The 2016 update of the WHO brain tumor classification

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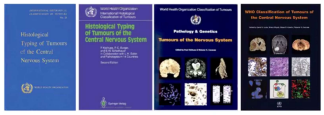
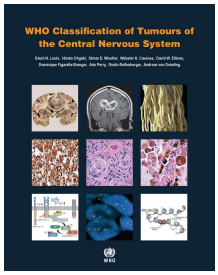
Outline

- The Making of the 2016 Update of the WHO brain tumor classification
- Update on most important changes
  - Diffuse glioma
  - Embryonal tumors
  - Other newly introduced entities and variants
- Implications on neuropathological practice & molecular marker testing

The WHO brain tumor classification



1st edition 1979 | 2nd edition 1993 | 3rd edition 2000 | 4th edition 2007

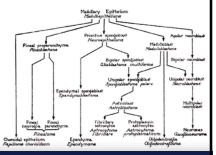


2016 update of the 4th edition

Prior to 2016

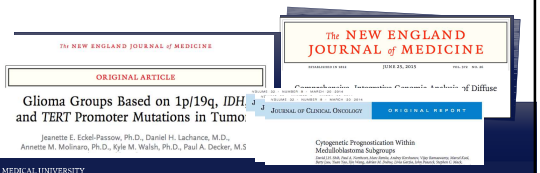
- Brain tumor classification based on histogenesis
  - Microscopic similarities of tumors with different cells of origin
- Based on hematoxylin and eosin-stained sections + immunohistochemical expression of lineage-associated proteins (+ ultrastructure)

Harvey Cushing



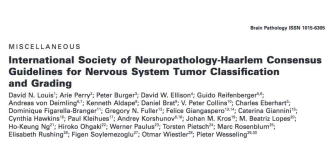
In the meantime

- Large-scale studies revealed the genetic basis of tumorigenesis of adult and pediatric brain tumors
- Molecular markers provide prognostic and/or predictive information *within* diagnostic categories
- Canonical genetic alterations may be used to define specific entities



2014 Haarlem Meeting, the Netherlands

- Under the auspices of the International Society of Neuropathology
- Aim: Providing guidelines for how to incorporate molecular findings into brain tumor diagnostics
- Set the stage for a major revision of the 2007 CNS WHO classification



Proposed format & overarching goal

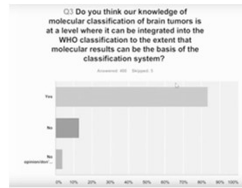
- Layer 1: Morphological classification
- Layer 2: WHO grade (reflects natural tumor history)
- Layer 3: Molecular information

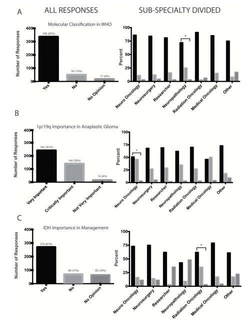
Integrated diagnosis

CAVE Diagnostic delay

- Adds a level of objectivity to the diagnostic process
- Stratifies tumors into biologically homogenous groups
- Enhances diagnostic accuracy & prognostic rating

Community Surveys (SNO & ISN)





Surveys provided overwhelmingly positive feedback

Classification based on histology & genetics

- International collaboration of 117 contributors from 20 countries
- Three-day consensus conference by a working group of 35 neuropathologists, clinical advisors and scientists from 10 countries

Austrian contributors:
Johannes A. Hainfellner
Matthias Preusser

How many brain tumor entities are differentiated according to the WHO 2016 classification?

- A1. 1-30
- A2. 40-70
- A3. 80-110
- A4. 120+

A4 is correct

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
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Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
Other astrocytic tumours	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumours	
Malignant peripheral nerve sheath tumour	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
Meningiomas	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Haemangioblastoma	9161/1
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma / PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumour	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
Melanocytic tumours	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
Lymphomas	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
MALT lymphoma of the dura	9699/3
Histiocytic tumours	
Langerhans cell histiocytosis	9751/3
Erdheim–Chester disease	9750/1
Rosai–Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
Germ cell tumours	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumour	9085/3
Tumours of the sellar region	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumour of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [742A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions. *These new codes were approved by the IARC/WHO Committee for ICD-O. *Italics*: Provisional tumour entities. **Grading according to the 2013 *WHO Classification of Tumours of Soft Tissue and Bone*.

2016

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2007

Diffuse astrocytomas more similar to oligodendrogliomas than pilocytic astrocytomas -> family trees redrawn

Protoplasmic astrocytoma 9410/3

Gliomatosis cerebri deleted (invasive growth of diffuse astrocytoma, oligodendroglioma or glioblastoma)

Anaplastic oligodendroglioma 9451/3

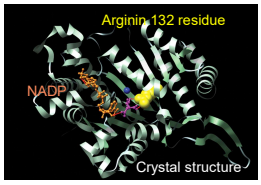
WHO grading II-III retained

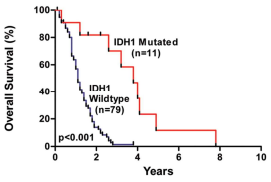
Anaplastic oligoastrocytoma 9382/3

Diffuse astrocytoma categories:
IDH-mutant
IDH-wildtype
NOS

Molecular markers now mandatory
IDH, 1p19q, H3K27

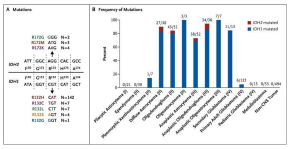
IDH 1/2 mutations

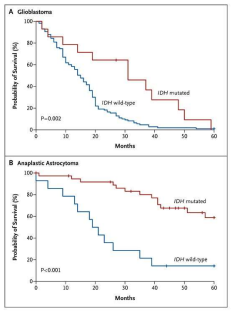




- Recurrent mutations in *IDH1* on chromosome 2q33 found in glioblastoma
- *IDH1* encodes isocitrate dehydrogenase 1 that catalyzes the oxidative carboxylation of isocitrate to alpha-ketoglutarate resulting in the production of NADPH
- Novel marker for *secondary glioblastoma*

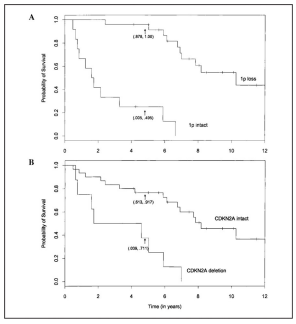
IDH mutations

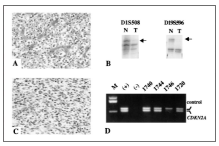


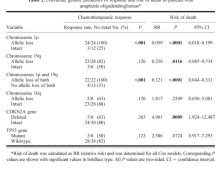


- IDH mutations implicated in the pathogenesis of malignant gliomas
- Common in lower grade gliomas
- IDH mutant tumors are genetically & clinically distinct

1p 19q deletion







What is the major reason for the observed discrepancy in chemotherapy sensitivity between oligodendroglioma and astrocytoma?

A1. Astrocytic cells show a higher number of multidrug resistant-associated ABC transporters

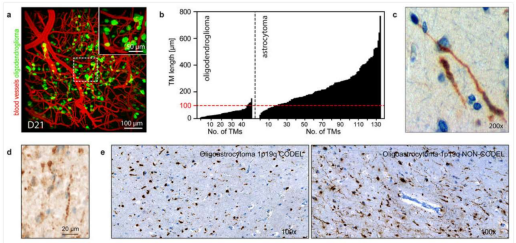
A2. Chromosome 1 encodes the temozolomide-resistance gene *zinc finger protein C2H2*

A3. Astrocytic cells communicate more efficiently in cellular networks

A4. Oligodendroglial cells show impaired mitochondrial metabolism

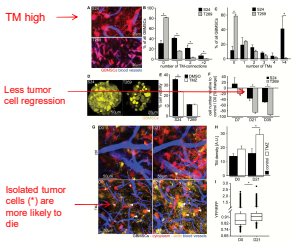
A3 is correct

Brain tumor cells interconnect to a functional and resistant networt



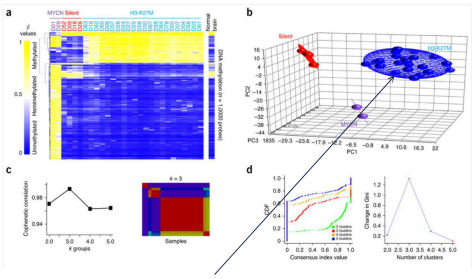
Oligodendrogliomas lack long 'tumor microtubes' that enable multicellular communication in astrocytomas

Tumor microtubes convey resistance to surgical lesions and chemotherapy in gliomas



Highly interconnected astrocytic tumor cells are more resistant to TMZ treatment

H3 K27M mutation



- Defines a subgroup of diffuse intrinsic pontine gliomas
- Mutation in histone protein -> epigenetic implications

Buczkowicz P et al, Nature Genetics 2014

2016

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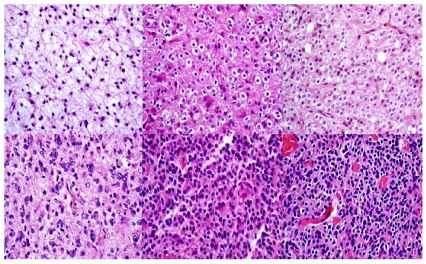
What happened to Oligoastrocytoma?

Oligoastrocytoma



Astrocytoma — *Difficult to define* — Oligodendroglioma

High interobserver discordance

Oligoastrocytoma

J Neuropathol Exp Neurol. 2007 Jun;66(6):545-51.

Panel review of anaplastic oligodendroglioma from European Organization For Research and Treatment of Cancer Trial 26951: assessment of consensus in diagnosis, influence of 1p/19q loss, and correlations with outcome.

Kros JM[1], Gorlia T, Kouwenhoven MC, Zheng PP, Collins VP, Figarella-Branger D, Giangaspero F, Giannini C, Mokhtari K, Mørk SJ, Paetau A, Reifenberger G, van den Bent MJ.

J Clin Oncol. 2015 Jun 10;33(17):1943-50. doi: 10.1200/JCO.2014.59.0168. Epub 2015 Apr 27.

Evidence-Based Diagnostic Algorithm for Glioma: Analysis of the Results of Pathology Panel Review and Molecular Parameters of EORTC 26951 and 26882 Trials.

Kros JM[1], Huizer K[2], Hernández-Laín A[2], Marucci G[2], Michotte A[2], Pollo B[2], Rushing EJ[2], Ribalta T[2], French P[2], Jaminé D[2], Bekka N[2], Lacombe D[2], van den Bent MJ[2], Gorlia T[2].

Acta Neuropathol. 2014 Oct;128(4):551-9. doi: 10.1007/s00401-014-1326-7. Epub 2014 Aug 21.

Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma.

Sahm F[1], Reuss D, Koelsche C, Capper D, Schittenhelm J, Heim S, Jones DT, Pfister SM, Herold-Mende C, Wick W, Mueller W, Hartmann C, Paulus W, von Deimling A.

Acta Neuropathol. 2015 Jan;129(1):147-9. doi: 10.1007/s00401-014-1353-4. Epub 2014 Oct 11.

Oligoastrocytomas: throwing the baby out with the bathwater?

Wilcox P[1], Li CC, Lee M, Shivalingam B, Brennan J, Suter CM, Kaufman K, Lum T, Buckland ME.

Oligoastrocytoma

- Using phenotype & genotype (i.e., *IDH* mutation and 1p19q codeletion) allows to allocate them to either astrocytic or oligodendroglial subtypes
- Discordant results of phenotype & genotype -> genotype trumps histological phenotype!

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"*

- Introduction of „not otherwise specified, NOS"

Is genotype alone sufficient for diagnosis?

- At this point in time: **No**
- WHO grading is still based on histologic criteria
- Challenges with respect to testing and reporting
  - Availability & choice of genotyping or surrogate genotyping assays

Cancer Cell
Previews

Fall of the Optical Wall: Freedom from the Tyranny of the Microscope Improves Glioma Risk Stratification

Vijay Ramaswamy[1] and Michael D. Taylor[2,3]
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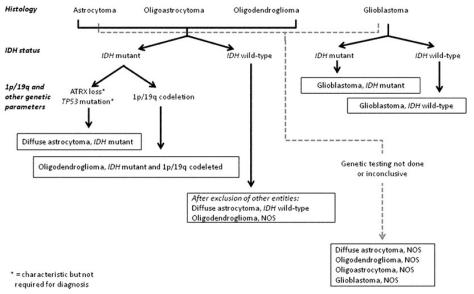
http://dx.doi.org/10.1016/j.ccell.2016.01.009

Diffuse gliomas



What is the correct 'integrated diagnosis' in the following case?

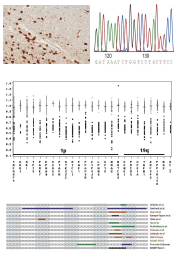
Histology: Oligoastrocytoma
WHO grade: II
Molecular markers: IDH2 mutant, 1p19q codeleted, TERT mutation, ATRX retained

- A1. Oligodendroglioma, WHO grade II, IDH2 mutant and 1p19q codeleted
- A2. Oligoastrocytoma, WHO grade II, IDH2 mutant and 1p19q codeleted
- A3. Astrocytoma, WHO grade II, IDH2 mutant and 1p19q codeleted
- A4. Oligodendroglioma, WHO grade II, NOS

A1 is correct

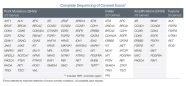
Commonly used molecular techniques

- *IDH* genes:
  - Step 1: mutation-specific IDH1 R132H antibody
  - Step 2: targeted IDH1/2 gene sequencing
    - **Screening of all lower grade gliomas (II-III)**
    - **Screening of GBM, IV only in patients aged <55 years**
- 1p 19q chromosomal arms:
  - Multiplex ligation probe amplification
  - Fluorescence in situ hybridization
- *MGMT* promoter methylation:
  - Pyrosequencing
  - Methylation-specific PCR

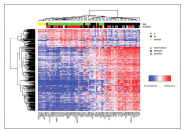


Advanced molecular techniques

- Gene-panel sequencing
- Exome/RNA sequencing



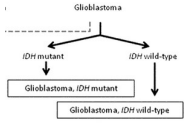
- DNA methylation array
  - G-CIMP/IDH, copy numbers, MGMT



- CAVE:
  - Quality control / data standardization
  - DNA quality of FFPE tissues

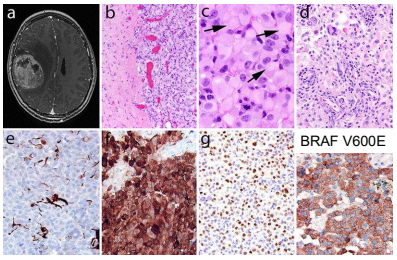
Glioblastoma

- Glioblastoma, IDH-wildtype (about 90% of cases)
- Glioblastoma, IDH-mutant (about 10% of cases) corresponds closely to secondary glioblastoma
- Glioblastoma, NOS in cases without full IDH assessment
  - Sequencing required for all patients > 55 years of age



Glioblastoma

- New variant: Epitheloid glioblastoma
- Stratifies into established diagnostic subsets upon molecular diagnosis

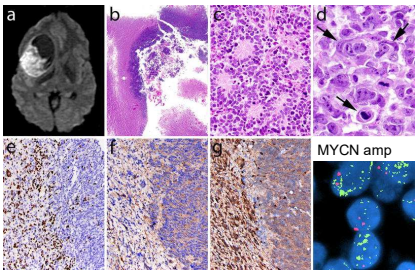


Louis et al, Acta Neuropath 2016

Variant = Subtype of an entity of clinical utility

Glioblastoma

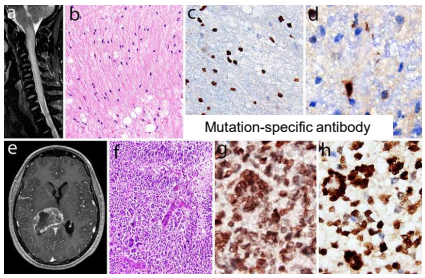
- New pattern: Glioblastoma with primitive neuronal component



Louis et al, Acta Neuropath 2016

Diffuse midline glioma

- K27M mutations in histone H3 gene *H3F3A* defines a group



Louis et al, Acta Neuropath 2016

Embryonal tumors

Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	9478/3
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	9508/3

Greatest conceptual challenge

Dismissal of "PNET, primitive neuroectodermal tumor"
-> "Embryonal tumor"

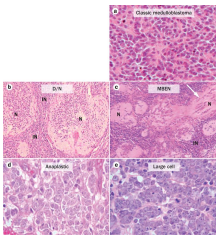
How many medulloblastoma groups are (currently) defined based on genetics?

- A1. 3
- A2. 4
- A3. 5
- A4. 9

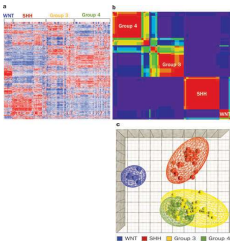
A2 is correct

Medulloblastoma

Long established histological groups

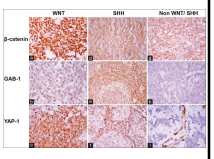


Four genetically defined groups



Medulloblastoma

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic / nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance



Surrogate IHC markers for pathway activation

+ TP53 sequencing
+ MYC amplification by FISH

Genetics & histology & clinical factors stratify patients into risk groups

New risk stratification since 2016

TABLE. Comparison between Risk Classification based on Clinical Criteria and New Patient Risk Groups based on the 2016 Expert Consensus Statement[19]

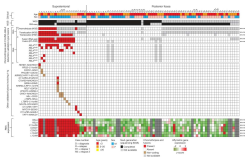
Current risk classification	Proposed new risk classification
Based on clinical criteria (children > 3 yr)	Integrating clinical and molecular criteria
Average risk	Low risk (>90% survival)
≤1.5 cm^2 of residual disease	Localized WNT MB (<16 yr)
No metastatic disease	Localized group 4 MB with chromosome 11 loss or whole chromosome 17 gain
High risk	Standard risk (75%–90% survival)
>1.5 cm^2 of residual disease	Localized p53 WT-SHH MB
Metastatic disease	Localized, non-*MYC* amplified group 3 MB
(Anaplasia)	Localized group 4 MB
	Localized group 4 MB without chromosome 11 loss or 17 gain
	High risk (50%–75% survival)
	Metastatic noninfant p53 WT-SHH or localized *MYCN*-amplified SHH MB
	Metastatic group 4 MB
	Very high risk (<50% survival)
	p53-mutated SHH MB
	Metastatic group 3 MB

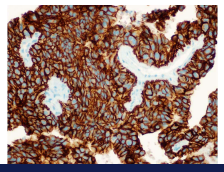
Other embryonal tumors

- Dismissal of PNET, primitive neuroectodermal tumor
- Instead:
  - ***C19MC*-amplified Embryonal tumor with multilayered rosettes**
    - ETANTR + ependymoblastoma + medulloepithelioma
    - Immunohistochemical marker LIN28
  - **Atypical teratoid/rhabdoid tumor (AT/RT)**
    - defined by *INI1* or very rarely *BRG1*
    - Immunohistochemical marker SMARCB1/INI1
  - Wastebasket category for all others: CNS embryonal tumor, NOS

Other tumors: Ependymoma

- WHO grading of unclear clinical significance
- One narrowly defined subgroup: Ependymoma, RelA gene fusion
  - Drives NFkappaB signaling (outside of the mutation box!)
  - Majority of supratentorial tumors in children, poor prognosis!
  - L1CAM expression as immunohistochemical surrogate

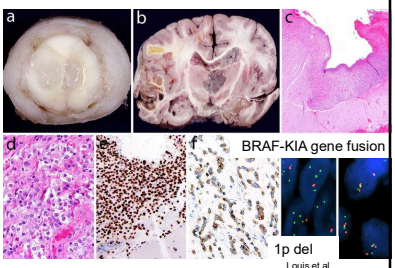




Neuronal and mixed neuronal-glial tumors

Diffuse leptomeningeal glioneuronal tumor

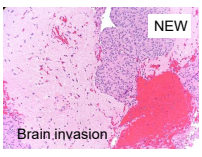
- Mostly in children and adolescents
- Histologically reminiscent of oligodendroglioma

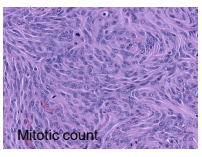


Louis et al, Acta Neuropath 2016

Meningioma

- Classification and grading not revised
- Except: *brain invasion* as a criterion for atypical meningioma, WHO grade II
  - Mitotic count (5 mitoses per 10 high-power fields) or
  - Brain invasion is sufficient





Solitary fibrous tumor - hemangiopericytoma

- Soft tissue pathologists moved away from the designation hemangiopericytoma
- Considered within the spectrum of solitary fibrous tumors
- Both share genetic constellations, most notably *STAT6* gene fusion -> one common entity
- Grade I-III
  - Grade I: highly collagenous, low cellularity
  - Grade II: more cellular, less collagenous „staghorn" vessels
  - Grade III: + 5 mitoses per 10 high-power fields

Summary

- Substantial step forward & paradigm change
- Introduction of molecular parameters
  - Challenge molecular marker testing!
- Associated changes of diagnostic format
  - Integrated diagnoses (CAVE time delay to molecular results)
- Greatest impact on diffuse gliomas & embryonal tumors
- More objective and precisely defined entities for enhanced patient management

Reactions

"H K, how can we cope with the new molecular requirements in the WHO ?" – Chitra Sarkar, India

"WHO 2016 has let the scientific world down" – Richard Gilbertson, ISPNO June 2016

"We are ten years ahead of WHO" – Martin van den Bent, EANO Oct 2016

Outlook next WHO classification

- Diffuse gliomas
  - WHO grading system will be revised
- Pediatric low-grade gliomas
  - Integrated diagnoses will be introduced, e.g., for *BRAF* gene fusion in pilocytic astrocytomas
- Ependymoma
  - WHO grading will be revised
- Meningioma
  - WHO grading will be revised
  - DNA methylation profiling might be introduced (?)

Asking neuropathologists in 2016 *post* WHO

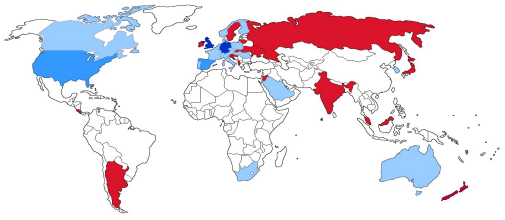
11th European Congress of Neuropathology, Bordeaux, France

Aim: Assessing practice patterns regarding adult diffuse glioma during times of transition

- Which molecular markers have already been incorporated in routine practice
- Which molecular techniques are in daily use or will be implemented in the near future
- Set a baseline for future assessments

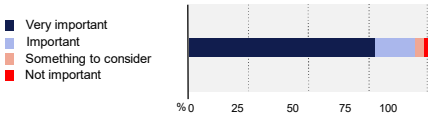
Methods: Structured survey distributed onsite and among Euro-CNS members

130 Respondents from 40 countries



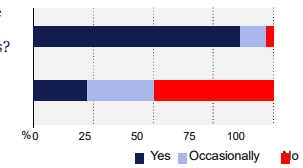
- 93.8 % indicate to work as (neuro-)pathologist
- 75 % report to work within Europe
- Single respondents from 17 different countries (in red)

1. How would you rate the relevance of molecular marker testing in diagnostic neuropathology?

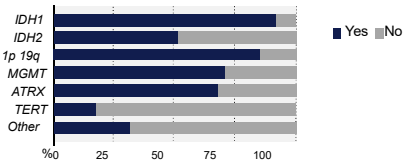


2. Do you currently use molecular information for diagnostic purposes?

3. Do you use „oligoastrocytoma" as histological diagnosis?



4. Which molecular markers do you routinely test for neuropathological work-up of diffuse gliomas?



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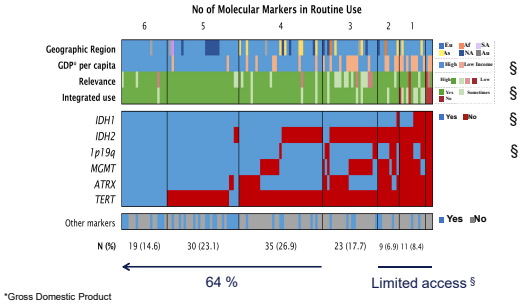
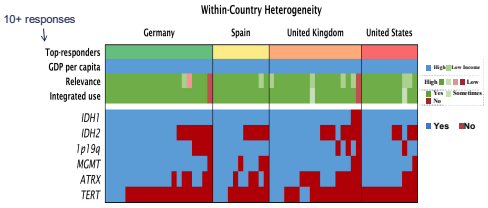


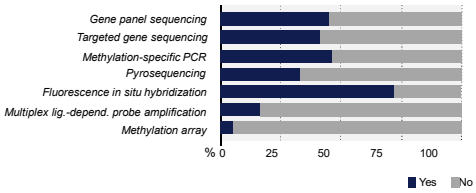
*Gross Domestic Product

4. Which molecular markers do you routinely test for neuropathological work-up of diffuse gliomas?



High within-country heterogeneity

5. Which molecular techniques and platforms do you currently use?



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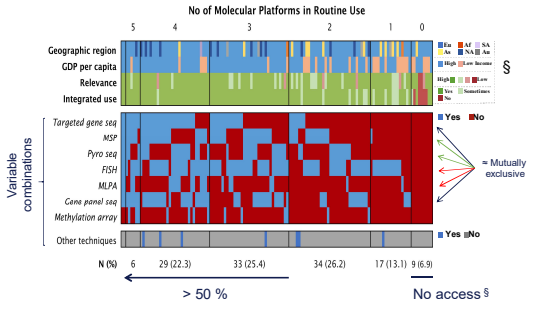

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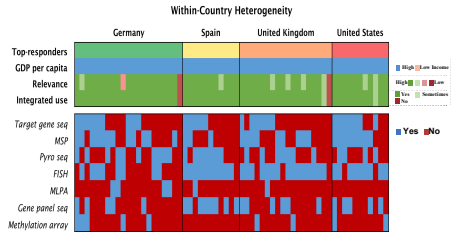
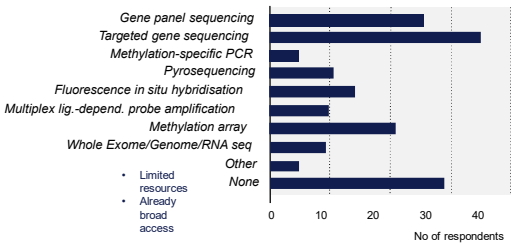


High within-country heterogeneity (might indicate centralization of diagnostic services)

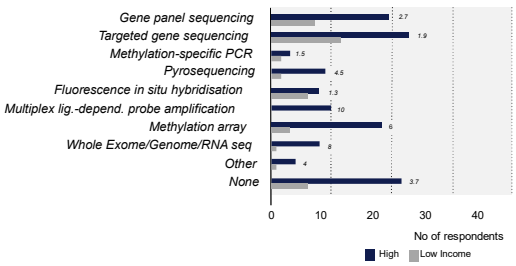
6. Which additional platforms are you going to implement within the next 1-2 years?



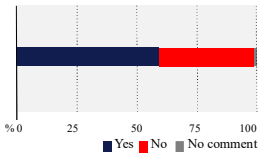
- Limited resources
- Already broad access

60 % of neuropathologists aim at implementing one additional technique

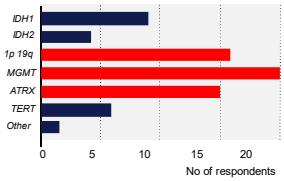
6. Which additional platforms are you going to implement within the next 1-2 years?



7. Are you concerned about the analytical test performance of any of those markers?

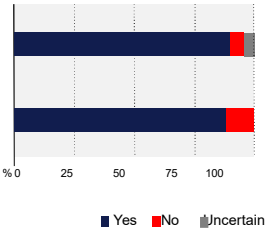


8. If yes, which marker would you rate most problematic?



9. Is there a need for guidelines on marker testing?

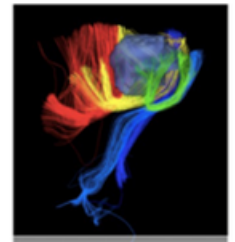
10. Would you be willing to participate in a ring trial?



Summary

- *Post 2016 WHO* survey focused on neuropathologists
- Neuropathologists uniformly rate **molecular marker testing as highly relevant** and **already incorporate molecular information** in their diagnostic assessments
- **Differences in access to crucial biomarkers and molecular techniques** across geographic regions AND within individual countries
- Concerns regarding the validity of test assays (with MGMT, 1p 19q, and ATRX being perceived most problematic) underline the **need for consensus guidelines** on molecular marker testing (cIMPACT now, Euro-CNS)

Thank you.



Modern Imaging of Brain Tumours

Mr Ranjeev Bhangoo
Consultant Neurosurgeon / Clinical Director Neuroscience
Mr Christian Brogna

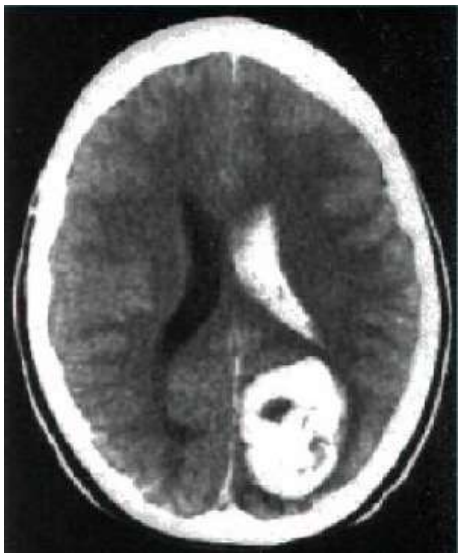
King's College Hospital
King's College London
London, United Kingdom

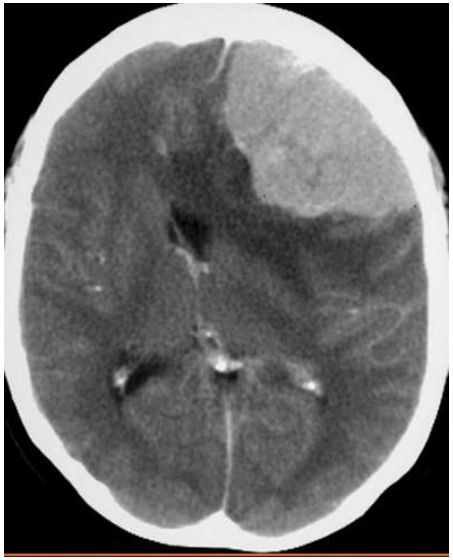
- CT and routine MRI protocol
- Anatomic Imaging
- Metabolic Imaging
- Physiological Imaging
- Functional Imaging
- Pros and Cons Imaging followup

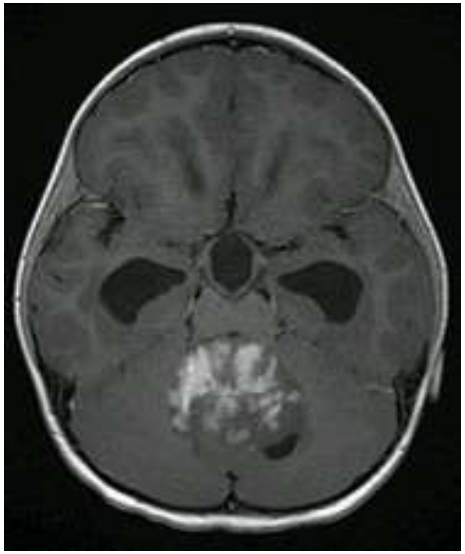
CT

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

⇨ Urgent Neurosurgical Treatment







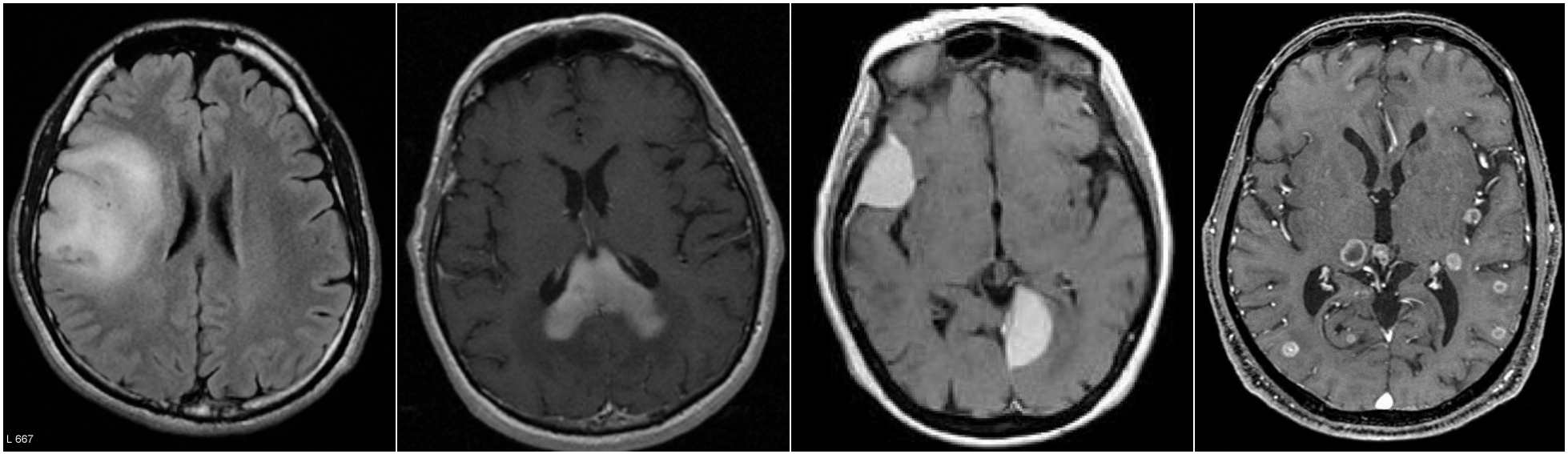
CONVENTIONAL STRUCTURAL MRI BRAIN TUMOURS

- **MRI**: routine protocol

  - 3D 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 Imaging (DWI)
  - Axial T2*-weighted sequence (sensitive to blood and calcifications)
  - Susceptibility-weighted imaging (SWI)
  - 3D Contrast enhanced T1 weighted sequences

CONVENTIONAL STRUCTURAL MRI

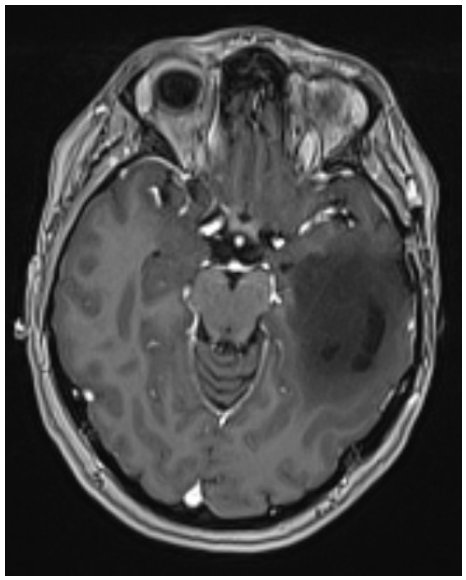
- Anatomical Location (Intra or extra-axial)
- Extent of tissue involvement
- Mass effect upon brain, ventricular system and vasculature
- Suggest a short list of differential diagnosis (particularly in t he clinical context)

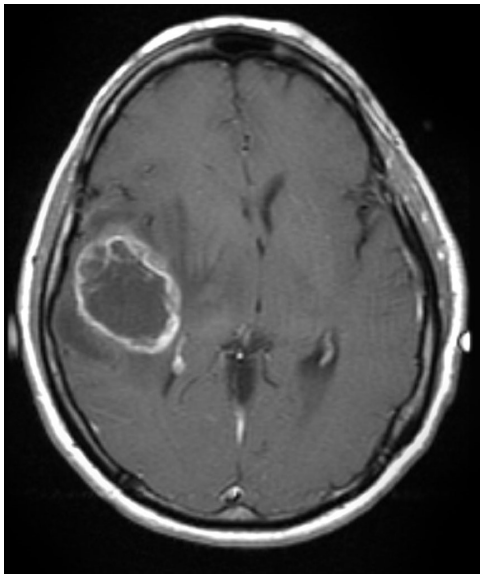


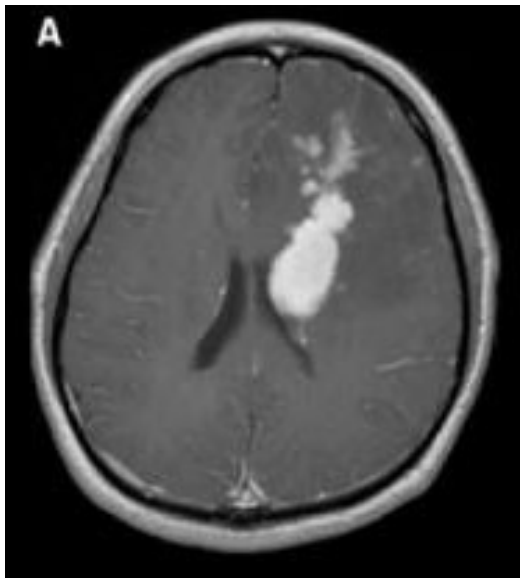
Oligodendroglioma | Lymphoma | Meningiomas | Multiple Mets

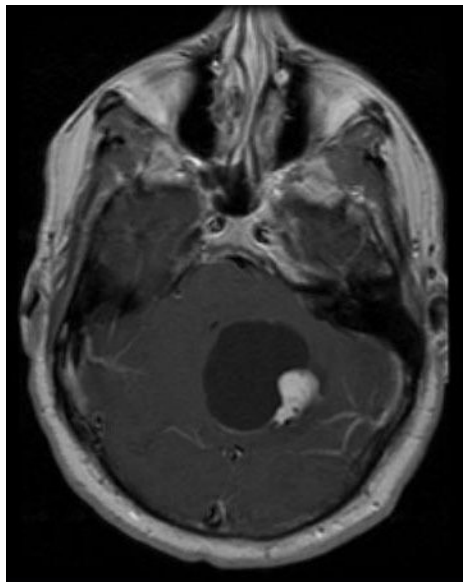
CONVENTIONAL STRUCTURAL MRI

- Pattern of enhancement









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

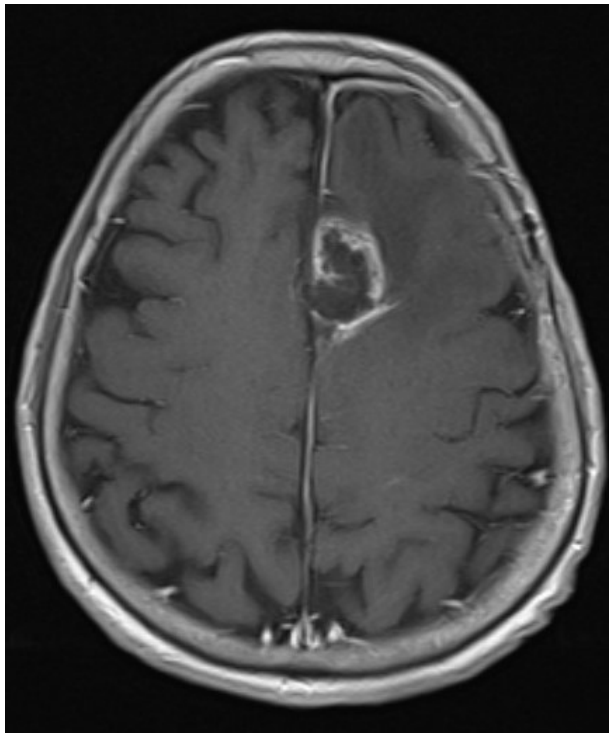
GBM

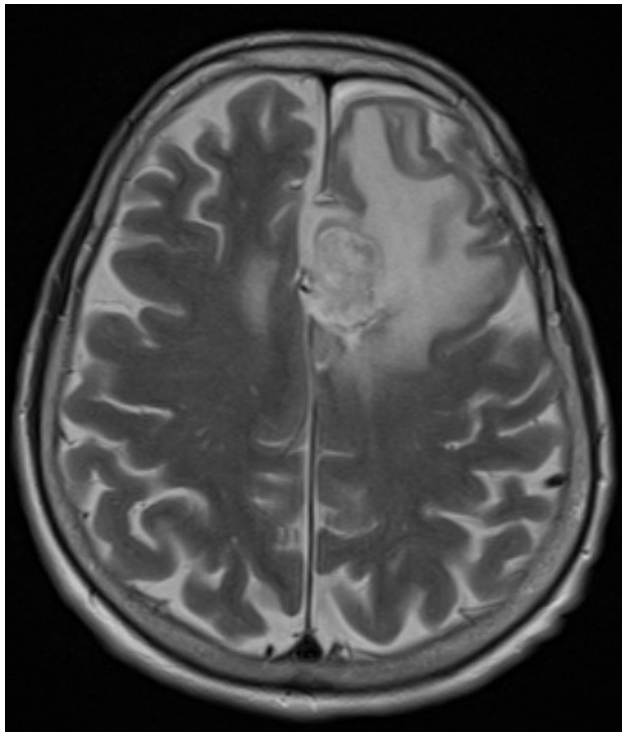
LYMPHOMA

HEMANGIOBLASTOMA

CONVENTIONAL STRUCTURAL MRI

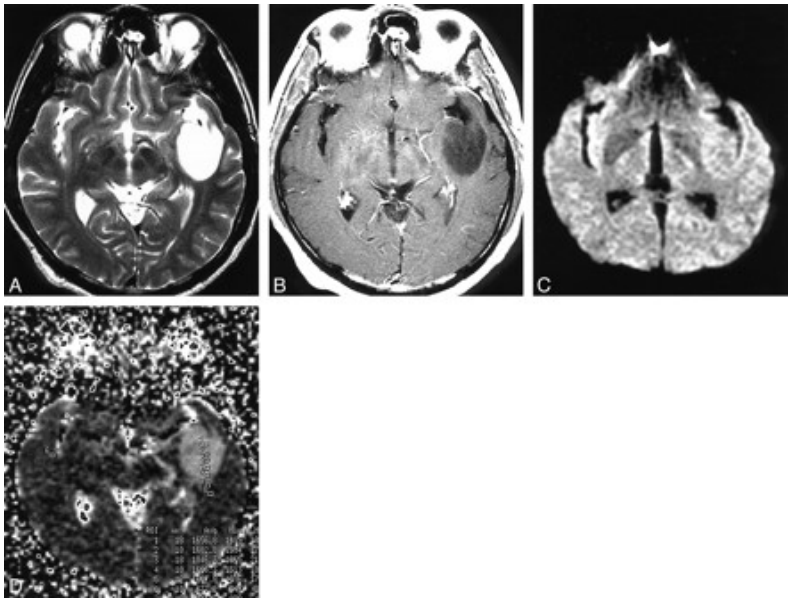
Pitfall: VASOGENIC EDEMA vs INFILTRATING TUMOUR





