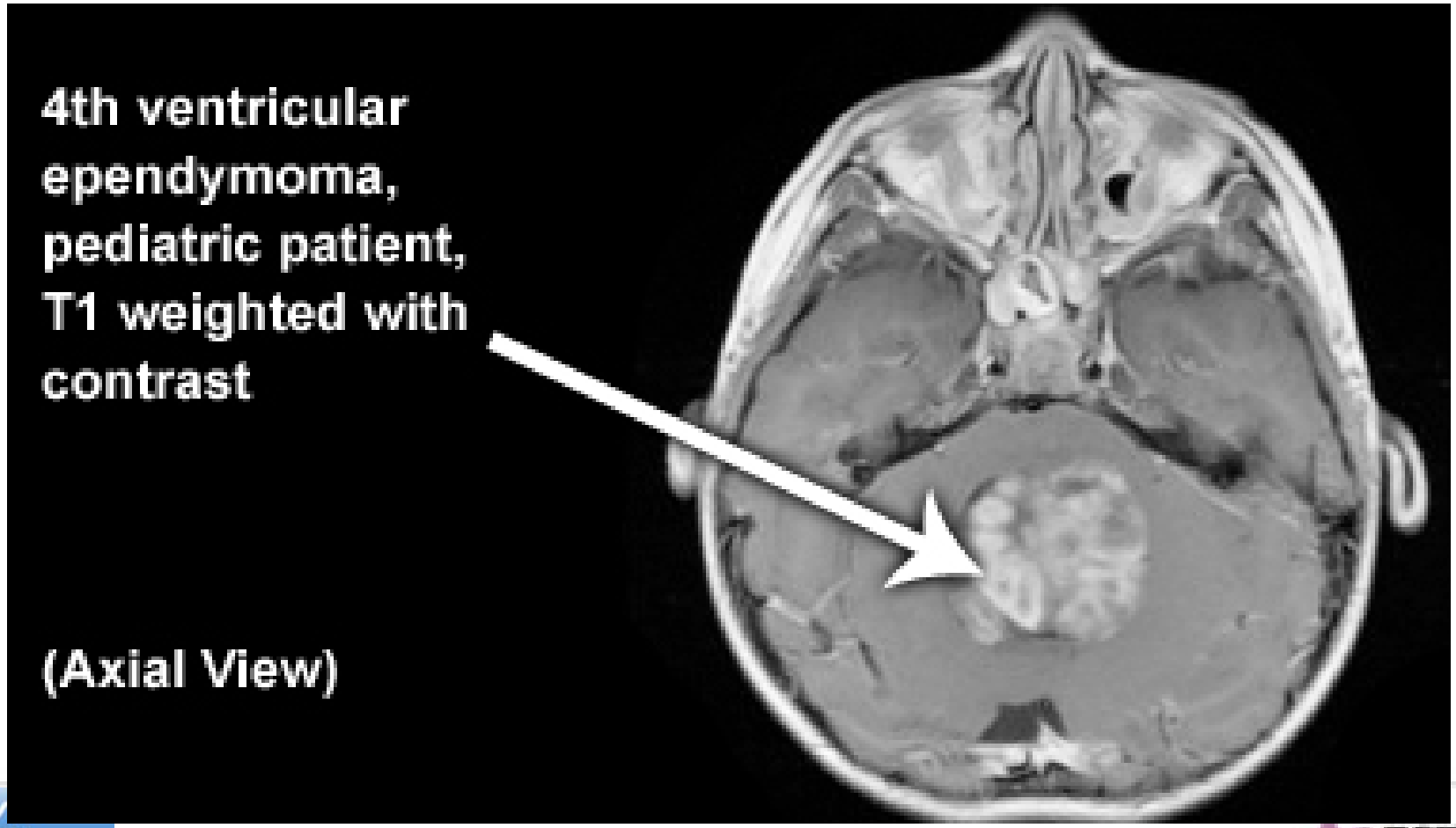
Exhibit more aggressive behavior than low grade ependymomas

Often require additional treatment after surgery and can recur

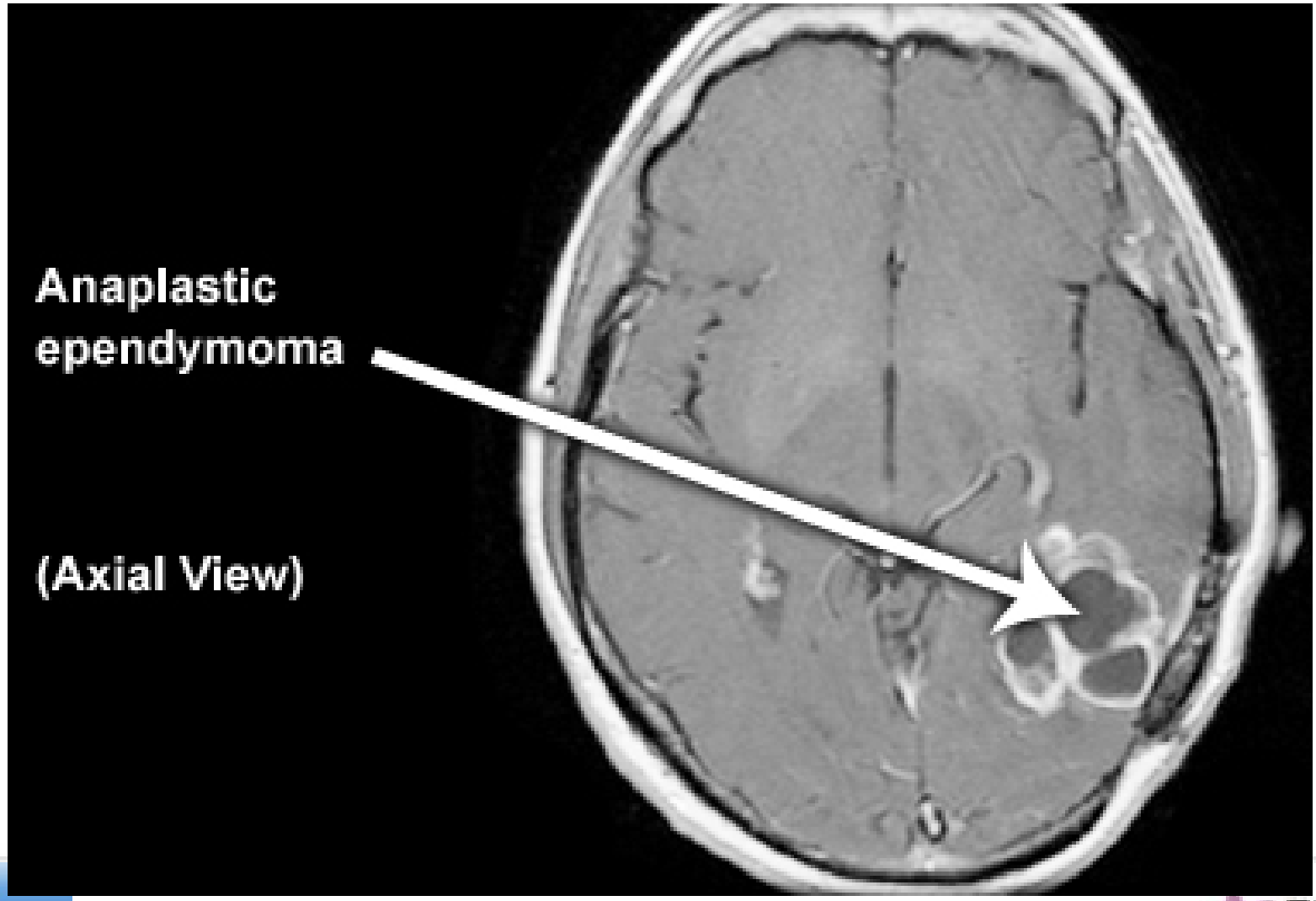
Paediatric Ependymoma



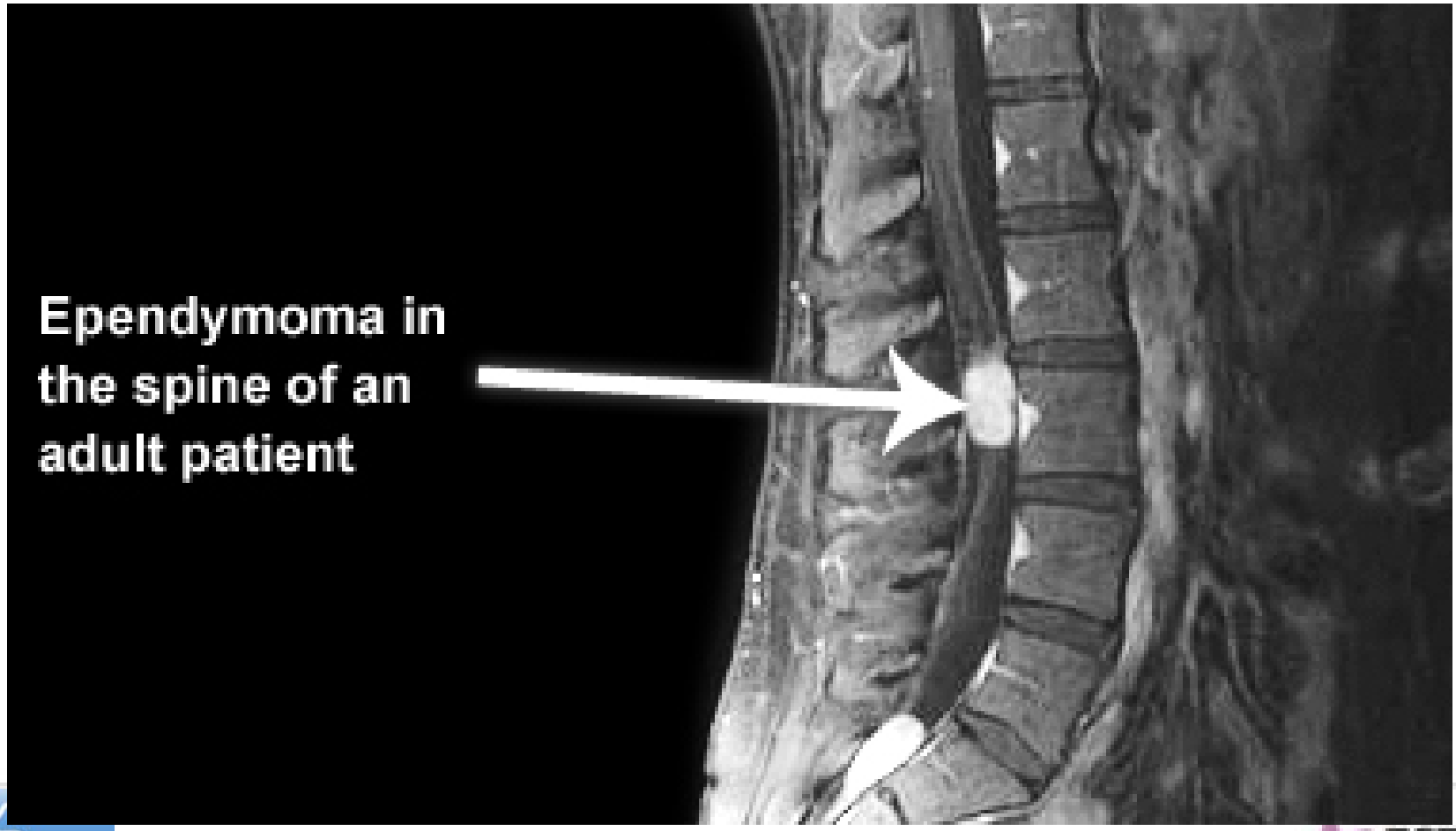
Paediatric Ependymoma



Adult Ependymoma



Drop Mets in Ependymoma



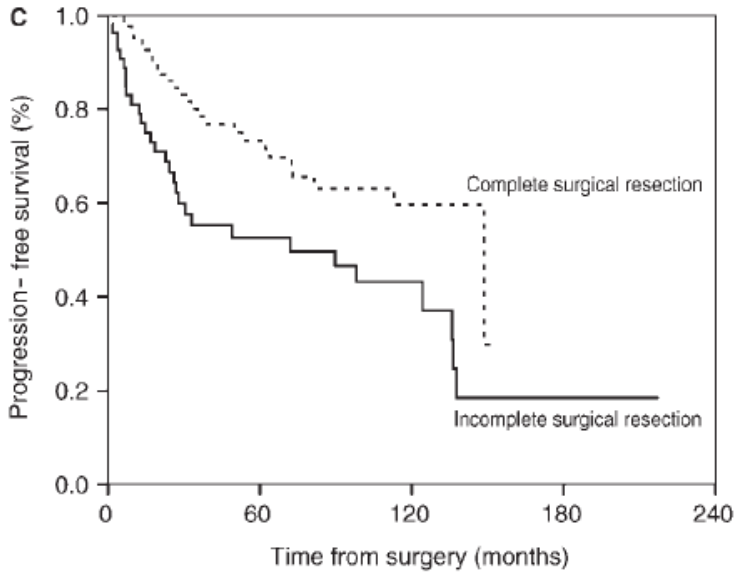
Treatment

- Treat any Hydrocephalus if needed
- Stage with Craniospinal MRI
- Macroscopic Resection if at all possible

Adult intracranial ependymomas

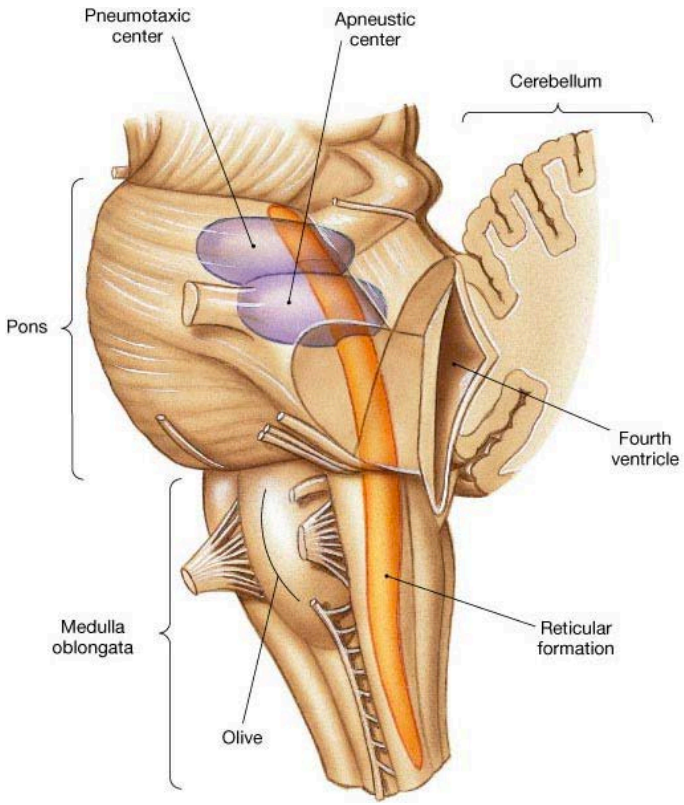
Multicentric French study on adult intracranial ependymomas: prognostic factors analysis and therapeutic considerations from a cohort of 152 patients

Philippe Metellus,[1] Marylin Barrie,[2] Dominique Figarella-Branger,[3] Olivier Chinot,[2] Roch Giorgi,[4] Joanny Gouvernet,[4] Anne Jouvet[5] and Jacques Guyotat[6]

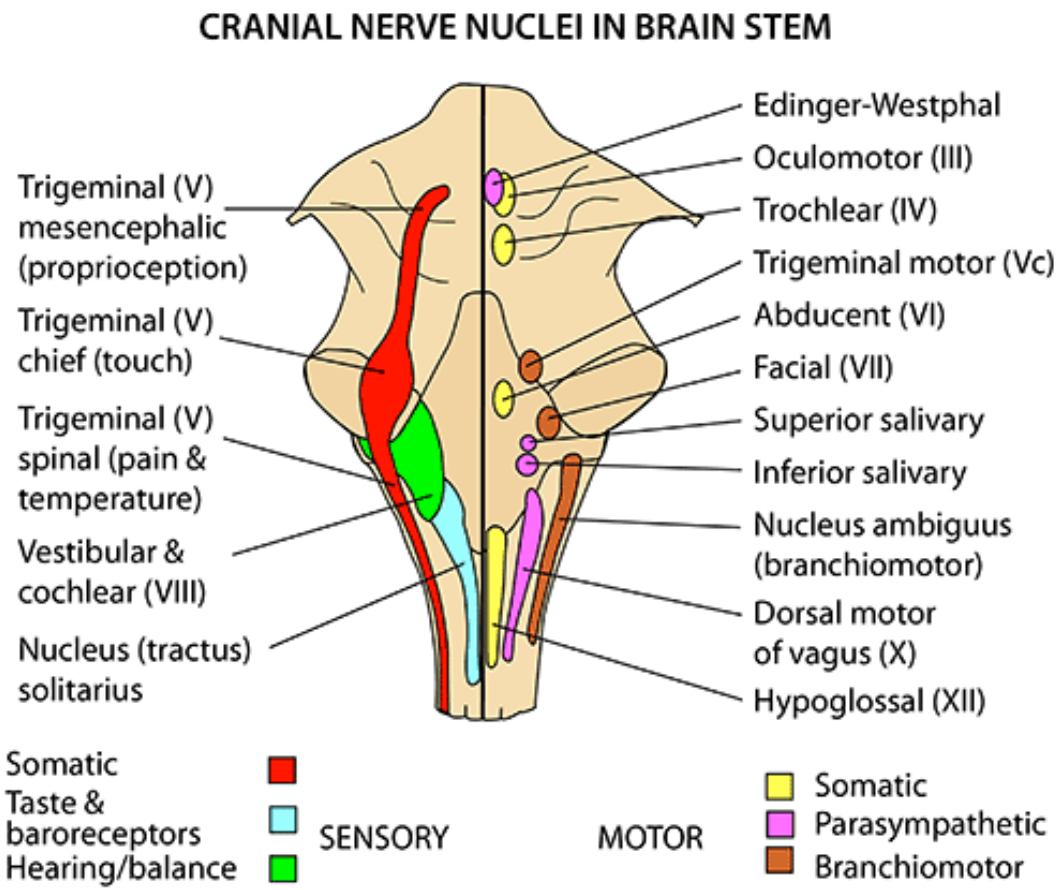


Metellus et al. Brain, 2007

Anatomy of the Brain Stem

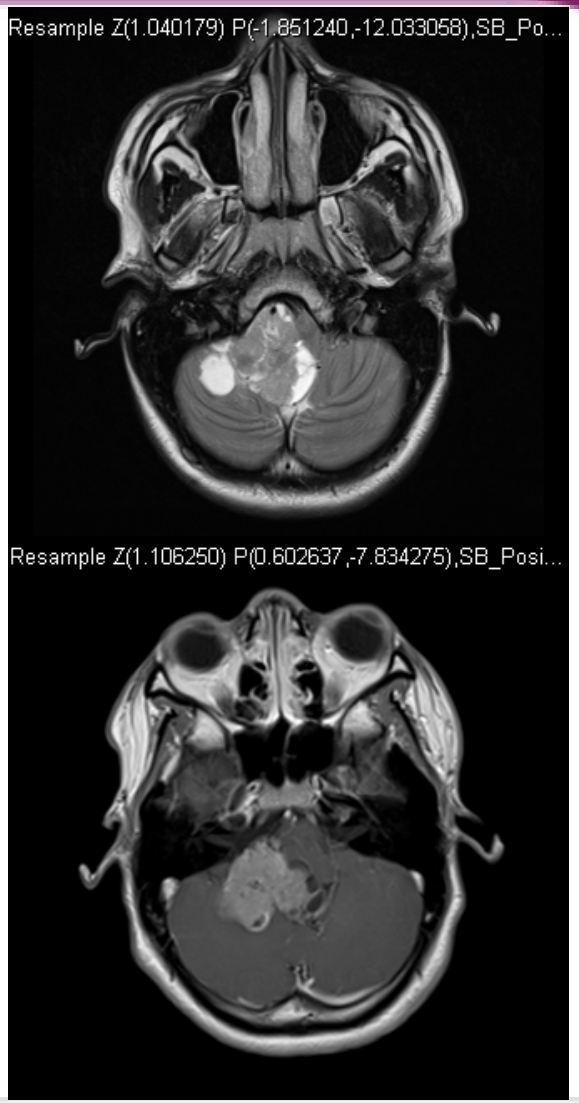


Anatomy of the Brain Stem

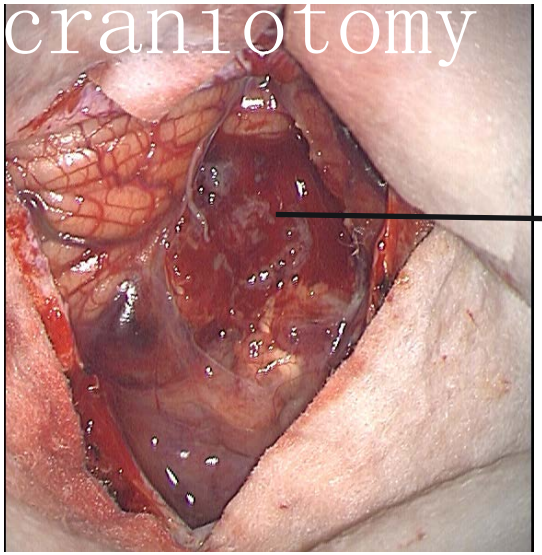


Illustrative

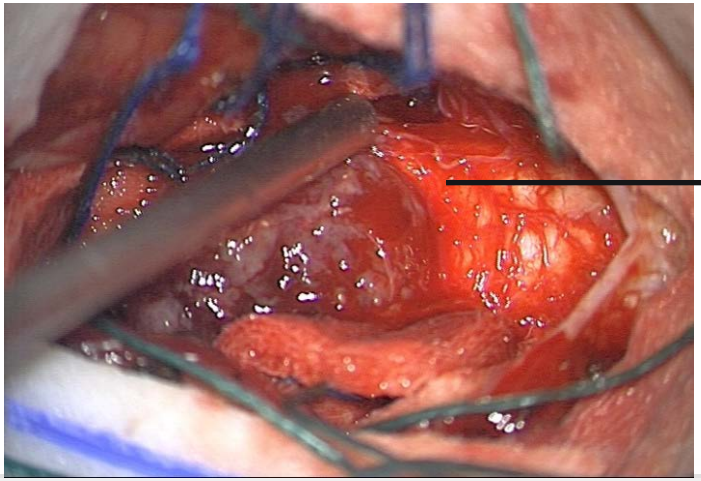
- 18 yrs old male
- 3/52 history of unsteadiness of gait poor coordination on right side
- MRI: right CP-angle lesion extending into IV ventricle



Posterior fossa craniotomy



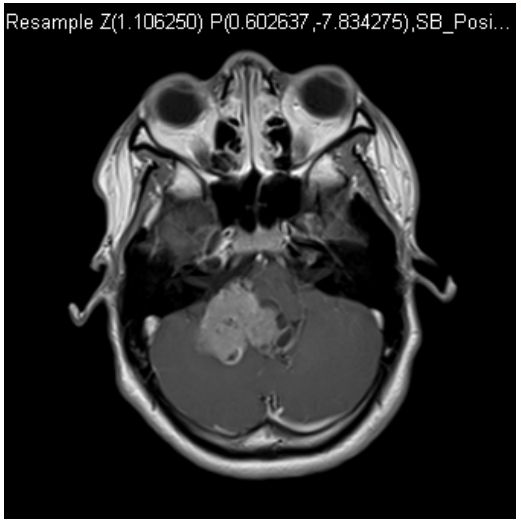
IV ventricle tumour extending from the obex

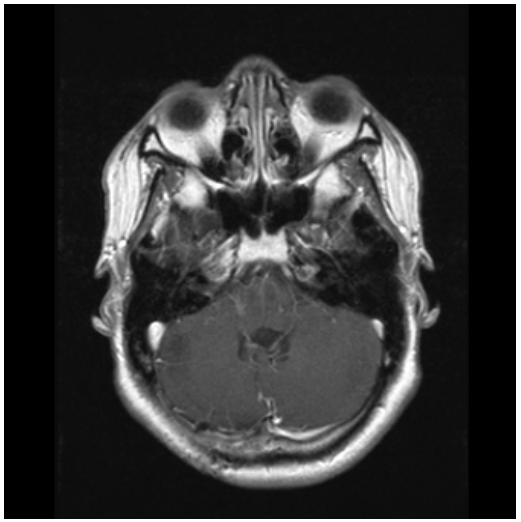


Plane of dissection between tumour and floor of the IV ventricle

Follow up

- Postop course initialy complicated by dysphagia requiring tracheostomy
- Dysphagia resolved at 3 months and tracheostomy removed
- Pt disease-free at 18 months follow-up





Spinal ependymomas – role of surgery

Contents lists available at ScienceDirect

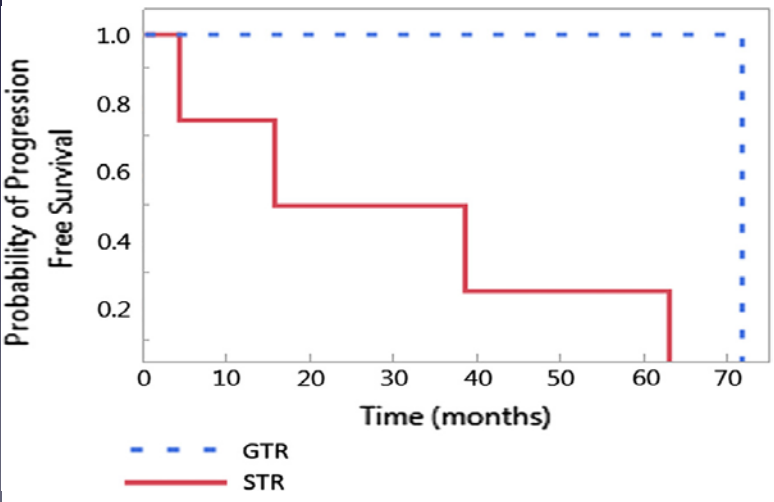
Journal of Clinical Neuroscience

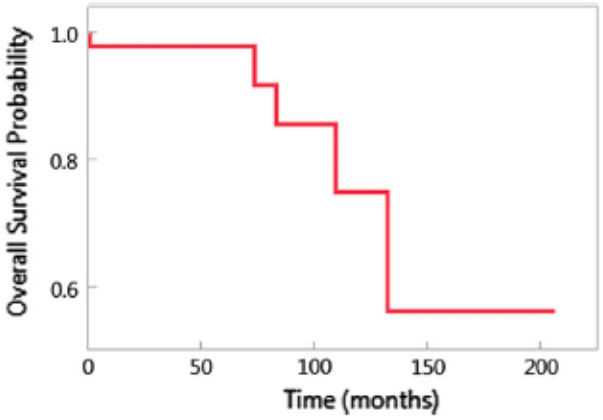
journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Progression free survival and functional outcome after surgical resection of intramedullary ependymomas

Kalil G. Abdullah [a,*], Daniel Lubelski [b], Jacob Miller [c], Michael P. Steinmetz [d], John H. Shin [e], Ajit Krishnaney [b], Thomas E. Mroz [b], Edward C. Benzel [b]





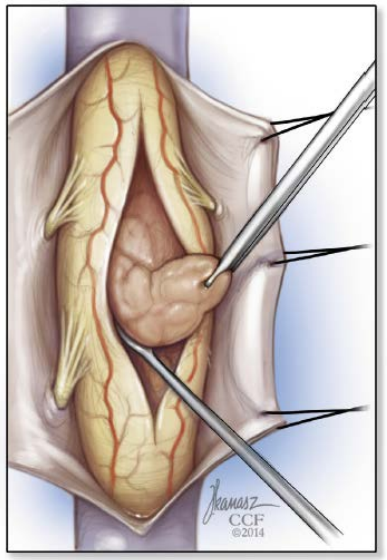
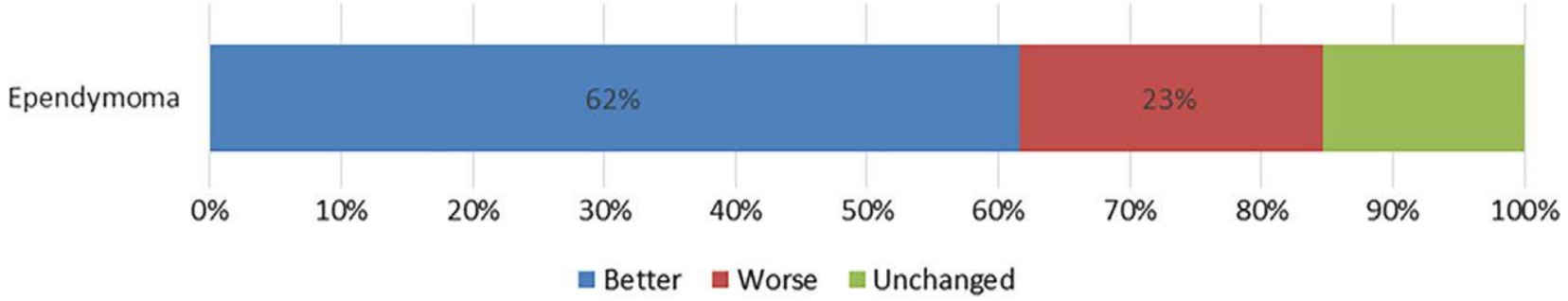


Fig 7. Plane of dissection during resection of an intramedullary ependymoma.

Neurological Outcome after Surgery



Adjuvant Treatment

- Complete Resection – Watch and Wait?
- Complete Resection – ? Radiotherapy
  - ➢ ? Local ? Craniospinal
- Incomplete Resection
  - ➢ What to offer?

Recurrence

- Re-operate
- Chemotherapy?
- Radiotherapy?

Conclusion

- Surgery – the First, the Best and the Only Chance

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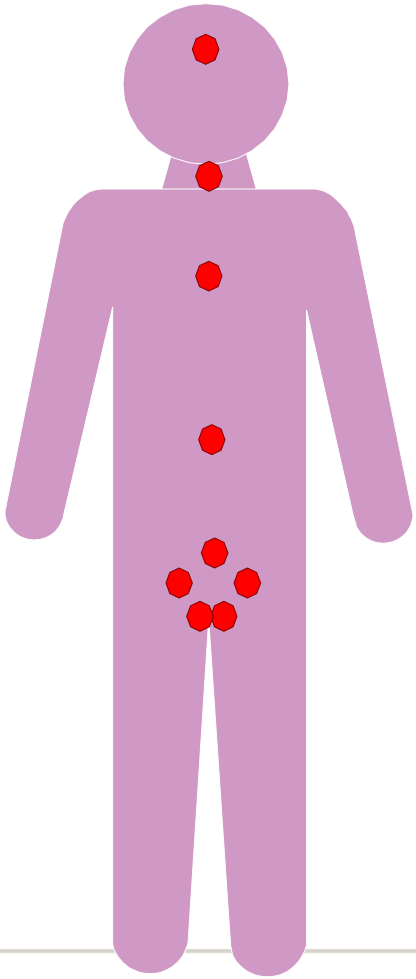
Turin, Italy

Management of CNS GCTs

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

Distribution of Germ Cell Tumors



brain: 21 %

neck: 2 %

mediastinum: 4 %

retroperitoneum: 3 %

coccyx: 19 %

ovary: 28 %

testis: 19 %

other: 4 %

Primary CNS Germ Cell Tumors

Frequency: 2 - 5 % of primary CNS tumours

Incidence: 0.02 - 0.07/ 100,000

0.6 per million per year in USA/Europe

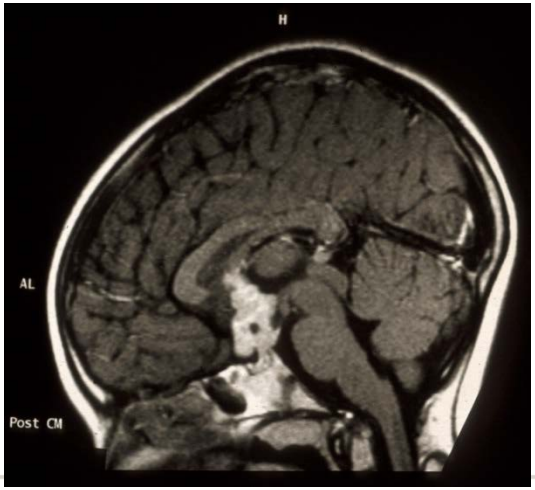
2.7 per million per year in Japan

Age: 75% of patients are 10-20 years

Male : female ratio 2 : 1

Presenting symptoms

- endocrine (e.g. DI)
- visual (e.g. Parinaud)
- neurological (e.g. raised ICP)



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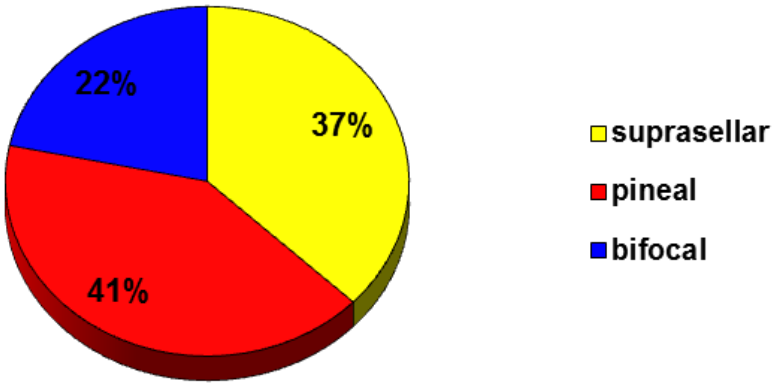
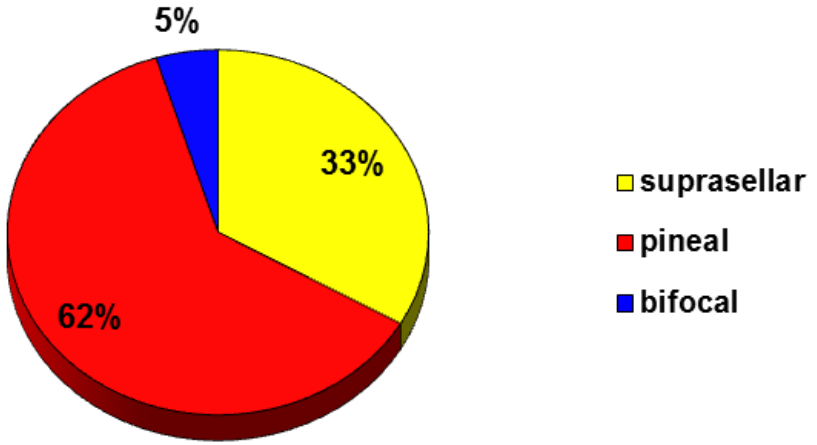
CNS GCTs – Location

Germinoma

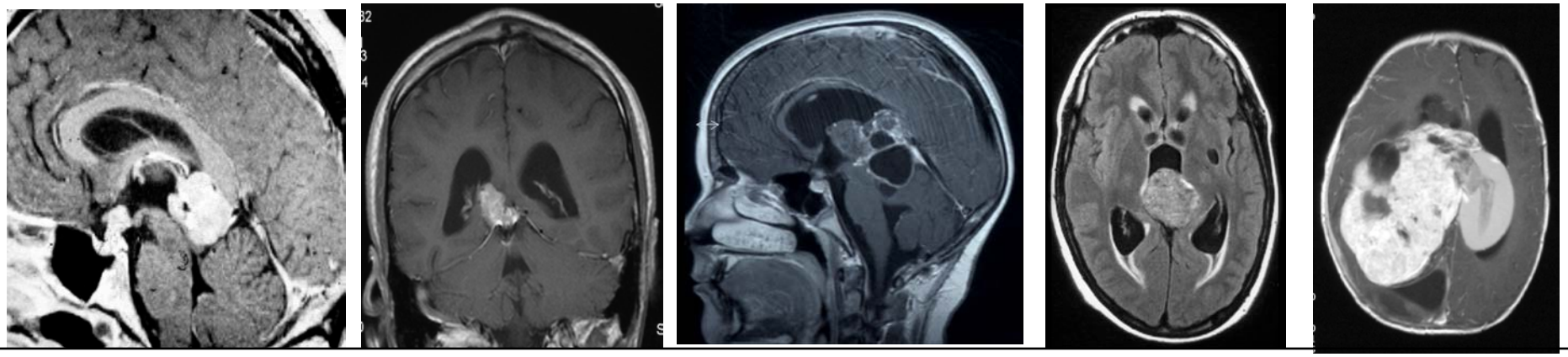


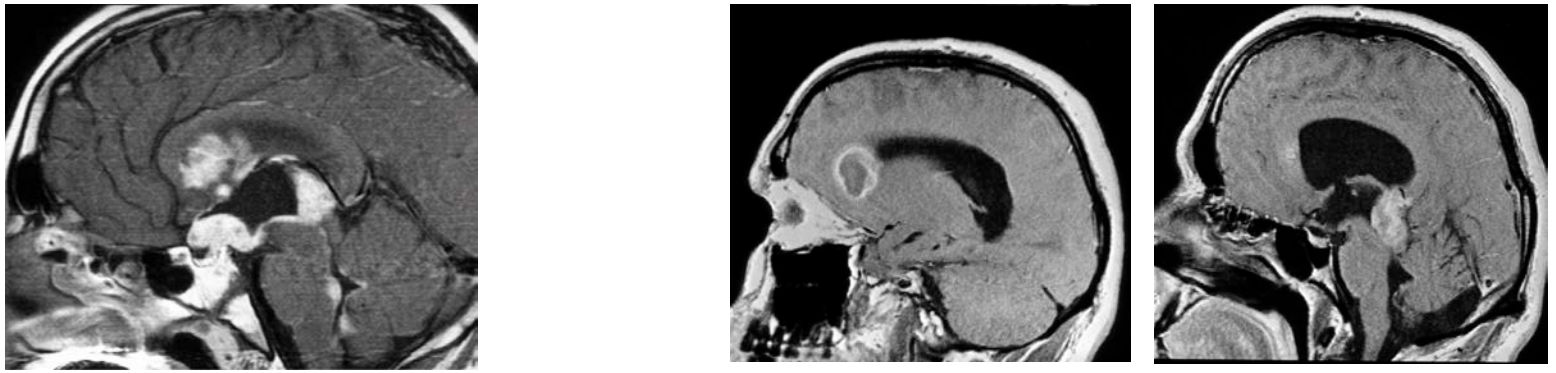
sGCT



Intracranial germ cell tumours (GCT)

Germinoma **Teratoma** **Embr. Ca. „Mixed“ GCT**





- ⇨ **Bifocal growth (pineal / suprasellar)**
- ⇨ **CSF spread**
- ⇨ **different histological subtypes**

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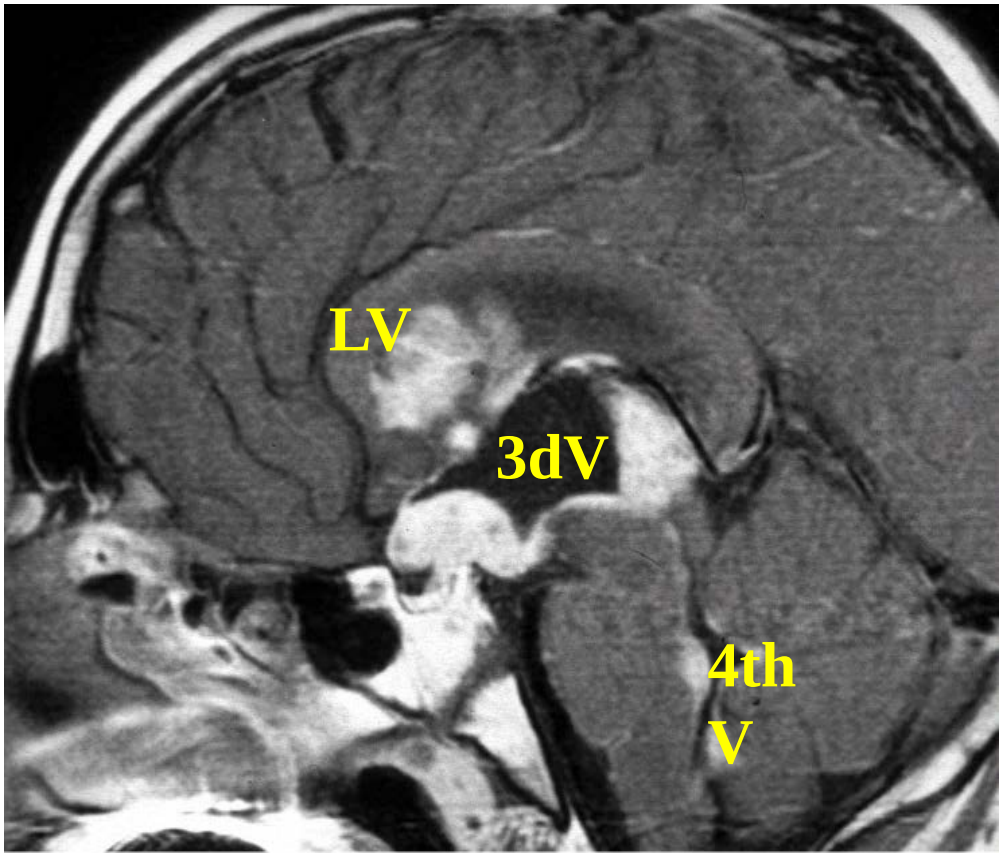
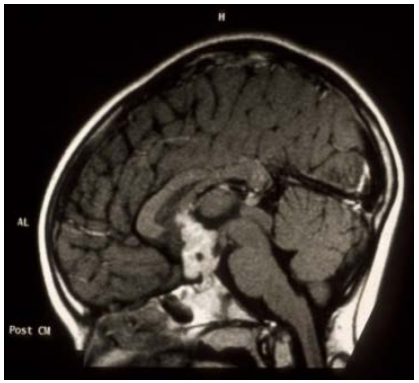
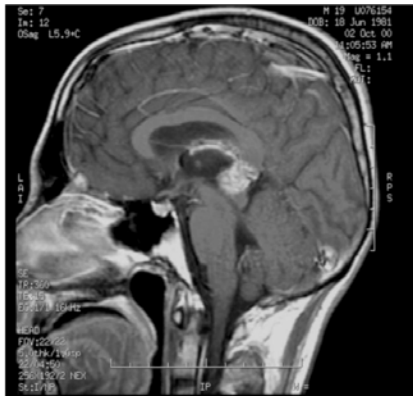
CNS GCT: a characteristic pattern of progression

Subependymal infiltration / CSF pathway dissemination







Intracranial extraventricular dissemination *exceptional*

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Intracranial germ cell tumours (GCT)

General strategy in diagnosis and management
Working Groups World wide

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SIOP CNS GCT working group

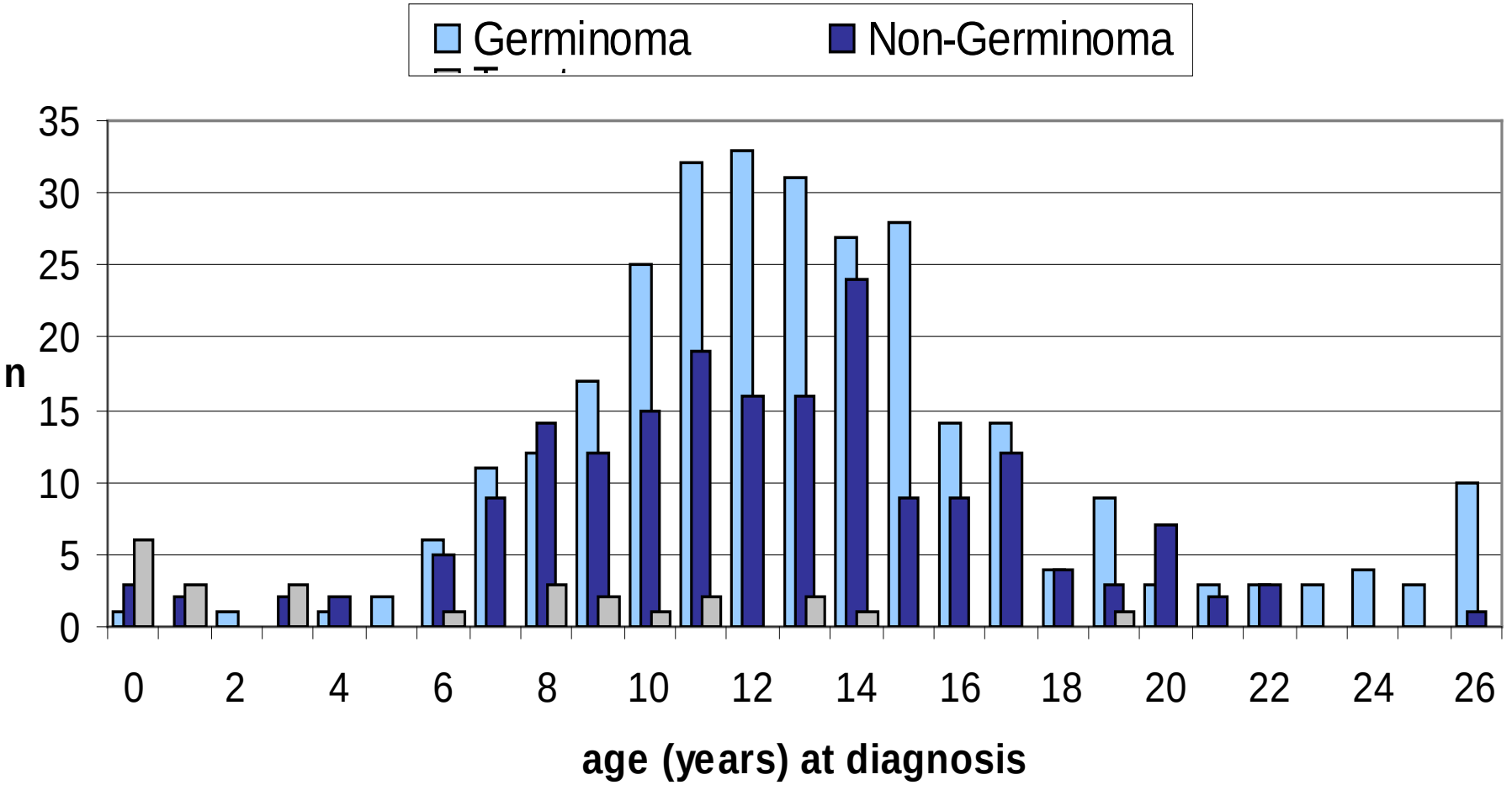
Gaby Calaminus, Rolf Kortmann (D)

Didier Frappaz, Claire Alapetite (F)

Maria Luisa Garré, Umberto Ricardi (I)

Frank Saran (UK), James Nicholson (UK)

Age distribution - diagnosis / SIOP CNS GCT 96



Intracranial germ cell tumours (GCT) – Tumor marker

Histology	*AFP*	*ß-HCG*
Germinoma	-	-/(+)
Embryonalcarcinoma	(+)	-
Yolk sac tumour	+++	-
Choriocarcinoma	-	+++
Teratom / matura od. immatura	-/(+)	-/(+)
Mixed GCT	-/(+)/+++	-/(+)/+++

General strategy in diagnosis and management

Europ. Consensus SIOP CNS GCT

Germinoma

If tumour markers are negative or slightly elevated, a histological diagnosis is mandatory

Secreting germ cell tumours

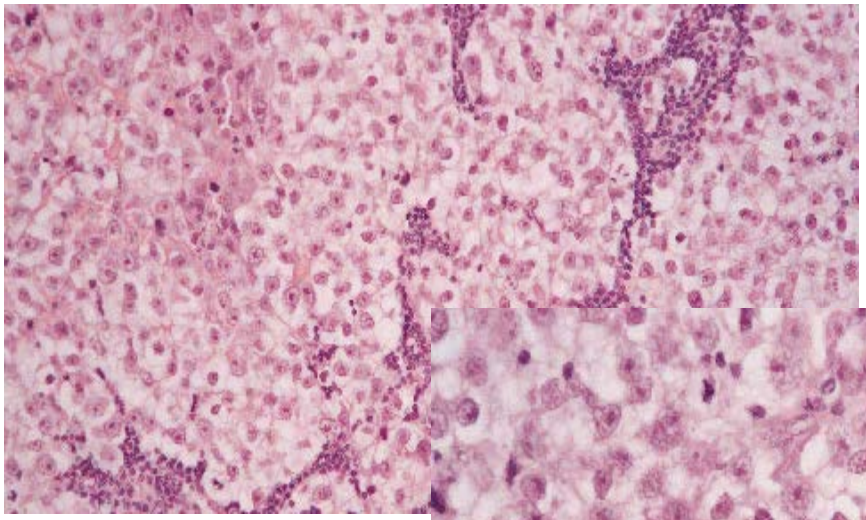
If tumor markers αFP and/or βHCG are elevated (αFP > 25 ng/ml; βHCG > 50 IU/L) and imaging shows a characteristic lesion, a secreting germ cell tumour is diagnosed and treatment should be started with chemotherapy (without histological confirmation)

CNS GCT: Extent of surgery

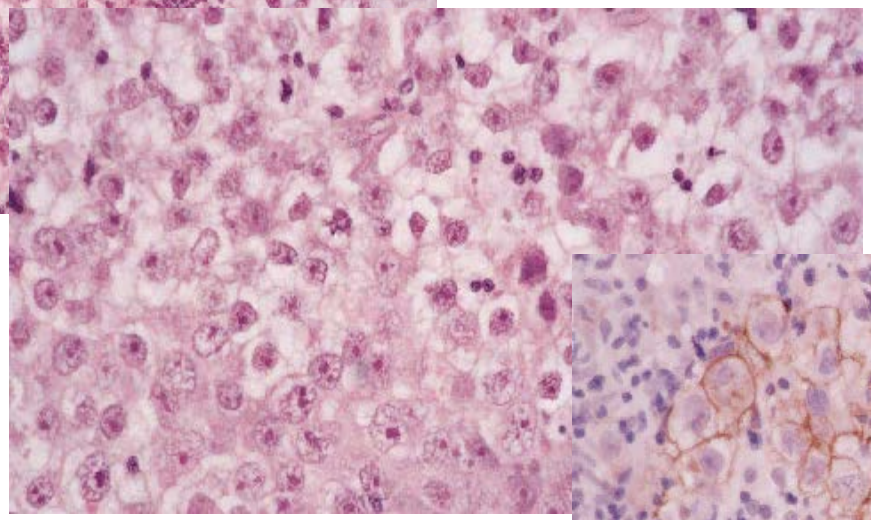
A beneficial role for more radical primary resection has not been established

Role of surgery for resection of residual disease after chemo (sGCT)

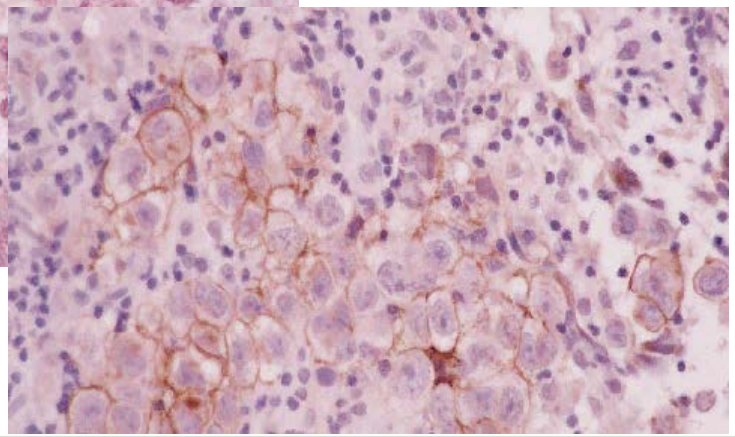
Primary CNS Germinoma- Pathology



lymphocytic infiltration



prominent nucleus

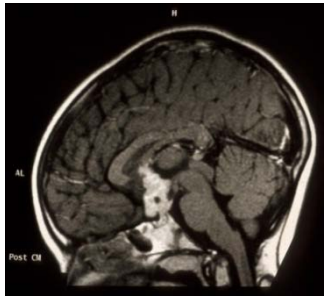


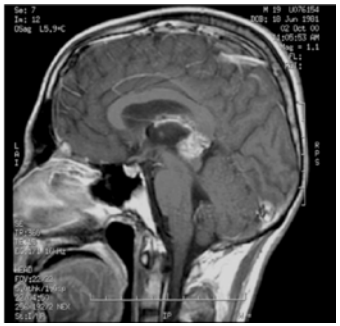
PLAP

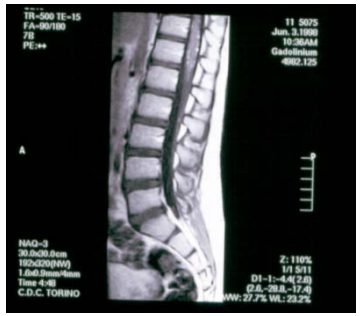
CNS GCT: Diagnostic work-up and Staging

MRI of the whole neuraxis
α-FP / β-HCG
- serum
- CSF

CSF cytology







Non metastatic (localized)
- unifocal disease
- bifocal disease

Metastatic
- microscopic (M1)
- macroscopic (M2,M3)

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Germinoma

Which is your proposal in a 14-yo male affected with localized pure germinoma of the pineal region?

1. Chemotherapy only
2. Radiotherapy alone (CSI followed by focal boost)
3. Chemo followed by same RT as above
4. Chemo followed by more limited RT

Germinoma

What do you mean as more limited RT?

1. CSI with lower doses
2. Smaller volumes: whole brain
3. Smaller volumes: WVI
4. Smaller volumes: focal irradiation only

Germinoma

Radiotherapy is the backbone in the treatment of pure intracranial germinoma

Germinoma: Management

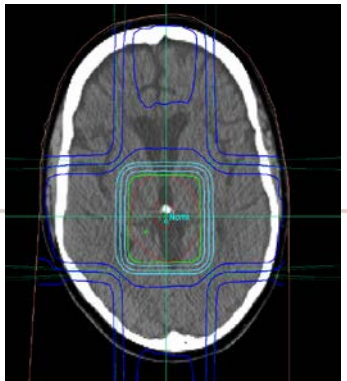
- Standard treatment has been RT alone, with cranio-spinal irradiation plus focal boost, resulting in DFS of 90-95%
  - Microscopic disease:

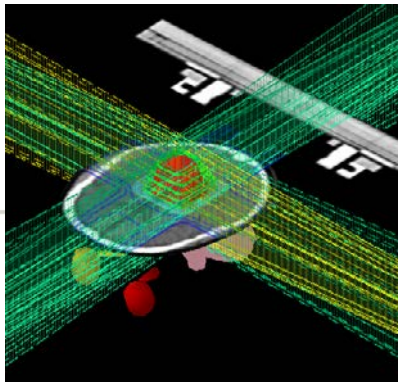
    30-36 Gy
  - Macroscopic disease:

    40-50 Gy

CSA

Boost to tumour site





CSI: risk for late toxicities

Two parallel developments to reduce late effects of CSI:

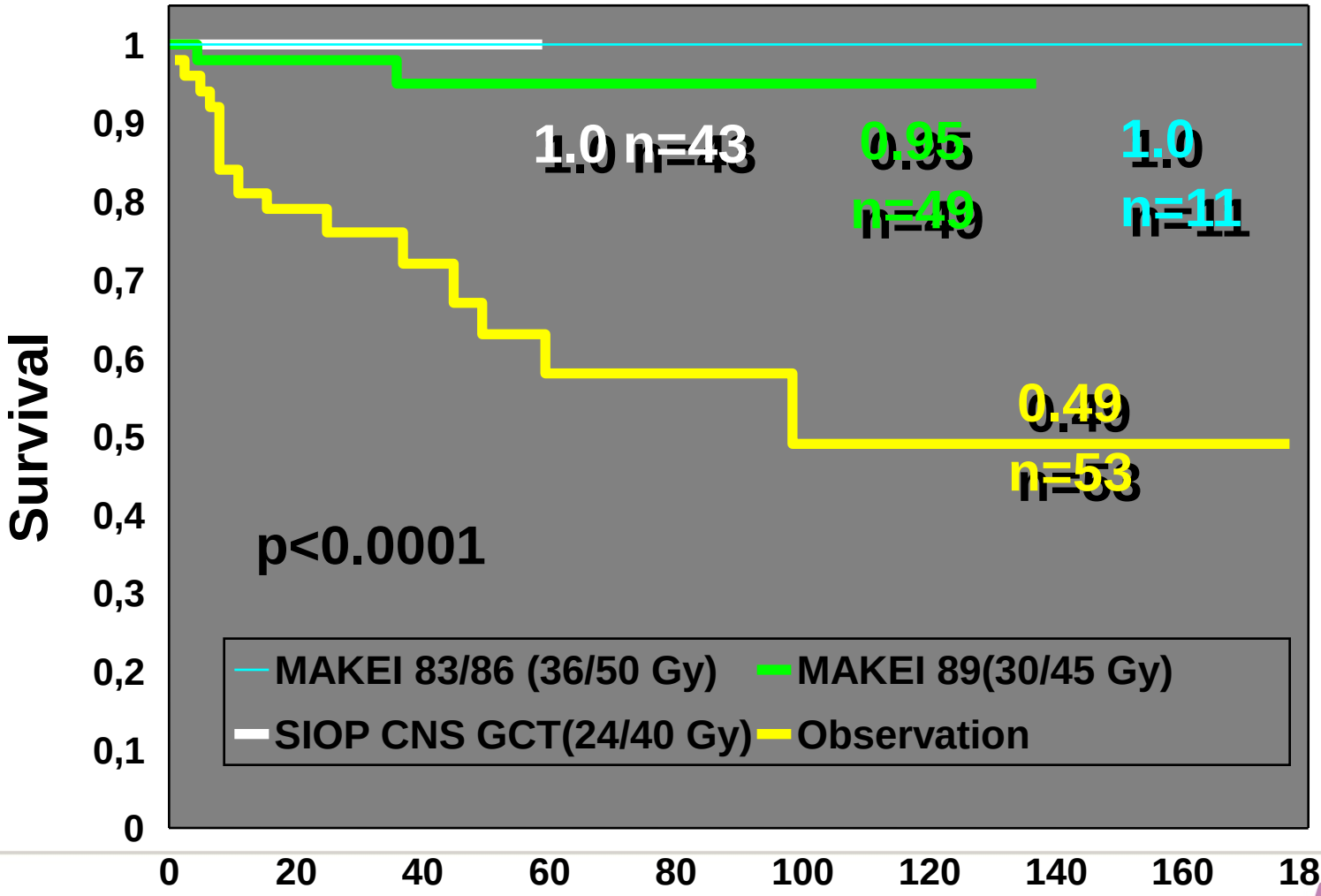
•evidence that with RT alone:

- ✓ irradiation to limited volumes (<CSI, but WVI/WBI) in well staged pts is equally effective (what is the real risk of spinal seeding?)
- ✓ lower RT doses (MAKEI 40 Gy --> 36 Gy --> 30 Gy) control subclinal disease

• reports of encouraging results using a combination of chemo followed by reduced-volumes RT

Radiotherapy in pure germinoma

Relapsefree survival (CNS) (n=155) (patients - germany)



Kortmann et al., 2001, abstr.

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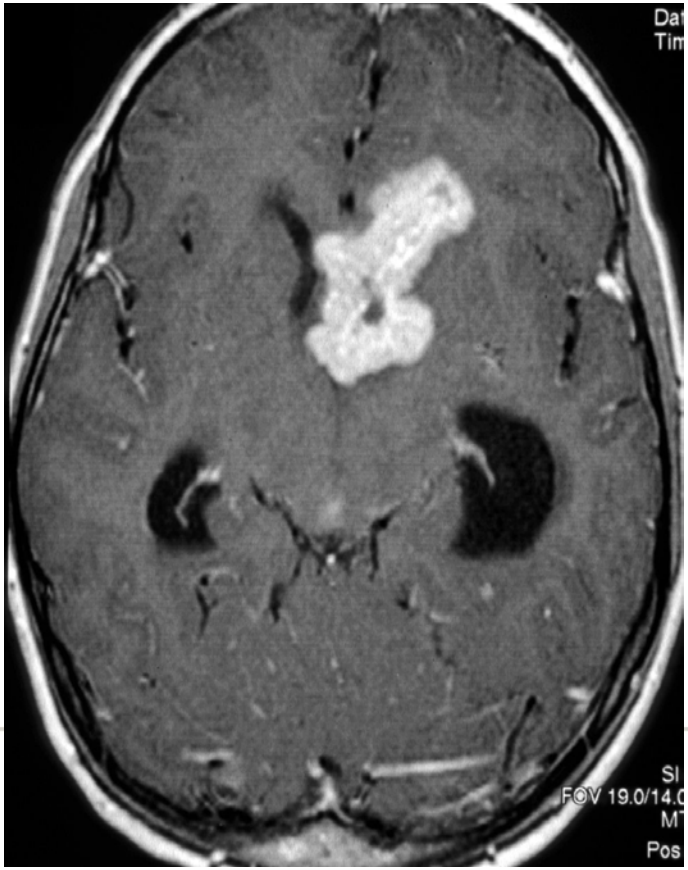
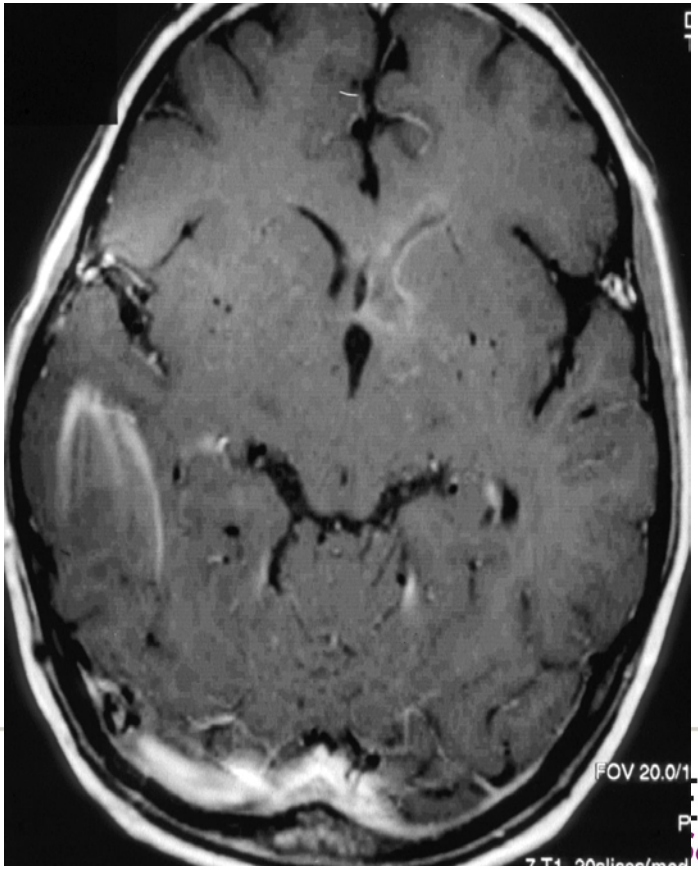
Germinoma

Response to chemotherapy

At diagnosis



After 2 x Carbo-PEI



Radiotherapy in pure germinoma

Outcome (RT alone, chx – RT, chx. alone)

Author	Pat.	Therapy	RFS (5 years)
Bamberg 1999	11 49	RT CSA 36 Gy+Tu 14 Gy RT CSA 30 Gy+Tu 15 Gy	100% 88.8%
Bouffet, 1999	44	Chx. + RT tumour	98% (3 years)
Balmaceda, 1996	45	Chx. alone	50%
Haddock, 1997	48	12 RT CSA/tumour 11 RT whole brain/tumour 24 RT ventricular system	10 y. 94% 94% 0%
Kitamura, 1999	13	Chx. / RT tumour : 24 Gy	100%
Aoyama, 1998	41	23 RT CSA/tumour 10 RT whole brain / tumour 8 RT tumour	10 y. 90% 76% 22%
Hardenbergh, 1997	40	30 RT CSA/tumour 10 RT whole brain/tumour	100% 100%
Cefalo, 1995	7	Chx. / RT tumour region	5 relapses (ventricles)
Kellie, 2004 Da Silva 2010	11 25	Chx. alone	47% 6 y : 45.6% / OS 75.3%
Kortmann, 2001	155	102 RT CSA 53 other treatments	99.5% (CNS) 49% (CNS)
Shikama, 2005	180	114 RT whole brain / Boost 66 RT CSA	8 y. EFS 89%, OS 91% (identical both groups)

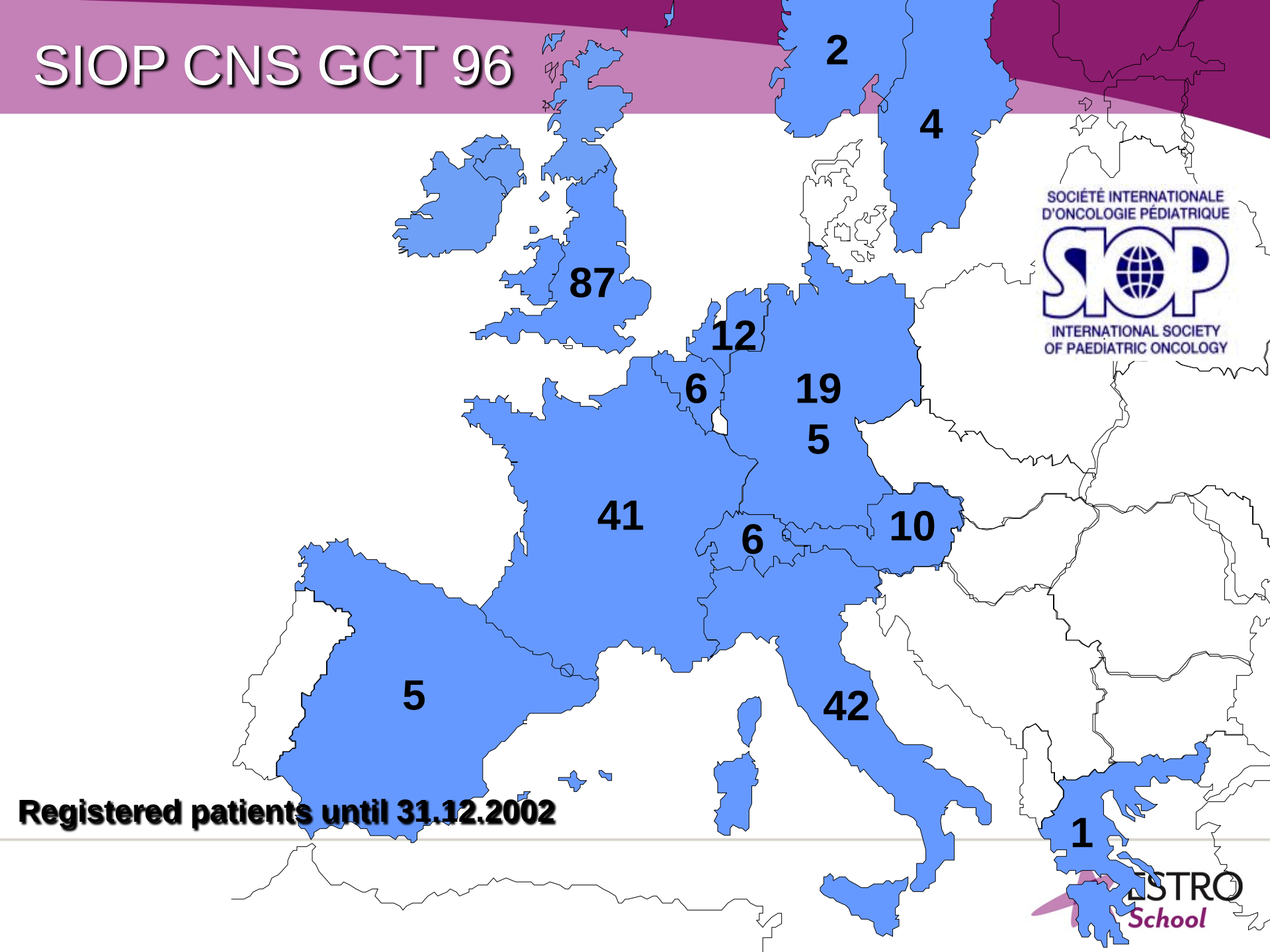
Treatment for biopsy proven germinoma

- Initial chemotherapy followed by reduced dose and/or reduced volume irradiation:

  sustained high EFS and OS (>90%)

  - improved QOL ?
  - reduced late effects ?

SIOP CNS GCT 96



SOCIÉTÉ INTERNATIONALE D'ONCOLOGIE PÉDIATRIQUE
SIOP
INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

Registered patients until 31.12.2002

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SIOP CNS GCT 96 / pure germinoma

Neuro-Oncology Advance Access published March 3, 2013
Neuro-Oncology
doi:10.1093/neuonc/not019
NEURO-ONCOLOGY

SIOP CNS GCT 96: final report of outcome of a prospective, multinational nonrandomized trial for children and adults with intracranial germinoma, comparing craniospinal irradiation alone with chemotherapy followed by focal primary site irradiation for patients with localized disease

Gabriele Calaminus, Rolf Kortmann, Jennifer Worch, James C. Nicholson, Claire Alapetite, Maria Luisa Garrè, Catherine Patte, Umberto Ricardi, Frank Saran, and Didier Frappaz

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Design of protocol

Option A :

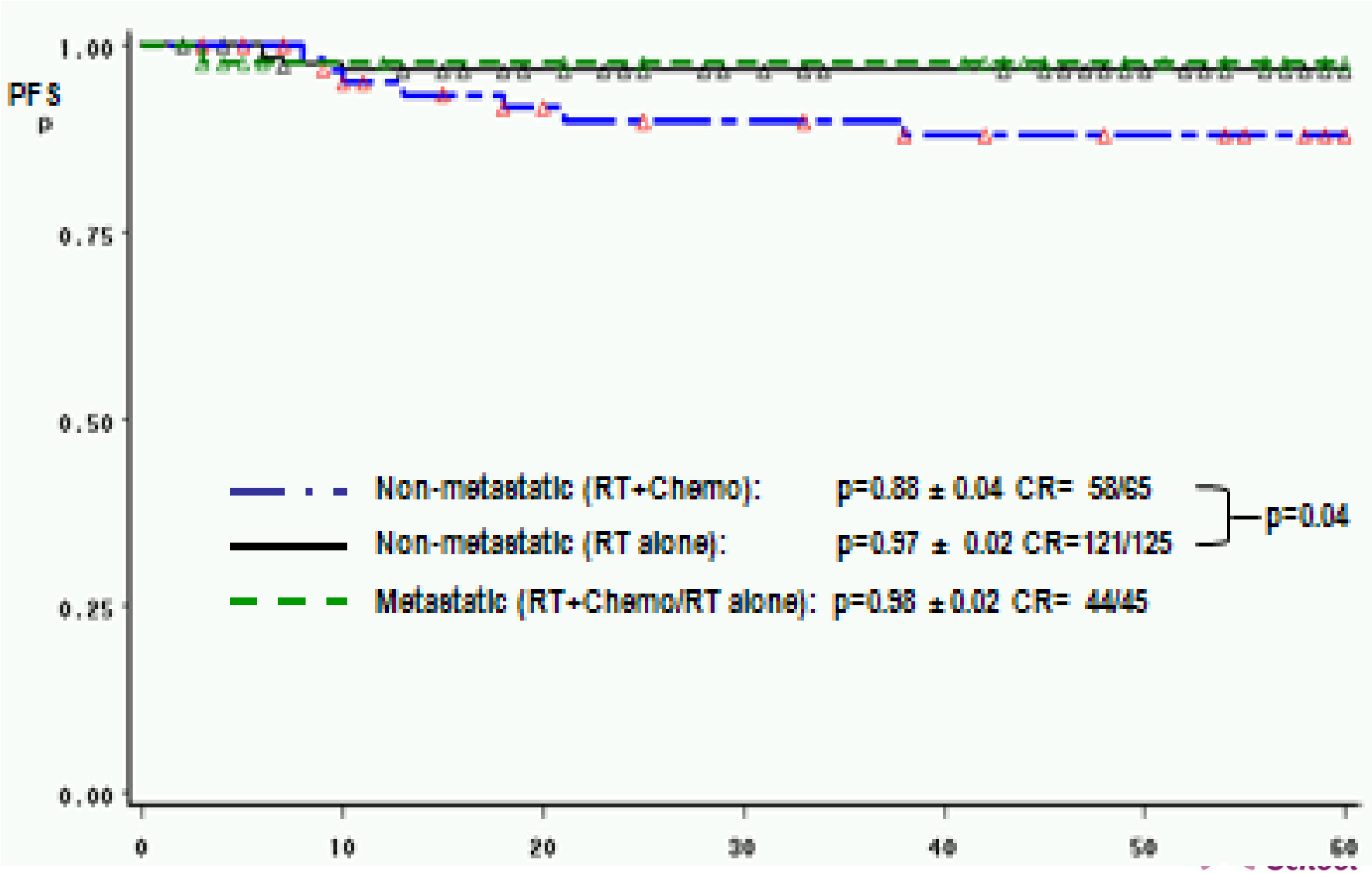
radiotherapy of craniospinal axis : 24 Gy (5 x 1.6 Gy / week)
followed by RT to tumour site : 16 Gy (5 x 1.6 Gy / week)
Total tumour dose : 40 Gy

Option B :

2 courses Carbo PEI
(600mg/m2 d1 -- VP16 150mg/m2 d1-3/22-24 – Ifosfam. 1800mg/m2 d22-26)
followed by RT to tumour site : 40 Gy (5 x 1.6 Gy / week)

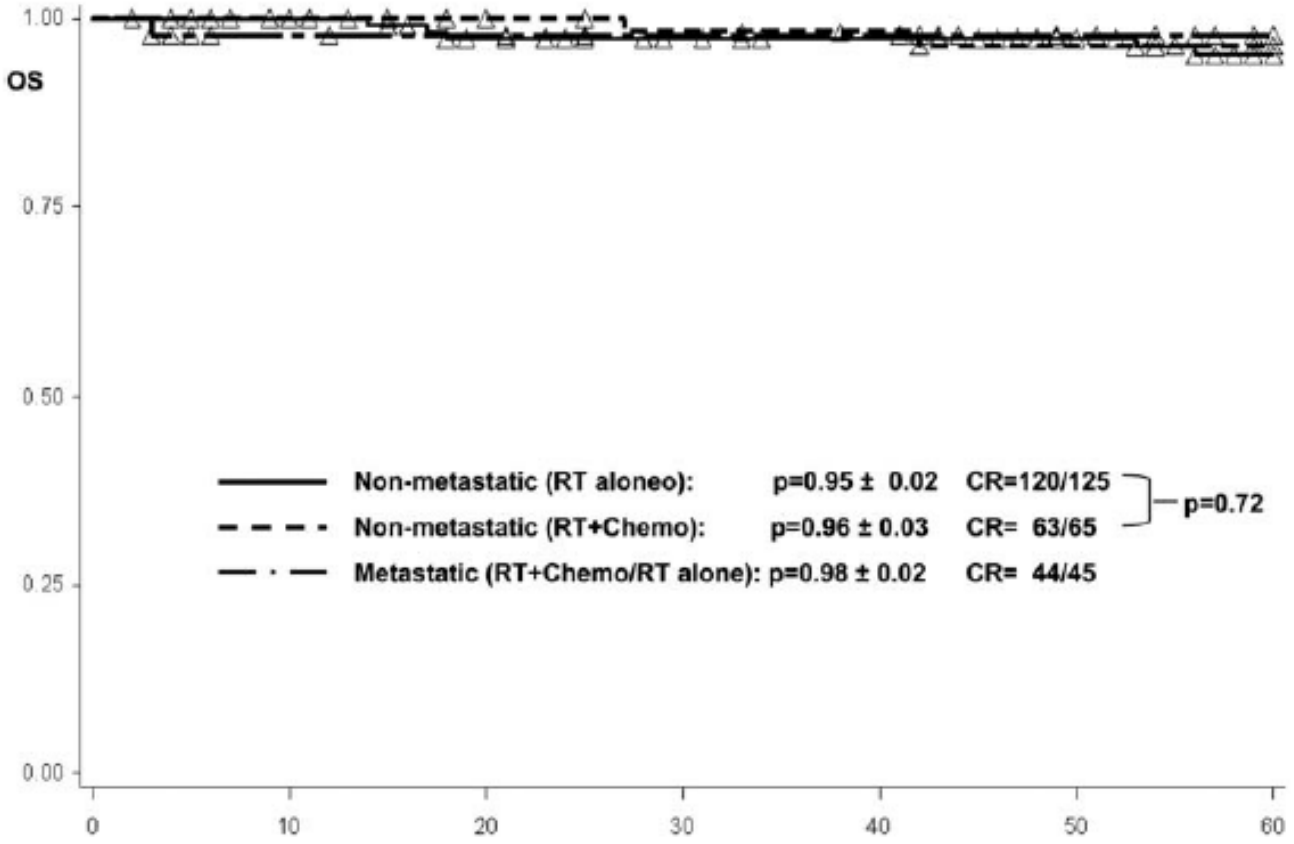
SIOP CNS GCT 96 / germinoma

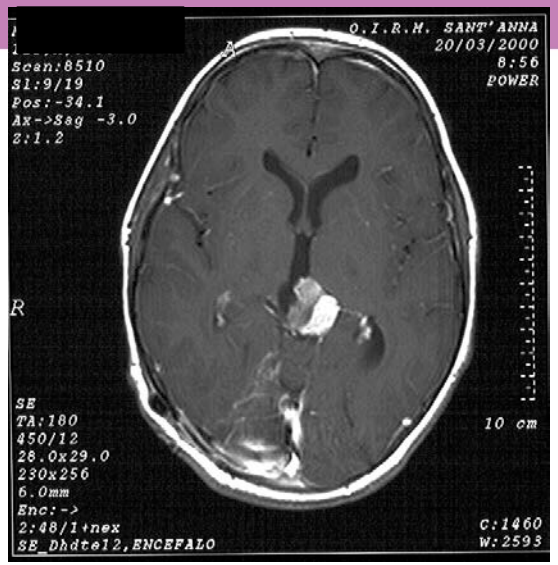
PFS / final analysis / including metastatic cases



SIOP CNS GCT 96 / germinoma

OS / final analysis / including metastatic cases

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230x256
6.0mm
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2:48/1+nex
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10 cm
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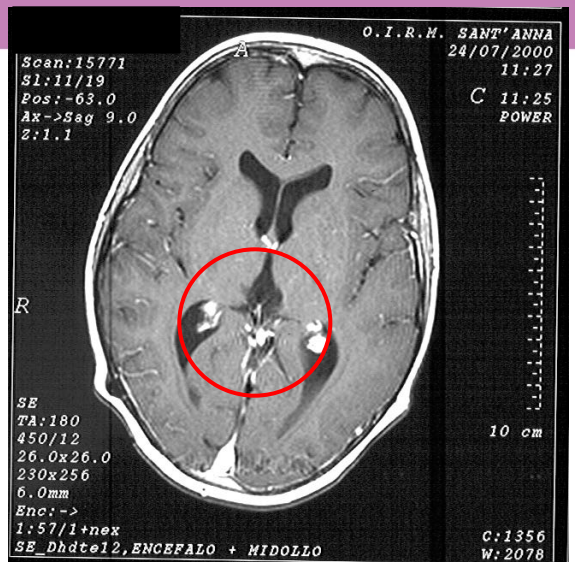
W:2593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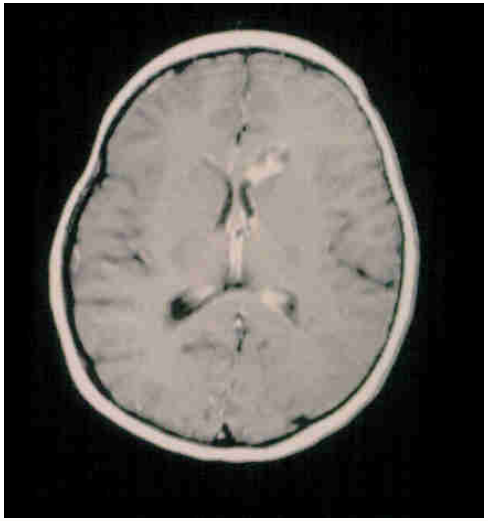
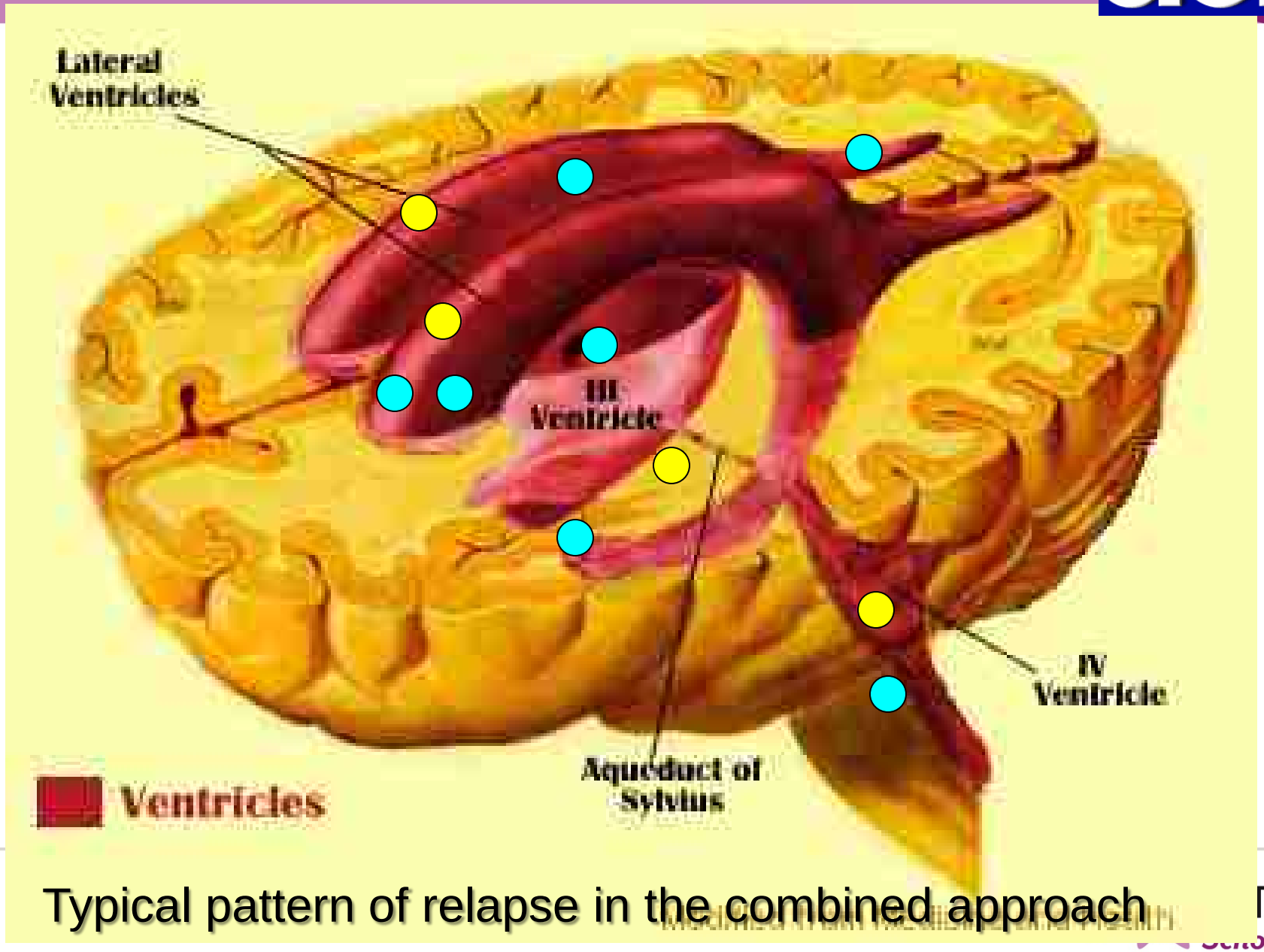


SIOP (7/65) SFOP (9/62)



Typical pattern of relapse in the combined approach

Radiotherapy in pure germinoma

Pattern of relapse after chx followed by RT
With respect to target volume (M0)
Local RT versus ventricular RT

Author	Pat.	Dose/Gy	RFS	OS	relapses
Cefalo, 1995	7	40 local	n.a.	100%	5 (71,5%)
Aoyama, 2002	28	24 local	66%	93,8%	6 (21%)
Lafay-Cousin 2006	6	24-40 WV	100%	100%	0 (0%)
Bouffet, 1999	57	40 local	96,4%	98%	4 (7%)
Matsutani, 2001	75	24 local	n.a.	n.a.	9 (12%)
Nguyen, 2006	9	30.6 local	n.a	89%	4 (44%)

Relapses (majority ventricular system) after local RT in all series 16% (6-71,5%)

Modified according to Aoyama et al., 2009

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CNS GCTs: SIOP CNS GCT 96

Germinoma
Take home message

CT + focal RT does not control subclinical ventricular disease

↳ whole ventricular RT

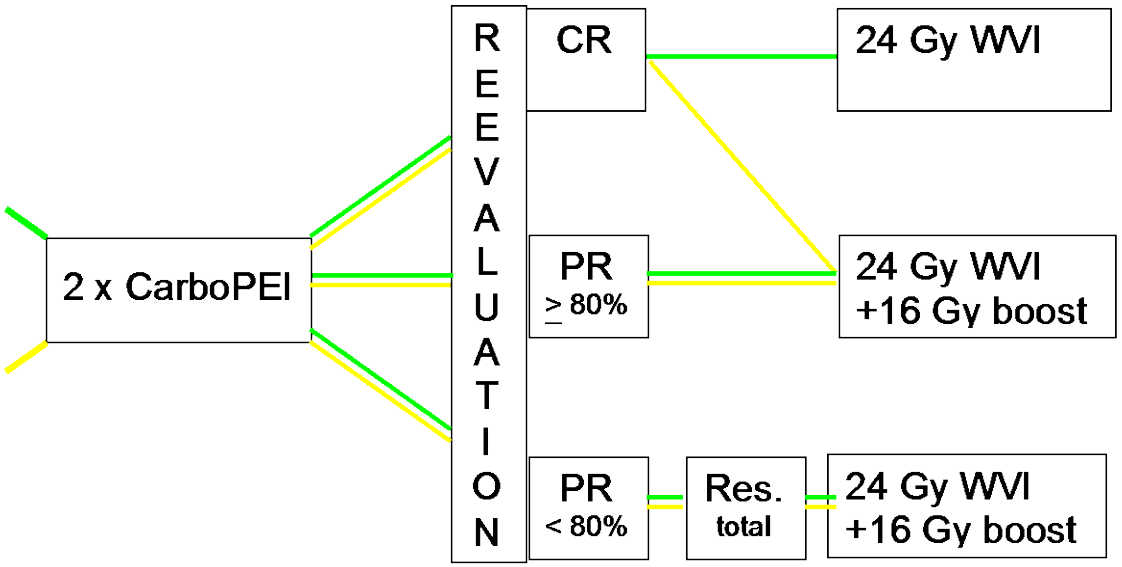
PLANNED THERAPY STRATEGY IN SIOP CNS GCT II

- GERMINOMA -

histologically proven, with or without teratoma,
AFP≤25 ng/ml and ßHCG≤50 IU/l in serum and CSF

non-metastatic, low risk
non-metastatic, unifocal and
pure germinoma and
AFP and ßHCG negative (normal)
in serum and CSF

non-metastatic, medium risk
non-metastatic, bifocal or
germinoma with teratoma or
AFP or ßHCG increased (in limits above)
in serum or CSF



metastatic, high risk
cranial or spinal metastases
or positive CSF-cytology or
incomplete staging according to
dissemination or tumor markers

24 Gy CSI + 16 Gy boost
to macroscopical disease

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Is radiotherapy alone to ventricular system / boost sufficient in non-metastatic disease ?

(no chemotherapy)

Radiotherapy in pure germinoma

Pattern of relapse after radiotherapy alone with respect to target volume (M0) (meta-analysis)

Technique	Pat.	Relapses (total)	Spinal
CSA	287	14 (4.8%)	3 (1%)
Whole brain	91	6 (6.5%)	3 (3.2%)
Ventricular system (boost)	54	3 (5.6%)	1 (1.8%)
Local only	130	31 (23.8%)	13 (10%)

Aoyama et al., 2009

SIOP CNS GCT II

Underlying philosophy:

Convert macroscopic to subclinical disease

by using chemotherapy before RT

Dose reduction from 40 to 24 Gy (primary tumour site)

(Japanese data, : overall tumor-free rate 92.9% (52 of 56 pat.)

Med.f-up, 2.1 years, 1 relapse outside RT area. Matsutani et al., 1998

Dose reduction to non-target brain

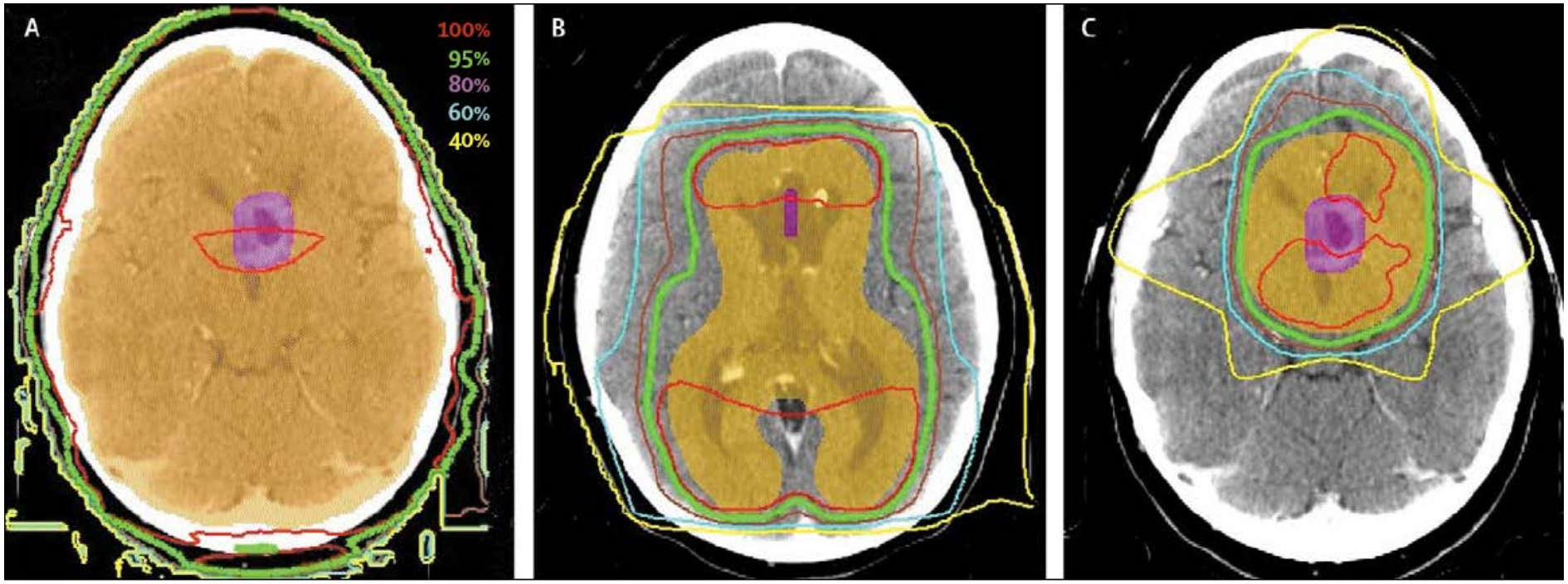
(dose reduction to functionally relevant areas)

⇨ **Reduction of risk for late effects**

Radiotherapy in pure germinoma

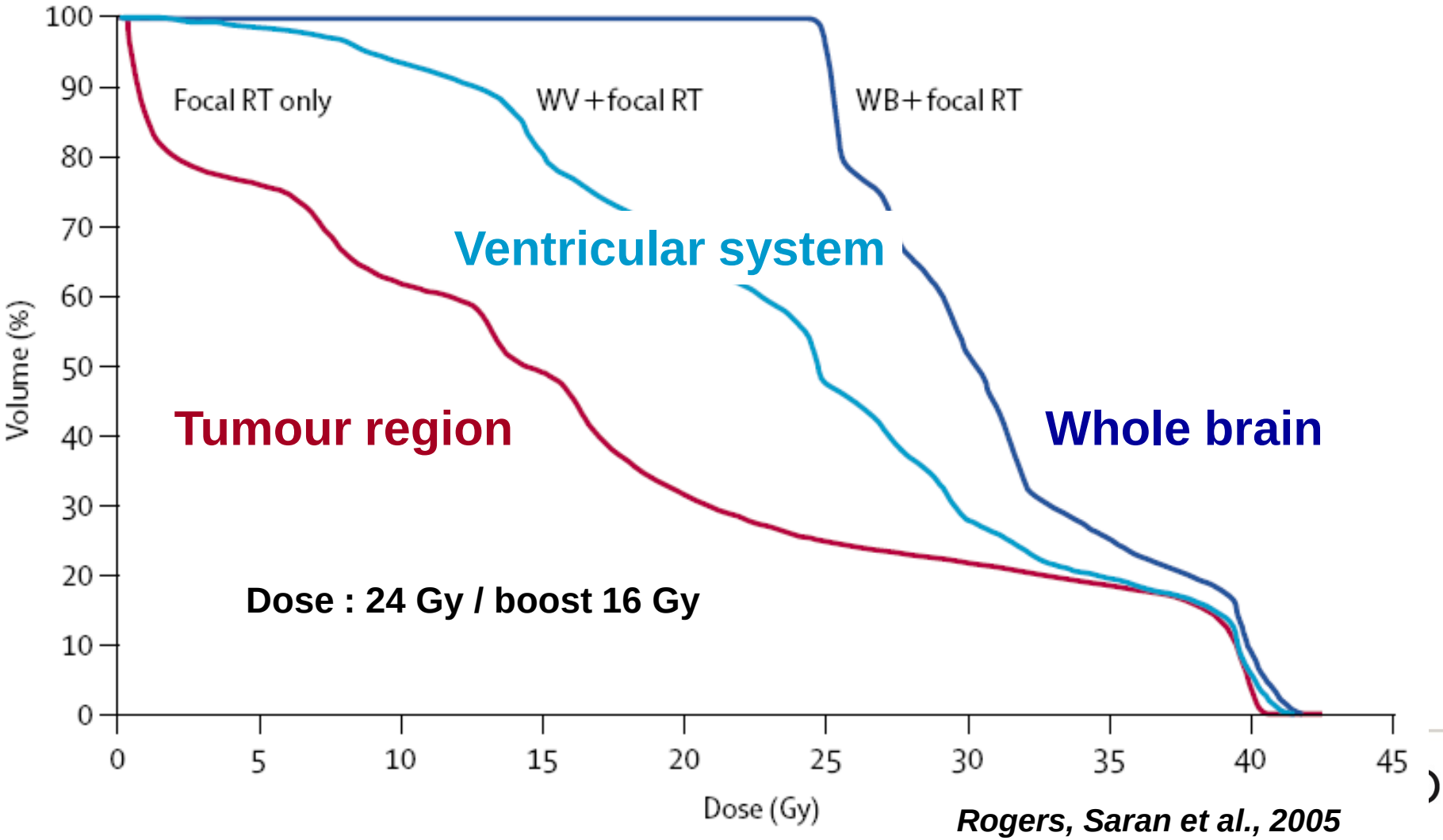
Dose distribution / target volumes

Whole brain **Ventricular system** **Tumour region**



Radiotherapy in pure germinoma

Dose distribution / target volume / DVH‘s (whole brain)



Rogers, Saran et al., 2005

Neurocognitive function
RT CSA versus ventricular RT

Domain	RT- CSA	Ventricular RT
Verbal comprehension	87.30	110.50
Perceptual reasoning	98.56	121.00
Full-scale IQ	91.78	115.17
Reading	85.38	106.17
Receptive vocabulary	85.56	106.20

Problem : total dose and dose distribution unknown
(RT CSA 25 - 30 Gy, boost doses up to 54 Gy ?)

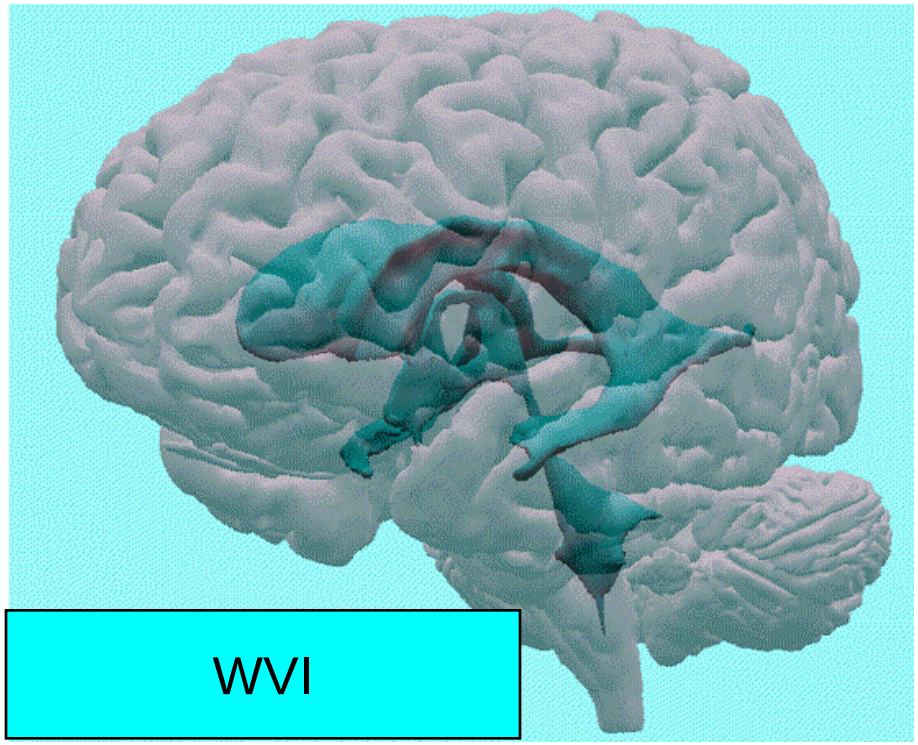
Mabott et al., 2011

WVI: definition

Third ventricle

Lateral ventricles

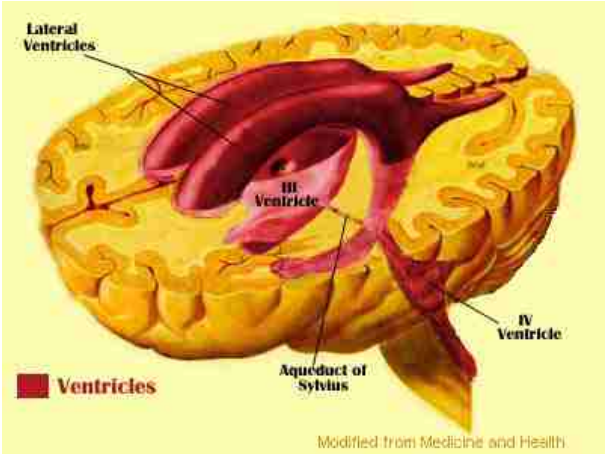
Fourth ventricle (regardless of primary tumor site)



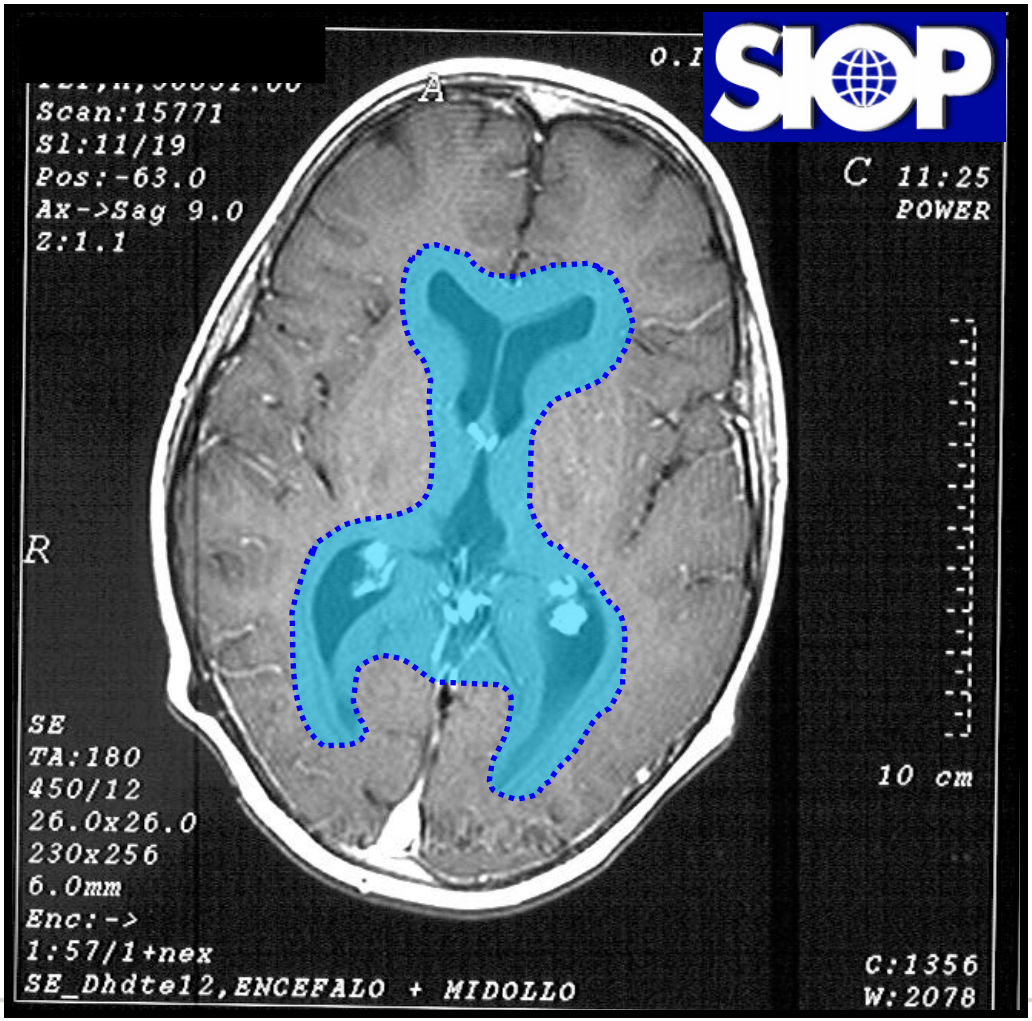
RT techniques for ventricular system irradiation

Very irregular shape of the target volume

New radiation modalities (IMRT) for the best conformity index (target coverage and normal brain sparing)



WVI: concave-shaped target for IMRT



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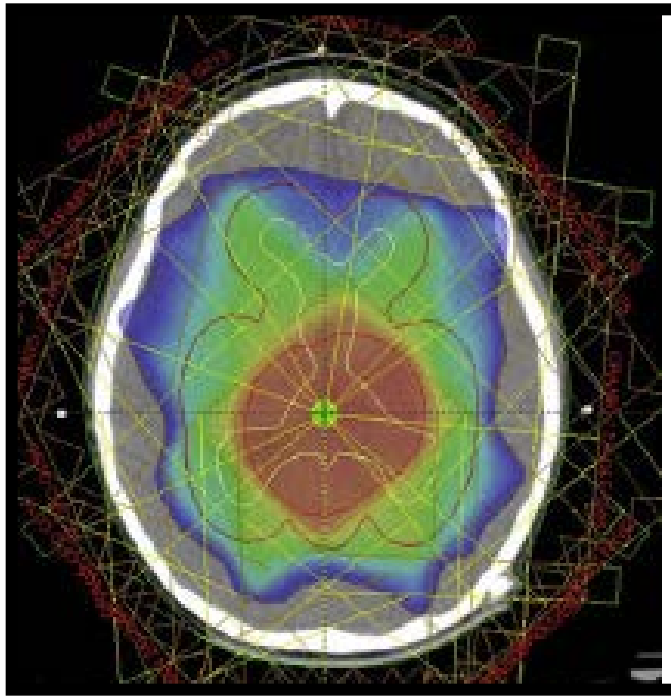
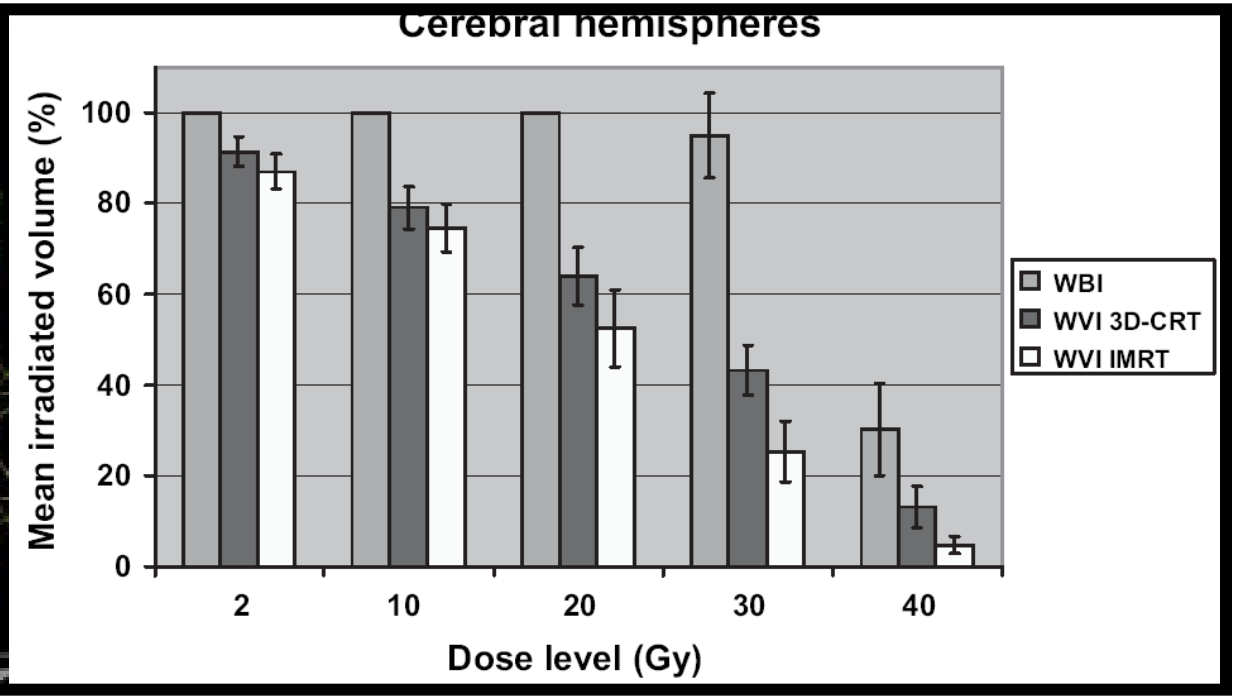
Radiotherapy in pure germinoma

RT ventricular system + boost / IMRT

Reduction of dose to „non-target brain“ / hemisheres

Comparison of plans / 10 patients





Chen et al., 2010

Longitudinal Evaluation of Neurocognitive Function After Treatment for Central Nervous System Germ Cell Tumors in Childhood

Donald J. Mabbott, PhD[1,2,3]; Eric Monsalves, BSc[3]; Brenda J. Spiegler, PhD[1,2,4]; Ute Bartels, MD[2,4]; Laura Janzen, PhD[1,2,4]; Sharon Guger, PhD[1,2]; Normand Laperriere, MD[2,5,6]; Nicole Andrews, PhD[1]; and Eric Bouffet, MD[2,4]

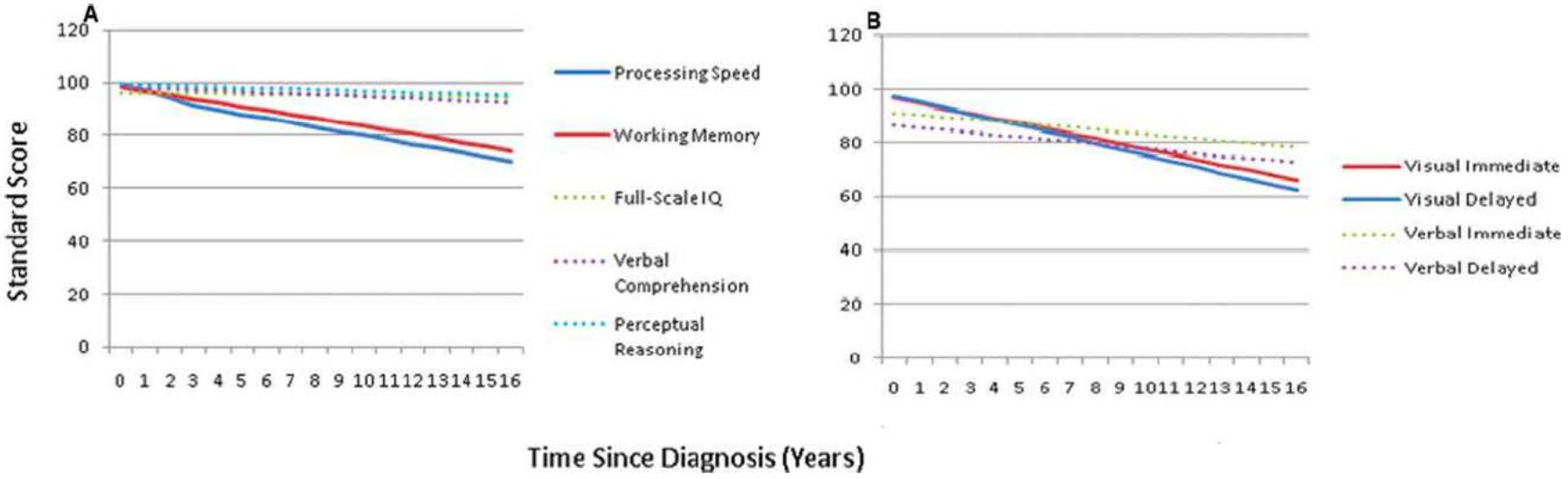
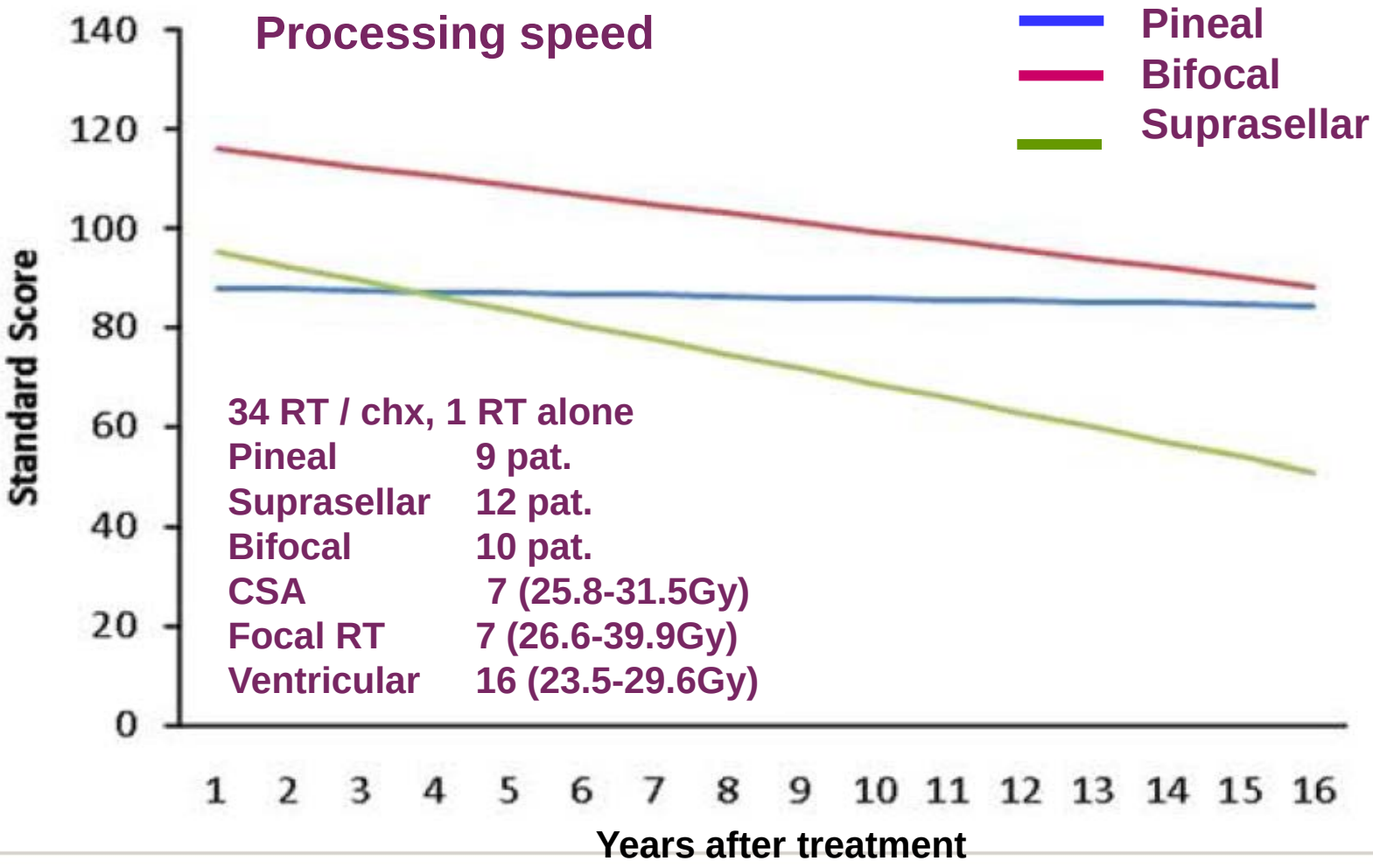


Figure 1. Estimated change over time based on linear models for the entire sample are shown for full-scale IQ, verbal comprehension, perceptual reasoning, working memory, and processing speed indices from the Wechsler Intelligence Scales for Children/ Wechsler Adult Intelligence Scales (A) and visual and verbal memory scores (B).

CONCLUSIONS: Although general cognitive abilities appeared stable and intact after treatment for most children with CNS GCT, a significant decline over time in working memory, processing speed, and visual memory was evident. Tumor location appeared to be important in understanding the trajectory of stability and decline in CNS GCT patients, as did radiation field. ***Cancer* 2011;117:5402–11.** © *2011 American Cancer Society.*

Intracranial germ cell tumours (GCT)

Neurocognitive function (29 germinoma, 7 non-germinoma)

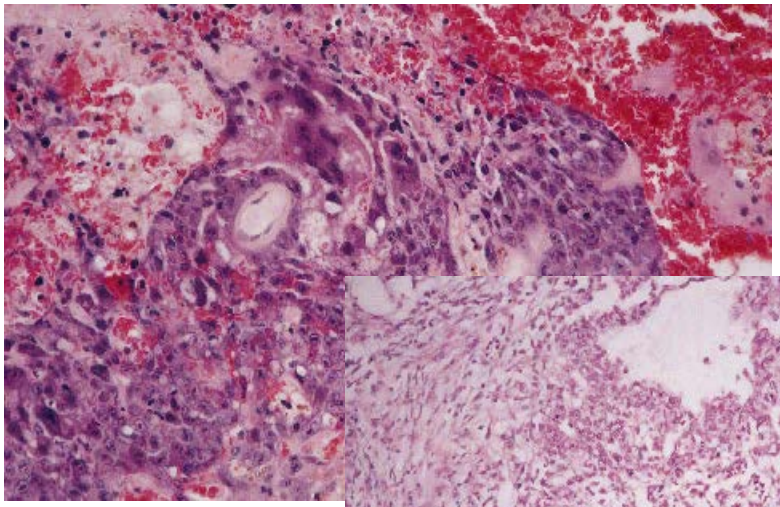


Mabott et al., 2011

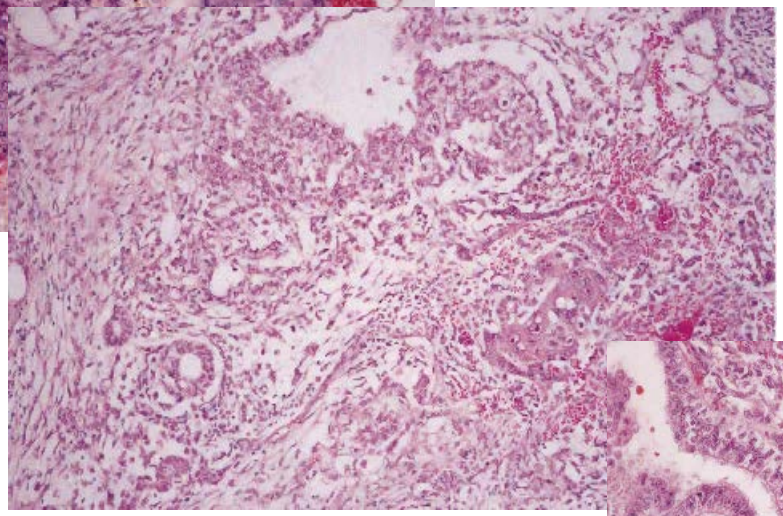
Intracranial germinoma - Conclusions

- ⇨ High cure rates
- ⇨ RT indispensable (Chx alone : app 50% relapse rate, high toxicity)
- ⇨ Chemotherapy is an effective strategy to avoid spinal RT and to reduce dose of RT
- ⇨ M + : RT CSA / boost alone (no chemotherapy)

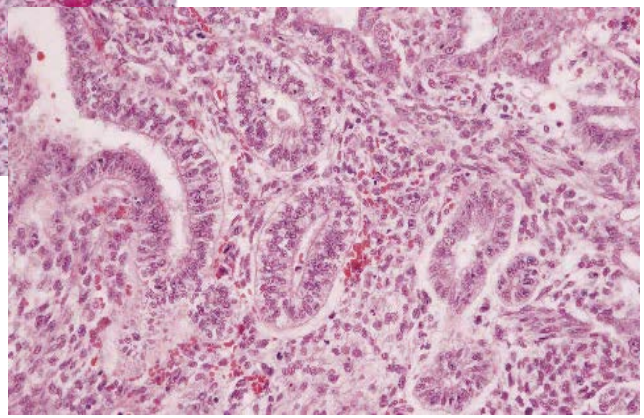
Primary CNS Secreting GCT's - Pathology



Choriocarcinoma
(βHCG)



Yolk sac tumour
(αFP)



embryonal
carcinoma
(αFP + βHCG)

Non - germinomatous GCT

SIOP CNS GCT 96 : secreting GCTs
Clinical diagnosis

α-FP > 25 ng/ml in serum and/or CSF

ß-HCG > 50 IU/l in serum and/or CSF

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Non - germinomatous GCT

Histological subtypes / tumour markers / sensivity to treatment

Histology	Clinical behaviour	Tumour markers		Sensitivity to	
		AFP	ßHCG	Chemo	RT (Gy)
Germinoma	malignant	–	(+)	+++	24
Embryonal CA Yolk sac tumour Choriocarc.	malignant malignant malignant	– +++ –	– – +++	+++ +++ +++	45 45 45
Teratoma	benign (potentially malignant)	–	–	–/?	>54/?

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Non-Germinoma GCT: Management

- Results very poor with radiotherapy alone (EFS 20-30%)
- Less sensitive to radiation than germinoma
- Chemotherapy alone: poorer results than with combined approach
- Standard of care: chemotherapy followed by radiotherapy (EFS 50-60%; OS 50%)
- First line surgery does not improve prognosis

Non - germinomatous GCT

SIOP CNS GCT 96 : therapy secreting GCTs

non-metastatic

4 x PEI → focal irradiation 54 Gy

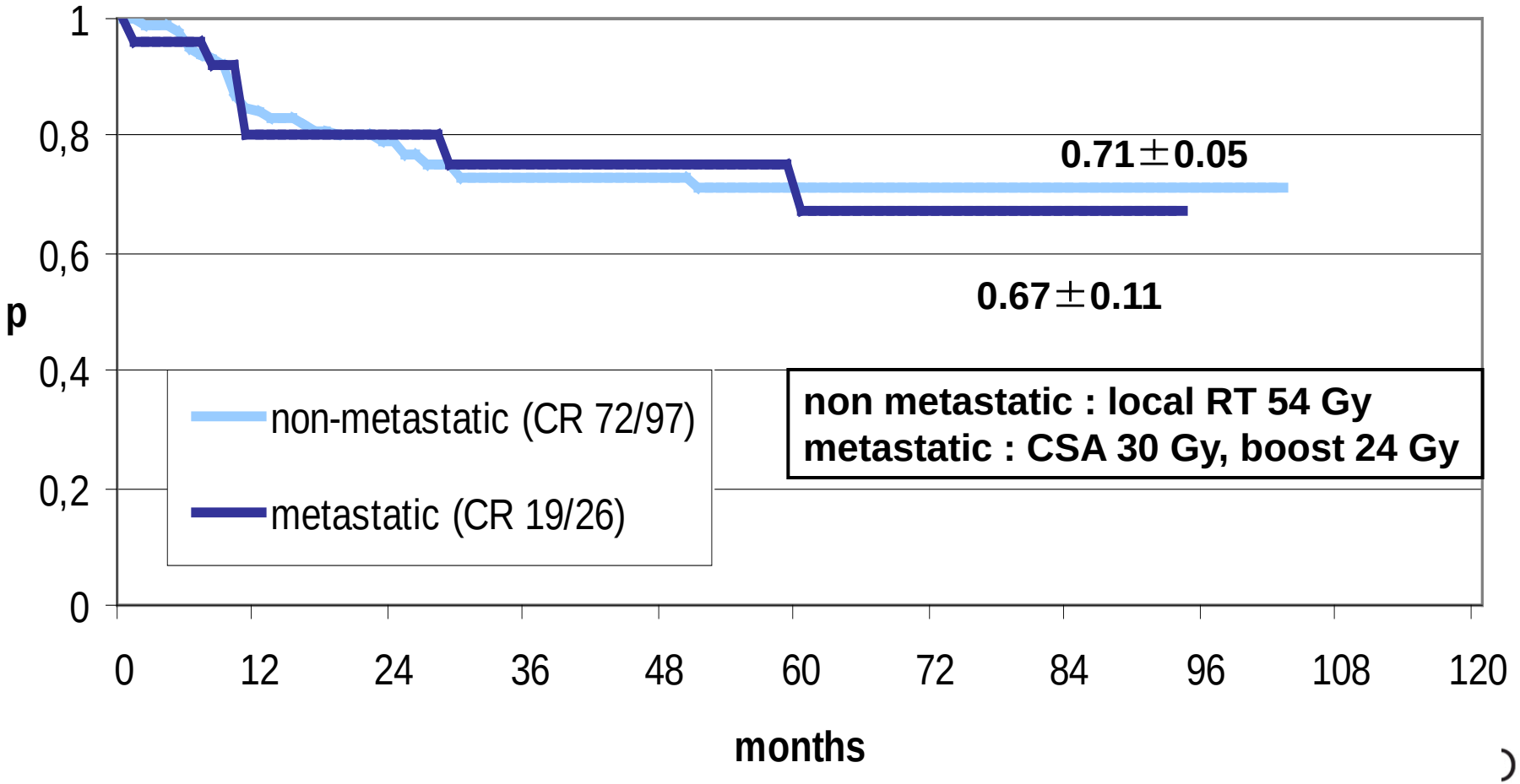
metastatic

4 x PEI → craniospinal irradiation 30 Gy

tumor site boost 24 Gy

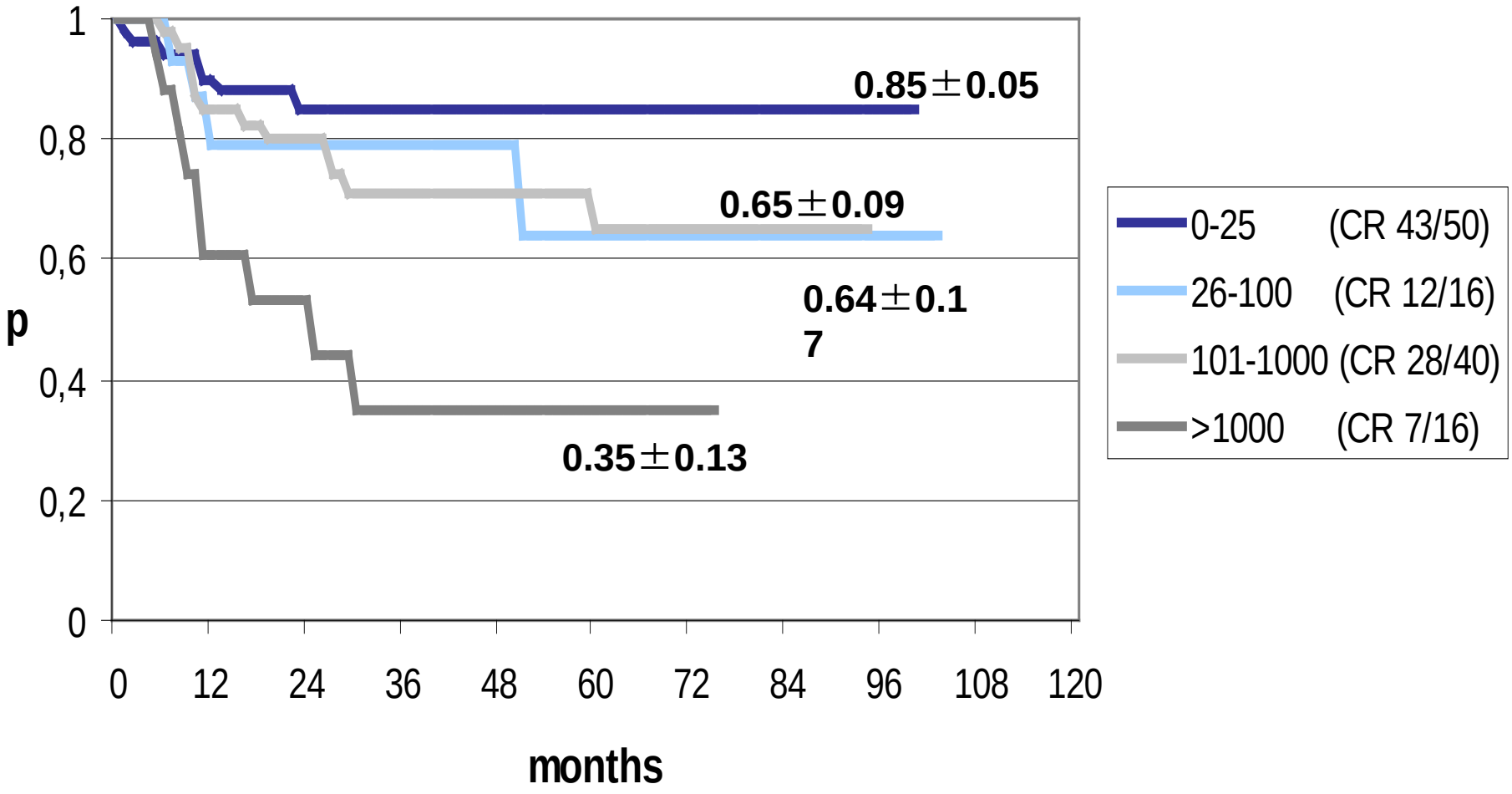
Non - germinomatous GCT

SIOP CNS GCT 96
EFS / non-metastatic versus metastatic disease



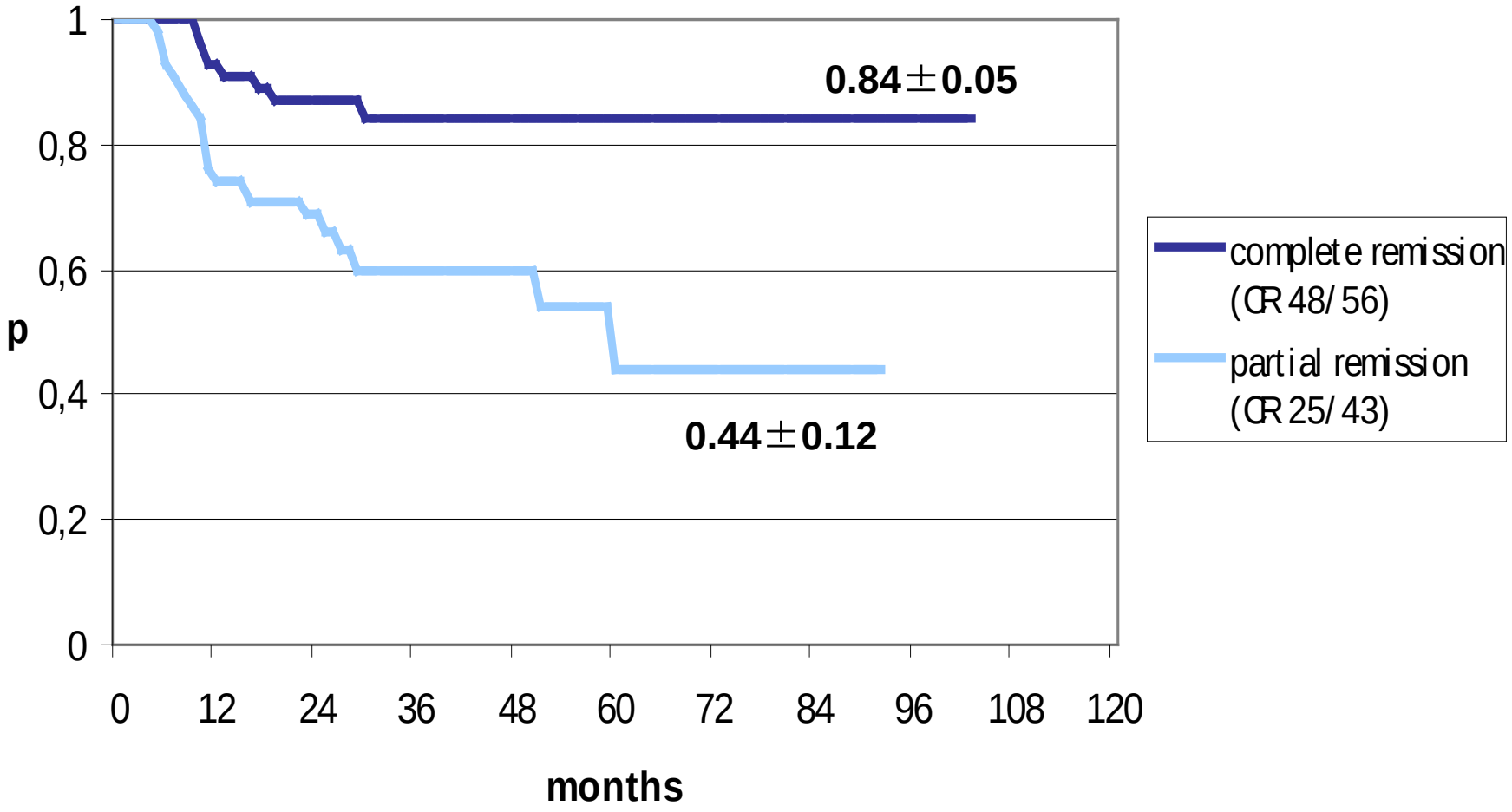
Non - germinomatous GCT

SIOP CNS GCT 96
AFP-value and EFS of protocol pts



Non - germinomatous GCT

SIOP CNS GCT 96
EFS / residual tumour



Non - germinomatous GCT

Target volume / conclusions

⇨ **Predominantly local failures**

⇨ **Conflicting data (Outcome / pattern of relapse)**

⇨ **High ventricular failure rates after chx. alone**

⇨ **sanctuary site for failures (like in germinoma) ?**

⇨ **Local and spinal failures independent of target volume (CSI versus local RT)**

⇨ **metastatic disease : CSI necessary**

⇨ **Local RT sufficient in non-metast. disease ?**

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Non - germinomatous GCT

Dose – response relationship / conclusions

⇨ **Data are scarce**

⇨ **Local doses of at least 50 Gy for all non germinoma GCT**

⟹ **Europe / North Am. : 54 Gy**
Asia (Japan) (54 – 60 Gy)

⇨ **Dose to areas with subclinical disease in CSI (prophylactic / metast. disease) unclear**

⟹ **30 Gy ?**

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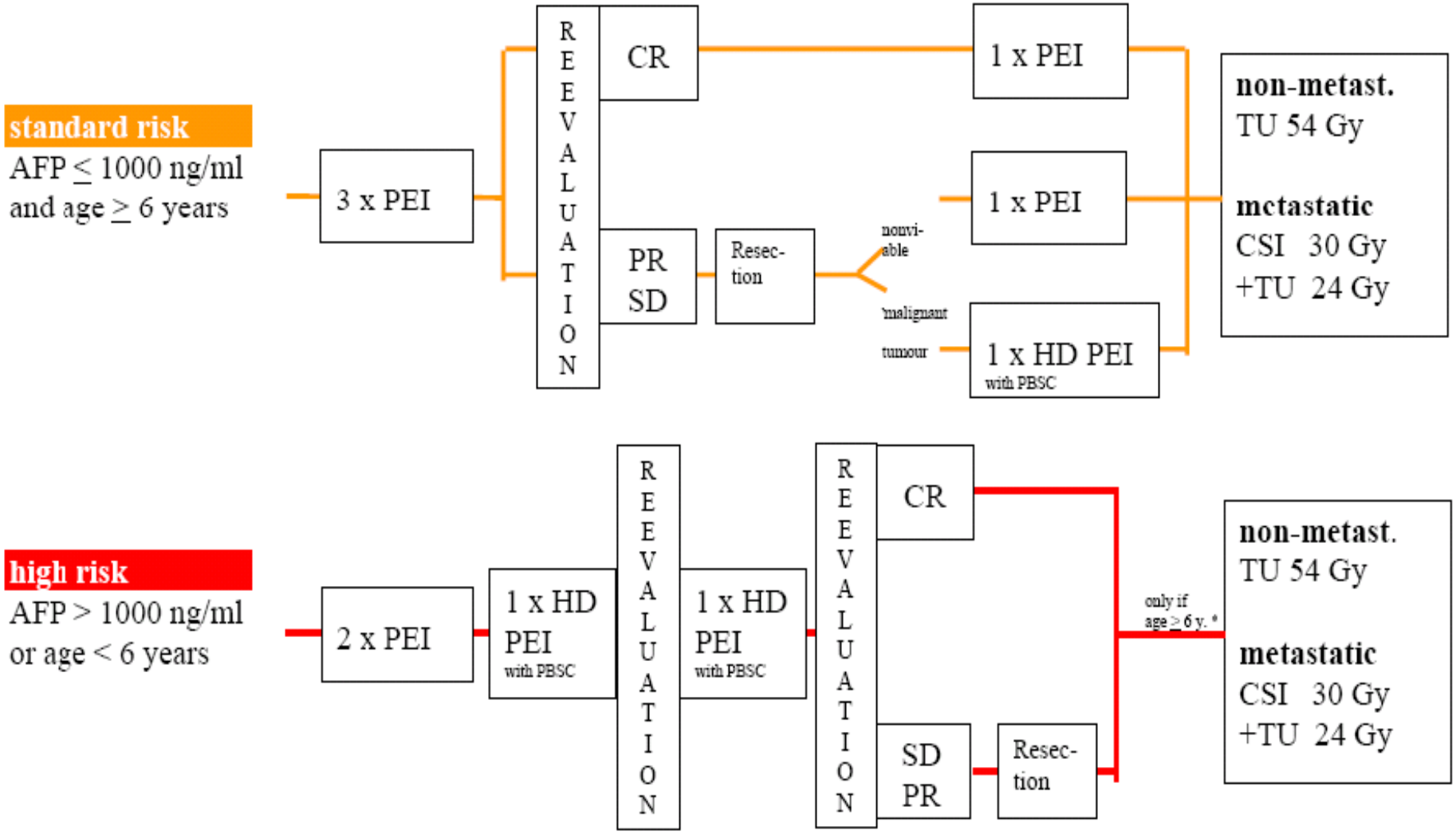
Non - germinomatous GCT

SIOP CNS GCT II

AFP > 25 ng/ml and or total HCG > 50 IU/l in serum and or CSF or hist proven CHC, YST,EC (+/- teratoma / germinoma



Non - germinomatous GCT

Protocols Europe / North America / Asia

Treatment	*Europe (SIOP GCT II)*	*North America (ACNS 1123)*	*Japan (Asia)*
RT volume	**Local (M0) CSI/boost (M+)**	**Whole ventricular / boost (M0) CSI / boost (M+)**	**CSI / boost (M0-M+)**
Dose prescription	**30 Gy CSI (M+) 54 Gy local (M0)**	**30.6 (WV-RT or CSI) 23.6 Gy boost**	**Japan (M0-M+) 30 Gy CSI 24-30 Gy (boost)**
Chx. protocol	**4 x PEI (cispl / etop / ifosph) HD chx in high risk pat. before RT**	**6 x carbopl. / etoposide / ifosfamide before RT&**	**Japan 5 x ICE (ifosph/, cisplatin /etop.) before RT**

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Consensus on the management of intracranial germ-cell tumours

Matthew J Murray, Ute Bartels*, Ryo Nishikawa, Jason Fangusaro, Masao Matsutani†, James C Nicholson†*

Lancet Oncol 2015; 16: e470–77

International Symposia:

- Kyoto, 2003
- Los Angeles, 2005
- Cambridge, 2013
- Tokyo, 2015

Primary CNS lymphoma

ESTRO teaching course
Management of brain tumours

Patrick Roth

Department of Neurology and Brain Tumor Center
University Hospital Zurich

Primary CNS lymphoma

- Lymphoma with exclusive manifestation in the CNS
- Median age: ~ 60 years
- Incidence: approximately 0.5/100.000

  => increasing for unkown reasons
- Particular situation: HIV-associated CNS lymphomas

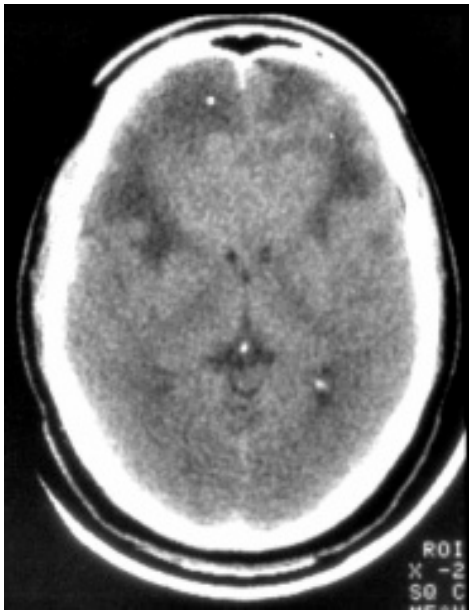
  => incidence decreasing since introduction of HAART
- Unclear pathogenesis => specific CNS tropism?

Clincal presentation

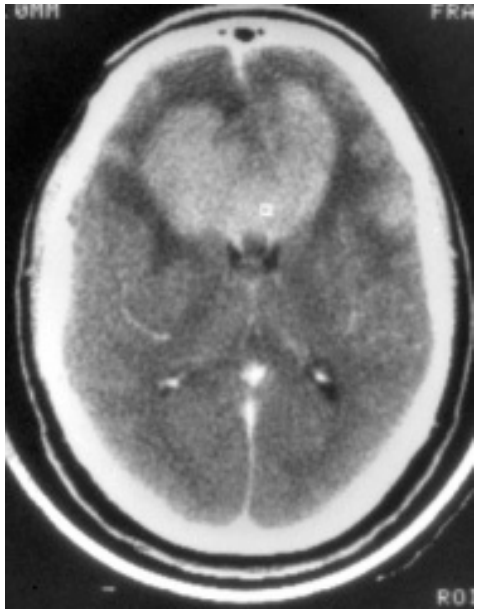
- Personality changes
- Symptoms associated with increased intracranial pressure
- Motor and sensory deficits
- Cranial nerve palsies
- Seizures (rare)
- Cerebellar symptoms

Imaging: CT

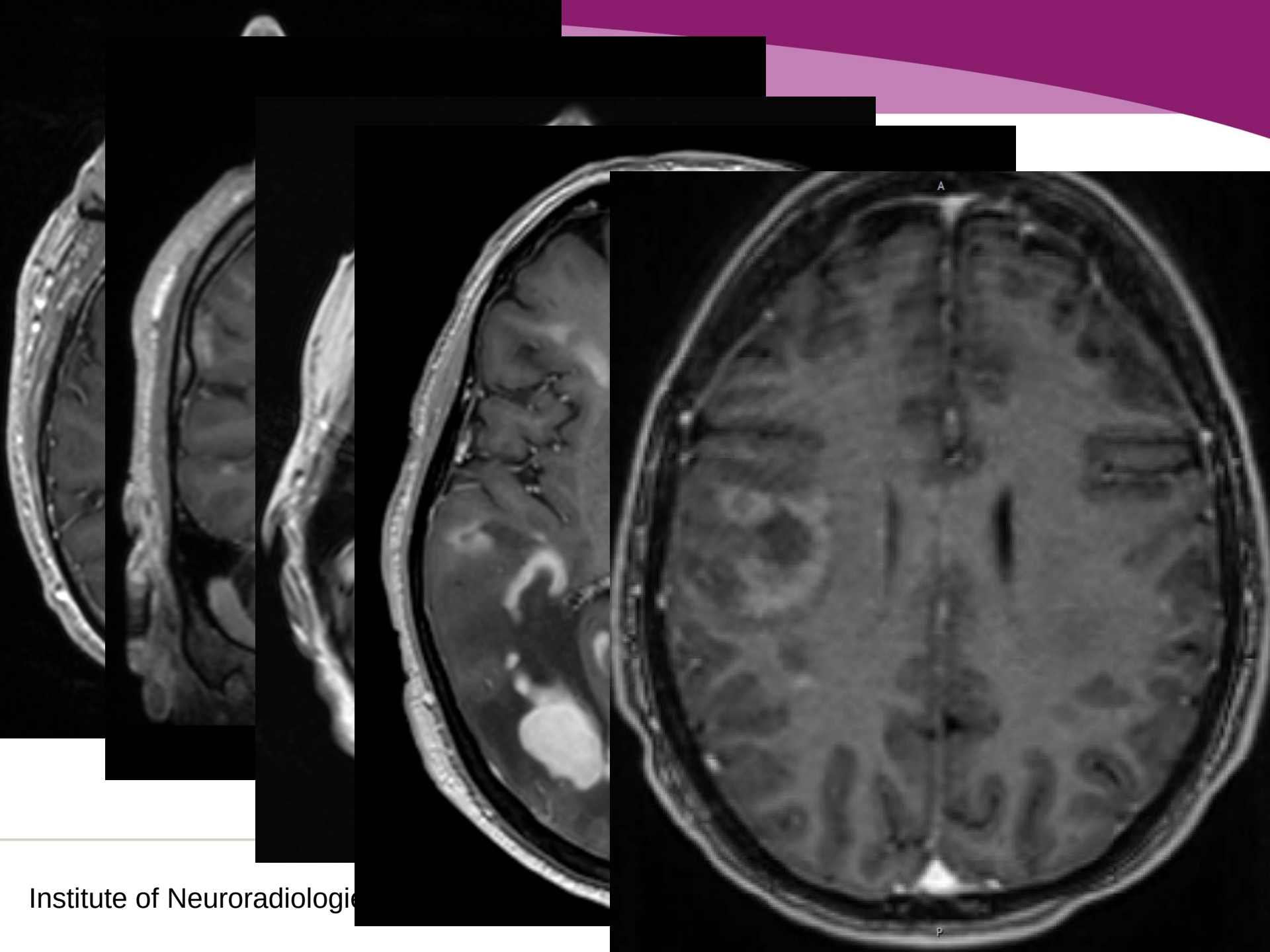
- Iso- or hyperdense mass
- Multiple lesions in about 30-40% of all patients



native



contrast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How to confirm the diagnosis

- Lumbar puncture: dissemination in the CSF in 20-30% of the patients with newly diagnosed PCNSL

  => Confirmation of a malignant B cell clone (FACS) or clonal IgH rearrangement using PCR

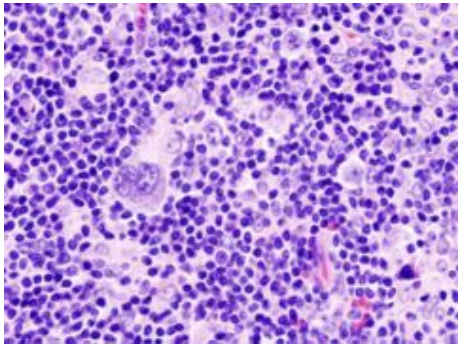
- Stereotactic biopsy: do not administer steroids before!
- Tumor resection does not affect survival – really…?

Staging:

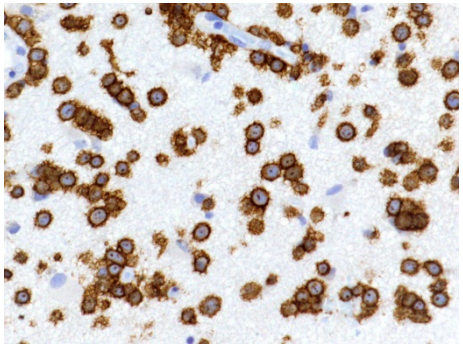
- Slit lamp examination (ocular involvement in 10-15%)
- CT scan chest and abdomen, bone marrow biopsy
- HIV testing

Histology

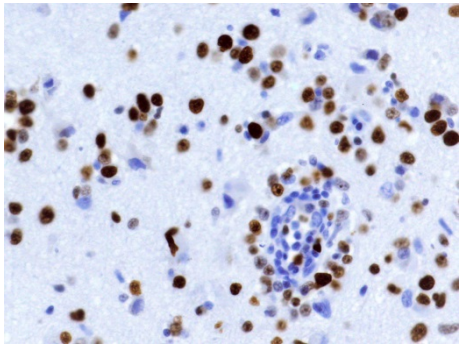
- Diffuse large B cell lymphoma (98%)



- $CD20^{+}$

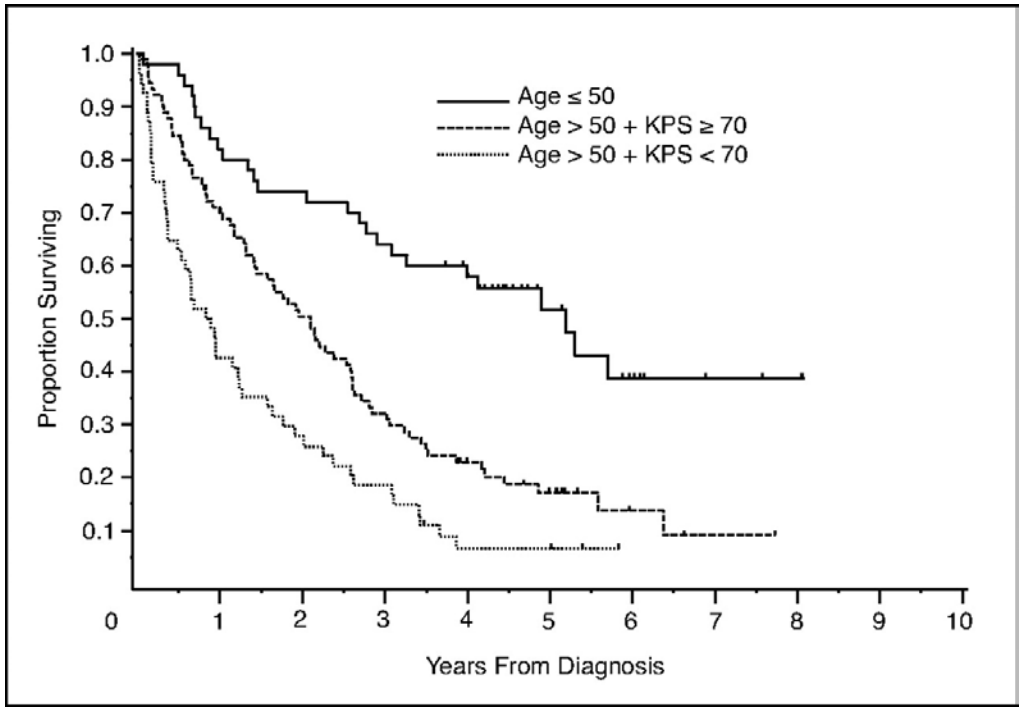


- High proliferation index (>50% $Ki\text{-}67^{+}$)



Prognosis

- Survival without treatment: weeks / few months
- Age and performance status are the most important prognostic factors



Abrey et al. J Clin Oncol 2006

- Histological subtype is **not** a prognostic factor

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Treatment of PCNSL

How would you treat a patient with newly diagnosed PCNSL?

1. Radiotherapy (WBRT)
2. Chemotherapy
3. Radio- and chemotherapy
4. Well, it depends…

Treatment of PCNSL: what do we know?

- WBRT (>40 Gy)

  Median OS 12 months, <5% 5-year survival (Nelson et al., 1992)

- High-dose methotrexate (HD-MTX): most active drug

  Median survival approximately 25 months

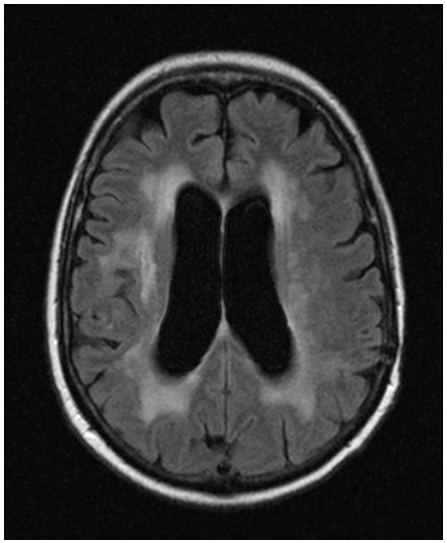
  ~25% surviving 5 years or more (Herrlinger et al., 2005)

- HD-MTX + intrathecal MTX + WBRT

  Median OS 42 months, 25% 5year survival (Abrey et al., 1998, DeAngelis et al., 2002)

  BUT: up to 60% of all patients (and virtually ALL elderly patients) suffer from severe **neurotoxicity** (Abrey et al., 1998; Herrlinger et al., 2001; Harder et al., 2004)

=> no longer appropriate



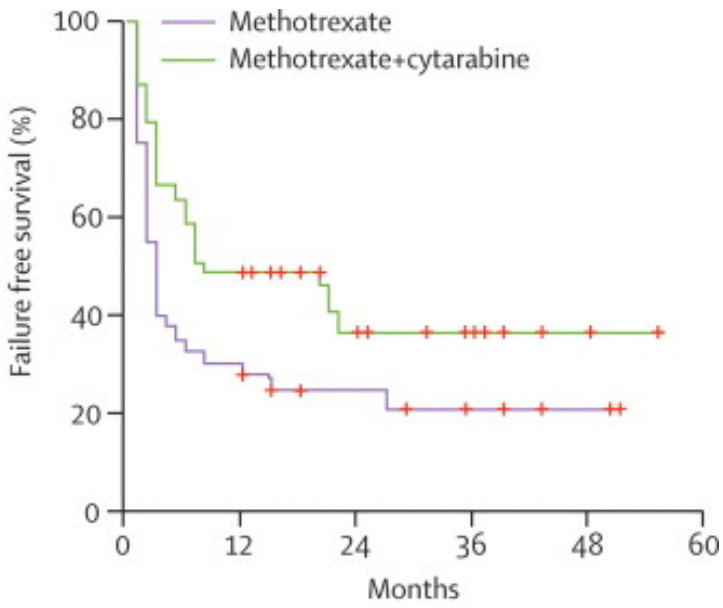
IELSG-20: MTX vs. MTX/Ara-C

- Randomized phase II trial, 24 centers, 6 countries
- 79 patients, age 18-75 Jahre
- 4 cycles of MTX, 3.5 g/m^2 alone **OR** MTX plus 4x Ara-C, 2 g/m^2 d2+3, every 3 weeks, followed by WBRT
- CR rate after MTX-based therapy:
  18% (MTX) versus 46% (MTX + Ara-C)
- Hematological toxicity more frequent and severe with combination

Ferreri et al., Lancet 2009

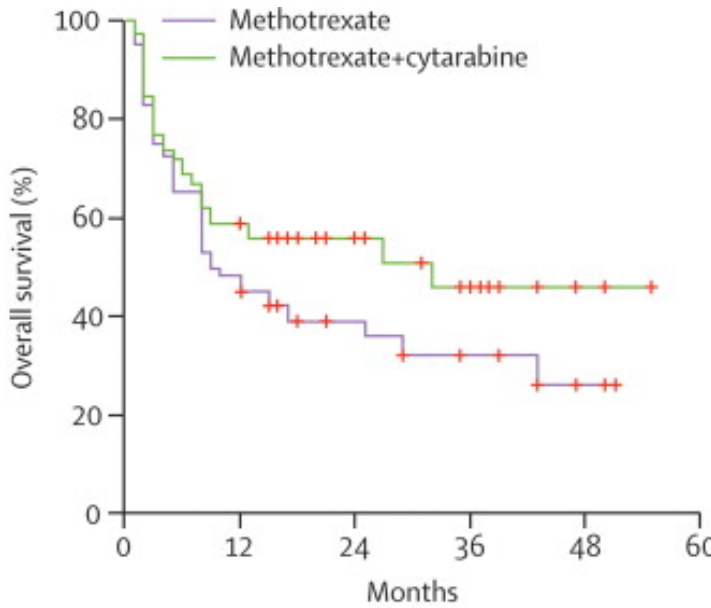
IELSG-20: MTX vs. MTX/Ara-C

PFS



Number at risk				
Methotrexate	11	7	4	2
Methotrexate+cytarabine	19	9	6	2

OS



Number at risk				
Methotrexate	19	12	7	3
Methotrexate+cytarabine	22	13	7	3

3 year survival rate 32% versus 46% (p = 0.07)

Ferreri et al., Lancet 2009

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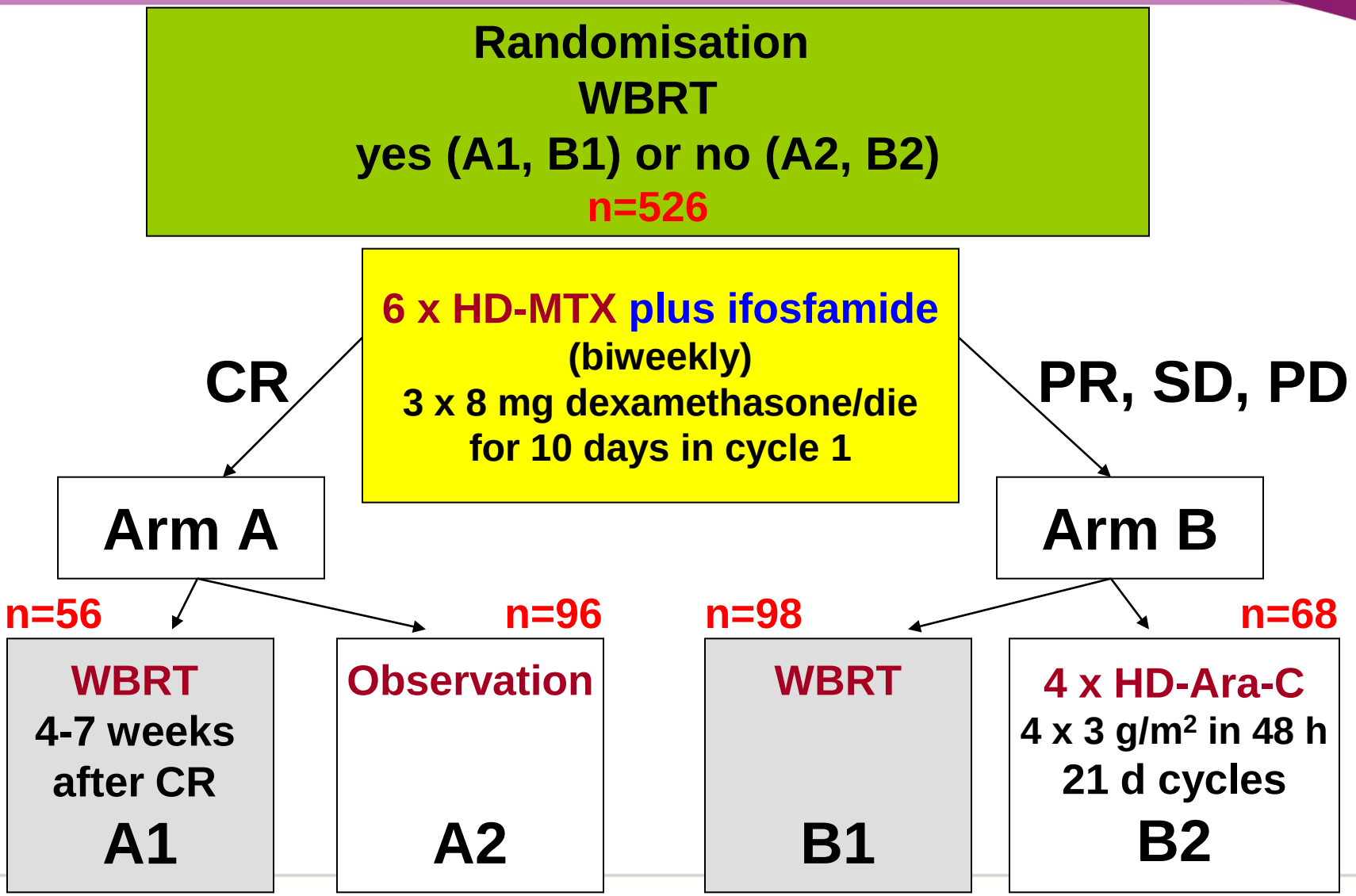
The G-PCNSL-SG1 trial



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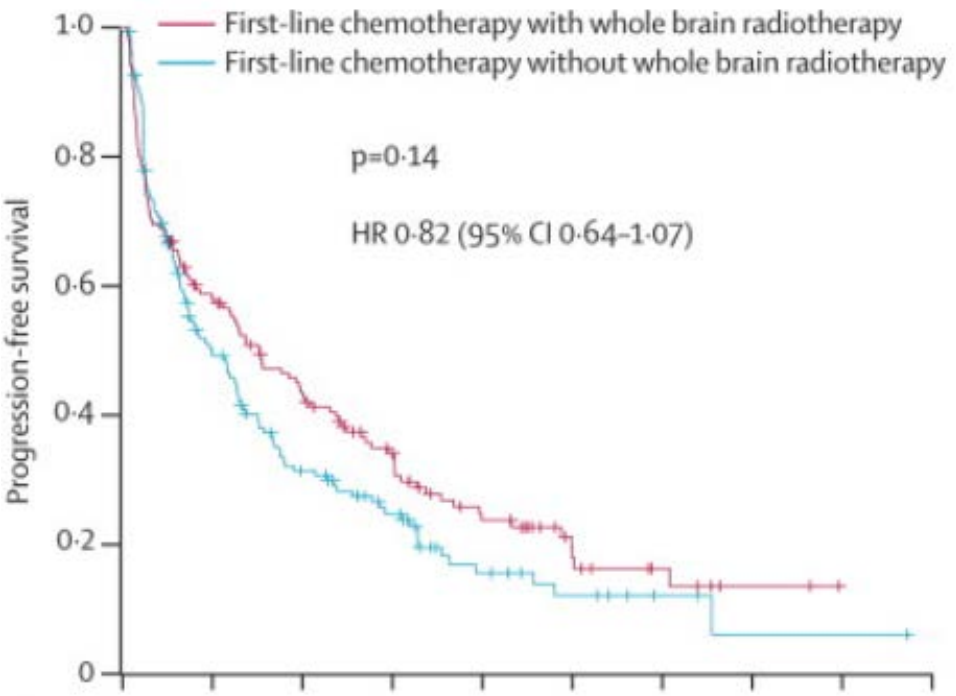
The G-PCNSL-SG1 trial

PFS



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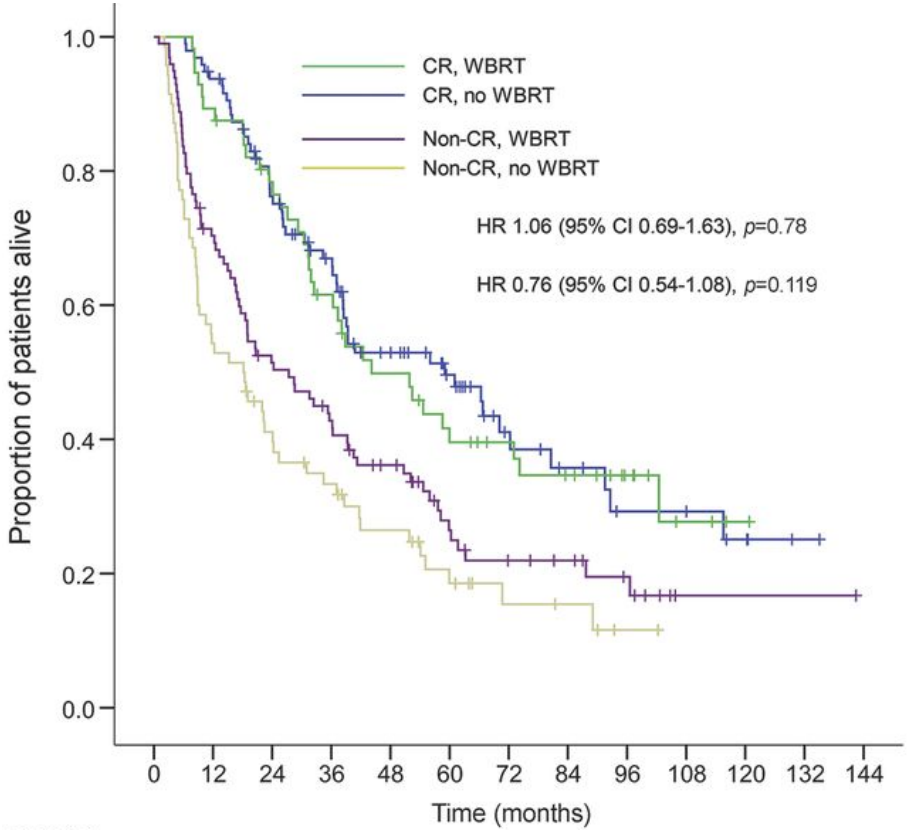

=> early WBRT does not prolong overall survival

Thiel et al., Lancet Oncol 2009
Korfel et al. Neurology 2015

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No role for resection – for 4 decades

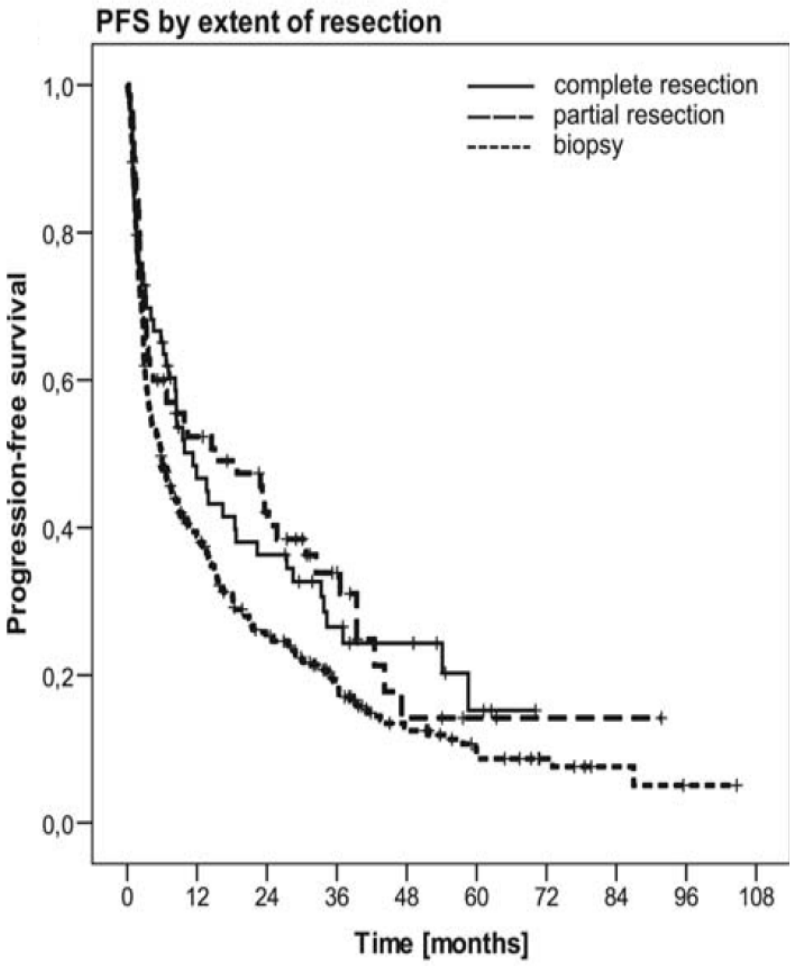
PRIMARY MALIGNANT LYMPHOMAS OF THE CENTRAL NERVOUS SYSTEM

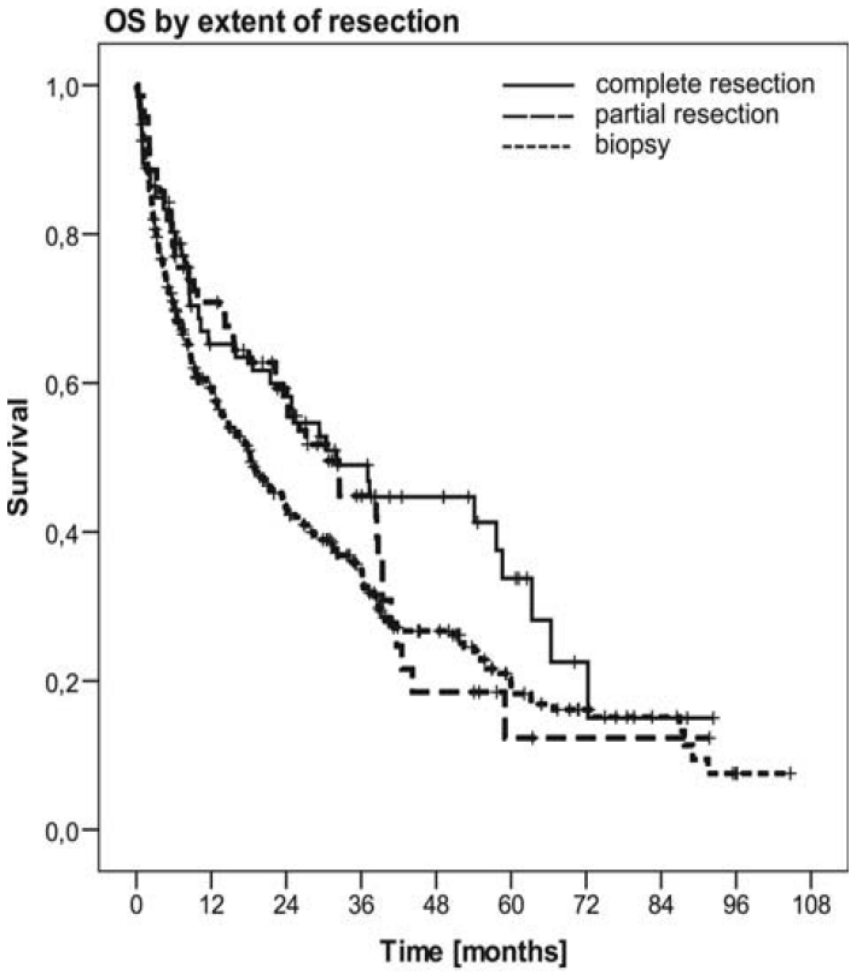
JAMES M. HENRY, MAJ, MC, USA, REID R. HEFFNER, JR, MD,
SAMUEL H. DILLARD, MAJ, MC, USA, KENNETH M. EARLE, MD,*
AND RICHARD L. DAVIS, MD†

Eighty-three cases of primary malignant lymphomas of the central nervous system (CNS) from the files of the AFIP were studied according to various clinical and pathologic parameters. The histologic patterns observed are analogous to those seen in the spectrum of malignant lymphomas arising in the reticuloendothelial system of other organs. The authors favor the diagnosis of primary malignant lymphoma of the CNS rather than that of "reticulum cell sarcoma" or "microgliomatosis" used in the past. Lesions are frequently multifocal, and surgery, other than for diagnostic biopsy, is not usually beneficial. The clinical course can be significantly prolonged by radiation therapy.

***Cancer* 34:1293–1302, 1974.**

Resection – may be considered…





Weller et al., Neuro Oncol 2012

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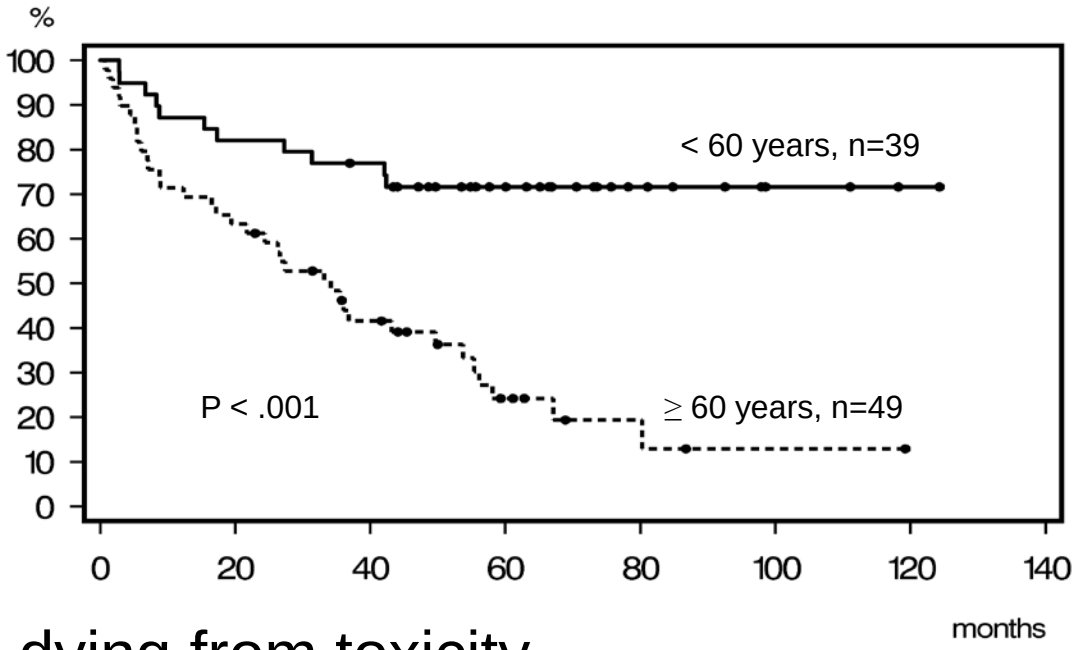
Bonn protocol - polychemotherapy

- 88 patients
- Polychemotherapy and intrathecal chemotherapy
- 60% CR, median OS 55 months



9% dying from toxicity
23% reservoir infection

Pels et al., J Clin Oncol 2003

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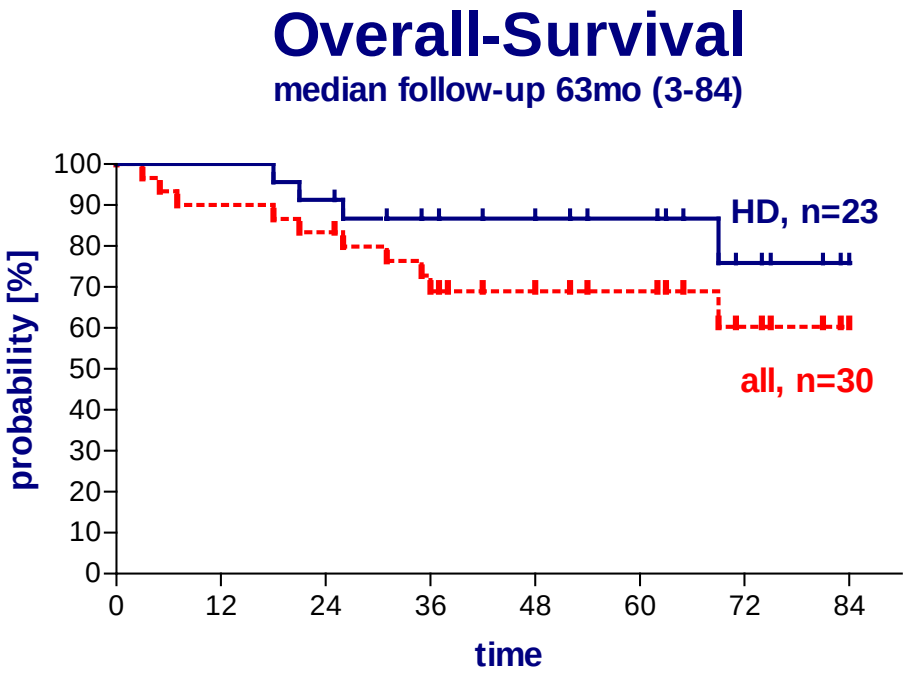
High-dose chemotherapy with stem cell support

- High-dose chemotherapy followed by autologous stem cell transplantation
- Only patients younger than 60 years



Illerhaus et al., J Clin Oncol 2006

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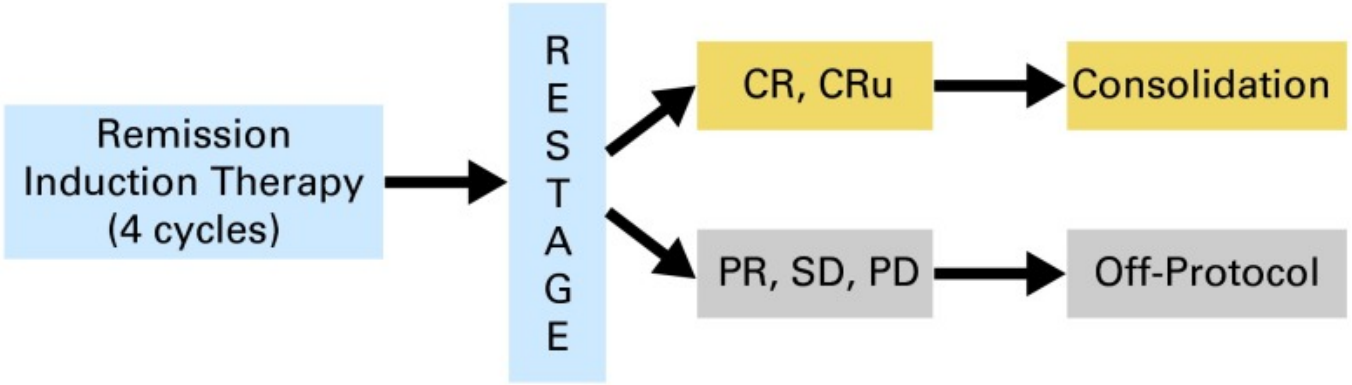
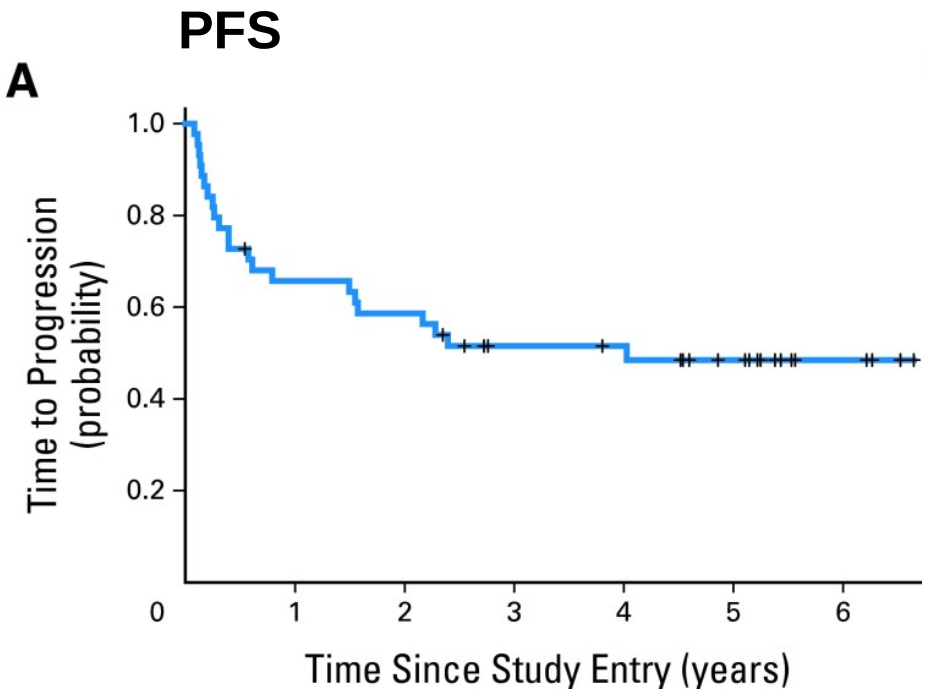
CALGB 50202: intensive chemotherapy + rituximab

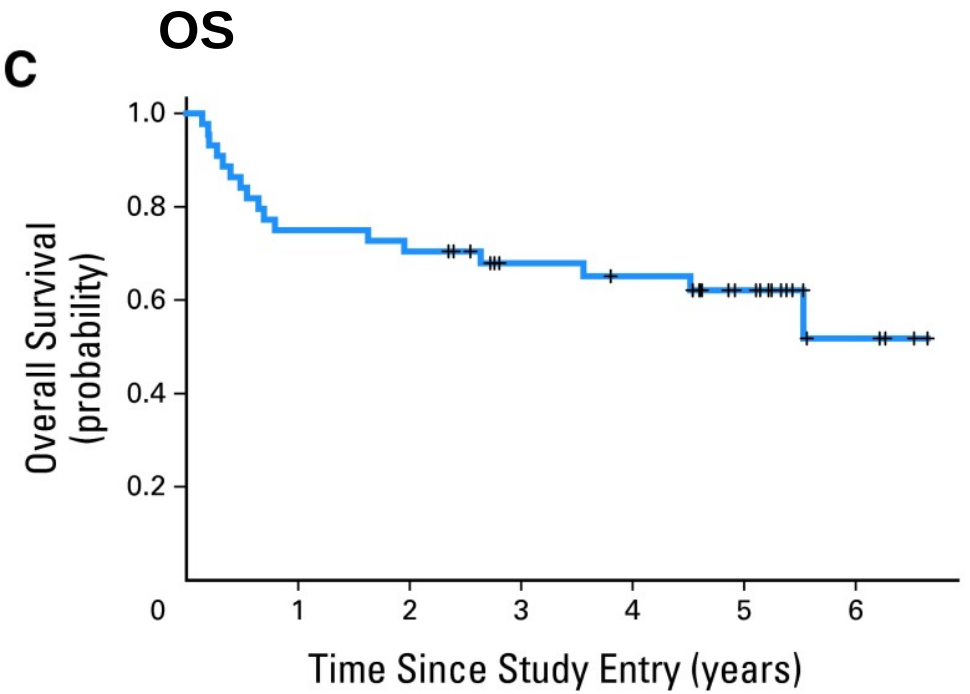


Remission Induction Therapy: MT-R (14-day cycle)	
Day 1	Methotrexate 8 grams/m^2 IV over 4 hrs
Day 2	Leucovorin 100 mg/m^2 every 6 hrs, until methotrexate < 0.05 mM
Day 3	Rituximab 375 mg/m^2 IV cycles 1 through 6
Day 7-11	Temozolomide 150 mg/m^2 PO (odd cycles only)
Consolidation Therapy: EA	
Day 1-4	Etoposide 40 mg/kg continuous IV over 96 hrs
Day 1-4	Cytarabine 2 gm/m^2 IV over 2 hrs every 12 hrs × 8 doses

Rubenstein et al., J Clin Oncol 2013

CALGB 50202: intensive chemotherapy + rituximab





Rubenstein et al., J Clin Oncol 2013

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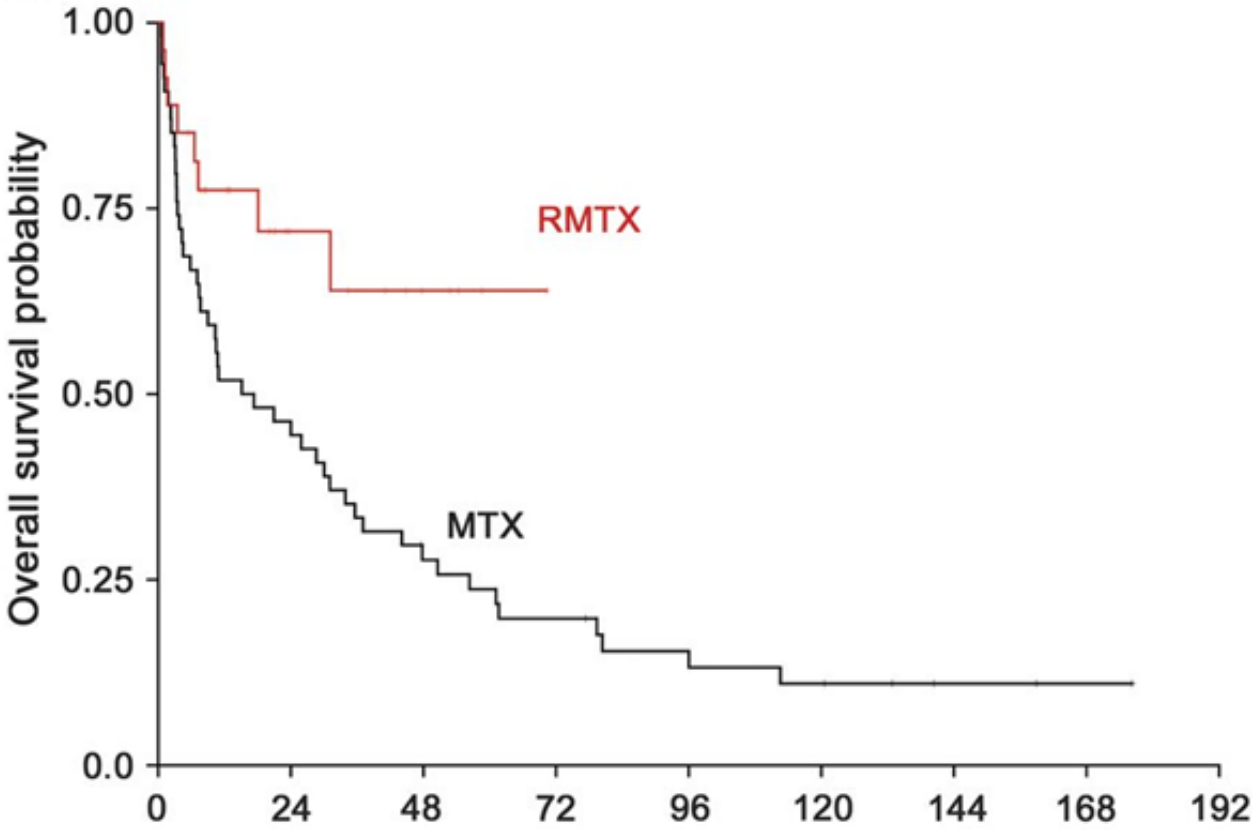
What is the role for rituximab in PCNSL?