PHYSIOLOGICAL IMAGING
DWI MRI

- Probes Brownian motion of water molecules
- Assess tumor cellularity, peritumoral edema, regions of tumor hypoxia, integrity of white matter
- Corresponding ADC values reflect the magnitude of diffusivity



Diffusion weighted image

	DWI	ADC	Examples
Diffusion restriction	○	●	*cytotoxic edema (acute ischemia), abscess/inflammation, acute demyelination*
Increased diffusion	●	○	*cerebrospinal fluid (CSF)*
T2 shine-through	○	○	*vasogenic edema, gallbladder, endometrium*

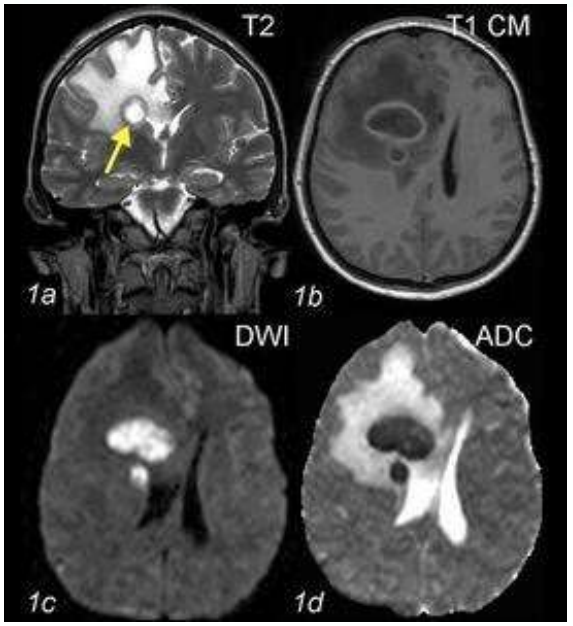
PHYSIOLOGICAL IMAGING
DWI MRI

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

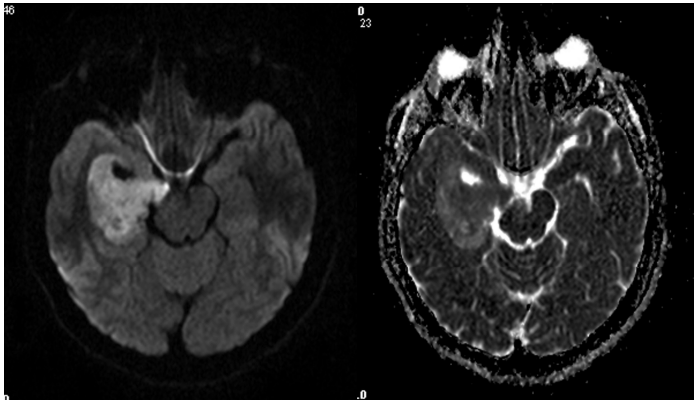
- Accurate interpretation of new abnormal contrast enhancement developing soon after tumor resection

- Postoperative ischemia

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



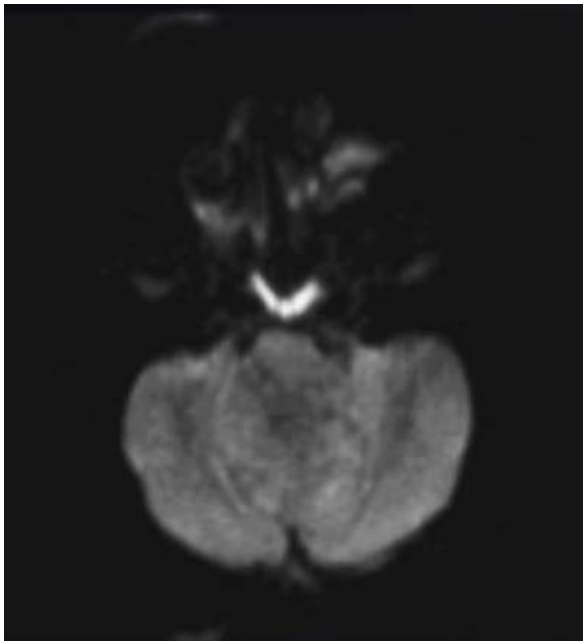
Brain abscess



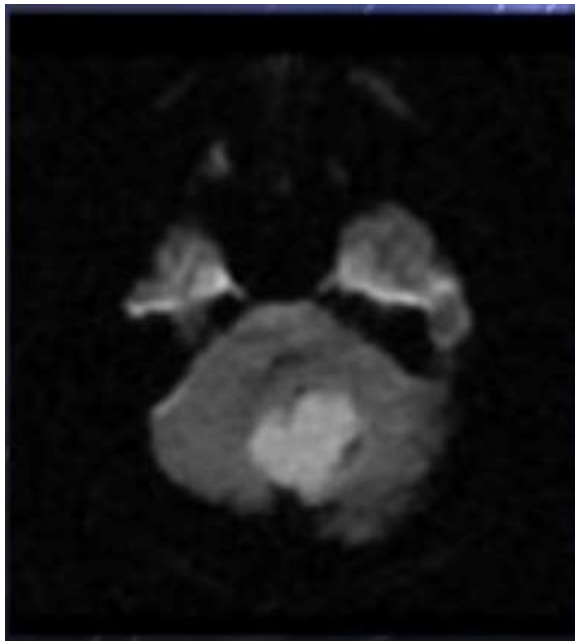
Epidermoid

PHYSIOLOGICAL IMAGING
DWI MRI

High ADC values
Ependymoma

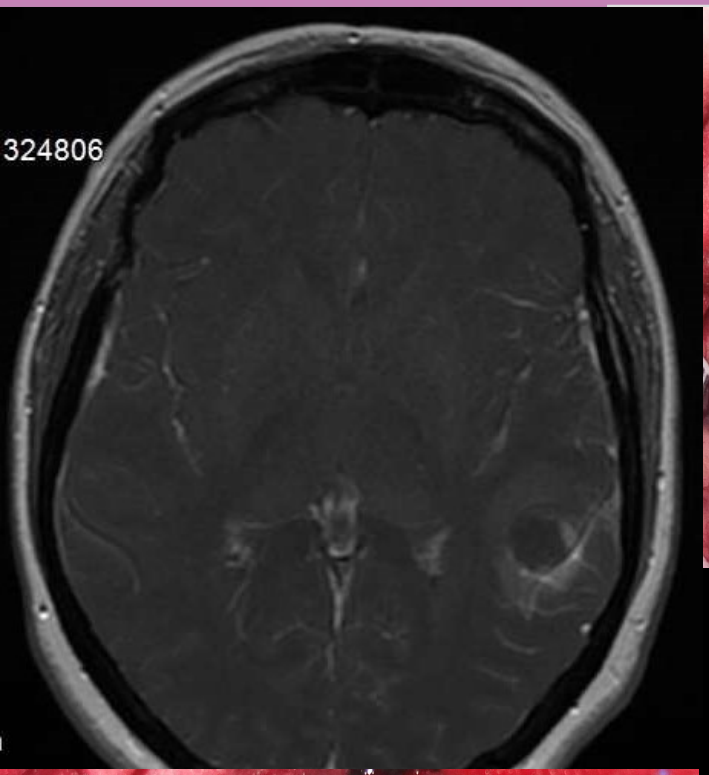


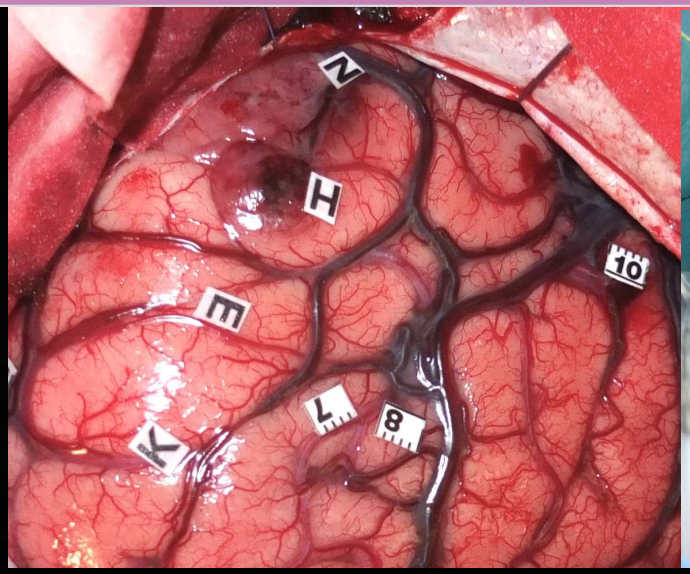
Low ADC values
Medulloblastoma

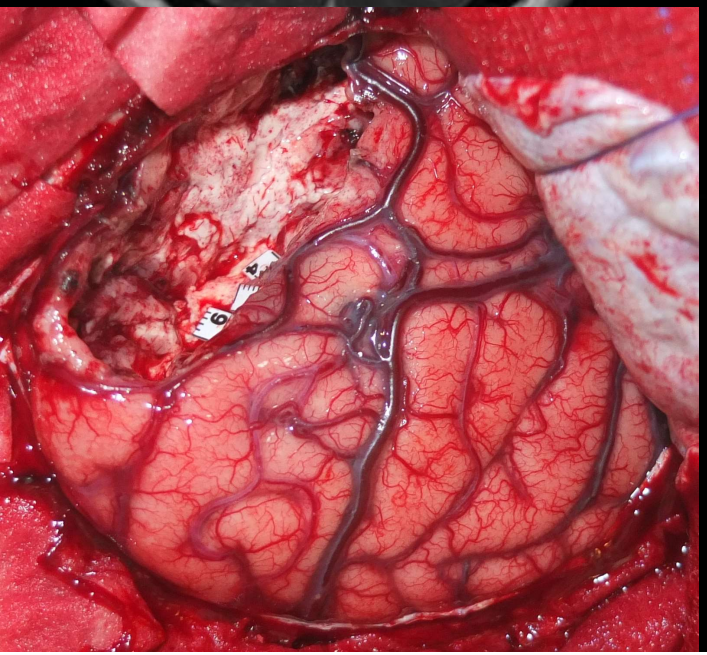


PHYSIOLOGICAL IMAGING

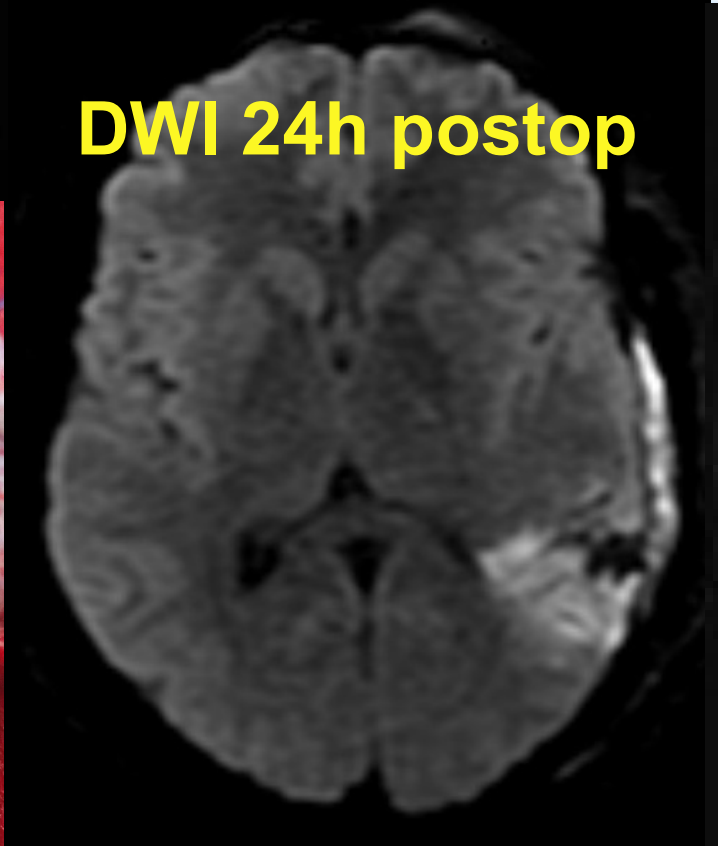
DWI- MRI



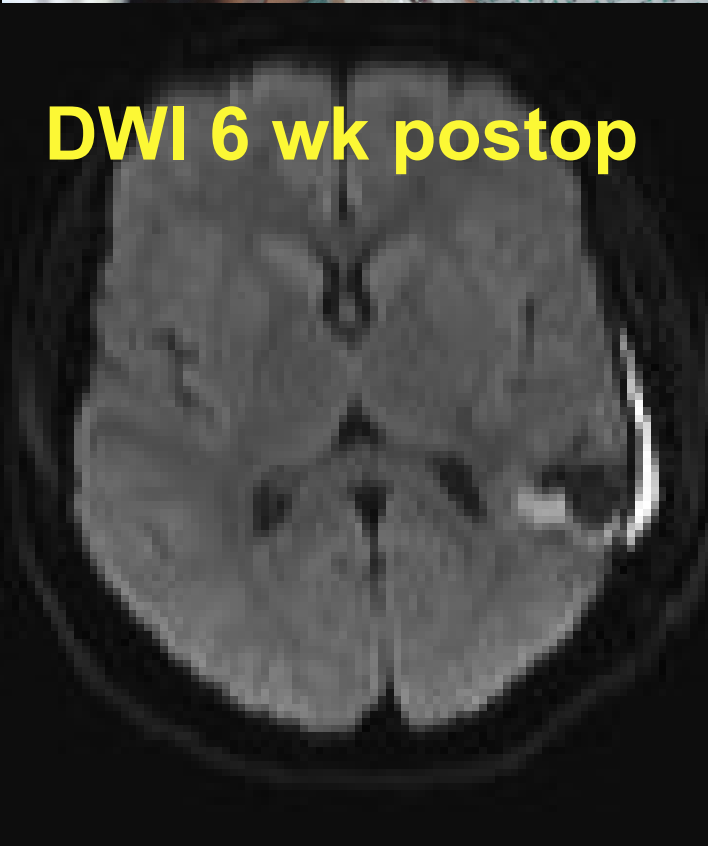




DWI 24h postop



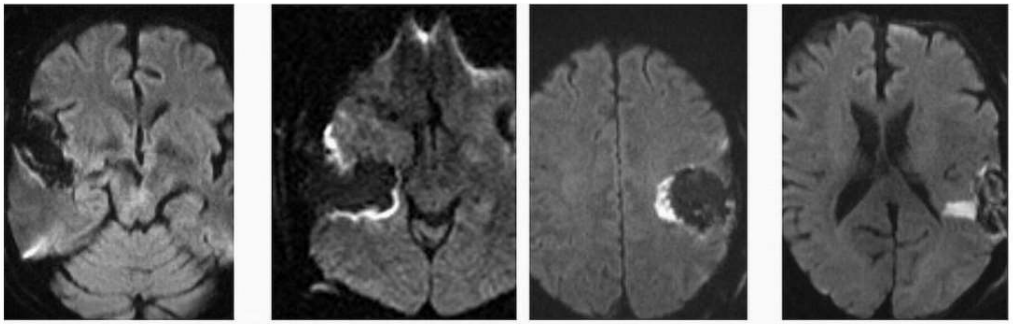
DWI 6 wk postop



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

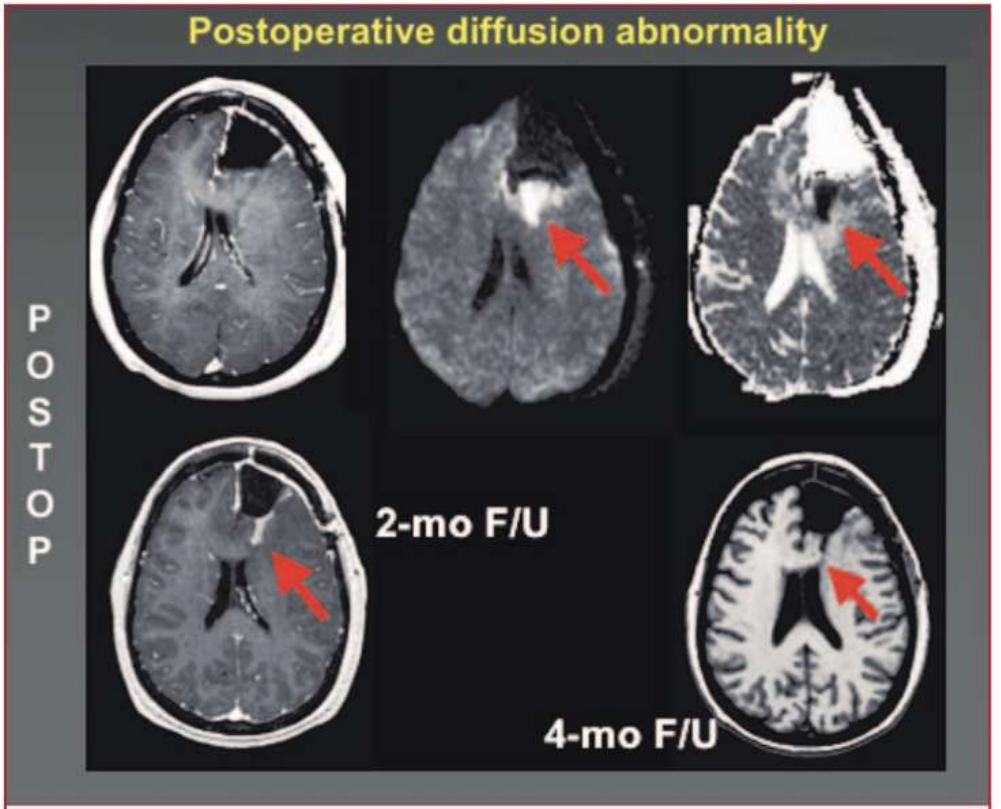
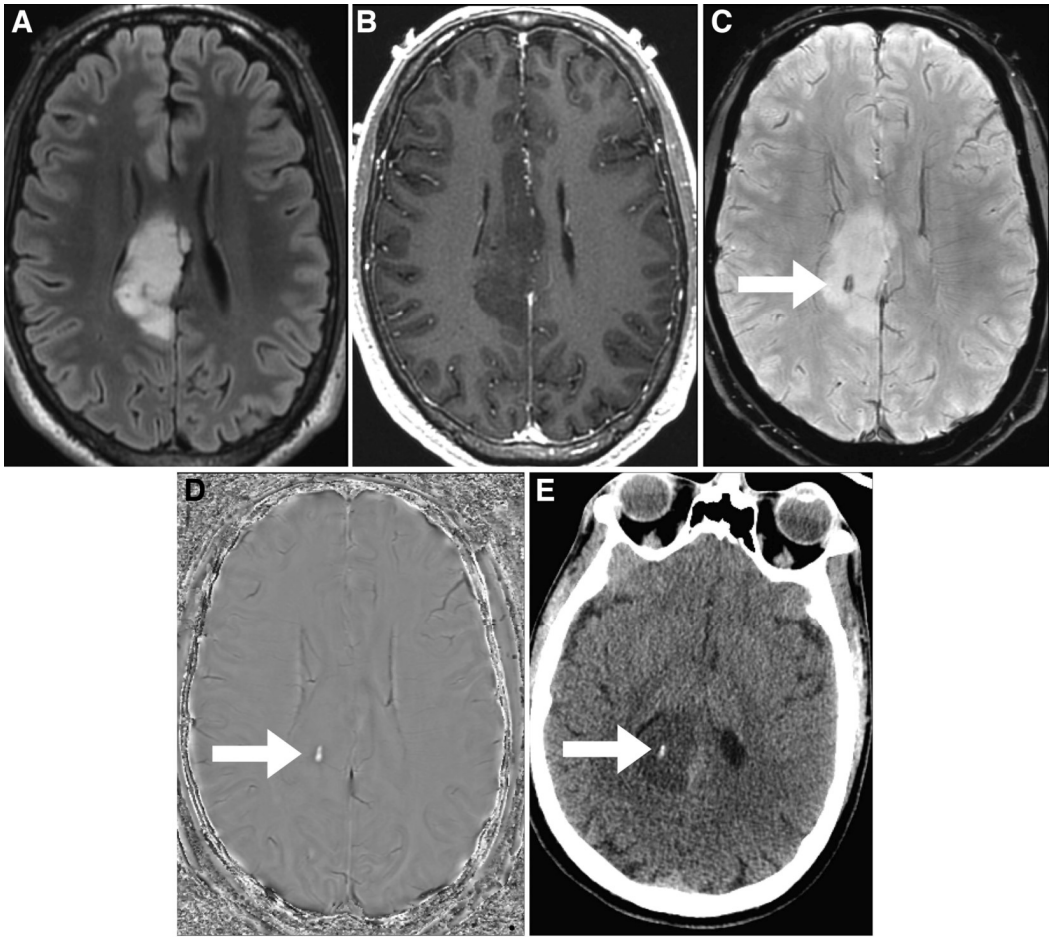


FIGURE 7. *DWI obtained 2 and 4 months postoperatively to identify areas of ischemia (bright signal DWI, dark signal void apparent diffusion coefficient) that enhances briefly postoperatively.*

M. Berger et al. Neurosurgery 2000

PHYSIOLOGICAL IMAGING
SWI-MRI

Sensitive to blood products, microvessels and calcium



Oligodendroglioma

PHYSIOLOGICAL IMAGING
PERFUSION MRI

- Provides hemodynamic informations and estimates the cerebral blood volume that reflect the underlying microvasculature, marker of angiogenesis
- 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

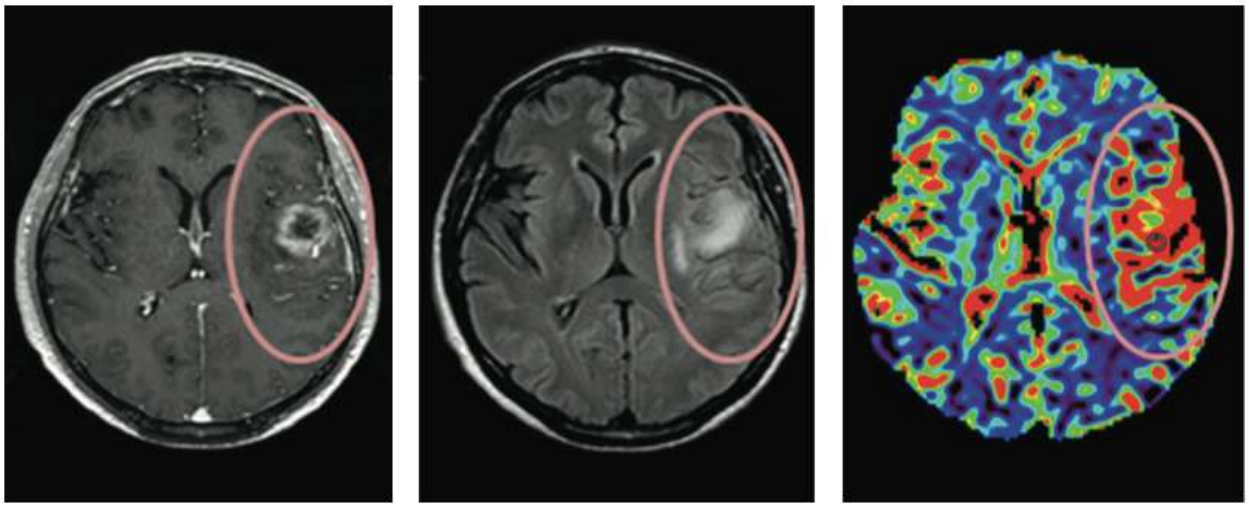
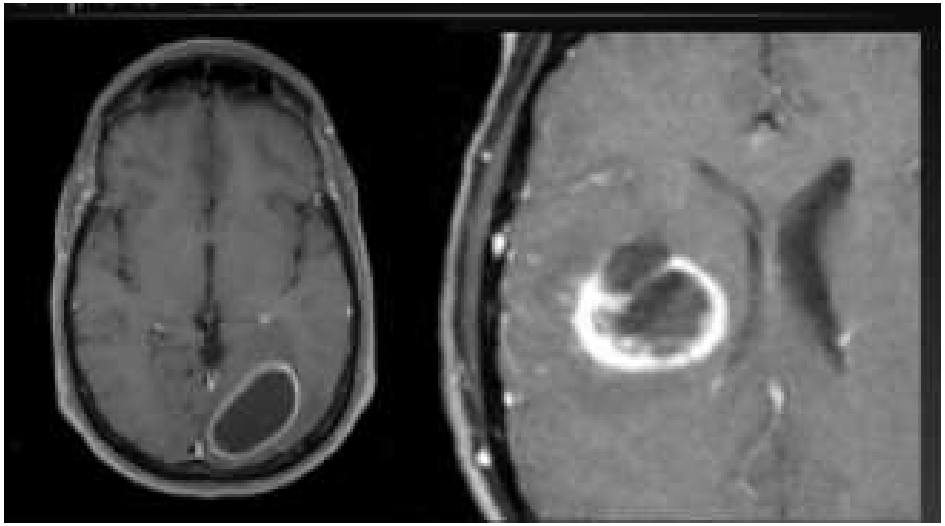


FIGURE 2: Axial coregistered contrast-enhanced axial T1-weighted image (a), FLAIR image (b), and CBV map (c) from a patient affected by glioma grade IV. In the CBV map (c) warmer colors indicate higher CBV values suggesting higher perfusion and neovascularization. Comparison of CBV map (c) and contrast-enhanced 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

TUMOR MIMICS

Ring- enhancing lesions

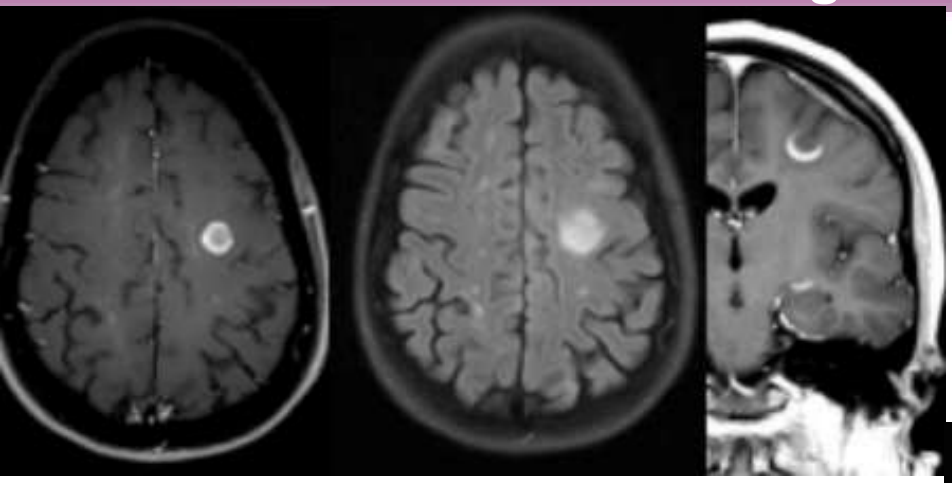


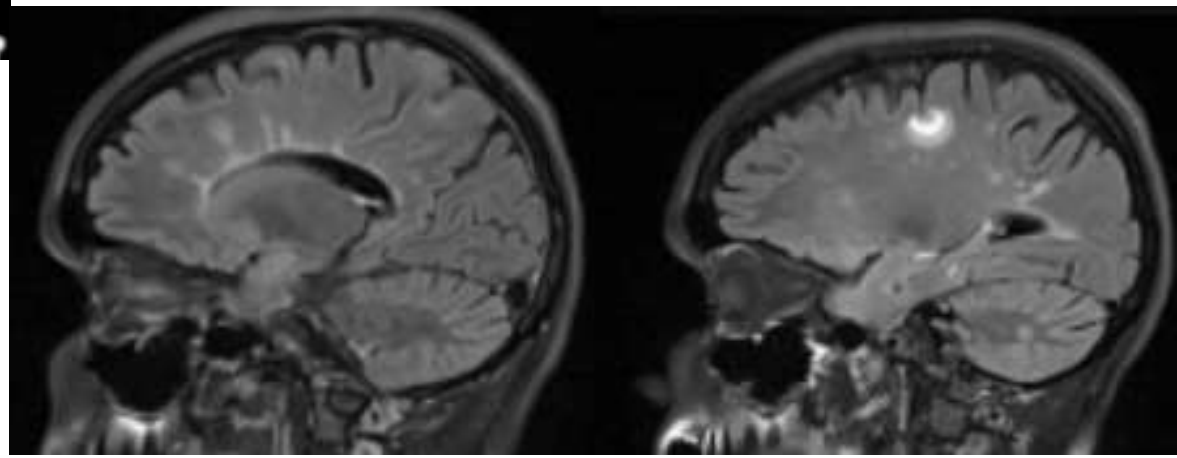
Met GBM

- **Demyelination**
  - Incomplete peripheral enhancement
- **GBM**
  - More irregular enhancement
- **Infection**
  - Toxoplasmosis, neurocysticercosis, TB, Abscess, Nocardia
- **Lymphoma**
  - Ring-enhancement if immunocompromised
- **Metastases**

TUMOR MIMICS

Ring- enhanicing lesions

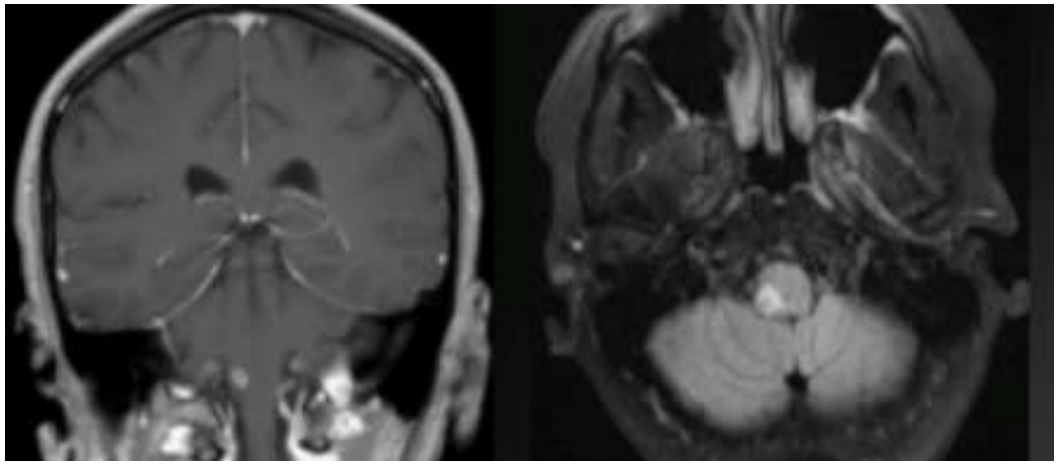


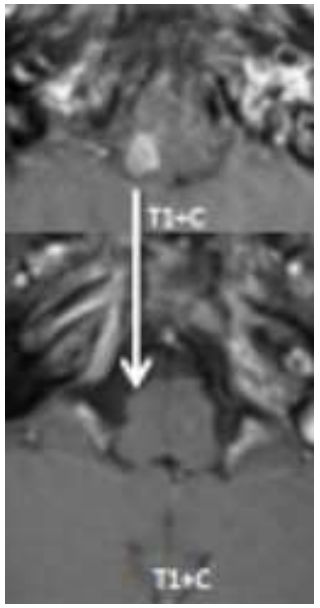


- 24 yy, Multiple sclerosis
- Ring-enhancement that opens toward the cortex

TUMOR MIMICS

Ring- enhanicing lesions

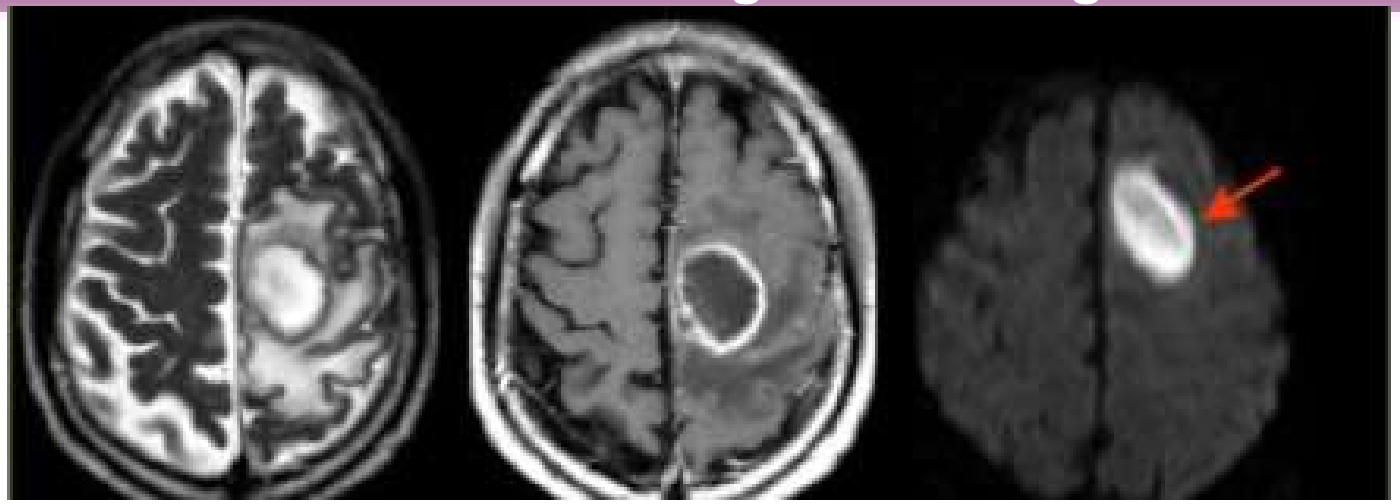




- ADEM
- 4 months later lesion resolved

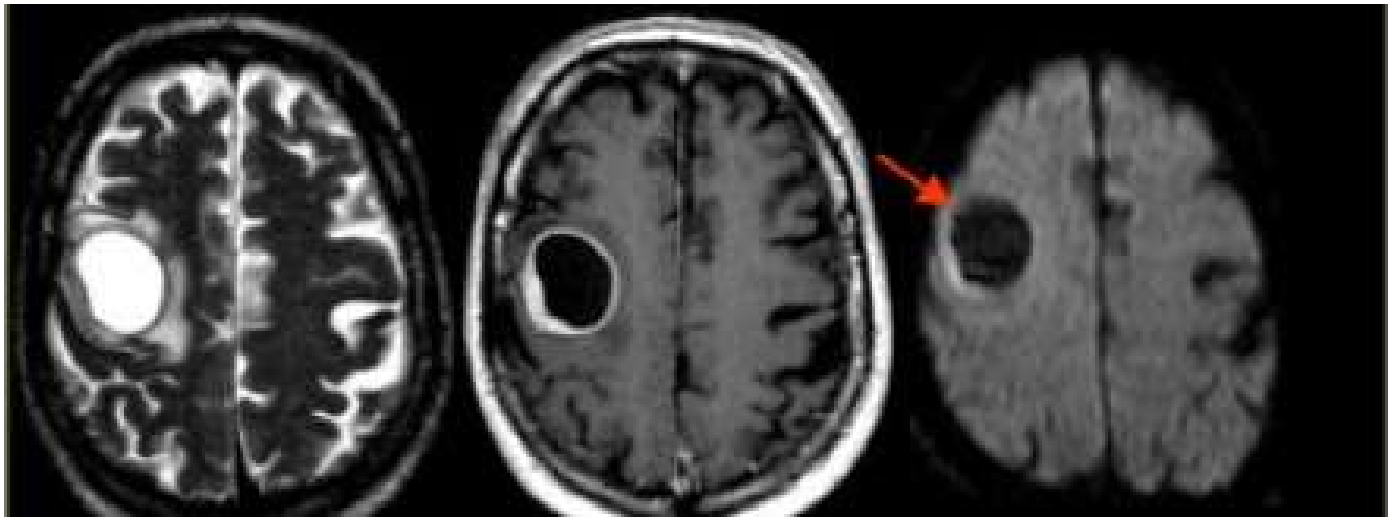
TUMOR MIMICS

Ring- enhanicing lesions



Abscess

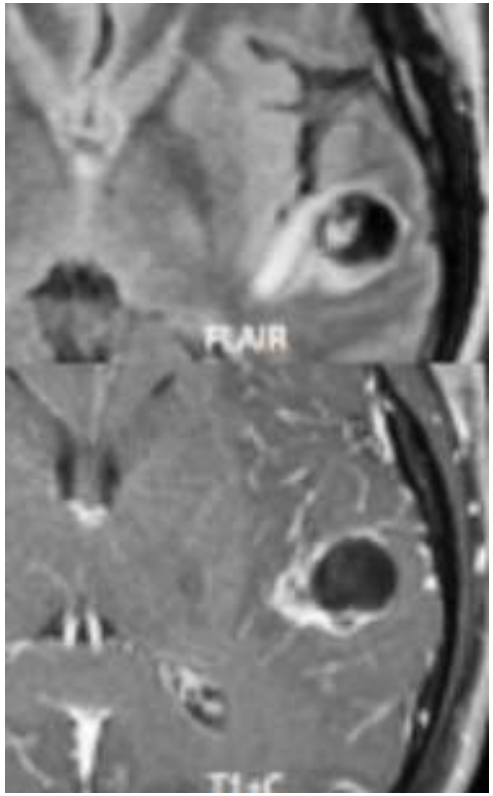
Vs



Lung Met

TUMOR MIMICS

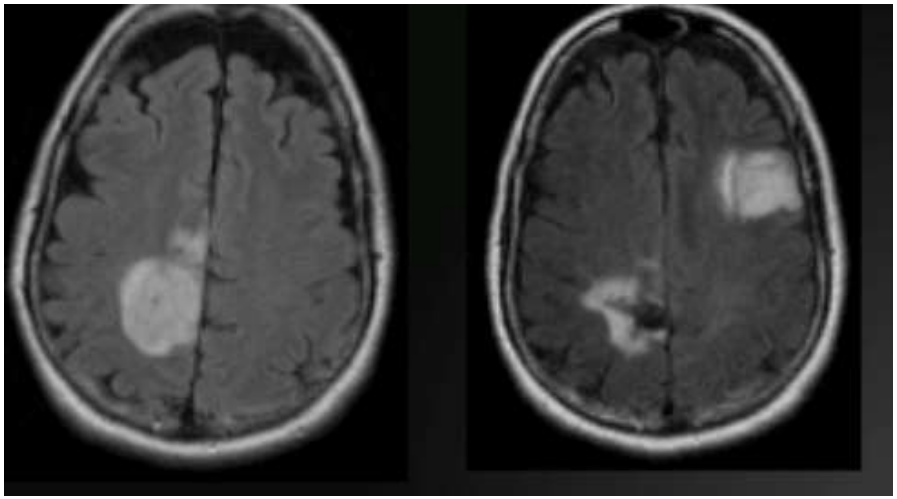
Ring- enhanicing lesions



- Neurocysticercosis as opposed to low grade solid neoplasm

TUMOR MIMICS

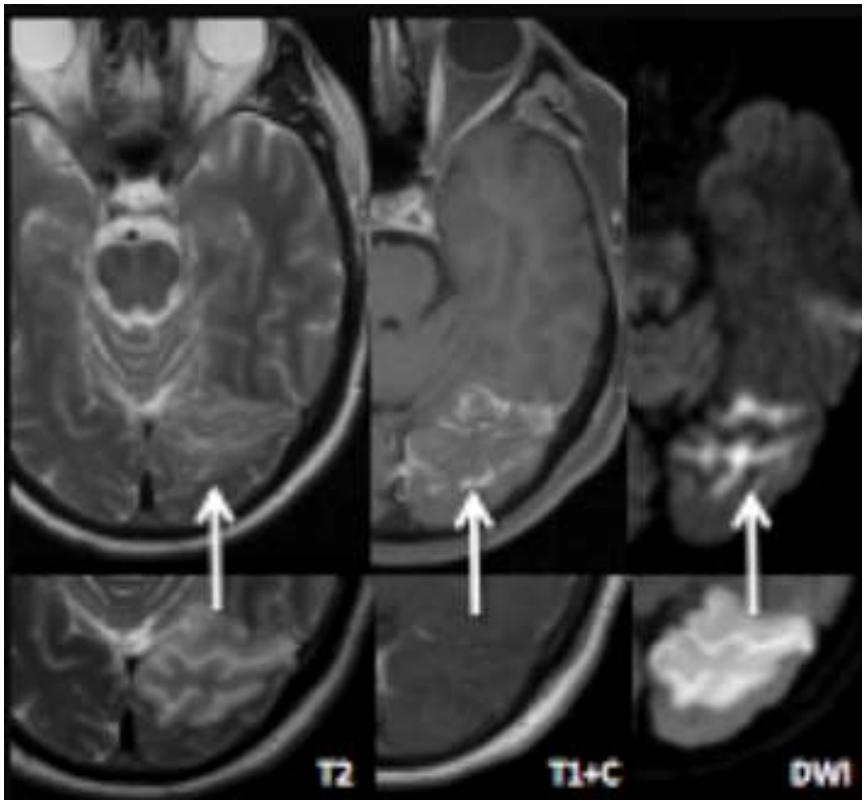
Ring- enhanicing lesions



3 months later

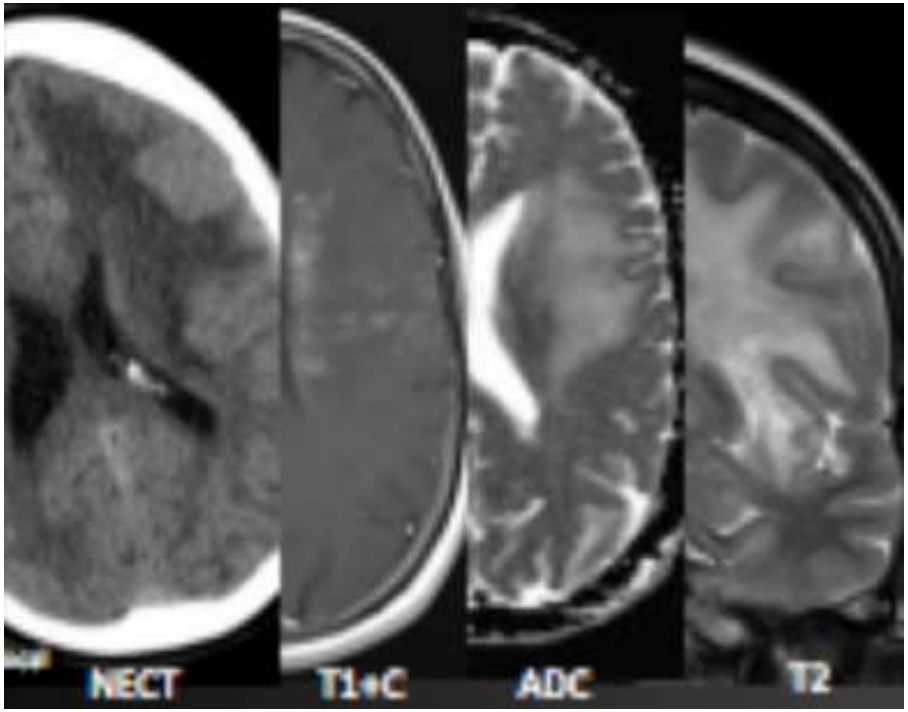
- Tumefactive demyelination as opposed to glioma