Data from prospective studies are lacking

Holdhoff et al., Neurology 2014

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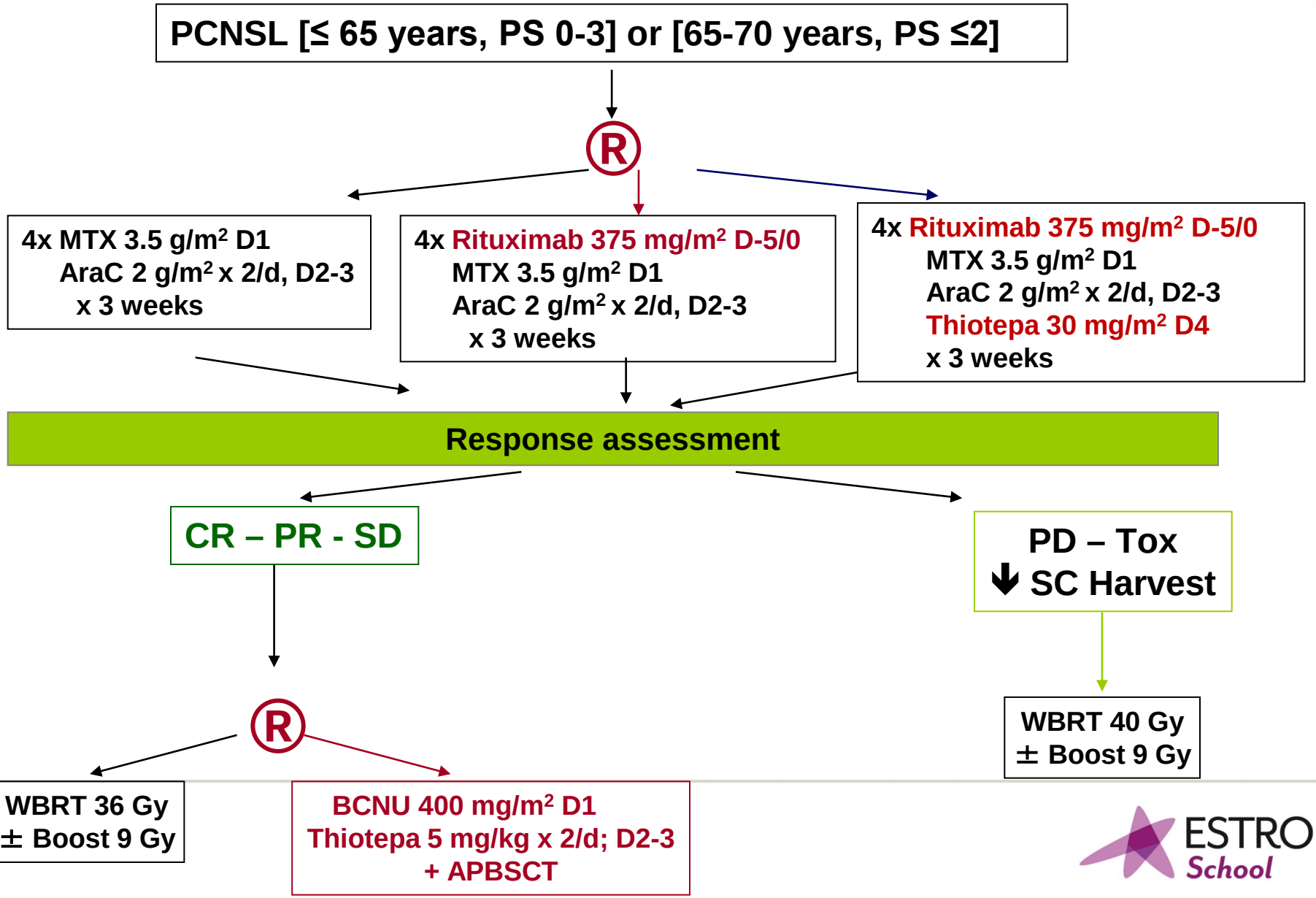
IELSG-32 trial



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Treatment at recurrence

- **No standard of care**

  Individual decision based on previous treatment, response to initial therapy, performance status, age….

- **Available options**

  HD-MTX re-challenge

  Other chemotherapeutic drugs (topotecan, temozolomide…)

  High-dose chemotherapy + stem cell transplantation

  WBRT

Elderly PCNSL patients: a particular challenge

- Median age of PCNSL patients: ~ 60 years
- Definition of “elderly“ is imprecise:

  ≥ 60 years?

  ≥ 65 years?

  ≥ 70 years?

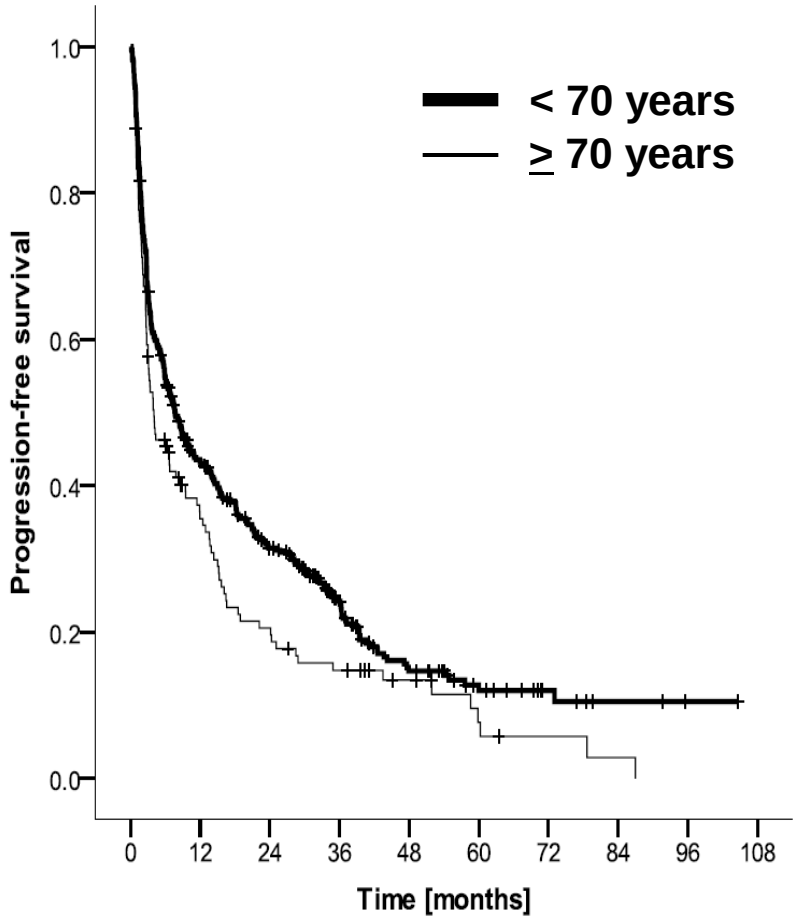


- Therapeutic relevance: age is an inclusion criterion in many trials
- (Neuro)toxicity is a particular concern in the elderly

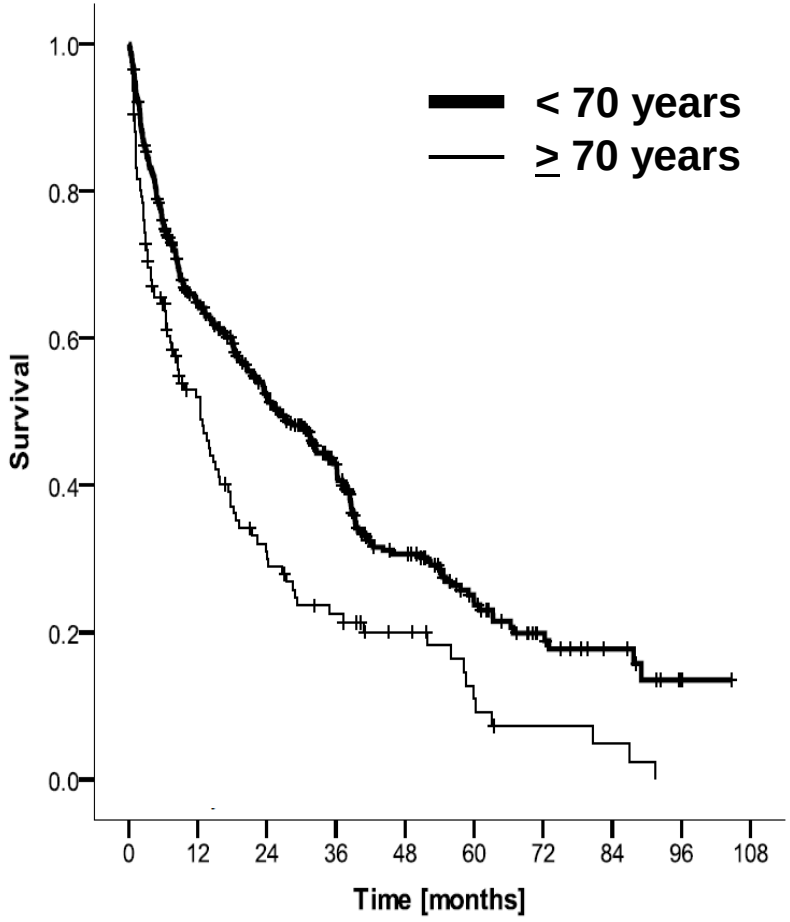
Elderly PCNSL patients in G-PCNSL-SG1

n=526

PFS



OS



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Elderly PCNSL patients in G-PCNSL-SG1

	PFS (months)	OS (months)
No-CR patients		
≥ 70 years	3.2	17.3
< 70 years	3.5	22.3
CR patients		
≥ 70 years	16.1	26.7
< 70 years	35.0	44.2

=> Relapses occur earlier in elderly patients

Roth et al., Neurology 2012

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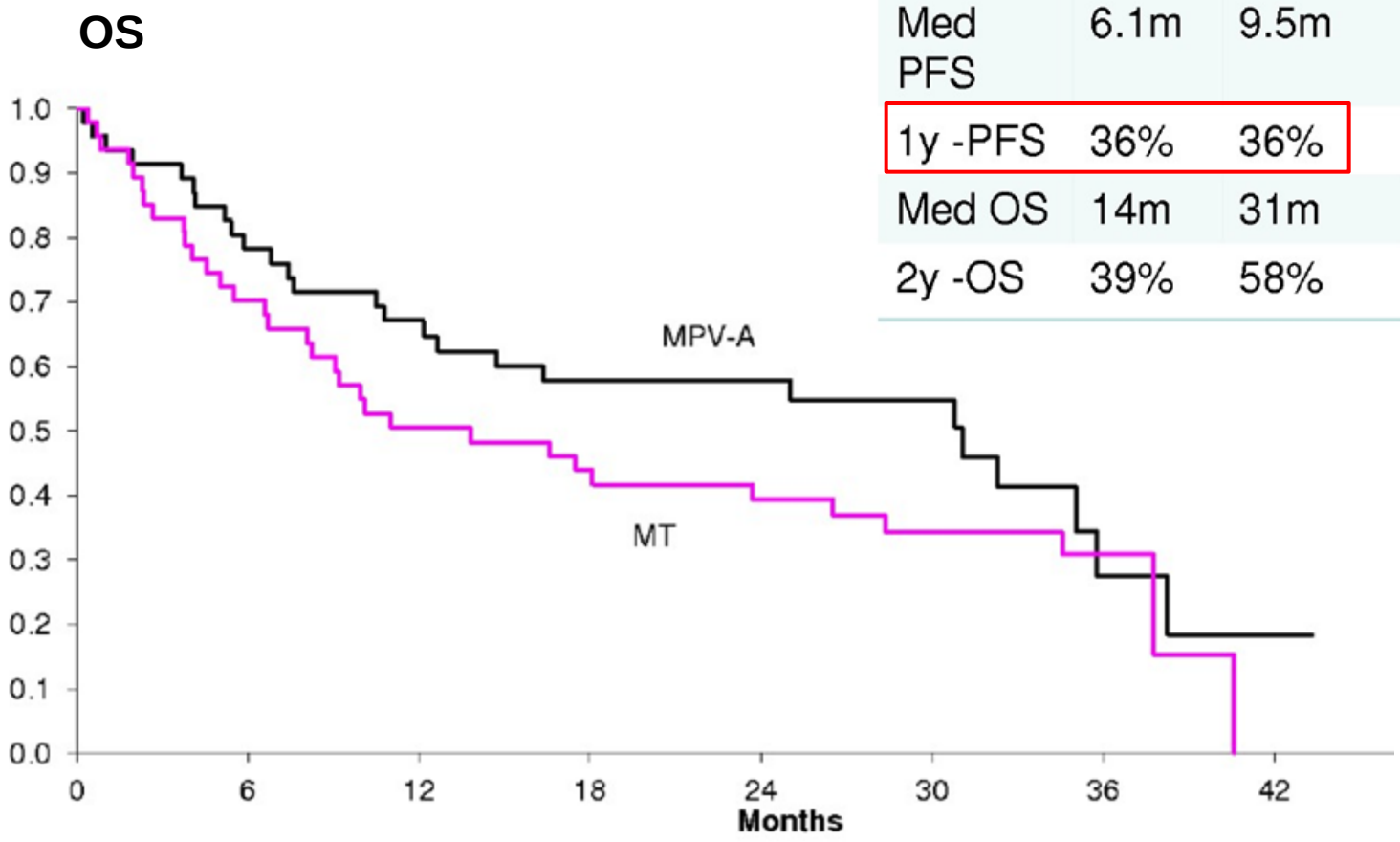
MTX/TMZ vs. MPV-A in elderly patients

- **Randomized phase II trial**
- **95 patients, median age 72 years (60–85)**
- **Treatment arms:**
  - **MTX 3.5 g/m^2 + Temozolomide**
  - **MTX 3.5 g/m^2 + Procarbazine, Vincristine, AraC**
- **Primary einpoint: PFS at 1 year (PFS-1)**
- **Toxicity (Grad 3/4): no difference**
- **CR rate: 45% (MT) vs. 62% (MPV-A)**

Omuro et al., Lancet Hematol 2015

MTX/TMZ vs. MPV-A in elderly patients

	MT	MPV-A	Pvalue
Med PFS	6.1m	9.5m	0.6
1y -PFS	36%	36%	
Med OS	14m	31m	0.2
2y -OS	39%	58%	



Omuro et al., Lancet Hematol 2015

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MTX-based therapy in elderly patients

Prospectively collected study data

	n	age	Treatment	CR	PR	PFS	OS
Omuro	23	68	MTX, Temozolomide	55%	0%	8	35
Hoang-Xuan	50	72	MTX, CCNU, PCZ, Prednisolone. MTX and AraC i.th.	42%	6 %	10.6	14.3
Illerhaus	30	70	MTX, CCNU, Procarbazine	44%	26%	5.9	15.4
Fritsch	28	76	MTX, CCNU, PCZ, Rituximab	64%	18%	16	17.5
Roth	126	73	MTX, ifosfamide, +/- WBRT	30%	14%	4.0	12.5
Omuro	95	73	MTX, PCZ, VCR, AraC	62%	26%	9.5	31
			MTX, TMZ	45%	20%	6.1	14

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Conclusions

- Cure is probably restricted to younger patients

  => cure might even be achieved when the tumor recurs

- Standard of care is only poorly defined

  => further trials are urgently needed

- Whenever possible, HD-MTX should be administered
- Avoid WBRT when possible
- Open questions:
  - Role for rituximab?
  - Optimal treatment for elderly/frail patients?

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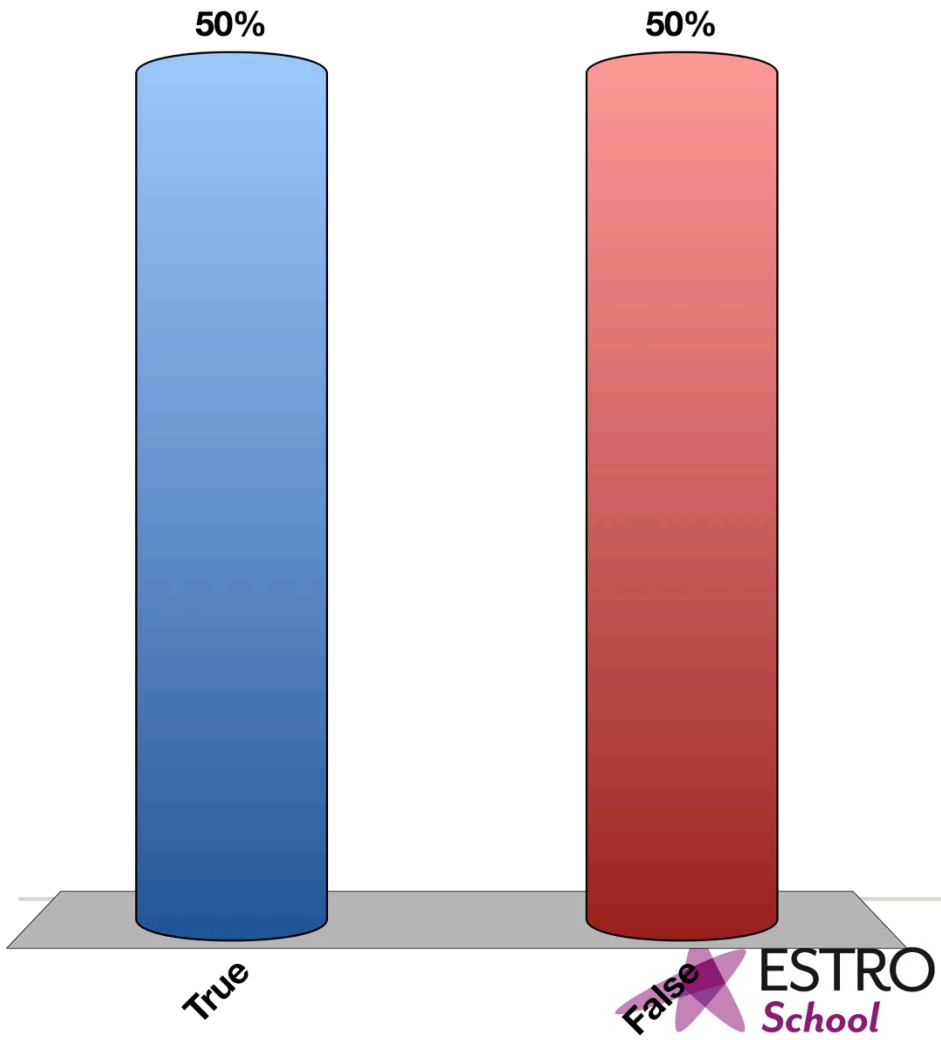
Biopsy of brainstem glioma is standard Ix!

A. True
B. False



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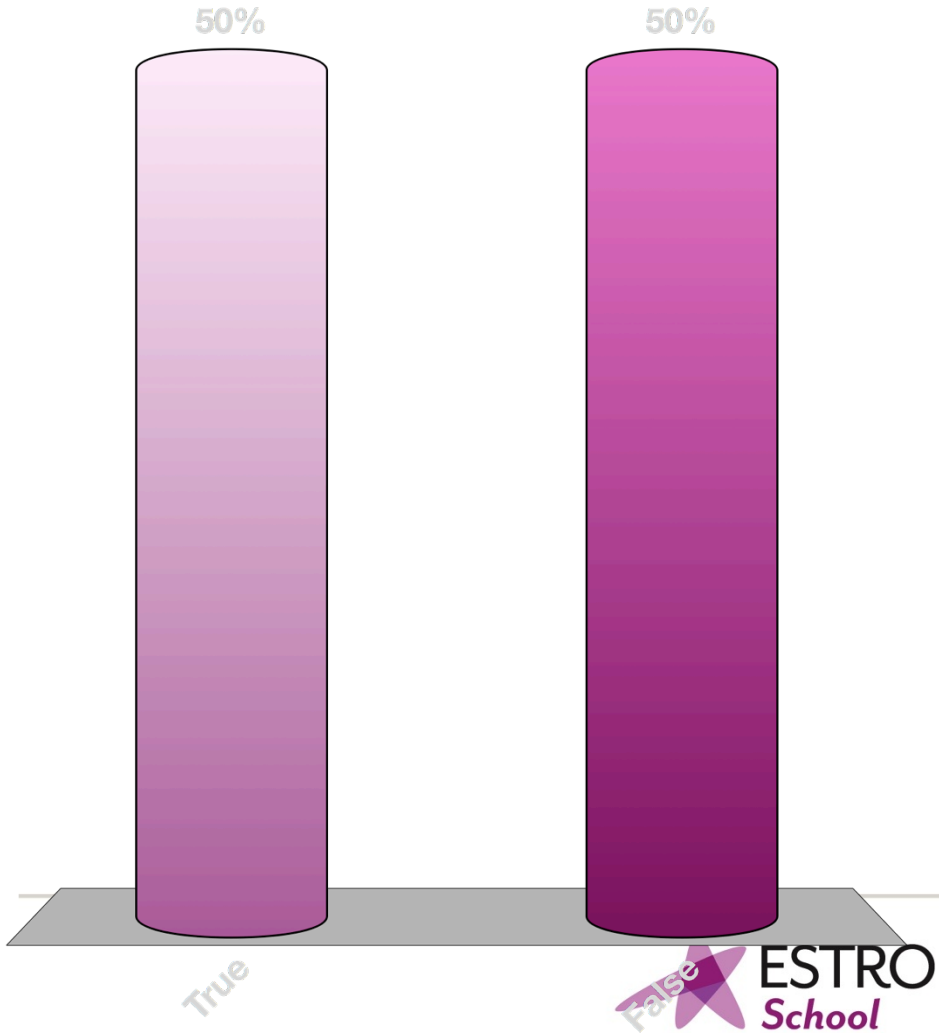
HGG biology is the same in children as in adults!

A. True
B. False



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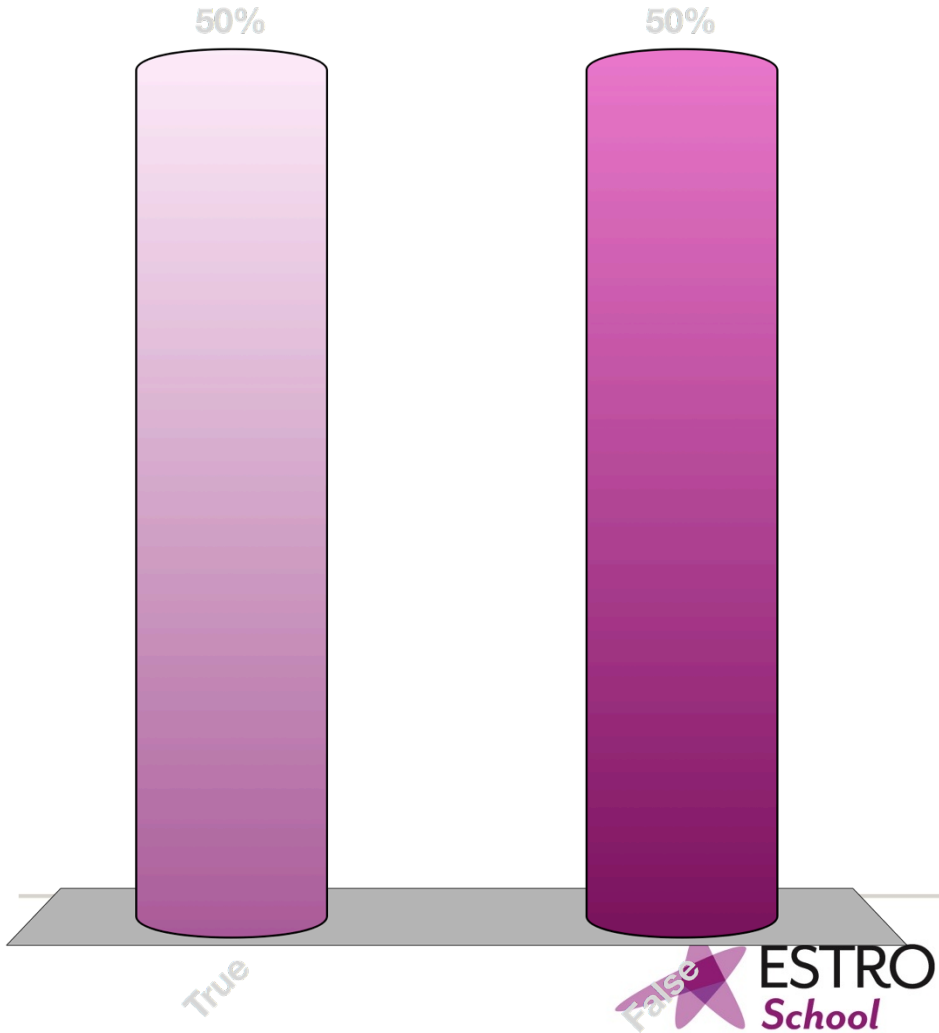
The brainstem is a frequent location of childhood HGG.

A. True

B. False



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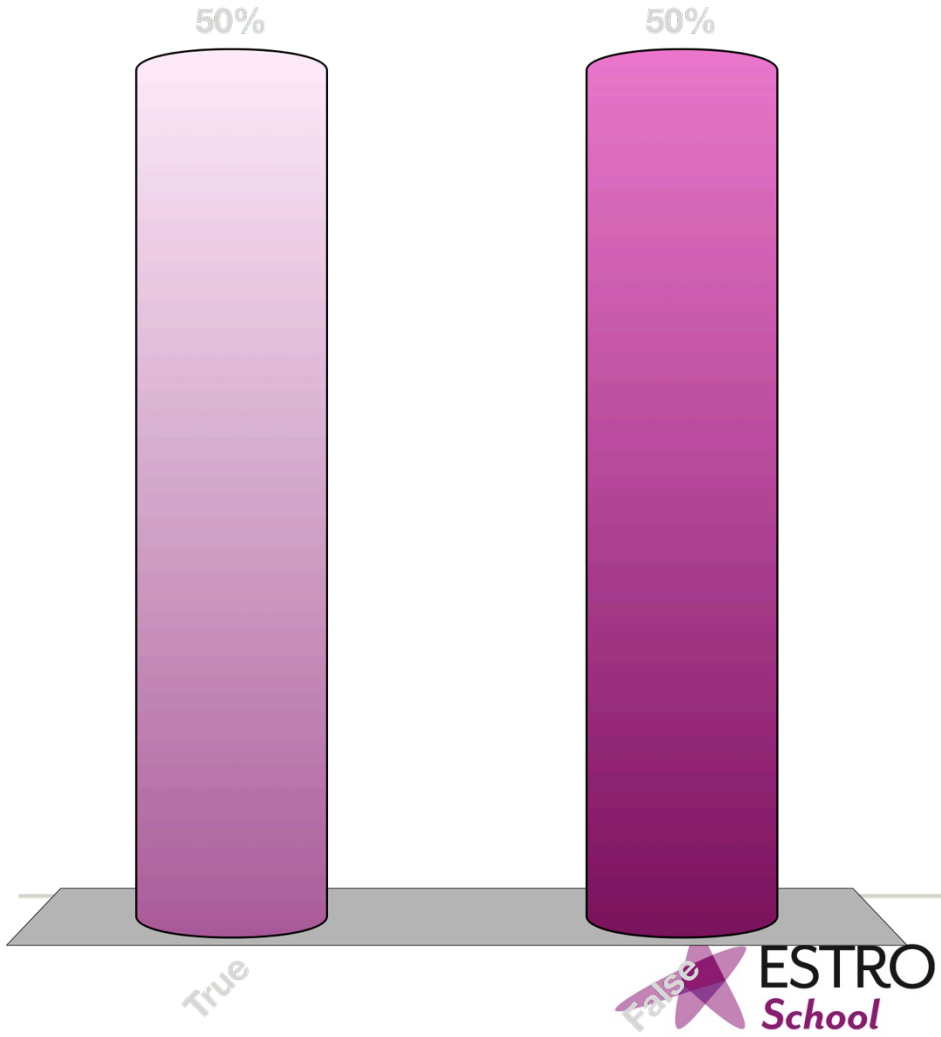
Infants (<3 yrs) with HGG have a worse prognosis than older child

A. True

B. False



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Management of high grade glioma in children

Darren Hargrave

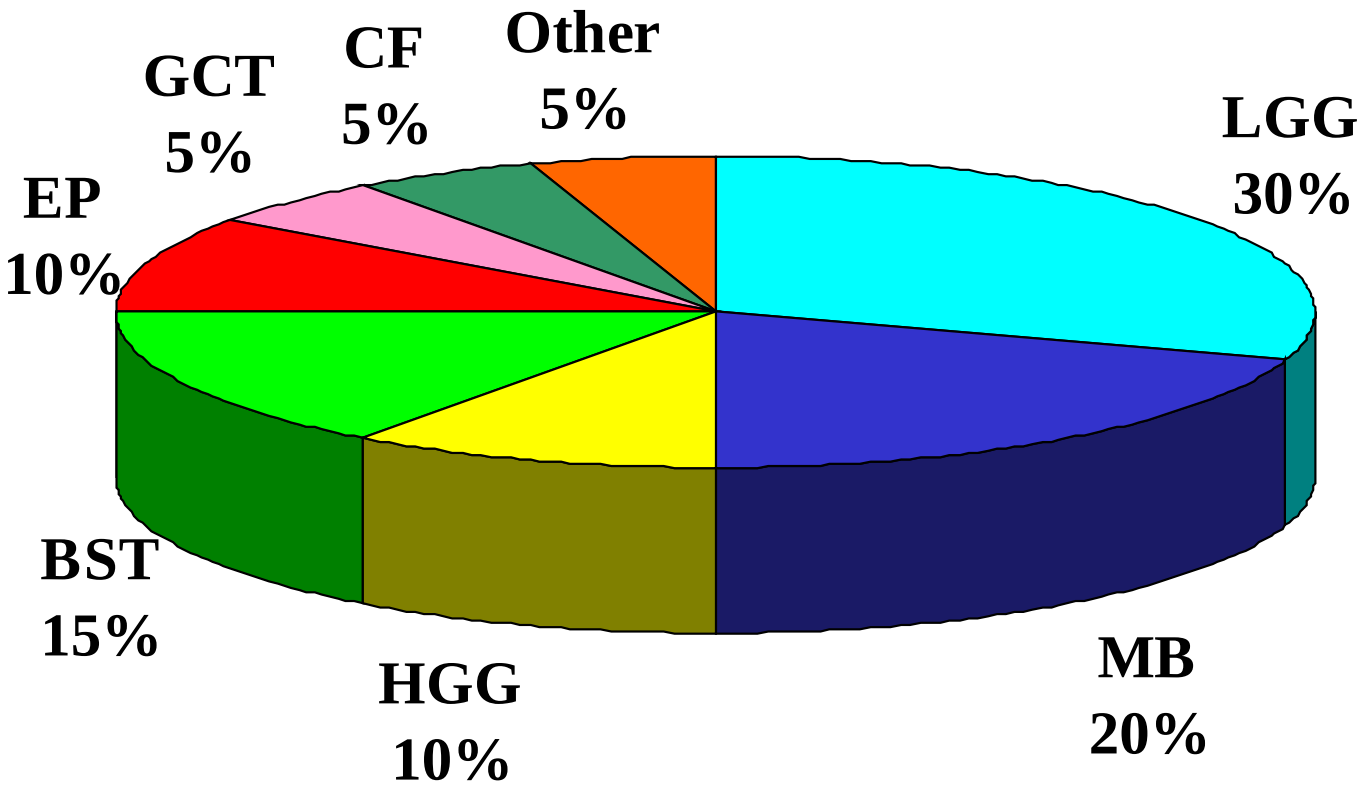
Consultant Paediatric Oncologist,

Neuro-oncology & Experimental Therapeutics

Great Ormond Street Hospital. London, UK.

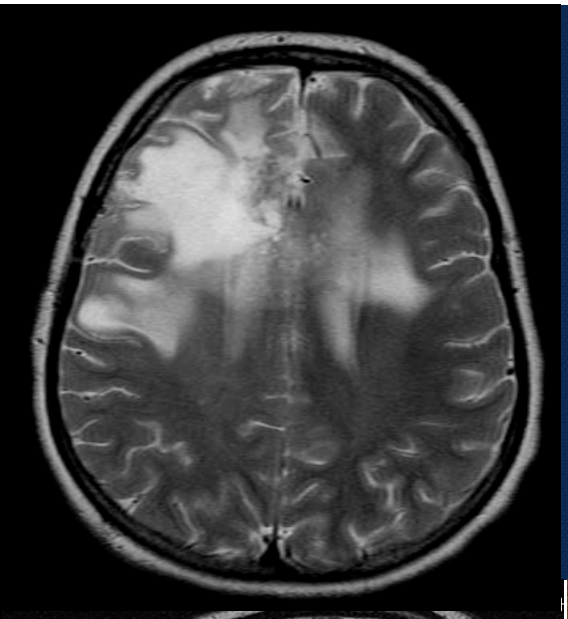
PAEDIATRIC HIGH GRADE GLIOMA:
BACKGROUND

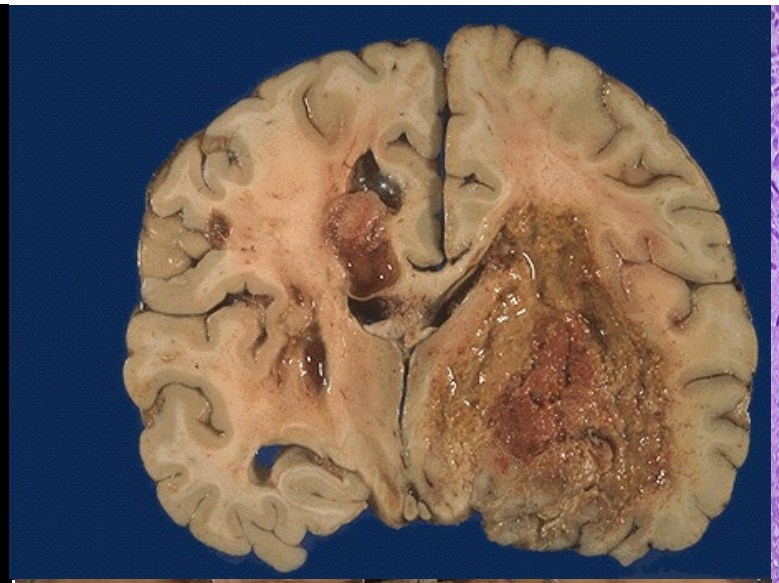
Paediatric brain tumours

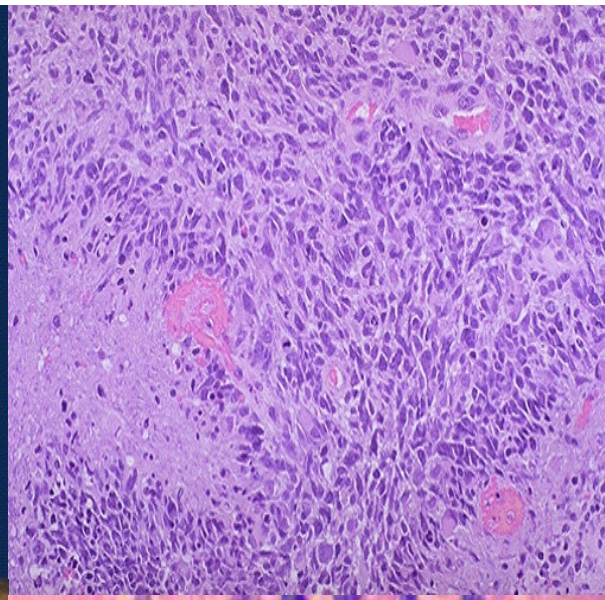


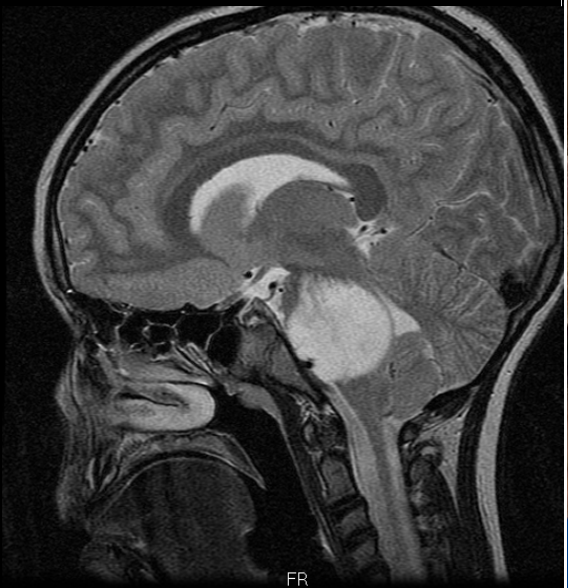
HGG (WHO grade III – IV): 15-25% of all CNS tumors in children

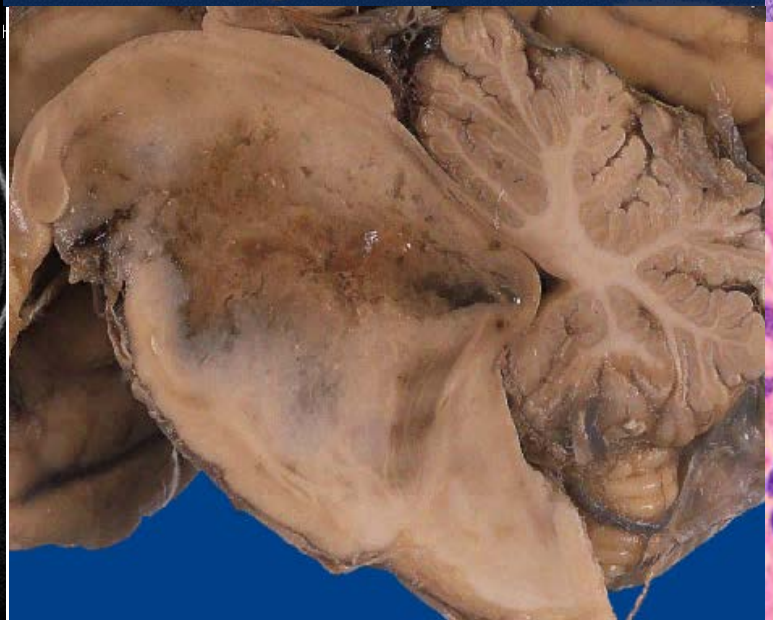
High Grade Glioma in children

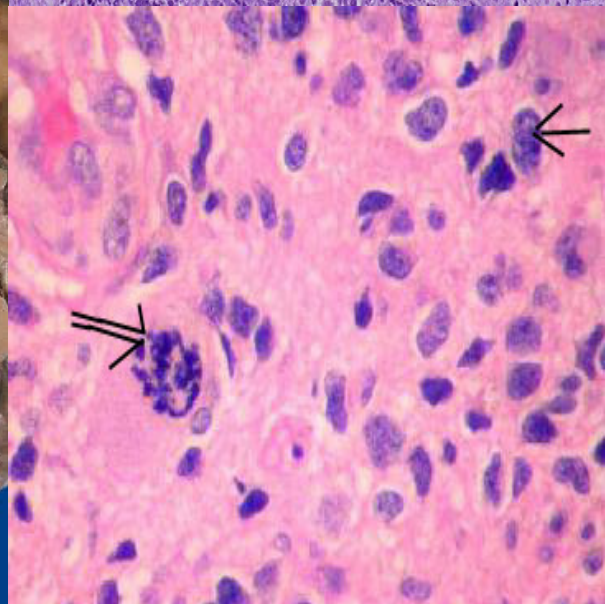












Pathology

- WHO Classification (2007)
  - Malignant Glioma- grade III & IV (High Grade)
  - Anaplastic Astrocytoma
  - Glioblastoma Multiforme
  - Gliosarcoma
  - Plus Mixed Oligo-Astrocytomas

High Grade Glioma: Aetiology

- In most cases is unknown
- Previous radiation treatment
- Genetic disease
  - Neurofibromatosis type I: mutation in the NF-1
  - Li-Fraumeni Syndrome: defect in TP53
  - Turcot syndrome: defect in the APC gene and/or a mutation in DNA mismatch repair (MMR) genes
  - Mismatch repair deficiency of the MSH6 mismatch repair

Epidemiology

- Incidence: 15-20% of all childhood CNS tumours

Table 1 | Rate (95% CI) of malignant glioma per 100,000 person years*

Age range (years)	Anaplastic astrocytoma	Anaplastic oligodendroglioma	Glioblastoma	Glioma malignant, NOS
0–4	0.06 (0.04–0.07)	NR‡	0.09 (0.07–0.11)	0.86 (0.79–0.92)
5–9	0.08 (0.06–0.11)	NR	0.14 (0.11–0.17)	0.77 (0.70–0.83)
10–14	0.09 (0.07–0.12)	NR	0.15 (0.12–0.18)	0.39 (0.35–0.44)
15–19	0.1 (0.08–0.12)	0.03 (0.02–0.05)	0.18 (0.15–0.21)	0.23 (0.20–0.26)
0–14	0.08 (0.07–0.09)	0.01 (0.01–0.02)	0.13 (0.11–0.14)	0.67 (0.63–0.70)
0–19	0.08 (0.07–0.09)	0.02 (0.01–0.02)	0.14 (0.13–0.15)	0.56 (0.53–0.58)
20–34	0.29 (0.27–0.32)	0.09 (0.08–0.11)	0.41 (0.38–0.44)	0.21 (0.19–0.23)
35–44	0.43 (0.40–0.46)	0.19 (0.17–0.21)	1.22 (1.17–1.28)	0.23 (0.21–0.25)
45–54	0.51 (0.48–0.55)	0.19 (0.17–0.21)	3.71 (3.62–3.80)	0.27 (0.25–0.30)
55–64	0.75 (0.70–0.80)	0.22 (0.20–0.25)	8.22 (8.05–8.38)	0.39 (0.35–0.42)
65–74	1.02 (0.95–1.10)	0.20 (0.17–0.24)	13.27 (13.01–13.54)	0.64 (0.58–0.70)
75–84	1.06 (0.97–1.16)	0.16 (0.13–0.20)	14.49 (14.15–14.82)	1.31 (1.21–1.41)
≥85	0.39 (0.31–0.49)	NR	8.3 (7.91–8.71)	1.48 (1.31–1.66)

*Data derived from Central Brain Tumor Registry of the United States Statistical Report 2011: the CDC National Program of Cancer Registries and the US National Cancer Institute Surveillance, Epidemiology and End Results program, 2004–2007, age-adjusted to the 2000 US standard population. ‡Fewer than 16 cases were reported. Abbreviations: NOS, not otherwise specified; NR, not reported.

Clinical Presentation- non-brainstem HGG

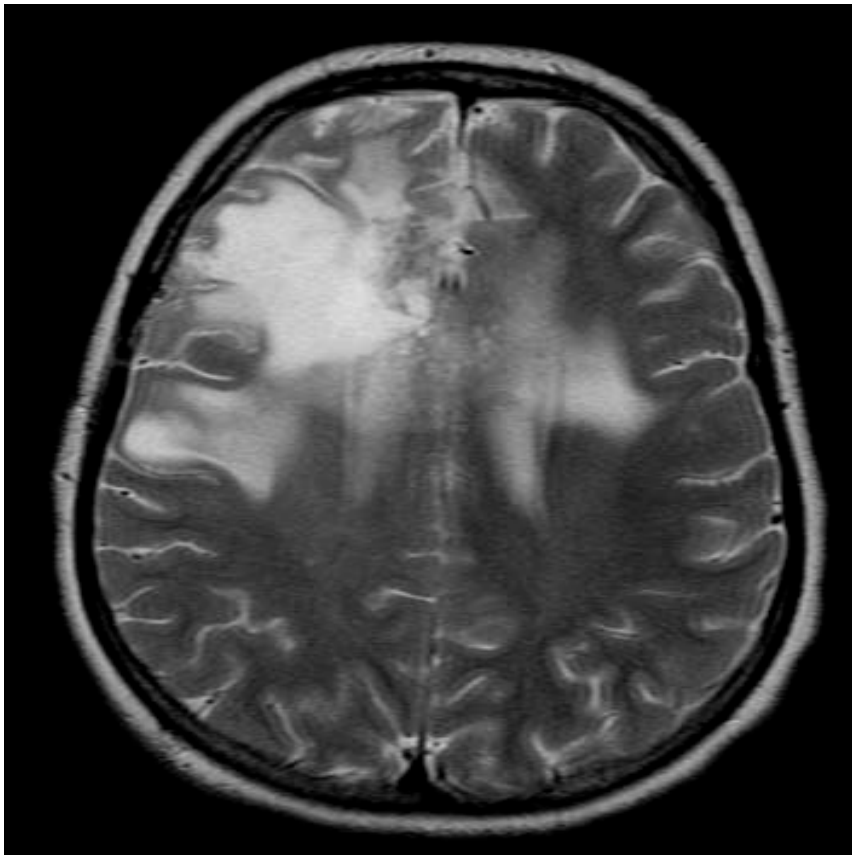
Raised ICP	Focal Signs	Focal Signs
	Post. Fossa	Hemispheric
Headache	Ataxia	Seizures
Vomiting	Nystagmus	Spasticity
Behavioural	Diplopia	Memory deficits
Conscious level	Brainstem	Behaviour
Papilloedema	Facial weakness	Mid-line
VI N palsy	Dysphagia	Growth deficits
Reduced Vision	Ocular palsies	Visual deficits
Head tilt	Spasticity	Appetite
Infant irritability	Behavioural	Endocrine
Head circumference	Ataxia	School performance

Diagnosis: HGG

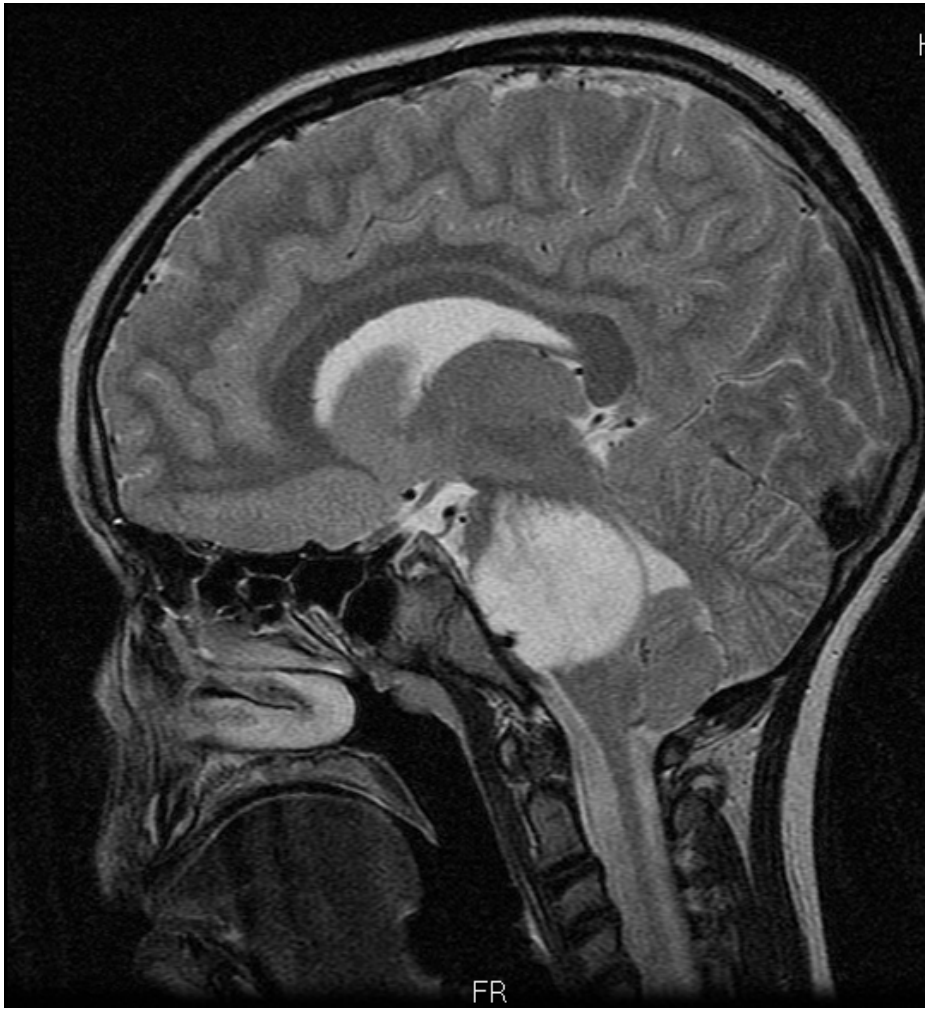
Clinical findings raise a diagnostic concern

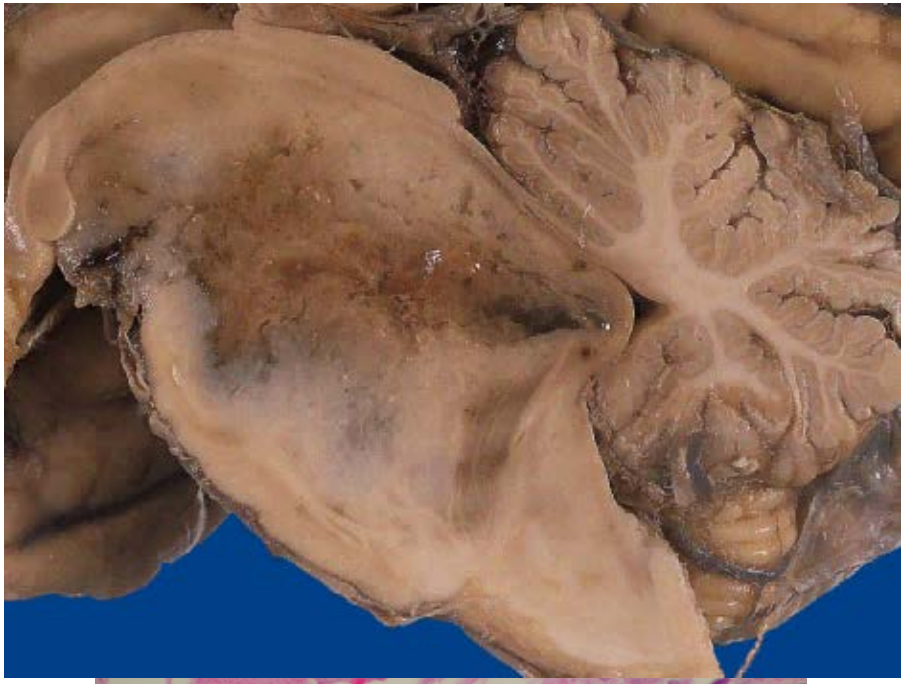
Diagnosis is corroborated by MRI

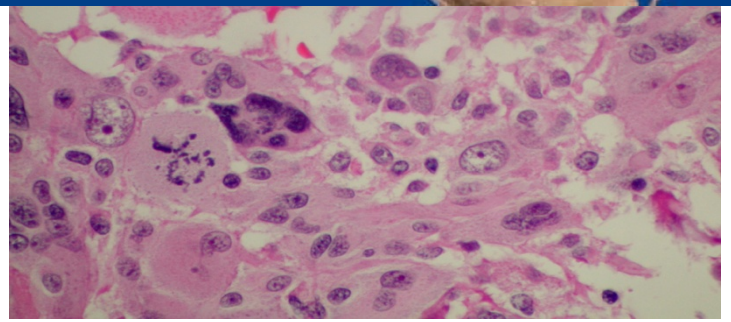
Surgery/biopsy is performed in majority of cases



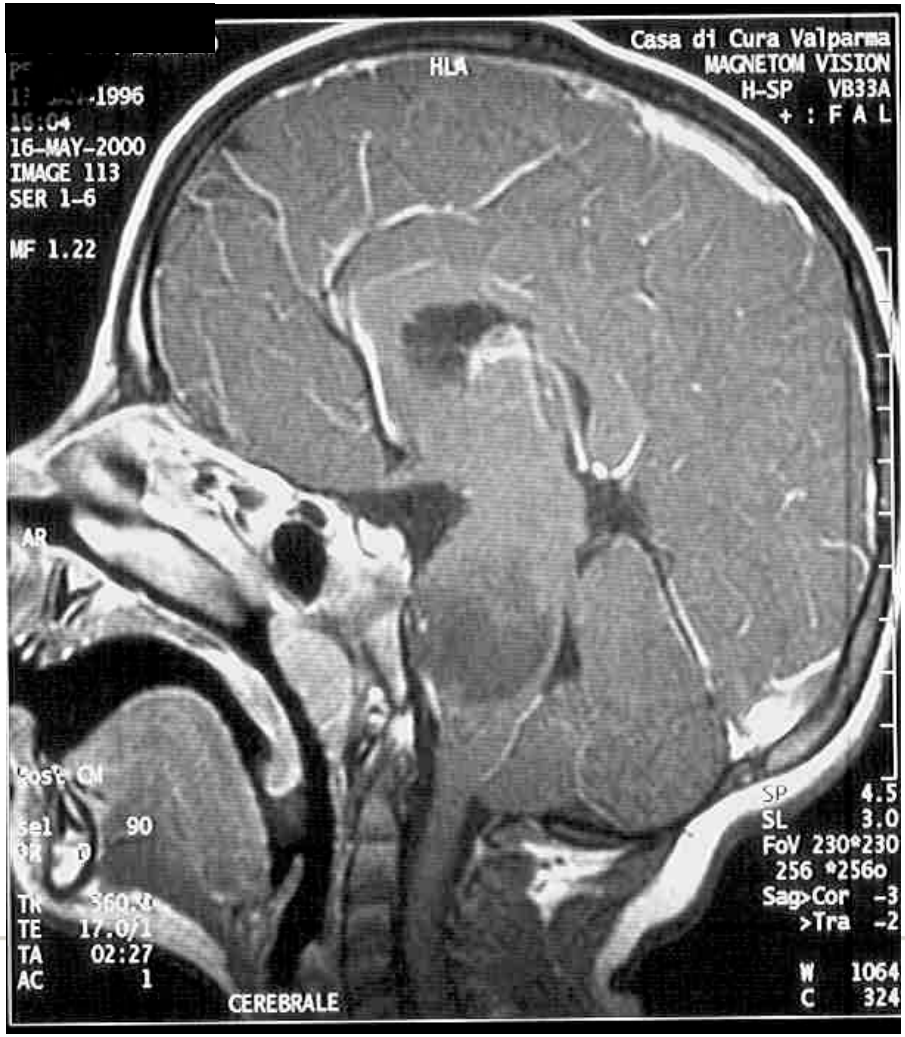
Brainstem Glioma in Children







Brainstem tumors



1) Diffuse intrinsic (75-85%)

2) Focal (5-10%)

3) Dorsal exophytic (10-20%)

4) Cervicomedullary (5-10%)

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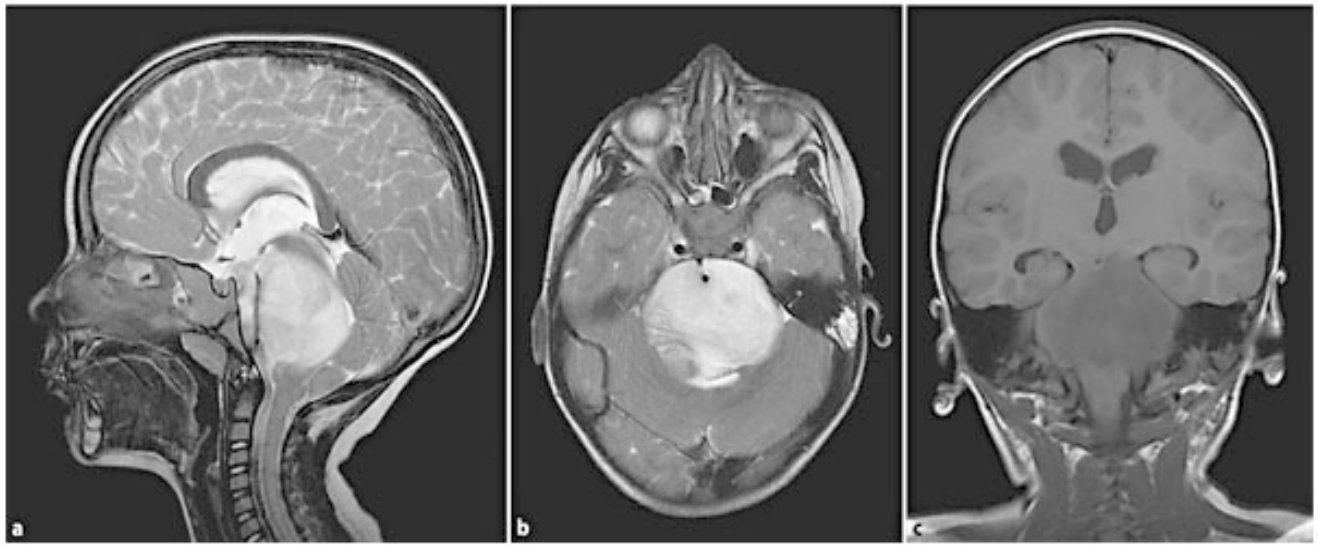
Diffuse Intrinsic Pontine glioma (DIPG)

Comprise 10-15% of childhood CNS tumours

- Incidence USA ~ 125 cases/year, UK ~ 25/year.
- Median age at presentation is 6-7 years

70% are diffusely infiltrating and involves the pons



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Focal or exophitic Brainstem glioma

- Symptoms often been present for months
- Typical histology is a low grade
- 5 years survival 50-60%
- Radiotherapy and chemotherapy can improve survival

DIPG: Clinical Presentation

- Short duration of symptoms (median 1-3 month)
- Hydrocephalus is not common
- Common triad
  - Cranial nerve palsies
  - Pyramidal tract signs
  - Cerebellar signs

DIPG: Clinical Presentation

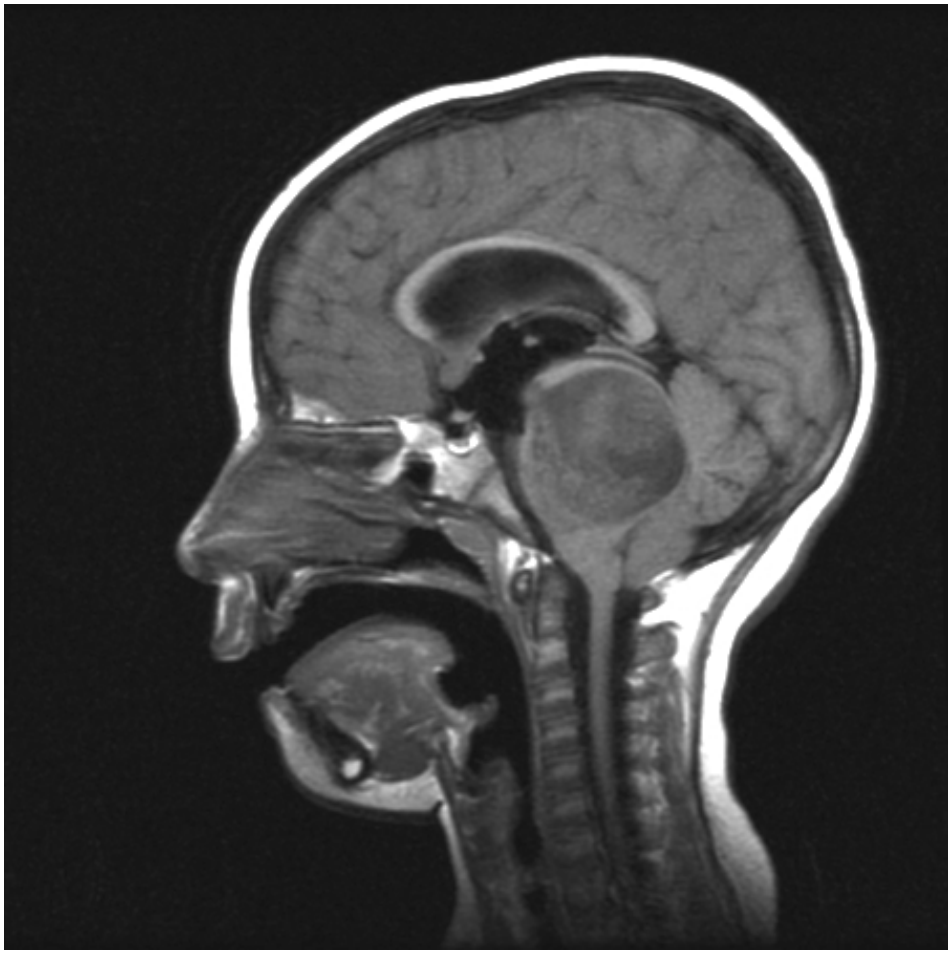
- A fluctuating course is not rare
- Changes in mood and behavior can precede obvious neurological features
  - pathological laughter
- Other presentation symptoms
  - Unexplained vomiting
  - Urinary problems
  - Respiratory insufficiency

Diagnosis: DIPG

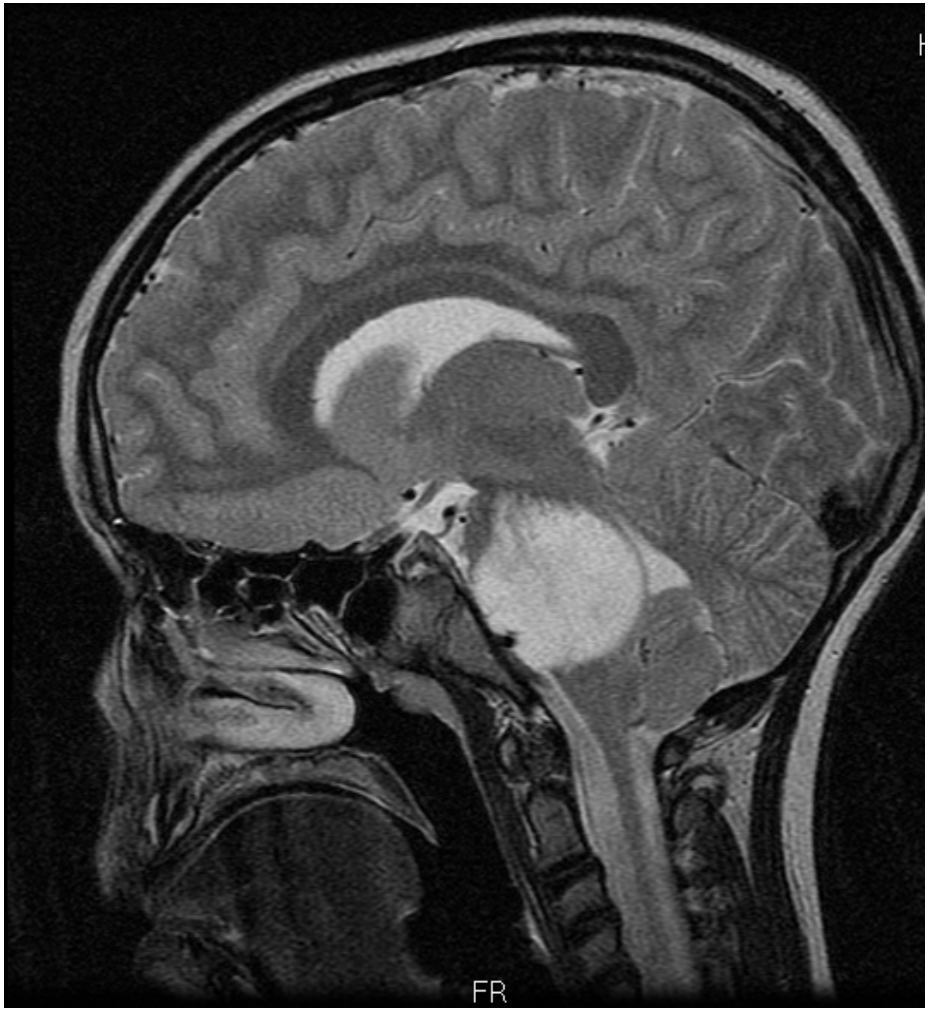
Clinical findings raise a diagnostic concern

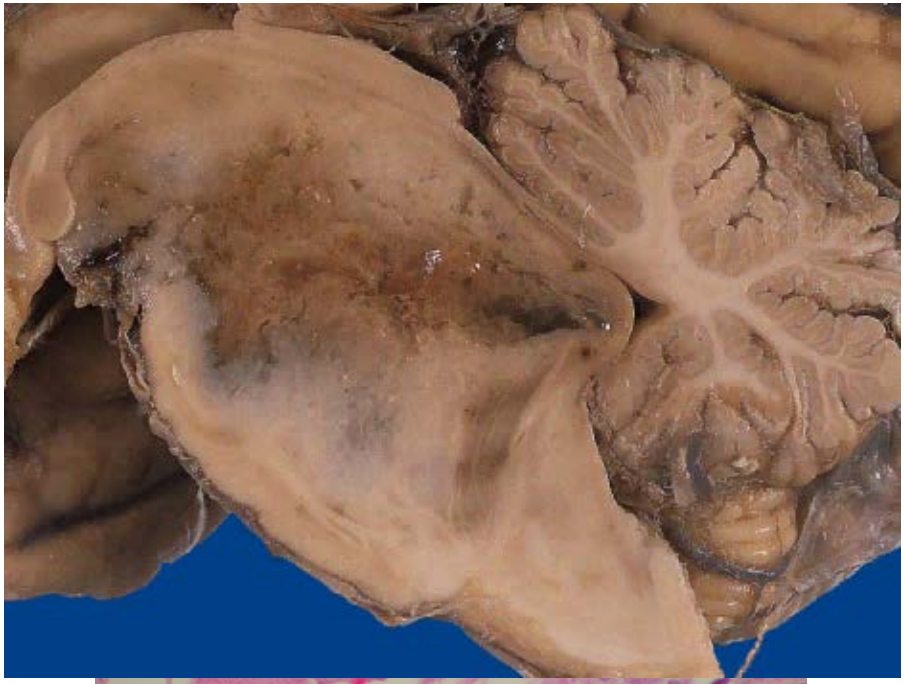
Diagnosis is corroborated by MRI

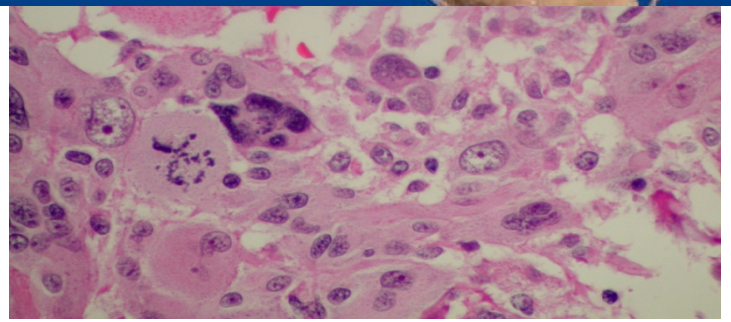
Biopsy is only performed if tumor has atypical radiological features



DIPG: To biopsy or not to biopsy?

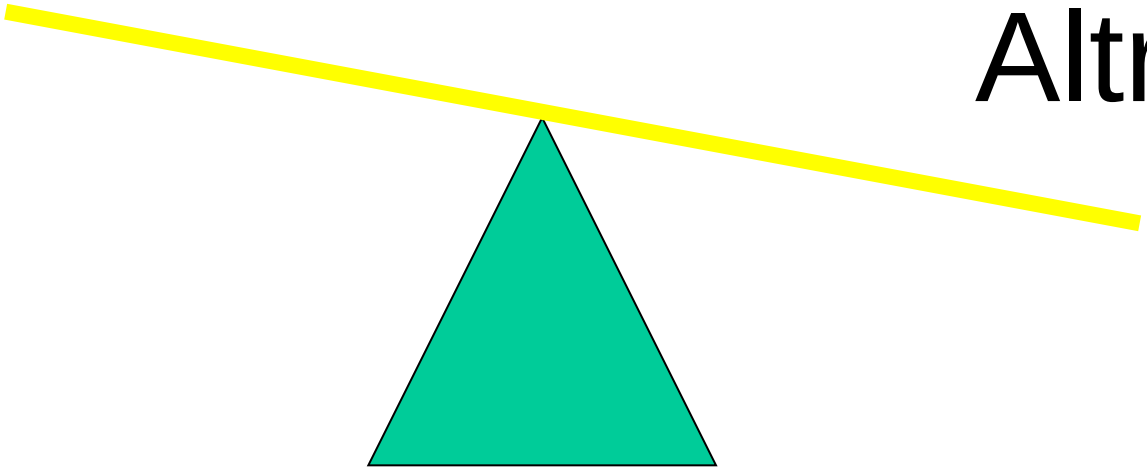






Ethics of Biopsy?

Individual benefit/ safety



Altruism

Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: a report from the Children's Cancer Group. Albright AL. Neurosurgery. 1993

Pontine glioma. To biopsy or not to biopsy: that is the question. Hargrave D. Br J Neurosurg. 2008

Is Biopsy Safe in Children with Newly Diagnosed Diffuse Intrinsic Pontine Glioma? Stephanie Puget. Am Soc Clin Oncol Educ Book. 2012.

Diffuse intrinsic pontine glioma (DIPG): time to biopsy again? MacDonald TJ. Pediatr Blood Cancer. 2012.

Time to rethink the unthinkable: Upfront biopsy of children with newly diagnosed diffuse intrinsic pontine glioma (DIPG). Kieran MW. Pediatr Blood Cancer. 2014

Childs Nerv Syst (2015) 31:1773–1780
DOI 10.1007/s00381-015-2832-1

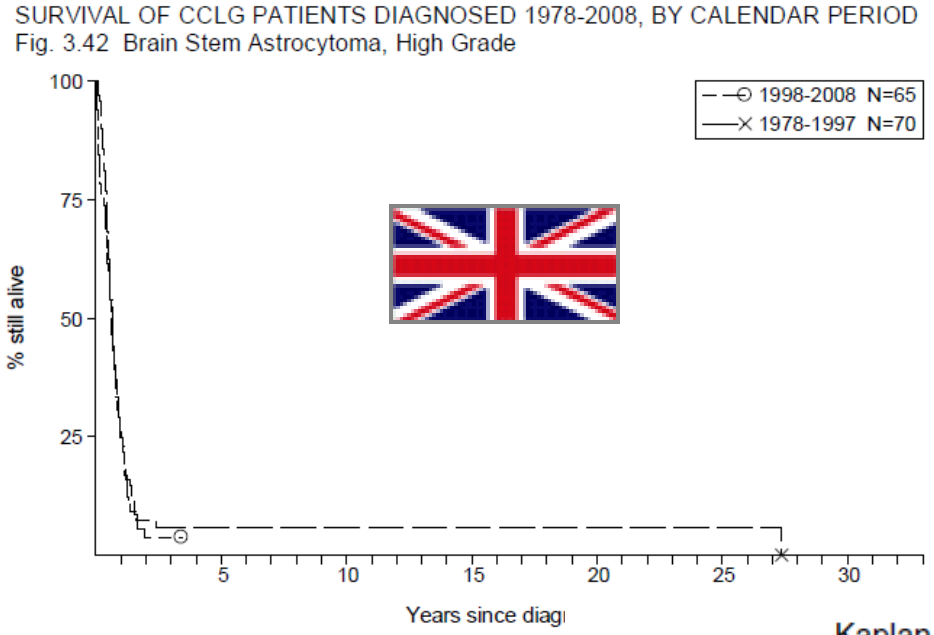
SPECIAL ANNUAL ISSUE

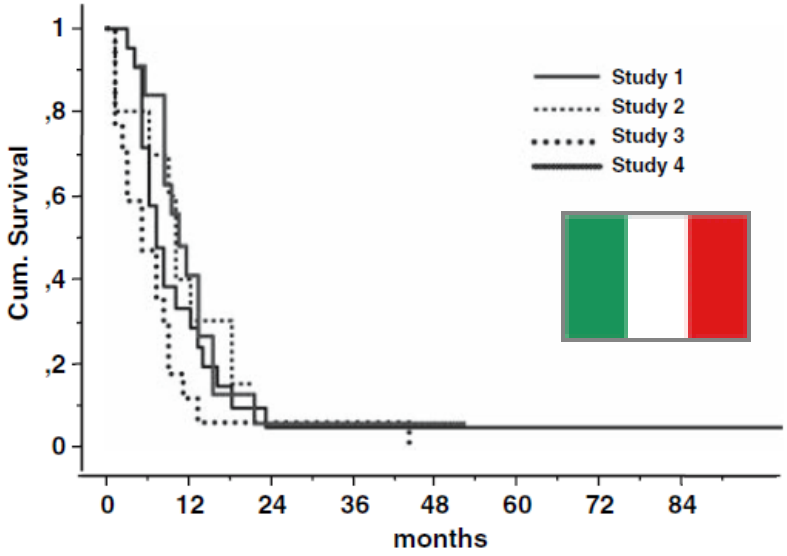
Biopsy in a series of 130 pediatric diffuse intrinsic Pontine gliomas

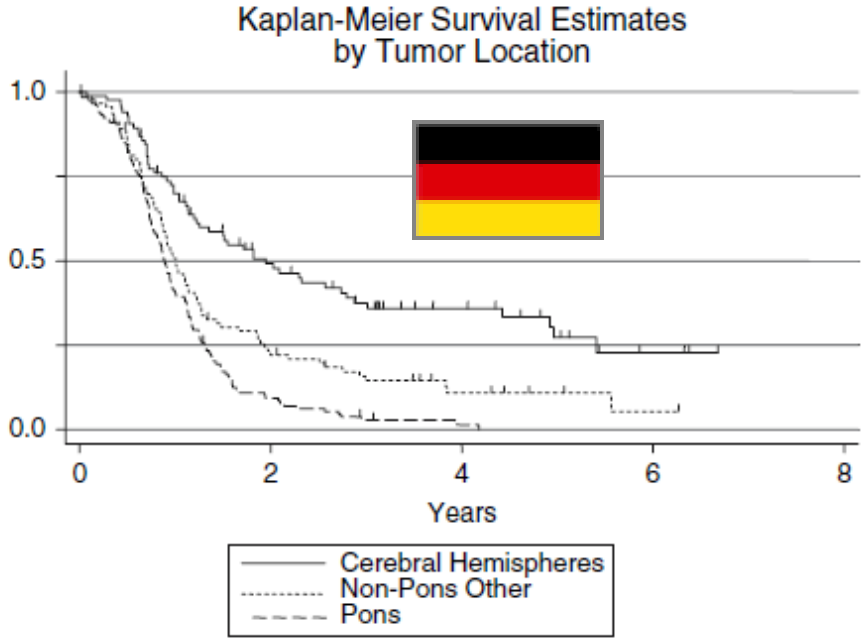
Stephanie Puget[1,2,5] · Kevin Beccaria[1,2] · Thomas Blauwblomme[1,2] · Thomas Roujeau[1,2] · Syril James[1,2] · Jacques Grill[3] · Michel Zerah[1,2] · Pascale Varlet[4] · Christian Sainte-Rose[1,2]

Results Reviewing our own 130 cases of DIPG biopsies and previous published data, these procedures appear to have a diagnostic yield and morbidity rates similar to those reported for other brain locations (3.9 % of transient morbidity in our series). In addition, the quality and the quantity of the material

Diffuse Intrinsic Pontine Glioma (DIPG)







What is the standard of care for DIPG?

Diffuse brainstem glioma in children: critical review of clinical trials

Darren Hargrave, Ute Bartels, Eric Bouffet

Lancet Oncol 2006; 7: 241–48

Contents lists available at ScienceDirect

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journal homepage: www.elsevierhealth.com/journals/ctrv

Tumour Review

Diffuse intrinsic pontine gliomas: A systematic update on clinical trials and biology

M.H.A. Jansen [a,c,*], D.G. van Vuurden [a,c,1], W.P. Vandertop [b,c,2], G.J.L. Kaspers [a,c,3]

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Brainstem glioma

Radiotherapy

Initial studies utilizing hyperfractionated radiation therapy with total doses up to 72 Gy (1 Gy twice day) suggested a modest improvement in survival of children with brainstem gliomas compared to radiation alone, and compared to radiation with neoadjuvant or adjuvant chemotherapy

Packer et al. 1993

However, subsequent trials using radiation doses up to 78 Gy did not confirm this finding

Packer et al. 1994

HFRT for DIPG

Toxicity included intralesional necrosis and steroid dependency at the intermediate and highest dose levels, as well as vascular events in a small # of pts treated at the highest dose levels

Doses as high as 78 Gy did not result in any significant improvement in time to progression, MST, or survival at 1 and 2 yrs

Hypofractionated Radiotherapy in DIPG?

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Hypofractionation vs Conventional Radiation Therapy for Newly Diagnosed Diffuse Intrinsic Pontine Glioma: A Matched-Cohort Analysis

Geert O. Janssens, MD,* Marc H. Jansen, MD,¶ Selmer J. Lauwers, BSc,* Peter J. Nowak, PhD,** Foppe R. Oldenburger, MD,†† Eric Bouffet, MD,‡‡ Frank Saran, MD,§§ Karin Kamphuis-van Ulzen, MD,† Erik J. van Lindert, PhD,‡ Jolanda H. Schieving, MD,§ Tom Boterberg, PhD,‖‖ Gertjan J. Kaspers, PhD,¶ Paul N. Span, PhD,* Johannes H. Kaanders, PhD,* Corrie E. Gidding, PhD,‖ and Darren Hargrave, MD¶¶

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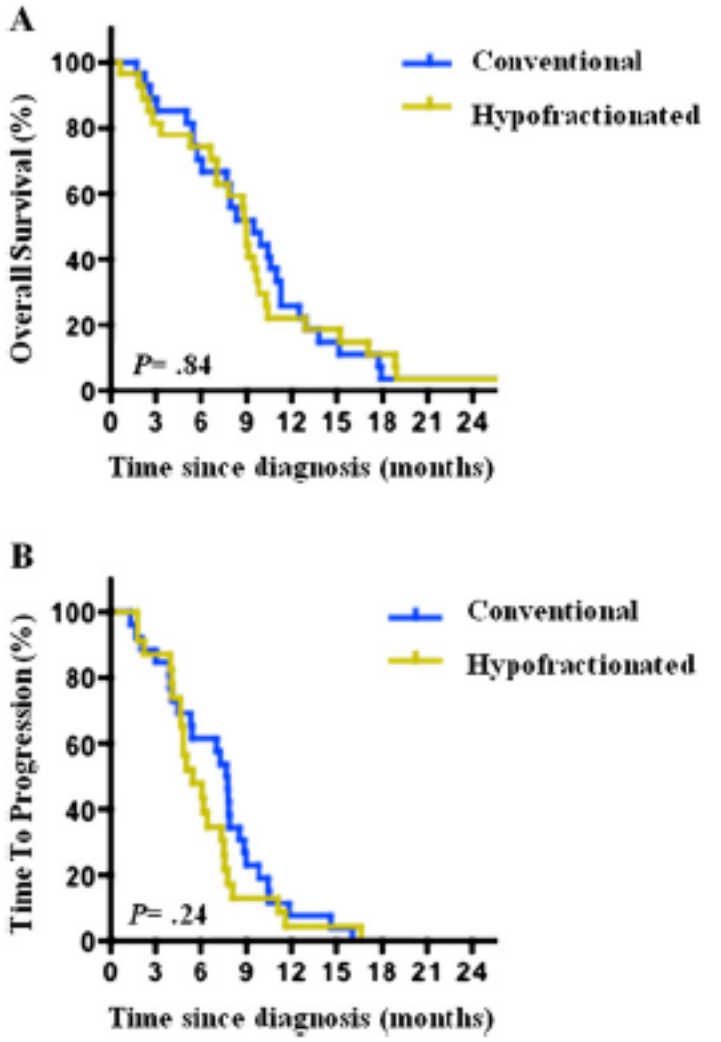

Fig. 2. Overall survival (2A) and time to progression (2B) for patients with newly diagnosed diffuse intrinsic pontine glioma after hypofractionation radiation therapy matched to a group receiving conventional radiation therapy.

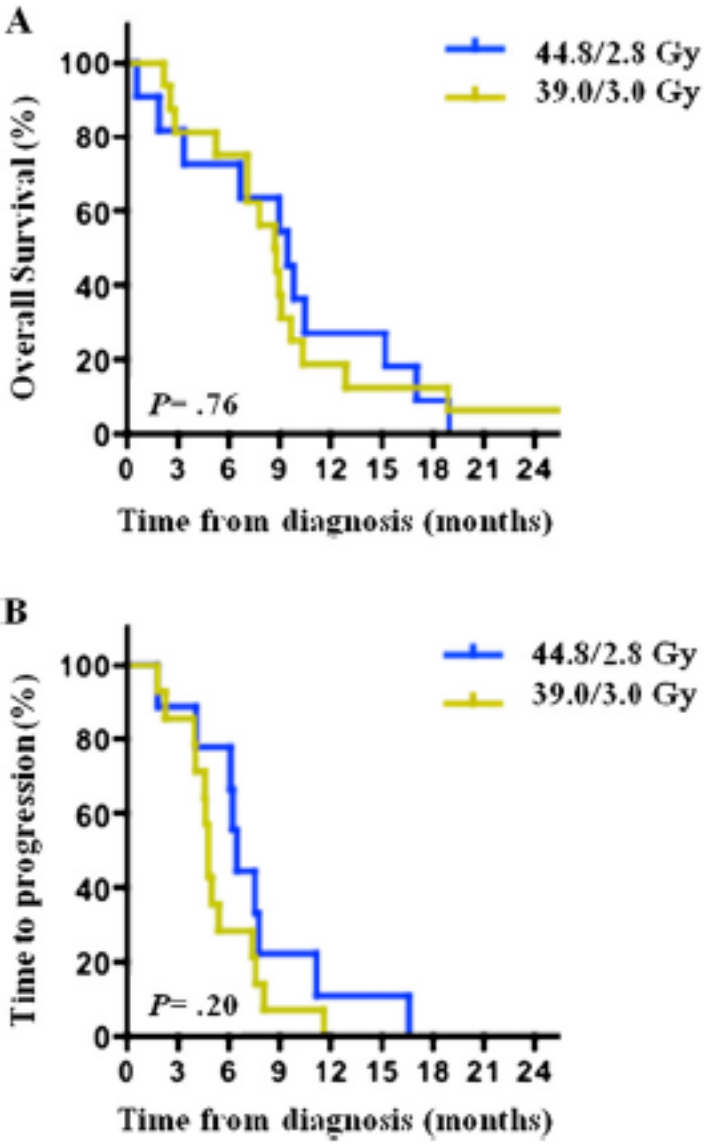

Fig. 3. Overall survival (3A) and time to progression (3B) after 39/3.0 Gy vs 44.8/2.8 Gy for patients with newly diagnosed diffuse intrinsic pontine glioma.

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journal homepage: www.thegreenjournal.com

Phase III randomised trial

Hypofractionated conformal radiotherapy for pediatric diffuse intrinsic pontine glioma (DIPG): A randomized controlled trial

Mohamed S. Zaghloul [a,*], Eman Eldebawy [a], Soha Ahmed [a], Amr G. Mousa [a], Amr Amin [a], Amal Refaat [b], Iman Zaky [b], Nada Elkhateeb [c], Mohamed Sabry [c]

[a] *Radiation Oncology Department;* [b] *Radiology Department, Children's Cancer Hospital, Egypt (CCHE) and National Cancer Institute, Cairo University; and* [c] *Research Department, Children's Cancer Hospital, Egypt*

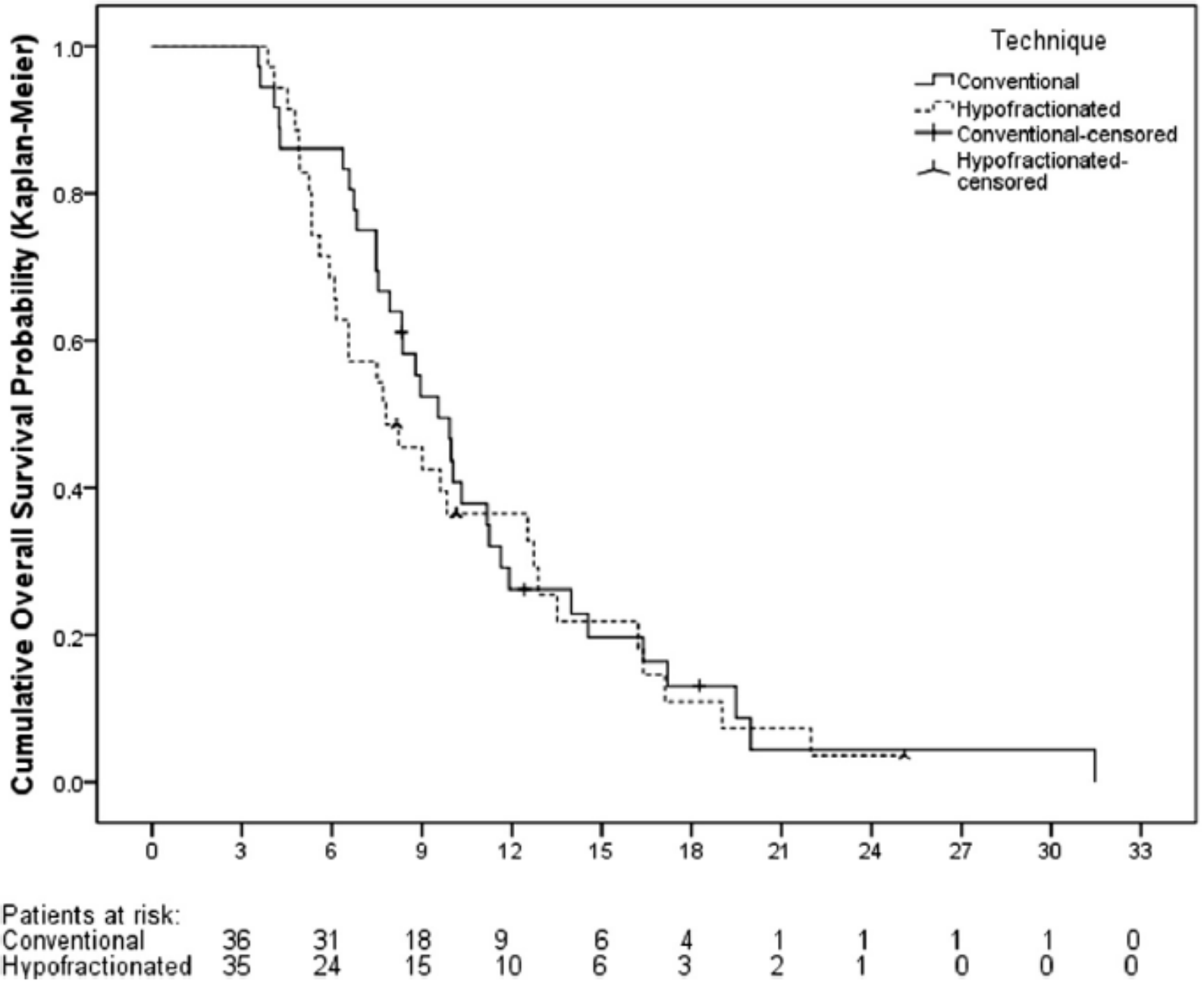


Fig. 2. The overall survival curves for the randomized arms: conventional fractionation and hypofractionation.

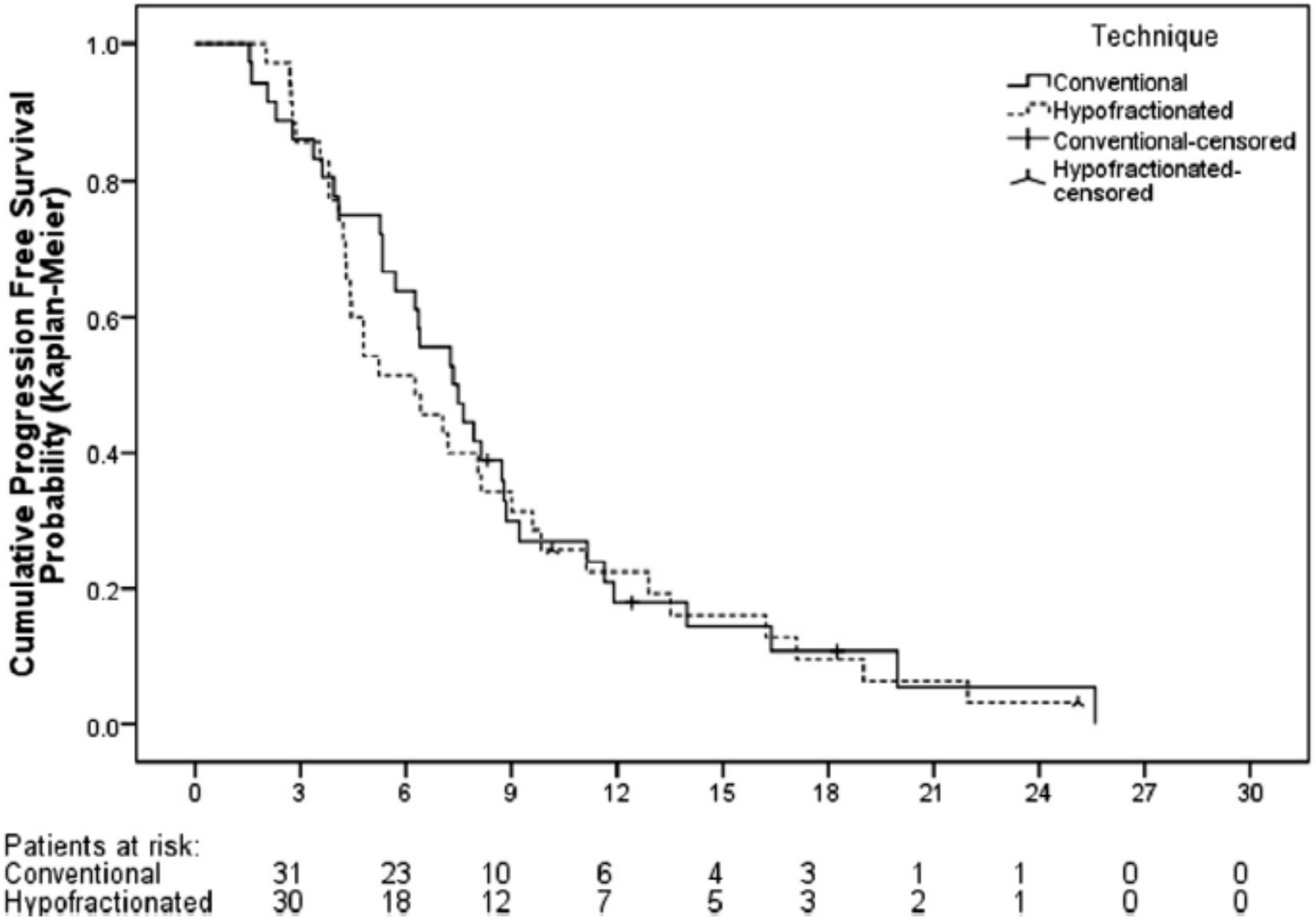


Fig. 3. The progression-free survival curves for the randomized arms: conventional fractionation and hypofractionation.

Childs Nerv Syst (2015) 31:1221–1222
DOI 10.1007/s00381-015-2678-6

LETTER TO THE EDITOR

Has hypofractionated radiotherapy become the standard of care in pediatric DIPG?

Mohamed Saad Zaghloul

Received: 23 December 2014 / Accepted: 2 March 2015 / Published online: 12 March 2015

Why have we failed?

Why have we failed?

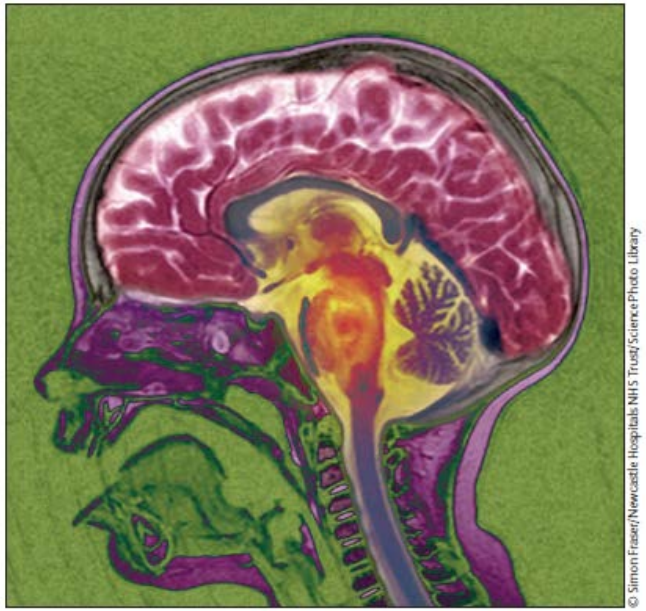
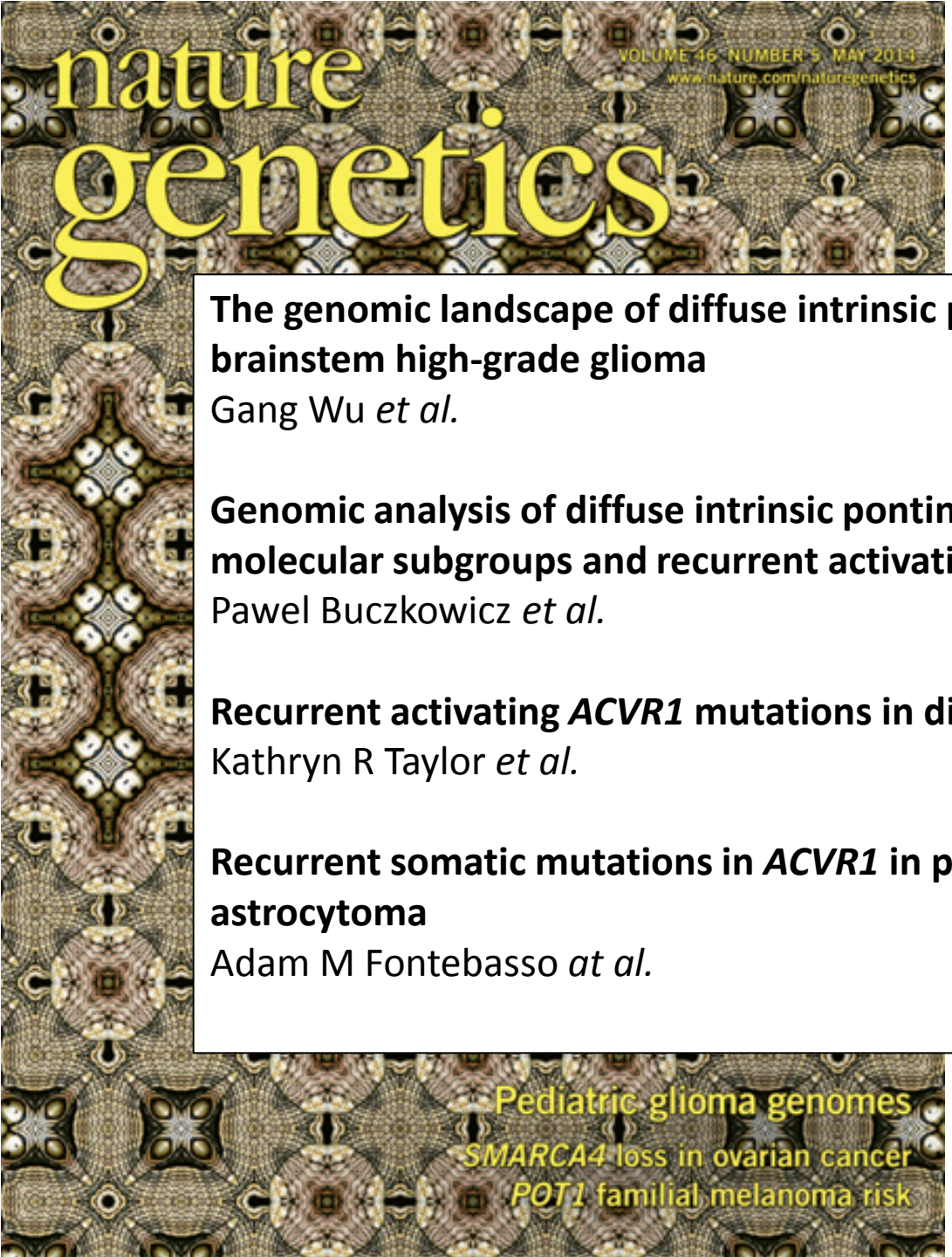


Figure 1: Gliomas are main cause of death from brain tumours in children

- Lack of biological knowledge!
  - Biopsy
  - Autopsy
- Lack of preclinical models!
  - Cell lines
  - Xenografts (orthotopic)
  - Transgenic models
- Lack of drugs!
  - Many possible targeted agents.
- Poor drug delivery!
  - Need solutions.



Lack of biological knowledge!

The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma
Gang Wu *et al.*

Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating *ACVR1* mutations
Pawel Buczkowicz *et al.*

Recurrent activating *ACVR1* mutations in diffuse intrinsic pontine glioma
Kathryn R Taylor *et al.*

Recurrent somatic mutations in *ACVR1* in pediatric midline high-grade astrocytoma
Adam M Fontebasso *at al.*

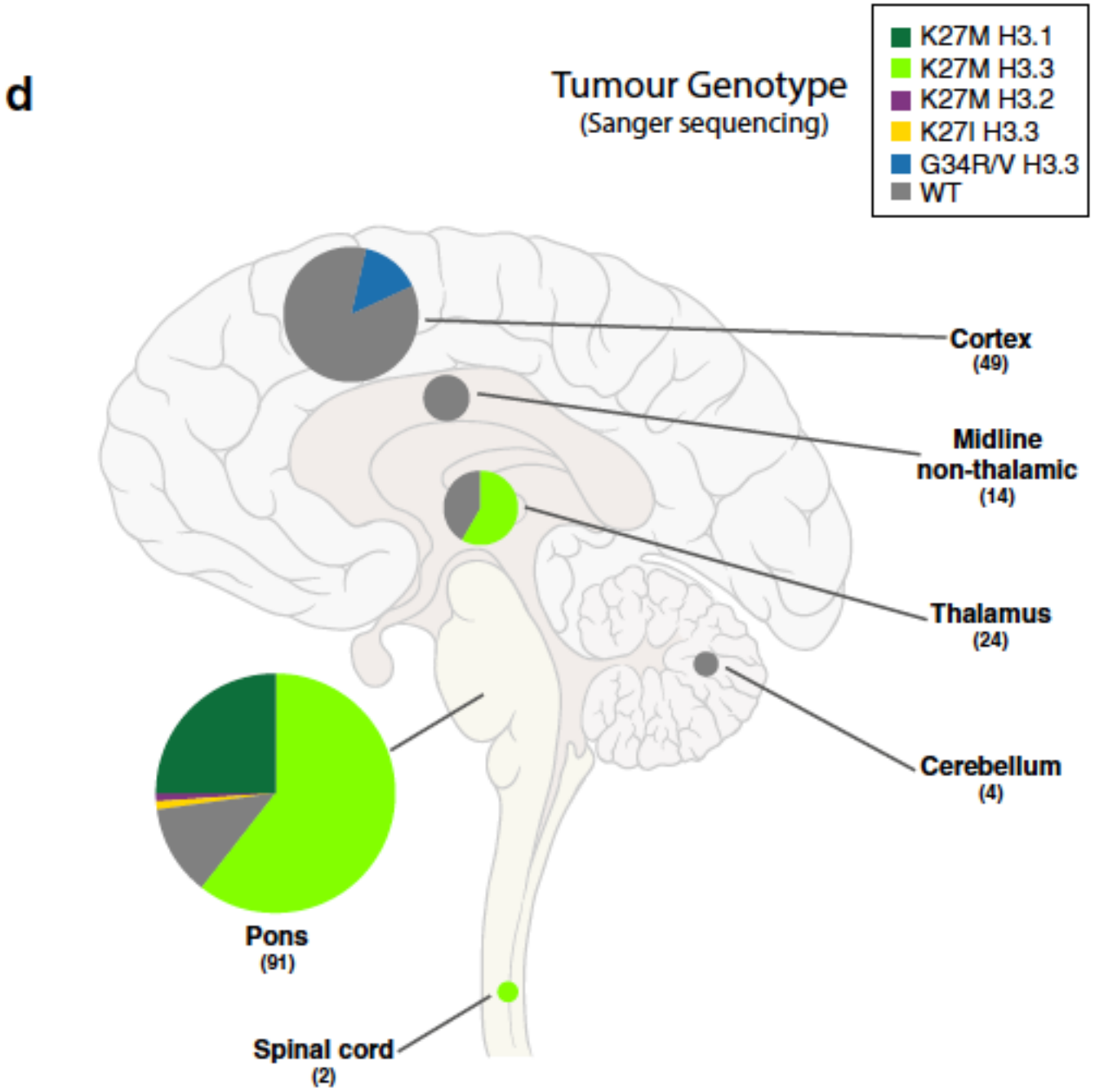
Acta Neuropathol
DOI 10.1007/s00401-015-1478-0

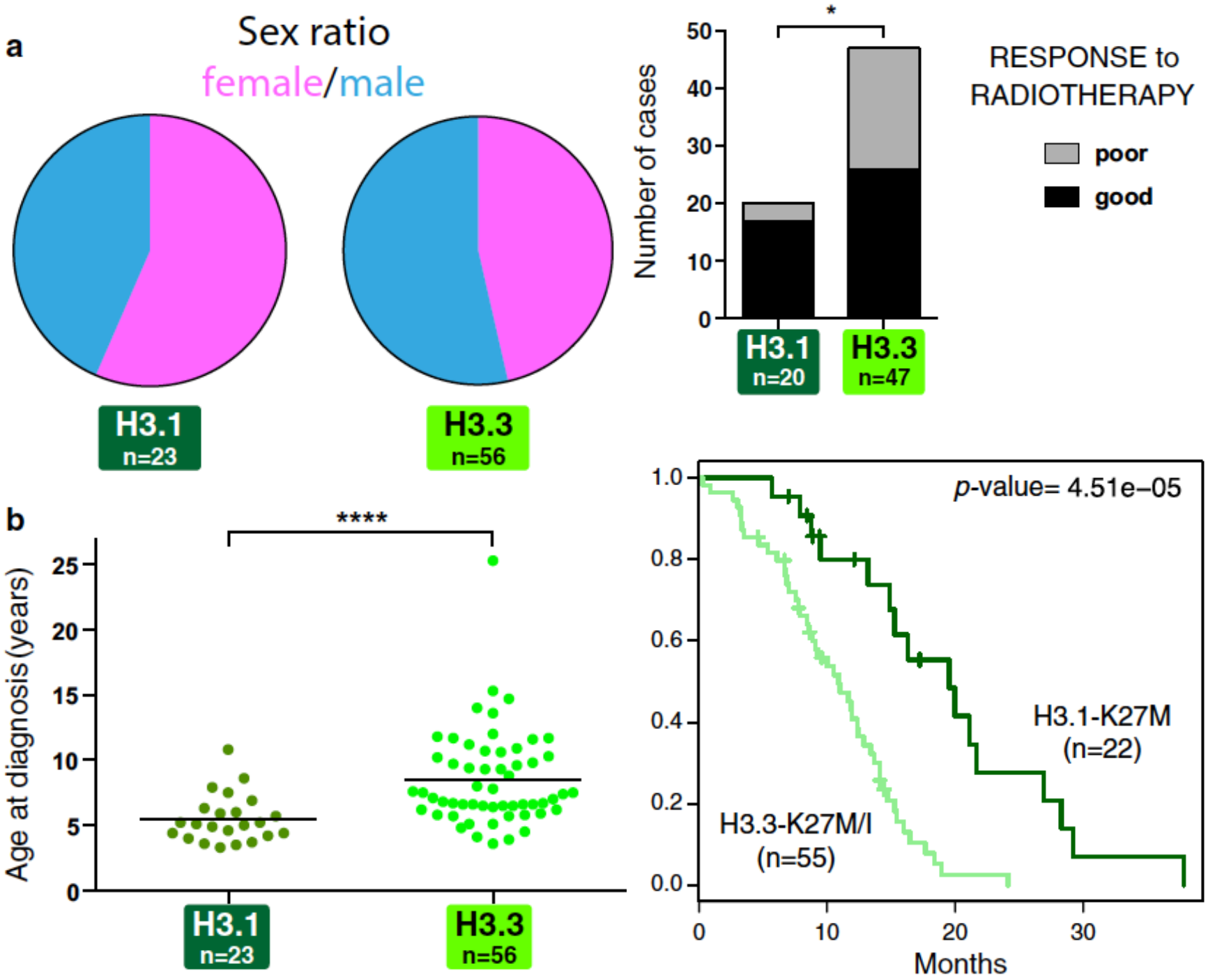
ORIGINAL PAPER

Histone *H3F3A* and *HIST1H3B* K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes

David Castel[1,2] · Cathy Philippe[1] · Raphaël Calmon[3] · Ludivine Le Dret[1] · Nathalène Truffaux[1] · Nathalie Boddaert[3] · Mélanie Pagès[7] · Kathryn R. Taylor[4] · Patrick Saulnier[5] · Ludovic Lacroix[5] · Alan Mackay[4] · Chris Jones[4] · Christian Sainte-Rose[6] · Thomas Blauwblomme[6] · Felipe Andreiuolo[7] · Stephanie Puget[6] · Jacques Grill[1,2] · Pascale Varlet[7] · Marie-Anne Debily[1,8]

Received: 24 June 2015 / Revised: 8 September 2015 / Accepted: 10 September 2015


d
Tumour Genotype
(Sanger sequencing)
K27M H3.1
K27M H3.3
K27M H3.2
K27I H3.3
G34R/V H3.3
WT
Cortex
(49)
Midline
non-thalamic
(14)
Thalamus
(24)
Cerebellum
(4)
Pons
(91)
Spinal cord
(2)


a
Sex ratio
female/male
H3.1
n=23
H3.3
n=56
*
Number of cases
50
40
30
20
10
0
H3.1
n=20
H3.3
n=47
RESPONSE to
RADIOTHERAPY
poor
good
b
****
Age at diagnosis (years)
25
20
15
10
5
0
H3.1
n=23
H3.3
n=56
p-value= 4.51e−05
1.0
0.8
0.6
0.4
0.2
0.0
H3.1-K27M
(n=22)
H3.3-K27M/I
(n=55)
0
10
20
30
Months

Why have we failed?

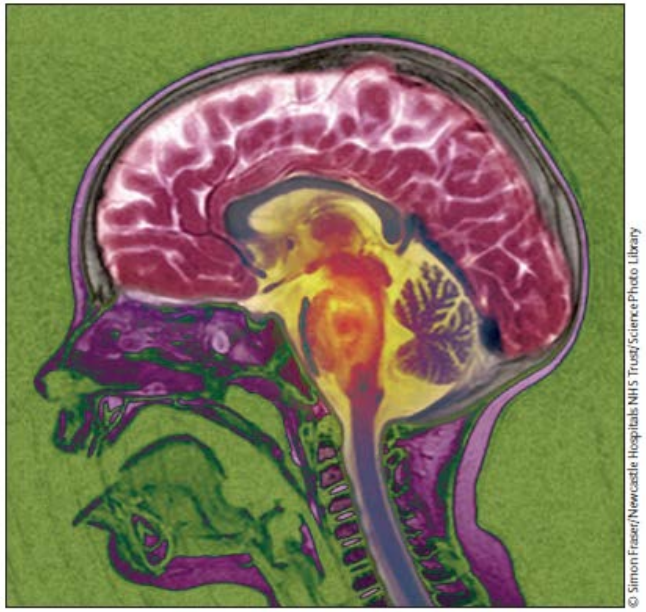


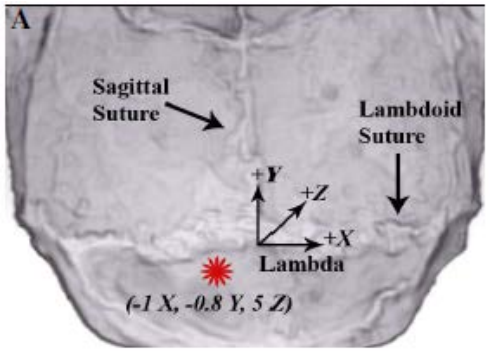
Figure 1: Gliomas are main cause of death from brain tumours in children

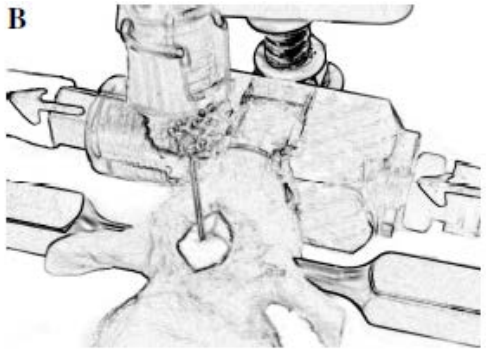
- **Lack of preclinical models!**
  - **Cell lines**
  - **Xenografts (orthotopic)**
  - **Transgenic models**

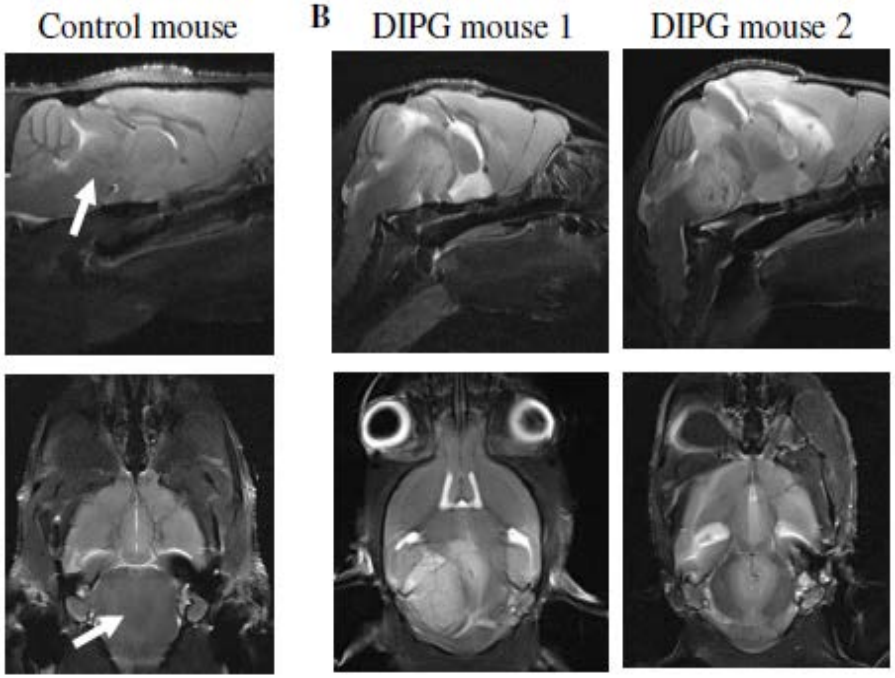
BRAIN PATHOLOGY

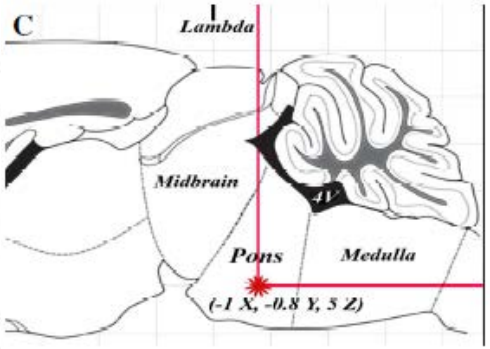
Monitoring of Tumor Growth and Post-Irradiation Recurrence in a Diffuse Intrinsic Pontine Glioma Mouse Model

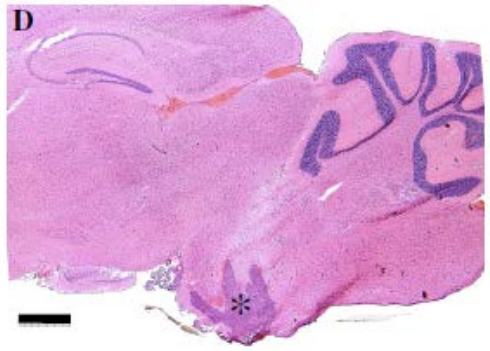
Viola Caretti[1,2,3], Ilse Zondervan[2,3], Dimphna H. Meijer[3,8], Sander Idema[2,3], Wim Vos[4], Bob Hamans[6], Marianna Bugiani[4], Esther Hulleman[1,2,3], Pieter Wesseling[7], W. Peter Vandertop[2], David P. Noske[2,3], GJ Kaspers[1], Carla F.M. Molthoff[5], Thomas Wurdinger[2,3,9,*]







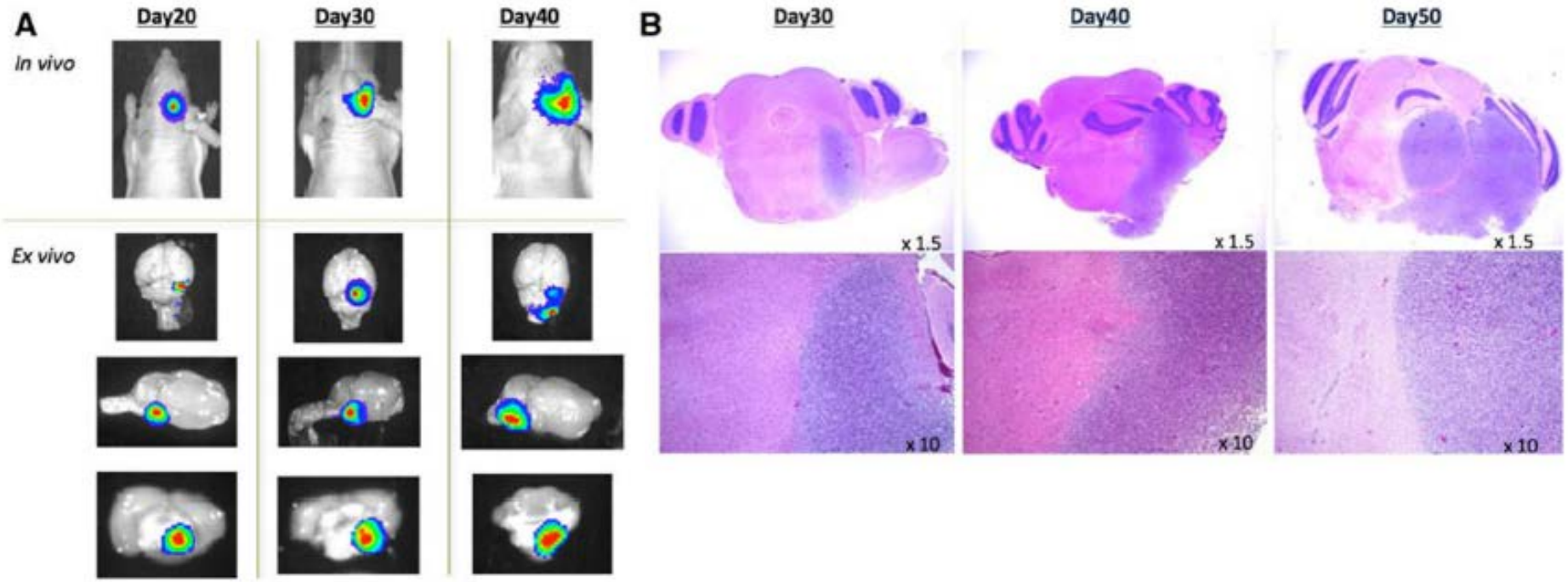




J Neurooncol. 2012 May ; 108(1): . doi:10.1007/s11060-011-0796-x.

An experimental xenograft mouse model of diffuse pontine glioma designed for therapeutic testing

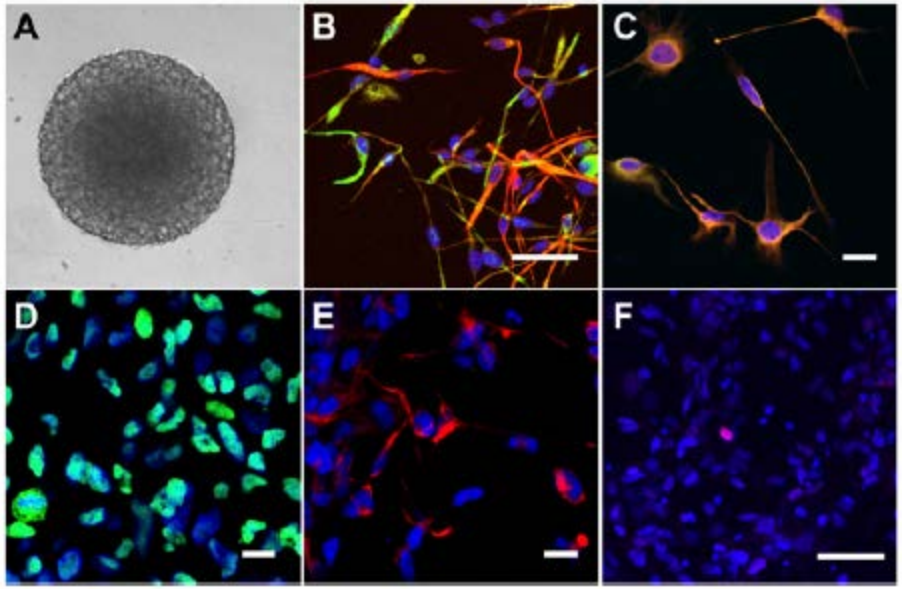
Yasuyuki Aoki,



Hedgehog-responsive candidate cell of origin for diffuse intrinsic pontine glioma

Michelle Monje[a,b,c,1,2], Siddhartha S. Mitra[c,d,1], Morgan E. Freret[a,b,c], Tal B. Raveh[c], James Kim[b,c], Marilyn Masek[e], Joanne L. Attema[c,3], Gordon Li[d], Terri Haddix[e], Michael S. B. Edwards[d], Paul G. Fisher[a], Irving L. Weissman[c,e], David H. Rowitch[f,g], Hannes Vogel[e], Albert J. Wong[d,h], and Philip A. Beachy[b,c,2]

Departments of [a]Neurology, [b]Developmental Biology, [d]Neurosurgery, [e]Pathology, and [h]Cancer Biology, and [c]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University Medical Center, Stanford, CA 94305; and Departments of [f]Neurological Surgery and [g]Pediatrics, University of California School of Medicine, San Francisco, CA 94143



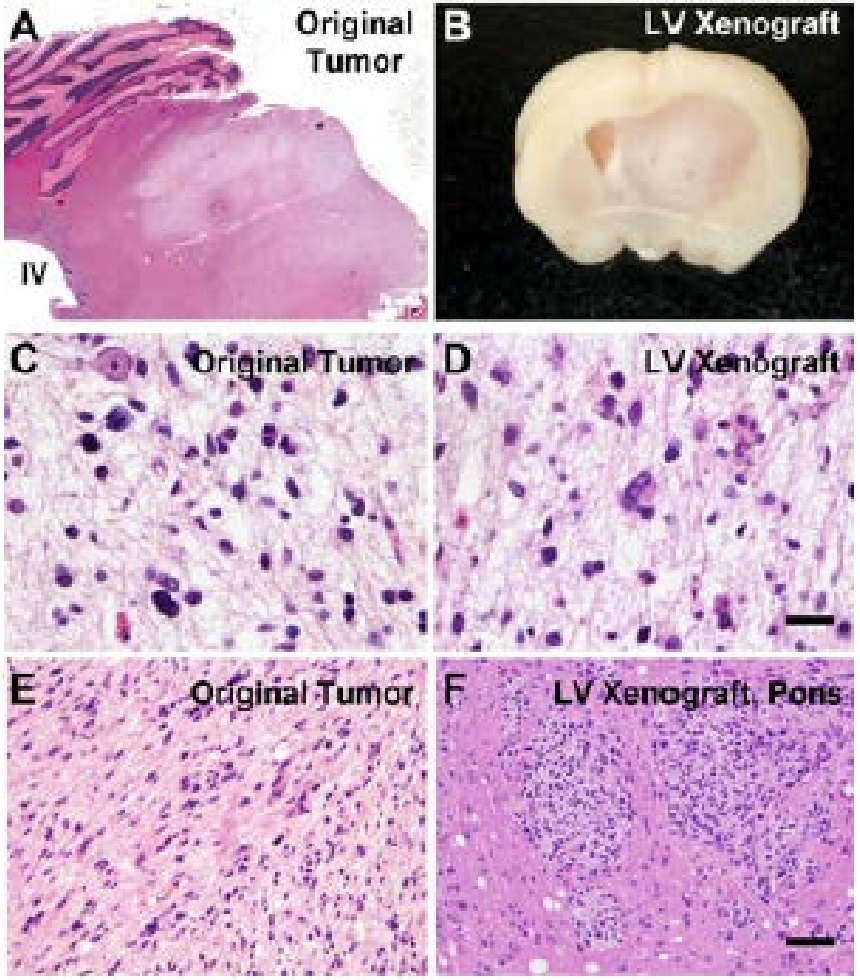


Fig. 4. DIPG neurosphere culture. (*A*) Tumor neurosphere is shown

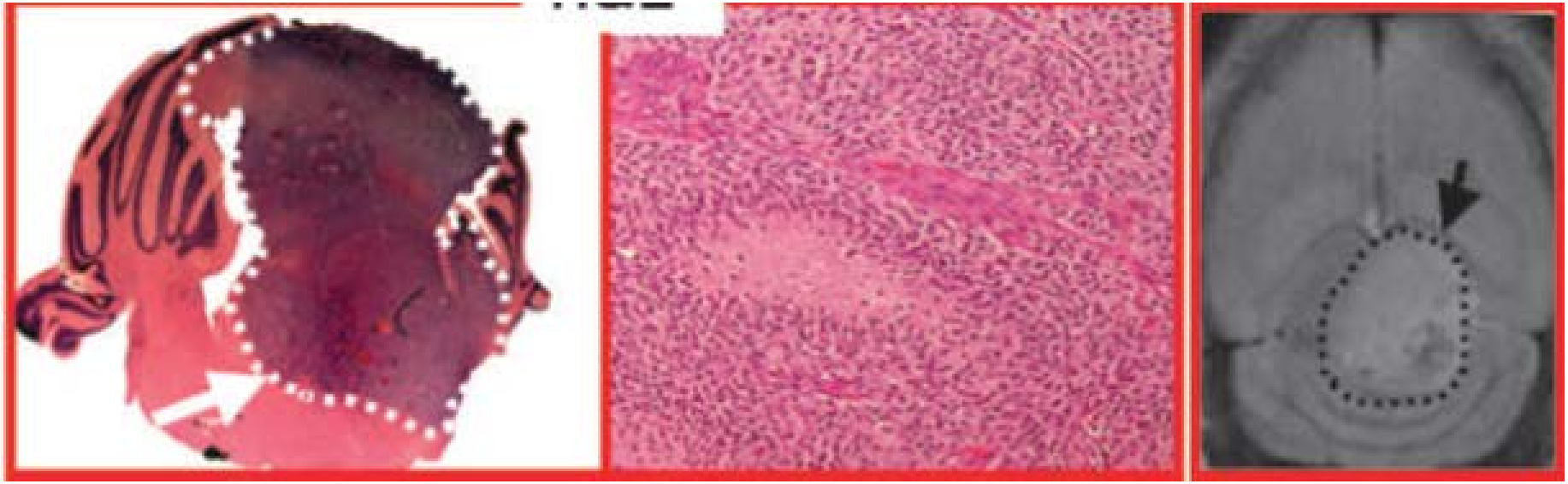
Pre-clinical Models

Tumor and Stem Cell Biology

Cancer Research

Preclinical Evaluation of Radiation and Perifosine in a Genetically and Histologically Accurate Model of Brainstem Glioma

Oren J. Becher[1,3,5], Dolores Hambardzumyan[2,5], Talia R. Walker[1,5], Karim Helmy[1,5], Javad Nazarian[6], Steffen Albrecht[7], Rebecca L. Hiner[3,5], Sarah Gall[8], Jason T. Huse[1,4,5], Nada Jabado[7], Tobey J. MacDonald[6], and Eric C. Holland[1,2,5]



Rapid Preclinical Development of a Targeted Therapy Combination for DIPG

CHILDREN'S ONCOLOGY GROUP

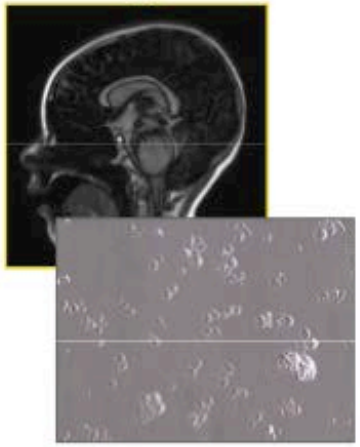
The world's childhood cancer experts

Preclinical Consortium

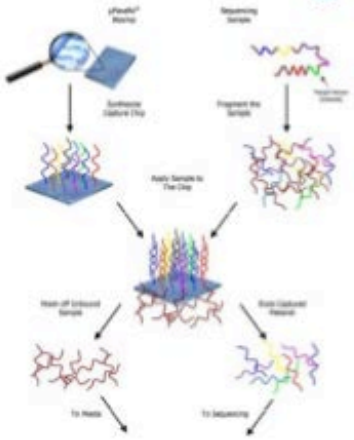
participants

experimental approach

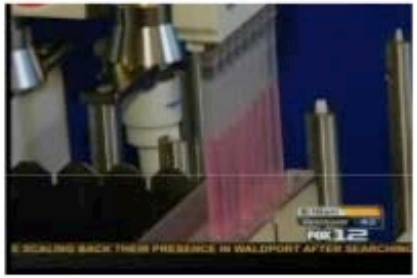
Primary Culture

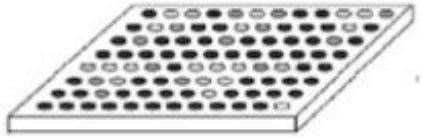


Molecular Credentialing



Single-Agent & Combination Screen





PPTP-friendly Preclinical Screen

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

version 2.0 screen for new leads

designed with input by Jim Olson, Maryam Fouladi, Chris Jones, Darren Hargrave, Jacques Grill, Esther Hullemen/Dannis van Vuurden

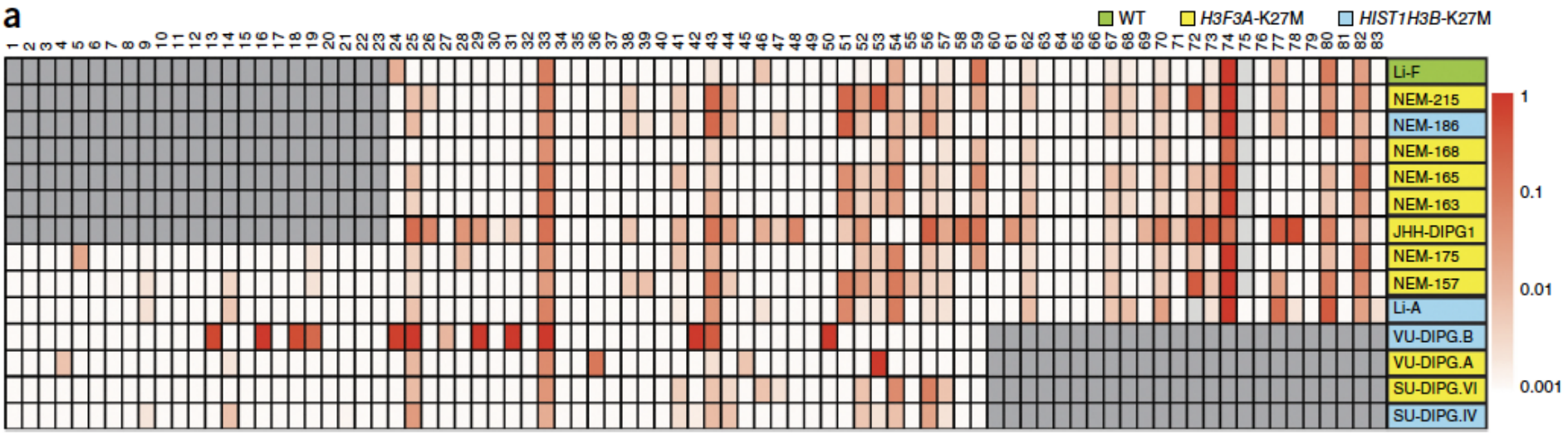
Drug	Target (s)
MK2206	Akt1,2,3
Pazopanib	VEGFRs, c-KIT, PDGFR beta
Temsirolimus (sirolimus prodrug & a	mTOR
Vandetanib	VEGFR-2, EGFR, RET
5-Aza-2 deoxycytidine (Decitabine)	DNA-methyl transferase
Bortezomib	Proteasome
Dasatinib	C-Kit, PDGFR, SFK, Bcr-Abl
OSI-906	Igf1r
ABT-888	PARP-1 and PARP-2
GDC-0449	Smoothened (Hedgehog pathway)
Panobinostat	HDAC
BMS-387032	CDK2, CDK7, CDK9
Imelelstat (GRN 163L)	Telomerase inhibitor
Lapatinib	Egfr, ErbB2
SAHA (Vorinostat)	HDAC
Sorafenib	VEGFR, PDGFR, RAF
AZD6244 (Selumetinib)	MEK1/2 inhibitor
AZD1152-HQPA (Barasertib)	Aurora kinase B
R115777 (tipifarnib, Zarnestra)	Enzyme(Farnesyl transferase - Enzyme)
CC-5013 (lenalidomide, Revlimid)	2, IL-6, IL-10, IL-12, IL-1beta, TNF-alpha, IFN-gamma -
Cediranib	VEGFR
RO4929097	Notch (gamma secretase)
EKB-569	Egfr, ErbB2
Obatoclax mesylate (GX15-070MS)	BCL2, BH3
BMS-754807	Igf1r
SCH-727965	CDK2, CDK5, CDK1, and CDK9
4-hydroxy-tamoxifen	estrogen receptor
Saracatinib (AZD0530)	Src Family Kinases
Flavopiridol (alvocidib)	Cycle(Cyclin-dependent kinases - Protein)
Sodium butyrate	HDAC

Sodium butyrate	HDAC
AP24534 (Ponatinib)	BCR-ABL, VEGFR2, FGFR1, PDGFRα
GANT61	Hedgehog (Gli1)
ATRA	differentiating agent
RO5045337	MDM2
MLN8237	Aurora kinase A
Crizotinib	C-Met, ALK
Carfilzomib	Proteasome
Quinacrine	autophagy pathway
SJ-172550	MDMX
SP600125	JNK 1,2 and 3
Cilengitide	αvβ3 and αvβ5 integrins
INCB018424(Ruxolitinib)	Jak1, Jak2
SB-431542	TGF beta
Enzastaurin	Protein Kinase Cβ
Trichostatin A	HDAC
ZD4054	Endothelin A receptor
Fenretinide	retinoid receptor
Fostamatinib (R788)	SYK kinase
BIX-01294	Histone-lysine methyltransferase
Nilotinib	PDGF-R, c-Kit, BCR-ABL
N-acetyl cysteine	Reactive oxygen species
VX-680	Aurora kinases
Entinostat	HDAC 1,2
PF-04554878	FAK inhibitor
BEZ 235	PI3K, mTOR
vemurafenib	BRAF
AP26113	ALK, EGFR
XL-184	EGFR, c-Met
AUY922	Hsp90
VER-155008	Hsp90, Hsp70

nature medicine

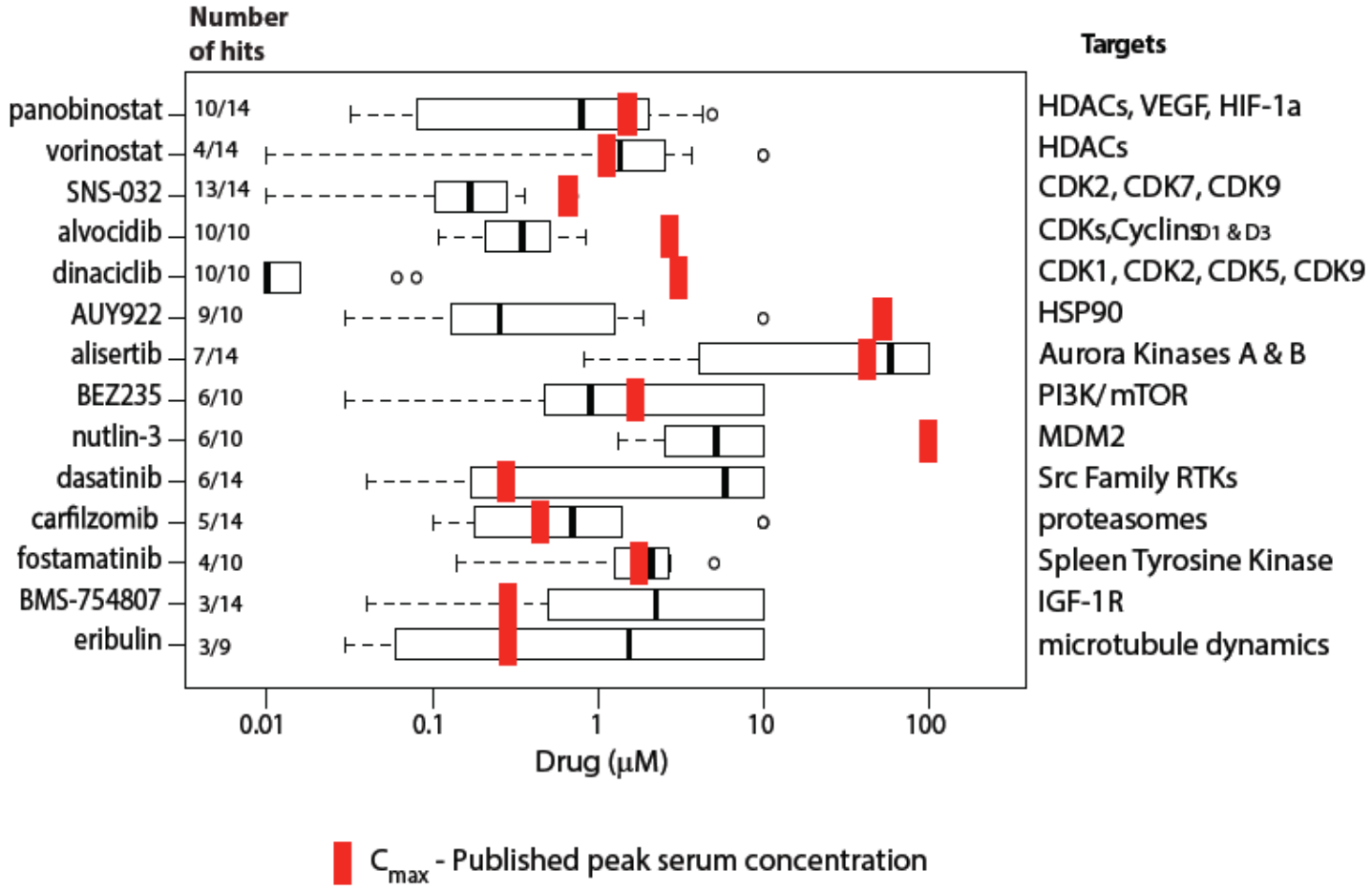
Functionally defined therapeutic targets in diffuse intrinsic pontine glioma

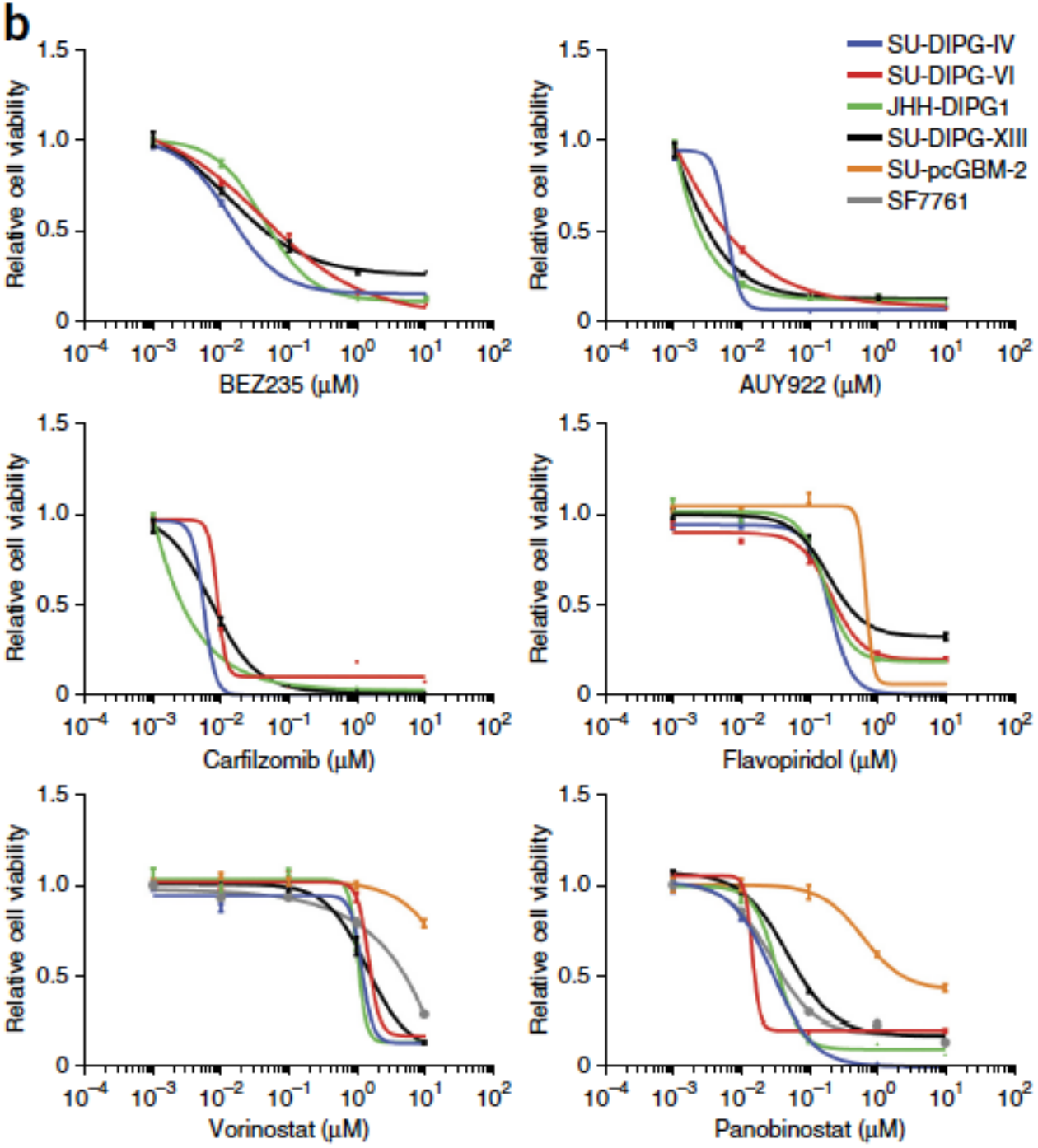
Catherine S Grasso[1,24], Yujie Tang[2–5,23,24], Nathalene Truffaux[6,24], Noah E Berlow[7], Lining Liu[2–5], Marie-Anne Debily[6,8], Michael J Quist[1], Lara E Davis[9], Elaine C Huang[9], Pamelyn J Woo[2–5], Anitha Ponnuswami[2–5], Spenser Chen[2–5], Tessa B Johung[2–5], Wenchao Sun[2], Mari Kogiso[10], Yuchen Du[10], Lin Qi[10], Yulun Huang[10,23], Marianne Hütt-Cabezas[11,12], Katherine E Warren[13], Ludivine Le Dret[6], Paul S Meltzer[13], Hua Mao[10], Martha Quezado[13], Dannis G van Vuurden[14,15], Jinu Abraham[9], Maryam Fouladi[16], Matthew N Svalina[1,17], Nicholas Wang[1], Cynthia Hawkins[18,19], Javad Nazarian[20], Marta M Alonso[21], Eric H Raabe[11,12], Esther Hulleman[14,15], Paul T Spellman[1], Xiao-Nan Li[10], Charles Keller[9,17,25], Ranadip Pal[7,25], Jacques Grill[6,22,25] & Michelle Monje[2–5,25]

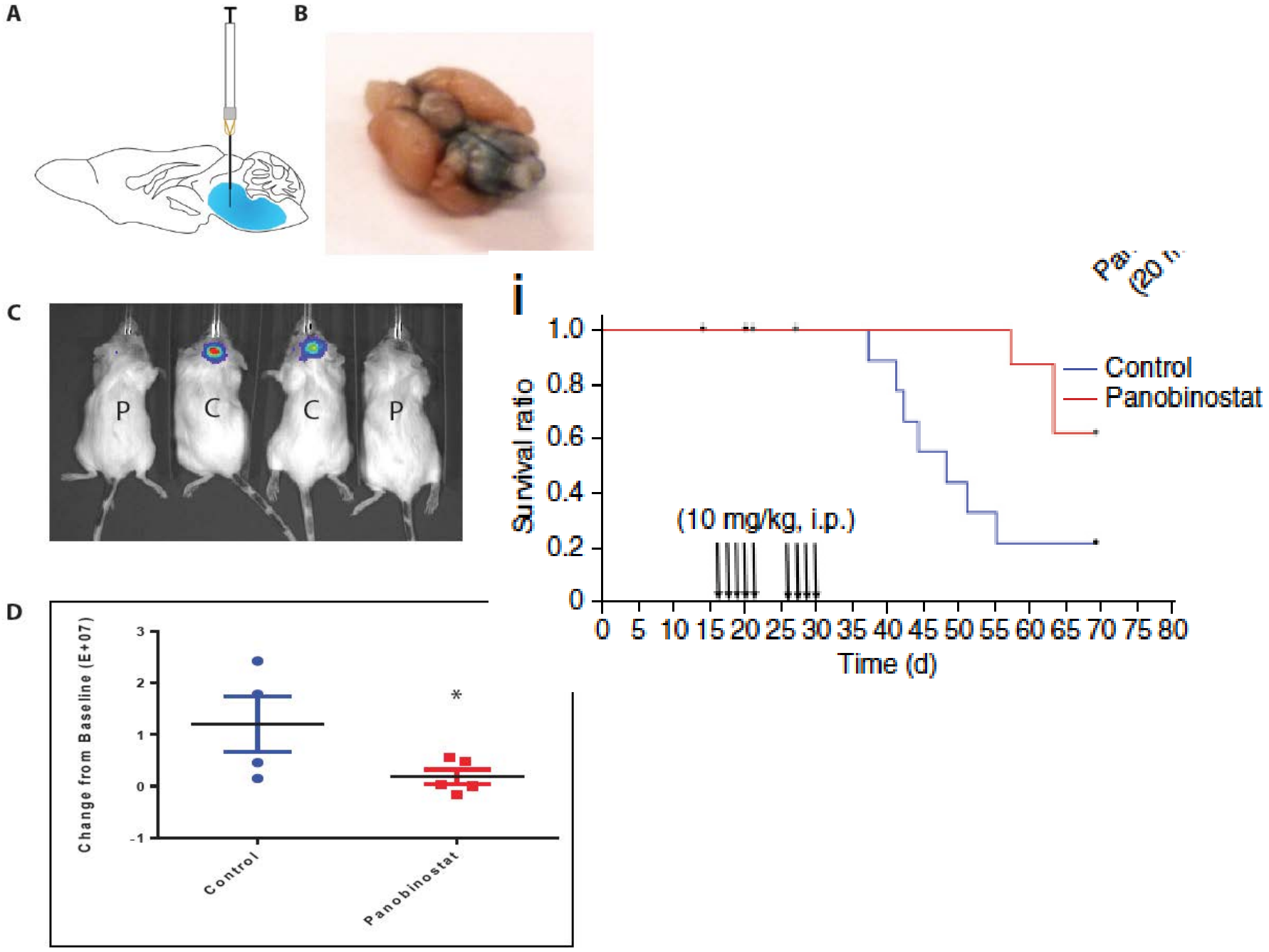


1 Vincristine
2 Valproic acid
3 Taurolidine
4 Sunitinib
5 Sod. ATM
6 Resveratrol
7 Rapamycin
8 Prednisone
9 PPP
10 PI-103
11 PD0332991
12 Nicotinamide
13 Itraconazole
14 Irinotecan
15 Imatinib
16 Erlotinib
17 Decitabine
18 Curcumin
19 Chromeceptin
20 Carboplatin
21 Bosutinib
22 BIX 02188
23 Actinomycin
24 Zibotentan
25 Vorinostat
26 Vismodegib
27 Veliparib
28 Tozasertib
29 Temsirolimus
30 SP600125
31 Sorafenib
32 Sodium butyrate
33 SNS-032
34 SJ-172550
35 Selumetinib
36 Ruxolitinib
37 RO4929097
38 Quinacrine
39 Ponatinib
40 Pazopanib
41 Trichostatin A
42 Pelitinib
43 Panobinostat
44 Obatoclax
45 *N*-acetyl cysteine
46 MK-2206
47 Linsitinib
48 Lapatinib
49 GANT 61
50 Enzastaurin
51 Dasatinib
52 Crizotinib
53 Cediranib
54 Carfizomib
55 Bortezomib
56 BMS-754807
57 BIX 01294
58 Barasertib
59 Alisertib
60 VER 155008
61 Vemurafenib
62 Vandetanib
63 Tamoxifen
64 SB-431542
65 Saracatinib
66 Revlimid
67 PF-562271
68 Nutlin-3
69 Nilotinib
70 Fostamatinib
71 Fenrentide
72 Eribulin
73 Entinostat
74 Dinaciclib
75 Cilengitide
76 Cabozantinib
77 BEZ235
78 AZD8931
79 Azacitidine
80 AUY922
81 ATRA
82 Alvocidib
83 ABT-737

Figure S2: Chemical screen 'hits' within the context of clinically-achievable serum drug levels.




b
Relative cell viability
1.5
1.0
0.5
0
10^{-4} 10^{-3} 10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2}
BEZ235 (μM)
AUY922 (μM)
Carfilzomib (μM)
Flavopiridol (μM)
Vorinostat (μM)
Panobinostat (μM)
SU-DIPG-IV
SU-DIPG-VI
JHH-DIPG1
SU-DIPG-XIII
SU-pcGBM-2
SF7761


A
B
C
P
C
C
P
i
Survival ratio
1.0
0.8
0.6
0.4
0.2
0
(10 mg/kg, i.p.)
Control
Panobinostat
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80
Time (d)
D
Change from Baseline (E+07)
3
2
1
0
-1
*
Control
Panobinostat

Why have we failed?

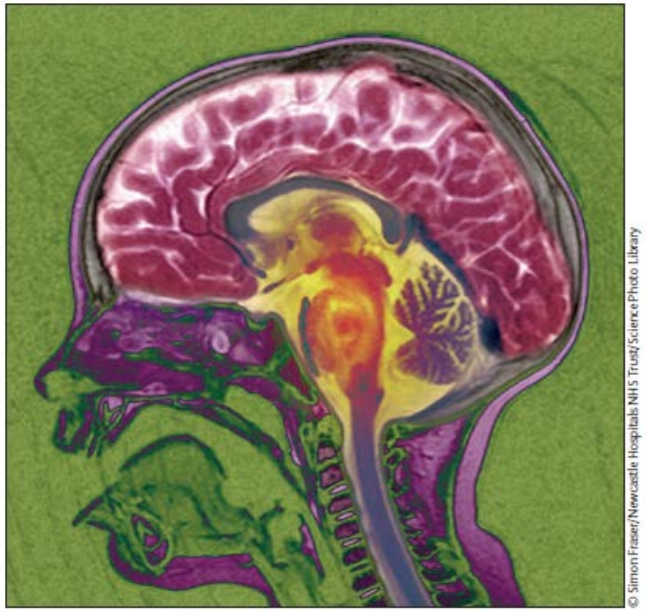
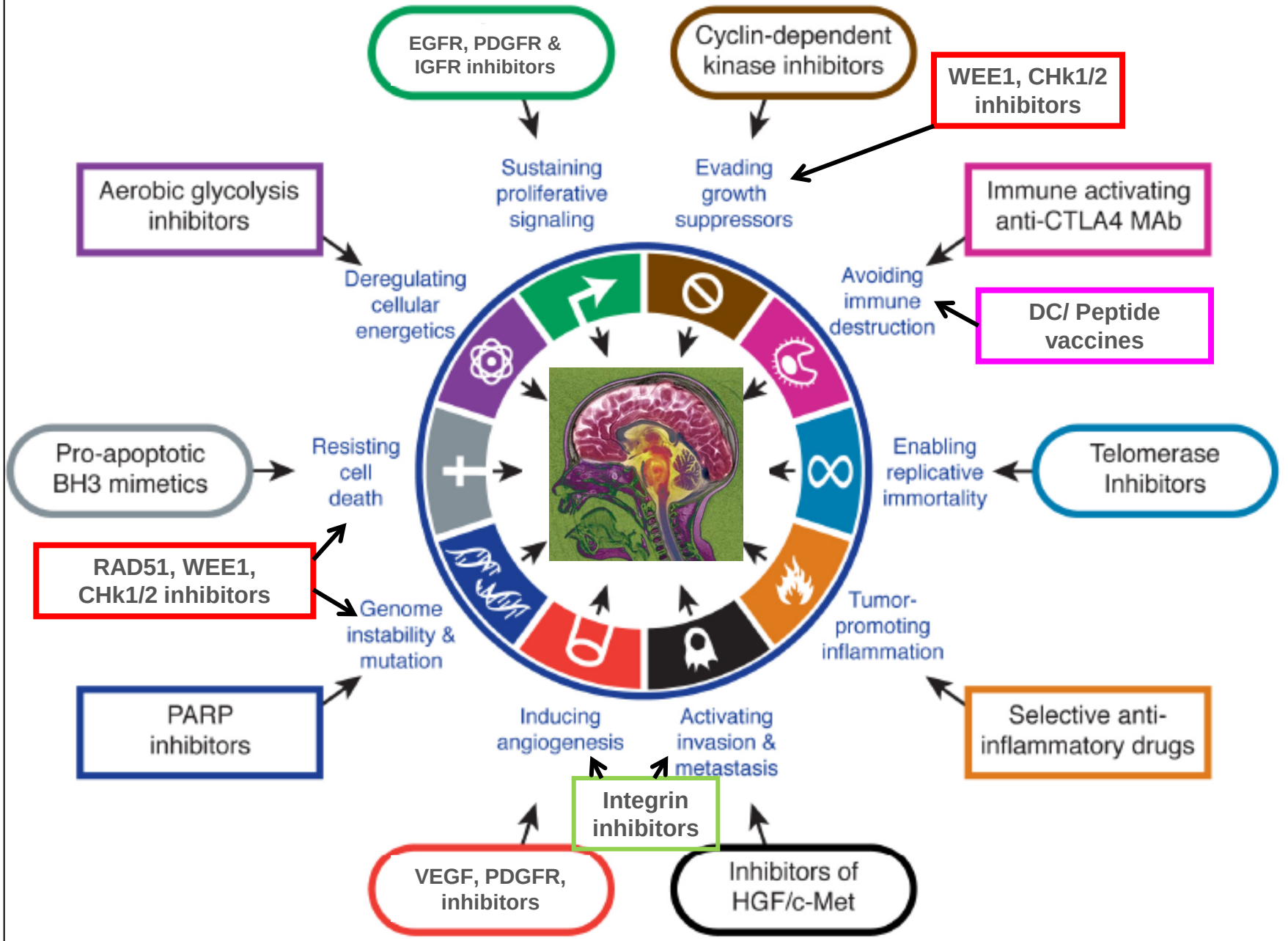


Figure 1: Gliomas are main cause of death from brain tumours in children

- **Lack of drugs!**
  - **Many possible targeted agents**
  - **Immunotherapy**



Hanahan and Weinberg, 2011

Cell PRESS

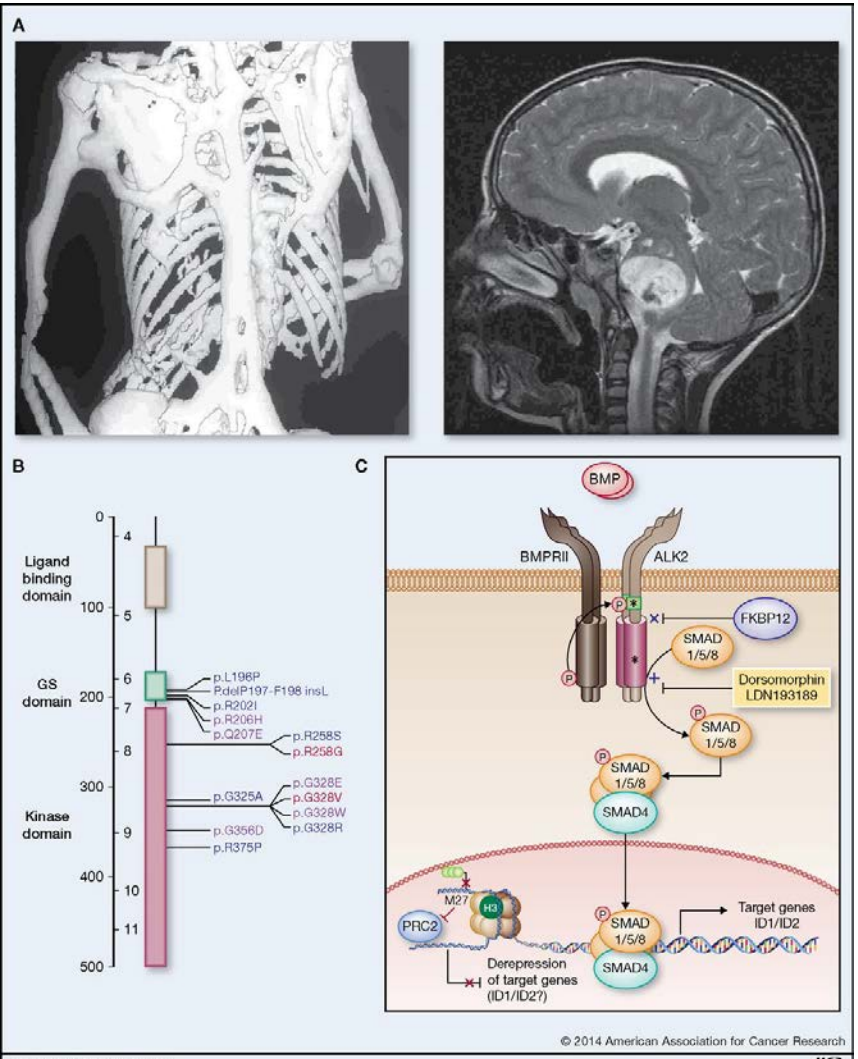
DIPG Specific Targets!

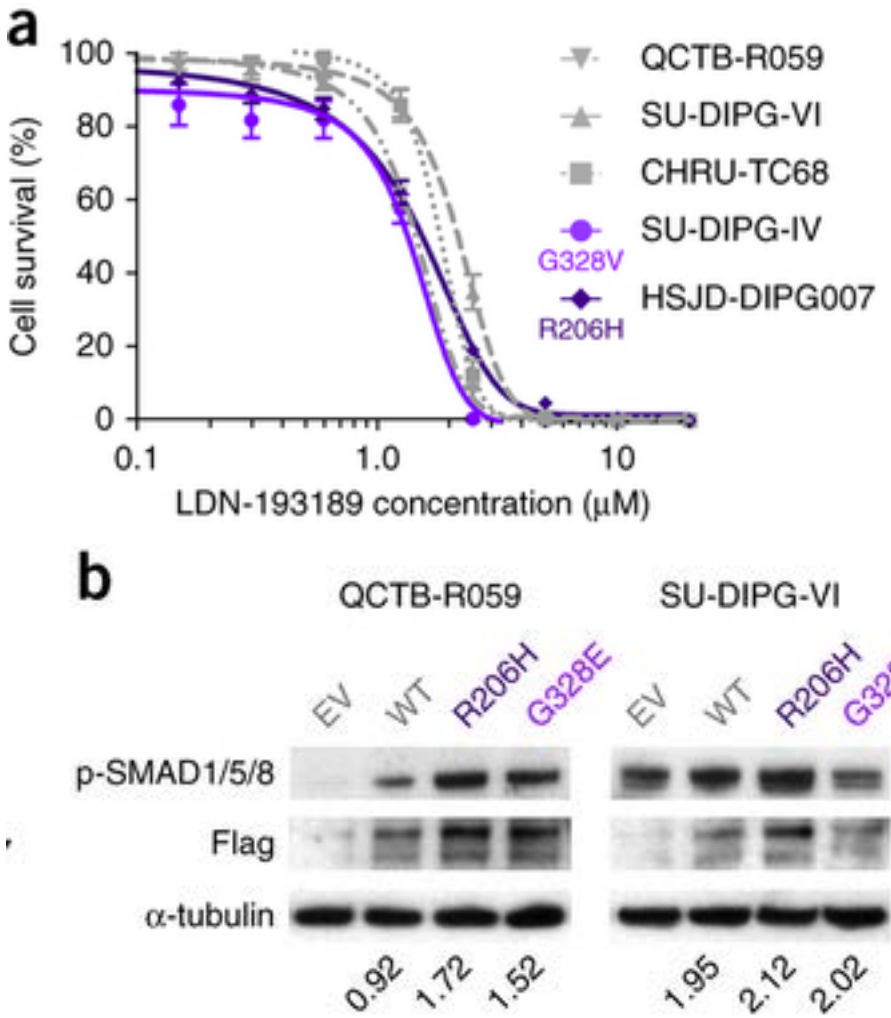
- Histone H3 mutations
  - restore H3K27 methylation? E.g. selective inhibitor of the H3K27 demethylase JMJD3
  - complex interplay of mutant histones ? Target histone acetylation but HAT or HDAC?
- ACVR1
- Immunotherapy

Cancer Research

ACVR1 Mutations in DIPG: Lessons Learned from FOP

Kathryn R. Taylor[1,2], Maria Vinci[1,2], Alex N. Bullock[3], and Chris Jones[1,2]





Why have we failed?

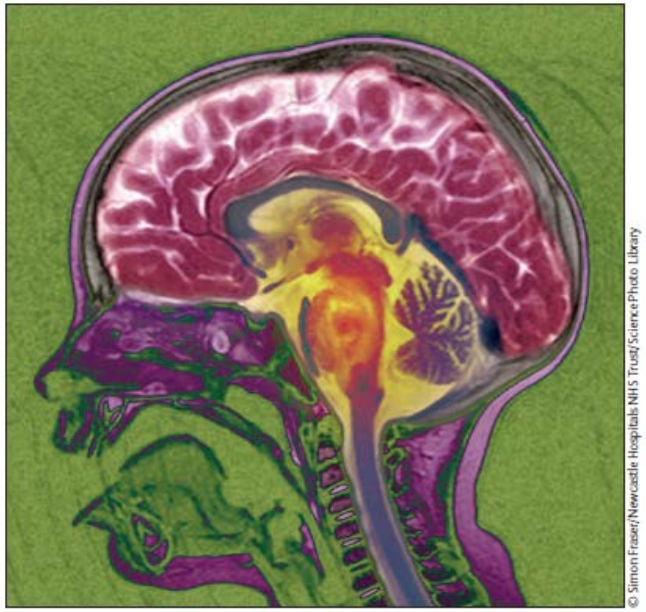
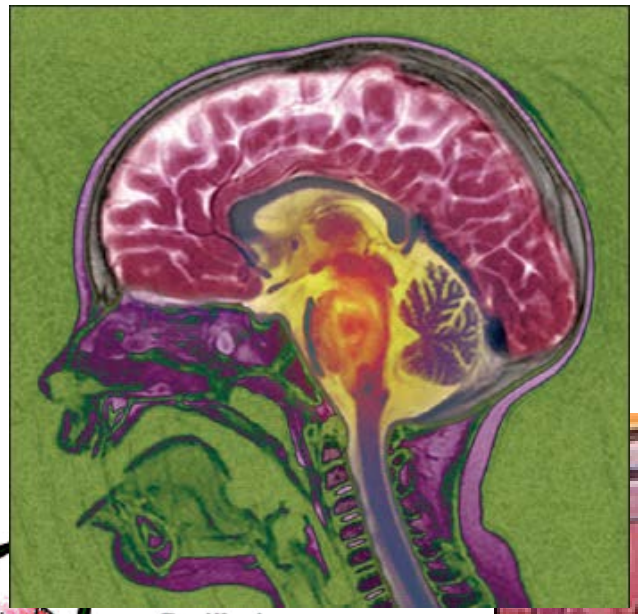
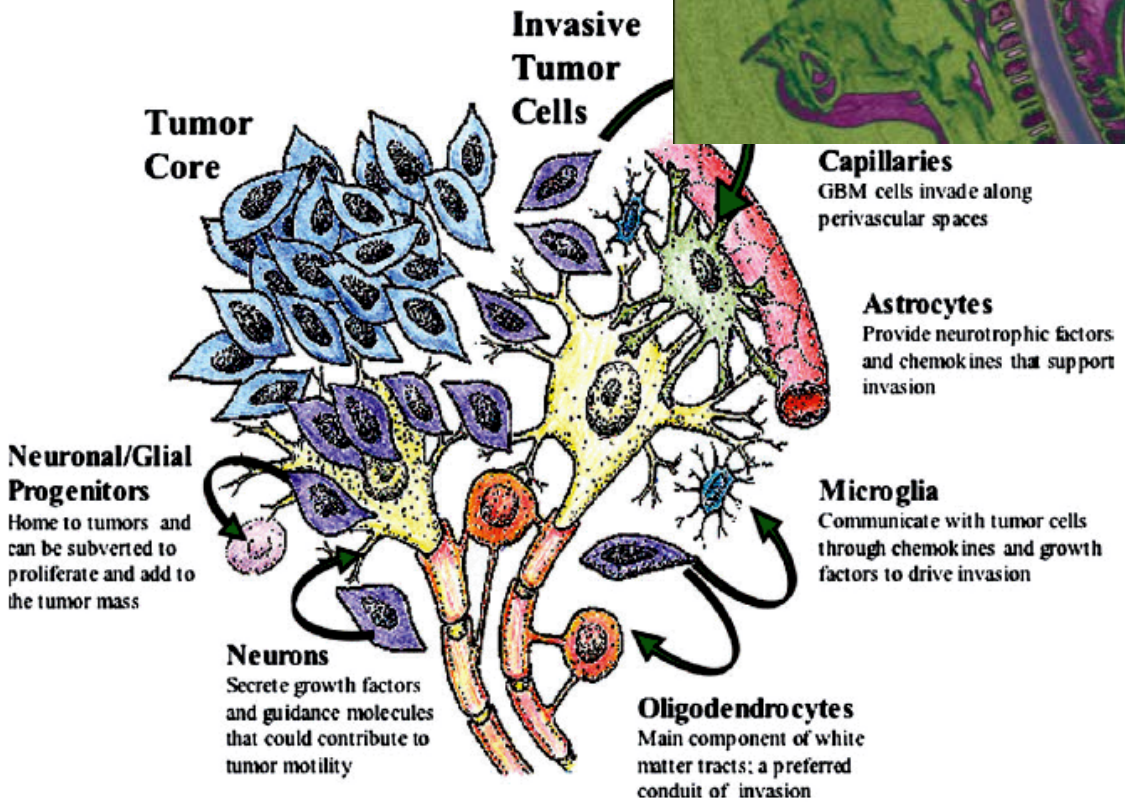


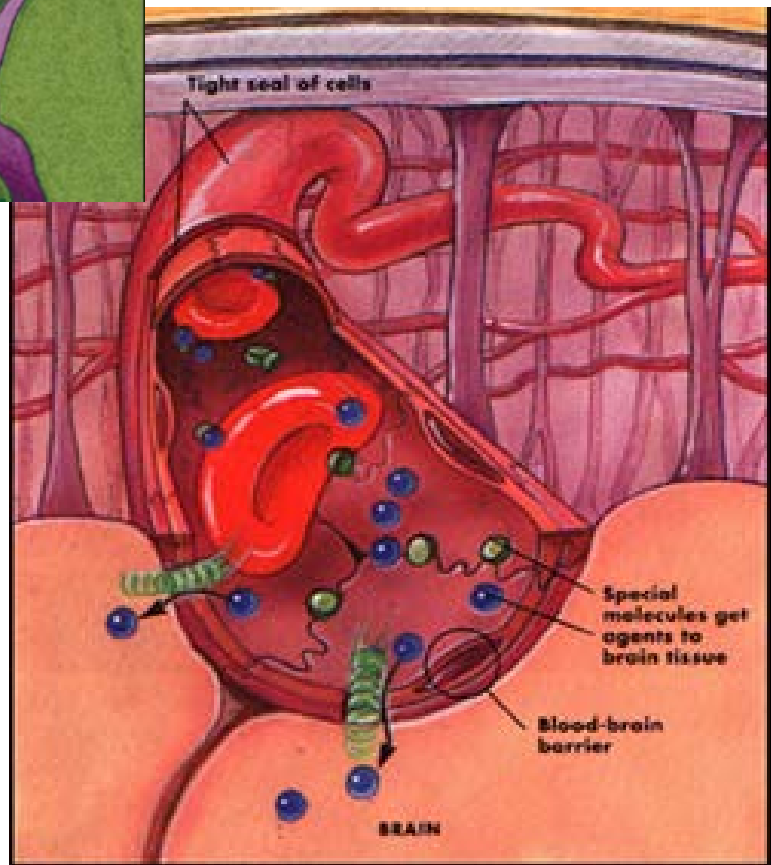
Figure 1: Gliomas are main cause of death from brain tumours in children

- **Poor drug delivery!**
  - **Is it a real problem?**
  - **Need solutions.**

Poor Drug Delivery



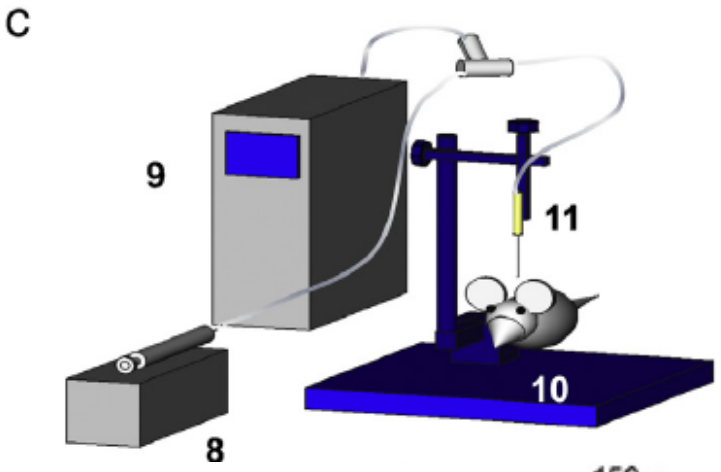


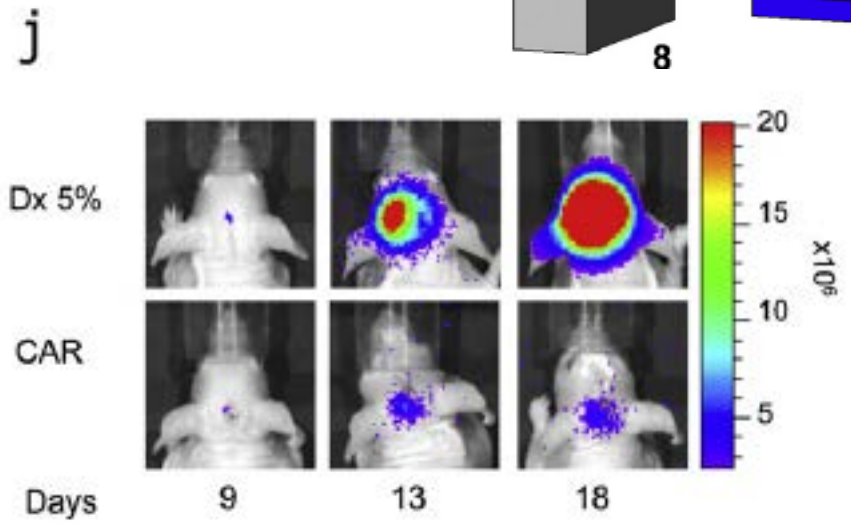


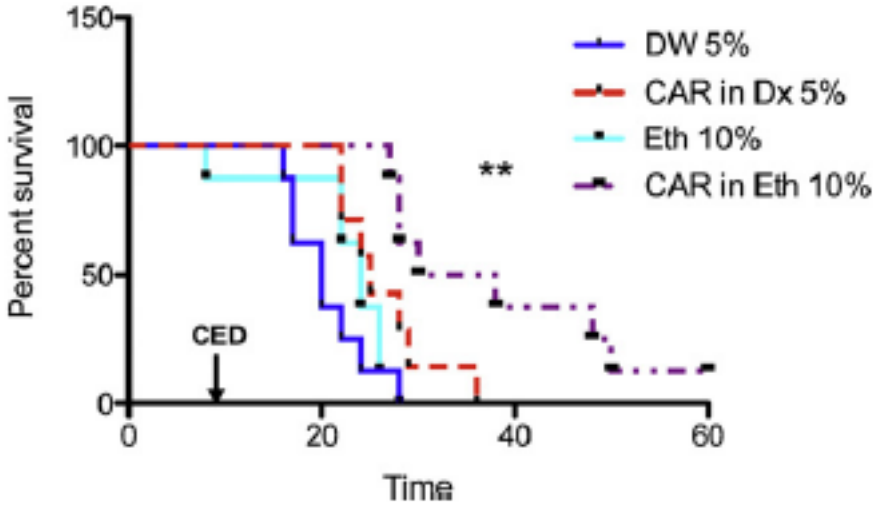
Convection enhanced delivery of carmustine to the murine brainstem: A feasibility study

Journal of Neuroscience Methods 238 (2014) 88–94

A. Charlotte P. Sewing[a,c,1], Viola Caretti[a,b,c,1,2], Tonny Lagerweij[a,b,c,1], Pepijn Schellen[a,b,c], Marc H.A. Jansen[a,c], Dannis G. van Vuurden[a,c], Sander Idema[b,c], Carla F.M. Molthoff[d], W. Peter Vandertop[b], Gertjan J.L. Kaspers[a], David P. Noske[b,c,1], Esther Hulleman[a,c,*,1]







CED DIPG Trials

- **An Open Label Dose Escalation Safety Study of Convection-Enhanced Delivery of IL13-PE38QQR in Patients With Progressive Pediatric Diffuse Infiltrating Brainstem Glioma and Supratentorial High-grade Glioma. NCT00880061**

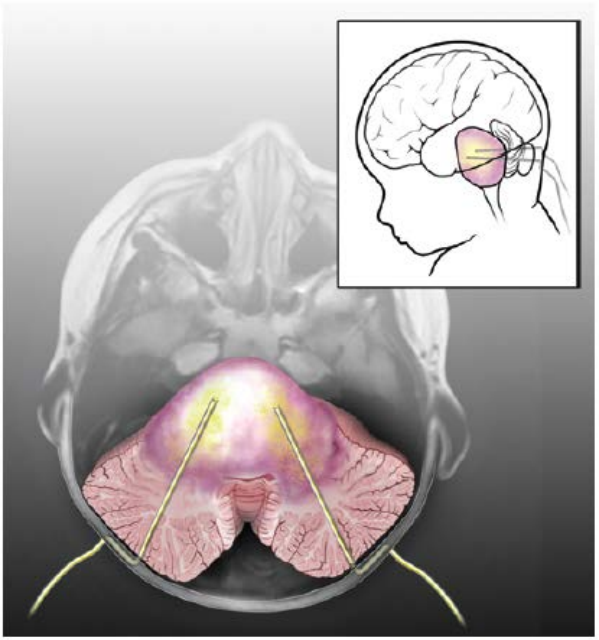
- **Convection-Enhanced Delivery of 124I-8H9 for Patients With Non-Progressive Diffuse Pontine Gliomas Previously Treated With External Beam Radiation Therapy. NCT01502917**

J Neurosurg Pediatrics 11:289–295, 2013

Convection-enhanced delivery of topotecan into diffuse intrinsic brainstem tumors in children

Report of 2 cases

Richard C. E. Anderson, M.D.,[1] Benjamin Kennedy, M.D.,[1] Candix L. Yanes, R.N.,[1] James Garvin, M.D., Ph.D.,[2] Michael Needle, M.D.,[2] Peter Canoll, M.D., Ph.D.,[3] Neil A. Feldstein, M.D.,[1] and Jeffrey N. Bruce, M.D.[1]

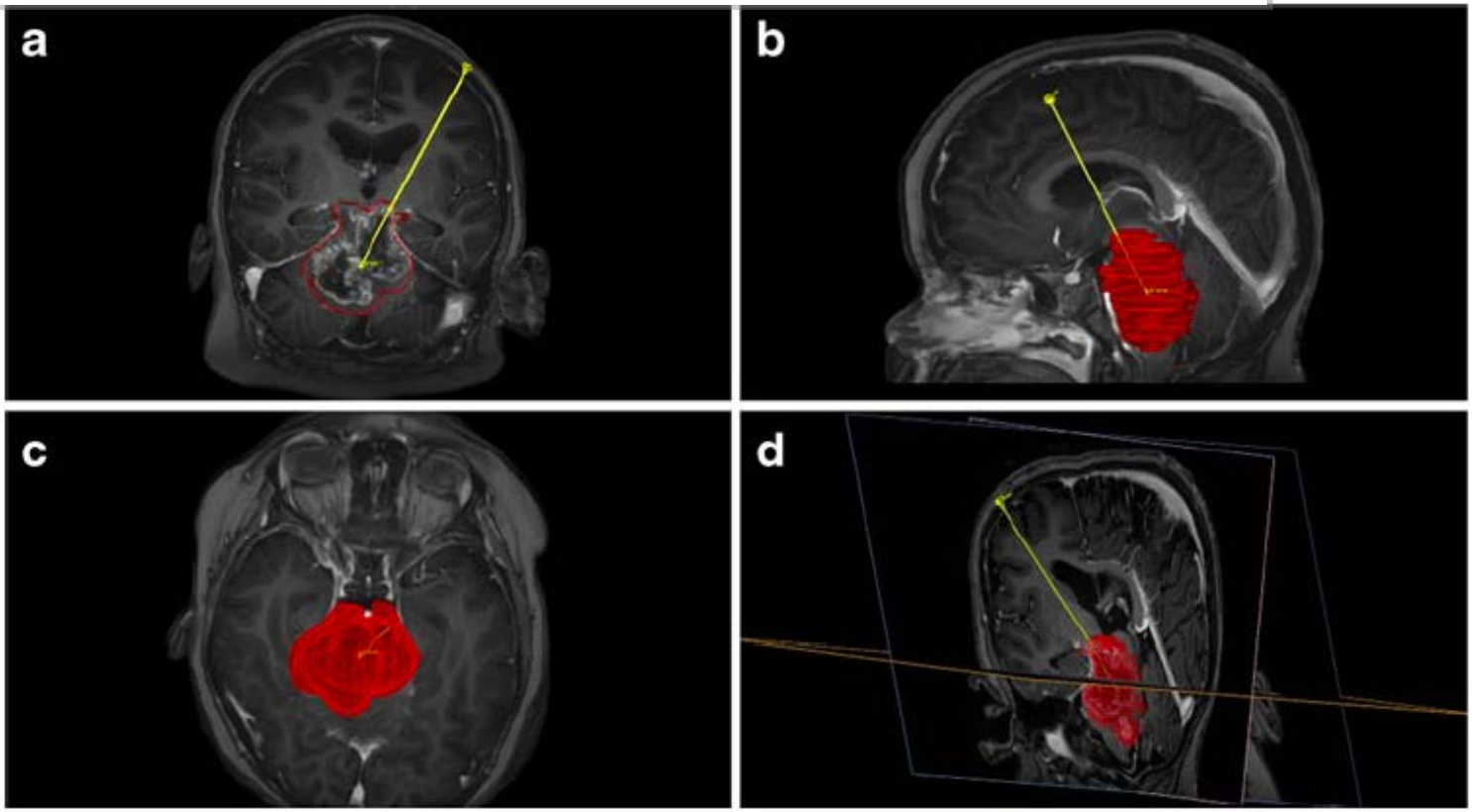


Acta Neurochir
DOI 10.1007/s00701-013-1700-6

TECHNICAL NOTE - PEDIATRICS

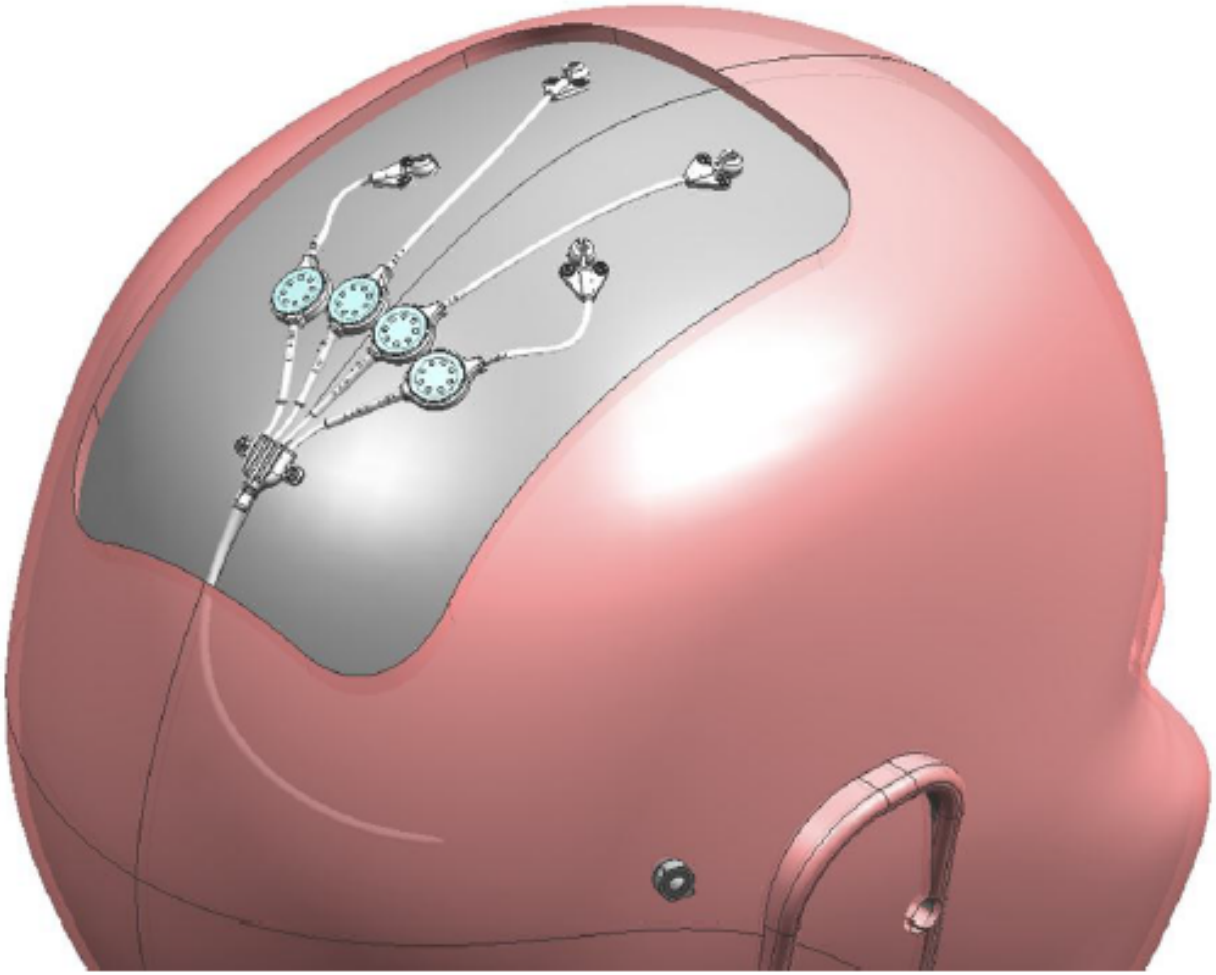
Robot-guided convection-enhanced delivery of carboplatin for advanced brainstem glioma

N. U. Barua · S. P. Lowis · M. Woolley · S. O'Sullivan · R. Harrison · S. S. Gill



Robot-guided catheter implantation

Chronic drug delivery system



Intermittent convection-enhanced delivery to the brain through a novel transcutaneous bone-anchored port N.U. Barua[a,b], M. Woolley[a,c], A.S. Bienemann[a], D.E. Johnson[a,c], O. Lewis[c], M.J. Wyatt[a], C. Irving[c], S. O'Sullivan[c], G. Murray[c], C. Fennelly[c], P. Skinner[c] & S.S. Gill[a,b]. J Neurosci Methods. 2013 Apr 15;214(2):223-32.

Intra-arterial Clinical Trials

- Intra-arterial Chemotherapy for the Treatment of Progressive Diffuse Intrinsic Pontine Gliomas (DIPG). NCT01688401
- Phase I/II Trial Of Super-Selective Intraarterial Infusion Of Erbitux (Cetuximab) And Avastin (Bevacizumab) For Treatment Of Relapsed/Refractory Intracranial Glioma In Patients Under 22 Years Of Age. NCT01884740

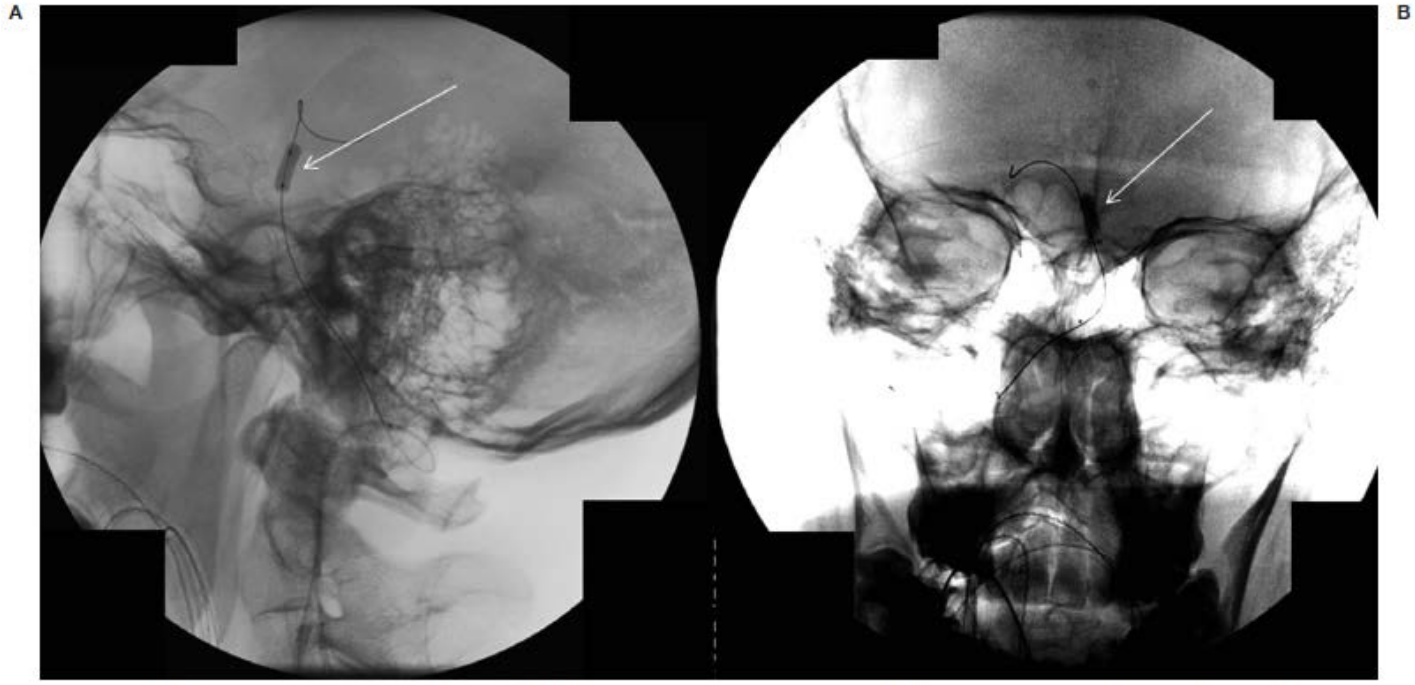


Figure 2 Fluoroscopy in lateral (A) and AP (B) projections demonstrating balloon (arrow) inflated in the distal basilar artery during selective infusion to prevent flow of chemotherapy to non-targeted areas in the distal posterior circulation.

Nanoparticles

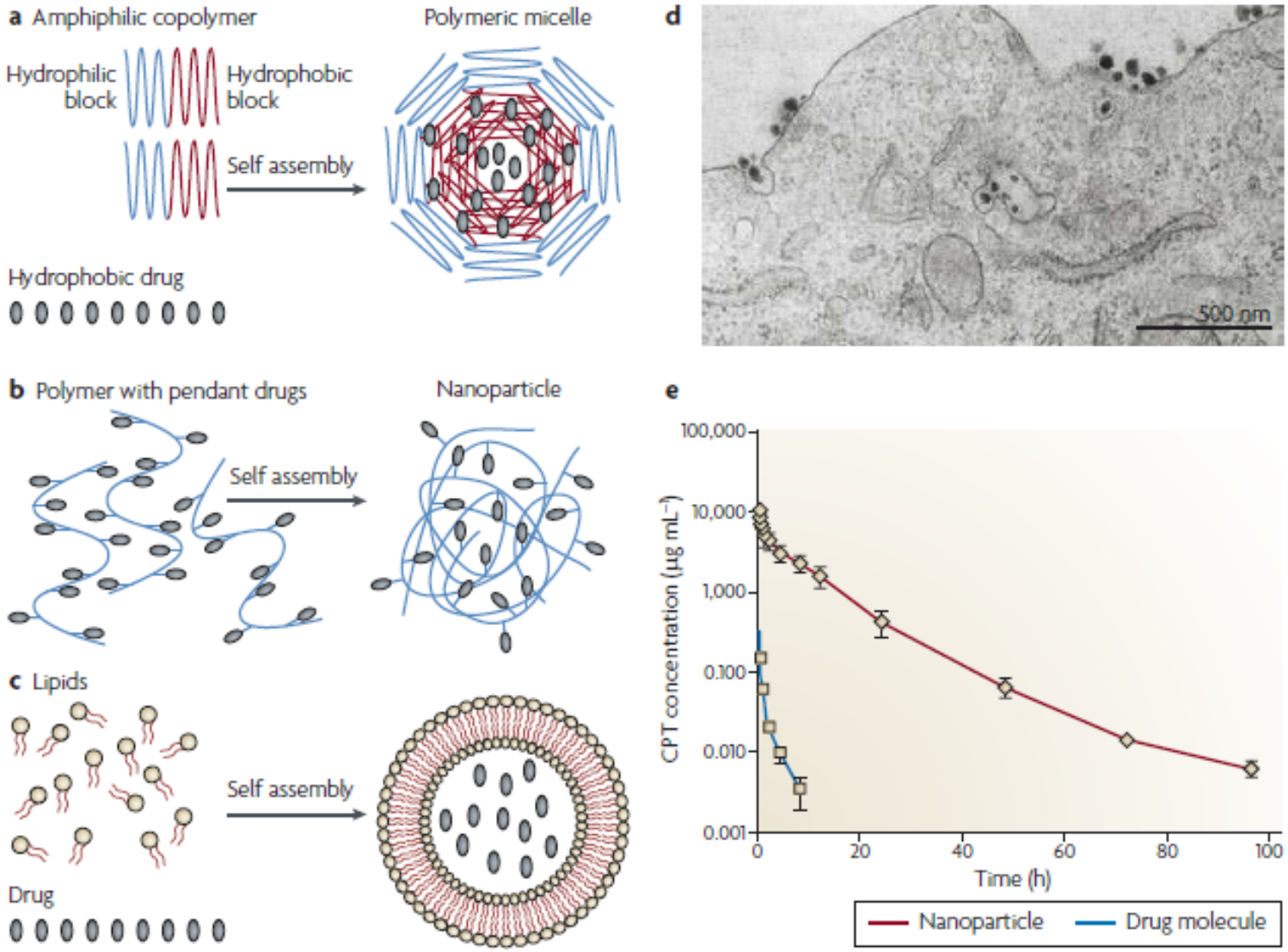
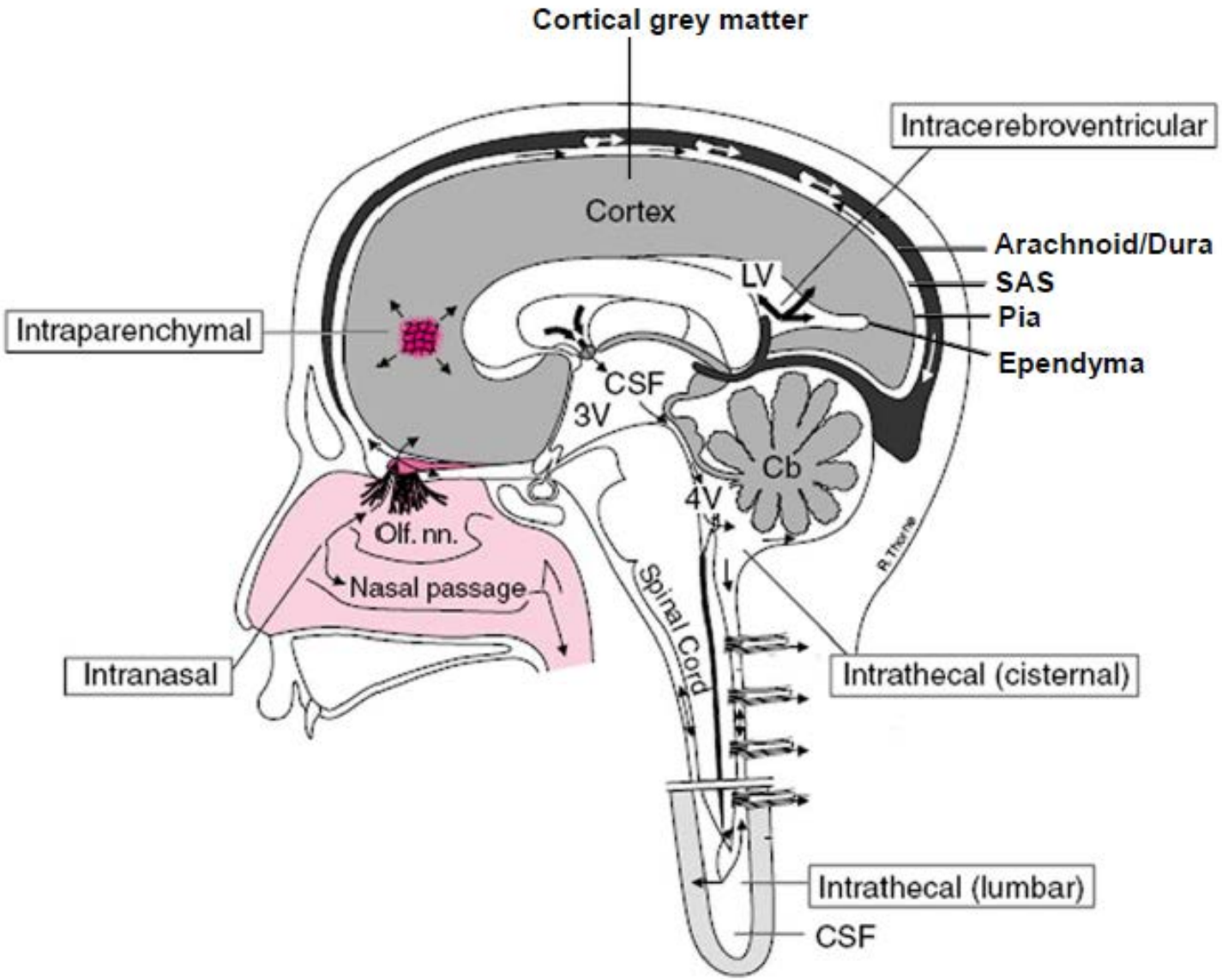


Figure 1 | **Major classes of nanoparticles that are in clinical trials and some of their properties. a** | Nanoparticles

Intranasal Delivery

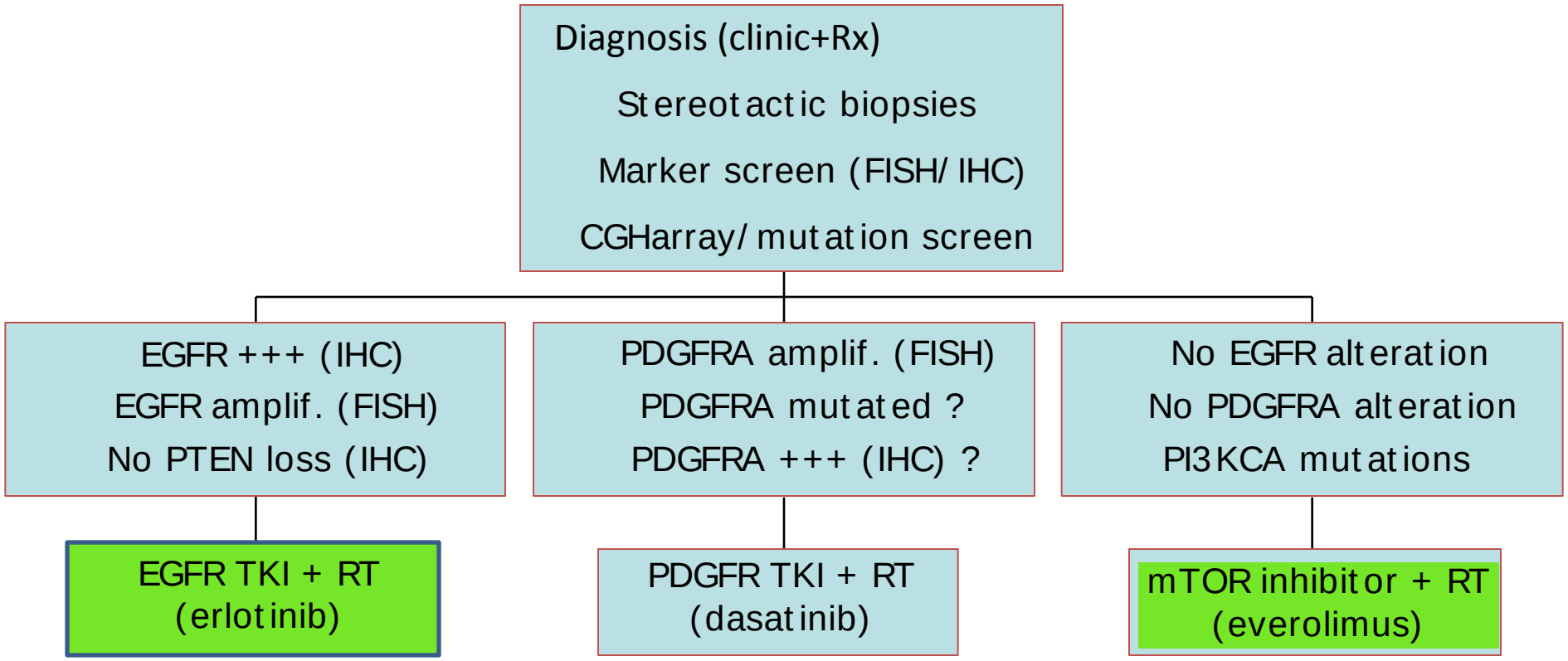


Biopsy directed therapies

- **Molecularly Determined Treatment of Diffuse Intrinsic Pontine Gliomas (DIPG).** NCT01182350
  - up-front stereotactic biopsy of classic DIPG used to stratify patients to different therapies based on the MGMT (temozolomide) and EGFR (erlotinib) expression in combination with focal radiation therapy and bevacizumab

- **BIOMEDE- Biologically-driven phase I/II study in children and adolescent with DIPG**

BIOMEDE Study

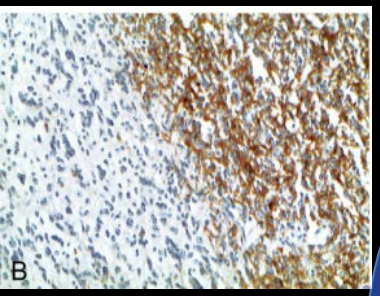


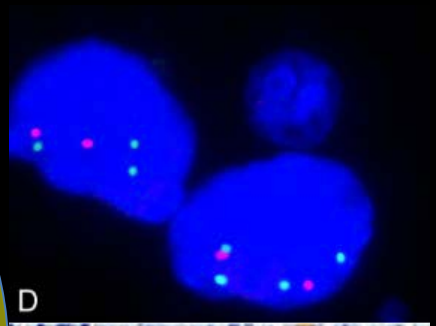
Three major targets selected

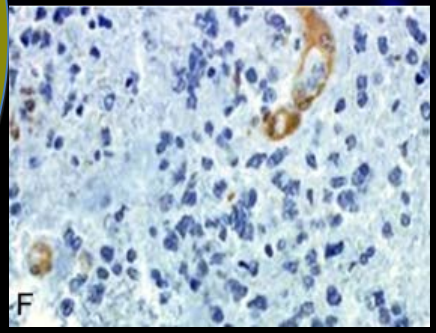
- **EGFR**
  - Rarely amp/mut, frequently overexpressed
- **mTOR pathway**
  - Activated by genomic alteration in ½ of DIPG (Taylor et al, Nat Genet in press).
  - PTEN loss in 80% of DIPG.
- **PDGFRA pathway**
  - PDGFRAamp/mut in 20% of DIPG

EGFR POS

PTEN LOSS







1%

30%

30%

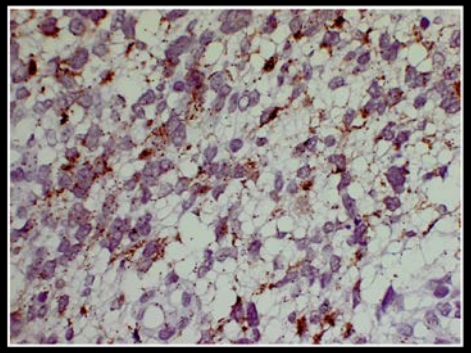
10%

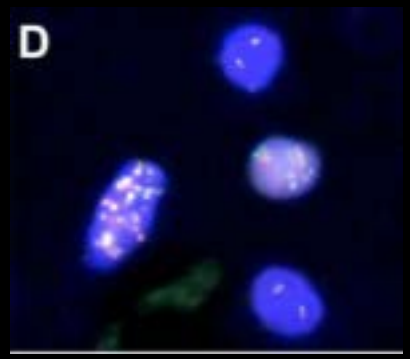
3%

10%

3%

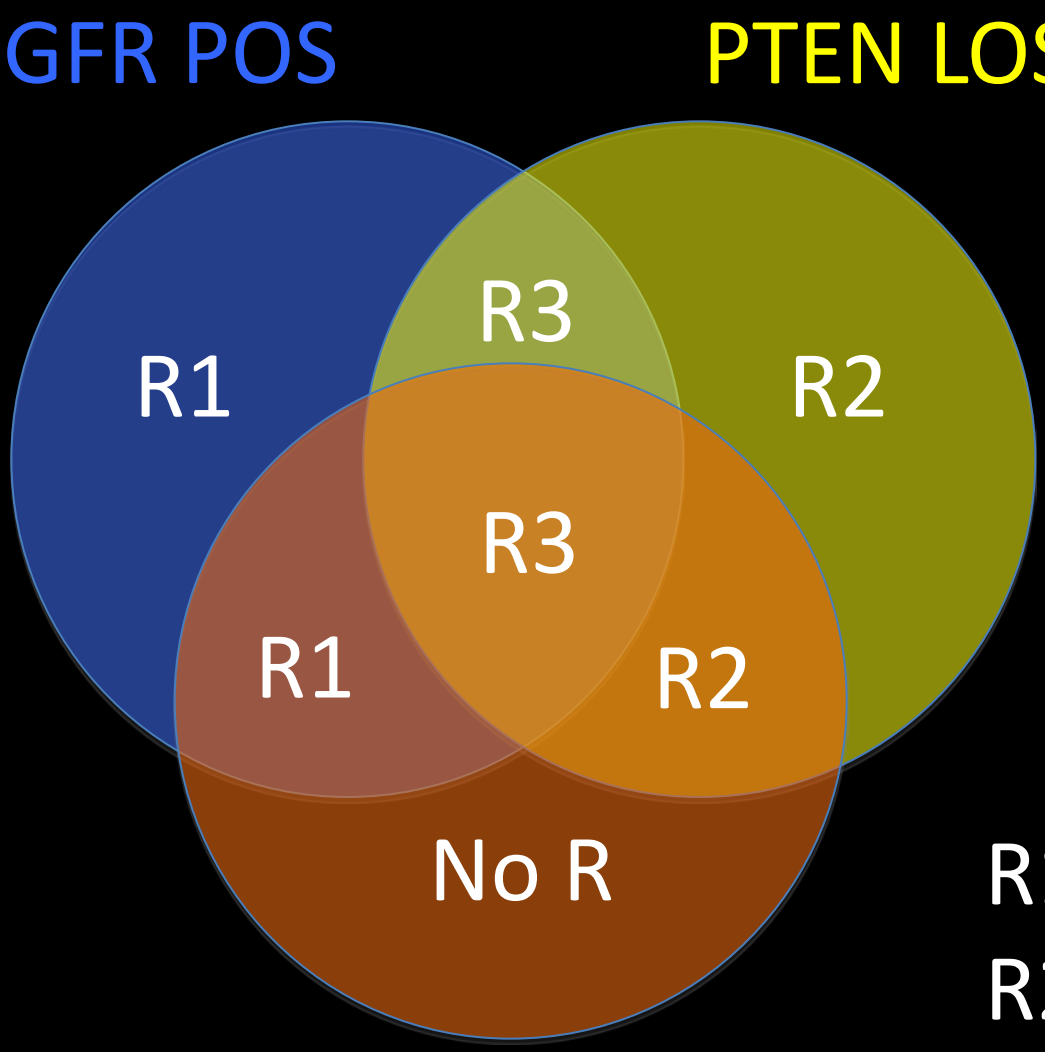
PDGFRA AMP



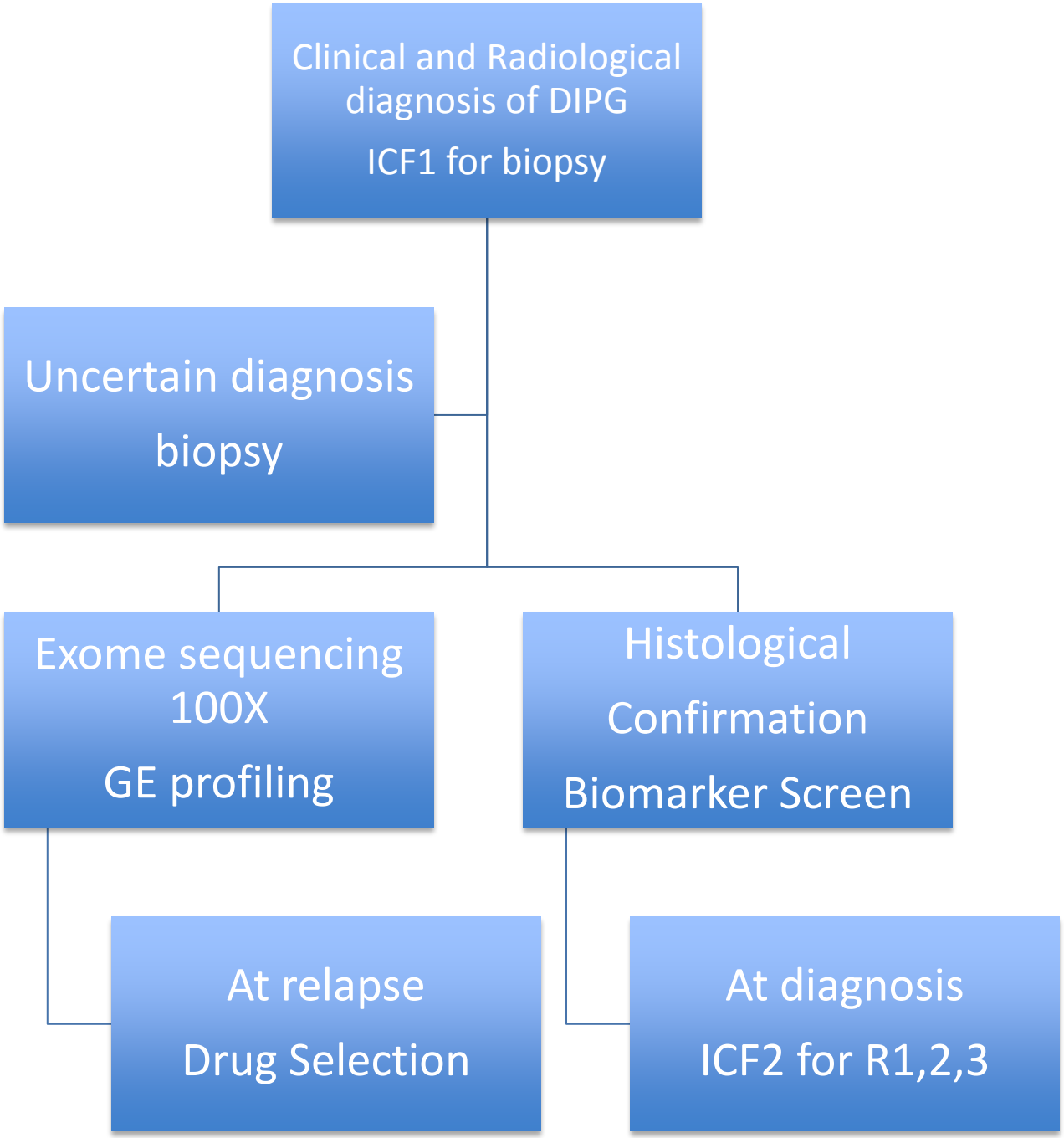


Three drugs selected

- ERLOTINIB to target EGFR
  - Geoerger N0 2010 and others.
- EVEROLIMUS to target mTOR pathway
  - Geoerger EJC 2011 in recurrent DIPG.
- DASATINIB to target PDGFRA pathway
  - Broniscer CCR 2013 in combo with vandetanib together with RT in newly diagnosed pts.
  - Dasatinib is also targeting other TKI.

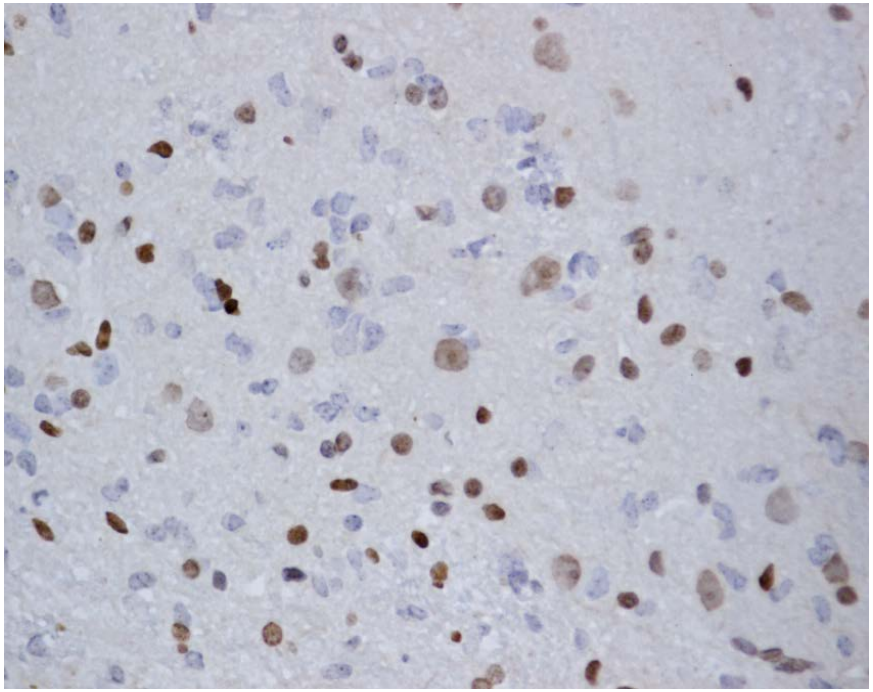


R1=Erlo/Dasa
R2=Ever/Dasa
R3=All three

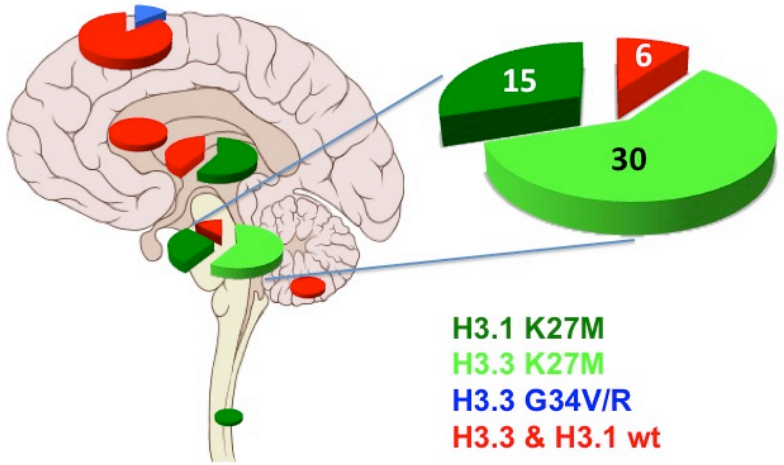

Clinical and Radiological diagnosis of DIPG
ICF1 for biopsy
Uncertain diagnosis biopsy
Exome sequencing 100X
GE profiling
Histological Confirmation
Biomarker Screen
At relapse
Drug Selection
At diagnosis
ICF2 for R1,2,3

Diagnostic workout

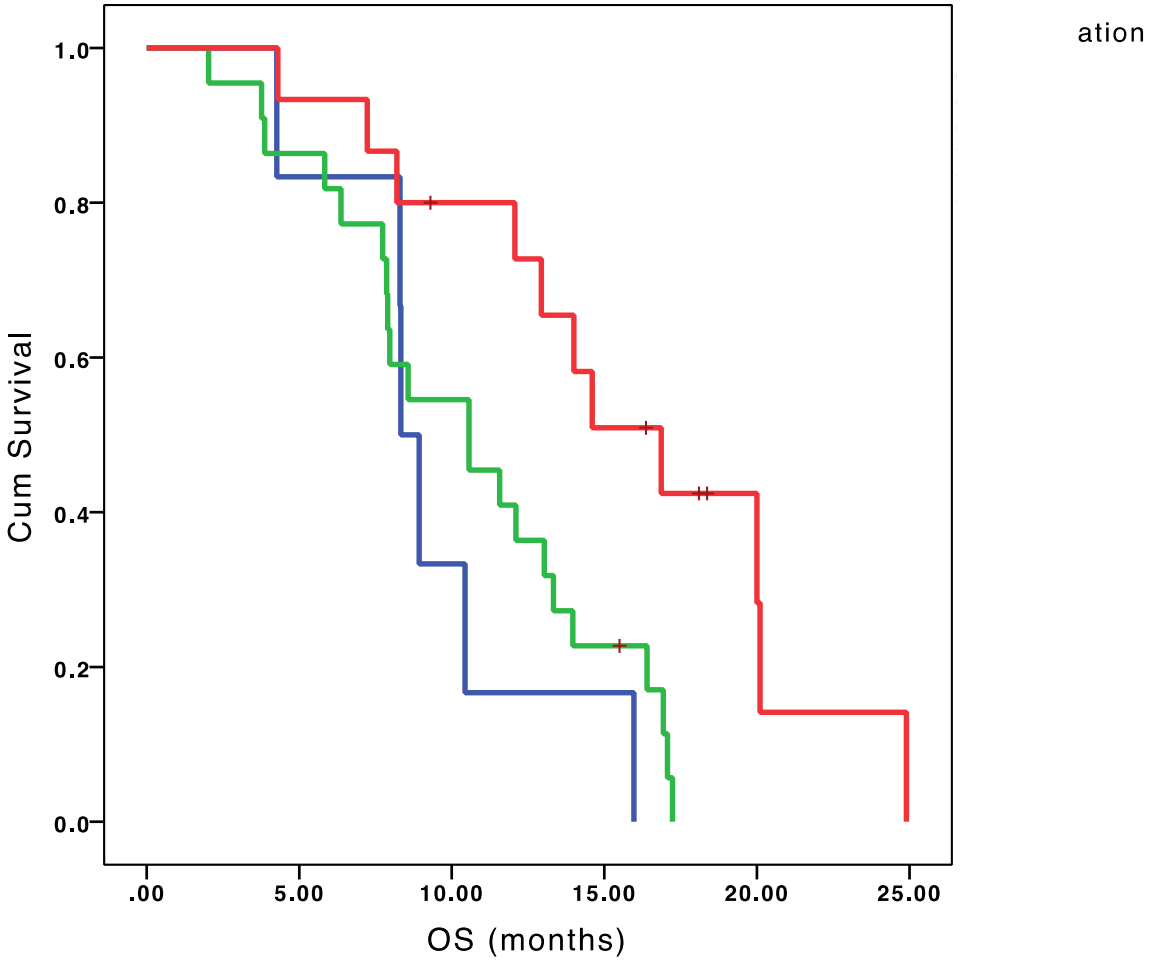
Loss of H3K27trimethylation mark



Histone H3 variant mutations

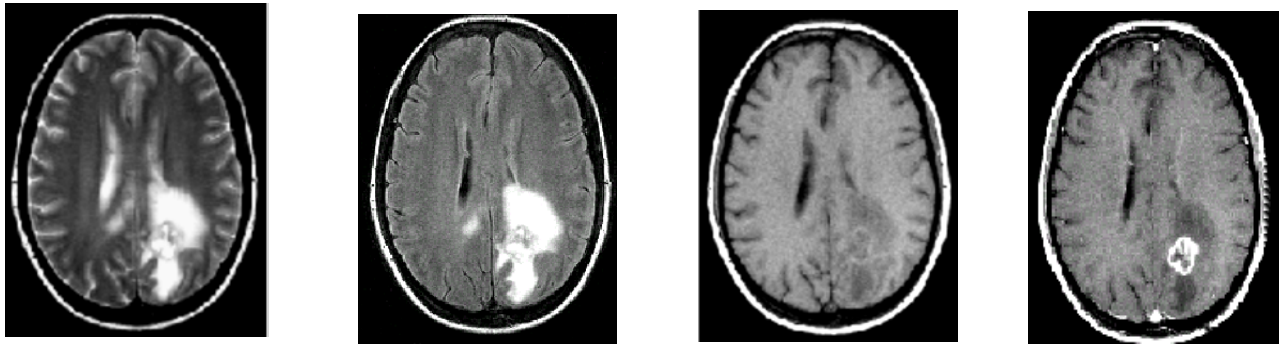


Prognostic impact of histone mutations

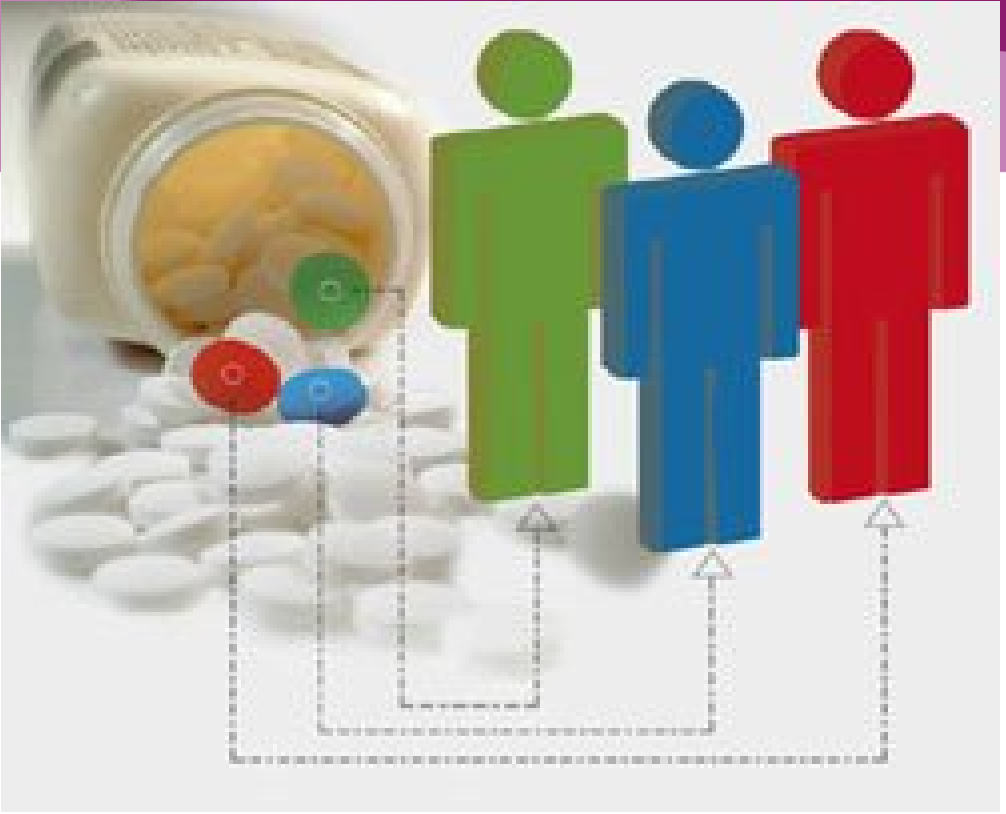


High grade glioma

Prognostic factors



- Extent of resection
- Histological grade (Grade III vs IV)
- Gender (female favourable)
- Radiation Dose > 54 Gy
- Proliferation index
- p53 overexpression (less favourable)
- Tumor location: with the poorest outcomes associated with pontine & thalamic locations



Current standard treatments & outcomes for pHGG

Surgery

The goal of the surgery is:

- obtain tissue for pathological analysis

-achieve an “uncomplicated” gross tumour resection (GTR)

-control possible neurological symptoms associated with mass effect

GTR (over 90% resection) is associated with a longer PFS

Surgery

Children's Cancer Group 945

131 patients with a diagnosis of AA or GBM

- **Surgery biopsy (<10% resection)**
- **Partial resection (10-50%)**
- **Subtotal resection (50-90%)**
- **Radical (90%)**

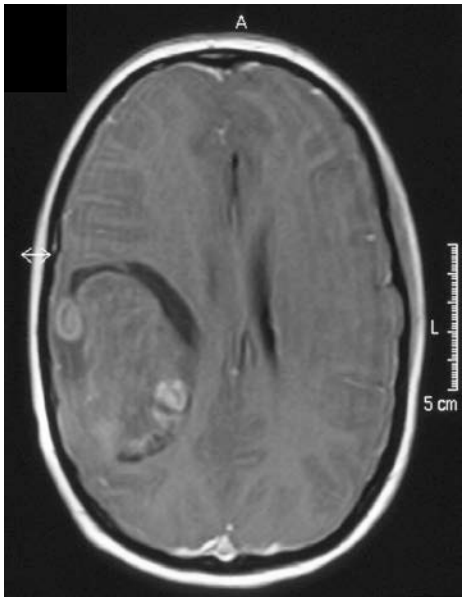
PFS at 5 years rate of 35% in radical resection compared with 17% in subtotal resection (p= 0.006)

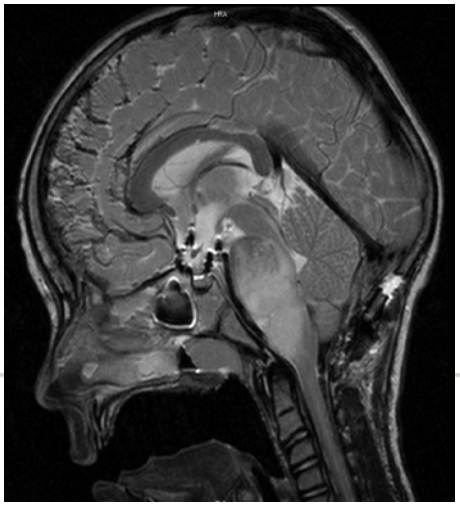
AAs PFS at 5 years 44% in radical vs. 22% in subtotal (p= 0.055)

GMB PFS at 5 years rate of 26% in radical vs. 4% in subtotal (p= 0.046)

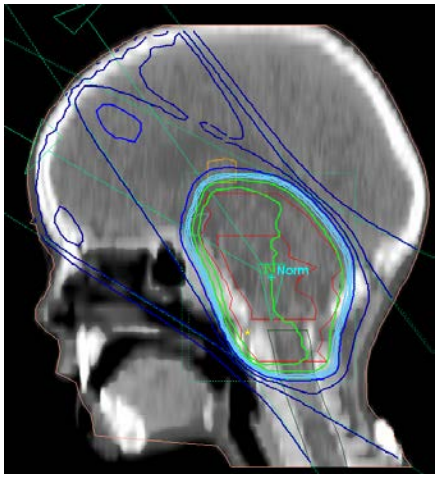
Wisoff et al. J Neurosurg 1998

High grade glioma + brainstem glioma





Aims of radiotherapy



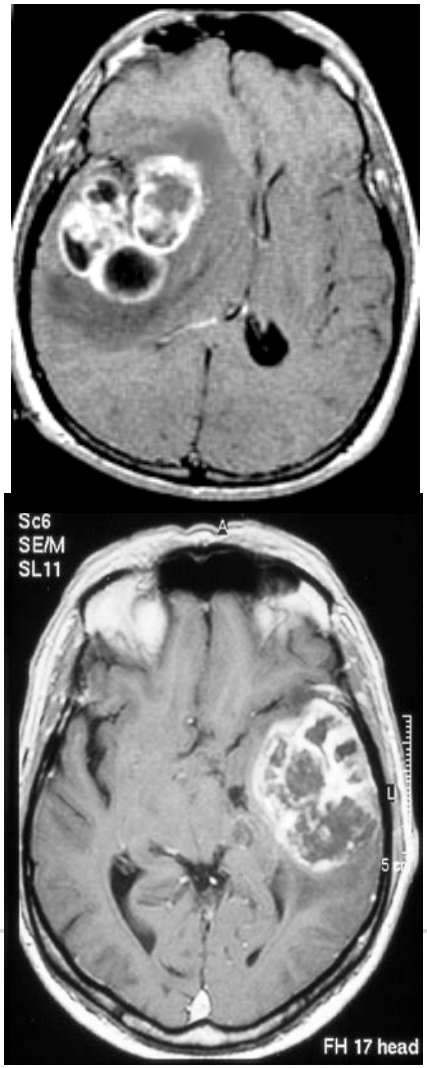
- **Improvement of local tumour control**
- **Using the advantages of modern treatment techniques**
- **Combination with chx. / „radiosensitizers“**

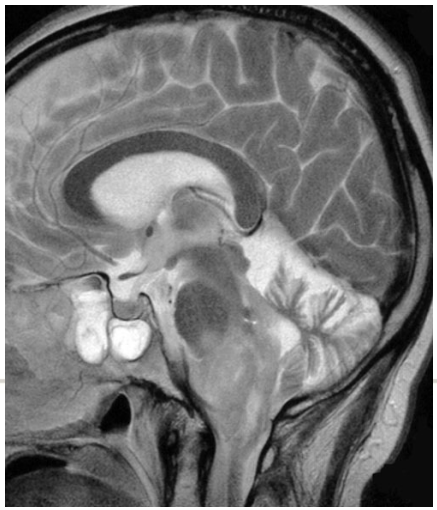
ESTRO School

High grade glioma

Criteria for treatment planning

- ⇨ **Location**
- ⇨ **Shape**
- ⇨ **Tendency to infiltration**
- ⇨ **Imaging**



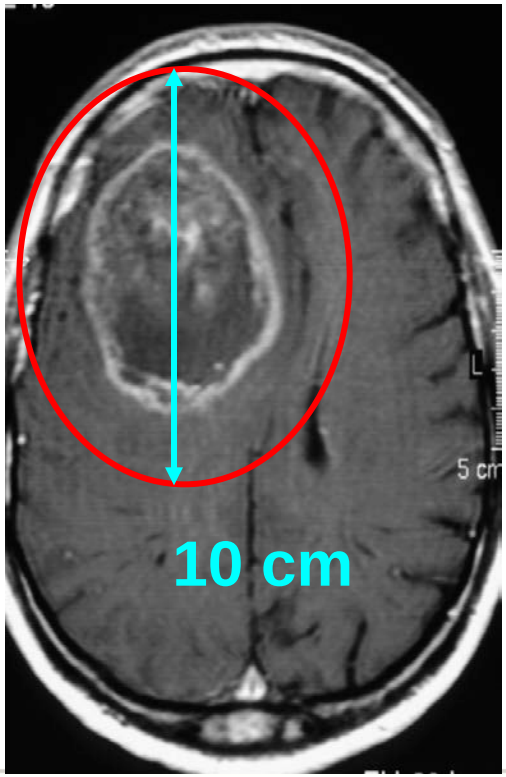


⇨ **Targeting**
Definition of GTV, CTV, PTV

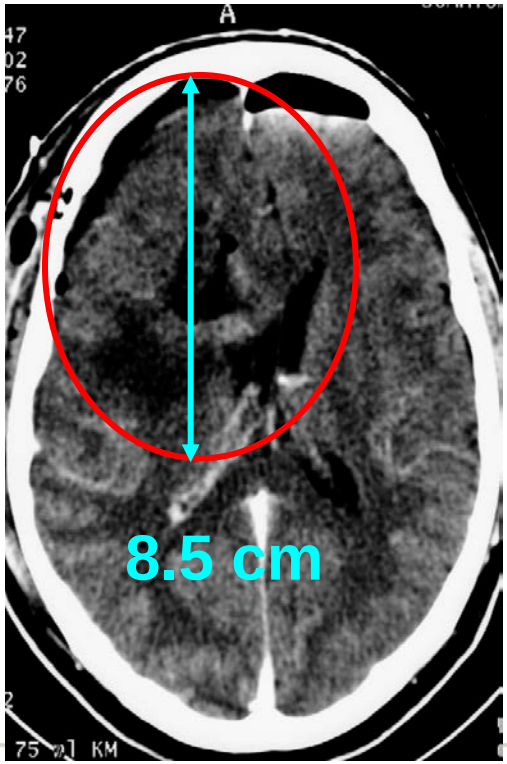
High grade glioma

⇨ Pre- or postoperative definition of CTV ?

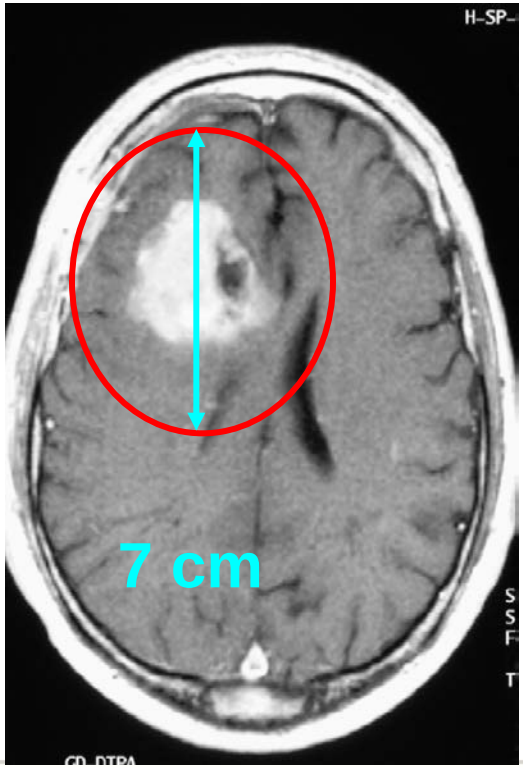
⇨ Technique / timing of imaging ?



MR pre-op.



CT 1 day postop.

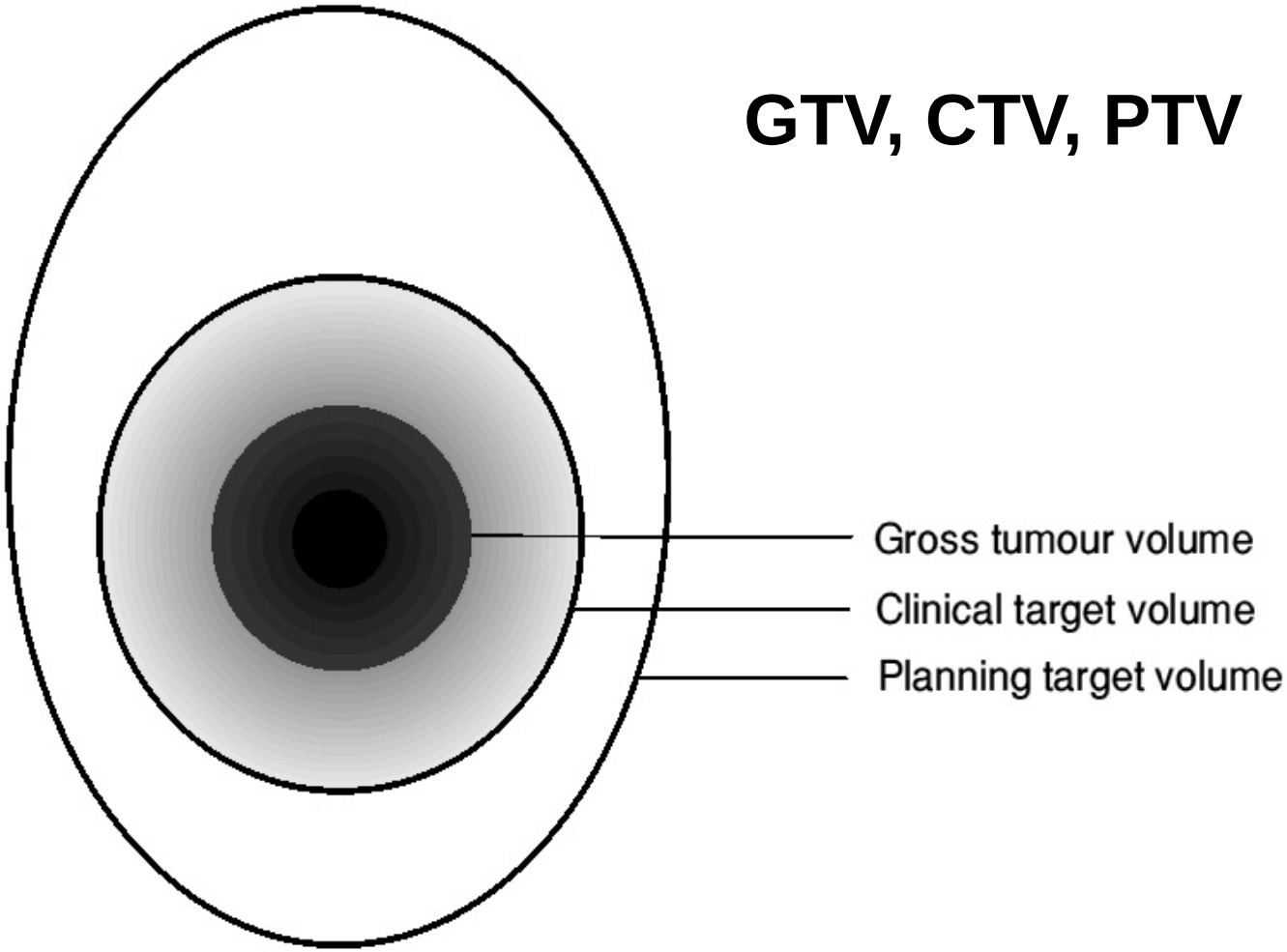


MR 2 weeks post-op.

Target volumes

ICRU 50 target volumes

The PTV can be eccentric



Chemotherapy in childhood HGG

Rationale

⇨ **Rationale for chx. before RT**
Open blood brain barrier (surgery)
lesser toxicity of agents, greater selection of protocols, reduction of tumour burden

⇨ **Rationale for chx. during RT**
Radiosensitization

⇨ **Rationale for chx. after RT**
Elimination of persistent tumour cells
Maintenance approach to prevent early relapse

High grade glioma

Phase III studies

Study	Pat.	survival	Signif.
CCG (1989) (WHO III+IV)	**58**	**EFS (5 years)**	**0.026**
RT		**18%**	
RT + (CCNU,VCR,Pred.)		**46%**	
CCG (1995) (WHO III+IV)		**PFS (5 years)**	
RT+ (CCNU,VCR,Pred.)	**85**	**33%**	**n.s.**
RT + „8 in 1“	**87**	**36%**	
HIT – GBM A (2001) (Gr. IV)		**med. survival**	
RT+ Troph/VP16	**22**	**12 mon**	
		(22% 4 y. EFS)	**n.s.**
RT / control (no chx.)	**13**	**12 mon.**	
		(4% 4 y. EFS)	

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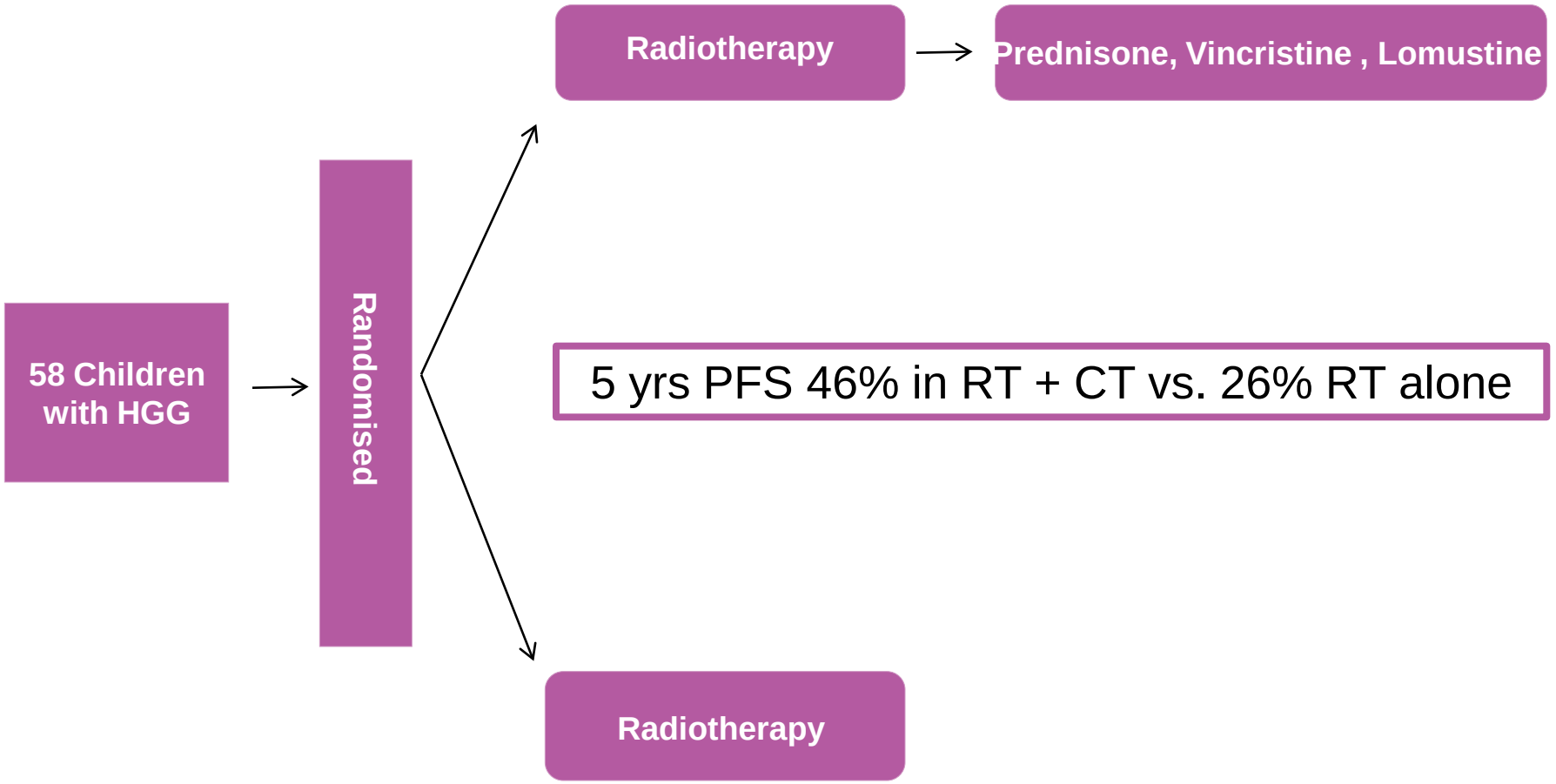
High grade glioma

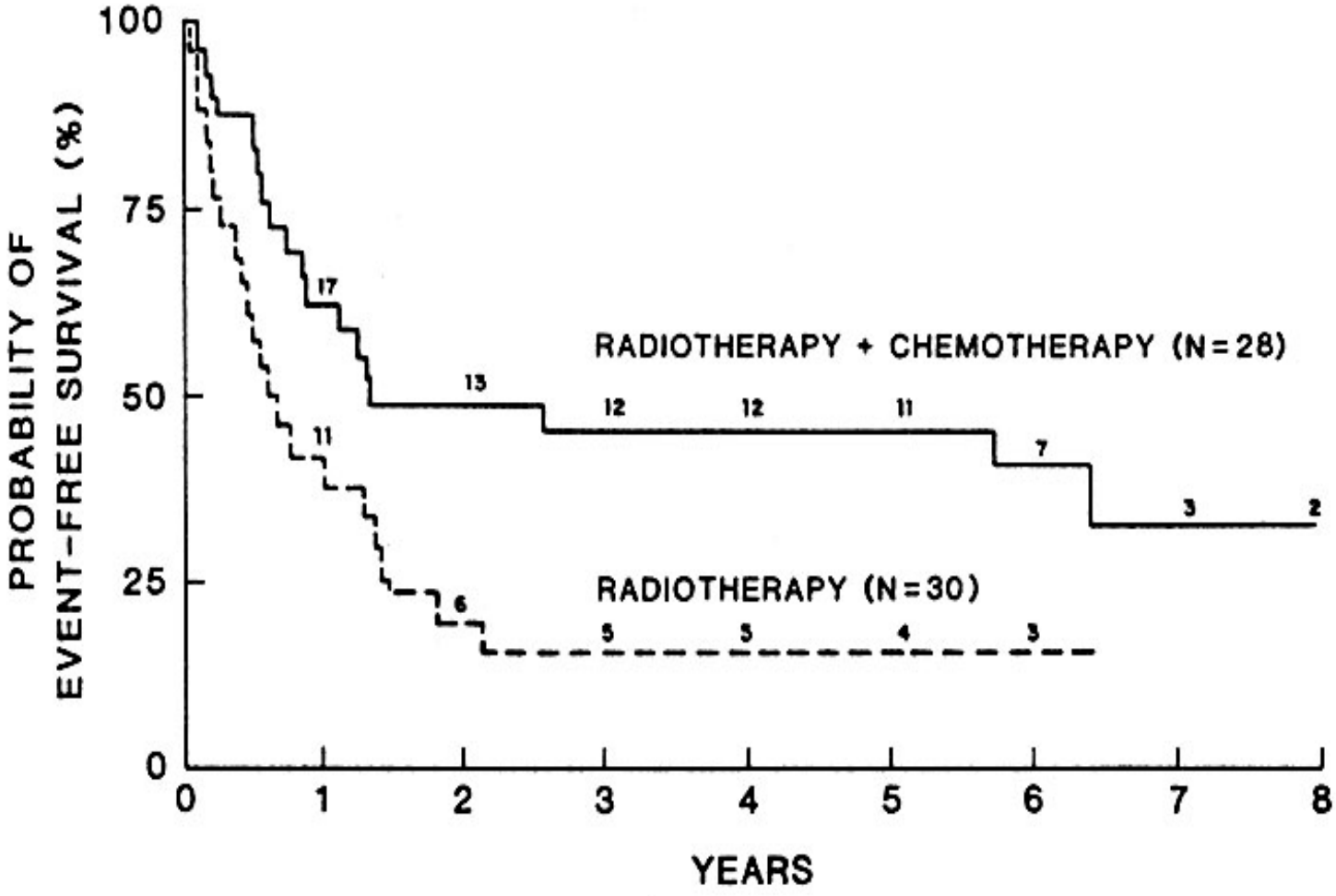
CCG 943 clinical trial



Sposto R et al. J Neurooncol 1989

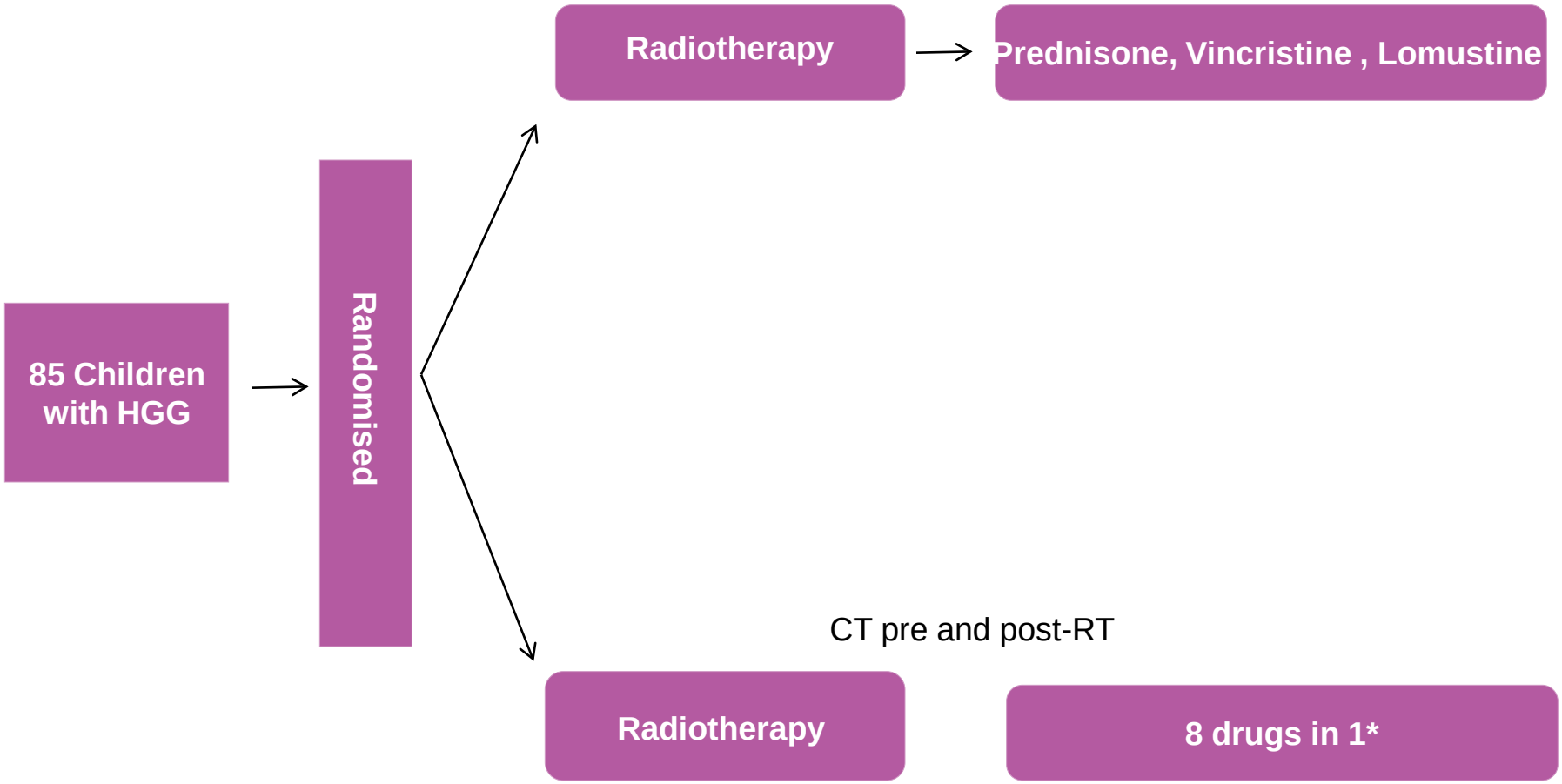
High grade glioma

Phase III study CCG943
RT + CCNU, Vincristine, Prednisone versus RT alone



High grade glioma

CCG 945 clinical trial



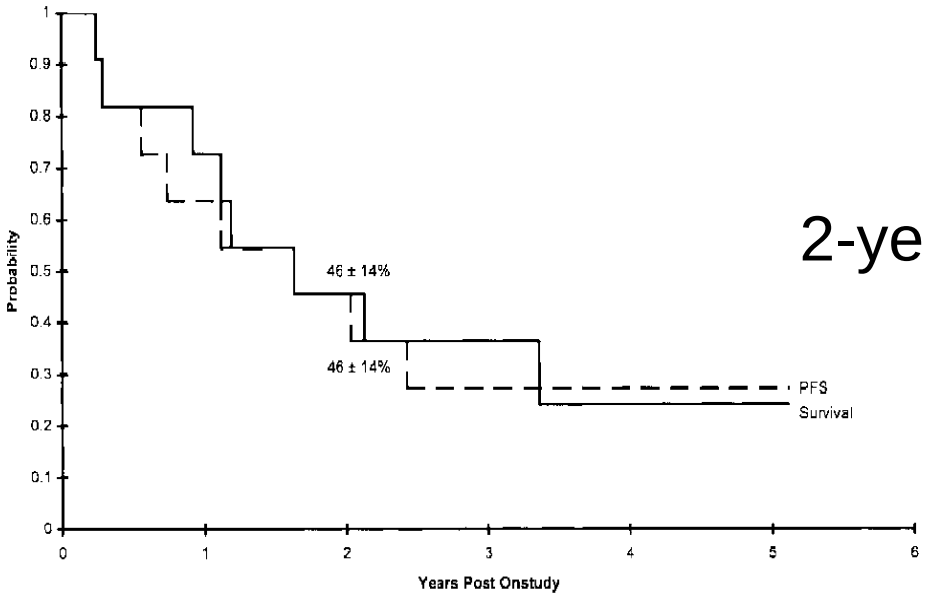
*vincristine, CCNU, procarbazine, hydroxyurea, cisplatin, mannitol, cytarabine, dacarbazine, methylprednisolone

Finlay JL et al. JCO 1995

Chemotherapy and autologous stem cell rescue

***Focal RT** daily — Total dose 54 Gy

11 Children with HGG → **Thiotepa, BCNU, and etoposide** → **ASCR** → **Focal RT***



2-year PFS rate of 46%

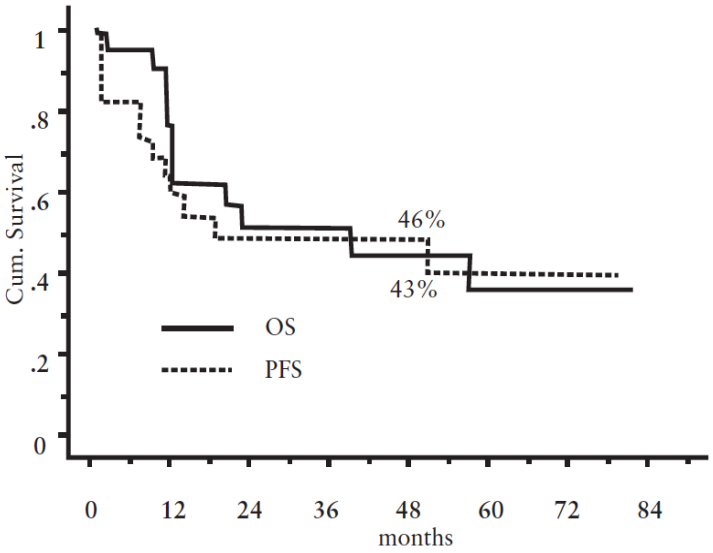
This study was closed early after 5 of the 11 treated. Patients developed significant pulmonary complications

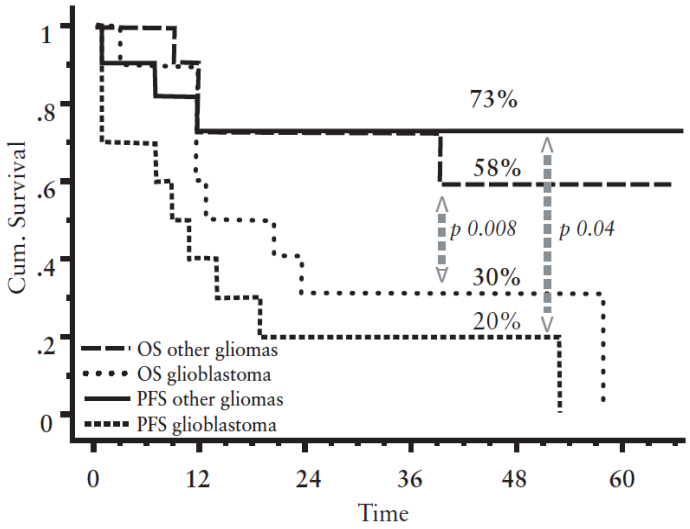
Grovas AC et al. Med Pediatr Oncol 1999

Chemotherapy and autologous stem cell rescue

***Focal RT** daily — Total dose 50-60 Gy

21 Children with HGG → **Cisplatin, etoposide, vincristine ,cyclophosphamide high-dose methotrexate, high-dose thiotepa** → **ASCR** → **Focal RT***





Chemotherapy and autologous stem cell rescue

The most appropriate candidates for ASCR are those with complete or near-complete resection before myeloablative therapy

The use of high-dose chemotherapy with ASCR may contribute to long-term disease control

But…

- At the expense of significant morbidity and mortality as a consequence of the regimens themselves.
- The associated side effects and resultant poor quality of life have led many investigators to question the benefit of high-dose chemotherapy with ASCR despite the potential for better disease control.

Infant HGG (< 3 years)
can be spared from radiation therapy with a good outcome

In children < 3 years:

French study BB-SFOP
(Dufour *et al.*, Eur J Oncol 2006)

Single arm phase II study of **radiation-sparing approach** in young children with newly diagnosed HGG

neurosurgery + carboplatin/procarbazine, cisplatin/etoposide and vincristine/ cyclophosphamide over a 16-month period

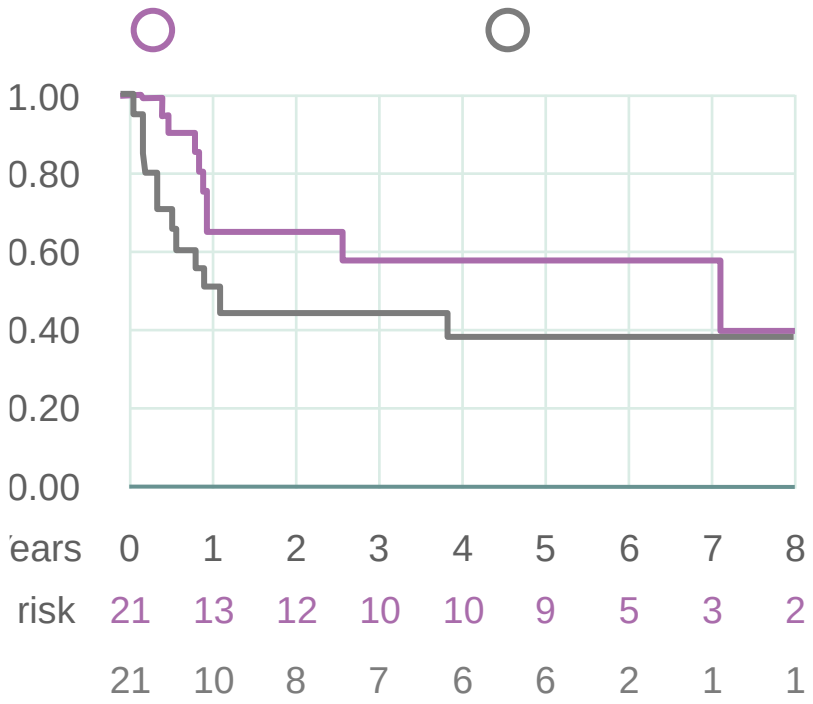
XRT only in case of recurrence or progression

Medium age = 23 months

5-year OS = 59%

5-year PFS = 35%

Median f/u = 5.2 years



Last f/u: 12/12 children alive (10 without XRT)

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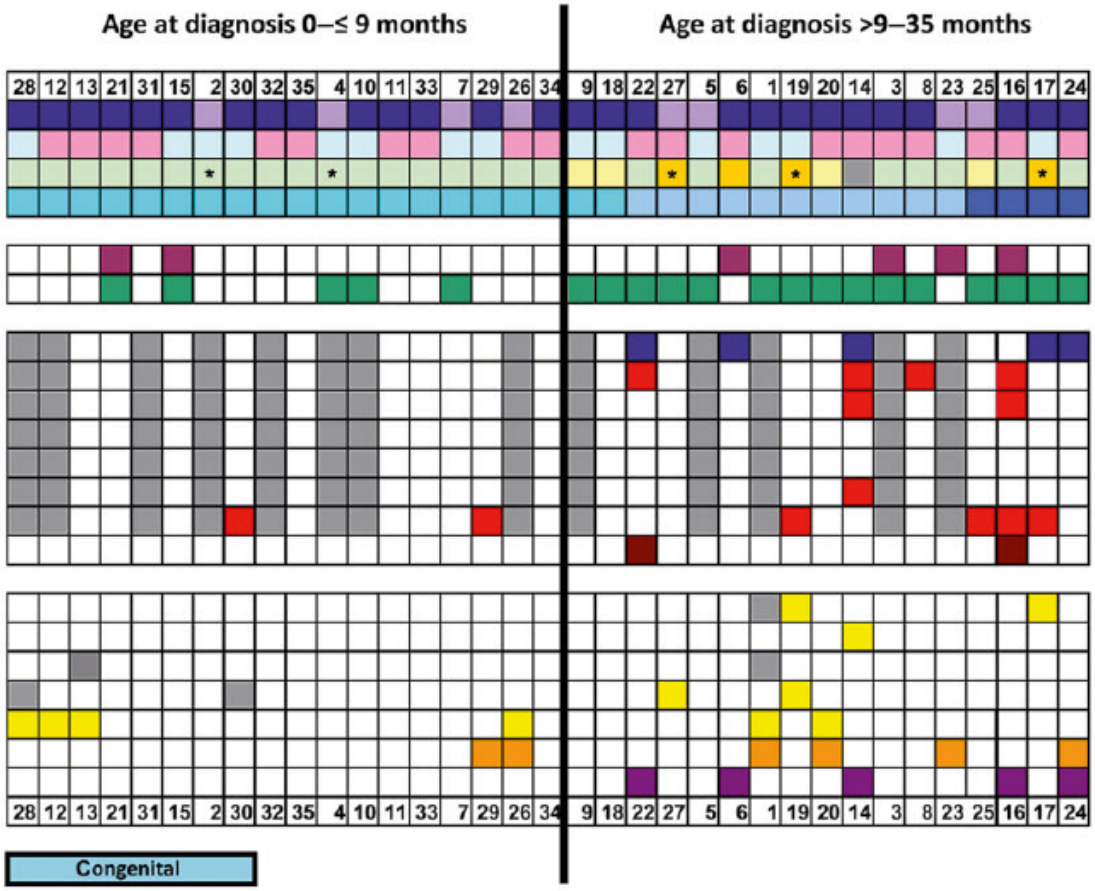
Brain Pathology ISSN 1015-6305

RESEARCH ARTICLE

Genetic Analysis of Diffuse High-Grade Astrocytomas in Infancy Defines a Novel Molecular Entity

Gerrit H. Gielen[1*]; Marco Gessi[1*]; Francesca R. Buttarelli[2]; Caterina Baldi[2]; Jennifer Hammes[1]; Anja zur Muehlen[1]; Evelyn Doerner[1]; Dorota Denkhaus[1]; Monika Warmuth-Metz[3]; Felice Giangaspero[4,5]; Libero Lauriola[6]; André O. von Bueren[7]; Christof M. Kramm[7†]; Andreas Waha[1†]; Torsten Pietsch[1†]



WHO grade	AA°III: 8; GBM°IV: 27	
Gender	m: 15; f: 20	
Localization		
Age at diagnosis		
p53 accumulation	6/35; 17.1%	IHC
Olig-2 expression	20/35; 57.1%	IHC
1q gain	5/22; 22.7%	Molecular inversion probe analysis
6q loss	4/22; 18.2%	Molecular inversion probe analysis
10q loss	2/22; 9.1%	Molecular inversion probe analysis
PDGFRα gain /ampl.	0/22; 0%	Molecular inversion probe analysis
EGFR gain / ampl.	0/22; 0%	Molecular inversion probe analysis
PTEN loss	1/22; 4.5%	Molecular inversion probe analysis
SNORD loss	6/22; 27.3%	Molecular inversion probe analysis
CDKN2A loss	2/35; 5.7%	MLPA
H3F3A K27M mut	2/34; 5.9%	Pyrosequencing
TERT mut	1/35; 2.9%	Pyrosequencing
FGFR1 mut	0/33; 0%	Pyrosequencing
BRAF V600E mut	2/33; 6.1%	MLPA
ATRX loss of expression	6/35; 17.1%	IHC
Alternate telomere lengthening	6/35; 17.1%	FISH
"non-infant like genotype"		

WHO grade III
WHO grade IV

Male
Female

Gain
Heterozygous loss
Homozygous deletion

Supratentorial
Posterior fossa
Spinal
Not analyzed

0-12 months
13-24 months
25-36 months

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What is the standard Rx in pHGG?

? Influence from Adult GBM studies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D.,Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

Adult Glioblastoma- 1st Line therapy

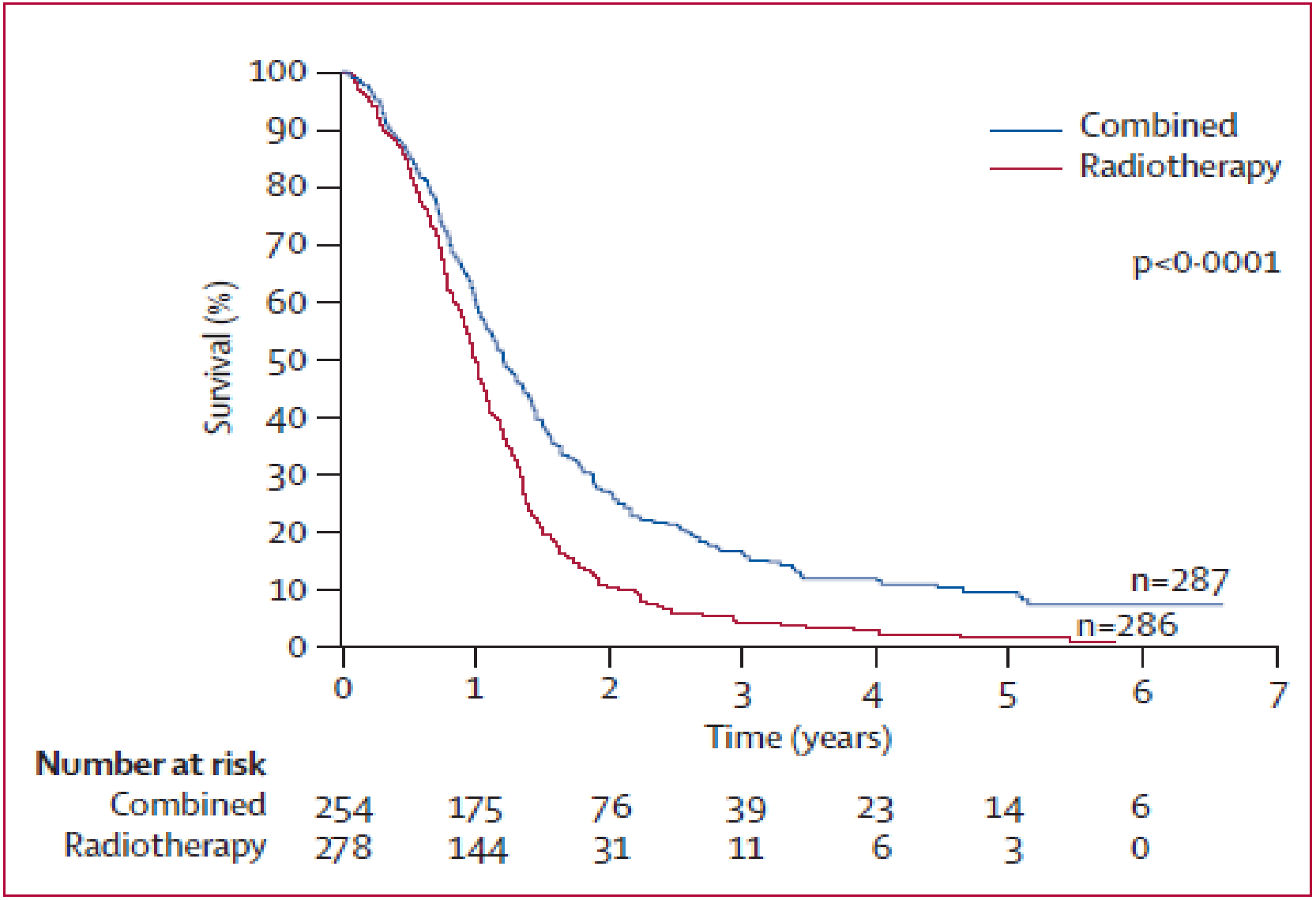


Figure 2: Kaplan-Meier estimates of overall survival by treatment group

Neuro-Oncology 13(3):317–323, 2011.
doi:10.1093/neuonc/noq191

NEURO-ONCOLOGY

Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group

Kenneth J. Cohen, Ian F. Pollack, Tianni Zhou, Allen Buxton, Emiko J. Holmes, Peter C. Burger, Daniel J. Brat, Marc K. Rosenblum, Ronald L. Hamilton, Robert S. Lavey, and Richard L. Heideman

EFS and OS rates of 90 HGG patients

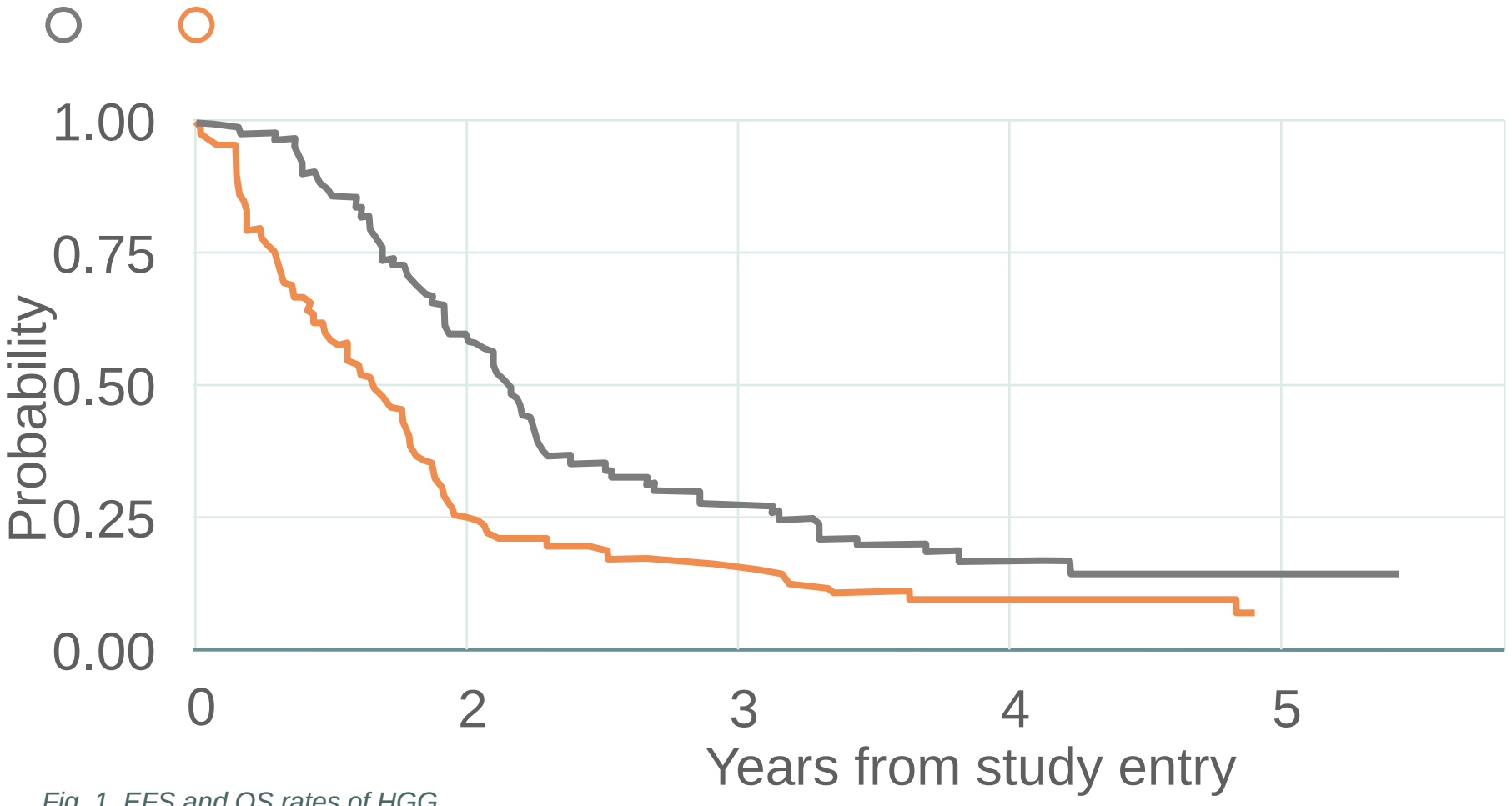
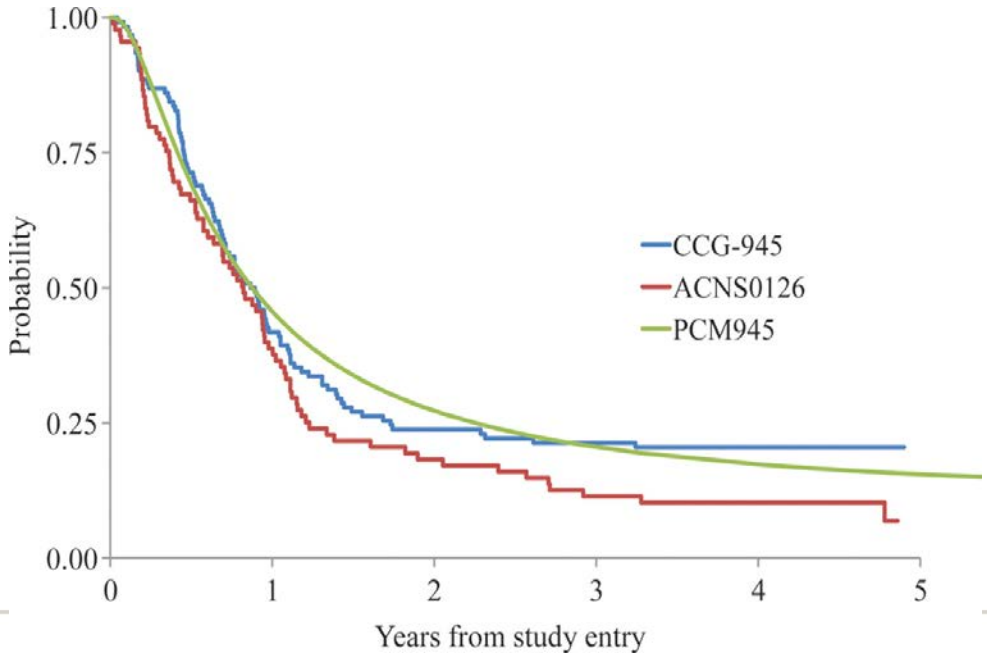


Fig. 1. EFS and OS rates of HGG patients enrolled in ACNS0126

High grade glioma

CCG ACNS0126 - Phase II trial

90 Children with HGG → **Radiotherapy + TMZ** → **TMZ (200 mg/m2)**



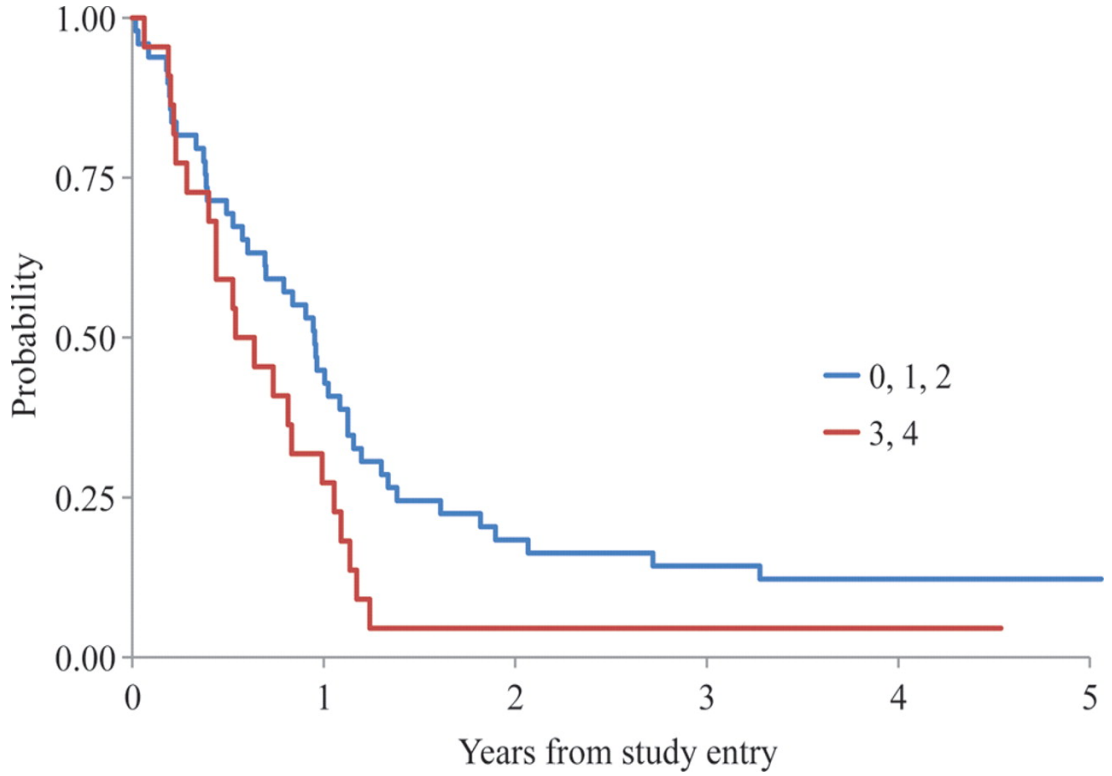
Focal RT daily — Total dose 54 Gy

TMZ 90 mg/m^2 for 6 weeks,
then 200 mg/m^2 5 day/28 day for 10 cycles

Cohen K et al. Neurooncol 2011

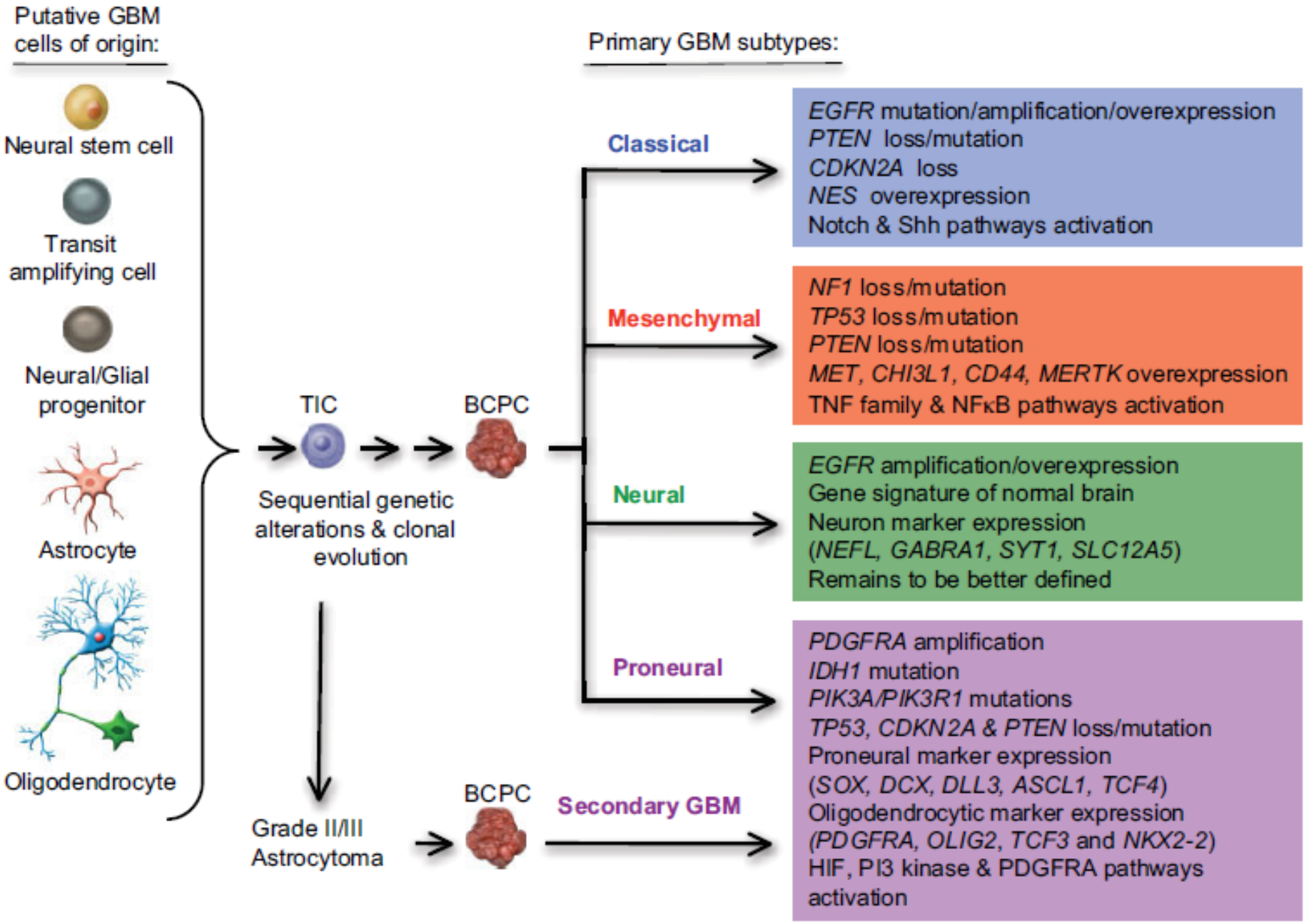
High grade glioma

At 2 yrs EFS 17% neg. MGMT Vs. 5% pos. MGMT (p = 0.045).



MGMT overexpression was adversely associated with survival

PAEDIATRIC HIGH GRADE GLIOMA:
ARE THEY THE SAME AS HGG IN ADULTS?



CA CANCER J CLIN 2010;60:166–193

Published Ahead of Print on May 17, 2010 as 10.1200/JCO.2009.26.7252
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.26.7252

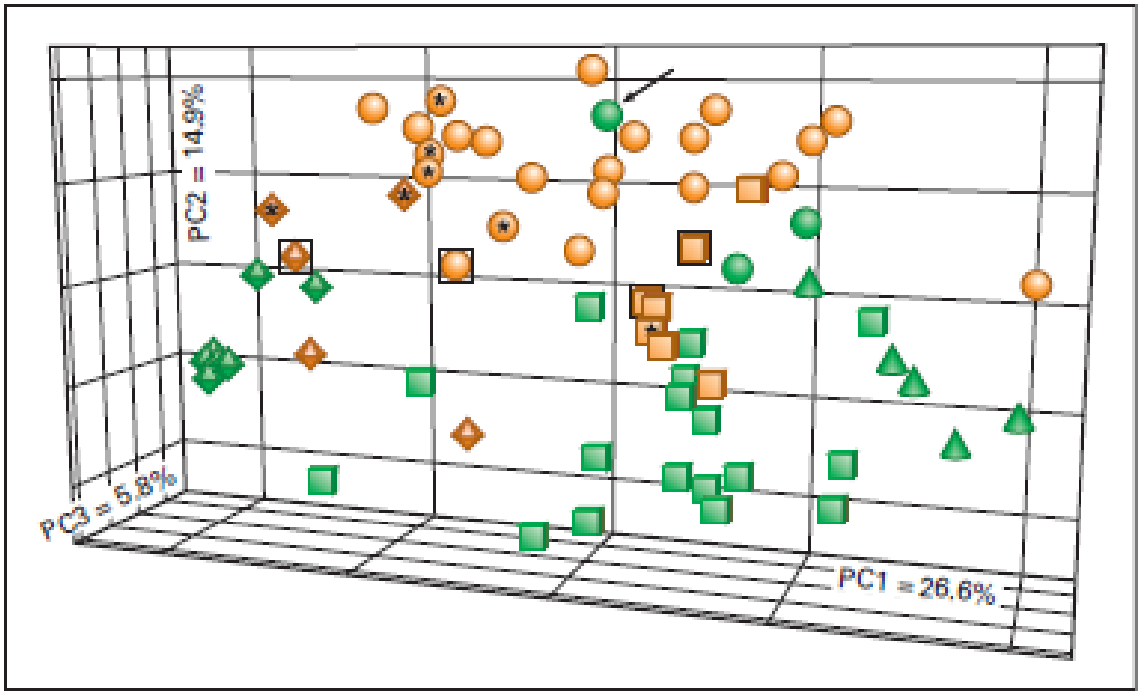
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Integrated Molecular Genetic Profiling of Pediatric High-Grade Gliomas Reveals Key Differences With the Adult Disease

Barbara S. Paugh, Chunxu Qu, Chris Jones, Zhaoli Liu, Martyna Adamowicz-Brice, Junyuan Zhang, Dorine A. Bax, Beth Coyle, Jennifer Barrow, Darren Hargrave, James Lowe, Amar Gajjar, Wei Zhao, Alberto Broniscer, David W. Ellison, Richard G. Grundy, and Suzanne J. Baker

From the St Jude Children's Research Hospital, Memphis, TN; Institute for Cancer Research; Royal Marsden National Health Service Foundation Trust,



ESTRO School

Paediatric and adult malignant glioma: close relatives or distant cousins?

Chris Jones, Lara Perryman and Darren Hargrave *Nat. Rev. Clin. Oncol.* 9, 400–413 (2012);

Table 2 | Location-specific and age-specific genetic differences in malignant glioma

Genetic abnormality	DIPG*	HGG‡				
		Infant (<3 years)	Child (3–14 years)	Adolescent (14–21 years)	Young adult (21–44 years)	Older adult (>45 years)
Transformation	NR	–	–	+	+++	+
Number alterations	++	–	+	+	++	+++
Gain of 1q	++	++	++	++	+	–
Loss of 16q	+	++	++	++	–	–
Stable genomes	–	++	++	++	–	–
Gain of 7	+	–	–	–	++	+++
Loss of 10q	++	+	+	+	++	+++
EGFR amplification	+	–	+	+	++	+++
PDGFRA amplification	+++	–	++	++	++	+
CDKN2A or *CDKN2B* deletion	–	+	++	++	+++	+++
p53 pathway alterations	+++	+++	++	++	++	++
PI3K pathway alterations	++	+	++	++	++	+++
Rb pathway alterations	++	+	+	+	++	+++
BRAF V600E	–	–	+	++	+	–
IDH1 R132X	–	–	–	+	+++	+
H3F3A K27M	+++	NR	+++	++	+	–
H3F3A G34R/V	–	NR	+	++	+	–
HIST1H3B K27M	++	NR	–	–	–	–

*Peak age 4–9 years. Grade not specified; ‡infratentorially located. ‡Supratentorially located. Abbreviations: –, low; +, moderate; ++, high; +++, very high; DIPG, diffuse intrinsic pontine glioma; HGG, high-grade glioma; NR, not reported.

STRO
hool

LETTER

2 | NATURE | VOL 000 | 00 MONTH 2012

doi:10.1038/nature10833

Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma

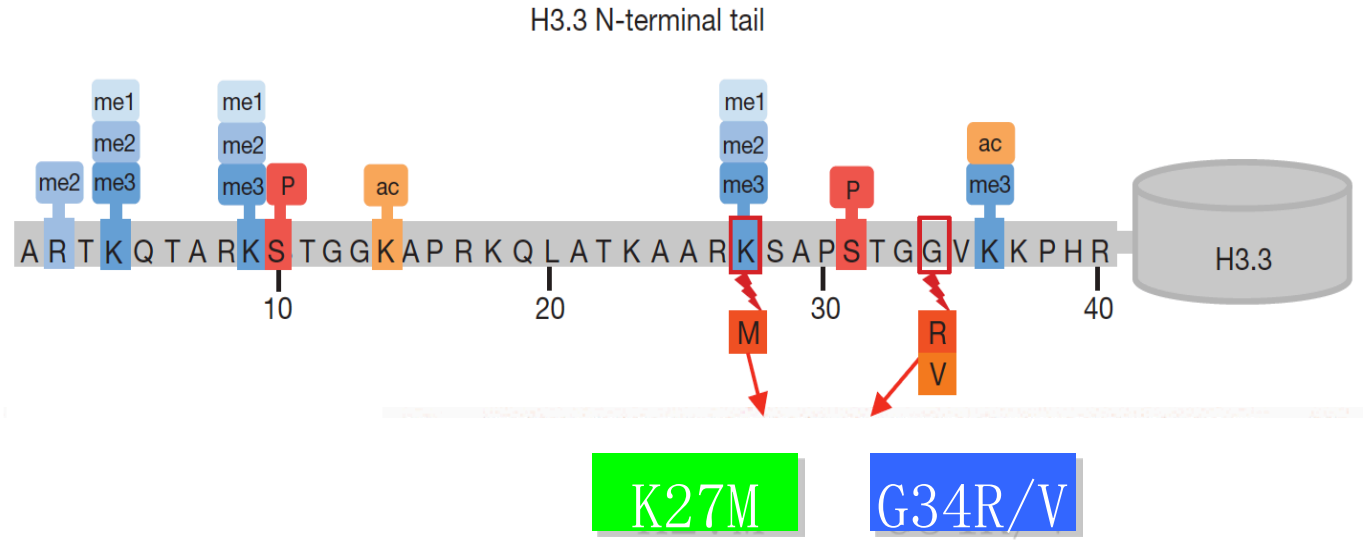
Jeremy Schwartzentruber[1]*, Andrey Korshunov[2]*, Xiao-Yang Liu[3]*, David T. W. Jones[4], Elke Pfaff[4], Karine Jacob[3],

Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas

Gang Wu[1,8], Alberto Broniscer[2,8], Troy A McEachron[3,8],

Received 21 December 2011; accepted 9 January 2012; published online 29 January 2012; doi: 10.1038/ng.1102

Identification of somatic *H3F3A* mutations



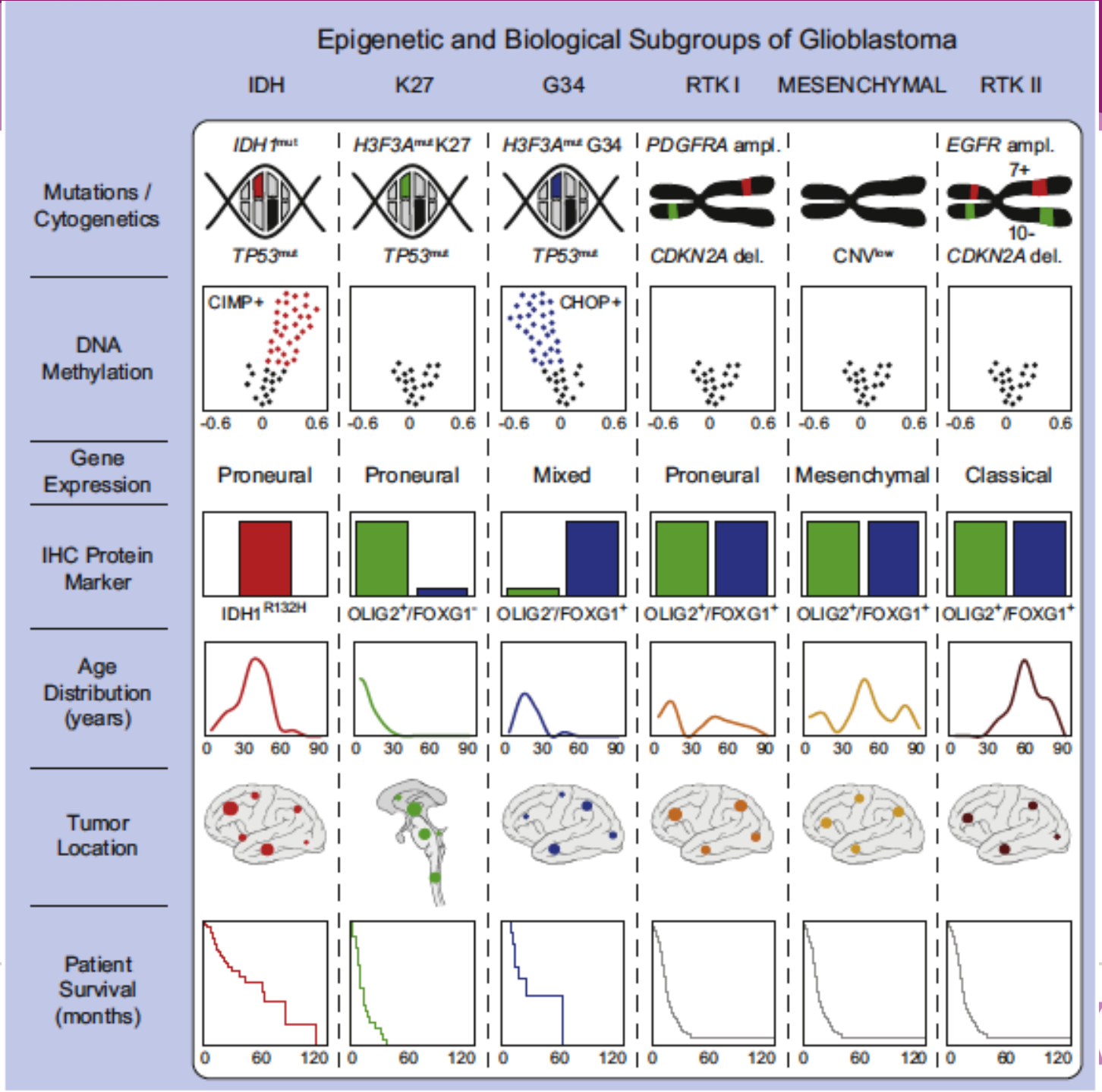
Novel, specific mutations at key histone H3.3 residues in paediatric GBM

ESTRO School

Cancer Cell
Article

Hotspot Mutations in *H3F3A* and *IDH1* Define Distinct Epigenetic and Biological Subgroups of Glioblastoma

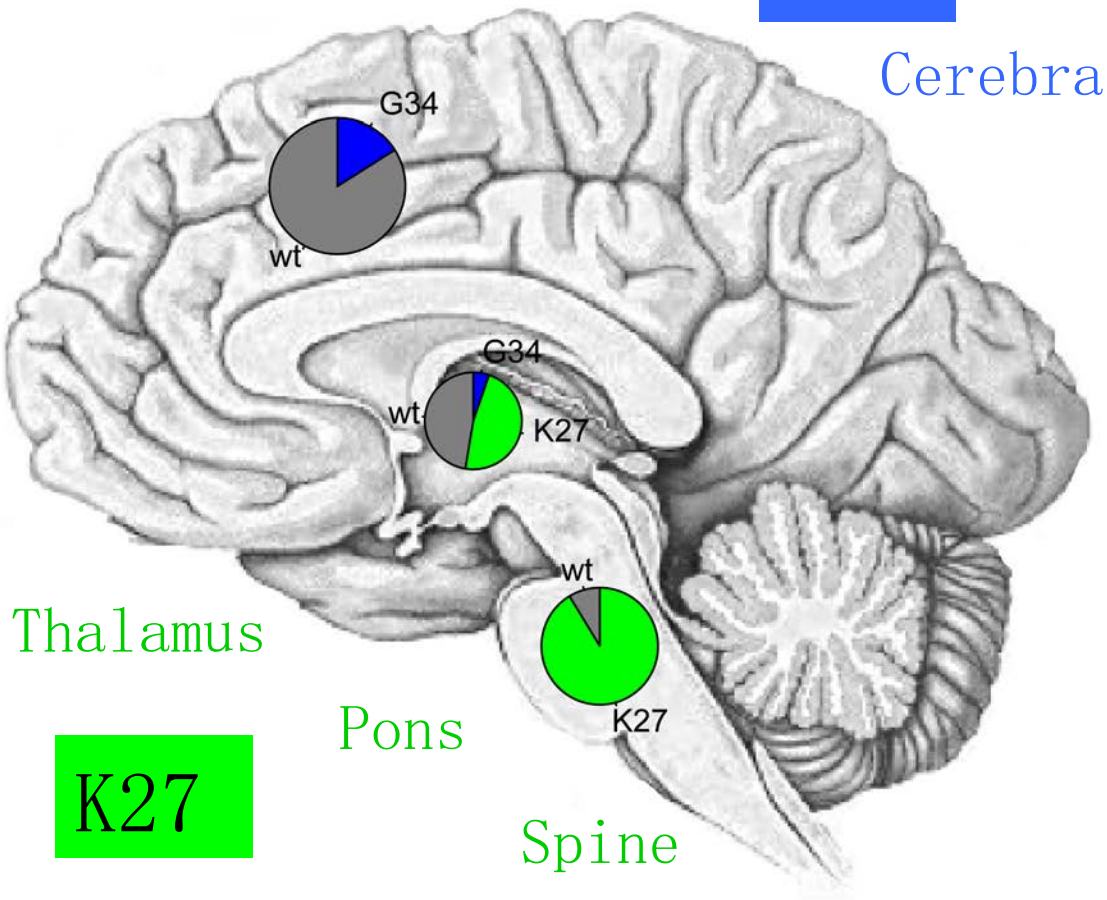
Dominik Sturm,[1,42] Hendrik Witt,[1,7,42] Volker Hovestadt,[2,42] Dong-Anh Khuong-Quang,[11,42] David T.W. Jones,[1] Carolin Konermann,[3] Elke Pfaff,[1] Martje Tönjes,[2] Martin Sill,[4] Sebastian Bender,[1] Marcel Kool,[1] Marc Zapatka,[2] Natalia Becker,[4] Manuela Zucknick,[4] Thomas Hielscher,[4] Xiao-Yang Liu,[11] Adam M. Fontebasso,[12] Marina Ryzhova,[13] Steffen Albrecht,[14] Karine Jacob,[11] Marietta Wolter,[15] Martin Ebinger,[16] Martin U. Schuhmann,[17] Timothy van Meter,[18] Michael C. Frühwald,[19] Holger Hauch,[20] Arnulf Pekrun,[21] Bernhard Radlwimmer,[2] Tim Niehues,[22] Gregor von Komorowski,[23] Matthias Dürken,[23] Andreas E. Kulozik,[7] Jenny Madden,[24] Andrew Donson,[24] Nicholas K. Foreman,[24] Rachid Drissi,[25] Maryam Fouladi,[25] Wolfram Scheurlen,[26] Andreas von Deimling,[5,9] Camelia Monoranu,[27] Wolfgang Roggendorf,[27] Christel Herold-Mende,[8] Andreas Unterberg,[8] Christof M. Kramm,[28] Jörg Felsberg,[15] Christian Hartmann,[29] Benedikt Wiestler,[10] Wolfgang Wick,[10] Till Milde,[6,7] Olaf Witt,[6,7] Anders M. Lindroth,[3] Jeremy Schwartzentruber,[30] Damien Faury,[11] Adam Fleming,[11] Magdalena Zakrzewska,[31] Pawel P. Liberski,[31] Krzysztof Zakrzewski,[32] Peter Hauser,[33] Miklos Garami,[33] Almos Klekner,[34] Laszlo Bognar,[34] Sorana Morrissy,[35] Florence Cavalli,[35] Michael D. Taylor,[35] Peter van Sluis,[36] Jan Koster,[36] Rogier Versteeg,[36] Richard Volckmann,[36] Tom Mikkelsen,[37] Kenneth Aldape,[38] Guido Reifenberger,[15] V. Peter Collins,[39] Jacek Majewski,[40] Andrey Korshunov,[5] Peter Lichter,[2] Christoph Plass,[3,41,*] Nada Jabado,[11,41,*] and Stefan M. Pfister[1,7,41,*]


Epigenetic and Biological Subgroups of Glioblastoma
IDH
K27
G34
RTK I
MESENCHYMAL
RTK II
Mutations / Cytogenetics
IDH1mut
H3F3Amut K27
H3F3Amut G34
PDGFRA ampl.
EGFR ampl.
7+
10-
TP53mut
TP53mut
TP53mut
CDKN2A del.
CNVlow
CDKN2A del.
DNA Methylation
CIMP+
CHOP+
-0.6 0 0.6
Gene Expression
Proneural
Proneural
Mixed
Proneural
Mesenchymal
Classical
IHC Protein Marker
IDH1R132H
OLIG2+/FOXG1-
OLIG2-/FOXG1+
OLIG2+/FOXG1+
OLIG2+/FOXG1+
OLIG2+/FOXG1+
Age Distribution (years)
0 30 60 90
Tumor Location
Patient Survival (months)
0 60 120

Tumour location & Shared Targets?

G34

Cerebral hemispheres



Thalamus

Pons

K27

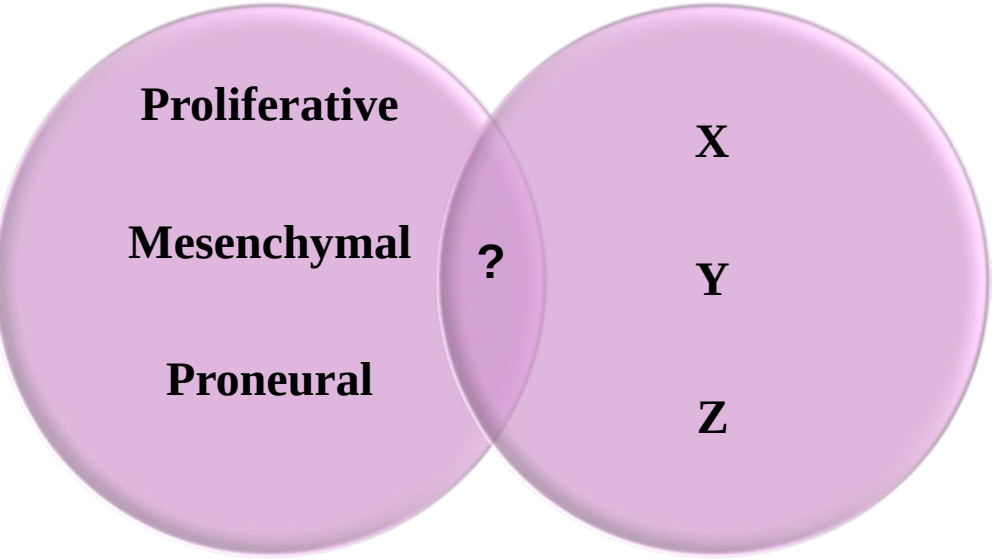
Spine

Histone H3.3 mutations produce anatomically distinct tumours

Paediatric and Adult HGG
Similarities and Differences

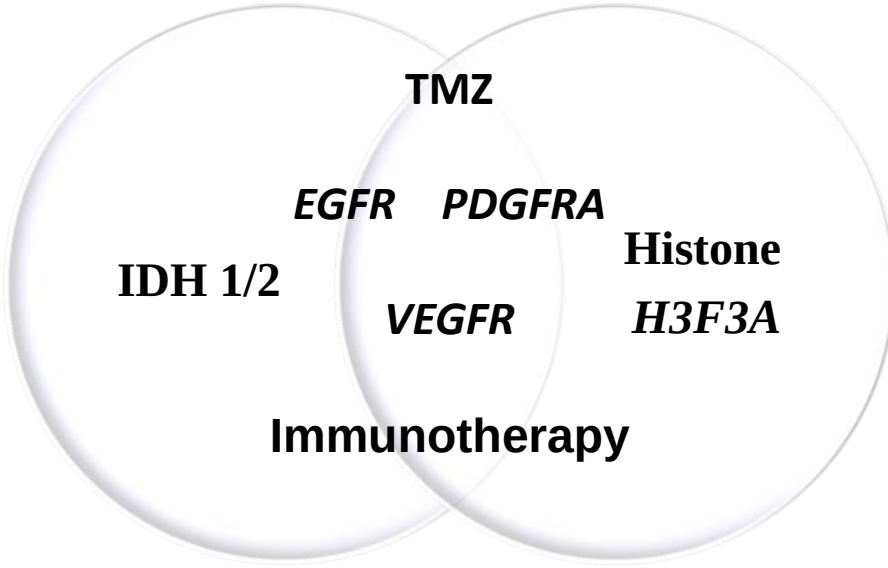
Distinct molecular categories

Adults | Paediatrics



Targets/Therapies

Adults | Paediatrics



SHARED TARGETS

Can extrapolate & even study together?

Define a common backbone!

At present for pHGG & aHGG

- Chemo-radiotherapy with temozolomide

DIPG- radiotherapy only

Common shared targets?

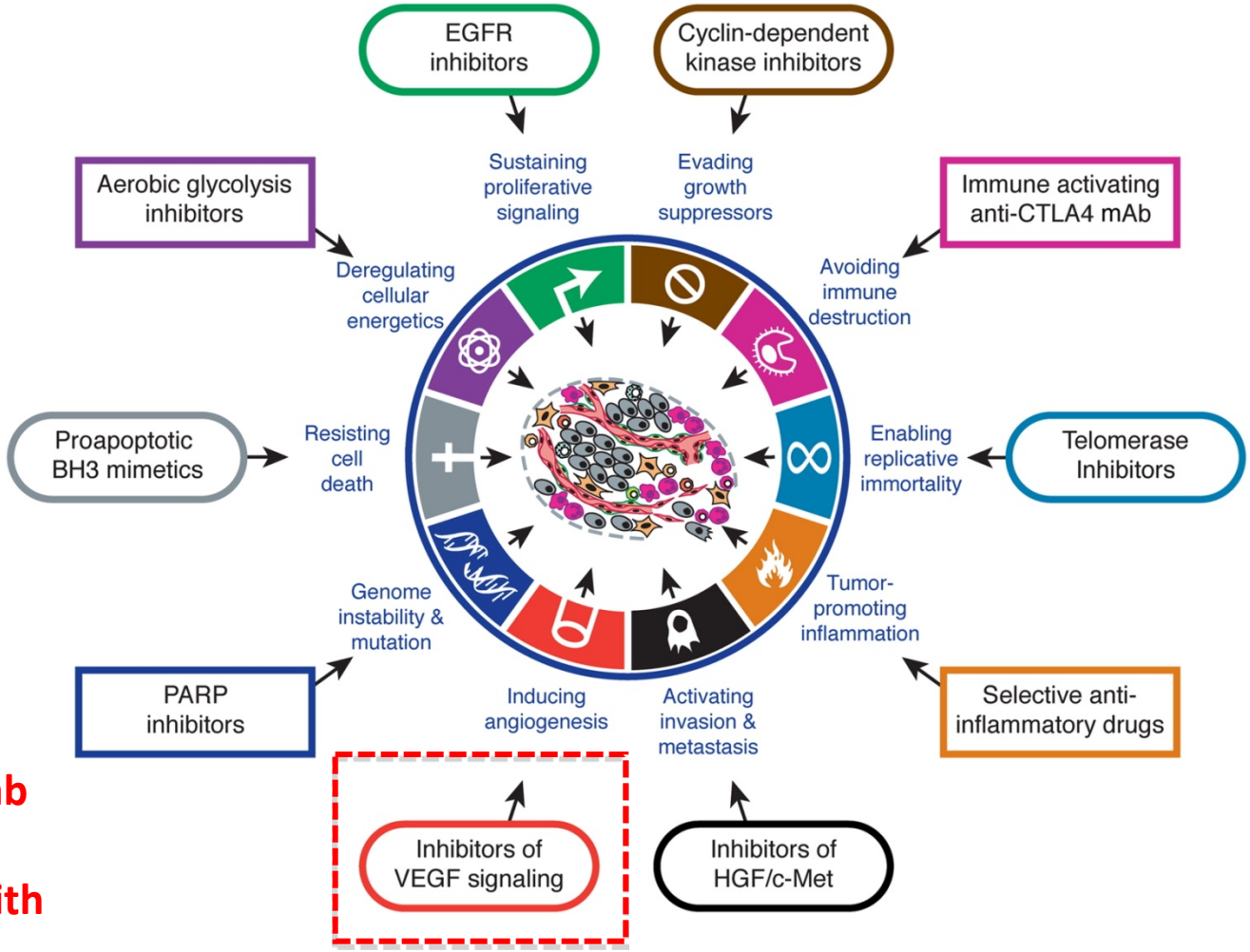
- Majority express target
- Histone *H3F3* as common target pHGG & DIPG?
- High target presence in both pHGG and aHGG?
  - E.g. ?VEGFR/ Integrins/ immunotherapy

Recent Trial in HGG

HGG Efficacy & Tolerability Research of Bevacizumab in Young children & adolescents

HERBY

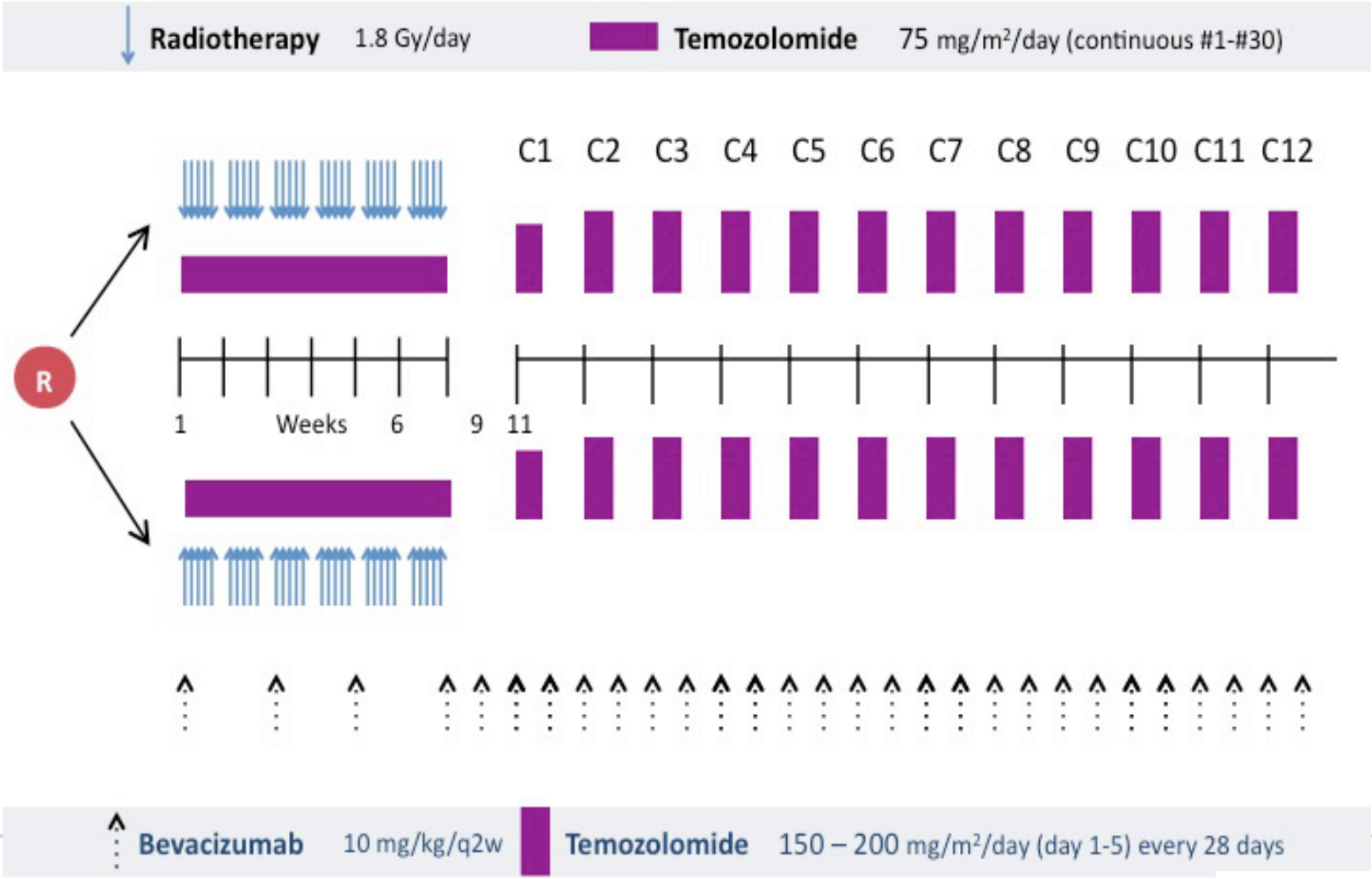
Anti angiogenesis in HGG



The anti-angiogenic properties of bevacizumab may have an important role to play in children with newly diagnosed HGG

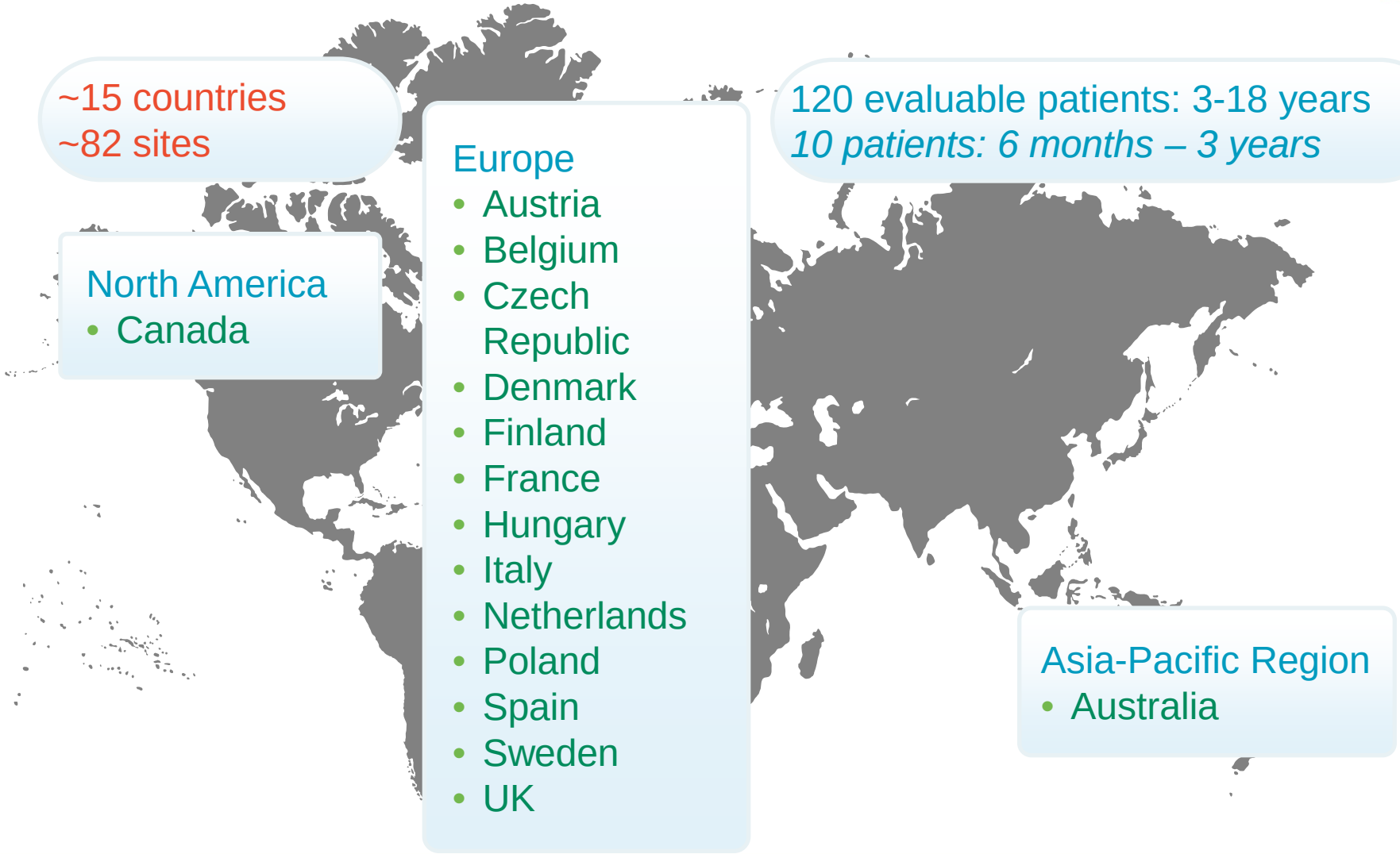
Adapted from Hanahan and Weinberg, *The Hallmarks of Cancer.* Cell (2011) 144, 5:646-674

HERBY Trial design



HERBY

Participating countries in this study



~15 countries
~82 sites

120 evaluable patients: 3-18 years
10 patients: 6 months – 3 years

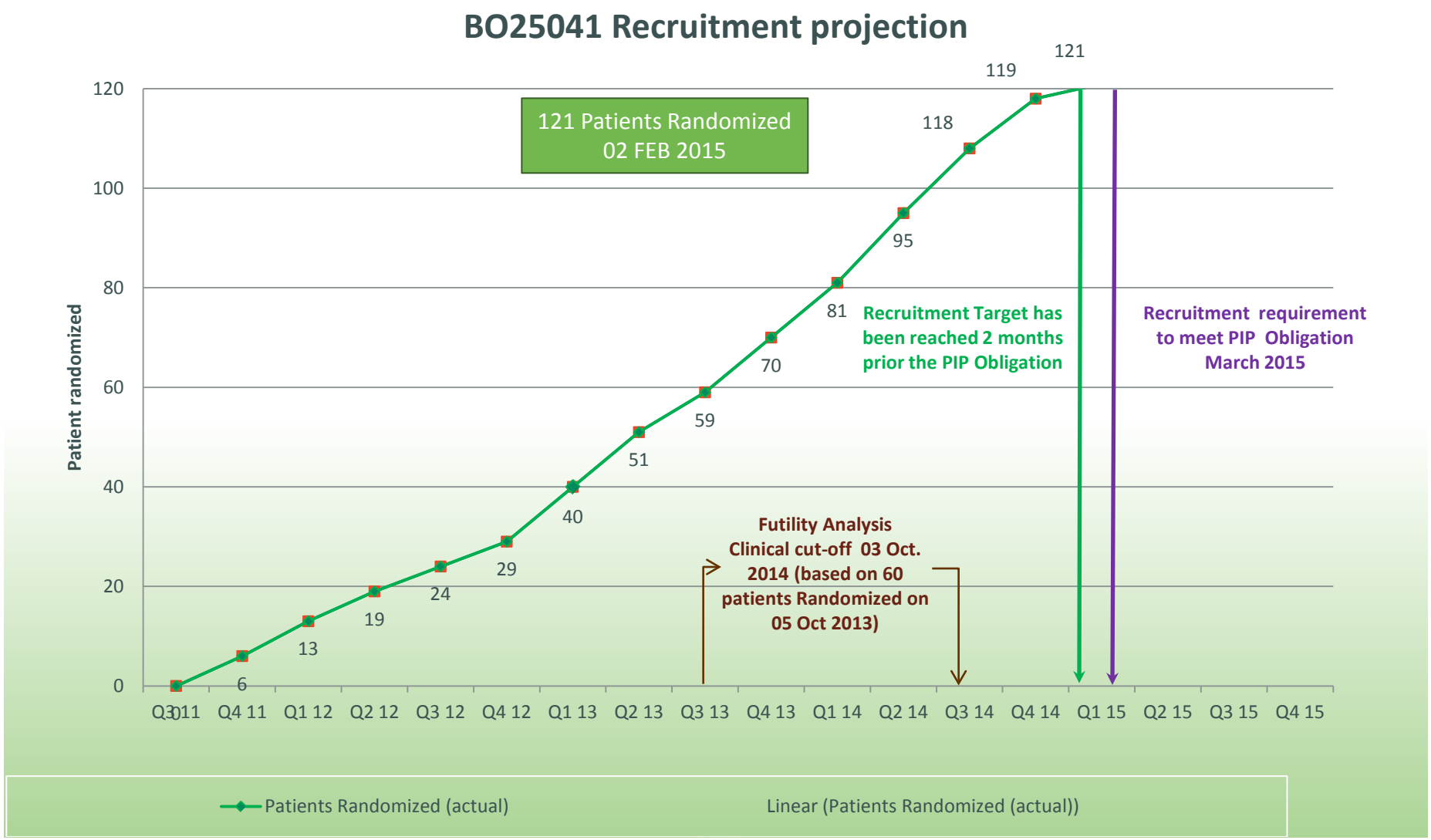
North America
- Canada

Europe
- Austria
- Belgium
- Czech Republic
- Denmark
- Finland
- France
- Hungary
- Italy
- Netherlands
- Poland
- Spain
- Sweden
- UK

Asia-Pacific Region
- Australia

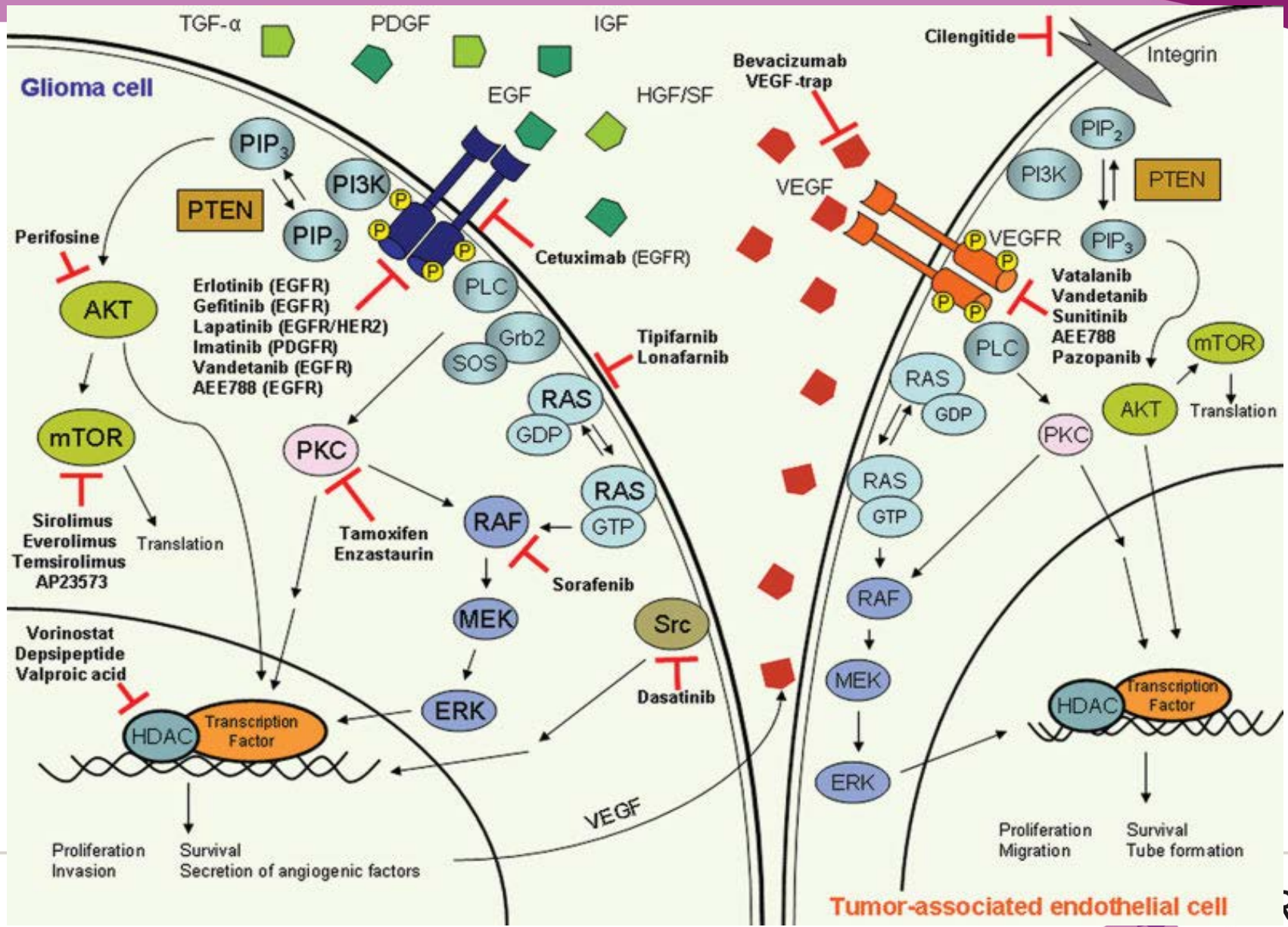
ESTRO School

Required Recruitment to fulfil PIP Requirement



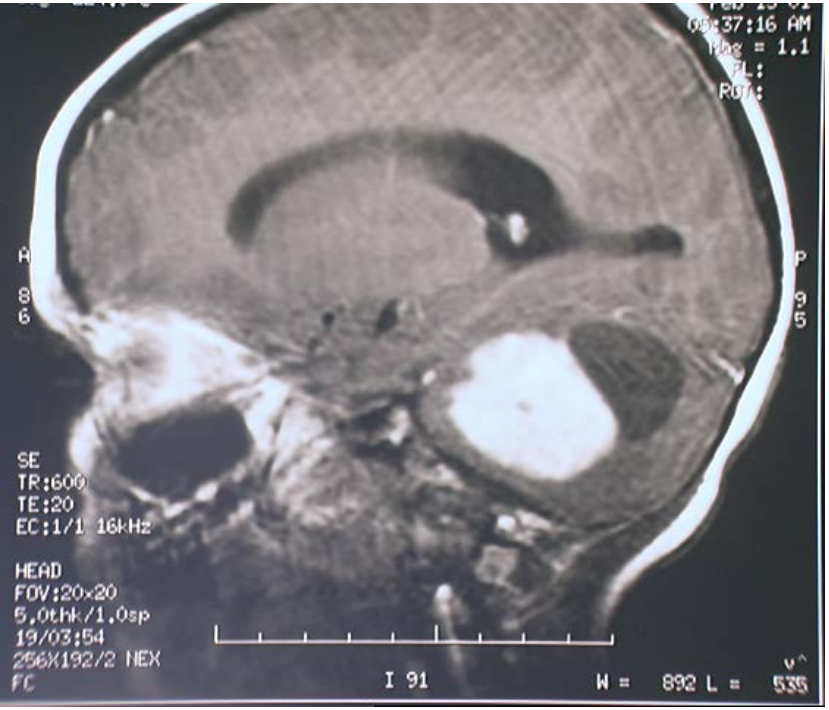
HERBY

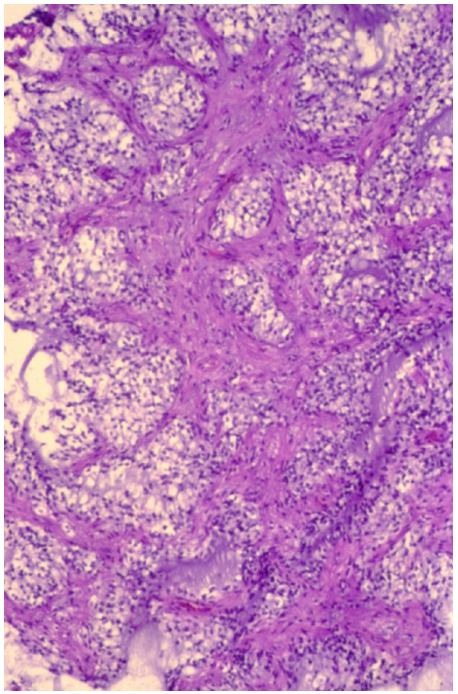
Novel approaches: Targeted agents and HGG

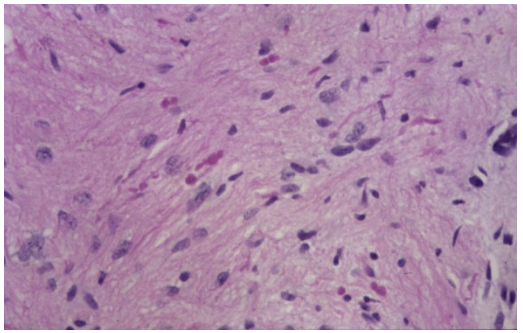


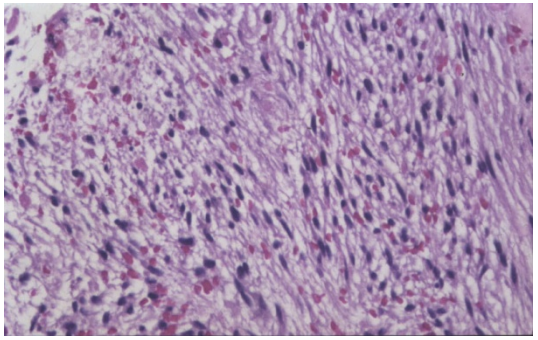
S.Sathornsumetee et al. Cancer 2007

BRAF in Paediatric CNS Tumours









NATURE | VOL 417 | 27 JUNE 2002 | www.nature.com/nature

Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14] Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]

Frequency of BRAF mutations

- ~8% of all Cancers
- 100% Hairy Cell Leukaemia
- 50% of Melanoma
- 45% Papillary Thyroid Cancer
- 30% Borderline Ovarian Ca.
- 10% Colorectal Cancer
- 2% NSCL Cancer

Most common mutation (BRAF V600E)—substitution of valine with glutamic acid at amino acid position 600 — locks BRAF into its active conformation, which has at >10 x higher activity than WT-type BRAF

Acta Neuropathol (2011) 121:397–405
DOI 10.1007/s00401-011-0802-6

ORIGINAL PAPER

Analysis of *BRAF* V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma and extra-cerebellar pilocytic astrocytoma

Genevieve Schindler · David Capper · Jochen Meyer · Wibke Janzarik · Heymut Omran · Christel Herold-Mende · Kirsten Schmieder · Pieter Wesseling · Christian Mawrin · Martin Hasselblatt · David N. Louis · Andrey Korshunov · Stefan Pfister · Christian Hartmann · Werner Paulus · Guido Reifenberger · Andreas von Deimling

OPEN ACCESS Freely available online

PLoS one

BRAF V600E Mutations Are Common in Pleomorphic Xanthoastrocytoma: Diagnostic and Therapeutic Implications

Dora Dias-Santagata[1], Quynh Lam[1], Kathy Vernovsky[2], Natalie Vena[3,4], Jochen K. Lennerz[1], Darrell R. Borger[2], Tracy T. Batchelor[2,5], Keith L. Ligon[3,4,6,7], A. John Iafrate[1], Azra H. Ligon[4,7], David N. Louis[1], Sandro Santagata[6,7]*

Cancer Res. 2010 January 15; 70(2): 512–519. doi:10.1158/0008-5472.CAN-09-1851.

Combined Oncogenic *BRAF* Mutation and *CDKN2A* Inactivation Is Characteristic of a Subset of Pediatric Malignant Astrocytomas

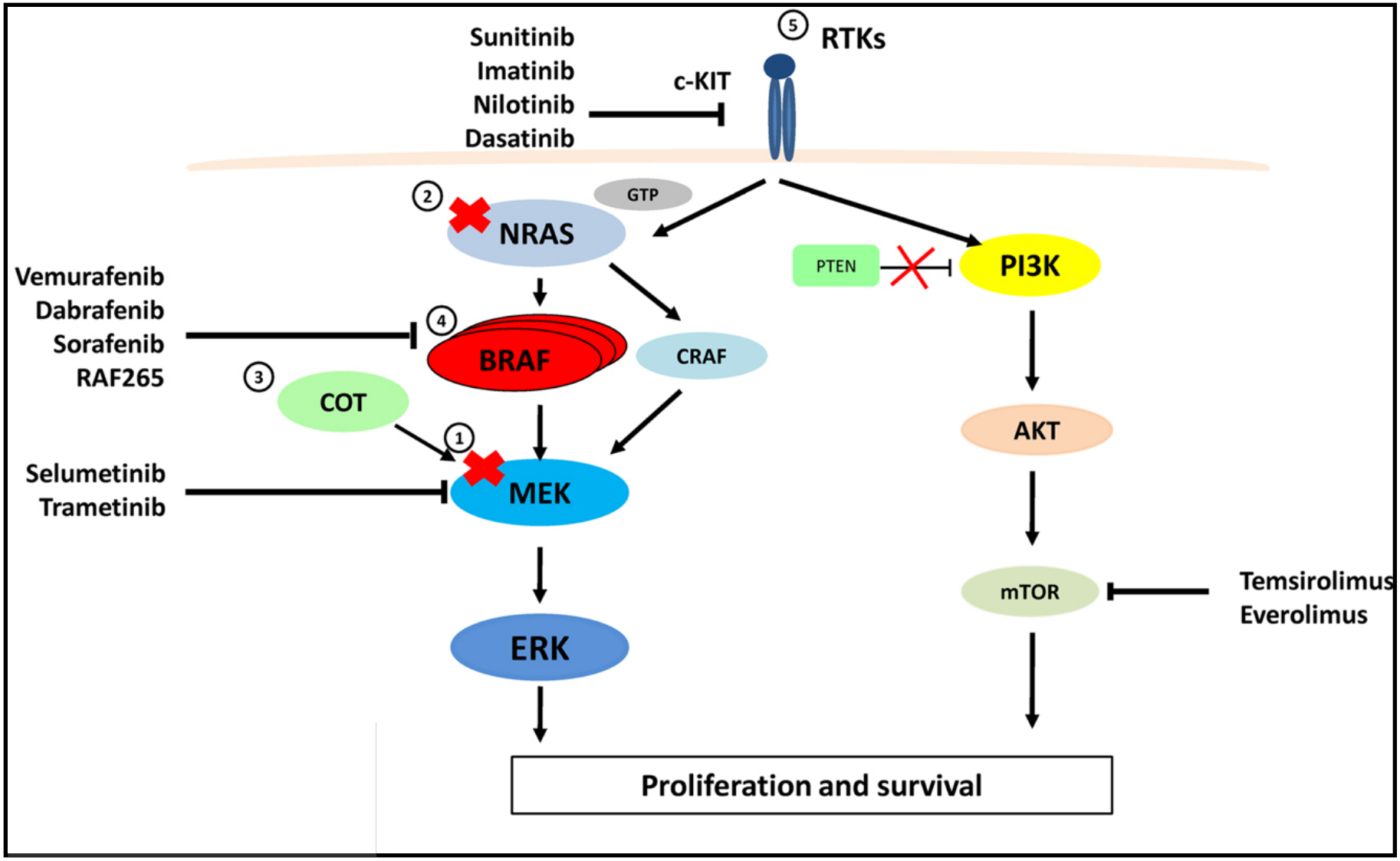
Joshua D. Schiffman[1], **J. Graeme Hodgson**[2,3], **Scott R. Vandenberg**[4], **Patrick Flaherty**[5], **Mei-Yin C. Polley**[2], **Mamie Yu**[2], **Paul G. Fisher**[6], **David H. Rowitch**[2,7], **James M. Ford**[8], **Mitchel S. Berger**[2], **Hanlee Ji**[8], **David H. Gutmann**[9], and **C. David James**[2]

ORIGINAL ARTICLE

Epithelioid GBMs Show a High Percentage of *BRAF* V600E Mutation

Bette Kay Kleinschmidt-DeMasters, MD,†‡ Dara L. Aisner, MD, PhD,* Diane K. Birks, MS,†§ and Nicholas K. Foreman, MD§*

MAPK Pathway Inhibitors



SELECTIVE BRAF INHIBITORS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 26, 2010 VOL. 363 NO. 9

Inhibition of Mutated, Activated BRAF in Metastatic Melanoma

Keith T. Flaherty, M.D., Igor Puzanov, M.D., Kevin B. Kim, M.D., Antoni Ribas, M.D., Grant A. McArthur, M.B., B.S., Ph.D., Jeffrey A. Sosman, M.D., Peter J. O'Dwyer, M.D., Richard J. Lee, M.D., Ph.D., Joseph F. Grippo, Ph.D., Keith Nolop, M.D., and Paul B. Chapman, M.D.

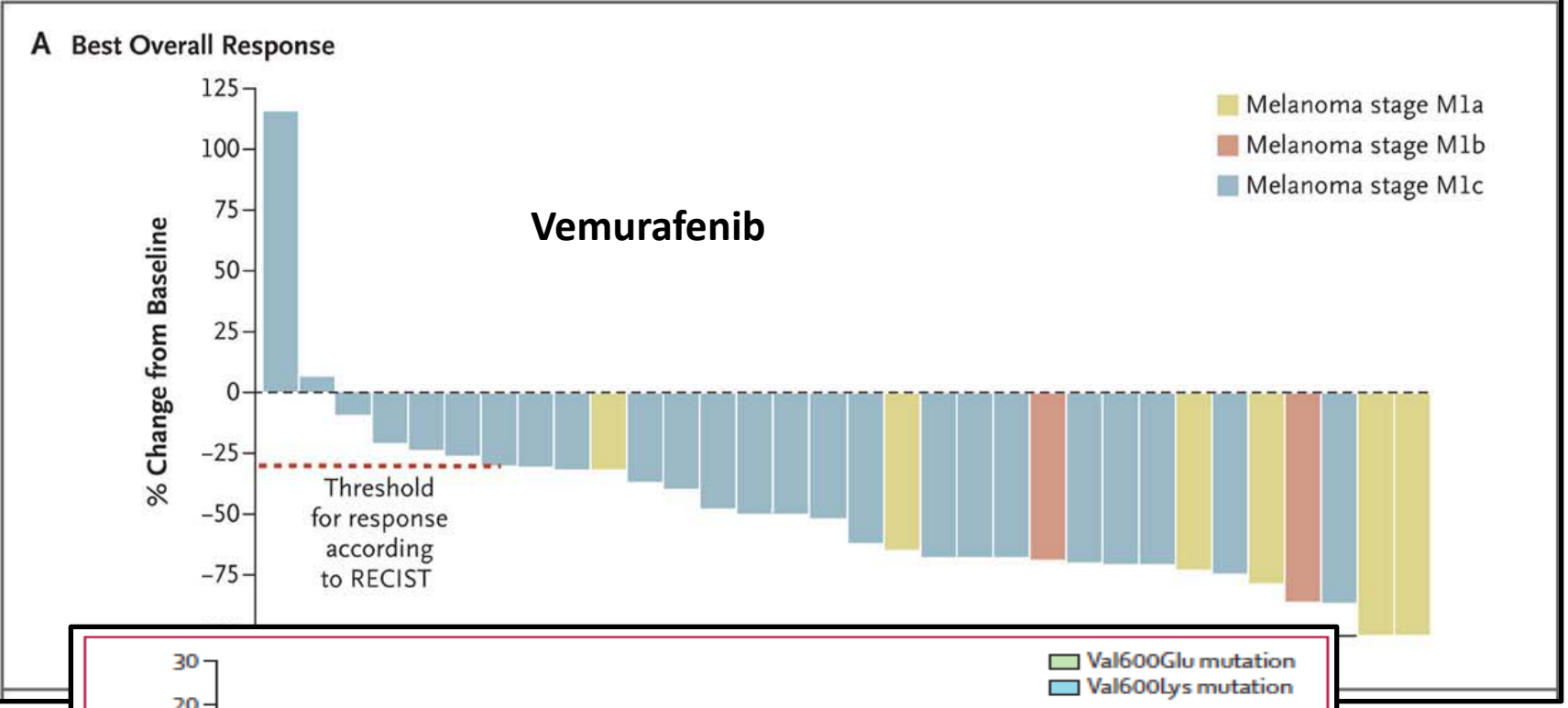
Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial

Gerald S Falchook, Georgina V Long*, Razelle Kurzrock, Kevin B Kim, Tobias H Arkenau, Michael P Brown, Omid Hamid, Jeffrey R Infante, Michael Millward, Anna C Pavlick, Steven J O'Day, Samuel C Blackman, C Martin Curtis, Peter Lebowitz, Bo Ma, Daniele Ouellet, Richard F Kefford*

Summary

Background Dabrafenib is an inhibitor of BRAF kinase that is selective for mutant BRAF. We aimed to assess its

Lancet 2012; 379: 1893–901



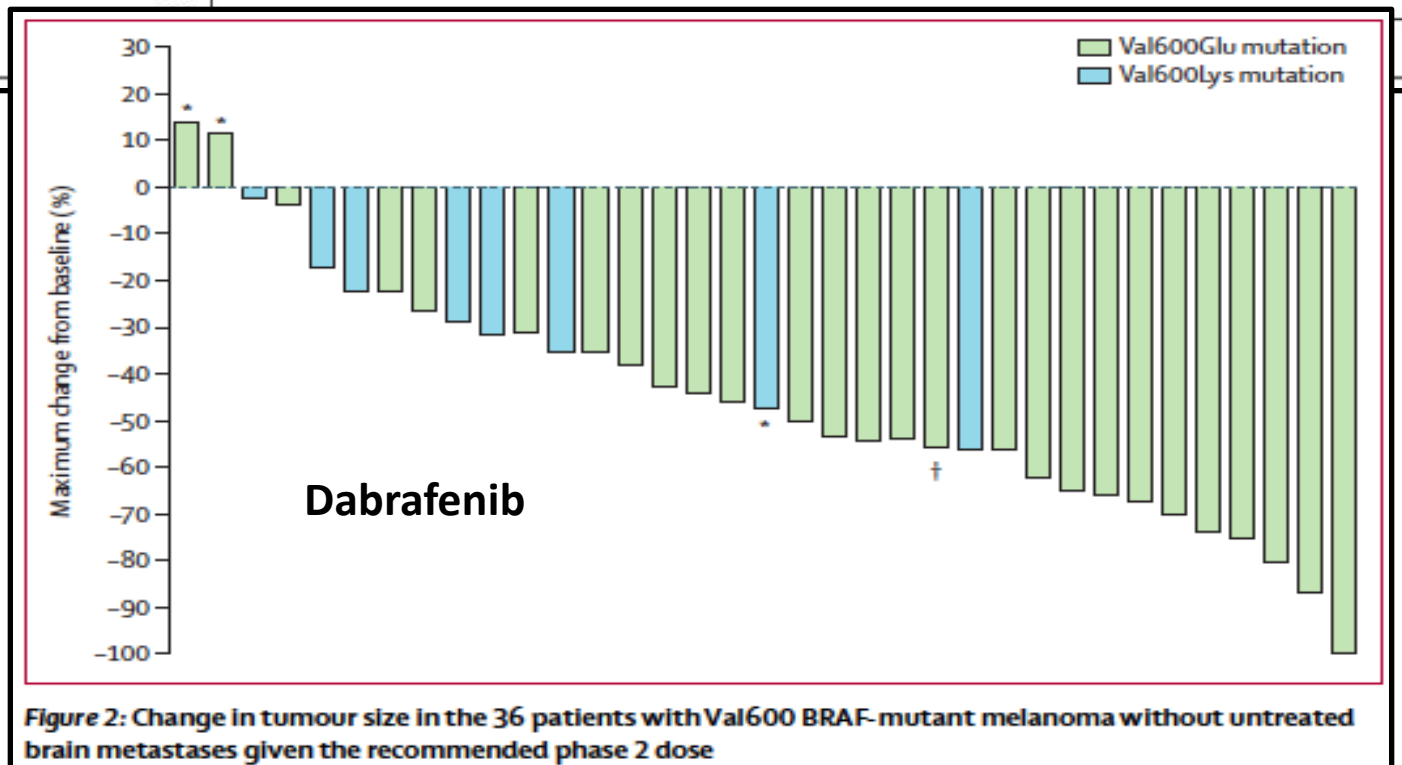


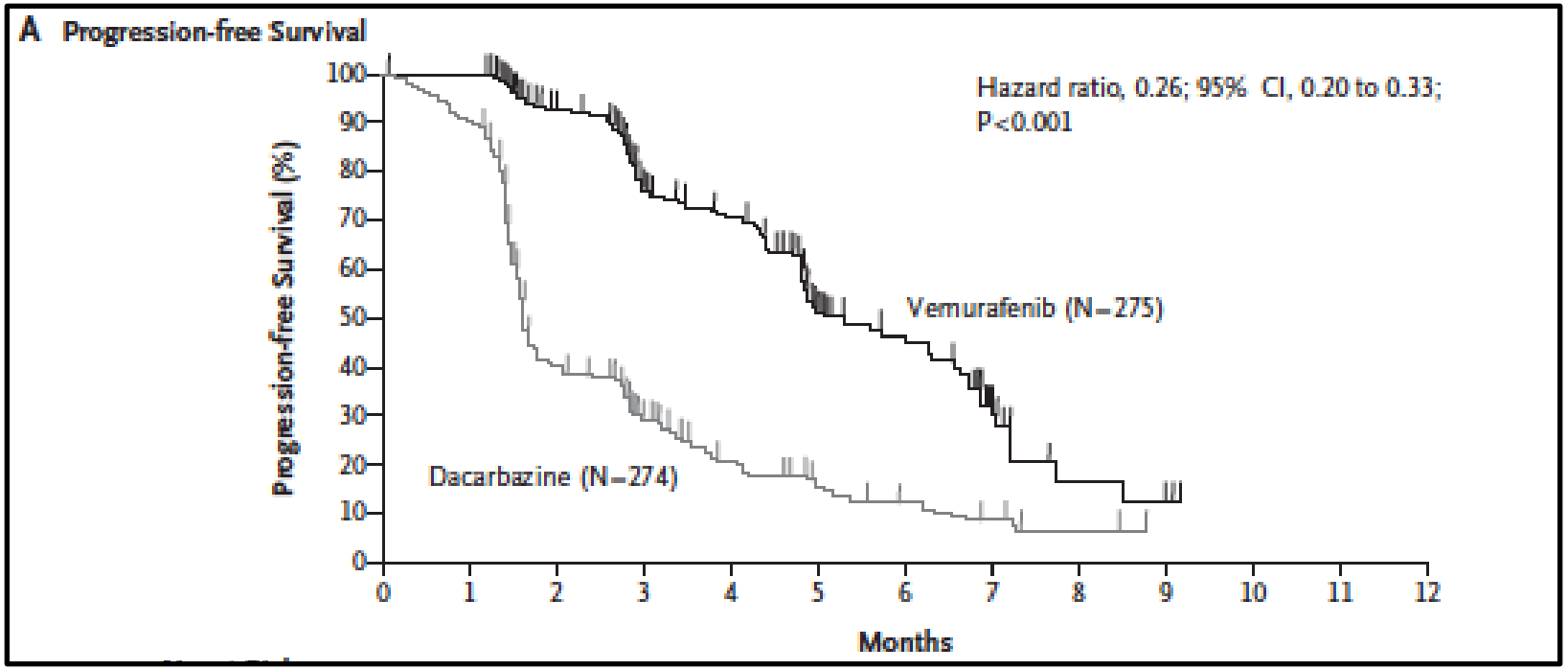
Figure 2: Change in tumour size in the 36 patients with Val600 BRAF-mutant melanoma without untreated brain metastases given the recommended phase 2 dose

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

N ENGL J MED 364;26 NEJM.ORG JUNE 30, 2011

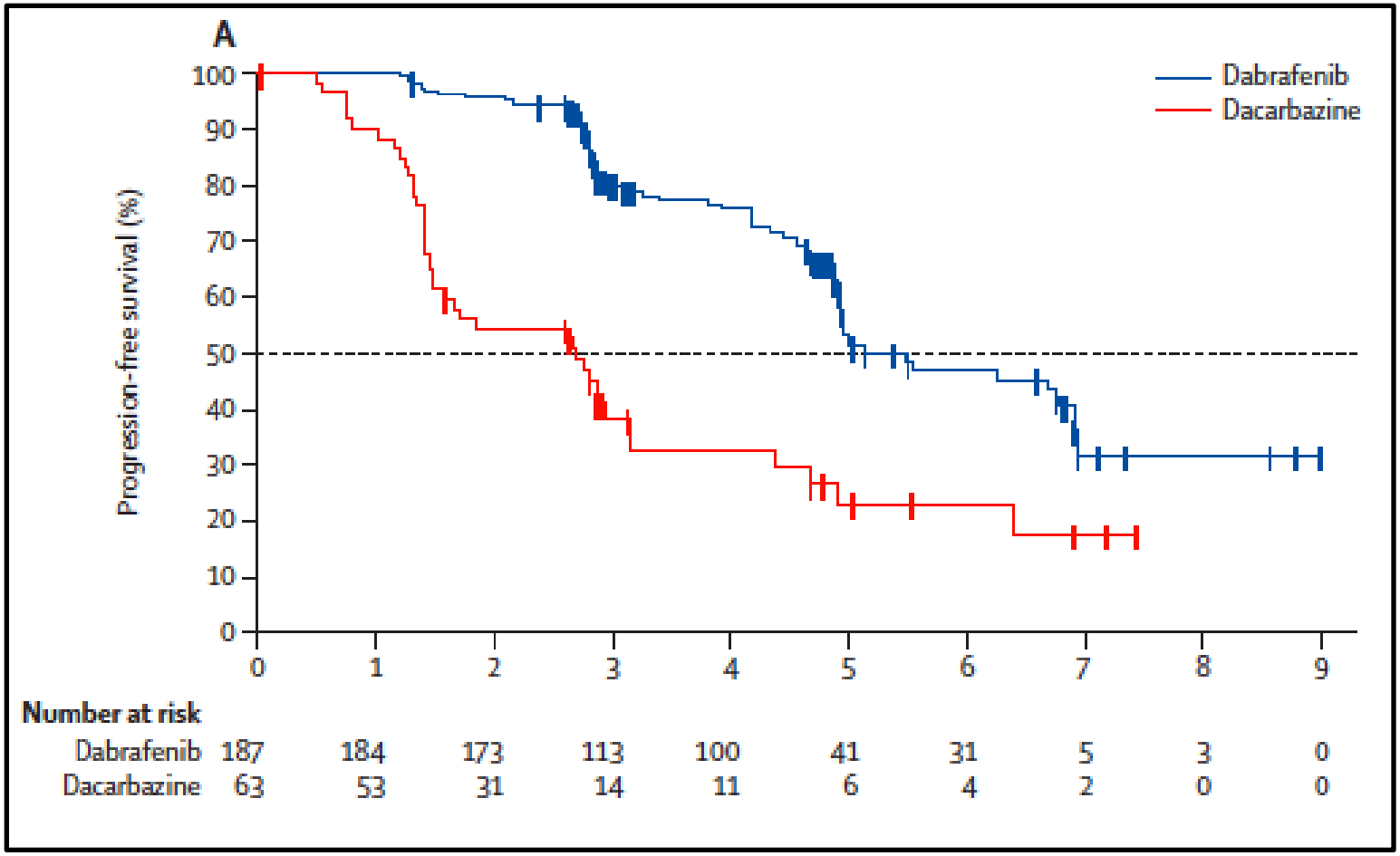
Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A.,



Dabrafenib in *BRAF*-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial

Axel Hauschild, Jean-Jacques Grob, Lev V Demidov, Thomas Jouary, Ralf Gutzmer, Michael Millward, Piotr Rutkowski, Christian U Blank, Wilson H Miller Jr, Eckhart Kaempgen, Salvador Martín-Algarra, Boguslawa Karaszewska, Cornelia Mauch, Vanna Chiarion-Sileni, Anne-Marie Martin, Suzanne Swann, Patricia Haney, Beloo Mirakhur, Mary E Guckert, Vicki Goodman, Paul B Chapman

Lancet 2012; 380: 358–65



BRAFV600 Mutations –pHGG Target?

- **Good Target?**
- **PROs**
  - Established oncogene with known mechanism
  - Established clinical drugs & validated biomarkers
  - Proof of mechanism and concept proven in melanoma
- **CONs**
  - Low prevalence in pHGG (6-8%)
  - Target can be heterogenous in tumours
  - Resistance can be inherent or acquired

BRAF PATHWAY

PAEDIATRIC EXPERIENCE

Brain Tumour Delivery with BRAFi?

Worked in Melanoma Brain Mets!

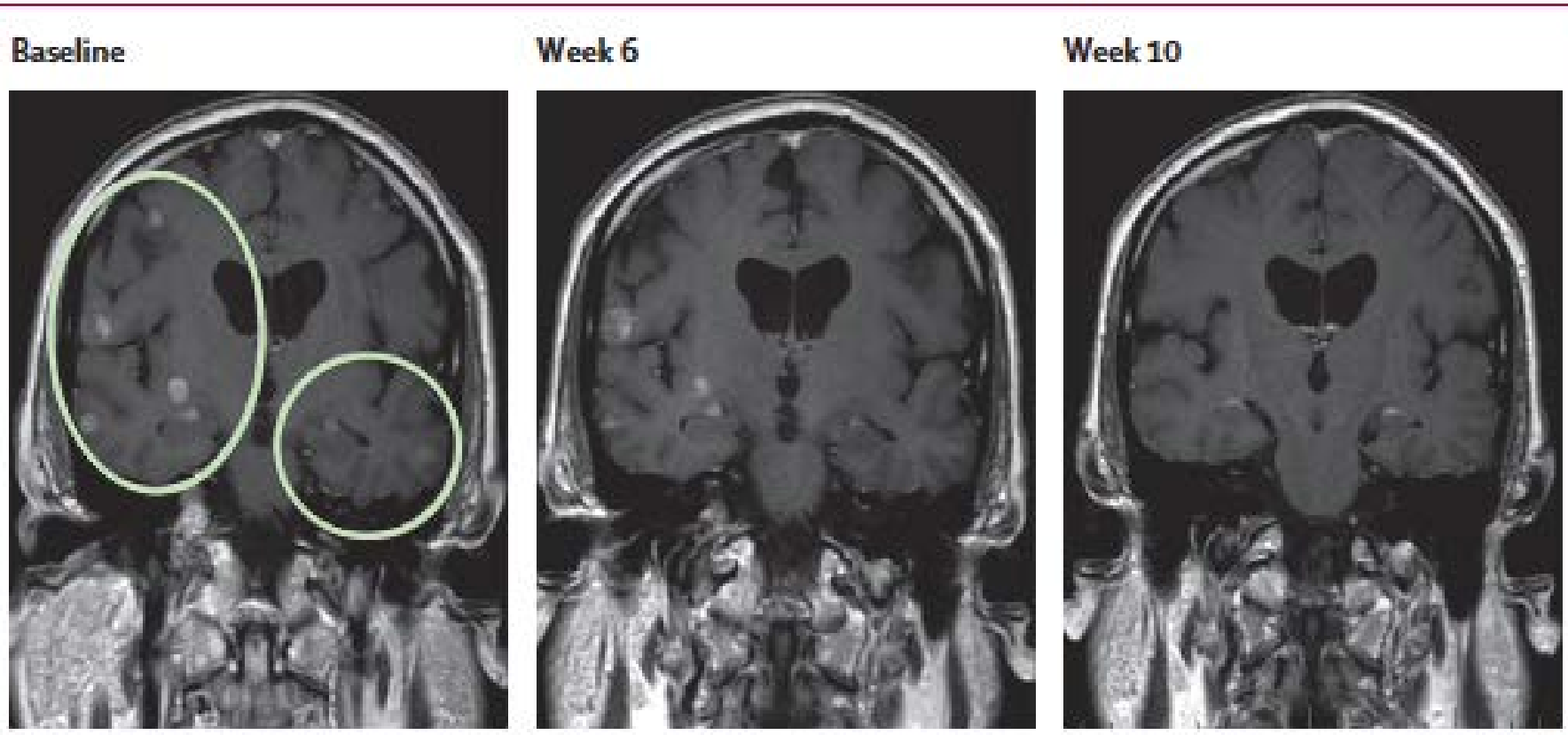


Figure 6: MRI images from one patient with Val600Glu BRAF-mutant melanoma and untreated brain metastases given the recommended phase 2 dose

Robinson et al. BMC Cancer 2014, 14:258
http://www.biomedcentral.com/1471-2407/14/258

BMC Cancer

CASE REPORT Open Access

Complete clinical regression of a BRAF V600E-mutant pediatric glioblastoma multiforme after BRAF inhibitor therapy

Giles W Robinson[1*], Brent A Orr[2] and Amar Gajjar[1]

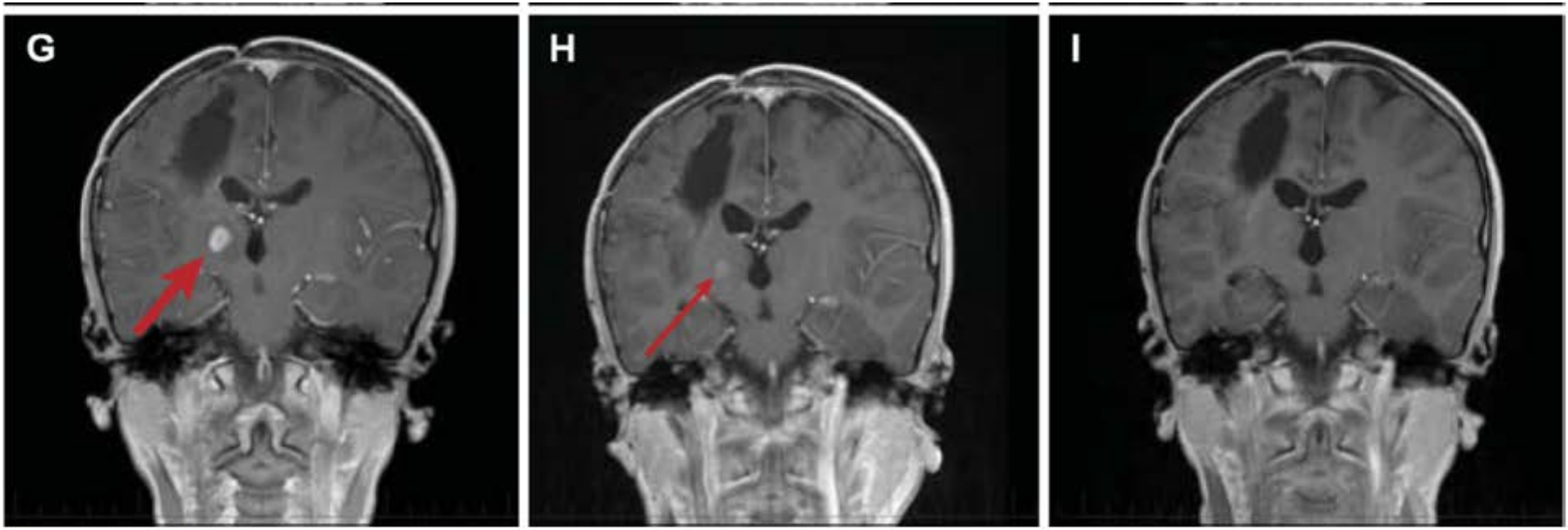


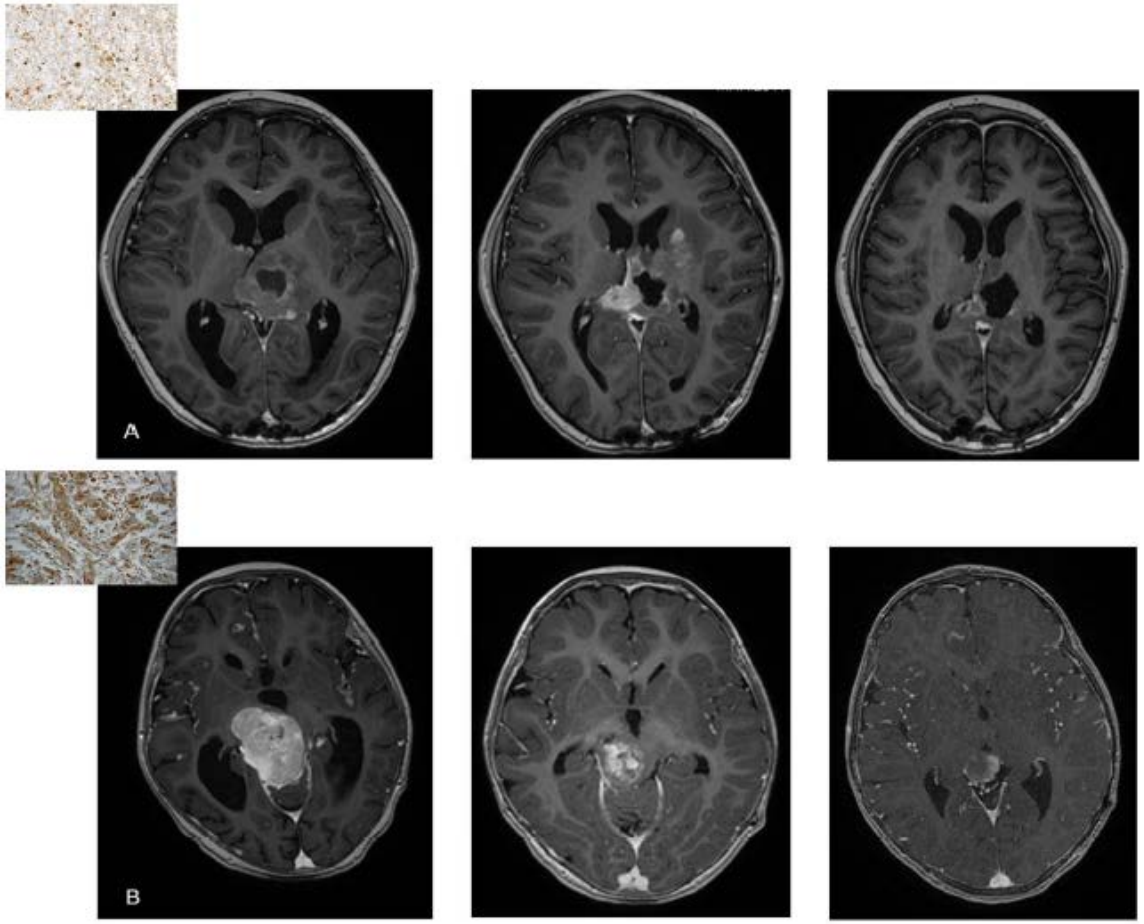
Figure 1 Chronological changes on magnetic resonance imaging (MRI) document the tumor recurrence and response. Coronal MRI T1-weighted images with gadolinium-based contrast were taken at the following times: **(A)** diagnosis, **(B)** post-operatively, **(C)** after completion of radiation therapy, **(D)** while receiving adjuvant chemotherapy, **(E)** at completion of therapy, **(F)** 4 months after completion of therapy, **(G)** upon start of vemurafenib therapy at relapse, **(H)** after 2 months of vemurafenib therapy, and **(I)** after 4 months of vemurafenib therapy.