TUMOR MIMICS



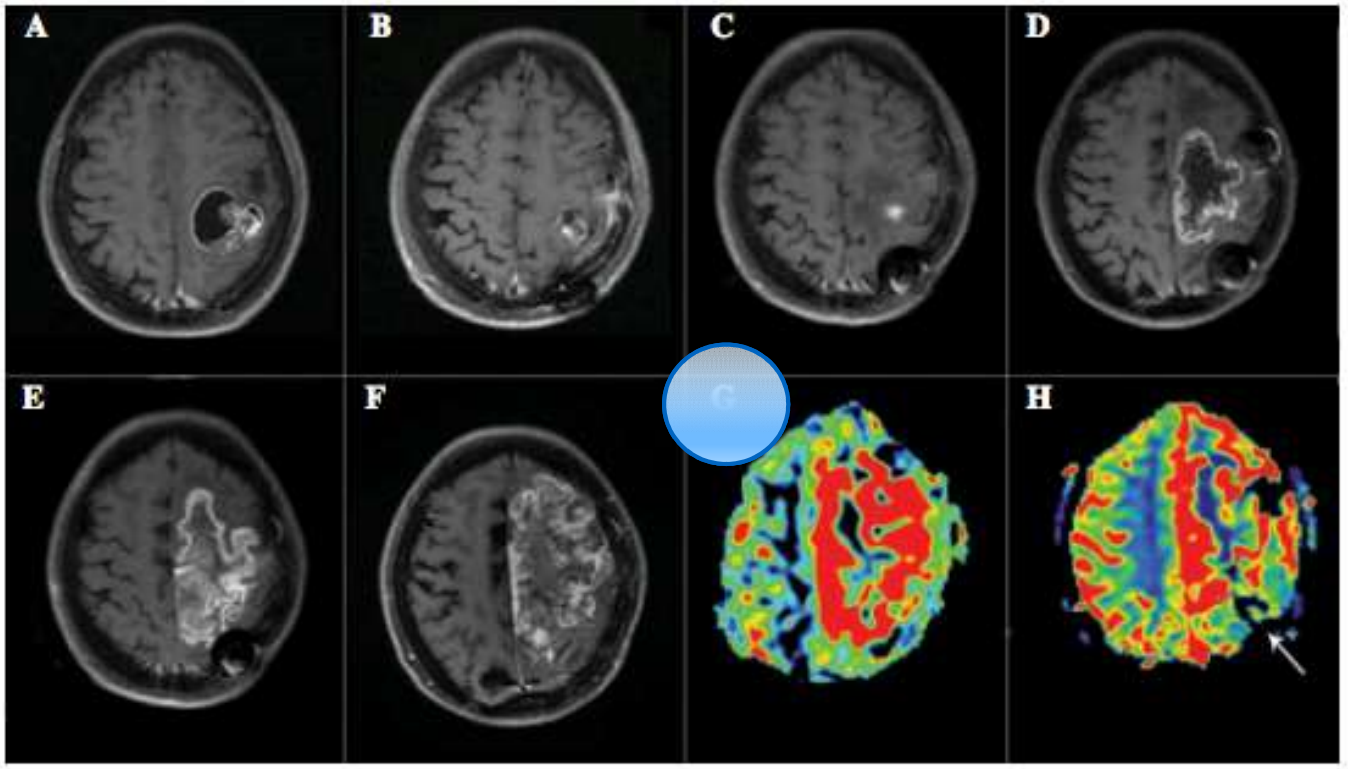
- Subacute stroke: in doubts re-image 2 weeks later

TUMOR MIMICS



- Vasculitis with microthrombosis as opposed to tumour

TUMOR MIMICS

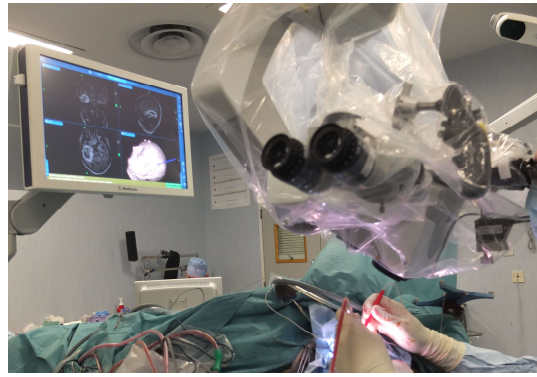


- Radiation Necrosis vs Recurrent High Grade:
- (G) Arterial Spin Labeling Perfusion Imaging

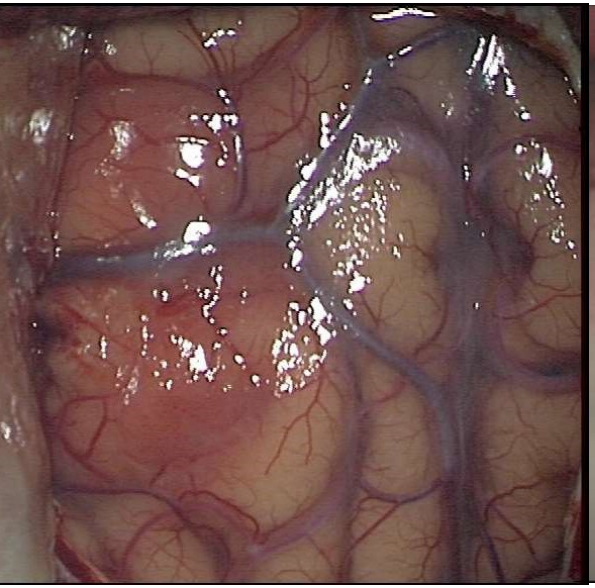
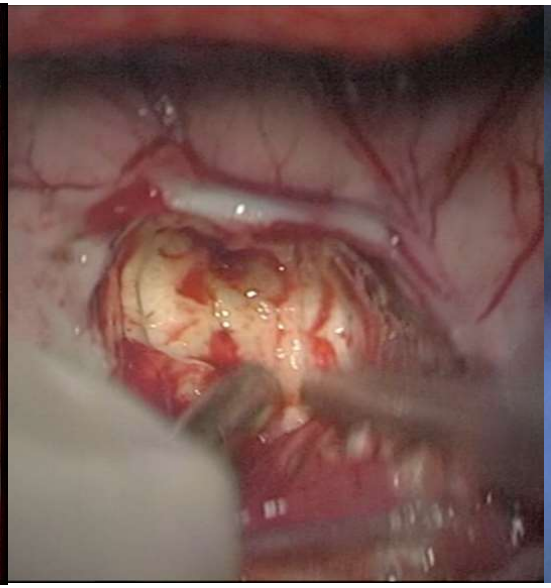
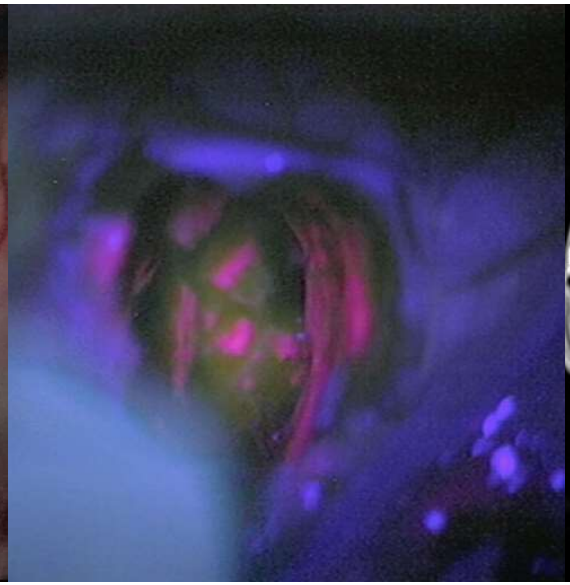
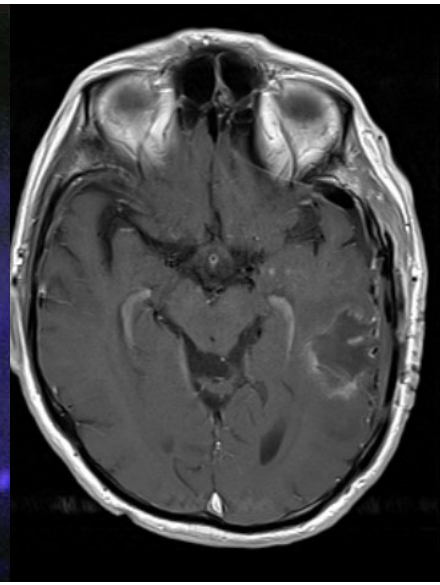
ASL-MRI: measure tumour perfusion. No Gd administered, No Gd extravasation

ANATOMIC IMAGING
EARLY POSTOP MRI

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



Post op imaging should be performed within 48h of surgery, the sooner the better

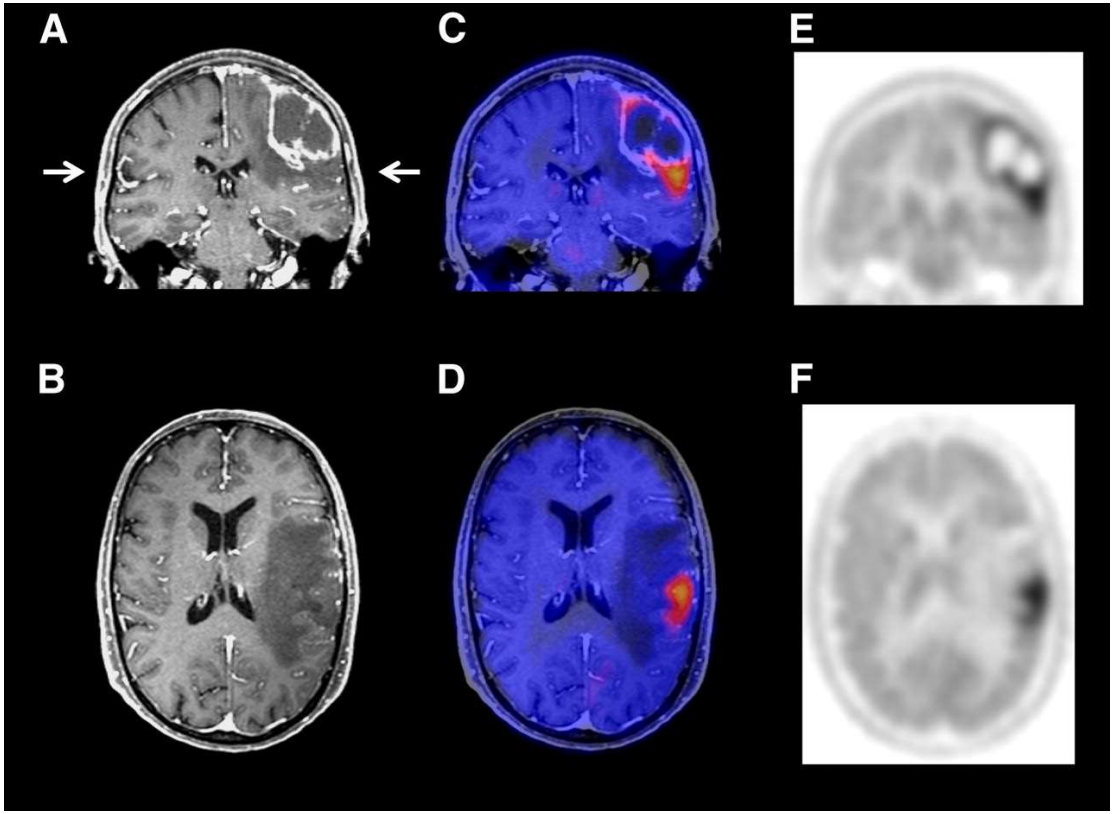





Pitfall: when comparing studies, the size and shape of a tumor can appear substantially different due to differences in the angle of imaging, slice thickness and gaps between slices

METABOLIC IMAGING

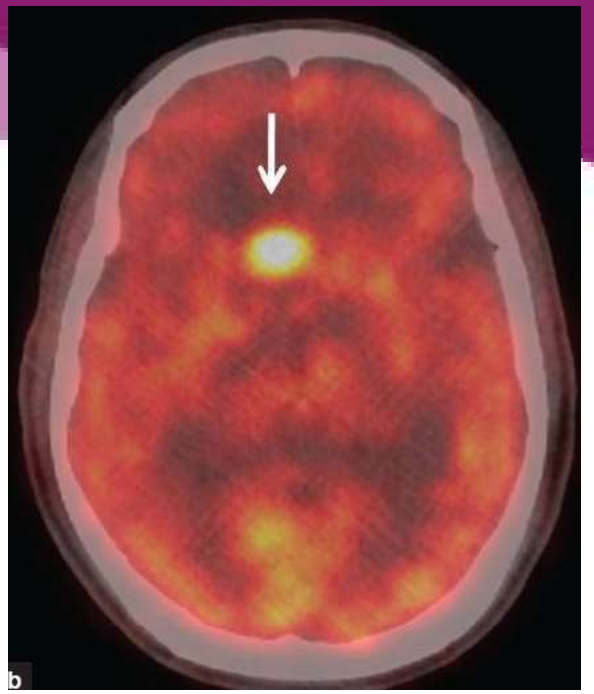
PET provides <u>metabolic in vivo measurement</u> of local tracer activity at a very high sensitivity

(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**

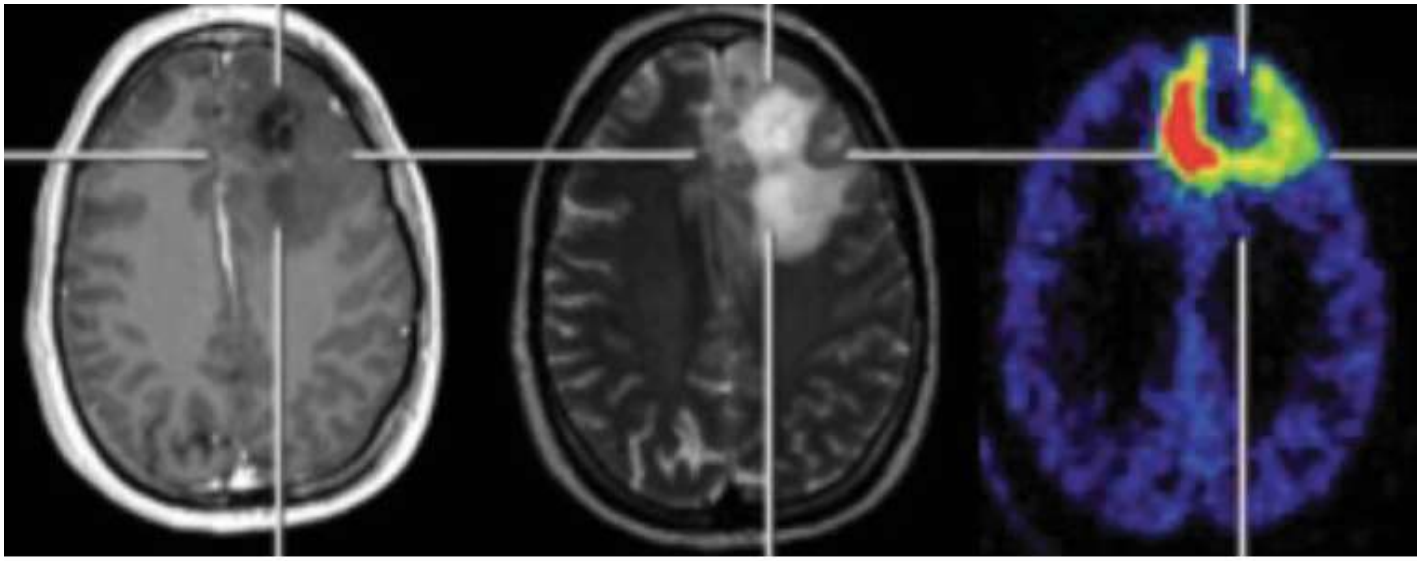
- **Cannot differentiate tumour vs inflammation vs acute stroke**
- **Radiation necrosis may be indistinguishable from recurrent tumour**

(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

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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 Recurrent tumour and Radiation Necrosis with high sensitivity and specificity (~75%): necrosis and glioses after therapy show a reduction of ammoniated uptake in contrast to recurrent and residual tumour growth.
- Deactivation of aminoacid transport is a early sign of response to chemotherapy (Galldicks N et al Mol Imaging 2010). PET responders with a decrease of tumour brain/ration of >10% had a significant longer TTP and OS than patient with increase tracer uptake after RT and CHT in GBM.

PITFALLS OF PET-MET

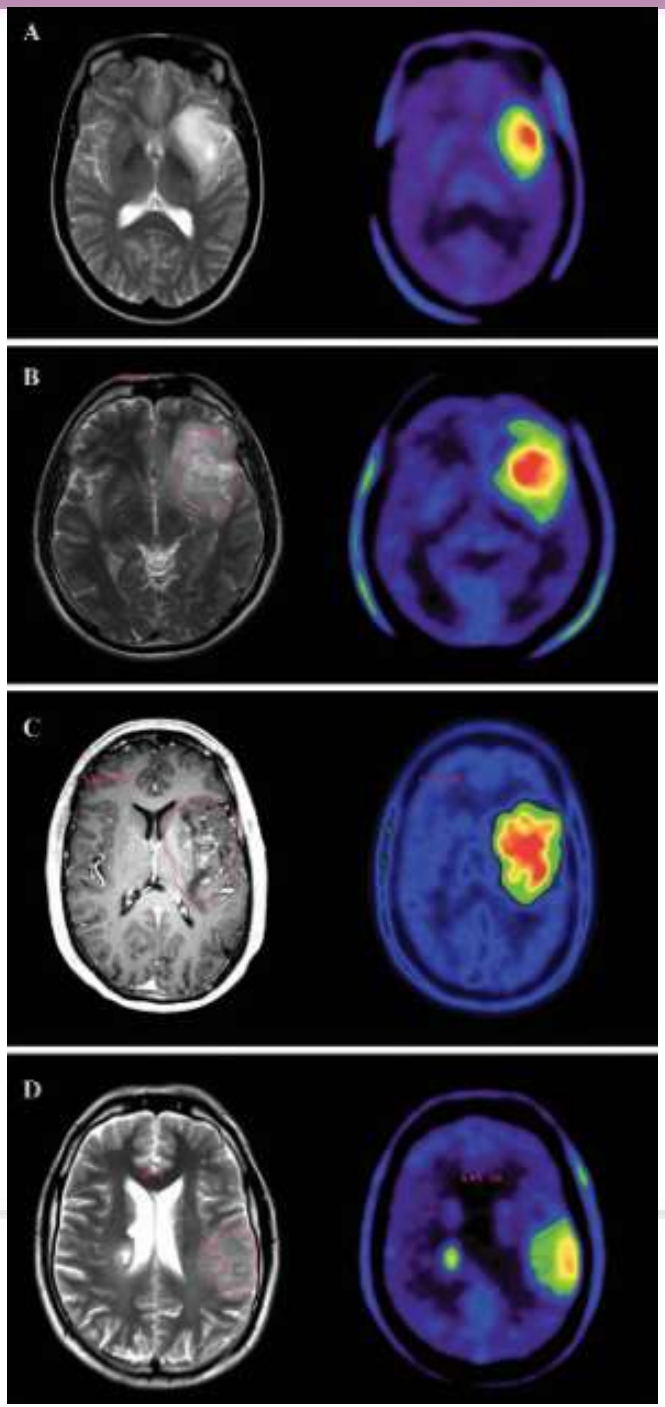
- some low grade astrocytomas demonstrates only low tracer uptake
- acute inflammation or ischemic stroke might manifest with increased aminoacid uptake
- NOT POSSIBLE TO PREDICT HISTOLOGICAL GRADE which is paramount in treatment decision making

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 III

GBM Grade IV

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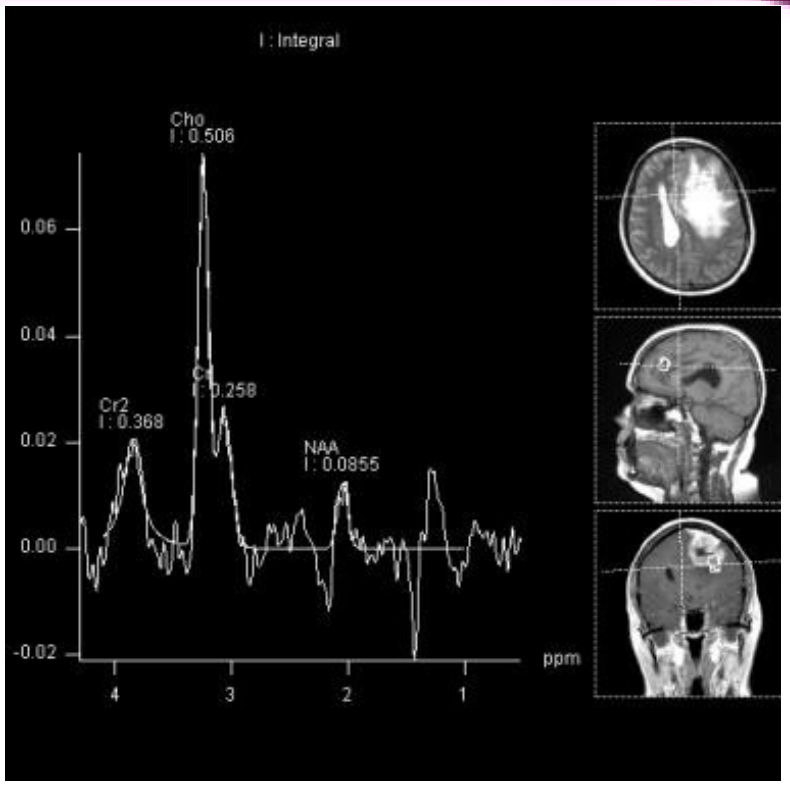
PHYSIOLOGICAL IMAGING
MRI SPECTROSCOPY

Provides insight into the biochemical profile

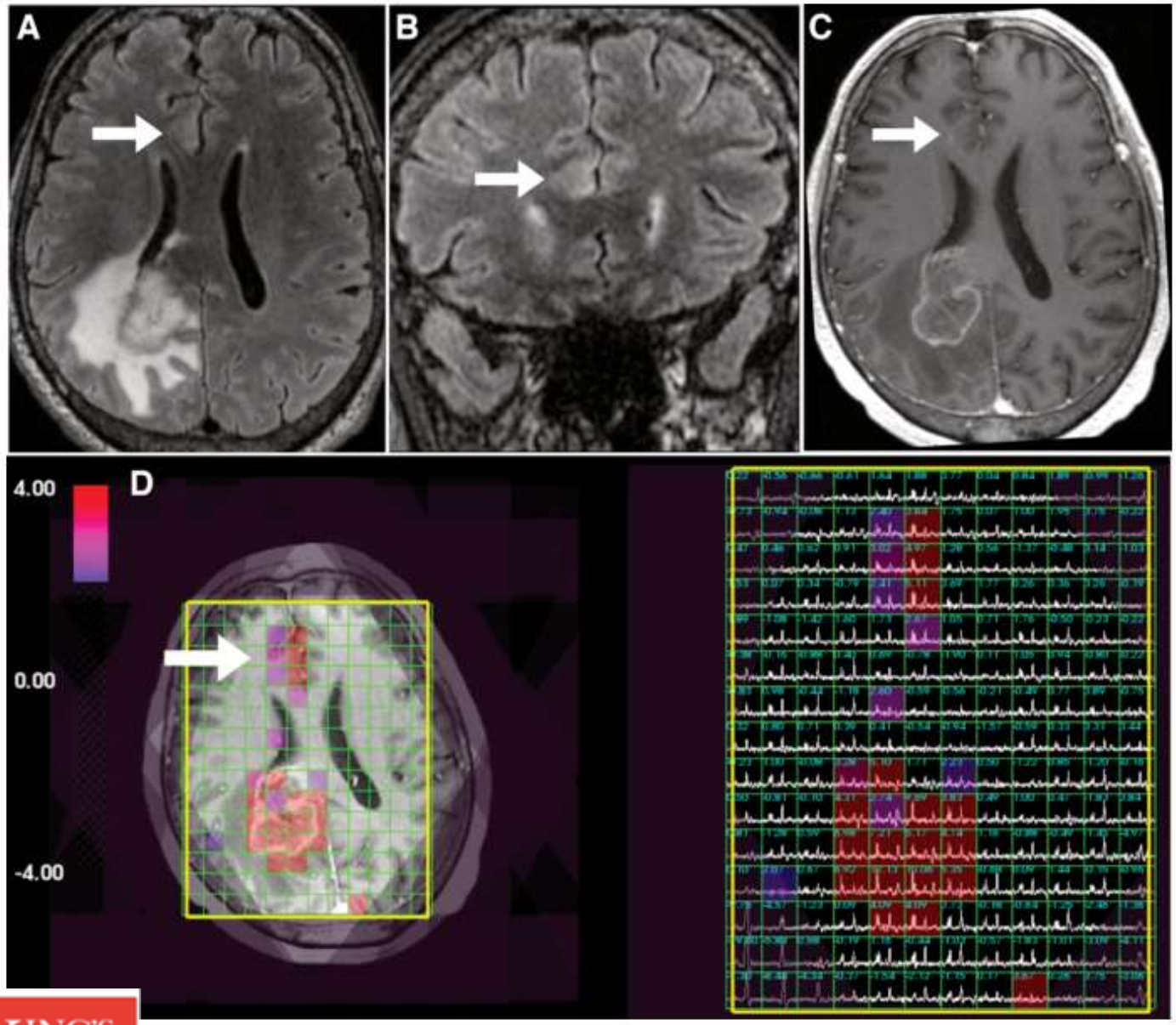
- **NAA**: marker of neural integrity
- **Choline**: membrane turnover
- Creatine: energetic
- **Myoinositol**: astrocytic marker
- **Lipid**: tissue destruction/necrosis marker
- Lactate: hypoxia marker
- Glutamine and Glutamate: excitatory markers



High choline correlates with high tumor proliferative index
Lower grades are associated with elevated MI/Cr ratio

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

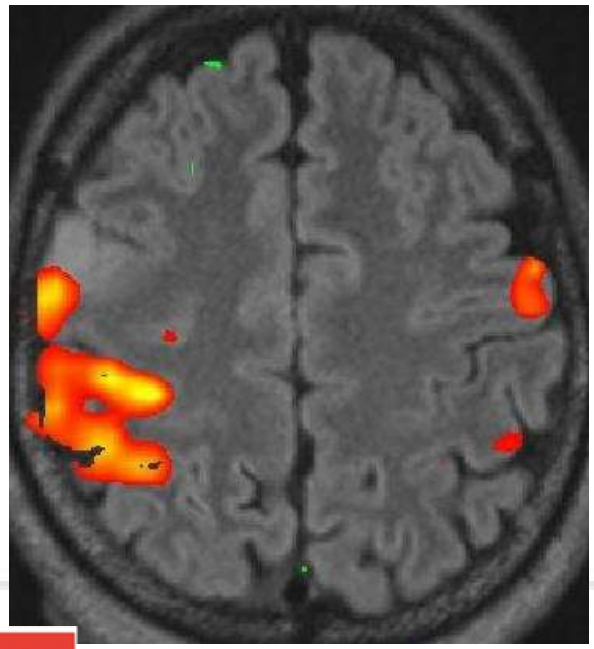
PHYSIOLOGICAL IMAGING
MRI SPECTROSCOPY



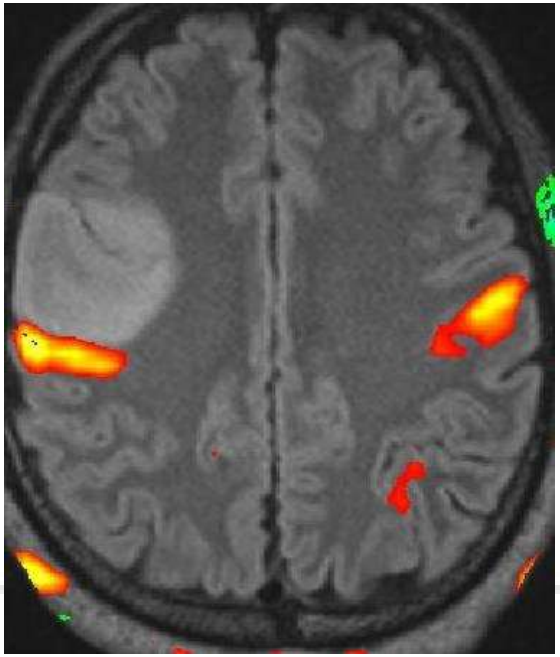
Villanueva-Meyer et al. Neurosurgery 2017

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

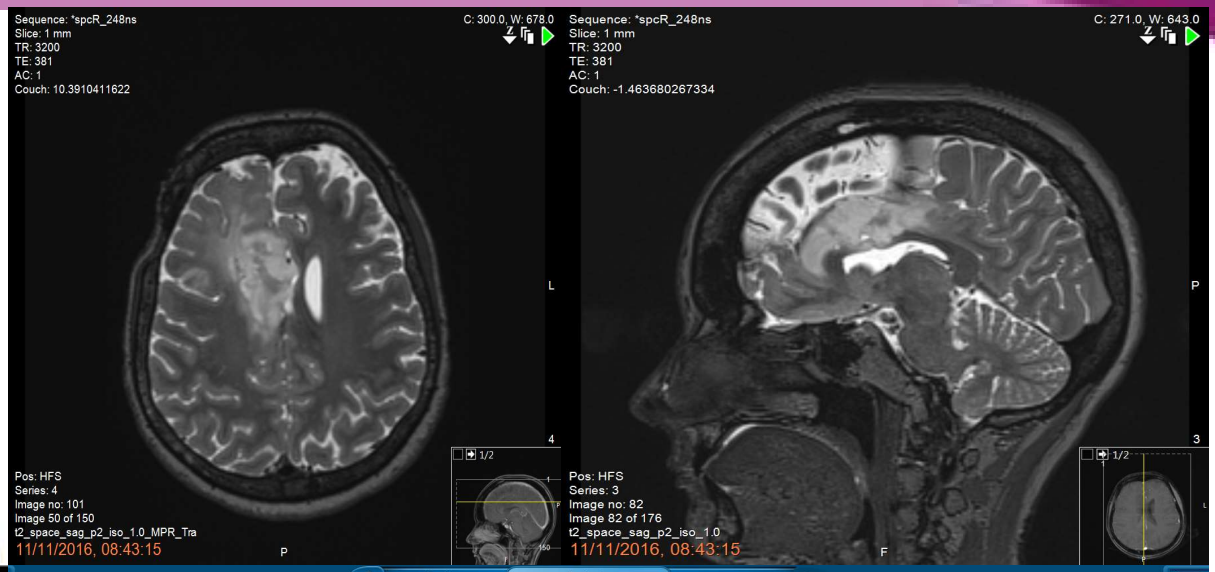


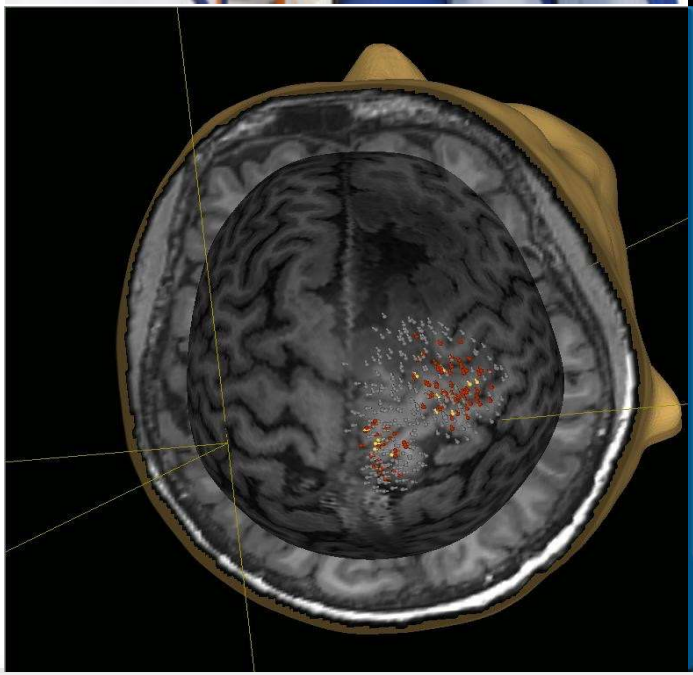
Finger Tapping

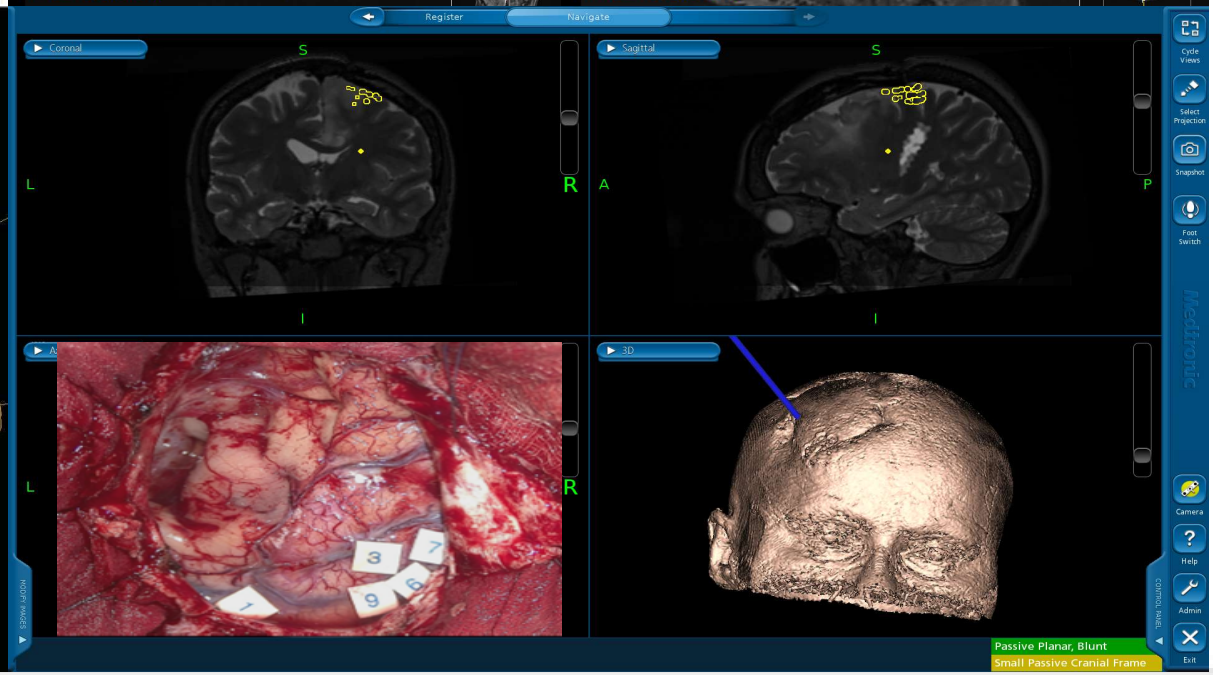


Semantic speech

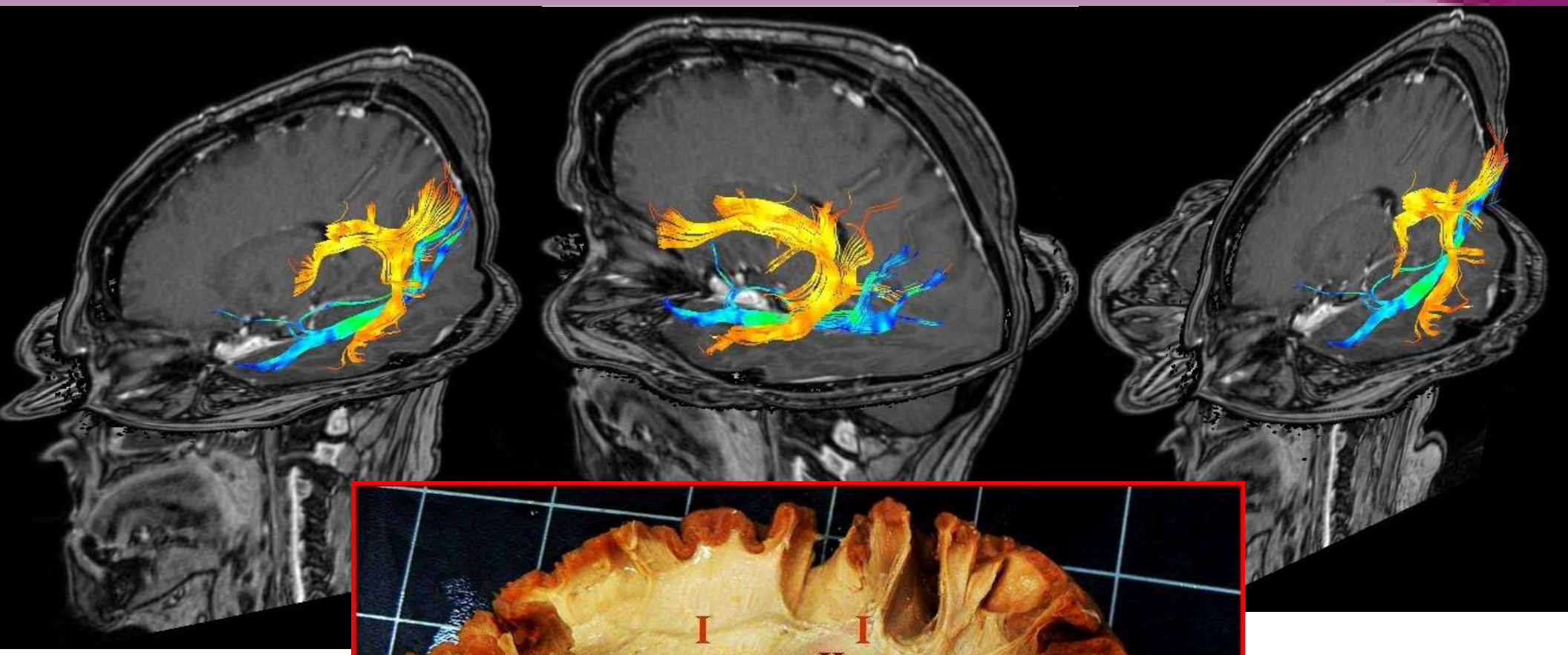
Navigated Trans-Cranial Magnetic Stimulation