Pediatr Blood Cancer 2014;61:1101–1103

BRIEF REPORT

Vemurafenib in Pediatric Patients With *BRAFV600E* Mutated High-Grade Gliomas

Francisco Bautista, MD,[1] Angelo Paci, PharmD, PhD,[2] Veronique Minard-Colin, MD, PhD,[1] Christelle Dufour, MD,[1] Jacques Grill, MD, PhD,[1] Ludovic Lacroix, MD, PhD,[3] Pascale Varlet, MD, PhD,[4] Dominique Valteau-Couanet, MD, PhD,[1] and Birgit Geoerger, MD, PhD[1]*

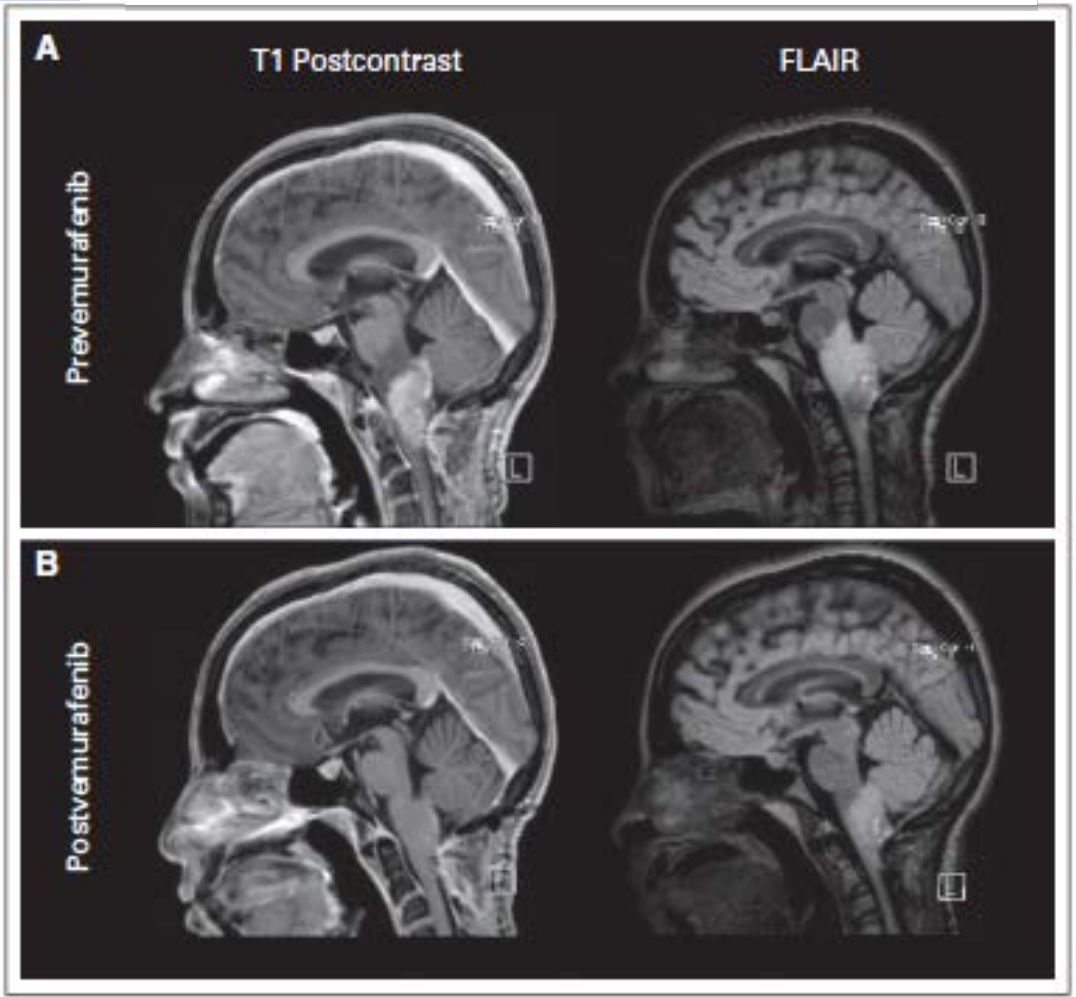


VOLUME 31 · NUMBER 10 · APRIL 1 2013

JOURNAL OF CLINICAL ONCOLOGY

DIAGNOSIS IN ONCOLOGY

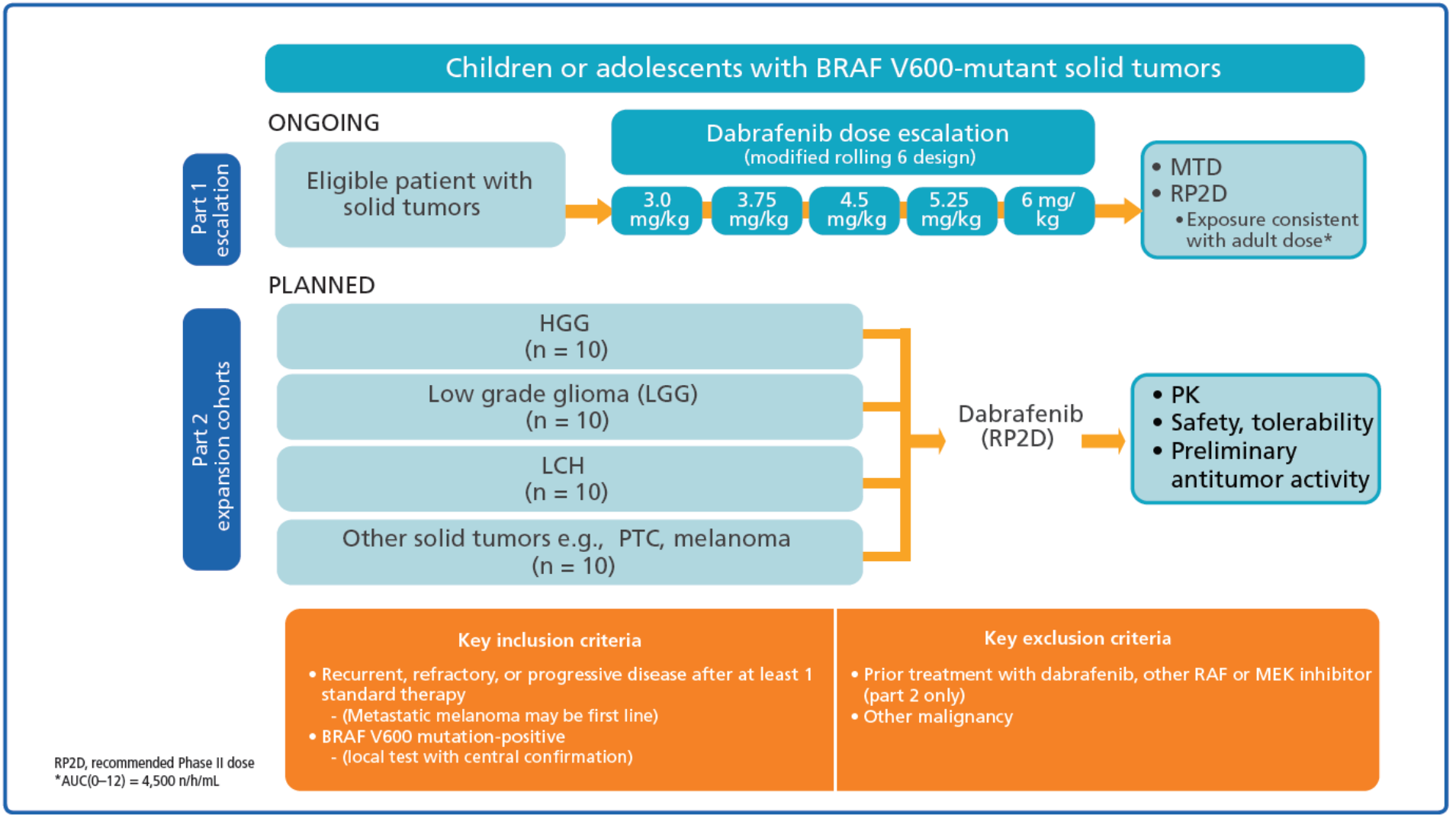
Brainstem Ganglioglioma Successfully Treated With Vemurafenib



Complete Radiographic Responses in Pediatric Patients with BRAF V600–Positive Tumors Including High Grade Gliomas: Preliminary Results of an Ongoing Phase I/IIa Safety and Pharmacokinetics (PK) Study of Dabrafenib

Mark W. Kieran[1], Kenneth J. Cohen[2], Francois Doz[3], Ira J. Dunkel[4], Darren R. Hargrave[5], Trent Ryan Hummel[6], Irene Jimenez[3], Sarah Leary[7], Andrew D.J. Pearson[8], Christine A. Pratilas[4], James Whitlock[9], Michael Durante[10], Diana M. Gibson[11], Patricia Haney[10], Mark W. Russo[10], A. Benjamin Suttle[11], Birgit Geoerger[12]

Figure 1. Study Design



RP2D, recommended Phase II dose
*AUC(0–12) = 4,500 n/h/mL

Figure 2. Preliminary Treatment Duration and Best Response

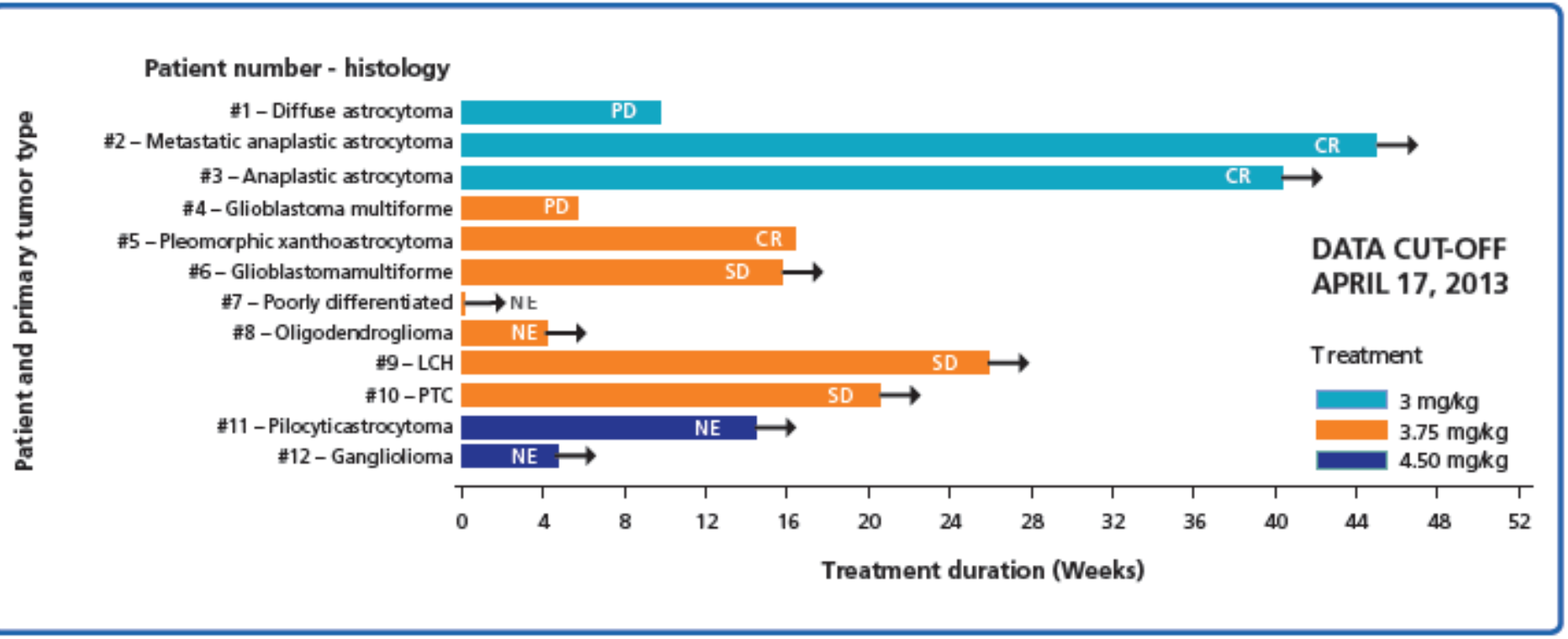
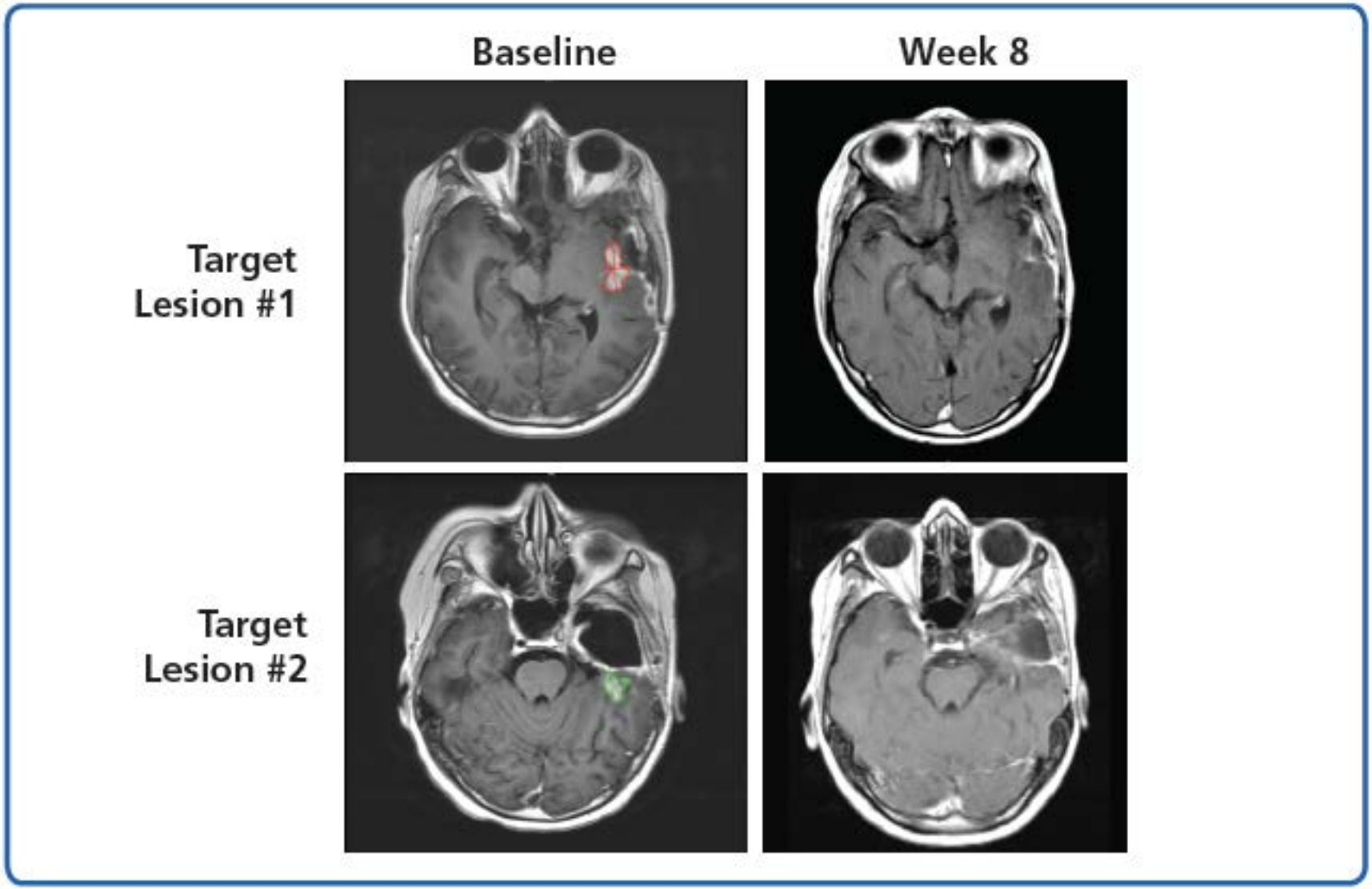


Figure 3. Radiologic Response, Patient 3



CONCLUSIONS

- Very encouraging preliminary activity seen in patients with relapsed/refractory V600 mutant glioma
  - CR or PR seen in 5/10 patients
    - Investigator-assessed best response
    - Follow-up confirmatory scans pending in 2 of the 5 patients with initial response
  - Trial is ongoing and includes expansion cohorts with plans to enroll additional patients with V600 mutant gliomas to confirm these preliminary findings
- Dose escalation continues
  - PK at 3.75 mg/kg does not satisfy pre-specified systemic exposure target
- Safety profile in children is similar to adults
  - 1 DLT event: maculopapular rash (onset day 1)

PAEDIATRIC HIGH GRADE GLIOMA:
CONCLUSIONS

Conclusions

In order to make progress in pHGG, DIPG or aHGG

- Biologically targeted therapies are needed
- Biomarkers are required for patient selection
- Accurate preclinical models needed

Extrapolation of data/ studies only possible for

- Shared targets and defined molecular groups
- Needs to be confirmed if these targets are relevant in different tumour entities

e.g. DIPG> pHGG > aHGG

Conclusions

Need to develop and validate new response criteria e.g. RANO & RAPNO

Must consider drug delivery as a vital component of neuro-oncology trials & possible reason for an active agent failing!

Efficient, adaptive and flexible clinical trial designs

- allow study of multiple arms
- combination targeted therapies
- parallel and sequentially

ESTRO School

Management of medulloblastoma in children

Umberto Ricardi

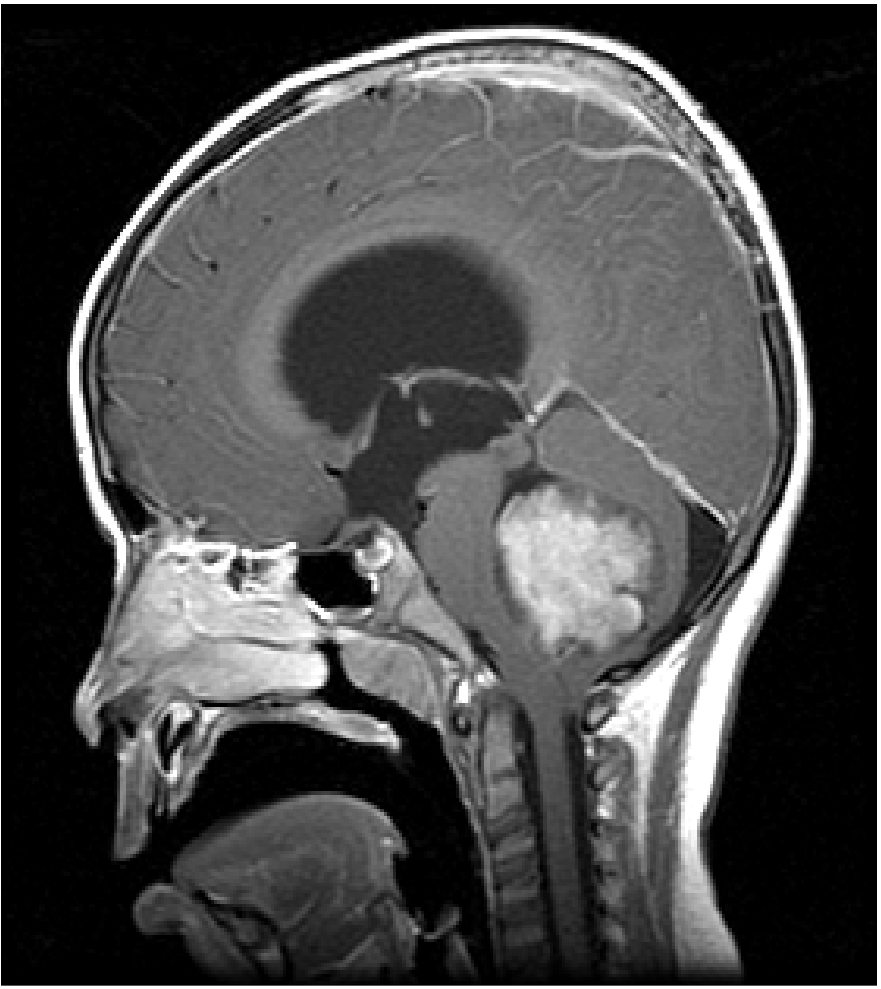
DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

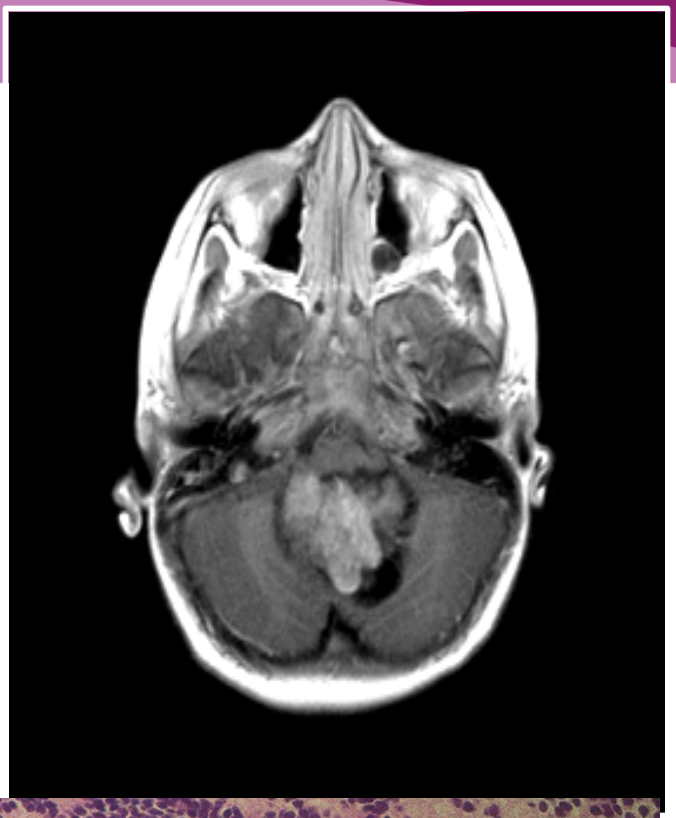
Medulloblastoma

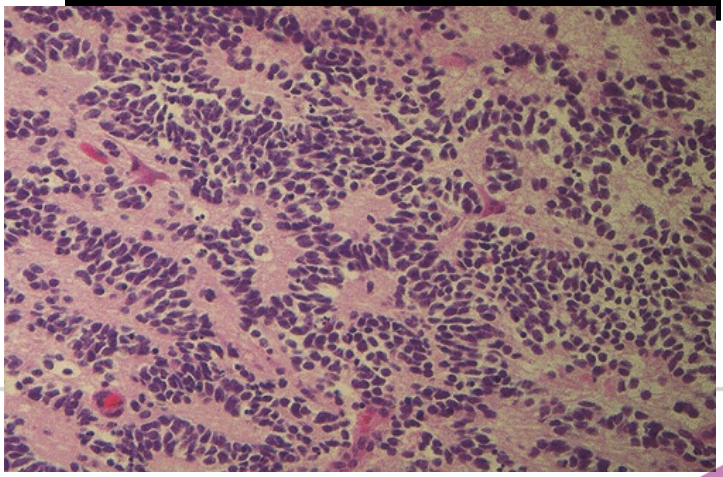
- Most common malignant CNS tumour in children

- Tremendous progress over last 20 years
  - Treatment
  - Biology >>> several distinct subtypes

Medulloblastoma







Posterior fossa PNET

Small round blue cells tumor

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Medulloblastoma

- 15-20% of all CNS tumors in children

- Bimodal peak incidences at ages 3-4 and 8-9 years

- 10/15% in infancy

- 70% <16 years

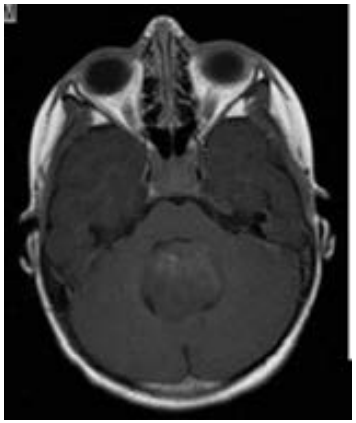
- Very rare after age 40

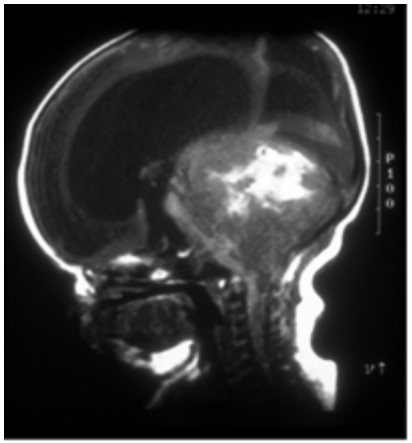
- Rate M:F 1.4 : 1

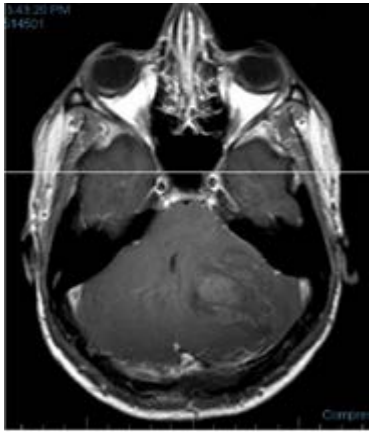
Medulloblastoma - Clinical presentation

- Typical midline location, arising in the vermis, causing IVth ventricle compression (symptoms and signs of raised intracranial pressure)

- Hemispheric location more common in very young children and adults



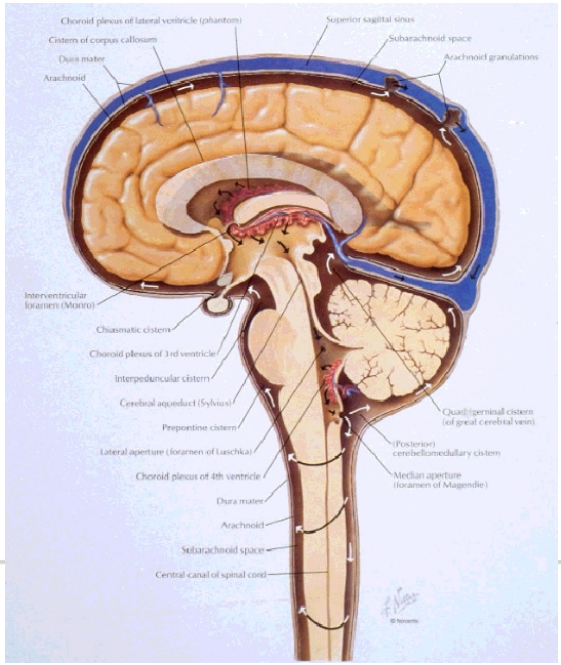


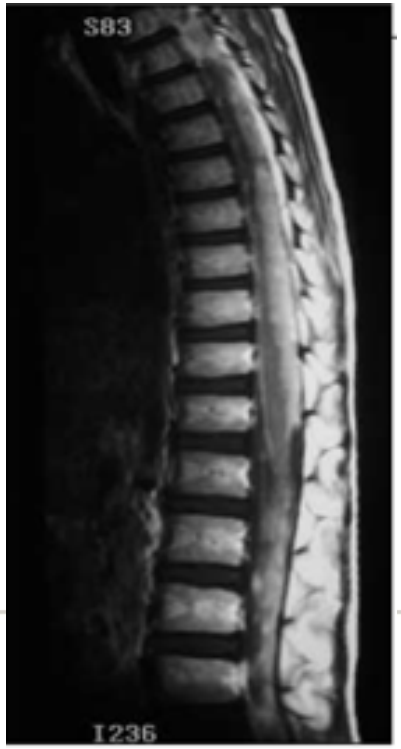


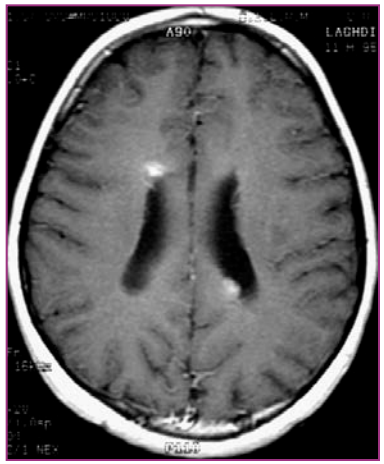
Medulloblastoma: pattern of spread

- Frequency of leptomeningeal seeding at diagnosis 30-35%

- Extra CNS metastases very uncommon (<5%) [lymph nodes, bone, bone marrow]







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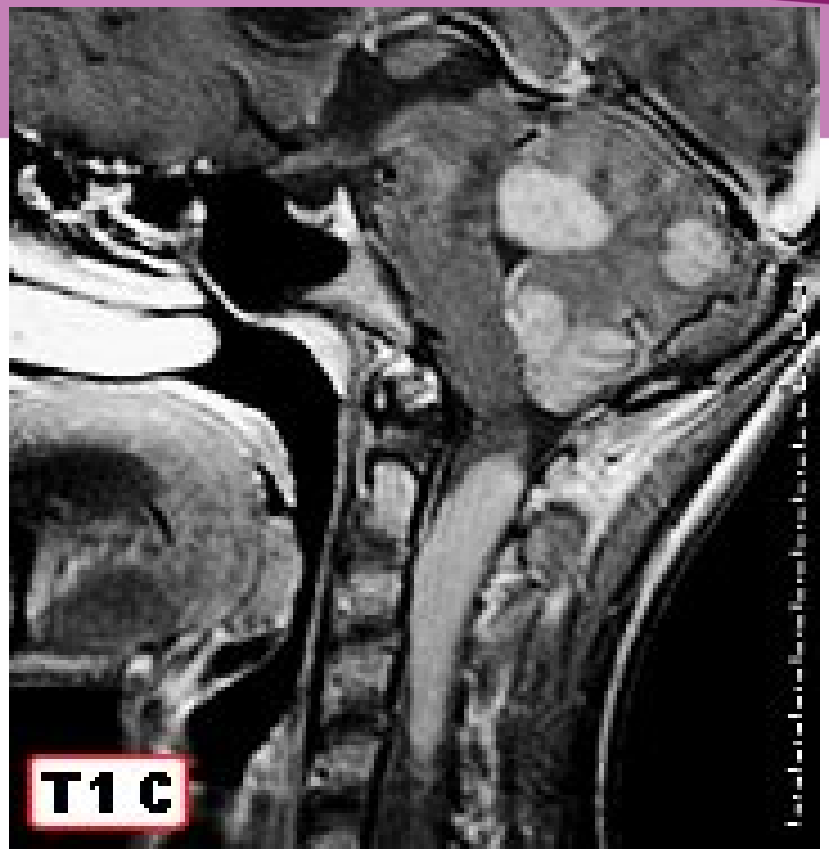
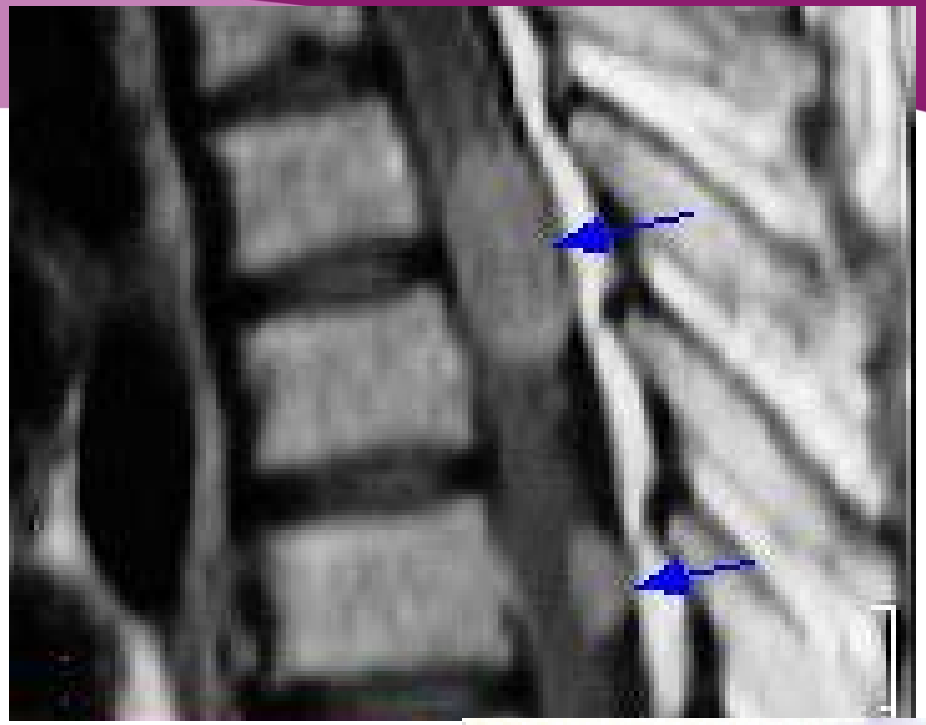
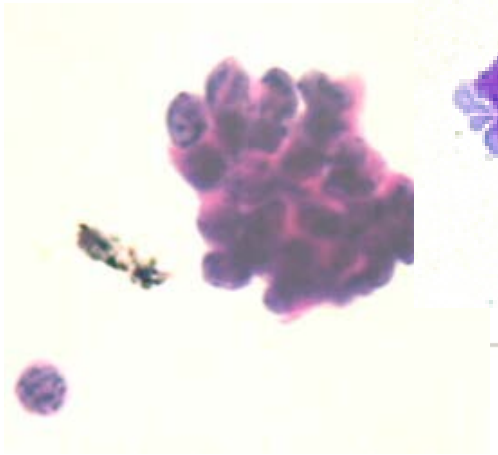
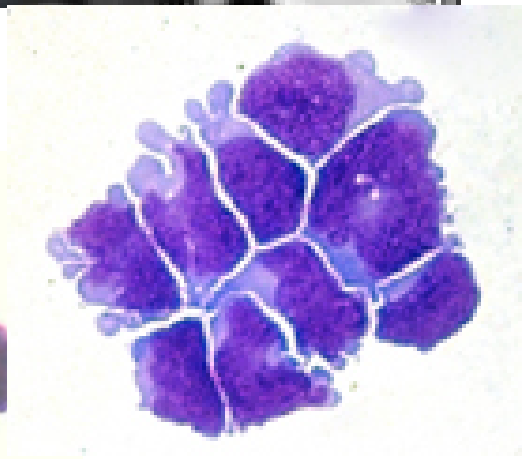




Chang staging system for metastases

- M0: no metastases
- M1: CSF cytology +ve
- M2: macroscopic seeding in subarachnoid space, IIIrd or lateral ventricles
- M3: macroscopic seeding along spinal axis
- M4: extra-CNS spread





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Medulloblastoma - Work-up

- Pre-op craniospinal MR imaging
- Post-op cranial MR (24-48 hours after surgery)
- Lumbar CSF cytology > 14 d post-op

Chang staging system for metastases

- M0: no metastases
- M1: CSF cytology +ve
- M2: macroscopic seeding in subarachnoid space, IIIrd or lateral ventricles
- M3: macroscopic seeding along spinal axis
- M4: extra-CNS spread

Medulloblastoma - Prognosis

Prognosis depends on…

- Extent of primary tumour/ completeness of surgical resection
- Presence or absence of leptomeningeal seeding

Also...

- Pathologic/molecular subtype

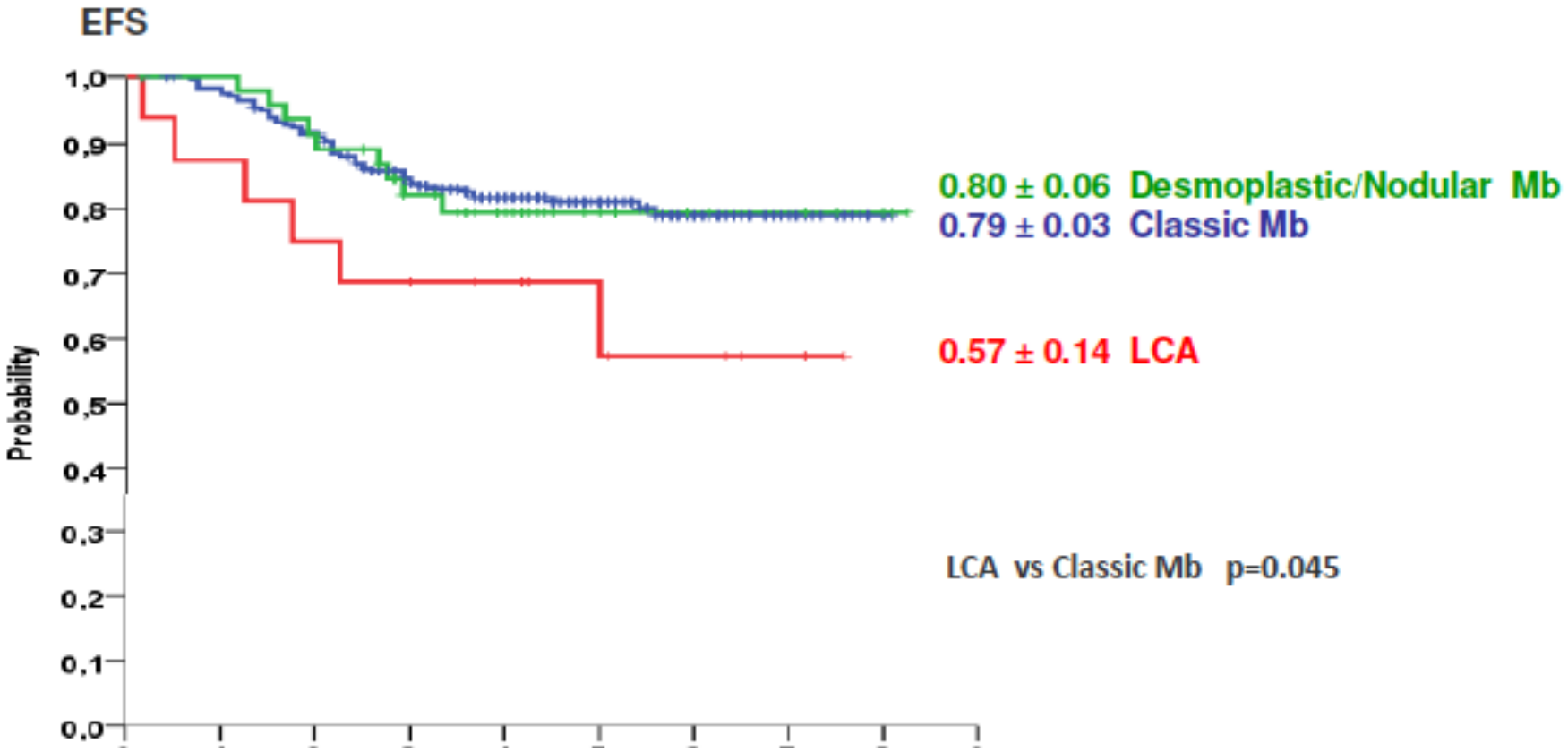
Medulloblastoma - Prognosis

Risk groups for management

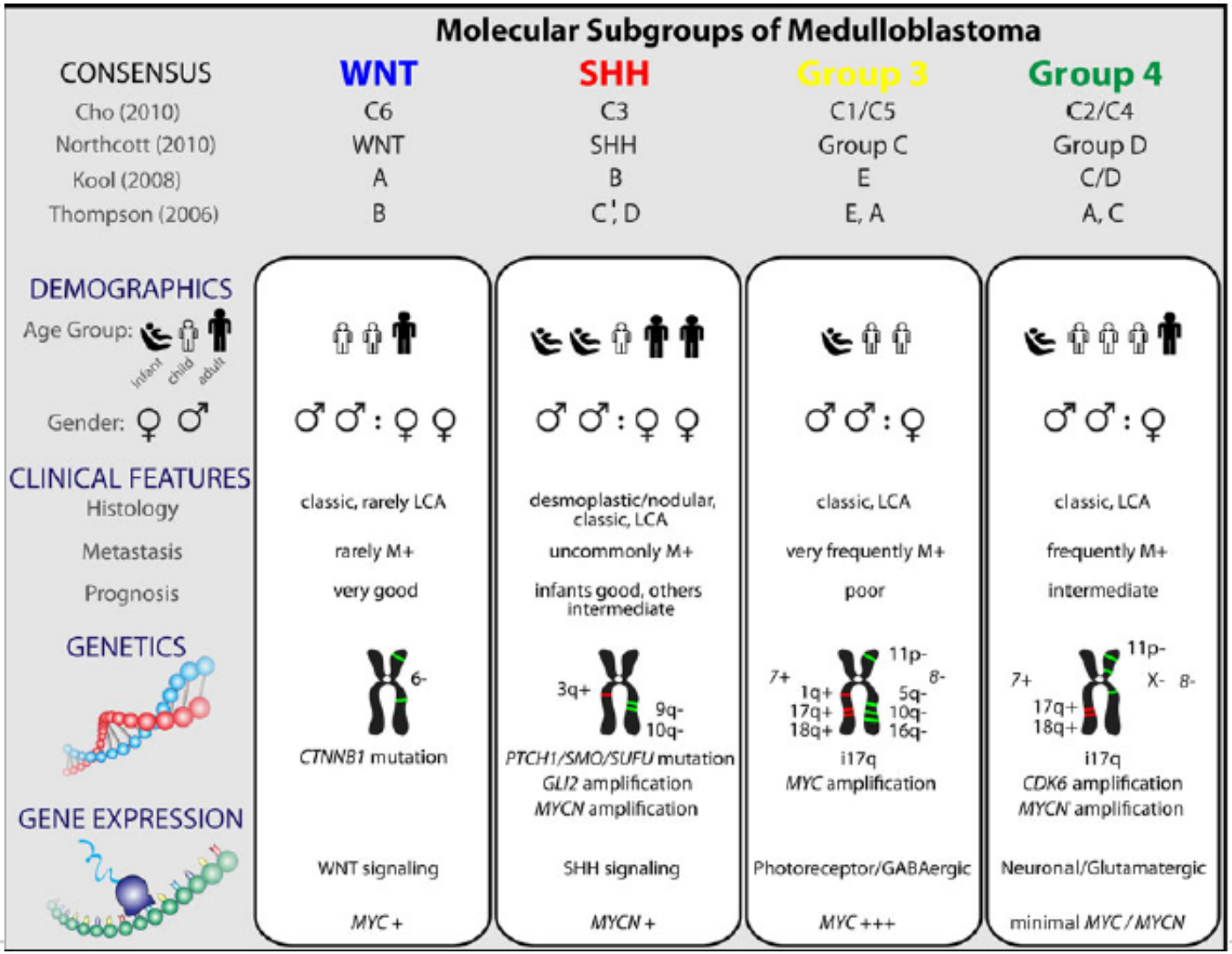
- Standard risk
  - GTR/residual tumour <1.5 cm^2 on post-op MRI
  - No leptomeningeal seeding by MRI of the spine or lumbar CSF cytology (M0)
- High risk
  - All others (1/3 to 1/2 all)
- Infants and very young children

SIOP PNET 4 : survival by histologic subtypes

Central Pathology Review



Comparison of the various subgroups of medulloblastoma including their affiliations with previously published papers on medulloblastoma molecular subgrouping



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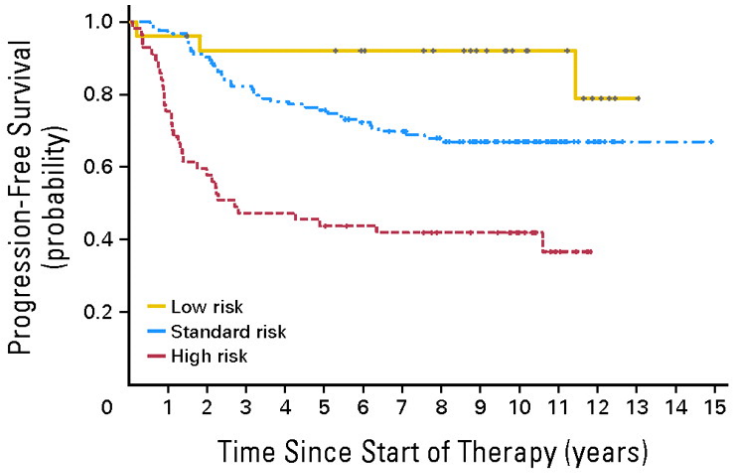
Histology + molecular variables

- 3 risk categories
  - Low (13%)
    - β-catenin+, M0, not large cell/anaplastic, no MYC amplification
  - High (28%)
    - M+ or
    - LC/A or
    - MYC amplification
  - Standard (59%)
    - All others



No. at risk														
Low risk	26	25	23	23	23	23	21	20	18	15	11	8	4	1
Standard risk	124	120	112	101	96	92	85	81	72	60	45	23	8	1	1
High risk	57	43	33	27	27	24	23	22	19	17	12	5			

Ellison JCO 2011

Medulloblastoma: the (near) future

- Patients will be stratified for treatment on the basis of biological markers
  - Low risk: reduce therapy → reduce risks associated with treatment
  - High risk: intensify treatment/use novel treatment approaches
- Possibility of developing agents that would target specific molecular aberrations

New risk groups

Risk Group	Definition of Risk Group	5 y EFS
1. Low "PNET5"	Nuclear ß-catenin +, no myc gene amplification, residual tumor ≤1.5 cm^2, no LC- or anapl. histology	91 %
2. Intermediate "PNET6"	Nuclear ß-catenin -, no myc gene amplification, residual tumor ≤1.5 cm^2, no LC- or anapl. histology	81 %
3. High "PNET-HR"	myc gene amplification, or residual tumor >1.5 cm^2, or LC- or anapl. histology	67 %

Medulloblastoma: the management

- **Standard risk Medulloblastoma**

- Standard risk
  - GTR/residual tumour <1.5 cm^2 on post-op MRI
  - No leptomeningeal seeding by MRI of the spine or lumbar CSF cytology (M0)

Post-operative treatments

- Craniospinal irradiation

  - ✓ Clinical target volume = whole brain + spinal cord with overlying meninges
  - ✓ CSI: 36 Gy, followed by local boost to 55 Gy
  - ✓ Cure rates: 60-80%

- ± Chemotherapy

Late toxicity related to CSI

- Due to radiotherapy to the brain
  - Neuro-cognitive deficits/effects on social interactions
  - Hypopituitarism
  - Alopecia
  - Cataracts
  - Hearing loss
- Due to radiotherapy to the spine
  - Short stature
  - Primary hypothyroidism
  - Impaired lung function
  - Effects on the heart
  - Primary ovarian failure
- Both
  - Second cancers…

How can we reduce the risks associated with CSI?

- Risk reduction
  - Reduce CSI dose
  - Use hyperfractionated RT?

Medulloblastoma

History of Chemotherapy Clinical Trials:

- 1970s-1980s:
- Adjuvant chemotherapy
- SIOP I,CCSG 942

Chemo better for high-risk subgroups
Standard dose RT (35-36 Gy established)

- 1980s-1990s:
- Pre-RT (Sandwich CT)
- SIOP II, SIOP/UKCCSG PNET 3
- Pre vs post RT chemotherapy : HIT 91,CCG 921
- CCG 9862 adjuvant chemotherapy (CVP)

Intensive sandwich CT better than RT alone (PNET 3)
Immediate RT better than delayed

Cisplatin, VCR,CCNU chemo standard and reduced dose RT (23.4 Gy) established

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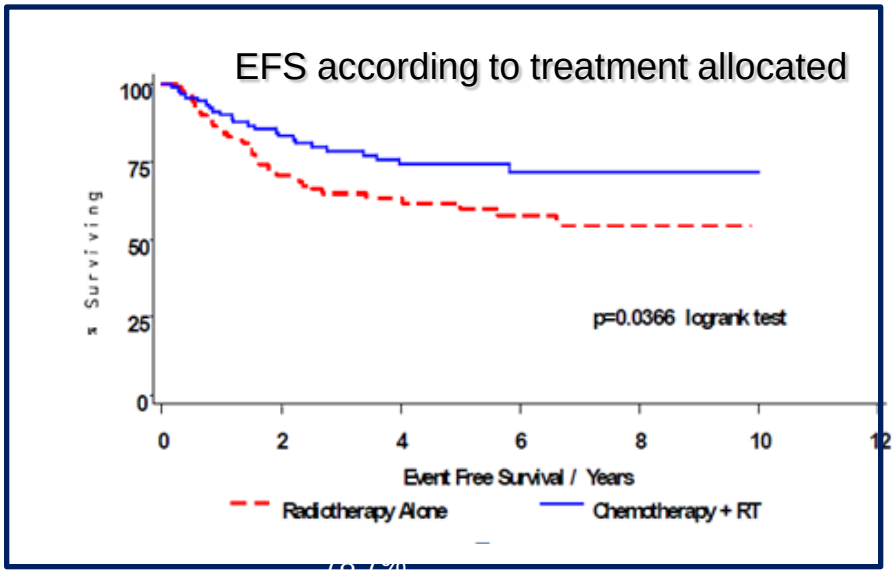
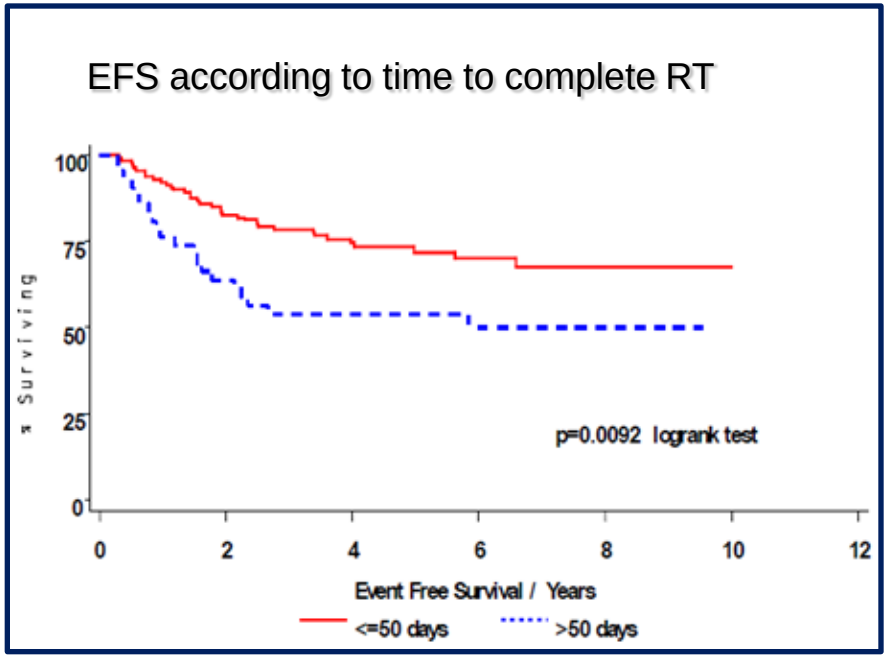
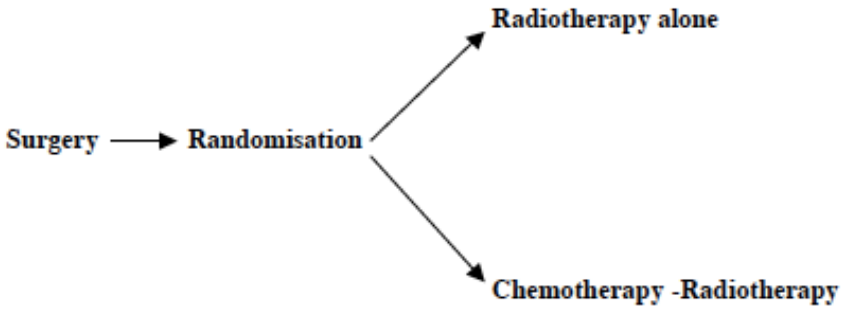
UKCCSG/SIOP PNET III







Combined CT-RT and completing RT within 50 days had a significant impact on EFS in multivariate analysis

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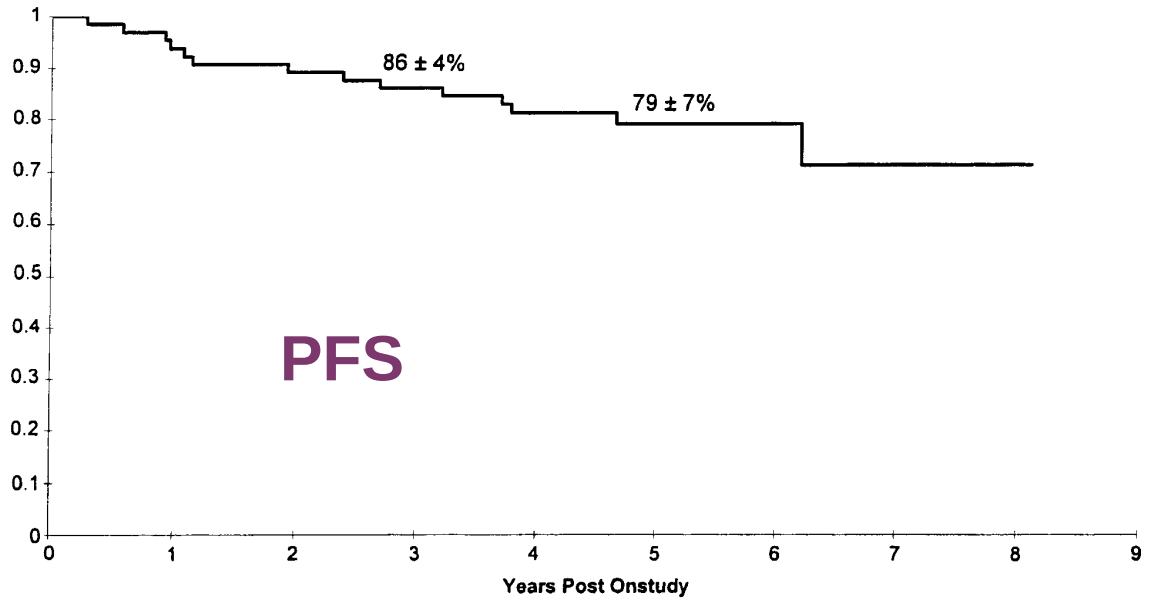
Reduced dose Cranio Spinal Irradiation with CT



- 65 “Standard-Risk” patients:
- RT doses
  Craniospinal: 23.4 Gy
  Posterior fossa: 55.2 Gy
- Concomitant CT:
  weekly Vincristine
- Adjuvant CT:
  Vincristine
  CCNU
  Cisplatin

“These overall survival rates compare favorably to those obtained in studies using full-dose radiation therapy alone”

Packer, J Clin Oncol 1999; 17:2127-36

Medulloblastoma- Randomised studies of CSI RT dose

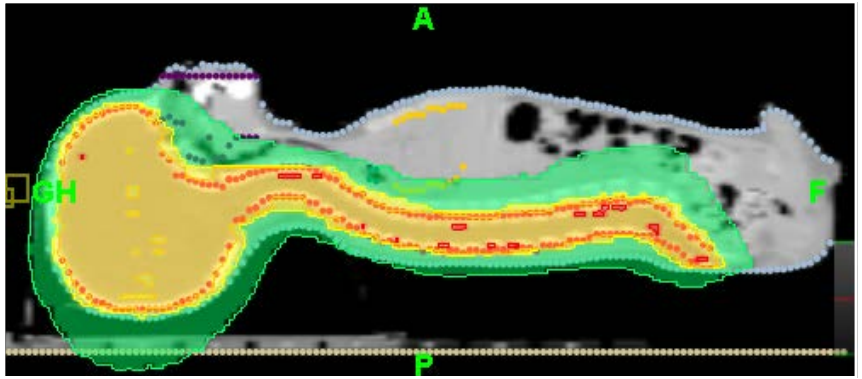
POG 8631/CCG 932 (1986-1990)

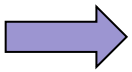
- 23.4 Gy – 52 % 5 year EFS
- 36 Gy – 67 % 5 year EFS
- p 0,08 (trial stopped for an increased risk of isolated neuraxis failure)

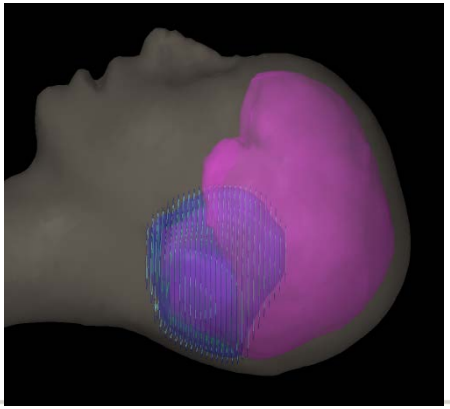
- 23.4 Gy – 52 % 8 year EFS
- 36 Gy – 60 % 8 year EFS
- p 0,141

Standard risk childhood MB

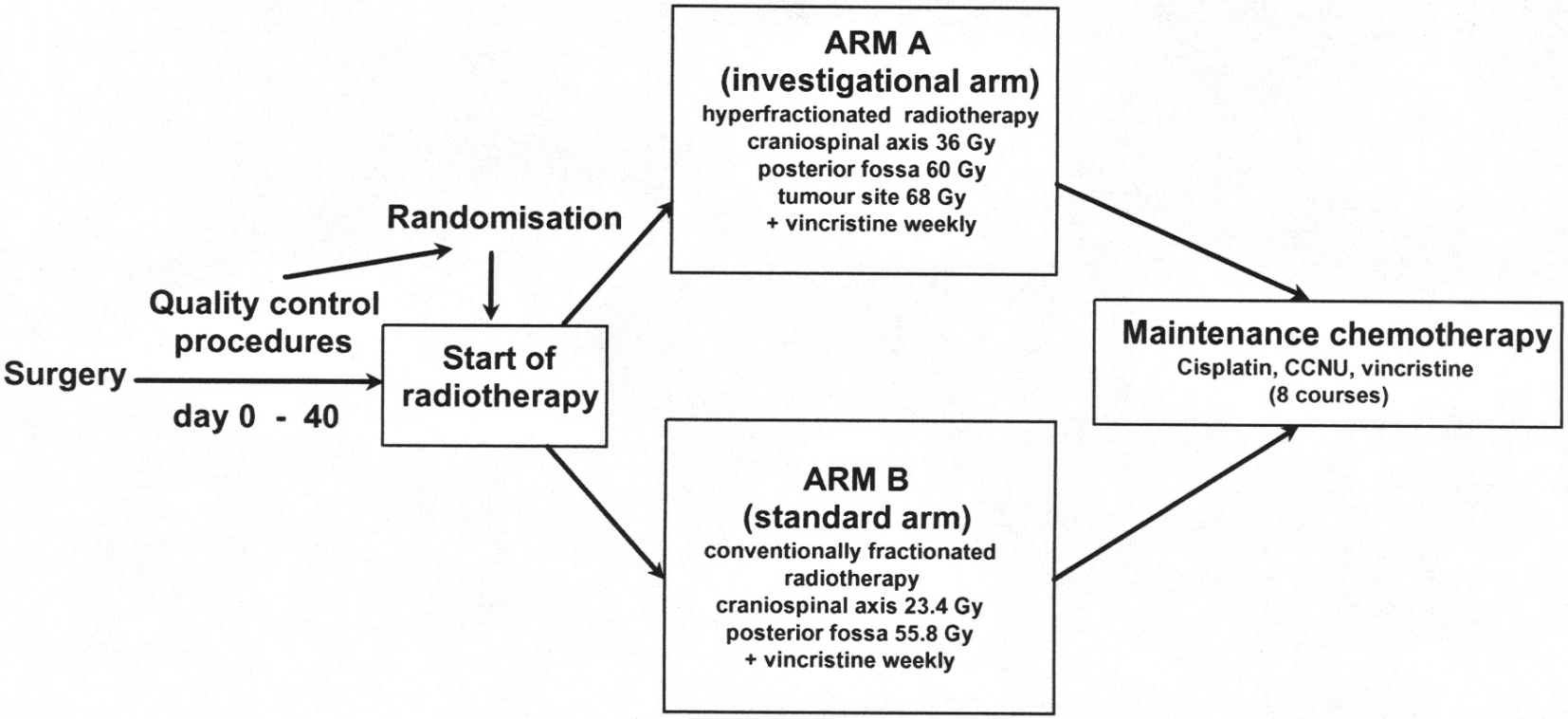
- CSI
  - Standard risk
    - 23.4Gy/13 daily fractions of 1.8 Gy
- Primary site
    - Total dose 54-55.8Gy
- Plus chemotherapy



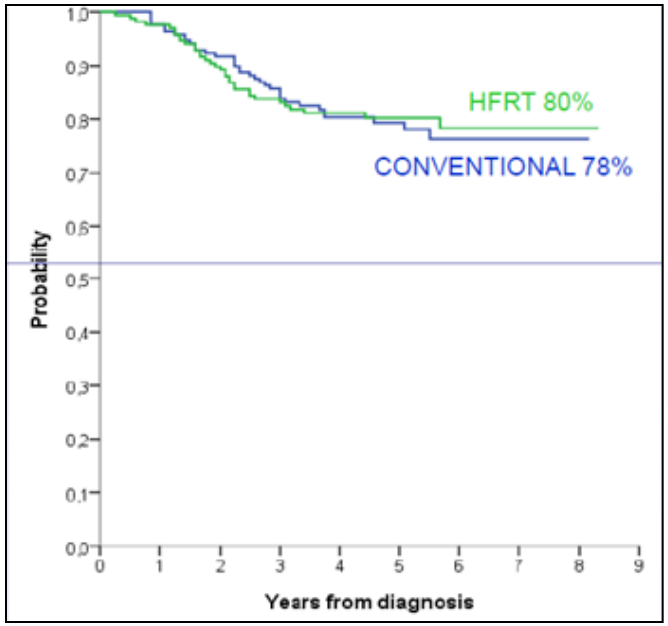




A prospective randomised controlled trial of hyperfractionated versus conventionally fractionated radiotherapy in standard risk medulloblastoma: SIOP Trial PNET 4



HIT2000/SIOP PNET-4 study for M0 medulloblastoma



Event Free Survival

- Pts with post-op residual tumor > 1.5 cc had a significantly inferior prognosis compared to pts without residual tumor (5 yrs-EFS 64% vs 82%, p<0,01)

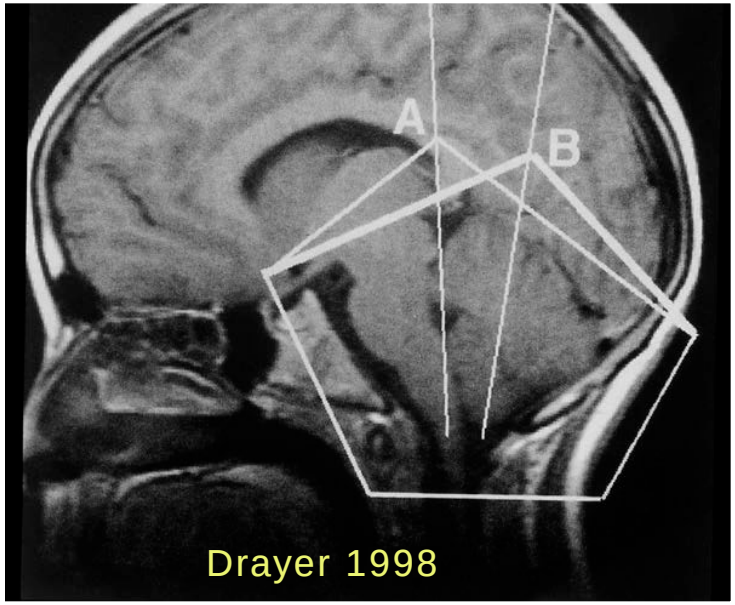
- Pts with RT starting < 49 days after surgery had a 5 year EFS of 81% compared with 67% for pts who commenced RT > 49 days after surgery (p=0.04)

The posterior fossa boost

- Whole posterior fossa
- Limited volume/tumour bed

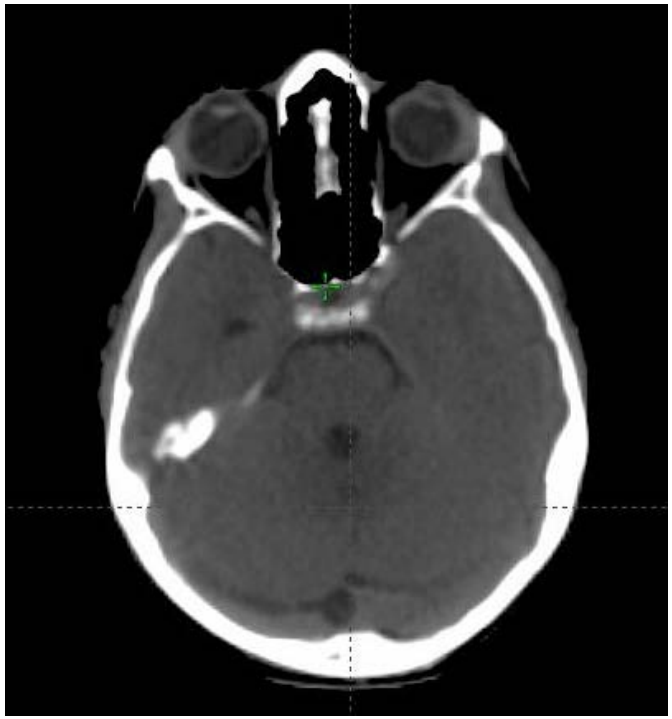
CTV for the posterior fossa boost

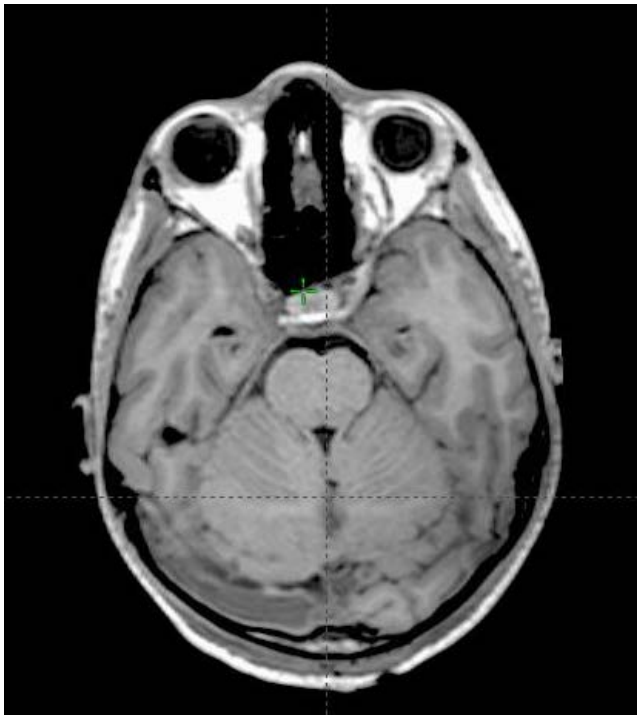
- Inferiorly
  - Bottom of C1
- Laterally
  - Bony walls of the occiput and temporal bones
- Superiorly
  - Tentorium cerebelli



The posterior fossa boost

- Whole posterior fossa

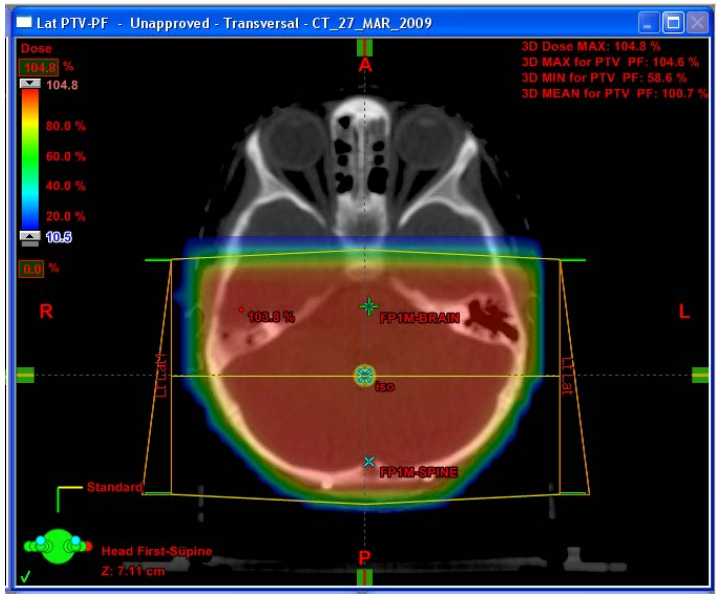


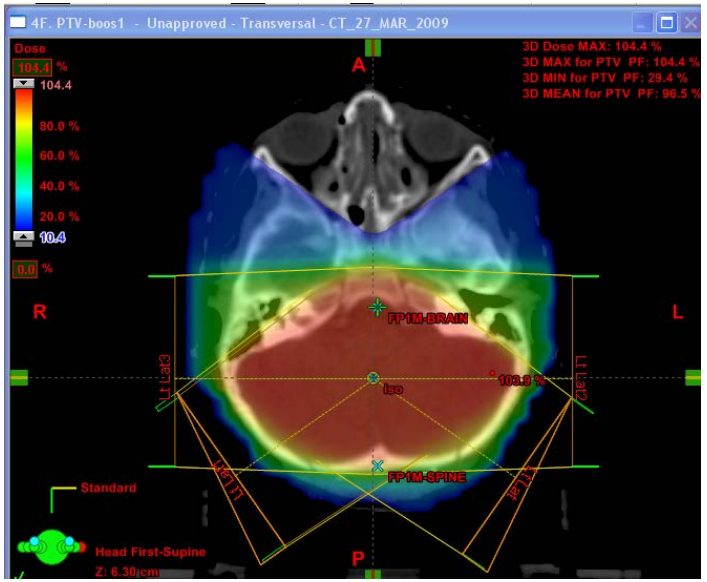


Radiotherapy technique

- Options include
  - Lateral opposed
  - Posterior obliques
  - 3D CRT
  - IMRT
- Principal consideration
  - Least dose to OARs

Whole PF: Lateral opposed → 3D CRT





- No sparing of cochlea
- Increased dose to hypothalamus/pituitary, optic chiasma, temporal lobes

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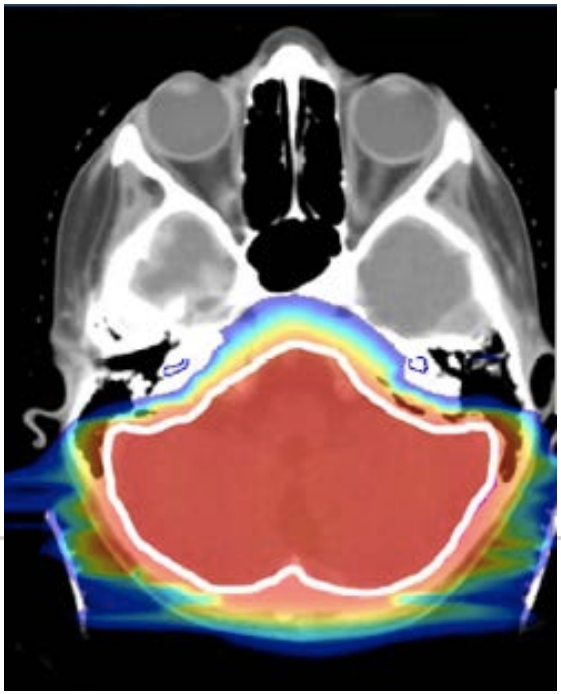
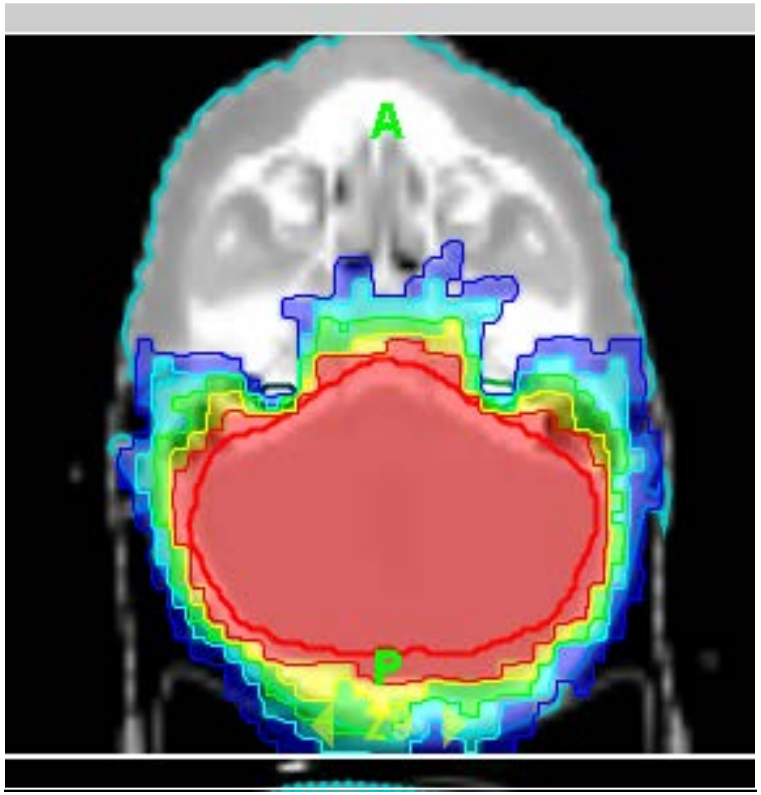
Whole PF: Lateral opposed → IMRT

Better sparing of cochlea

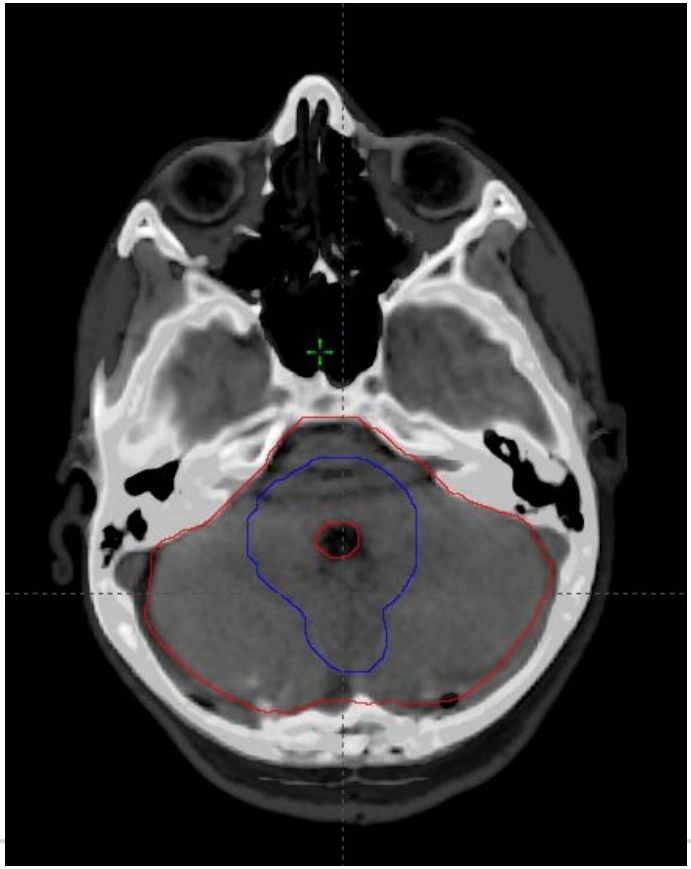
Reduced volume of supratentorial brain receiving high dose

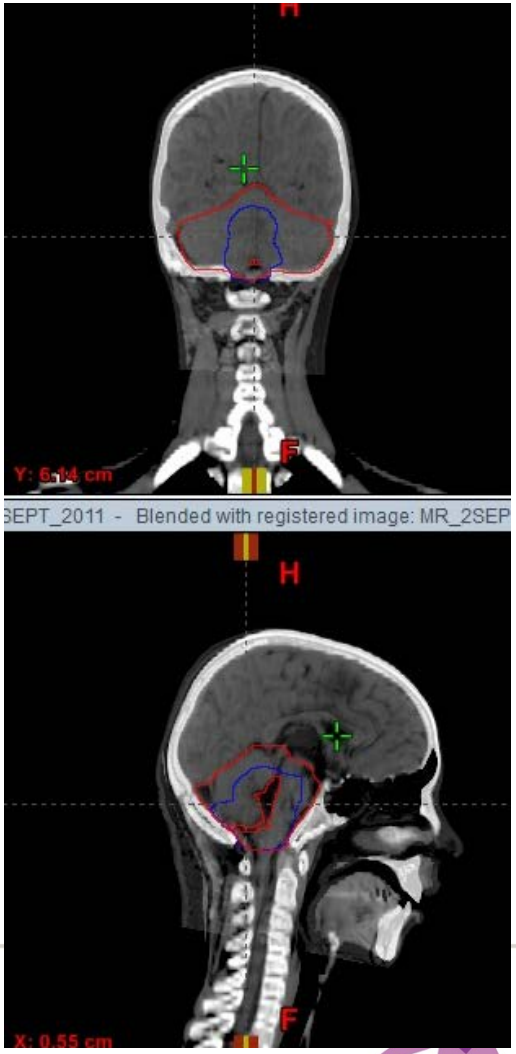




Whole PF vs tumour bed boost: ongoing trials

Benefit: less dose to surrounding healthy tissues





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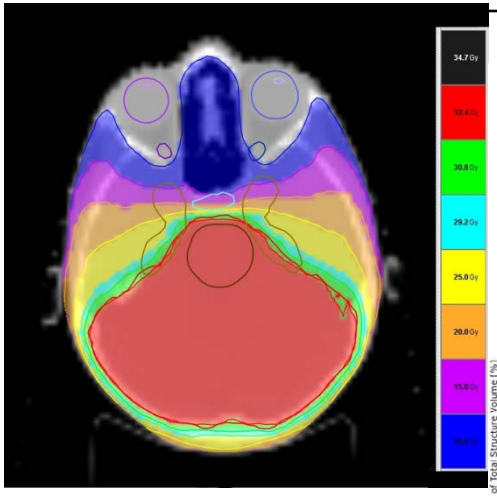
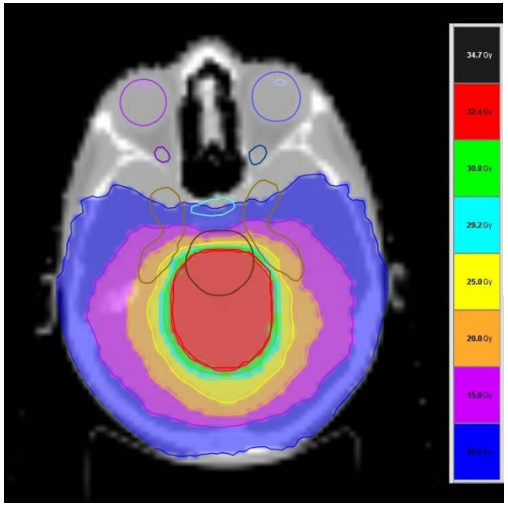
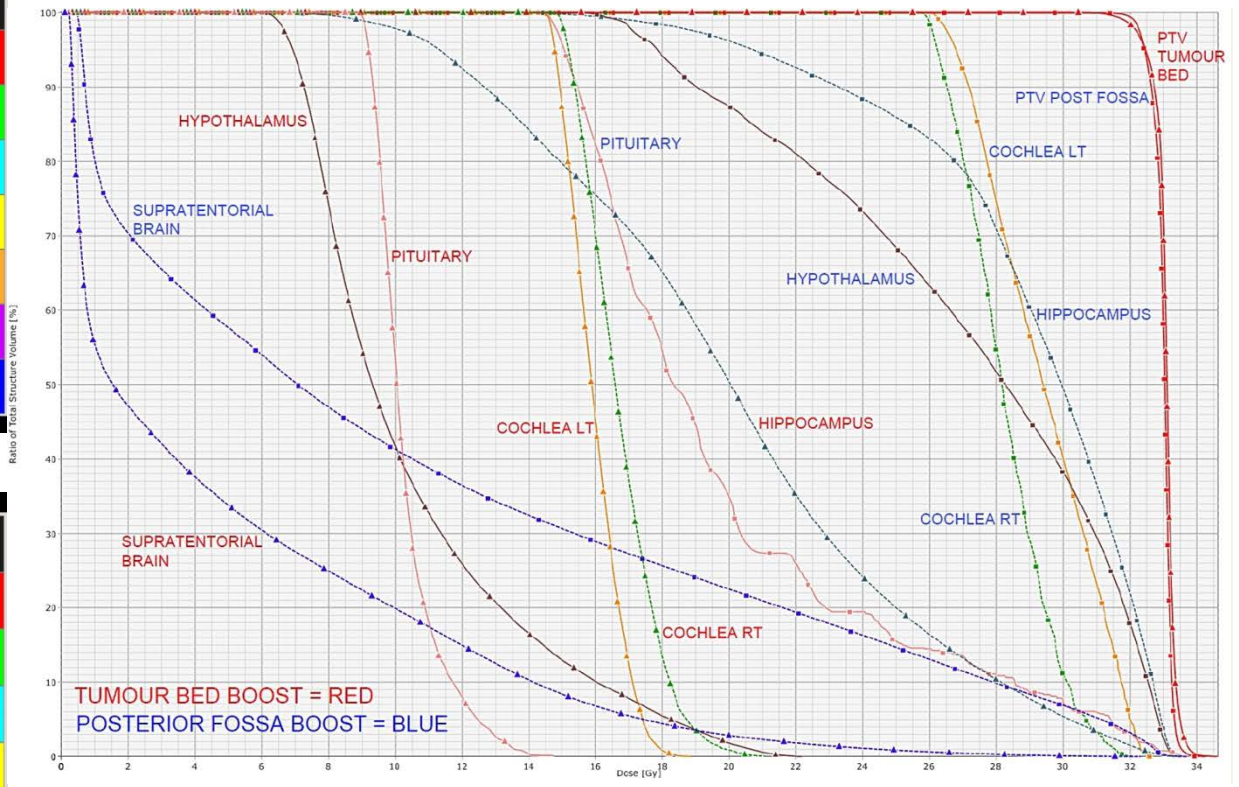
Whole PF vs tumour bed







+ med dose of 15.4Gy to cochlea

+ med dose of 6.4Gy to hypothalamus

+ med dose of 18.4Gy to R hippocampus

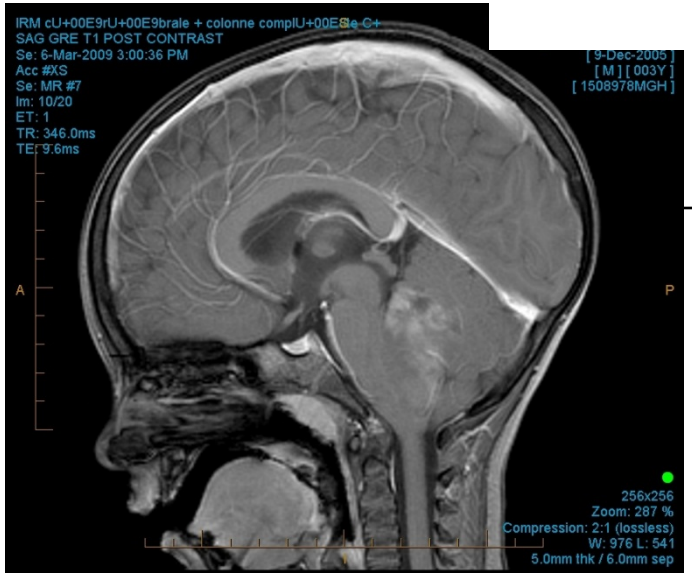
+ med dose of 2.4Gy to R supratentorial brain

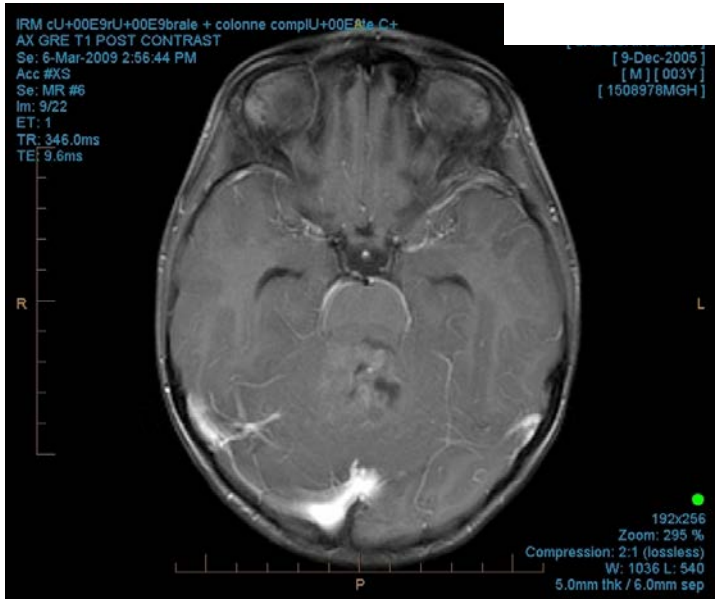
Reduced volume tumour bed boost

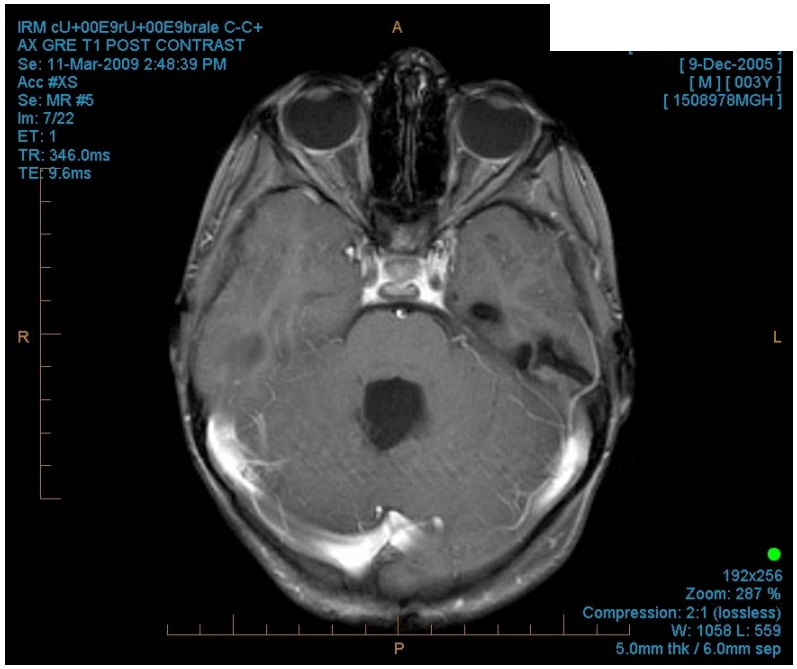
	Years of study	Number of patients	CSI/ whole PF dose	Treatment volume for tumour bed boost	Isolated failures in PF outside boost volume
Merchant 1999	1994-1996	10	0-36Gy	TB + 1-2 cm + 0.5 cm	0
Wolden 2003	1994-2002	32	23.4-36Gy	TB + 1-2 cm + 0.5 cm	1 (@ 84 mo)
Douglas 2004	1994-2001	33	23.4Gy	TB + 2 cm to block edge	0
Carrie 2005	1998-2001	48	36Gy/36 fx (HFRT)	TB + 1.5 cm	0
Merchant 2008	1996-2003	86	23.4Gy/36 Gy	TB + 2 cm + 0.5 cm	max 3

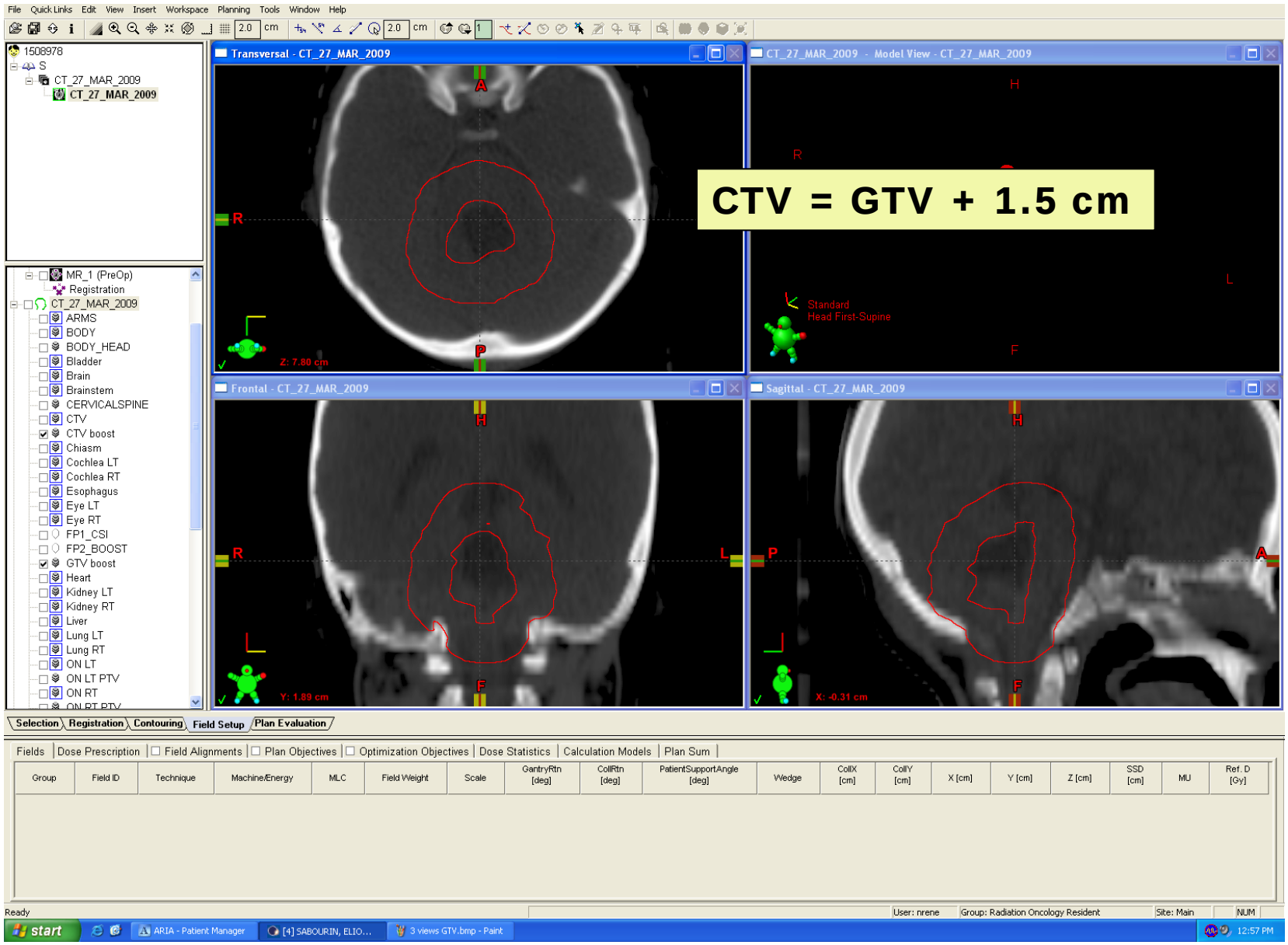
Limit volume boost (ACNS0331)

- 3D planning mandatory using CT-MRI co-registration
- GTV based on pre-op extent of disease, taking account of shifts that have taken place since surgery i.e., any macroscopic residual + wall of surgical cavity
- Margin for CTV of 1.5 cm


IRM cU+00E9rU+00E9brale + colonne complU+00E9te C+
SAG GRE T1 POST CONTRAST
Se: 6-Mar-2009 3:00:36 PM
Acc #XS
Se: MR #7
Im: 10/20
ET: 1
TR: 346.0ms
TE: 9.6ms
[9-Dec-2005]
[M] [003Y]
[1508978MGH]
A
P
256x256
Zoom: 287 %
Compression: 2:1 (lossless)
W: 976 L: 541
5.0mm thk / 6.0mm sep


IRM cU+00E9rU+00E9brale + colonne complU+00E9te C+
AX GRE T1 POST CONTRAST
Se: 6-Mar-2009 2:56:44 PM
Acc #XS
Se: MR #6
Im: 9/22
ET: 1
TR: 346.0ms
TE: 9.6ms
[9-Dec-2005]
[M] [003Y]
[1508978MGH]
R
L
P
192x256
Zoom: 295 %
Compression: 2:1 (lossless)
W: 1036 L: 540
5.0mm thk / 6.0mm sep


IRM cU+00E9rU+00E9brale C-C+
AX GRE T1 POST CONTRAST
Se: 11-Mar-2009 2:48:39 PM
Acc #XS
Se: MR #5
Im: 7/22
ET: 1
TR: 346.0ms
TE: 9.6ms
A
[9-Dec-2005]
[M] [003Y]
[1508978MGH]
R
L
P
192x256
Zoom: 287 %
Compression: 2:1 (lossless)
W: 1058 L: 559
5.0mm thk / 6.0mm sep


CTV = GTV + 1.5 cm
Transversal - CT_27_MAR_2009
CT_27_MAR_2009 - Model View - CT_27_MAR_2009
Frontal - CT_27_MAR_2009
Sagittal - CT_27_MAR_2009
Standard
Head First-Supine
Z: 7.80 cm
Y: 1.89 cm
X: -0.31 cm
1508978
S
CT_27_MAR_2009
MR_1 (PreOp)
Registration
ARMS
BODY
BODY_HEAD
Bladder
Brain
Brainstem
CERVICALSPINE
CTV
CTV boost
Chiasm
Cochlea LT
Cochlea RT
Esophagus
Eye LT
Eye RT
FP1_CSI
FP2_BOOST
GTV boost
Heart
Kidney LT
Kidney RT
Liver
Lung LT
Lung RT
ON LT
ON LT PTV
ON RT
Selection
Registration
Contouring
Field Setup
Plan Evaluation
Fields
Dose Prescription
Field Alignments
Plan Objectives
Optimization Objectives
Dose Statistics
Calculation Models
Plan Sum
Group
Field ID
Technique
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MLC
Field Weight
Scale
GantryRtn [deg]
CollRtn [deg]
PatientSupportAngle [deg]
Wedge
CollX [cm]
CollY [cm]
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Group: Radiation Oncology Resident
Site: Main
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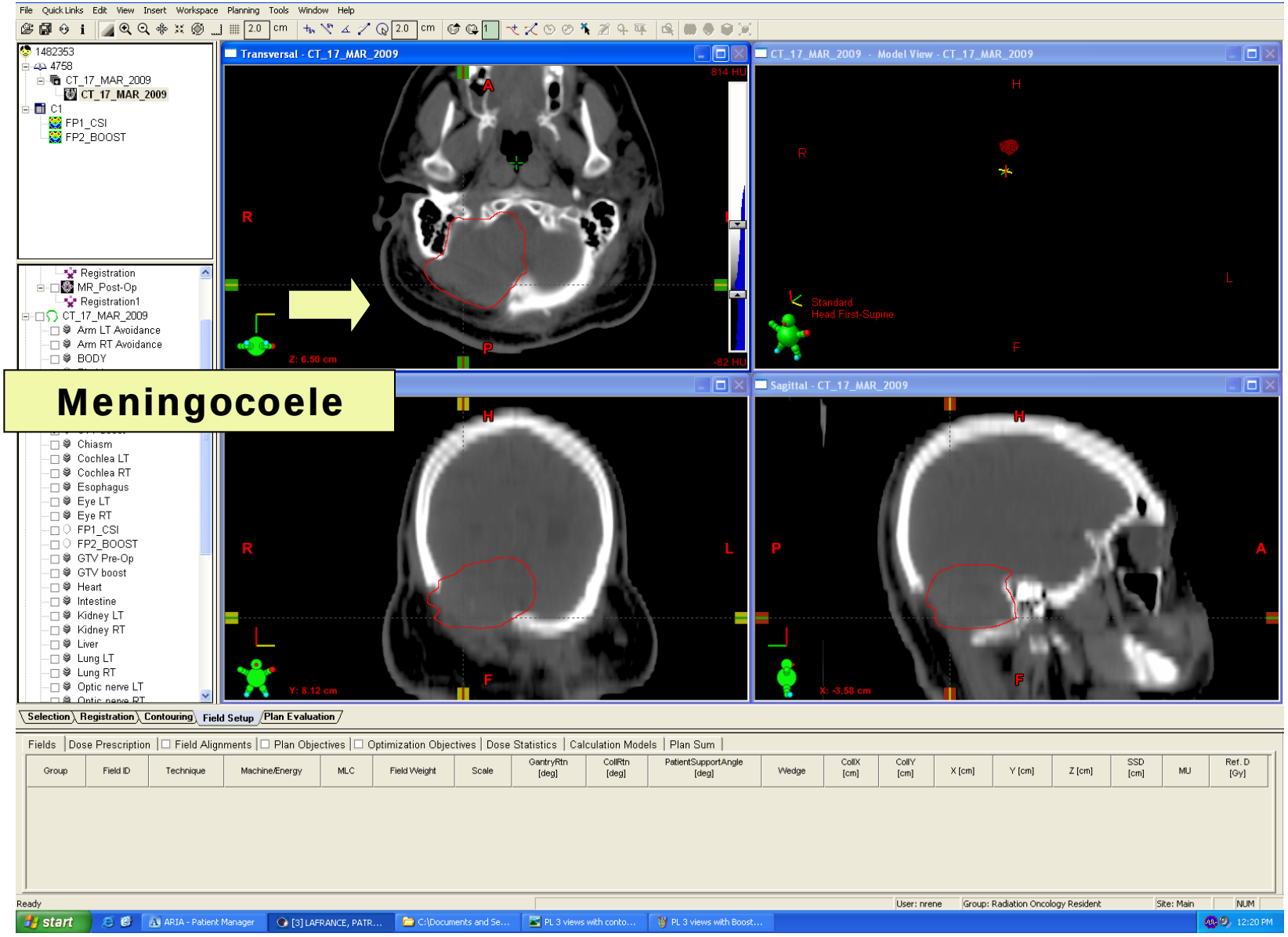
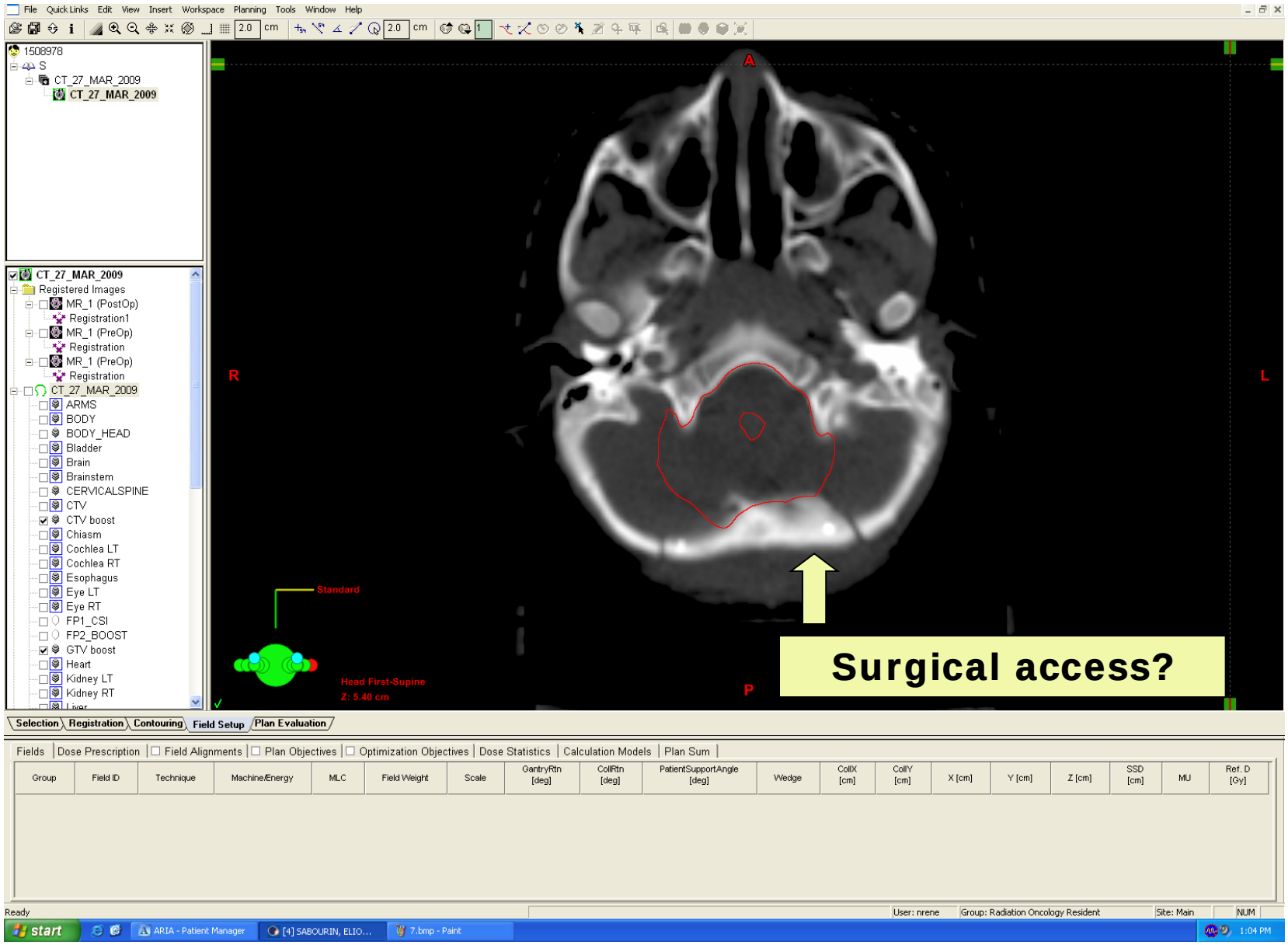


Meningocoele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Field Weight
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Ref. D [Gy]
Ready
User: nrene
Group: Radiation Oncology Resident
Site: Main
NUM
start
ARIA - Patient Manager
[4] SABOURIN, ELIO...
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Medulloblastoma: the management

- **High risk medulloblastoma**

Medulloblastoma

- High risk: intensify treatment/use novel treatment approaches

Historic outcome for conventional RT and chemotherapy for M2-M3 MB

Study	Entry Period	Outcome at 3 years
SIOP 2	1984-1989	43% EFS
HIT-91	1991-1997	30% PFS
PNET-3	1992-2000	39.7% EFS

Milan HART Study

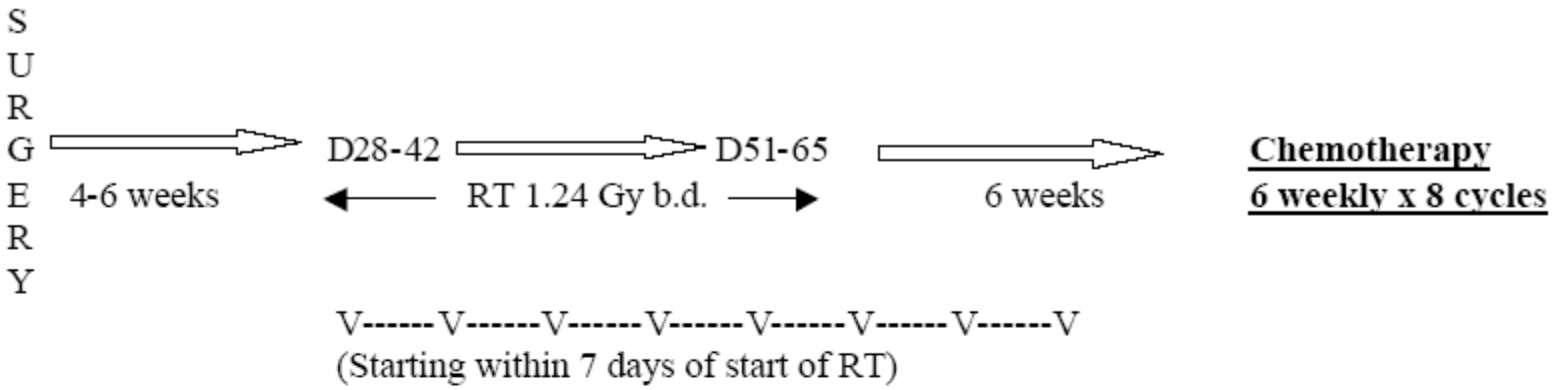
- 1998-2007
- 33 pts (M1 9, M2 6, M3 17, M4 1)
- High dose chemotherapy approach
- HART: CSI 39 Gy; 1.3 Gy bid
  posterior fossa boost up to 60 Gy; 1.5 Gy bid

- 7 pts aged < 10 yrs who achieved CT after chemo received a lower dose to the neuraxis (31.2 Gy)

- Median 82 months follow-up

- 5 yr EFS 70%
- 5 yr PFS 72%
- 5 yr OS 73%

UK HART: High Risk



***Radiotherapy (RT)**

Brain – 39.68 Gy in 32 fractions of 1.24 Gy over 16 treatment days
Spine - 39.68 Gy in 32 fractions of 1.24 Gy over 16 treatment days
Primary tumour boost – 22.32 Gy in 18 fractions of 1.24 Gy over 9 treatment days
Total dose to primary – 62.00 Gy in 50 fractions of 1.24 Gy
Boost to metastases – 9.92 Gy in 8 fractions of 1.24 Gy over 4 treatment days

Chemotherapy

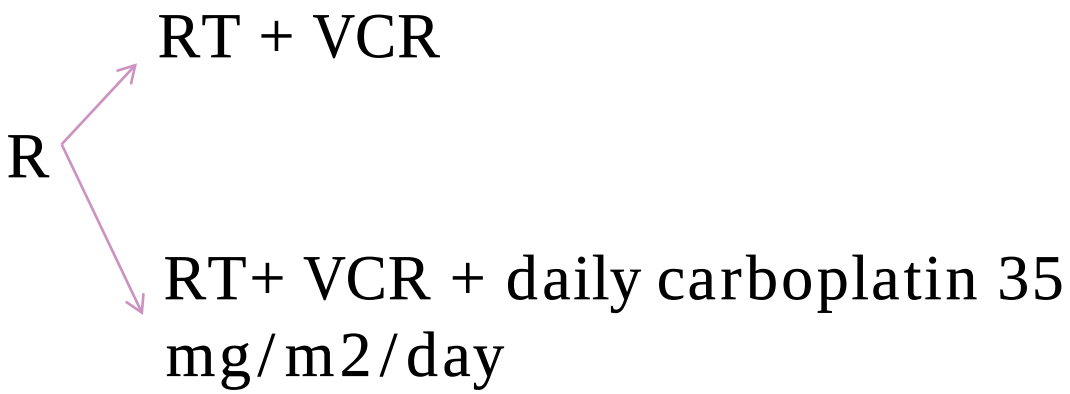
V – Vincristine 1.5 mg/m^2 (maximum 2 mg)
C – Lomustine (CCNU) 75 mg/m^2
P - Cisplatin 70 mg/m^2

Weeks					
1	2	3	4	5	6
V------	V------	V------	------	------	------
C					
P					

ESTRO School

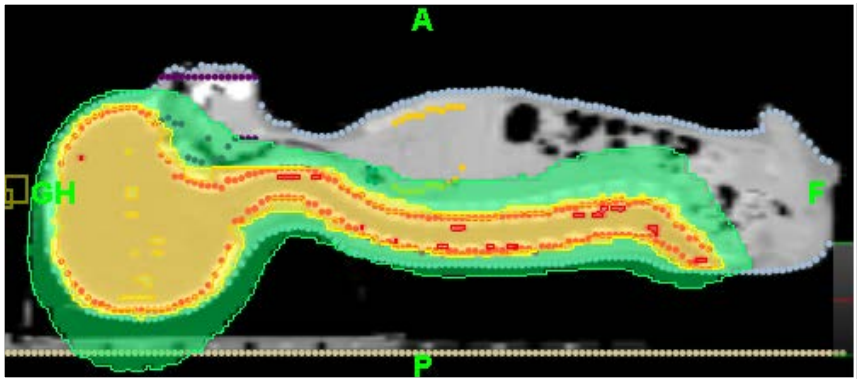
COG ANS0332 - Radiosensitisation study

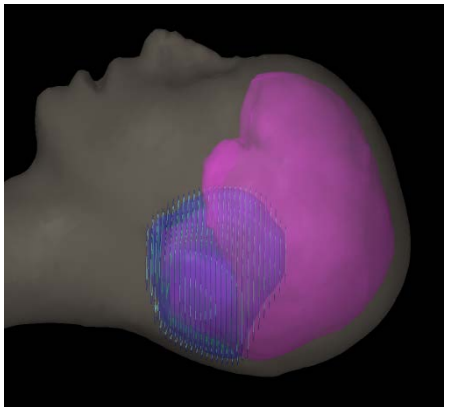
- Opened March 2007
- Planned recruitment 300
- RT: CSRT 36 Gy, post fossa 55.8 Gy
- Maintenance chemo cisplatin/VCR/Cy



Radiotherapy dose

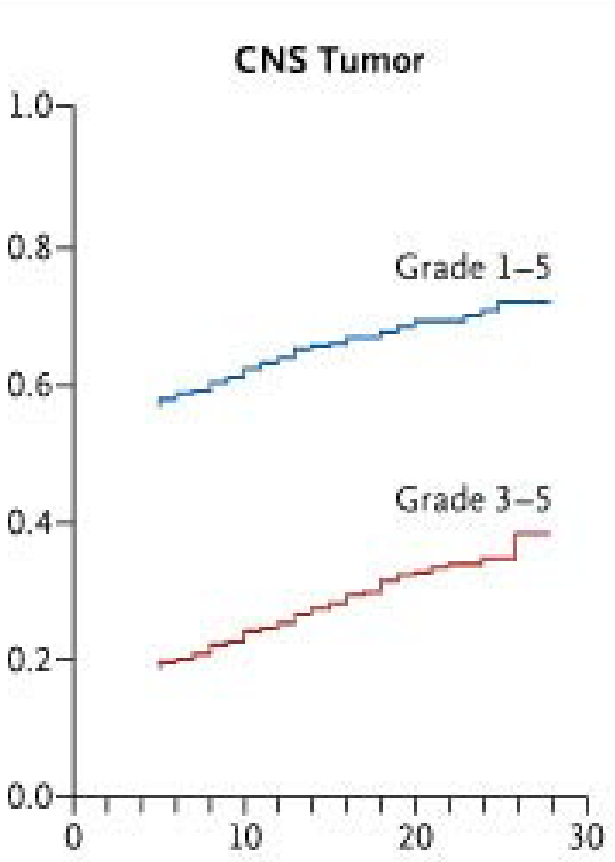
- CSI
  - High risk
    - 36(-39.4)Gy/20(-23) daily fractions of 1.8Gy
- Primary site
    - Total dose 54-55.8Gy





Long-term complications of treatment

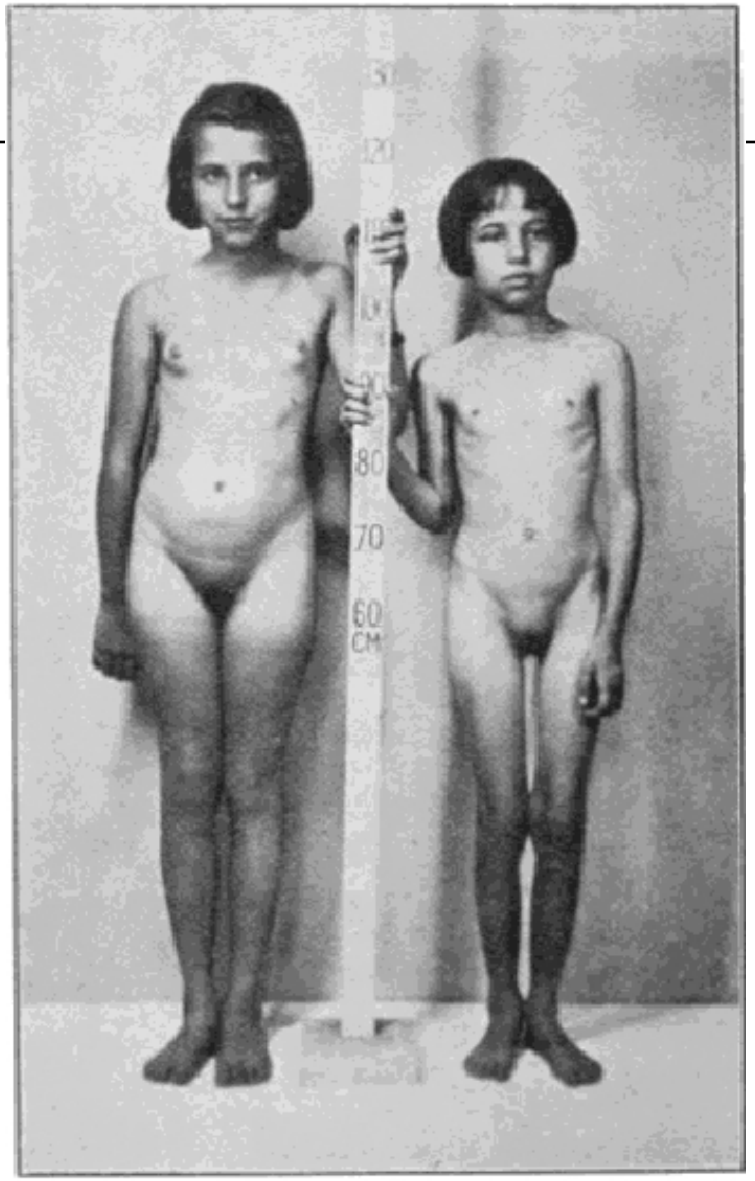
- Overall 62.3% of survivors of childhood cancer have at least one chronic health problem and 27.5% have a severe/life-threatening one
- Survivors of CNS tumours most likely to be functionally impaired



Oeffinger, N Engl J Med 2006

- MB poorest overall health of all CNS tumours
- Multiple health problems
  - Very frequent
  - Some related to tumour, surgery
  - Worse with chemo-RT than with RT alone

Late effects of CSI



Late toxicity related to CSI

- Due to radiotherapy to the brain
  - Neuro-cognitive deficits/effects on social interactions
  - Hypopituitarism
  - Alopecia
  - Cataracts
  - Hearing loss
- Due to radiotherapy to the spine
  - Short stature
  - Primary hypothyroidism
  - Impaired lung function
  - Effects on the heart
  - Primary ovarian failure
- Both
  - Second cancers…

How can we reduce the risks associated with CSI?

- Second cancers
  - Patients with MB at highest risk of a 2nd malignancy of all CNS tumours
    - Actuarial risk at 20-30 years 4-10%
  - Especially
    - 2nd CNS tumour (glioma, meningioma)
    - Soft tissue sarcoma incl desmoid
    - Thyroid
    - Skin cancers
- Risk reduction
  - Reduce dose outside the target
    - New techniques

IMRT for the spine field

- IMRT reduces high dose exposure to all organs at risk:
  - Thyroid
  - Lungs
  - Heart
  - Liver
  - Kidneys
  - Ovaries

- ... at the expense of increased low dose exposure

Concluding remarks

- Radiotherapy is an indispensable component in medulloblastoma treatment
- CSI is a complex treatment that for optimal results must be done properly
- Reduced dose to OARs is possible using new techniques
- Tremendous progress in medulloblastoma treatment over the last 20 years

Management of low grade glioma in children

Darren Hargrave

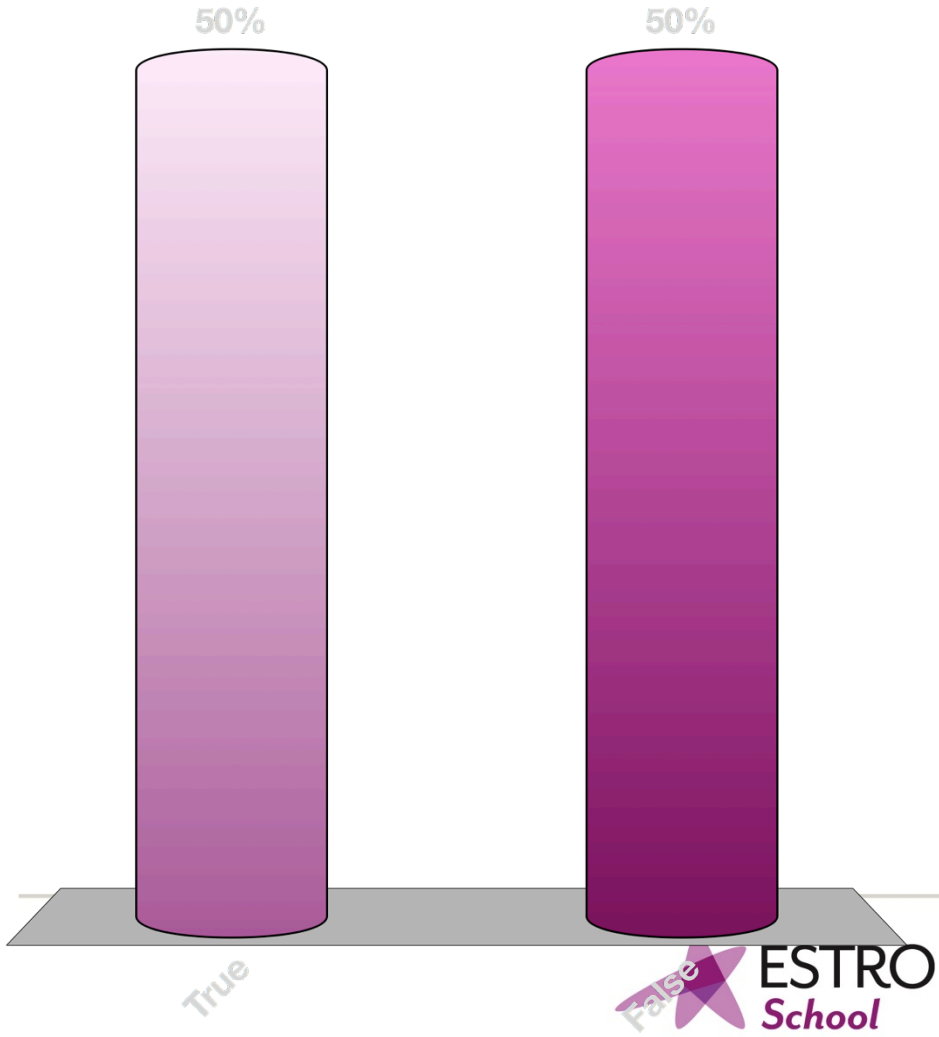
Consultant Paediatric Oncologist,

Neuro-oncology & Experimental Therapeutics

Great Ormond Street Hospital. London, UK.

Pathology of LGG in adults and children is usually the same!

A. True
B. False

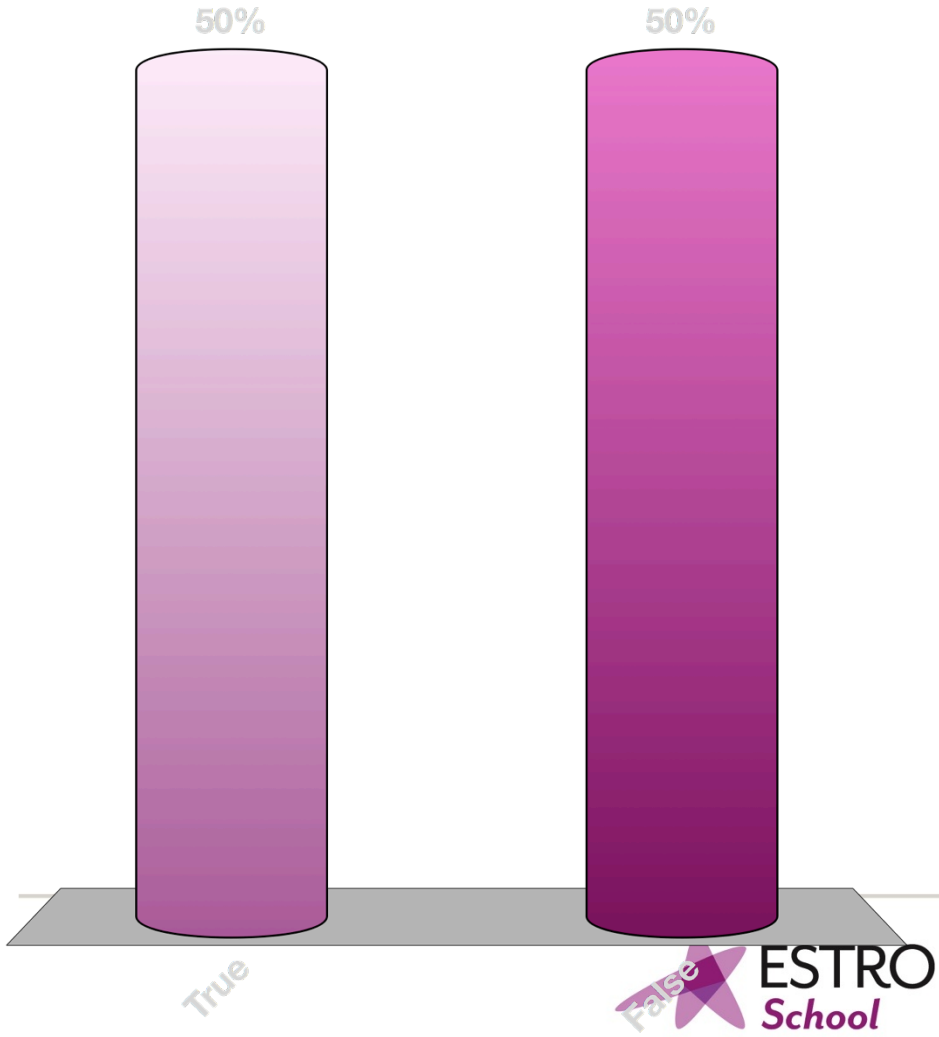


ESTRO School

Most common location for childhood LGG is cerebral hemisphere

A. True

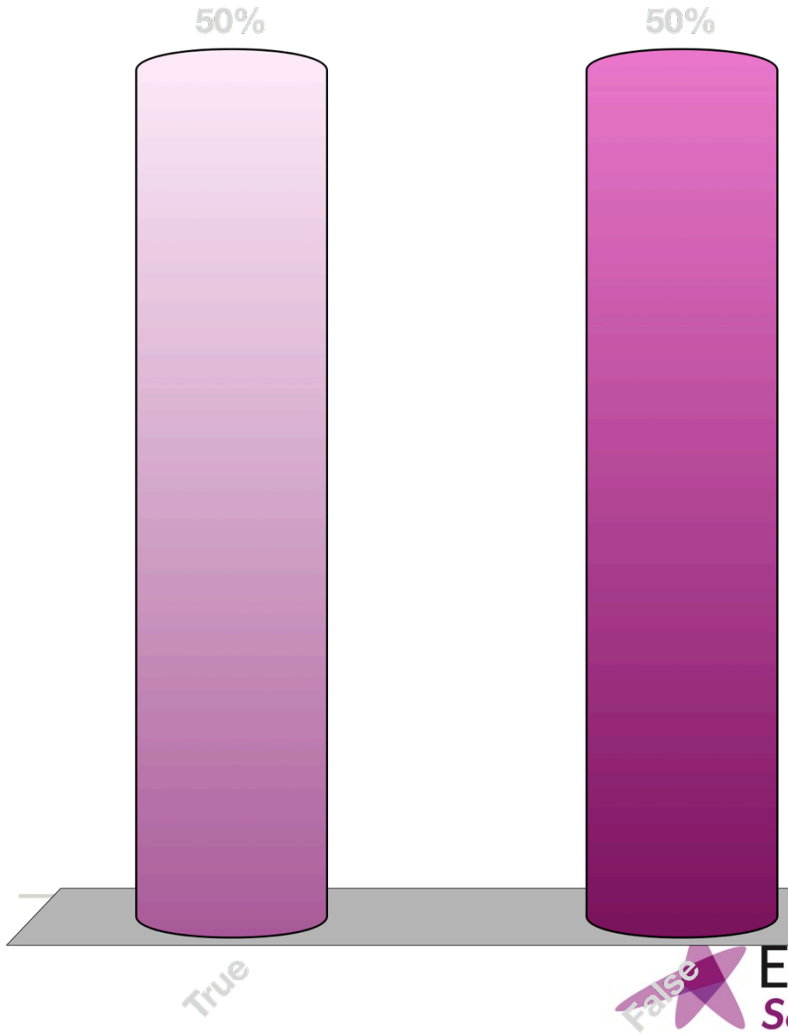
B. False



ESTRO School

LGG in children <1 year has a better prognosis!

A. True
B. False



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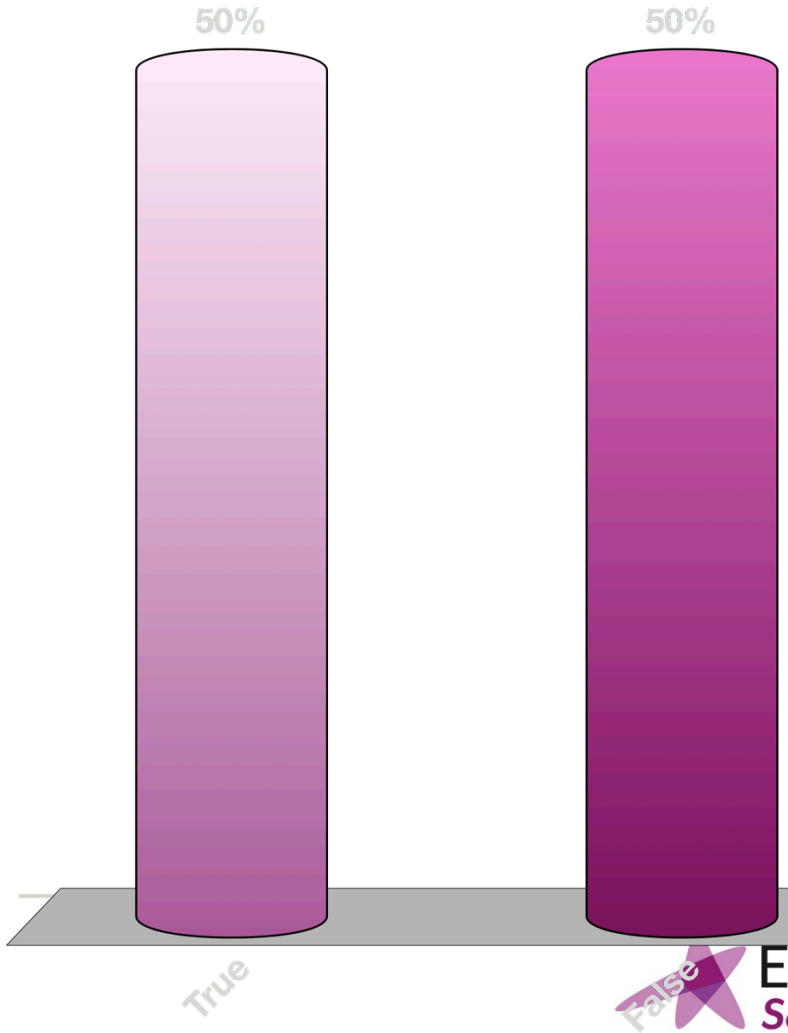
Malignant transformation rate in childhood LGG is ~30%.

A. True
B. False



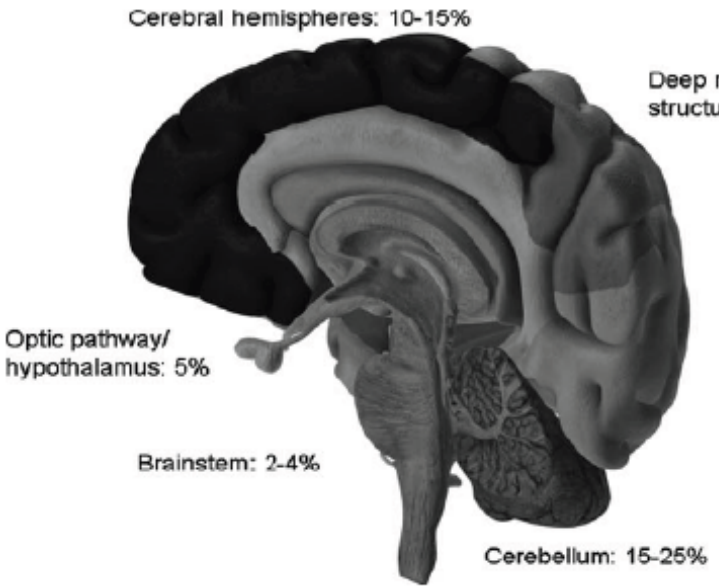
ESTRO School

Low Grade Glioma in Children

- Heterogeneous set of tumors characterised by an indolent clinical course

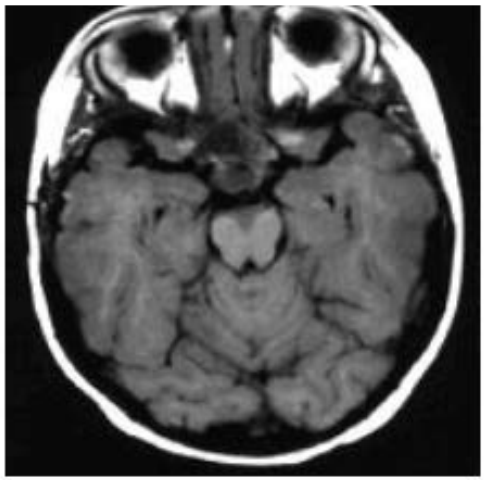
- They account for one third of all CNS tumours in the pediatric age group

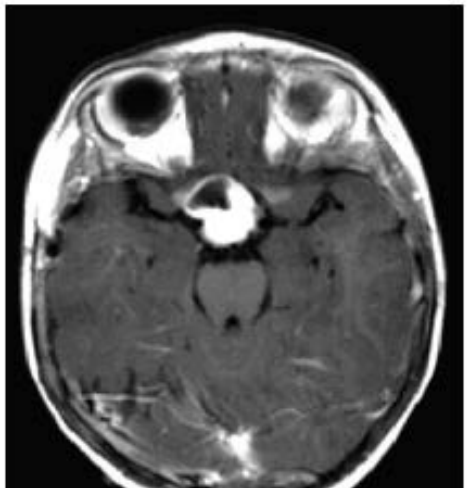
- The 2 most common low-grade glioma histologies in children are the pilocytic (WHO grade 1) and diffuse fibrillary astrocytoma (WHO grade 2)

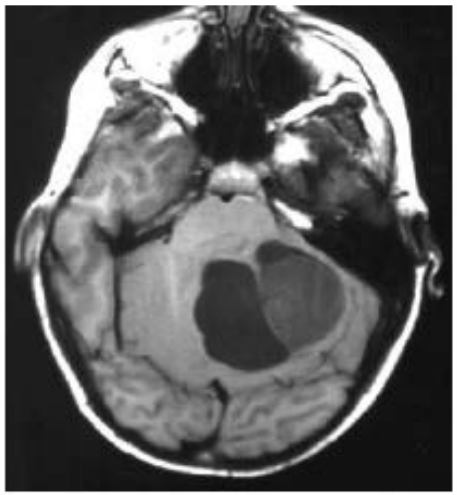


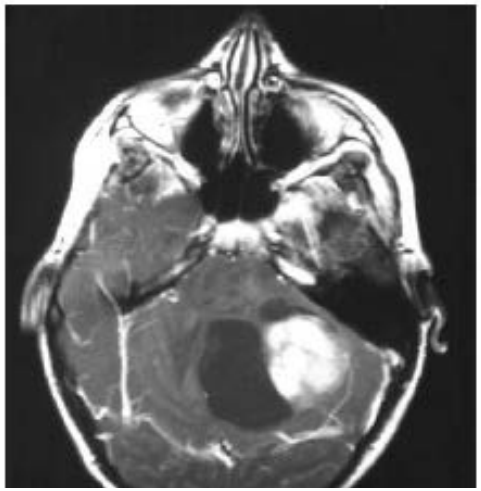
Distribution by location of LGGs

Low Grade Glioma in Children





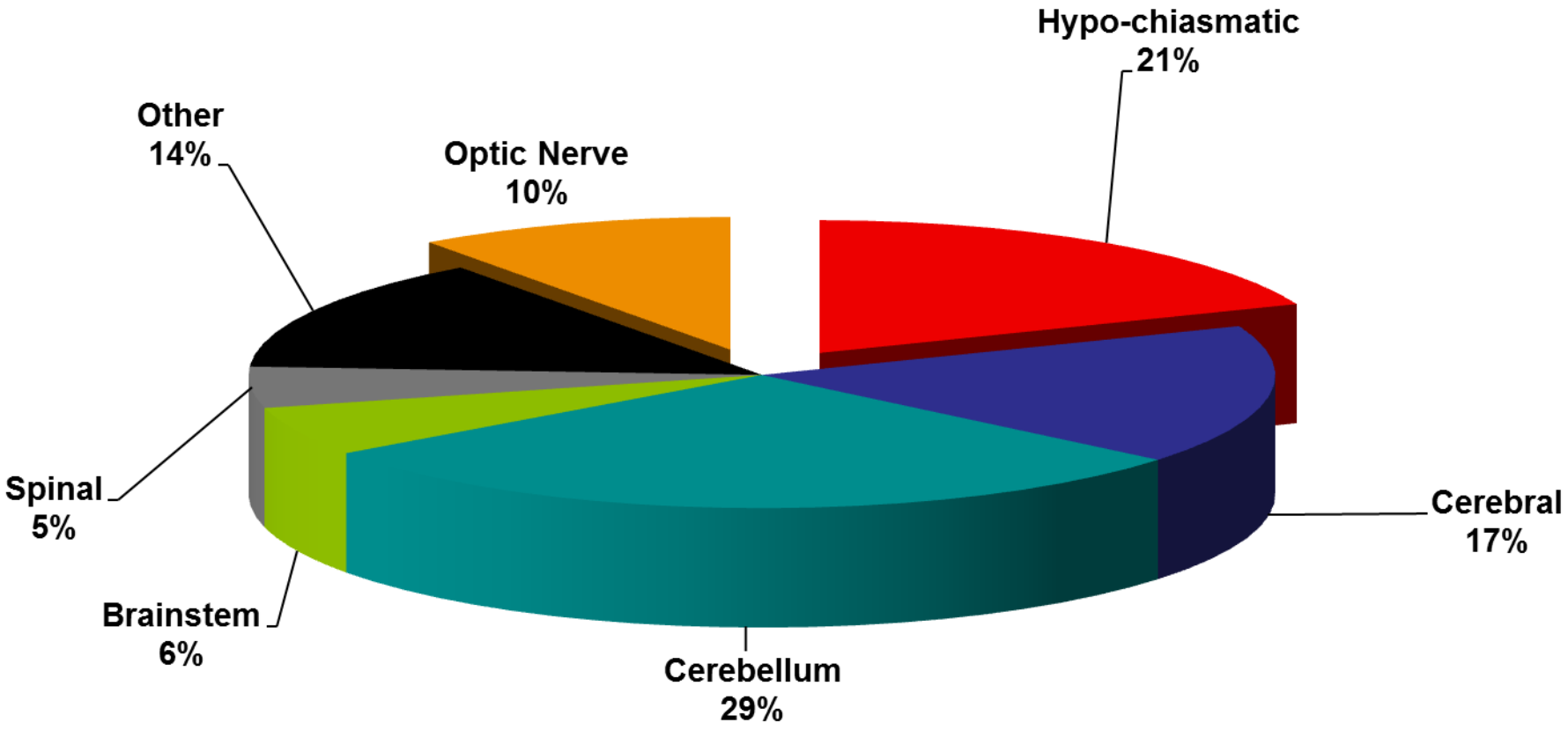




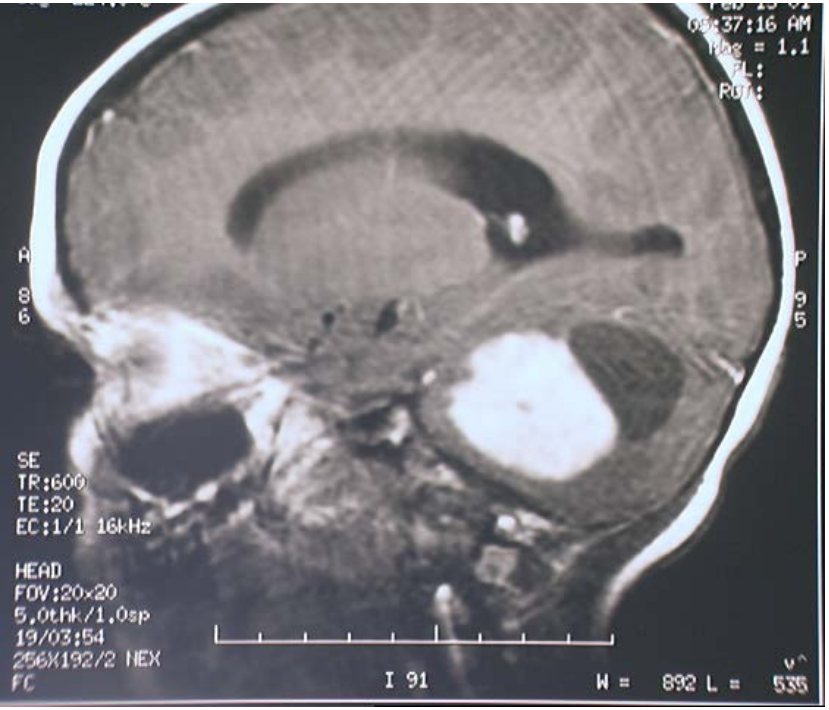
Childhood LGG

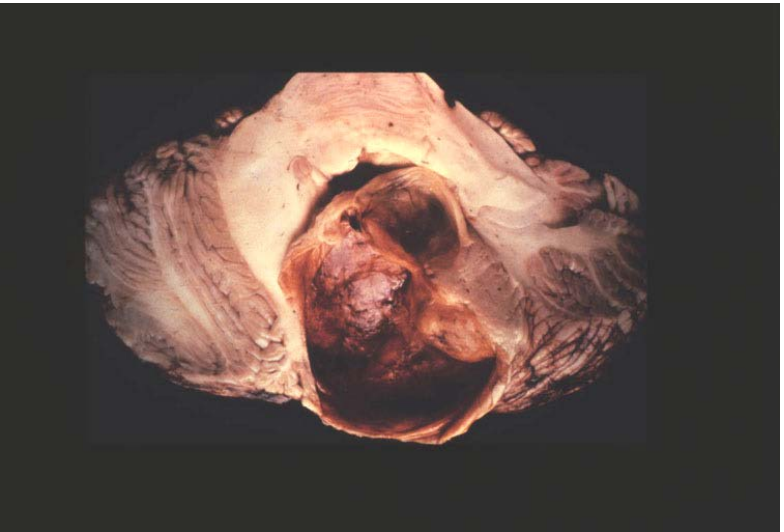
30-40% of CNS tumors

Primary Site of Low Grade Glioma

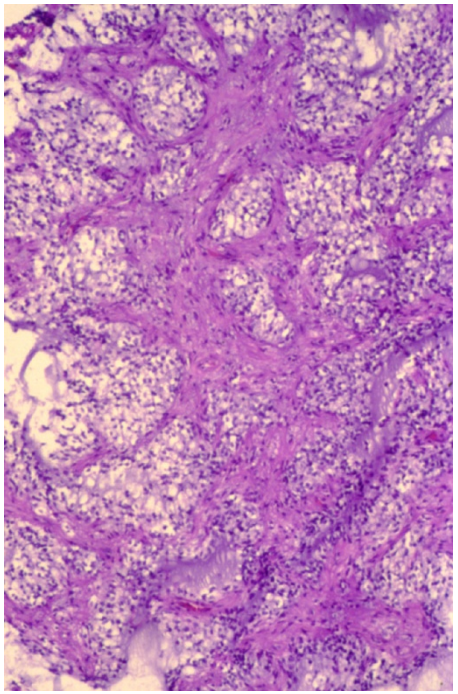


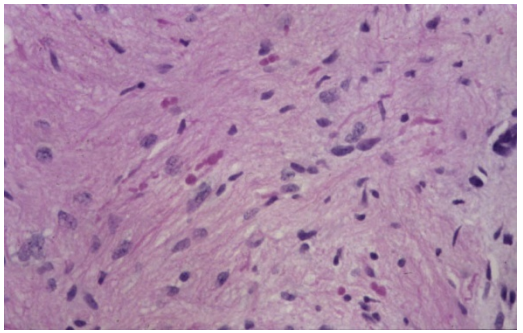
Low Grade Glioma

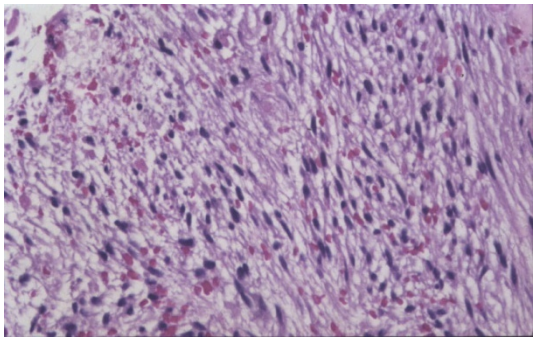




Pilocytic astrocytomas





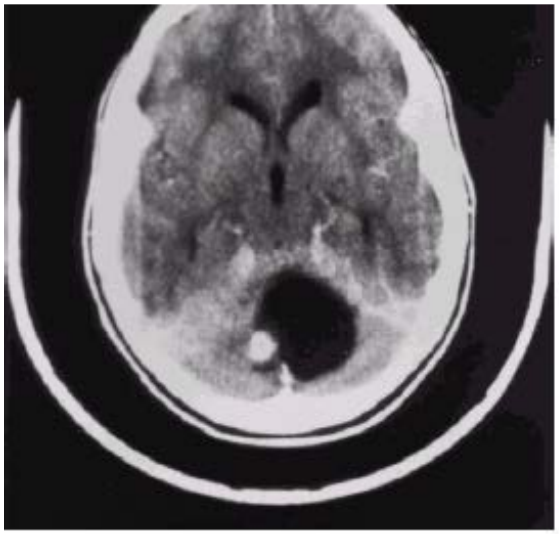


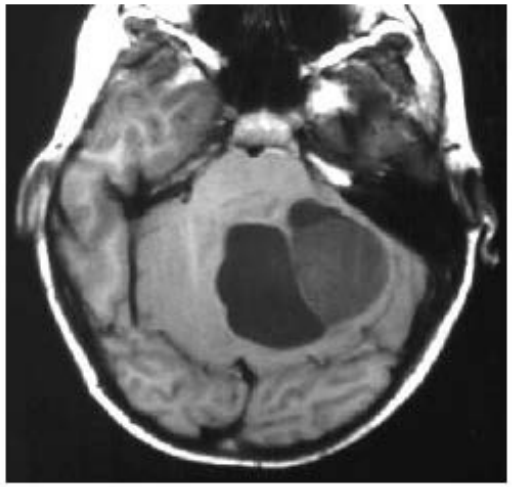
Tumor of cerebellum, often with cyst, biphasic, Rosenthal fibers, piloid cells

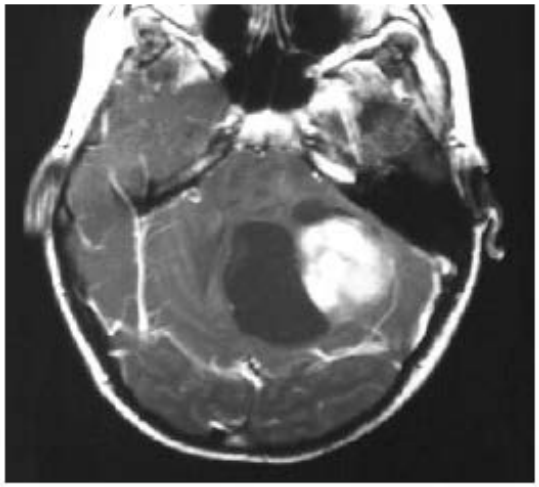
Juvenile Pilocytic Astrocytoma

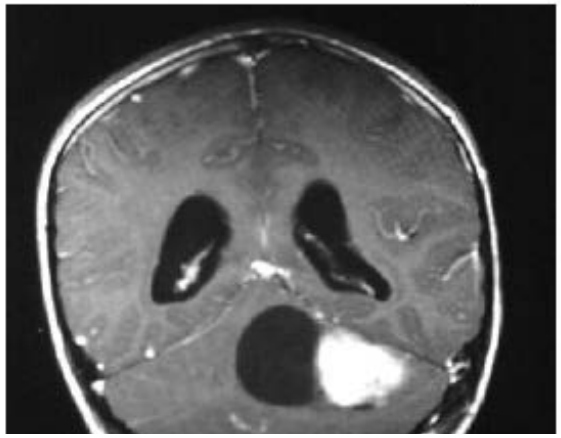
- Most common type in children
- Seen predominantly in younger children (median ~ 4 years)
- Usually well circumscribed, often partially cystic, with little oedema, no mass effect
- Enhance brightly and uniformly with contrast material
- Gross total resection often possible

Low Grade Glioma in Children

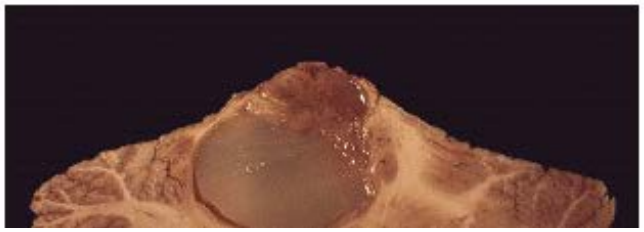


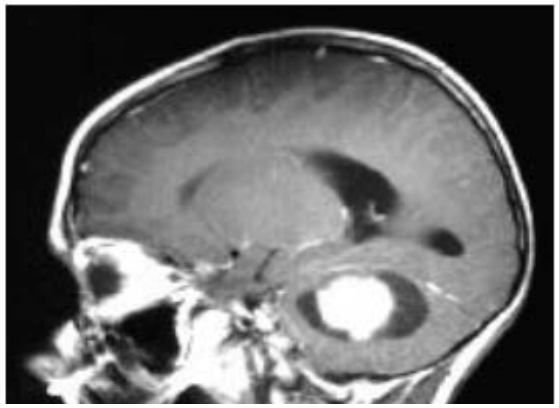






JPA

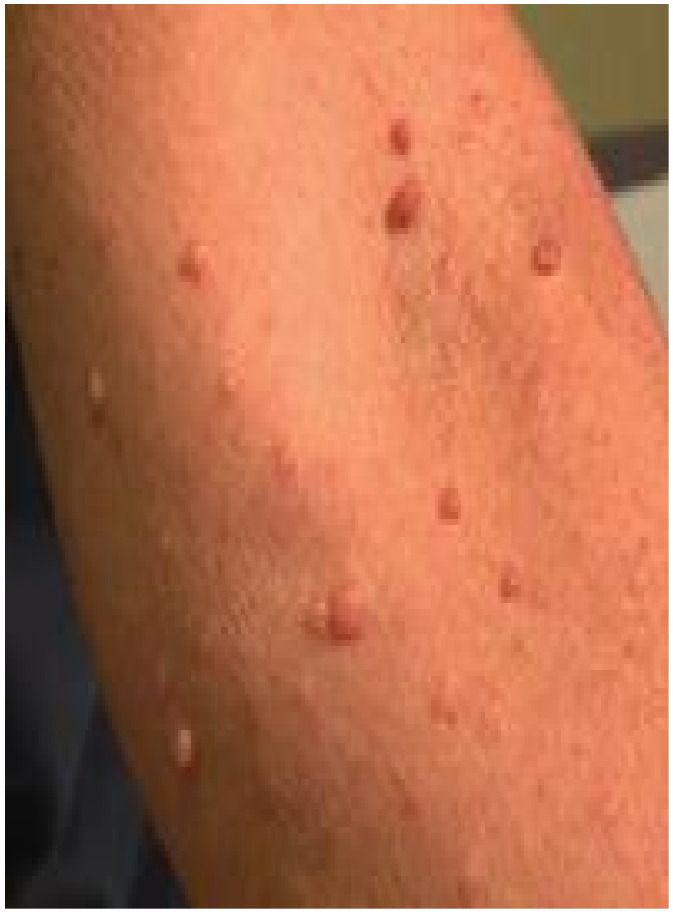


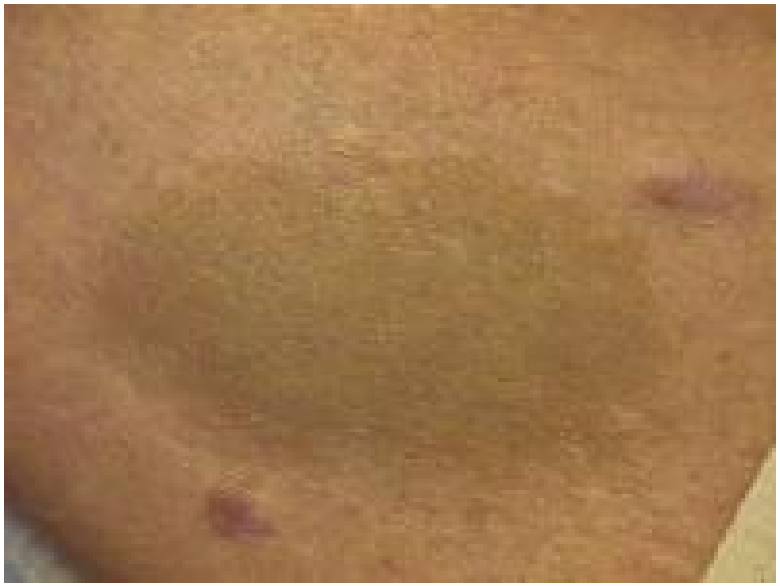


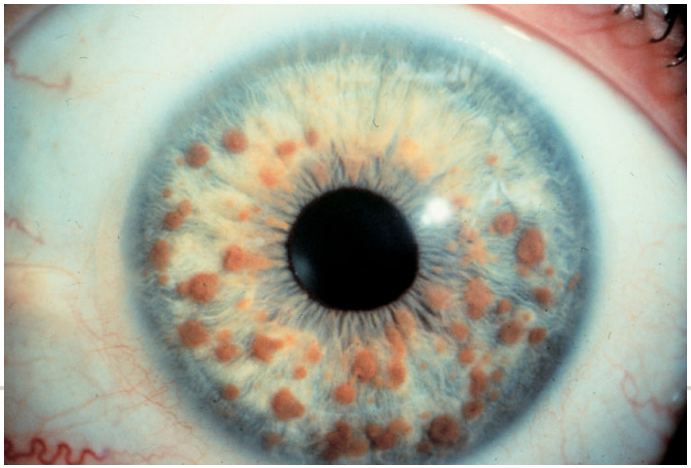
Low Grade Glioma in Children

- 30-40% of paediatric brain tumours
- Heterogeneous pathologically, anatomically, clinically and biologically
- < 5% present with leptomeningeal metastases
- Frequently protracted clinical course
- Balance between anti-tumour effects and long-term morbidity of therapy

Aetiology of Childhood LGG

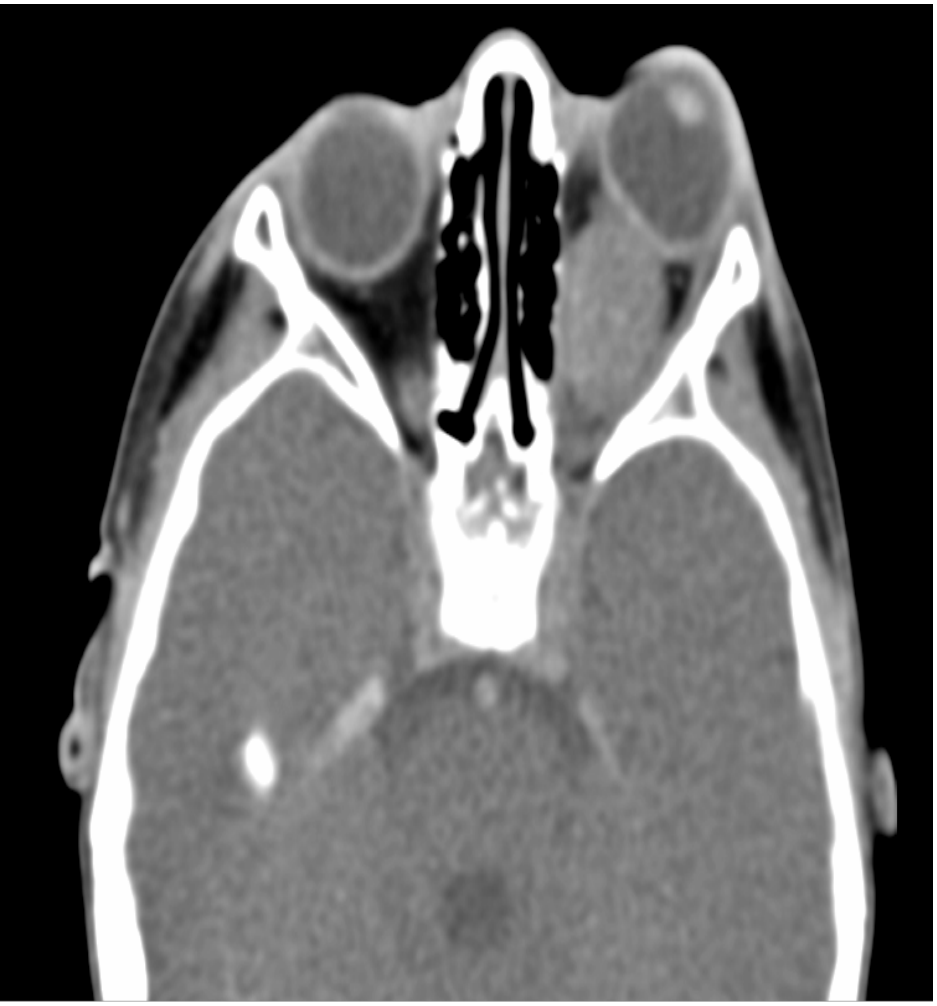


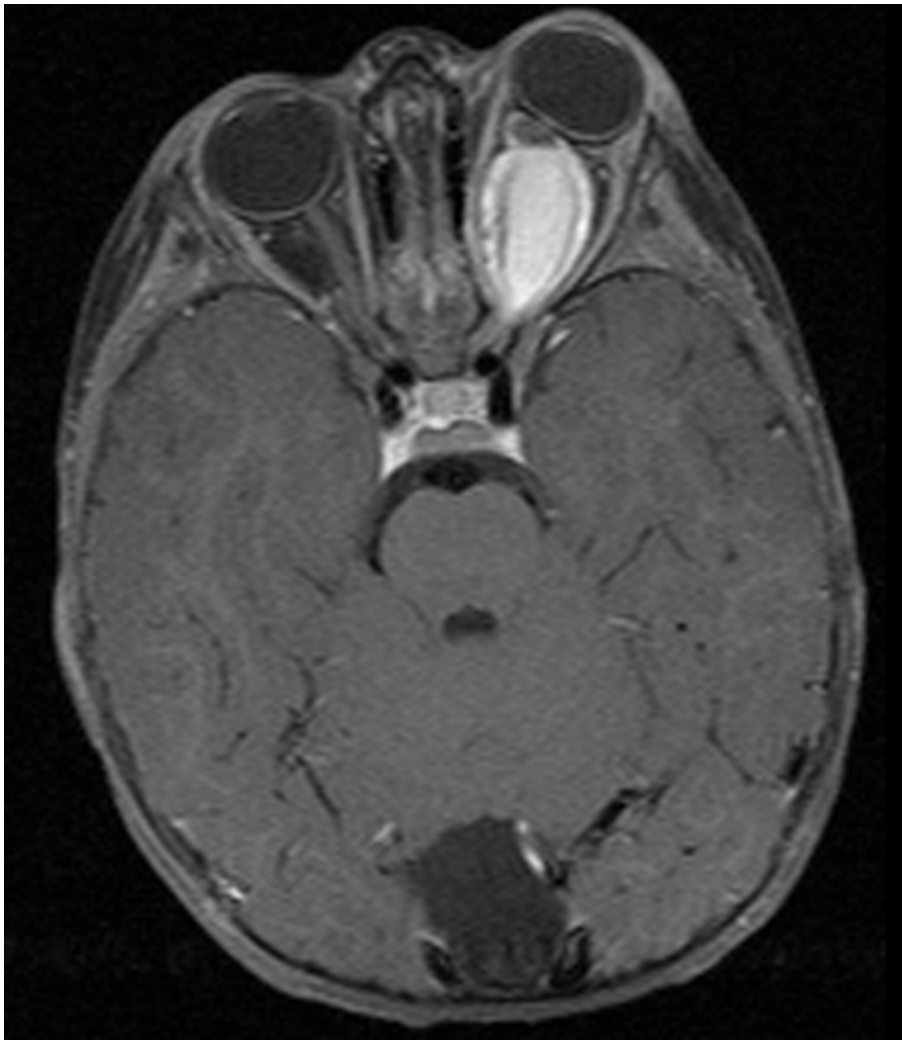




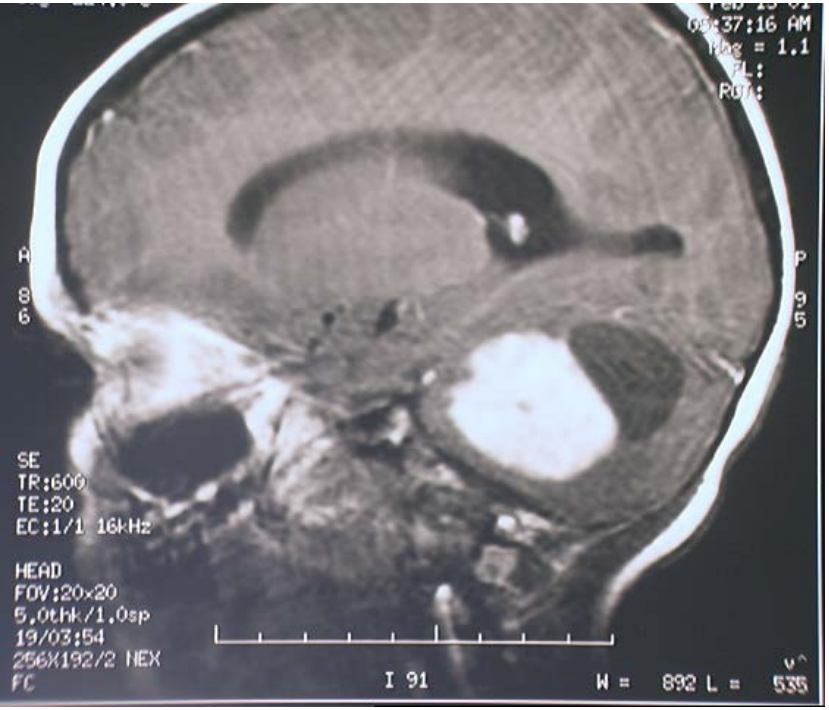
NF-1

Optic Pathway Glioma





MAPK in pLGG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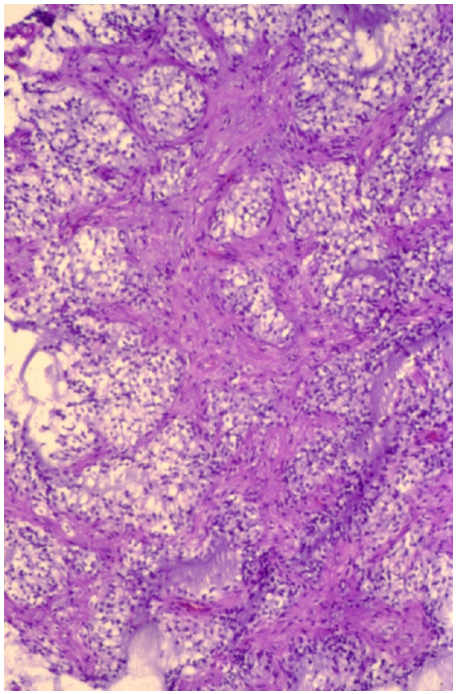
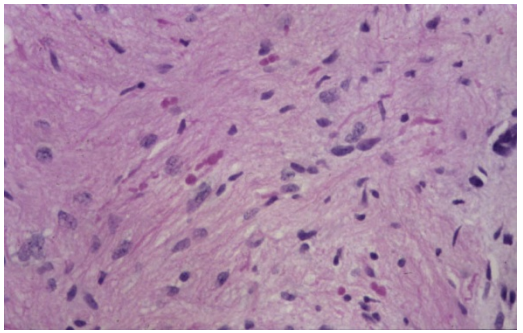
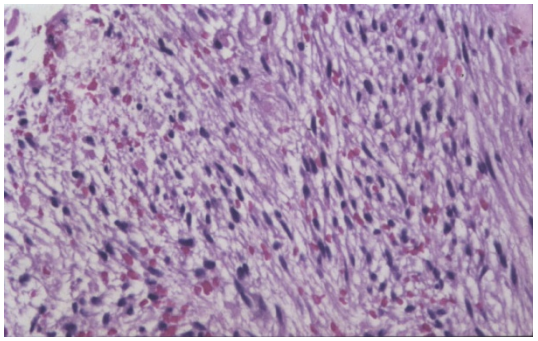
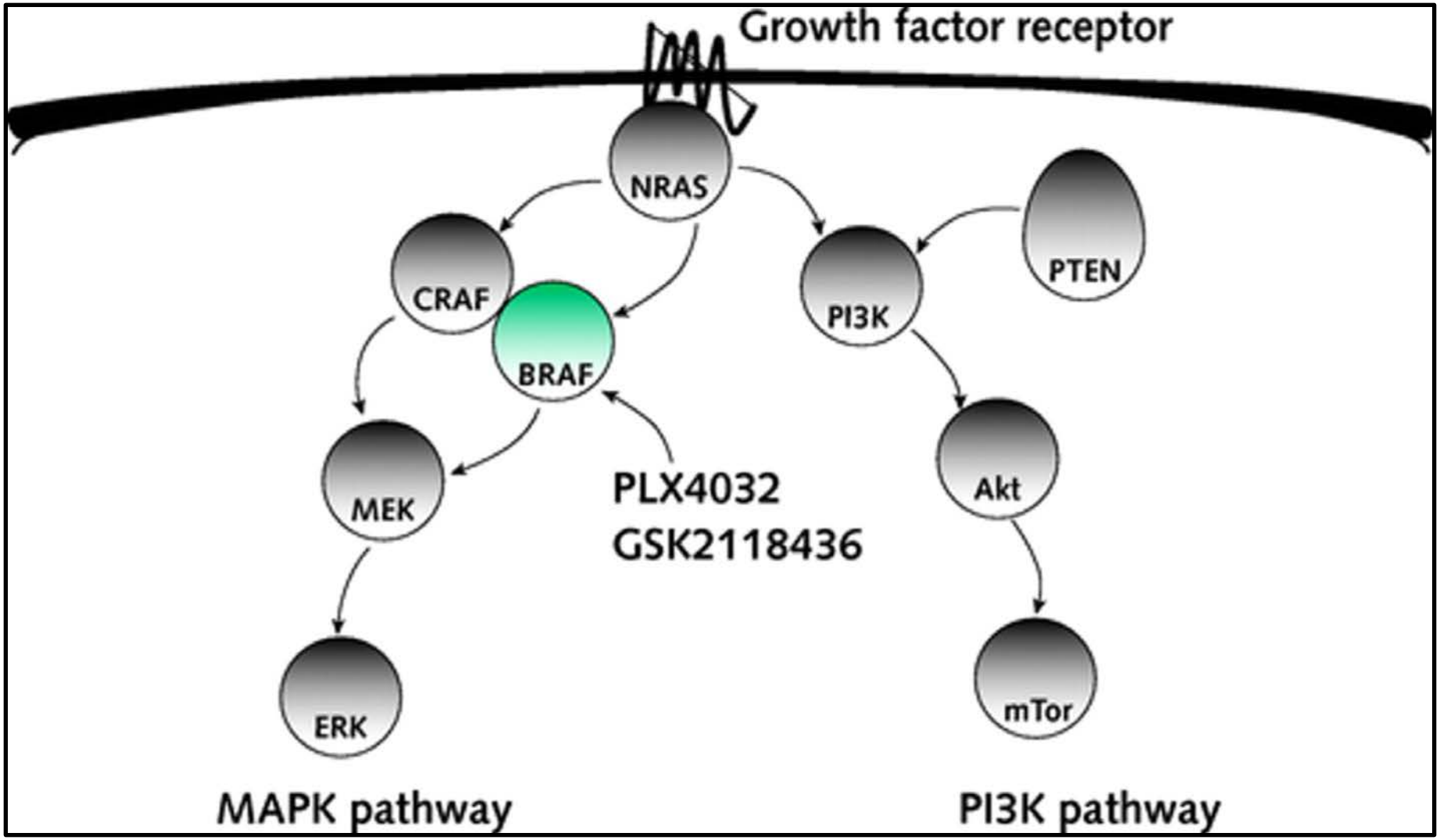
FC
I 91
W = 892 L = 535





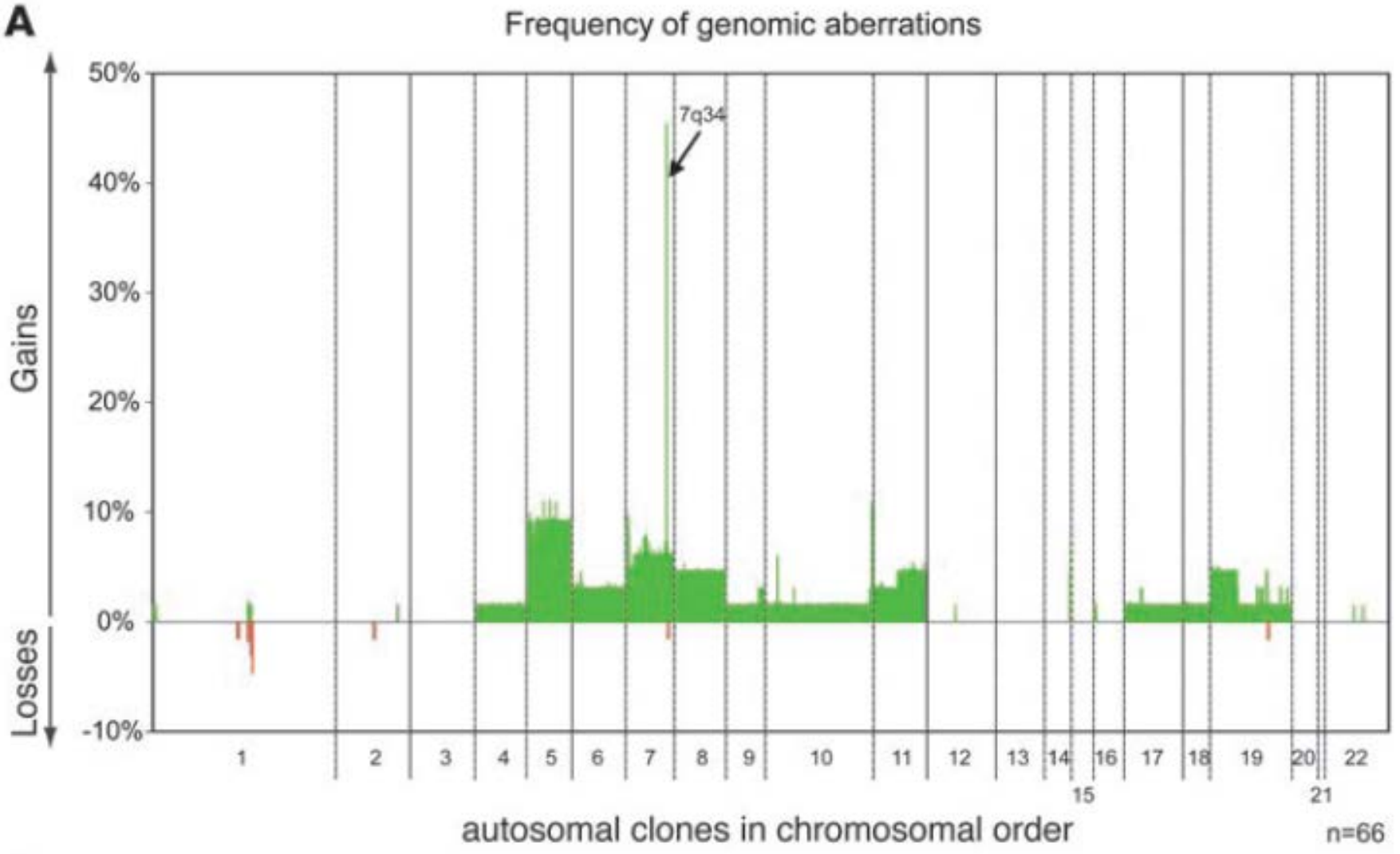


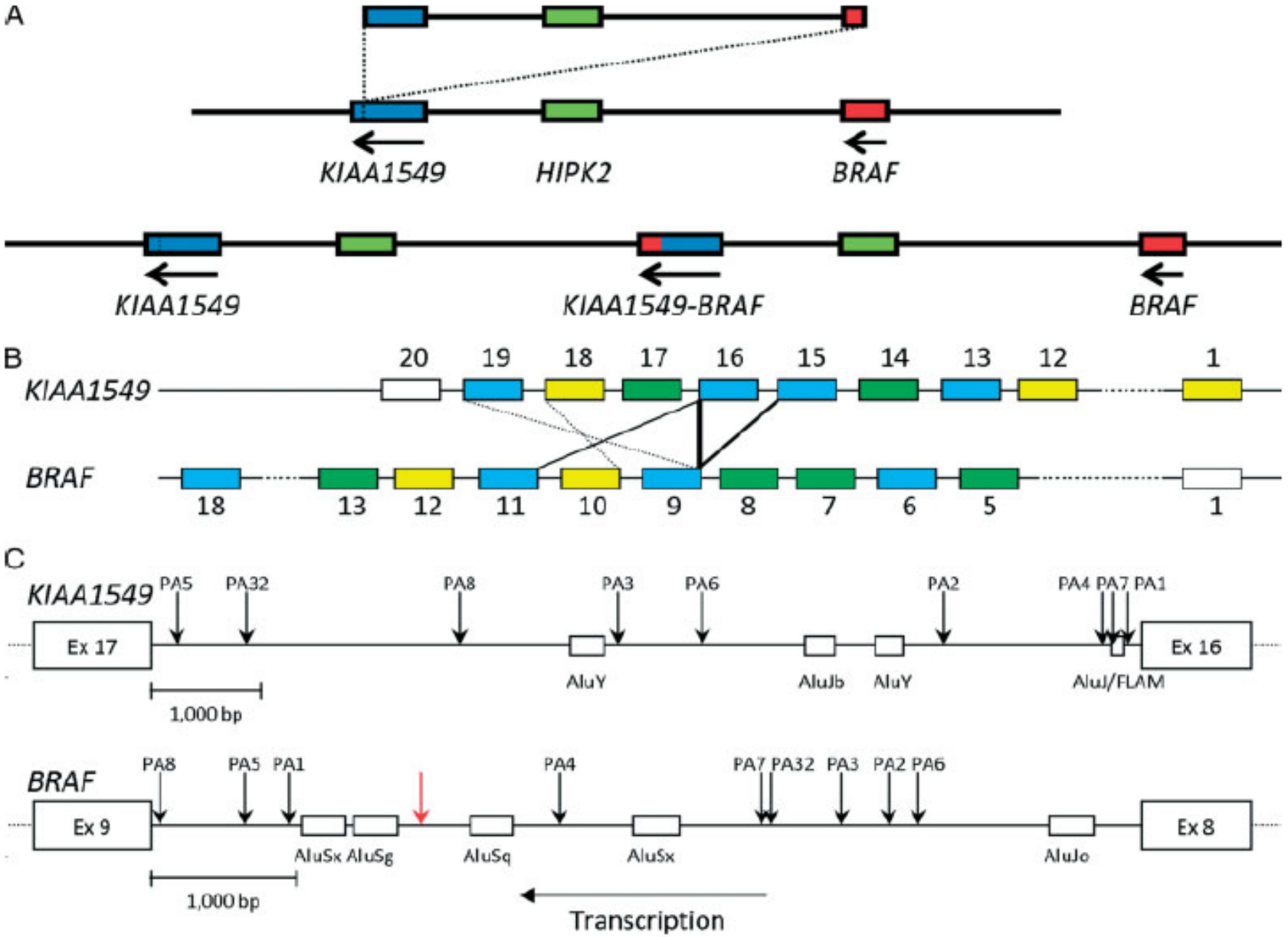
MAPK Pathway



From: Narrative Review: BRAF Opens the Door for Therapeutic Advances in Melanoma

Ann Intern Med. 2010;153(9):587-591. doi:10.7326/0003-4819-153-9-201011020-00008


A
Frequency of genomic aberrations
Gains
Losses
50%
40%
30%
20%
10%
0%
-10%
7q34
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
autosomal clones in chromosomal order
n=66


A
KIAA1549
HIPK2
BRAF
KIAA1549
KIAA1549-BRAF
BRAF
B
KIAA1549
20 19 18 17 16 15 14 13 12 1
BRAF
18 13 12 11 10 9 8 7 6 5 1
C
KIAA1549
PA5 PA32 PA8 PA3 PA6 PA2 PA4 PA7 PA1
Ex 17
Ex 16
AluY AluJb AluY AluJ/FLAM
1,000 bp
BRAF
PA8 PA5 PA1 PA4 PA7 PA32 PA3 PA2 PA6
Ex 9
Ex 8
AluSx AluSg AluSq AluSx AluJo
1,000 bp
Transcription

Recurrent somatic alterations of *FGFR1* and *NTRK2* in pilocytic astrocytoma

David T W Jones[1,39], Barbara Hutter[2,39], Natalie Jäger[2,39], Andrey Korshunov[3,4], Marcel Kool[1],

NATURE GENETICS VOLUME 45 | NUMBER 8 | AUGUST 2013

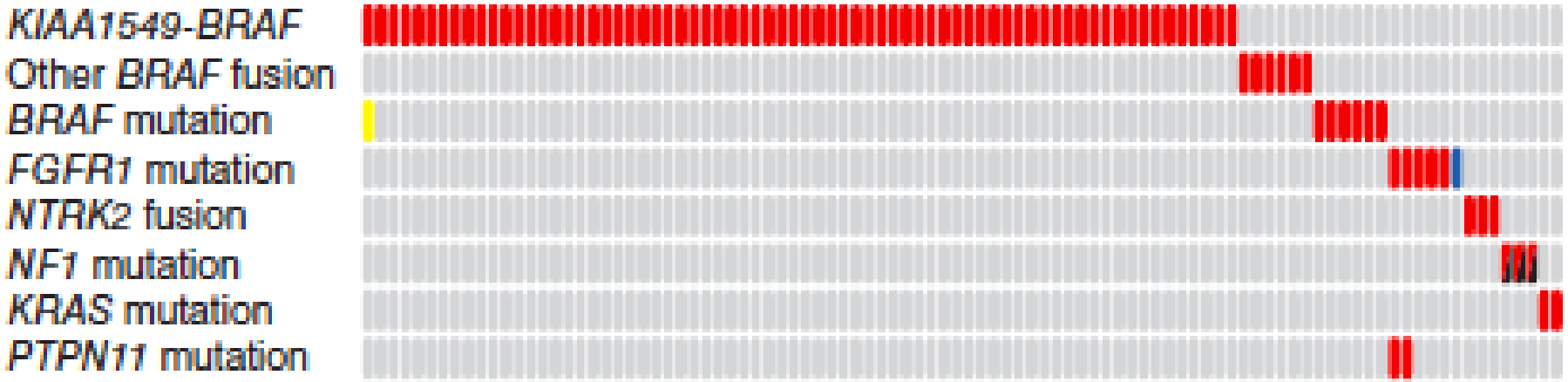


Figure 4 Summary of MAPK pathway alterations in pilocytic astrocytoma.