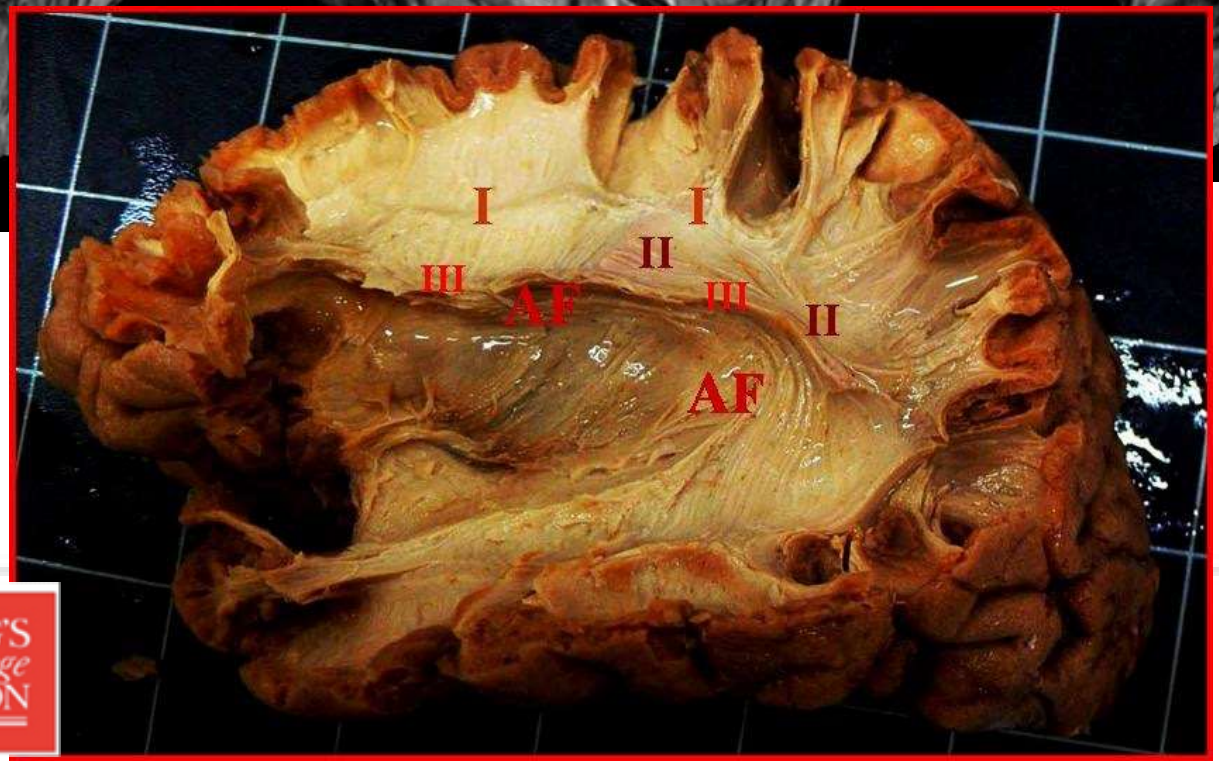




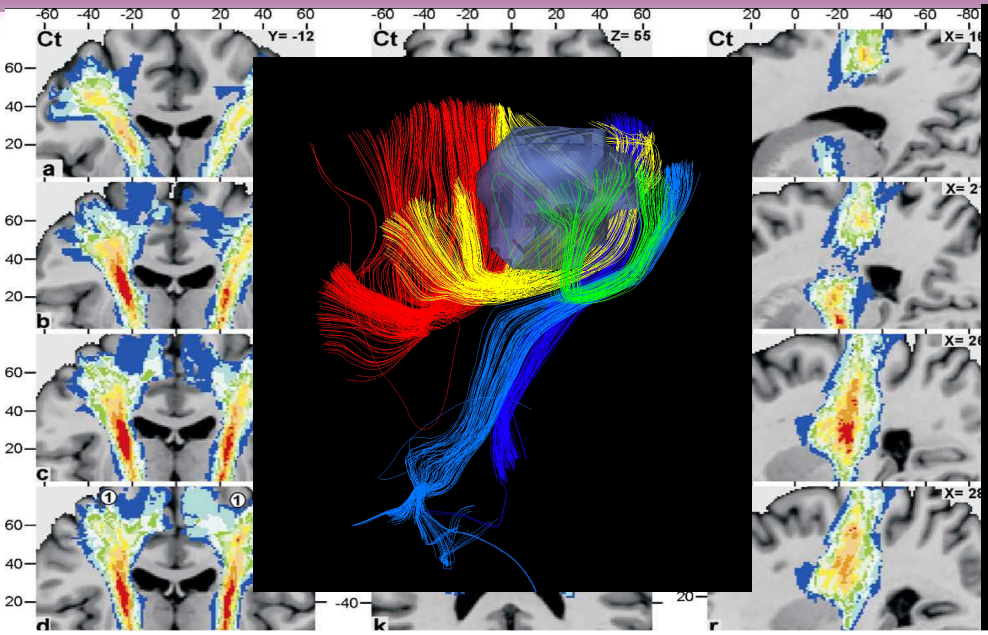


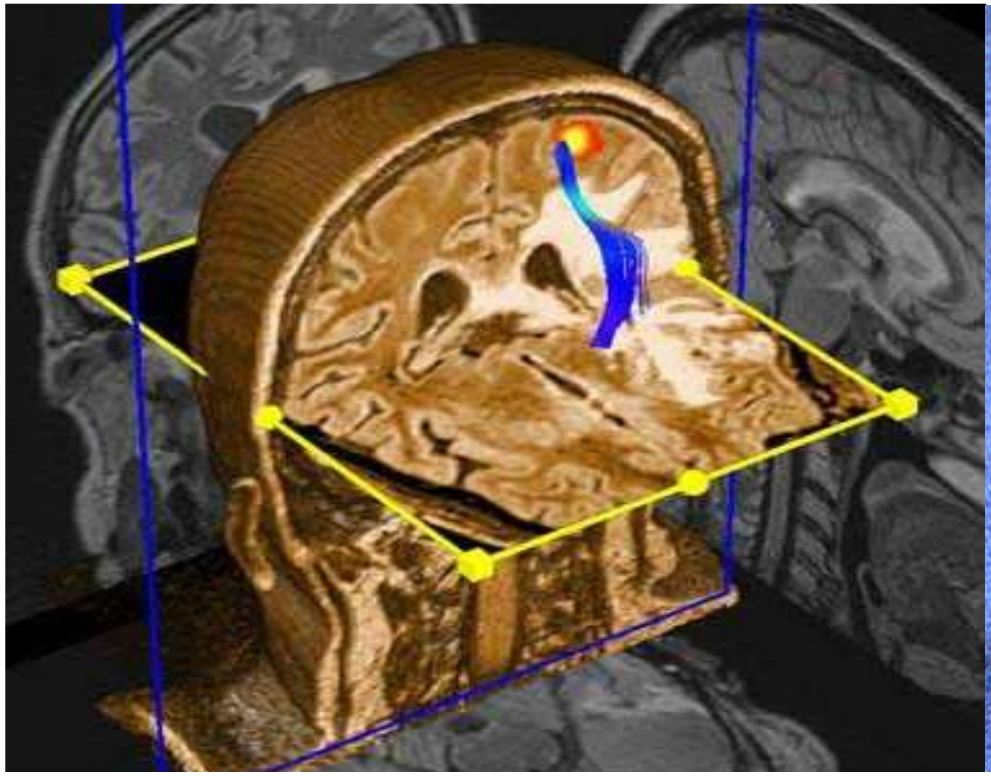
WHITE MATTER TRACTS – DTI MR

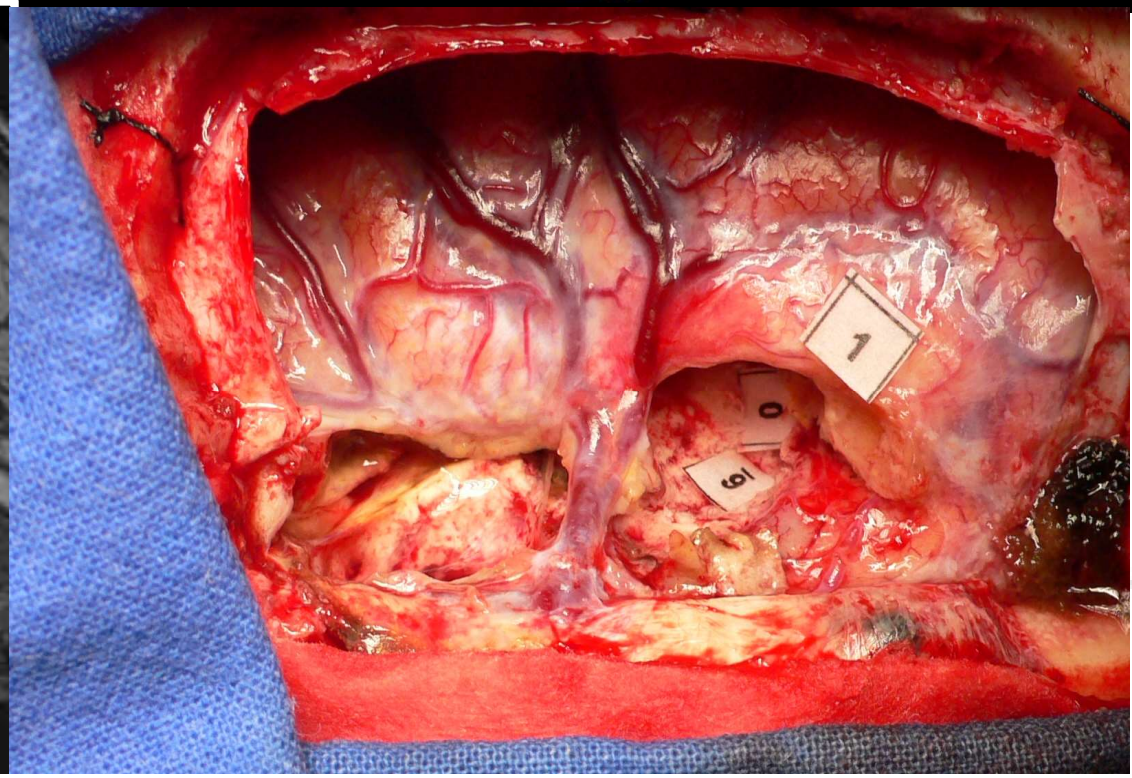




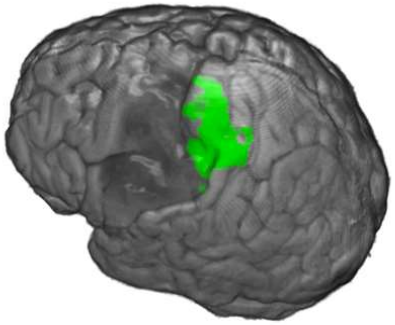
WHITE MATTER TRACTS - fMRI+DTI

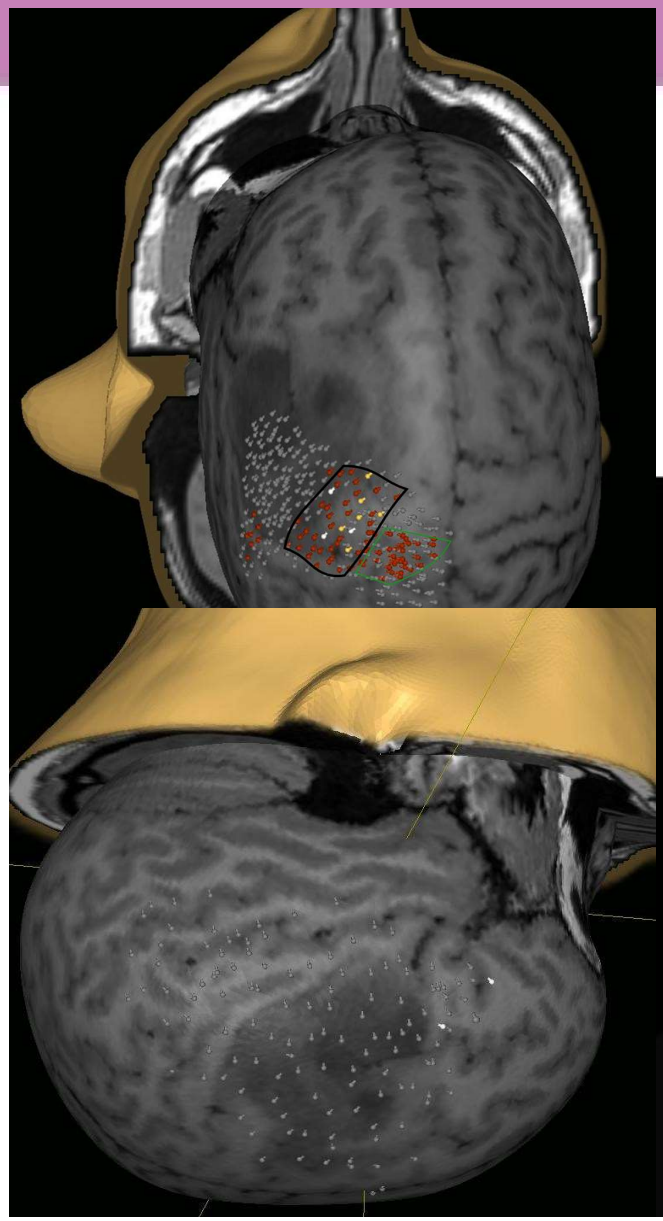






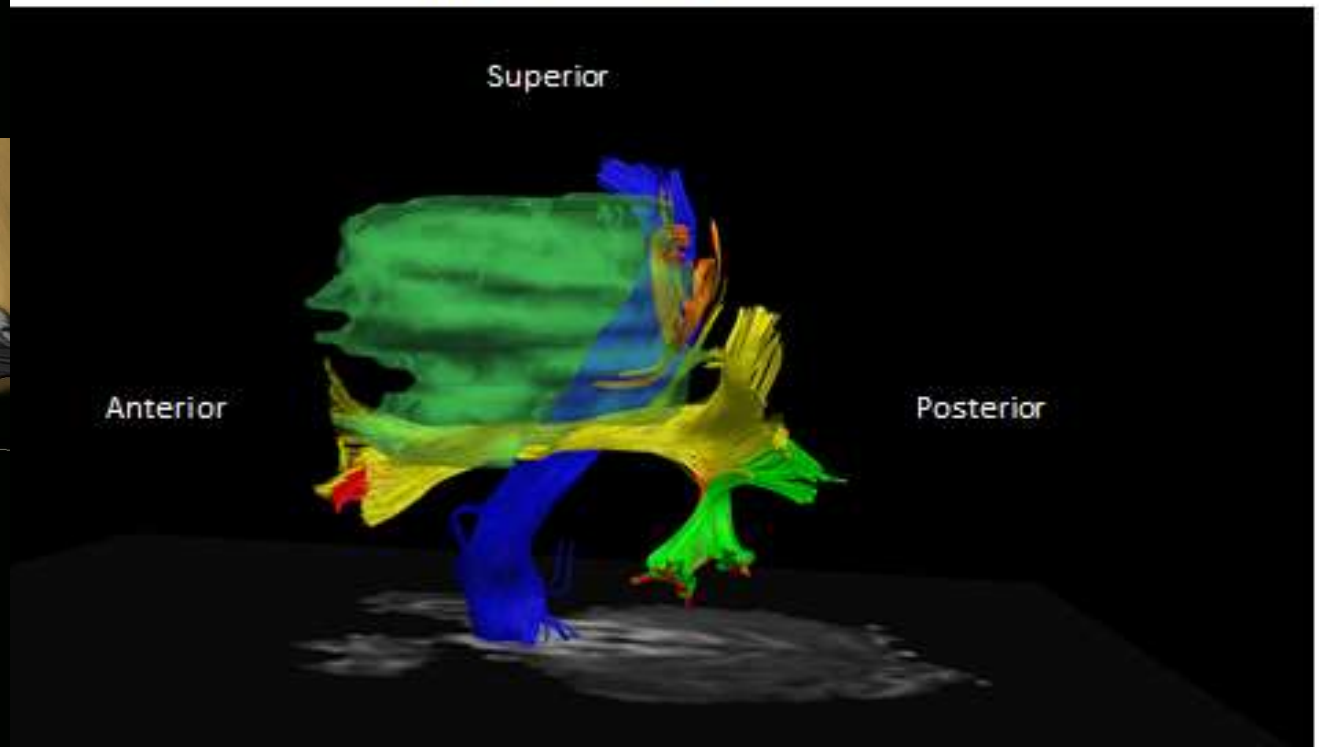
fMRI
hand





Tractography: lateral view

Yellow, green and red: segments of arcuate fasciculus
Blue: cortico-spinal
Orange: U-fibers of central lobule



TMS for movement (above) with hand and foot region outlined (black and green circles, respectively. TMS for language (below), with 2 spots where hesitation was found (white spots)

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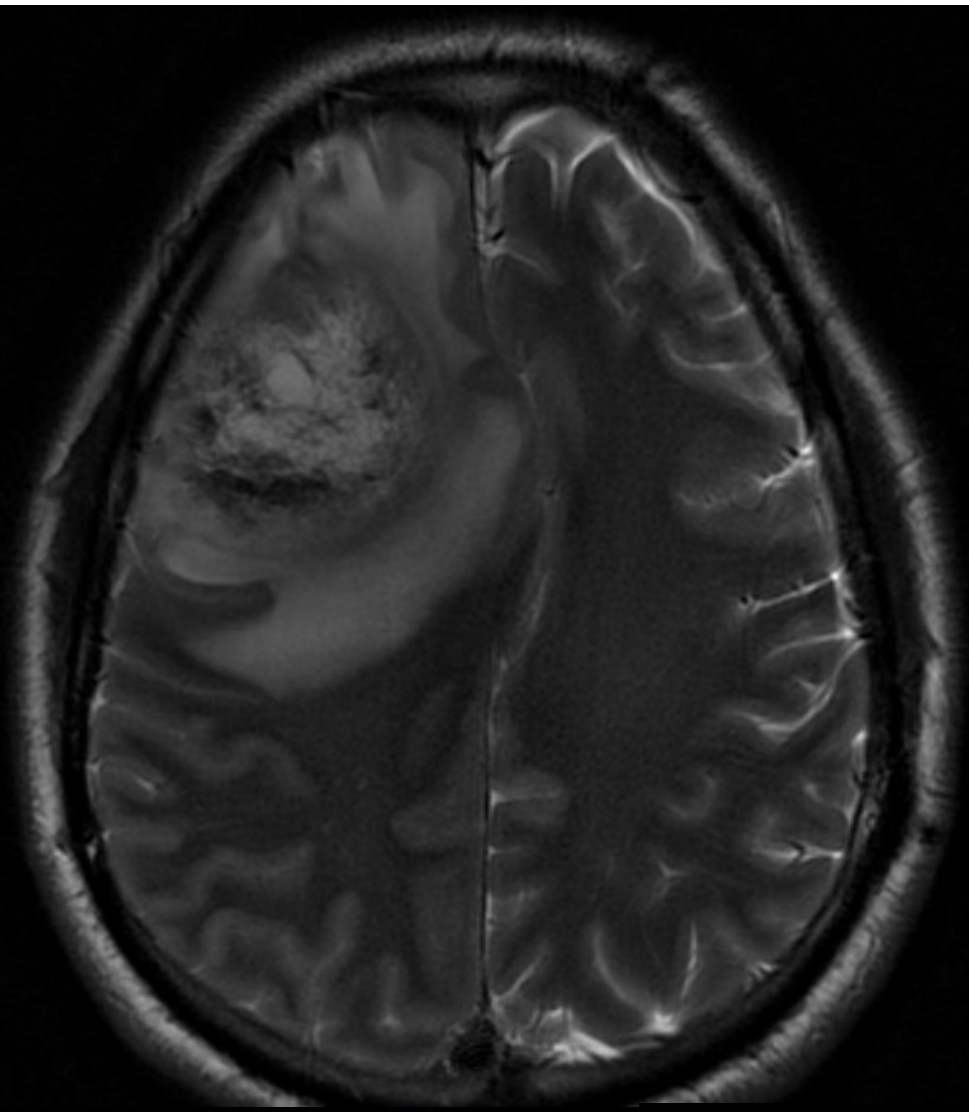

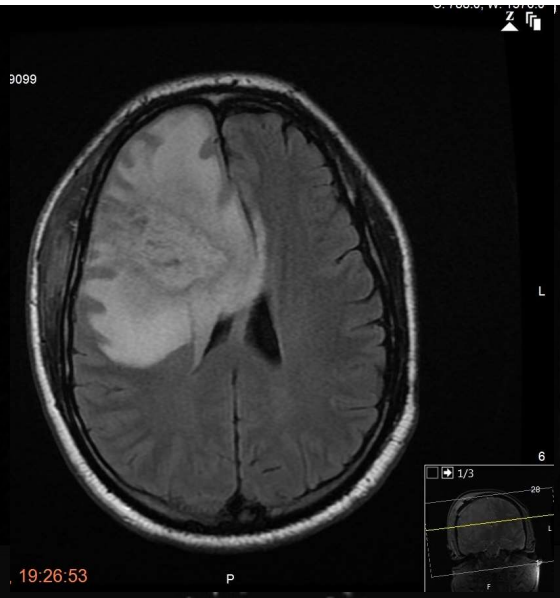
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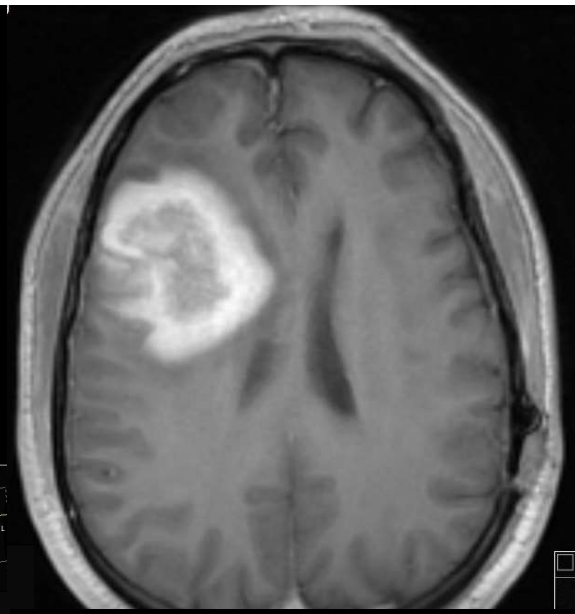

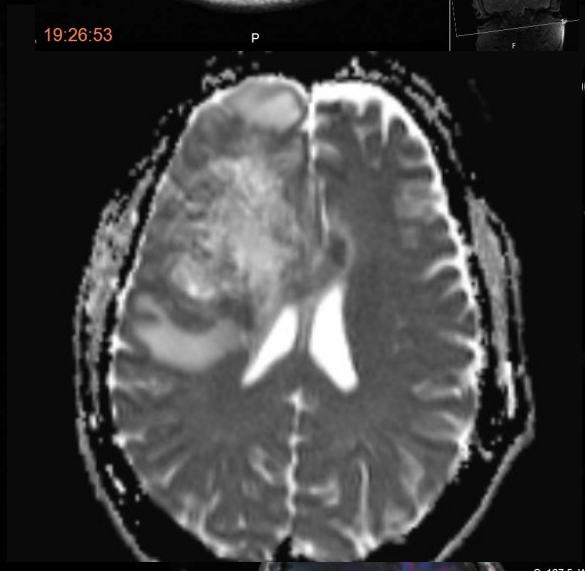

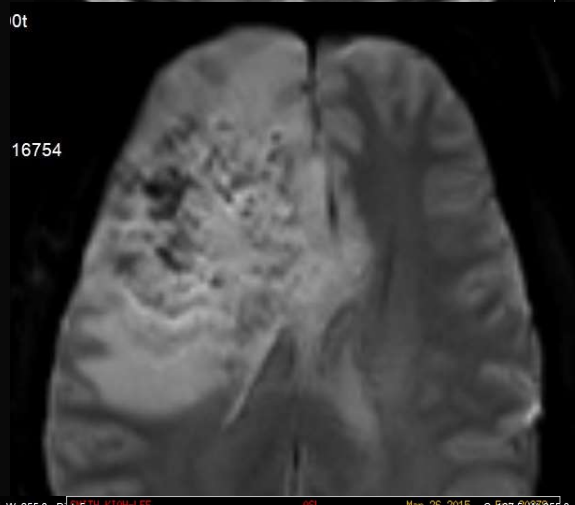
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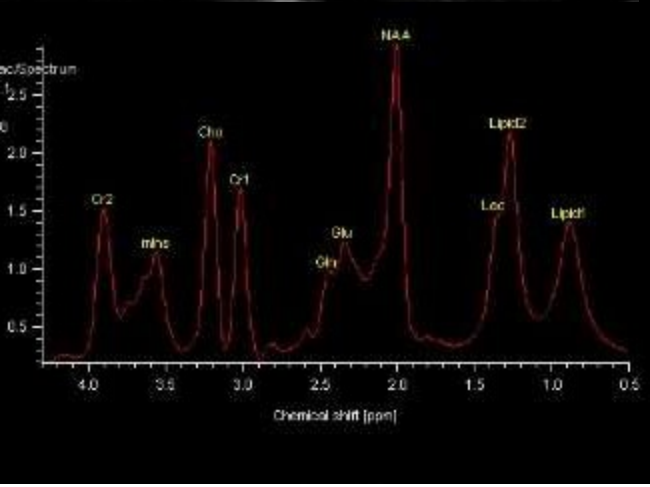
NAA
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Cr1
Cr2
mIns
Glu
Gln
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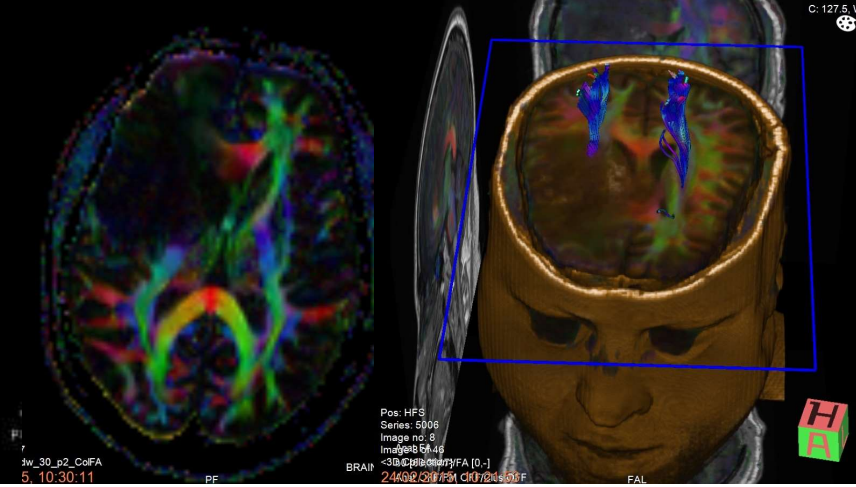
Chemical shift [ppm]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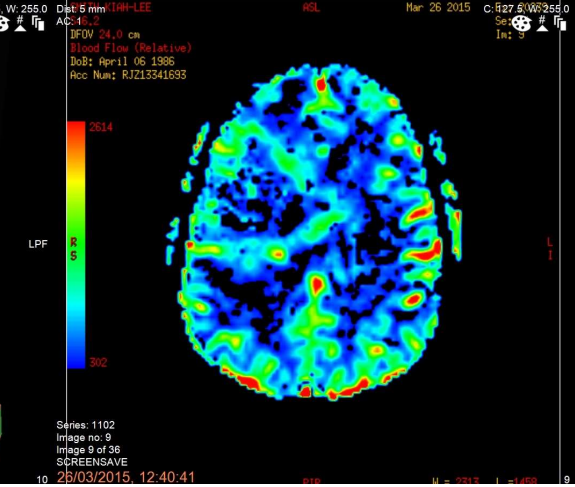
Mar 26 2015
DFOV 24.0 cm
Blood Flow (Relative)
DoB: April 06 1986
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302
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Image 9 of 36
SCREENSAVE
26/03/2015, 12:40:41

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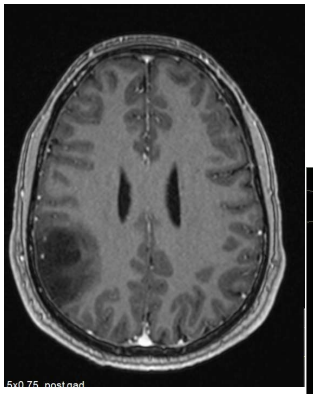
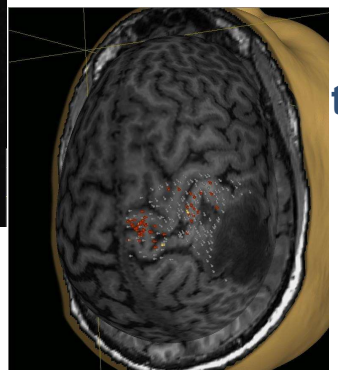
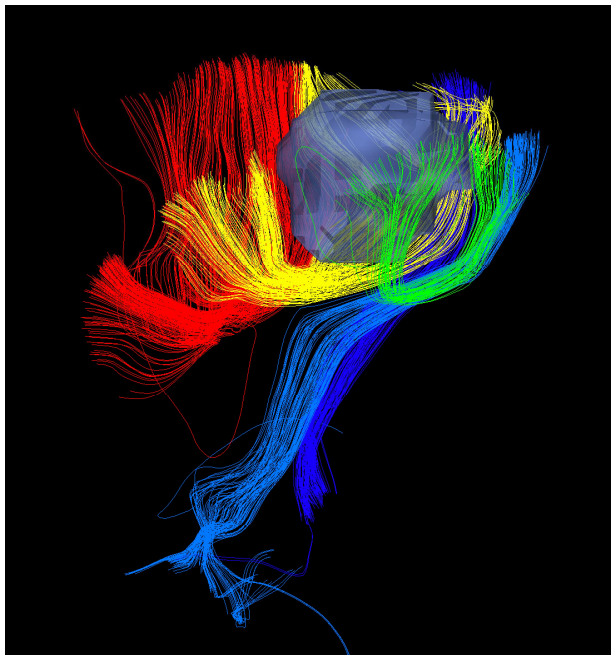
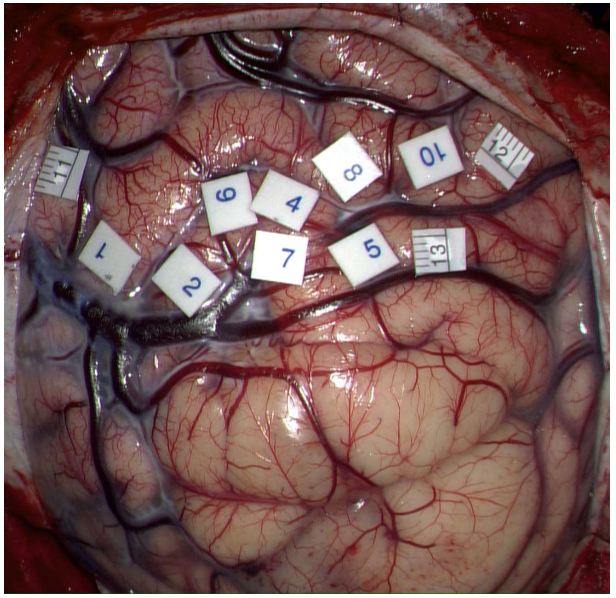
Neuro-oncology

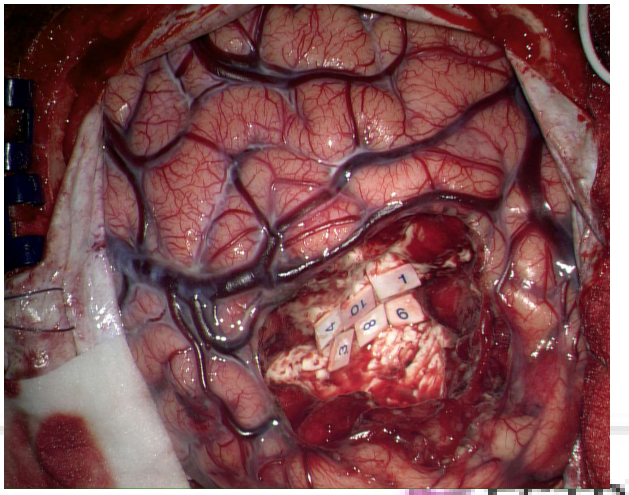
Multimodal imaging and Intraoperative mapping to maximise extent of resection











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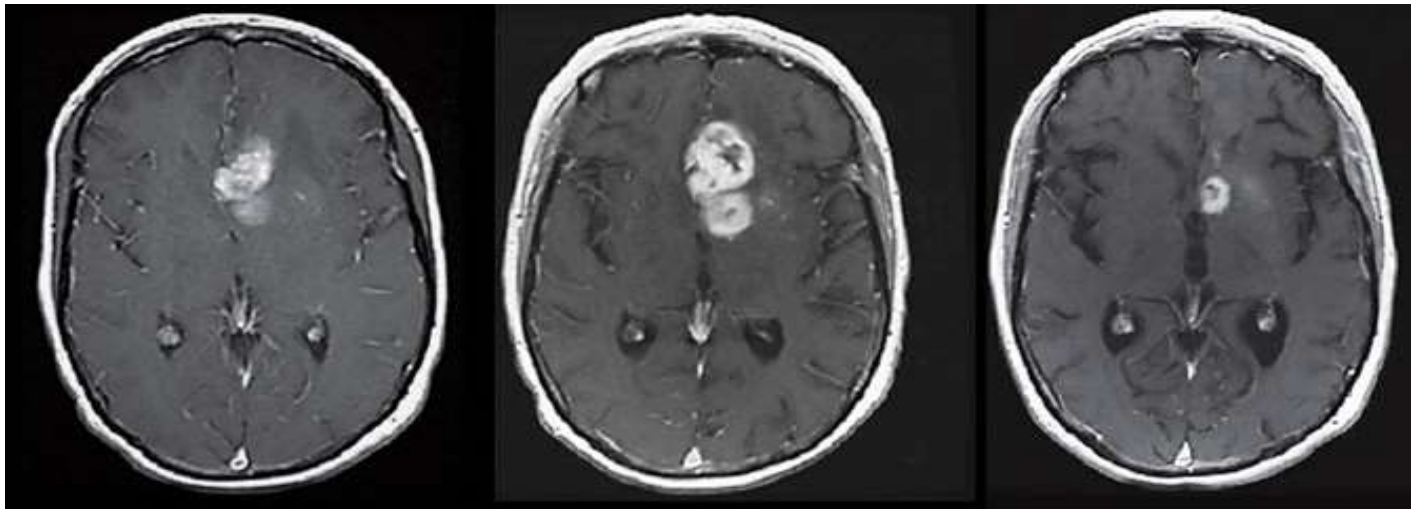
PROGRESSION

- Multifocality
- Signal abnormality extending across corpus callosum
- Subependymal involvement
- Low ADC values

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) – up to 30% of high grade gliomas, also seen in low grade gliomas-*

-more frequent in MGMT Met tumours



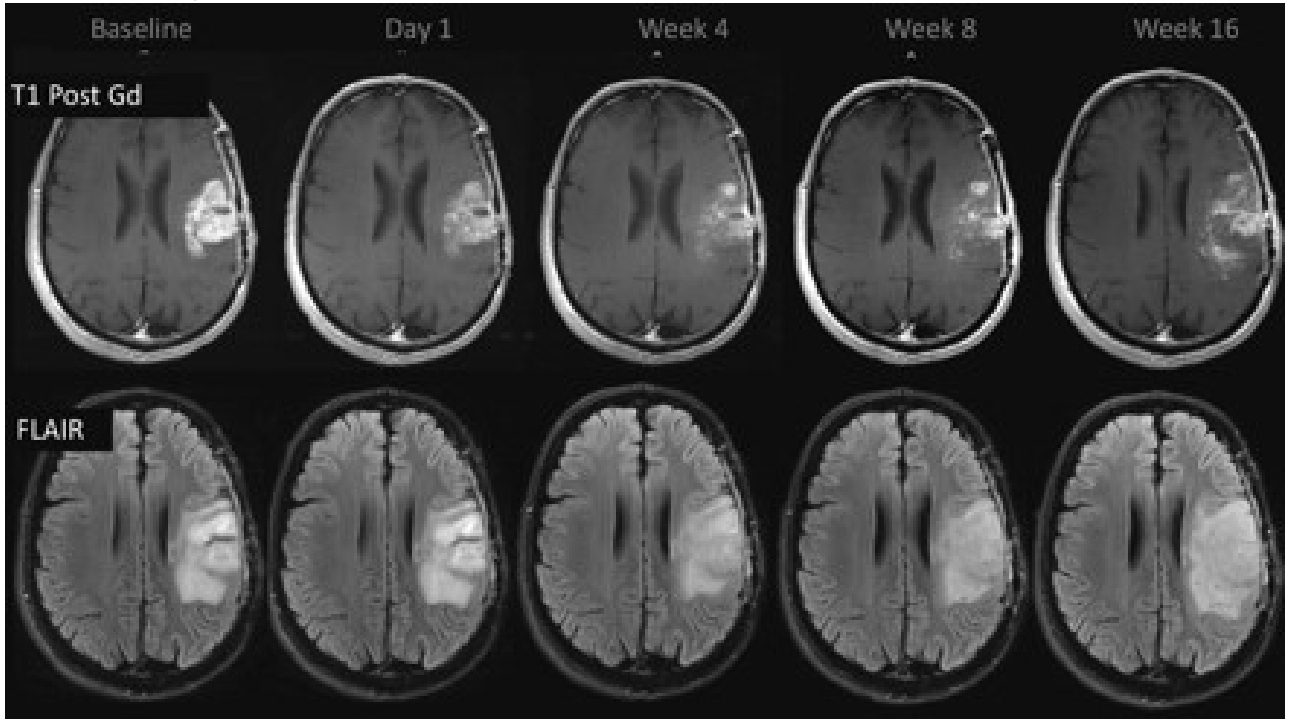
Before RT+TMZ | Before adjuvant TMZ | After 2 cycles adj TMZ

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

RANO criteria: within the first 12 weeks following completion of radiotherapy, progression can only be determined if new enhancement is seen outside of the radiation field or if there is histopathological confirmation

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).*



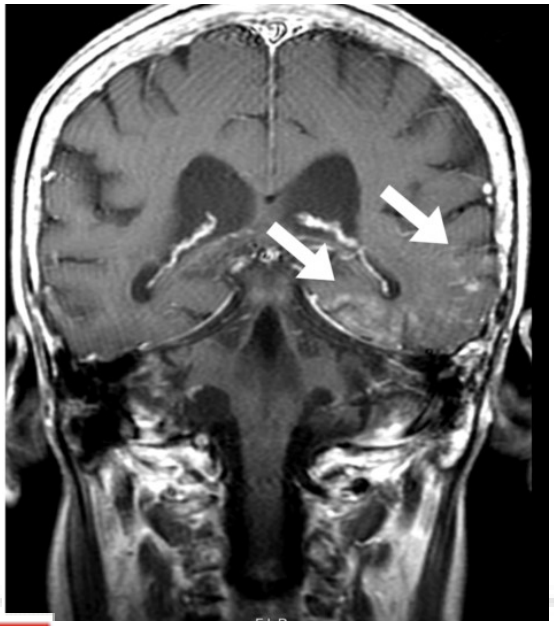
A 47-year-old man with GBM. A reduction of the enhancing portion of the lesion is observed 1 day after initiation of cediranib treatment. Four weeks later, besides a continuing reduction in the enhancing portion, an expansion is observed in the FLAIR images. Expansions in both the enhancing area and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

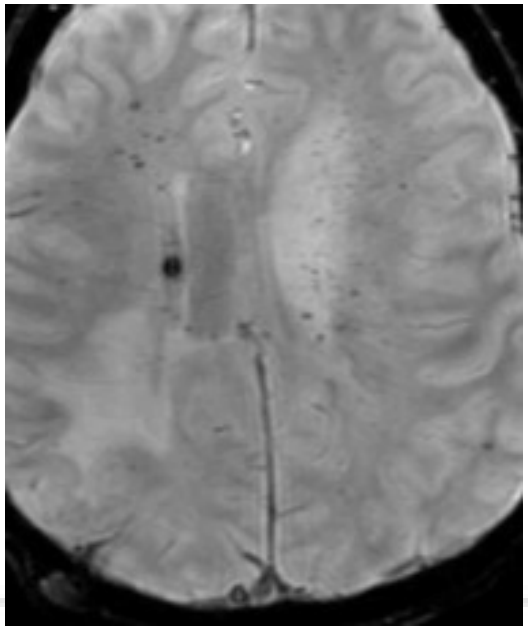
Pseudo-response might be an indicator of subsequent favourable response

RANO Criteria for pseudoresponse: greater than 50% reduction in contrast enhancement without a significant decrease in nonenhancing tumour.
Decreased enhancement should persist more than 4 weeks to be considered true response.

SMART SYNDROME

- Remote history of intracranial irradiation
- Headaches and neurological deficits
- Cortical contrast-enhancement
- SWI – Microhemorrhages (delayed radiation toxicity on cerebral microvasculature)



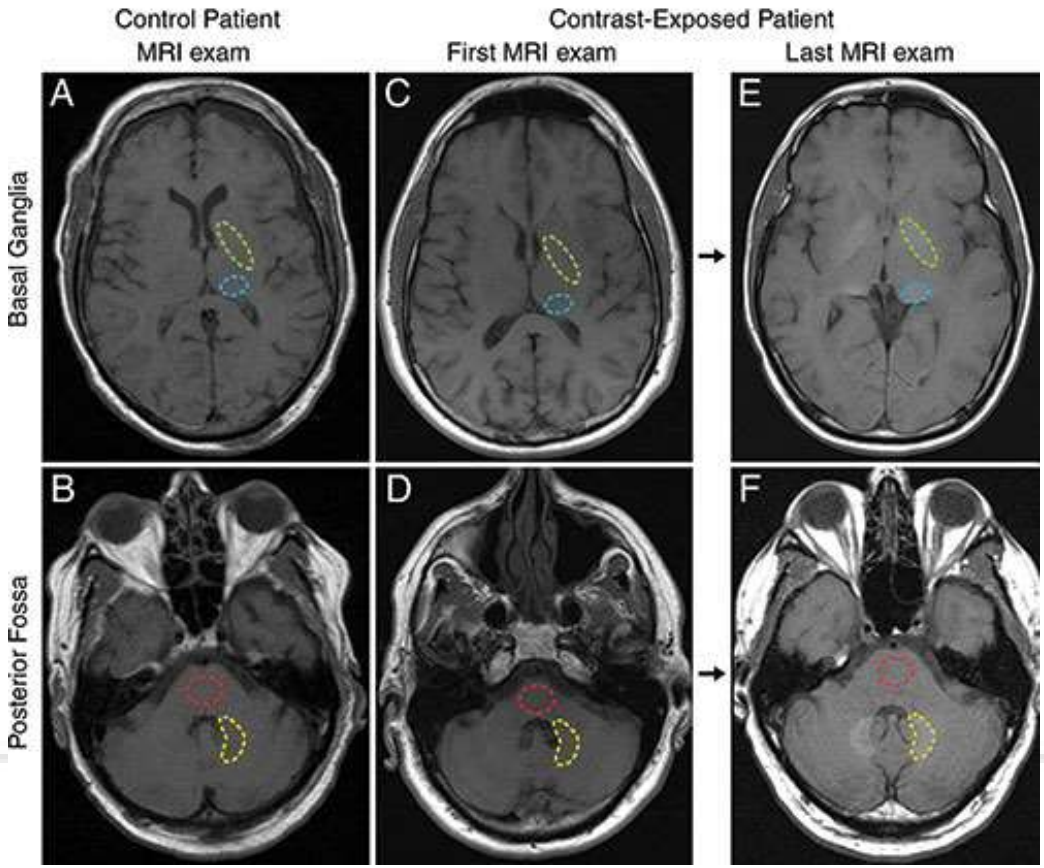


IMAGING LONG-TERM COMPLICATIONS OF MRI Gad

Gadolinium deposition in the brain: summary of evidence and recommendations

Vikas Gulani, Fernando Calamante, Frank G Shellock, Emanuel Kanal, Scott B Reeder, on behalf of the International Society for Magnetic Resonance in Medicine

Lancet Neurol 2017; 16: 564-70



Deposition in perivascular glial cells

?Clinical Significance

MODERN IMAGING OF BRAIN TUMOURS
TAKE HOME MESSAGE

- **Modern imaging offers a series of extraordinary complementary tools in diagnosis, treatment and followup 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>**

MODERN IMAGING OF BRAIN TUMOURS
TAKE HOME MESSAGE

Thank You!

Acknowledgements

King's Neuro-oncology Team

Neurosurgery

- K Ashkan
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- L Mullens
- C Kennedy
- J La

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- R Laxton

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- L Brazil
- A Swampillai
- C Cikurel
- G Finnerty

Therapists

- SLT/OT/Physio

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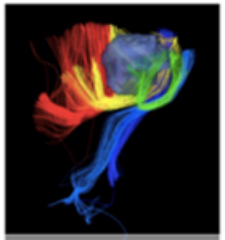

King's College London

NEURO-ONCOLOGY
NEUROSURGERY

KING'S HEALTH PARTNERS

Pioneering better health for all

Current Surgical Approaches

in

Brain Tumours

Mr Ranjeev Bhangoo
Consultant Neurosurgeon / Clinical Director of Neuroscience
Mr Christian Brogna

Department of Neurosurgery
King's College Hospital – King's College London
London, United Kingdom

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Declarations

- I am a Neurosurgeon !

Role of the Neuro-oncological Surgeon

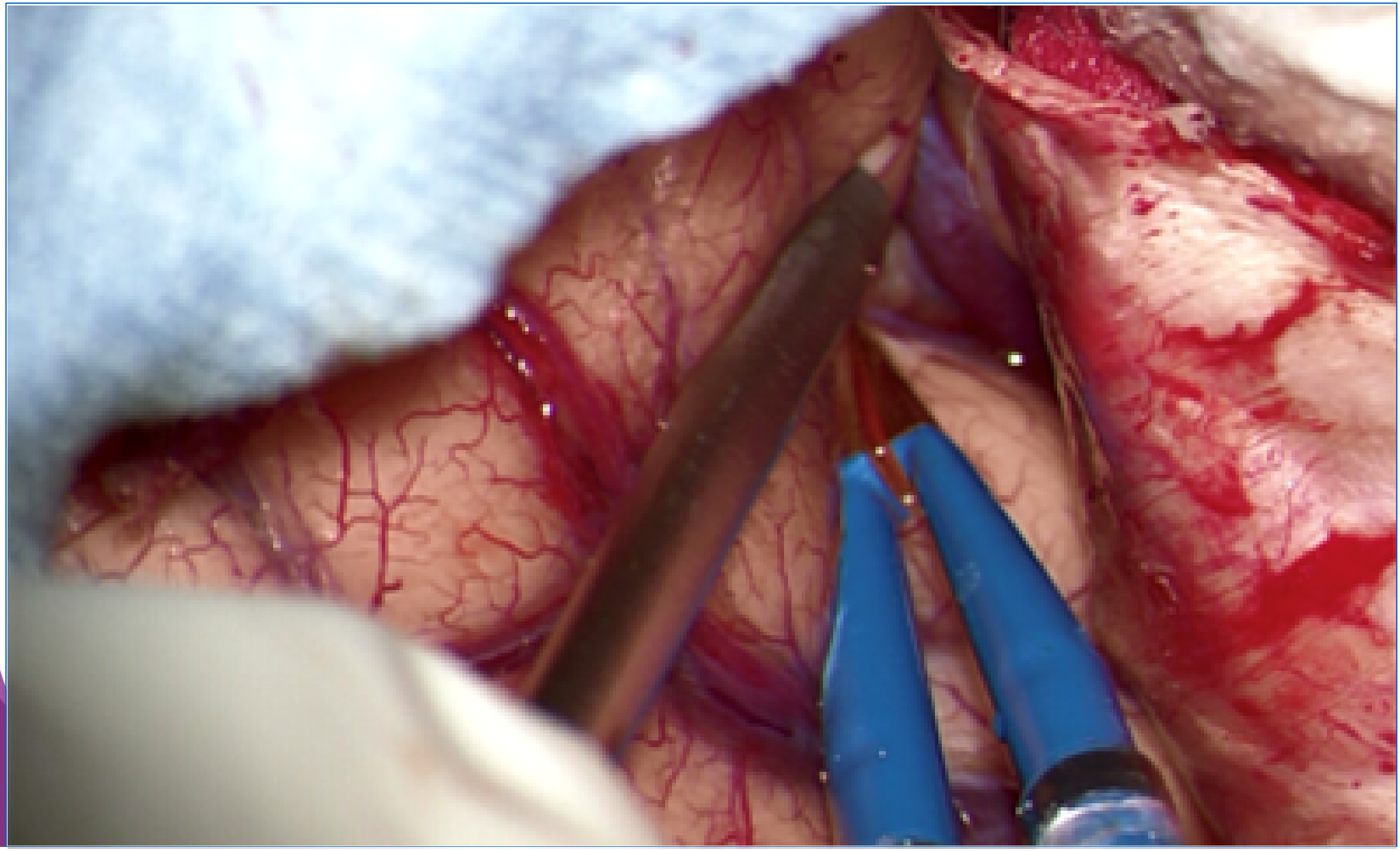
- Relieve mass effect and intracranial pressure
- Symptoms relief
- Solve or prevent hydrocephalus
- Allow steroids withdrawal
- Provide tissue for histological and molecular diagnosis
- Support adjuvant treatments
- Improve PFS and OS
- Preserve Quality of Life

Mastering Neurosurgical Oncology

Anatomy – White Matter Fiber Dissection

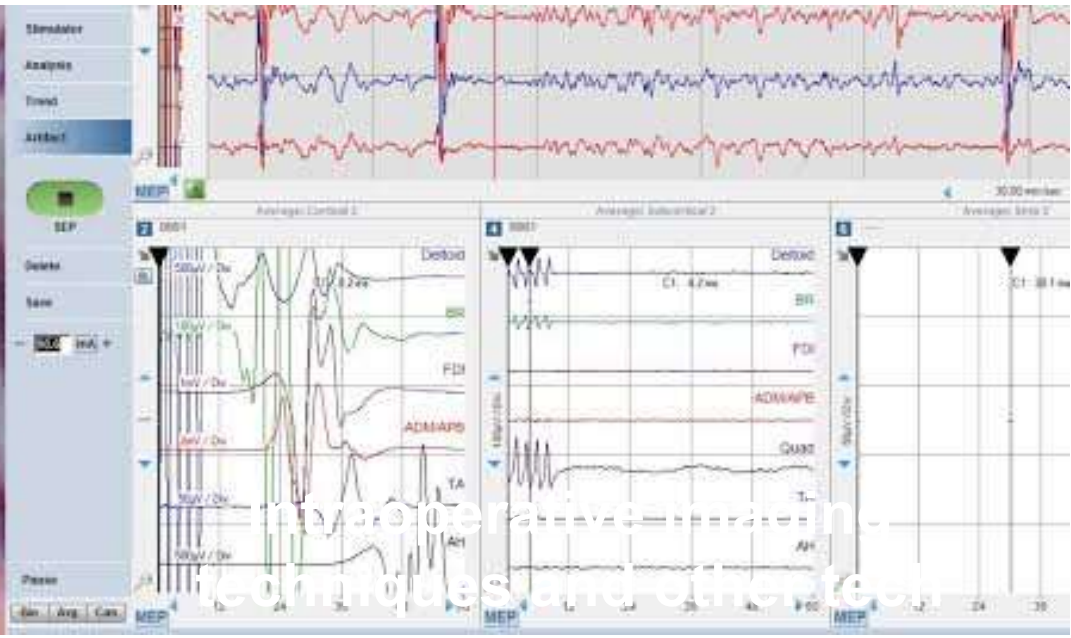
Mastering Neurosurgical Oncology

Advanced Microsurgical Techniques



Mastering Neurosurgical Oncology

Mapping Techniques and Neuromonitoring



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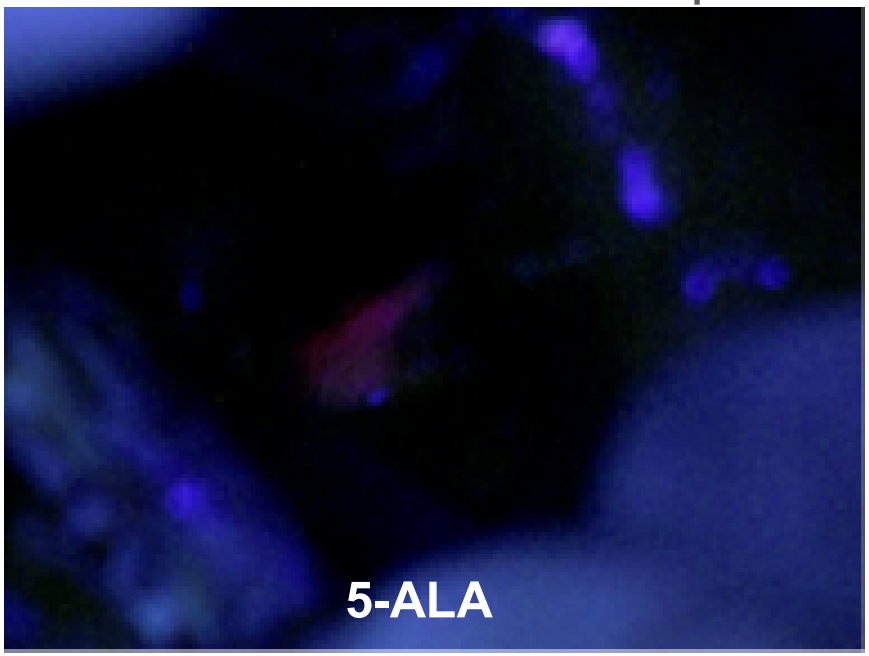
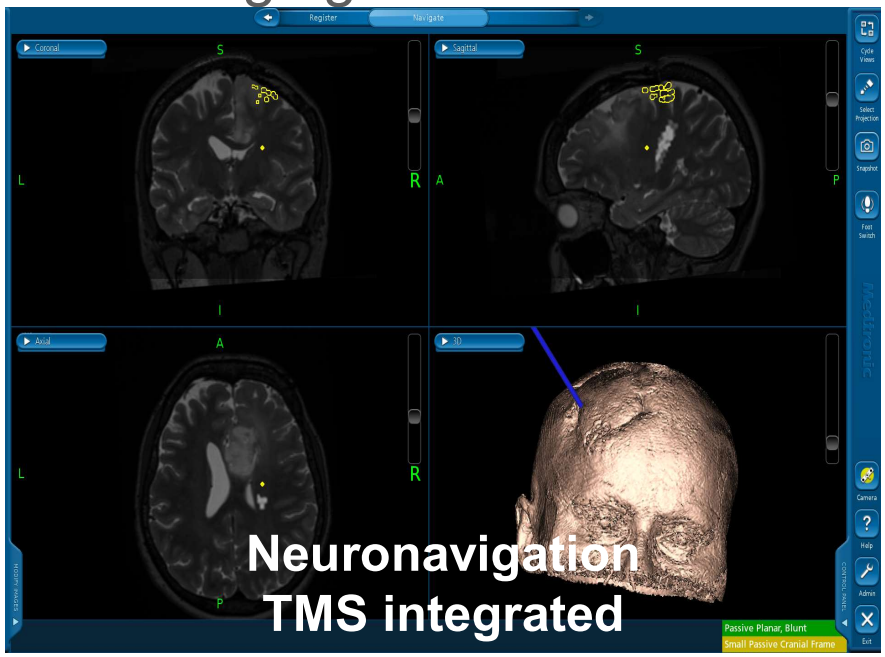
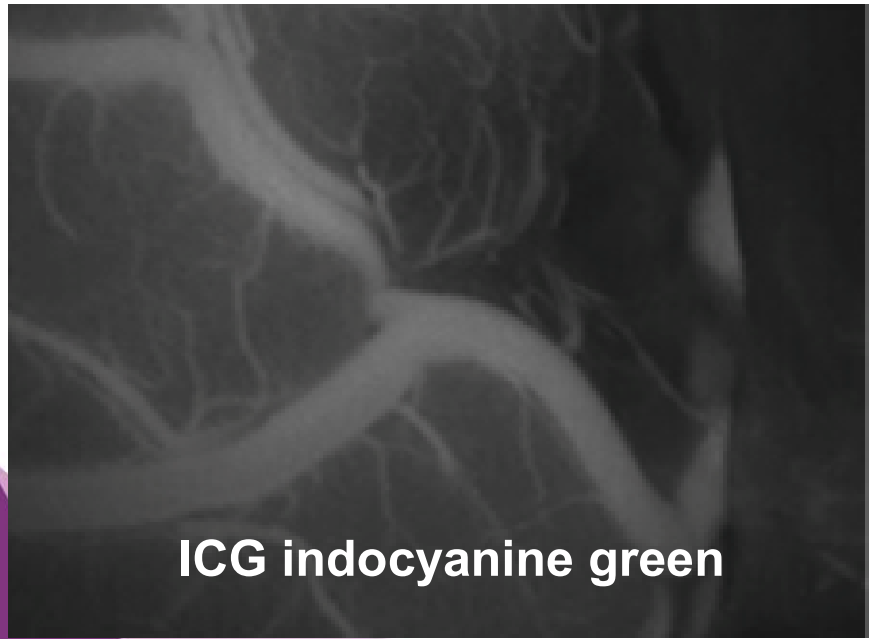
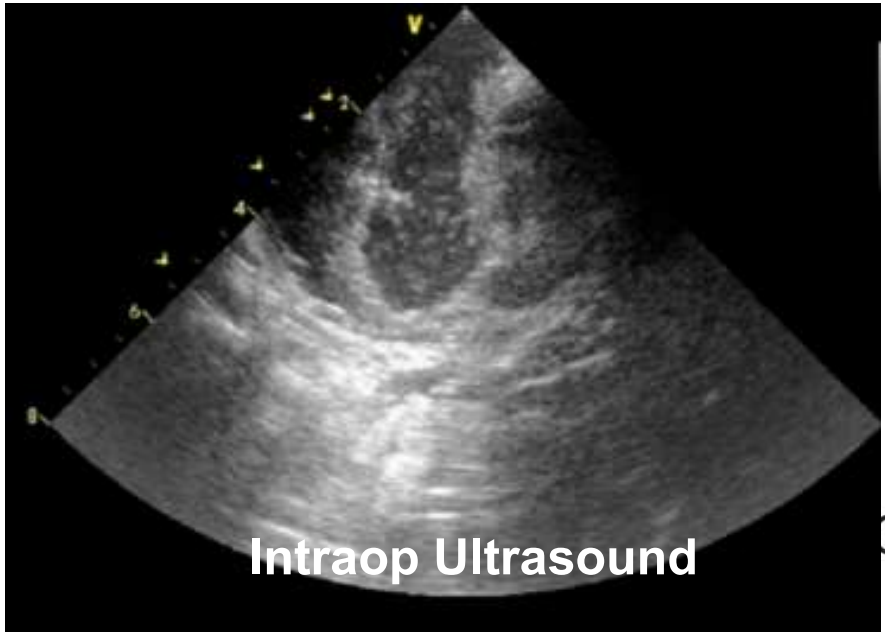
Intraoperative Enhanced Imaging









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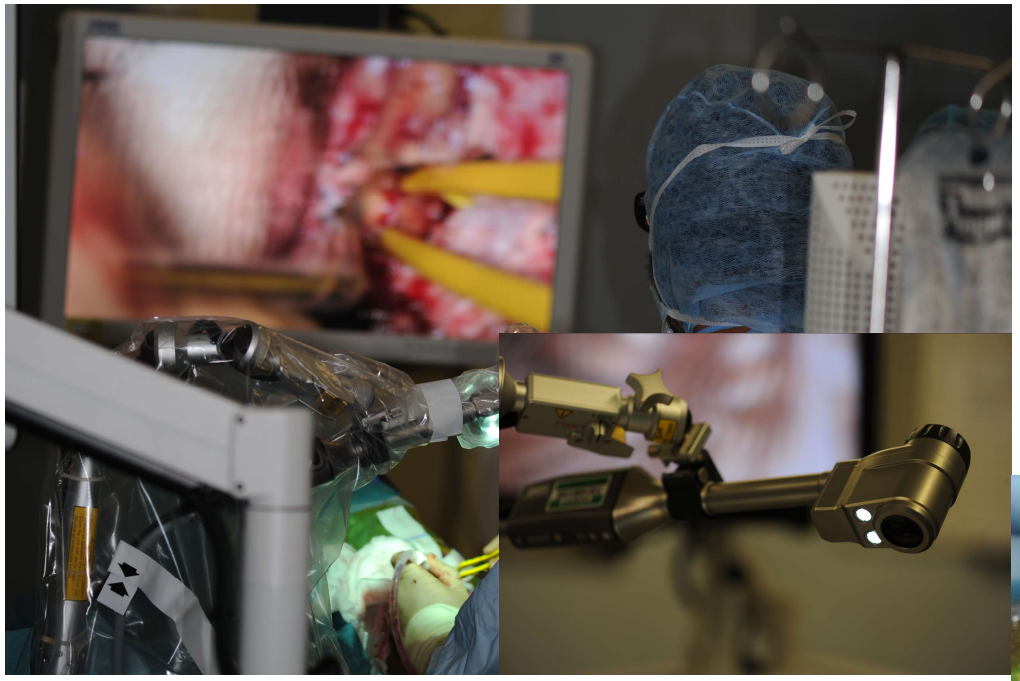
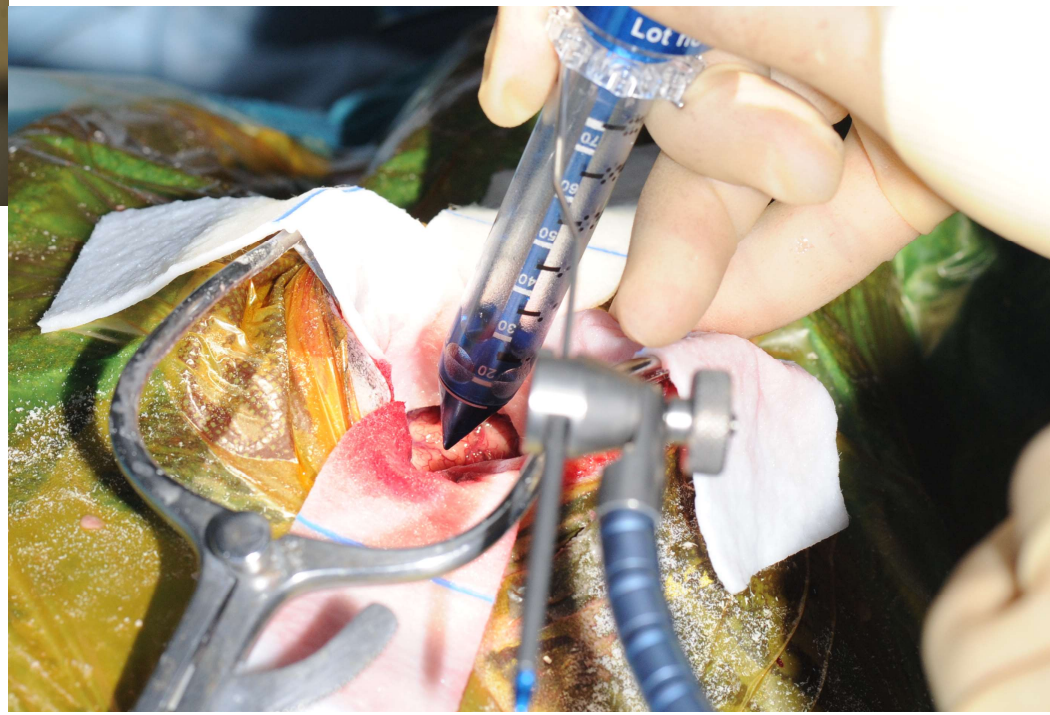
Minimally Invasive Techniques for deep seated lesions

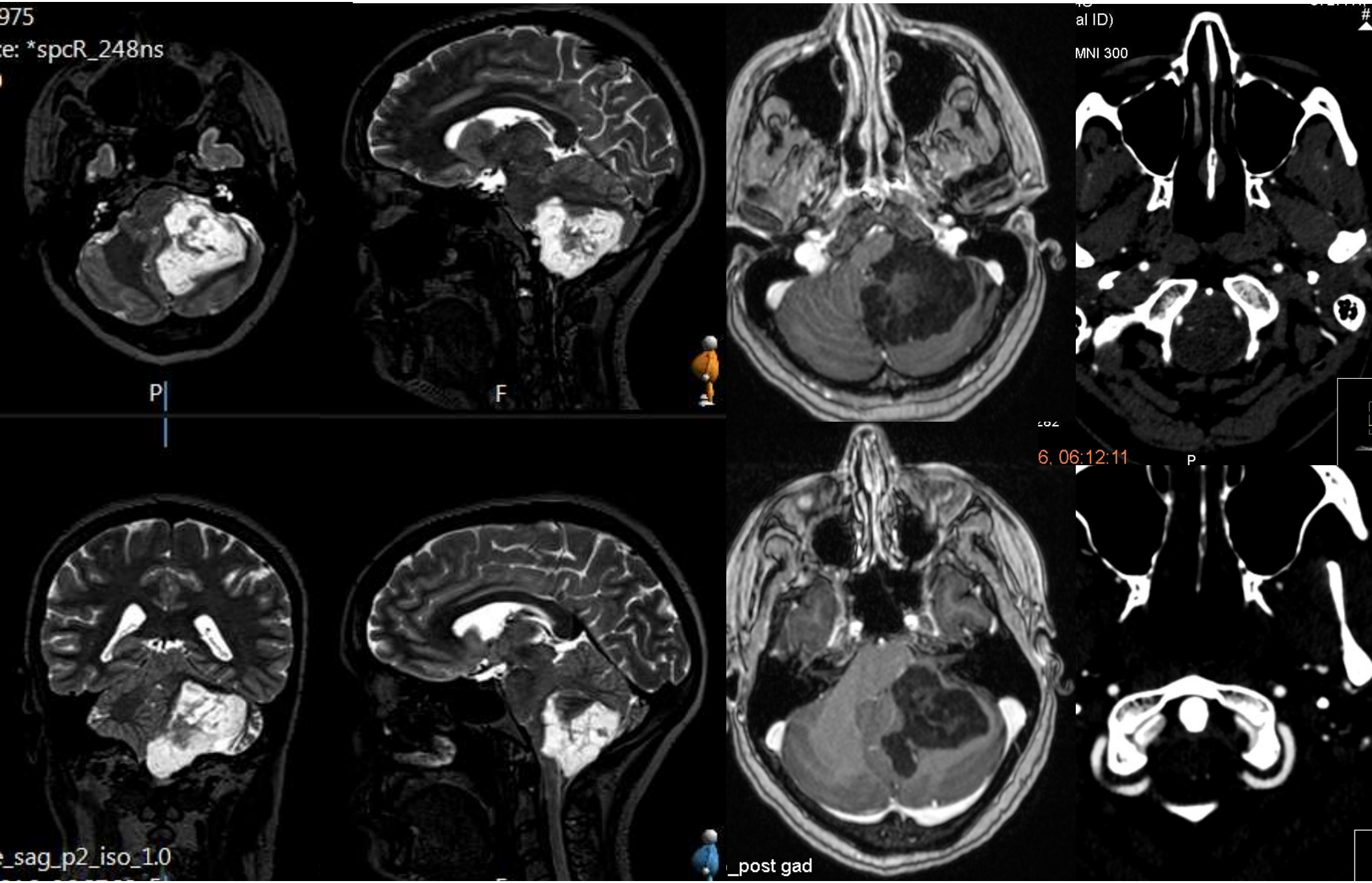


3D Exoscope
Brainpath
Nico



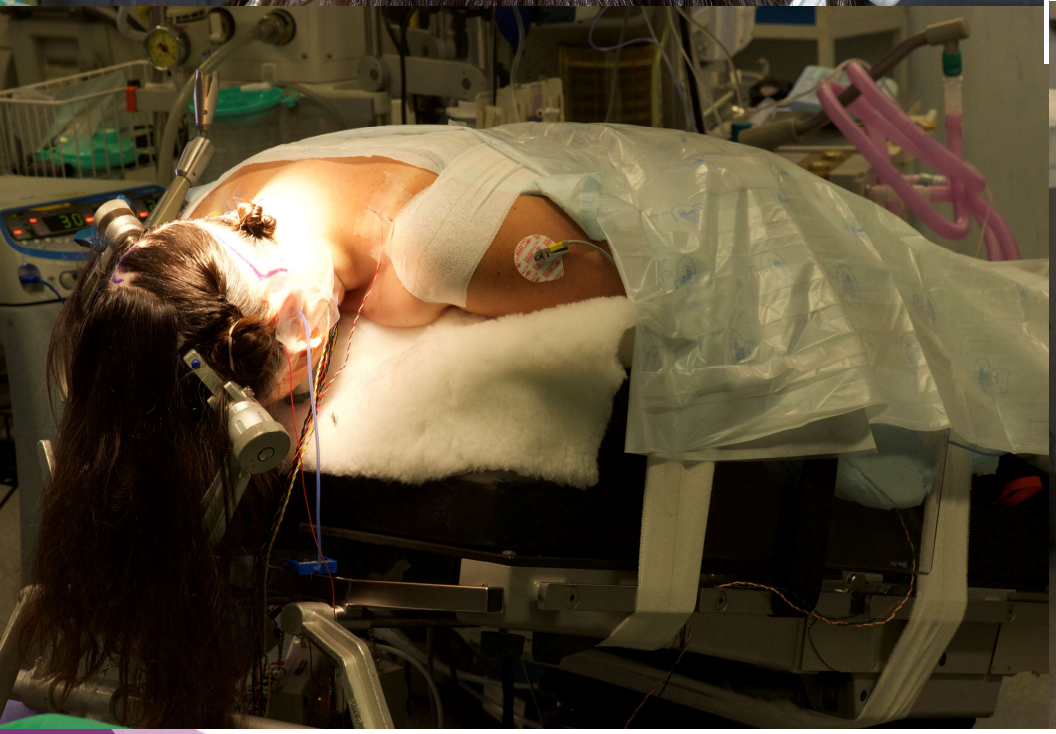
Posterolateral Approach

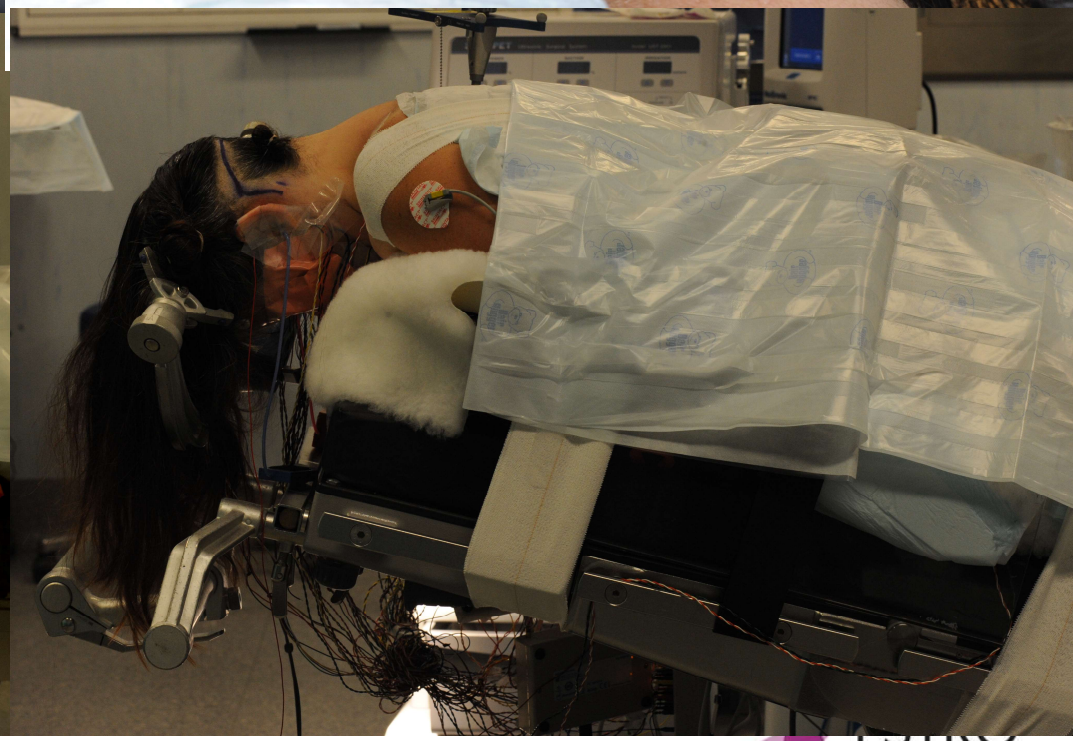
Anatomy + Microsurgical techniques + Monitoring



Posterolateral Approach

Anatomy + Microsurgical techniques + Monitoring





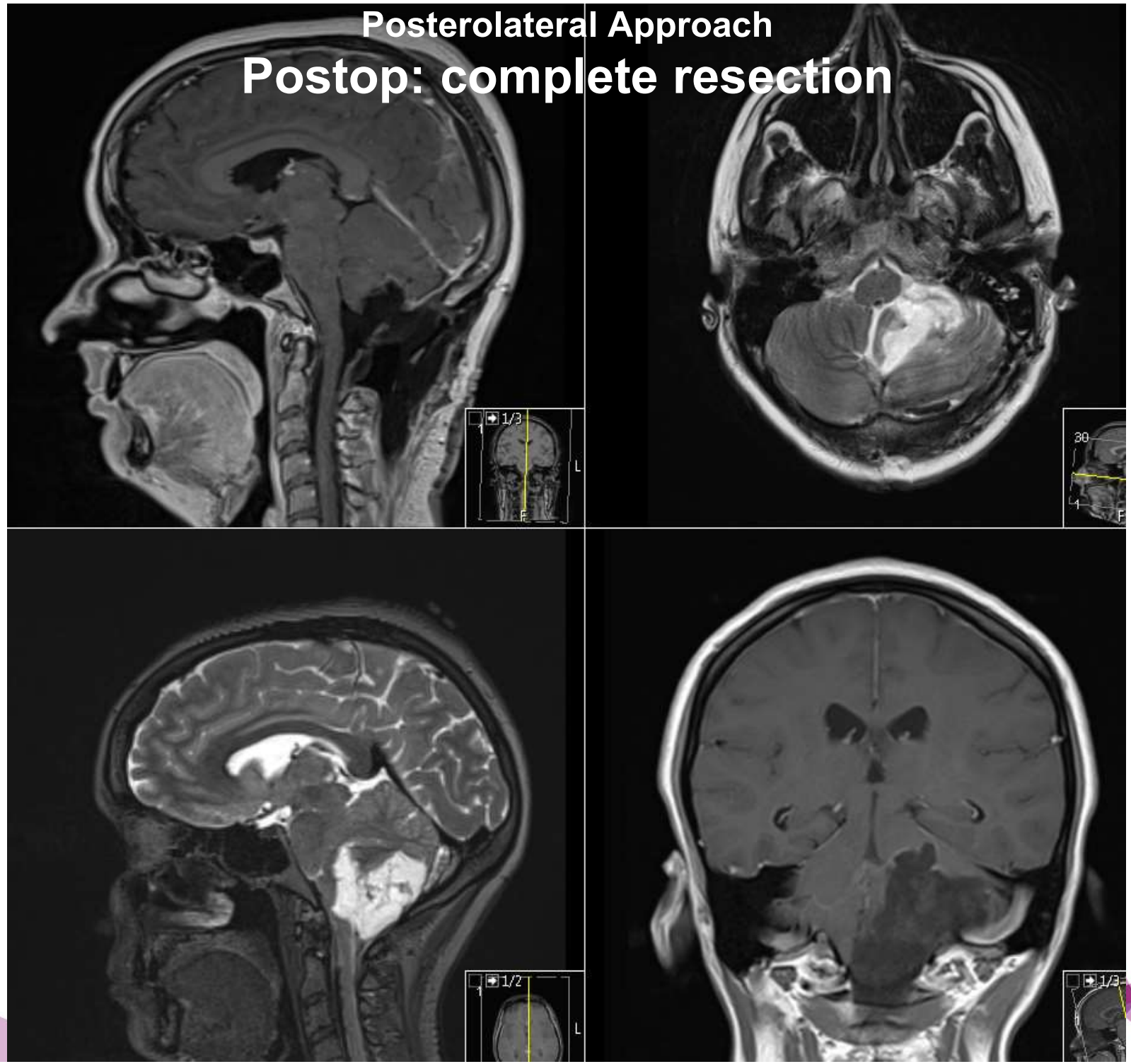
Hockey Stick suboccipital incision

Posterolateral Approach

Anatomy + Microsurgical techniques + Monitoring

Posterolateral Approach

Postop: complete resection



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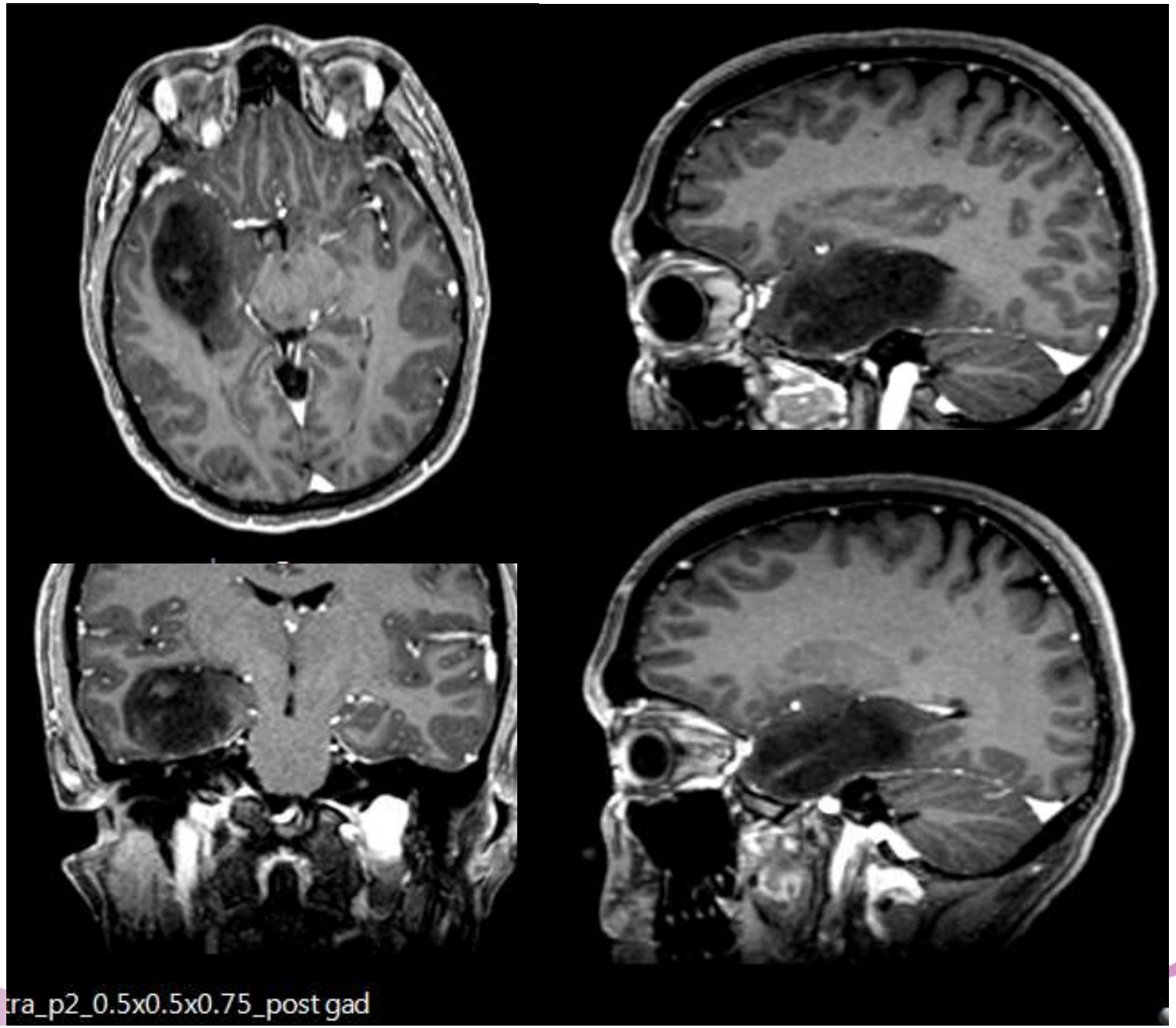
Transylvian Approach Oligo IDH1+ 1p;19q codel, ATRX not mut of the anterior fusiform gyrus

Anatomy + White Matter + Microsurgery



ESTRO School

Transylvian Approach Oligo IDH1+ 1p;19q codel, ATRX not mut of the anterior fusiform gyrus

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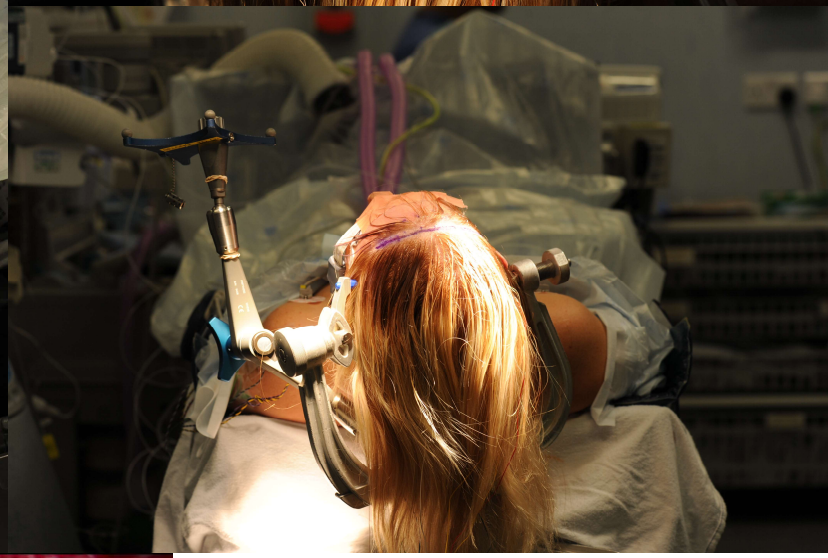

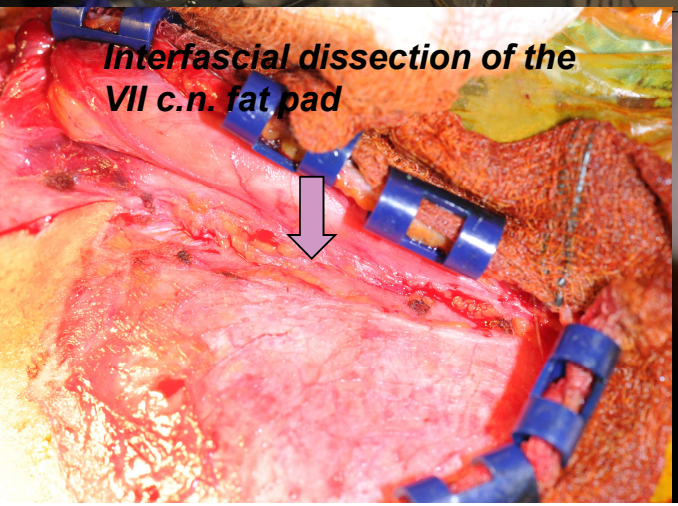

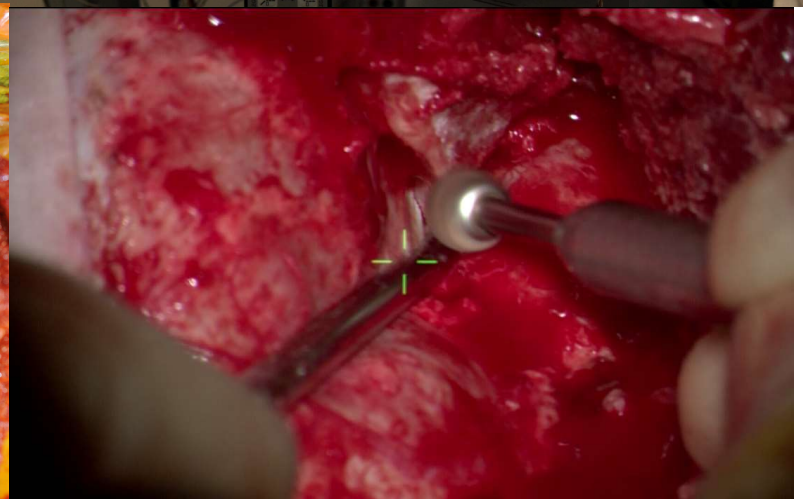

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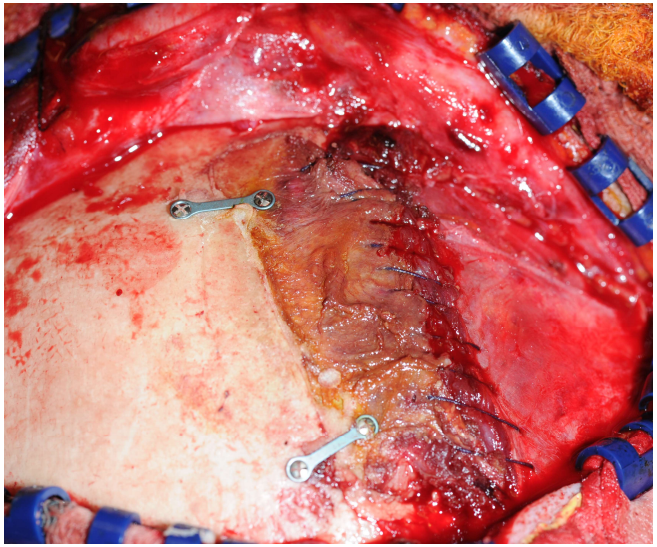
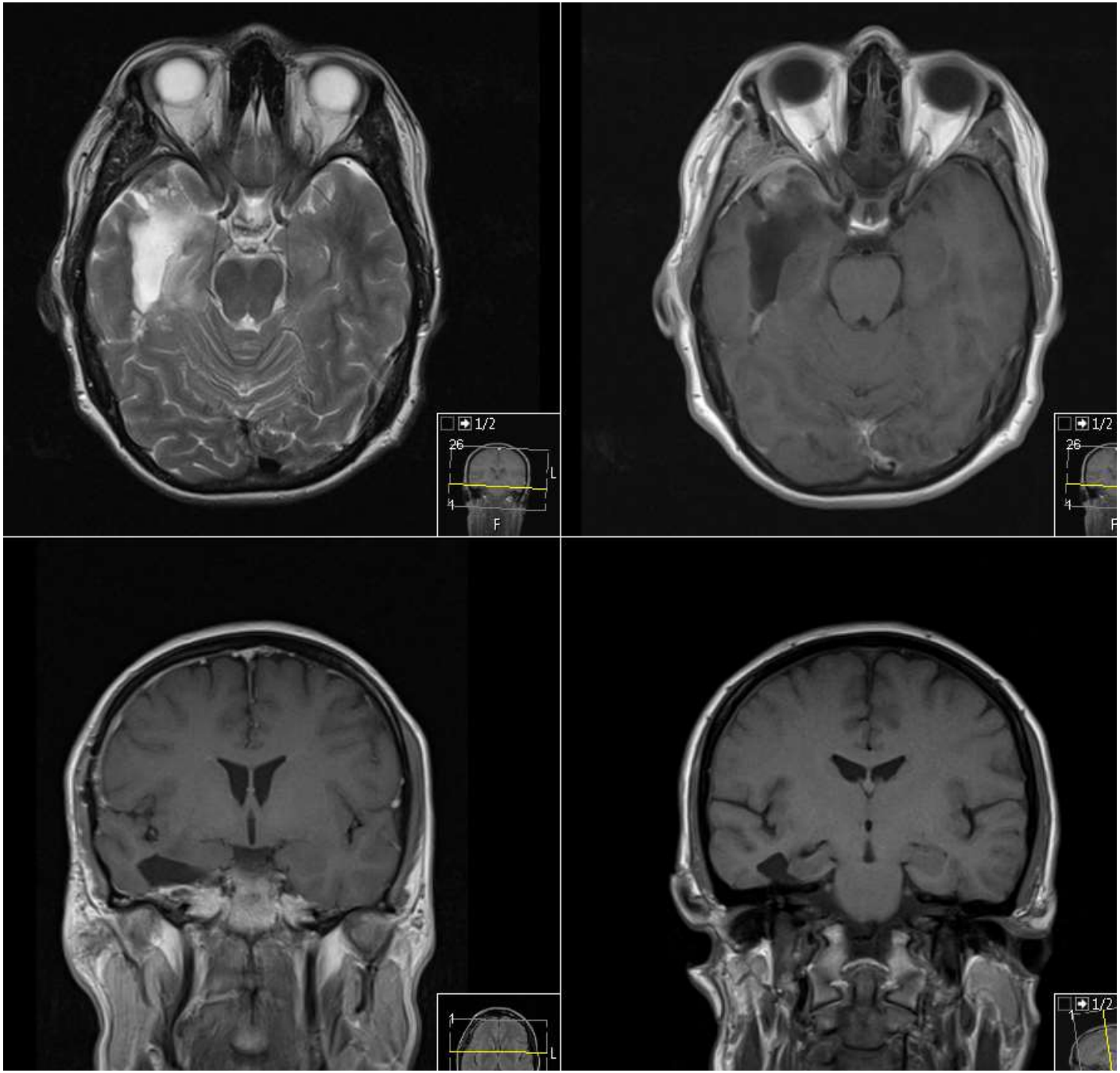
Transylvian Approach