Surgery in LGA

- Surgery is the mainstay of treatment
- Advances in neurosurgical techniques including computer-assisted resections have resulted in much higher rates of complete resection than in the past, even for tumours in locations previously considered inaccessible (thalamus, brain stem)
- EFS and OS after complete resection 90-100%

Pylocitic astrocytoma- Management

- Surgery remains the mainstay of therapy and GTR is the most consistent prognostic factor for prolonged PFS and OS

- Adjuvant treatment? (CT/RT)

- In case of GTR → no further therapy (10-year OS rates of 90% or greater and rare tumor recurrences)

- In case of PTR → a «wait and see policy» with follow-up brain MRI at 3-6-month intervals and adjuvant treatment postponed until there is either measurable progression by neuroimaging or clinical symptoms

- In case of biopsy/no surgical approach → observation until radiographic progression if there are minimal clinical symptoms

Low grade glioma in children

- Importance of recognizing behaviour specific to particular tumor type
- Timing of intervention
- Role of adjuvant therapy following incomplete resection
- Choice of modality (Chemo/RT) for adjuvant therapy
- Issues specific to RT (target volume, treatment technique and dose)

Criteria for non-intervention in LGA

- Asymptomatic and non-progressive lesions in patients with neurofibromatosis

- Lesions in the tectal region

Eras of LGG Management
SIOP Studies

- [Pre-LGG1]
- LGG1
- LGG2
- Current/Future

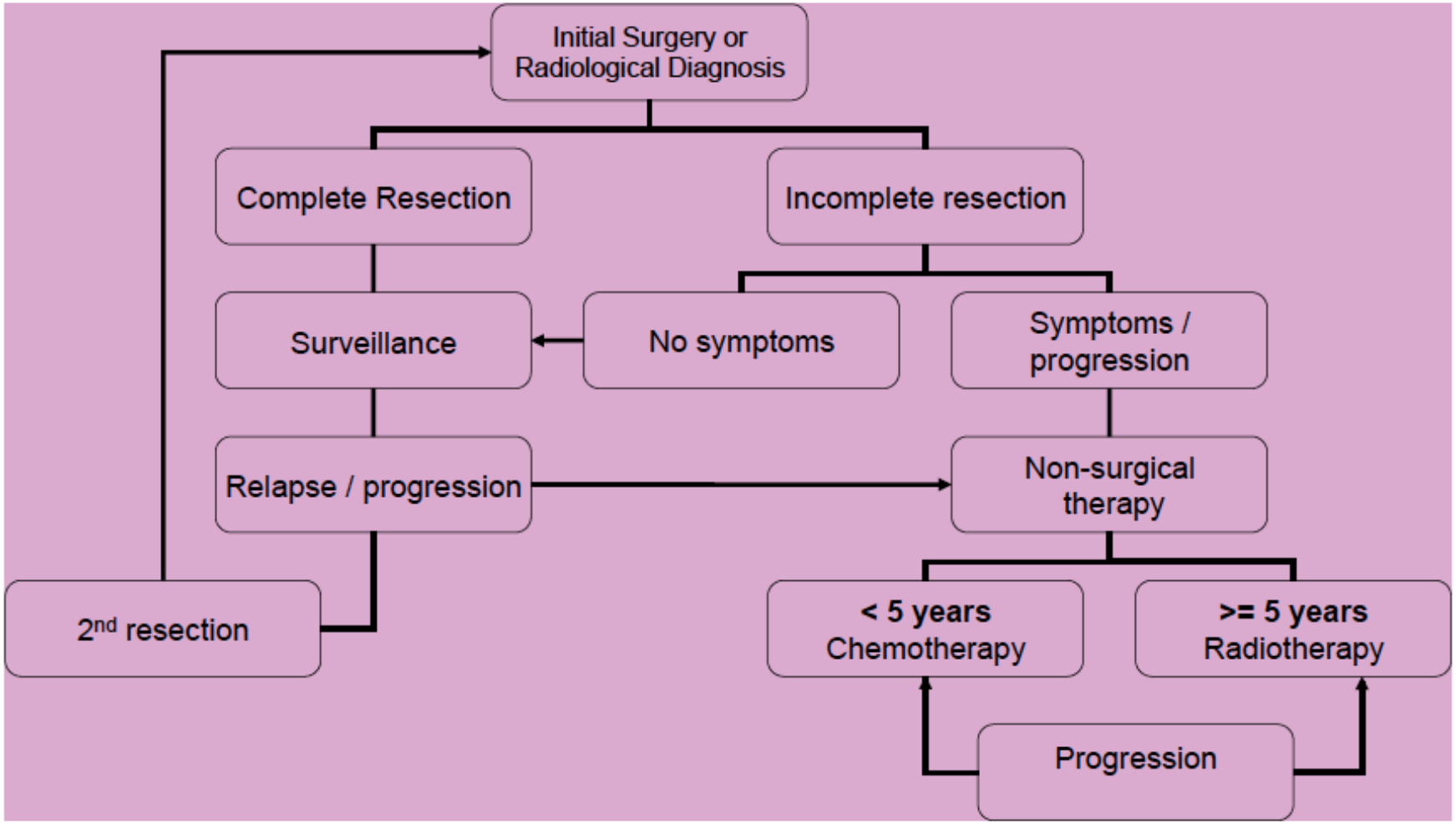
LGG1

October 1996 – March 2004

LGG1

- 1996 – 2004
- International Consortium
  - Germany, Italy, UK
- New paradigm in LGG management
- Standardised schema:
- Initial period of observation after surgery or radiological diagnosis (based on typical appearances of optic pathway glioma)
- Standardised RT and chemotherapy protocols

LGG1 Schema

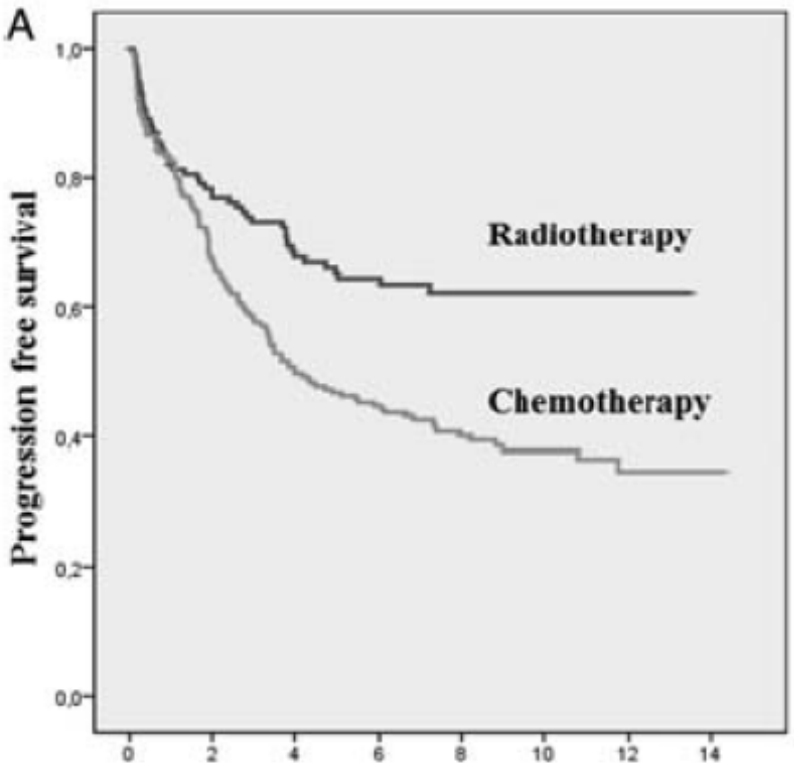


ESTRO School

LGG1 - RT

- MR imaging – T2
- 1 cm margin for CTV (2 cm if only CT scan used)
- Intracranial primaries: 54 Gy in 30 fractions of 1.8 Gy
- Spinal primaries: 50.4 Gy
- Children aged <5: 50 Gy in 30 fractions of 1.67 Gy

LGG1 German Cohort



- Ten-year PFS 62% following RT and 44% following chemotherapy
- 61 of 216 chemotherapy patients received RT 0.3–8.7 years after initial diagnosis
- Approximately 75% of surviving chemotherapy patients had not received RT at time of analysis

ESTRO School

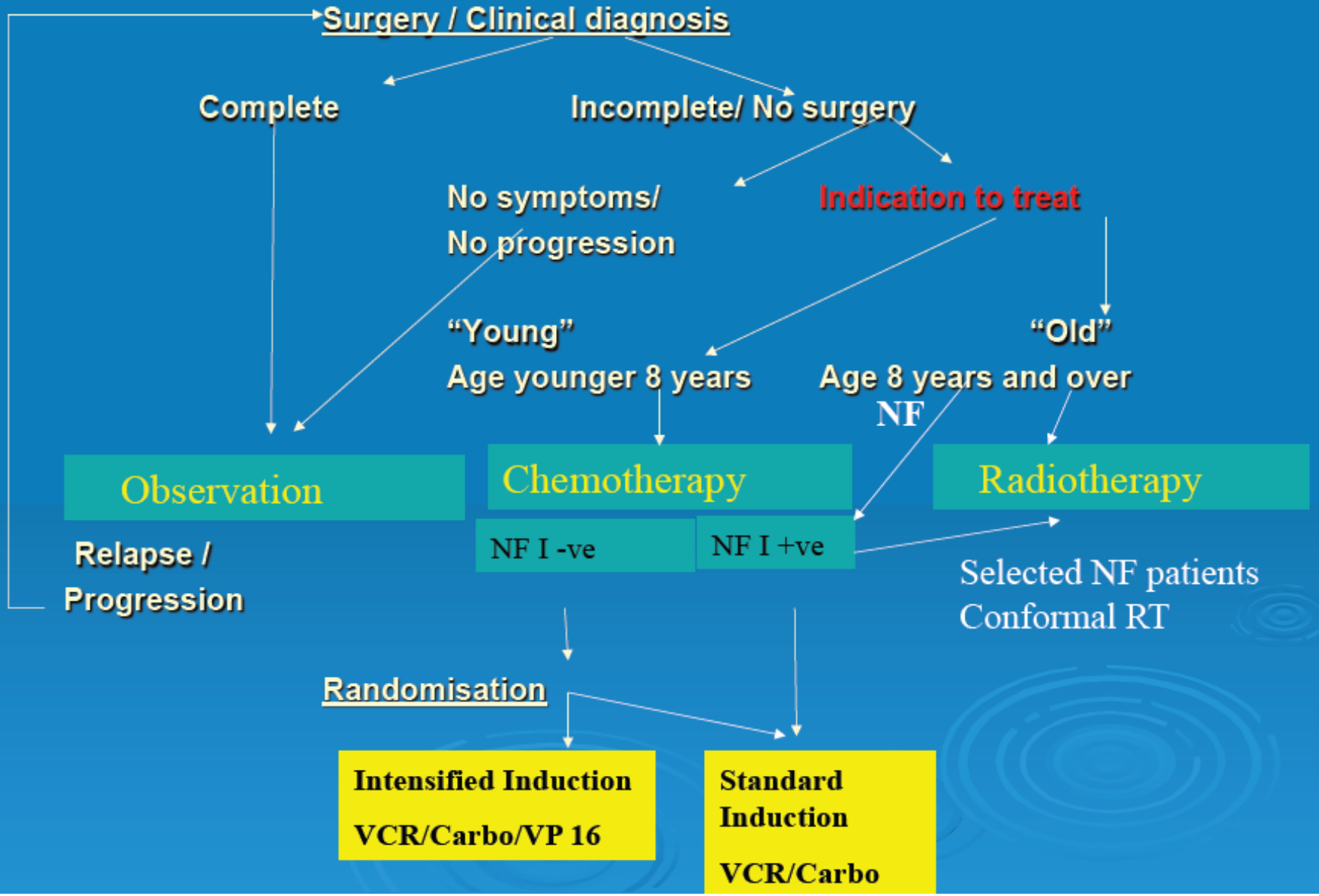
LGG1 German Cohort

- Analysis of clinical factors for progression and survival
- LGG1 patients recruited October 1996 – March 2004
- Main tumour location: supratentorial midline (40.4%)
- Main histology: pilocytic astrocytoma (67.9%)
- Following a median observation of 9.3 years, 10-year OS was 94% and 10-year EFS was 47%
- Infants with or without diencephalic syndrome and dissemination bear the highest risk for death and progression following diagnosis or treatment

LGG2 Study Aims

- Opened 2004
- Closed 2012
- Built upon achievements of LGG1
- Standardised approach for LGG
- Initial observation policy
- Non-surgical treatment for radiological progression or severe symptoms (RT age > 8)
- **Chemotherapy Study:**
- Randomisation between Carboplatin +/- Etoposide with the aim of increasing PFS

Overview of SIOP LGG 2003 treatment strategy



LGG2 RT Protocol Aims

- To utilize modern treatment techniques to reduce the integral radiation dose to normal tissue
- To record the integral dose to tumor and normal tissue as a basis for future assessment of QoL of long-term survivors
- To assess response of tumour and clinical symptoms to radiotherapy with respect to primary treatment or after chemo failure
- To assess the pattern of relapse, when using modern treatment techniques
- To assess the efficacy of CSRT for metastatic disease

LGG2 - RT Doses

Target volume	Number of fractions	Dose per fraction	Total dose	Duration (weeks)
Intracranial	30	1.8 Gy	54.0 Gy	6
Spinal	28	1.8 Gy	50.4 Gy	5 ½

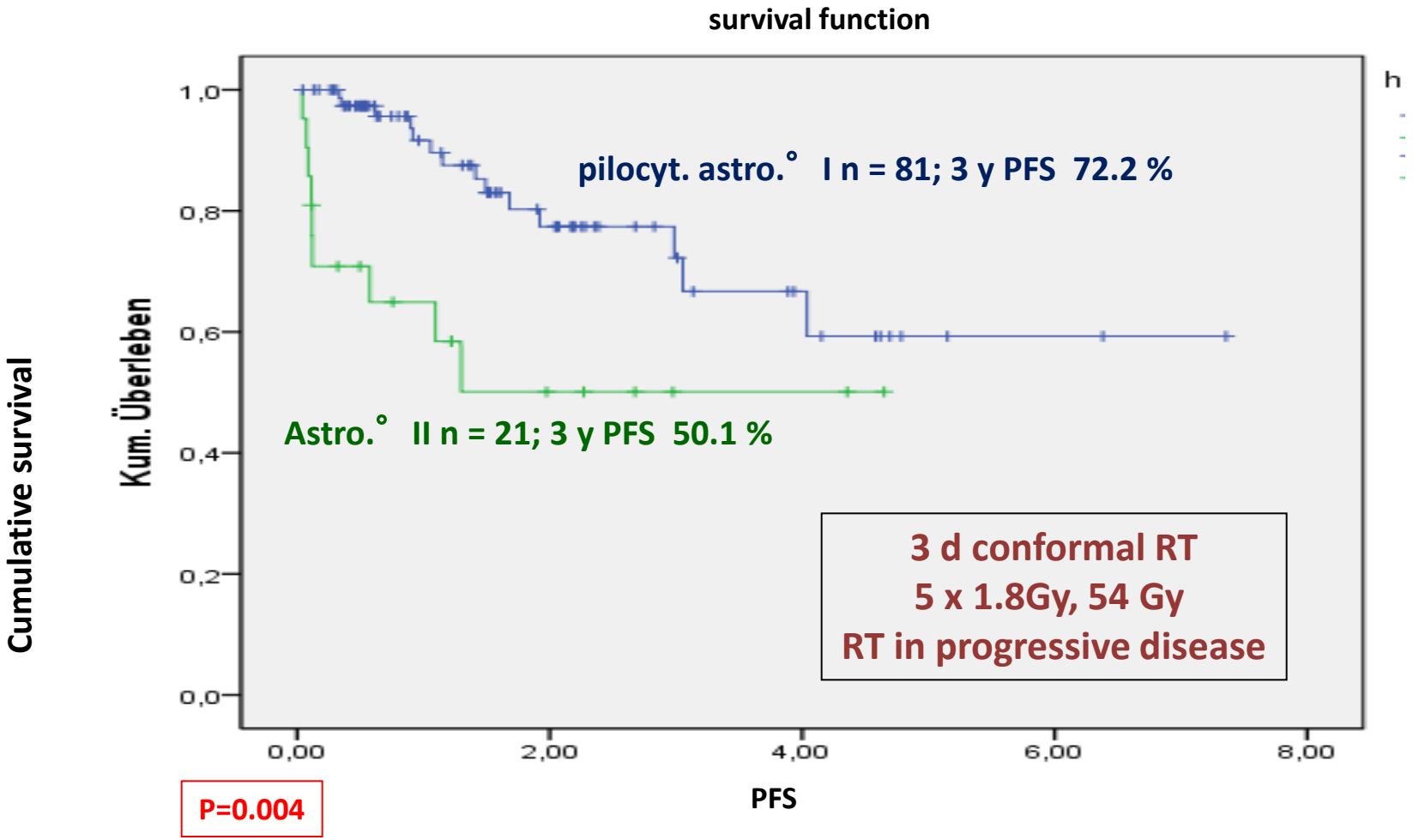
LGG Outcome Following RT

Author	Dose prescription	Pat.	Results	F-up
Debus et al., 1999	Median 52.4 Gy/1.6-2.0 Gy	10	5 y. PFS: 90 %, 5 y. OS: 100 % No acute toxicities	12-72 mon.
Saran et al., 2002	Median 50-55 Gy/30-33 Fr.	14	3 y. PFS: 87 %, 3 y. OS: 100 % 1 relapse within GTV	33 mon.
Hug et al., 2002	Protons 50.4-63.0 CGE 1,8 Gy.	27	Local control survival Hemisph. 71 % 86 % Dienceph. 87 % 93 % Brain stem 60 % 60 %	3.3 years
Marcus et al., 2005	Ster. Conv RT Median 52,2 Gy/1,8Gy	81	5 y./8 y. PFS: 82.5 %/65 % 5 y./8 y. OS: 97.8 %/82 % 6 local	6.9 years
Combs et al., 2005	3D conformal RT Med. 52.2 Gy / 1.8Gy	15	3y. / 5 y. PFS : 92 % / 72 % 5 y. OS : 90 %	97 mon.
Merchant et al., 2009	3D conformal RT Median 54 Gy/1.8 Gy	78	5/10 y. EFS: 87.4 %/74.3 % 5 / 10 y. OS: 98.5 %/95.9 %	89 mon.
Paulino et al., 2013	IMRT 45-60 Gy	39	8 y. EFS/OS: 78.2 % and 93.7 %	n.a.
Muller et al., 2013	Conventional/3D planning Median 54 Gy/1.8 Gy Margin 1-2 cm	75	Pilocytic astrocytoma 5/10 y. PFS: 76.5 % 5/10 y. OS: 96.2 % Relapse pattern: n.a.	8.4 years

Courtesy: Rolf Kortmann

Radiotherapy in low grade glioma / children

HIT LGG 2004 PFS – astrocytoma WHO I vs WHO II



Kortmann et al., unpublished, last update Nov 2011

Fig. 1: Low grade glioma Study: Progression free survival in patients treated with chemotherapy.

The 3-year PFS of the entire population is 57.5%(95% CI 49.7-65.3).

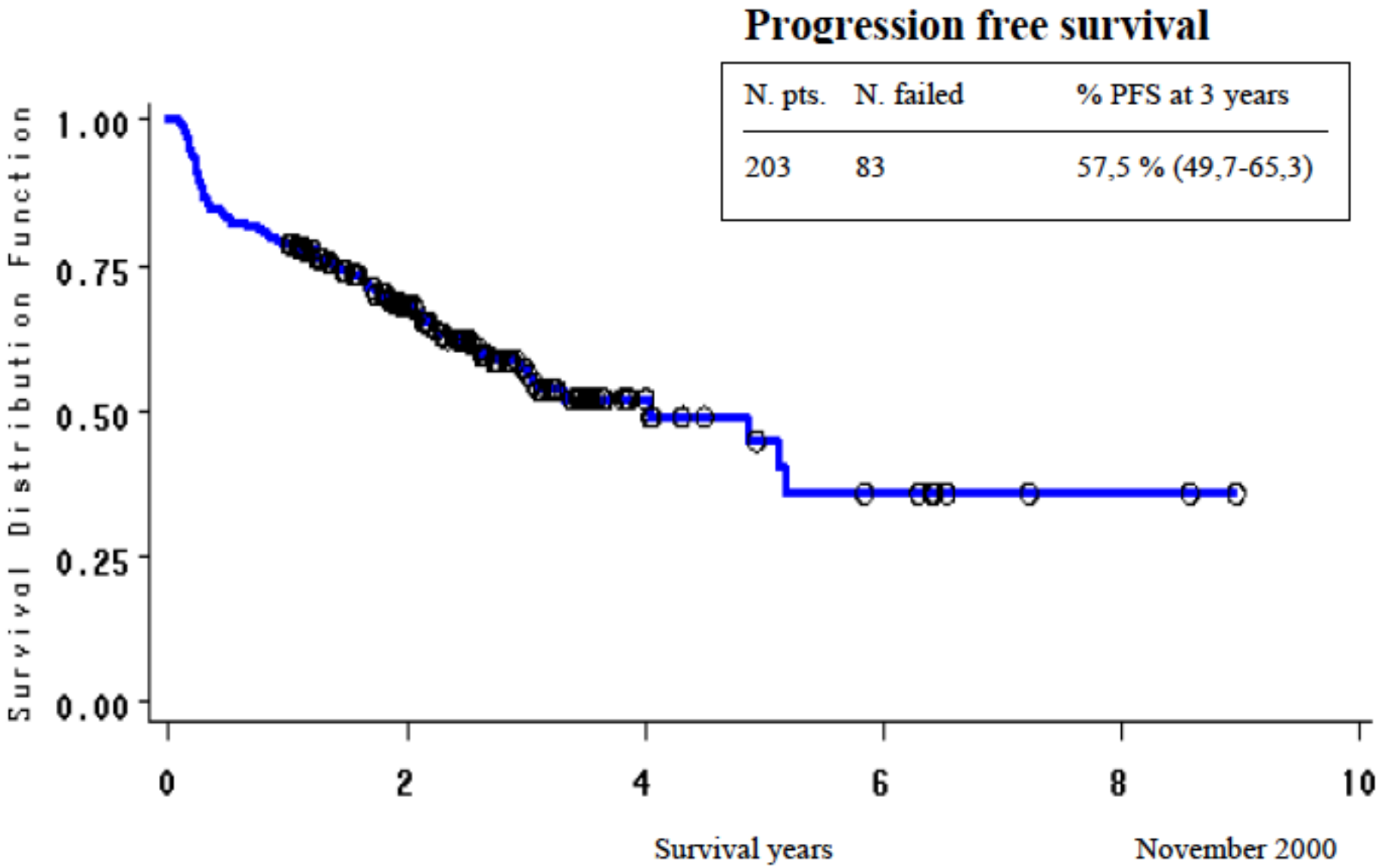
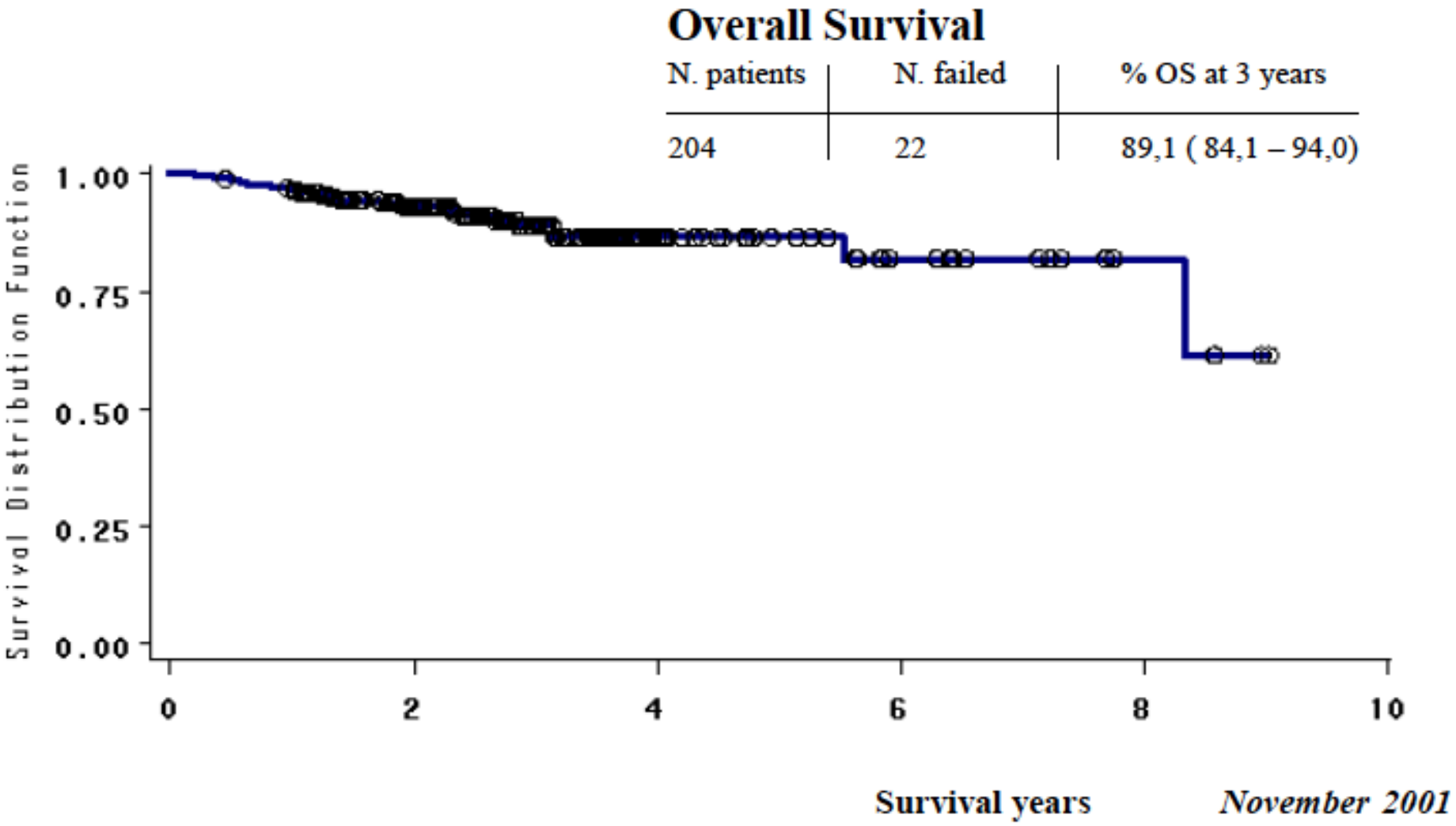


Fig. 2: Low grade glioma Study: Overall free survival in patients treated with chemotherapy.
The 3-year OS of the entire population is very good: 89.1% (95% CI 84.1-94.0).



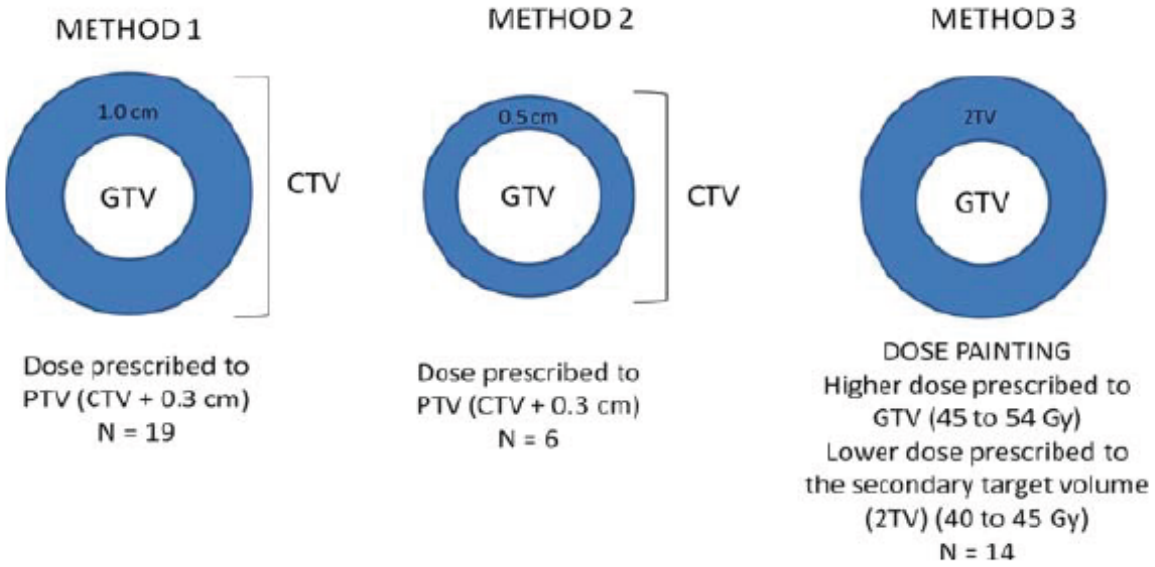
Cancer July 15, 2013

Intensity-Modulated Radiotherapy (IMRT) in Pediatric Low-Grade Glioma

Arnold C. Paulino, MD[1,2]; Ali Mazloom, MD[1]; Keita Terashima, MD[2]; Jack Su, MD[2]; Adekunle M. Adesina, MD, PhD[3]; M. Faith Okcu, MD, MPH[2]; Bin S. Teh, MD[1]; and Murali Chintagumpala, MD[2]

n=39

Margins Around GTV



8y-PFS rate 78.2%

Margins 1 cm added to the GTV may not be necessary, because excellent local control was achieved by adding a 0.5-cm margin and by dose painting

VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Conformal Radiation Therapy for Pediatric Low-Grade Glioma

Thomas E. Merchant, Larry E. Kun, Shengjie Wu, Xiaoping Xiong, Robert A. Sanford, and Frederick A. Boop

Materials and Methods

Between August 1997 and August 2006, 78 pediatric patients with LGG and a median age of 8.9 years (range, 2.2 to 19.8 years) received 54 Gy CRT by using a 10-mm CTV and by targeting with systematic magnetic resonance imaging (MRI) registration. Tumor locations were diencephalon (n = 58), cerebral hemisphere (n = 3), and cerebellum (n = 17). Sixty-seven patients had documented or presumed WHO grade 1 tumors, 25 patients had prior chemotherapy, and 13 patients had neurofibromatosis type 1.

Conclusion

This large, prospective series of irradiated children with LGG demonstrates that CRT with a 10-mm CTV does not compromise disease control. The results suggest that CRT should be delayed in young patients to reduce the risk of vasculopathy.

VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

n=78

Phase II Trial of Conformal Radiation Therapy for Pediatric Low-Grade Glioma

Thomas E. Merchant, Larry E. Kun, Shengjie Wu, Xiaoping Xiong, Robert A. Sanford, and Frederick A. Boop

Table 2. Pediatric Low-Grade Glioma Chemotherapy and Radiotherapy Series

Author by Type of Treatment	Year of Study	Treatment Regimen	No. of Patients	Event- or Progression-Free Survival (%)				
				2-Year	3-Year	5-Year	8-Year	10-Year
Chemotherapy								
Ater[21]	2008	CV	137			35		
		TPCV	137			48		
Gnekow[20]	2004	CV	198			61		
Massimino[19]	2002	CisVP	31		78			
Prados[18]	1997	TPCV	42	50				
Packer[17]	1997	CV	78		68			
Radiation therapy								
Marcus[27]	2005	52.2 Gy	50			82	65	
Saran[26]	2002	50-55 Gy	14		87			
Grabenbauer[29]	2000	45-60 Gy	25					69
Erkal[28]	1997	50 Gy	30			82		77
Merchant	2008	54 Gy	78			85		74

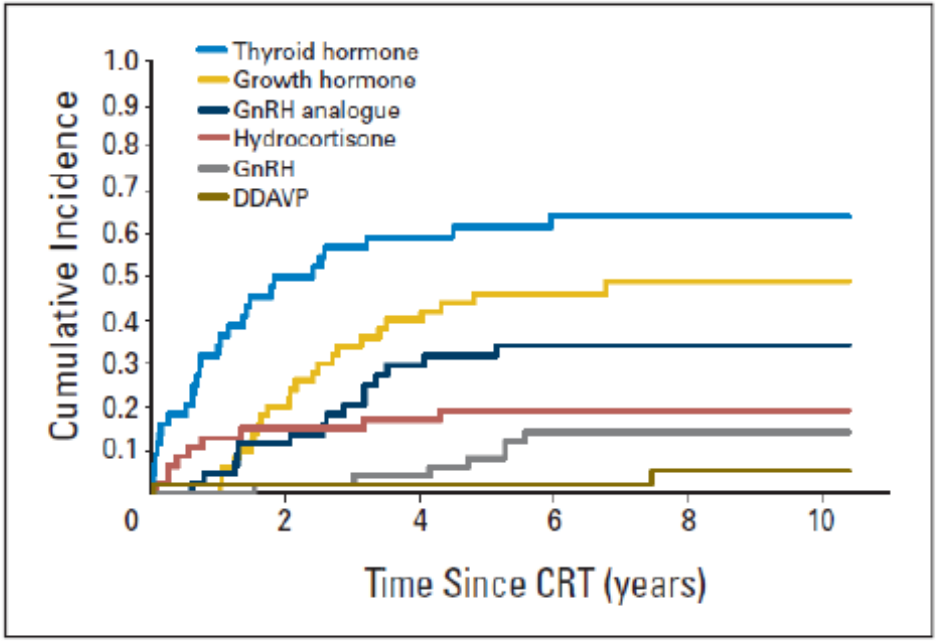
C, carboplatin; V, vincristine; T, thioguanine; P, procarbazine; Cis, cisplatin; VP, etoposide.

Late Effects

Merchant et al, 2009

J Clin Oncol 2009; 27: 3691-3697

- GH impaired in 24% prior to RT
- 12% precocious puberty
- 10-year cumulative incidence of GH replacement: 48.9%, thyroid replacement: 64.0%, glucocorticoid replacement: 19.2%,
- GHRH: 34.2%.
- Cumulative incidence of years 5.7%



VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Late Effects of Conformal Radiation Therapy for Pediatric Patients With Low-Grade Glioma: Prospective Evaluation of Cognitive, Endocrine, and Hearing Deficits

Thomas E. Merchant, Heather M. Conklin, Shengjie Wu, Robert H. Lustig, and Xiaoping Xiong

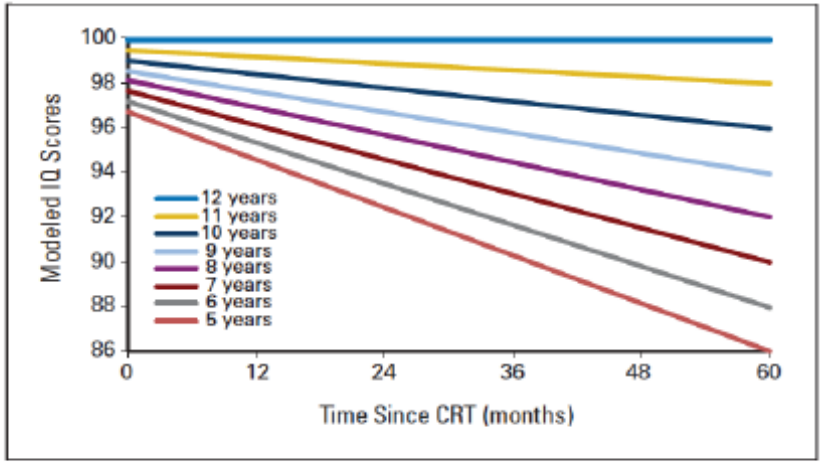


Fig 1. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age for pediatric low-grade glioma. Age is measured in years, and time is measured in months after the start of CRT.

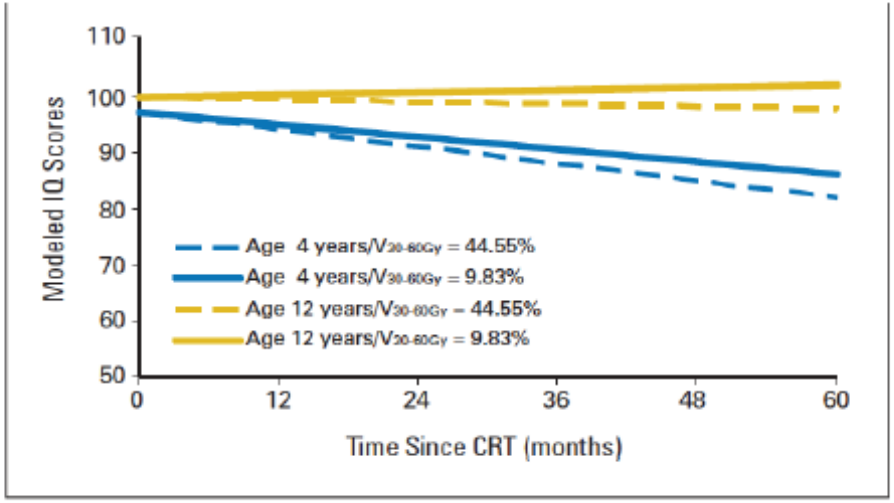


Fig 2. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age and supratentorial brain dose-volume intervals for pediatric low-grade glioma. Age is measured in years, and time is measured in months after CRT. The dose-volume intervals $V_{0\text{-}30Gy}$ and $V_{30\text{-}60Gy}$ represent the percent volume of the supratentorial brain that received dose within the specified interval.

CHILDREN'S ONCOLOGY GROUP

Radiation Therapy in Treating Young Patients With Gliomas

NCT00238264 trial

CTV= GTV plus a 0.5 cm margin

VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Late Effects of Conformal Radiation Therapy for Pediatric Patients With Low-Grade Glioma: Prospective Evaluation of Cognitive, Endocrine, and Hearing Deficits

Thomas E. Merchant, Heather M. Conklin, Shengjie Wu, Robert H. Lustig, and Xiaoping Xiong

Table 1. Models of Cognitive Effects After CRT for Pediatric Low-Grade Glioma

Evaluation	No. of Patients Who Had at Least Two Measures	Score*			
		Baseline	Change per Month	Month 60	P†
IQ	55	98.9642	−0.0591	95.4182	
Math	55	96.9703	−0.0435	94.3603	
Reading	56	98.9448	−0.0989	93.0108	.0039
Spelling	56	98.2341	−0.1434	89.6301	.0014
Memory	53	47.5523	0.0164	48.5363	
Behavior problems‡	55	49.2340	−0.0556	45.8980	.0641
Externalizing‡	58	43.9829	−0.0099	43.3889	
Internalizing‡	58	51.5753	−0.0550	48.2753	.0248
Activities	55	43.2365	0.0031	43.4225	
School	53	41.8430	−0.0515	38.7530	.0479
Socialization	56	44.5348	−0.0084	44.0308	
Communication	57	94.6115	−0.1308	86.7635	.0041
Composite	57	94.4170	−0.1026	88.2610	.0433
Daily living	57	94.0500	−0.0635	90.2400	
Socialization	57	98.7889	−0.0559	95.4349	
Visual auditory learning	30	92.2834	0.1768	102.8914	< .0001

NOTE. Instruments for each evaluation are as follows: IQ, Bayley second edition; Wechsler Preschool and Primary Scale of Intelligence revised; Wechsler Intelligence Test for Children third edition or Wechsler Adult Intelligence Scale revised, as appropriate for age; math, reading, and spelling: Wechsler Individual Achievement Test; memory: California Verbal Learning Test: Child Version; behavior problems, externalizing, internalizing, activities, school, socialization: Child Behavior Checklist; communication composite, daily living, socialization: Vineland Adaptive Behavior Scale; and visual auditory learning: Woodcock Johnson revised, visual auditory learning subtest.

Abbreviations: CRT, conformal radiation therapy; IQ, intelligence quotient.

*Score = baseline + ([change per month] × time).

†*P* value for change per month.

‡Increasing scores represent worsening performance.

Five years after CRT, only the decline in spelling scores was clinically significant

Influencing factors

RT related

- Dose: Total tumour dose, but dose to critical structures more important
- Fraction size: Hypo-fractionation or hyper-fractionation
- **Volume**: Whole brain Vs CSI Vs Partial brain
- Technique: Conformal, margins, accuracy of execution
- Energy: Photons Vs particle beam…..Telecobalt
- Planning: Dose constraint models to minimise cognitive impairment

Proton Therapy

Advantages

⇒ **reduction of integral dose to organs at risk (highly conformal even to irregular tumour shapes)**

⇒ **reduction of late effects is expected (neurocog., endocrin., hearing, sec. malignancies..)**

Disadvantages

⇒ **limited information regarding tumour control rates and reduction of late effects**

⇒ **limited access (will change in future)**

Prospective, european wide studies necessary

Courtesy: Rolf Kortmann

Role of Chemotherapy

VOLUME 30 · NUMBER 21 · JULY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Study of Two Chemotherapy Regimens for Treatment of Low-Grade Glioma in Young Children: A Report From the Children's Oncology Group

Joann L. Ater, Tianni Zhou, Emiko Holmes, Claire M. Mazewski, Timothy N. Booth, David R. Freyer, Ken H. Lazarus, Roger J. Packer, Michael Prados, Richard Sposto, Gilbert Vezina, Jeffrey H. Wisoff, and Ian F. Pollack

Table 3. Tumor Response at End of Chemotherapy by Central Review

Review Response	CV			TPCV		
	No.	%	95% CI	No.	%	95% CI
Complete/partial	33	35	27 to 46	31	30	22 to 40
Minor	14	15	9 to 24	23	22	15 to 31
Stable disease	16	17	11 to 26	16	16	10 to 24
Progressive disease/recurrence/off study because of progressive disease	30	32	26 to 42	33	32	24 to 42
Total	93	100		103	100	

Abbreviations: CV, carboplatin and vincristine; TPCV, thioguanine, procarbazine, lomustine, and vincristine.

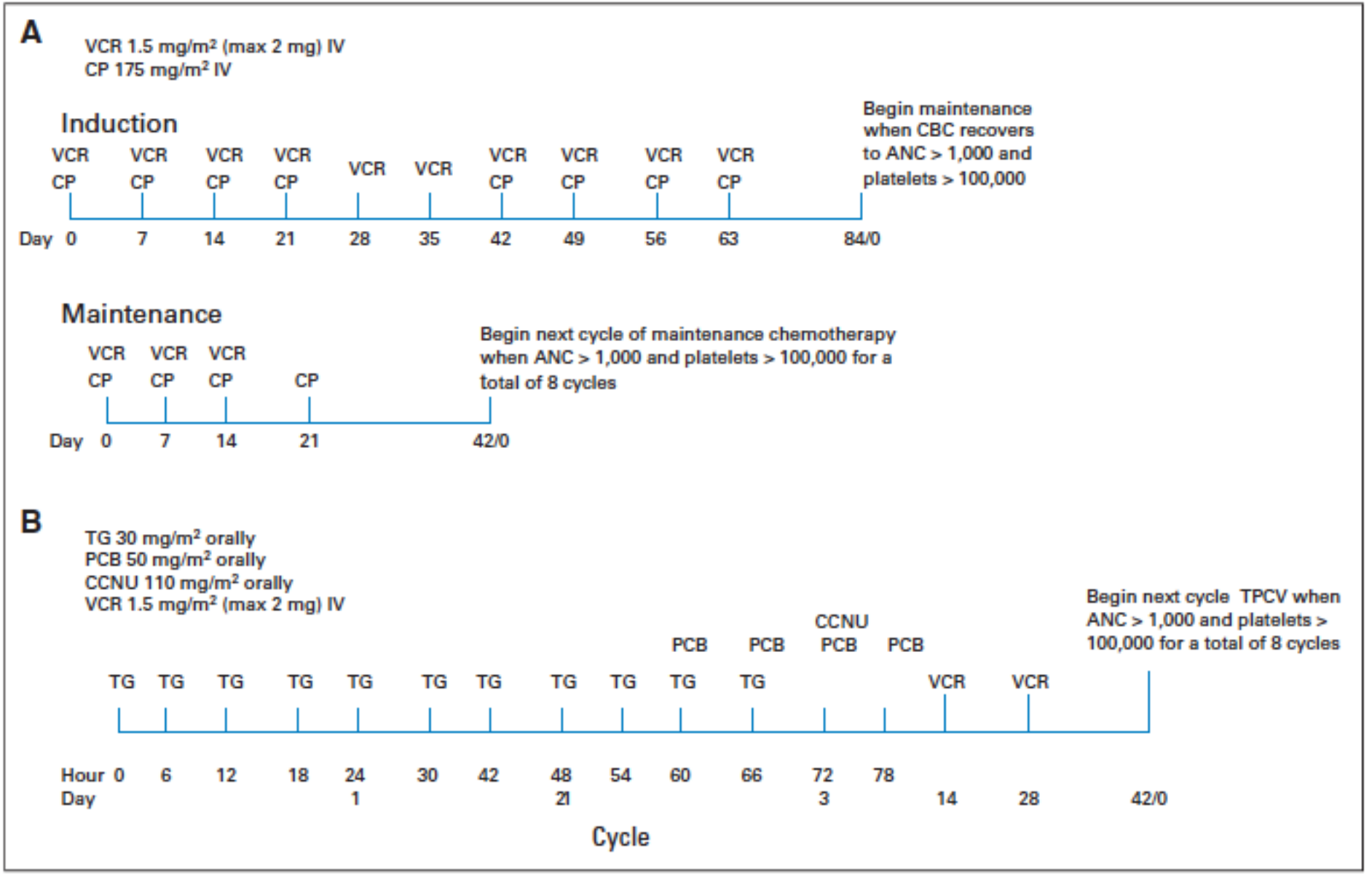


Fig 2. Treatment schema for induction and maintenance therapy for two regimens. Regimen A: carboplatin (CP) and vincristine (VCR). Regimen B: TPCV, thioguanine (TG), procarbazine (PCB), CCNU (lomustine), and vincristine (VCR). ANC, absolute neutrophil count.

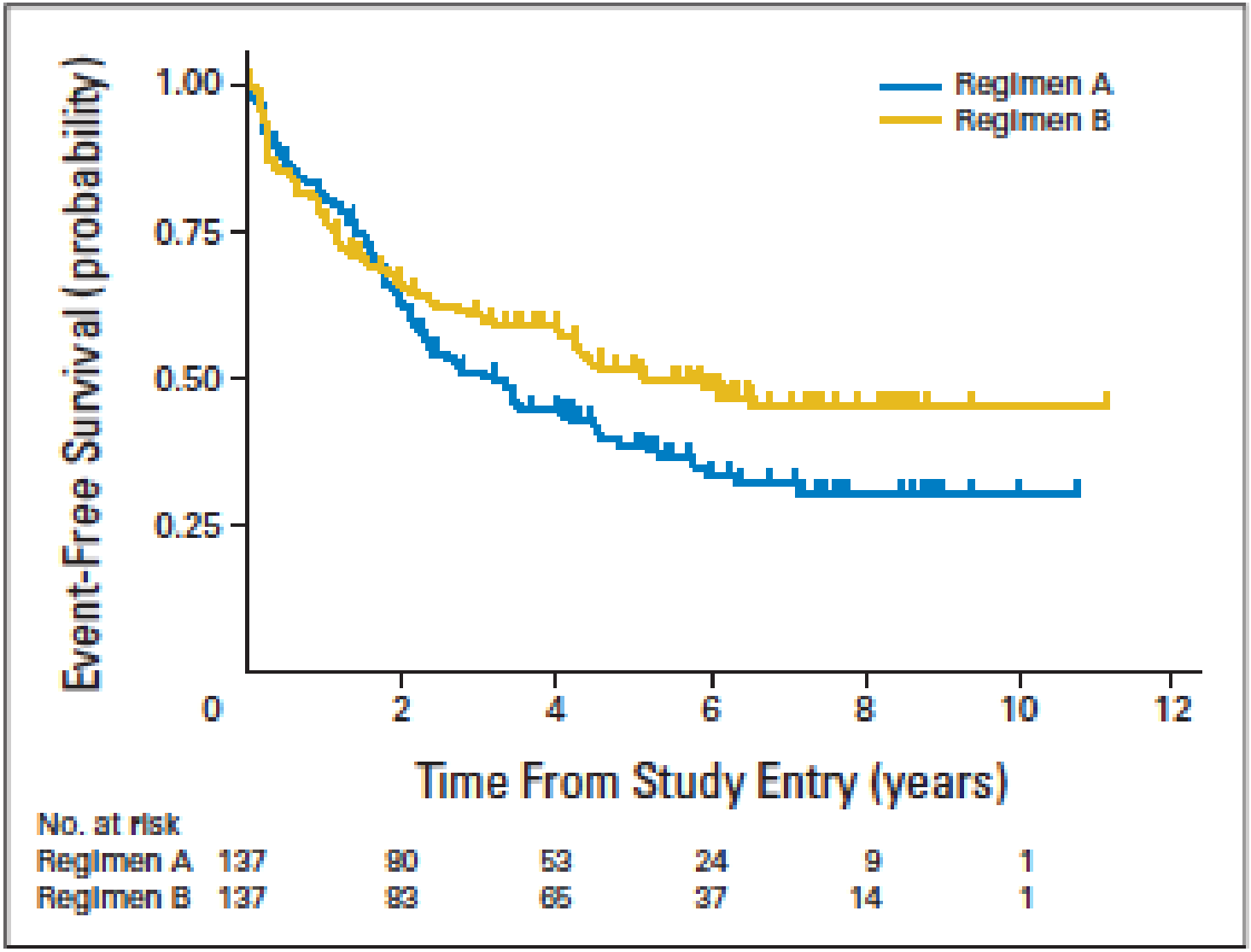


Fig 3. Event-free survival for patients randomly assigned to regimen A (CV: carboplatin and vincristine) or regimen B (TPCV: thioguanine, procarbazine, CCNU [lomustine], and vincristine).

VOLUME 30 · NUMBER 12 · APRIL 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Weekly Vinblastine in Recurrent or Refractory Pediatric Low-Grade Glioma

Eric Bouffet, Regina Jakacki, Stewart Goldman, Darren Hargrave, Cynthia Hawkins, Manohar Shroff, Juliette Hukin, Ute Bartels, Nicholas Foreman, Stewart Kellie, Joanne Hilden, Michael Etzl, Beverly Wilson, Derek Stephens, Uri Tabori, and Sylvain Baruchel

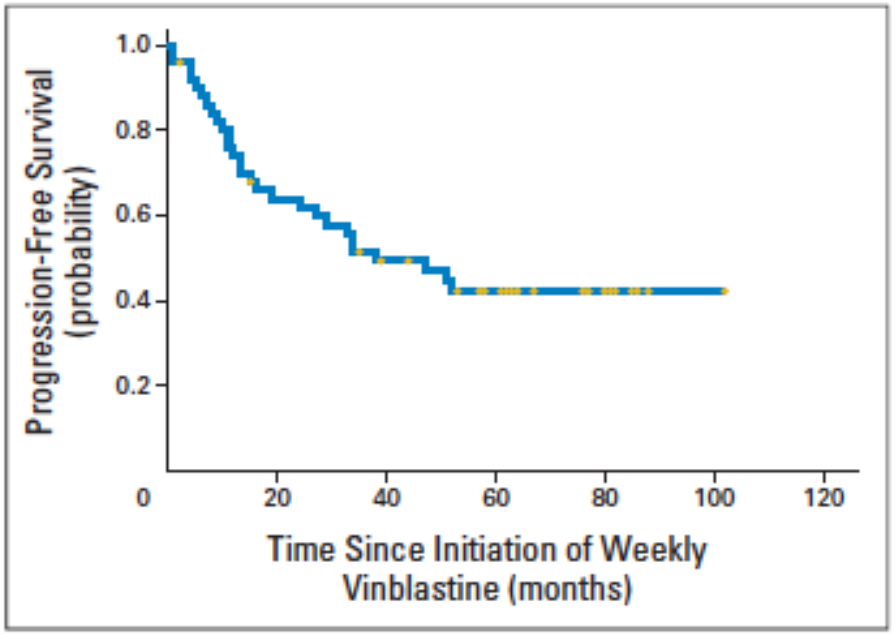


Fig 2. Progression-free survival in 51 patients treated with vinblastine.

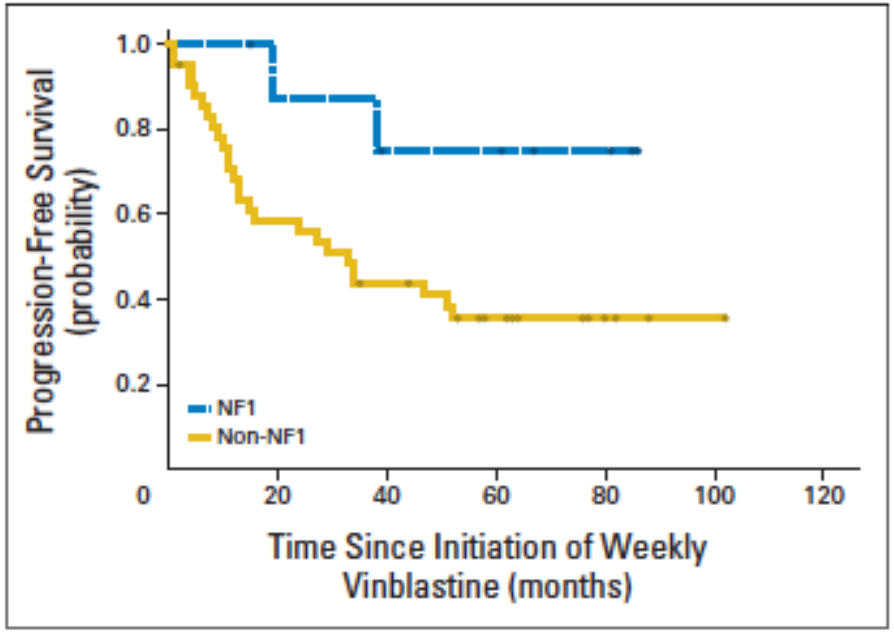


Fig 3. Progression-free survival in patients with and without neurofibromatosis type 1 (NF1; $P = .04$).

J Neurooncol (2015) 121:405–412
DOI 10.1007/s11060-014-1652-6

CLINICAL STUDY

Single agent vinorelbine in pediatric patients with progressive optic pathway glioma

Andrea Maria Cappellano · Antonio Sergio Petrilli · Nasjla Saba da Silva · Frederico Adolfo Silva · Priscila Mendes Paiva · Sergio Cavalheiro · Eric Bouffet

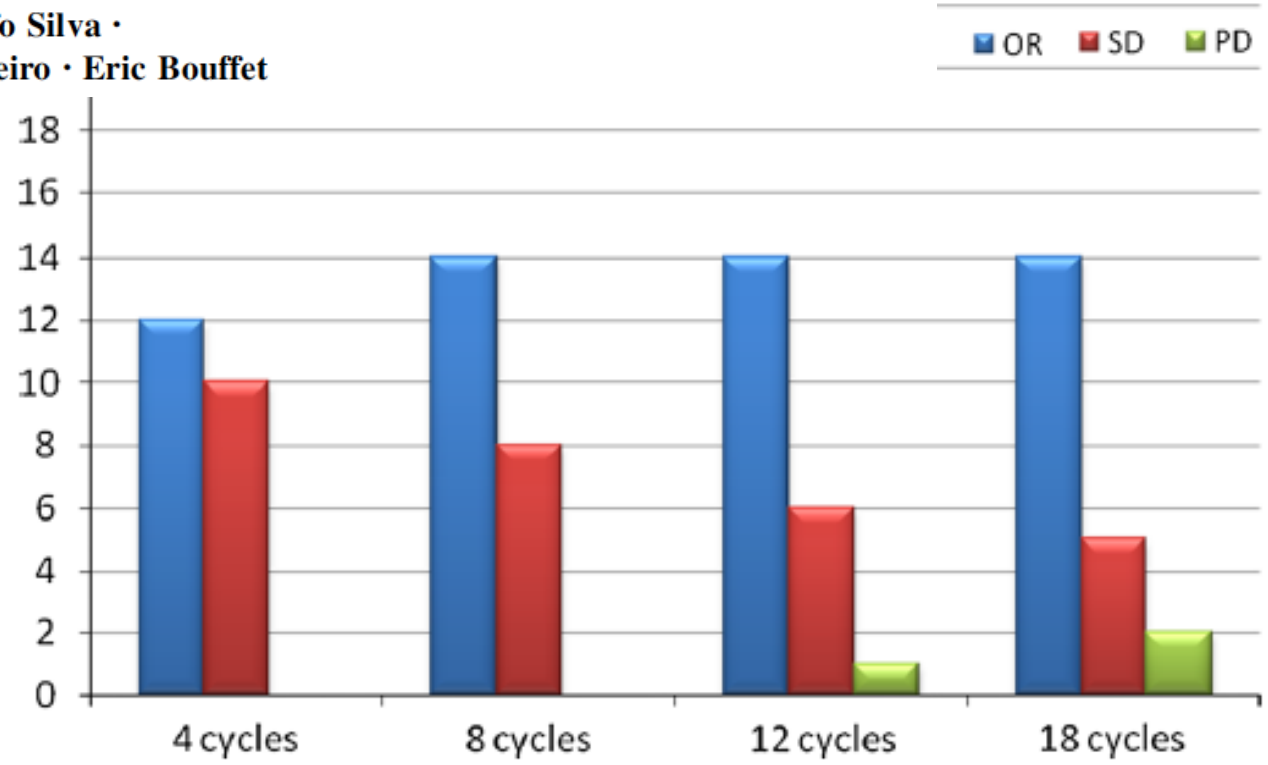
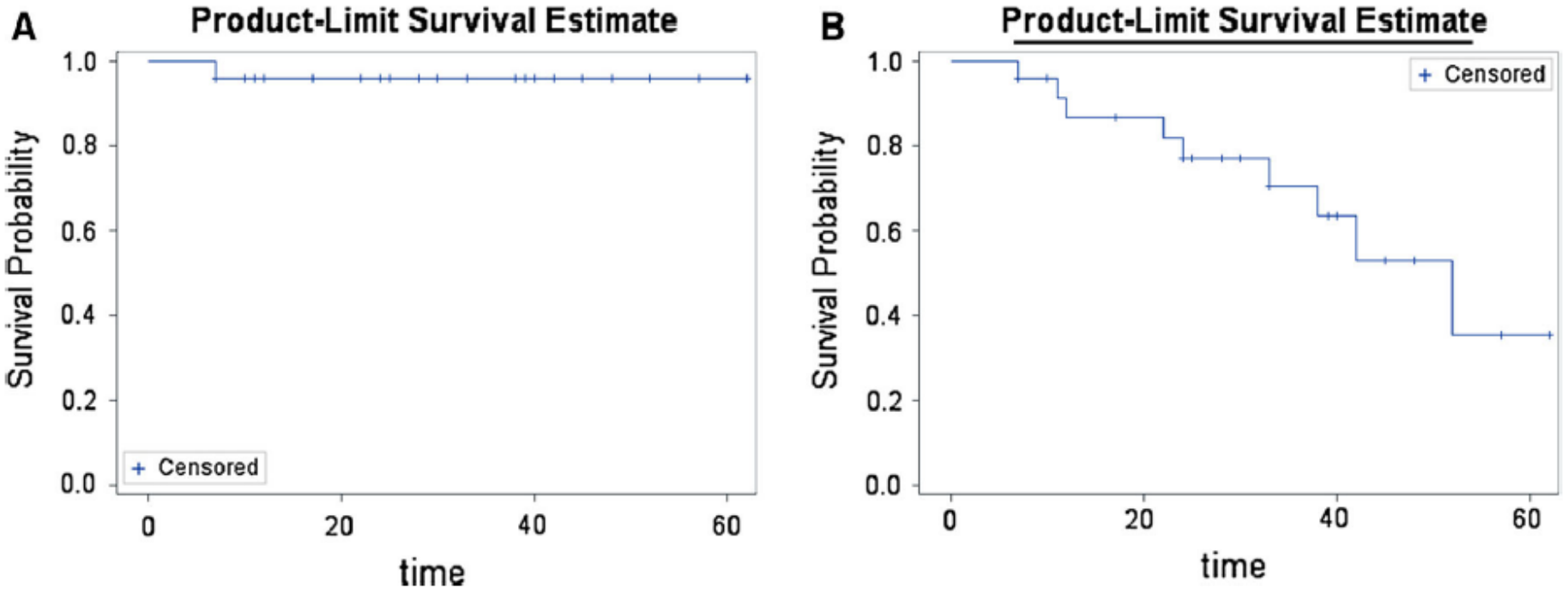


Fig. 1 Assessable patient's response according to cycles. *OR* objective response, *SD* stable disease, *PD* progressive disease



a Overall survival and **b** progression free survival of the 22 evaluable patients

Low-Dose Cisplatin-Etoposide Regimen for Patients with Optic Pathway Glioma: A Report of Four Cases and Literature Review

Stefania Cardellicchio[1] Giacomo Bacci[2] Silvia Farina[1] Lorenzo Genitori[3] Maura Massimino[4] Maurizio de Martino[1] Roberto Caputo[2] Iacopo Sardi[1]

Table 1 Clinical characteristics of optic pathway gliomas

ID	Sex (M/F)	Age at diagnosis, y	NF-1	Number of total courses	Response (MRI)	Response (VA/VF)	Follow-up (mo)
OPG1	F	10	No	10	SD	PR	26
OPG2	M	4	No	10	SD	PR	38
OPG3	F	10	Yes	10	SD	CR	54
OPG4	M	6	No	10	SD	CR	21

Abbreviations: CR, complete response; MRI, magnetic resonance imaging; NF-1, neurofibromatosis type 1; PR, partial response; SD, stable disease; VA, visual acuity; VF, visual field.

Case Report/Case Series

Marked Recovery of Vision in Children With Optic Pathway Gliomas Treated With Bevacizumab

Robert A. Avery, DO, MSCE; Eugene I. Hwang, MD; Regina I. Jakacki, MD; Roger J. Packer, MD

IMPORTANCE Children with optic pathway gliomas (OPGs) frequently experience vision loss from their tumors. Standard front-line treatment using carboplatin-based chemotherapy typically produces only a modest benefit (eg, stabilization or 0.2 logMAR improvement) in visual acuity (VA). Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor and acts primarily as an anti-angiogenic agent. Recent reports suggest a qualitative improvement in vision after bevacizumab-based treatment in children with OPGs.

OBSERVATIONS We report 4 cases of pediatric OPGs (2 neurofibromatosis type 1–related and 2 sporadic cases) that received treatment with bevacizumab due to progressive VA or visual field (VF) loss despite prior treatment with chemotherapy or proton-beam radiation. All 4 subjects demonstrated a marked improvement in their VA, VF, or both while receiving bevacizumab-based therapy. Three patients had complete resolution of their VA or VF loss in at least 1 eye—2 of whom had previously received bevacizumab therapy.

CONCLUSIONS AND RELEVANCE Given that most patients with OPG-related visual impairment will show modest or no visual improvement with standard treatment, the incorporation of bevacizumab in these cases may greatly improve visual outcomes and should be considered in appropriate clinical situations.

JAMA Ophthalmol. 2014;132(1):111-114. doi:10.1001/jamaophthalmol.2013.5819
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Author Affiliations: Author affiliations are listed at the end of this article.

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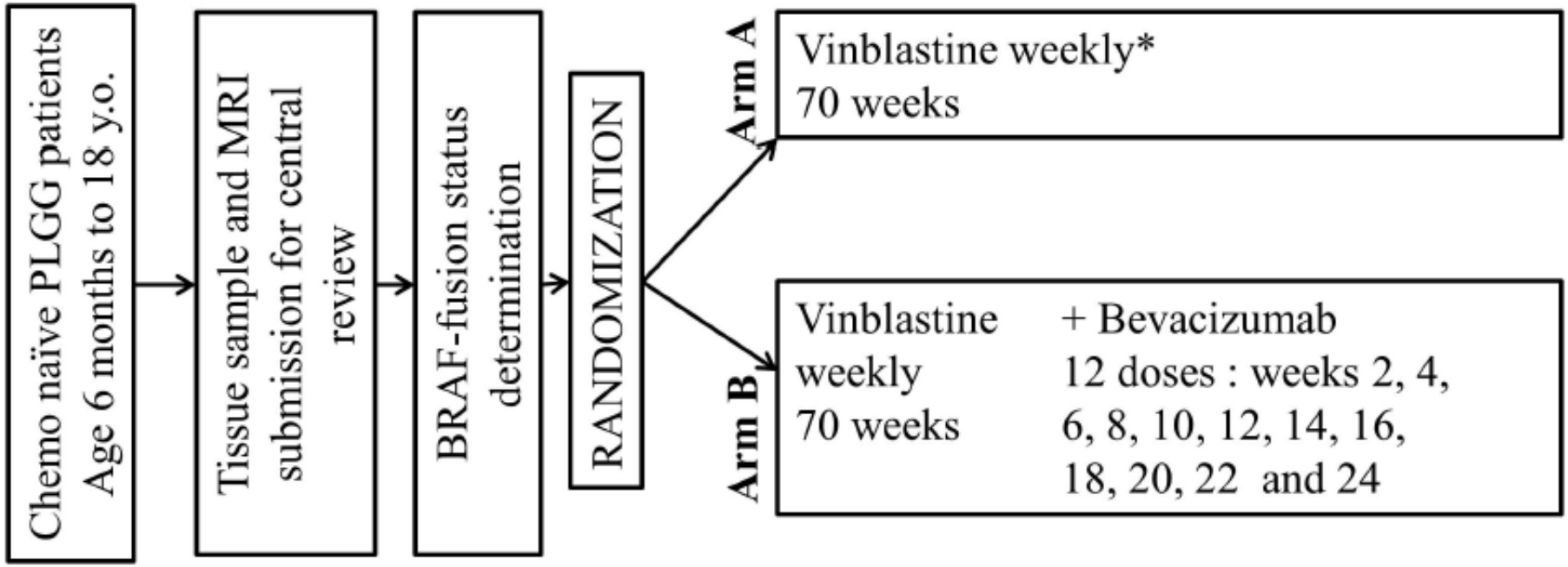
Vinblastine-Bevacizumab protocol – February 7, 2015

A PHASE II, OPEN-LABELED, MULTI-CENTER, RANDOMIZED CONTROLLED TRIAL OF VINBLASTINE +/- BEVACIZUMAB FOR THE TREATMENT OF CHEMOTHERAPY-NAÏVE CHILDREN WITH UNRESECTABLE OR PROGRESSIVE LOW GRADE GLIOMA (LGG)

EXPERIMNTAL DESIGN SCHEMA



Assessments:

MRI:** baseline, weeks 12, 24, 36, 48, 60, 72

Visual*:** start of therapy, q3 months on therapy and 1 year off therapy, then q6 months year 2-5 off therapy

QOL: start of therapy, weeks 15 and 30, end of therapy, 6 months and 1 year off therapy

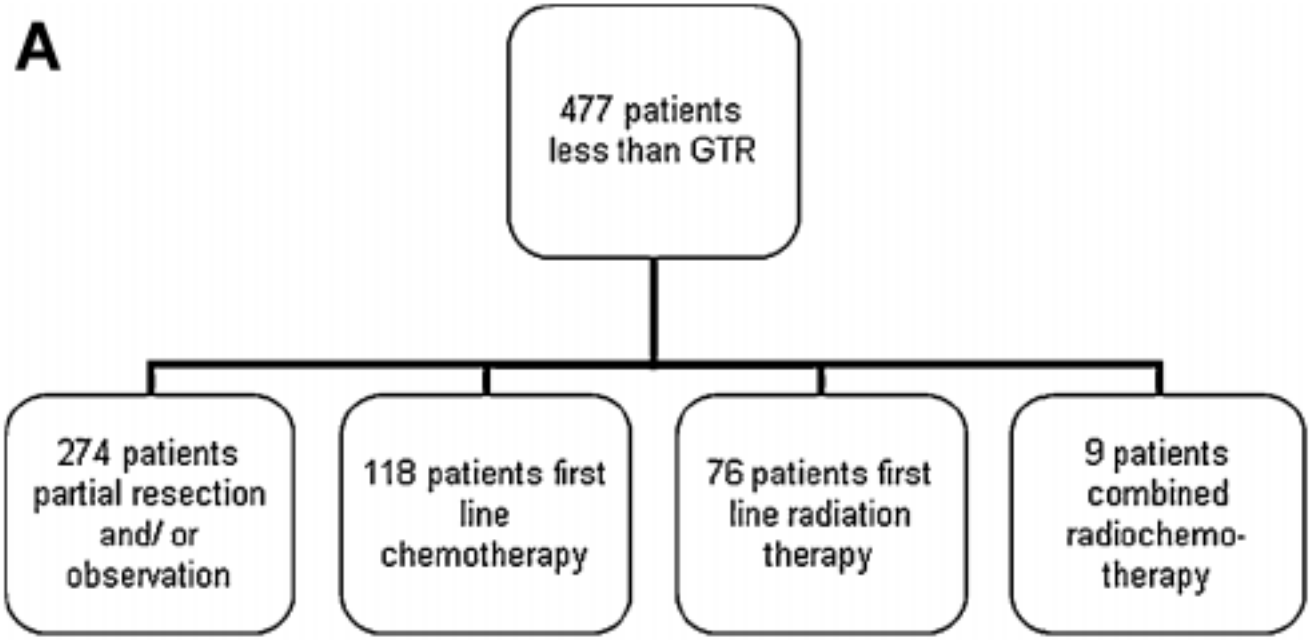
Table 2 EFS and OR with chemotherapy in clinical trials for children with progressive unresectable LGG

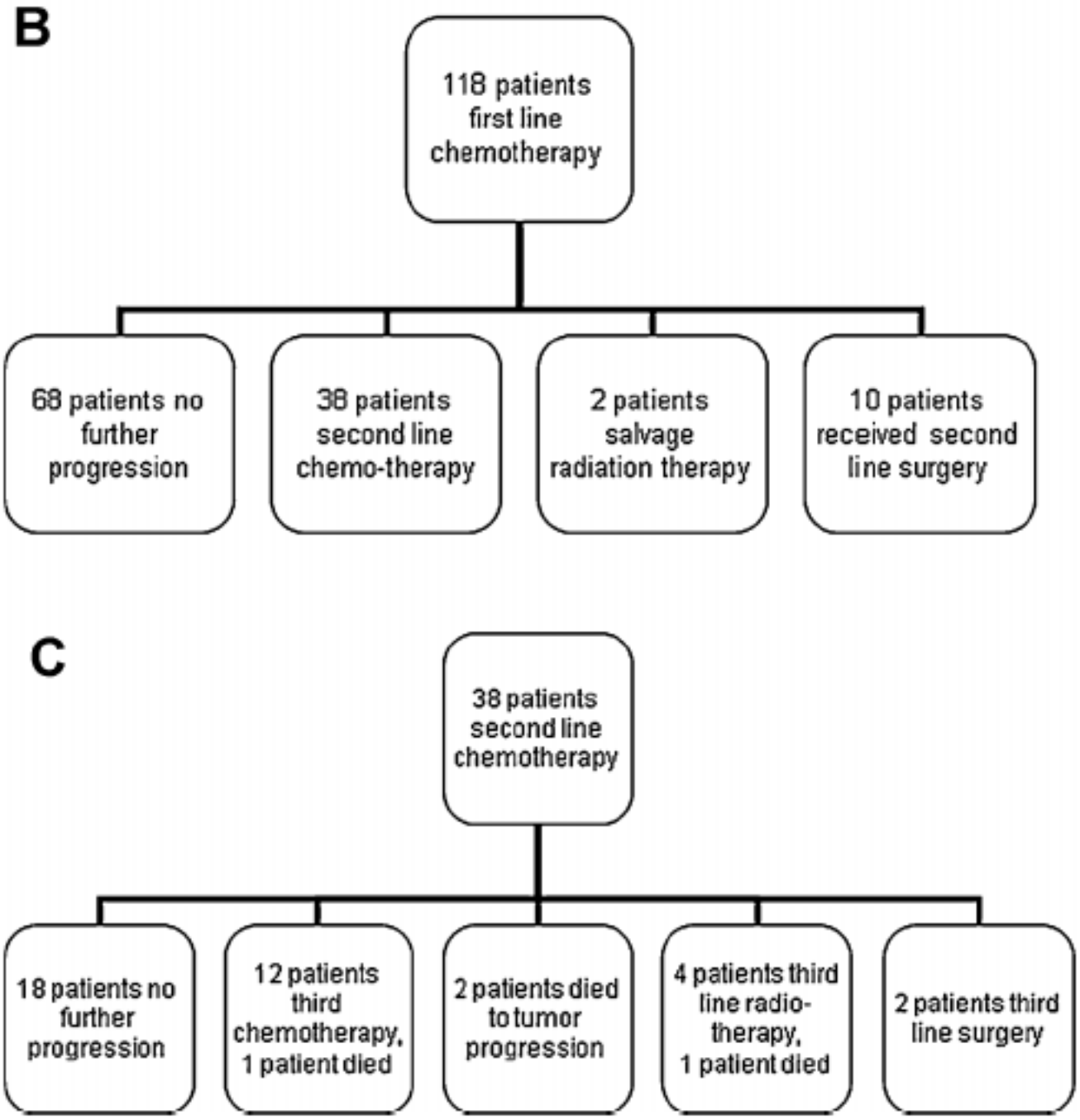
Single agent/regimen	No. of patients	OR	EFS (%)	Reference
Vincristine	10 (1 LGG)	1	NA	[19]
Vinblastine	51	18 (36 %)	42 at 5 years	[18]
Carboplatin	81	23 (29 %)	64 at 3 years	[11]
Temozolomide	30	3 (11 %)	31 at 4 years	[15]
Vincristine–Carboplatin (1st line)	78	44 (56 %)	68 at 3 years	[9]
TPCV	42	15 (36 %)	45 at 3 years	[10]
Etoposide–Cisplatin	34	24 (70 %)	78 at 3 years	[12]
Bevacizumab-irinotecan	10	07 (78 %)	NA	[16]
Vinorelbine	22	14 (63 %) (95 % CI 43–81 %)	64 at 3 years/37 at 5 years	Present study

Pediatr Blood Cancer 2011;57:84–88

Feasibility and Efficacy of Repeated Chemotherapy for Progressive Pediatric Low-Grade Gliomas

Katrin Scheinemann, MD,[1,2] Ute Bartels, MD,[1] Elena Tsangaris, BSc,[1] Cynthia Hawkins, MD, PhD,[3] Annie Huang, MD, PhD,[1] Peter Dirks, MD, PhD,[4] Iris Fried, MD,[1] Eric Bouffet, MD,[1] and Uri Tabori, MD[1]*




B
118 patients first line chemotherapy
68 patients no further progression
38 patients second line chemo-therapy
2 patients salvage radiation therapy
10 patients received second line surgery
C
38 patients second line chemotherapy
18 patients no further progression
12 patients third chemotherapy, 1 patient died
2 patients died to tumor progression
4 patients third line radio-therapy, 1 patient died
2 patients third line surgery

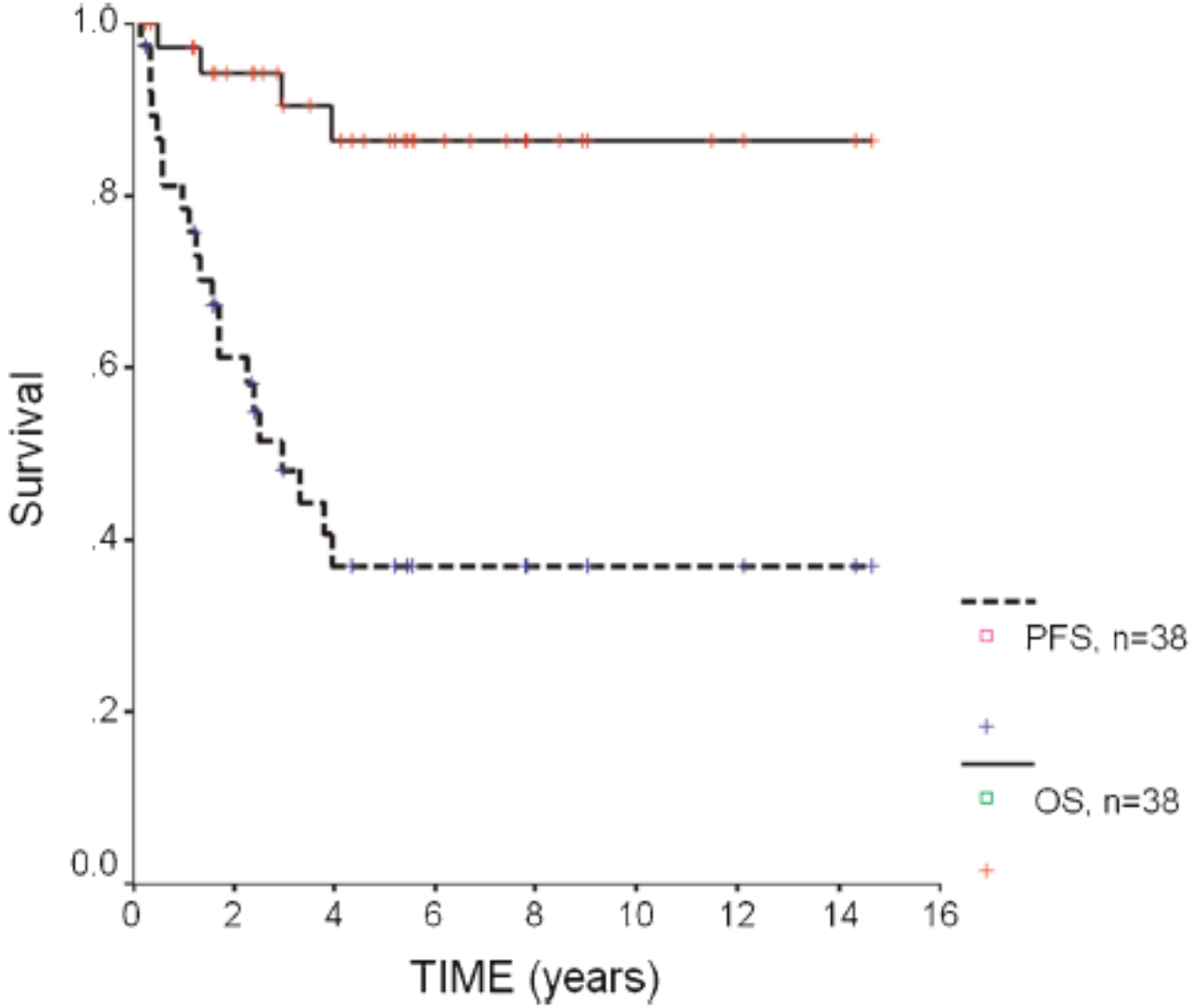


Fig. 2. Kaplan–Meier figure for overall (OS) and progression free survival (PFS) for 38 patients with second line chemotherapy. Five-year OS 86 ± 6%, 5-year PFS 37 ± 8%.

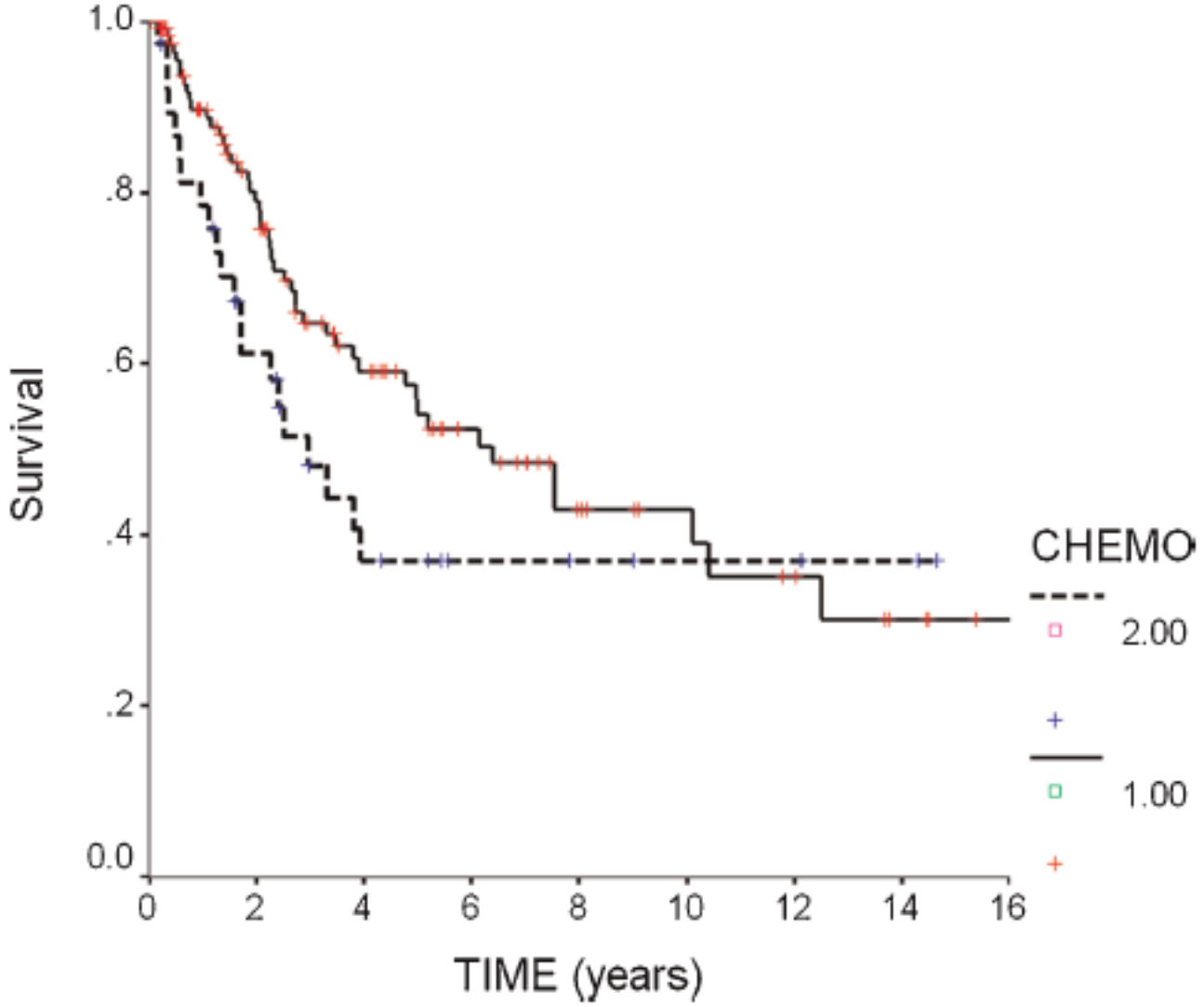


Fig. 3. Kaplan–Meier figure for progression free survival for first (1) and second line (2) chemotherapy. First line chemotherapy 5-year EFS $52 \pm 6\%$, second line chemotherapy 5-year EFS $37 \pm 8\%$ ($P = 0.14$).

FUTURE MANAGEMENT OF LGG

LO GIC

EUROPE

... because function & biology matters

Update
LOGGIC Europe trial

Olaf Witt & Netteke Schouten van Meeteren
on behalf of the SIOP LGG Trial Protocol Working Group

We Care for **all** LGG Patients ….

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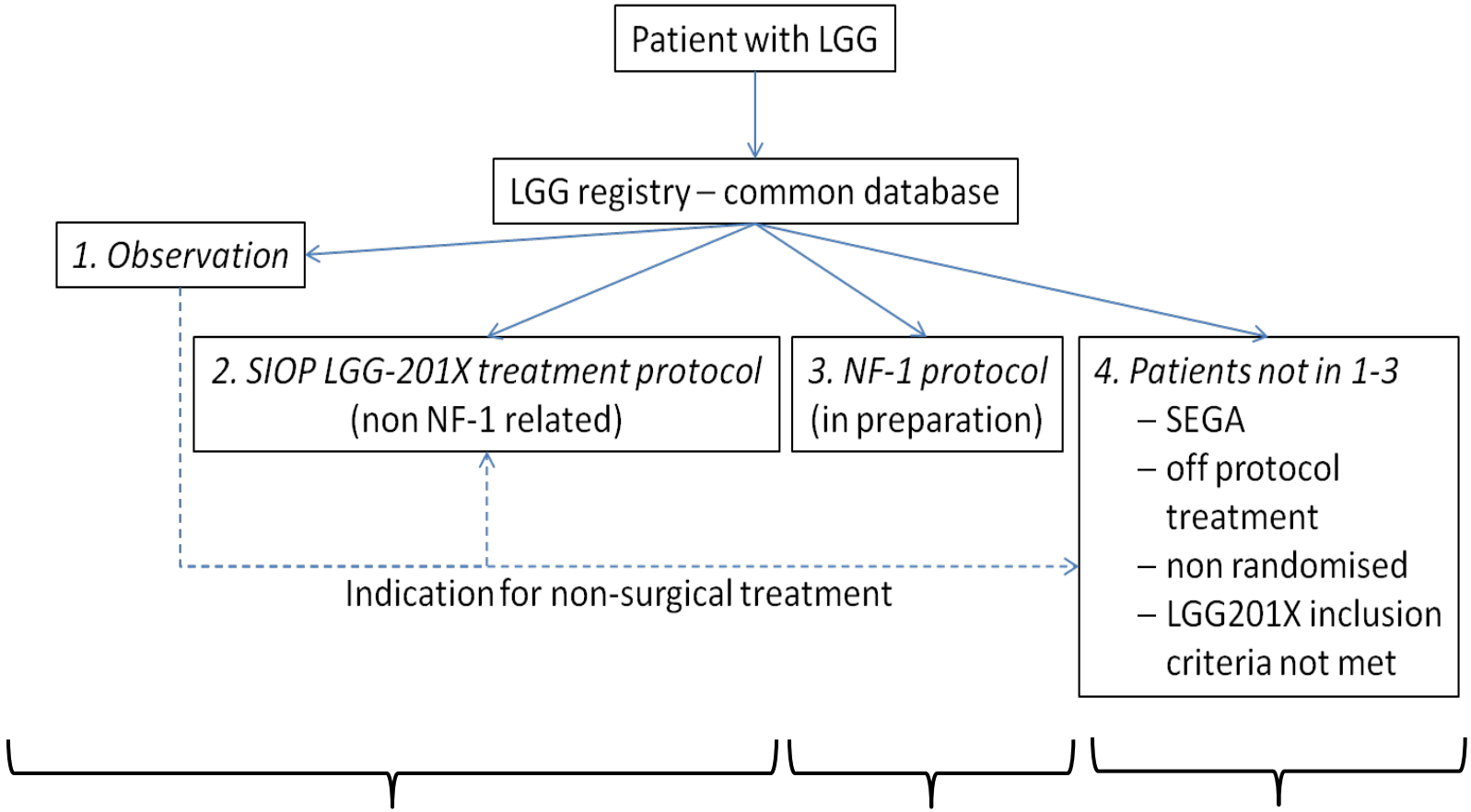
EUROPE



LGG principles….

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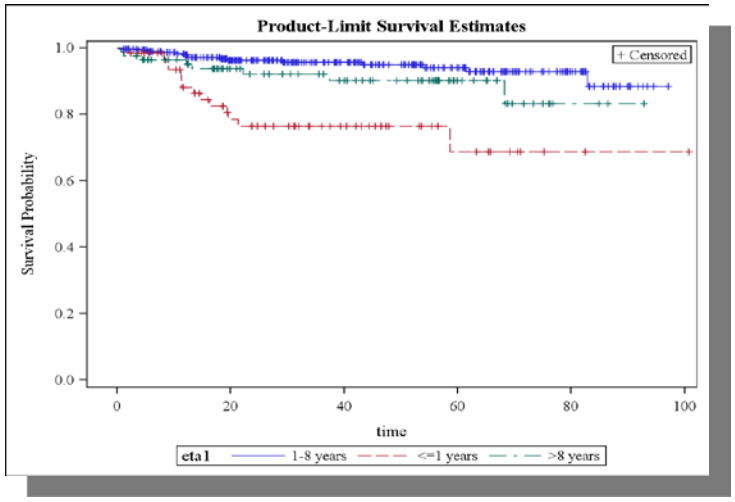
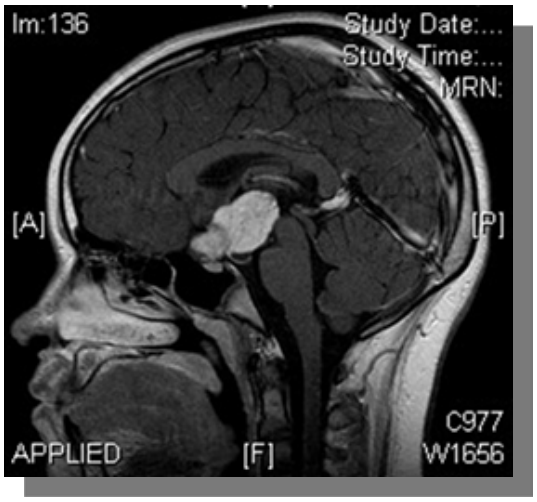
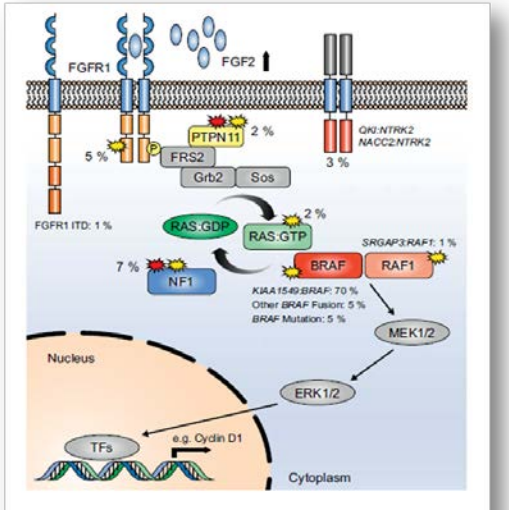
1. Chronic disease
2. Brain function matters
3. Biology is key







Aims of the Trial

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EUROPE

- Reduction of neurotoxicity
- Introduce **combined primary endpoint**:
  + PFS (MRI)
  + neurological function (VABS II)
  + visual function (VA, LogMAR)
- **Biology:** biomarker for prediction of natural course of LGG, prediction response to chemotherapy/targeted therapy
- Introduction of **targeted compounds** asap after promising phase II data

Trial design

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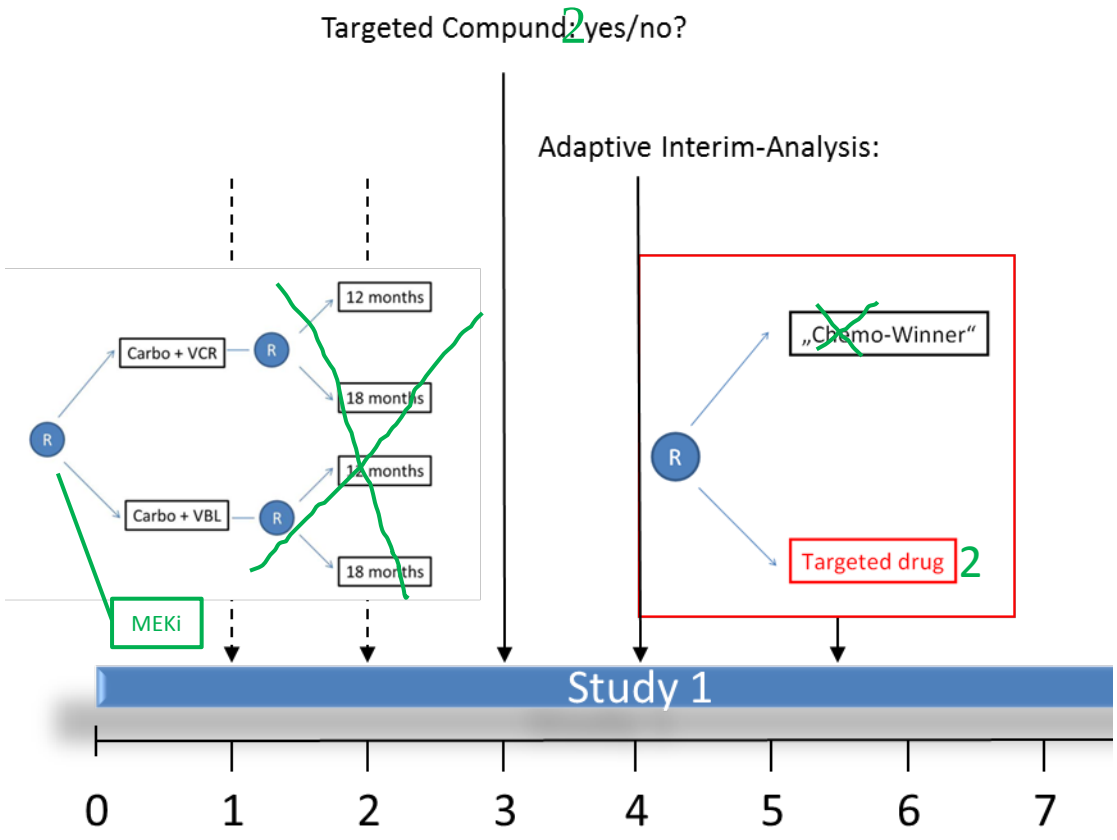
EUROPE



Primary objectives:

=> PFS & CNS & visual function

=> biomarker driven prediction of overall course of disease

Secondary objectives:

=> PA, DG2, infants, other LGGs

=> outcome in molecular subgroups

=> neuro-psychology, endocrinology, diencephalic syndrome, neurotox+pharmacogenomics

under discussion:

- Introduce MEKi now
- skip 12 vs 18 months randomization
- keep adaptive design

Key inclusion criteria

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EUROPE

- age: 0 -20.99 years
- histologically verified LGG
- collection of **fresh frozen tumor tissue** for biomarker determination **mandatory**.

Exception: single cases of stereotactic biopsy in which larger biopsy would impose unacceptable risk to patient

- Indication to start chemotherapy: progressive disease on MRI, neurological function, visual function,
- all infants **< 1 year**

no default first line radiation therapy

Why biomarkers mandatory?

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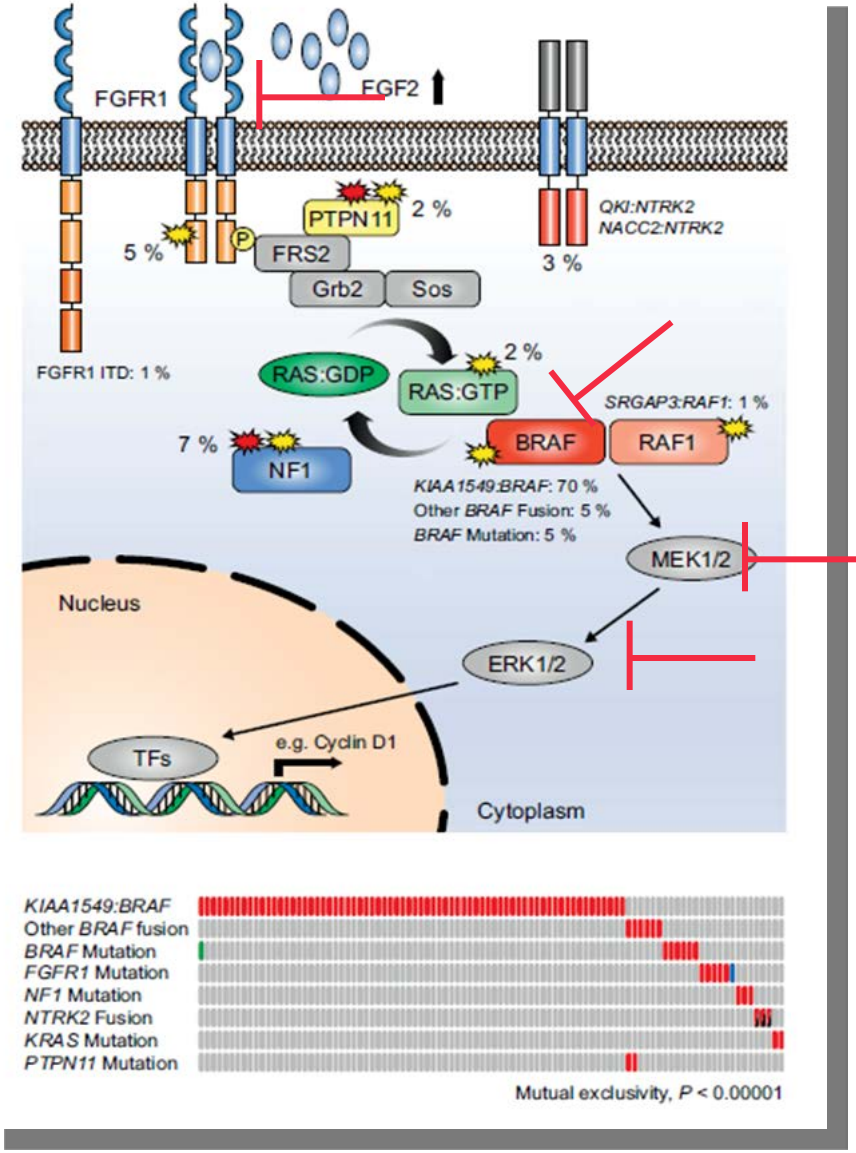

=> Primary endpoint:
multistate model
=> Response prediction
=> Target available at relapse
=> Planning targeted trials
=> No increased risk

ICGC PedBrain Tumor

Jones et al.
Nature Genetics 2013

Why molecular biomarkers II ?

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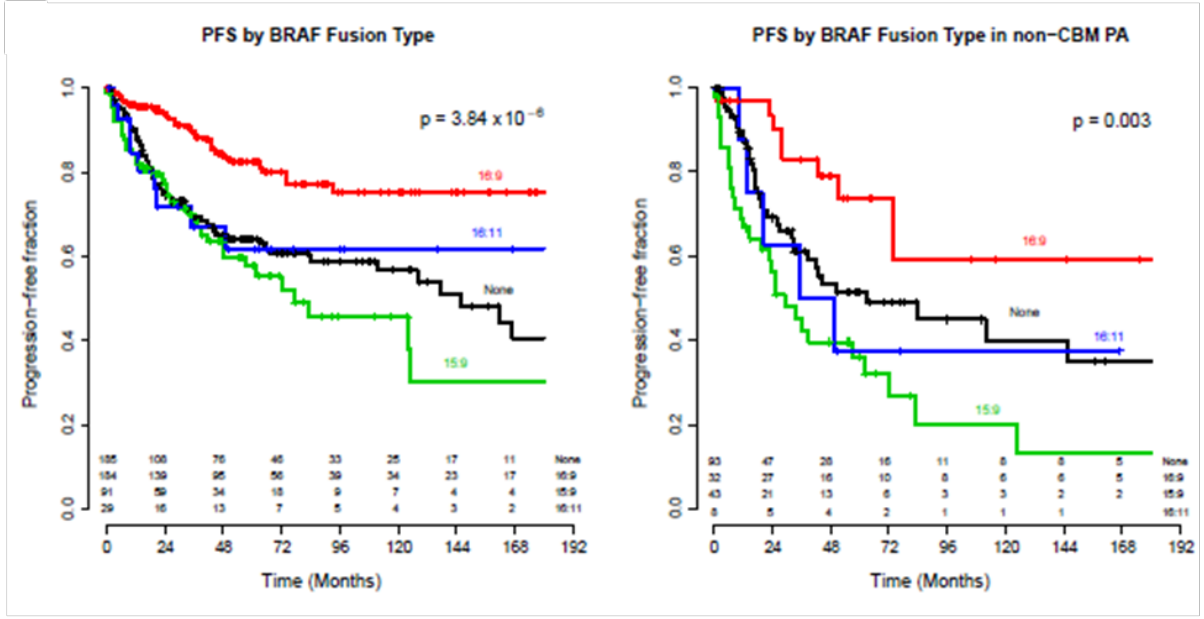
EUROPE

Meta-analysis SIOP LGG pre-clinical working group:

⇒ BRAF KIAA fusions type independent prognostics factor (multivariate analysis: age, location, histology, extend of resection)



KIAA1549:BRAF breakpoint:

15_9

16_9

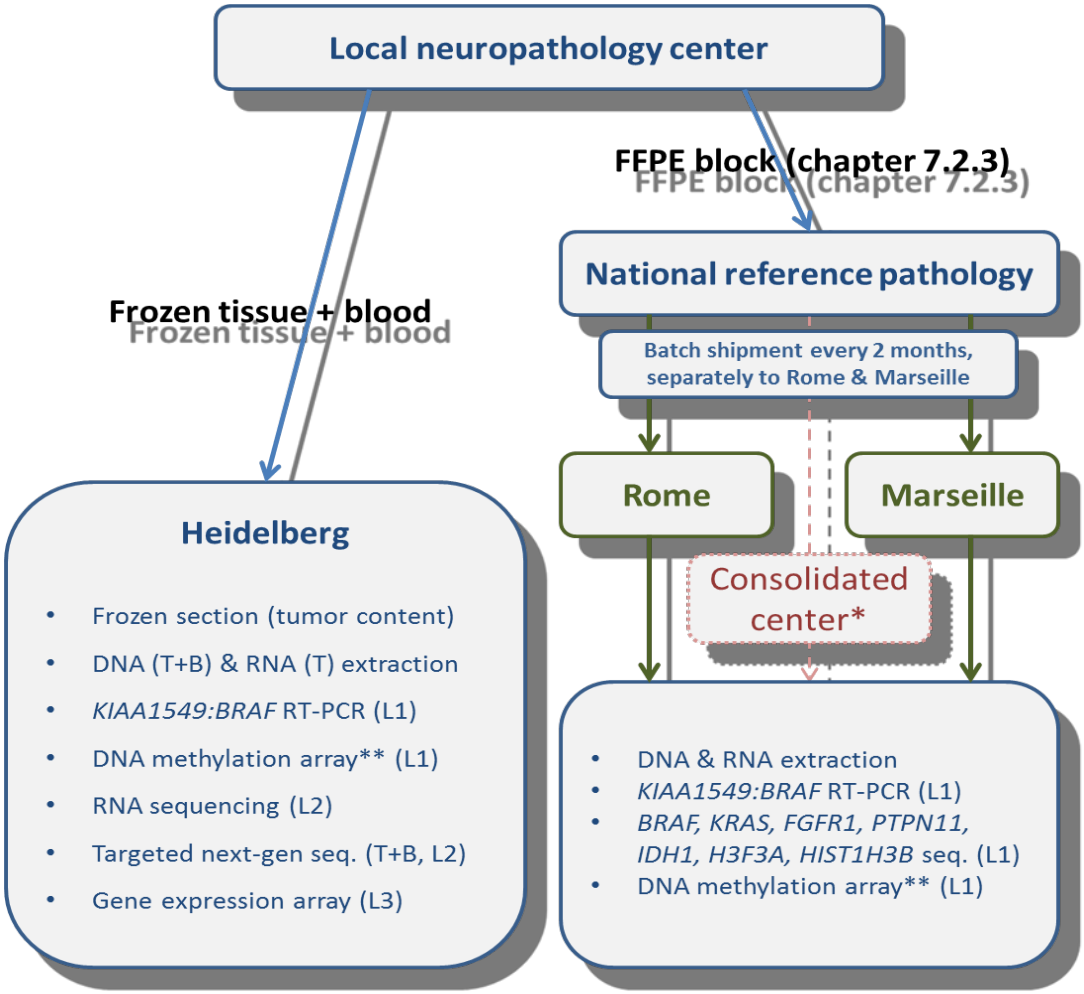
16_11

None

SIOP LGG Preclinical Working Group: Manuscript in preparation

Tumor sample workflow

LOGIC EUROPE



A Kids' Brain Tumor Cure
PLGA Foundation

L1 – Level 1; highest priority use of material
L2 – Level 2; performed if no alteration identified in L1
L3 – Level 3; performed if material remaining after L1 & L2

Why Vinblastine?

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- Single agent activity
  Bouffet et al., JCO 2012, Phase II, n=51, 5 year PFS 42%
- Low neurotoxicity
  => OPG/Thalamic tumors
- Anti-angiogenic activity at low doses
  Klement et al., JCI 2000; Vacca et al., Blood 2004
- Phase I Carbo+VBL
  Jakacki et al., 2011, Carbo +VBL at 400mg/m2/d + VBL 4mg/m2/d
  1 PR=>CR, 6 OR (1PR), 11 SD, 3 PD (total 21)
  7/9 OPG: improvement of vision

Visual acuity (VA) as the primary measure

- Aim to "*measure the **best possible corrected** VA under the **best possible conditions** at every time point using an **age-appropriate** test*"
- Use a quantitative **continuous scal**e (logMAR based)
- In case of poor cooperation and/or suspected visual decline "*it is mandatory to **retest the child*****"** (within 1-2 weeks)
- it is crucial to "***exclude** refractive error, amblyopia, or other non-OPG-related causes*"
- A **national reference ophthalmologist** necessary

Visual indications to treatment

Additional criteria only for OPG subgroup

(other criteria may influence treatment indication i.e. infant age, radio progression, neurologic symptoms…)

At diagnosis

- Presence of visual-related "severe symptoms"

During observation

- Visual decline (0.2 logMAR or more) in one or both eyes)

Vision-related severe symptoms (WHO def)

Named Ranges of Vision Loss (ICO, 1978 and ICD-9-CM)		Numbered ranges (WHO, ICD-9)		Visual Acuity: Decimal notation	Visual Acuity: U.S. notation	Visual Acuity: 6 m notation	Linear scales: Letter count	Linear scales: Log MAR
(Near-)Normal Vision	Range of Normal Vision	(The ICD does not code normal conditions)		1.6	20/12	6/4	110	-0.2
				1.25	20/16	6/5	105	-0.1
				1.0	**20/20**	**6/6**	100	0
				0.8	20/25	6/7.5	95	0.1
	Mild Visual Impairment (near-normal vision)			0.63	20/32	6/10	90	0.2
				0.5	20/40	6/12	85	0.3
				0.4	20/50	6/15	80	0.4
				0.32	20/63	6/18	75	0.5
Low Vision	Moderate Visual Impairment	Low Vision - WHO	Group 1	0.25	20/80	6/24	70	0.6
				0.2	20/100	6/30	65	0.7
				0.16	20/125	6/36	60	0.8
				0.125	20/160	6/48	55	0.9
	(20/200) Severe Visual Impairment		(6/60)	**0.1**	**20/200**	**6/60**	**50**	**1.0**
			Group 2	0.08	20/250		45	1.1
				0.063	20/300		40	1.2
				0.05	20/400	3/60	35	1.3
	Profound Visual Impairment	Blindness - WHO	Group 3	0.04	20/500		30	1.4
				0.032	20/600	2/60	25	1.5
				0.025	20/800		20	1.6
				0.02	20/1000		15	1.7
(Near-) Blindness	Near-Blindness		Group 4	less	less	1/60 or less	10	1.8
							5	1.9
	Blindness		Group 5	0.0	NLP	NLP	0	2.0

Abnormal VA (≥0.2 logMAR)in both eyes (bilateral threat)

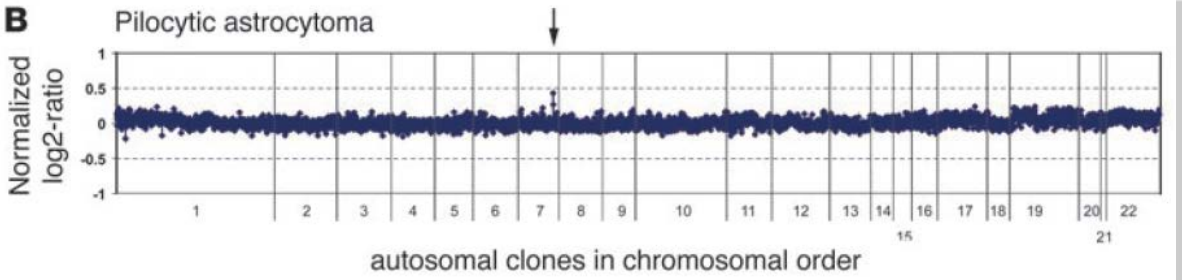
Low vision (> 0.5 logMAR) in the worse eye (threat to vision)

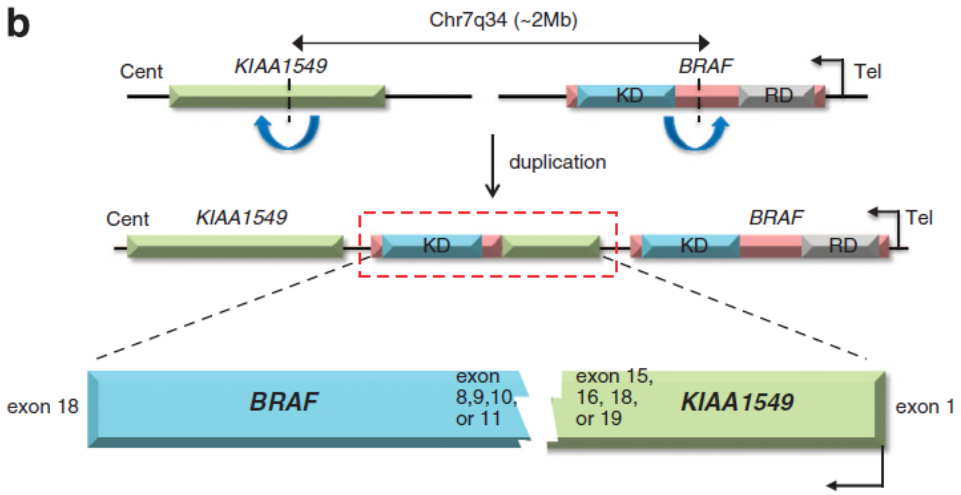
Targeting BRAF and MEK pathway in LGG

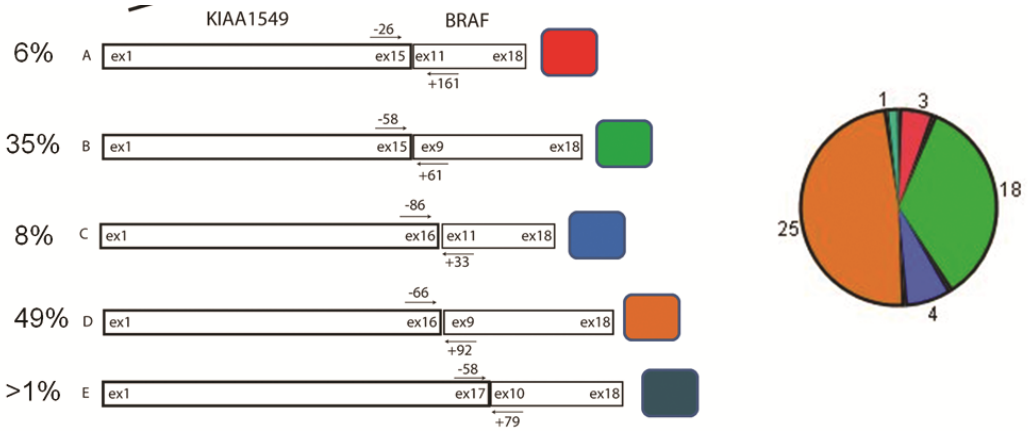
Outline

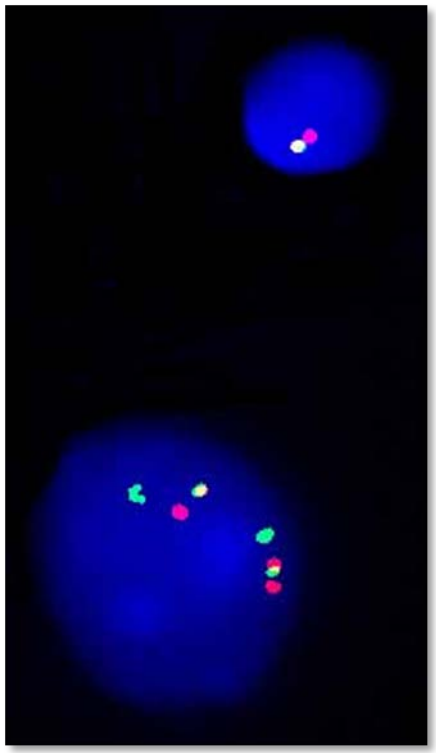
- Biology of Low Grade Glioma
- Sorafenib (NYU and collaborating Institutions)
- Sunitinib (PBTC – NCI Sponsored Trial)
- Dabrafenib (Company Sponsored – GSK; Transatlantic accrual)

BRAF abnormalities – hallmark signature for PA





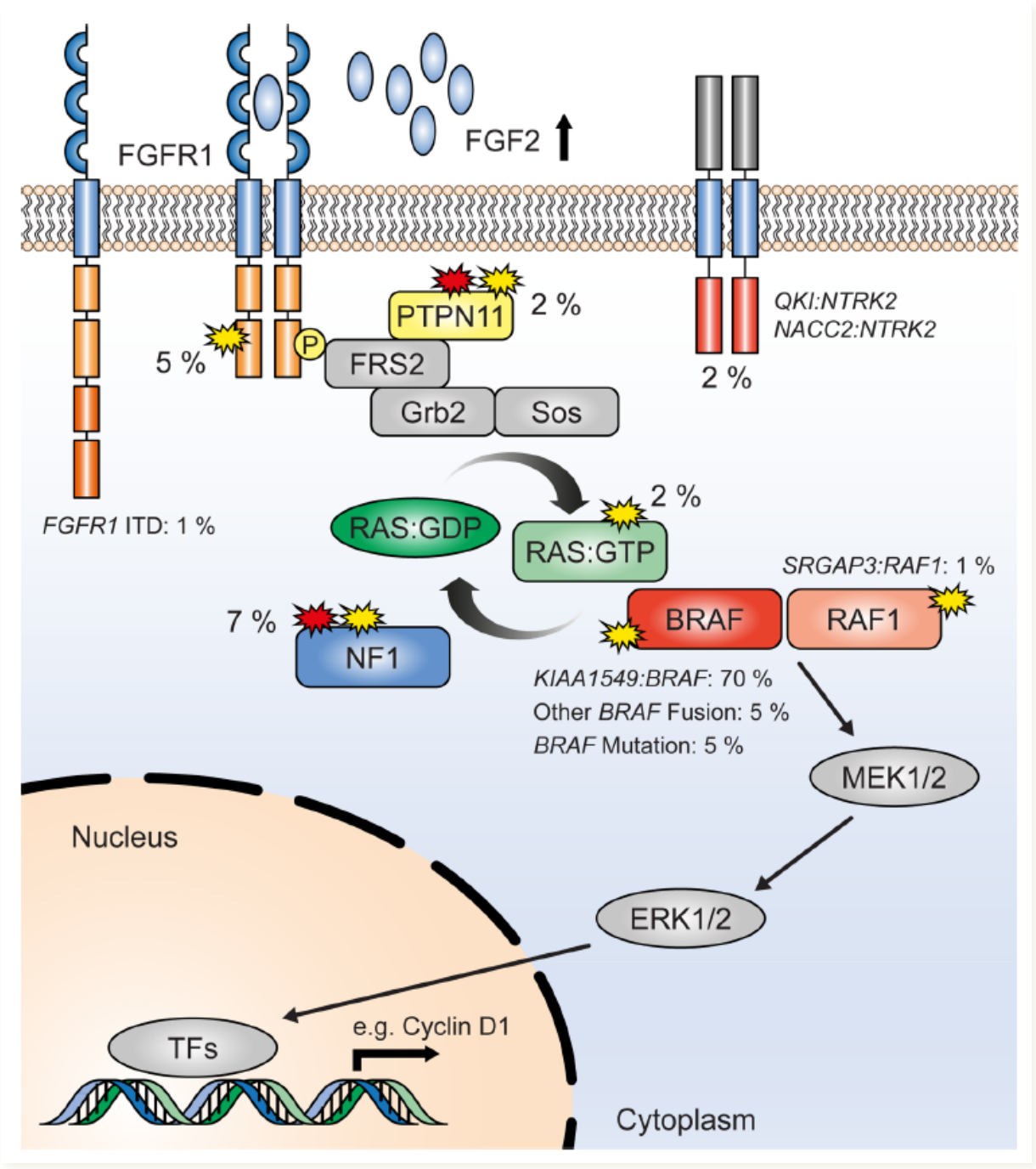




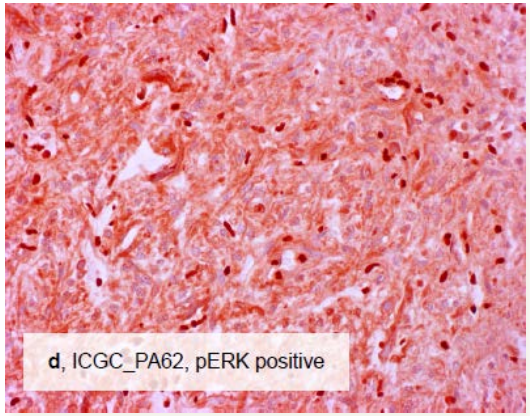
Pfister *et al.*, JCI 2008

Chen and Guttmann, Oncogene 2013

Lin *et al.*, J Neuropathol Exp Neurol 71, 2012



Germline and Somatic mutations in PA

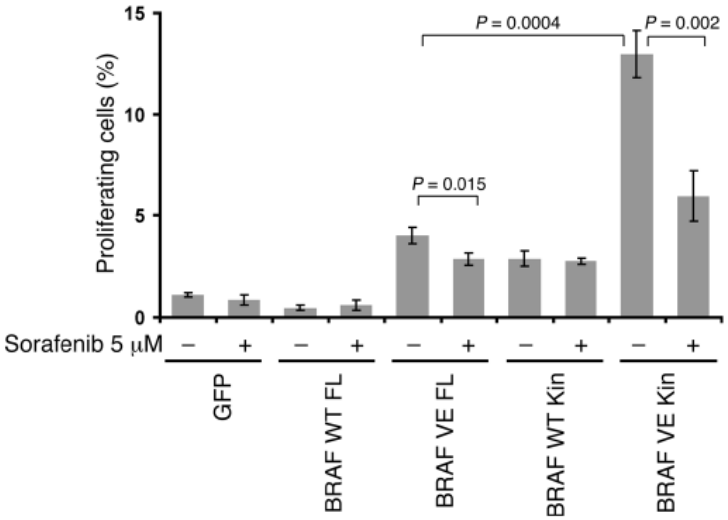


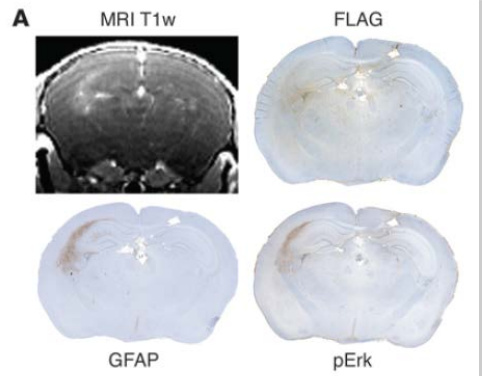
BRAF driven mouse model of PA

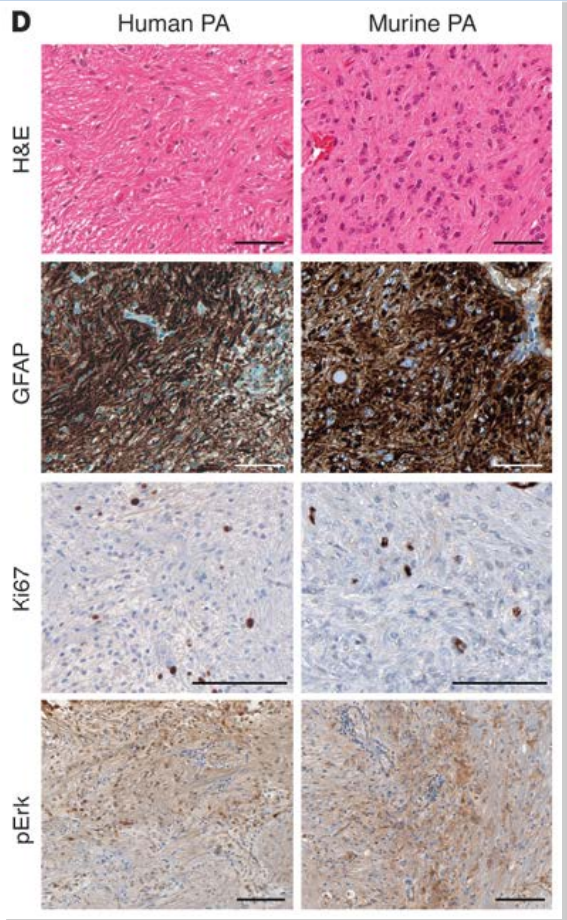
Brief report

An activated mutant BRAF kinase domain is sufficient to induce pilocytic astrocytoma in mice

Jan Gronych,[1] Andrey Korshunov,[2] Josephine Bageritz,[1] Till Milde,[3,4] Manfred Jugold,[5] Dolores Hambardzumyan,[6] Marc Remke,[1,4] Christian Hartmann,[2] Hendrik Witt,[1,4] David T.W. Jones,[1] Olaf Witt,[3,4] Sabine Heiland,[7] Martin Bendszus,[7] Eric C. Holland,[6] Stefan Pfister,[1,4] and Peter Lichter[1]

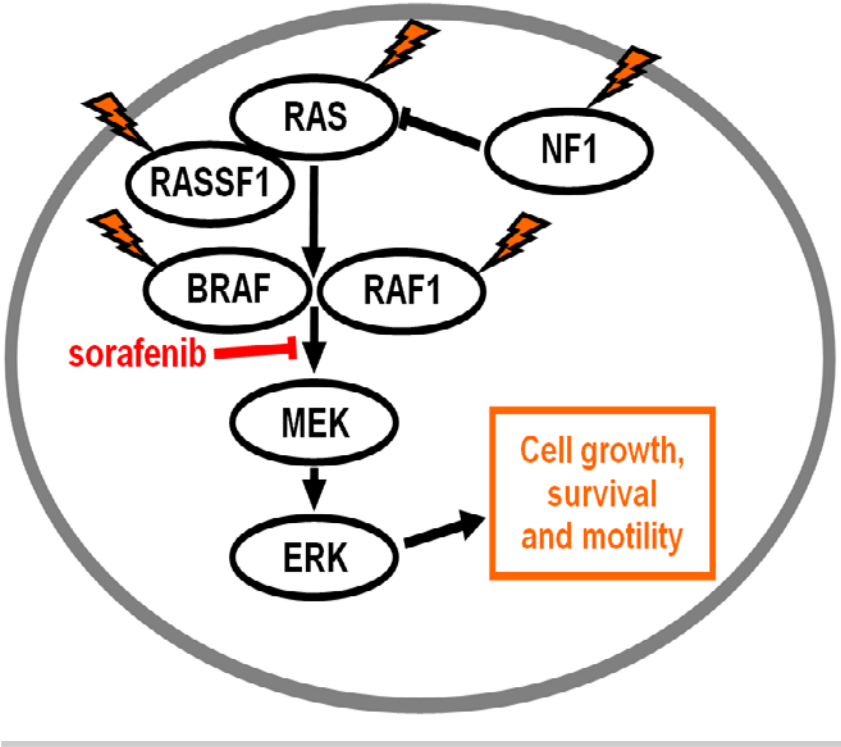


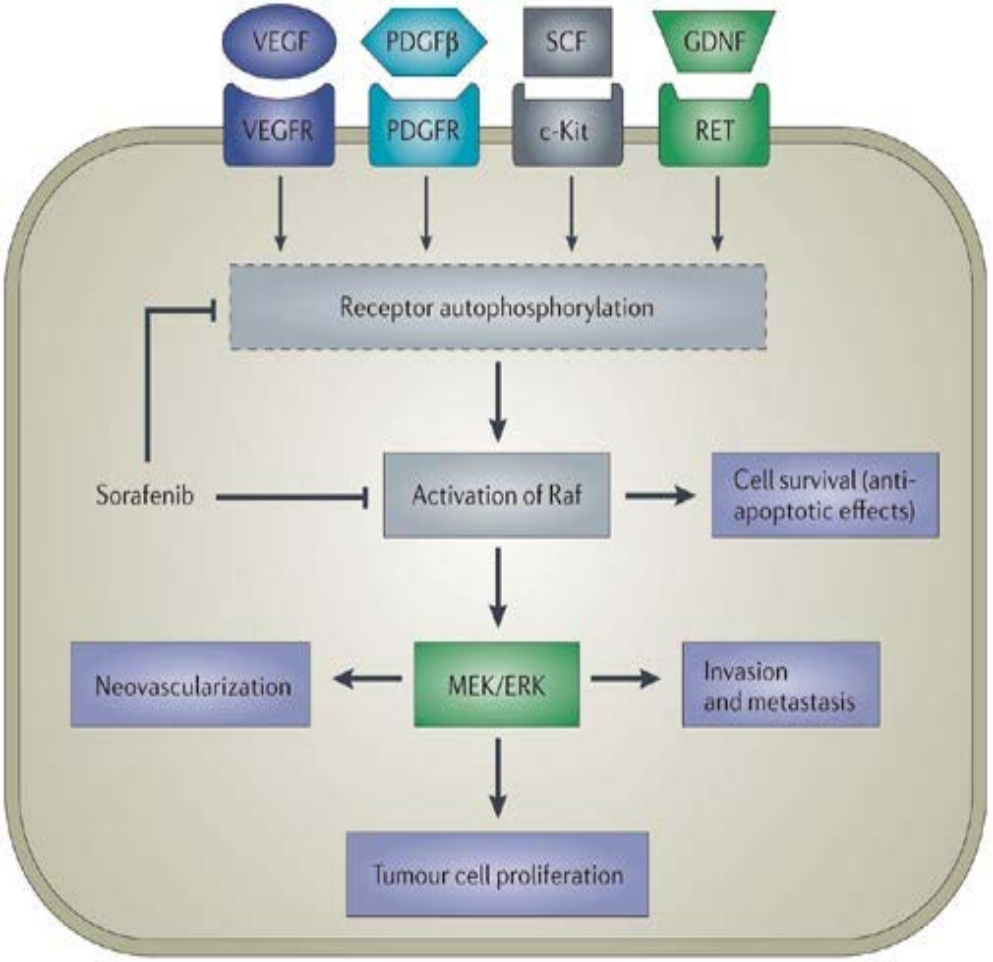




Construct	Incidence	Histology
BRAF WT FL	0/10 (0%)	–
BRAF VE FL	0/10 (0%)	–
BRAF WT kin	0/10 (0%)	–
BRAF VE kin	21/23 (91%)	Pilocytic astrocytoma

Sorafenib as a MEK inhibitor





Sorafenib

- Developed as a selective ATP-competitive RAF inhibitor
- Inhibits CRAF (RAF-1) and BRAF , including BRAF ^{v600E} at low nanomolar concentrations
- Also targets VEGF2/3, PDGFR, FGFR-1, FLT3 and c-KIT
- Preclinical data suggest good CNS bioavailability (10% of systemic exposure)
- Most advanced RAF inhibitor in clinical space
- FDA approved for treatment of renal cell carcinoma and hepatocellular carcinoma
- Pediatric MTD determined and safety data established in Phase I trials

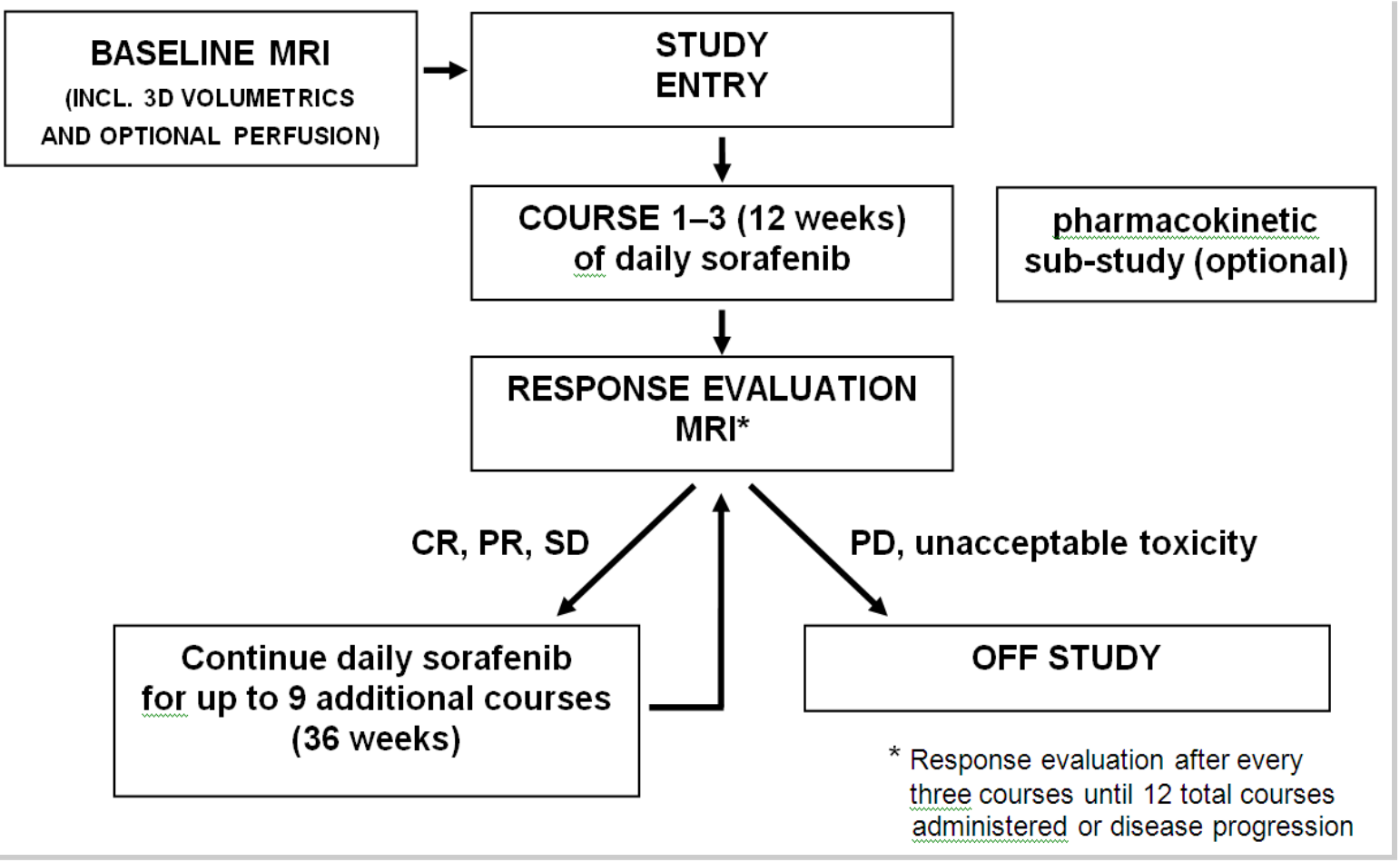
Sorafenib – in vitro inhibitory concentrations

Table 2: *in vitro* inhibitory profile of sorafenib (from: Voliotis and Dumas in: Tumor Angiogenesis, Springer 2007, 655-671)

Kinase target (biochemical kinase assay)	***In vitro* IC_{50} value (nM)**	***Kinase target (cellular kinase assay)***	***In vitro* IC_{50} value (nM)**
RAF1 (CRAF)	6	MEK phosphorylation in MDA MB 231 cells	40
Wild-type BRAF	25	ERK 1/2 phosphorylation in MDA MB 231 cells	90
Oncogenic BRAF V600E	38	MEK 1/2, and p44/p42 MAPK phosphorylation in FRO cells	500
VEGFR-1	26	RET phosphorylation in NIH3T3 fibroblasts	47
VEGFR-2	90	Oncogenic V804L RET human thyroid carcinoma cells	110
Murine VEGFR-1	20	Oncogenic V804M RET human thyroid carcinoma cells	147
Murine PDGFR-β	57	Oncogenic BRAF V600E in human thyroid carcinoma cells	1000
Flt-3	33	VEGFR-2 phosphorylation in NIH 3T3 fibroblasts	30
p38	38	VEGF-ERK 1/2 phosphorylation in HUVEC cells	60
c-Kit	68	PDGFR-β phosphorylation in HAoSMC	80
FGFR-1	580	VEGFR-3 phosphorylation in HEK-293 cells	100
MEK-1, ERK-1, EGFR, Her2, c-met, IGFR-1, PKA, PKB, cdk1/cyclin B, pim-1, PKC-α, PKC-γ	>10,000	Flt-3 phosphorylation in HEK-293 cells with human ITD	20

Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas

Matthias A. Karajannis, Geneviève Legault, Michael J. Fisher, Sarah S. Milla, Kenneth J. Cohen, Jeffrey H. Wisoff, David H. Harter, Judith D. Goldberg, Tsivia Hochman, Amanda Merkelson, Michael C. Bloom, Angela J. Sievert, Adam C. Resnick, Girish Dhall, David T. W. Jones, Andrey Korshunov, Stefan M. Pfister, Charles G. Eberhart, David Zagzag, and Jeffrey C. Allen



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PATIENT STRATIFICATION

A non-NF1: LGA *positive* for constitutive BRAF activation (*KIAA:BRAF* fusion or *BRAF*$^{V600E/ins598T}$)

B non-NF1: LGA *negative* for constitutive BRAF activation

C non-NF1: LGA with *unknown/indeterminate* BRAF status (including OPGs without available tissue)

D NF1

Molecular analysis:

- PCR *BRAF:KIAA* (frozen) and *BRAF*^{V600E} (frozen/FFPE)
- array CGH
- FISH (FFPE)

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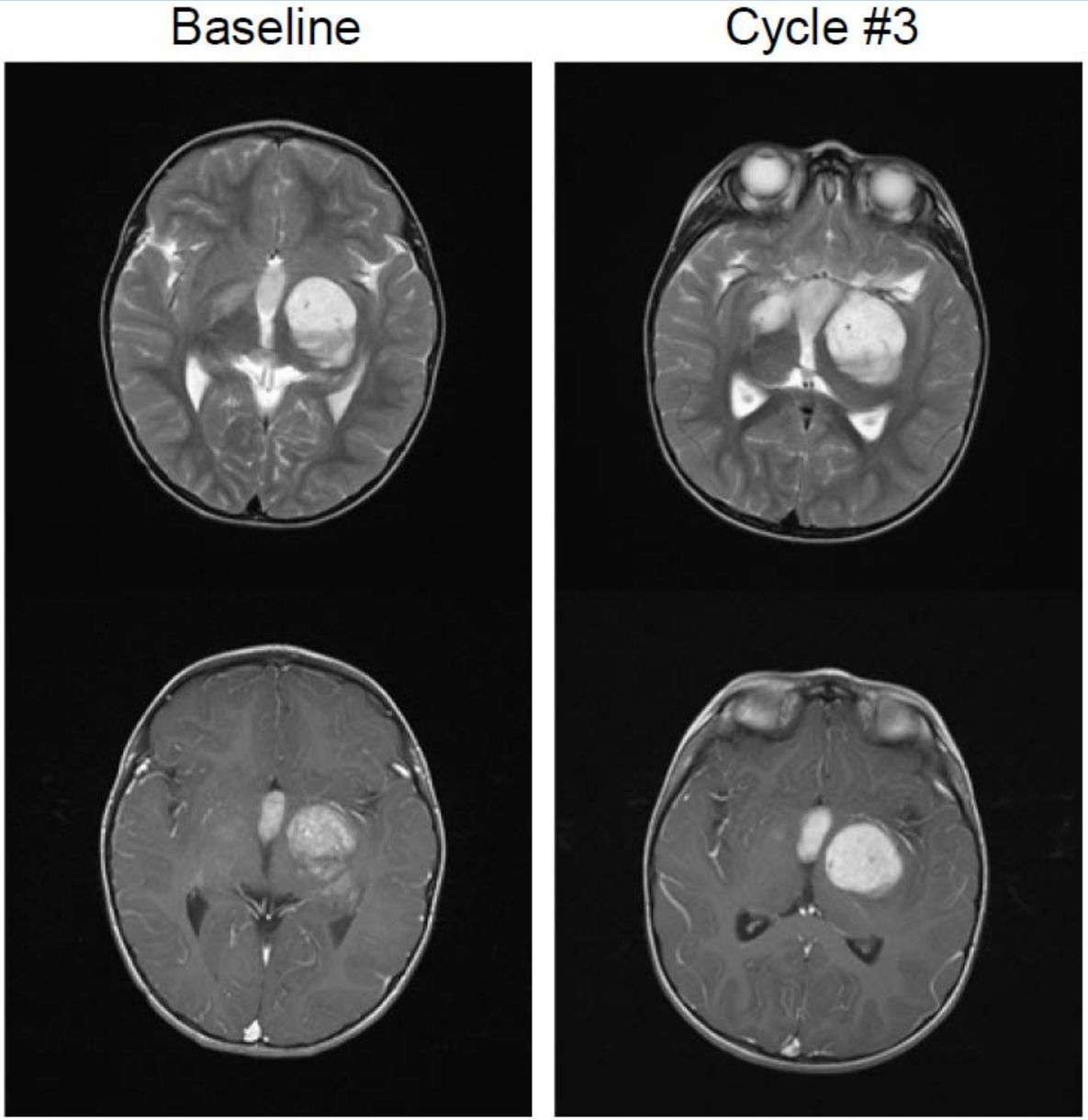
Table 3. Summary of evaluable patient treatment outcomes on study

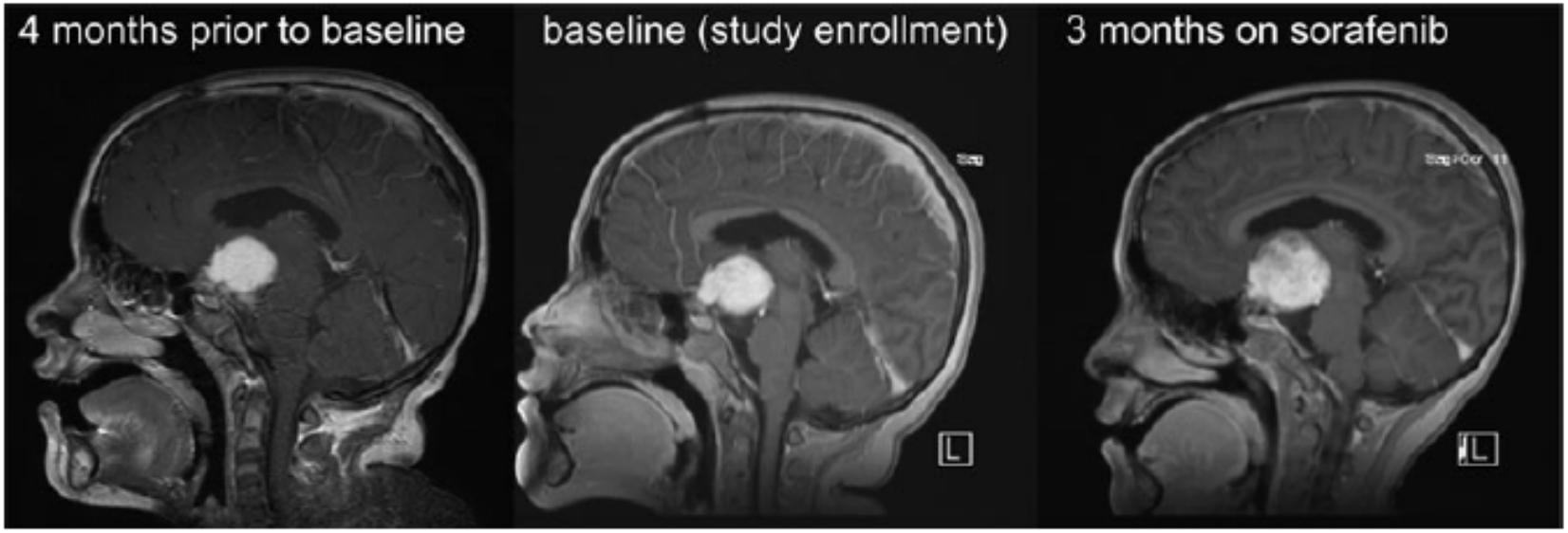
Patient	Treatment Duration [cycles]	Best Tumor Response	Tumor Volume Change	Reason for Treatment Discontinuation
1	7	SD	−4%	Patient preference
2	3	PD	+122%	Progression
3	2	PD	N/A*	Progression
4	9	PR	−43%	Toxicity (hand-foot skin syndrome)
5	3	PD	+21%	Progression
6	2	PD	+326%	Progression
7	2	PD	+26%	Progression
8	3	PD	+59%	Progression
9	2	PD	+53%	Progression
10	3	PD	+61%	Progression
11	3	PD	+24%	Progression

Abbreviations: N/A, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.
*Patient developed new lesion.

B. Patient #10, BRAF-KIAA, PD



C: Patient #8 – NFI; no biopsy; PD



Vol 464|18 March 2010|doi:10.1038/nature08902 nature

LETTERS

RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF

Poulikos I. Poulikakos[1], Chao Zhang[2], Gideon Bollag[3], Kevan M. Shokat[2] & Neal Rosen[1]

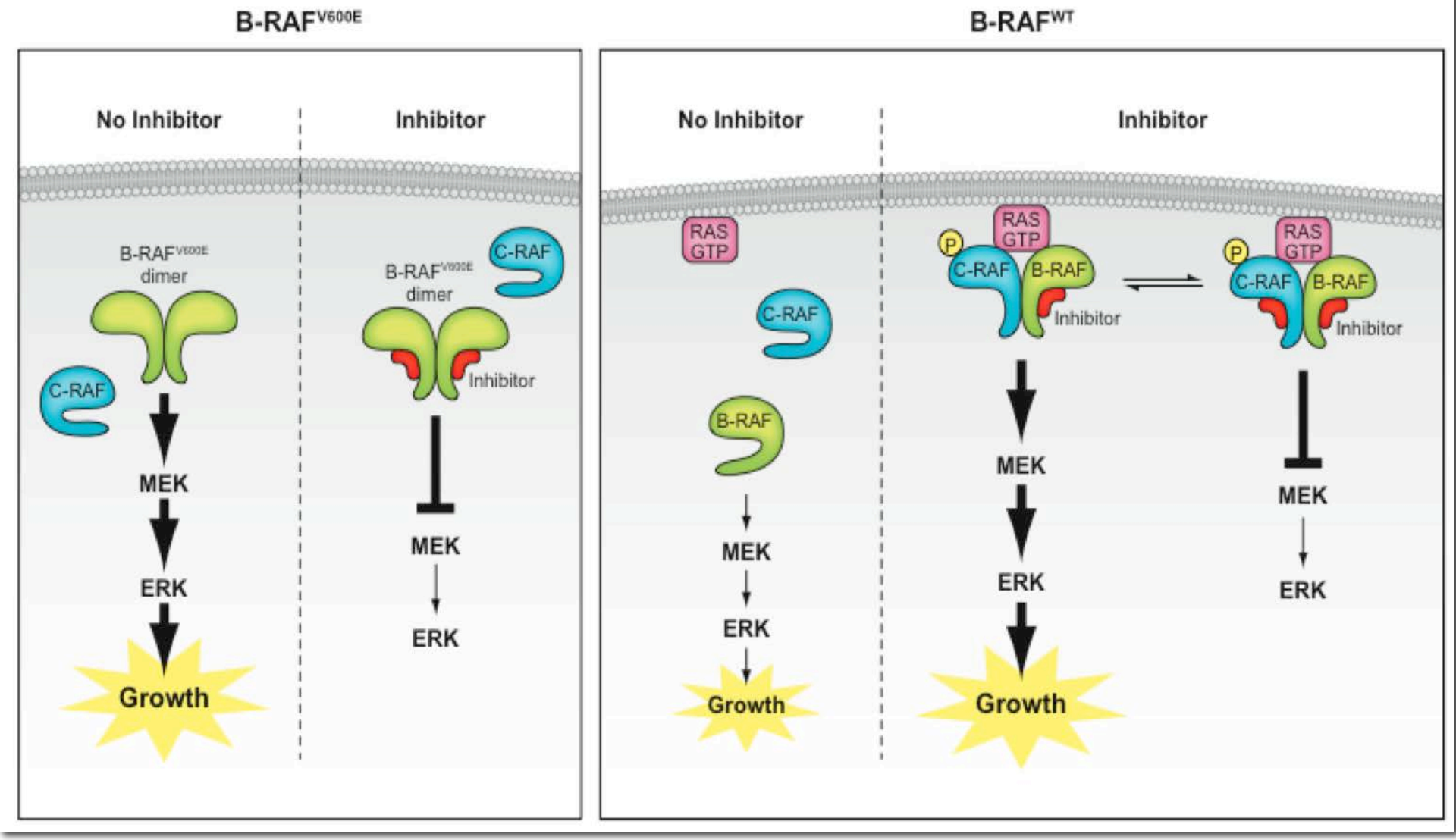
Vol 464|18 March 2010|doi:10.1038/nature08833 nature

LETTERS

RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth

Georgia Hatzivassiliou[1], Kyung Song[1], Ivana Yen[1], Barbara J. Brandhuber[2], Daniel J. Anderson[1], Ryan Alvarado[1], Mary J. C. Ludlam[1], David Stokoe[1], Susan L. Gloor[2], Guy Vigers[2], Tony Morales[2], Ignacio Aliagas[1], Bonnie Liu[1], Steve Sideris[1], Klaus P. Hoeflich[1], Bijay S. Jaiswal[1], Somasekar Seshagiri[1], Hartmut Koeppen[1], Marcia Belvin[1], Lori S. Friedman[1] & Shiva Malek[1]

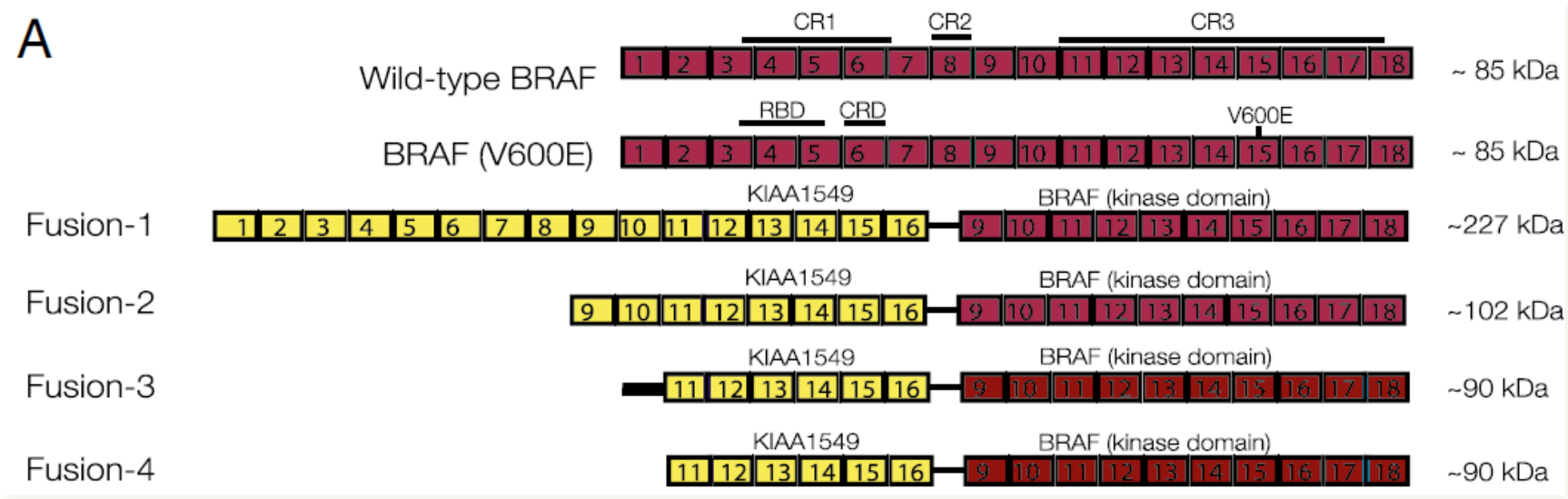
RAF inhibitors prime wild-type RAF to activate MAPK signaling and enhance tumor growth



Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas

Angela J. Sievert[a,b,1], Shih-Shan Lang[c,1], Katie L. Boucher[d], Peter J. Madsen[c,d], Erin Slaunwhite[d], Namrata Choudhari[d], Meghan Kellet[d], Phillip B. Storm[c,d], and Adam C. Resnick[c,d,2]

[a]Division of Oncology, The Children's Hospital of Philadelphia, Philadelphia, PA 19104; [b]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104; [c]Department of Neurosurgery, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104; and [d]Division of Neurosurgery, The Children's Hospital of Philadelphia, Philadelphia, PA 19104



A Phase 1 Study of AZD6244 in Children with Recurrent or Refractory Low Grade Gliomas: A Pediatric Brain Tumor Consortium Report.

Anuradha Banerjee, Regina Jakacki, Arzu Onar-Thomas, Shengjie Wu, Theodore Nicolaides, David C. Turner, Stacye Richardson, Tina Young-Poussaint, Joanna Phillips, Michael Prados, Roger Packer, Ibrahim Qaddoumi, Sridharan Gururangan, Stewart Goldman, Ian Pollack, Austin Doyle, Clinton F. Stewart, James Boyett, Larry Kun, Maryam Fouladi

- Age > 3 and < 21 years with recurrent or refractory low grade glioma that has failed prior chemo or radiotherapy
- Drug administered by mouth, daily, BID continuously
- One course=28 days, up to 26 courses of treatment allowed
- Dose limiting toxicity (DLT) observation period is end of 1st 28 day cycle
- 3 dosage levels (DL) investigated
  - DL0, 25 mg/m2/dose, BID
  - DL1, 33 mg/m2/dose, BID
  - DL2, 43 mg/m2/dose, BID

A Phase 1 Study of AZD6244 in Children with Recurrent or Refractory Low Grade Gliomas: A Pediatric Brain Tumor Consortium Report.

Subject characteristics

- 38 eligible subjects
- Pilocytic astrocytoma most common diagnosis (22/38)
- Median age 13.3 years

AGE at Registration (Years): Median (Min, Max)	13.3 (5.6, 20.8)	
	Number	***Percentage***
SEX		
Males	19	50.0
Females	19	50.0
ETHNICITY		
Non-Hispanic	35	89.7
Hispanic or Latino	3	7.7
Unknown	1	2.6
RACE		
White, Non-Hispanic	33	86.8
Black	3	7.9
Unknown	2	5.3
DIAGNOSIS		
Pilocytic Astrocytoma	22	57.9
Glioma, Nos (Except Nasal Glioma, Not Neoplastic)	8	21.1
Astrocytoma, Nos	4	10.5
Ganglioglioma	2	5.3
Oligodendroglioma, Nos	1	2.6
Pleomorphic Xanthoastrocytoma	1	2.6

A Phase 1 Study of AZD6244 in Children with Recurrent or Refractory Low Grade Gliomas: A Pediatric Brain Tumor Consortium Report.

Toxicity

- Dose limiting toxicities were headache, rash, mucositis, and elevation of amylase and lipase
- Maximum tolerated dosage = 25 mg/m2/dose
- At dose levels above 25mg/m2/dose, toxicities resulted in treatment discontinuation rate of 36%

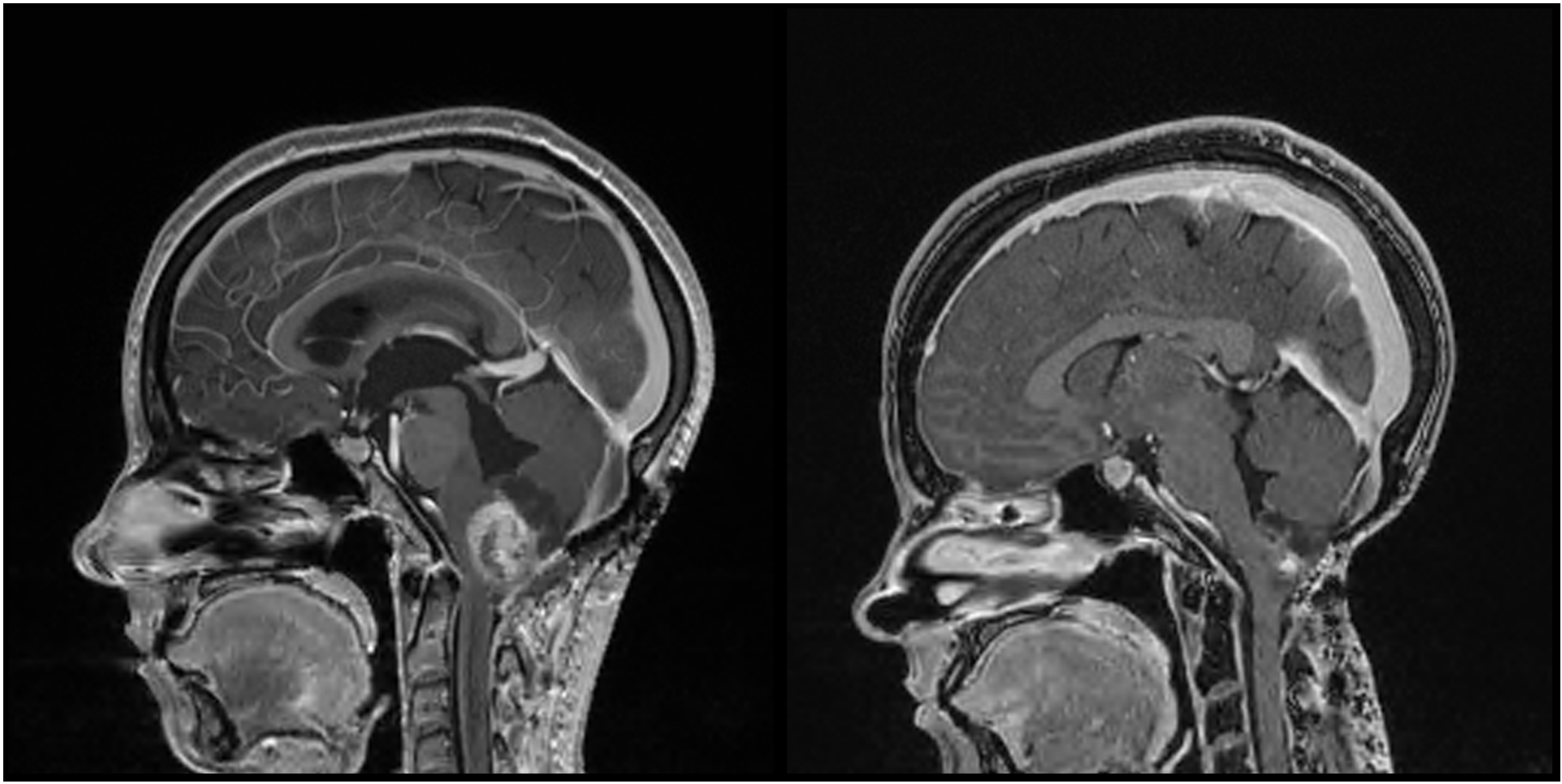
Stratum I				
Dose level (mg/m^2/dose BID)	*Number of eligible patients*	*Number of evaluable Patients*	*Number of patients with DLTs*	*Description of DLTs*
25	25	24	3	Grade 3 Elevation of Amylase\ Lipase (n=1) Grade 3 Rash (n=1) Grade 3 Mucositis (n=1)
33	10	10	4	Grade 3 Headache (n=1) Grade 2 Rash (n=1) Grade 3 Rash (n=2)
43	3	3	2	Grade 3 Rash (n=2) Grade 3 Mucositis (n=1)

A Phase 1 Study of AZD6244 in Children with Recurrent or Refractory Low Grade Gliomas: A Pediatric Brain Tumor Consortium Report

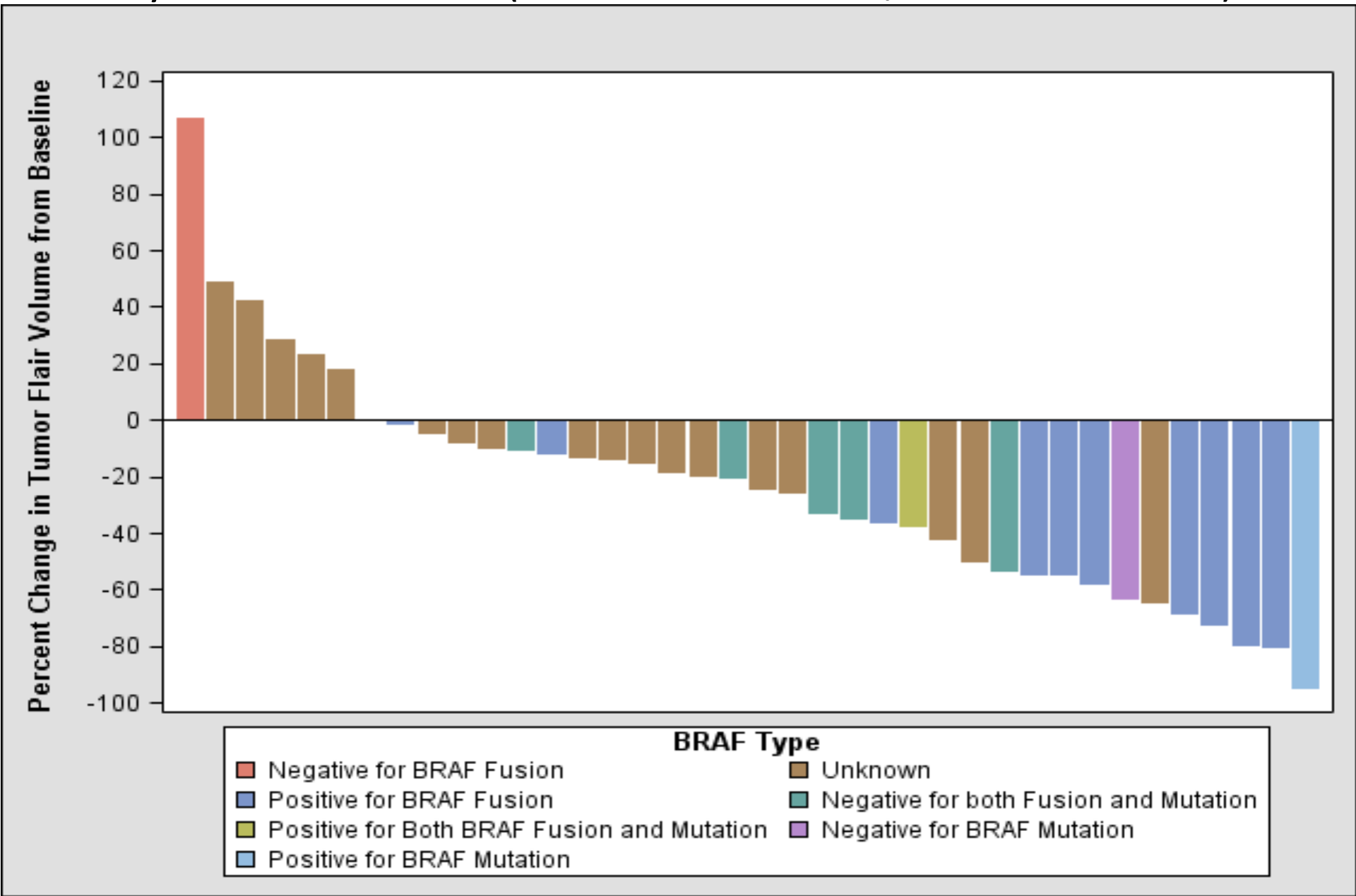
Responses

- 8 subjects with radiographic partial response
- 6 of 8 PRs observed in subjects treated at MTD (**25** mg/m2/dose)
- **Objective response rate at MTD = 6/24 (25%)**
- 5 of 8 subjects with PR had sufficient tissue for BRAF studies; 4 of these 5 had a BRAF mutation (n=1) or fusion (n=3)

AZD 6244 - RESPONSE



Largest Percentage Reduction in Tumor Volume from Baseline by BRAF Aberration (Min Tumor Volume/Baseline Volume)



A Phase 1 Study of AZD6244 in Children with Recurrent or Refractory Low Grade Gliomas: A Pediatric Brain Tumor Consortium Report

Conclusions

- The maximum tolerated dosage of AZD6244 in children and adolescents is 25 mg/m2/dose
- Pharmacokinetic analysis shows that this dosage results in plasma exposures similar to those known to inhibit phospho-ERK in peripheral blood cells
- Radiographic responses observed in this cohort demonstrates that therapeutic targeting of pediatric low grade glioma with the MEK inhibitor AZD6244 has promise as a novel treatment

Pediatric Brain Tumor Consortium

PBTC29 – Phase II study

Stratum 1	Stratum 2	Stratum 3	Stratum 4	Stratum 5	Stratum 6
Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma **with** pre-trial tumor material available and **with** a BRAF aberration, excluding patients with optic pathway glioma NON NF1 With BRAF aberration	Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma **with** pre-trial tumor material available and **without** BRAF aberration, excluding patients with optic pathway glioma NON NF1 without BRAF aberration	Patients with NF-1 associated progressive, recurrent or refractory low grade glioma (WHO I or II), **with or without** tissue NFI with or without Tissue – non OPG	Patients with non NF-1 associated progressive, recurrent or refractory optic pathway glioma (OPG) **with or without** tissue available for BRAF evaluation. NFI with or without tissue - OPG	Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than pilocytic astrocytoma or optic pathway glioma). These patients‟ tumors must have BRAF aberrations which will be determined by screening prior to enrollment on the treatment protocol. Non NF-1; Non PA Must have BRAF aberrations	Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than OPG) with tissue available for BRAF analyses who cannot be classified into Stratum 1, 2 or 5 due to inadequate tissue quality, assay failure, etc Non NF-1; Must have BRAF Aberrations Does not qualify for Stratum 1,2,5

Phase 1 study of dabrafenib in pediatric patients with relapsed or refractory BRAFV600-mutant high-grade gliomas, low-grade gliomas, histiocytosis, and other solid tumors

Mark W Kieran[1], Darren Hargrave[2], Ken Cohen[3], Isabelle Aerts[4], Ira J Dunkel[5], Trent R Hummel[6], Irene Jimenez[4], Andrew Pearson[7], Christine Pratilas[3], James Whitlock[8], Eric Bouffet[8] , Violet Shen[9], Alberto Broniscer[10], Anne-Isabelle Bertozzi[11], Joan Sandberg[12*], Allison Florance[12*], Benjamin Suttle[12 §] , Patricia Haney[12†], Mark Russo[12*], Birgit Geoerger[13]

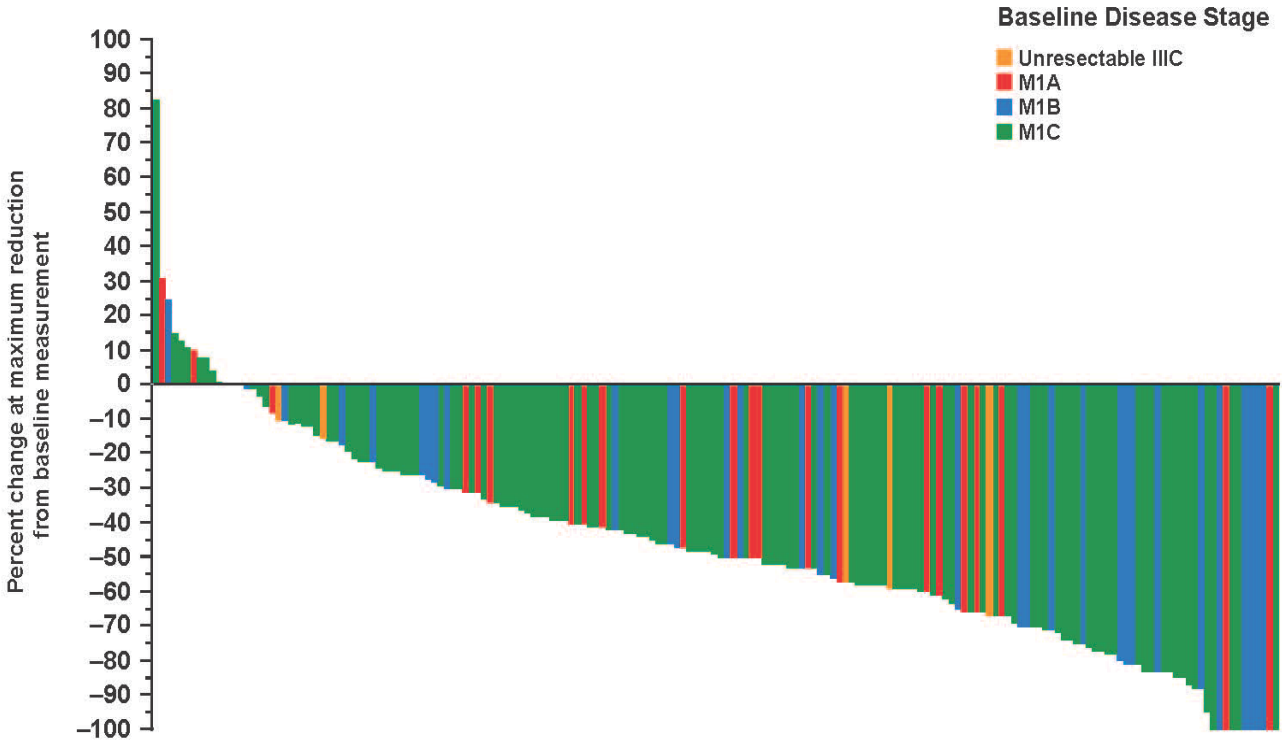
[1]Dana-Farber Cancer Institute and Boston Children's Hospital, Boston, MA, USA; [2]Great Ormond Street Hospital for Children, London, UK; [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Curie Institute, Paris France; [5]Memorial Sloan Kettering Cancer, New York, NY, USA; [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [7]The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK; [8]Hospital for Sick Children, Toronto, Ontario, Canada; [9]Children's Hospital of Orange County, Orange, CA, USA; [10]St. Jude Children's Research Hospital, Memphis, TN, USA; [11]CHU de Toulouse - Hôpital des Enfants, Toulouse, France; [12]GlaxoSmithKline, RTP, NC, USA; [13]Gustave Roussy, Villejuif, France

*_Current affiliation_: Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA;

§ _Current affiliation_: Salix Pharmaceuticals, Raleigh, NC, USA;

† _Current affiliation_: Pfizer Inc, New York, NY, USA

Dabrafenib Activity in Adults With *BRAF*V600-mutant Melanoma

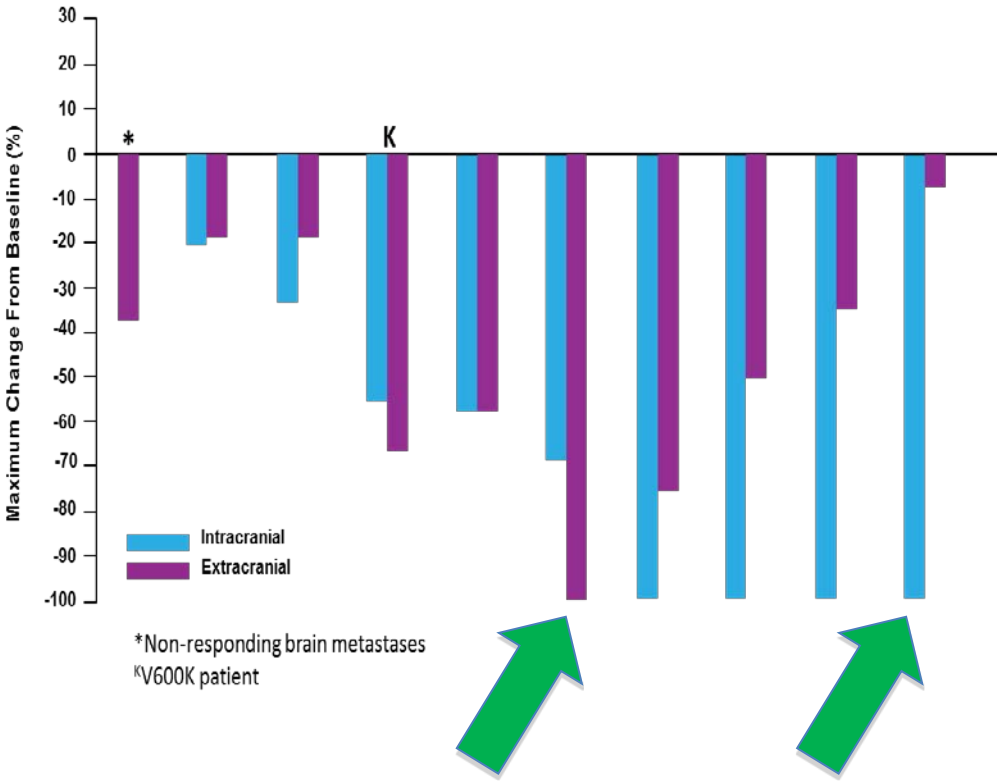


- Best tumor response from baseline in adult patients with melanoma treated with dabrafenib

Hauschild A, et al., *Lancet* 2012;380:358-365.

Dabrafenib Activity in Brain Metastases

- Dabrafenib, at the recommended phase 2 dose, has activity against brain metastases in adult patients with melanoma[1]
  - Nine of ten (90%) melanoma patients with untreated brain metastases showed reduction in brain lesion size



1. Falchook GS, *et al*. *Lancet* 2012;379:1893–1901.

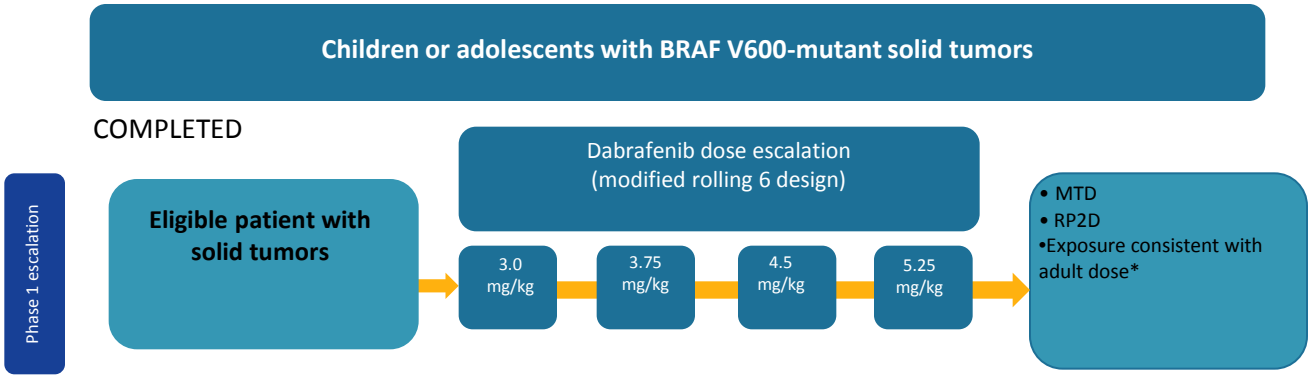
BRAFV600 Mutations in Pediatric Tumors

- ~60% papillary thyroid carcinoma[1]
- ~60% Langerhans cell histiocytosis[2]
- ~50% melanoma[3,4]
- ~10% Low grade gliomas
  - ~10% fibrillary astrocytoma, pilocytic astrocytoma[5]
  - ~60% pleomorphic xanthoastrocytoma[6]
  - ~60% gangliogliomas[7]
- ~10% malignant astrocytomas[8]

1. Henke LE, et al. *Pediatr Blood Cancer* 2014;61:1168–1172;. **2** Badalian-Very G, et al. *Blood* 2010;116:1919–1923; **3**.Daniotti M, et al. *J Invest Dermatol* 2009;129: 1759–1768; **4**. Lu C, et al. *J Invest Dermatol* 2015;135:816–823; **5**. Bergthold G et al. *Neuro Oncol* 2015;pii:nov045; **6**. Dias-Santagata D, et al. *PLoS One* 2011; 6:e17948; **7**. MacConaill LE, et al. *PLoS One* 2009; 4:e7887; **8**. Nicolaides TP, et al. *Clin Cancer Res* 2011;17:7595-7604.

Study Objectives

- Determine the recommended pediatric phase 2 dose (<18 years)
  - Maximum tolerated dose, or if not seen
  - Similar steady-state systemic exposure to adults (AUC, 4000–5500 ng•h/mL)
- Assess dabrafenib safety and efficacy in pediatric population



Key inclusion criteria

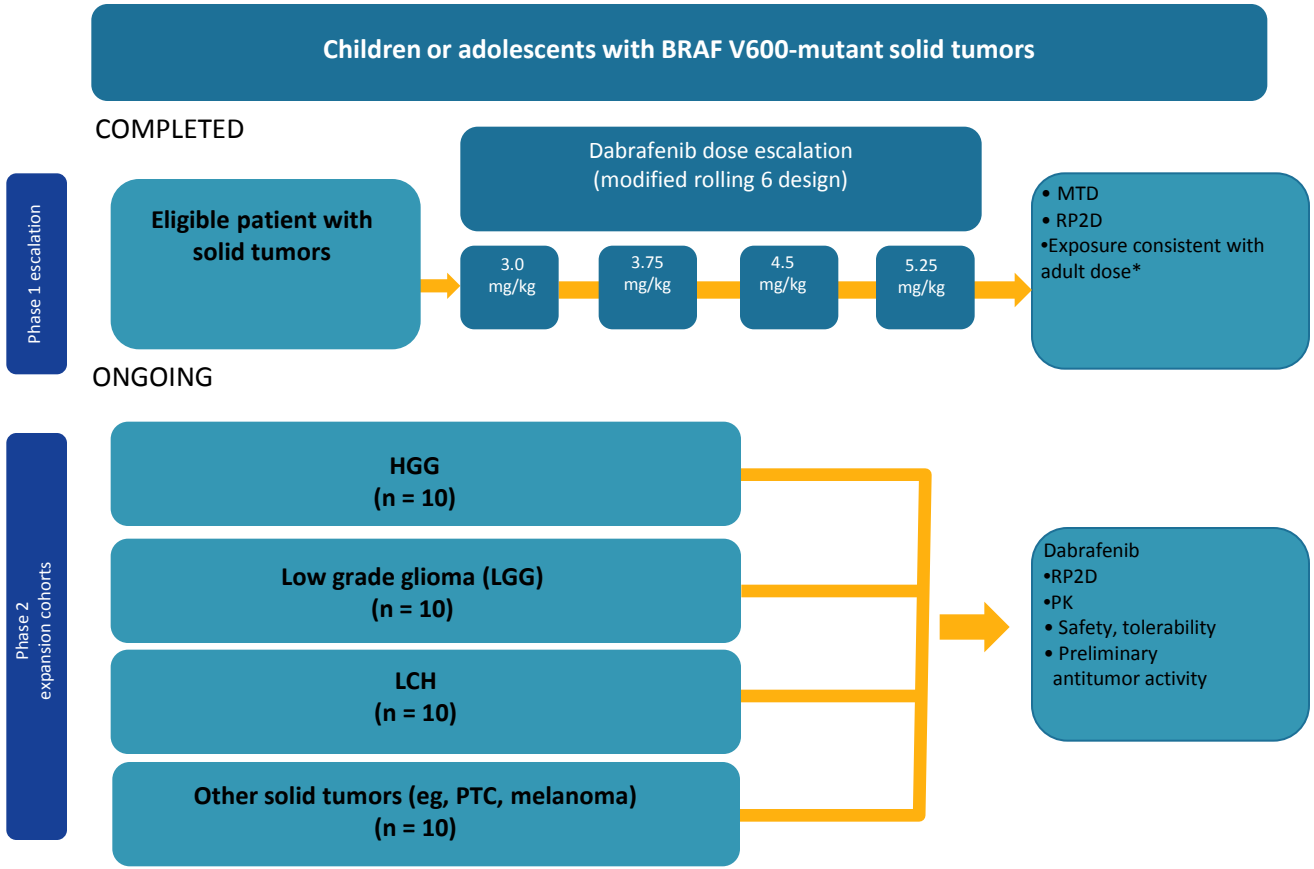
- Recurrent, refractory, or progressive disease after at least 1 standard therapy
  - (metastatic melanoma may be first line)
- BRAF V600 mutation positive
  - (local test with central confirmation)

Key exclusion criteria

- Prior treatment with dabrafenib, other RAF or MEK inhibitor (part 2 only)
- Other malignancy

RP2D, recommended phase 2 dose.
*$AUC_{(0\text{-}12)}$ = 4,000-5,500 ng•h/mL.

Registered at clinicaltrials.gov as NCT01677741



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RP2D, recommended phase 2 dose.
*$AUC_{(0\text{-}12)}$ = 4,000-5,500 ng•h/mL.

Registered at clinicaltrials.gov as NCT01677741

Methods

- V600 mutation status established locally; central confirmation available
- Dabrafenib given orally twice daily, starting dose of 3.0 mg/kg/day
  - Formulations HPMC capsules (10, 25, 50, 75 mg strengths) and powder for suspension in water
- Toxicity, pharmacokinetics, and response assessed at each dose level for patients aged ≥12 months to ≤12 years and >12 years
- During assessment of filled dose level, enrollment allowed into lower tolerable dose levels (backfill)
- Therapy to continue as long as patient is benefitting
- Intrapatient dose escalation permitted

Baseline Patient Characteristics

	Dose cohort				
	3 mg/kg (n = 3)	3.75 mg/kg (n = 10)	4.50 mg/kg (n = 8)	5.25 mg/kg (n = 6)	Total (N = 27)
Mean age (years) **Range**	8.7 4–14	11.6 3–17	6.5 1–17	7.7 3–12	8.9 1–17
Sex **Female** **Male**	 1 2	 5 5	 3 5	 3 3	 12 15
Tumor type	3 HGG	5 HGG; 3 LGG 1 LCH; 1 PTC	6 LGG; 1 LCH 1 NB	6 LGG	8 HGG; 15 LGG; 2 LCH; 1 PTC; 1 NB
- HGG histology	2 AA; 1 AG	2 GBM; 1 AGG 1 AA; 1 APXA			
- LGG histology		1 JPA; 1GG; 1 PMA	4 JPA; 2 GG	1 PXA; 1 JPA; 1 GG; 3 LGG	

AA, anaplastic astrocytoma; **AG**, anaplastic glioma; **AGG**, anaplastic ganglioglioma; **APXA**, anaplastic pleomorphic xanthoastrocytoma ; **GBM**, gliobastoma multiforme; **GG**, ganglioglioma; **HGG**, high grade glioma; **JPA**, juvenile pilocytic astrocytoma; **LCH**, Langerhans cell histiocytosis; **LGG**, low grade glioma; **NB**, neuroblastoma; **PMA**, pilomyxoid astrocytoma; **PTC**, papillary thyroid carcinoma; **PXA**, pleomorphic xanthoastrocytoma.

Results

- Phase 1 portion completed
  - N = 27 patients
  - May 2013 to November 2014
- Clinical data cut 7 March 2015
- Duration on study from 9 weeks to 23 months (ongoing)
- 20 of 27 patients remain on dabrafenib

Adverse Events

- Most common AE class
  - Skin and subcutaneous tissue disorders 25 (93%) patients
- Most common AE terms
  - Pyrexia 14 (52%) patients
  - Fatigue 12 (44%) patients
  - Vomiting 12 (44%) patients
  - Headache 11 (41%) patients
- Dose-limiting toxicity (1 event)
  - Grade 3 transient maculopapular rash at 4.5 mg/kg/day dose
    - Patient remains on study at reduced dose (3.75 mg/kg/day)

Investigator-assessed Best Confirmed Response[a] by Tumor Type

Tumor type	High-grade glioma n = 8	Low-grade glioma n = 15	LCH n = 2	Other solid tumor n = 2	Total N = 27
Best response, n					
Complete response (CR)	**3** (2AA, 1 APXA)		**2**		**5**
Partial response (PR)	**2** (GBM, AGG)	**5** (2 PA, PMA, GG, LGG)			**7**
Stable disease (SD)		**7** (3 PA, GG, PXA, 2 LGG)		**1** (PTC)	**5**
Progressive disease	**3** (GBM, AG, AA)	**1** (PA)		**1** (NB)	**5**
Not evaluable		**2** (GG[b], GG[c])			**5**
Response rate, n (%)					
CR+PR	**5** (63)	**5** (33)	**2** (100)	**0**	**12** (44)

[a]Extracranial solid tumors assessed by RECIST (Response Evaluation Criteria In Solid Tumors); brain tumors assessed by RANO (Response Assessment in Neuro-Oncology); [b]missing data in eCRF: PI reports SD weeks 8-16; [c]missing data in eCRF: PI reports PR weeks 16-24.

AA, anaplastic astrocytoma; **AG**, anaplastic glioma; **AGG**, anaplastic ganglioglioma; **APXA**, anaplastic pleomorphic xanthoastrocytoma ; **GBM**, gliobastoma multiforme; **GG**, ganglioglioma; **LGG**, low grade glioma; **NB**, neuroblastoma; **PA**, pilocytic astorcytoma; **PMA**, pilomyxoid astrocytoma; **PTC**, papillary thyroid carcinoma; **PXA**, pleomorphic xanthoastrocytoma.

Summary

- Dabrafenib was well tolerated in pediatric patients
- Phase 2 recommended doses were identified and different in children ≤12 years and children >12 years based on PK parameters
- Radiographic responses (44%) and prolonged stable disease (19%) were seen across a number of tumor types driven by BRAFV600 mutations
- The multistrata phase 2 component of trial is open and accruing around the world

Conclusions

- MEK inhibitors are exciting new agents for low grade gliomas.
- Imaging responses can be documented after prolonged exposure to therapy (4-6 months)
- BRAF V600E specific inhibitors being tested in low-grade and high-grade gliomas; responses have been observed in patients with progressive disease
- Phase I/II studies ongoing with mTOR inhibitors, BRAF V600E inhibitors; MEK inhibitors and combination of BRAF inhibitors and MEK inhibitors
- New paradigm for treatment of LGG that uses tumor biology to direct therapy

Conclusions

Low grade gliomas have a good prognosis (especially with NF1)

Aim is to preserve function at least cost.

Possible targeted therapies in the future.

Adult Medulloblastoma

Darren Hargrave

Consultant Paediatric Oncologist,

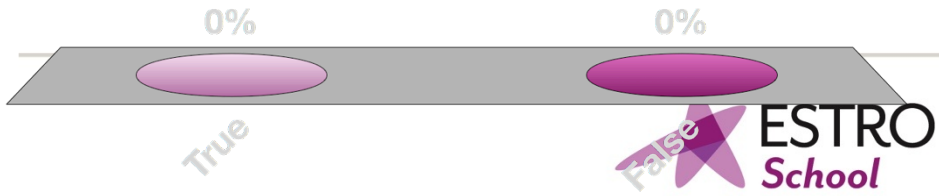
Neuro-oncology & Experimental Therapeutics

Great Ormond Street Hospital. London, UK.

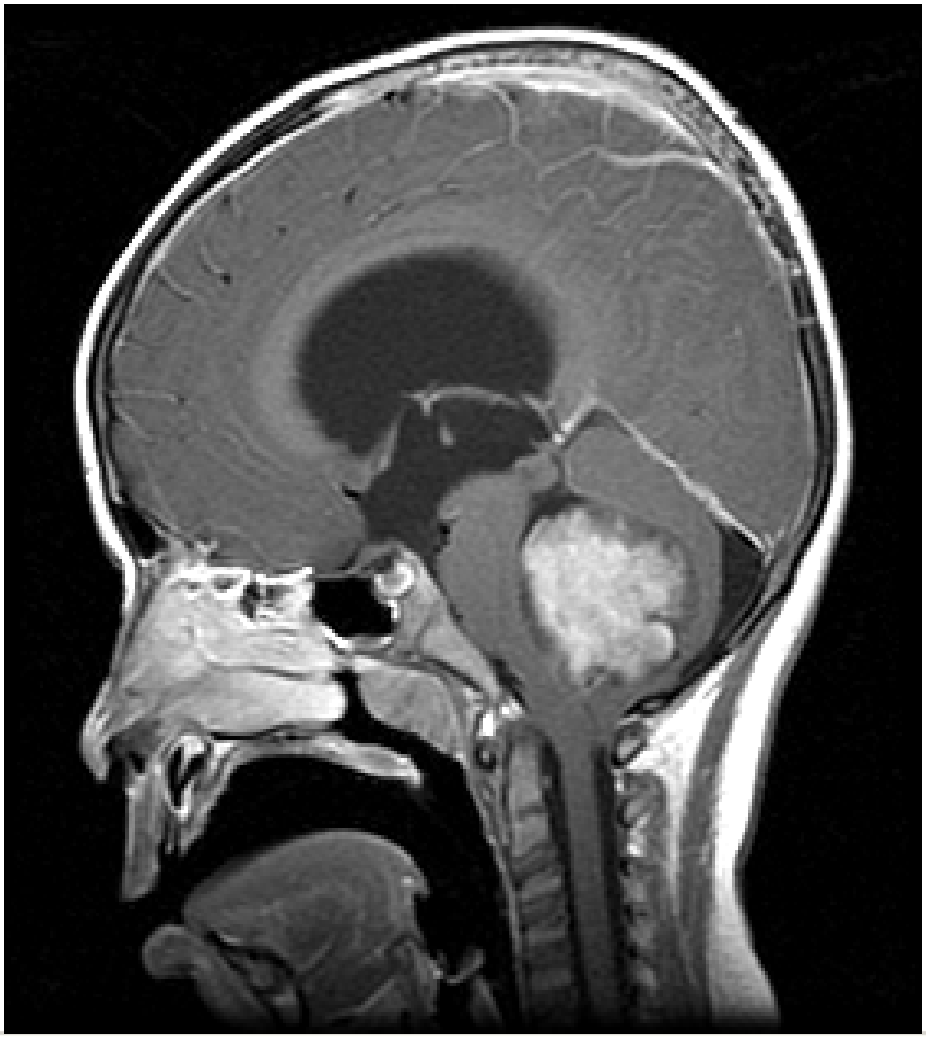
Have you ever treated an adult MB patient?

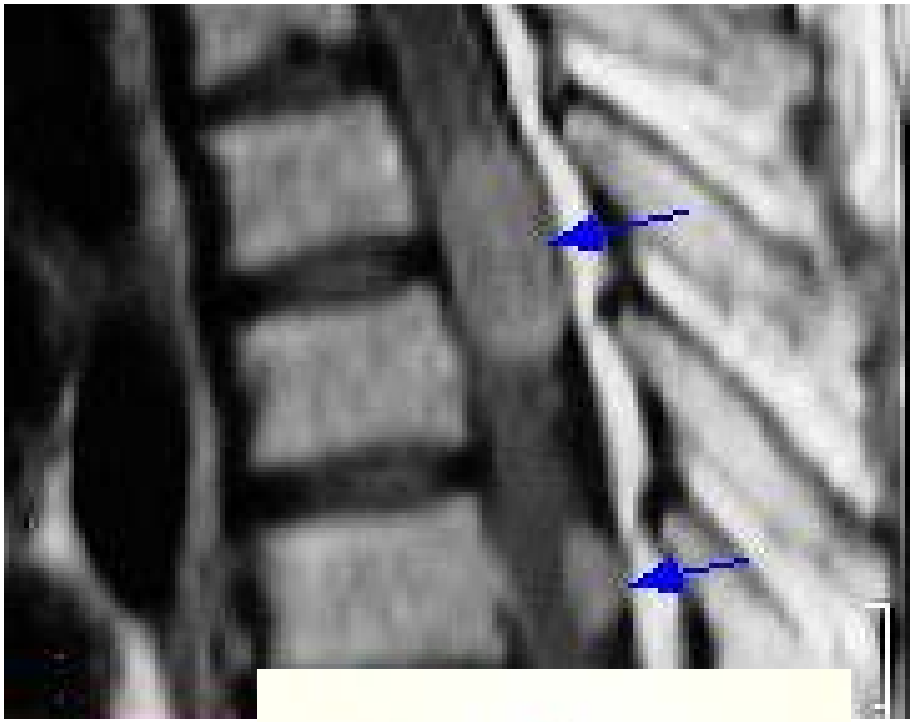
A. True

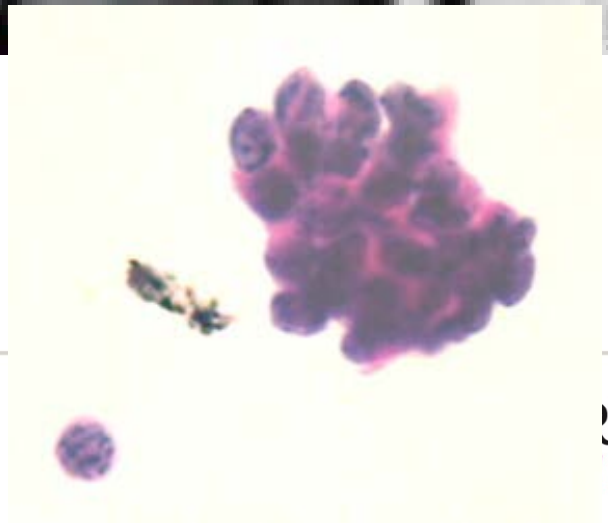
B. False



Adult Medulloblastoma: Data?







Adult data needed for Clinical Trial Design?

- Incidence?
- Risk groups?
- What is standard treatment?
- Outcomes?
- Biology & Novel therapy options?

Incidence of adult medulloblastoma?

Journal of Clinical Neuroscience 19 (2012) 1541–1544

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Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

The incidence of medulloblastomas and primitive neurectodermal tumours in adults and children

Nicolas R. Smoll [a,*], Katharine J. Drummond [b,c]

SEER database from 1973 to 2007: 369 adult MBs
Approx 11/year (children 10 x more likely to have MB)

Risk Groups

- Use same risk group as children
  - i.e. Chang staging metastatic disease
  - Pathology- LCA
  - Biology MYC amplified
  - Residual disease >1.5cm2
- 33% adult MB High Risk

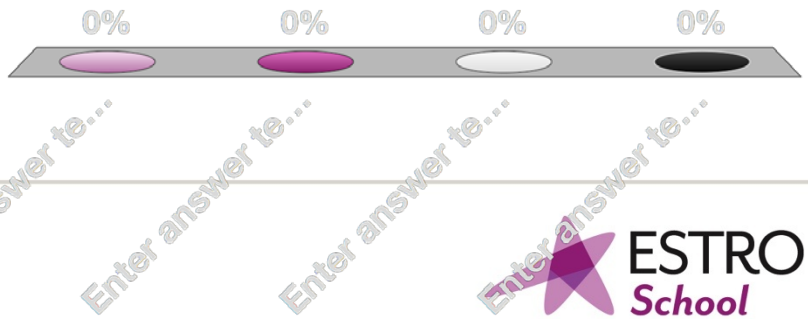
What would be your standard Rx for adult SR-MB

A. CSI only 36Gy (54Gy PF).

B. CSI only 23.4Gy (54Gy PF).

C. CSI 36Gy (54Gy PF) + ChemoRx.

D. CSI 23.4Gy (54Gy PF)+ ChemoRx.



THE TREATMENT OF ADULTS WITH MEDULLOBLASTOMA: A PROSPECTIVE STUDY

ALBA A. BRANDES, M.D.,* MARIO ERMANI, M.D.,† PIETRO AMISTA, M.D.,‡ UMBERTO BASSO, M.D.,* FRANCESCA VASTOLA, M.D.,* MARINA GARDIMAN, M.D.,§ PAOLO IUZZOLINO,‖ SERGIO TURAZZI, M.D.,¶ ANTONINO ROTILIO,# LORENZO VOLPIN, M.D.,** CARLO MAZZA, M.D.,‖ LAURA SAINATI, M.D.,†† FRANCO AMMANNATI,‡‡ AND FRANCO BERTI, M.D.§§

Departments of *Medical Oncology, †Neurological Sciences, ‡Neuroradiology, §Pathology, #Neurosurgery, ††Pediatrics, and §§Radiotherapy, Azienda Ospedale-Università of Padova, Padova, Italy; Departments of ‖Pathology and ¶Neurosurgery, Azienda Ospedale-Università of Verona, Verona, Italy; **Department of Neurosurgery, San Bortolo Hospital, Vicenza, Vicenza, Italy; ‡‡Department of Neurosurgery, Azienda Ospedale-Università of Firenze, Florence, Italy

Treatment protocol

Low-risk patients. In low-risk patients, radiation therapy alone was planned and started within 28 days of surgery. For patients receiving craniospinal radiation therapy, the radiation dose was 36 Gy in 20 fractions of 1.8 Gy/5 fractions per week, followed by a boost of 18.8 Gy in 10 fractions to the posterior fossa, including the entire tentorium, with the anterior aspect of the field extending to the posterior clinoid process (up to a total dose of 54.8 Gy).

Table 1. Cisplatin-based chemotherapy: Dose levels

	Level −2	Level −1	Level 0	Level +1
Cyclophosphamide (mg/m^2/ on Day 4)	600	750	1000	1000
Etoposide (mg/m^2 on Days 1 to 4)	26	32	40	50
Cisplatin (mg/m^2 on Days 1 to 4)	20	25	25	25

Outcomes?

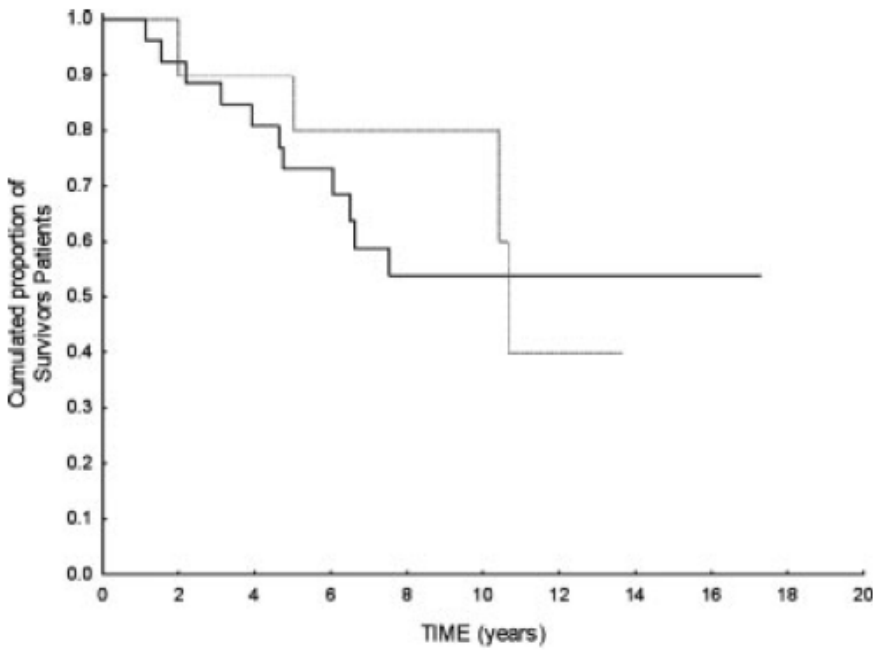


FIGURE 2. These overall survival curves were calculated according to the risk-assessment method described in Chang et al., 1969[4] (black line, high-risk group; gray line, low-risk group).

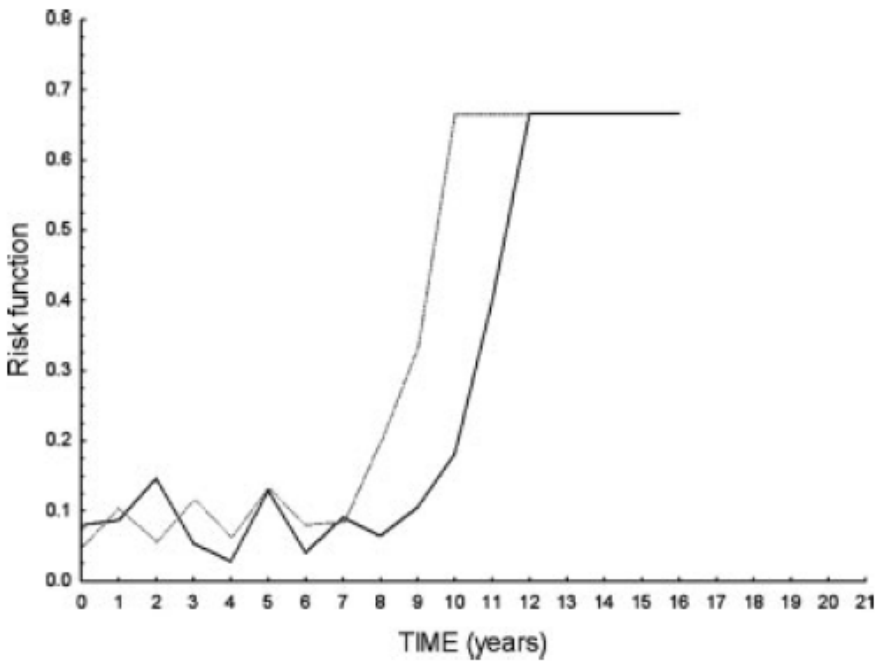


FIGURE 3. These curves illustrate the risk of recurrence according to the risk-assessment method described in Chang et al., 1969[4] (black line, high-risk group; gray line, low-risk group).

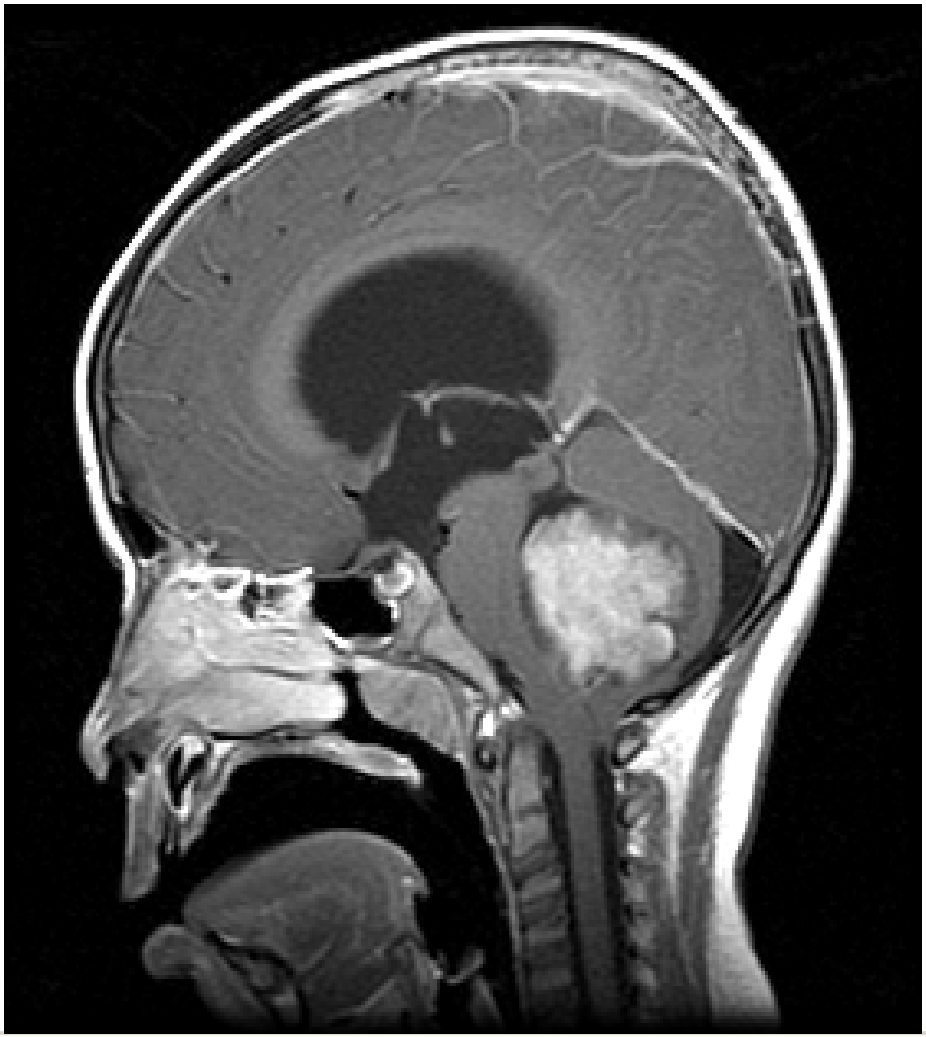
Outcomes?

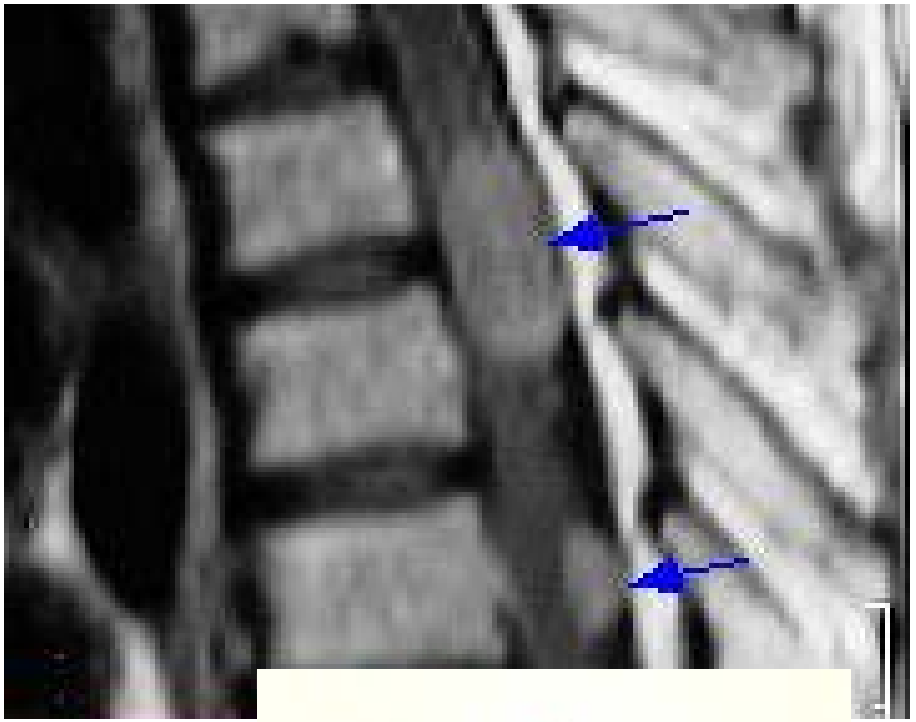
TABLE 3
Largest Adjuvant Adult Medulloblastoma Chemotherapy Trials in the Literature

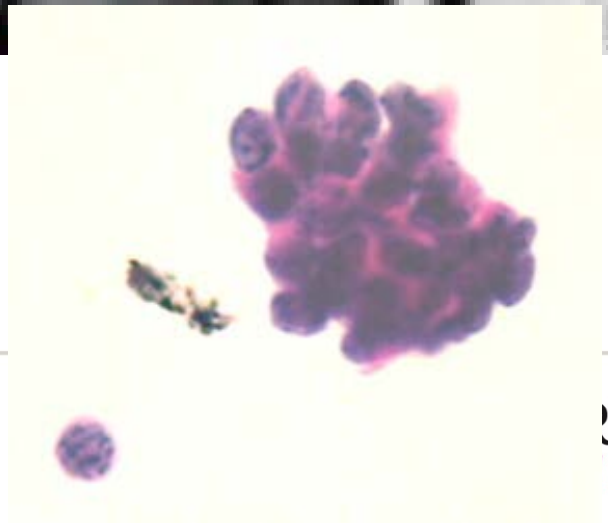
Study	No.	Chemotherapy	Outcome
Carrie et al., 1994[11]	156	75 Patients, 8 in 1 CT: SIOP protocol; IFO/CDDP/VCR	5-Y PFS rate: 58% in M0 group vs 51% in M+ group; 59% in R0 group vs 64% in R+ group
Prados et al., 1995[12]	47	32 Patients	5-Y PFS 5 rate: 54% in LR group vs 38% in HR group
Chan et al., 2000[13]	32	24 Patients: 3-5 cycles of CT	5-Y PFS rate: 59% in M0 group vs 47% in M+ group; 86% in R0 group vs 27% in R+ group
Louis et al., 2002 (unpublished results)	51	24 SR patients, no CT; 27 HR patients, CT with CARBO/VP-16	5-Y PFS rate: 60% in SR group vs 63% in HR group
Abacioglu et al., 2002[1]	30	10 Patients	5-Y PFS rate: 69% in CT-treated patients; 60% in untreated patients
Greenberg et al., 2001[14]	17	17 Patients: Packer regimen or POG protocol	PFS, 48 mo

CT indicates chemotherapy; SIOP, International Society of Pediatric Oncology; IFO, ifosfamide; CDDP, cisplatin, VCR, vincristine; PFS, progression-free survival; M0, negative for metastasis; M+, positive for metastasis; R0, curative resection; R+, noncurative resection; LR, low risk; HR, high risk; SR, standard risk; CARBO, carboplatin; VP-16, etoposide; POG, Pediatric Oncology Group.

Adult Medulloblastoma: Biology/ Novel Rx?







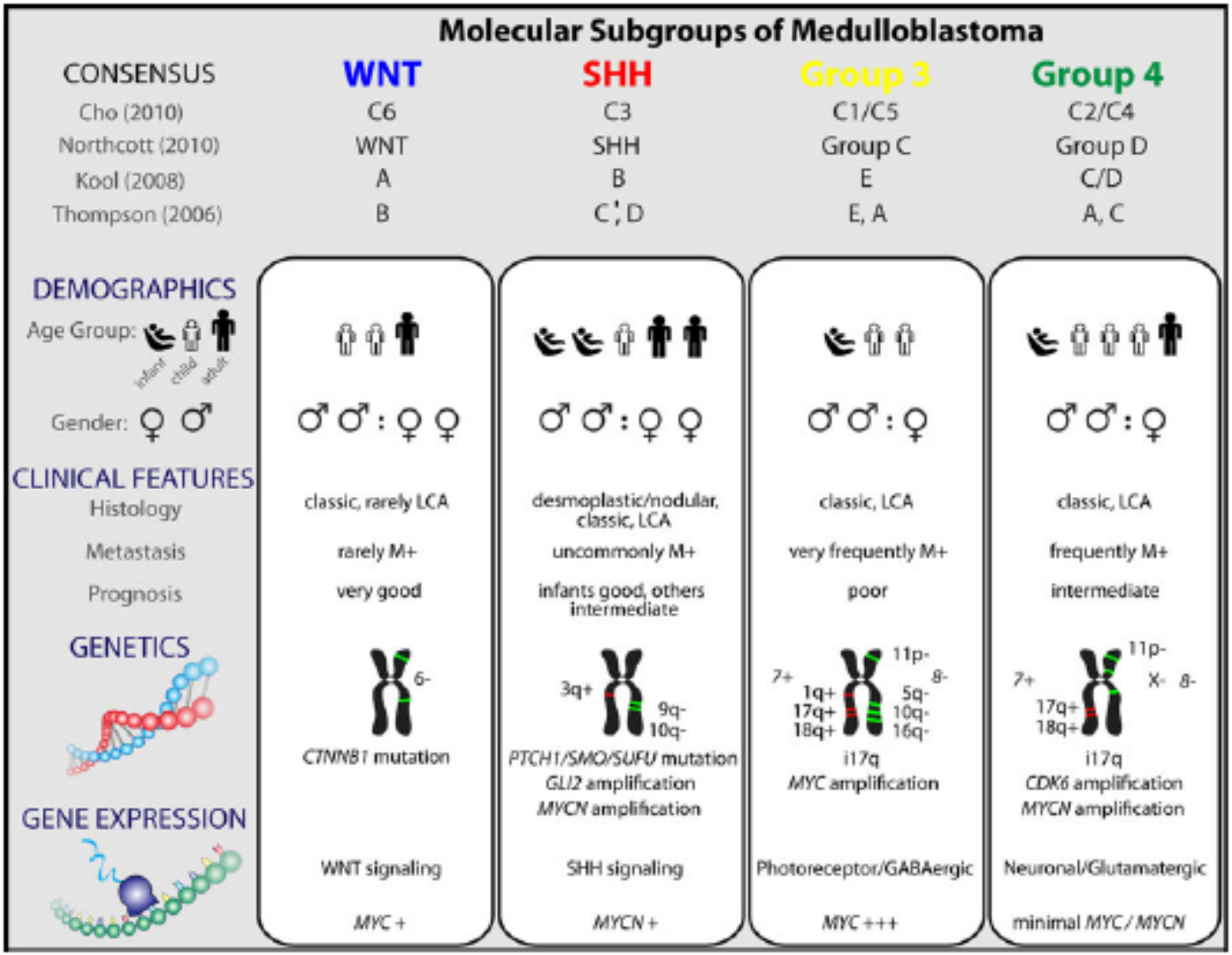


Fig. 2 Comparison of the various subgroups of medulloblastoma including their affiliations with previously published papers on medulloblastoma molecular subgrouping

Northcott, P. A. *et al. Nat. Rev. Neurol.* advance online publication 8 May 2012; doi:10.1038/nrneurol.2012.78

memo (2012) 5:228–232
DOI 10.1007/s12254-012-0037-9

memo
magazine of european medical oncology

Update on molecular and genetic alterations in adult medulloblastoma

Marcel Kool, Andrey Korshunov, Stefan M. Pfister

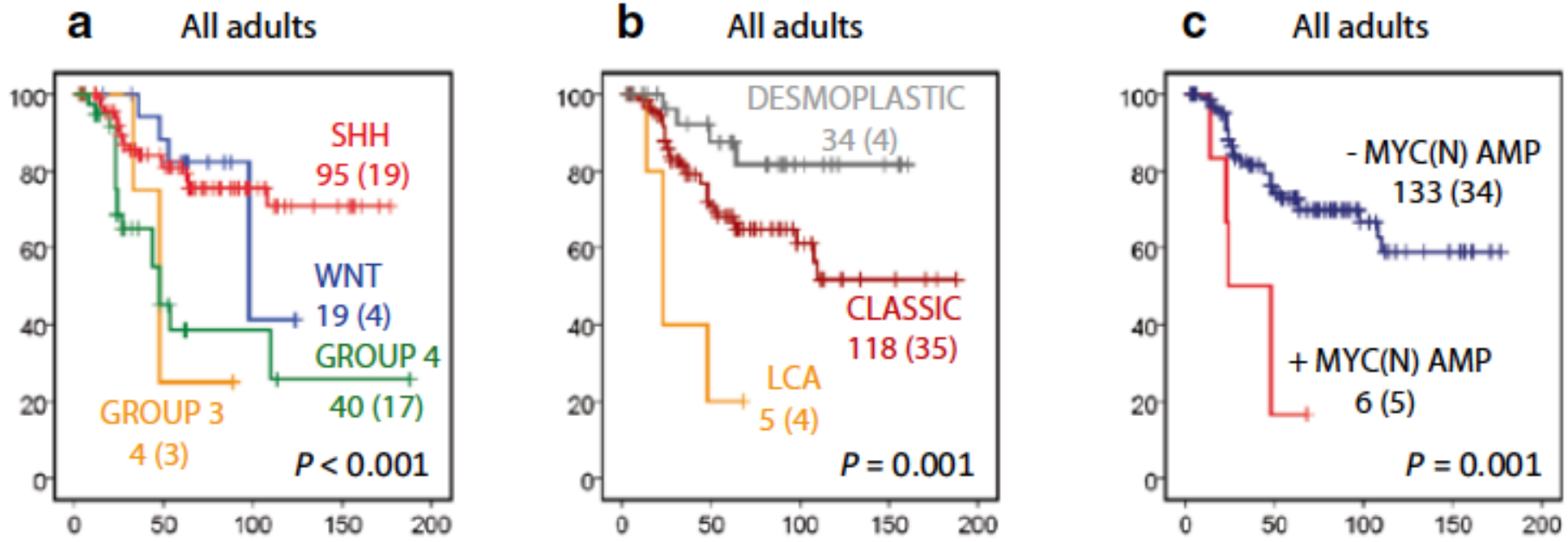


Table 1 verview of medulloblastoma molecular subgroup distribution, histological subgroup distribution, and metastatic groups in infants (age <4 years), children (age 4–16), and adults (age >16)

	Infants		Children		Adults	
	Percentage[a]	OS[b]	Percentage[a]	OS[b]	Percentage[a]	OS[b]
Molecular subgroups						
WNT	1	NA	12	96	13	82
SHH	57	77	18	81	57	81
Group 3	34	29	26	55	2	25
Group 4	8	57	44	78	28	39
Histological subgroups	Percentage[a]	OS[b]	Percentage[a]	OS[b]	Percentage[a]	OS[b]
Classic	43	49	80	79	79	68
Desmoplastic	43	88	8	86	18	88
Large cell/Anaplastic	15	26	12	48	3	20
Metastatic stage	Percentage[a]	OS[b]	Percentage[a]	OS[b]	Percentage[a]	OS[b]
M0	68	66	68	81	93	71
M+	32	50	32	65	7	52

Data are from meta-analyses performed on published datasets of medulloblastomas analyzed and categorized into subgroups either by gene expression profiling or immunohistochemistry [6]

OS overall survival

[a]Numbers indicate the frequency each subgroup occurs within that age category

[b]For each subgroup the percentage of patients is shown that is still alive 5 years after medulloblastoma diagnosis as determined by Kaplan Meier analysis

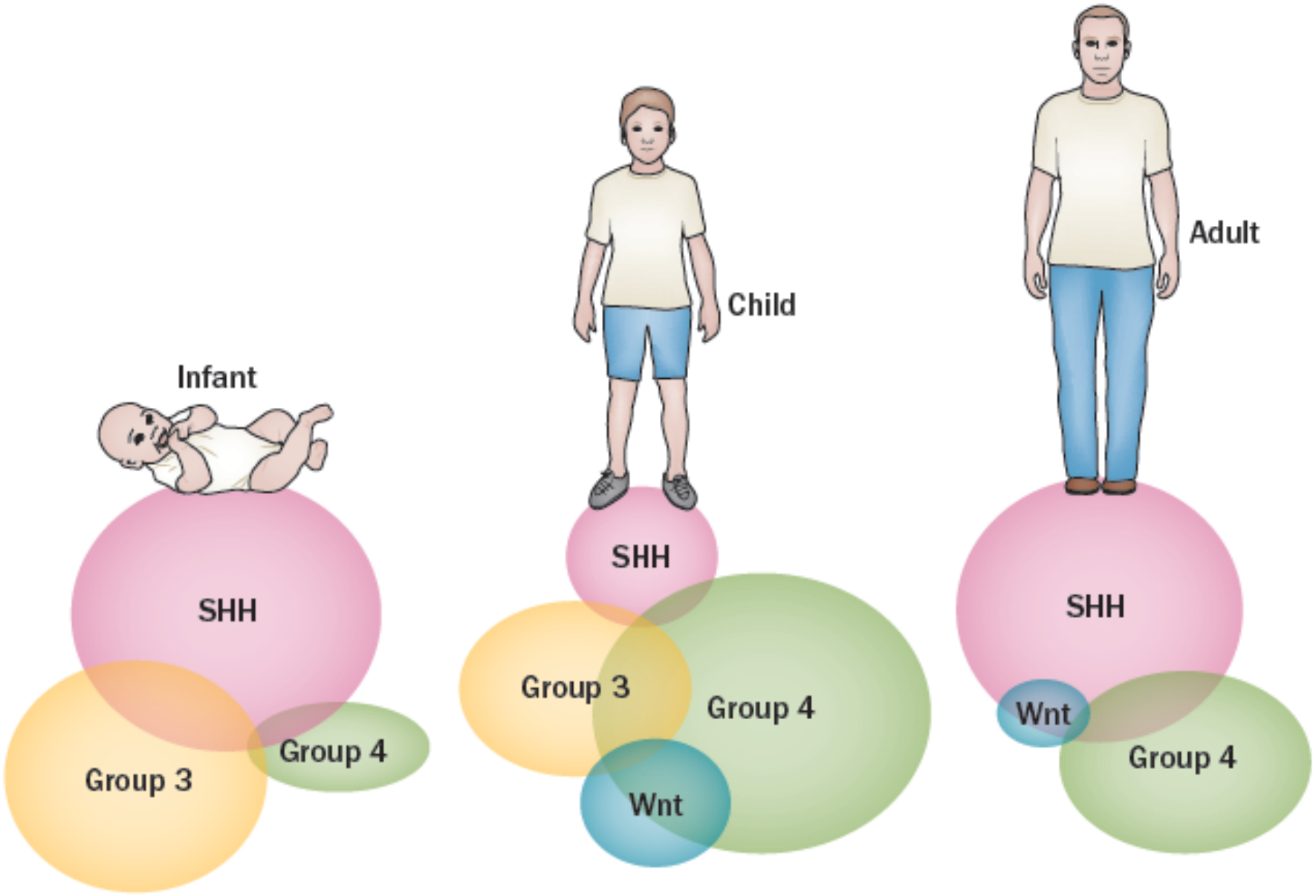


Figure 2 | Schematic distribution of the prevalence of the molecular medulloblastoma subtypes among different age groups. The approximate frequency

Rare cancer syndromes identify genes commonly mutated in sporadic medulloblastoma

Syndrome	Gene	Locus	Tumour susceptibilities
Turcot's syndrome	*APC*	5q21-q22	Medulloblastoma Multiple colorectal adenomas
Naevoid basal cell carcinoma syndrome (NBCCS) / Gorlin syndrome	*PTCH*	9q22.3	Medulloblastoma Basal cell carcinoma
Li-Fraumeni syndrome	*TP53*	17p13.1	Medulloblastoma Multiple primary neoplasms, including: Soft tissue sarcomas Osteosarcoma Breast carcinoma Brain tumours Leukaemias Adenocortical carcinoma

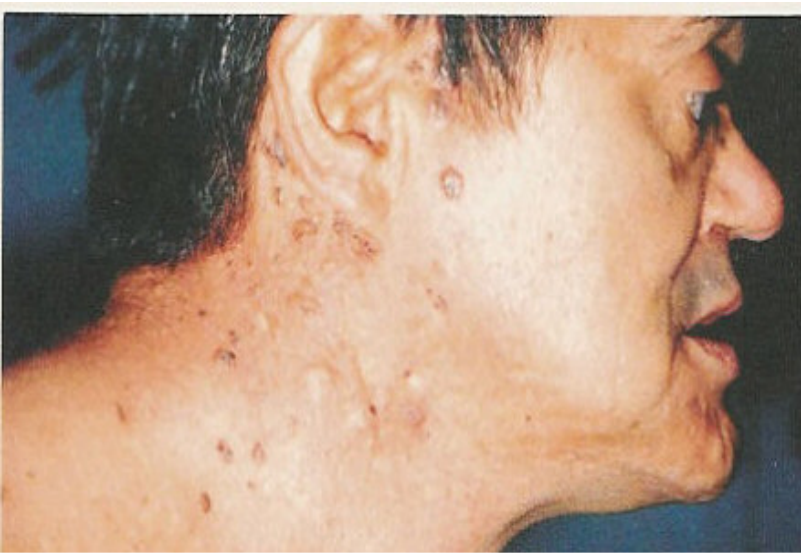
APC in 5% of cases

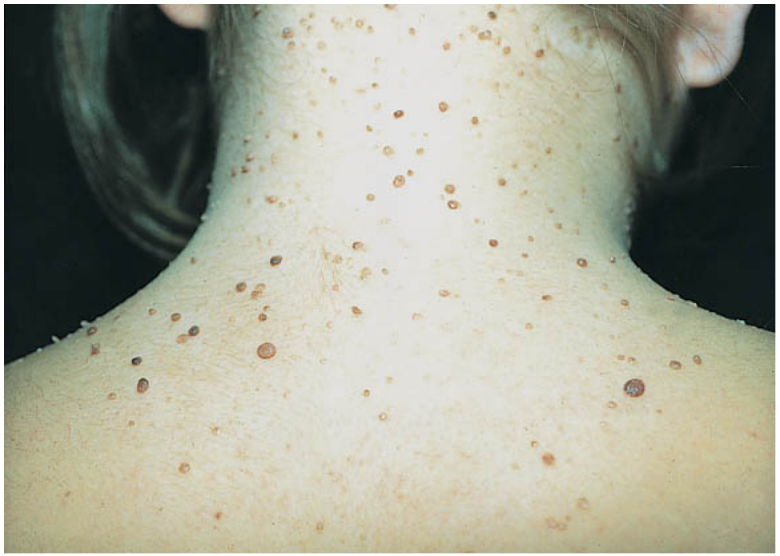
PTCH in 10% of cases

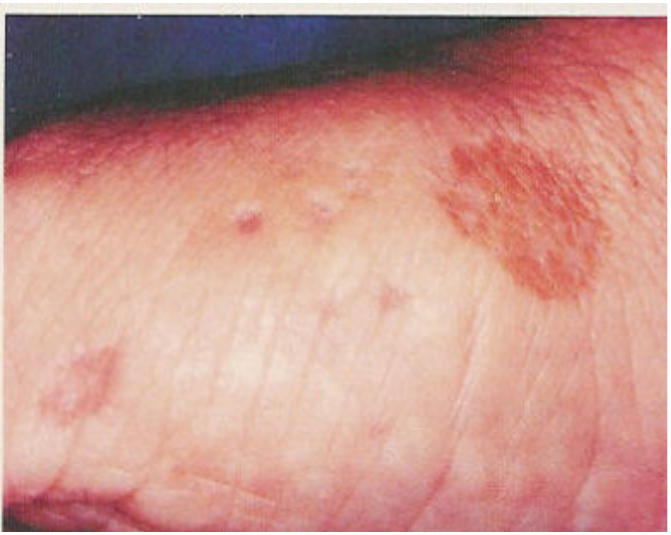
TP53 in 10% of cases

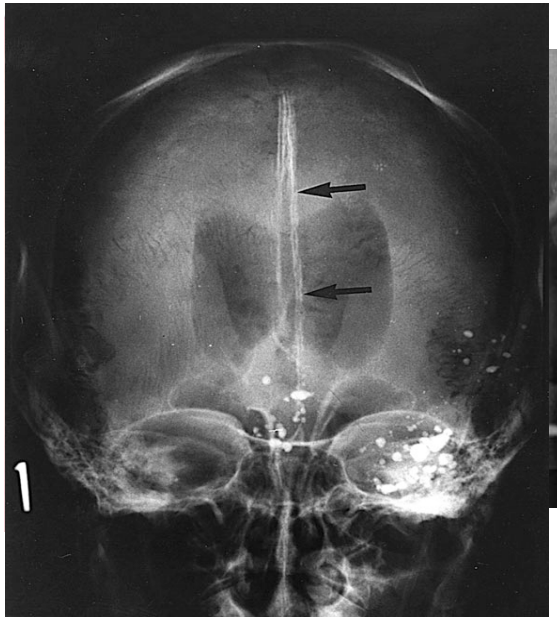
ESTRO School

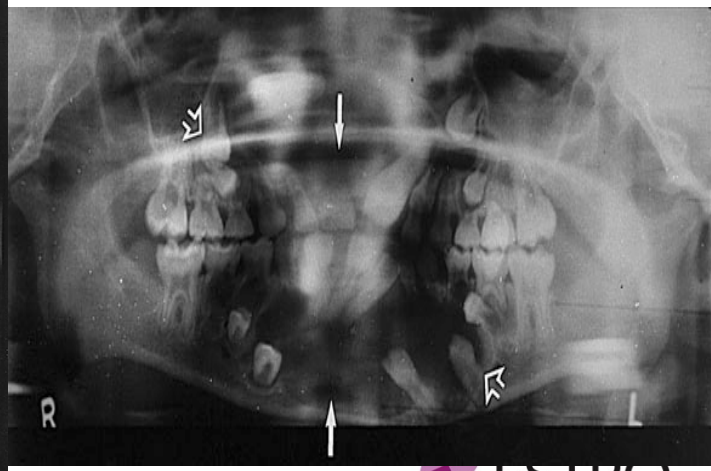
Gorlin Syndrome





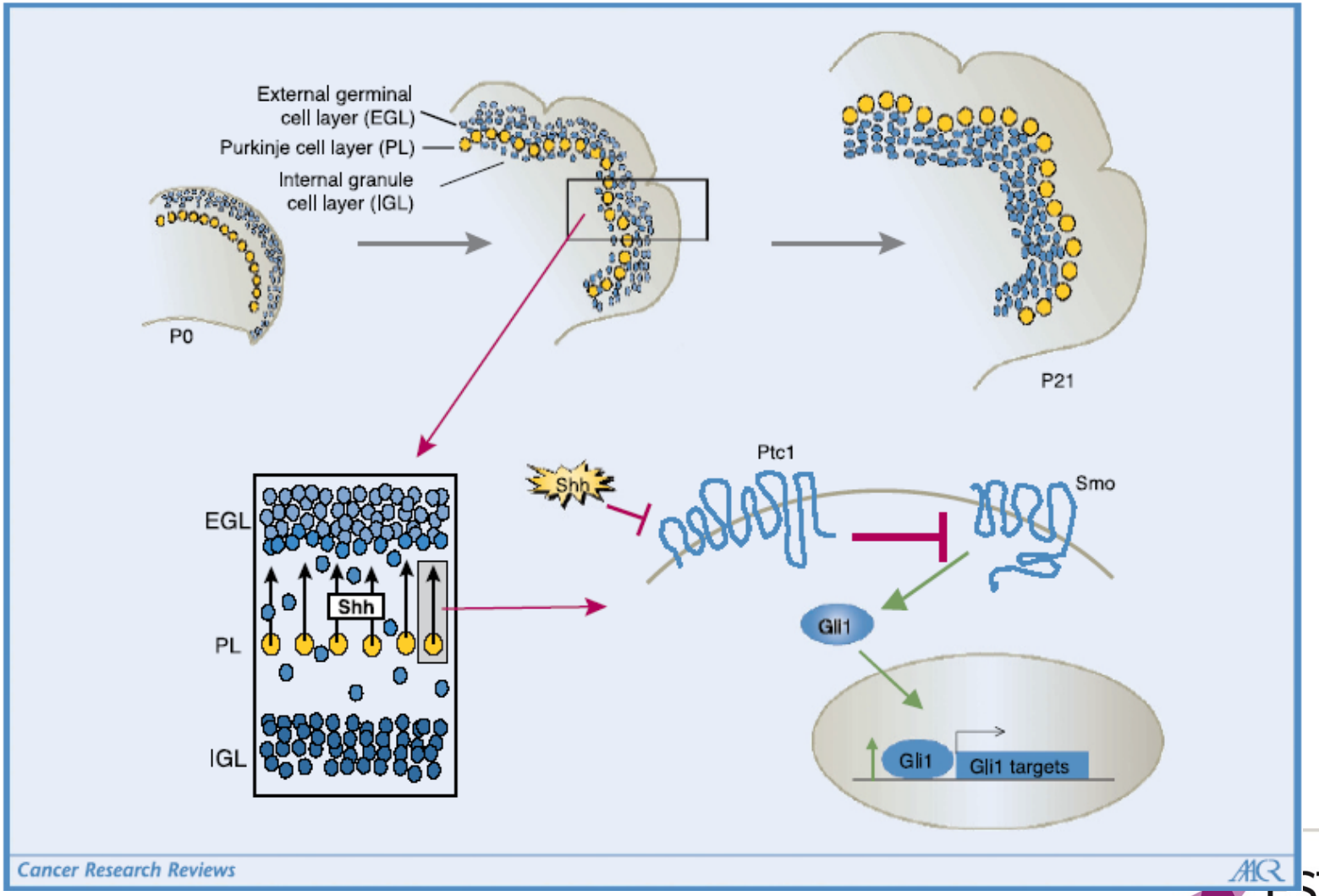




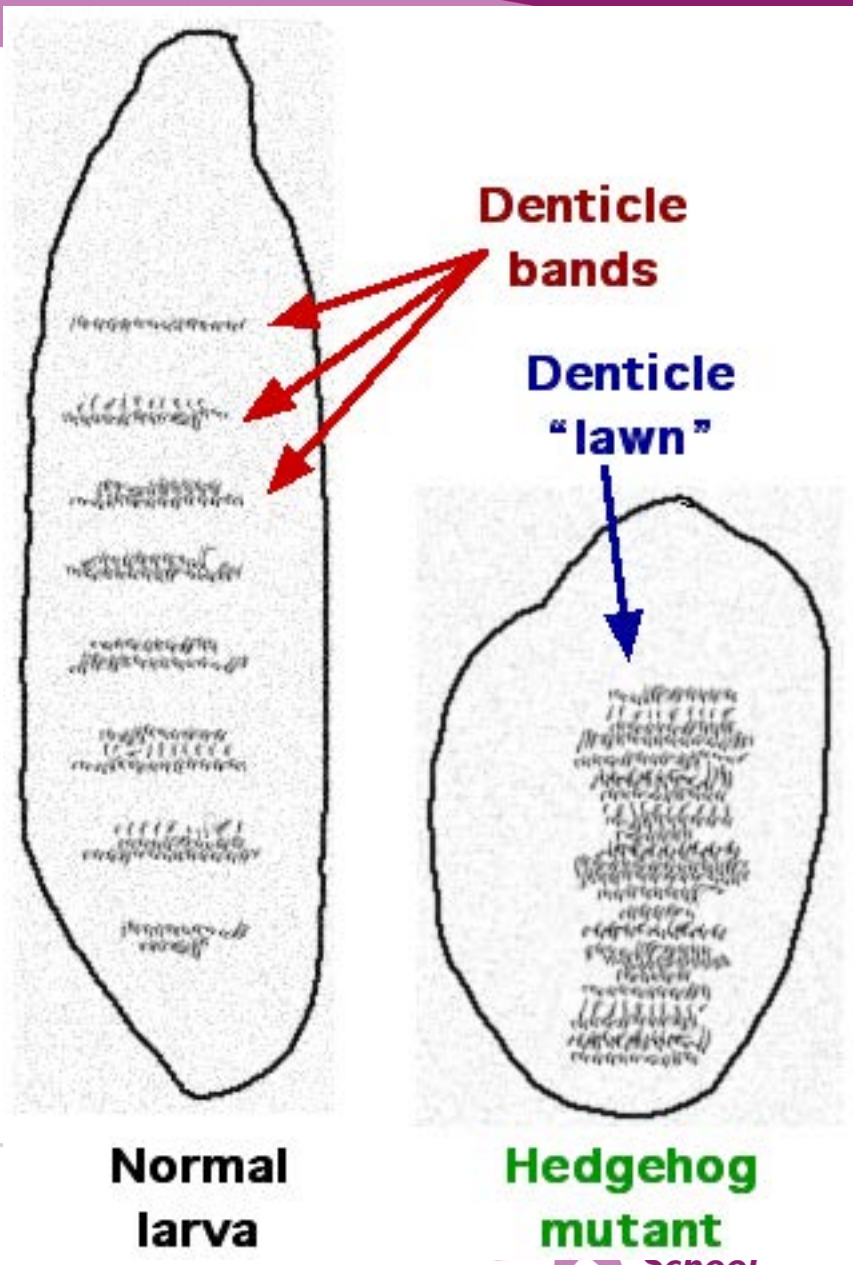


ESTRO School

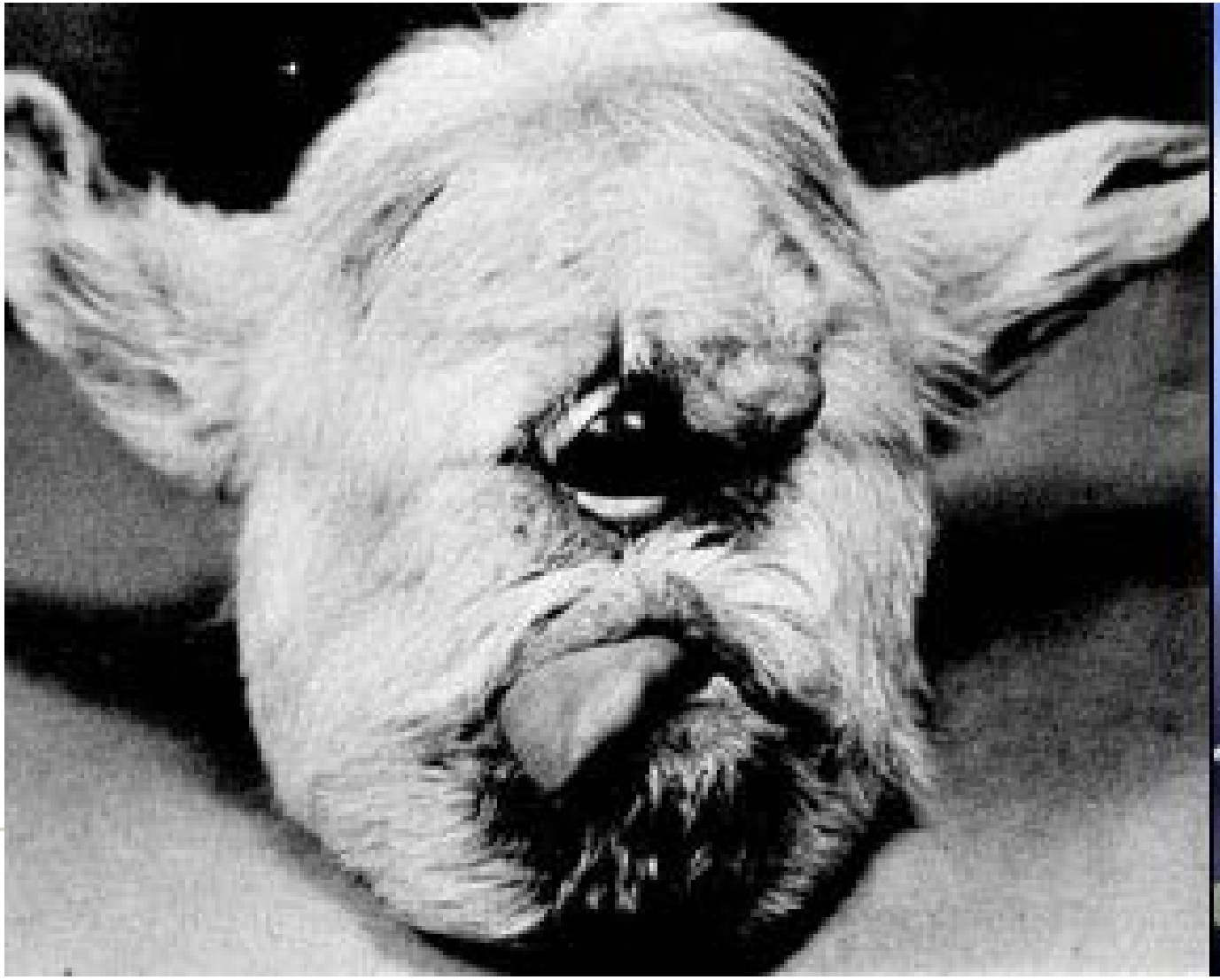
The *SHH* signalling pathway



Romer, J and Curran, T (2005). *Cancer Research.* **65:** 4975.


Denticle bands
Denticle "lawn"
Normal larva
Hedgehog mutant

Sonic Hedgehog & Corn Lillies



ARTICLE

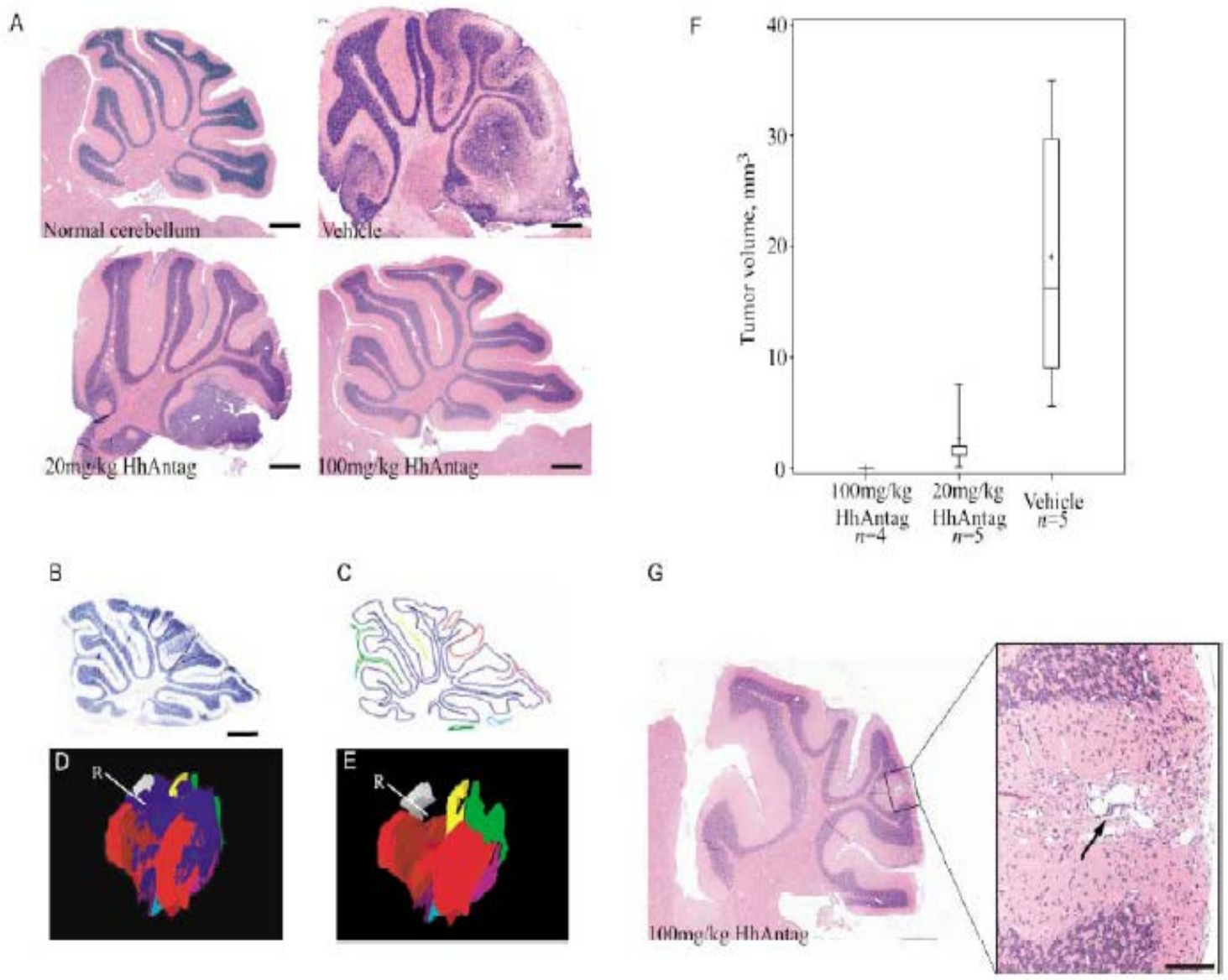
Suppression of the Shh pathway using a small molecule inhibitor eliminates medulloblastoma in *Ptc1*$^{+/-}$*p53*$^{-/-}$ mice

Justyna T. Romer,[1] Hiromichi Kimura,[1] Susan Magdaleno,[1] Ken Sasai,[1] Christine Fuller,[1] Helen Baines,[1] Michele Connelly,[1] Clinton F. Stewart,[1] Stephen Gould,[2] Lee L. Rubin,[2] and Tom Curran[1,*]

[1]Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105
[2]Curis, Inc., Cambridge, Massachusetts 02478
*Correspondence: tom.curran@stjude.org

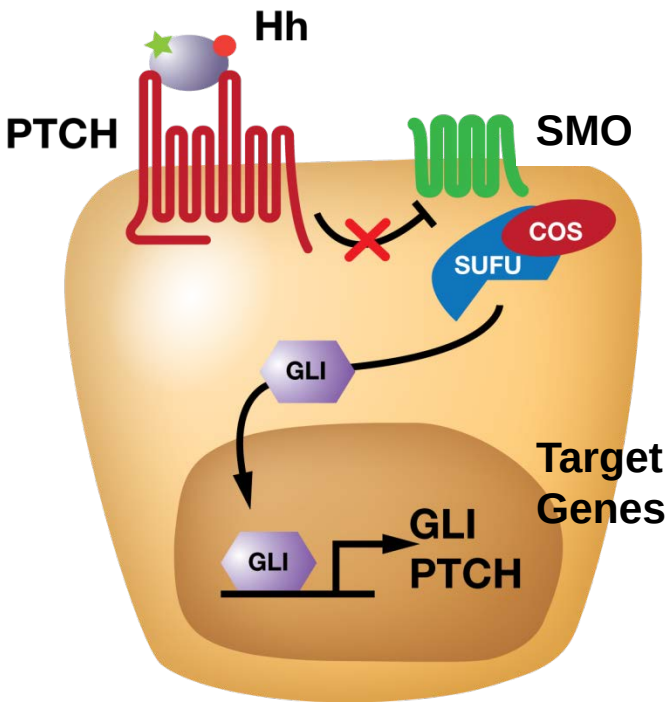
Cancer Cell. **6:** 229-240, 2004.

- HhAntag691 (Curis/Genentech)
- Blocks SMO function (10x cyclopamine)
- Blood-brain penetration
- Assessment using PTCH (+/-) mouse MB model



Cancer Cell. **6:** 229-240, 2004.

The Hedgehog (Hh) Pathway

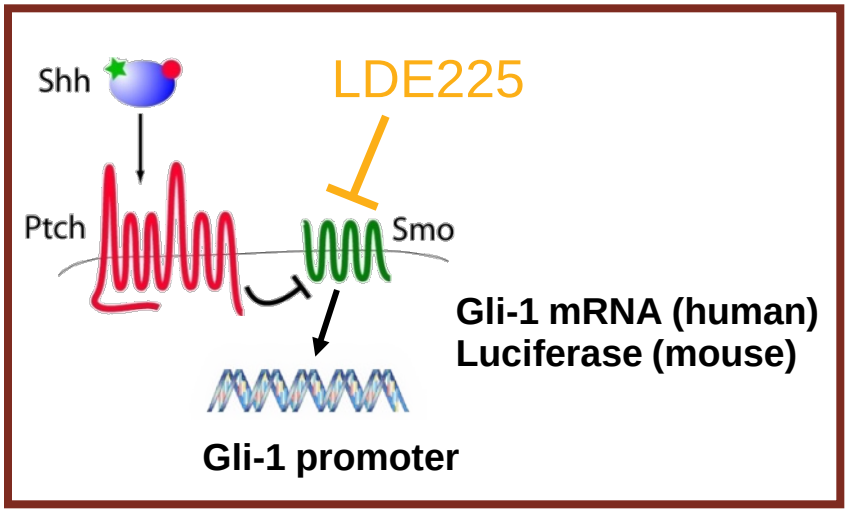


- Hh signaling pathway is essential in mammalian embryonic development and adult tissue homeostasis[1]
- Mechanism:[2,3]
  - PTCH inhibits SMO
  - Hh ligand binding to PTCH relieves inhibition of SMO
  - SMO signaling, via SUFU, activates GLI transcription factors
- Constitutive activation can result from mutations (*PTCH*, *SMO* or *SUFU*) or overexpression of the ligands[4–8]
  - Hypermethylation of *PTCH* and the negative regulator HIP1 can lead to pathway activation[9,10]

COS, conserved ortholog set; GLI, glioma-associated oncogene; Hh, hedgehog; HIP1, hedgehog interating protein 1; PTCH, patched; SMO, smoothened; SUFU, suppressor of fused

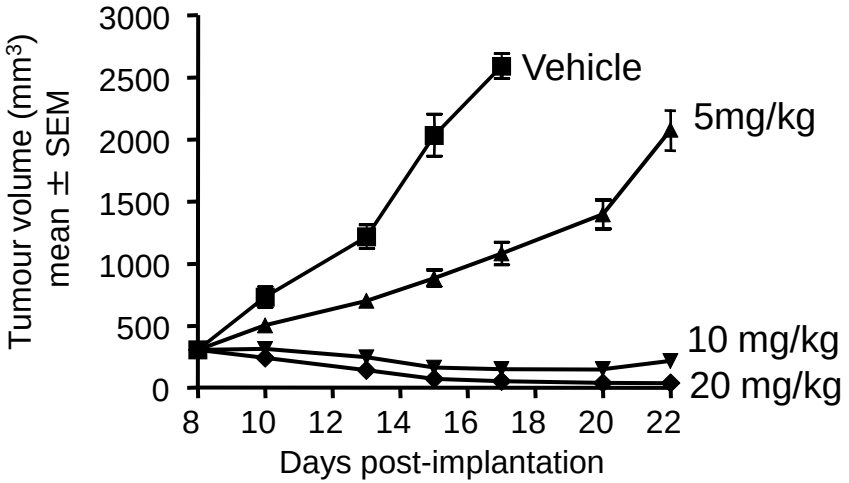
1. Jiang J, Hui C. Dev Cell 2008; 2. Epstein EH. Nat Rev Cancer 2008; 3. Xie J. Acta Biochim Biophys Sin (Shanghai) 2008; 4. Slade I , et al. Fam Cancer 2011; 5. Lee Y , et al. Cancer Res 2003; 6. Scott DK , et al. Cell Cycle 2006; 7. Zurawel RH, et al. Genes Chromosomes Cancer 2000; 8. Thompson MC, et al. JCO 2006; 9. Shahi MH, et al. BMC Cancer 2010; 10. Shahi MH, et al. J Neurooncol 2011.

LDE225: Preclinical Summary



Assay	Cell line	IC_{50}(nM)
Shh-induced Gli-1 mRNA	Human HEPM	13
Shh-induced Gli-1 Luciferase	Mouse TM3	7

Ptch +/-, p53 -/- MB model

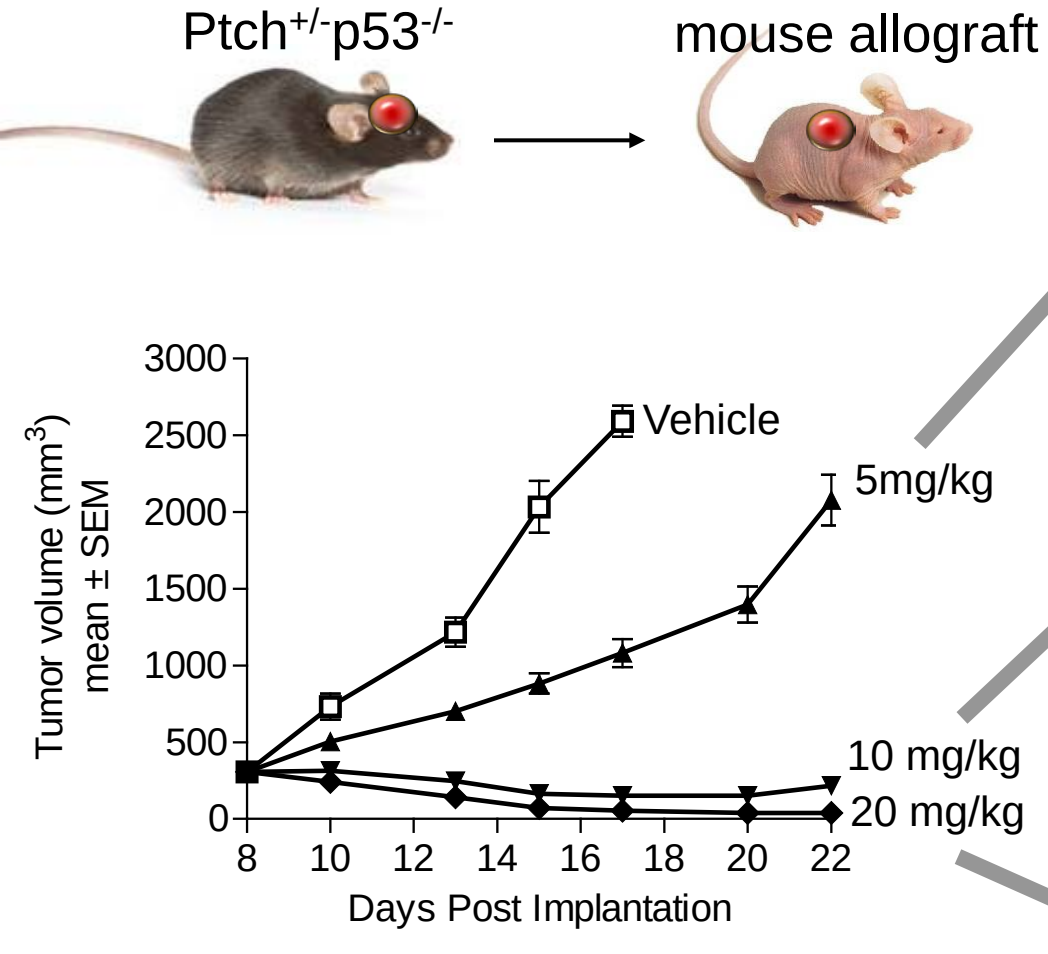


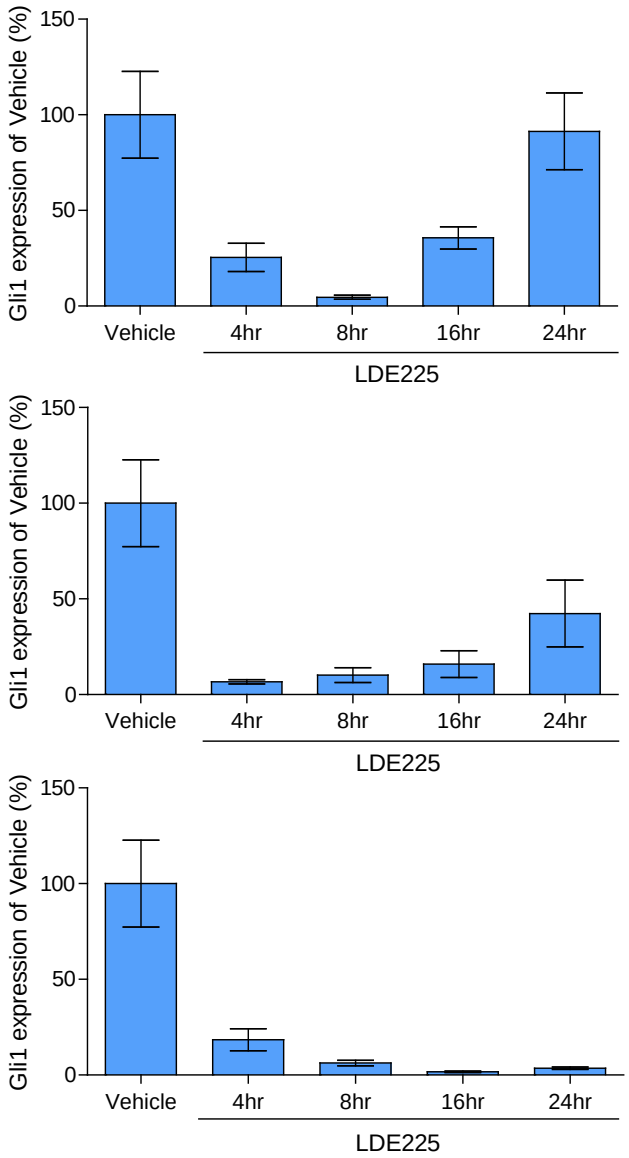
- LDE225 is a novel oral inhibitor of Smo that potently inhibits Smo-dependent proliferation *in vivo* in preclinical studies

Gli, glioma-associated oncogene homolog zinc finger protein; Shh, Sonic Hedgehog

LD
E22
5C2

LDE225 induced tumor regression is associated with Gli1 suppression in tumor





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The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Treatment of Medulloblastoma with Hedgehog Pathway Inhibitor GDC-0449

Charles M. Rudin, M.D., Ph.D., Christine L. Hann, M.D., Ph.D., John Laterra, M.D., Ph.D., Robert L. Yauch, Ph.D., Christopher A. Callahan, M.D., Ph.D., Ling Fu, M.D., Thomas Holcomb, M.S., Jeremy Stinson, B.S., Stephen E. Gould, Ph.D., Barbara Coleman, R.N., C.C.R.P., Patricia M. LoRusso, D.O., Daniel D. Von Hoff, M.D., Frederic J. de Sauvage, Ph.D., and Jennifer A. Low, M.D., Ph.D.

This article (10.1056/NEJMoa0902903) was published on September 2, 2009, at NEJM.org.

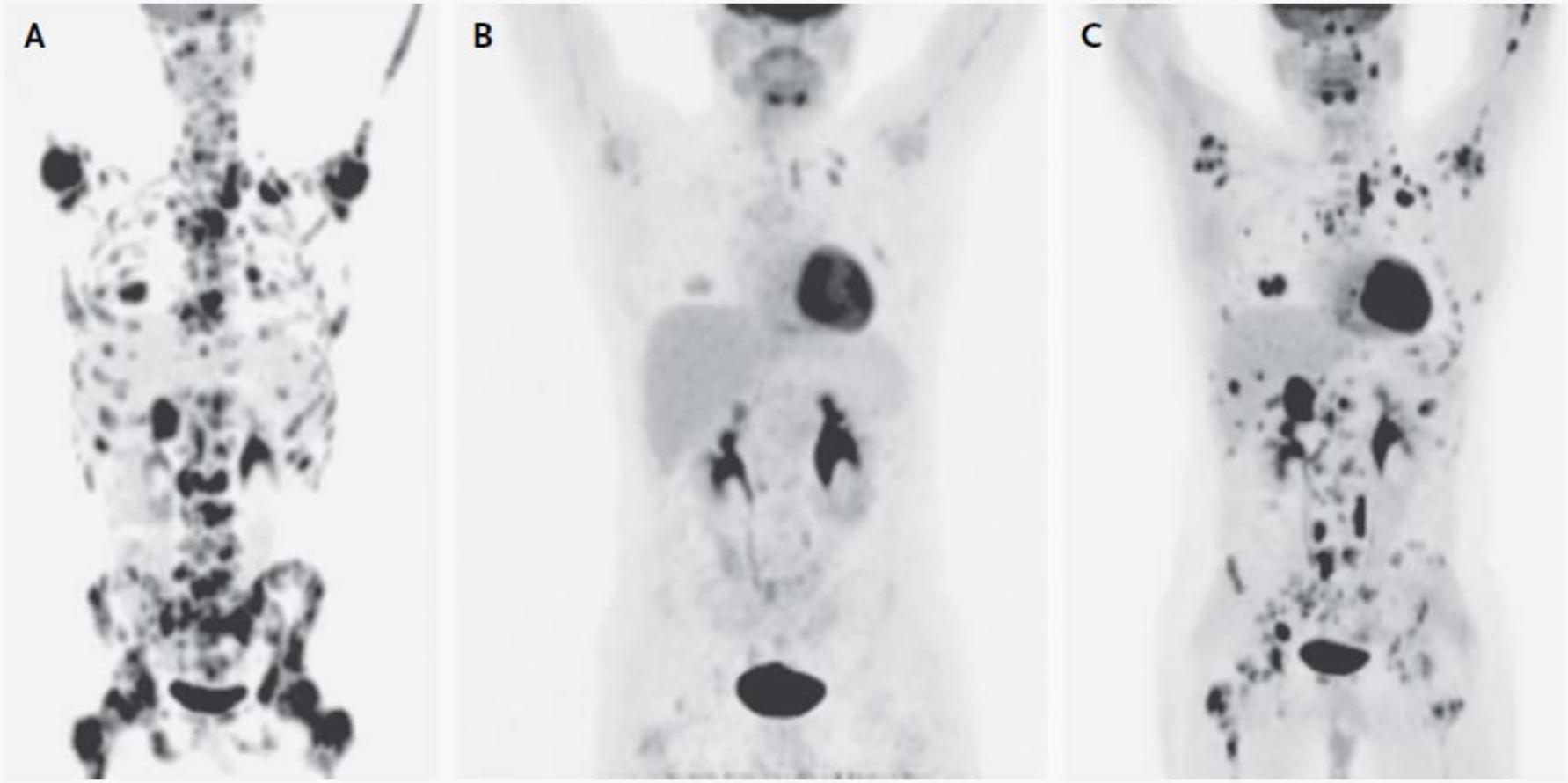


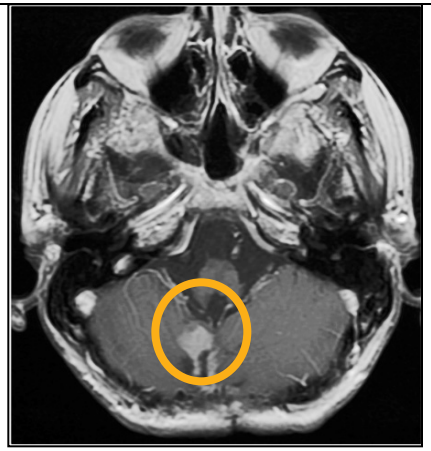
Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning.

Whole-body projections from ^{18}F-fluorodeoxyglucose (FDG)–PET scans are shown. Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.

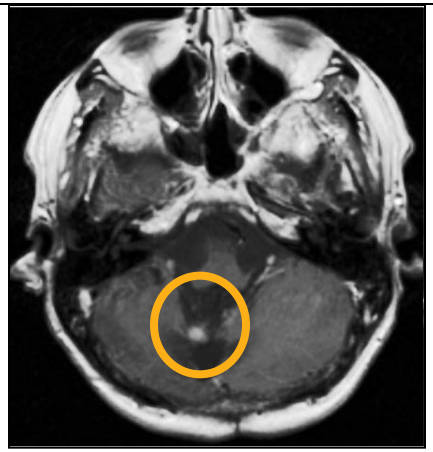
LDE225: responses in medulloblastoma

Patient A (200 mg QD)

- Prior surgery, radiation, 4 chemotherapy regimens and autologous BMT
- Partial response maintained for 4 months



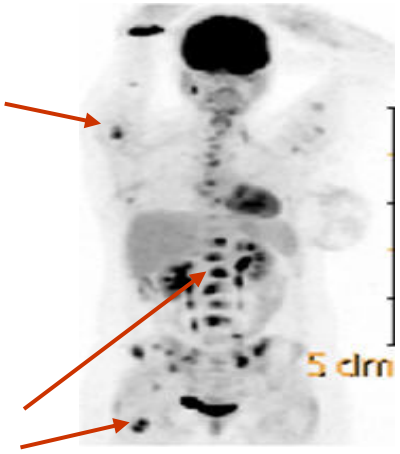
Pre-treatment



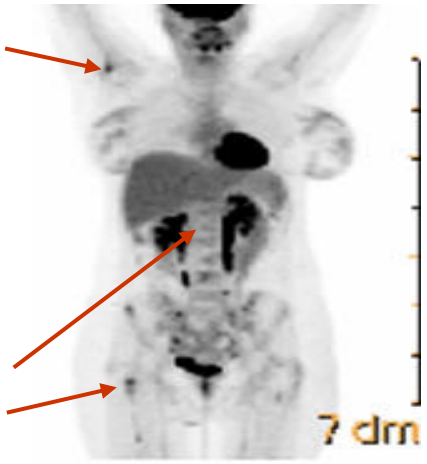
Cycle 2

Patient B (1500 mg QD)

- Prior surgery, radiation, 4 chemotherapy regimens and autologous BMT
- Partial response by PET scan maintained more than 7months



Pre-treatment



Cycle 2

Phase I/II: Study Design

Phase I→ Pediatric patients with recurrent/refractory MB, rhabdomyosarcoma, neuroblastoma, hepatoblastoma, high-grade glioma, or osteosarcoma

Dose escalation

Oral, once-daily LDE225 in 28-day cycle
Starting dose = 372 mg/m^2

Bayesian logistic regression model using overdose control*
DLT evaluation at 6 weeks

MB enrichment
Enrollment to previously tested lower dose levels

→ **Declaration of MTD** →

Safety expansion (n = 12)

Once-daily LDE225 at declared MTD

Primary endpoint – MTD, DLTs
Secondary endpoints – Safety, PK, ORR, PD/biomarkers (validation of Hh gene expression signature)

Phase II→ Pediatric patients with recurrent or refractory MB

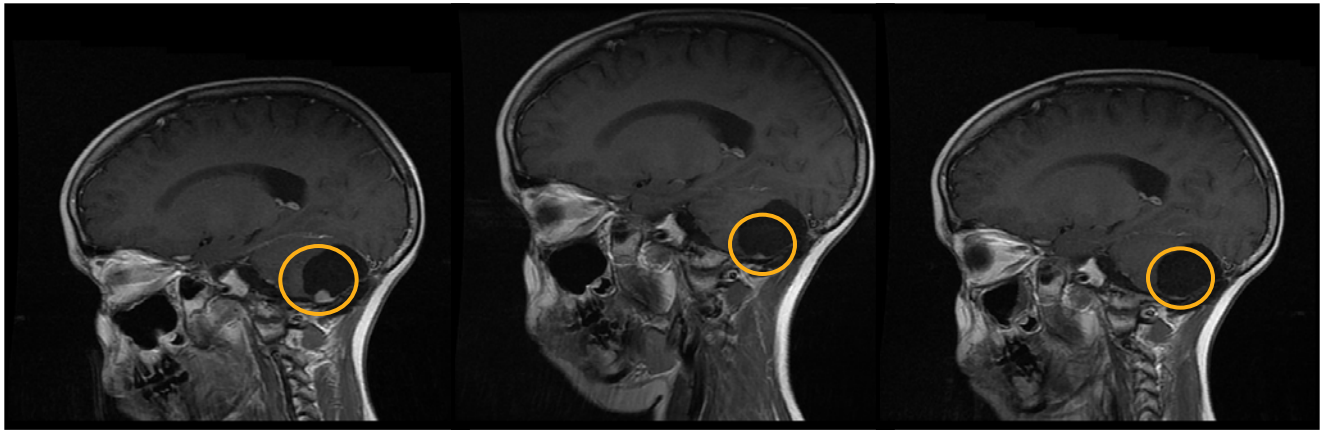
Recommended Dose LDE225
Pediatric MB patients (n = 30)

Primary endpoint – ORR (regardless of Hh pathway status)
Secondary endpoints – ORR and duration of response as a function of Hh pathway status, safety, PK

DLT, dose-limiting toxicity; Hh, hedgehog; MB, medulloblastoma; MTD, maximum tolerated dose; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response

NOVARTIS

Phase I: Complete Tumor Responses in MB

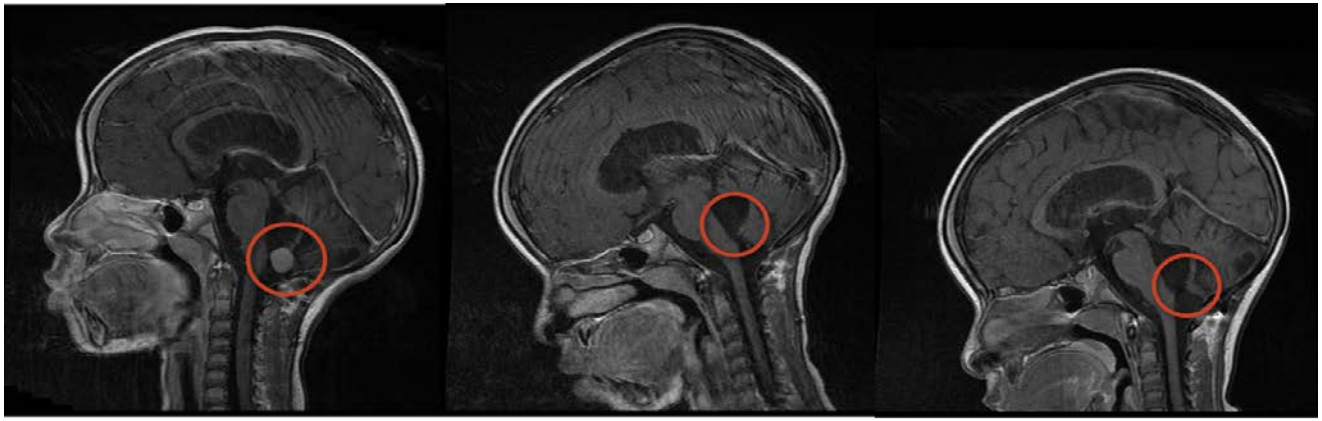


Baseline | Cycle 2 | Cycle 3

11-year-old with recurrent desmoplastic MB

372 mg/m^2

Treatment duration: 254 days



Baseline | Cycle 2 | Cycle 5

4-year-old with recurrent desmoplastic MB

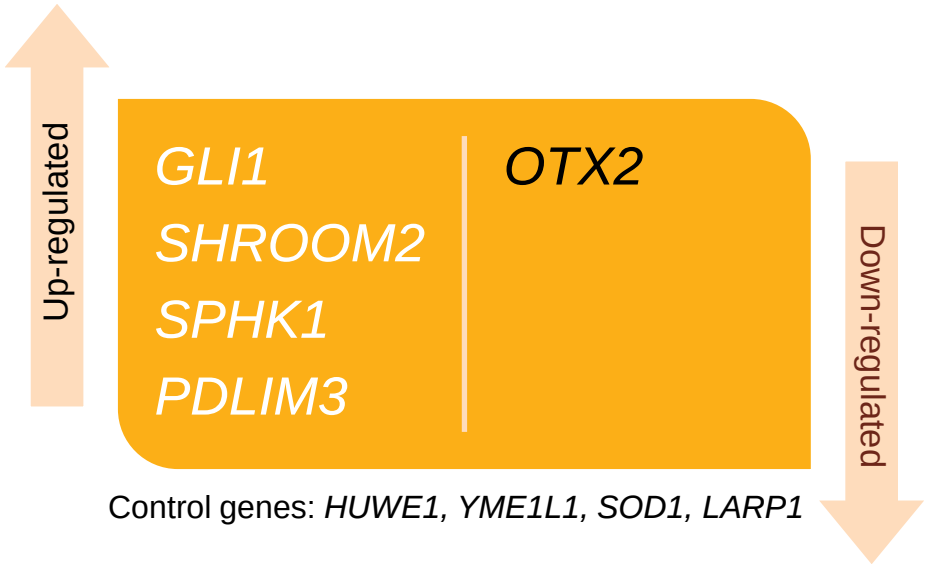
425 mg/m^2

Treatment duration: 280 days

NOVARTIS

The 5-Gene Hh Signature

- The 5-gene Hh signature can robustly identify Hh-pathway activation in FFPE tumor samples by standard RT-PCR
- Hh activation status determined by the 5-gene Hh signature is in 100% agreement with the Hh status determined by Affymetrix
- A robust patient pre-selection tool for LDE225 treatment



Control genes: *HUWE1, YME1L1, SOD1, LARP1*

GLI1, glioma-associated oncogene homolog 1; HUWE1, HECT, UBA and WWE domain containing 1; LARP1, la ribonucleoprotein domain family, member 1;OTX2, orthodenticle homeobox 2; SHROOM2, shroom family member 2; SOD1, superoxide dismutase 1, soluble; PDLIM3, PDZ and LIM domain 3; SPHK1, sphingosine kinase 1; YME1L1, YME1-like 1; ZP2, zone pellucida sperm-binding protein 2.

Amakye D, et al. AACR 2012. Abstract #4818.

NOVARTIS

Phase I: Best Overall Tumor Response and Correlation With 5-Gene Hh Signature in MB

	Responders/Hh-activated	Responders/Hh-non-activated
Adults	3/3 (3 PR)	0/4
Children	2/2 (2 CR)	0/12
Total	**5/5**	**0/16**

CR, complete response; Hh, hedgehog; MB, medulloblastoma; PR, partial response
Amakye D, et al. AACR 2012. Abstract #4818.

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Clinical Trial Design Options?

- Newly diagnosed versus relapse?
- Randomised versus single arm?
- Biomarker selected versus all comers?
- Age groups?

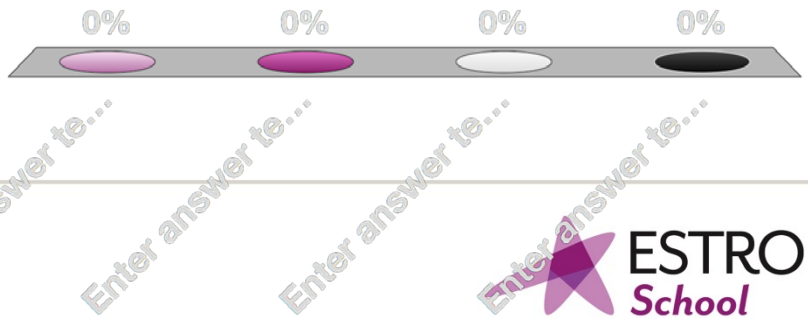
Which of the following trials do you prefer?

A. Upfront randomised study?

B. Upfront single arm study?

C. Relapse randomised study?

D. Relapse single arm study?



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Discussion on which trial is best/ feasible?

Dr Darren Hargrave

Consultant Paediatric Oncologist

Neuro-oncology & Experimental Therapeutics

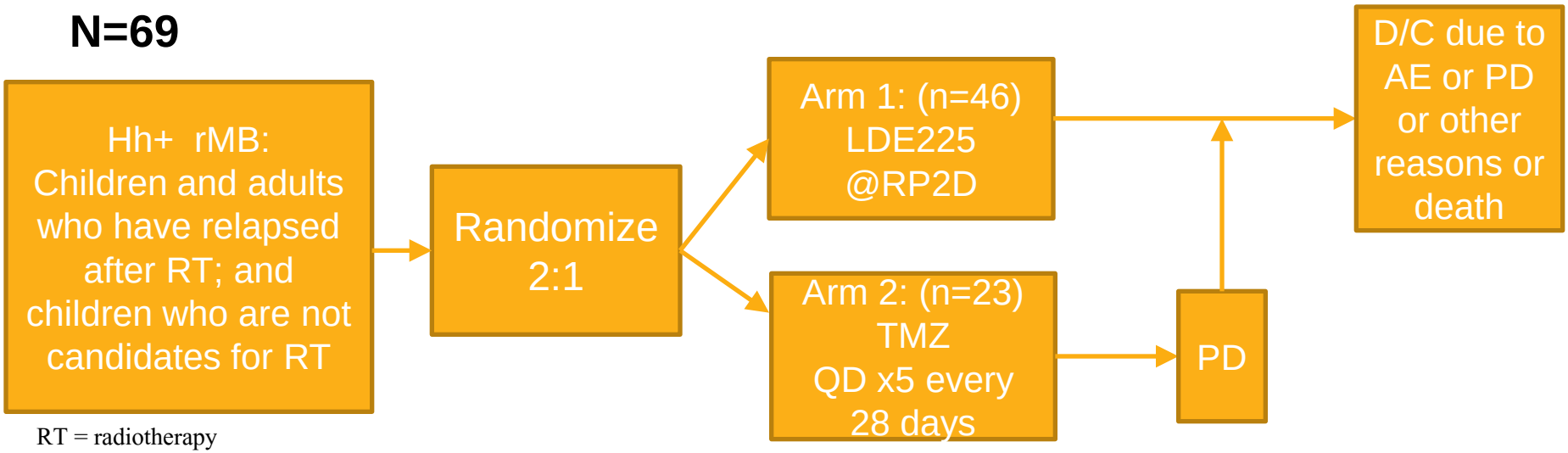
Great Ormond Street Hospital for Children, London

NOVARTIS

Randomized Phase II C2201 Study Design

Hh-pathway activated relapsed MB in children and adults

N=69



RT = radiotherapy

Primary endpoints: ORR

Secondary endpoints: DoR, PFS, safety, OS, QoL

Randomization stratified by age (adults/children)
Patients on TMZ may cross-over to LDE225 at progression. Patients not previously treated with RT will be analyzed as a separate subgroup. Safety data will be analyzed by age (children/adults)

Conclusions

Population –problems with rarity how to overcome

Right target- patients selection

Right drug(s)-

Different schedules

Different trial designs

Outcomes / endpoints

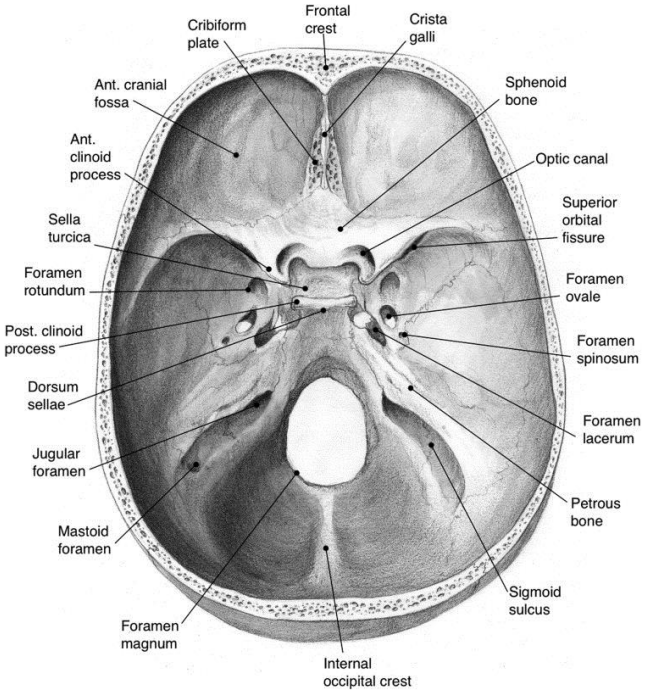
Management of Skull base tumors

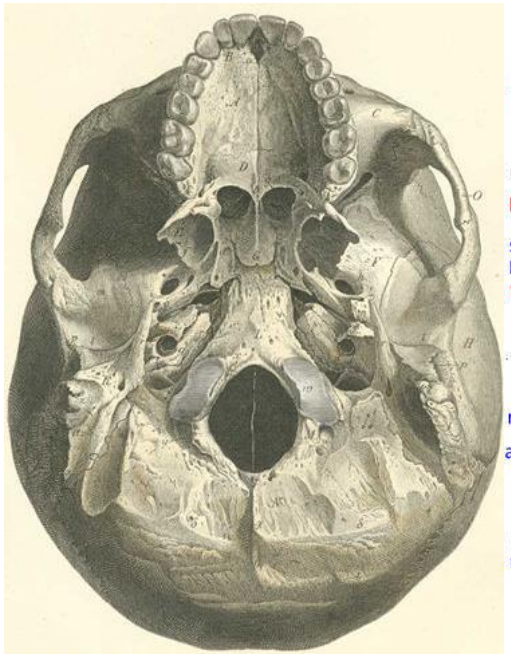
Prof. Dr.med. Damien Charles Weber

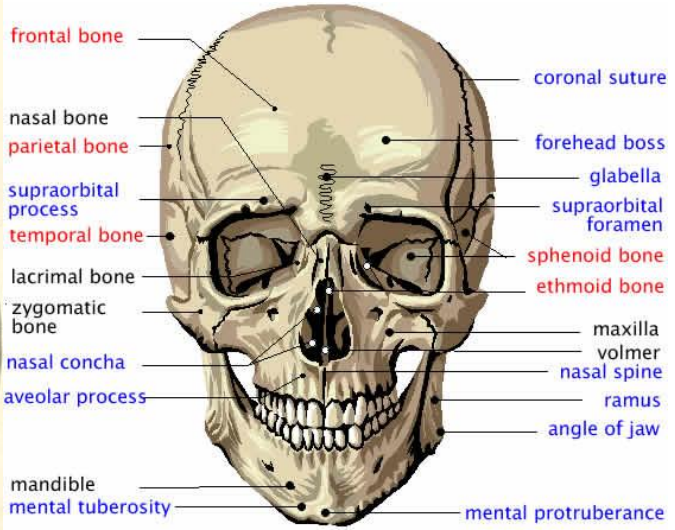
Center for Proton Therapy

Paul Scherrer Institute

Anatomy


Cribiform plate
Frontal crest
Crista galli
Ant. cranial fossa
Sphenoid bone
Ant. clinoid process
Optic canal
Sella turcica
Superior orbital fissure
Foramen rotundum
Foramen ovale
Post. clinoid process
Foramen spinosum
Dorsum sellae
Foramen lacerum
Jugular foramen
Petrous bone
Mastoid foramen
Sigmoid sulcus
Foramen magnum
Internal occipital crest




frontal bone
coronal suture
nasal bone
parietal bone
forehead boss
glabella
supraorbital process
supraorbital foramen
temporal bone
sphenoid bone
lacrimal bone
ethmoid bone
zygomatic bone
maxilla
volmer
nasal concha
nasal spine
aveolar process
ramus
angle of jaw
mandible
mental tuberosity
mental protruberance

DD

- **Primary tumors**
  - **Chordoma, Chondrosarcoma**

- **Secondary infiltration or involvement by intracranial tumors**
  - **Meningioma**
  - Craniopharyngioma

- **Secondary infiltration by primary H&N tumors**
  - Esthesioneuroblastoma
  - Adenoid cystic carcinoma
  - Ca Nasopharynx
  - Ca nasal cavity and paranasal sinus
  - Sarcoma: rhabdomyosarcoma/osteosarcoma/Ewing's

Skull base meningioma

- Meningioma: Most common (nonglial) primary brain tumor
- Predominantly benigh (90%) grade WHO 1
- SBM: 30% of all meningiomas
- Skull base: Complete resection rarely feasible
- Adjuvant treatment should be discussed

Clinical Trials Database

EORTC The future of cancer therapy

EORTC Brain Tumor Group(Coordinating Group)
EORTC Radiation Oncology Group
NCIC Clinical Trial Group
Trans-Tasman Radiation Oncology Group Inc

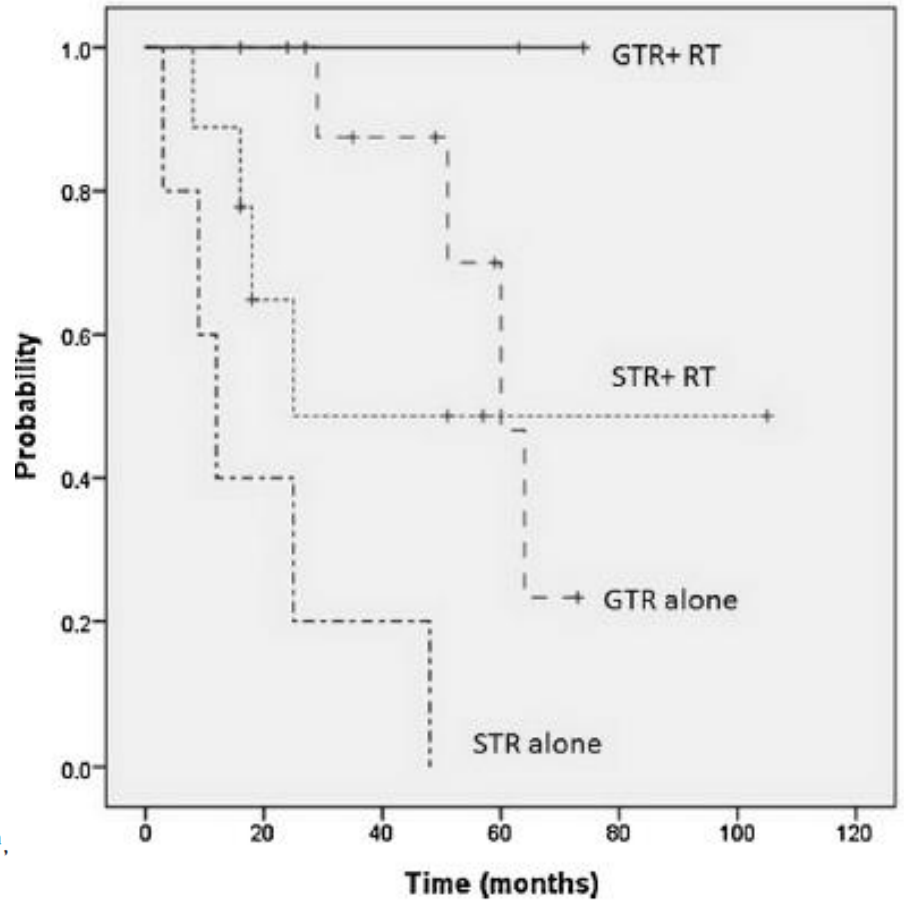
EORTC-26021-22021-BTG-ROG

Observation versus conventional-fractionated radiotherapy or radiosurgery after non-radical surgery for benign intracranial meningiomas : a phase III study

Targeted Sample size EORTC Groups: 153 - All Groups: 478

Skull base meningioma

Clinical Neurology and Neurosurgery 128 (2015) 112–116



Skull base atypical meningioma: Long term surgical outcome and prognostic factors

Yu-Chi Wang[a], Chi-Cheng Chuang[a], Kuo-Chen Wei[a], Yung-Hsin Hsu[a], Peng-Wei Hsu[a], Shih-Tseng Lee[a], Chieh-Tsai Wu[a], Chen-Kan Tseng[b], Chun-Chieh Wang[b], Yao-Liang Chen[c], Shih-Min Jung[d], Pin-Yuan Chen[a,*]

Characteristics	Number (%)
Gender	
Male	139 (27)
Female	368 (73)
Age	
Mean (range)	53 (16–83)
Histologic classification	
No histology	238 (47)
WHO Grade I	234 (46)
WHO Grade II	20 (4)
WHO Grade III	15 (3)
Predominant clinical symptoms	
Headache	106 (21)
Double vision	131 (26)
Vision impairment	134 (26)
Exophthalmia	64 (13)
Seizures	24 (5)
Trigeminal impairment	178 (35)
Facial impairment	171 (34)
Time of radiation	
Definitive	145 (28.6)
Postoperatively	231 (45.6)
For tumor progression	131 (25.8)

Skull base meningiomas: Long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT)

Stephanie E. Combs[a], Sebastian Adeberg[a], Jan-Oliver Dittmar[a], Thomas Welzel[a], Stefan Rieken[a], Daniel Habermehl[a], Peter E. Huber[a, b], Jürgen Debus[a]

Skull base meningioma

Many radiation techniques

1. **EBRT**
2. **Radiosurgery**
3. **FSRT**
4. **Protons**

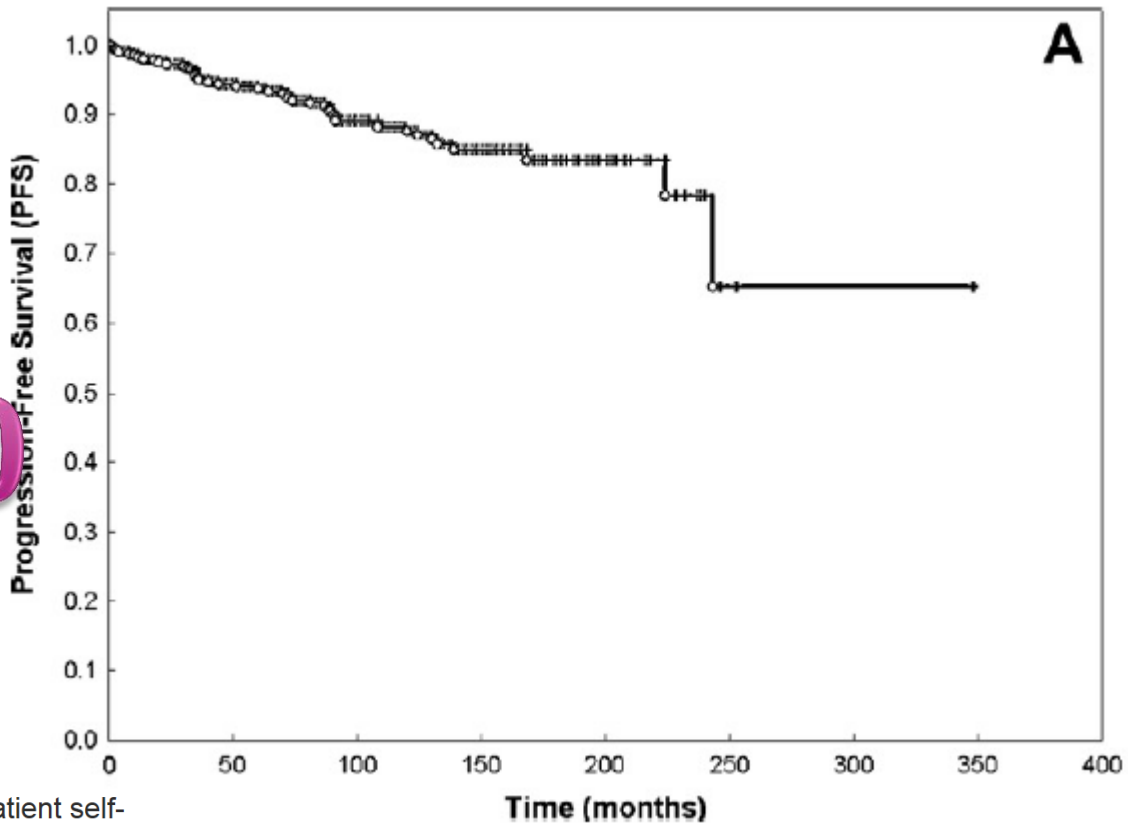
Radiological response rate different when using SRS vs. EBRT

Study	Mean/medianFU (range)	No. Of SBM patients	No change	Decreased	Increased
Starke RM J Neurosurg 2015:122(2):363	6.5 years (0.5-21)	465	49%	**35%**	16%
Pollock BE Int J Radiat Oncol Biol Phys. 2012 Aug 1;83(5):1414-8	62.9± 43.9 mo	251	26.7%	**72.1%**	1.2%

Skull base meningioma-Results

95% at 5 years

88% at 10 years



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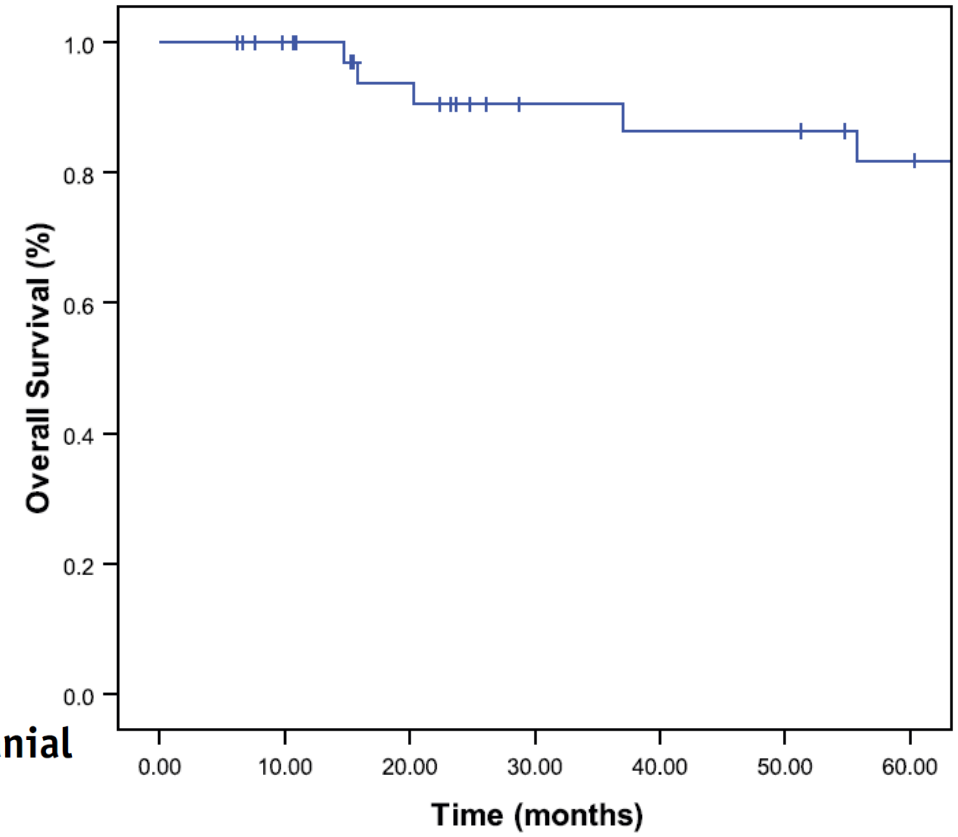
Skull base meningioma-Results

N=220 SBM patients
Median FU: 32 months (range, 7-97 months)

	Volume	dose	fractions	Radiographic tumor control	P value
SRS	2.8	12.5 (80% IDL)	1	91%	0.25
SFRT	4.8	25.0 (90% IDL)	5	94%	
EBRT	11.1	50.4 (90% IDL)	28	95%	

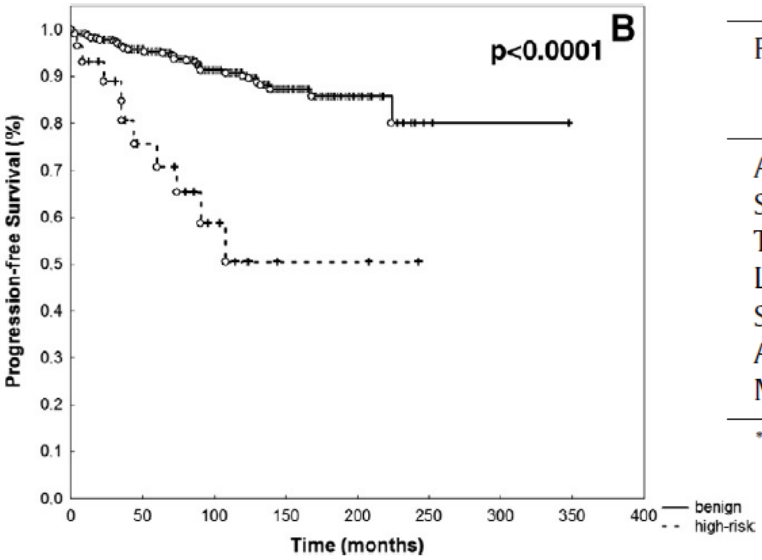
Characteristic	Number of patients (%)
Gender	
Female/male	30 (76.9%)/9 (23.1%)
Age (y)	
median	48.3
range	3.2–76.1
Histology (n = 34)	
Benign meningioma (WHO Grade I)	23 (67.6%)
Atypical (WHO Grade II)	9 (26.5%)
Anaplastic (WHO Grade III)	2 (5.9%)
Simpson (n = 34)	
<3	3 (8.8%)
3	3 (8.8%)
>3	20 (58.8%)
unknown	8 (23.6%)
Indication SSPT	
Postoperative	24 (61.6%)
Exclusive	8 (20.5%)
Salvage	6 (15.4%)
Adjuvant	1 (2.5%)
GTV (cm^3)	
Median	21.5
Range	0.76–546.5
Tumor site	
Skull base meningioma*	32 (82.1%)
Non-skull base meningioma	7 (17.9%)



Spot Scanning-Based Proton Therapy for Intracranial Meningioma: Long-Term Results From the Paul Scherrer Institute

Damien C. Weber, M.D.,* Ralf Schneider, M.D.,† Gudrun Goitein, M.D.,† Tamara Koch, M.Sc.,† Carmen Ares, M.D.,† Jan H. Geismar, M.D.,†

Skull base meningioma-Prognostic factors



Factors associated with progression free survival.

Factors	*p* value	
	Univariate analysis	Multivariate analysis
Age	0.024*	0.052
Sex	0.491	–
Tumor diameter	0.413	–
Location	0.076	–
Surgical extent	0.011*	0.005*
Adjuvant RT	0.376	–
MIB index	0.031*	0.030*

* $p < 0.05$

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Skull base meningioma-Complications

Surgery

10%

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Yu-Chi Wang[a], Chi-Cheng Chuang[a], Kuo-Chen Wei[a], Yung-Hsin Hsu[a], Peng-Wei Hsu[a], Shih-Tseng Lee[a], Chieh-Tsai Wu[a], Chen-Kan Tseng[b], Chun-Chieh Wang[b], Yao-Liang Chen[c], Shih-Min Jung[d], Pin-Yuan Chen[a,*]

Tumor location	Tumor diameter (cm)	Resection extent	Complication
Sphenoid ridge	8.3	GTR	Hemiparesis
Petroclivus	5.5	GTR	Facial palsy
Petroclivus	4.2	STR	Facial palsy

Complications	**%**
New craniopathies	44
New craniopathies permanent	**14**
Hydrocephalus	16
CSF leak	**2**

50 SBM undergoing Sx
36% treated by GKS

J Neurosurg. 2011 May;114(5):1268-77. doi: 10.3171/2010.11.JNS10326. Epub 2010 Dec 24.

Petroclival meningiomas: study on outcomes, complications and recurrence rates.

Nanda A[1], Javalkar V, Banerjee AD.

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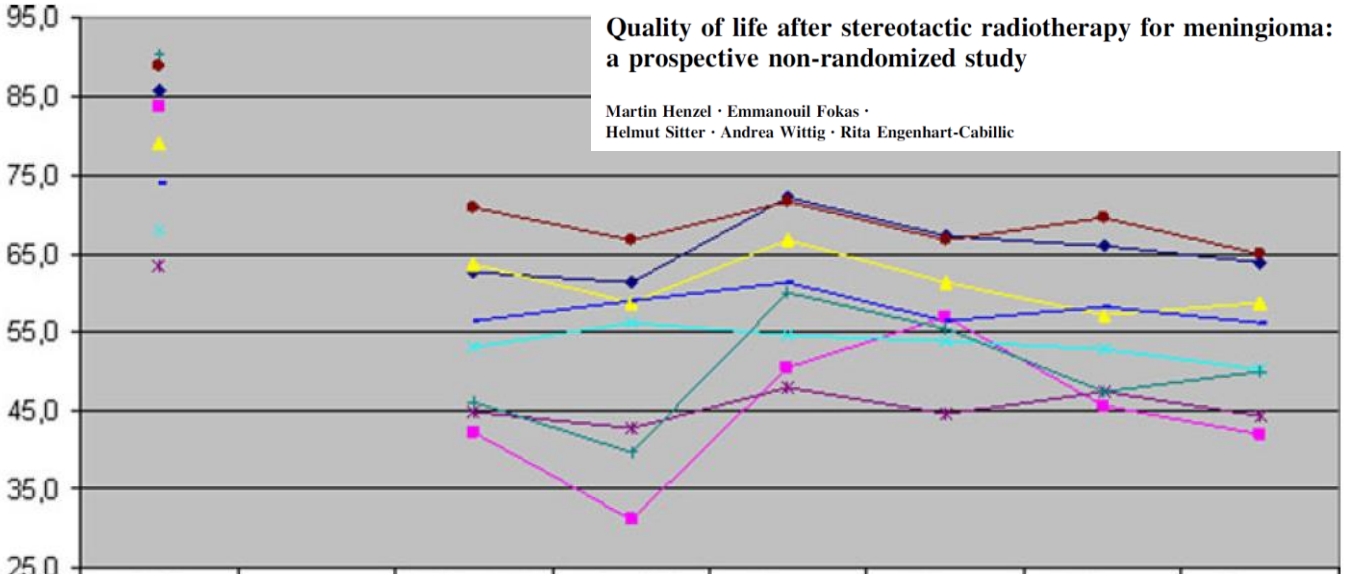
Skull base meningioma-QoL



Quality of life after stereotactic radiotherapy for meningioma: a prospective non-randomized study

Martin Henzel · Emmanouil Fokas · Helmut Sitter · Andrea Wittig · Rita Engenhart-Cabillic

	GNP		before RT	after RT	6 mo	12 mo	18 mo	24 mo
pf	85,7		62,7	61,4	72,0	67,1	65,8	63,9
rolph	83,7		42,3	31,3	50,5	56,9	45,6	42,0
pain	79,1		63,7	58,7	66,6	61,2	57,2	58,7
ghp	68,1		53,0	56,2	54,5	53,8	52,8	50,2
vital	63,3		44,7	42,7	48,0	44,6	47,4	44,3
social	88,8		70,7	66,8	71,6	66,8	69,4	64,8
rolem	90,4		46,2	39,7	59,9	55,3	47,4	50,0
mh	73,9		56,5	59,0	61,3	56,5	58,2	56,1

J Neurooncol (2013) 113:135–141
DOI 10.1007/s11060-013-1099-1

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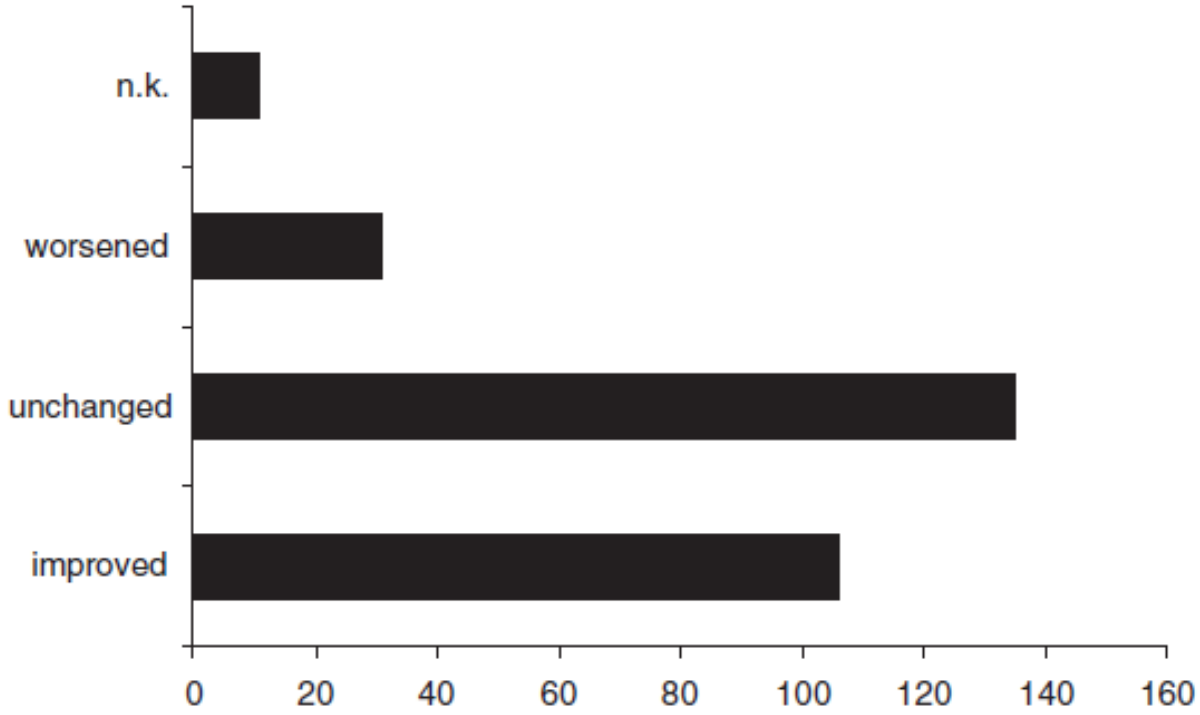
Skull base meningioma-QoL



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Chordoma and Chondrosarcoma

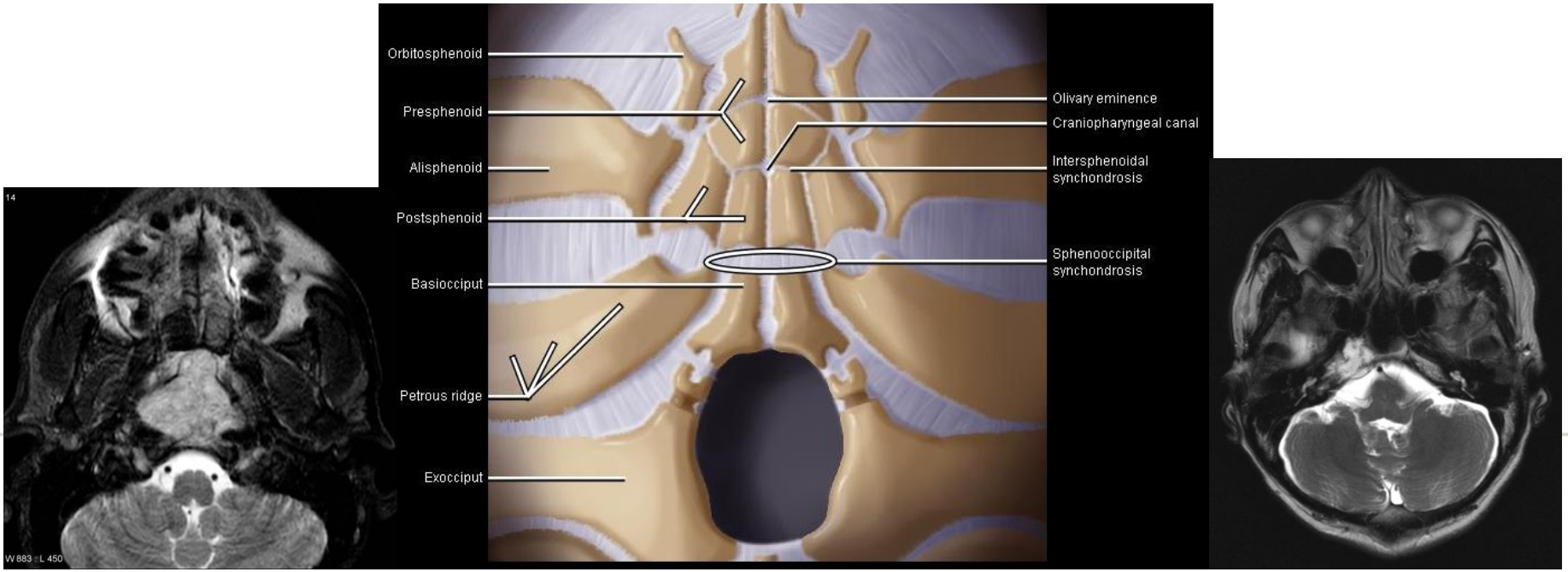
CHORDOMA

Presumed to arise from remnants of primitive notochord, an embryonic precursor replaced by mesodermal elements to form vertebrae and skull base

Typically midline

CHONDROSARCOMA

- Arise from embryonal rests of cartilaginous matrix that escape reabsorption during endochondral ossification
- Off-midline and originate within the temporal bone and petroclival fissure



Chordoma Chondrosarcoma

EPIDEMIOLOGY

CHORDOMA

0.84 per 1'000'000 (M>F)*

Median age 58 (3 - 95)

Intracranial chordomas invariably involve the clivus

Those arising from :

(a) the most rostral notochordal extension in the dorsum sellae present as sellar/parasellar tumors

(b) the most ventral part of the clivus present as nasopharyngeal tumors

(c) those associated with body and dorsal aspect of clivus manifest as spheno-occipital or petrosal lesions

(d) those related to the lower clivus will present at the ventral portion of the foramen magnum

Direct dural invasion responsible for extension to posterior fossa

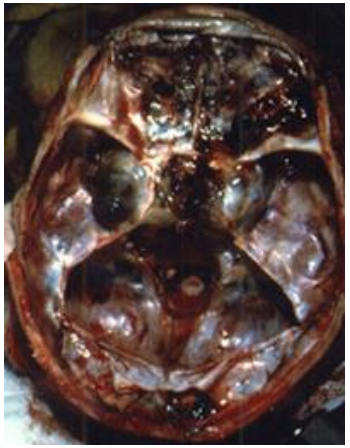
CHONDROSARCOMA

- 5 per 1'000'000 (M>F)
- Median age 51 (1 – 102)
- Appendicular > axial > soft tissue

*Incidence and relative survival of chordomas: the standardized mortality ratio and the impact of chordomas on a population.

NR, Gautschi OP, Radovanovic I, Schaller K, **Weber DC**. Cancer. 2013 Jun 1;119(11):2029-37. doi: 10.1002/cncr.28032. Epub 2013 Mar 15

Chordoma Chondrosarcoma



CHORDOMA - Pathology

Macroscopically:

Chordomas are soft, gelatinous, lobulated neoplasms

Microscopically:

Vacuolated, bubble-containing cytoplasm: **physaliphorous cells**

Express S-100, EMA and cytokeratin

Notochordal developmental transcription factor, **BRACHYURY** *(when combined with cytokeratin staining, sensitivity of 98% and specificity of 100% for chordoma)*

Chondroid Chordoma:

Favorable prognosis (UNRESOLVED ISSUE)

About 20% were later found to be chondrosarcomas

Mayo clinicopath study revealed no difference in survival (attributed to occurrence in younger pts)

Chordoma Chondrosarcoma

NATURAL HISTORY

CHORDOMA

5 yr and 10 yr DFS 70% and 45%

Exhibit locally destructive growth

Recurrences may be noted many years after treatment

Distant metastasis extremely rare (6% - 22%)

Metastasis higher in the presence of recurrent disease

After recurrence, 3-yr and 5-yr OS about 43% and 7%

CHONDROSARCOMA

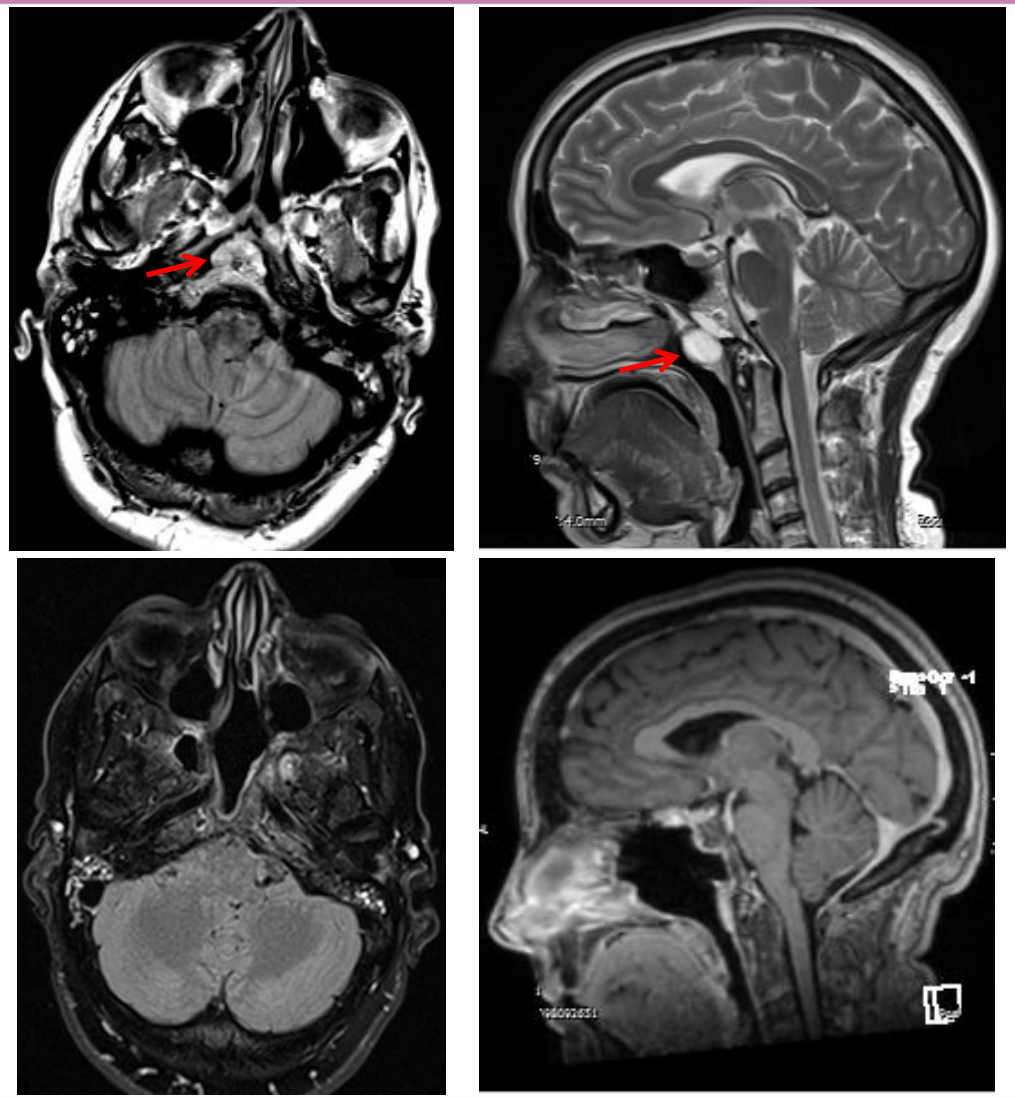
- More **indolent** and associate with much more favorable prognosis
- 10-yr local control and disease-specific survival 98-99%
- No relationship between histological subtype and grade

Treatment - Surgery

- Goal is to remove as much of the tumor while minimizing complications
- Whenever brainstem compression present, decompress
- Fat graft as spacer to increase distance between clivus and contiguous brainstem to facilitate safe delivery of radiation

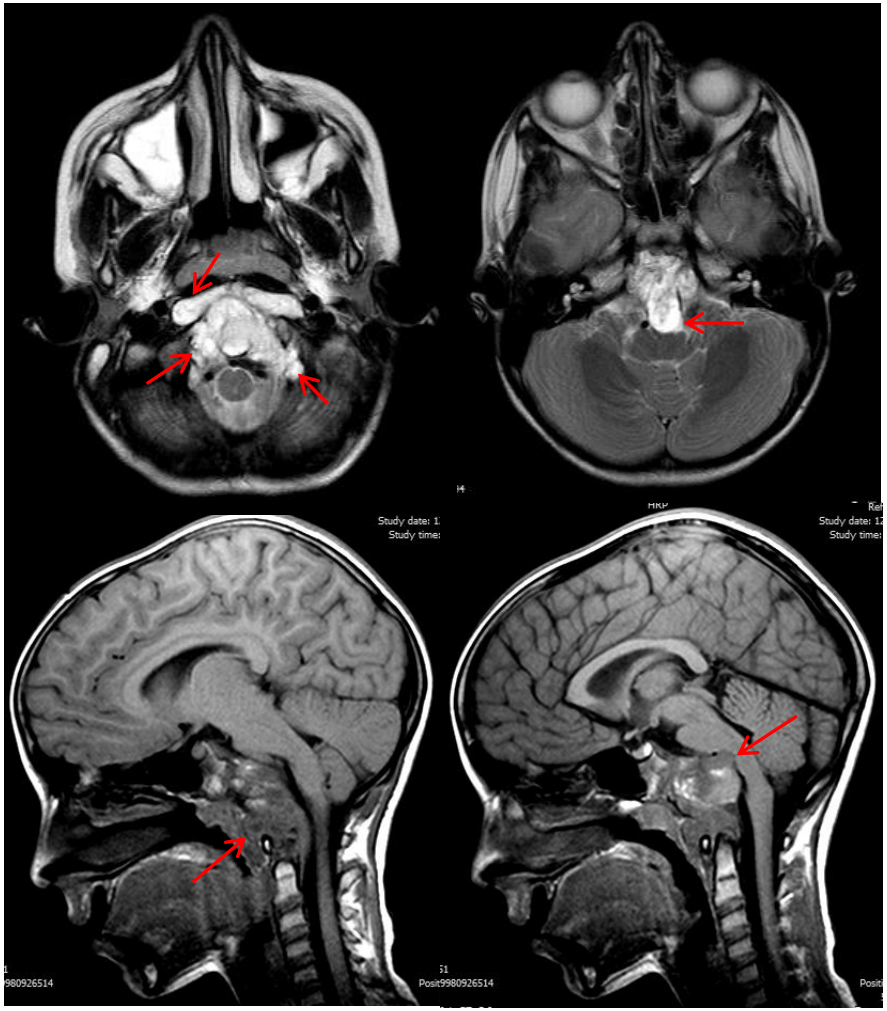
Chordoma Chondrosarcoma

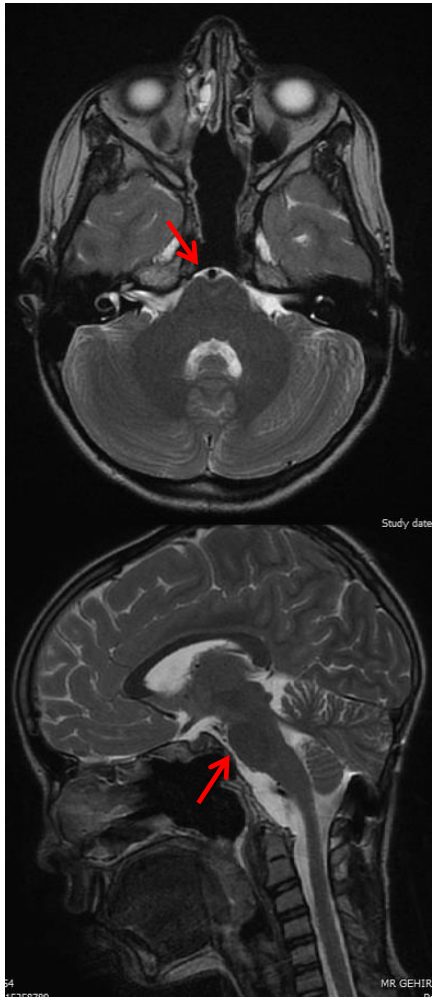
Goal of Surgery - Chordoma



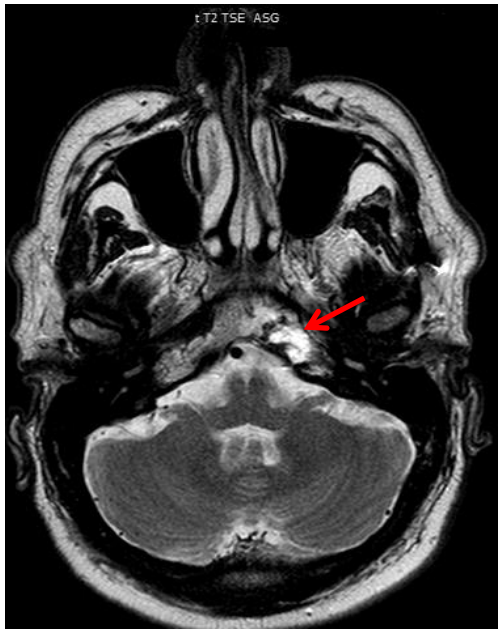
Chordoma Chondrosarcoma

Goal of Surgery - Chordoma

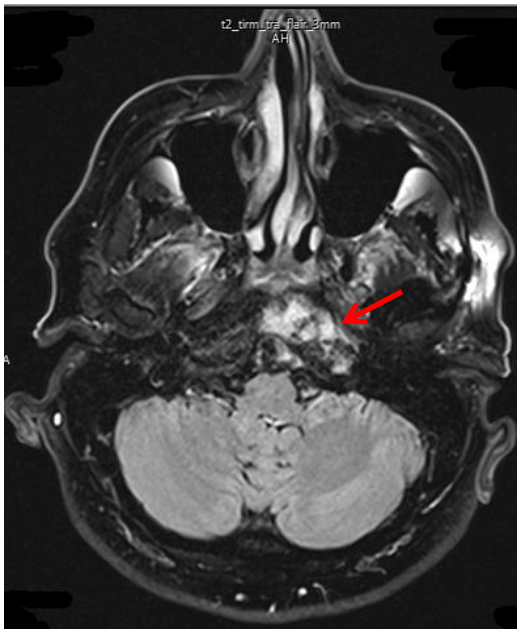




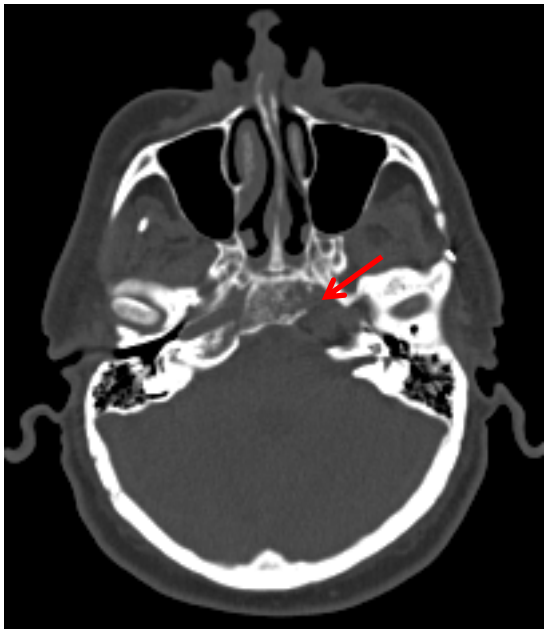
Goal of Surgery - Chondrosarcoma



2007



2015



Planning CT

Chordoma - Surgery

	Radical Resection (No tumor)	Subtotal Resection (>90% resected)	Partial Resection (<90% resected)	Biopsy
Al-Mefty	43%	48%	9%	
Watkins		89%		11%
Gay	47% (total) 20% (near total)	23%	10%	

-Multiple retrospective studies have suggested **improved local control and survival in those patients with optimal surgical debulking**

- Tzortzidis reported that in patients with chordomas who underwent surgery aimed at performing a complete resection, GTR could be accomplished in only 72%.
- The 10-year recurrence-free survival was 31% indicating that **even after GTR, the likelihood of tumor control is low with surgery alone**

Chordoma: Surgery + Radiation

Tai et al, Cancer, 1995:
159 patients with cranial chordomas treated by various regimens:

- Subtotal resection followed by adjuvant radiation had a significantly improved survival over surgery alone (p=0.011)

- No difference when compared to radiation alone (p=0.271)

- The survival curves for the combined treatment separate with follow up and suggest a benefit to include surgery in the management

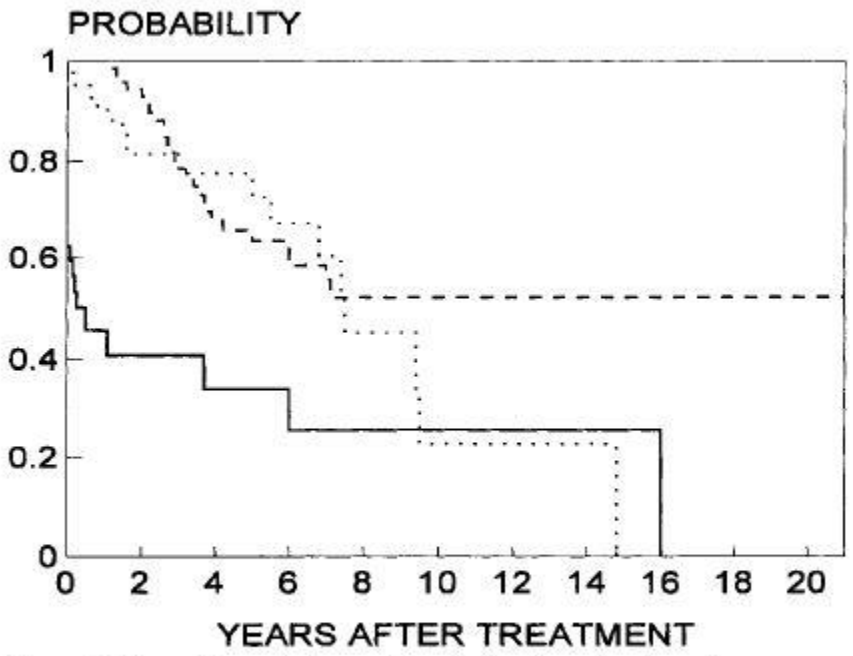


Figure 3. Overall survival according to the three treatments: ——, surgery alone, · · · ·, radiation alone; and – – – –, combined surgery and postoperative radiation.

Chordoma: Radiation

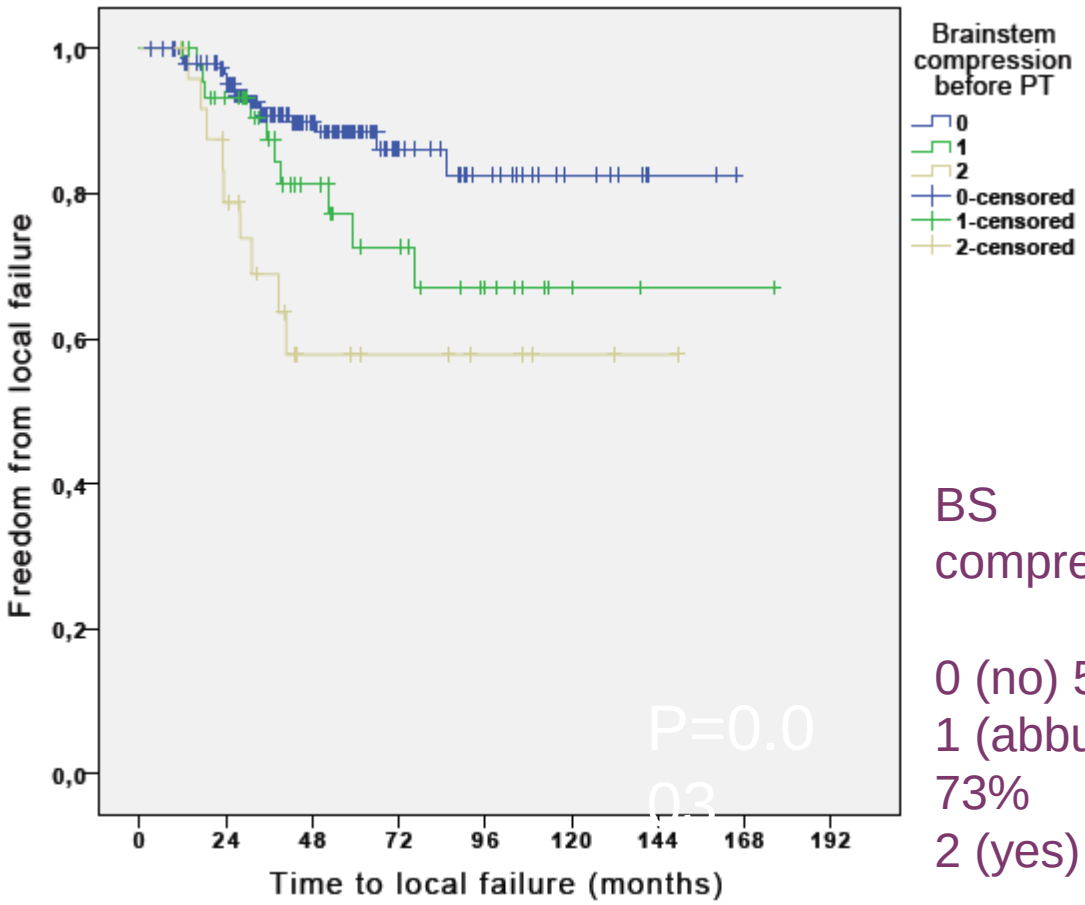
- The primary role of radiation therapy following maximal surgical resection is to improve local control
- There have been no randomized studies investigating optimal dose
- Initial results in the 1960s and 1970s suggest an improvement in symptomatic response and local control with increasing dose
- Used antiquated techniques and often included multiple sites in their reports
- In 1970 Pearlman and Friedman: Decrease in local failure with ↑ dose

Dose	Rates of Failure
<40 Gy (n=47)	85%
40 – 60 Gy (n=18)	60%
60-80 Gy (n=8)	43%
>80 Gy (n=2)	0%

Chordoma Chondrosarcoma

Author	Year/pts	Therapy	Dose Gy (Range)	Outcome
Romero J *et al.*	1993/17	photons	50 (median) (29.9-64.8)	PFS@5y: **17%***
Catton C *et al.*	1996/48	photons	50 25-60	LC@5y: **23%**
Debus J *et al.*	2000/65	FSRT	66.6	LC@5y:**50%**
Author	**Year/pts**	**Therapy**	**Dose Gy (Range)**	**Outcome**
Noel G *et al.*	2003/100	PT and photon	67 (60-70)	**LC@4y: 53.8%**
Munzenrider *et al.*	1999		72.1 (64.2-79.6)	**LC@5y:73%**
PSI	2014	Protons	74	**LC@5y:76%**

Chordoma Chondrosarcoma



BS compression:

0 (no) 5y 88%
1 (abbuts) 5y 73%
2 (yes) 5y 58%

N=222 Chordoma and CS patients, PSI *unpublished data*

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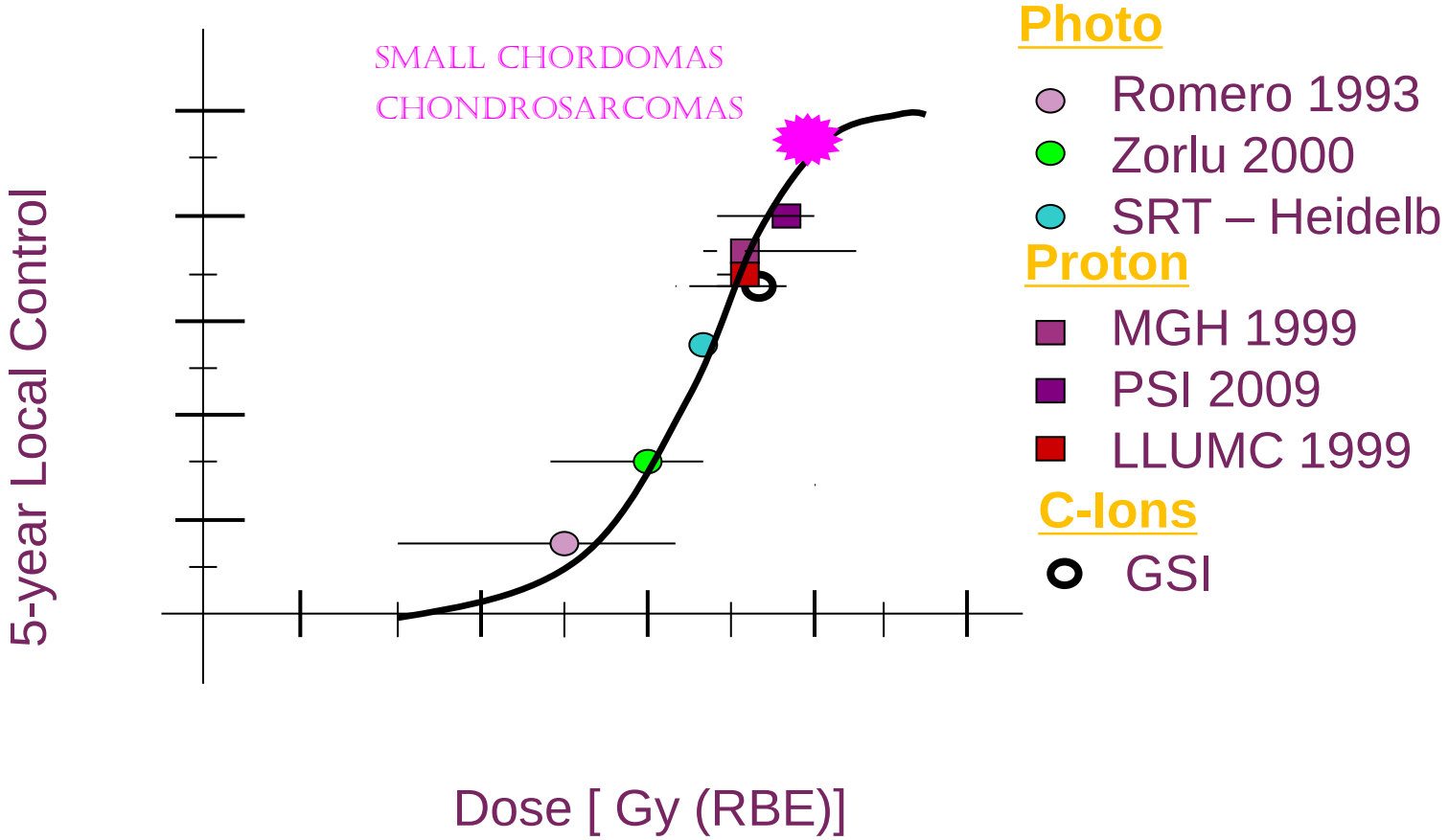
Chordoma Chondrosarcoma

Chordomas of the Base of Skull



Chordoma Chondrosarcoma

Fractionated Photon Radiation

Author	Period	N (Patients)	Site(s)	Tumor Dose (Gy)	% Local Control (Year)		% Overall Survival (Year)	
					5	10	5	10
Cummings et al, 1983 [50]	1958–1979	24	Multiple	25–67	–	–	62 (Ch)	28 (Ch)
Amendola et al, 1986 [51]	1962–1982	21	Multiple	50–66	–	–	50 (Ch)	20 (Ch)
Fuller et al, 1988 [32]	1952–1981	25	Multiple	30–70	33 (Ch)	20 (Ch)	44 (Ch)	17 (Ch)
Magrini et al, 1992 [52]	1955–1990	12	Multiple	35–60	17 (Ch)	17 (Ch)	58 (Ch)	35 (Ch)
Forsyth et al, 1993 [23]	1960–1984	39	BOS	23–67	39 (Ch)	31 (Ch)	51 (Ch)	35 (Ch)
Romero et al, 1993 [53]	1975–1990	18	Multiple	30–65	17 (Ch)	–	38 (Ch)	–
Catton et al, 1996 [54]	1958–1992	48	Multiple	25–60	23 (Ch)	15 (Ch)	54 (Ch)	20 (Ch)
Zorlu et al, 2000 [55]	1979–1997	18	BOS	50–64	23 (Ch)	–	35 (Ch)	–
Debus et al, 2000 [56]	1990–1997	45	BOS	Med. 66.6 (Ch) Med. 64.6 Gy (CS)	50 (Ch) 100 (CS)		82 (Ch) 100 (CS)	

Abbreviations: BOS, base of skull; Ch, Chordoma; CS, Chondrosarcoma.

Stereotactic RT

Mehta: Principles and Practice of Neuro-Oncology

Chordoma Chondrosarcoma

Stereotactic Radiosurgery

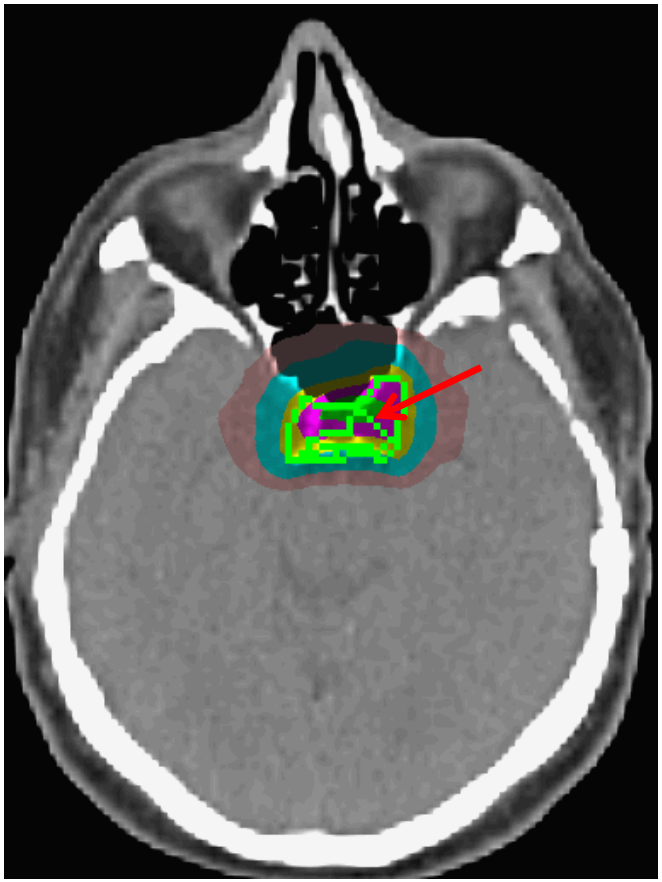
Author	Period	N (Patients)	Tumor Dose (Gy)	% Local Control (Year)		% Overall Survival (Year)	
				5	10	5	10
Krishnan et al, 2005 [62]	1990–2002	29	10–20	32 (Ch/CS)	–	–	–
Hasegawa et al, 2007 [63]	1991–2006	37	9–20	76 (Ch/CS)	67 (Ch/CS)	80 (Ch/CS)	53 (Ch/CS)
Martin et al, 2007 [64]	1987–2004	28	10–25	53 (Ch) 80 (CS)	–	63 (Ch)	–

Abbreviations: Ch, Chordoma; CS, Chondrosarcoma; SRS, Stereotactic radiosurgery.

- Response correlated to only small volumes
- Increased marginal failures
- Increased morbidity: cranial nerve dysfunction, brain necrosis

Chordoma - Small Tumor Volume

In contrast to SRS, even in small tumors treated with protons, consistently a CTV and a PTV are created



Chordoma Chondrosarcoma

Target definition

- GTV (gross tumor volume)= gross residual tumor (and high-risk area in immediate proximity)
  - MRI (T1, T1GD, T2)
  - CT (bone window)
- CTV (clinical target volume) = postop. tumor bed (taking in account pre-op. extension), modifying for anatomical boundaries and compartments.

Prescription dose to targets

- PTV1 (CTV): 54 Gy(RBE) at 2 Gy/fr
- PTV2 (GTV): 74 Gy(RBE) Chordoma / 70 Gy(RBE) Chondrosarcoma at 2 Gy/fr

Skull Base Chordoma and Chondrosarcoma

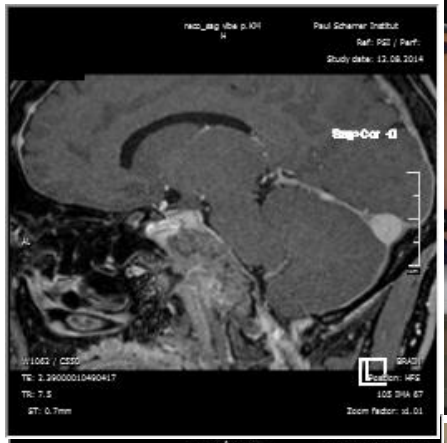
OAR Constraints:

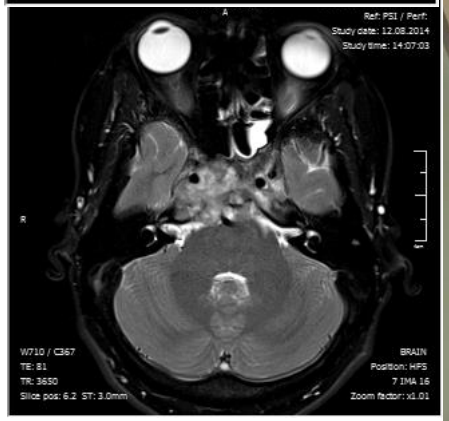
Optic chiasm and nerves: max 60 Gy(RBE)
Brainstem surface: max 64 Gy(RBE)
Brainstem center: max 54 Gy(RBE)
Cochlea: max 36 Gy(RBE), mean 30 Gy(RBE)
Temporal Lobe (outside PTV): ≤ 20 Gy(RBE)
Spinal cord surface: max 60 Gy(RBE)(generally ≤54 Gy(RBE)
Spinal cord center: ≤50.4 Gy(RBE)
Hippocampus: V_{40} = <7.3 Gy(RBE

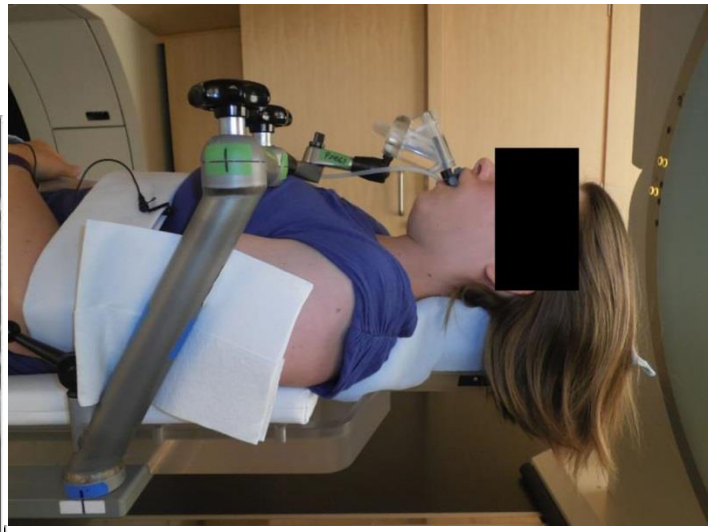
Chordoma Chondrosarcoma

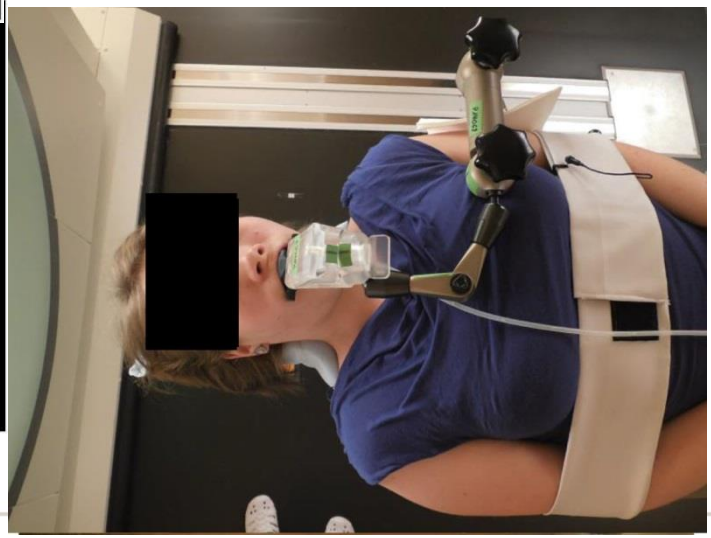
Skull Base Chordoma and Chondrosarcoma - **IMMOBILIZATION**

ADULTS

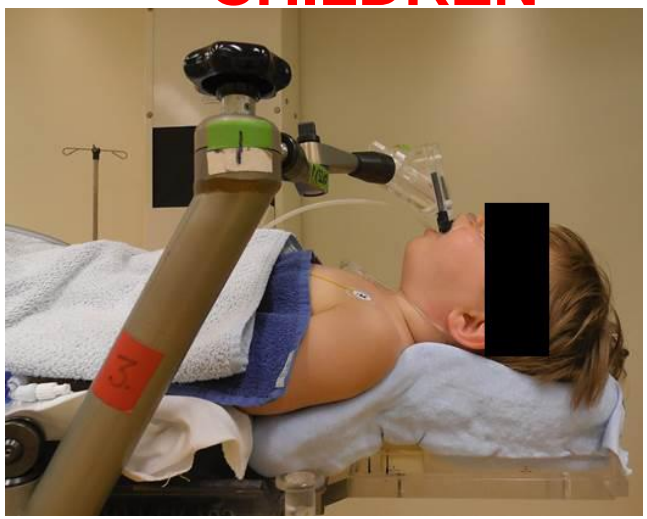


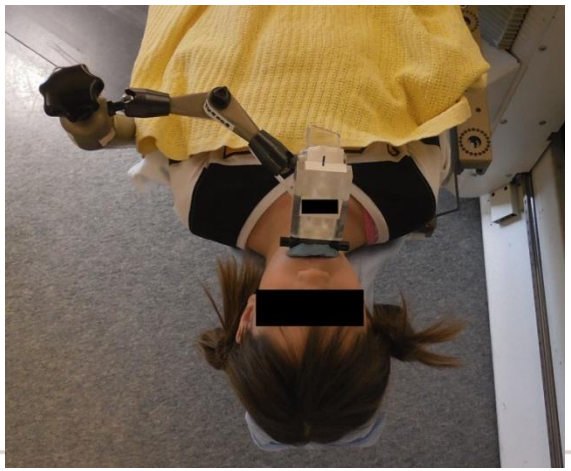






CHILDREN





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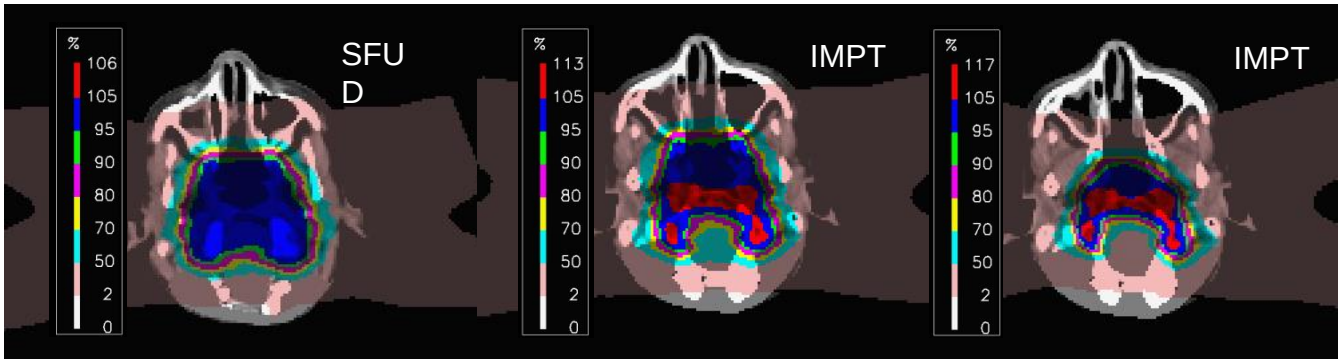
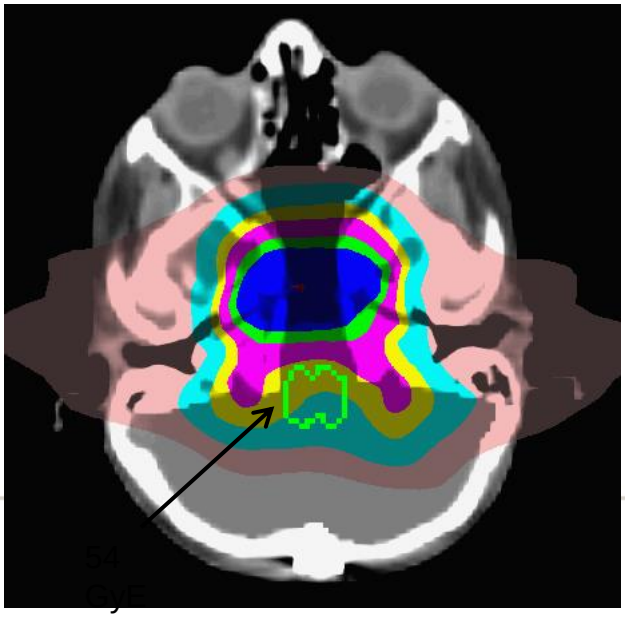
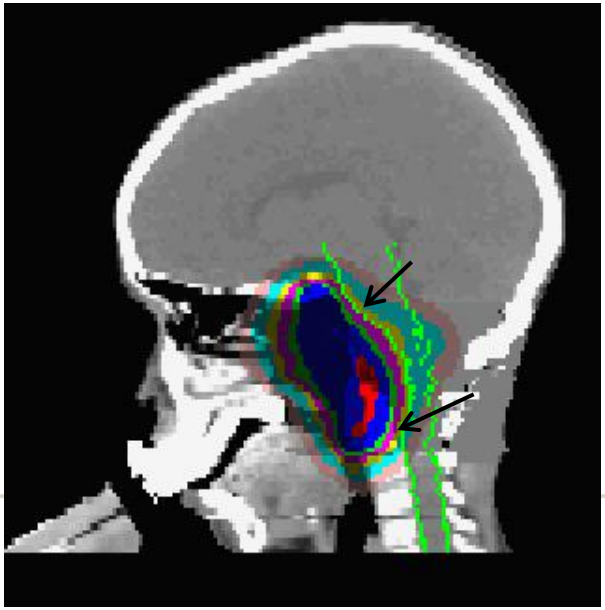
Post-op Proton Therapy for Clivus Chordoma

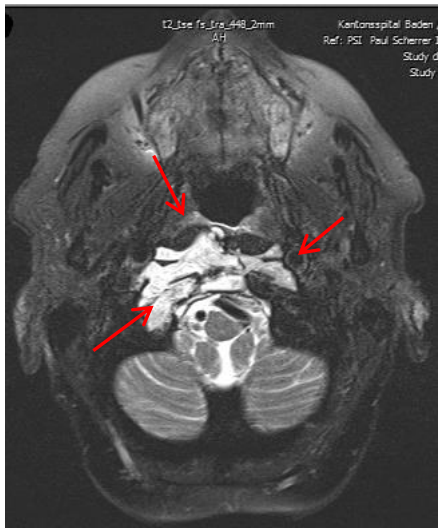


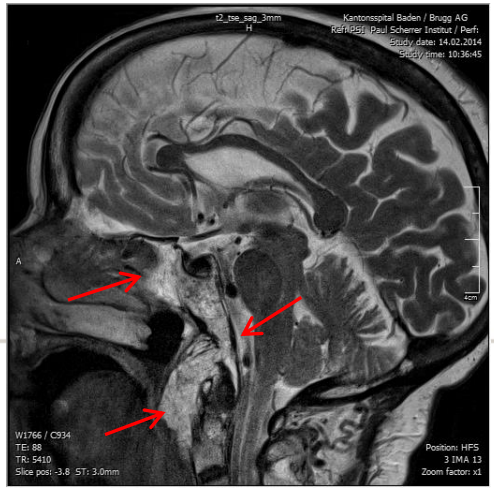


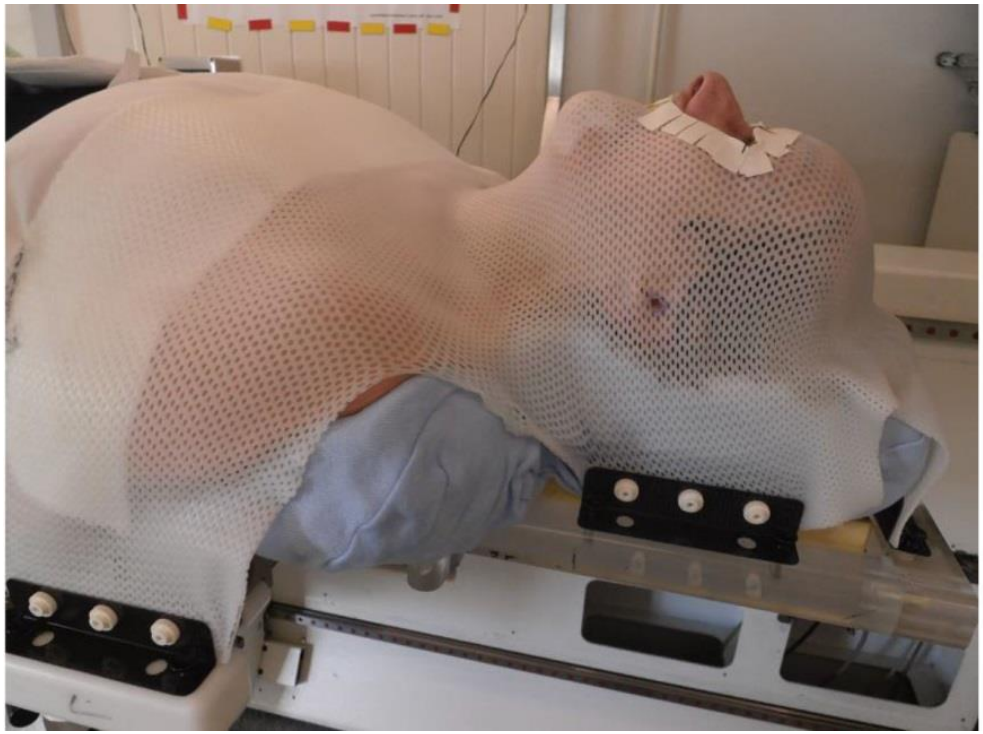


Chordoma Chondrosarcoma

Skull Base Chordoma and Chondrosarcoma - **IMMOBILIZATION**







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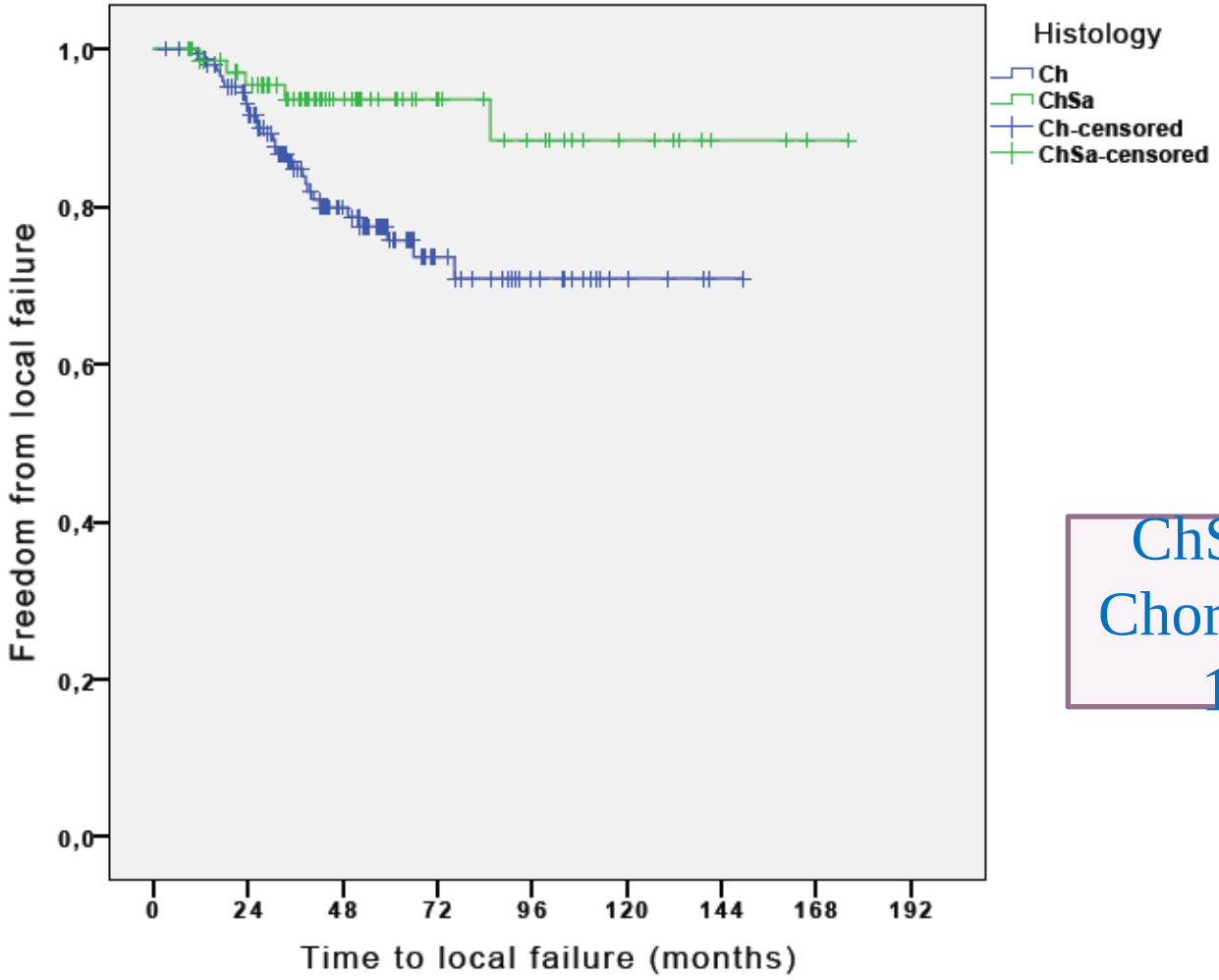
Primary Skull Base tumors: PSI Experience



ChSa=71
Chordoma=151

Chordoma Chondrosarcoma

Ares *et al*. IJROBP 2009;75(4):1111-8

Prognostic Factors Significant for Local Control in CHORODMA

- Residual tumor volume >25 c.c.
- Brainstem compression

Radiation-induced Late Toxicity

- Asymptomatic MRI white matter changes (G1) = 5 patients

- High grade late toxicity = 4 patients (all diagnosed with chordoma)
  - optic pathway: G4 (1 patient) – unilateral blindness
    G3 (1 patient) – unilateral visual deficit, steroid dependent
  - neurologic: G3 (2 patients) – **symptomatic brain necrosis**

Actuarial 5-year freedom from high-grade toxicity: 94%

Chordoma Chondrosarcoma

Protons: Improved Local Control for “Smaller Size Tumors”

LLUMC: < 25 c.c. vs. > 25 c.c. (100% vs. 56%)

- **CPO: <29 c.c. vs. > 29 c.c.**
- **PSI: > 25 c.c. vs. > 25 c.c. (90% vs. 74%)**
- **MGH: < 70 c.c. vs. > 70 c.c. (disease-free survival)**

Chordoma Chondrosarcoma

Risk of severe (>Grade 3) following high-dose proton therapy

- **Tumor size**
- **Compression of: chiasm, optic N, brainstem, brain**
- **Number of surgeries**
- **Diabetes, HTN, smoking**
- **KPS**

Summary of Prognostic Factors

- (+++) Skull base: Chondrosarcomas versus Chordomas
- (+++) Tumor Size
- (++) Skull Base versus Spine
- (+) Primary versus recurrent disease
- (+) Chondroid versus Non-Chondroid Pathology
- (?) Gender
- (+) Age
- (+) Pediatric versus Adult
- (+++) Ability versus Inability to deliver dose: Optimal / suboptimal dose distribution by involvement or abutment of critical structures
- (+++) Radiation Dose
- (+++) Protons versus Photons

Skull Base Chordoma: Comparison of Literature

	n	Radiation	Mean dose	LC 3-yr	LC 5-yr	LC 10-yr
Munzenrider, 1999	**169**	**PT, RT**	**76**		**73**	**54**
Terahara, 1999	**115**	**PT, RT**	**69**		**59**	**44**
Hug, 1999	**33**	**PT, RT**	**71**	**67**	**59**	
Noel, 2005	**100**	**PT, RT**	**67**	**86@2y**	**53@4y**	
Igaki, 2004	**13**	**PT, RT**	**72**	**67**	**46**	
Schulz-Ertner, 2007	**96**	**Carbon, RT**	**60 ***	**81**	**70**	
Mizoe, 2009	**33**	**Carbon**	**57 ***		**85**	**64**
Unpublished, (PSI) 20xx	**151**	**PT**	**74**	**87**	**76**	**71**
Deraniyagala, 2014	33	PT	78	86@2y		

* @ 3 Gy/fraction

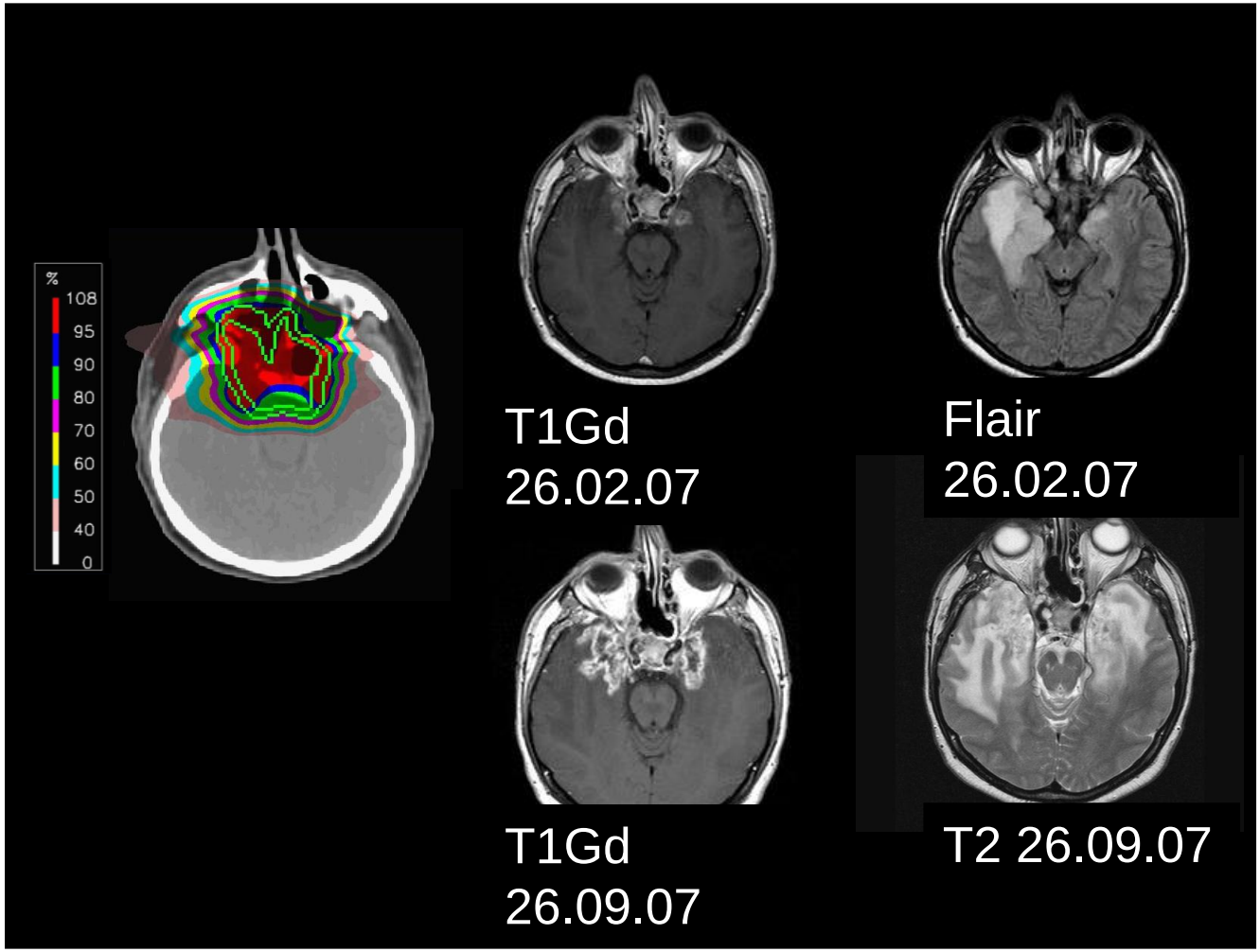
Skull Base Chondrosarcoma: Comparison of Literature

	n	Radiation	Mean dose	LC 3-yr	LC 5-yr	LC 10-yr
Munzenrider, 1999	**229**	**PT, RT**	**72**		**98**	**94**
Hug, 1999	**25**	**PT, RT**	**71**	**94**	**75**	
Johnson, 2002	58	PT, RT	71		91	
Noel, 2003	**26**	**PT, RT**		**94**	**75@4y**	
Schulz-Ertner, 2007	**96**	**Carbon, RT**	**60 ***	**81**	**70**	
Unpublished, (PSI) 20xx	**71**	**PT**	**68**	**94**	**94**	**88**

* @ 3 Gy/fraction

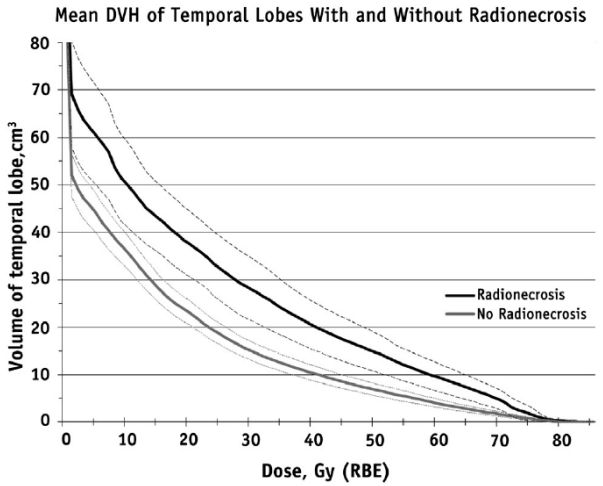
Chordoma Chondrosarcoma

Pehlivan B, Ares C, Lomax AJ, et al. IJROBP 2012;83(5):1432-40



Example of Grade 3 bilateral temporal lobe toxicity in a patient with skull base chordoma treated up to 74 Gy(RBE)
Occurrence = 6%

Chordoma Chondrosarcoma



Necrosis @ 3 year	12.4%
Necrosis @ 3 year (grade 2 and higher)	5.7%

Dose–Volume Relationships Associated With Temporal Lobe Radiation Necrosis After Skull Base Proton Beam Therapy

Mark W. McDonald, MD,*,† Okechukwu R. Linton, MD, MBA,* and Cynthia S.J. Calley, MA‡

Mean dose–volume information to area of radiation necrosis by grade of radiation necrosis

	Grade 1/asymptomatic	Grade 2 or higher	*P* value
Volume, cm^3	2.15	3.66	.51
Minimum dose	54.0	50.2	.58
Maximum dose	75.0	82.9	<.01
Mean dose	68.6	73.0	.02
Epicenter dose	70.9	76.7	<.01

Dose is given in Gy (relative biological effectiveness).

Dose–volume levels associated with 3-year risk of any-grade temporal lobe radiation necrosis

Risk level	aV40	aV50	aV60	aV70
10%	16.5	9.0	5.1	1.2
15%	16.5	9.6	5.5	1.7
20%	16.6	10.1	5.8	2.0
30%	16.7	10.8	6.3	2.5
40%	16.7	11.4	6.8	3.1
50%	16.8	12.2	7.2	3.9

Abbreviations: aV = absolute volume of temporal lobes exposed to dose in Gy (RBE); RBE = relative biological effectiveness. Volume is expressed in cubic centimeters (cm^3).