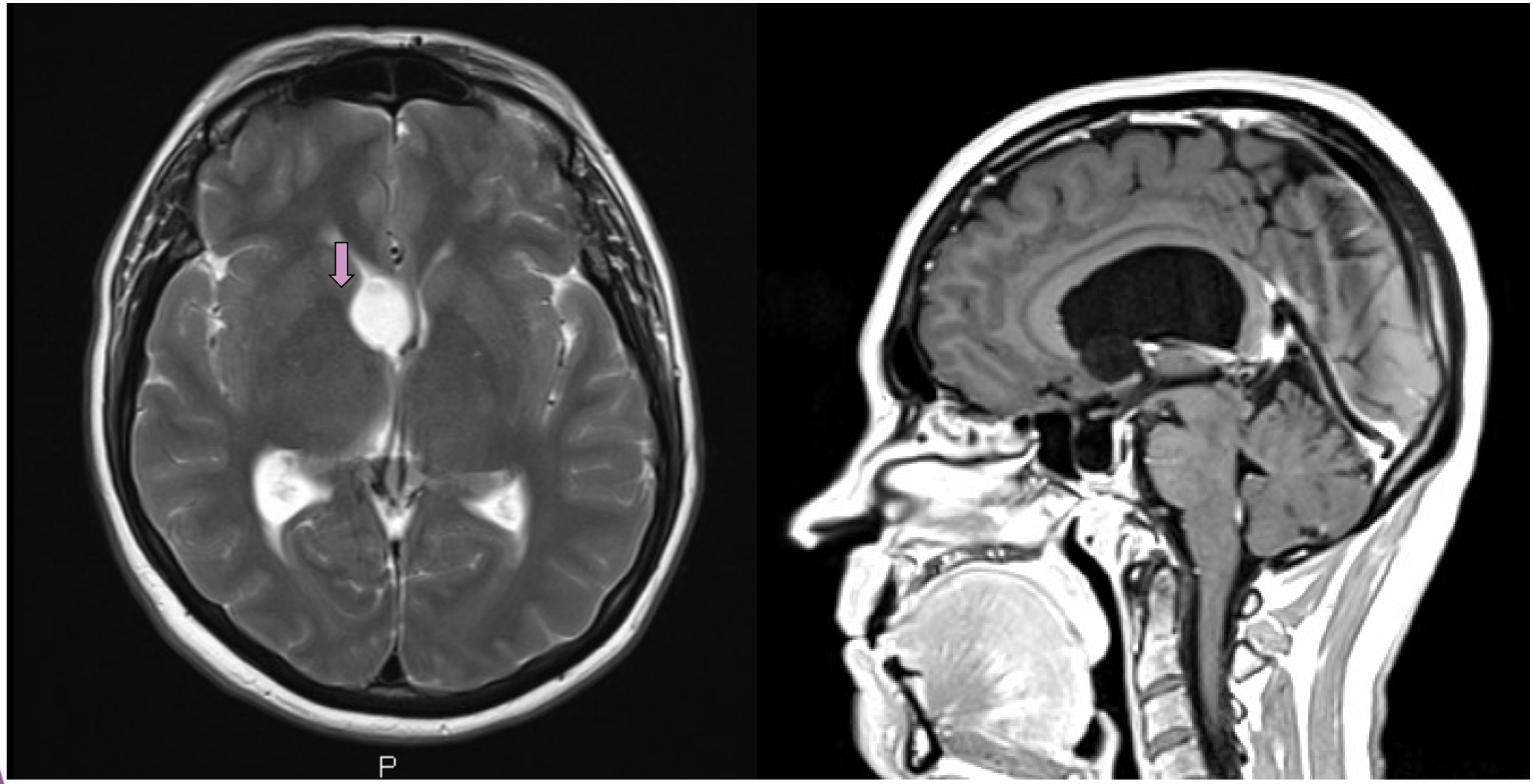
Postop: complete resection





Anterior Interhemispheric: Rosette-forming Glioneural tumour WHO grade I/II

Anatomy + Microsurgery



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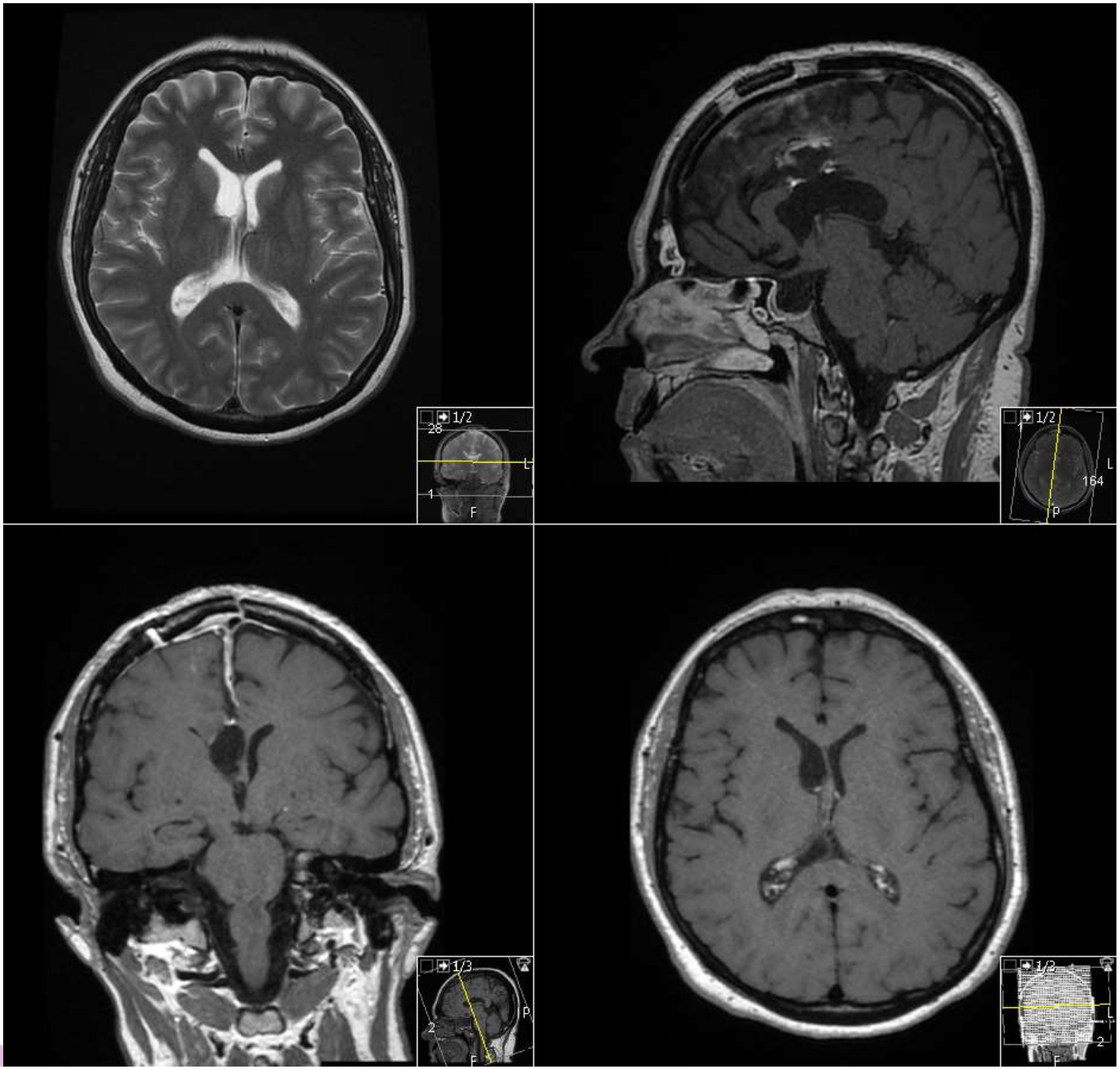
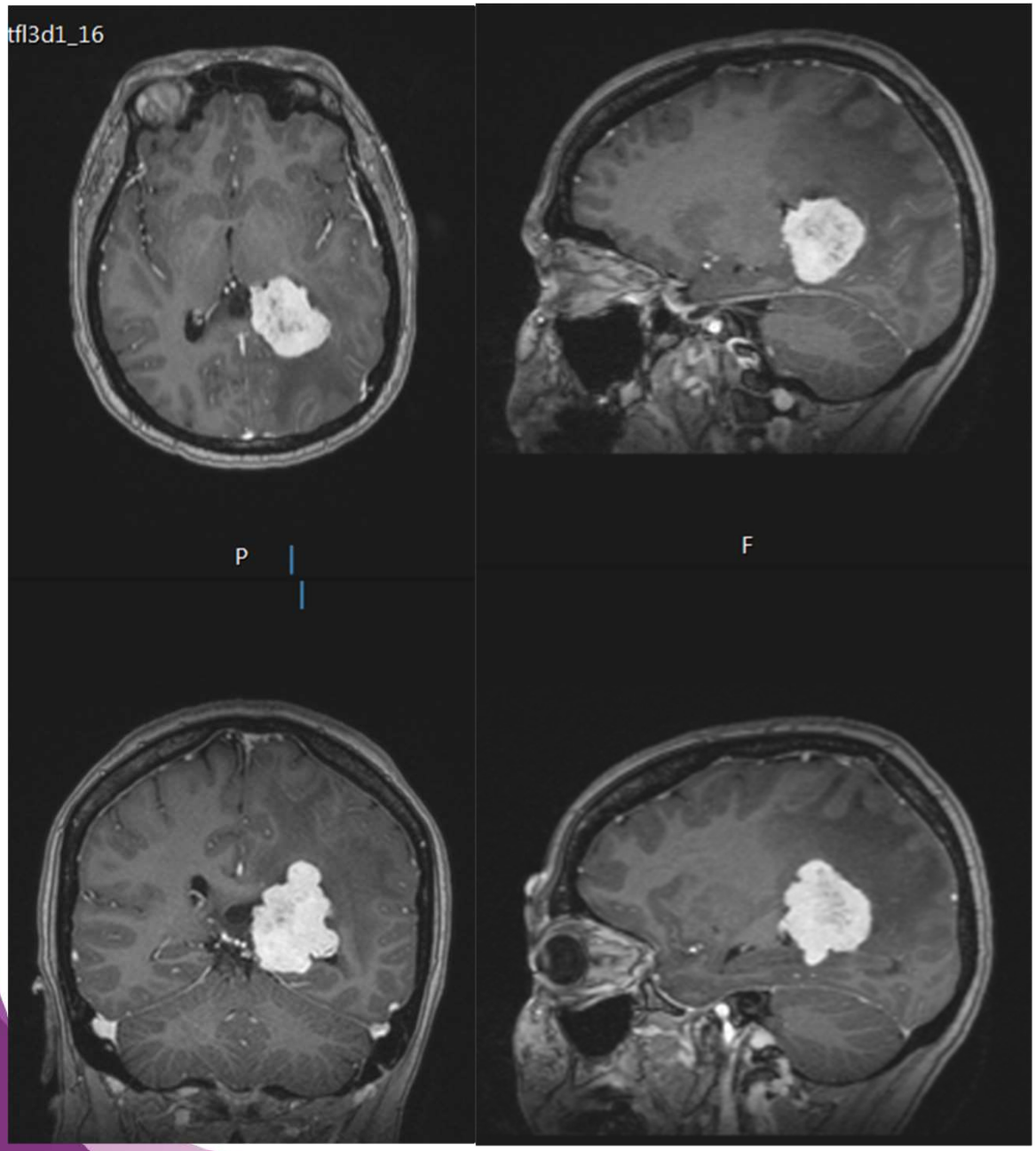
Anterior Interhemispheric

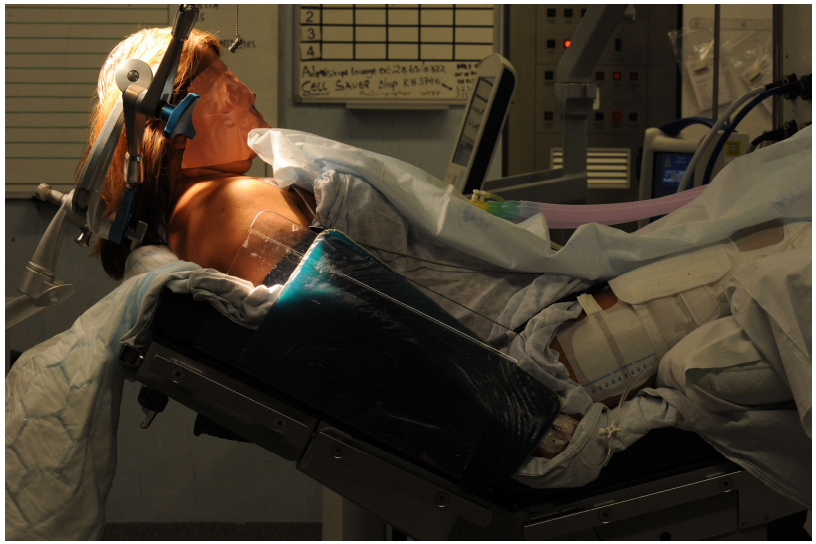
Post-op: complete resection

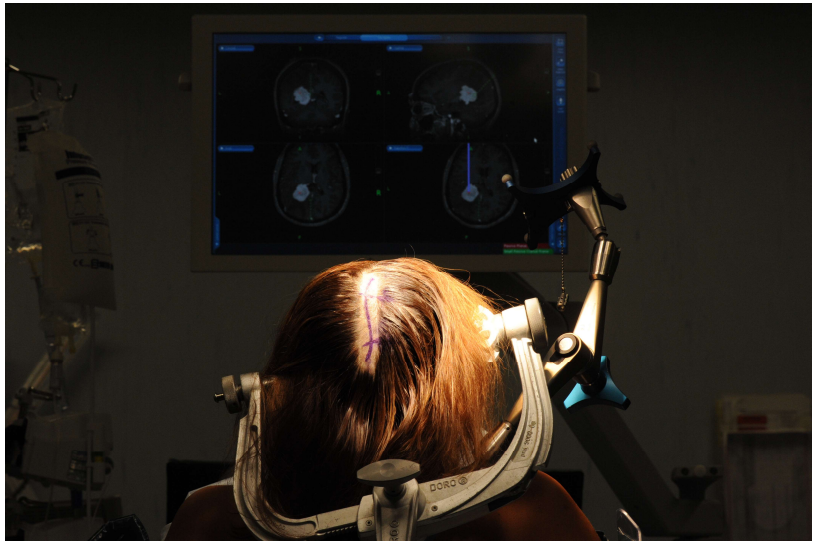


Interhemispheric Transpecuneous Approach Dominant side: meningioma grade I WHO

Anatomy + white fibers + Microsurgery + image guidance







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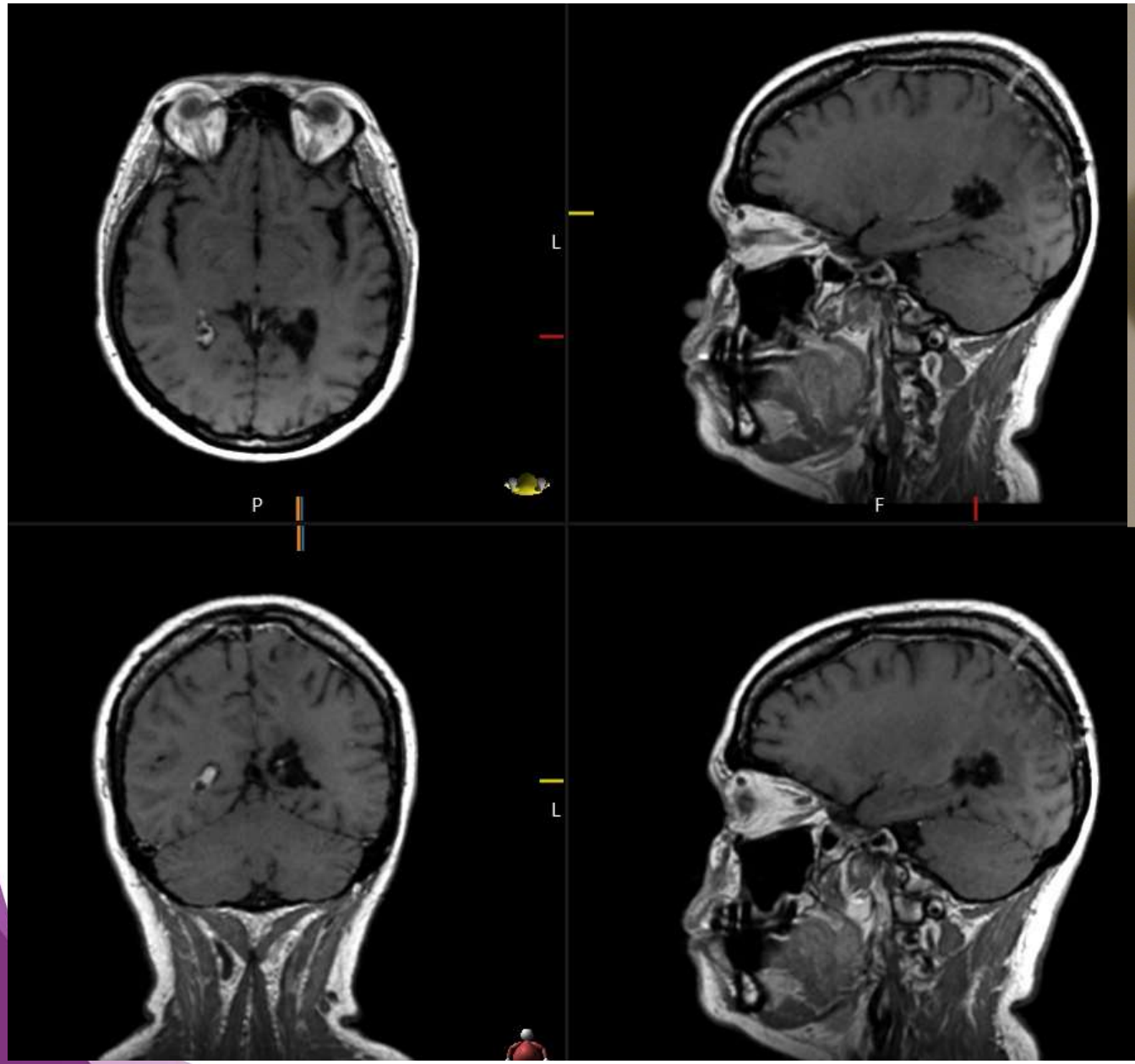
Interhemispheric transprecuneous approach

Left Intraventricular Meningioma: complete resection



Preservation of visual and language pathways

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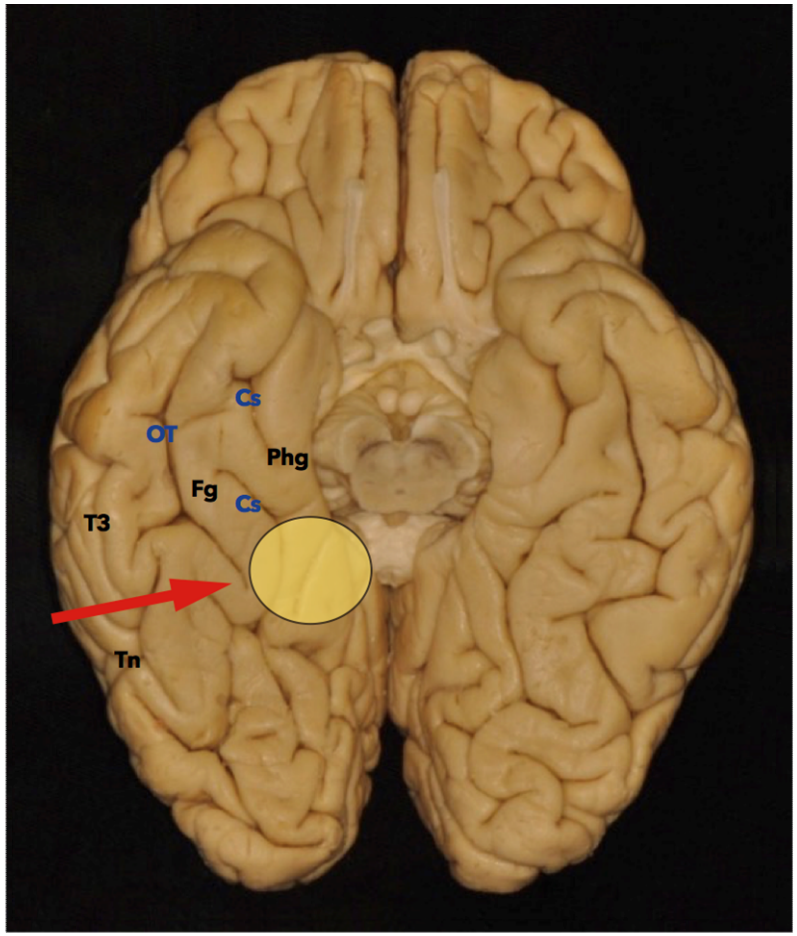
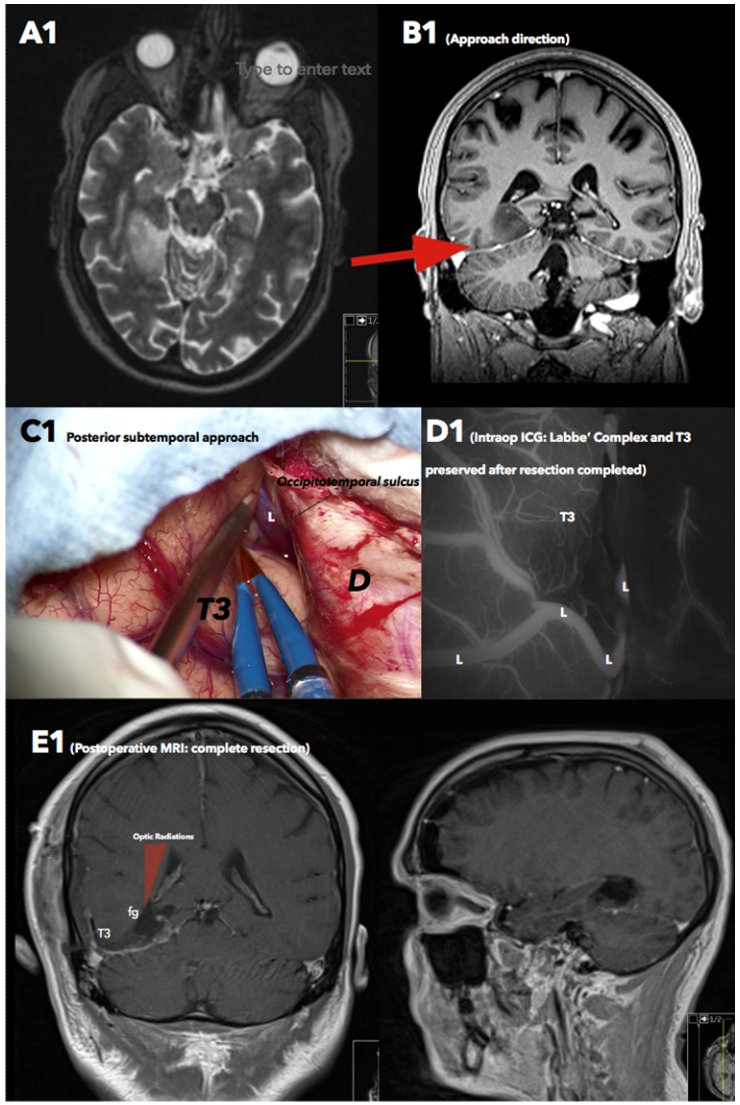
Subtemporal Approach to the posterior fusyform gyru: low grade

Anatomy + Microsurgery + ICG



Inferior surface of the brain: posterior subtemporal approach direction. *Tn: temporal notch, T3: inferior temporal gyrus, OT:occipitotemporal sulcus, Fg: fusiform gyrus; Cs: collateral sulcus;Phg: parahippocampal gyrus.*



Case 1: 36yy, presented with generalised seizures. E1: MRI 24h post showing complete resection. No visual field defects postoperatively. *D=temporal dura reflected toward the transverse sinus, which is exposed in the craniotomy to gain basal access.* L=Labbe' Vein

C.Brogna, R. Bhangoo et al. 2015

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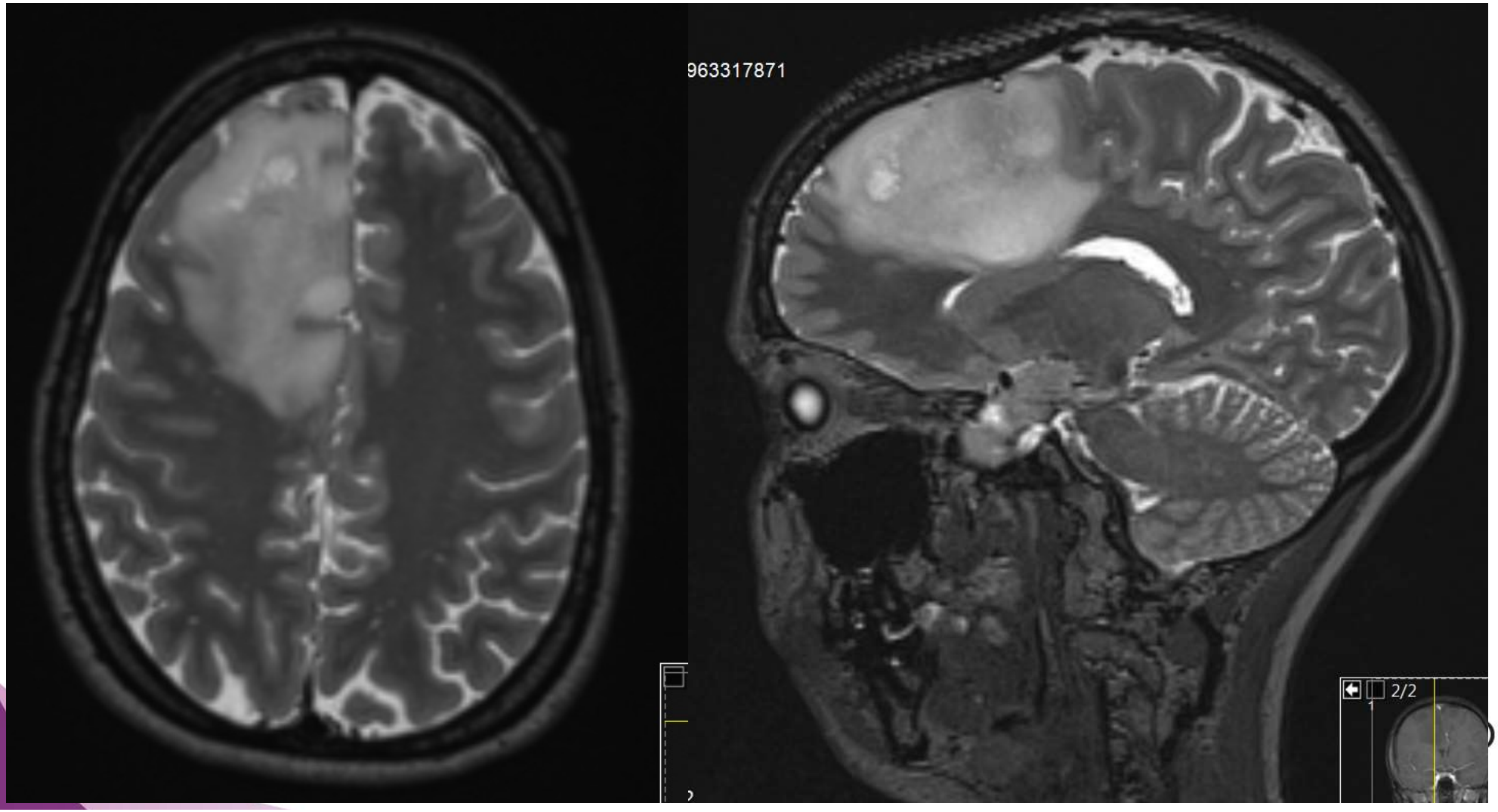
Low Grade Glioma of the Right SMA+Cingulum+Corpus Callosum

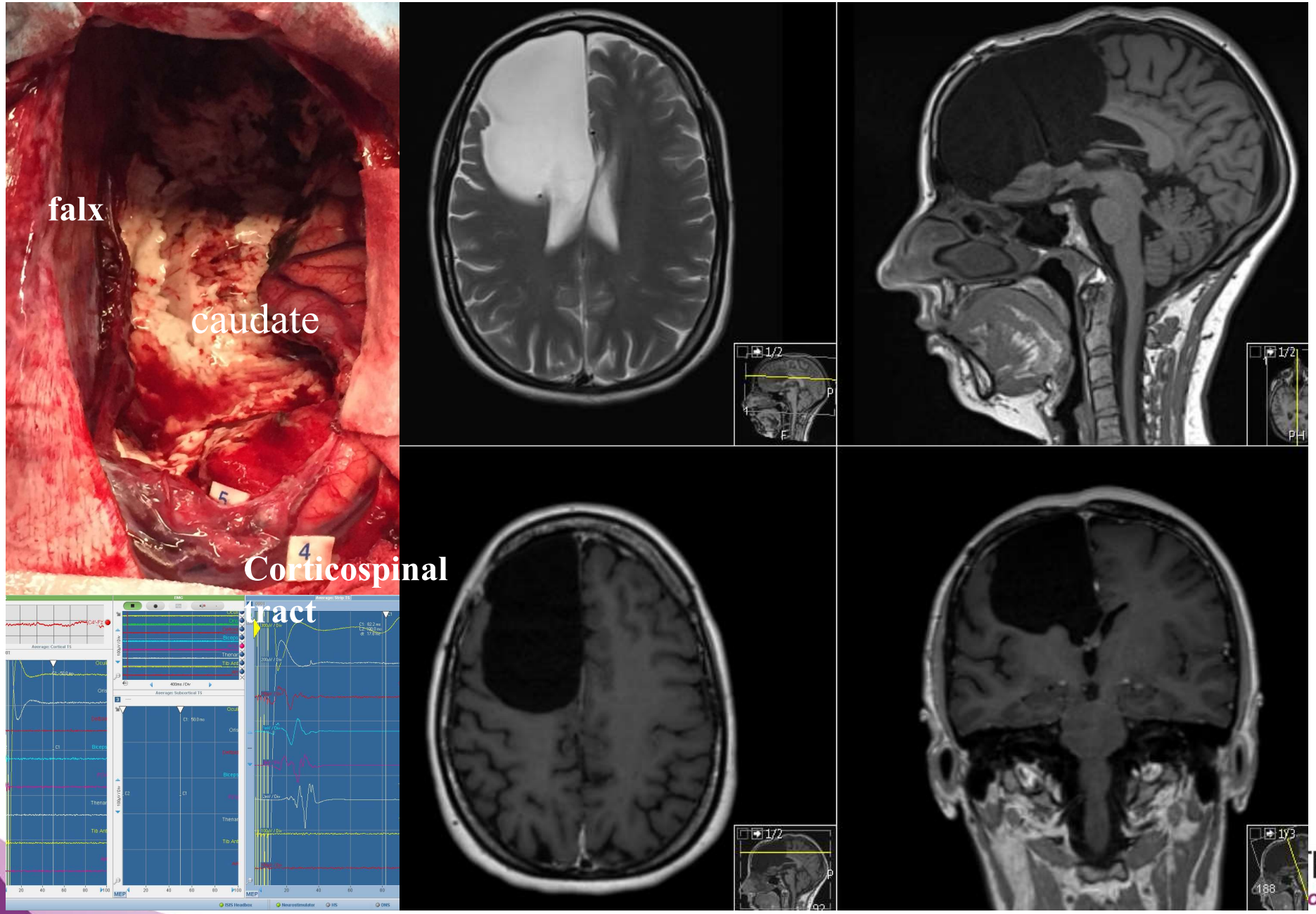
Anatomy + White matter + Microsurgery + Intraop Mapping

- 30yy
- Li-Fraumeni syndrome
- Previous bilateral mastectomy



Low Grade Glioma of the Right SMA+Cingulum+Corpus Callosum

Anatomy + White matter + Microsurgery + Intraop Mapping

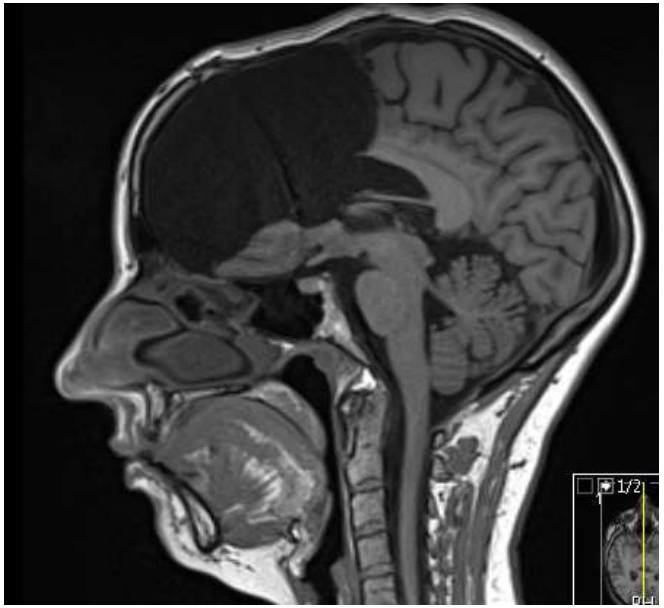


Department of Neuropsychology
Neuropsychological Report

King's College Hospital NHS
NHS Foundation Trust

CONCLUSION:

On the WAIS-IV M[redacted]s shows a large difference between her verbal and nonverbal skills, in favour of nonverbal skills. Her score on the Verbal Comprehension subscale fell into the average range and her score on the Perceptual Reasoning subscale fell at the upper end of the high average range. Although it is possible that this reflects a longstanding pattern of strengths and weaknesses, given that her verbal score is consistent with her estimated 'average' optimal level of ability based on her reading score, a difference of the size found is unusual. Her scores on the Working memory and Processing Speed subscales also fell into the average range. Verbal recall memory scores are mixed, with below average story recall but average list learning. Verbal and visual recognition memory is satisfactory. Language, perceptual functions and performance on selected executive tests are satisfactory.



Verbal Comprehension
Perceptual Reasoning
Working Memory
Processing Speed

AVERAGE
SCORING

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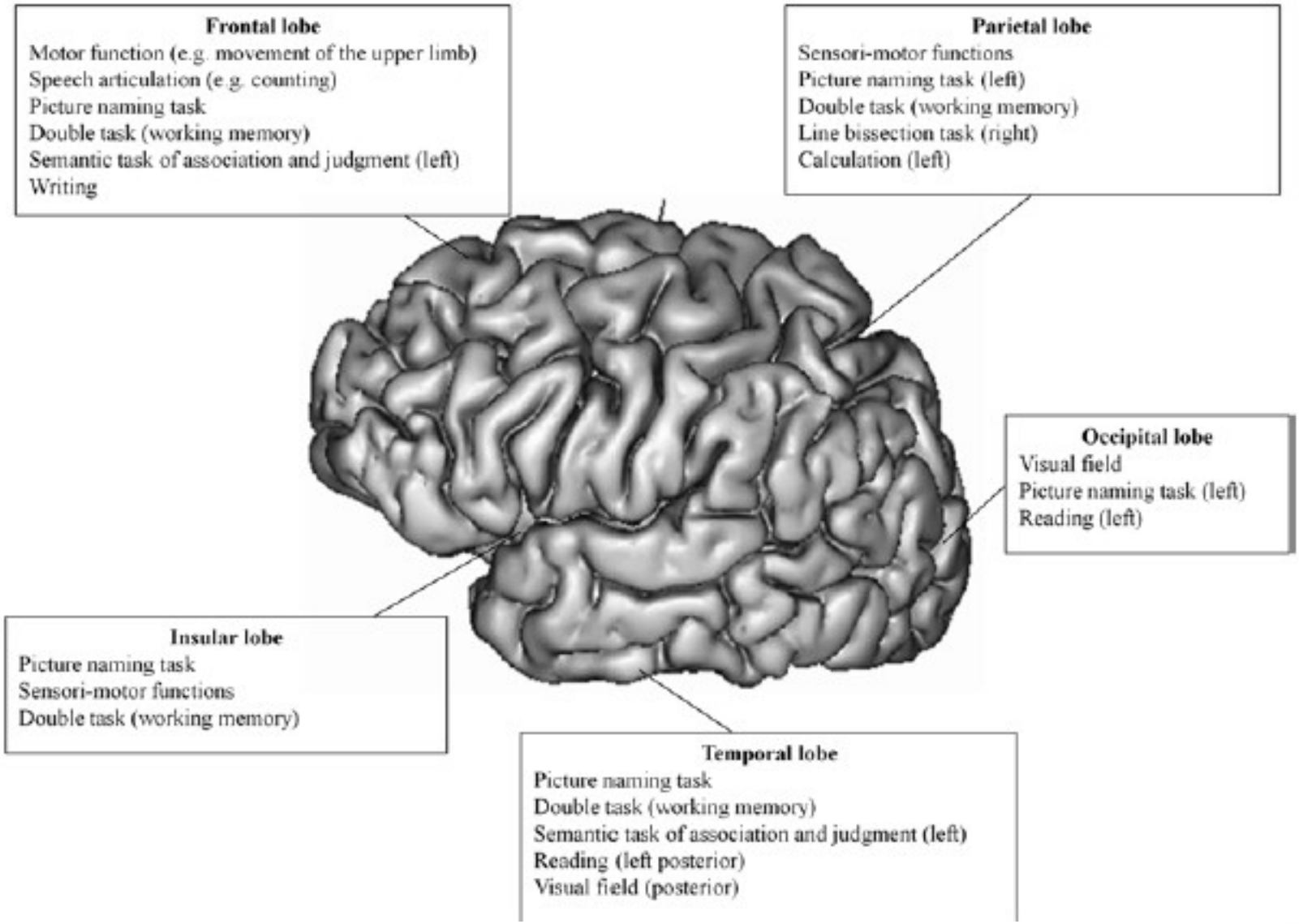
Beyond Motor and Language



Fernandez-Coello et al. J Neurosurg, 2013

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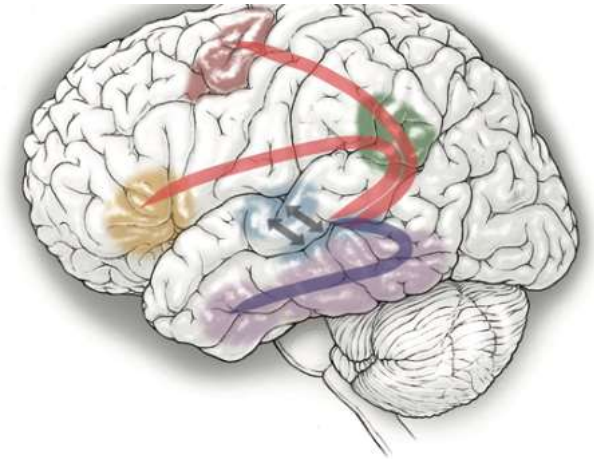
JNS
LITERATURE REVIEW
J Neurosurg 122:250–261, 2015

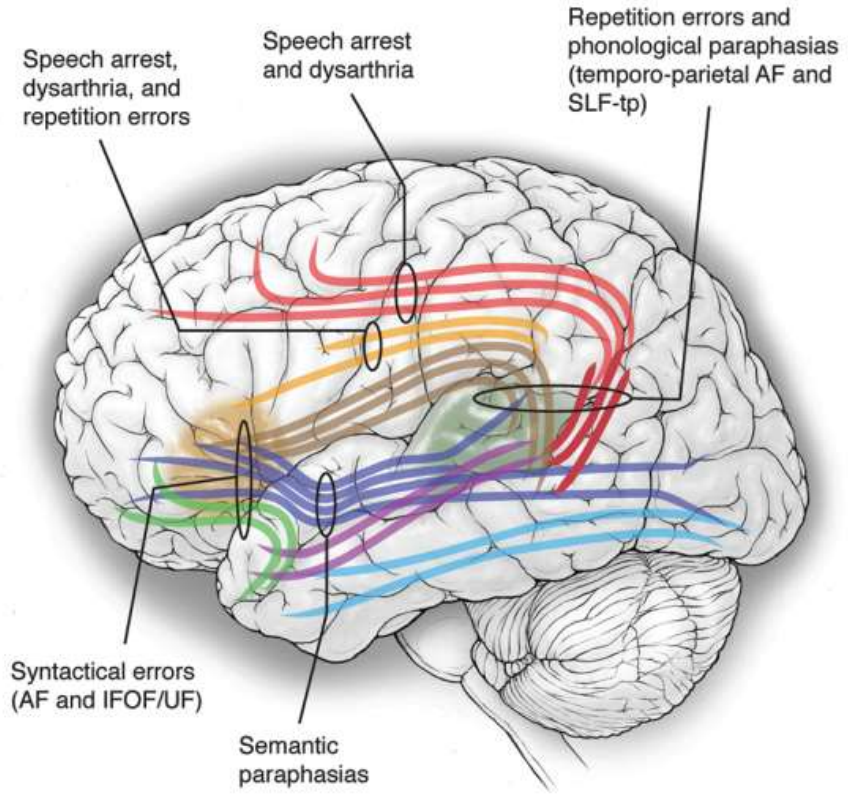
Contemporary model of language organization: an overview for neurosurgeons

Edward F. Chang, MD, Kunal P. Raygor, AB, and Mitchel S. Berger, MD



Dorsal stream for sensorimotor integration (mostly dominant)

Ventral stream for speech comprehension (bilateral)