Int J Radiation Oncol Biol Phys, Vol. 91, No. 2, pp. 261–267, 2015

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Summary

1. Excellent tumor control with for SBM with various radiotherapeutic modalities
2. SBM: Increase tumor response with radio-surgery
3. SBM: Increase radiation-induced toxicity with SRS
4. QoL in meningioma patients ill-assessed
5. High-dose radiation therapy necessary to control Chordomas
6. No PRT (level I evidence)
7. Prognostic factors: Chordoma, volume, tumor size, compression of BS, photons
8. Main toxicity of PT is brain necrosis


THANK
YOU


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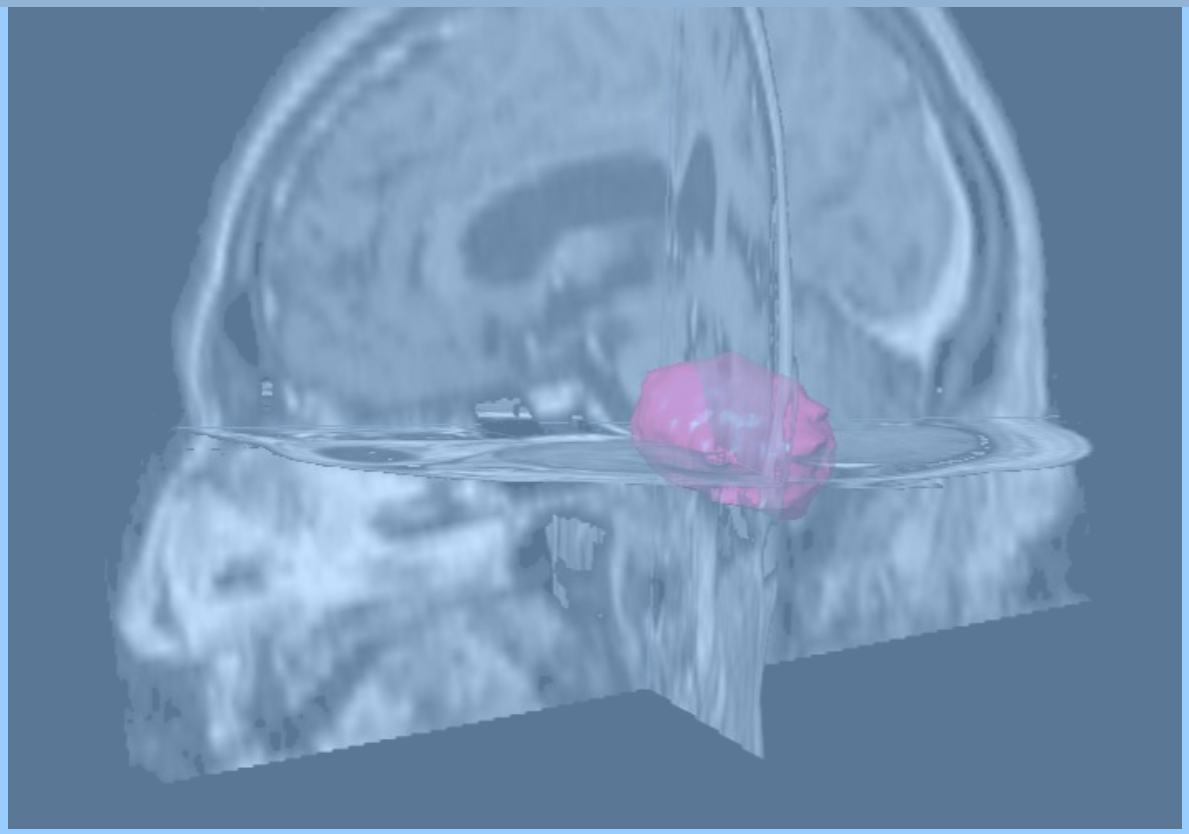
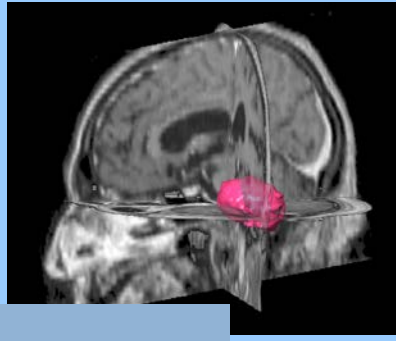
Benign Brain Tumours



Principles



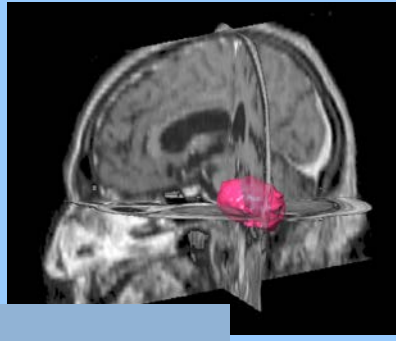
indolent tumours

long natural history

rarely life threatening

radiotherapy - one of available options

Radiotherapy prerequisites



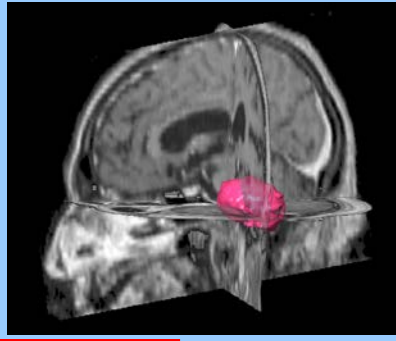
need to understand:

natural history

imaging

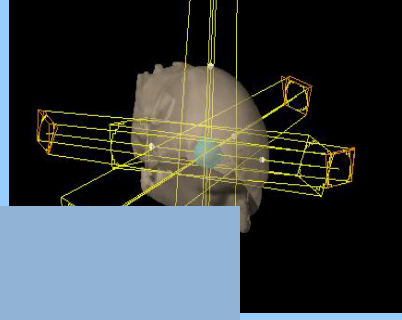
other treatment options

balance of risks



Surveillance	Surgery
Radiotherapy	Medical therapy

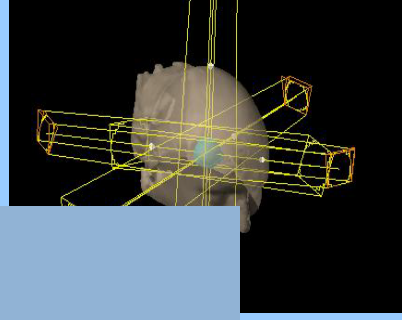
Management options in benign brain tumours



radiotherapy issues

technical

clinical



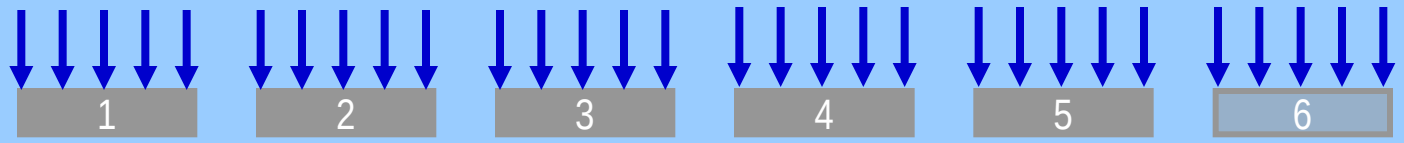
radiotherapy issues - technical

technical aspects of delivery

target definition

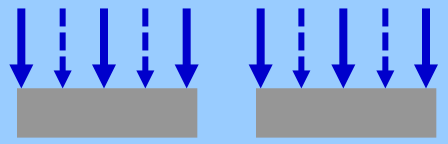
dose fractionation

Fractionated radiotherapy

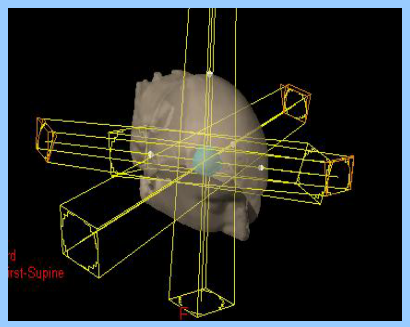


45 - 55Gy in 25 - 33 fractions

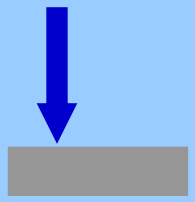
Hypofractionated radiotherapy



20 - 30Gy in 3 - 10 fractions



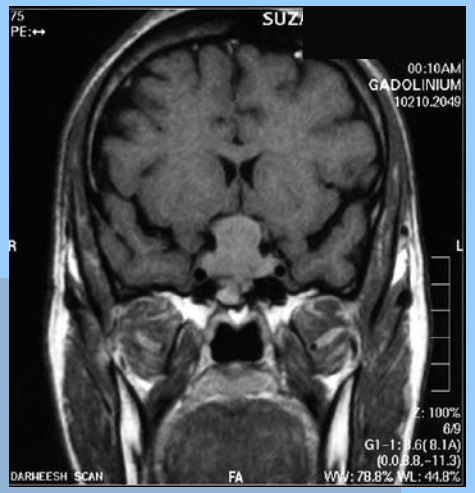
Single fraction radiotherapy (radiosurgery)



10 - 25Gy in 1 fraction

Dose fractionation in benign brain tumours

Benign brain tumours



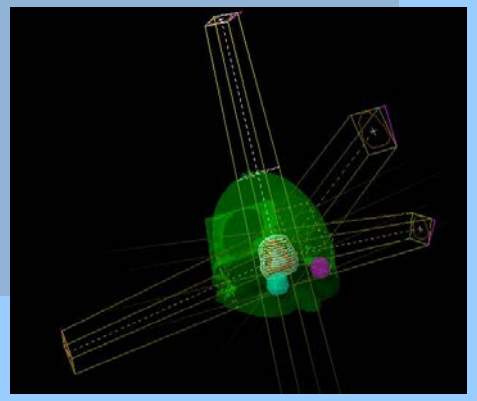
pituitary adenoma

craniopharyngioma

acoustic neuroma

skull base meningioma

childhood low grade glioma



Management of benign brain tumours

Benign brain tumours

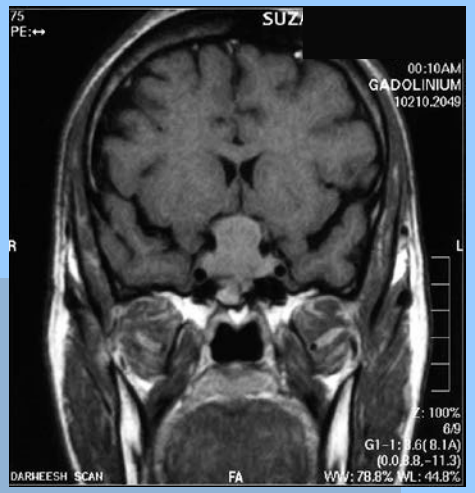
pituitary adenoma

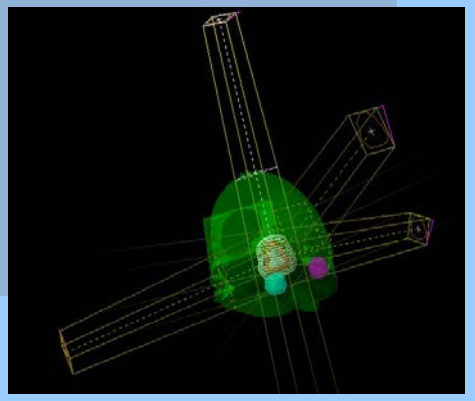
craniopharyngioma

acoustic neuroma

skull base meningioma

childhood low grade glioma





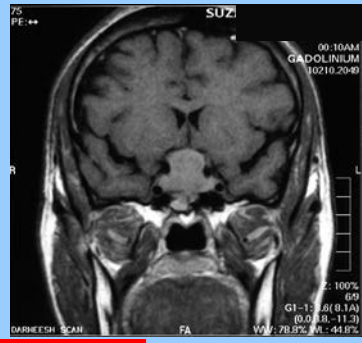
Management of benign brain tumours

Radiotherapy in patients with non-functioning pituitary adenoma

1. prolongs survival
2. should be given soon after incomplete resection
3. should avoid hypothalamus
4. all of these
5. none of these

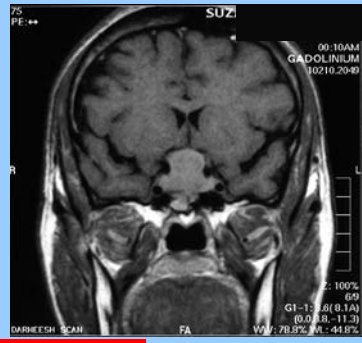
Radiotherapy in patients with secreting pituitary adenoma

1. is the primary treatment for persistent elevation of GH after surgery for acromegaly
2. higher total dose leads to faster hormone decline
3. radiosurgery compared to fractionated treatment leads to faster hormone decline
4. all of these
5. none of these



Surveillance	Surgery
Radiotherapy	Medical therapy

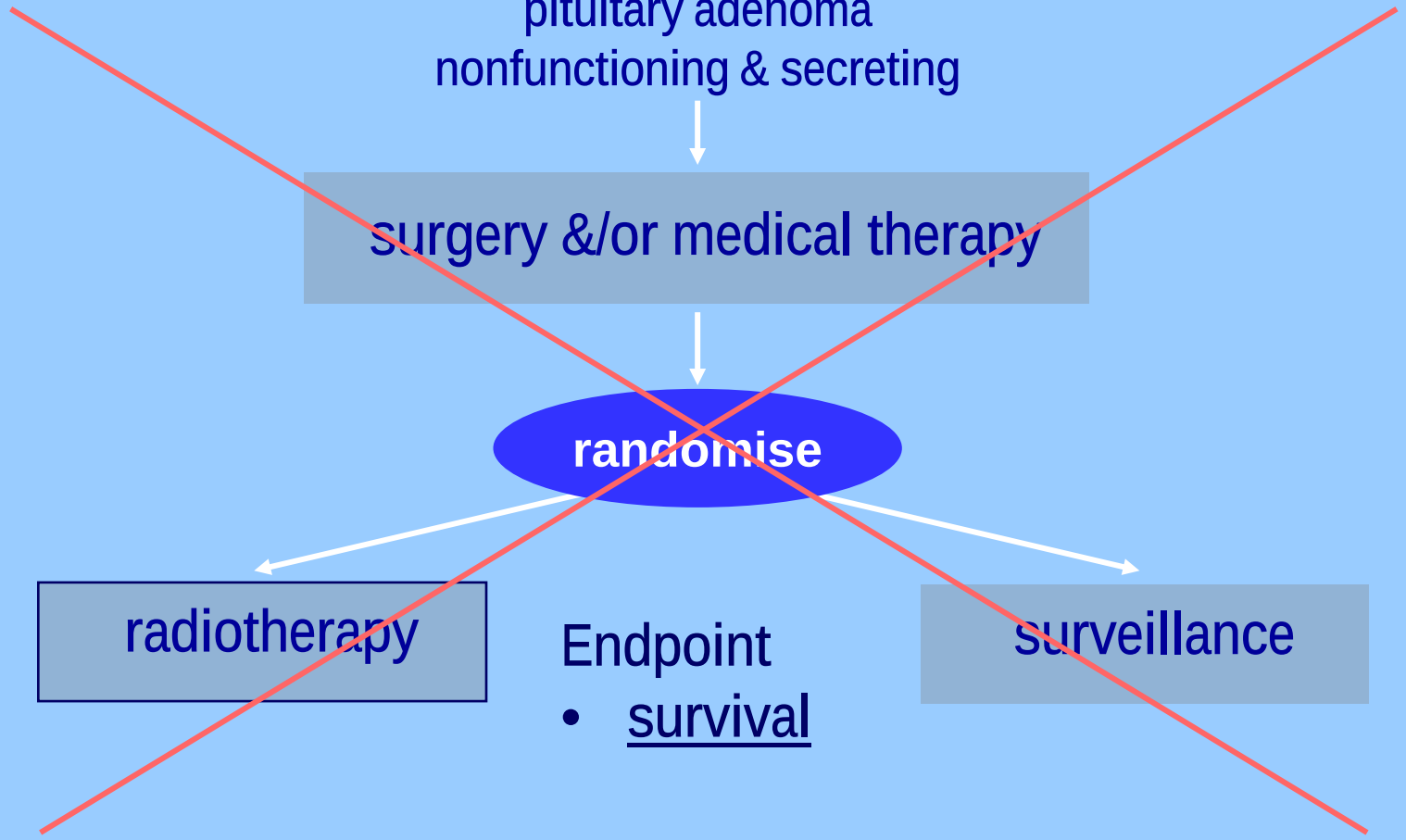
Management options in pituitary adenoma



Surveillance	Surgery
Radiotherapy	Medical therapy

Management options in pituitary adenoma

Benefit of radiotherapy

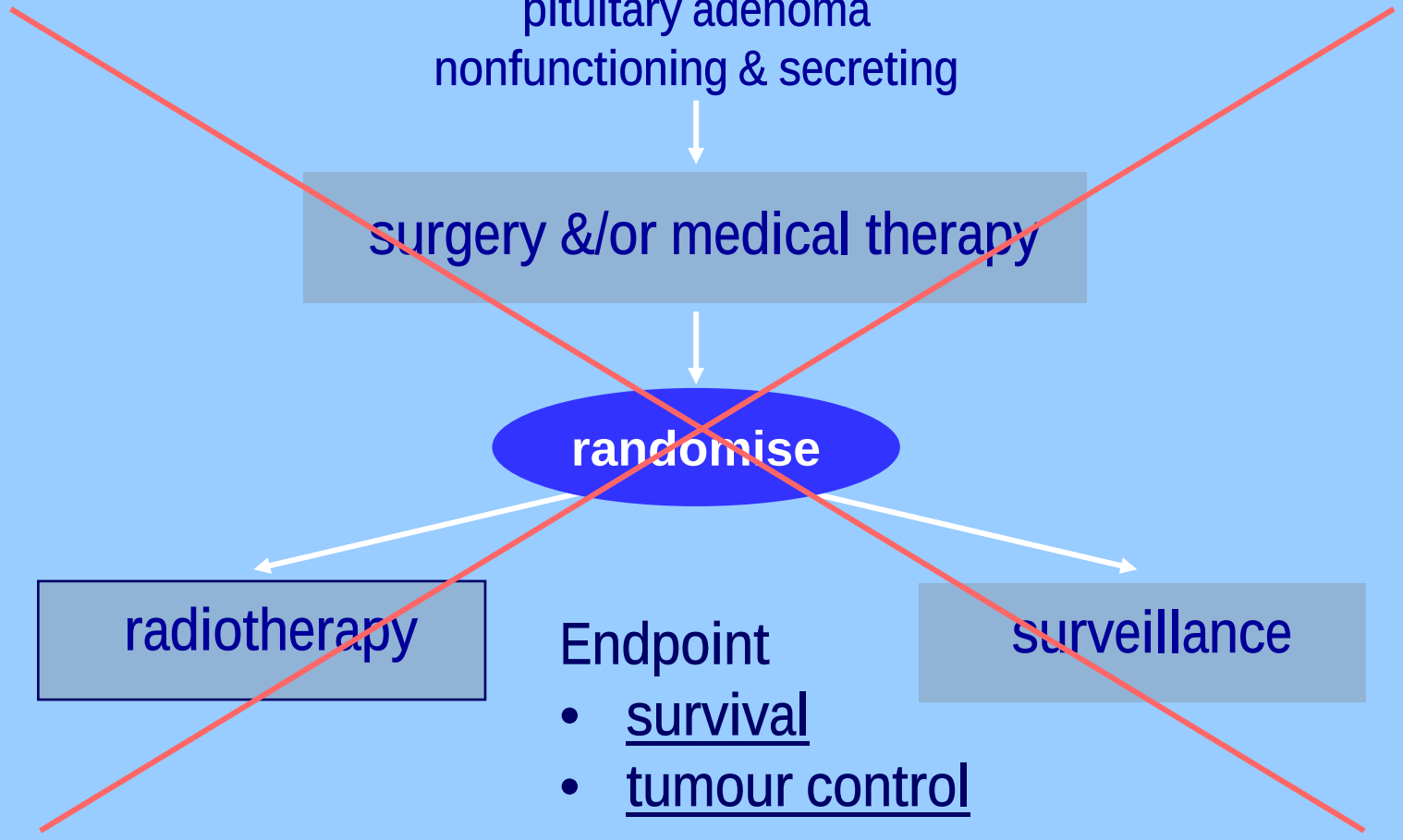


Endpoint

- survival

Radiation for pituitary adenoma

Benefit of radiotherapy

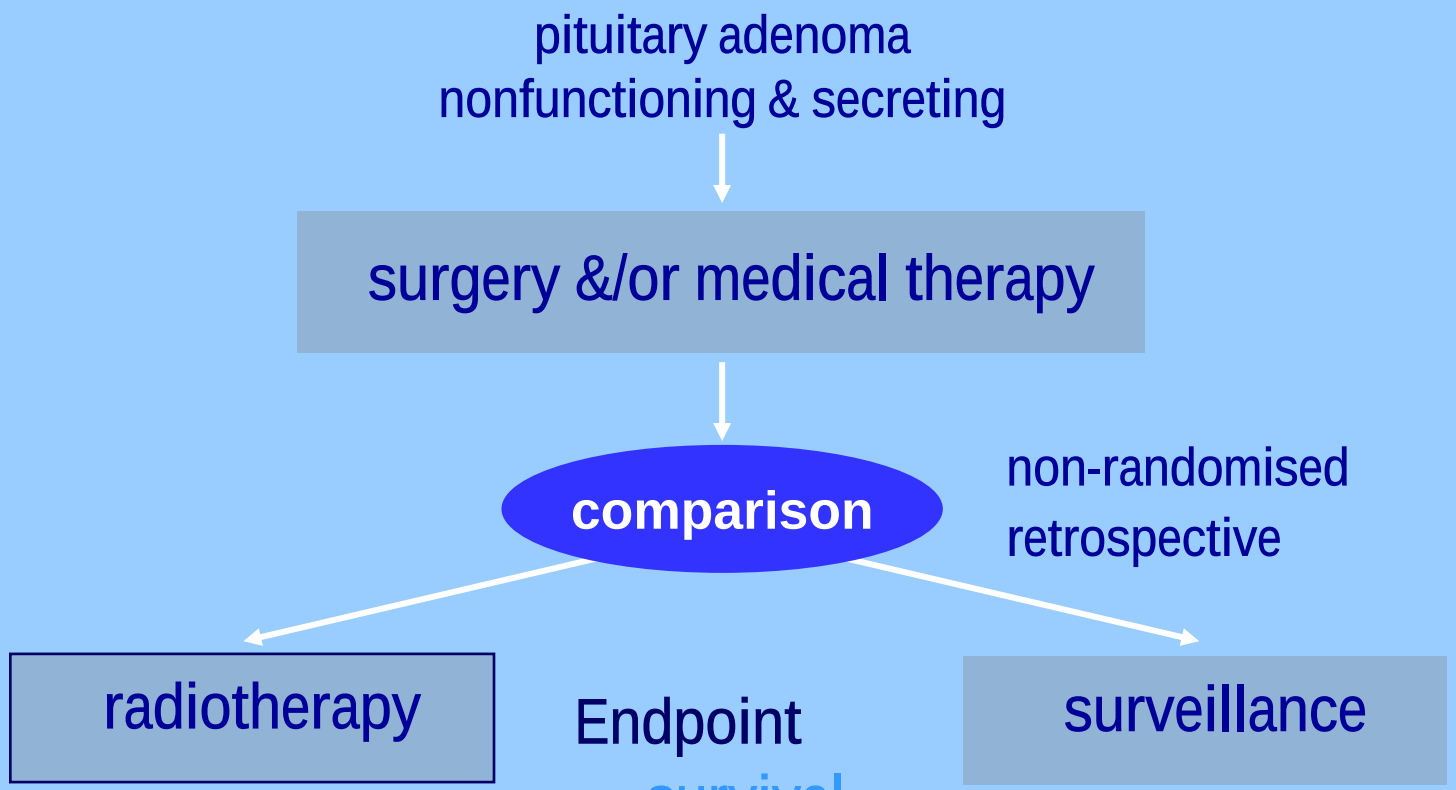


Endpoint

- survival
- tumour control

Radiation for pituitary adenoma

Benefit of radiotherapy

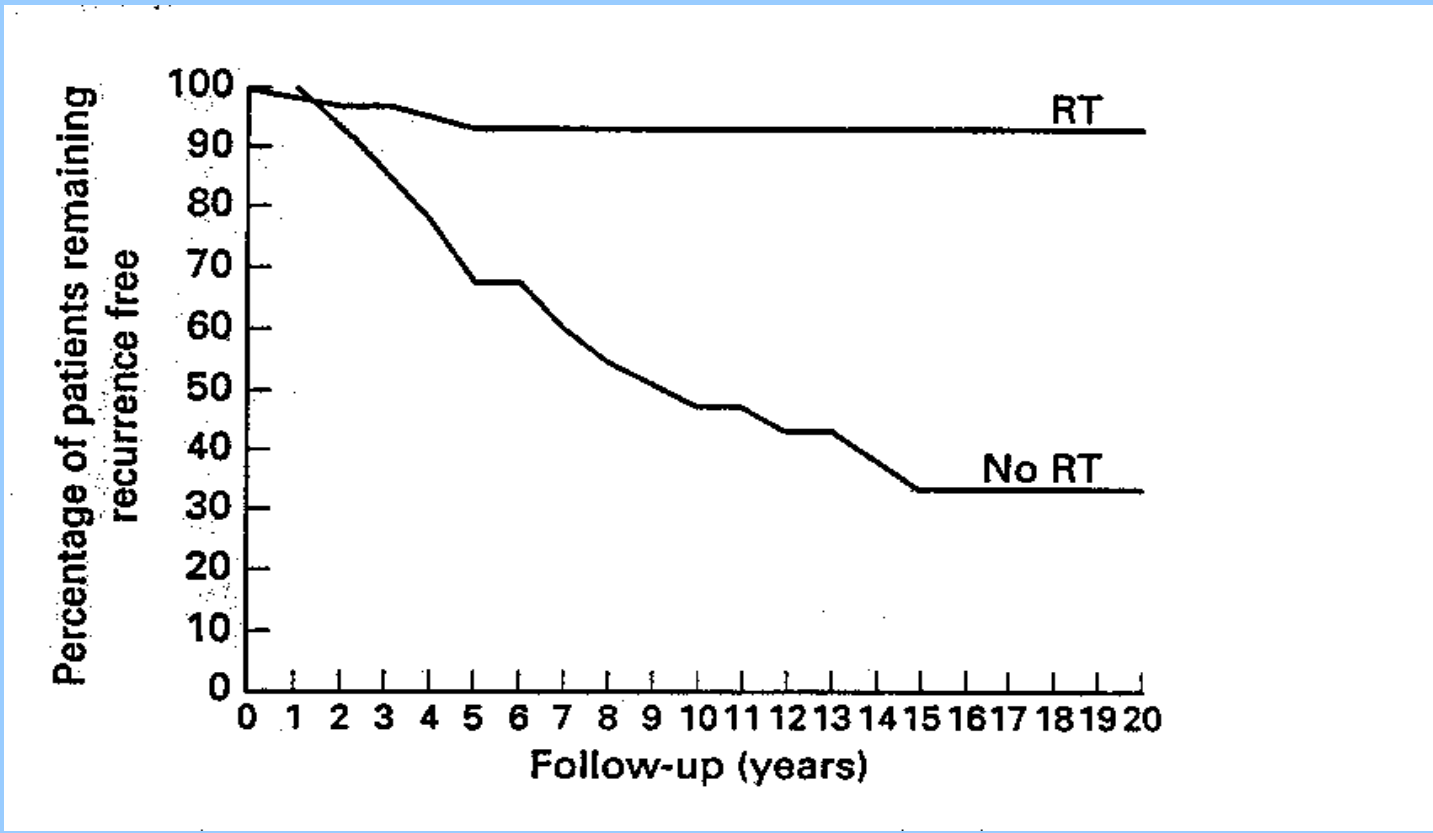


Endpoint

- survival
- tumour control

Radiation for pituitary adenoma

Progression after surgery

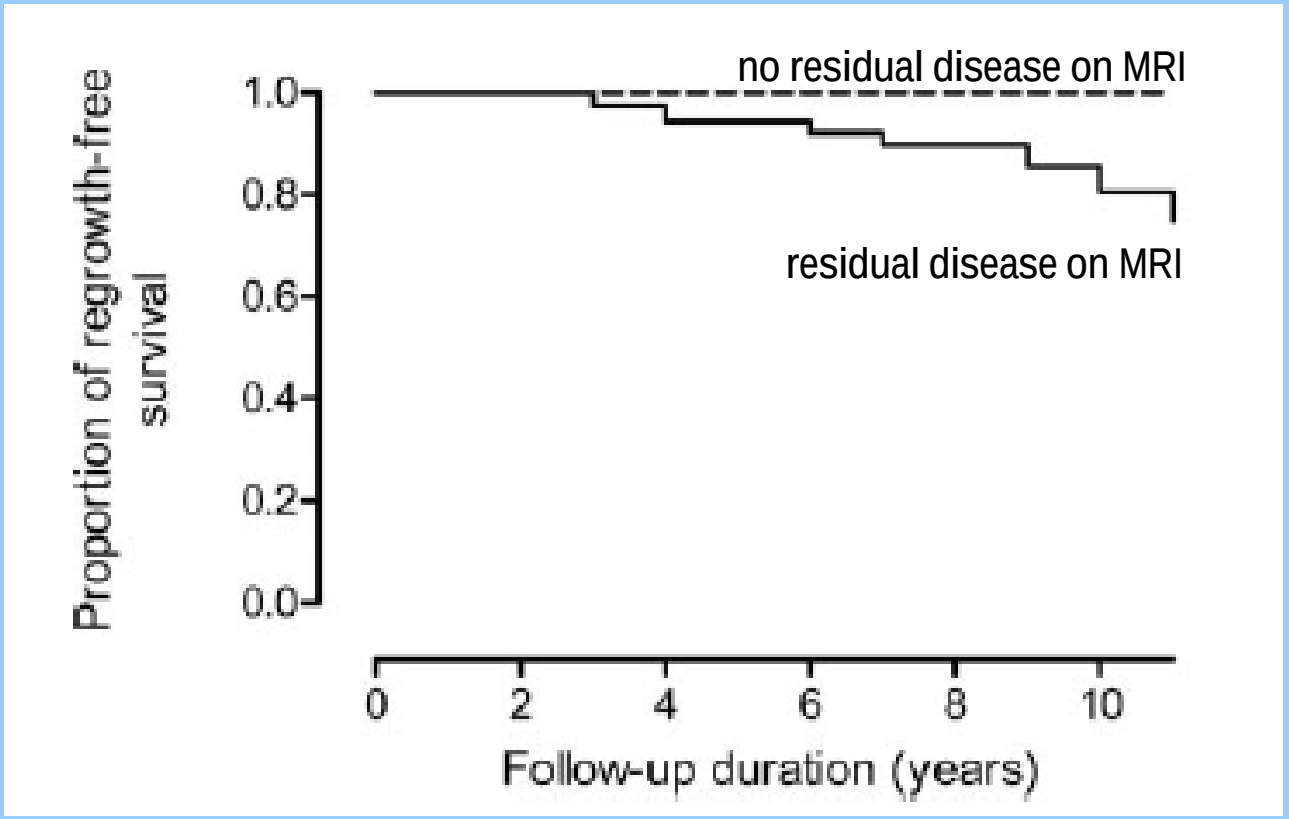


2 centre policy (non-randomized), 126 patients

Residual pituitary adenoma

Gittoes et al 1998

Progression after surgery

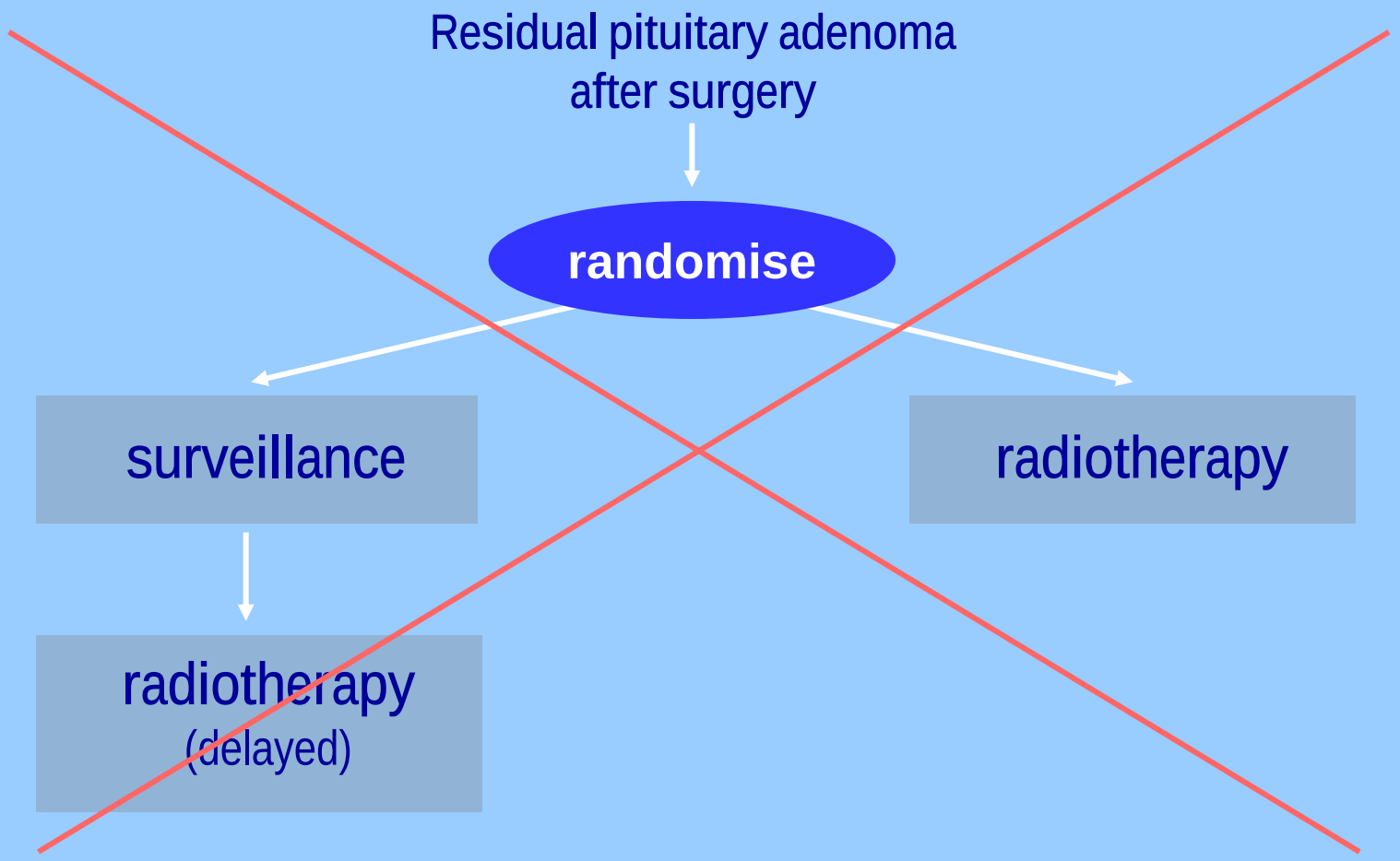


109 pts with non-functioning adenoma, median FU 6 years

Residual pituitary adenoma

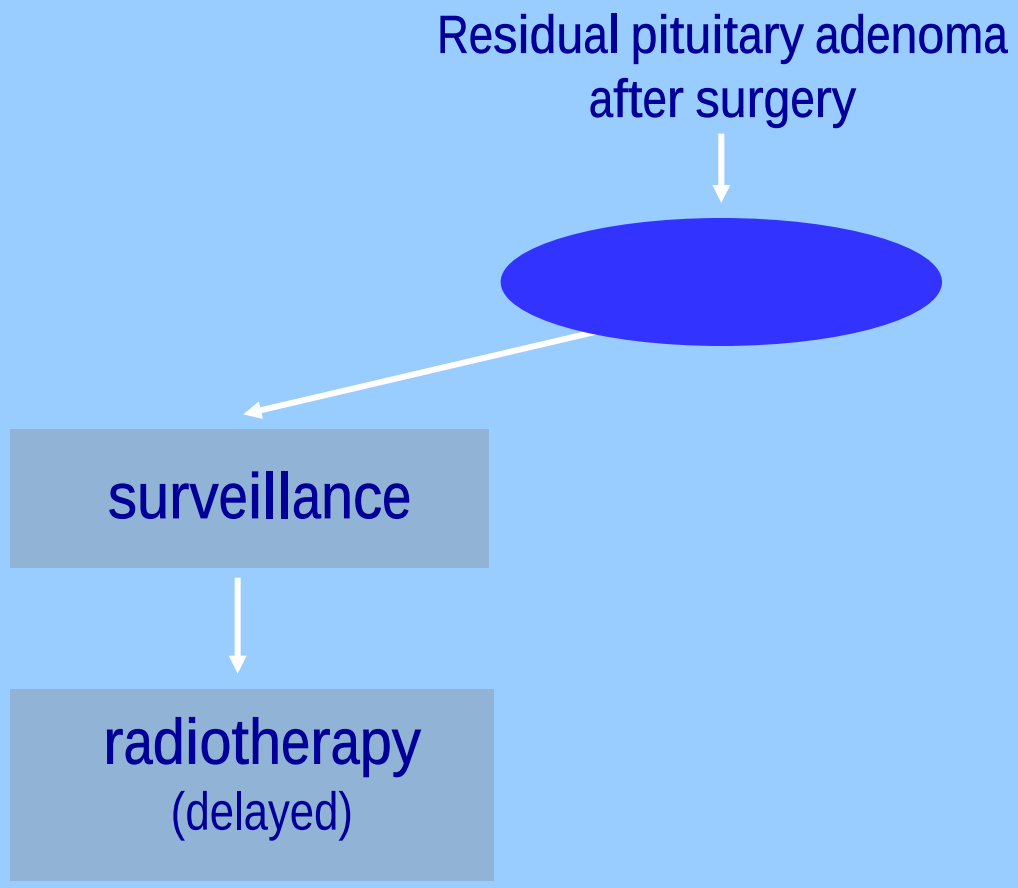
Dekkers et al 2008

Timing of radiotherapy



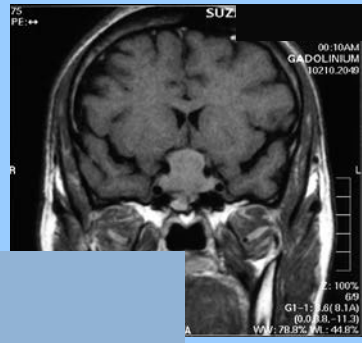
Radiation for pituitary adenoma

Timing of radiotherapy



Radiation for pituitary adenoma

Indications for radiotherapy

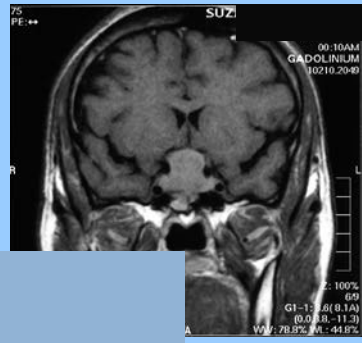


Non-functioning pituitary adenoma

- progressive tumour
- following primary surgery
- presumed threat to function

Management options in pituitary adenoma

Indications for radiotherapy



Non-functioning pituitary adenoma

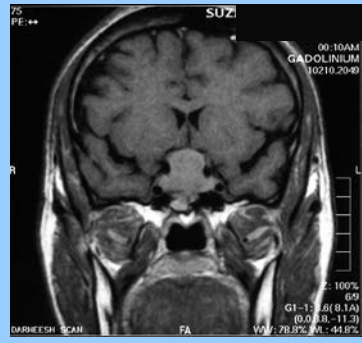
- progressive tumour
- following primary surgery
- presumed threat to function

Hormone secreting pituitary adenoma

- persistent hormone elevation after surgery
- to withdraw medical treatment

Management options in pituitary adenoma

Pituitary adenoma



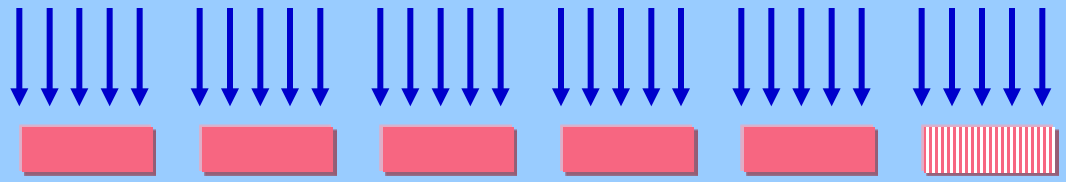
Efficacy

- Actuarial tumour control
- Endocrine control

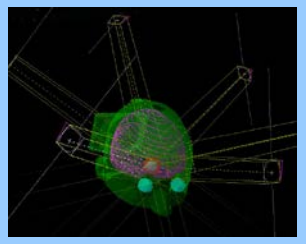
Toxicity

Endpoints in the evaluation of irradiation

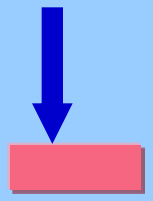
Fractionated high precision conformal radiotherapy



45 – 50 Gy in 25 - 30 fractions



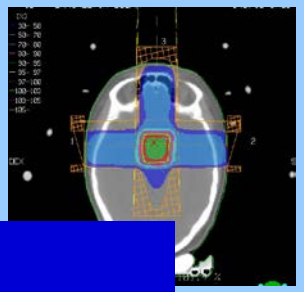
Single fraction radiosurgery

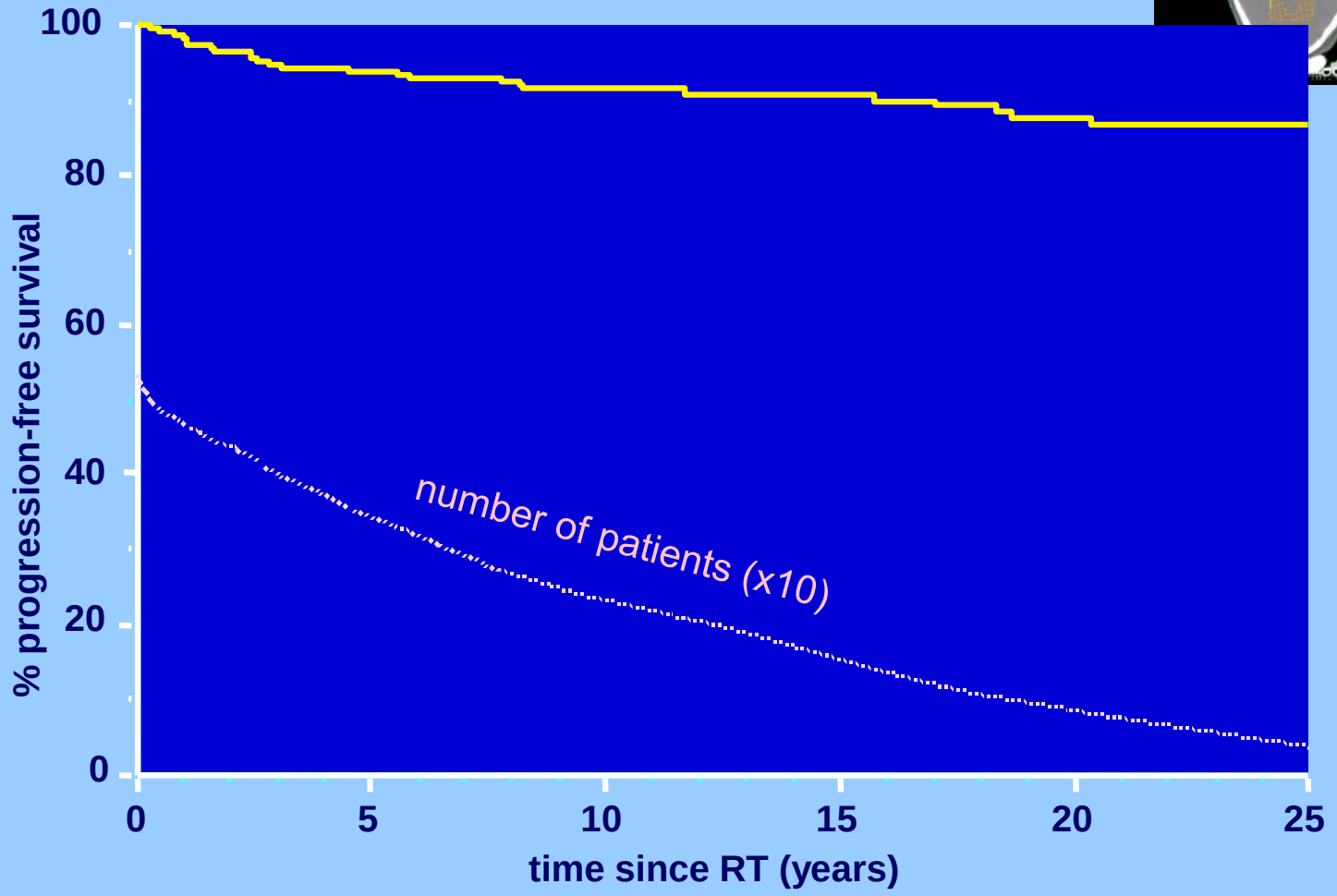


10 – 25 Gy in 1 fraction

Comparison of high precision techniques

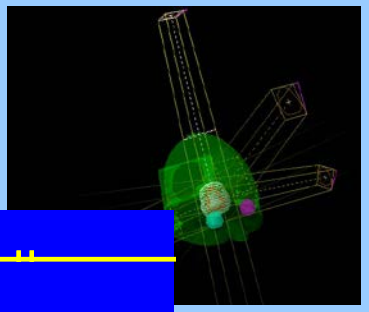
Tumour control

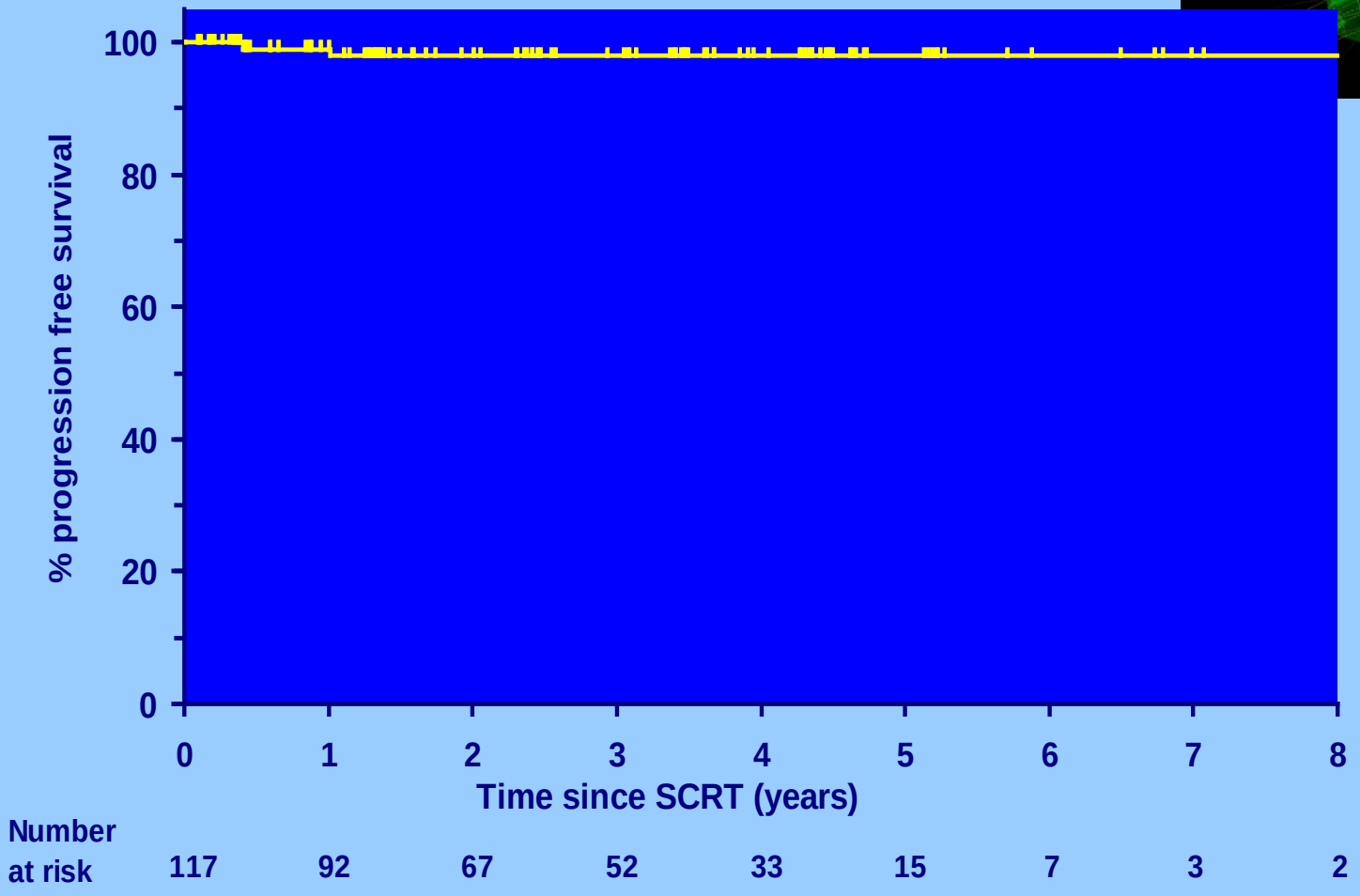




Conventional radiotherapy

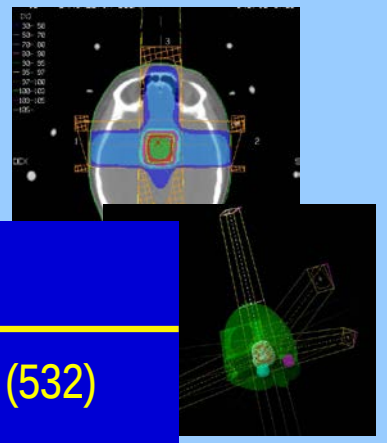
Tumour control

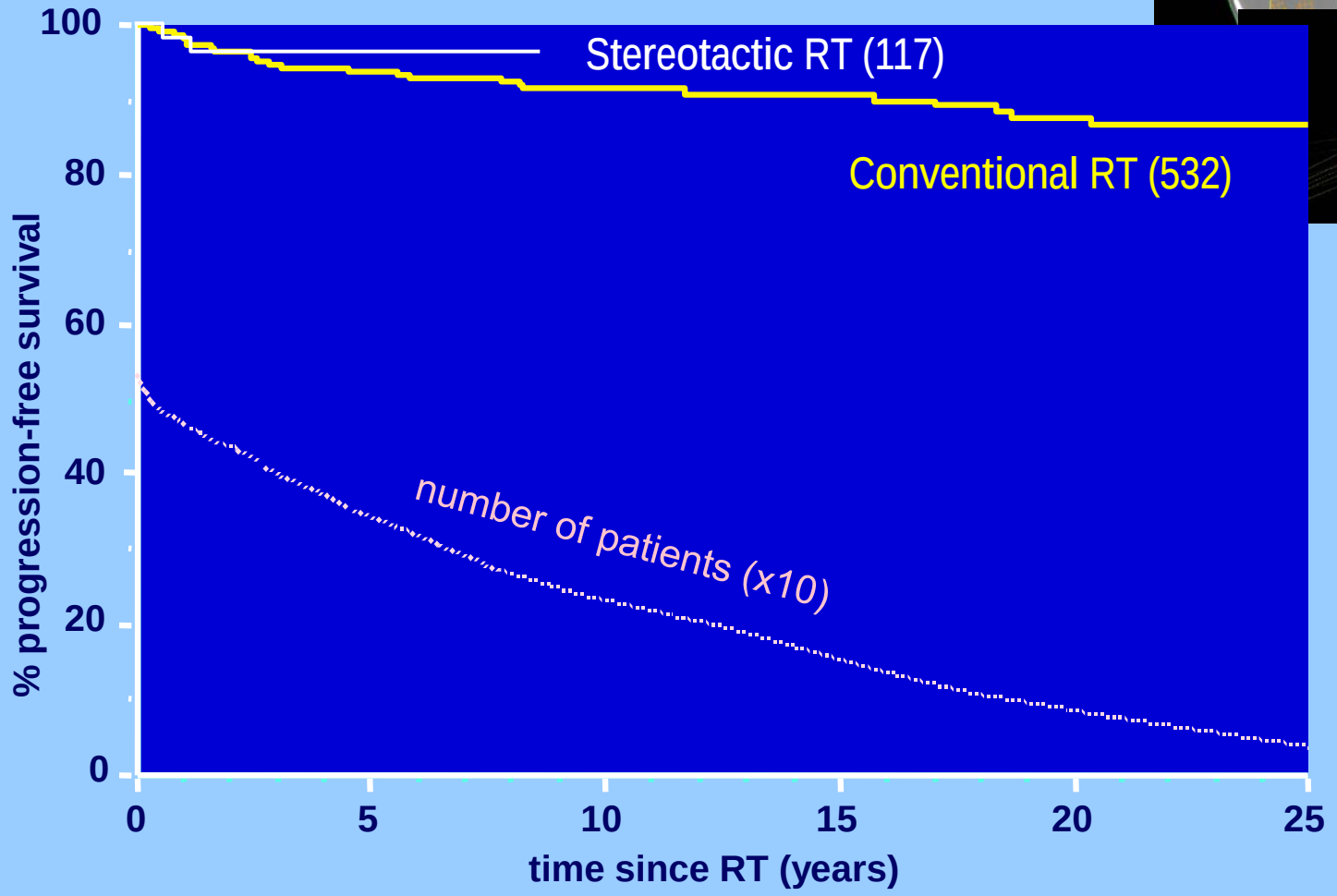




Fractionated stereotactic radiotherapy (SCRT)

Tumour control





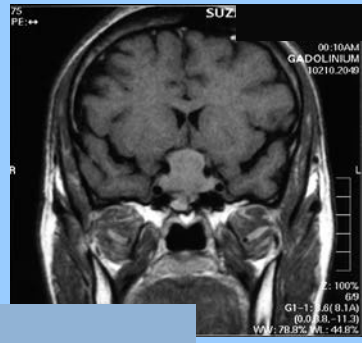
Conventional & stereotactic radiotherapy

Systematic review of published literature

Nonfunctioning pit. adenoma	Number of patients	5 year PFS
Weighted mean	393	92%

Gamma knife radiosurgery in nonfunctioning p.a.

Brada & Jankowska
Endocrinol Metab Clin N Am 37 (2008) 263–275



Pituitary adenoma

Efficacy

- Actuarial tumour control
- Endocrine control

Toxicity

Stereotactic radiotherapy similar to conventional RT

GK radiosurgery worse than fractionated RT

Endpoints in the evaluation of irradiation

Pituitary adenoma

Efficacy

- Actuarial tumour control
- Endocrine control

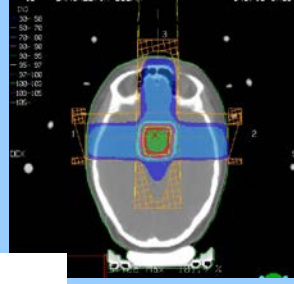
Toxicity

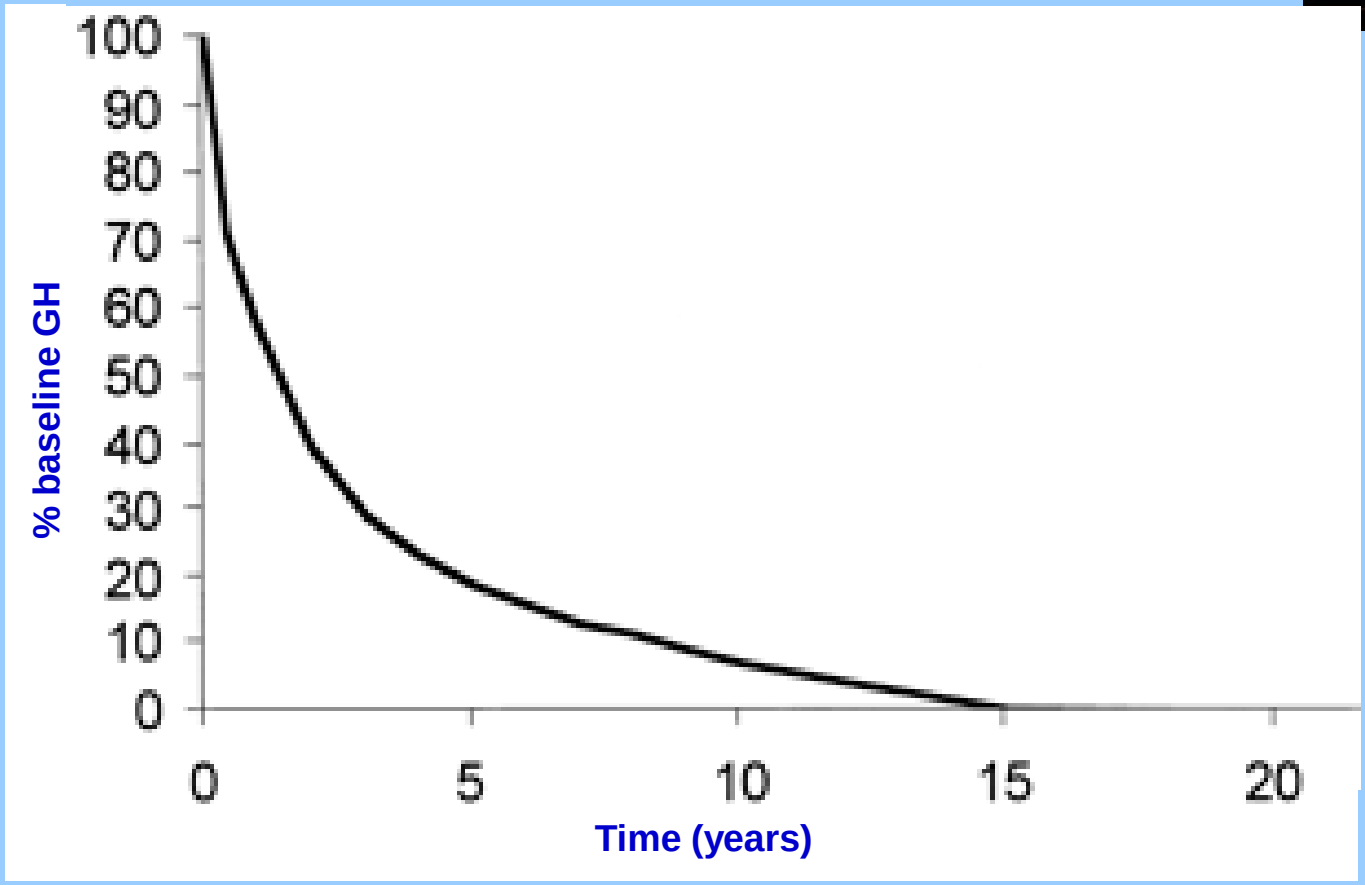
Endpoints in the evaluation of irradiation

The best measure for assessing effectiveness of different forms of radiotherapy in a cohort of patients with acromegaly is

1. median time to normalisation of GH
   (time when half of the patients achieve normal GH)
2. median time to normalisation of IGF-1
3. median time to halving of GH
4. tumour control at 5 years
5. all of these
6. none of these

GH control in acromegaly



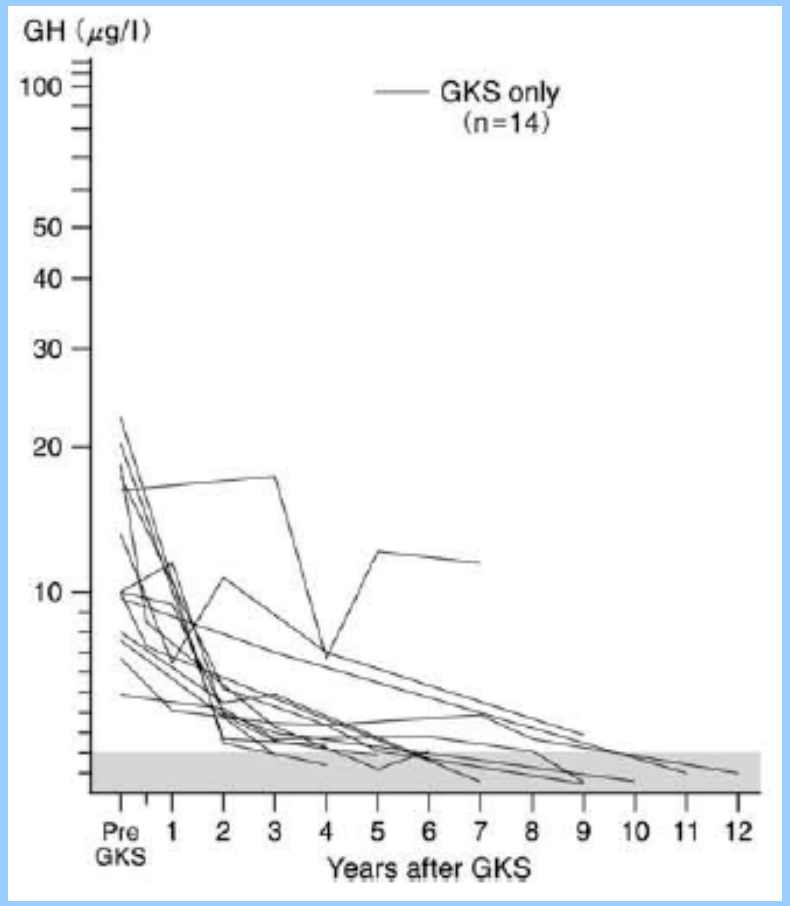


128 patients
mean FU 11 yrs

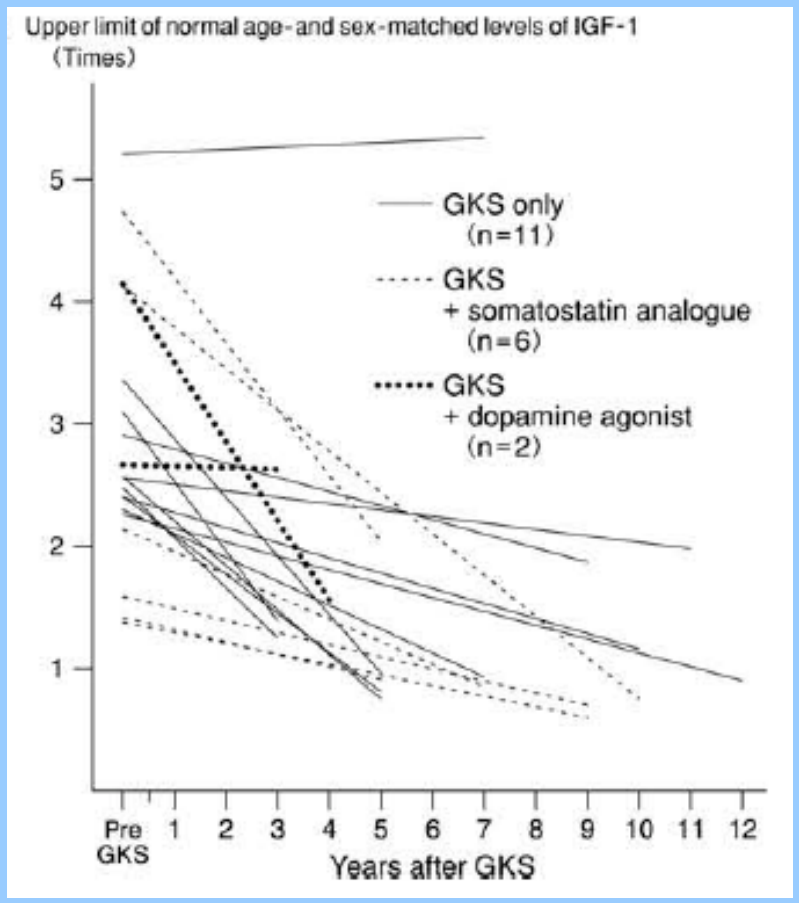
Conventional radiotherapy for acromegaly

Barrande et al 2000

GH & IGF1 control in acromegaly



GH



IGF-1

GK radiosurgery for acromegaly

Iwai et al 2010

Pituitary adenoma

Efficacy

- Actuarial tumour control
- Endocrine control

Toxicity

Stereotactic radiotherapy similar to conventional RT

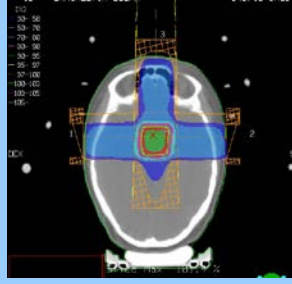
GK radiosurgery no better than fractionated RT

Endpoints in the evaluation of irradiation

Pituitary adenoma

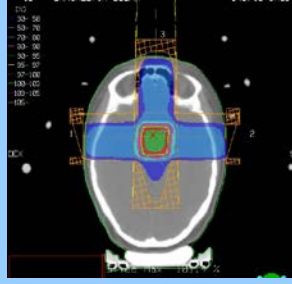
- Efficacy
  - Actuarial tumour control
  - Endocrine control
- Toxicity

Endpoints in the evaluation of irradiation



Toxicity

- Neurological damage
  - Vision
  - Temporal lobe damage
  - Cognitive function
- Endocrine failure
- Second malignancy
- Cerebrovascular accident (CVA)



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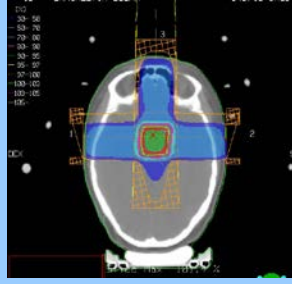

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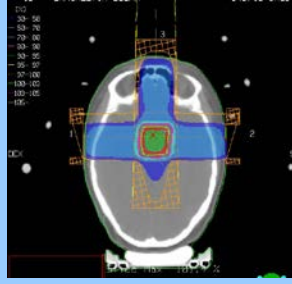

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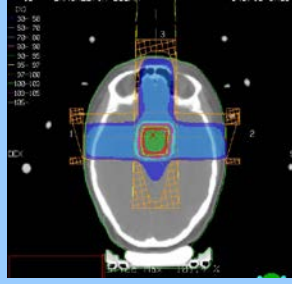
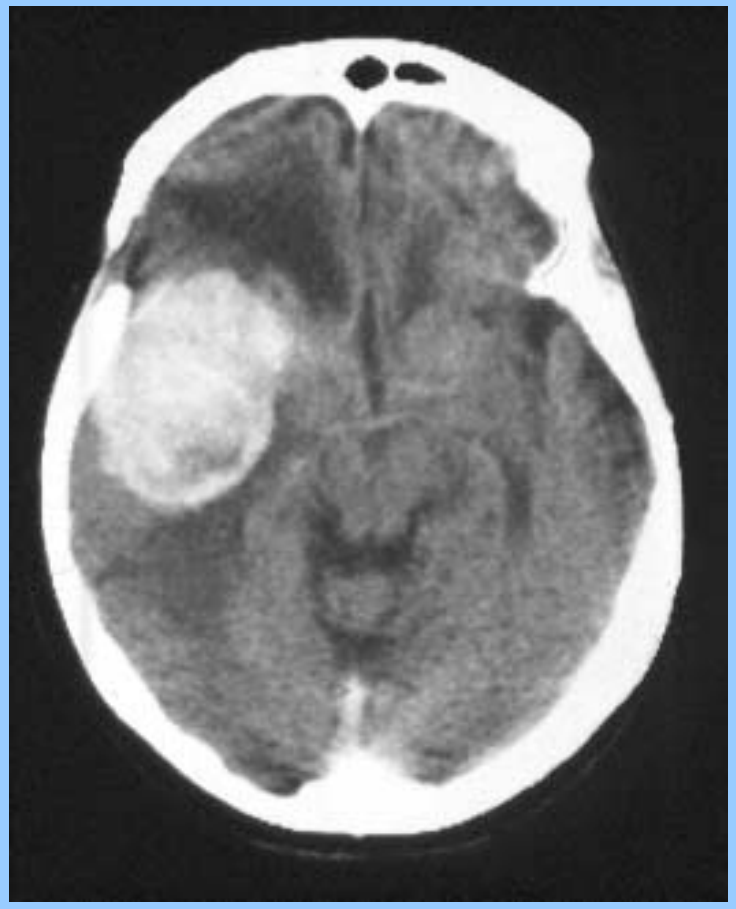
- Second malignancy
- Cerebrovascular accident (CVA)

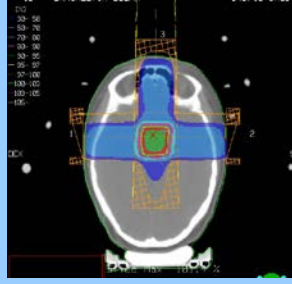


Toxicity

- Neurological damage
  - Vision
  - Temporal lobe damage
  - Cognitive function
- Endocrine failure
- Second malignancy
- Cerebrovascular accident (CVA)

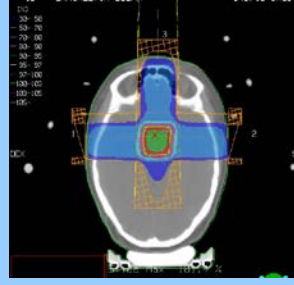
Radiation induced second malignancy

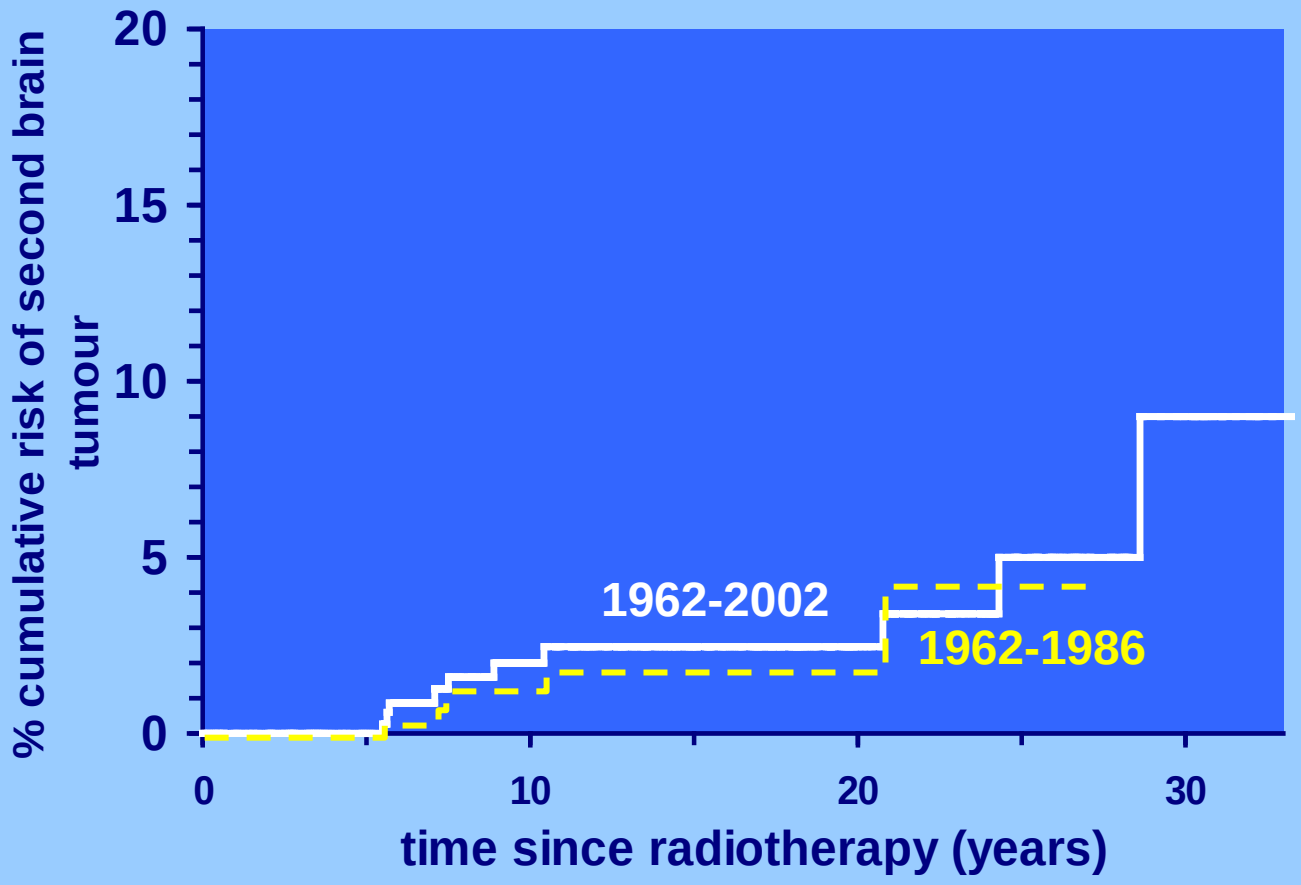




Radiotherapy for pituitary adenoma

Radiation induced second malignancy

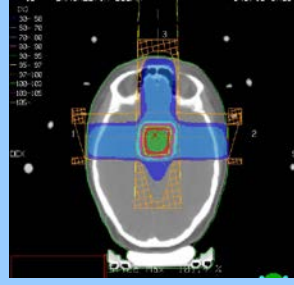


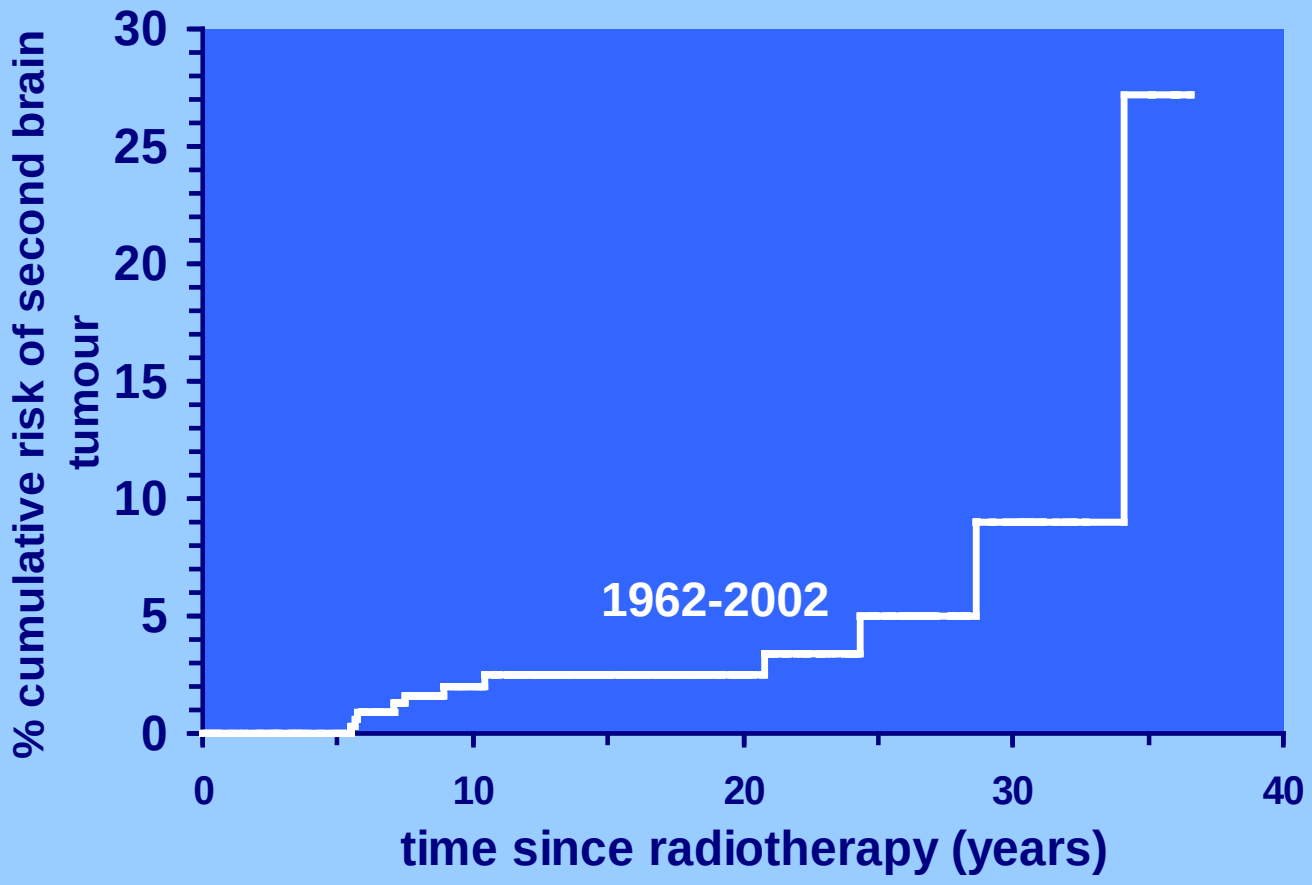


Radiotherapy for pituitary adenoma

Brada et al 1992
Minniti et al 2005

Radiation induced second malignancy

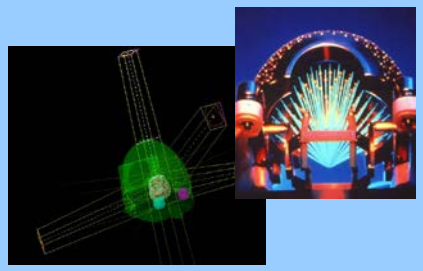




Radiotherapy for pituitary adenoma

Brada et al 1992
Minniti et al 2005

Toxicity of new techniques



- Neurological damage
  - Vision
  - Temporal lobe damage
  - Cognitive function
- Endocrine failure
- Second malignancy
- Cerebrovascular accident (CVA)

High precision RT & radiosurgery for pituitary adenoma

Efficacy

- Actuarial tumour control
- Endocrine control

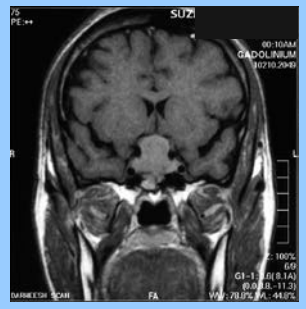
Toxicity

Stereotactic radiotherapy – potential reduction in toxicity requires long term follow up

Single fraction radiosurgery more toxic for larger tumours

Endpoints in the evaluation of irradiation

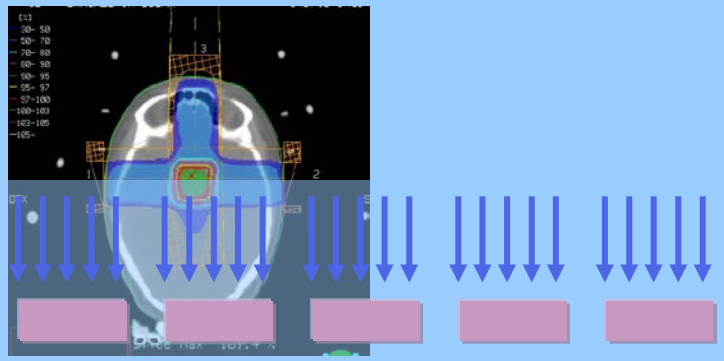
Pituitary adenoma



Efficacy
- Actuarial tumour control
- Endocrine control

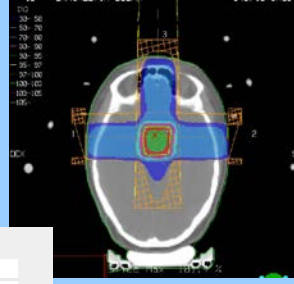
Toxicity

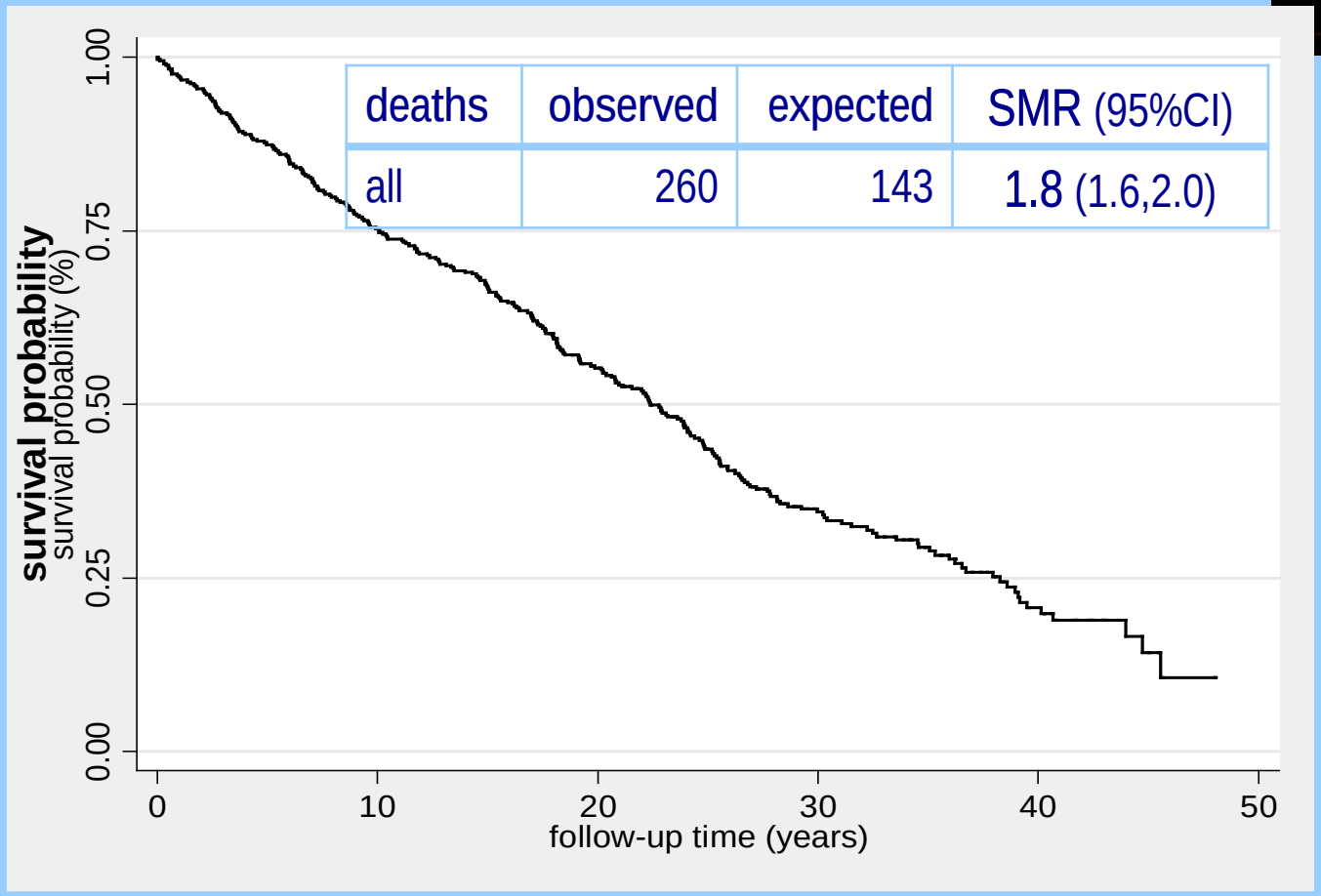
→ **survival**



Endpoints of efficacy

Risk of death as standardised mortality ratio (SMR)





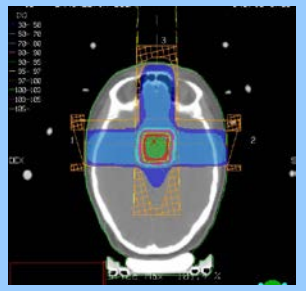
deaths	observed	expected	SMR (95%CI)
all	260	143	1.8 (1.6,2.0)

426 patients
treated 1962 - 1994

Survival following conventional radiotherapy

Brada et al 2012 unpublished

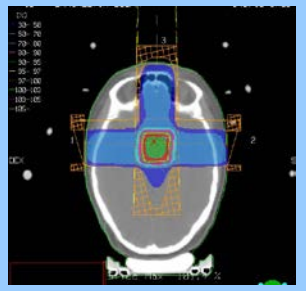
Causes of excess mortality



- disorders of pituitary
  - endocrine
  - tumour
- second brain tumours
- cerebrovascular

Pituitary adenoma

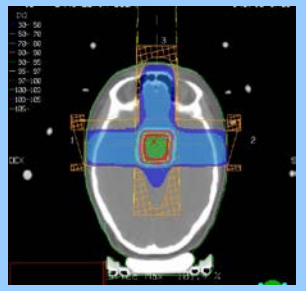
Causes of excess mortality



- disorders of pituitary
  - endocrine
  - tumour
- second brain tumours
- cerebrovascular

Pituitary adenoma

Deaths from cerebrovascular causes

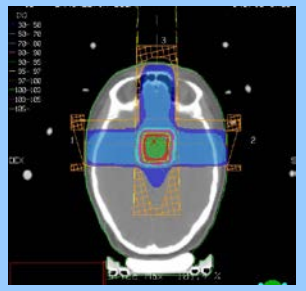


observed	33
expected	8
relative risk	4.11
95%CI	2.84-9.75

Pituitary adenoma

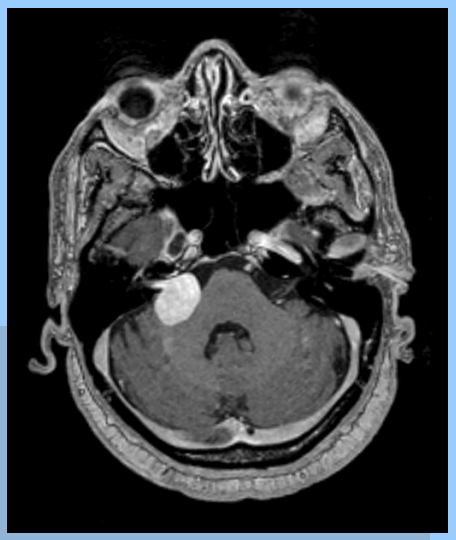
Brada et al 2002

Toxicity



- Neurological damage
  - Vision
  - Temporal lobe damage
  - Cognitive function
- Endocrine failure
- Second malignancy
- Cerebrovascular accident (CVA)

Benign brain tumours



pituitary adenoma

craniopharyngioma

acoustic neuroma

skull base meningioma

childhood low grade glioma

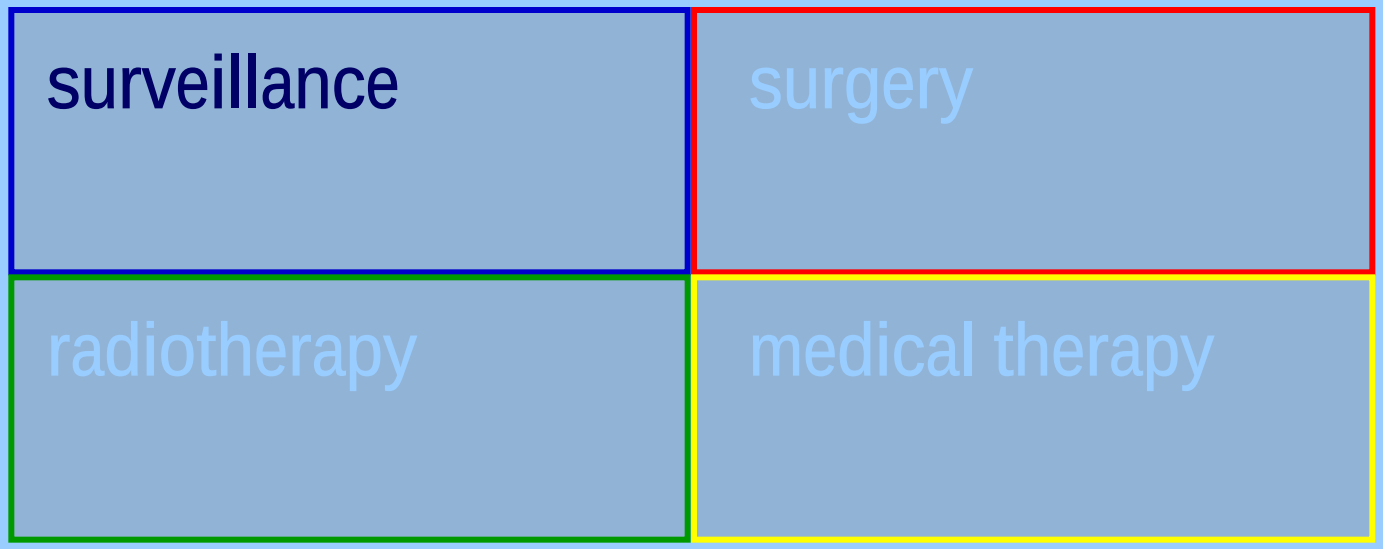
Management of benign brain tumours

Acoustic neuroma and radiotherapy

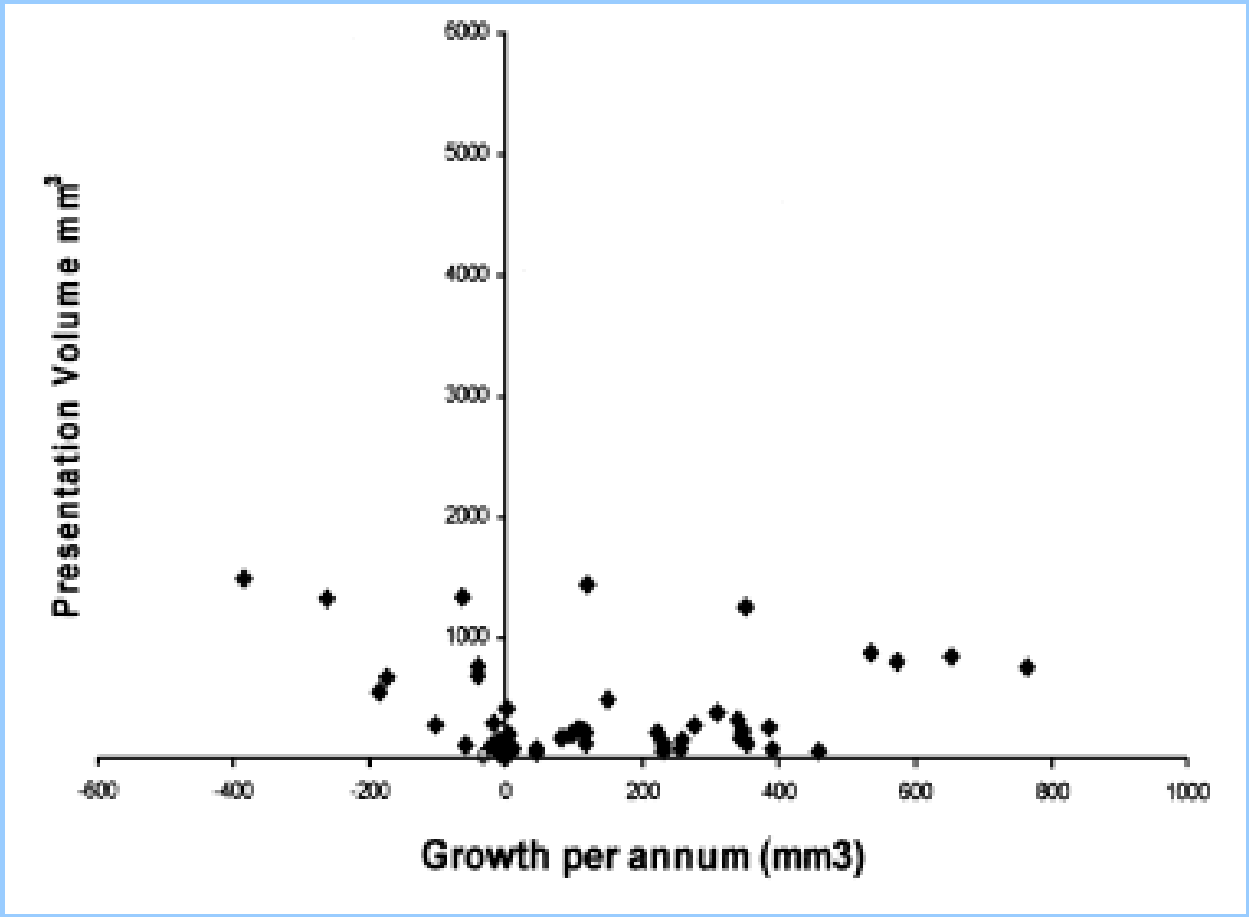
1. tumour control is dose dependent (dose/response)
2. radiotherapy can be associated with life threatening complications
3. surveillance prior to RT is associated with risk of facial palsy
4. early radiotherapy preserves hearing
5. all of these
6. none of these

surveillance	surgery
radiotherapy	medical therapy

Management options in vestibular schwannoma



Management options in vestibular schwannoma



Surveillance

Herwadker et al 2005
Manchester

patients with AN (1977 –2005)

≤ 2cm max diameter (sporadic)

	number of patients
total	1989
observation	729
at least 2 scans	552
intrameatal	230
extrameatal	322

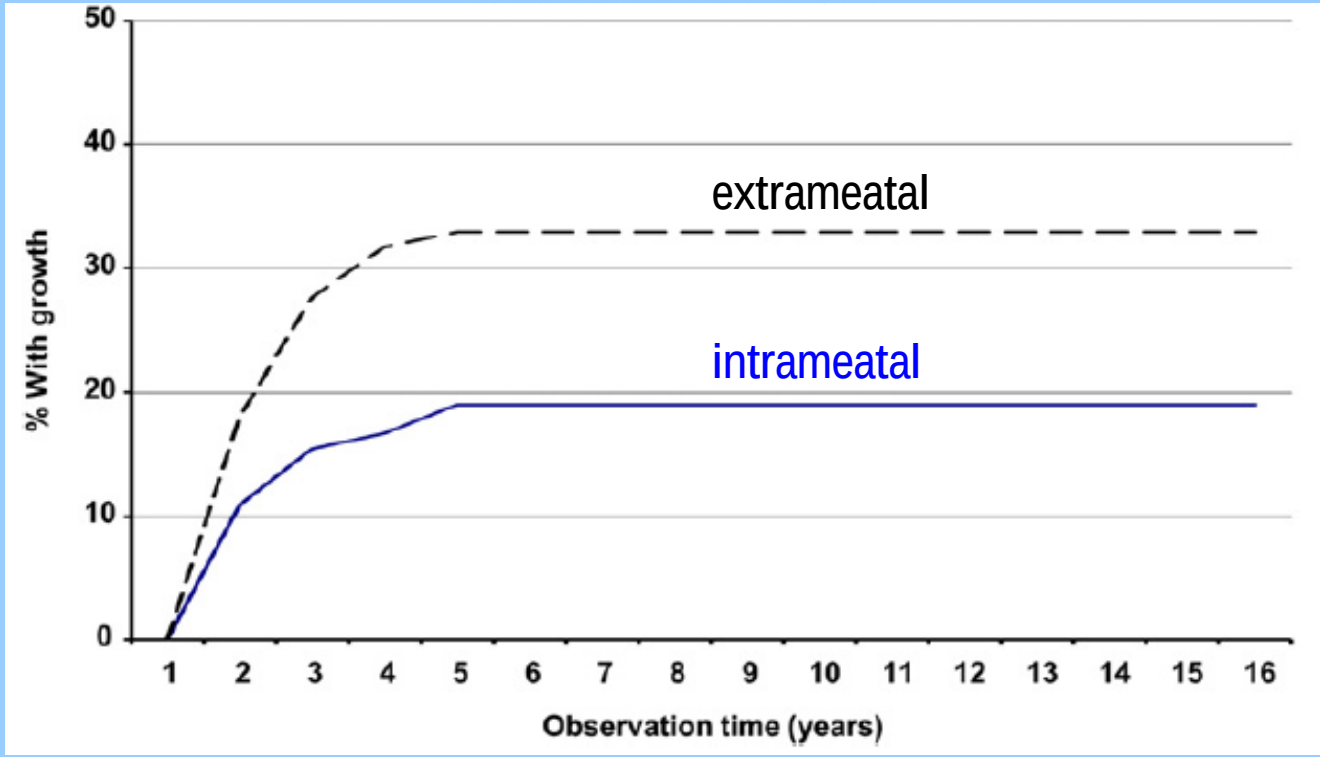
Surveillance

Stangerup et al 2006
Copenhagen

growth on surveillance

Danish cohort

AN ≤ 2cm max diameter (sporadic)



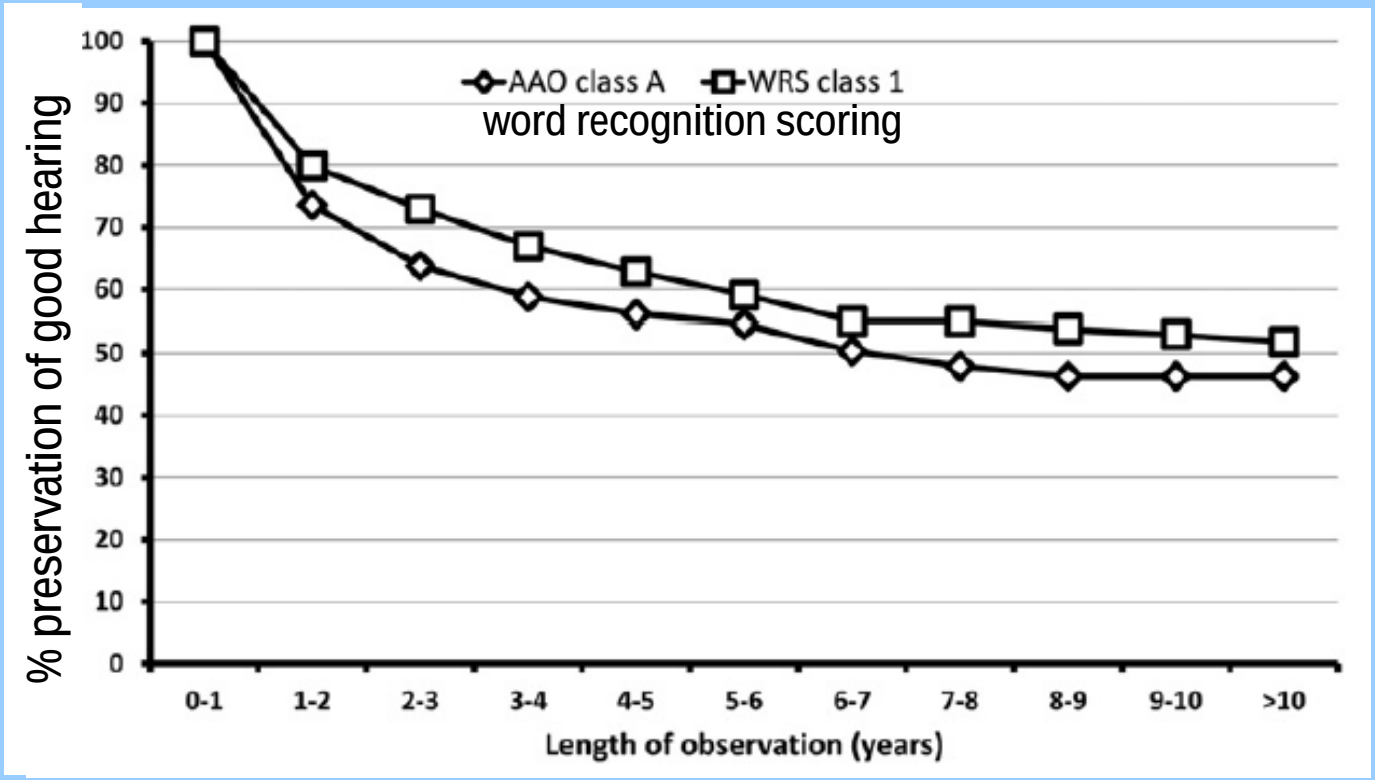
Surveillance

Stangerup et al 2012
Copenhagen

hearing loss on surveillance

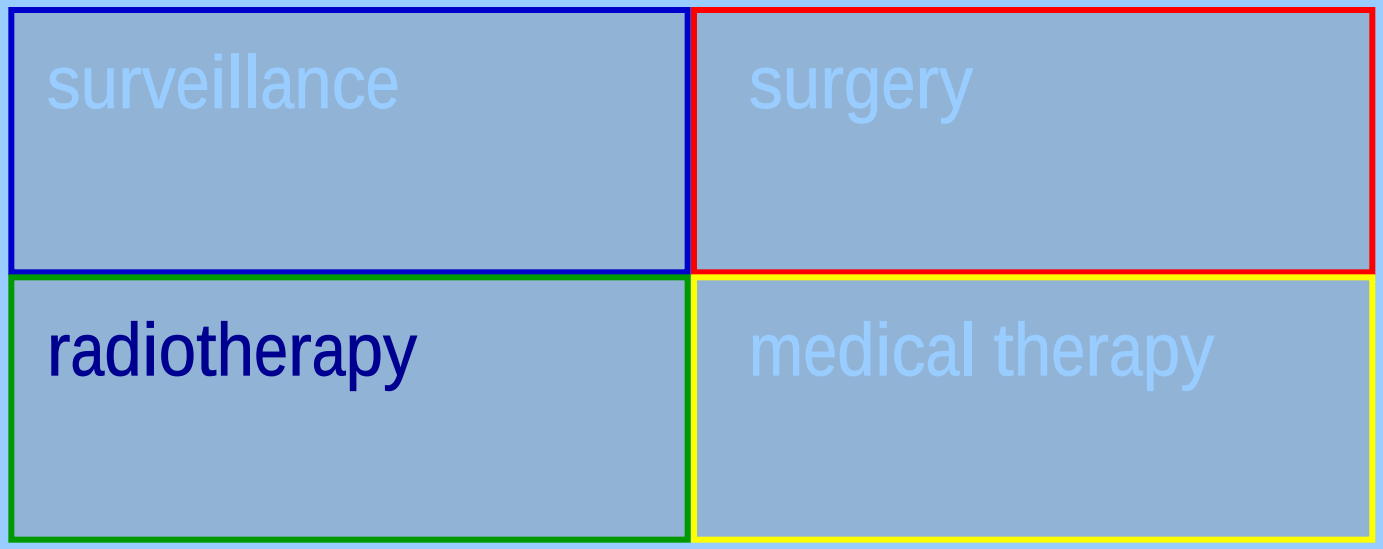
Danish cohort

AN ≤ 2cm max diameter (sporadic)



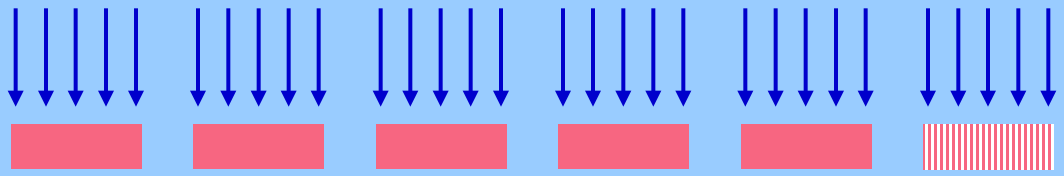
Surveillance

Stangerup et al 2012
Copenhagen



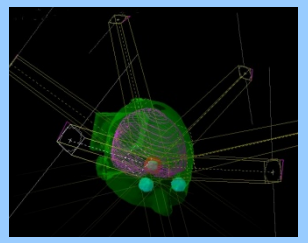
Management options in vestibular schwannoma

Fractionated “stereotactic” radiotherapy

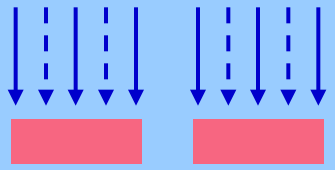


fractions
weeks

45 - 50Gy in 25 - 30 fractions

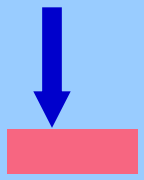


Hypofractionated “stereotactic” radiotherapy



20 - 30Gy in 6 - 10 fractions

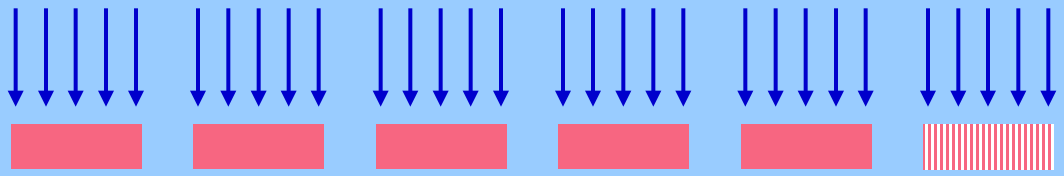
Single fraction radiosurgery



10 - 25Gy in 1 fraction

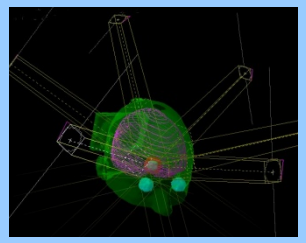
Fractionation in high precision radiotherapy

Fractionated “stereotactic” radiotherapy

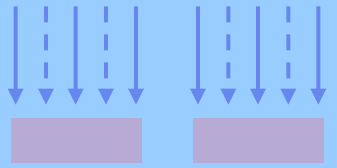


fractions
weeks

45 - 50Gy in 25 - 30 fractions

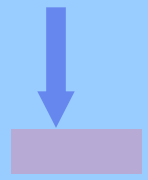


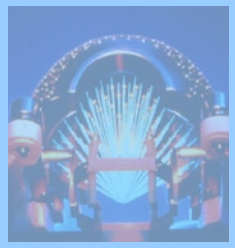
Hypofractionated “stereotactic” radiotherapy



20 - 30Gy in 6 - 10 fractions

Single fraction radiosurgery

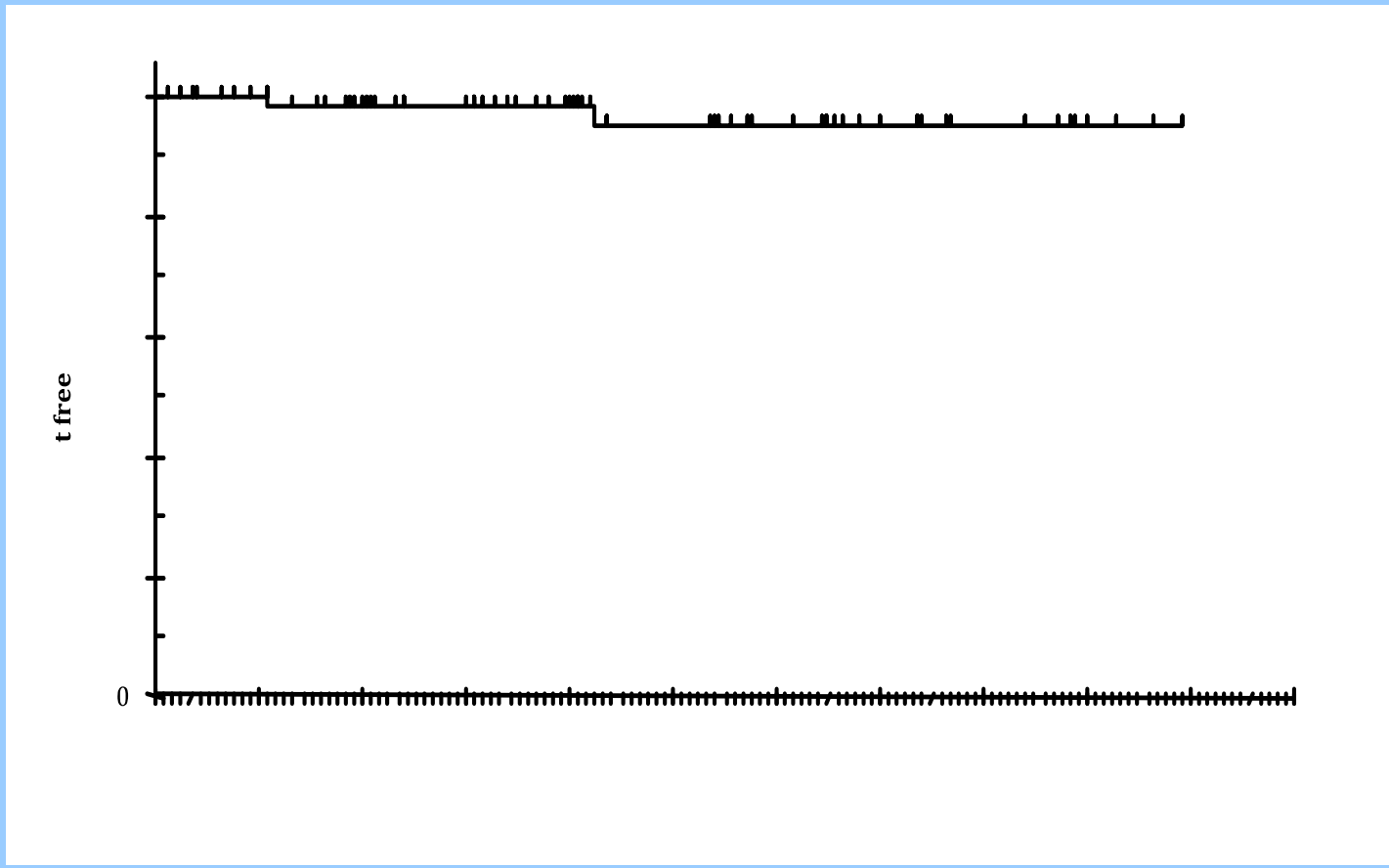




10 - 25Gy in 1 fraction

Fractionation in high precision radiotherapy

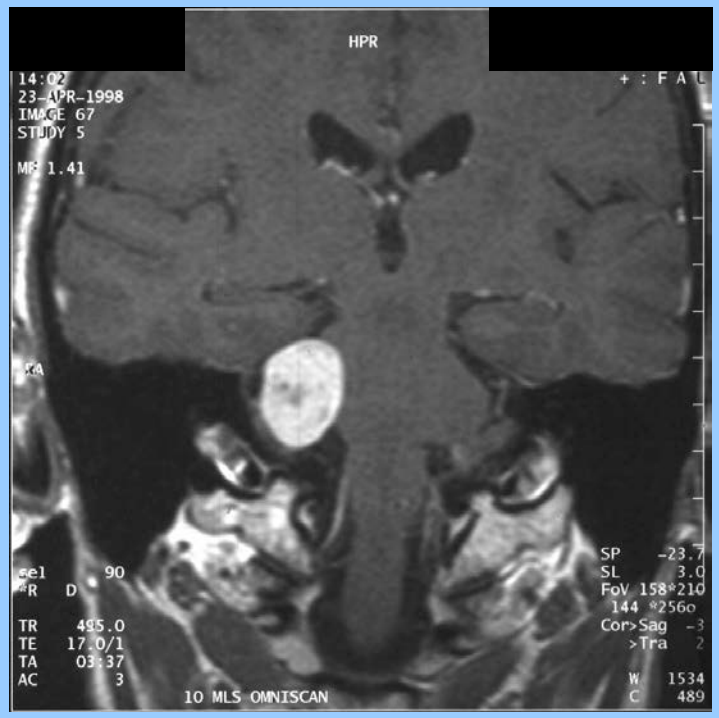
Tumour control



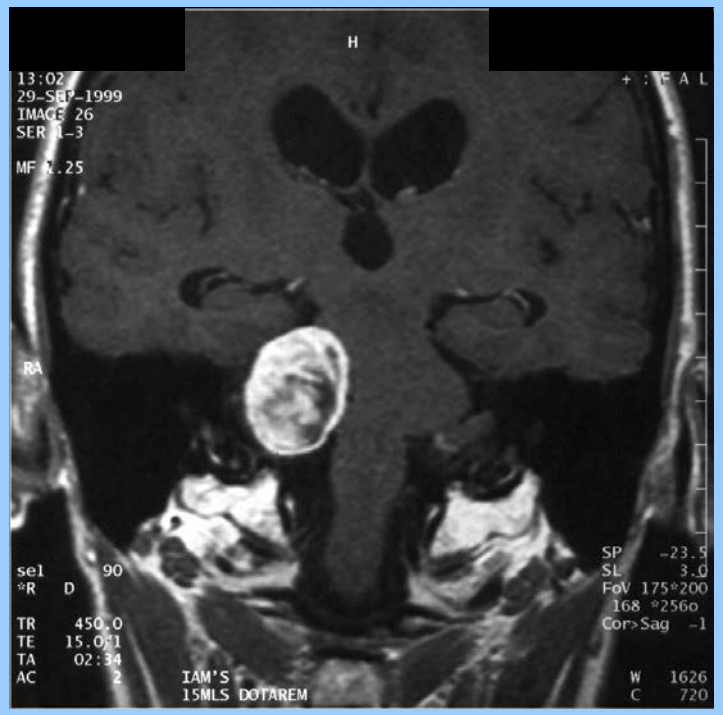
Powell et al 2010 IJROBP
72 patients with acoustic neuroma
Royal Marsden Hospital

Stereotactic RT for acoustic neuroma

Transient enlargement & hydrocephalus



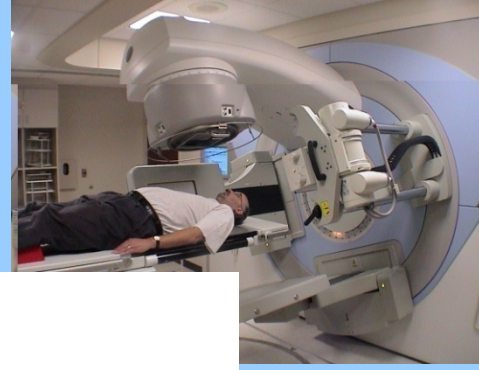
23/4/1998

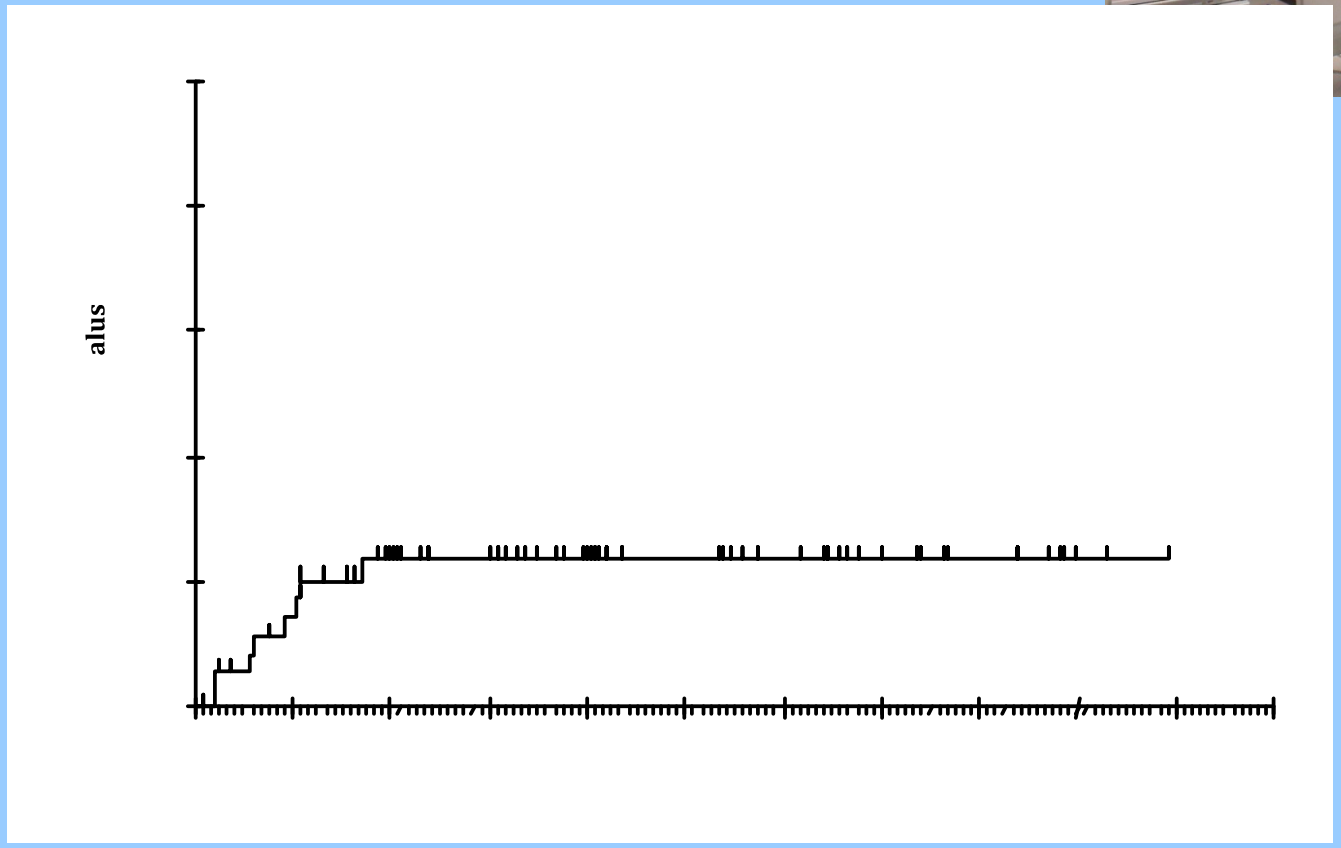


29/9/1999

Stereotactic RT for acoustic neuroma

Incidence of hydrocephalus





Powell et al 2010 IJROBP
72 patients with acoustic neuroma
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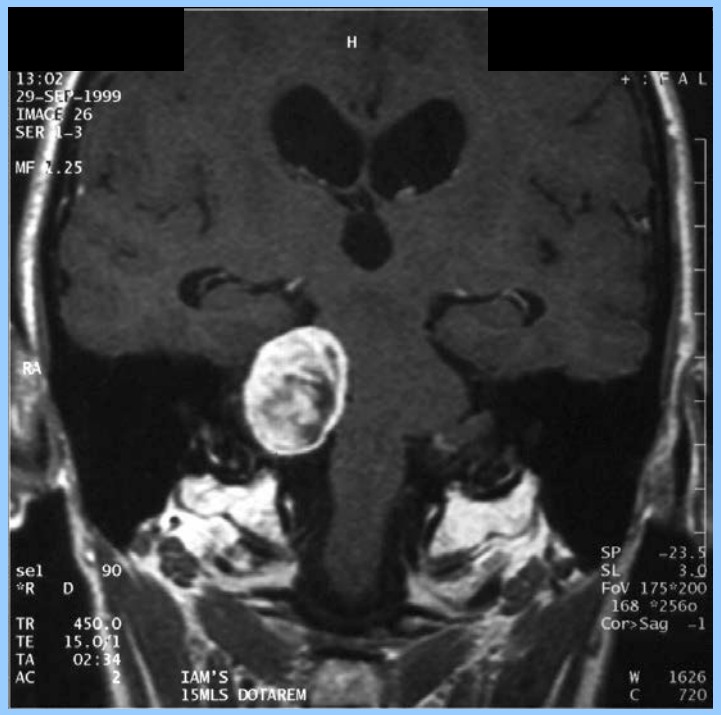
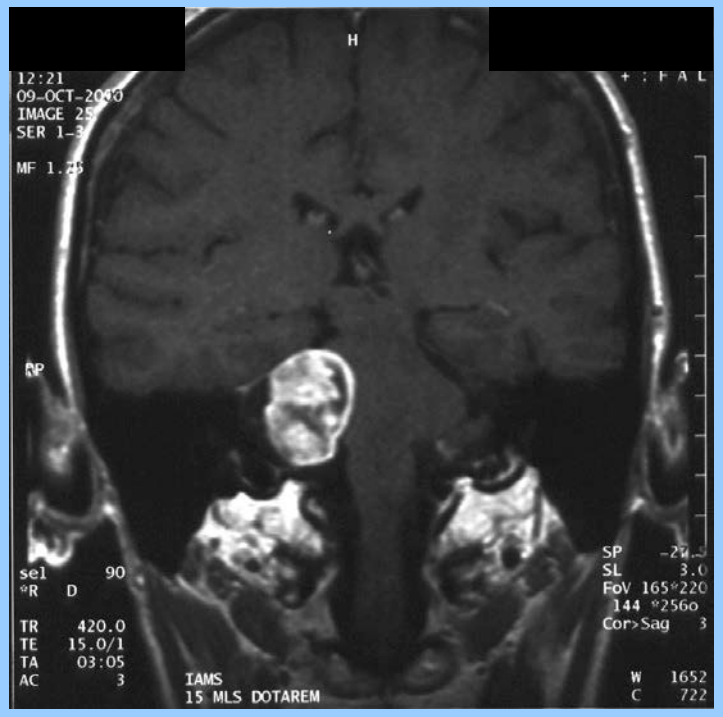
Stereotactic RT for acoustic neuroma

Transient enlargement resolution



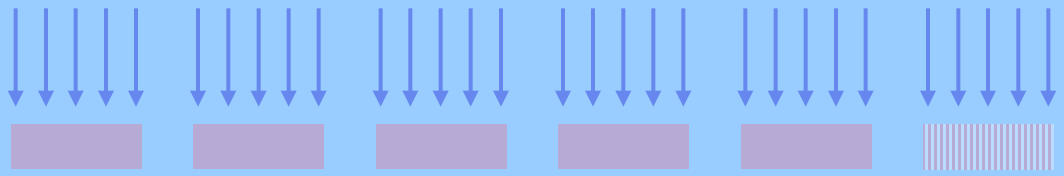
29/9/1999



9/10/2000

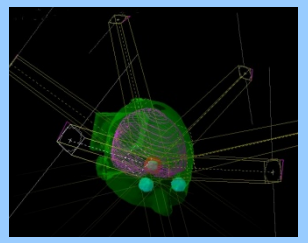
Stereotactic RT for acoustic neuroma

Fractionated “stereotactic” radiotherapy

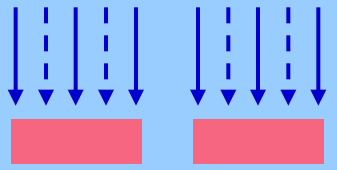


45 - 50Gy in 25 - 30 fractions

fractions
weeks

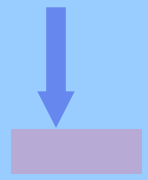


Hypofractionated “stereotactic” radiotherapy

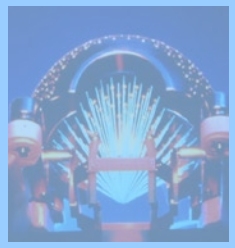


20 - 30Gy in 6 - 10 fractions

Single fraction radiosurgery

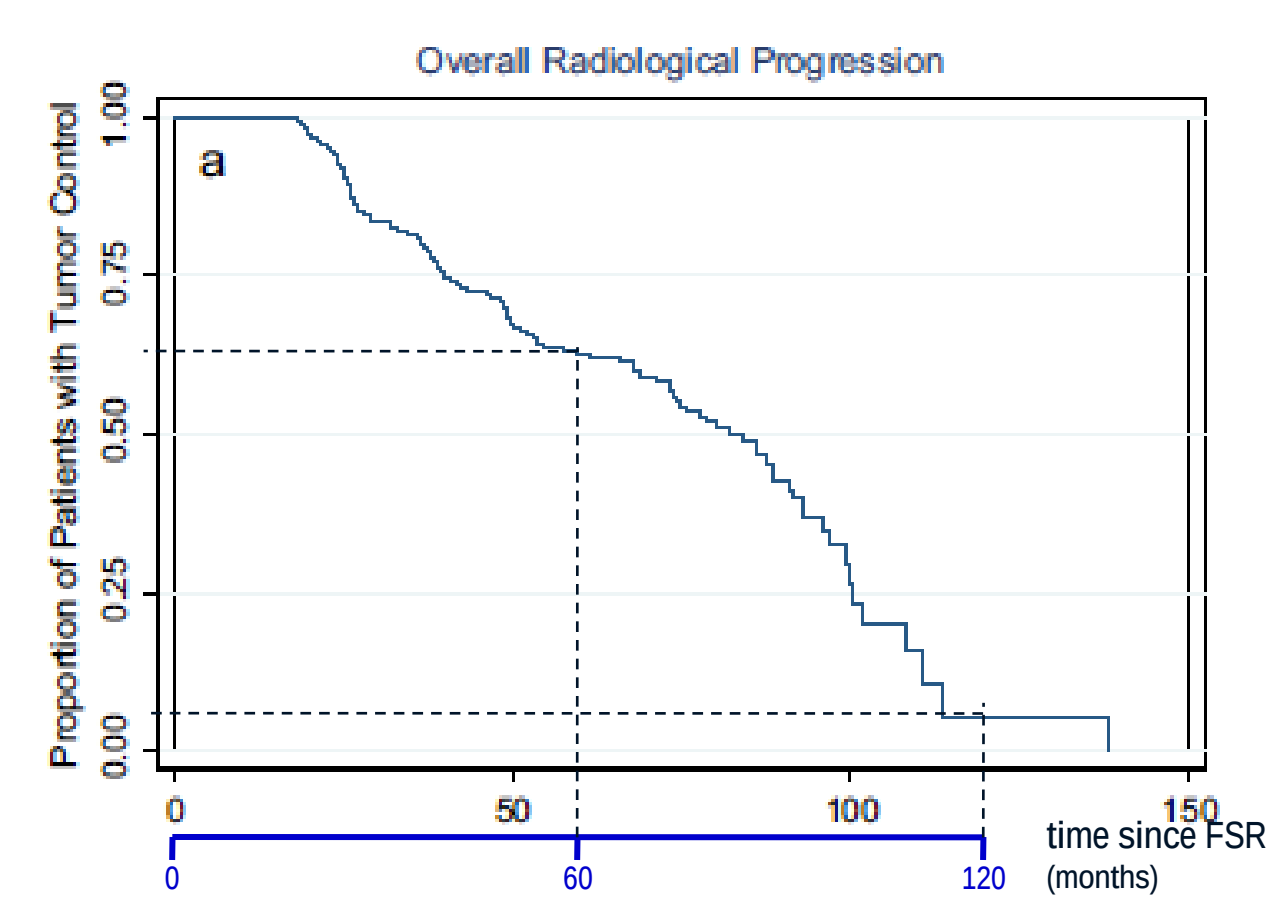


10 - 25Gy in 1 fraction



Fractionation in high precision radiotherapy

Tumour control



Fractionated stereotactic RT for acoustic neuroma

Kapoor et al 2010, Int J Rad Oncol Biol Phys, Johns Hopkins experience

Benign brain tumours

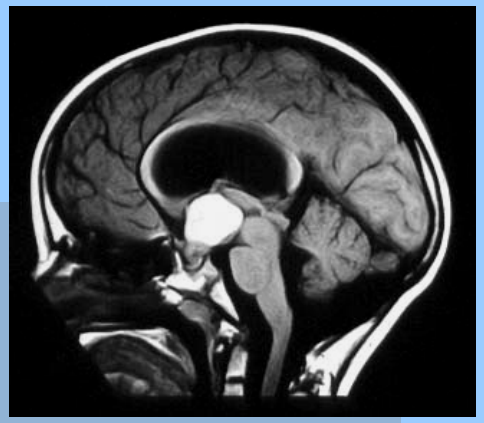
pituitary adenoma

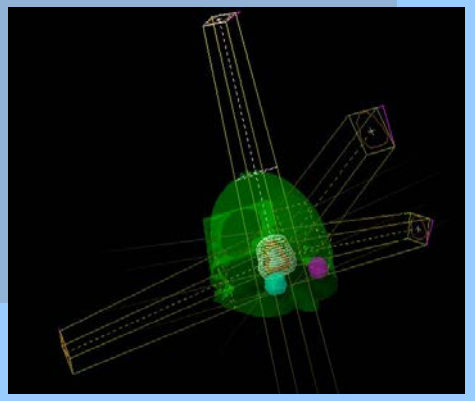
craniopharyngioma

acoustic neuroma

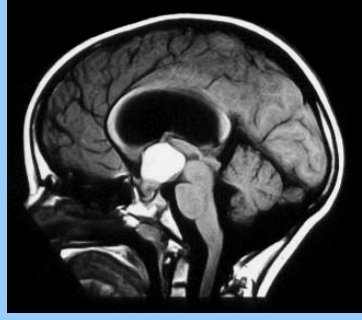
skull base meningioma

childhood low grade glioma





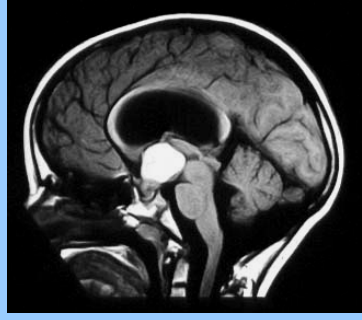
Management of benign brain tumours



Primary therapy

Surveillance	Surgery
Radiotherapy	Medical therapy

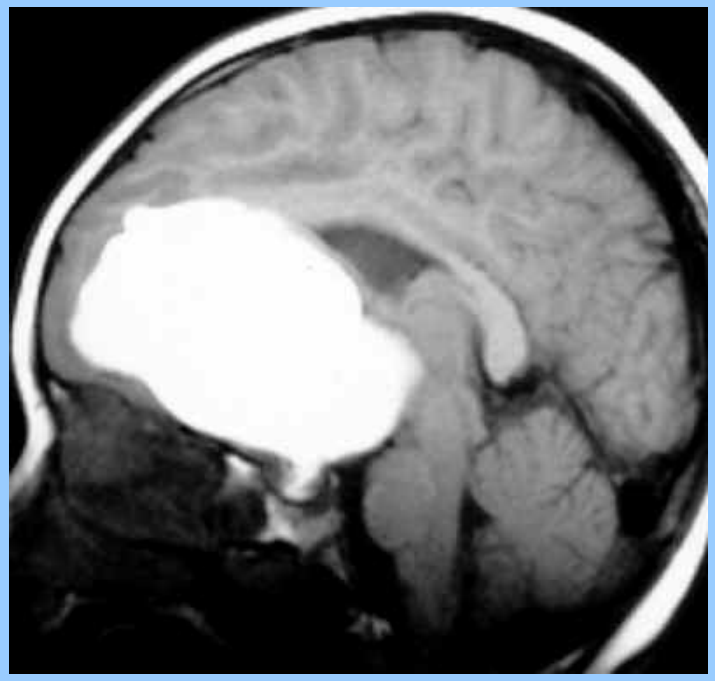
Management options in craniopharyngioma

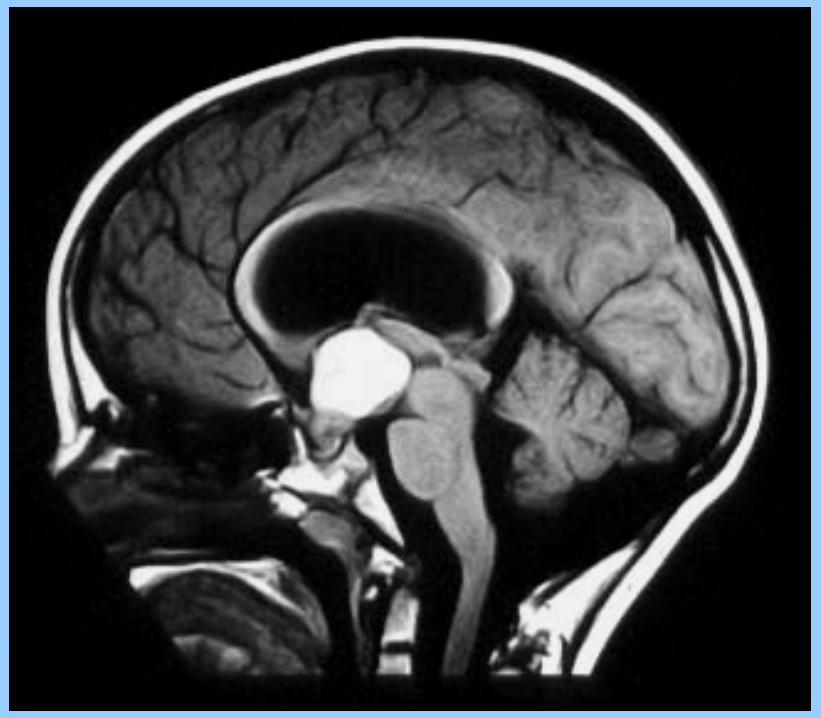


Primary therapy

Surveillance	Surgery
Radiotherapy	Medical therapy

Management options in craniopharyngioma





Surgery for craniopharyngioma

Practical issues

target volume

cystic enlargement

image guidance

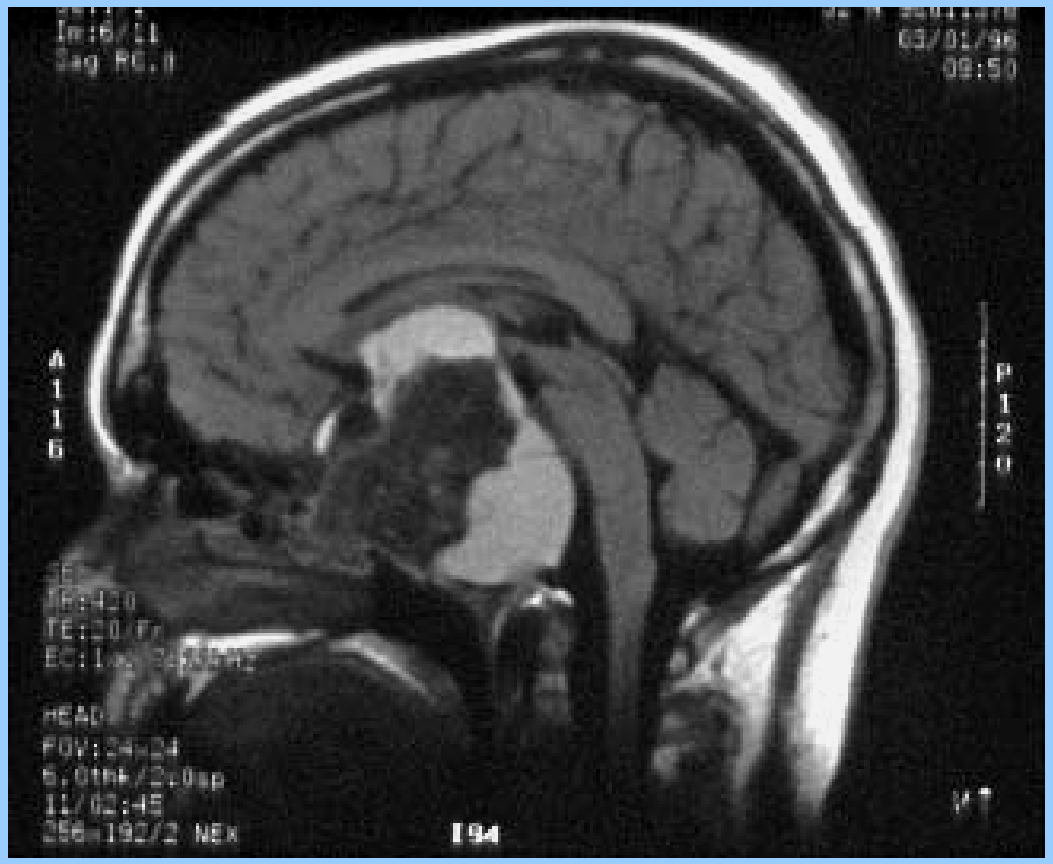
Practical issues

target volume

cystic enlargement

image guidance

Target volume



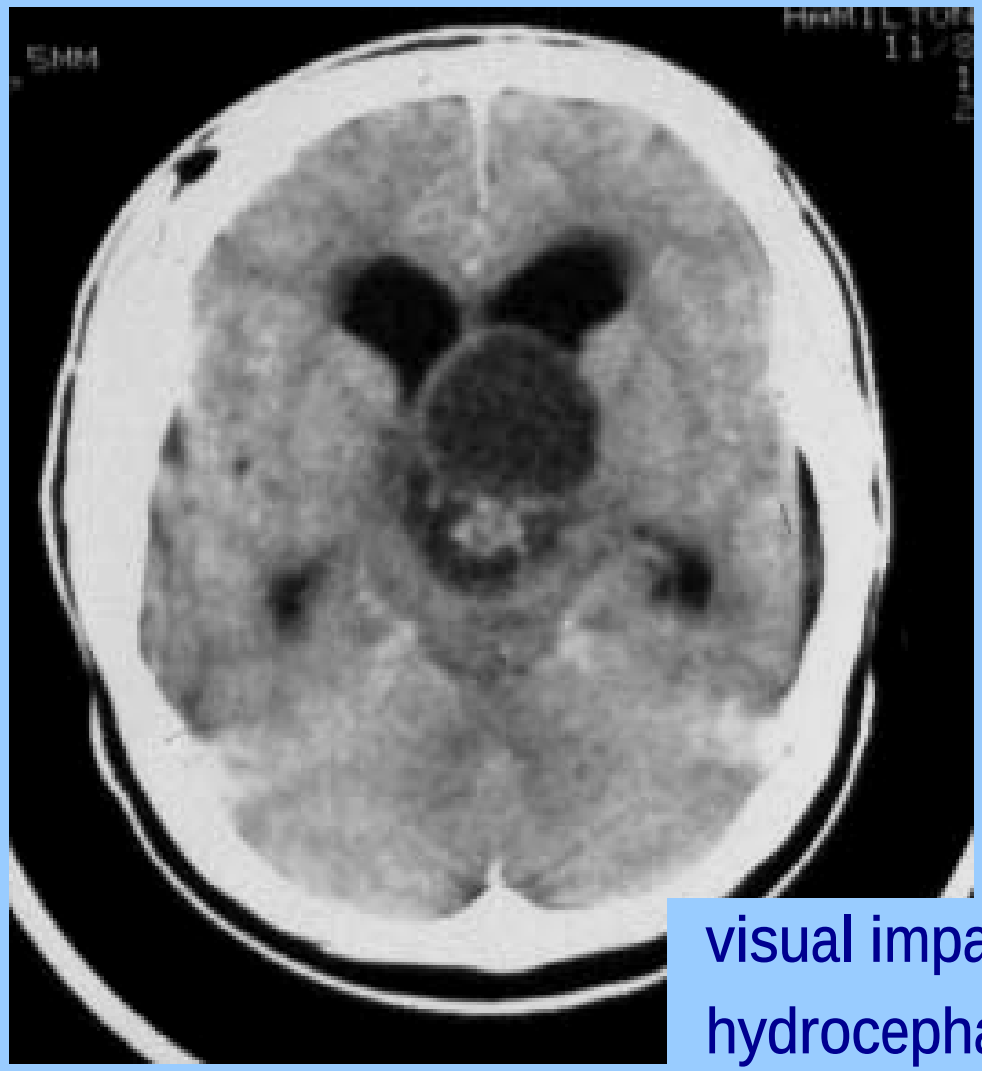
Craniopharyngioma management

Practical issues

target volume

cystic enlargement

image guidance



visual impairment

hydrocephalus

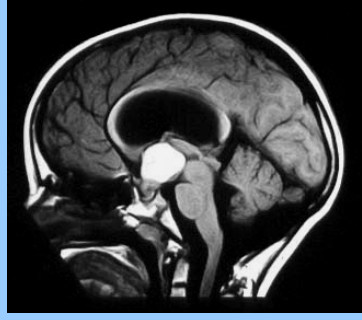
Craniopharyngioma management

Practical issues

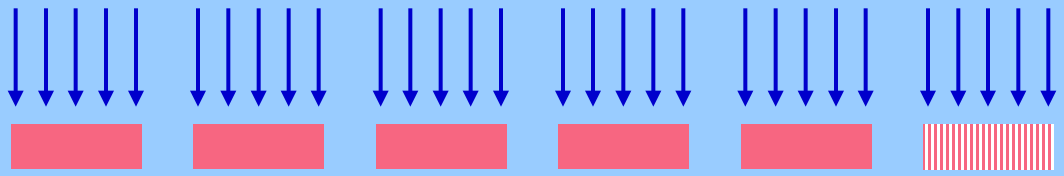
target volume

cystic enlargement

image guidance

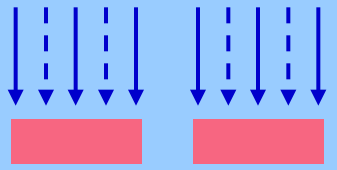


Fractionated “stereotactic” radiotherapy



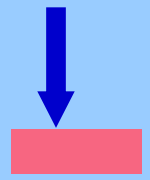
45 - 50Gy in 25 - 30 fractions

Hypofractionated “stereotactic” radiotherapy



20 - 30Gy in 6 - 10 fractions

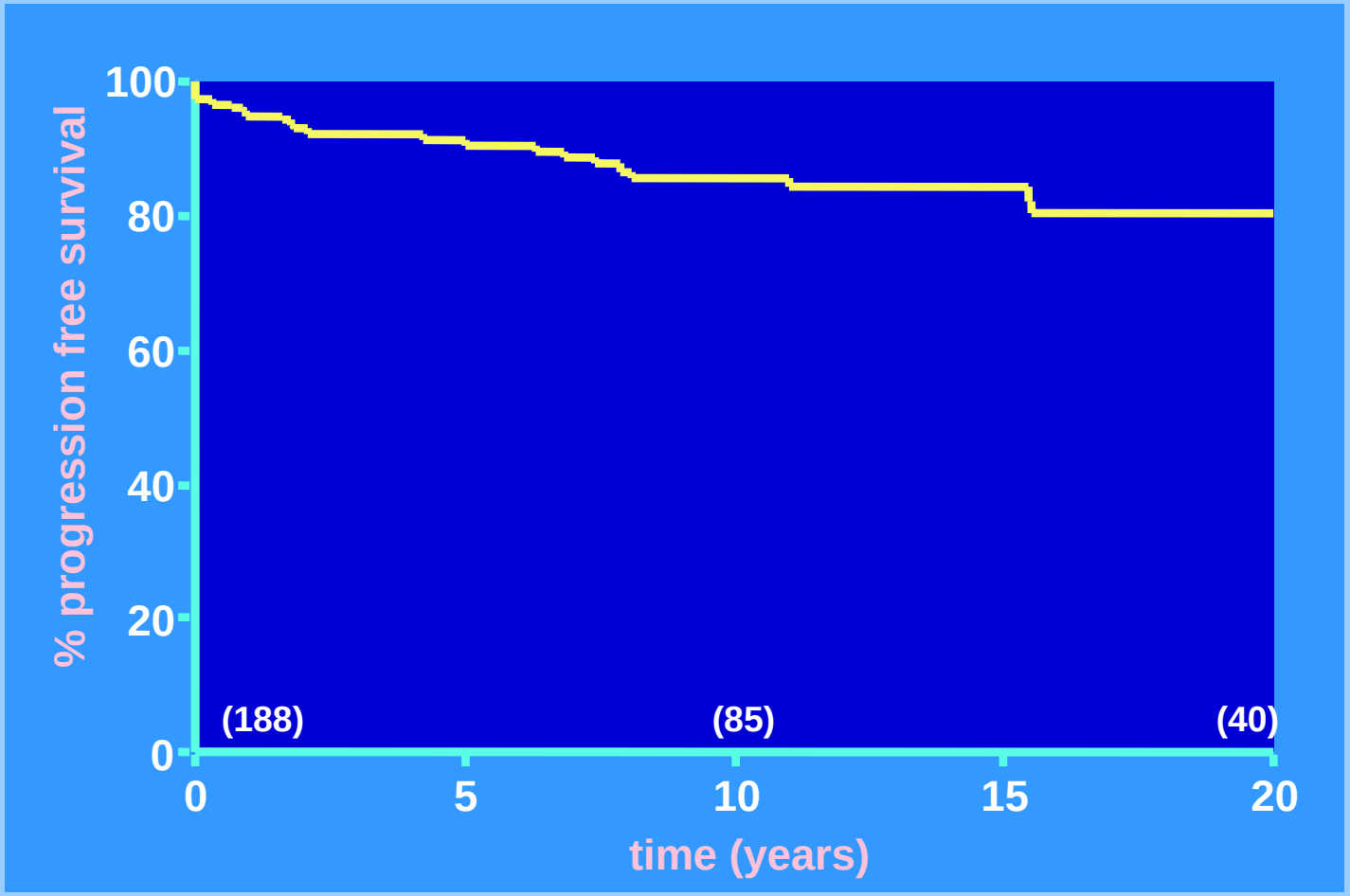
Single fraction radiosurgery



10 - 25Gy in 1 fraction

Radiotherapy for craniopharyngioma

Tumour control

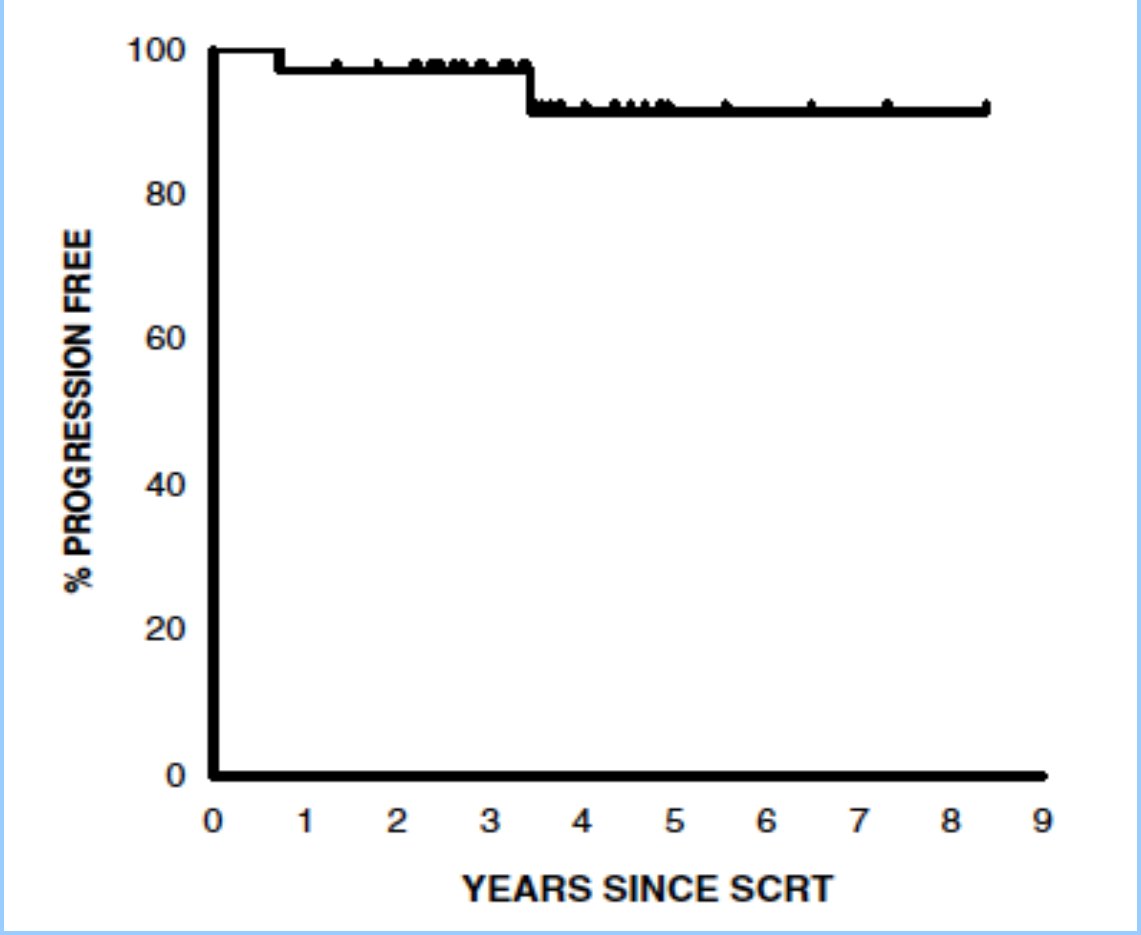


188 patients conservative surgery and radiotherapy

Conventional radiotherapy for craniopharyngioma

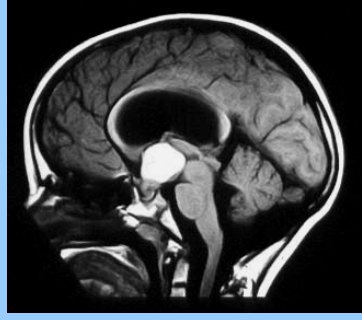
Rajan et al 1993

Tumour control



High precision radiotherapy for craniopharyngioma

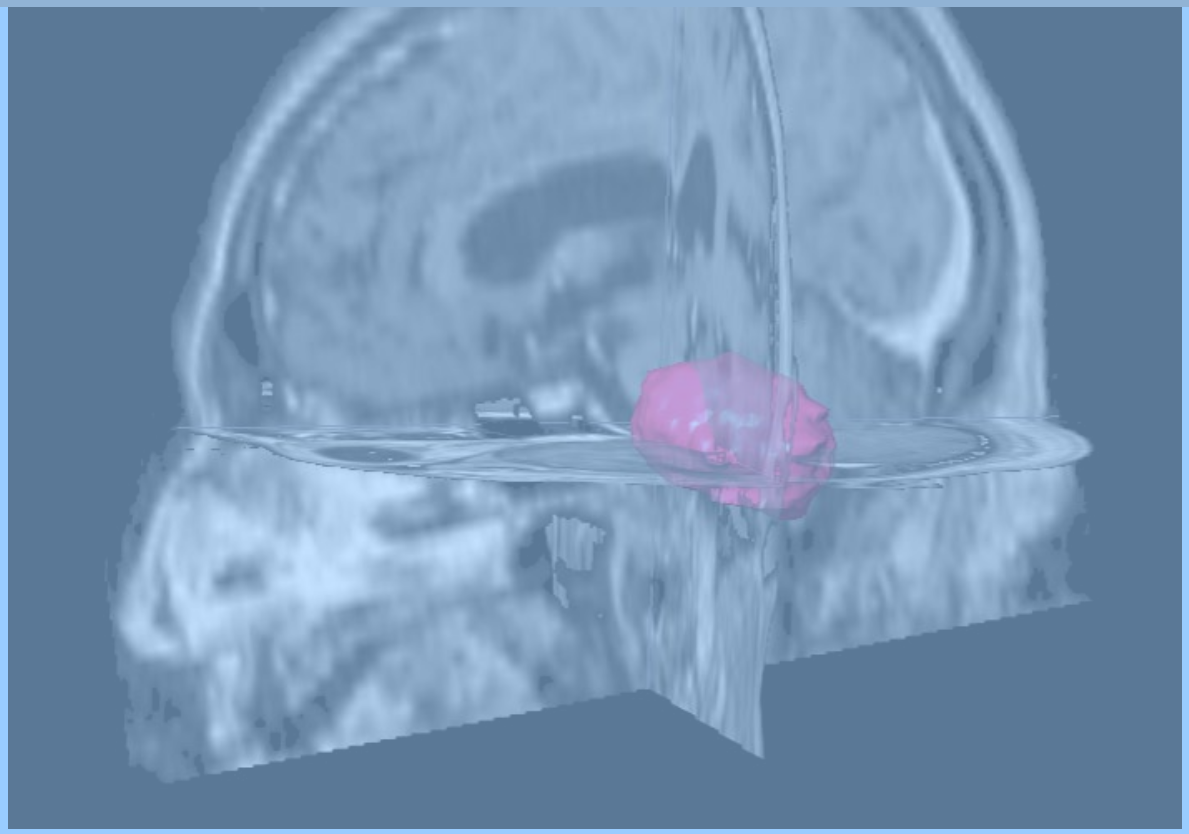
Minniti et al 2007



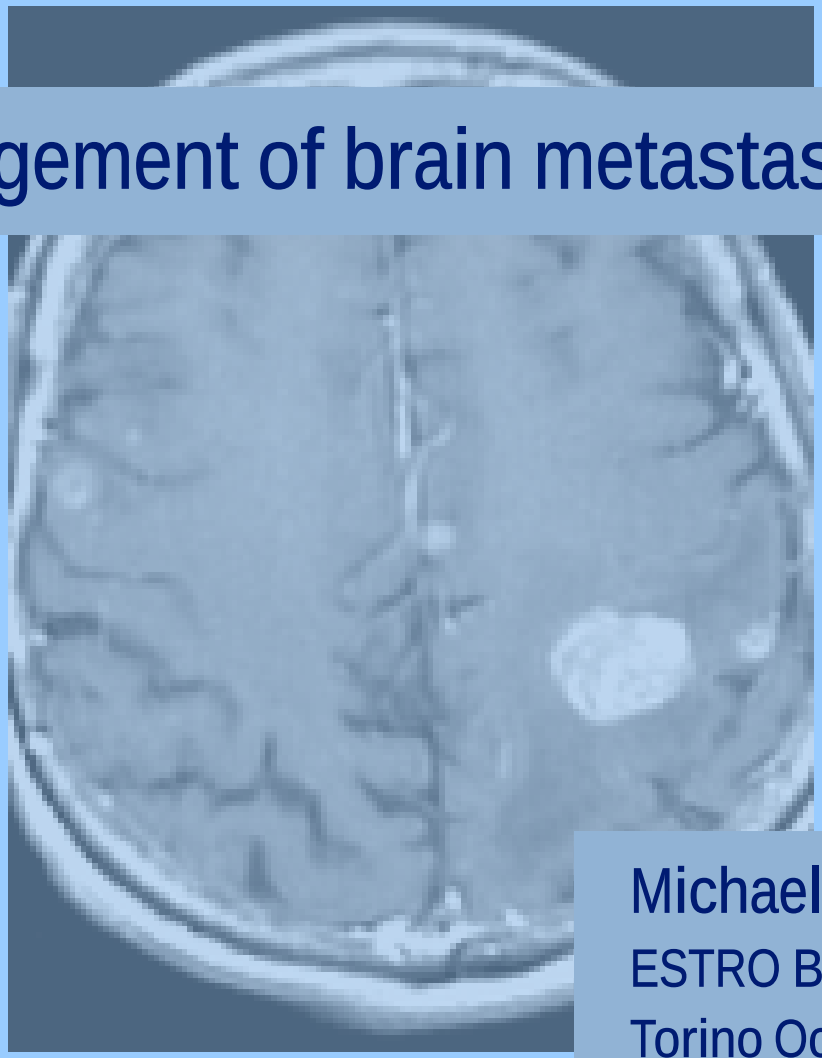
Author	Patients (n)	Dose (Gy)	Mean Tumour size (cm^3)	Control (%)
Gamma knife				
Xu et al[41]	37	14.5	1.6	**67% at 5 yrs**
Niranjan et al[42]	46	13	1	**68% at 5 yrs**
Kobayashi et al[34]	98	11.6	3.5	**61% at 5 yrs** **54% at 10 yrs**
Yomo et al[43]	18	11.5	1.8	(94%)
Amendola et al[36]	14	14	3.7	(86%)
Ulfarsson et al[21]	21	3-25	7.8	(36%)
Chiou et al[37]	10	16.4	1.7	(58%)
Chung et al[35]	31	9.5-16	9	(87%)
Mokry[44]	23	8-9.7	7	(74%)
Prasad et al[45]	9	13	10	(63%)
Cyberknife				
Iwata et al[39]	40	13-25	2	**85% at 3 yrs**
Miyazaki et al[46]	13	22.7	NA	(84%)
Lee et al[38]	11	21.6	6	(91%)
fSRT				
Kaneska et al[48]	16	30	1.8	**82% at 3 yrs**
Combs et al[16]	40	52.2	13.3	**100% at 10yrs**
Minniti et al[15]	39	50	10.2	**92% at 5 yrs**
Schulz-Ertner et al[33]	26	52.2	5.2	**100% 10 yrs**
Selch et al[49]	16	55	7.7	**75% at 3 yrs**

Tumour control following radiotherapy

Benign Brain Tumours



Management of brain metastases



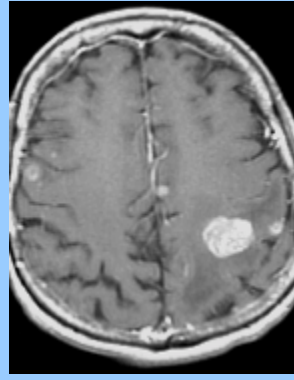
Michael Brada

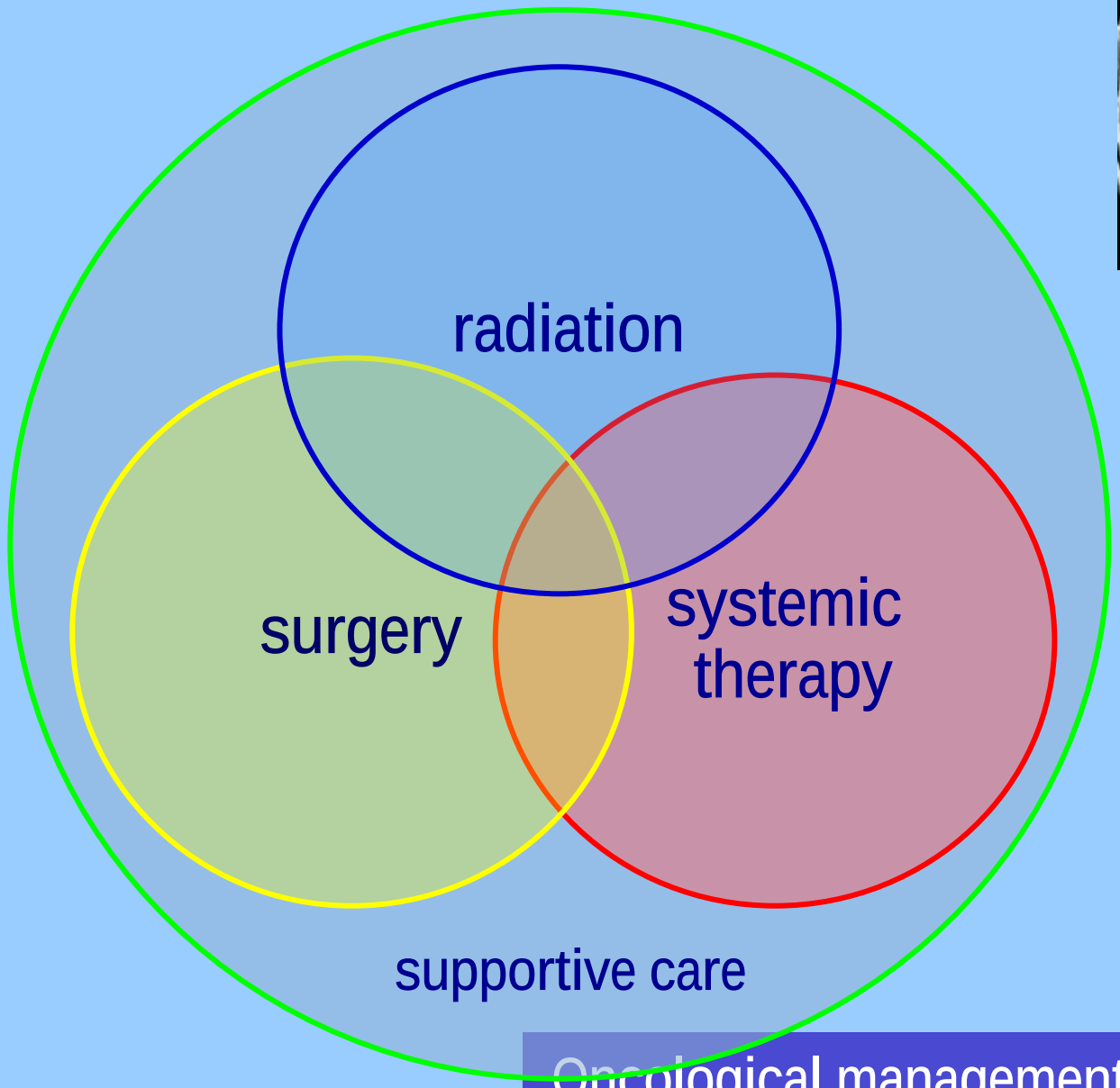
ESTRO BT course

Torino October 2015

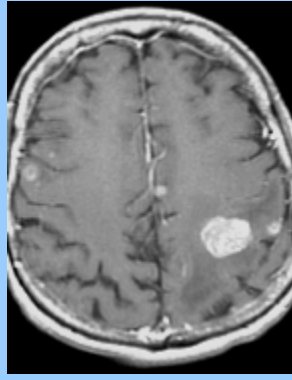
UNIVERSITY OF LIVERPOOL

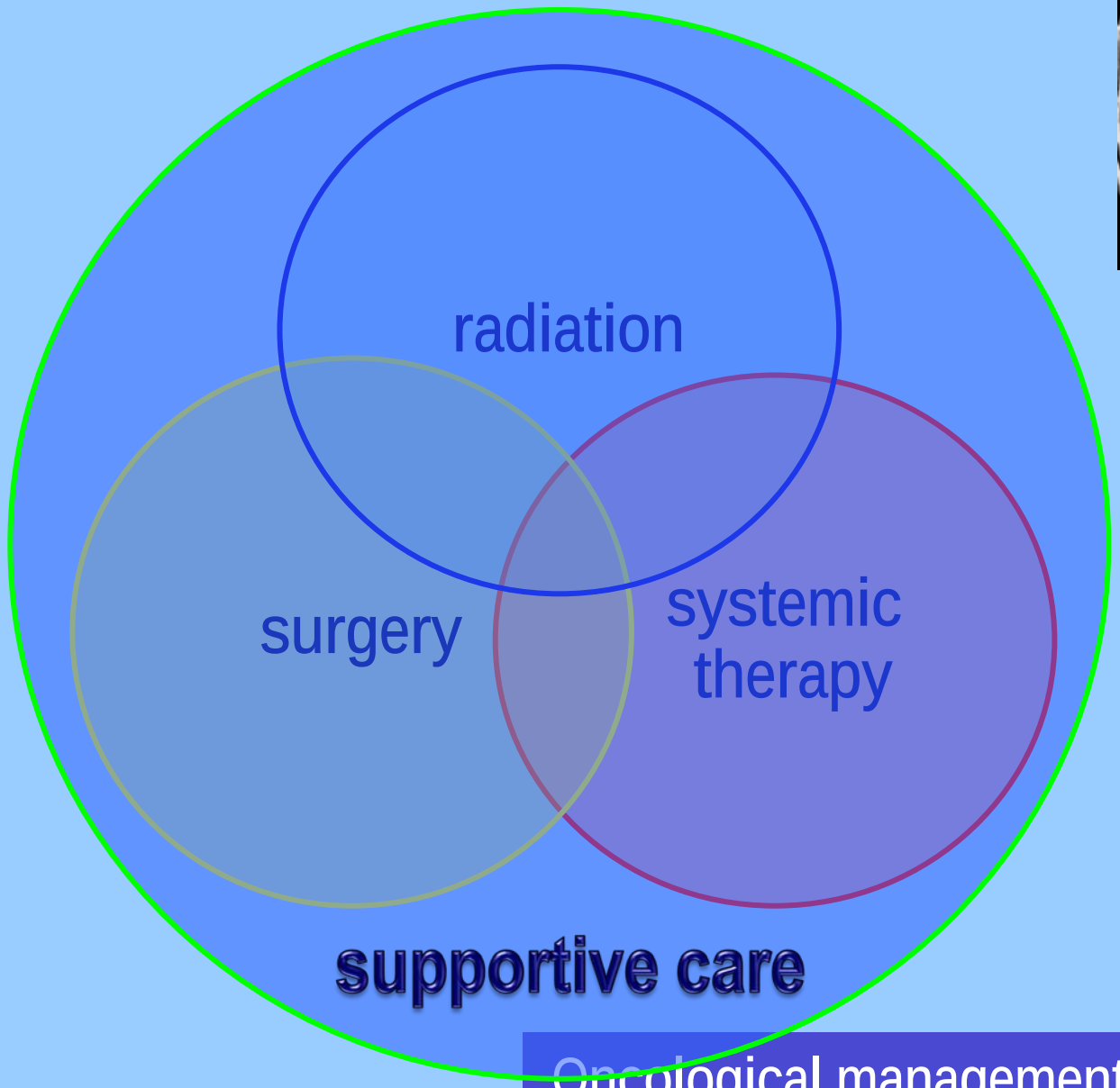
The Clatterbridge Cancer Centre NHS Foundation Trust



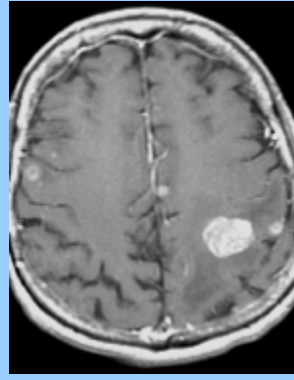


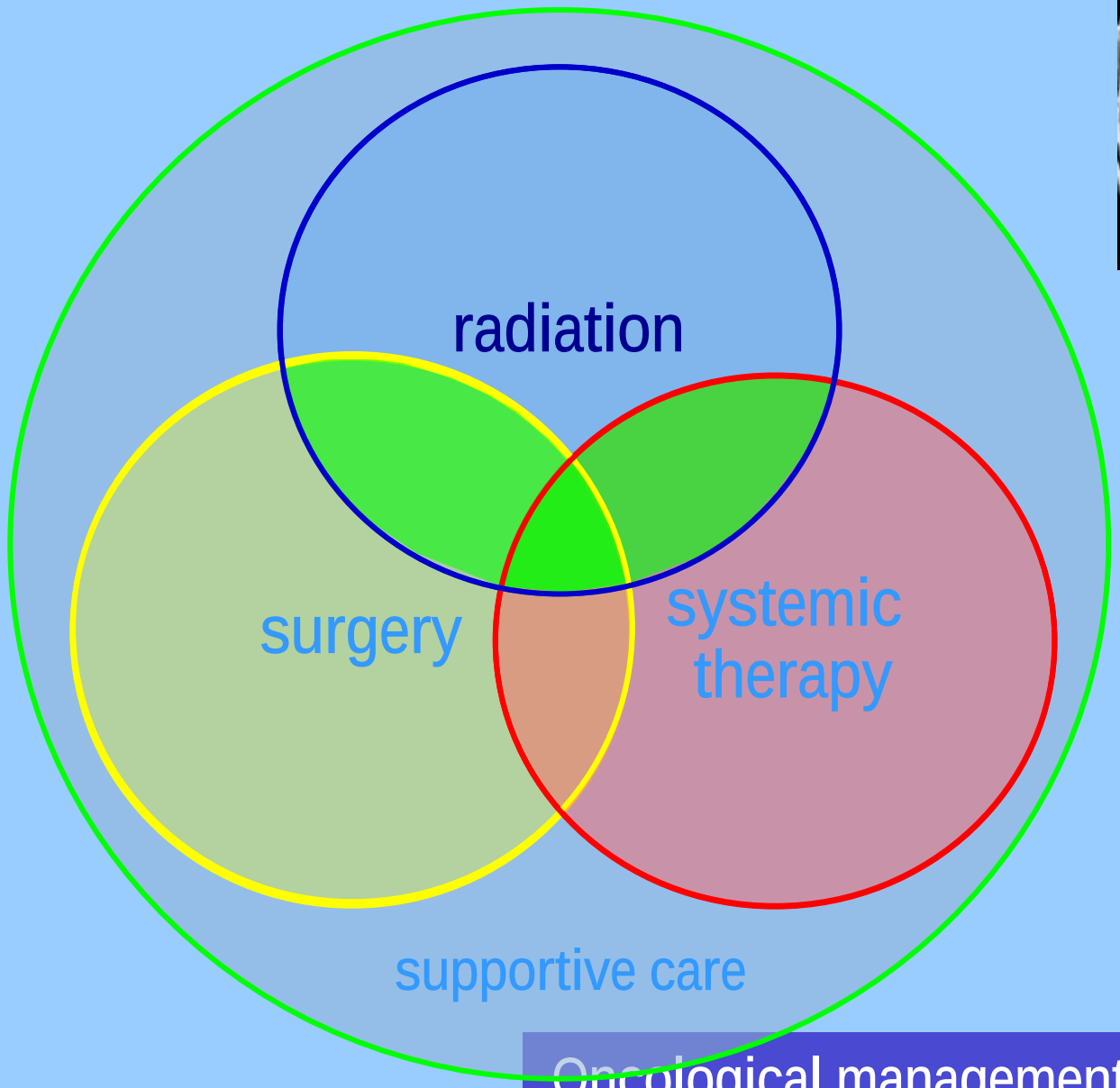
Oncological management options



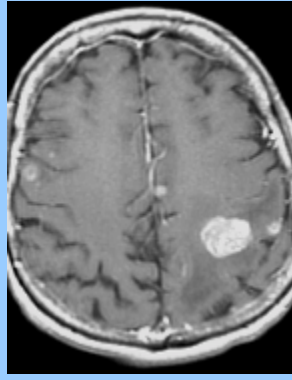


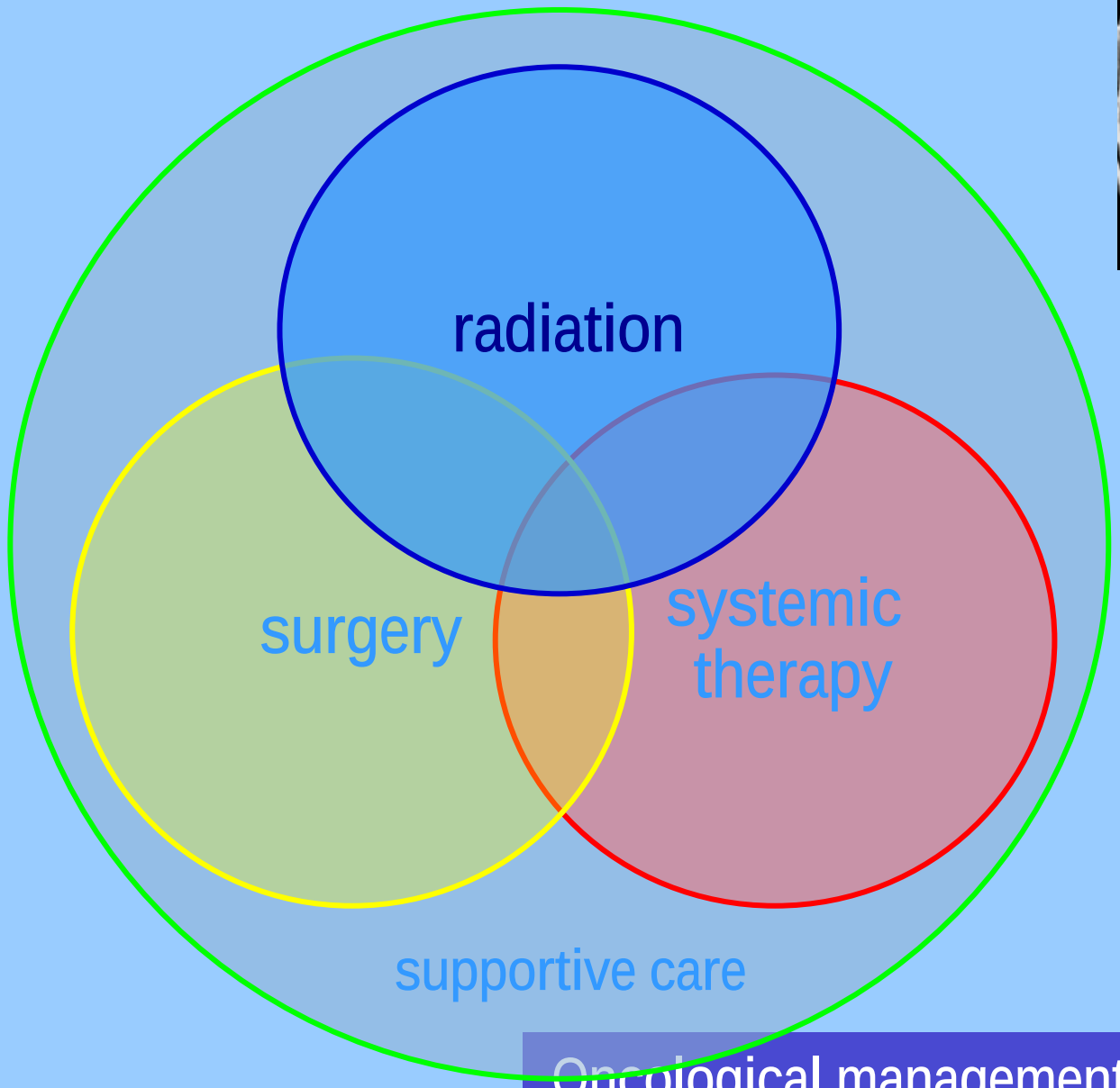
Oncological management options





Oncological management options





Oncological management options

- Radiotherapy technologies
- Context and endpoints
- Clinical issues - evidence base

Radiotherapy in the treatment of brain metastases

- Radiotherapy technologies
- Context and endpoints
- Clinical issues - evidence base

Radiotherapy in the treatment of brain metastases

Extent of irradiation

whole brain radiotherapy (WBRT)

partial brain radiotherapy (PBRT)

focal radiotherapy (SRT) & radiosurgery (SRS)

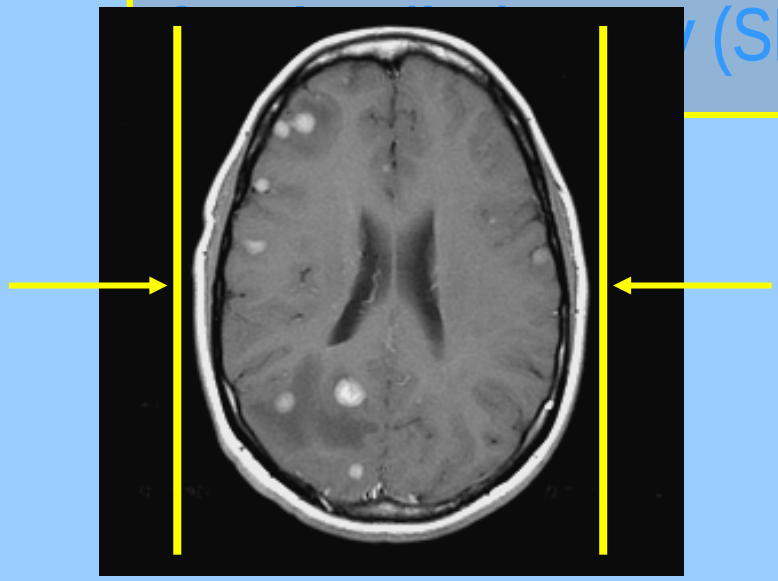
Radiotherapy options

Extent of irradiation

whole brain radiotherapy (WBRT)

partial brain radiotherapy (PBRT)

(SRT) & radiosurgery (SRS)



Radiotherapy options

Whole brain radiotherapy for multiple brain metastases

1. higher dose achieves better tumour control
2. 30Gy in 10 fractions is the best regimen
3. more protracted fractionation is less toxic
4. causes somnolence and fatigue
5. all of these
6. none of these

Extent of irradiation

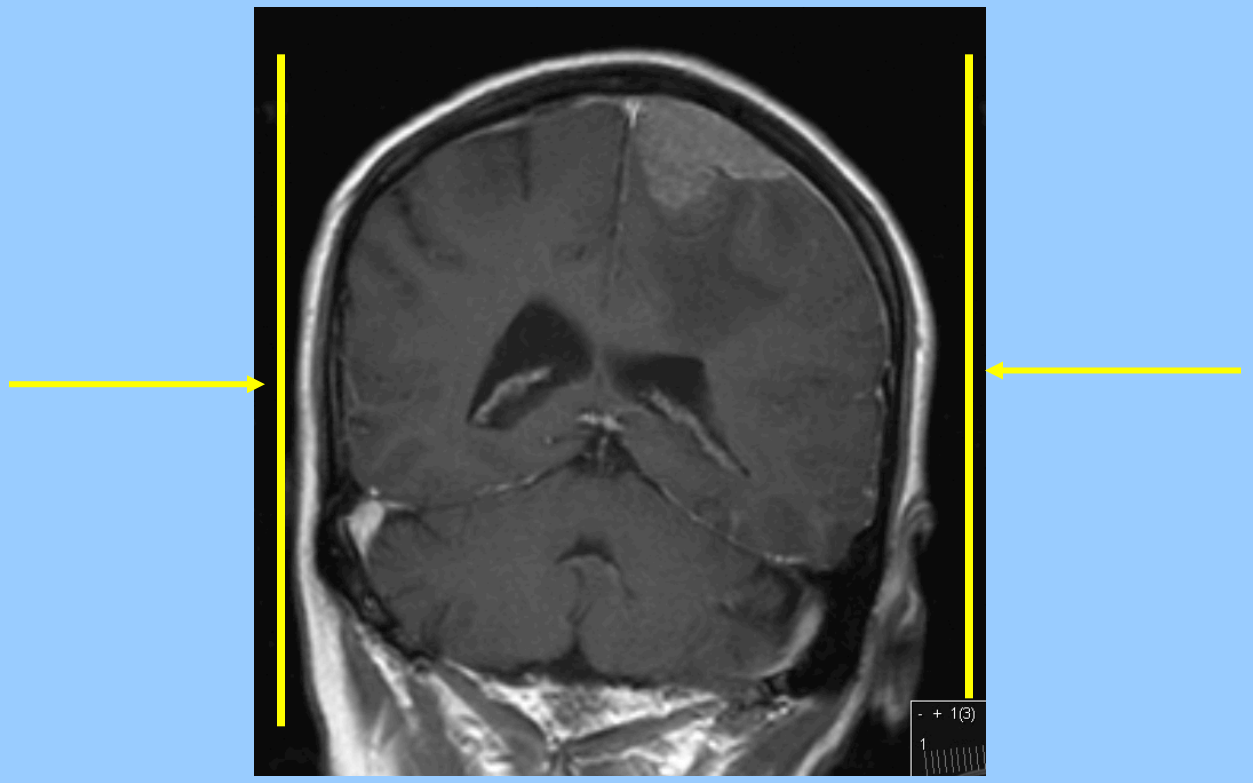
whole brain radiotherapy (WBRT)

partial brain radiotherapy (PBRT)

focal radiotherapy (SRT) & radiosurgery (SRS)

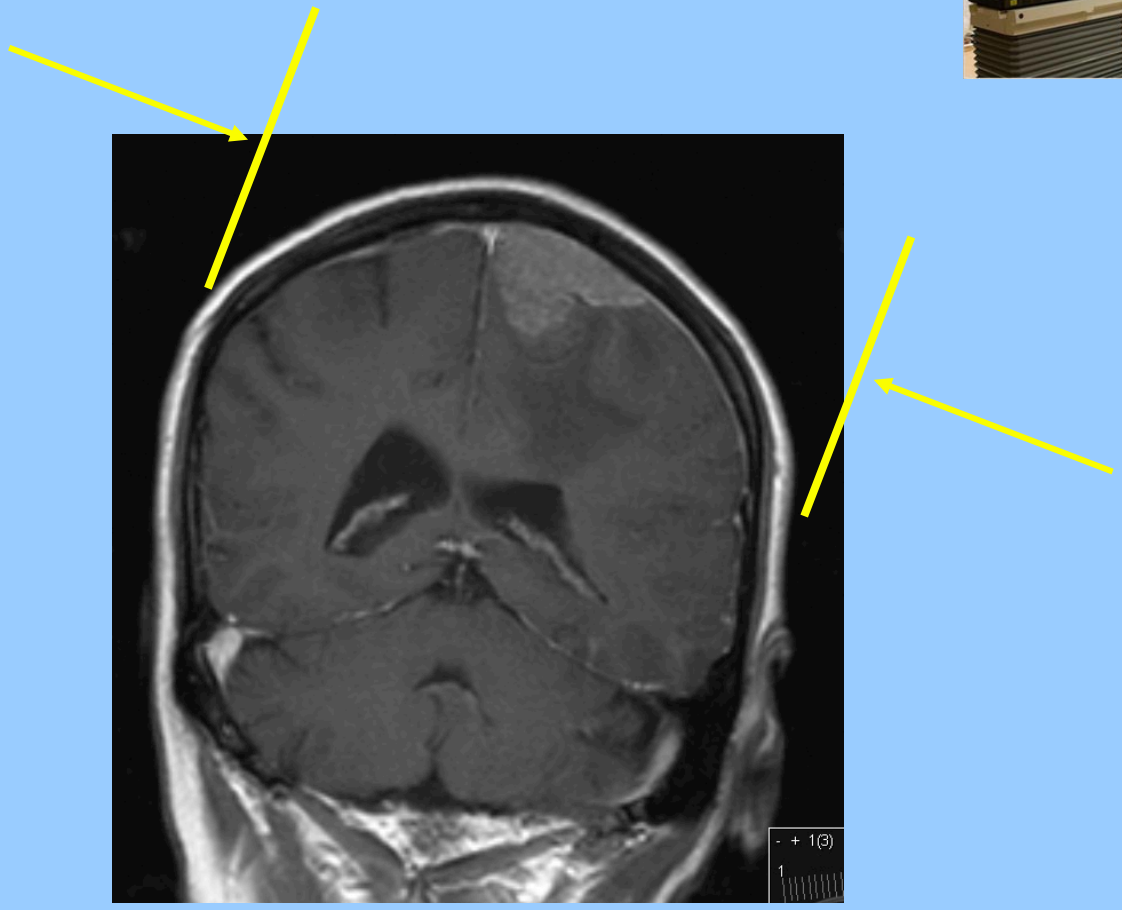
Radiotherapy options

whole brain radiotherapy



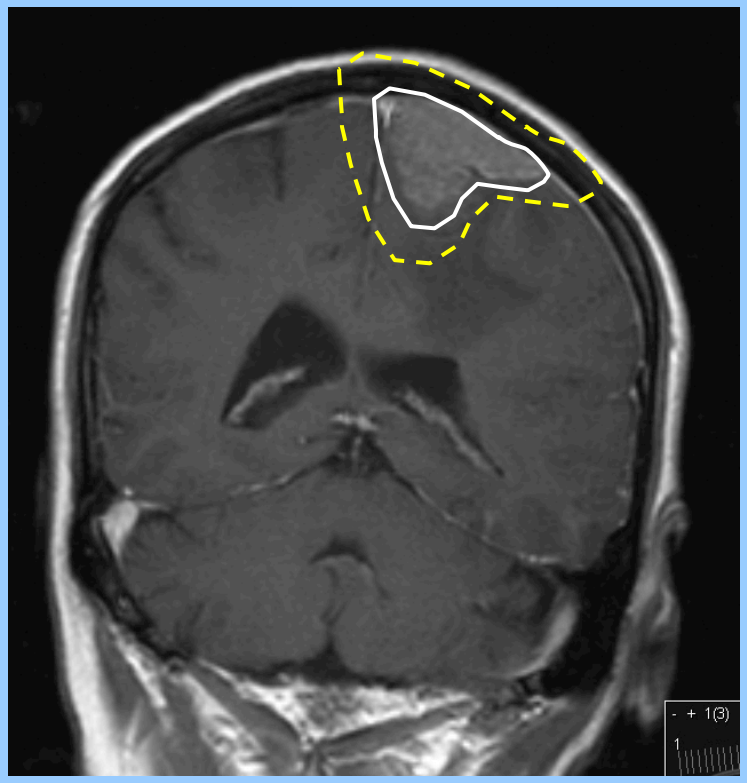
Radiotherapy options

partial brain radiotherapy



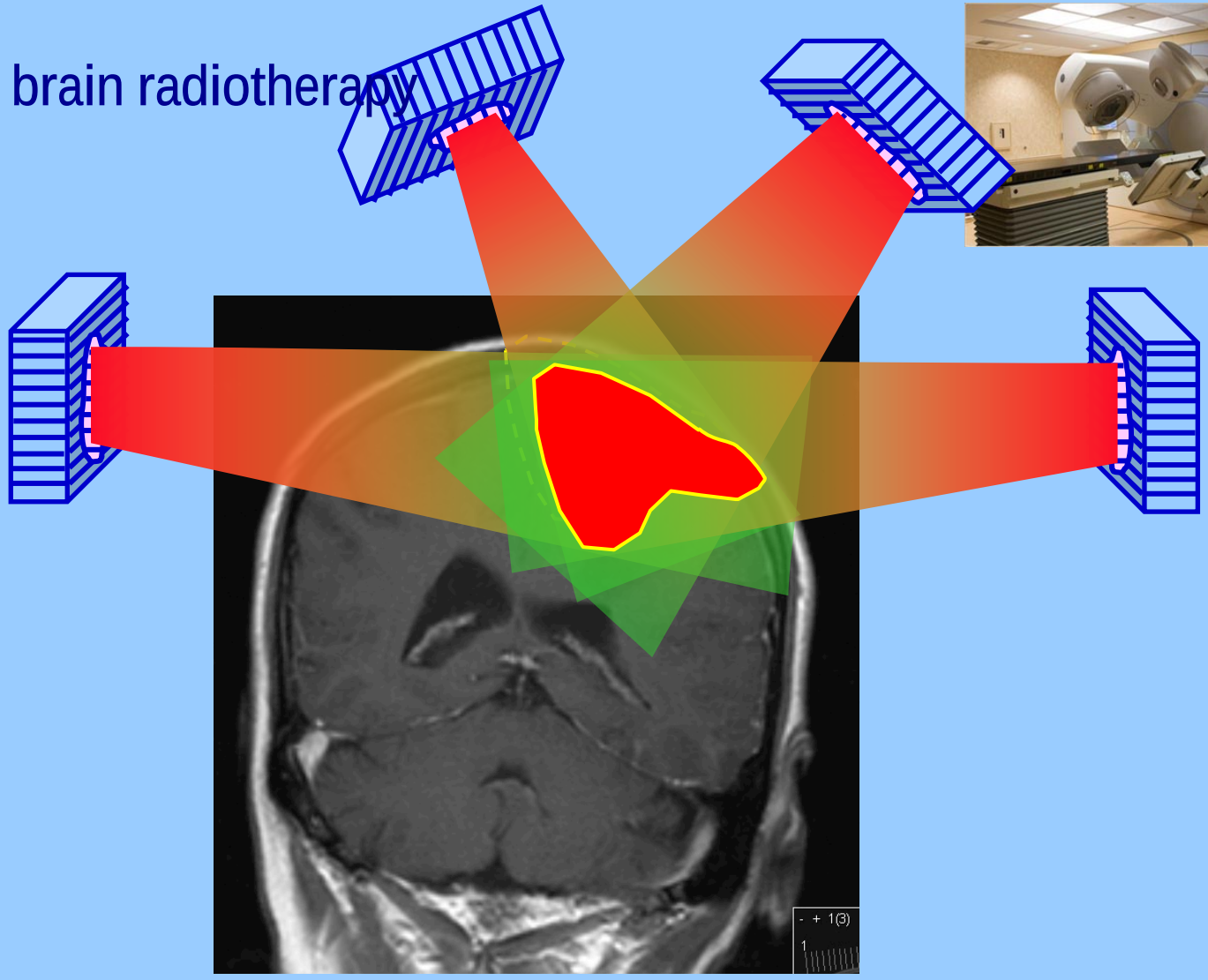
Radiotherapy options

partial brain radiotherapy



Radiotherapy options

partial brain radiotherapy



Radiotherapy options

Terminology

Extent of irradiation

whole brain radiotherapy (WB

partial brain radiotherapy (PBRT)

focal radiotherapy (SRT) & radiosurgery (SRS)

conformal RT

IMRT

tomotherapy

VMAT/RapidArc

……

Radiotherapy options

whole brain vs partial brain radiotherapy

patients with brain metastases
whole brain radiotherapy

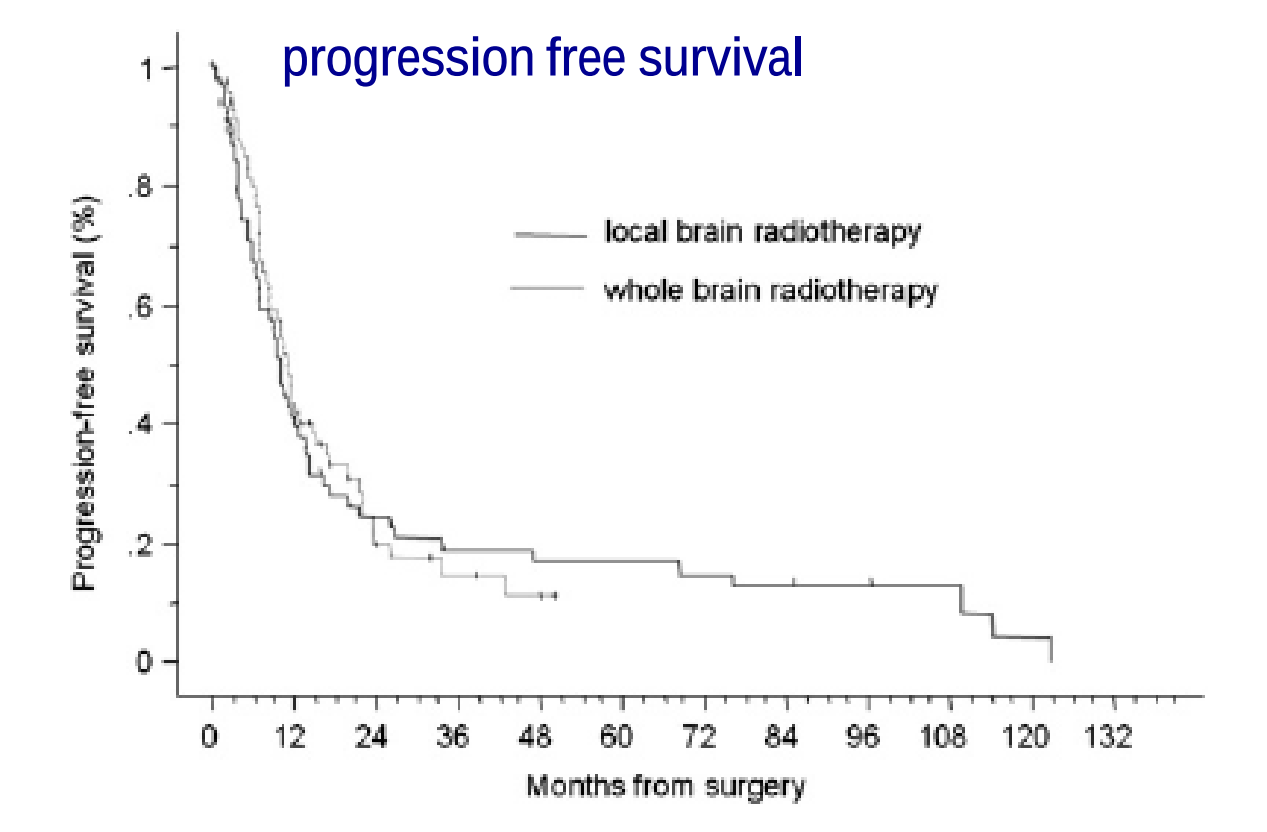
Whole brain

Partial brain

Comparison of whole brain and partial brain RT

Partial brain vs whole brain radiotherapy

after surgery – retrospective comparison (126 patients)

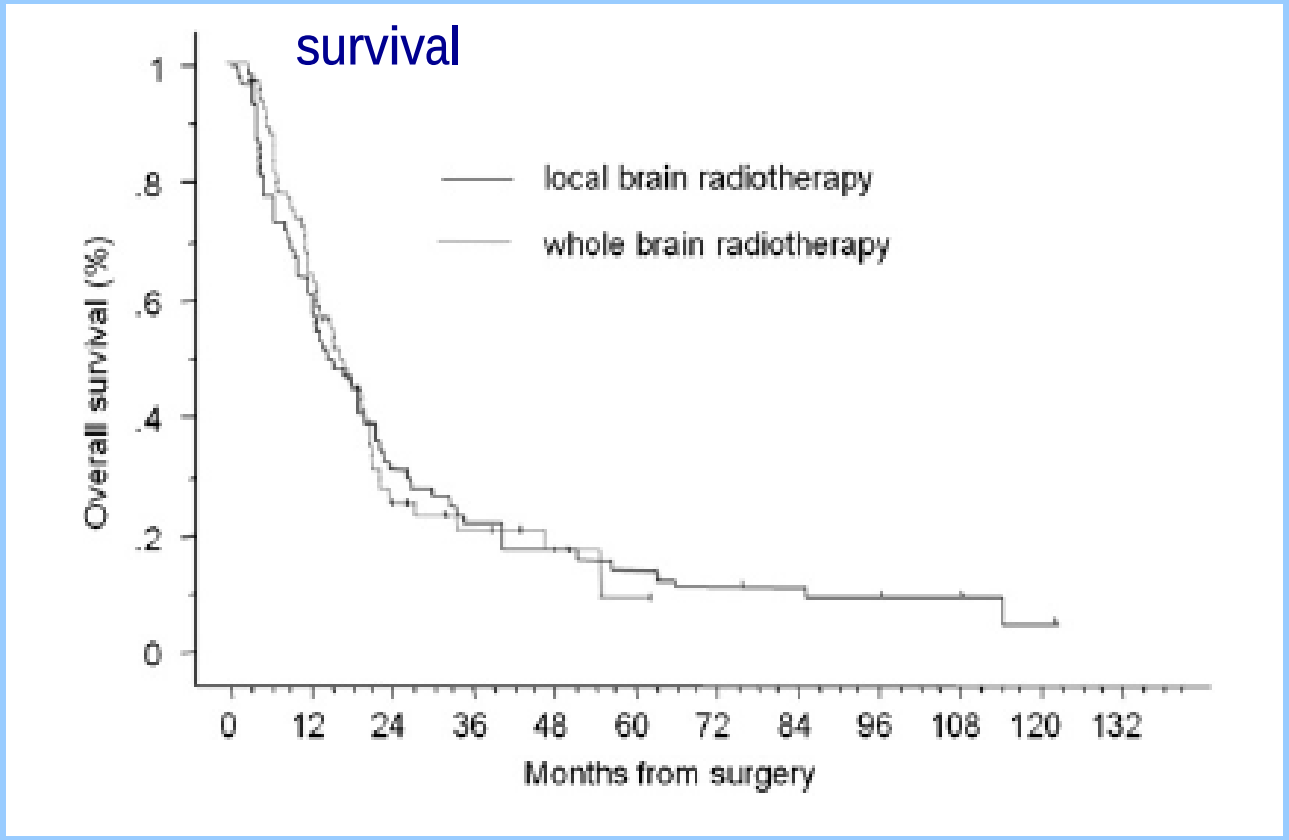


Partial brain RT after surgery for solitary brain metastases

Hashimoto et al 2011

Partial brain vs whole brain radiotherapy

after surgery – retrospective comparison (126 patients)



Partial brain RT after surgery for solitary brain metastases

Hashimoto et al 2011

Extent of irradiation

whole brain radiotherapy (WBRT)

partial brain radiotherapy (PBRT)

focal radiotherapy (SRT) & radiosurgery (SRS)

Terminology

Extent of irradiation

stereotactic radiosurgery (single fraction) SRS

stereotactic radiotherapy (fractionated) fSRT

partial brain radiotherapy (PBRT)

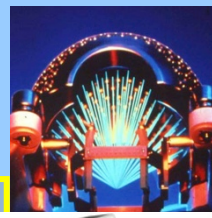
focal radiotherapy (SRT) & radiosurgery (SRS)

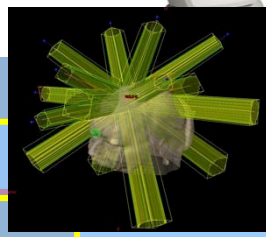
Radiotherapy options

Terminology

Extent of irradiation

multiheaded cobalt unit	gamma knife
robotic arm mounted linear accelerator	cyberknife
conventional linear accelerator	linac





focal radiotherapy (SRT) & radiosurgery (SRS)

Radiotherapy options

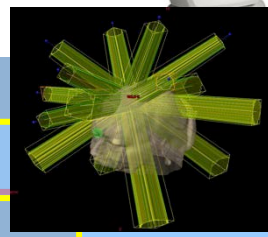
Terminology

Extent of irradiation

multiheaded cobalt unit — gamma knife

robotic arm mounted linear accelerator — cyberknife

conventional linear accelerator — linac



focal radiotherapy (SRT) & radiosurgery (SRS)

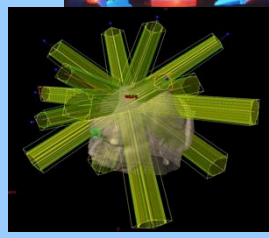
multiple fixed field conformal radiotherapy

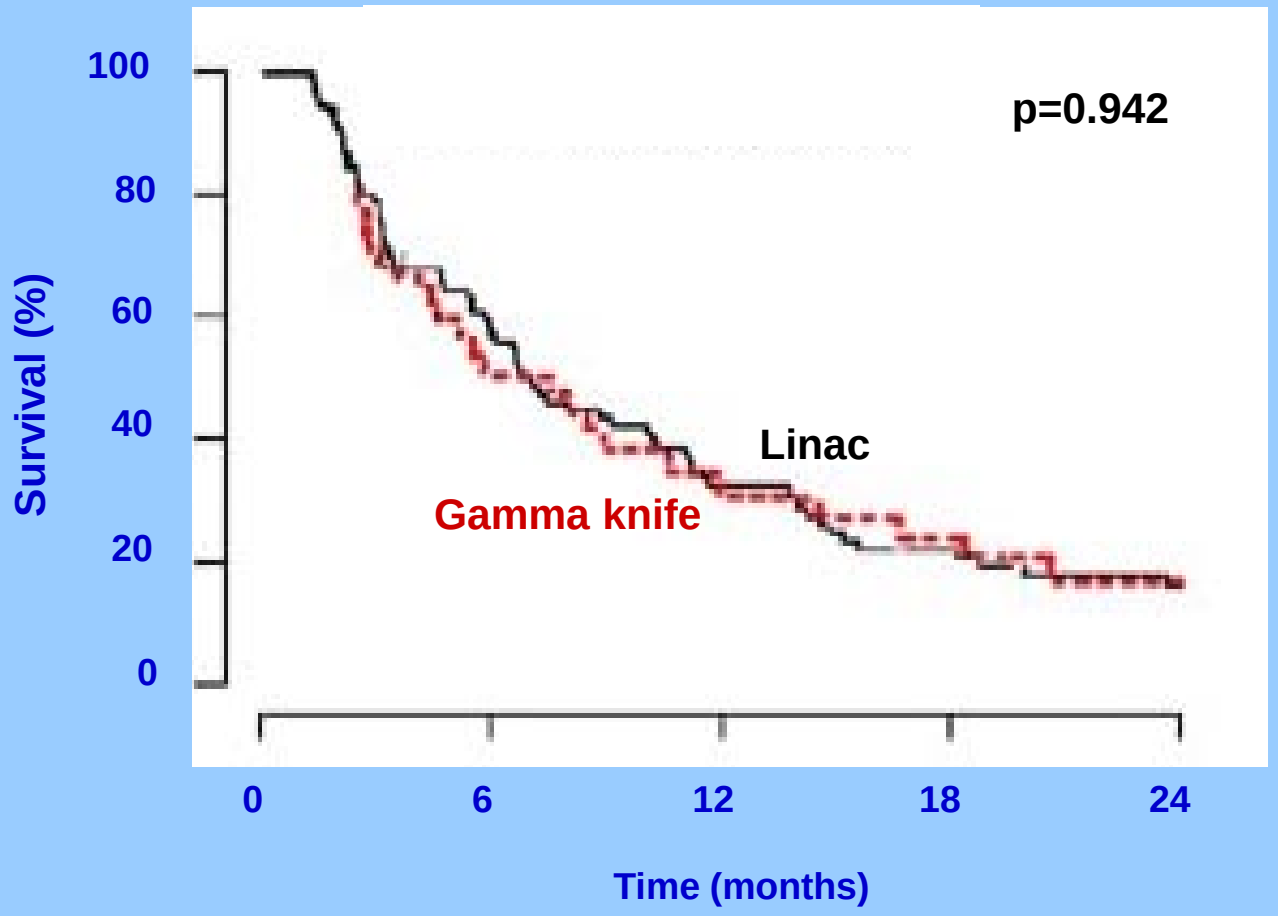
intensity modulated radiotherapy (IMRT)

rotating volumetric IMRT (VMAT®/RapidArc®)

Radiotherapy options

survival – by treatment unit



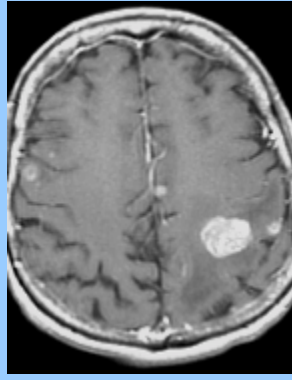


Radiosurgery for solitary brain metastases

Andrews et al 2004, Lancet 363: 1665–72

- Radiotherapy technologies
- Context and endpoints
- Clinical issues - evidence base

Radiotherapy in the treatment of brain metastases



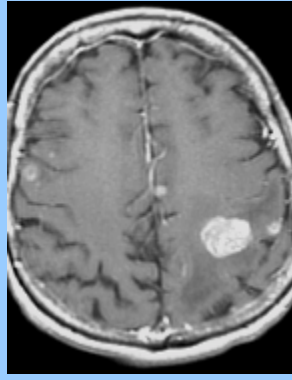
Context

prognosis

primary tumour type

timing in the course of disease

Oncological management options



Context

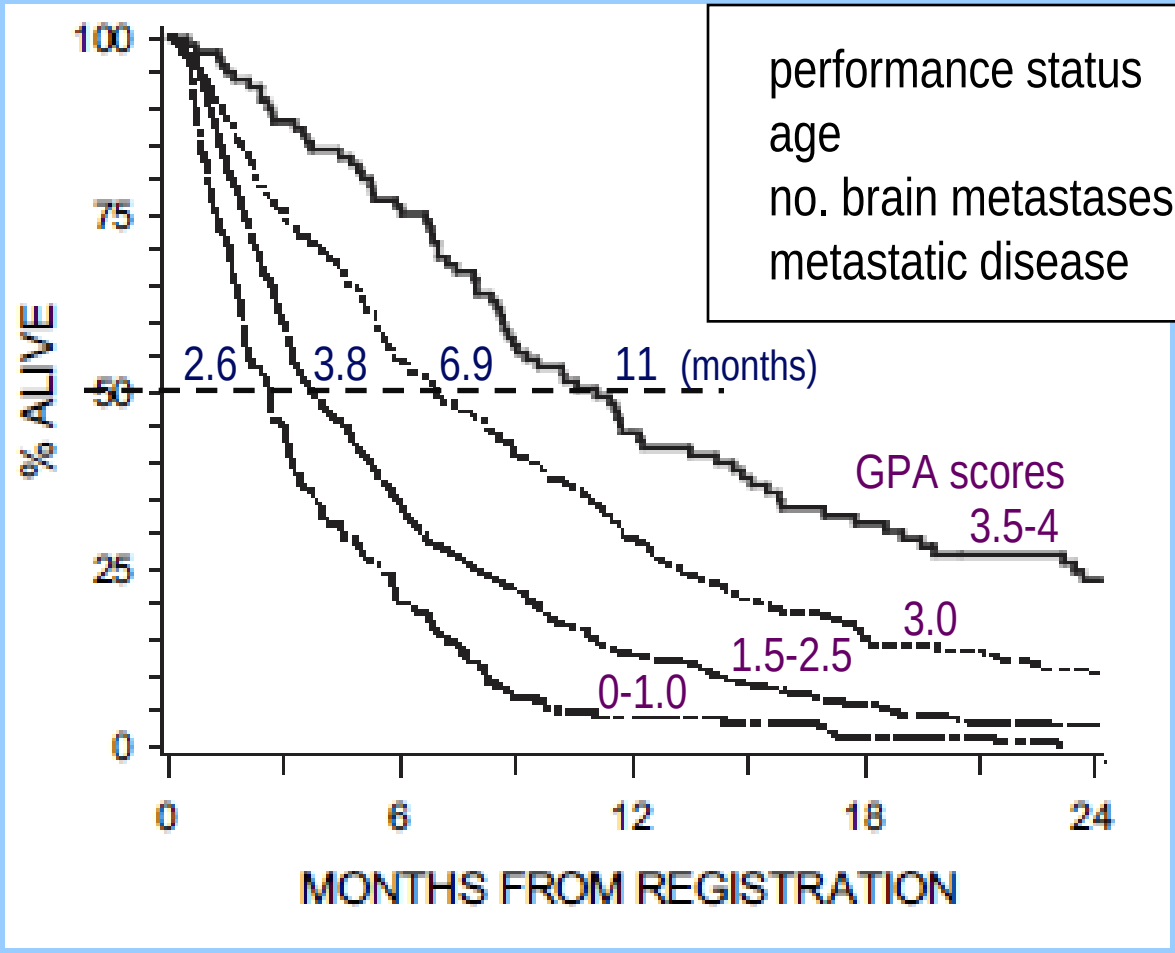
prognosis

primary tumour type

timing in the course of disease

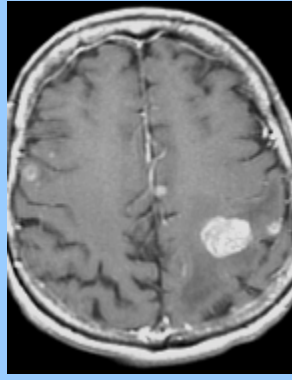
Oncological management options

Graded prognostic assessment (GPA)



Prognosis in patients with brain metastases

Sperduto et al Int J Radiat Oncol Biol Phys 2008; 70: 510-514



Context

prognosis

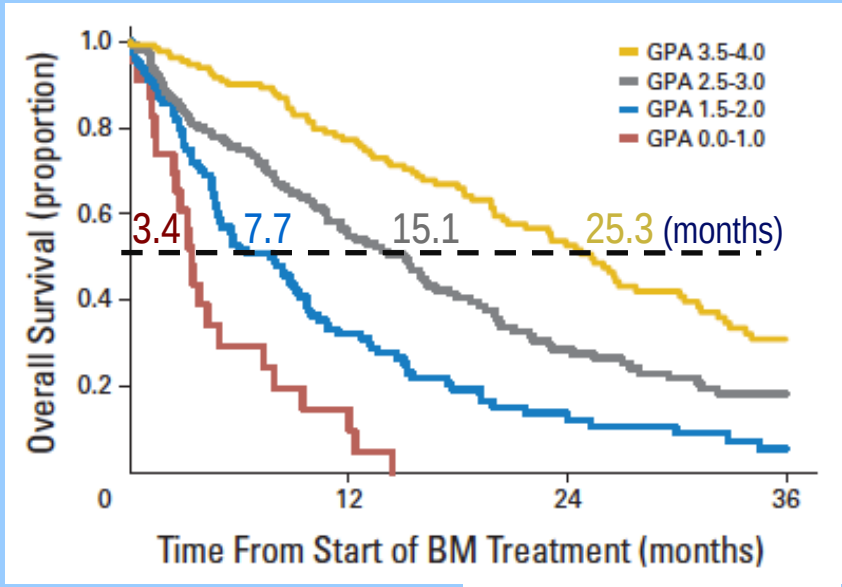
primary tumour type

timing in the course of disease

Oncological management options

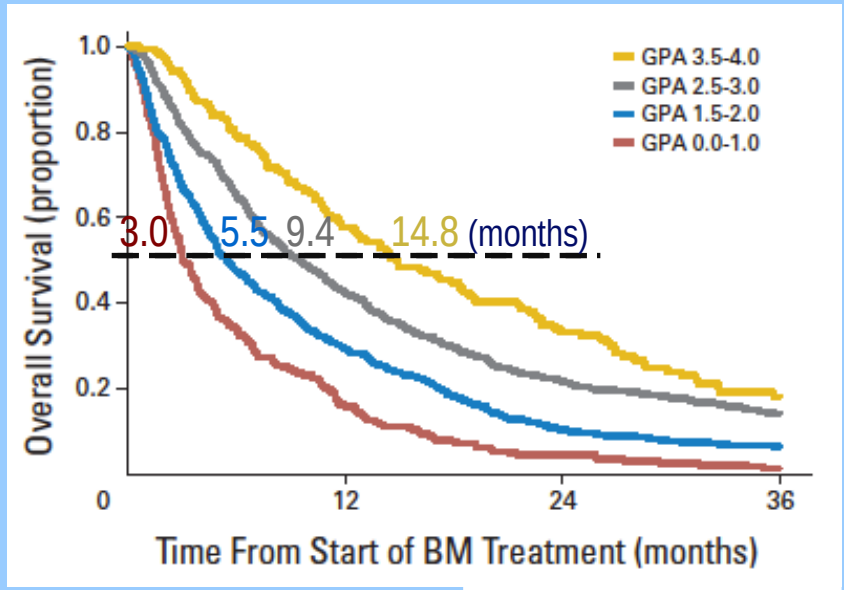
Graded prognostic assessment (GPA)

Breast



performance status
age
tumour subtype

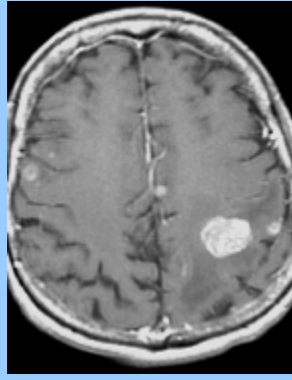
NSCLC



performance status
age
no. brain mets
metastatic disease

Prognosis in patients with brain metastases

Sperduto et al 2012 J Clin Oncol, 30: 419 - 425



Context

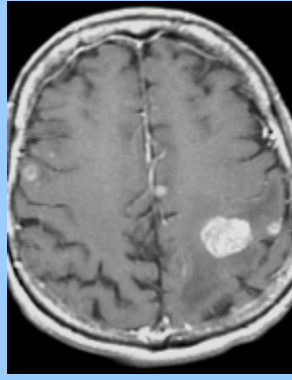
prognosis

primary tumour type

timing in the course of disease

Oncological management options

Course of malignant disease



Brain metastases

Diagnosis

Local recurrence or dissemination

Progression

primary disease

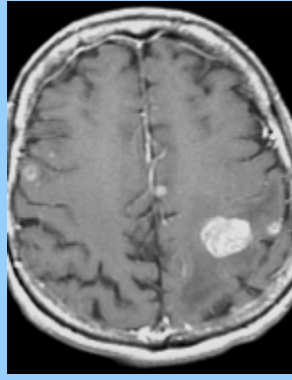
recurrent disease

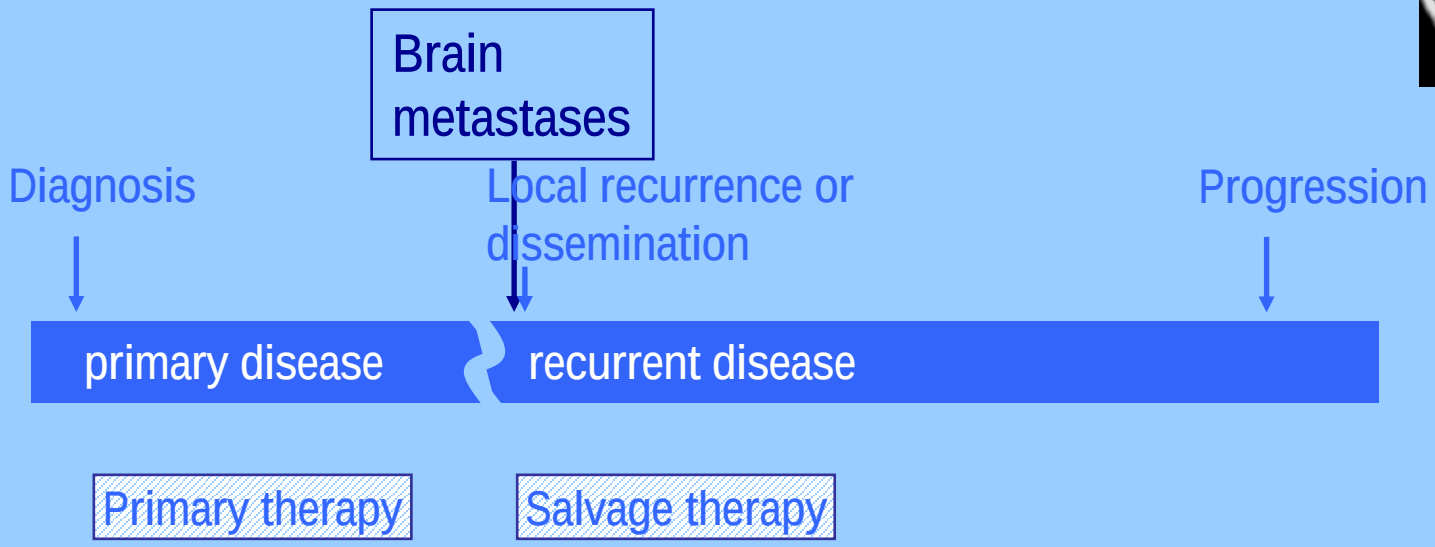
Primary therapy

Salvage therapy

Brain metastases in malignancy

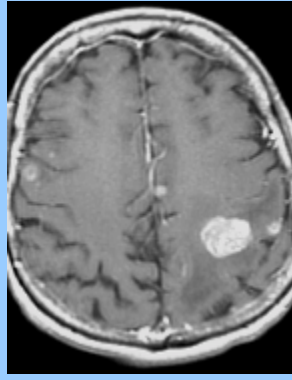
Course of malignant disease



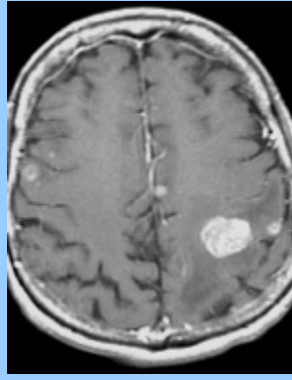


Brain metastases in malignancy

Course of malignant disease



Brain metastases in malignancy



Context

prognosis

primary tumour type

timing in the course of disease

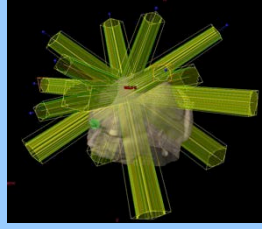
Endpoints

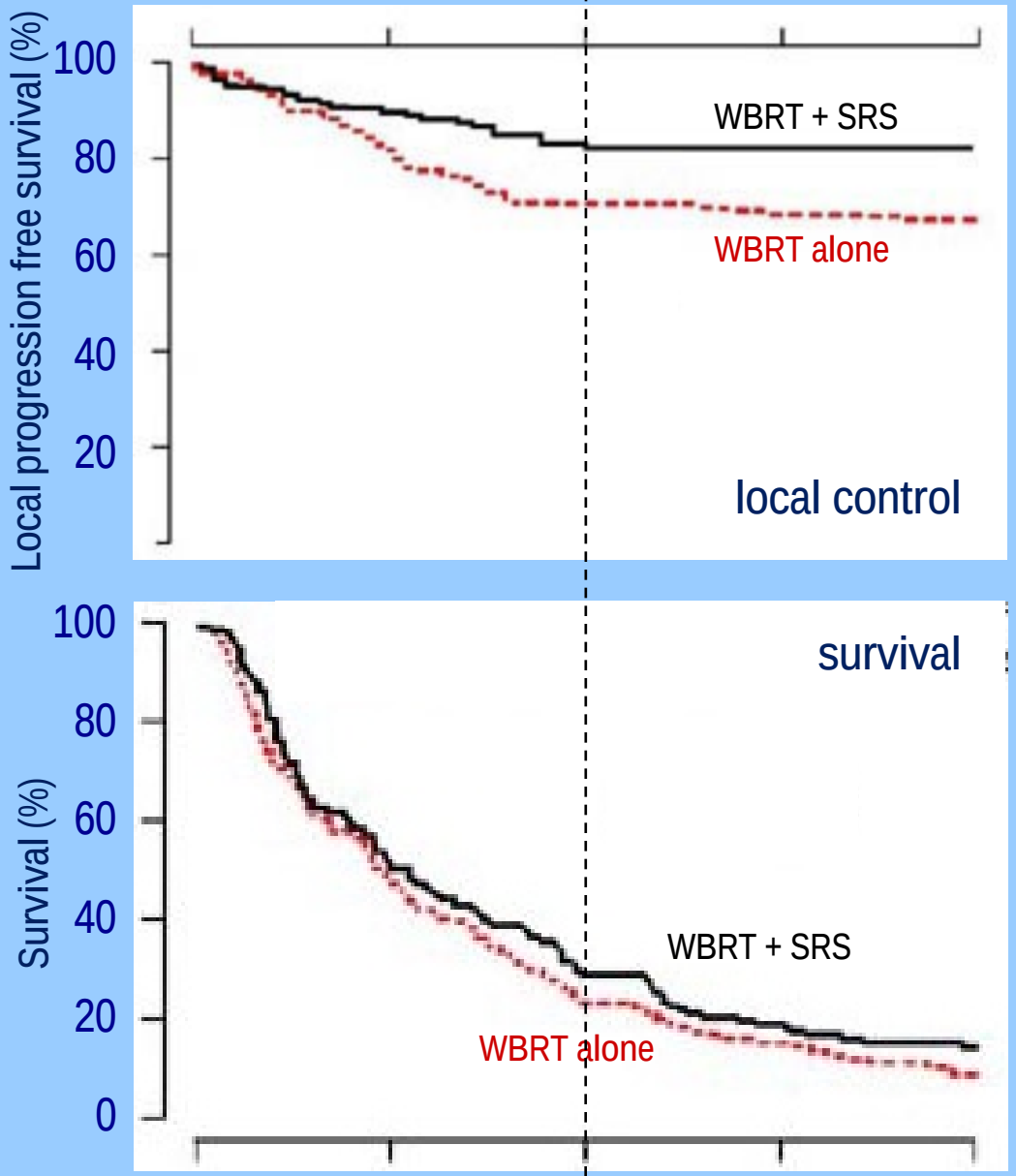
survival

quality of life

Oncological management options

WBRT +/- radiosurgery for brain metastases





RTOG 9508

Andrews et al 2004, Lancet; 363: 1665–72

WBRT whole brain RT
SRS stereotactic radiosurgery

- Radiotherapy technologies
- Context and endpoints
- Clinical issues - evidence base

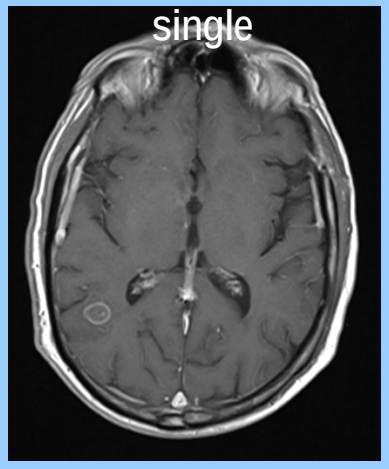
Radiotherapy in the treatment of brain metastases

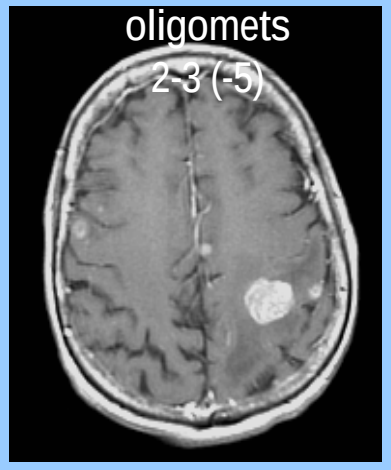
Radiotherapy options

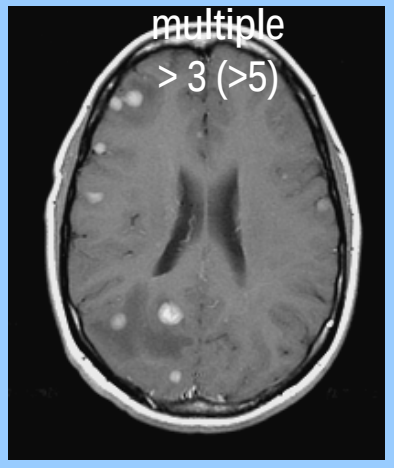
- whole brain radiotherapy (WBRT)
- partial brain radiotherapy (PBRT)
- focal radiotherapy (SRT) & radiosurgery (SRS)

Evidence base for radiotherapy in the treatment of brain metastases

radiotherapy options



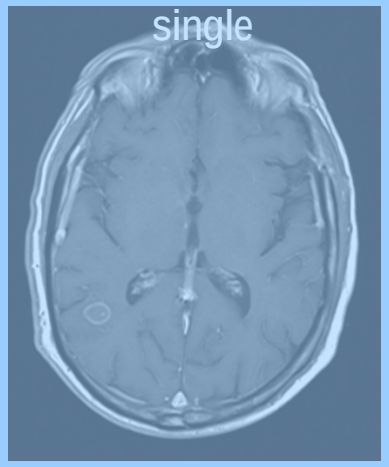


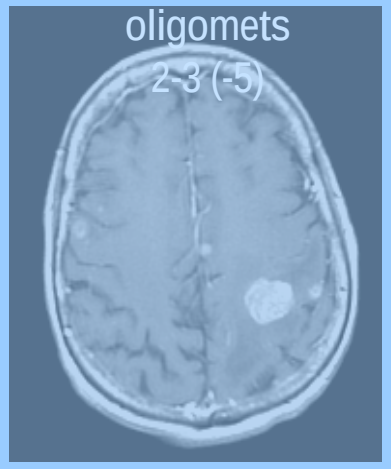


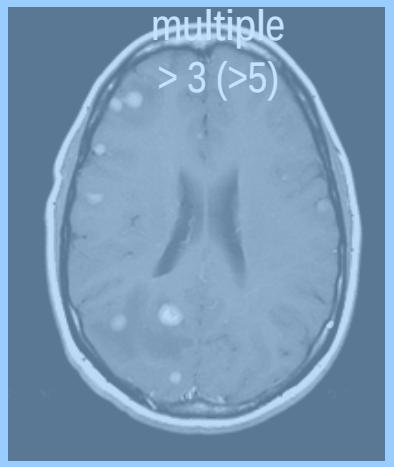
Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			







Evidence base for radiotherapy in the treatment of brain metastases

Radiosurgery plus whole brain radiotherapy
compared to whole brain radiotherapy alone
for brain metastases

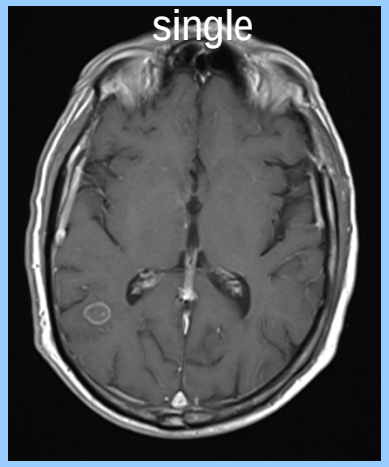
1. prolongs survival in patients with oligometastastases
2. prolongs time to functional deterioration in patients with oligometastases
3. prolongs survival in patients with single brain metastases
4. none of these
5. all of these

Whole brain radiotherapy after radiosurgery *is important* because it

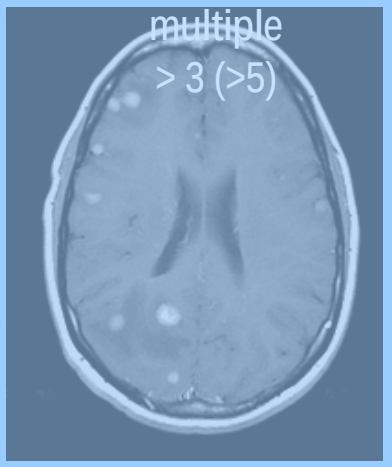
1. prolongs survival
2. prolongs time to functional deterioration
3. prolongs intracranial tumour control
4. none of these
5. all of these

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single	good	any	
oligomets			
multiple			

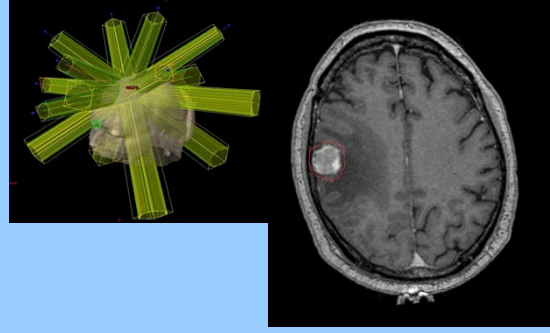


surgery
radiosurgery



Evidence base for radiotherapy in the treatment of brain metastases

RTOG trial 9508



1 - 3 brain metastases

oligometastases

randomise

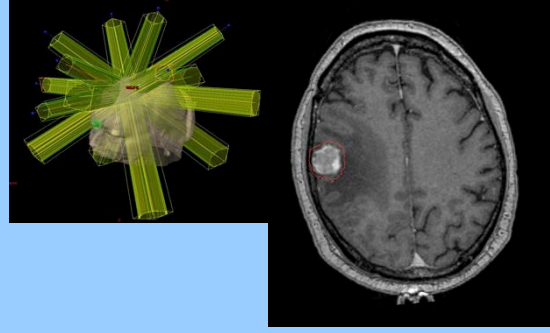
whole brain radiotherapy & radiosurgery (SRS)	whole brain radiotherapy (WBRT)
167 patients	164 patients

331 patients

Radiosurgery for “solitary” brain metastases

Andrews et al 2004, Lancet; 363: 1665–72

RTOG trial 9508



1 brain metastasis

randomise

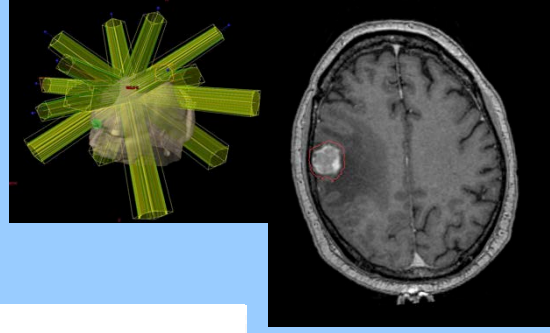
whole brain radiotherapy & radiosurgery (SRS)	whole brain radiotherapy (WBRT)
92 patients	94 patients

186 patients

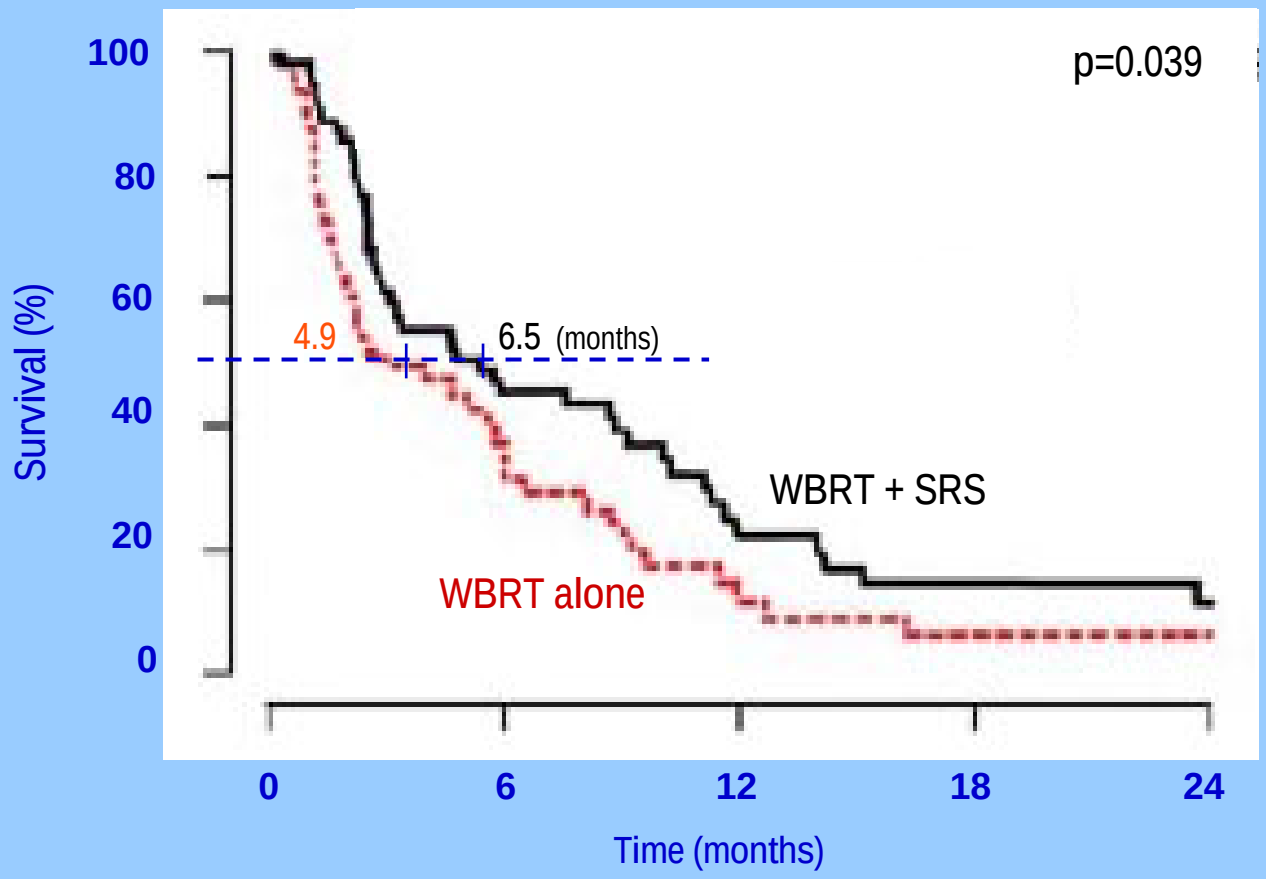
Radiosurgery for solitary brain metastases

Andrews et al 2004, Lancet; 363: 1665–72

RTOG trial 9508



survival – single brain metastases



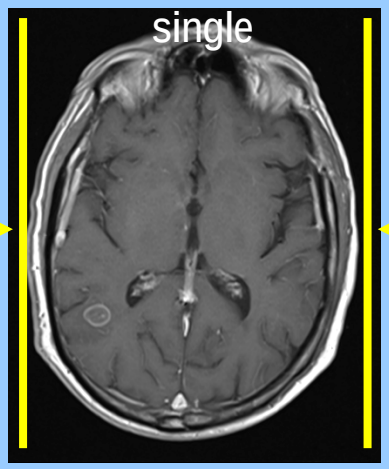
Radiosurgery for solitary brain metastases

Andrews et al 2004, Lancet; 363: 1665–72

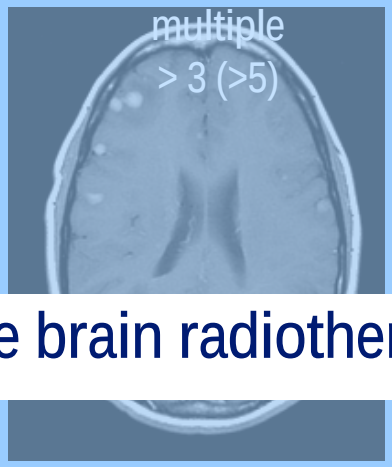
WBRT	whole brain radiotherapy
SRS	stereotactic radiosurgery

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single	good	any	
oligomets			
multiple			



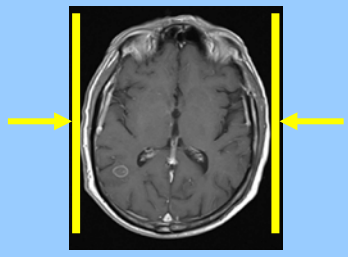
surgery
radiosurgery



additional whole brain radiotherapy ?

Evidence base for radiotherapy in the treatment of brain metastases

Japanese Radiation Oncology Study Group (JROSG 99-1)



radiosurgery

(for 1-4 mets)

randomise

whole brain radiotherapy

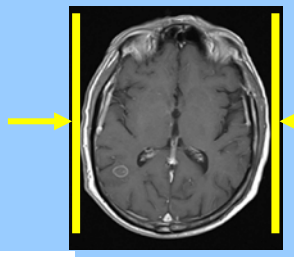
observation

132 patients

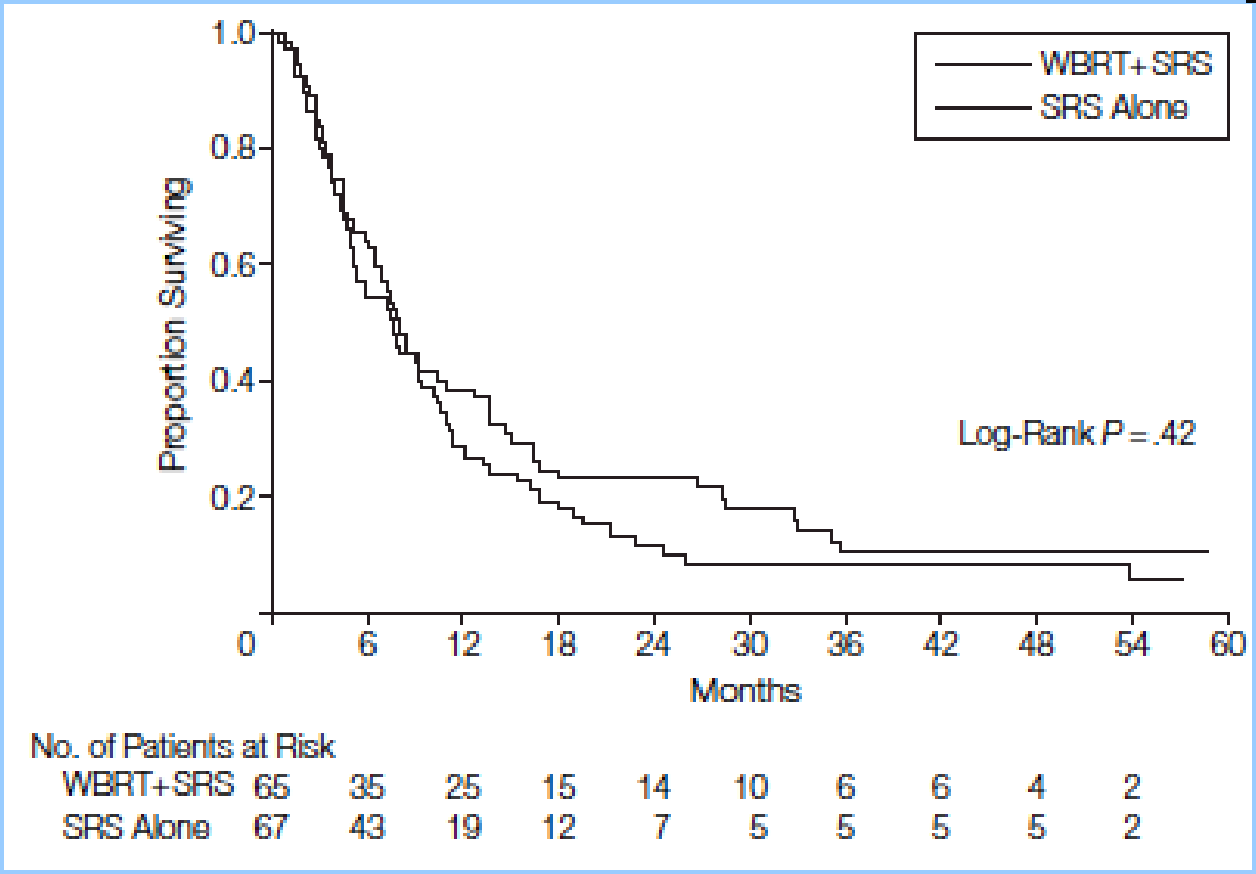
Whole brain radiotherapy following surgery or radiosurgery

Aoyama et al 2006, JAMA; 295: 2483-2491

Japanese Radiation Oncology Study Group (JROSG 99-1)



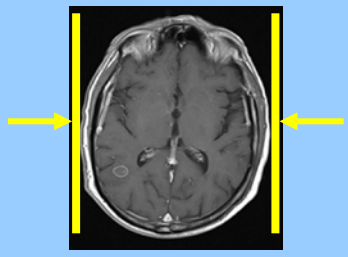
survival



Whole brain radiotherapy following surgery or radiosurgery

Aoyama et al 2006, JAMA; 295: 2483-2491

EORTC 22952-26001



surgery or radiosurgery

(for 1-3 mets)

randomise

whole brain radiotherapy

observation

180 patients

179 patients

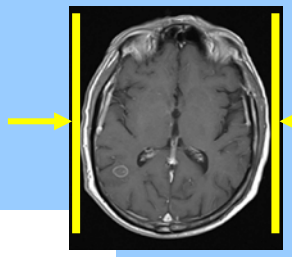
359 patients

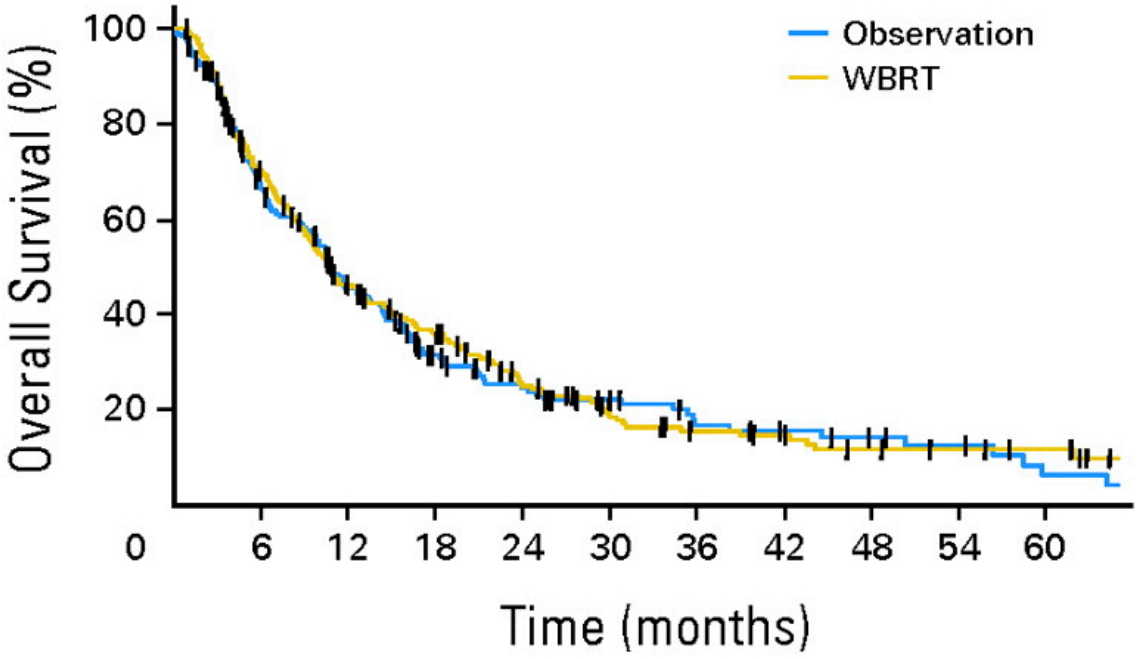
Whole brain radiotherapy following surgery or radiosurgery

Kocher et al 2011 J Clin Oncol 29:134-141

EORTC 22952-26001

survival





Randomized treatment	0	N	No. of patients at risk									
Observation	143	179	117	75	44	31	22	15	12	9	7	3
WBRT	149	180	124	80	61	38	25	18	15	11	9	7

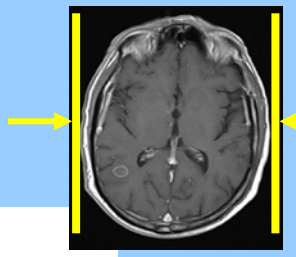
Whole brain radiotherapy following surgery or radiosurgery

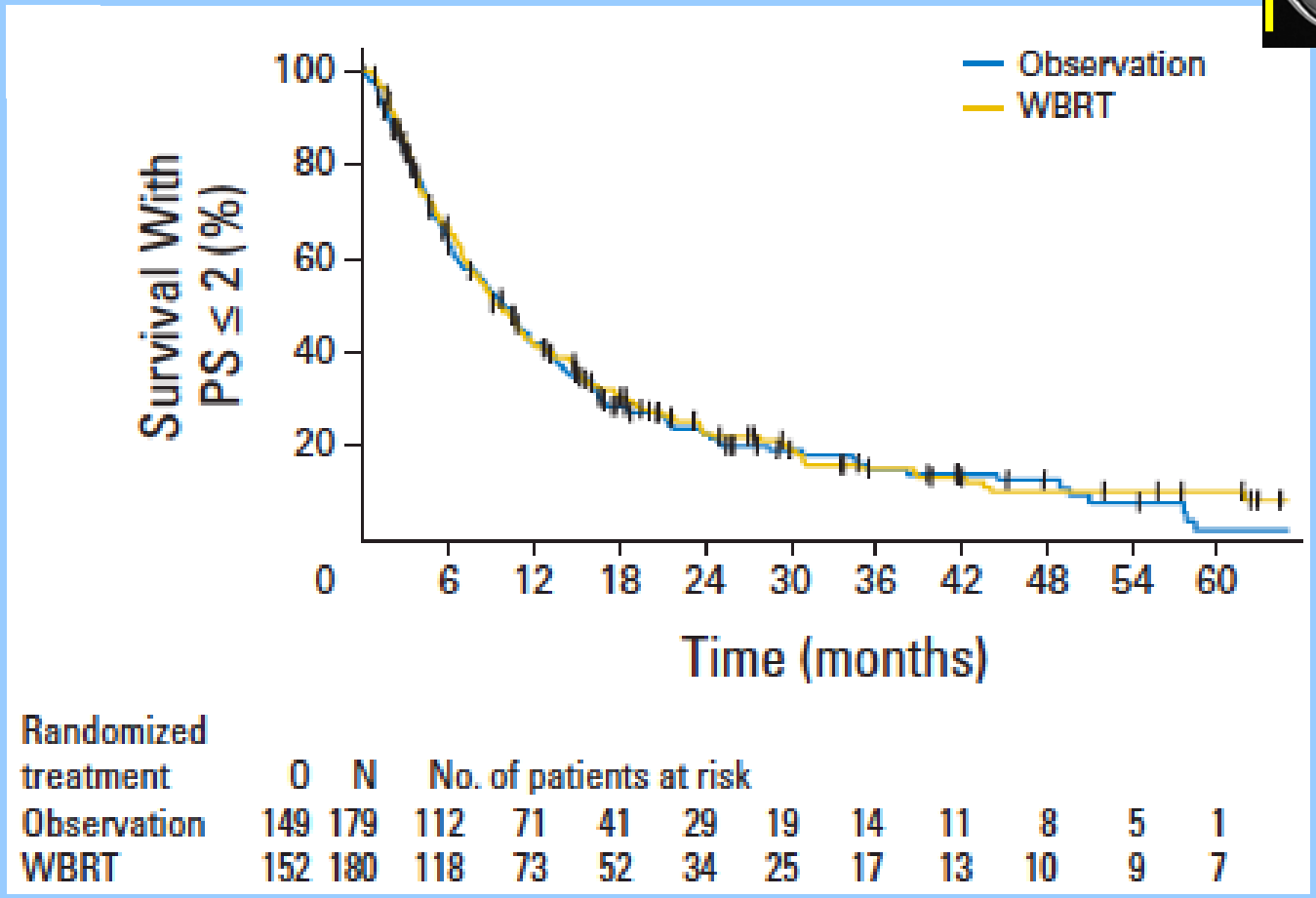
WBRT – whole brain radiotherapy

Kocher et al 2011 J Clin Oncol 29:134-141

EORTC 22952-26001

survival with good performance status





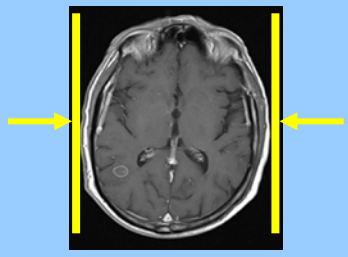
Randomized treatment	0	N	No. of patients at risk								
Observation	149	179	112	71	41	29	19	14	11	8	5	1
WBRT	152	180	118	73	52	34	25	17	13	10	9	7

Whole brain radiotherapy following surgery or radiosurgery

WBRT – whole brain radiotherapy

Kocher et al 2011 J Clin Oncol 29:134-141

NCCTG N0574 (Alliance) trial



1 - 3 brain metastases

randomise

213 patients

radiosurgery & whole brain radiotherapy

radiosurgery alone

1° endpoint: cognitive progression after treatment

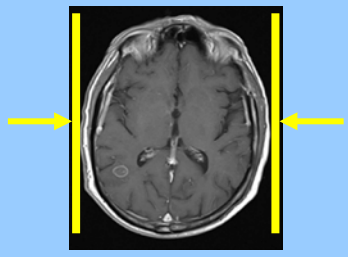
2° endpoint Survival

Cognitive progression
cognitive function tests - drop in 1SD in one test

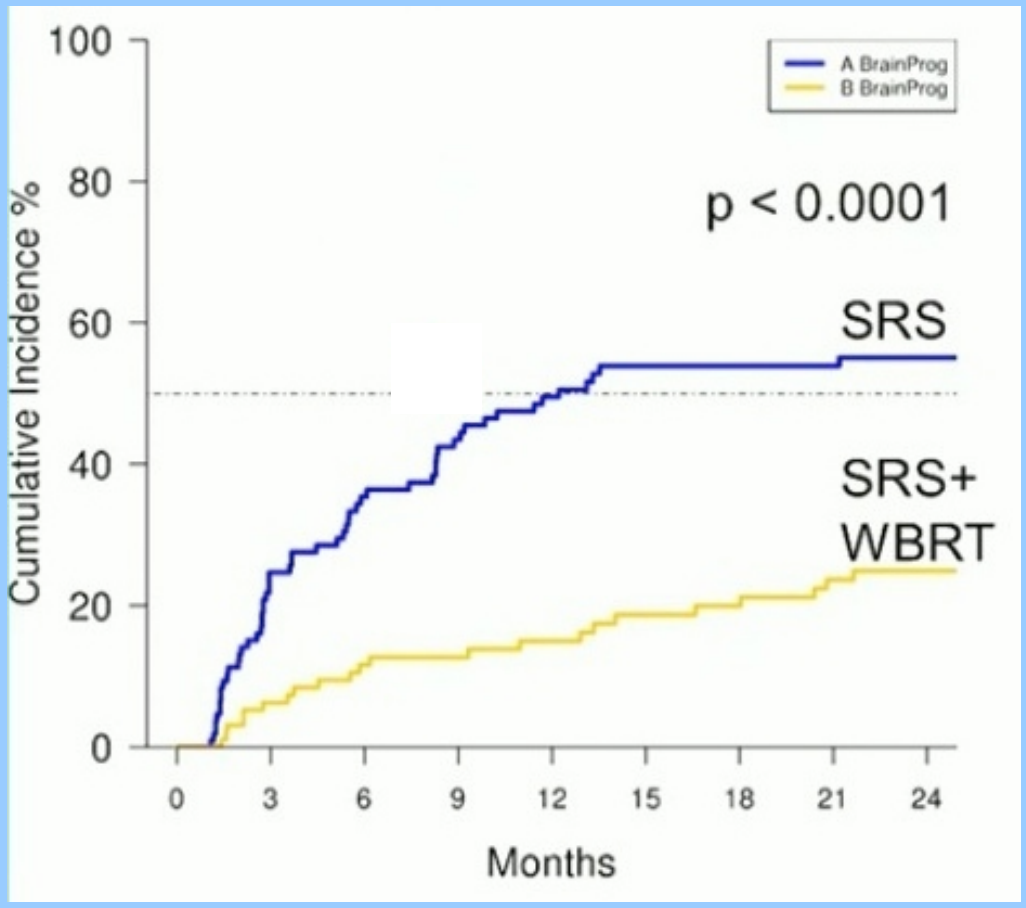
Whole brain radiotherapy following radiosurgery

Brown et al 2015 ASCO abstract #LBA4

NCCTG N0574 (Alliance) trial



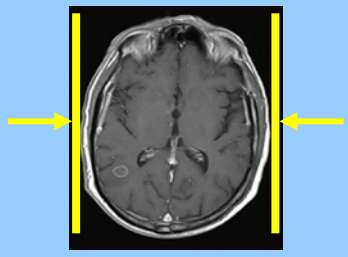
Intracranial progression



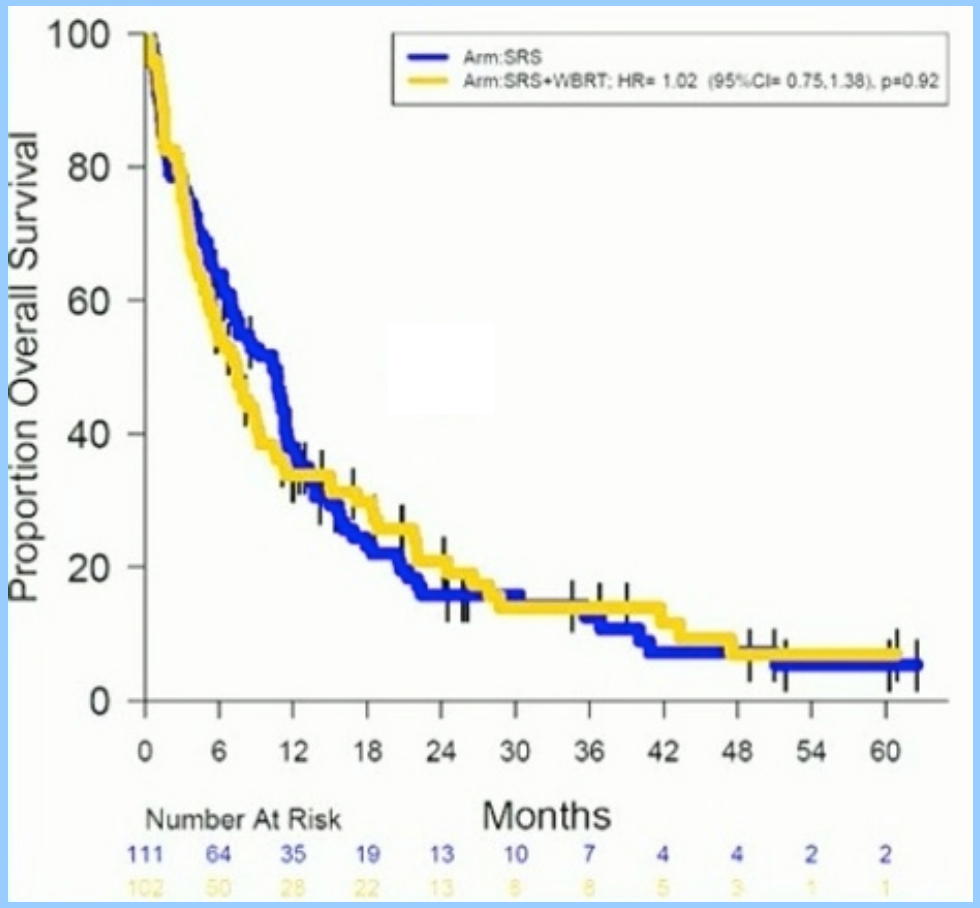
Whole brain radiotherapy following radiosurgery

Brown et al 2015 ASCO abstract #LBA4

NCCTG N0574 (Alliance) trial



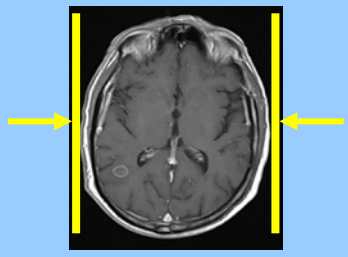
Survival



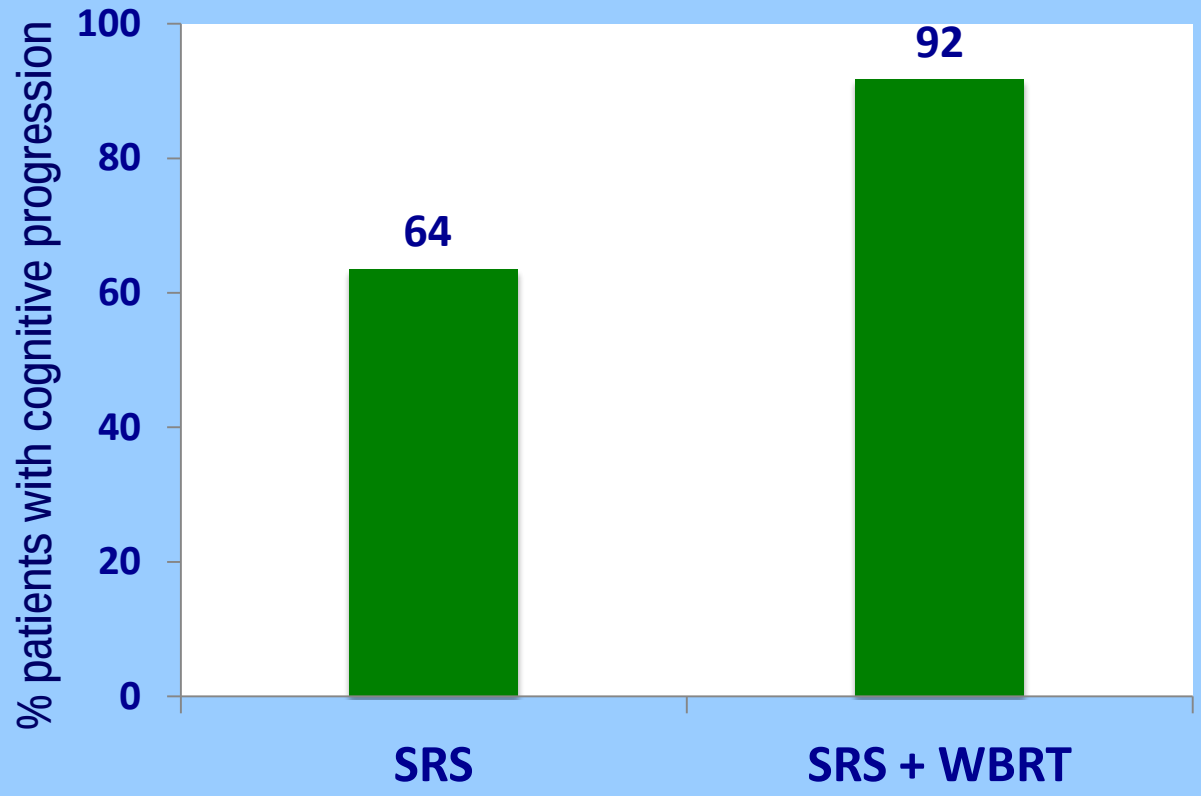
Whole brain radiotherapy following radiosurgery

Brown et al 2015 ASCO abstract #LBA4

NCCTG N0574 (Alliance) trial



Cognitive progression at 3 months

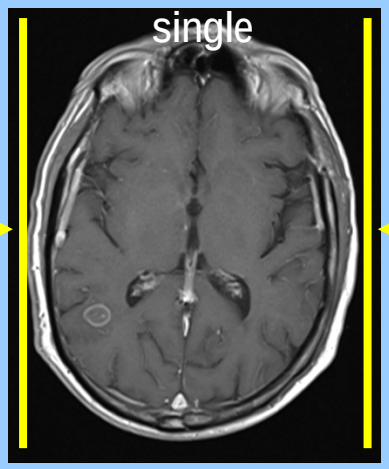


Whole brain radiotherapy following radiosurgery

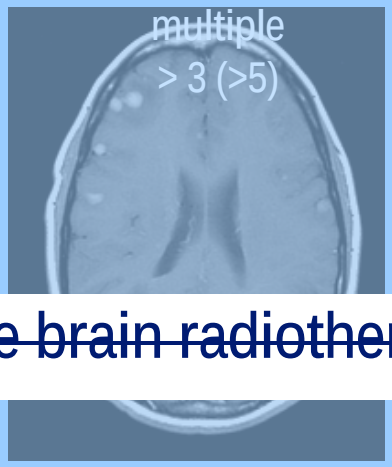
Brown et al 2015 ASCO abstract #LBA4

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single	good	any	
oligomets			
multiple			



surgery
radiosurgery

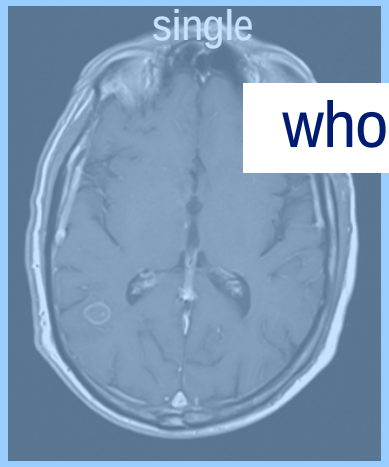


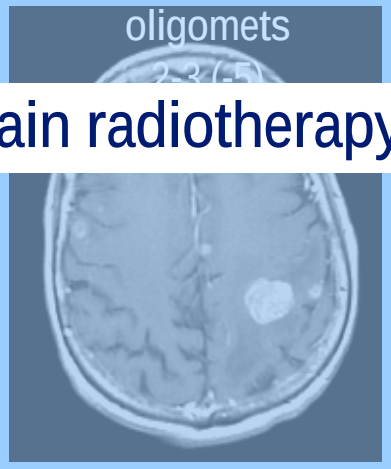
~~additional whole brain radiotherapy~~

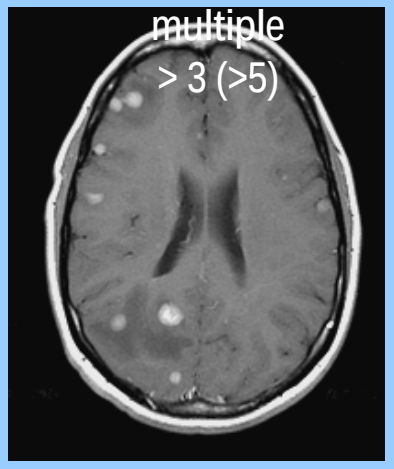
Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			



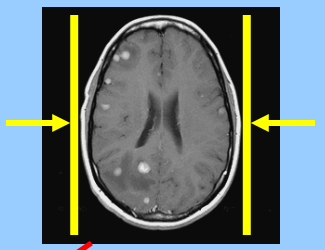




whole brain radiotherapy

Evidence base for radiotherapy in the treatment of brain metastases

whole brain radiotherapy and survival



patients with brain metastases

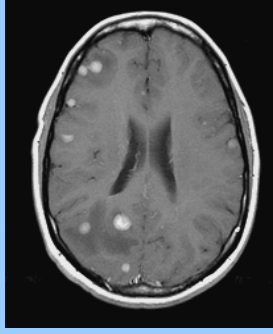
randomise

palliative radiotherapy & supportive care

supportive care alone

Effect of whole brain radiotherapy on survival

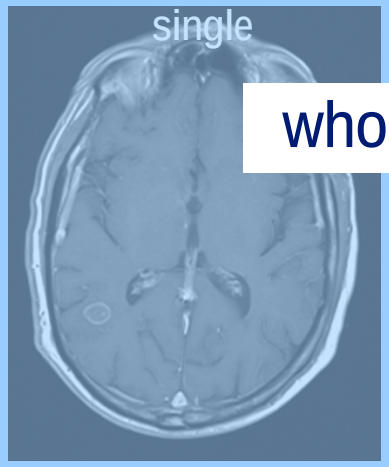
Course of malignant disease

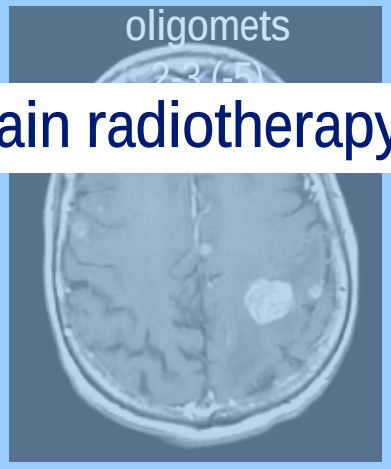


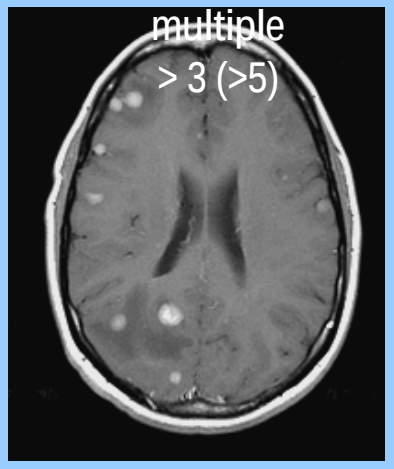
Brain metastases in malignancy

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single oligomets			
multiple	poor		end stage



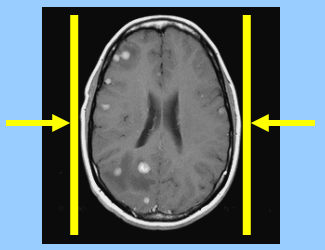




whole brain radiotherapy

Evidence base for radiotherapy in the treatment of brain metastases

QUARTZ trial CR UK & TROG



brain metastases in NSCLC
& poor prognostic factors

randomise

palliative radiotherapy & supportive care

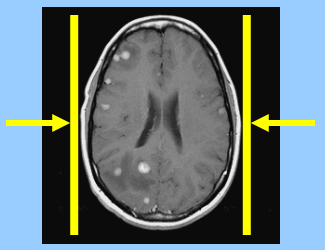
supportive care alone

endpoints: palliative efficacy (QOL, Barthel), survival free of neurological progression, survival

Effect of whole brain radiotherapy on survival & QOL

Mulvenna et al 2015 ASCO Abstract #8005

QUARTZ trial CR UK & TROG



brain metastases in NSCLC
& poor prognostic factors

randomise

538

palliative radiotherapy & supportive care

269

supportive care alone

269

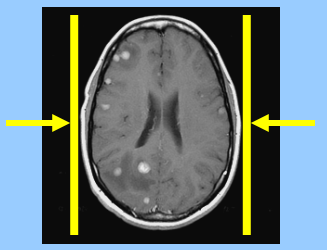
endpoints: palliative efficacy (QOL, Barthel), survival free of neurological progression, survival

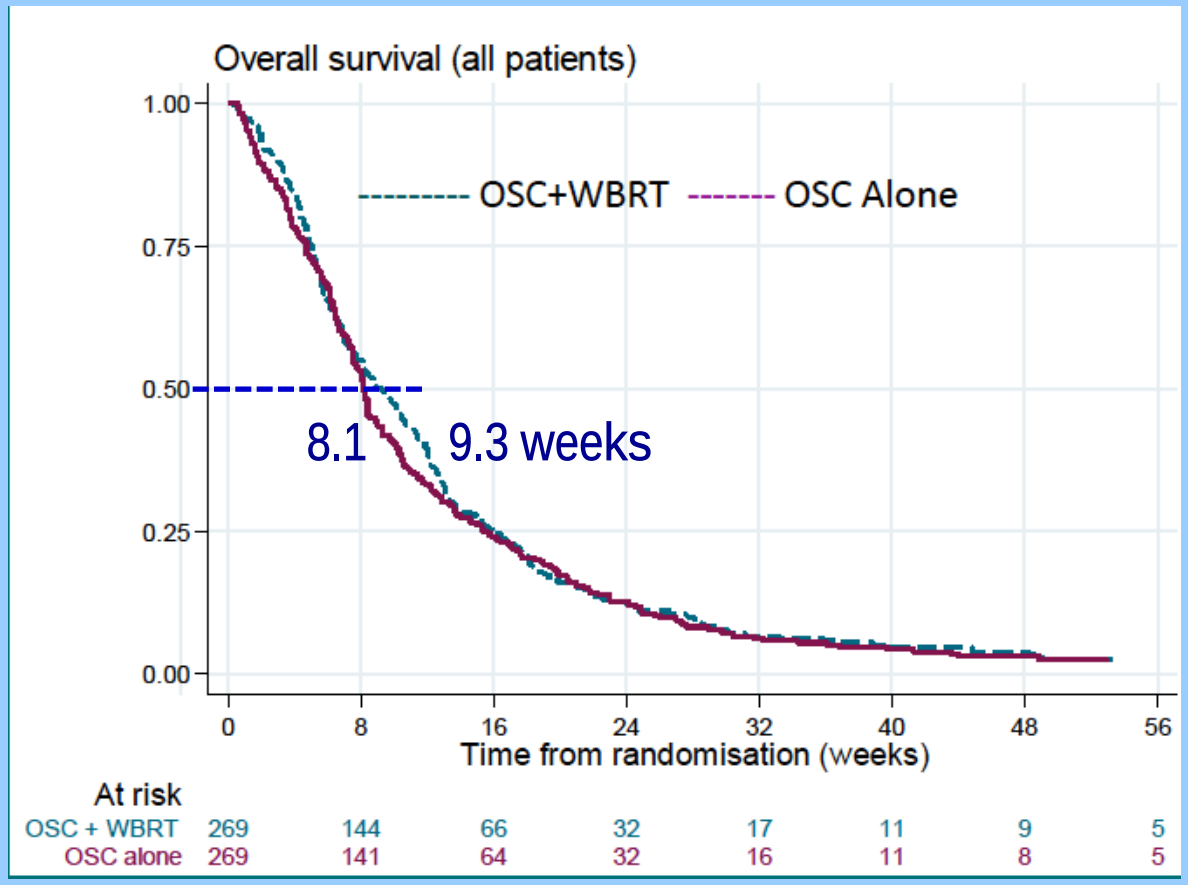
Effect of whole brain radiotherapy on survival & QOL

Mulvenna et al 2015 ASCO Abstract #8005

QUARTZ trial CR UK & TROG

survival



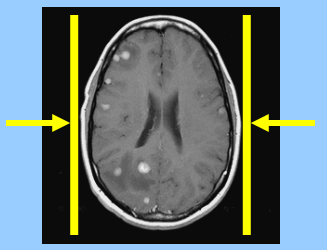


Effect of whole brain radiotherapy on survival & QOL

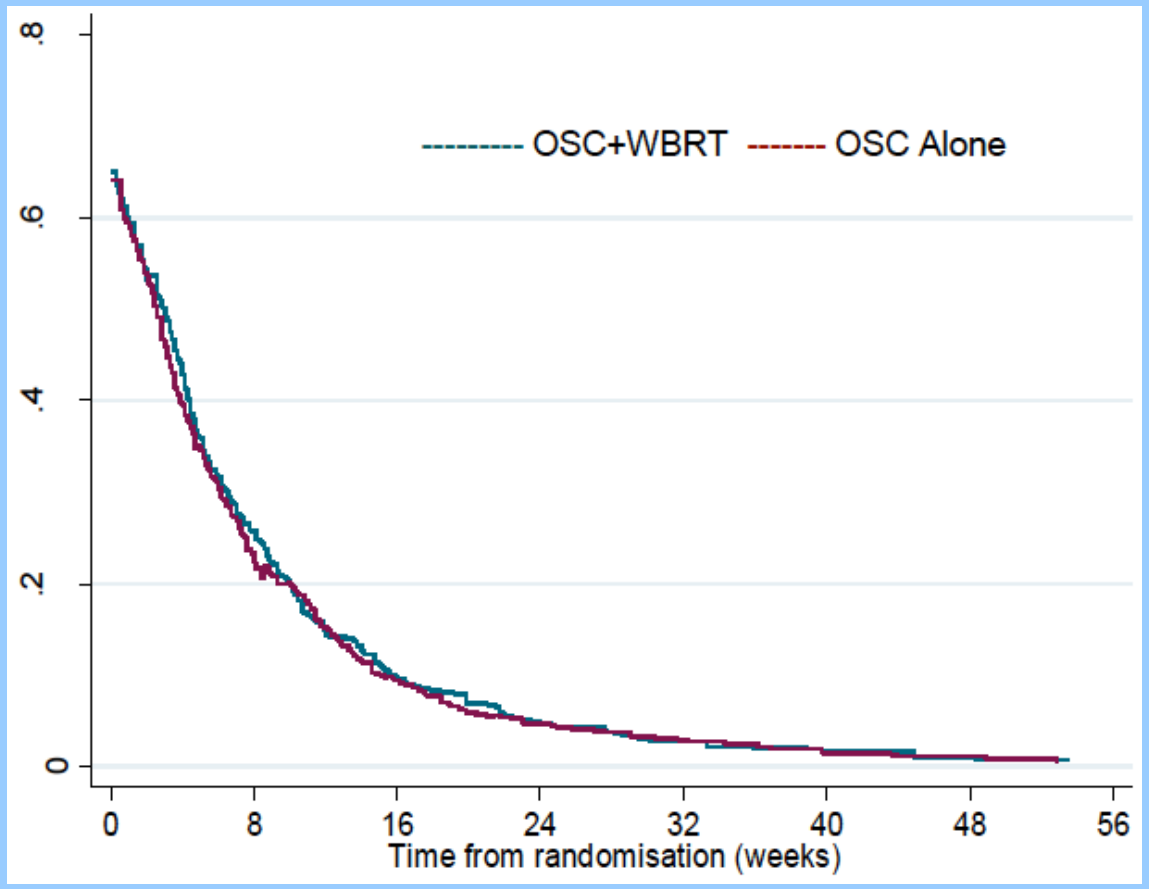
Mulvenna et al 2015 ASCO Abstract #8005

QUARTZ trial CR UK / TROG

quality adjusted life years (QALY)



QALY

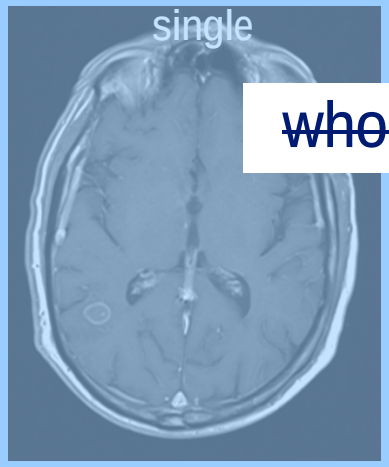


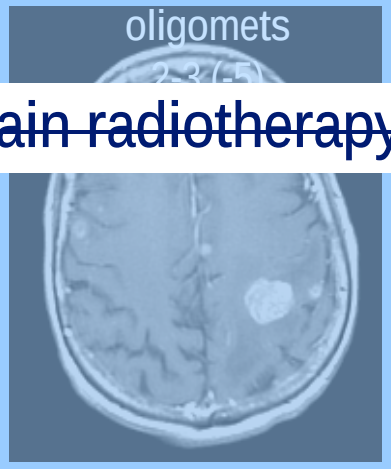
Effect of whole brain radiotherapy on survival & QOL

Mulvenna et al 2015 ASCO Abstract #8005

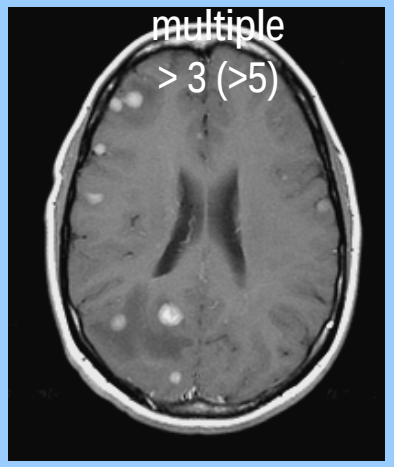
Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple	poor		end stage





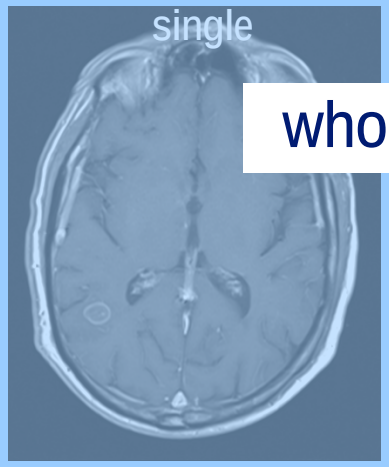
~~whole brain radiotherapy~~

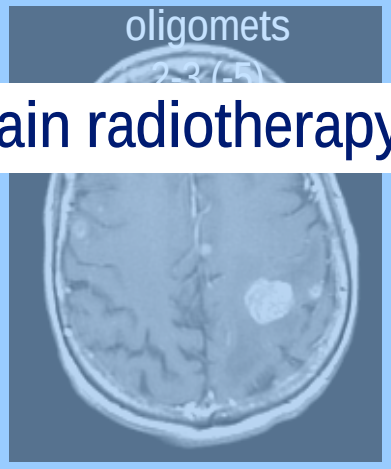


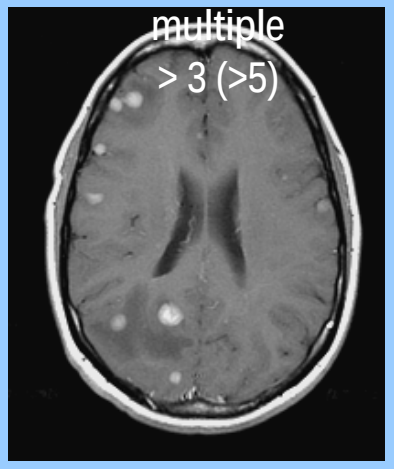
Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			





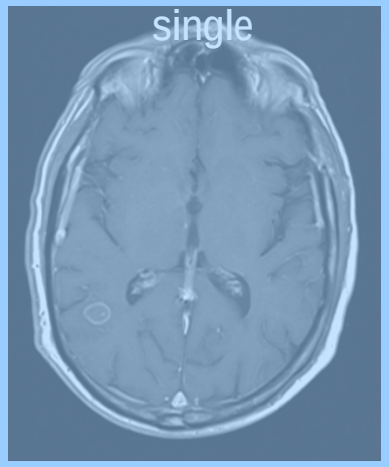


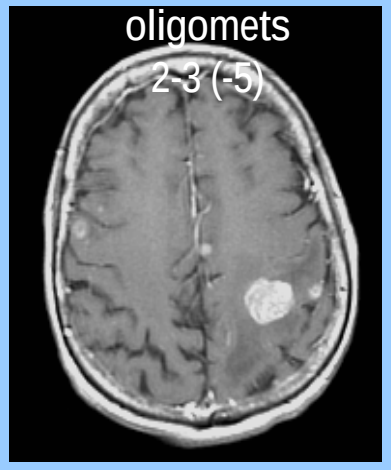
whole brain radiotherapy

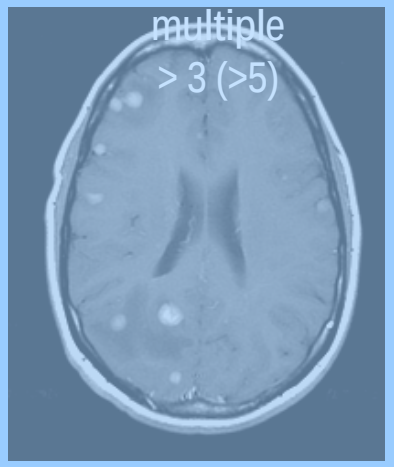
Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			



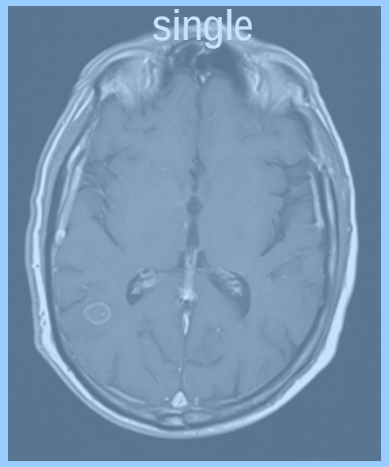


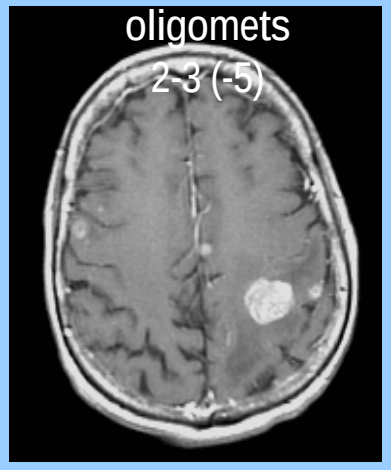


Evidence base for radiotherapy in the treatment of brain metastases

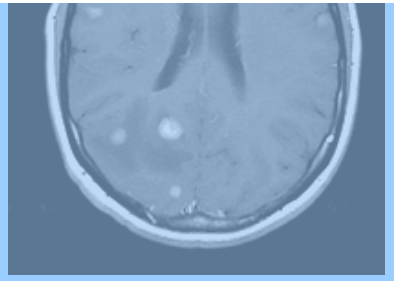
Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets	good		
multiple			



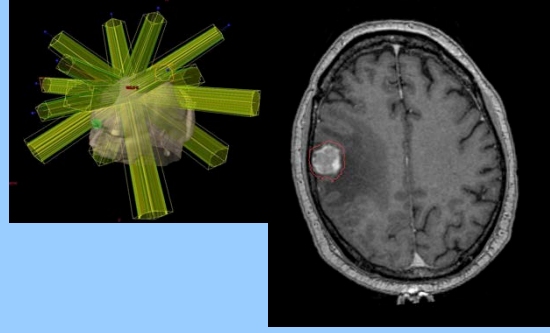


whole brain radiotherapy
or radiosurgery (or both)



Evidence base for radiotherapy in the treatment of brain metastases

RTOG trial 9508



1 - 3 brain metastases

oligometastases

randomise

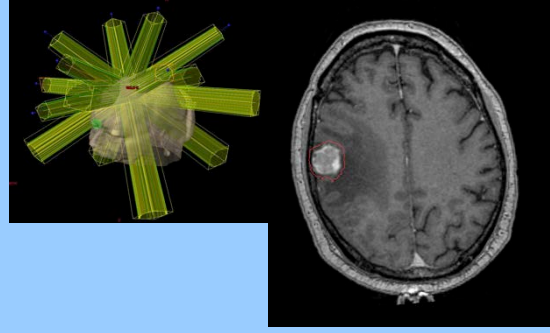
whole brain radiotherapy & radiosurgery (SRS)	whole brain radiotherapy (WBRT)
167 patients	164 patients

331 patients

Radiosurgery for “solitary” brain metastases

Andrews et al 2004, Lancet; 363: 1665–72

RTOG trial 9508



oligometastases

(2-3 mets)

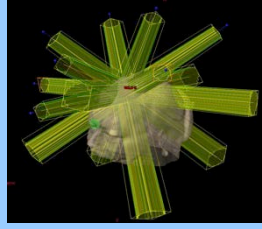
randomise

whole brain radiotherapy & radiosurgery (SRS)	whole brain radiotherapy (WBRT)
73 patients	72 patients

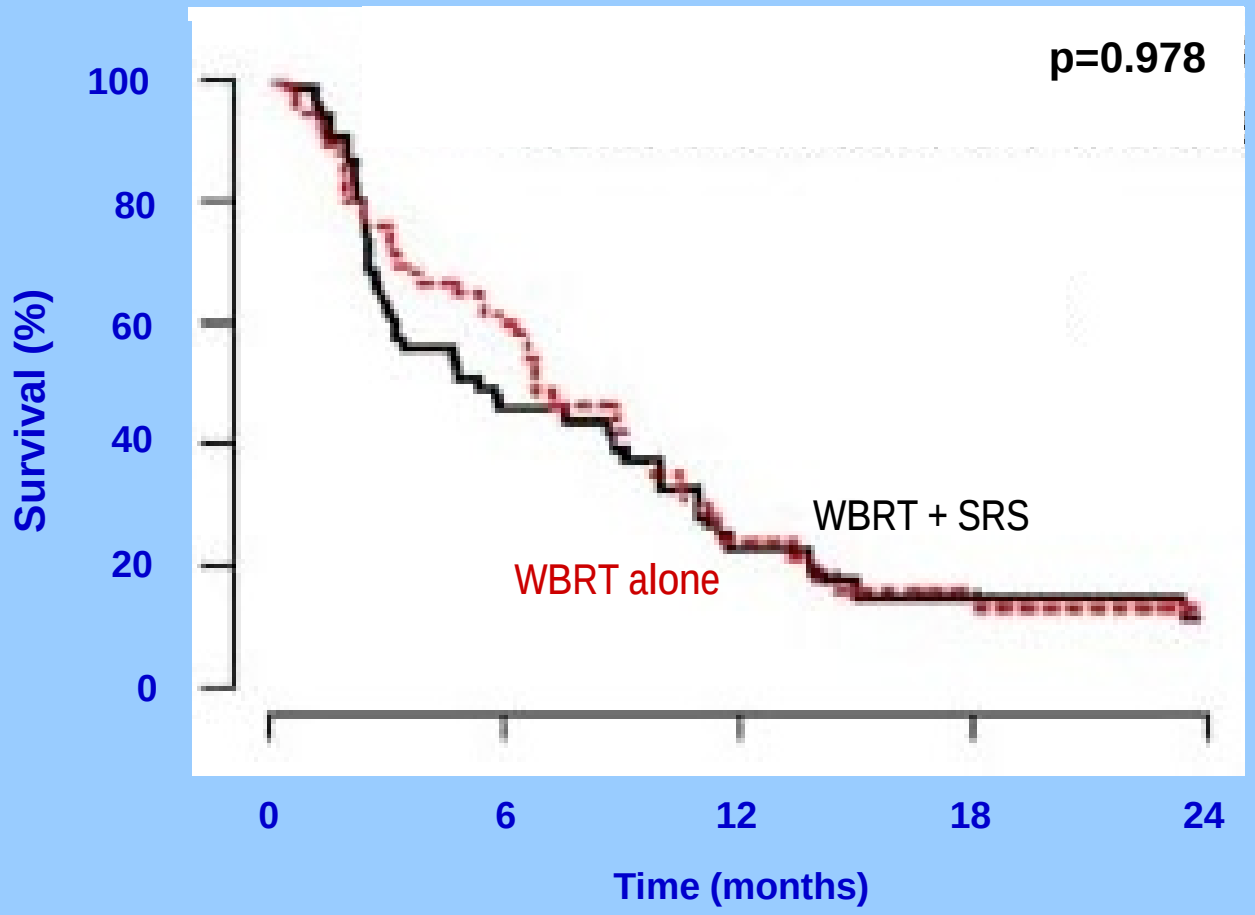
145 patients

Radiosurgery for oligometastases in the brain

Andrews et al 2004, Lancet; 363: 1665–72



survival 2 – 3 brain metastases



Radiosurgery for oligometastases in the brain

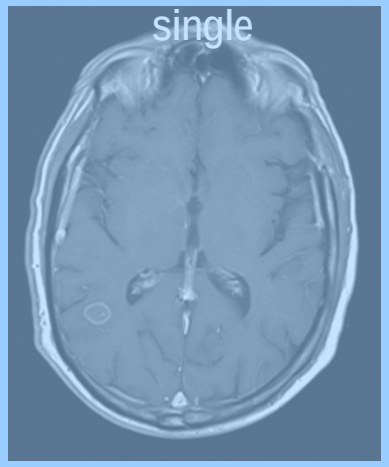
RTOG 9508

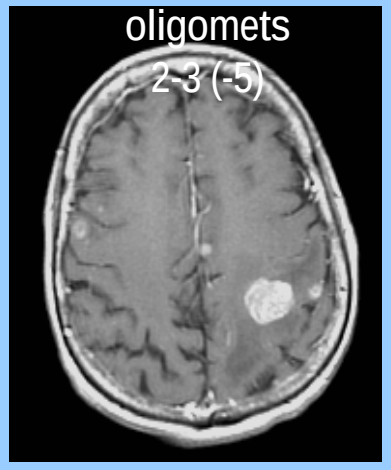
Andrews et al 2004, Lancet; 363: 1665–72

WBRT	whole brain radiotherapy
SRS	stereotactic radiosurgery

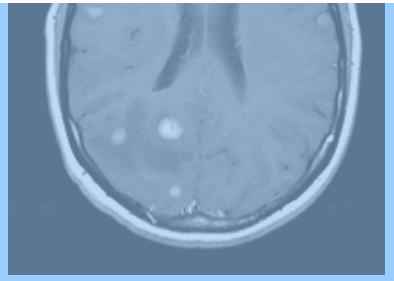
Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets	good		
multiple			



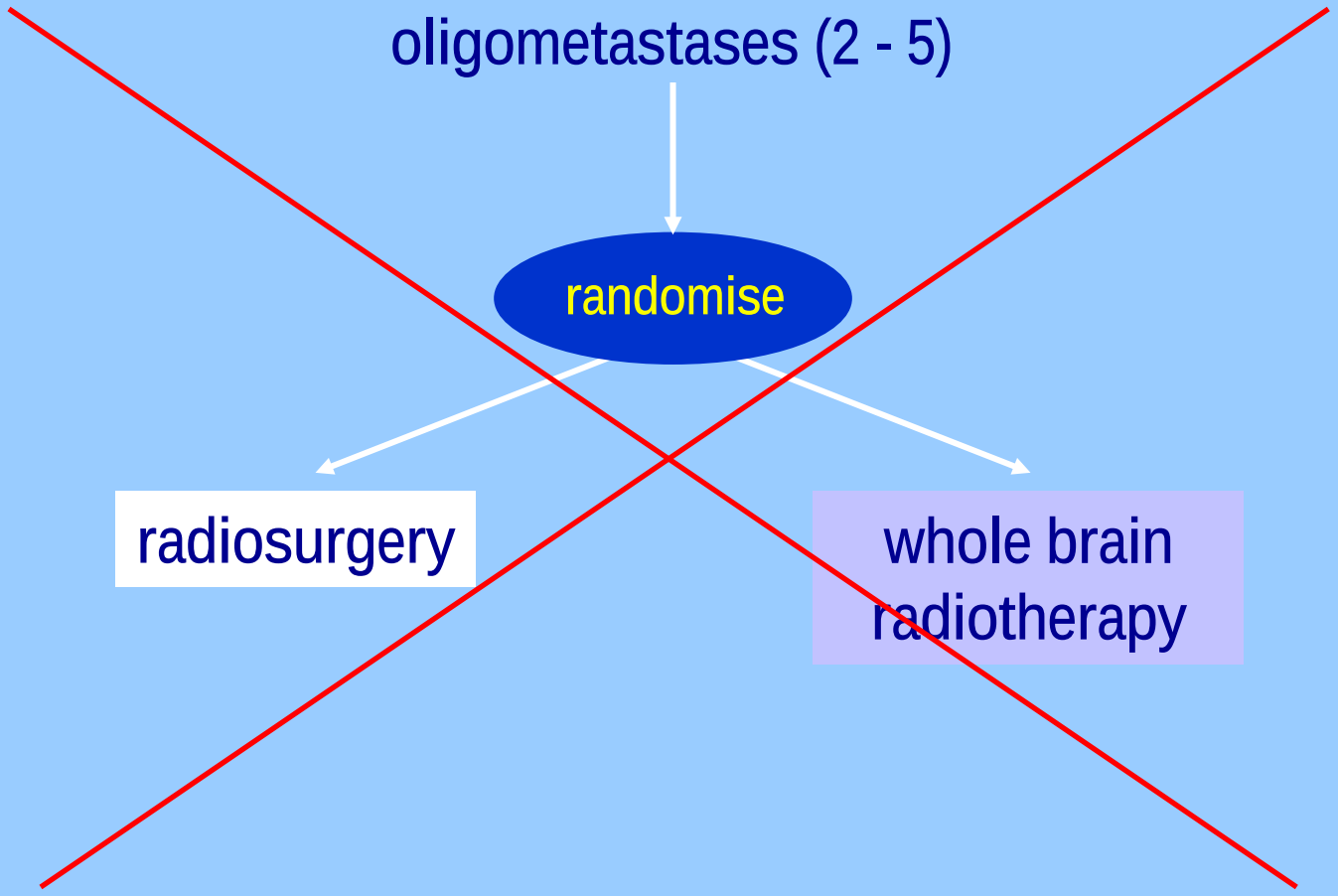


whole brain radiotherapy
or radiosurgery (or both)



Evidence base for radiotherapy in the treatment of brain metastases

Oligometastases



Radiosurgery for oligometastases in the brain

Radiosurgery after whole brain radiotherapy

Proportion receiving radiosurgery (SRS)
7.8%

sample of 898 patients of 3030 patients receiving radiotherapy for brain mets

Stereotactic radiotherapy utilisation

Hodgson et al 2012 multicentre survey of Canadian centres

Independent factors associated with higher chance of receiving SRS

Availability of on-site SRS

Fewer brain metastases

Controlled extracranial disease

Age

sample of 898 patients of 3030 patients receiving radiotherapy for brain mets

Stereotactic radiosurgery utilisation

Hodgson et al 2012 multicentre survey of Canadian centres

SEERS study

year	Proportion receiving radiosurgery (SRS)
2000	3.0%
2005	8.2%

SEERS-Medicare database, patients with NSCLC and diagnosed with brain metastases
7708 patients treated with RT within 2 months of brain mets diagnosis, age >65

Stereotactic radiotherapy utilisation

Halasz et al 2011 ASTRO abstract

SEERS study

Independent factors associated with higher chance of receiving SRS

Year of diagnosis

Higher socio-economic status

Number of sites of systemic disease

Longer progression free interval

Admission to teaching hospital

No history of low income status

SEERS-Medicare database, patients with NSCLC and diagnosed with brain metastases
7708 patients treated with RT within 2 months of brain mets diagnosis, age >65

Stereotactic radiosurgery utilisation

Halasz et al 2011 ASTRO abstract

SEERS study

Independent factors associated with higher chance of receiving SRS

Year of diagnosis

Higher socio-economic status

Number of sites of systemic disease

Longer progression free interval

Admission to teaching hospital

No history of low income status

prognosis

SEERS-Medicare database, patients with NSCLC and diagnosed with brain metastases
7708 patients treated with RT within 2 months of brain mets diagnosis, age >65

Stereotactic radiosurgery utilisation

Halasz et al 2011 ASTRO abstract

SEERS study

Independent factors associated with higher chance of receiving SRS

Year of diagnosis — prognosis

Higher socio-economic status — availability

Number of sites of systemic disease — prognosis

Longer progression free interval — prognosis

Admission to teaching hospital — availability

No history of low income status — availability

SEERS-Medicare database, patients with NSCLC and diagnosed with brain metastases
7708 patients treated with RT within 2 months of brain mets diagnosis, age >65

Stereotactic radiosurgery utilisation

Halasz et al 2011 ASTRO abstract

SEERS study

Independent factors associated with higher chance of receiving SRS

Year of diagnosis

Higher socio-economic status

Number of sites of systemic disease

Longer progression free interval

Admission to teaching hospital

No history of low income status

prognosis

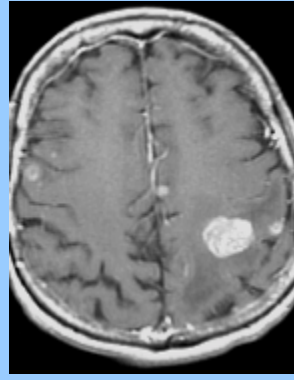
availability

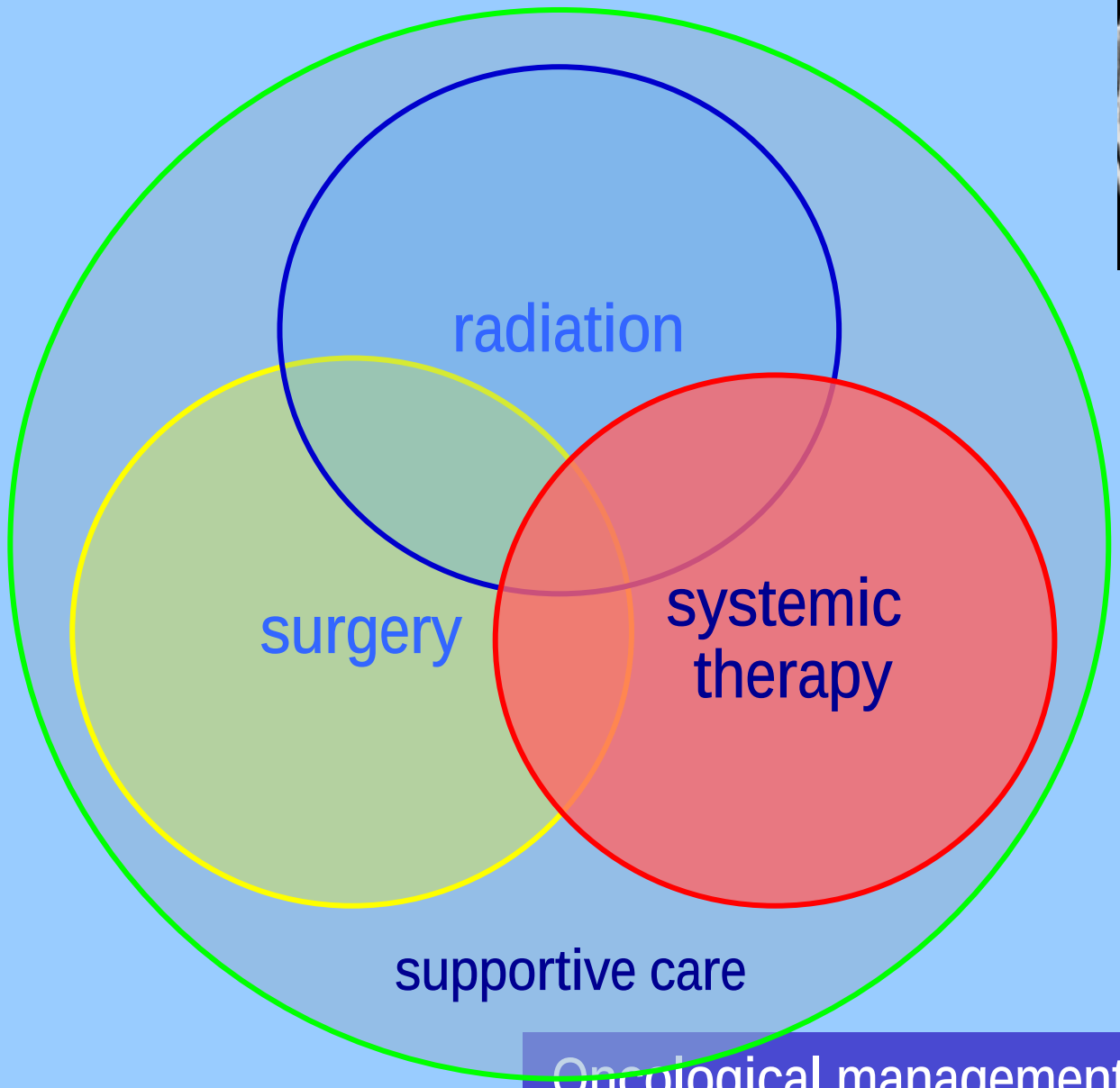
inequity

SEERS-Medicare database, patients with NSCLC and diagnosed with brain metastases
7708 patients treated with RT within 2 months of brain mets diagnosis, age >65

Stereotactic radiosurgery utilisation

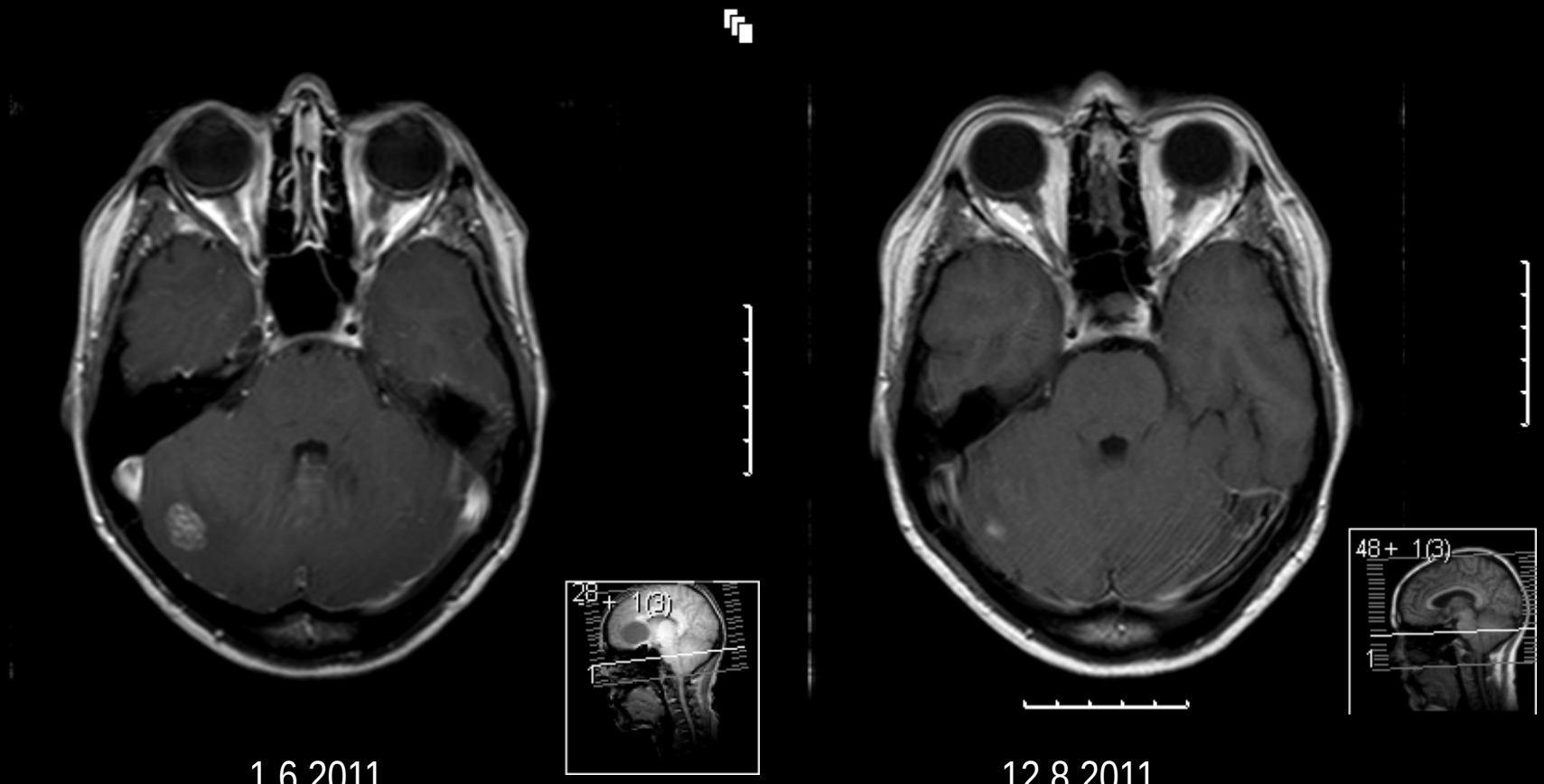
Halasz et al 2011 ASTRO abstract





Oncological management options

ER+ metastatic breast cancer

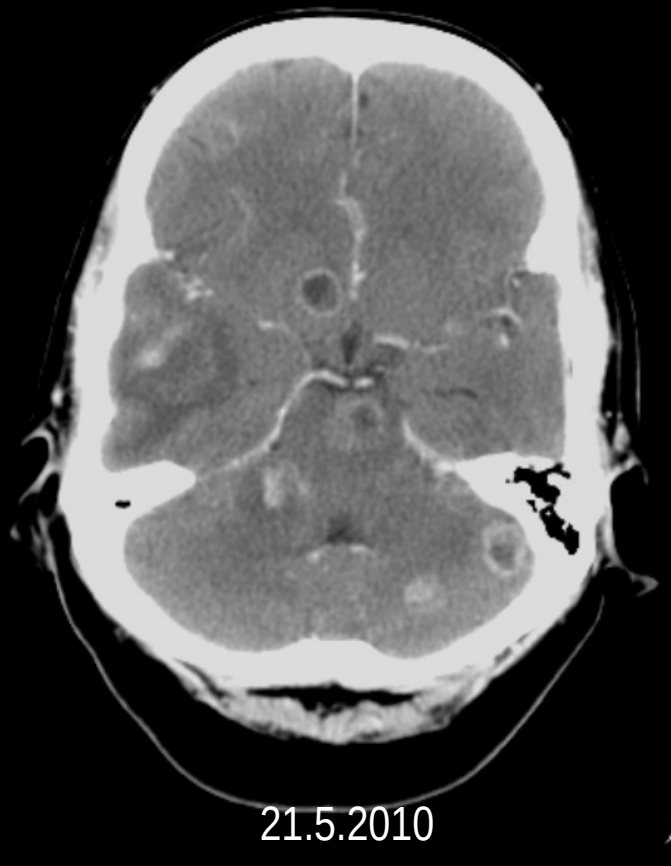


1.6.2011

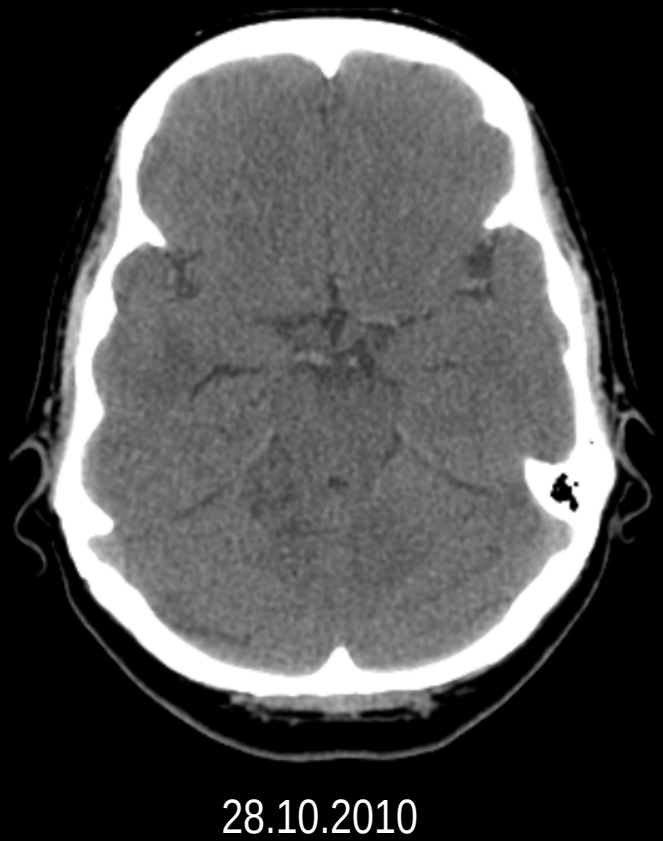
12.8.2011

response to Anastrazole & Goserelin

lung adenocarcinoma with EGFR mutation



21.5.2010



28.10.2010

response to Erlotinib

primary therapy in sensitive tumours

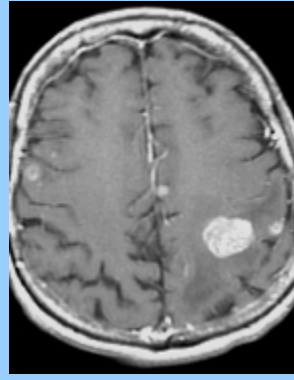
in common cancers (eg breast, NSCLC)

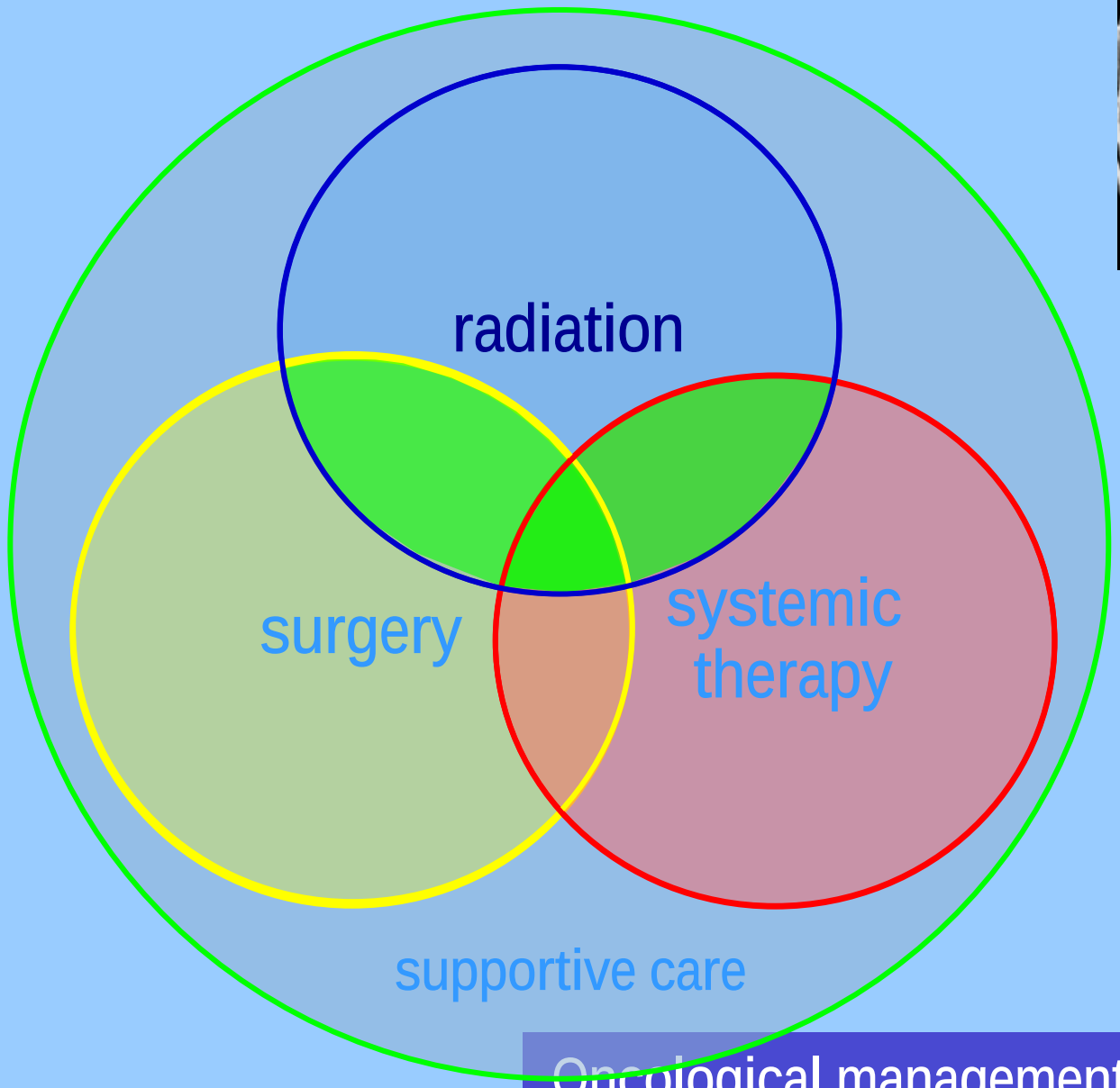
response of enhancing brain mets

similar magnitude as

response of systemic disease

Systemic therapy for brain metastases





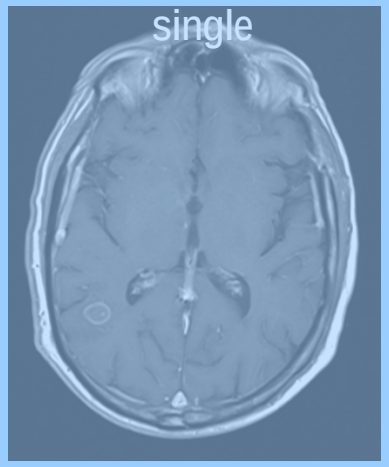
Oncological management options

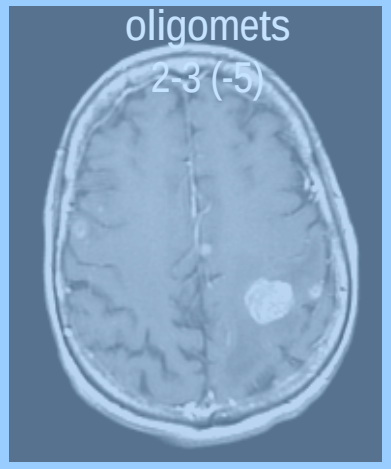
In patients with non-small cell lung cancer and brain metastases

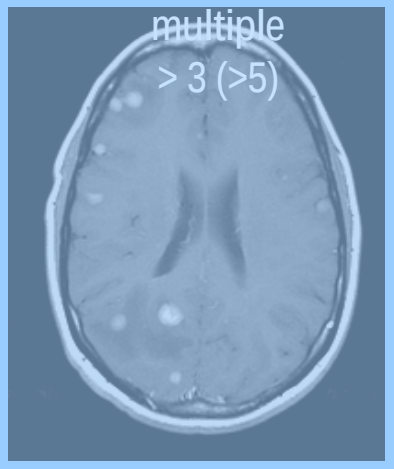
1. at presentation (stage IV disease) radiotherapy
   is the best treatment
2. chemotherapy is the best treatment in patients with
   poor performance status
3. in ALK mutated adenocarcinoma
   crizotinib is the appropriate treatment
4. in ALK mutated adenocarcinoma
   crizotinib prolongs survival compared to whole brain RT
5. none of these

Matrix - radiotherapy options

No. met's	prognosis 1^0 tumour timing
single oligomets multiple	responsive to systemic treatment



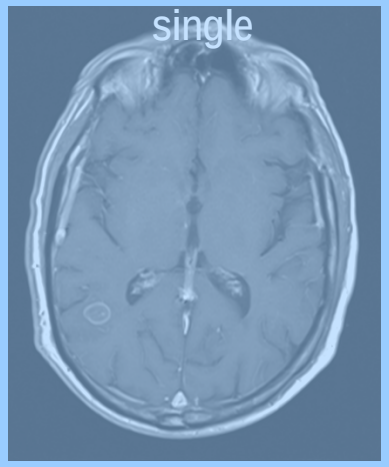


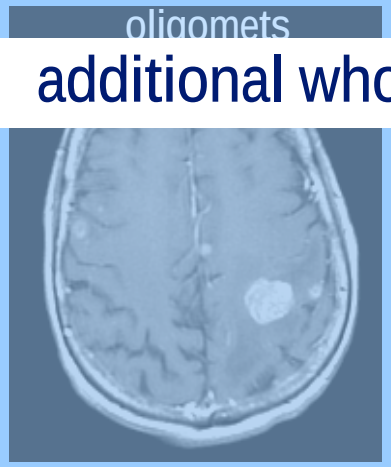


Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

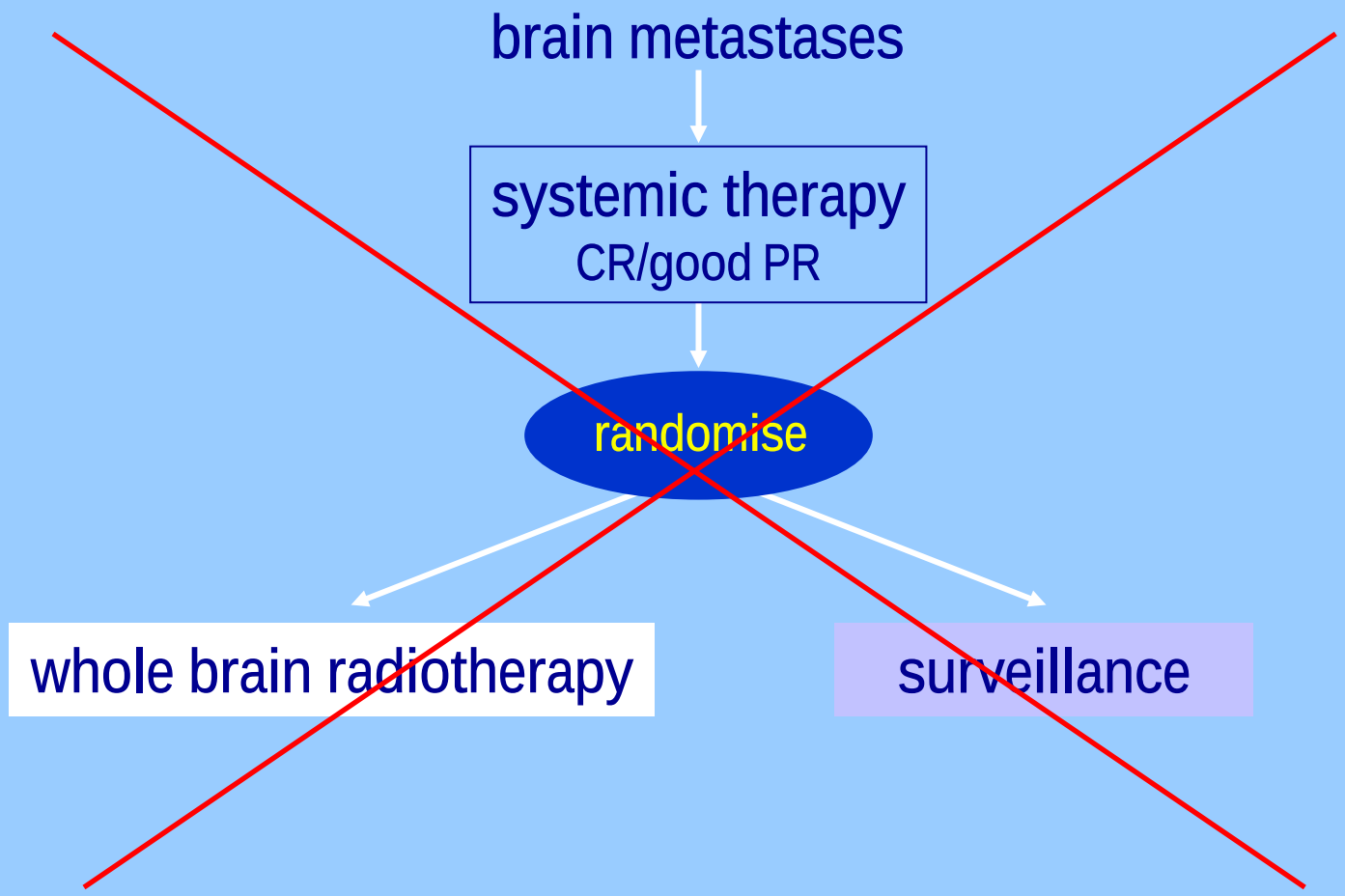
No. met's	prognosis 1^0 tumour timing
single oligomets multiple	responsive to systemic treatment





additional whole brain radiotherapy?

Tumours responsive to systemic treatment

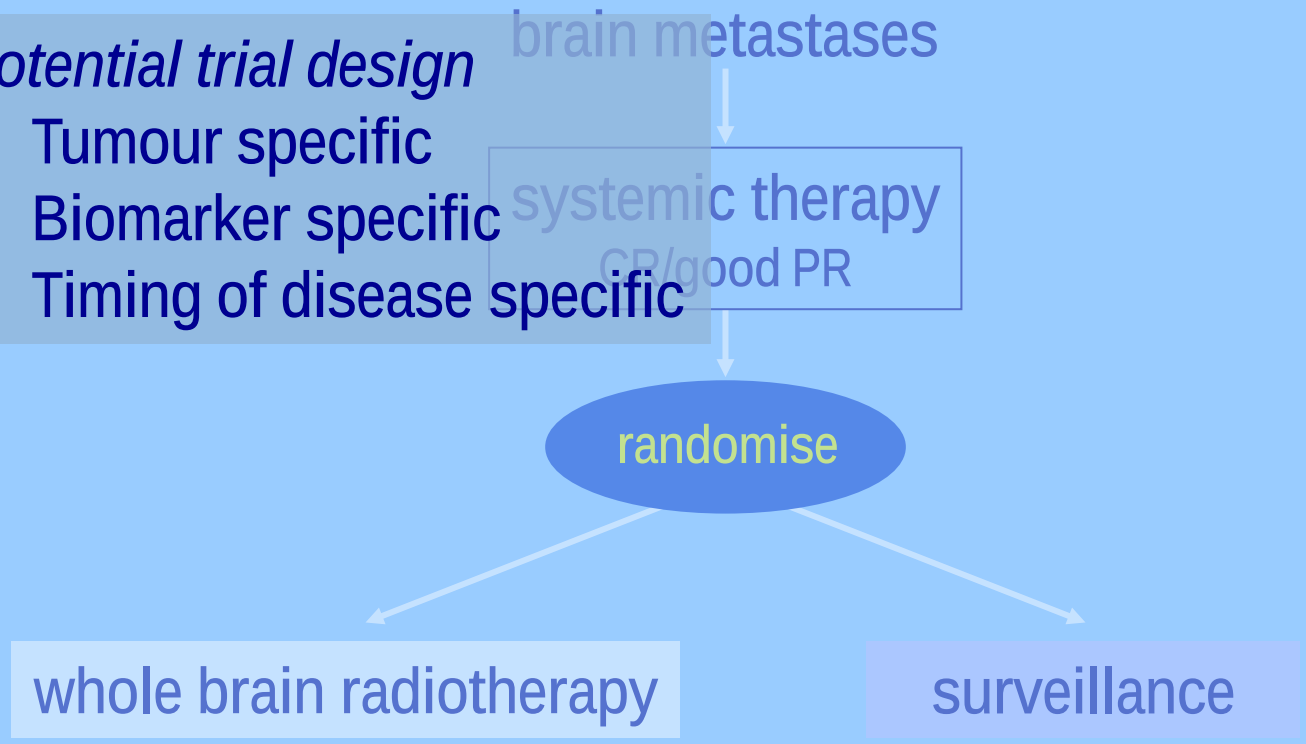


Role of radiotherapy in responsive tumours

Tumours responsive to systemic treatment

Potential trial design

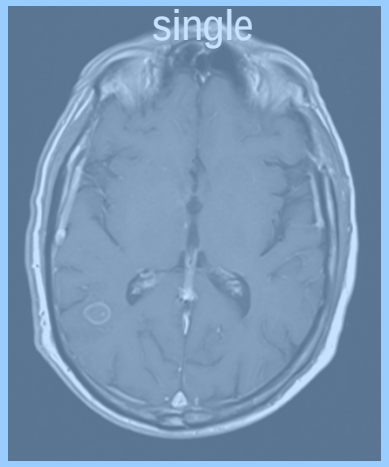
- Tumour specific
- Biomarker specific
- Timing of disease specific

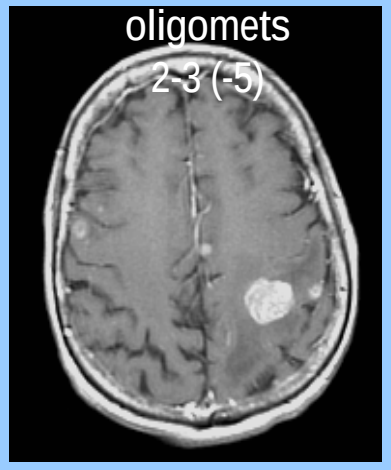


Role of radiotherapy in responsive tumours

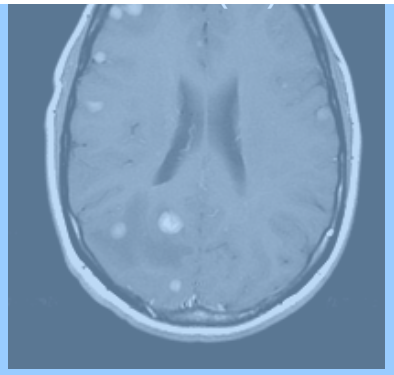
Matrix - radiotherapy options

No. met's	prognosis 1^0 tumour timing
single	
oligomets	responsive to systemic treatment
multiple	



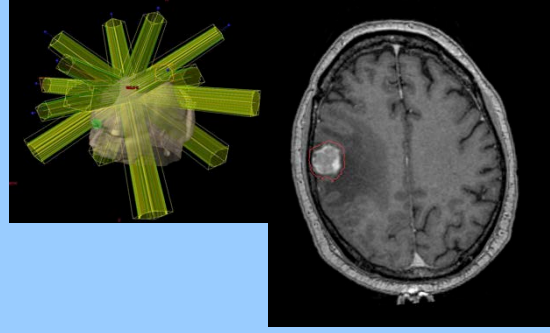


additional radiosurgery ?



Evidence base for radiotherapy in the treatment of brain metastases

Synchronous oligometastases in non-small cell lung cancer



1 - 4 brain metastases

oligometastases

randomise

radiosurgery (SRS) (49)

chemotherapy

chemotherapy (49)

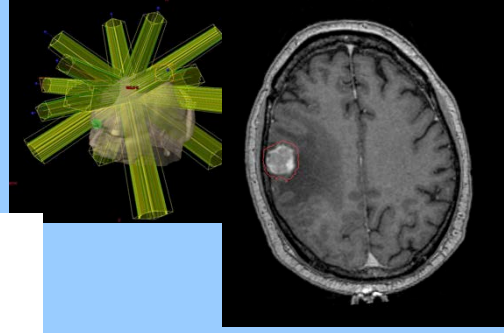
98 patients - synchronous asymptomatic brain metastases

Samsung Medical Centre, Seoul 2008 - 13

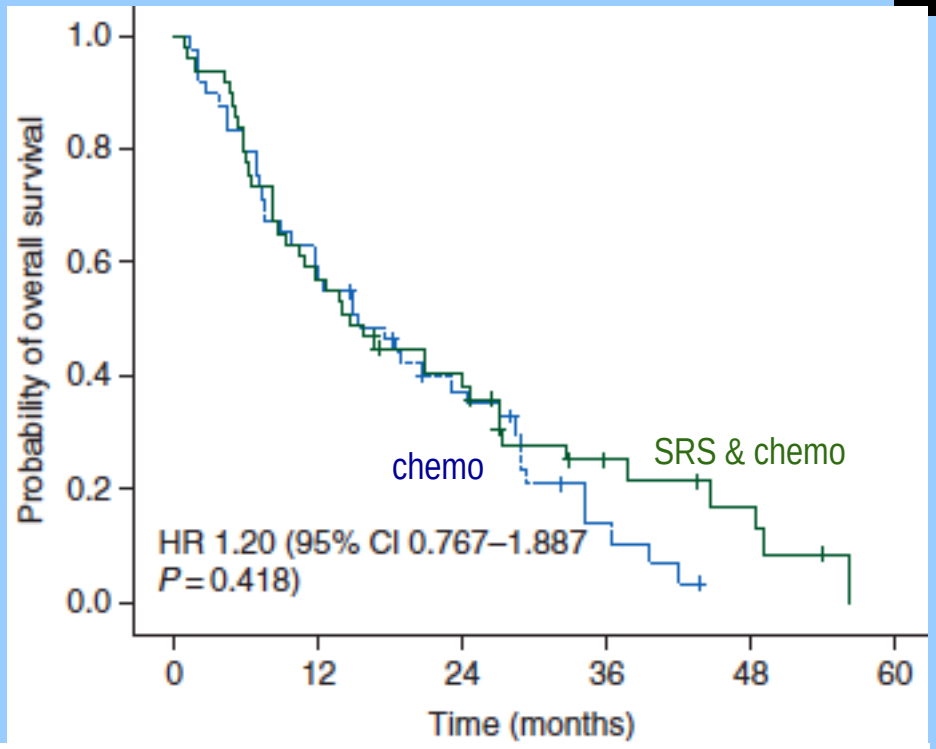
Radiosurgery for synchronous brain oligometastases

Lim et al 2015, Annals of Oncology 26: 762–768

Synchronous oligometastases in NSCLS



survival



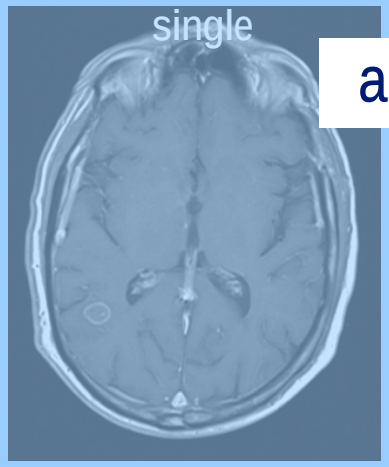
Number at risk						
GKS	49	31	20	10	6	2
Upfront chemotherapy	49	31	19	7	2	0

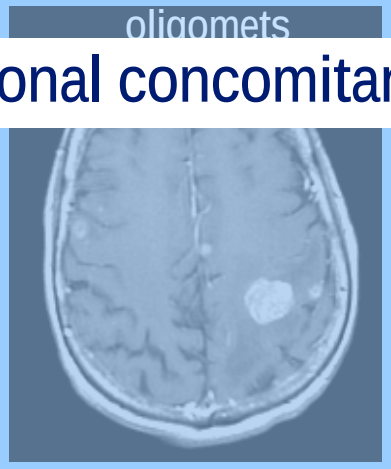
Radiosurgery for synchronous brain oligometastases

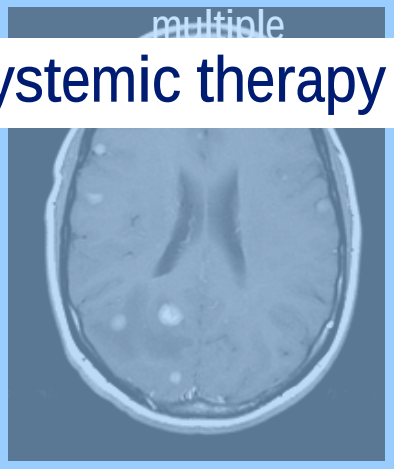
Lim et al 2015, Annals of Oncology 26: 762–768

Matrix - radiotherapy options

No. met's	prognosis 1^0 tumour timing
single oligomets multiple	treated with radiotherapy



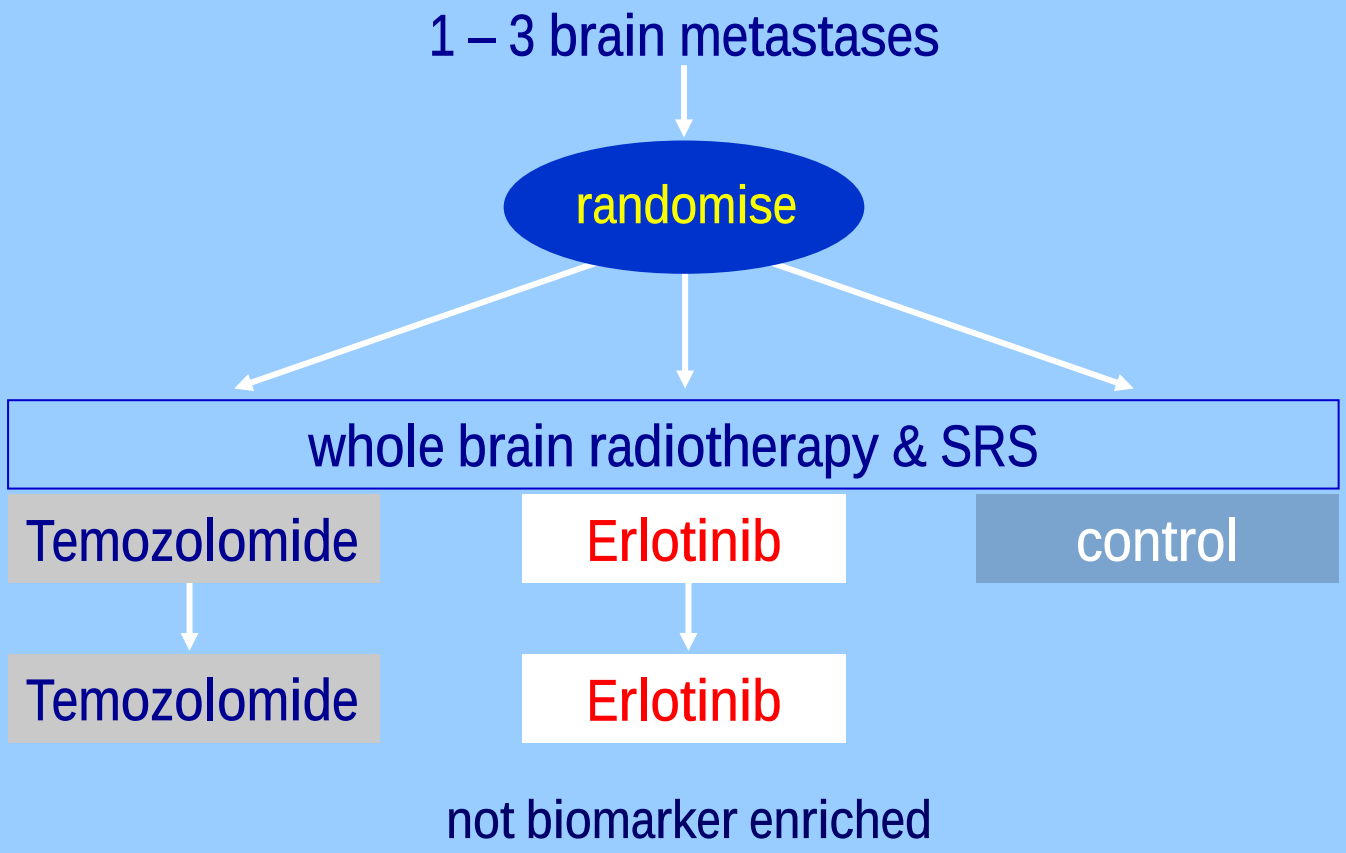




additional concomitant systemic therapy ?

Evidence base for radiotherapy in the treatment of brain metastases

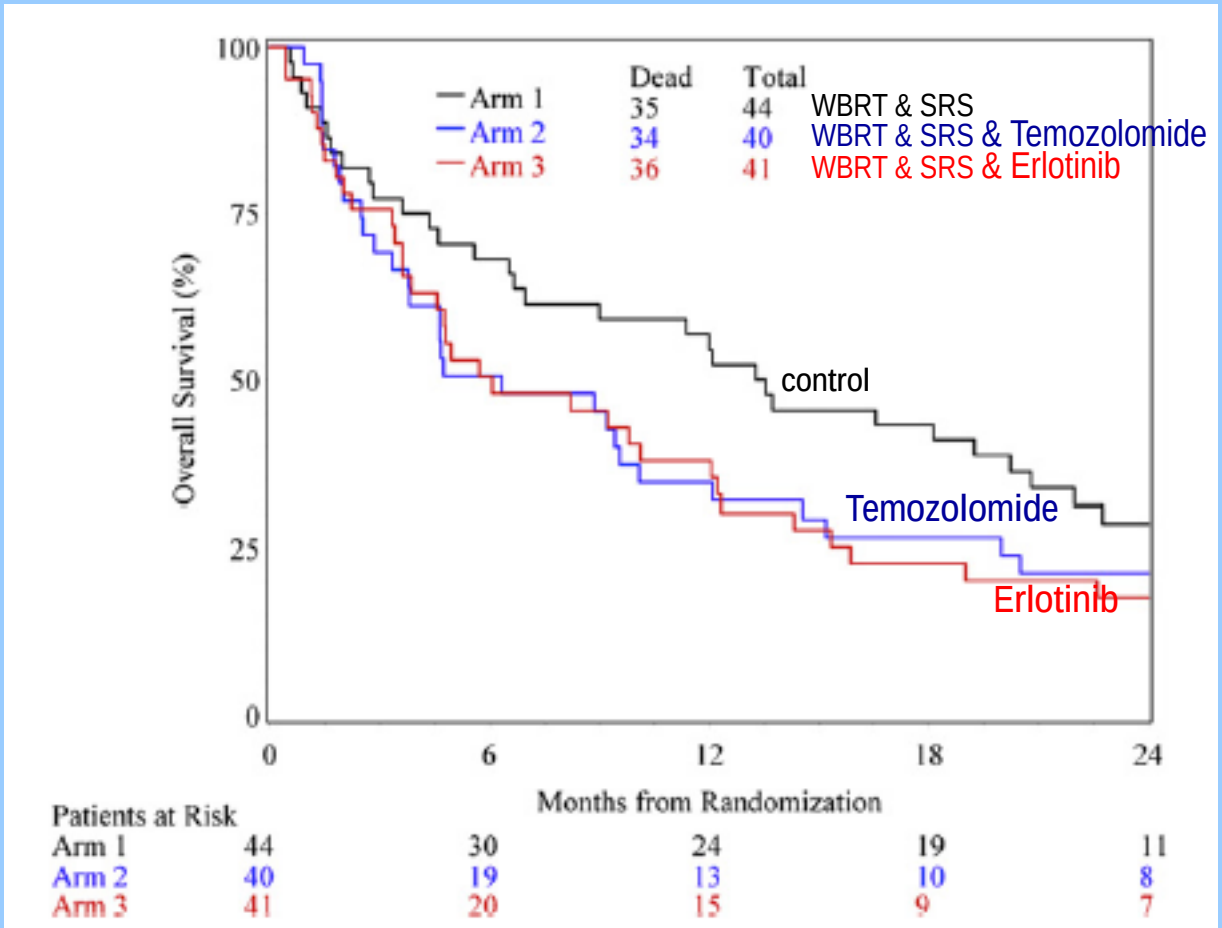
non-small cell lung cancer brain metastases
RTOG 0320



Additional systemic therapy in NSCLC brain metastases

Sperduto et al 2013, Int J Radiat Oncol Biol Phys, 85(5): 1312-8

non-small cell lung cancer brain metastases
RTOG 0320

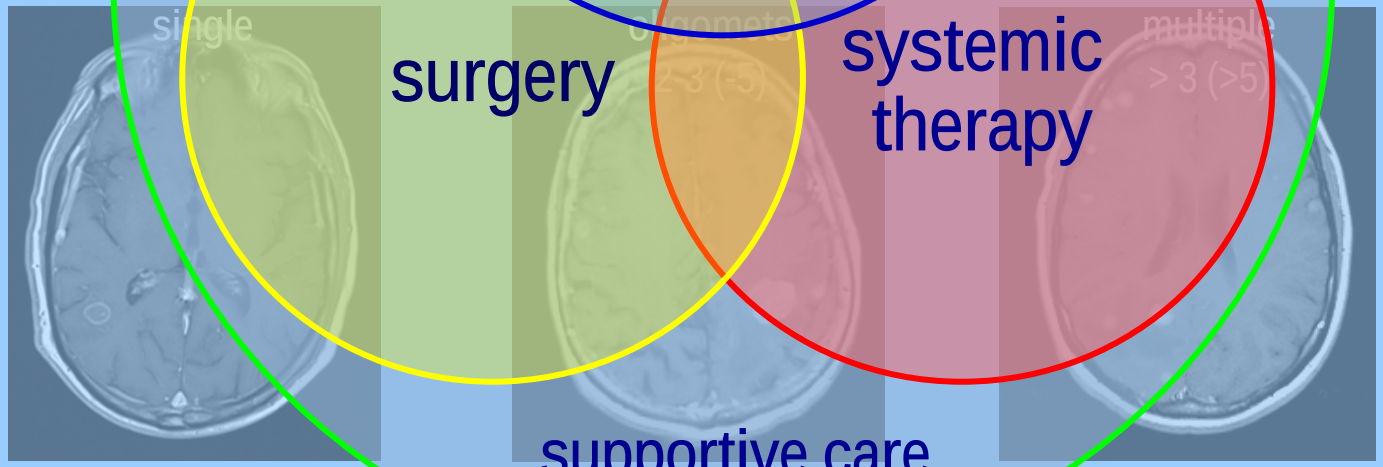


Additional systemic therapy in NSCLC brain metastases

Sperduto et al 2013, Int J Radiat Oncol Biol Phys, 85(5): 1312-8

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			



radiation

surgery

systemic therapy

supportive care

Evidence base for radiotherapy in the treatment of brain metastases

Management of brain metastases

Michael Brada
University of Liverpool

Department of Molecular and Clinical Cancer Medicine
& Department of Radiation Oncology
Clatterbridge Cancer Centre NHS Foundation Trust
Bebington, Wirral, CH63 4JY

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Supportive care of brain tumor patients

ESTRO teaching course
Management of brain tumours

Patrick Roth

Department of Neurology and Brain Tumor Center
University Hospital Zurich

Overview

- Management of pain
- Antiemesis
- Treatment of seizures
- Steroids for the treatment of tumor-associated edema

Seizures in brain tumor patients

Background

- Incidence of brain tumor-associated epilepsy
- Tumor-mediated epileptogenesis

Medical treatment

- Available drugs
- Treatment recommendations
    - Interaction with other drugs / tumor-specific treatment
    - Appropriate antiepileptic drugs
- Duration of treatment

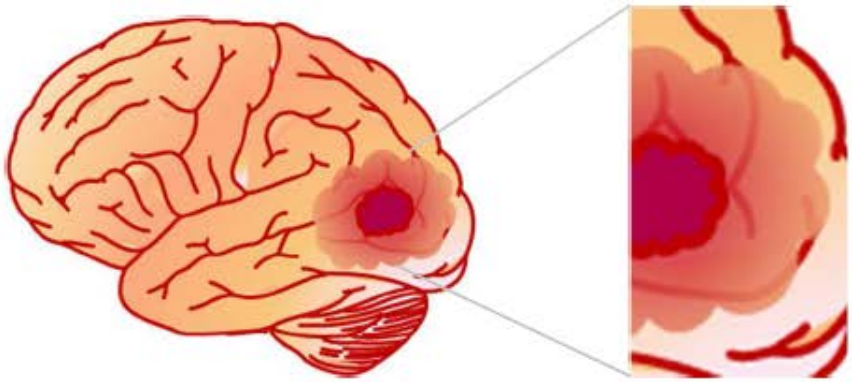
Epilepsy in brain tumor patients

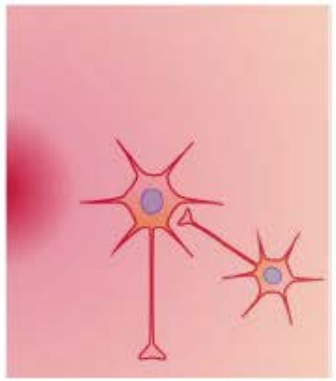
- Approx. 30-50% of all brain tumor patients are affected by seizures
  => frequently first clinical manifestation of a brain tumor

- Seizures are particularly common in slowly growing tumors and tumors of glial origin

• **DNET**	**100%**
• **Ganglioglioma**	**80-90%**
• **Low-grade glioma**	**70-80%**
• **Meningeoma**	**30-60%**
• **Glioblastoma**	**30-50%**
• **Metastases**	**20-35%**
• **CNS lymphoma**	**10-15%**

Brain tumors & epileptogenesis





- Blood-brain barrier
- Edema
- Intracranial pressure
- Hemosiderin

- Alkalinization
- Deafferentiation
- Glial excitability ↑

- Glutamate ↑
- GABA-mediated inhibition ↓
- Adenosine ↓

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Impact of tumor-specifc therapy on epilepsy

- **Radiotherapy: may increase edema, necrotic areas may also enhance the excitability**

- **Chemotherapy: increased risk of infections => fever => may trigger seizures**

- **Concomitant medication:**

  Steroids may alter glucose and electrolyte levels

  Neuroleptics may trigger seizures

Which antiepileptic drugs (AED) are appropriate?

Basic considerations

- Antiepileptic activity
- Side effects
- Interaction with other drugs
- Approval for monotherapy

Specifically for brain tumors

- Interaction with tumor-specific treatment
- Direct effects on the tumor
- i.v. administration

Numerous AED are available

Drug	Trade name (CH)	Dose (mg)	costs/day (CHF)
Phenobarbital	Luminal®	50-300	0.1-0.5
Phenytoin	Phenhydan®	200-350	0.15-0.5
Carbamazepine	Tegretol®	600-2000	0.7-2.5
Valproic acid	Orfiril®	1200-2400	1-2
Lamotrigine	Lamictal®	100-300	3-7
Gabapentin	Neurontin®	900-2400	2-5
Topiramate	Topamax®	50-200	2-5
Levetiracetam	Keppra®	1000-3000	4-13
Lacosamide	Vimpat®	100-400	4-13
Zonisamide	Zonegran®	300-500	5-12

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Which AED do you choose?

45 yo patient with a low-grade glioma has 2 generalized tonic-clonic seizures.

Which drug will you prescribe?

1. **Phenytoin**
2. **Valproic acid**
3. **Levetiracetam**
4. **Any other AED**
5. **The neurologist should tell me**

AED in brain tumor patients: where is the evidence?

THE COCHRANE COLLABORATION®

Antiepileptic drugs for treating seizures in adults with brain tumours (Review)

Kerrigan S, Grant R

Cochrane Database Syst Rev 2011

"There is a lack of robust, randomised, controlled evidence to support the choice of antiepileptic drug for the treatment of seizures in adults with brain tumors"

"There is a need for further large randomised, controlled trials in this area"

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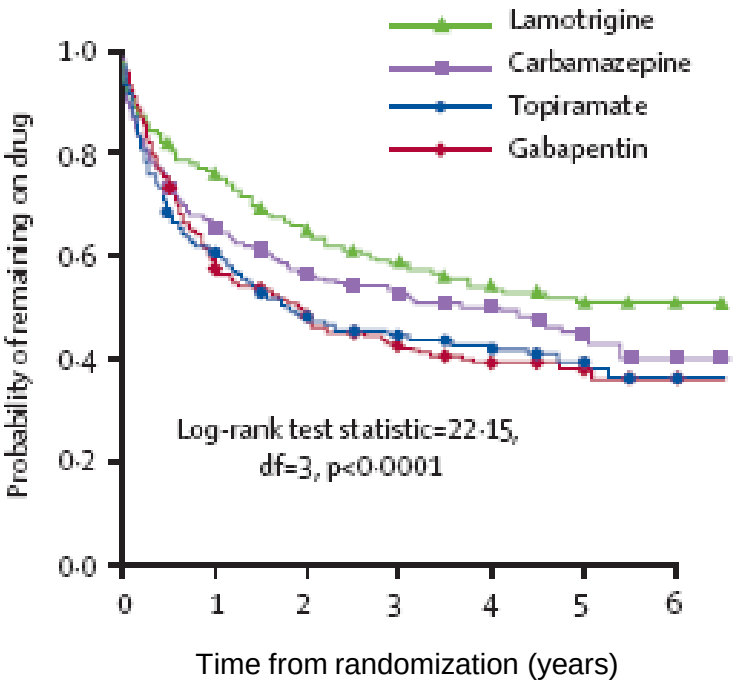
How to choose the best AED



„time to treatment failure“:
LTG > CBZ, GBP und TPM

Marson et al., Lancet 2007

„seizure control“
LEV = CBZ

Brodie et al., Neurology 2007

1.	Carbamazepine	CBZ
2.	Gabapentin	GBP
3.	Lacosamide	LAC
4.	Lamotrigine	LTG
5.	Levetiracetam	LEV
6.	Oxcarbazepine	OXC
7.	Perampanel	PER
8.	Phenobarbital	Pb
9.	Primidon	PRM
10.	Phenytoin	PHT
11.	Pregabalin	PGB
12.	Topiramate	TPM
13.	Valproic acid	VPA
14.	Zonisamide	ZON

Old AED: pros and cons

Phenobarbital	Sedation, allergic reactions Enzyme induction (cytochrome P450)
Phenytoin	Vertigo, allergic reactions, liver enzymes ↑, gingival hyperplasia, cerebellar degeneration Enzyme induction (cytochrome P450)
Carbamazepine	Vertigo, Nausea, Ataxia, low blood sodium, nystagmus, allergic reactions, Enzyme induction (cytochrome P450)
Valproic acid	Tremor, gain of weight, coagulation disorders, thrombopenia, teratogenicity Enzyme inhibition

New(er) AED: pros and cons

Lamotrigine	Skin reactions, tremor, sedation
Gabapentin	Fatigue, vertigo
Pregabalin	Vertigo
Levetiracetam	Fatigue, psychiatric disorders
Topiramate	Fatigue, loss of appetite, cognitive impairment
Lacosamide	Vertigo

Further considerations

- Enzym-inducing drugs may reduce the activity of chemotherapeutic drugs and steroids
- VPA (enzyme inhibition): impact is unclear
- Probably no interaction of lamotrigine, gabapentin, pregabalin, levetiracetam, topiramate or lacosamide with chemotherapeutic agents

1.	Carbamazepine	CBZ
2.	Gabapentin	GBP
3.	Lacosamide	LAC
4.	Lamotrigine	LTG
5.	Levetiracetam	LEV
6.	Oxcarbazepine	OXC
7.	Perampanel	PER
8.	Phenobarbital	Pb
9.	Primidon	PRM
10.	Phenytoin	PHT
11.	Pregabalin	PGB
12.	Topiramate	TPM
13.	Valproic acid	VPA
14.	Zonisamide	ZON

Which drugs are approved for monotherapy?

Monotherapy (CH):

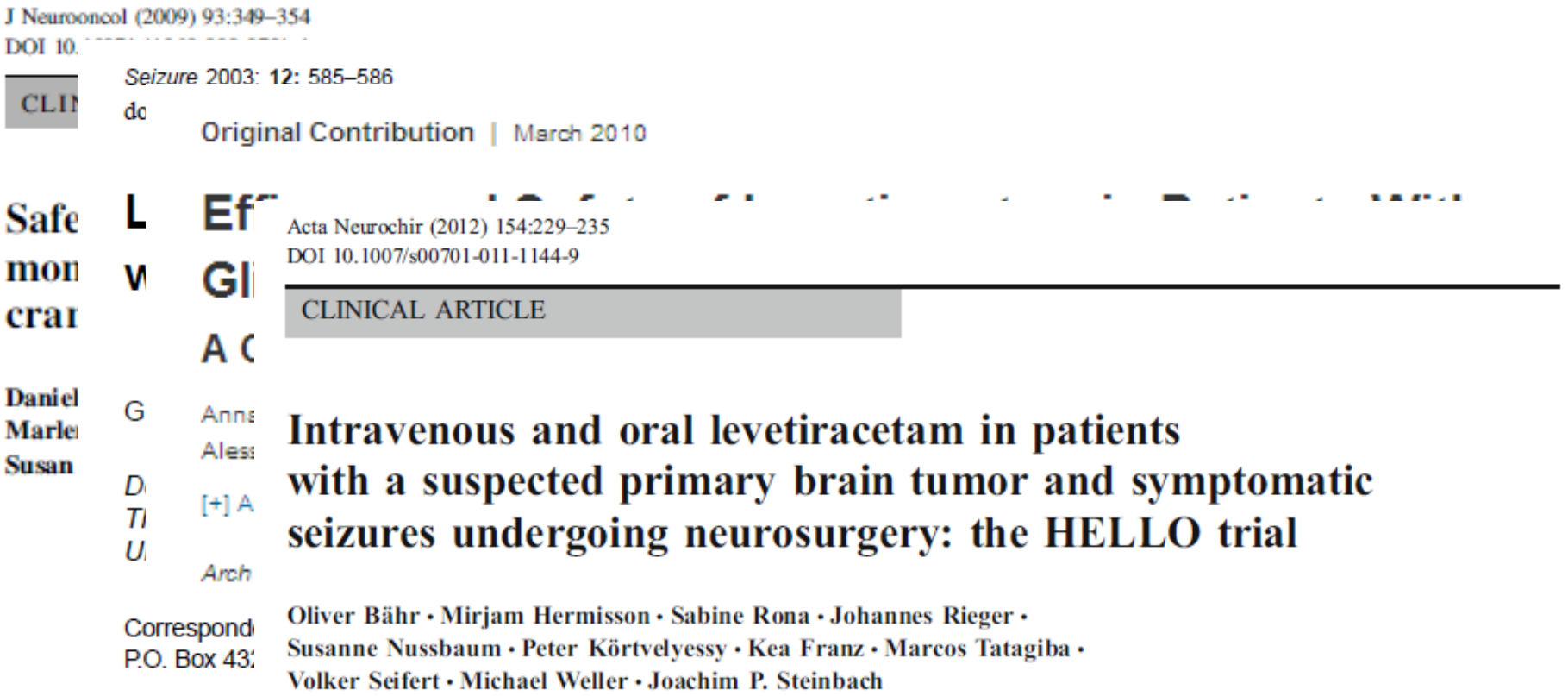
CBZ, GBP, LTG, LEV, OXC, Pb, PHT, PRM, TPM, VPA, ZON

i.v. administration:

LAC, LEV, Pb, PHT, VPA

1.	Carbamazepine	CBZ
2.	Gabapentin	GBP
3.	Lacosamide	LAC
4.	Lamotrigine	LTG
5.	Levetiracetam	LEV
6.	Oxcarbazepine	OXC
7.	Perampanel	PER
8.	Phenobarbital	Pb
9.	Primidon	PRM
10.	Phenytoin	PHT
11.	Pregabalin	PGB
12.	Topiramate	TPM
13.	Valproic acid	VPA
14.	Zonisamide	ZON

Data from clinical trials: brain tumors and AED



J Neurooncol (2009) 93:349–354
DOI 10.

Seizure 2003; **12**: 585–586
do

Original Contribution | March 2010

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Daniel
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Susan

Acta Neurochir (2012) 154:229–235
DOI 10.1007/s00701-011-1144-9

CLINICAL ARTICLE

Intravenous and oral levetiracetam in patients with a suspected primary brain tumor and symptomatic seizures undergoing neurosurgery: the HELLO trial

Oliver Bähr · Mirjam Hermisson · Sabine Rona · Johannes Rieger · Susanne Nussbaum · Peter Körtvelyessy · Kea Franz · Marcos Tatagiba · Volker Seifert · Michael Weller · Joachim P. Steinbach

Correspond
P.O. Box 43

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Levetiracetam vs. Pregabalin

Table 3. Study endpoints

	Levetiracetam	Pregabalin
Randomized patients	25	27
Composite endpoint	9 (36%)	12 (44%)
Status epilepticus	0	0
2 seizures with consciousness impairment	1 (4%)	1 (4%)
Need to interrupt study drug	7 (28%)	7 (26%)
Need to add on a second antiepileptic drug	1 (4%)	4 (15%)
Seizure free from enrollment until last follow-up	17 (65%)	18 (75%)
Lost to follow-up	0	3 (11%)
Death	7 (28%)	5 (19%)
Survival in the study, days, median (range)	286 (9–431)	166 (0–410)

- 52
- Ra
- „c

econd AED;

3.

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Who to treat and for how long?

- **Shall all brain tumor patients be treated with an AED?**
  No
- **Prophylaxis in all patient who undergo surgery?**
  No – or only transiently
- **Treatment following a seizure?**
  Yes
- **How long shall patients be treated with an AED?**
  Depends on histology, overall prognosis, tolerance…

Conclusions: brain tumors and epilepsy

- Hardly any data from randomized trials
- **Levetiracetam**: may be overall well tolerated and have good activity against seizures in brain tumor patients
- **Lamotrigine**: no comprehensive testing in brain tumor patients; overall good antiepileptic activity, well tolerated
- **Pregabalin**: may be considered as an alternative drug, probably not approved as monotherapy in most countries
- **Valproic acid**: active, moderate tolerability, may have anti-tumor properties (?)

Overview

- Management of pain
- Antiemesis
- Treatment of seizures
- **Steroids for the treatment of tumor-associated edema**

Steroids in neurooncology: history

CORTISONE AND ACTH AS AN ADJUNCT TO THE SURGERY OF CRANIOPHARYNGIOMAS*

FRANC D. INGRAHAM, M.D.,† DONALD D. MATSON, M.D.,‡ AND ROBERT L. MCLAURIN, M.D.§

BOSTON

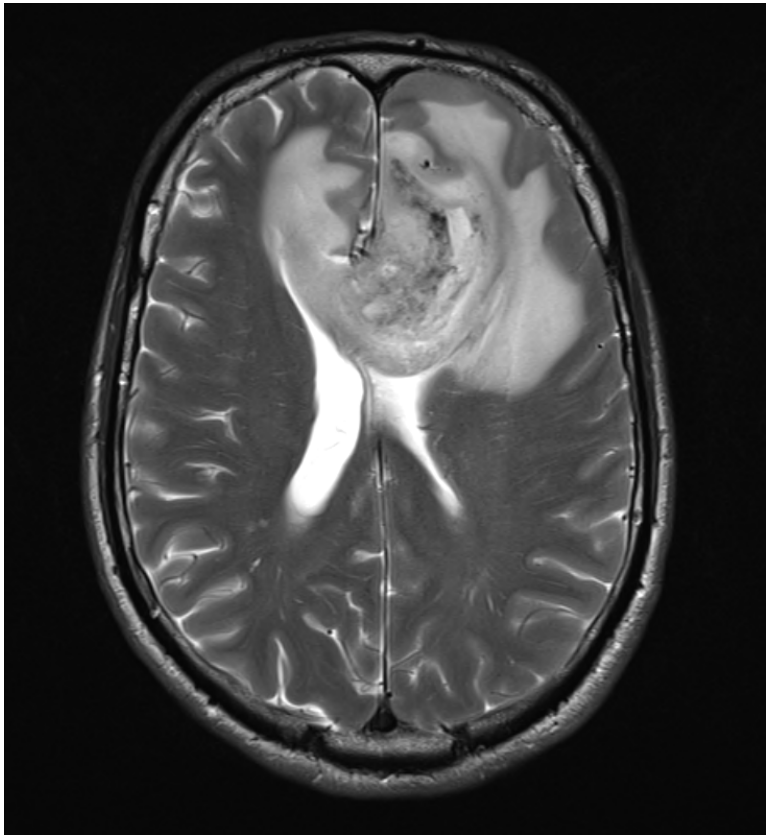
THE surgical management of craniopharyngiomas, whether radical or conservative, has always been hazardous. Gordy, Peet and Kahn[1] reported a series of 51 cases in which the operative mortality was 41 per cent, due principally to severe hypothalamic reactions incident to the surgical manipulation. Grant,[2] in summarizing the results of 40 operations on 30 patients, found a case mor-

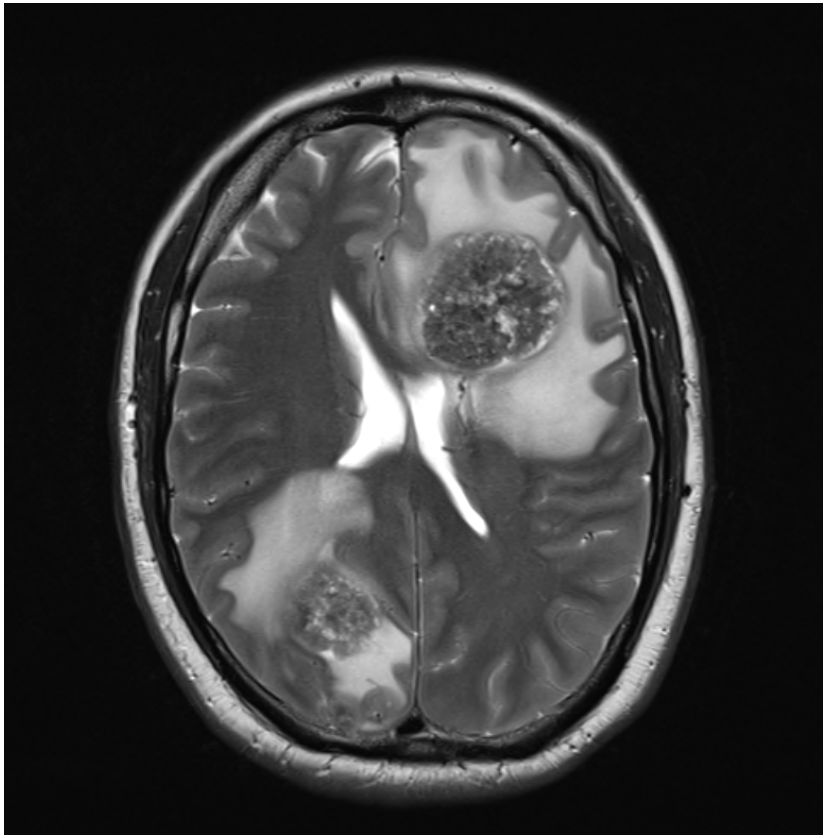
pacity of the pituitary adrenal system were, of course, not employed.

It is apparent that most of the operative complications in the treatment of craniopharyngioma result from the proximity of the lesion to the pituitary gland and the hypothalamus. Manipulation in this region is perilous at all times, but the danger is accentuated in the majority of these cases because

Treatment of edema

Primary or secondary brain tumors with surrounding edema





Which steroid and which dose?

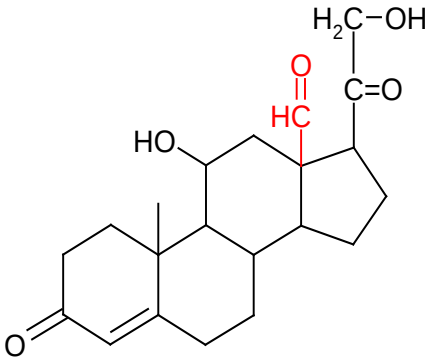
57 yo patient with a recurrent glioblastoma and pronounced edema requires treatment with steroid because of increasing hemiparesis on the right side.

What will you do?

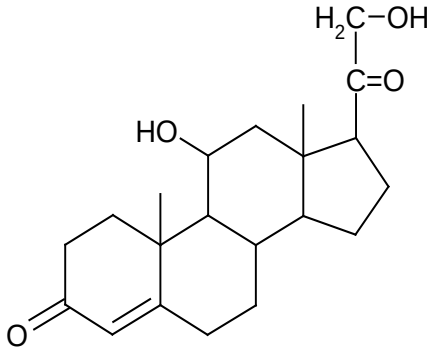
1. **Hydrocortisone 30 mg/d**
2. **Prednisone 100 mg/d**
3. **Dexamethasone 4 x 4 mg**
4. **Dexamethasone 16 mg**

Physiological steroid hormones

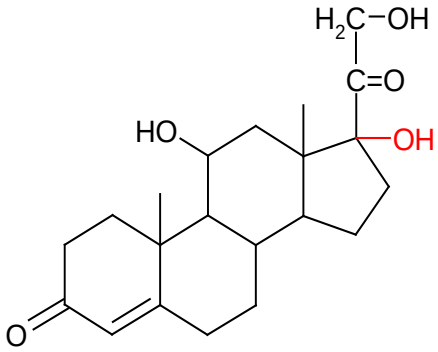
glucocorticoid activity



aldosterone



corticosterone



cortisol/hydrocortisone

mineralocorticoid activity

Steroids: which compound?

	Glucocorticoid Potency	Plasma half-life (h)	Biological half-life (h)	Mineralo-corticoid effects
Hydrocortisone	1		8-12	1
Prednisone	5	3-4	12-36	0.8
Methylprednisolone	4	1.5-3	12-36	0.5
Dexamethasone	~ 30	2-5	36-54	0

Advantages of dexamethasone:

- Least amount of mineralocorticoid activity
  => Low rate of fluid retention
- Long biological half-life
  => frequent dosing not required

ESTRO School

Dexamethasone dosing

Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors:

A randomized study of doses of 4, 8, and 16 mg per day

Ch.J. Vecht, MD, PhD; A. Hovestadt, MD, PhD; H.B.C. Verbiest, MD; J.J. van Vliet; and W.L.J. van Putten, MSc

Neurology®

- 96 patients; 2 randomized, double-blind trials
- Dexamethasone: 4 vs. 16 mg/d
  8 vs. 16 mg/d
- Primary endpoint: KPS => no difference
- Side effects: more frequent in patients taking 16 mg/d

Vecht et al., Neurology 1994

Steroids: side effects

- **Hyperglycemia ("steroid diabetes": > 50% of all patients)**

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JOURNAL OF CLINICAL ONCOLOGY

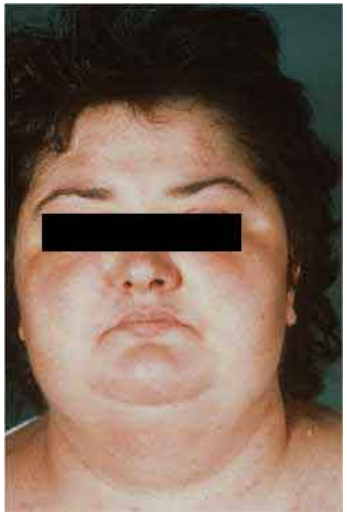
ORIGINAL REPORT

Association Between Hyperglycemia and Survival in Patients With Newly Diagnosed Glioblastoma

Rachel L. Derr, Xiaobu Ye, Melissa U. Islas, Serena Desideri, Christopher D. Saudek, and Stuart A. Grossman

Cushing's syndrom:

- **Central obesity**
- **"moon face"**
- **Arterial hypertension**



Osteoporosis & myopathy

Osteoporosis:

- **Development of osteoporosis is particularly high in patients taking other osteoporosis-inducing drugs (e.g. loop diuretics, thyroxine)**

- **Prophylaxis: Calcium, vitamine D, biphosphonates**

Myopathy:

- **Weakness of the proximal muscles of the upper and lower limbs**
- **No data supporting the hypothesis that myopathy occurs more frequently when „fluorinated“ steroids are used**
- **Prophylaxis: physiotherapy**

Side effects: many more…

- Gastrointestinal symptoms (peptic ulcers)
- Steroid cataract
- Psychiatric side effects (depression, psychosis, insomnia)
- Increased risk for infections (e.g. Pneumocystis jirovecii) (particularly in patients who receive radio- and/or chemotherapy)

=> Steroid toxicity may reduce the benefit from other treatment modalities, e.g. radio- and chemotherapy

Guidelines for the use of steroids

- **Regular check of blood pressure and glucose levels**
- **Proton pump inhibitor and thrombosis prophylaxis should be considered**
- **PJP prophylaxis, particularly in patients on radio-/chemotherapy**
  - **Trimethoprim/sulfamethoxazole (Co-trimoxazole)**
  - **Pentamidine inhalation**
- **Check interaction(s) with other drugs**

Steroid tapering

- **Tapering should be persued as soon as clinically possible**
- **Short treatment => rapid tapering**
- **Long duration of therapy => slow tapering**

  => Watch for signs of hypocortisolism!

  - **Nausea, vomiting, headaches**
  - **Myalgia, hypotension**

- **Manifest hypocortisolism: substitution with hydrocortisone**

  => average daily dose: 20-30 mg

Can we avoid/replace steroids?

- **H15 (Boswellia serrata): limited activity**

Boswellia serrata Acts on Cerebral Edema in Patients Irradiated for Brain Tumors

A Prospective, Randomized, Placebo-Controlled, Double-Blind Pilot Trial

Simon Kirste, MD[1]; Markus Treier, MD[2]; Sabine Jolie Wehrle, MD[1]; Gerhild Becker, MD[3]; Mona Abdel-Tawab, PhD[4]; Kathleen Gerbeth[4]; Martin Johannes Hug, PhD[5]; Beate Lubrich, PhD[5]; Anca-Ligia Grosu, MD[1]; and Felix Momm, MD[1]

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Steroid-Sparing Effect of Corticorelin Acetate in Peritumoral Cerebral Edema Is Associated With Improvement in Steroid-Induced Myopathy

Lawrence Recht, Laszlo L. Mechtler, Eric T. Wong, Patrick C. O'Connor, and Bruce E. Rodda

Conclusions