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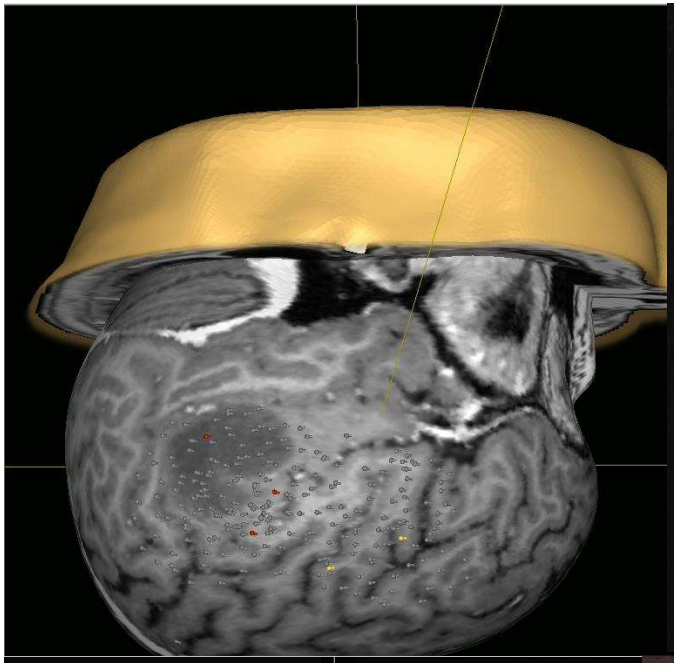
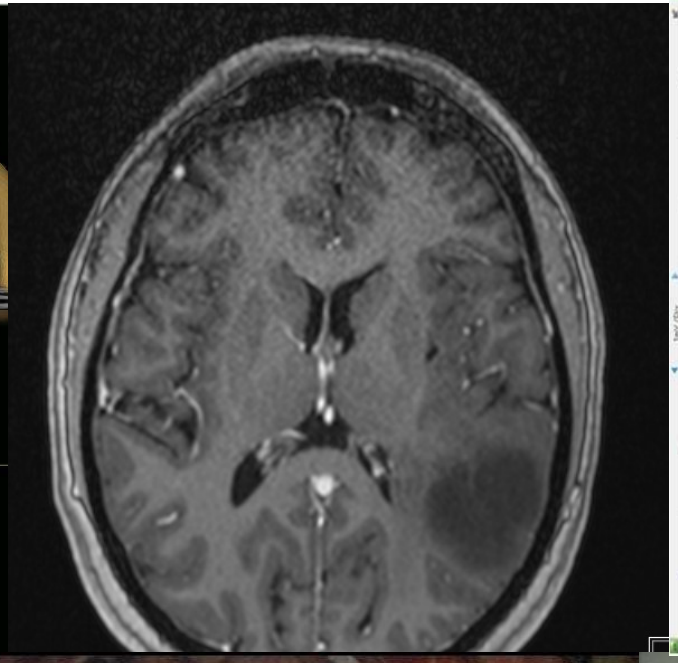
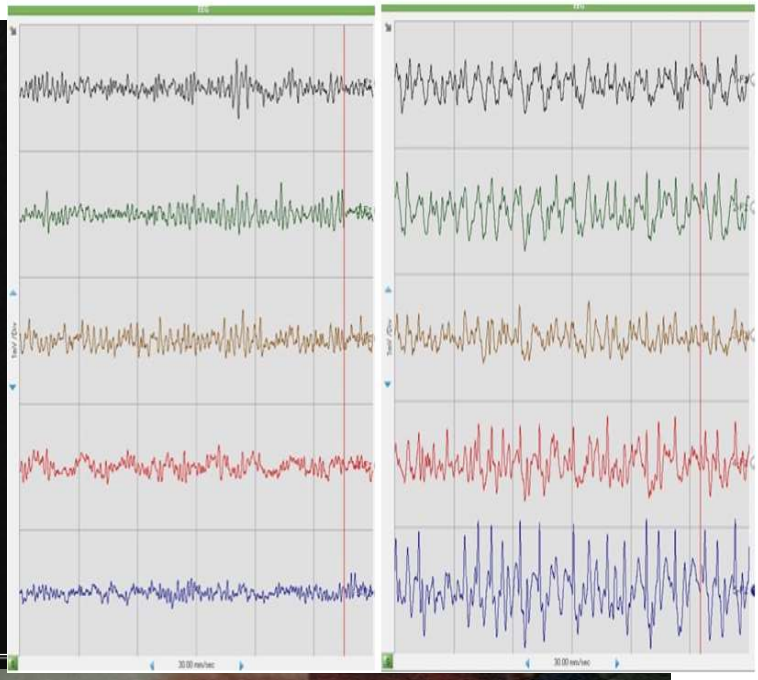
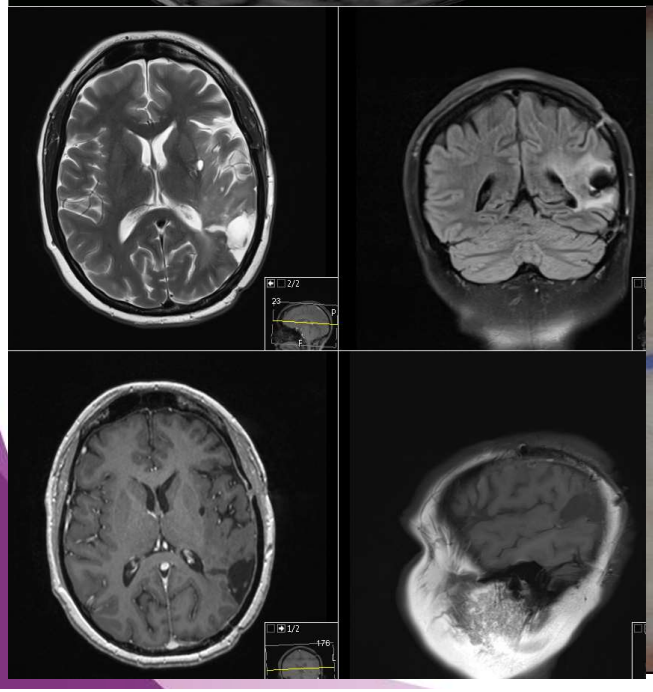
Aleep-Awake-Asleep Left Supramarginal Low Grade

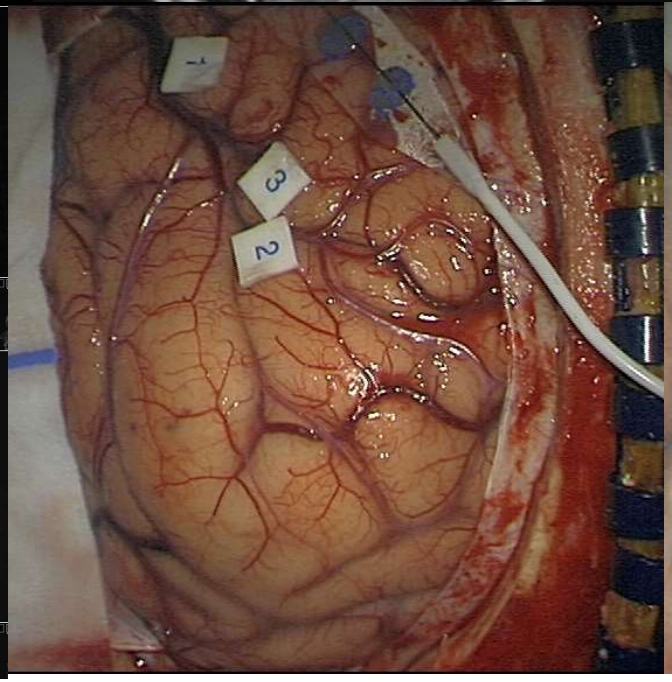
Anatomy – Functional networks – Mapping – Neuronav

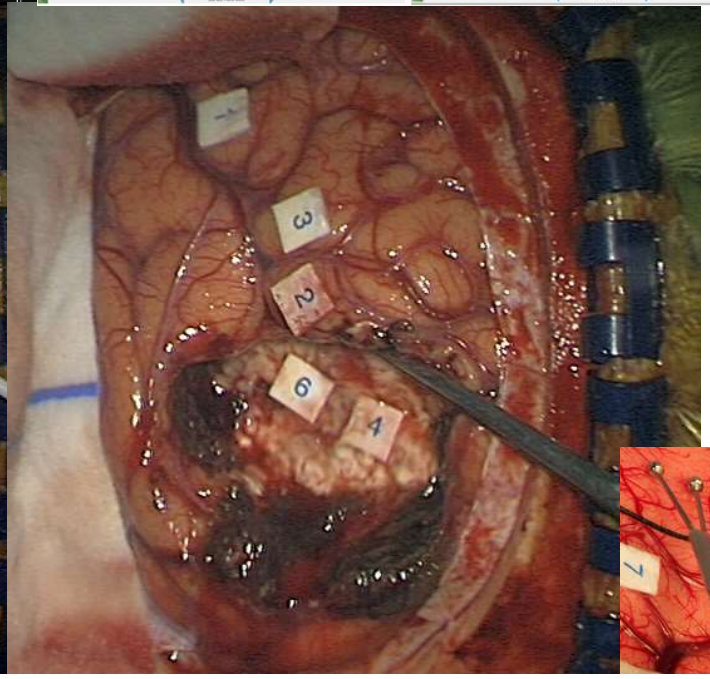








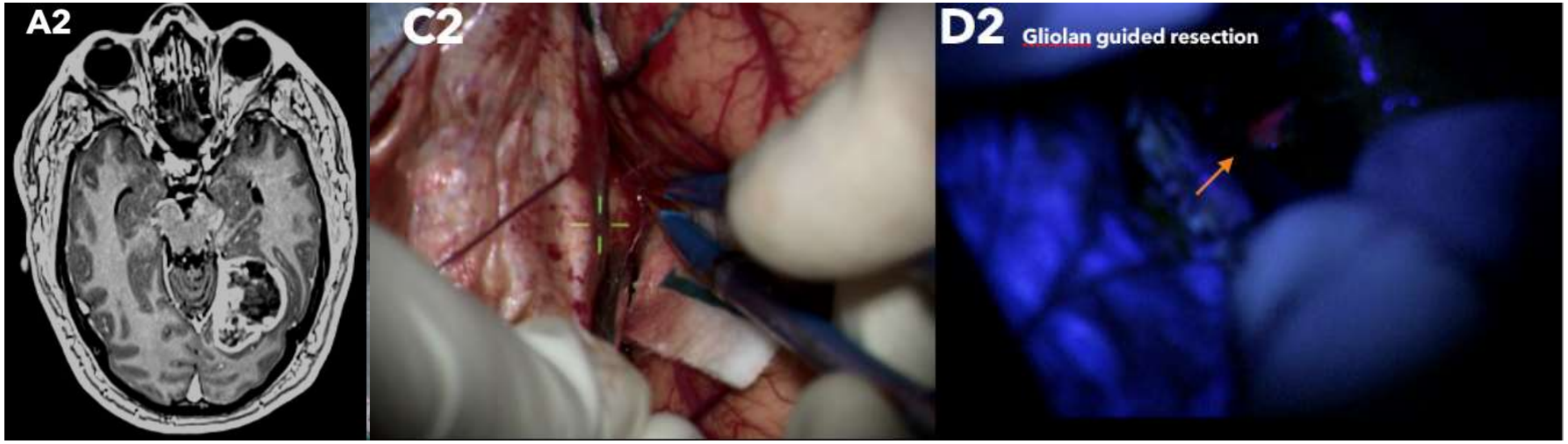


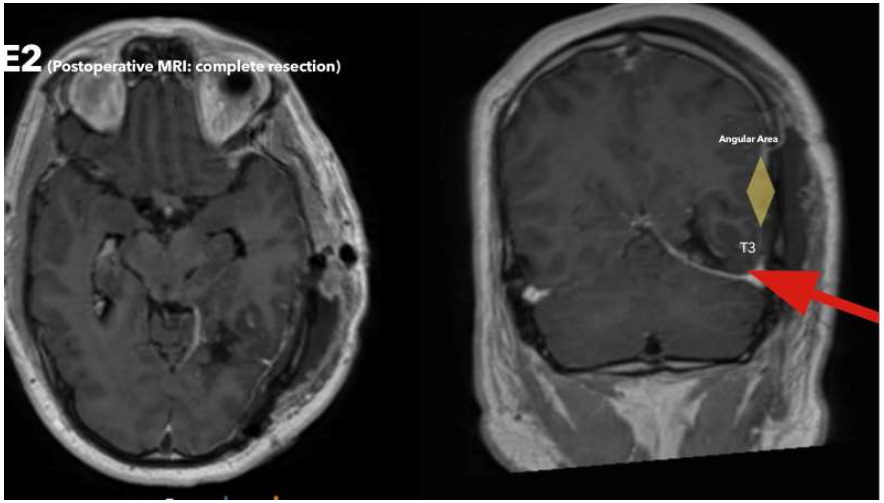


Subtemporal Approach to the fusyform gyrus

High grade Glioma - Preservation of the lateral dominant neocortex

Anatomy + White Matter + Microsurgery + 5-ALA





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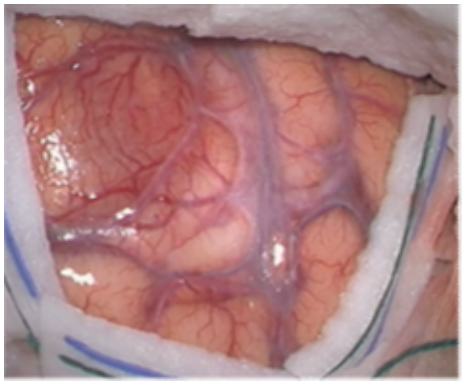
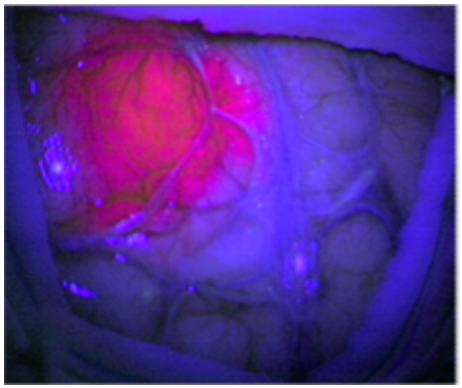
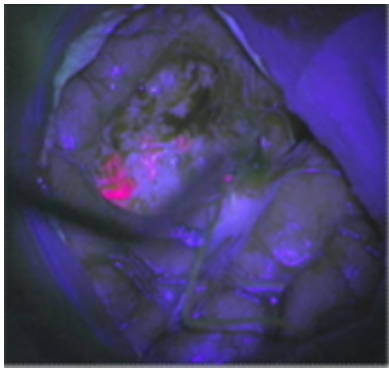
Intraoperative use of 5-ALA

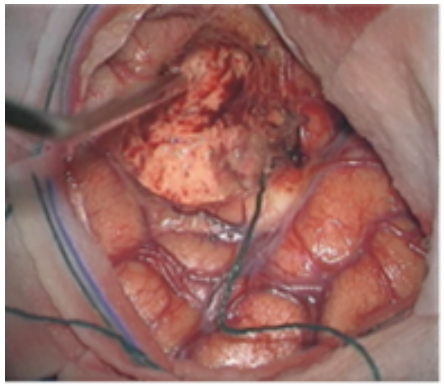
Tumour Identification

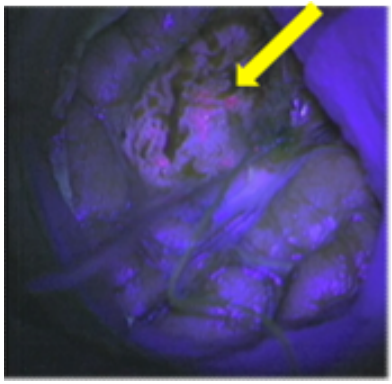




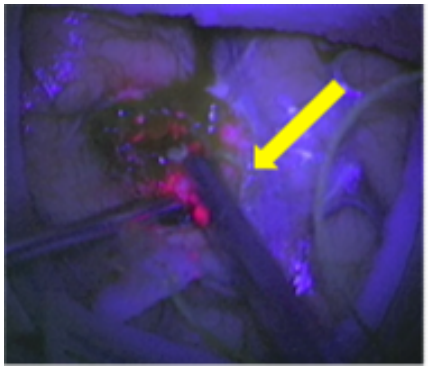
Residual tumour







Tumour sampling



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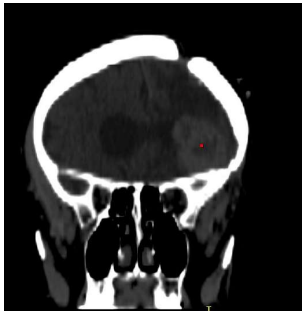
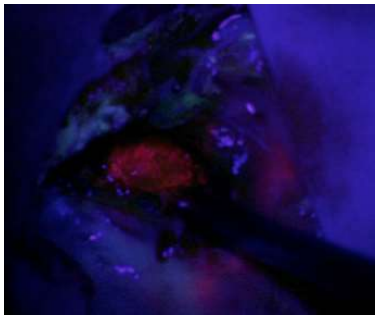
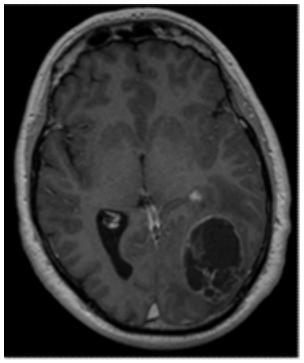
Fluorescent tumours…

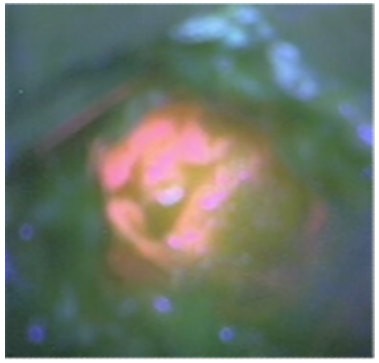
Malignant Meningioma



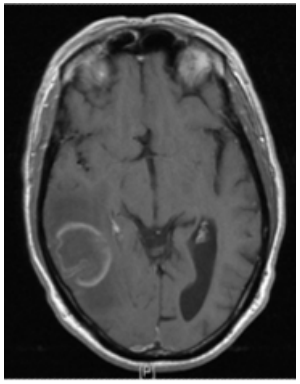


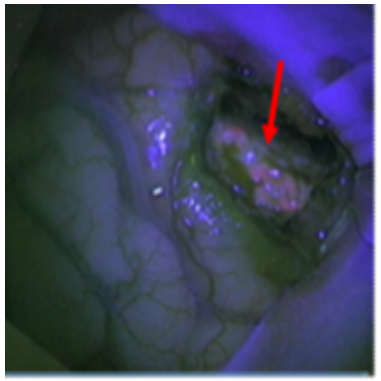
Ependymoma





Lymphoma





Acta Neurochir (Wien). 2017 Aug;159(8):1511-1515. doi: 10.1007/s00701-017-3213-1. Epub 2017 May 27.

5-ALA fluorescence in intraparenchymal endodermal cysts.

Lavrador JP[1], Brogna C[2,3], Vergani F[2], Greenway F[2], Aizpurua M[4], Bhangoo R[2].

⊕ **Author information**

Abstract

In recent years, new indications have been suggested for 5-ALA, particularly for cystic lesions. We report the use of 5-ALA fluorescence in an intraparenchymal supratentorial endodermal cyst of a 52-year-old female presenting with headache, progressive right side hemiparesis and anomic aphasia. She underwent an image-guided 5-ALA-assisted left minicraniotomy for fenestration of the cystic lesion into the ventricular system. The capsule of the cyst was noted to fluoresce with 5-ALA. She recovered from the previous deficits and the cyst decreased in size. To the best of our knowledge, this is the first time 5-ALA fluorescence is reported in a case of endodermal cyst.

KEYWORDS: 5-ALA; Endodermal cyst; This work has not been presented in a conference.; Tumour

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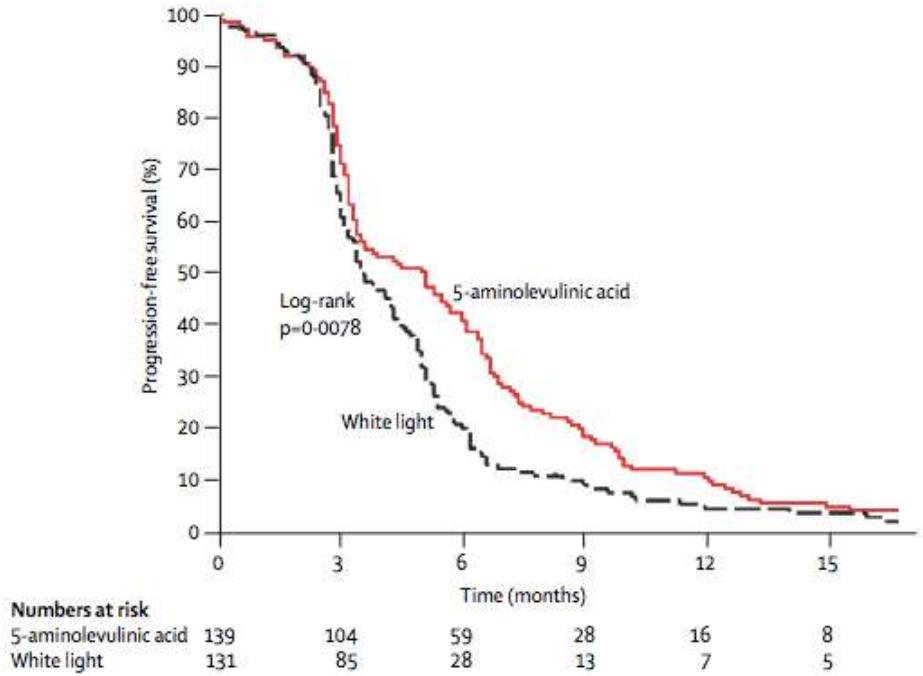
Lancet Oncol 2006; 7: 392–401

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)



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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

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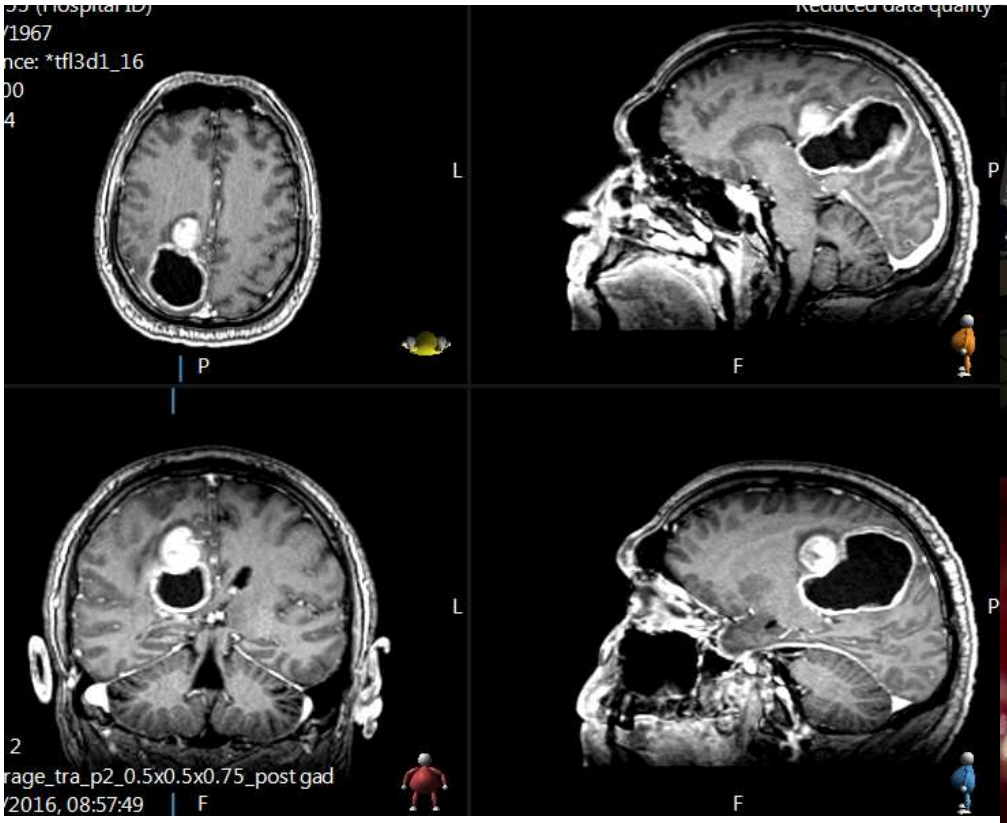
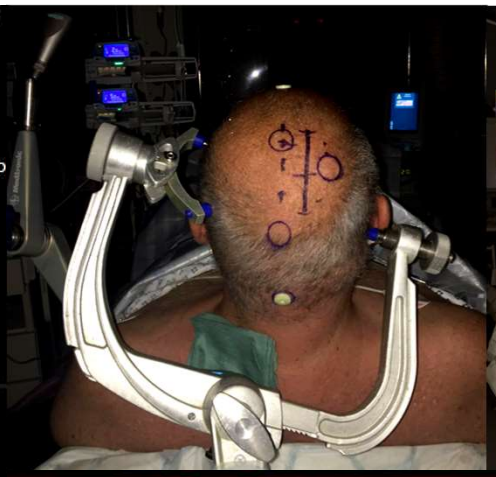
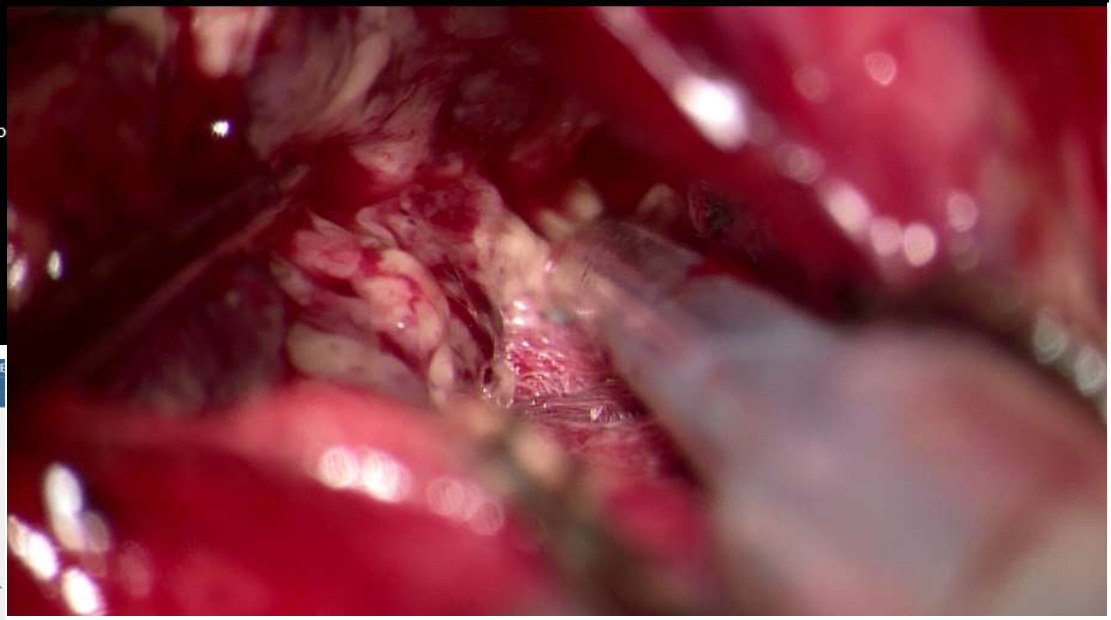
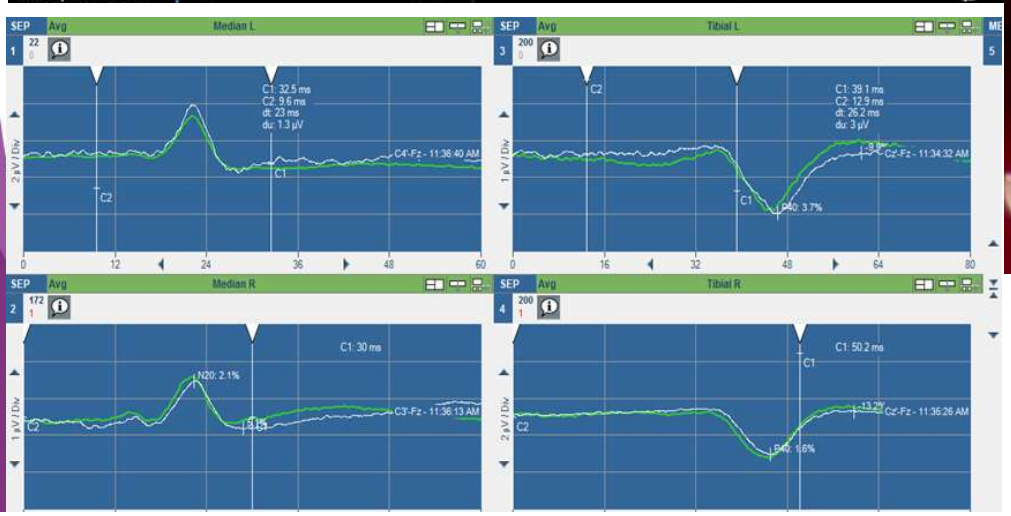
Right Quadrangular/Central Lobe High Grade

Anatomy + Functional networks + Mapping + Neuronav + 5-ALA + Ultrasound









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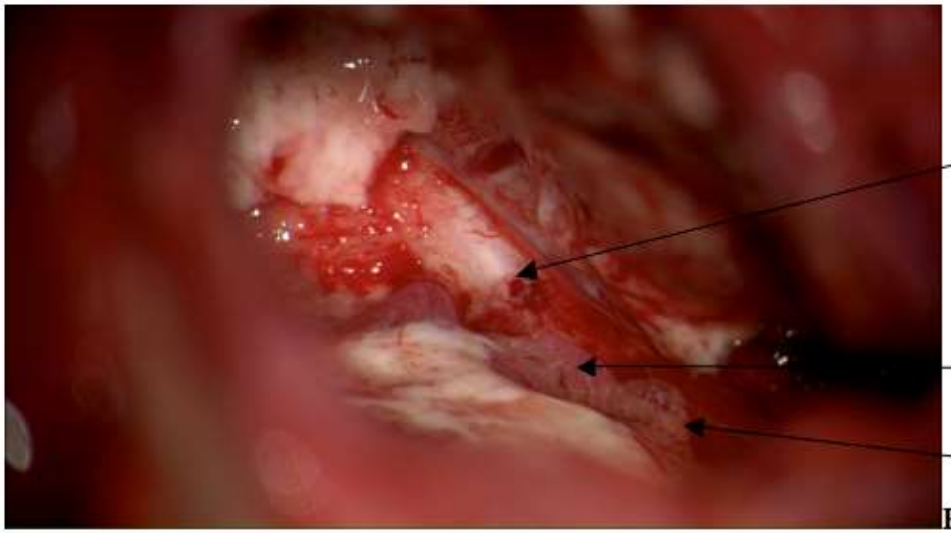
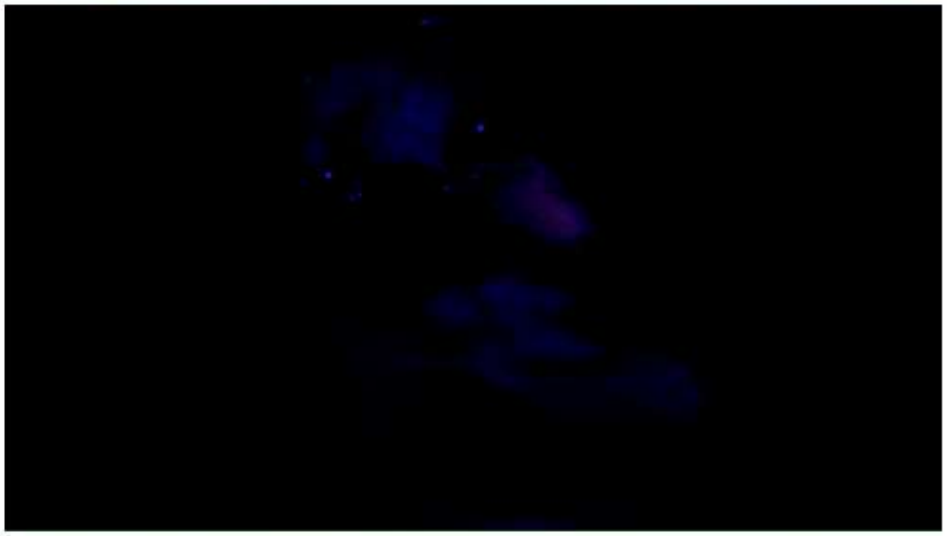
Right Quadrangular/Central Lobe High Grade

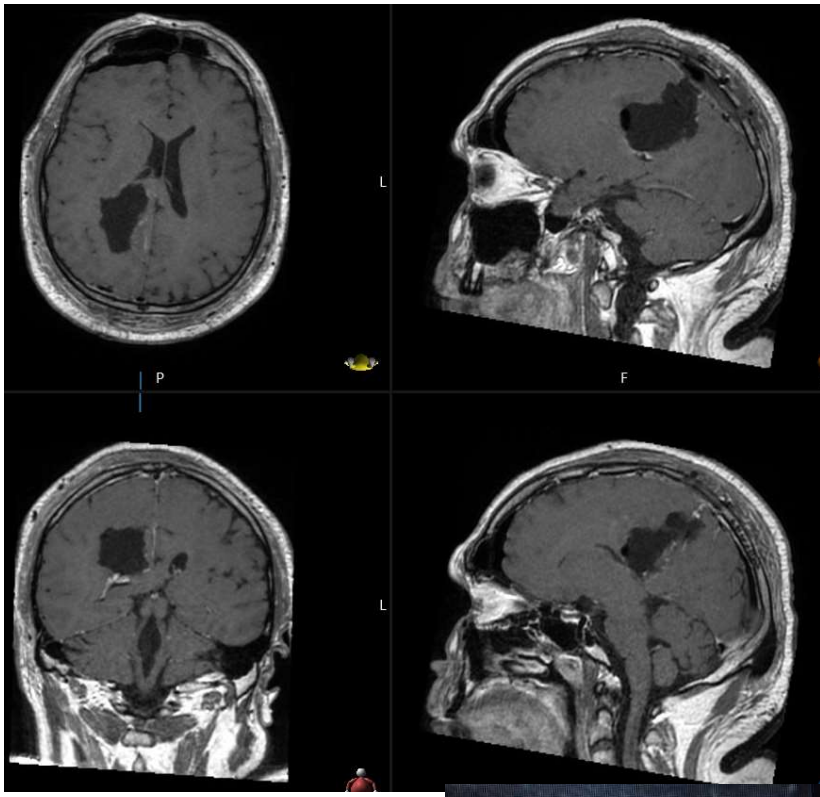
Anatomy + Functional networks + Mapping + Neuronav +5-ALA

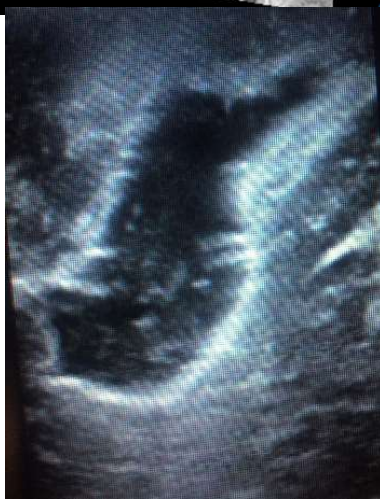


Right Trigone



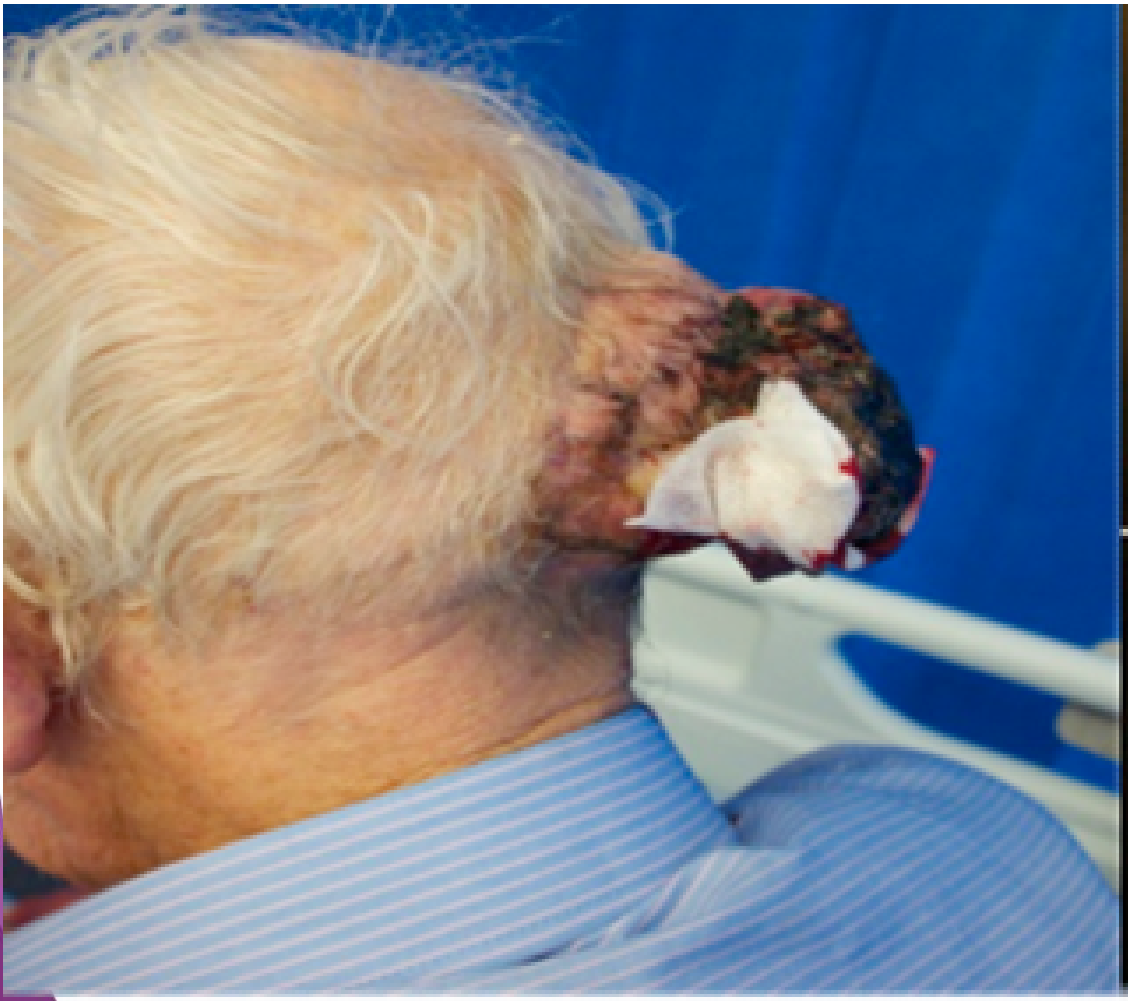
Trigone of the right ventricle opened. The picture above shows the fluorescence belonging to the ependyma of the ventricle and not to the tumor.

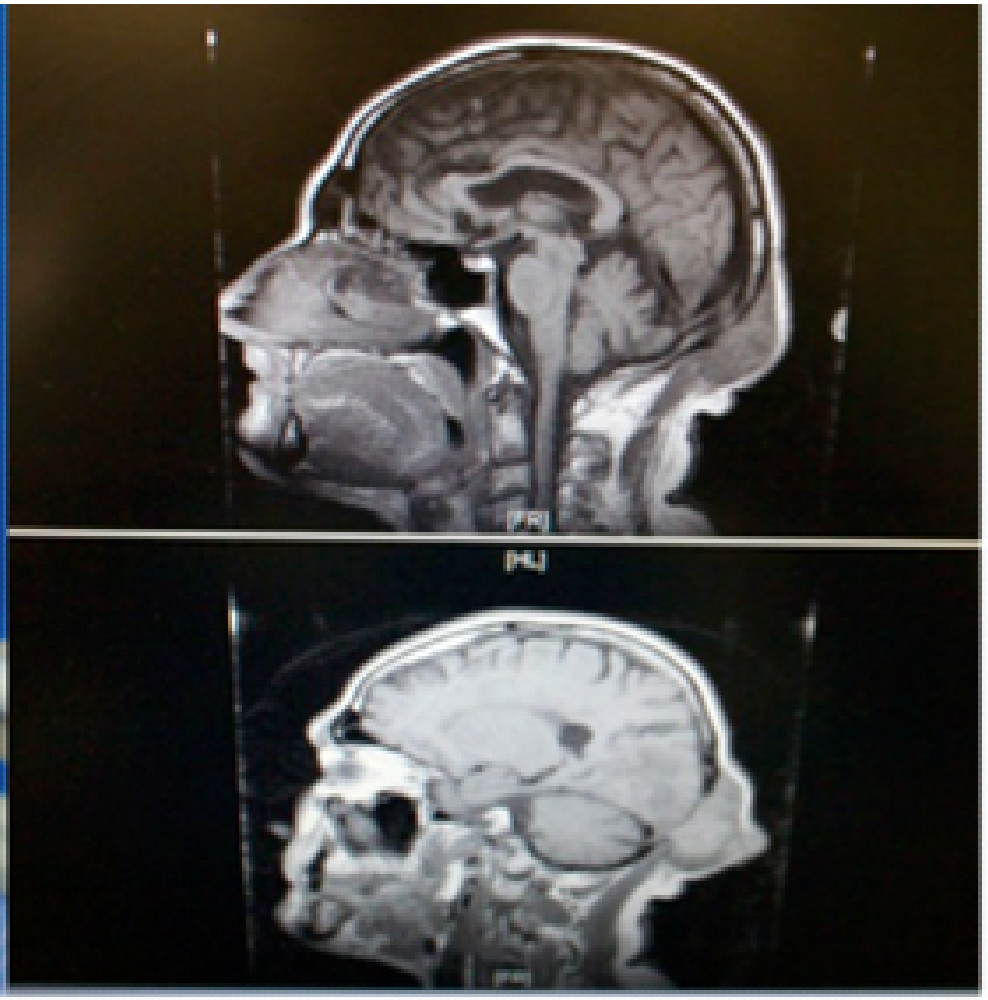




Giant Exophytic Meningioma

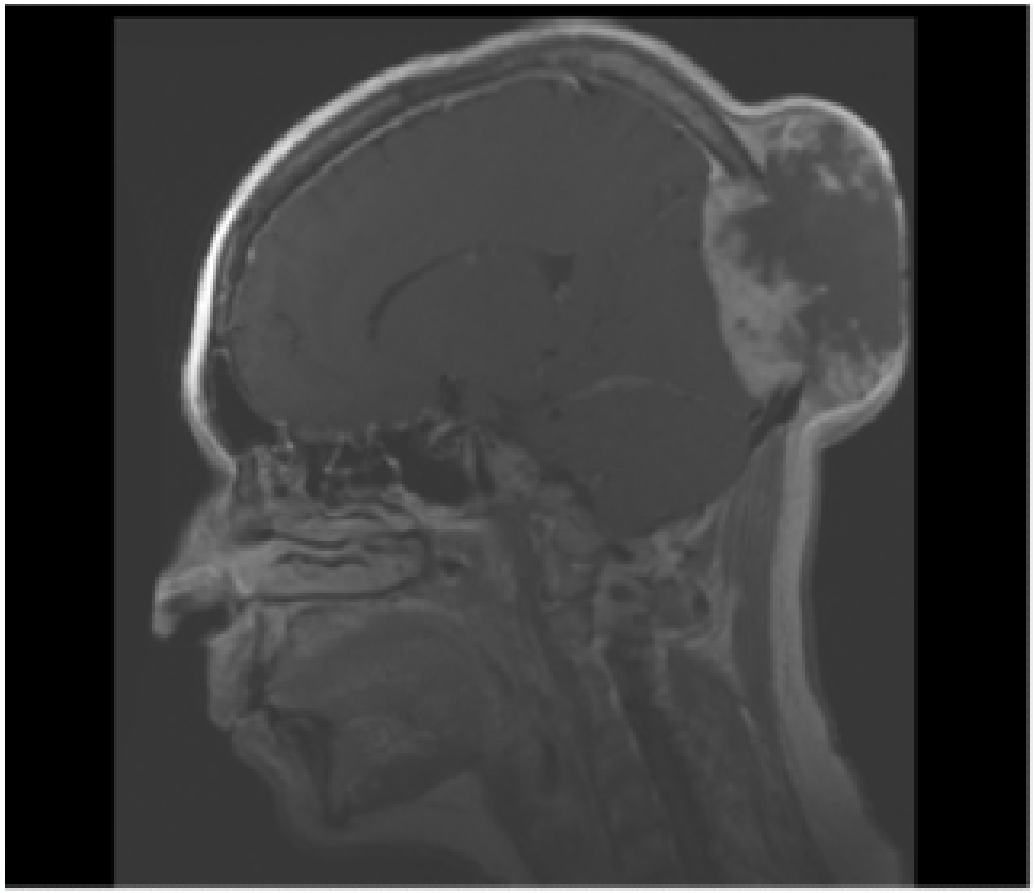
Planning ahead, Radiosurgery/Reconstructive Surgery

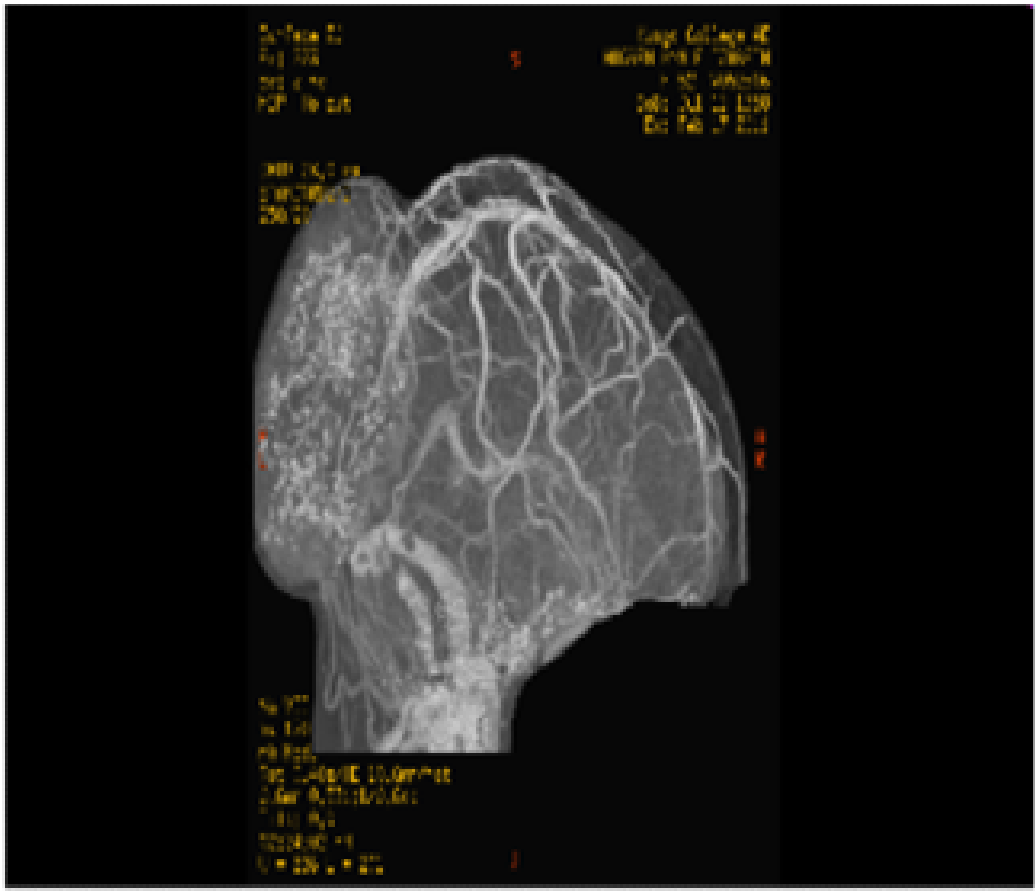




Giant Exophytic Meningioma

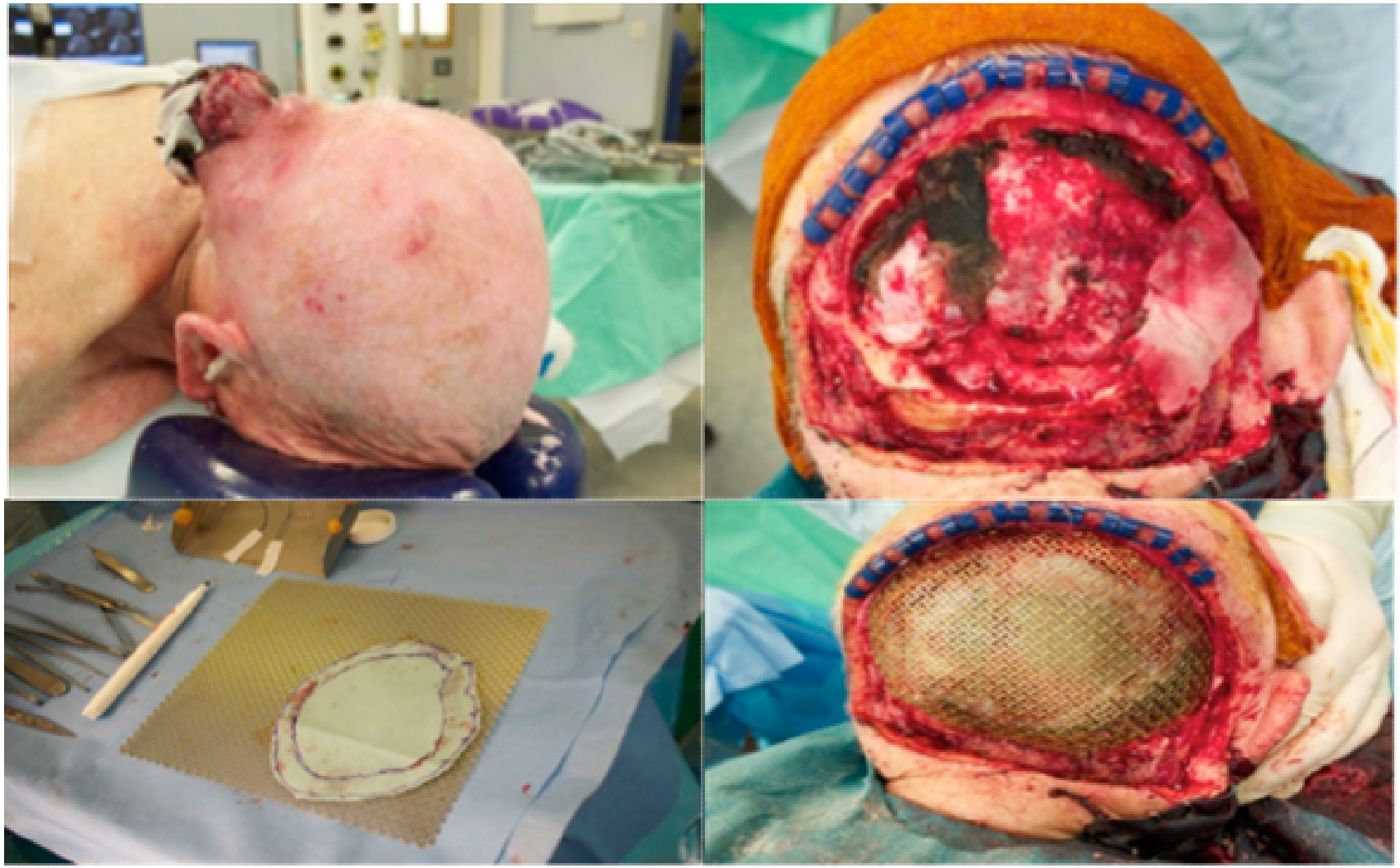
Planning ahead, Radiosurgery/Reconstructive Surgery





Giant Exophytic Meningioma

Planning ahead, Radiosurgery/Reconstructive Surgery



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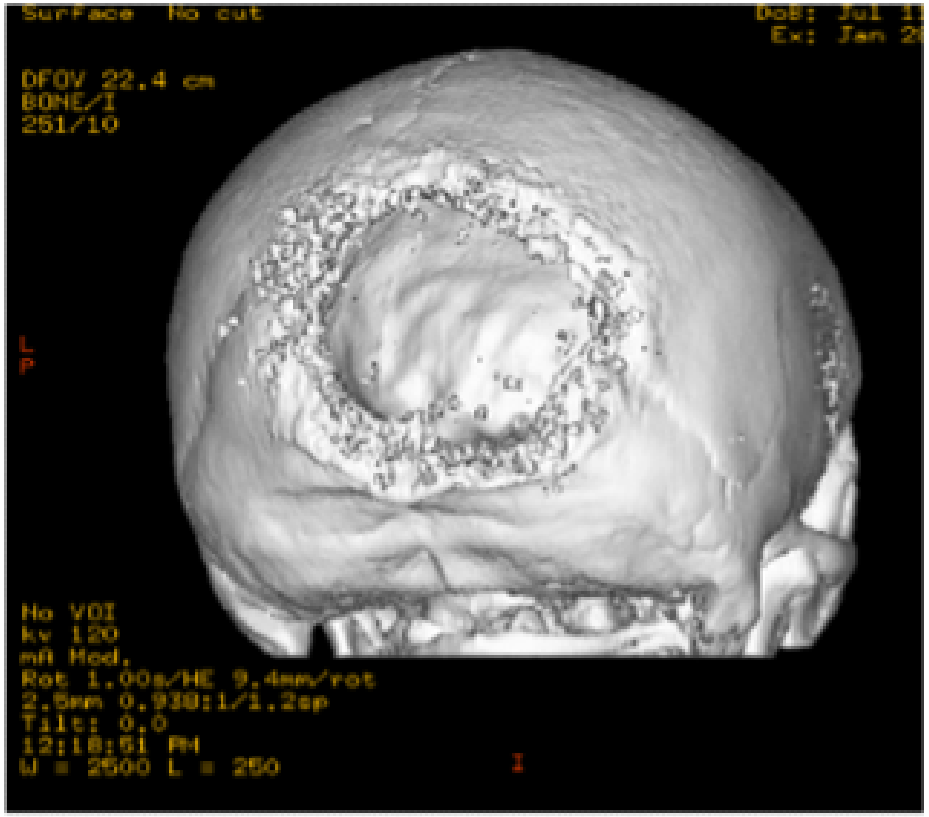
Exophytic Meningioma
Planning ahead, Radiosurgery/Reconstructive Surgery

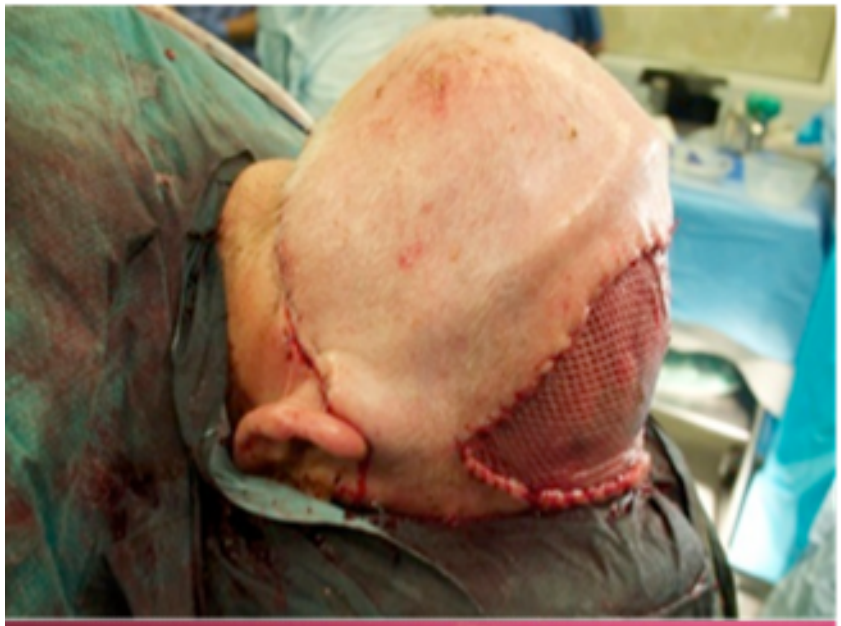
- Underwent planned Craniectomy with optimal debulking and Simultaneous Cranioplasty

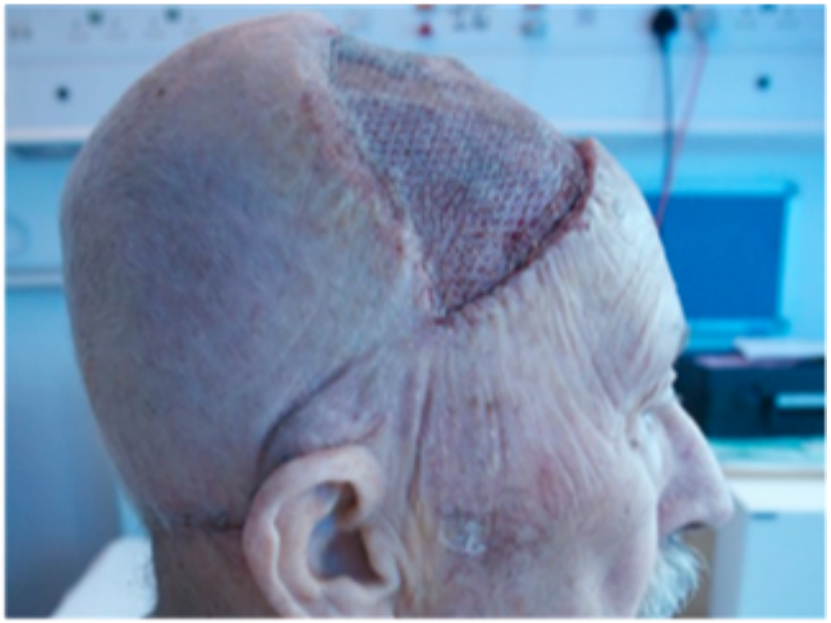
- Followed Cyberknife© radiosurgery to intra-sinus remnant

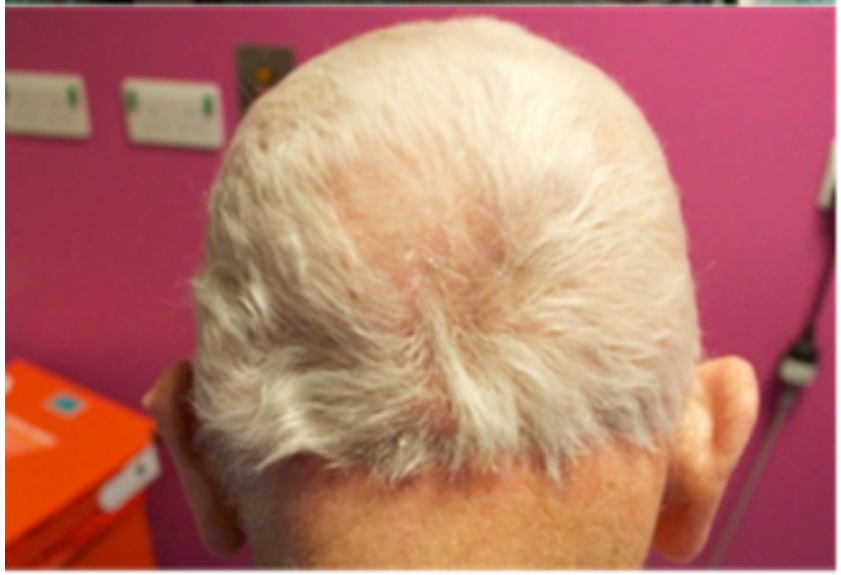


Exophytic Meningioma

Planning ahead, Radiosurgery/Reconstructive Surgery







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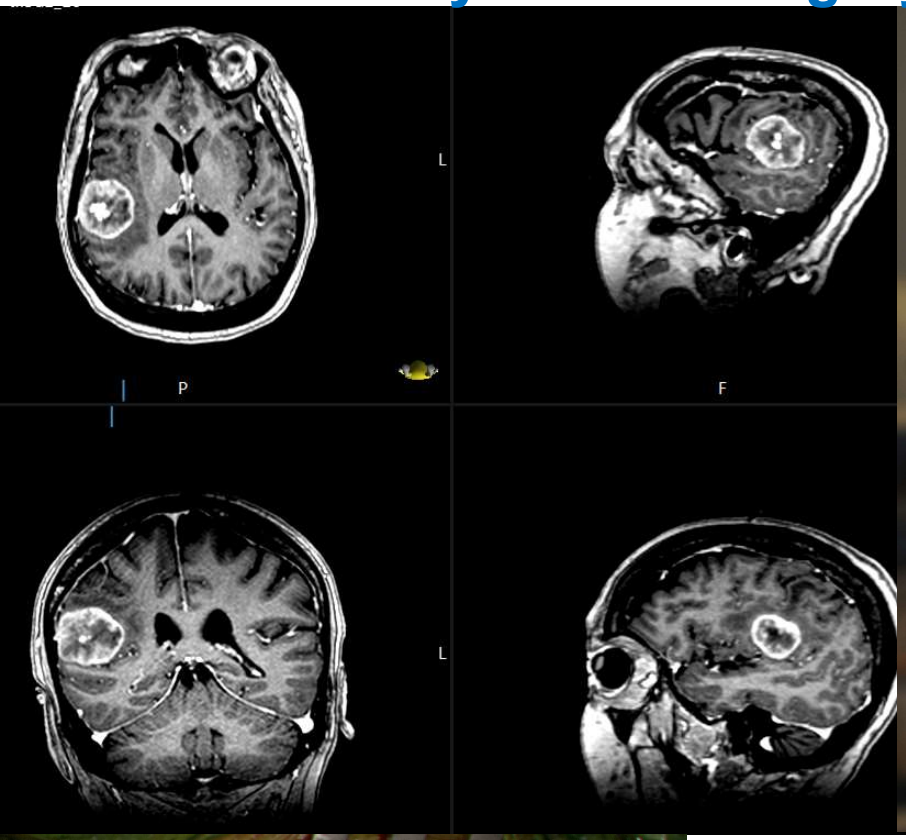
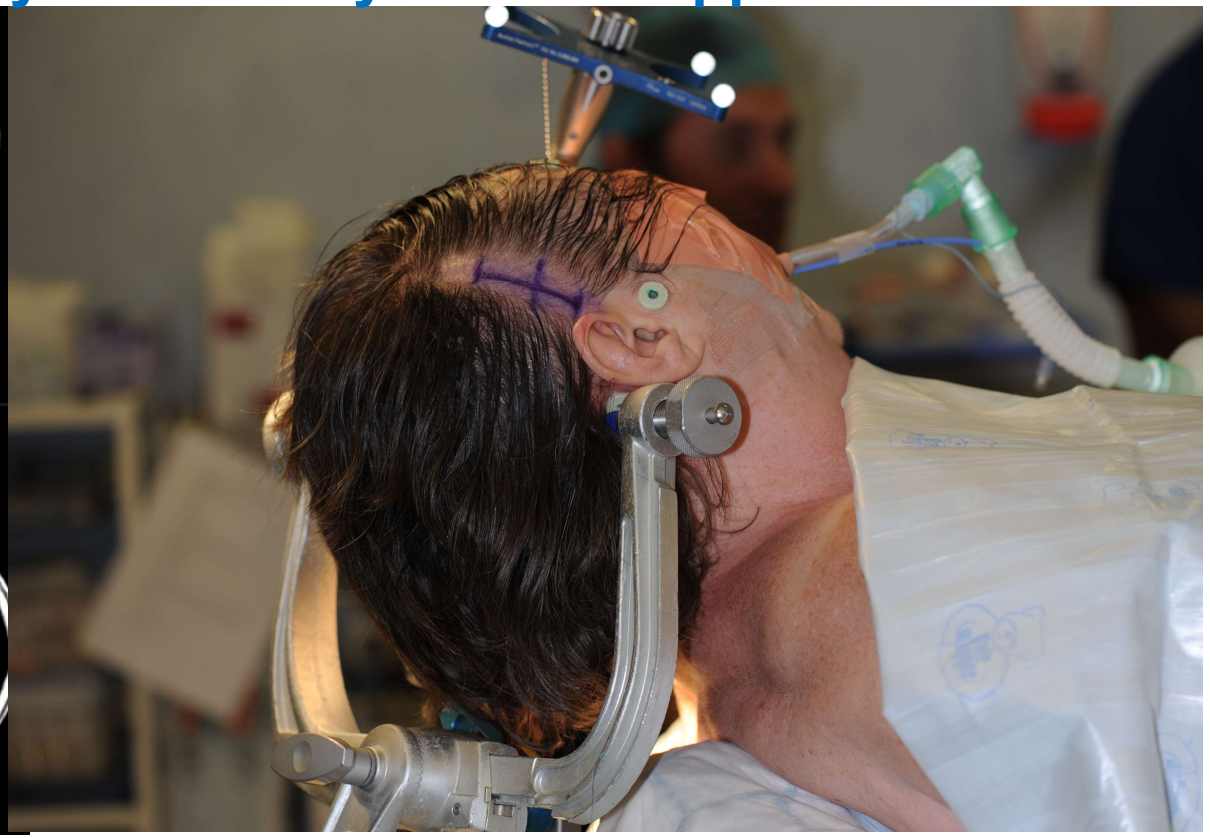
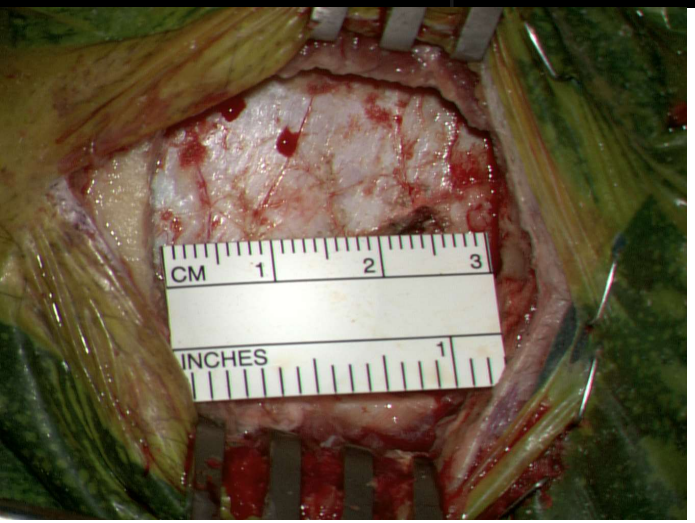
Subcentral Gyrus Metastasis

Anatomy + Microsurgery + Minimally Invasive appraoch







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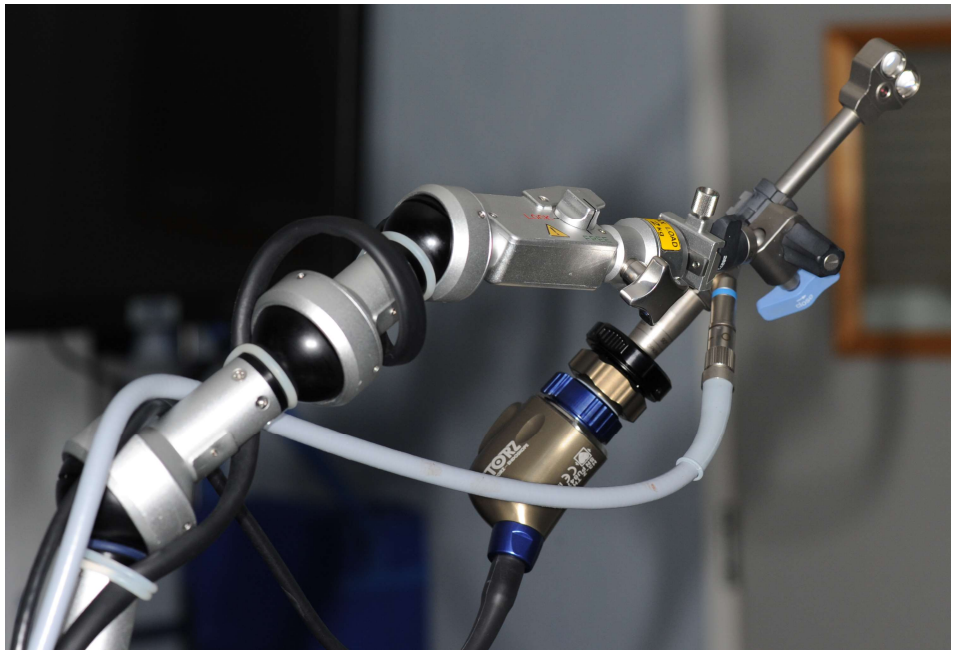
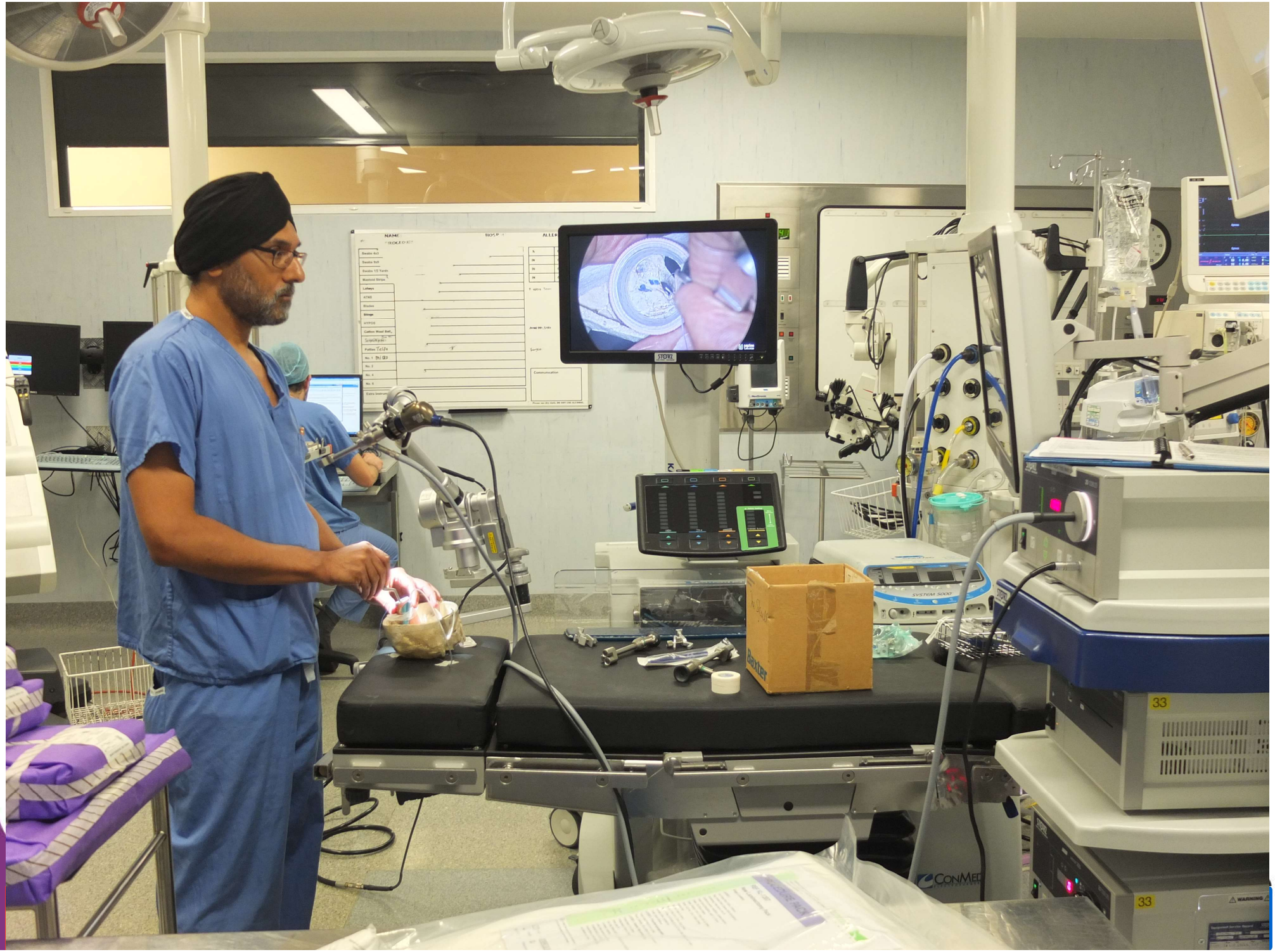
Exo-scope *VS* Endo-scope

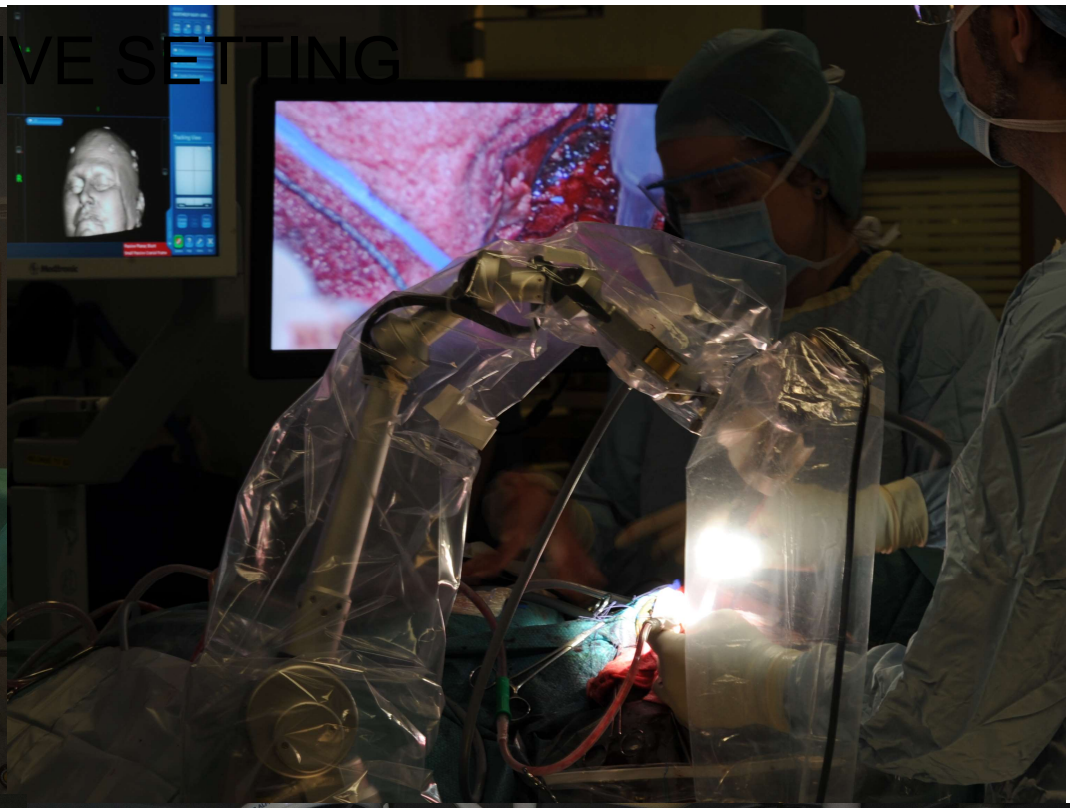


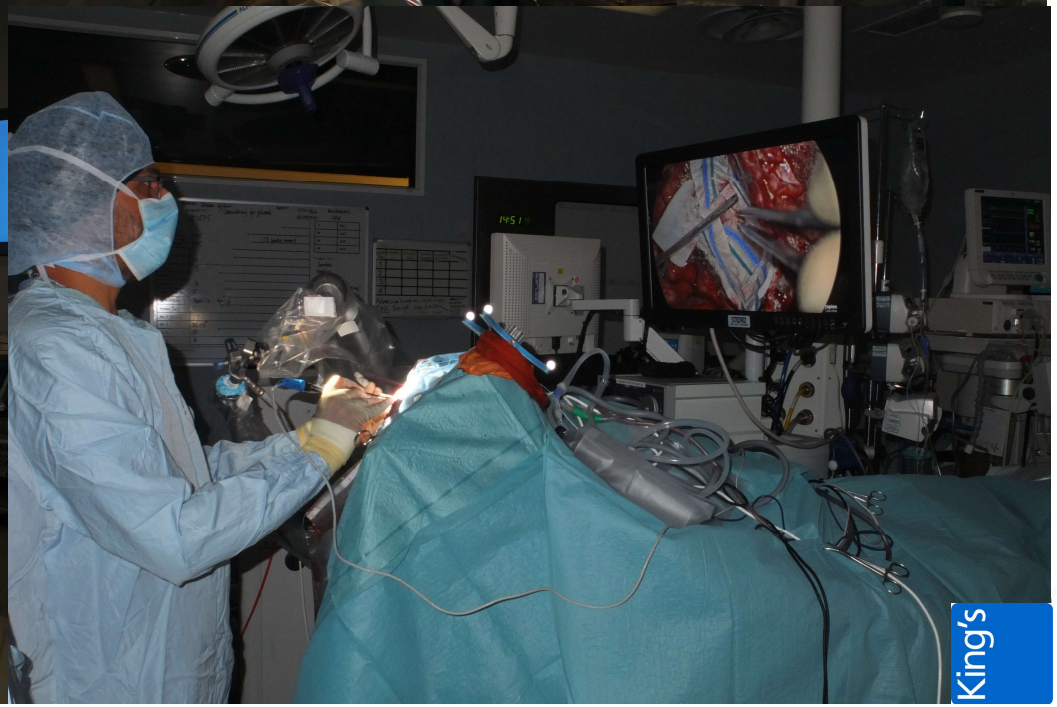
First European Clinical Experience with a

3D High-Definition Exoscope System for Microneurosurgery


STORZ
Baxter
ConMed
33
33

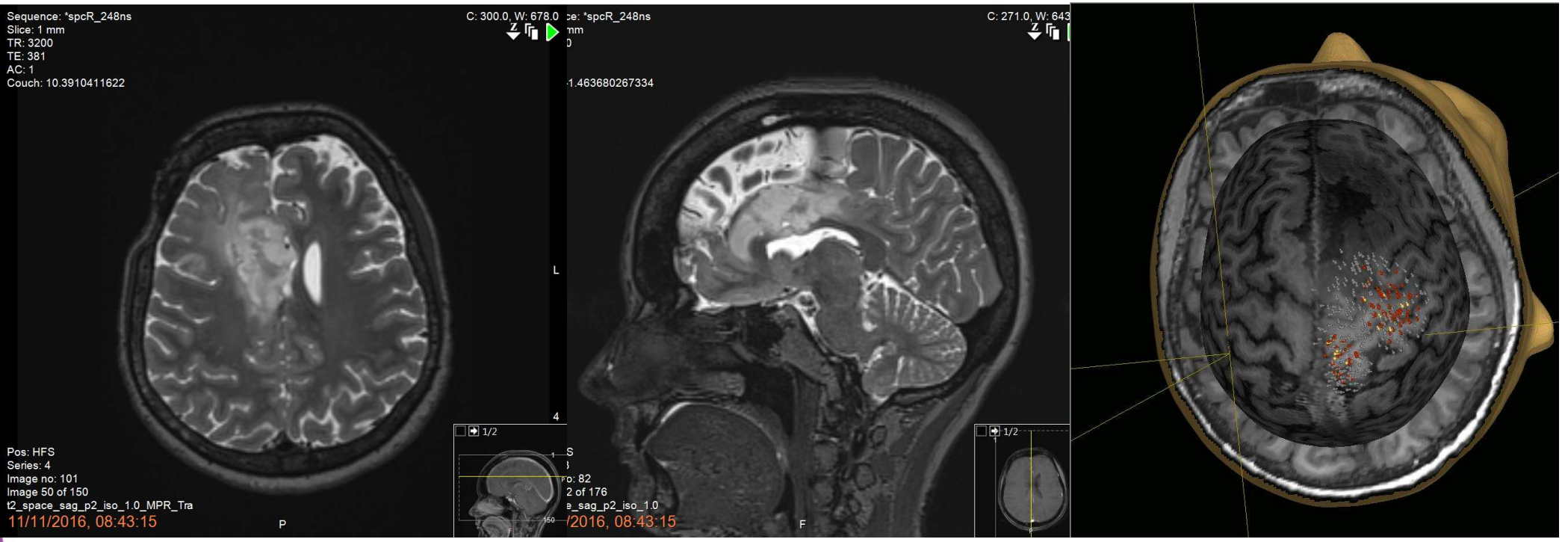
EXOSCOPE INTRAOPERATIVE SETTING





Aleep-Awake-Asleep Right SMA/Cingulum Low Grade

Anatomy – Functional networks – Mapping – Neuronav+TMS



- Known oligodendroglioma grade II
- Epilepsy

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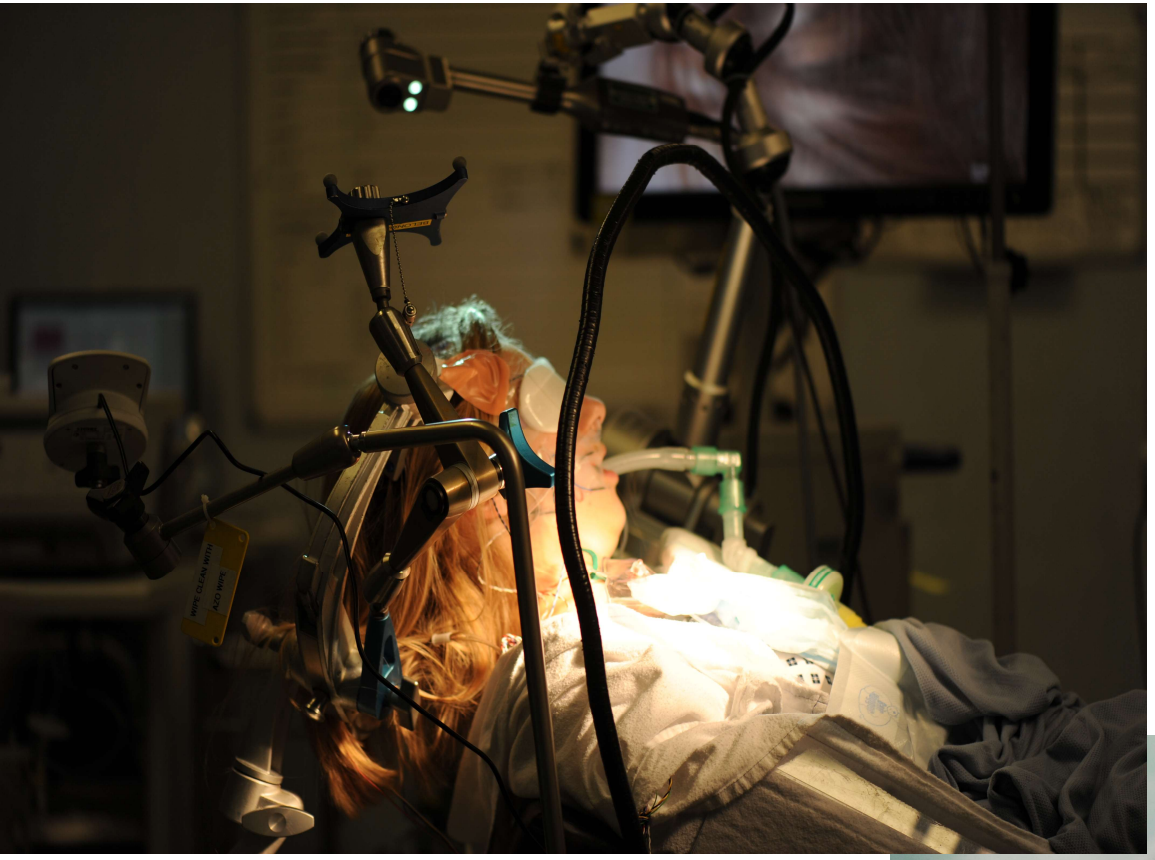

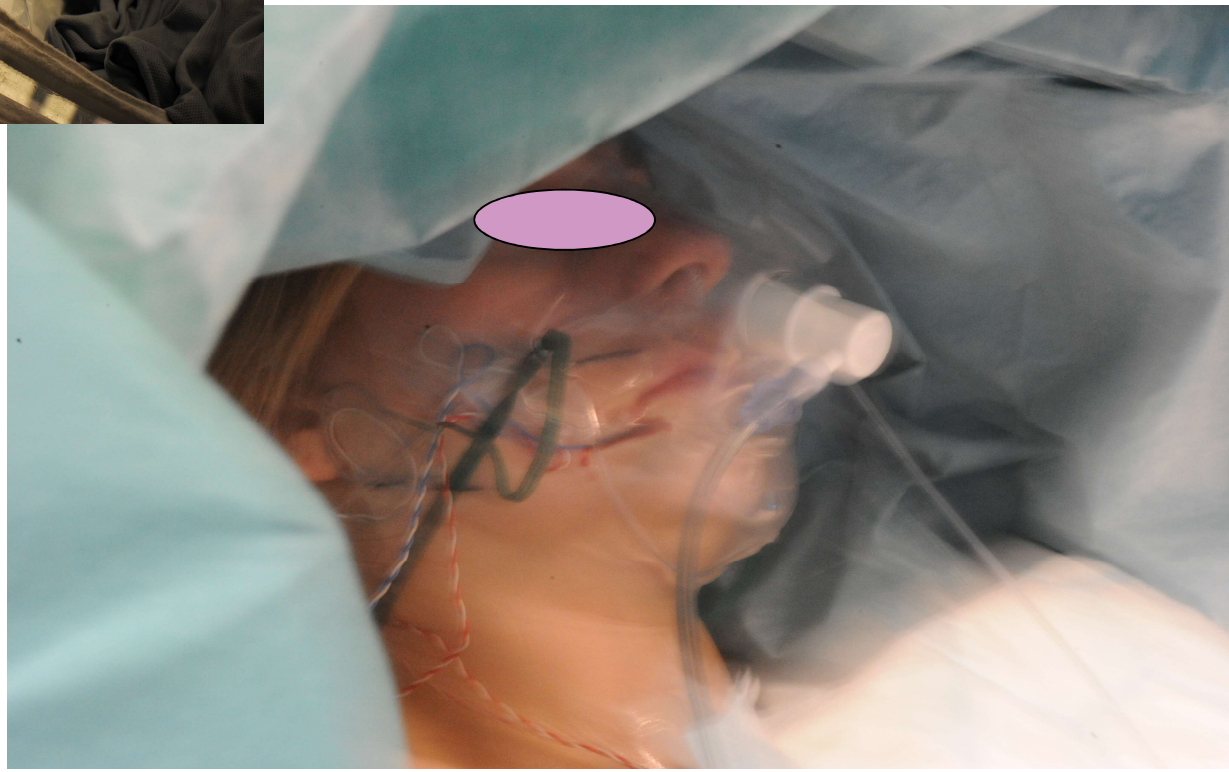

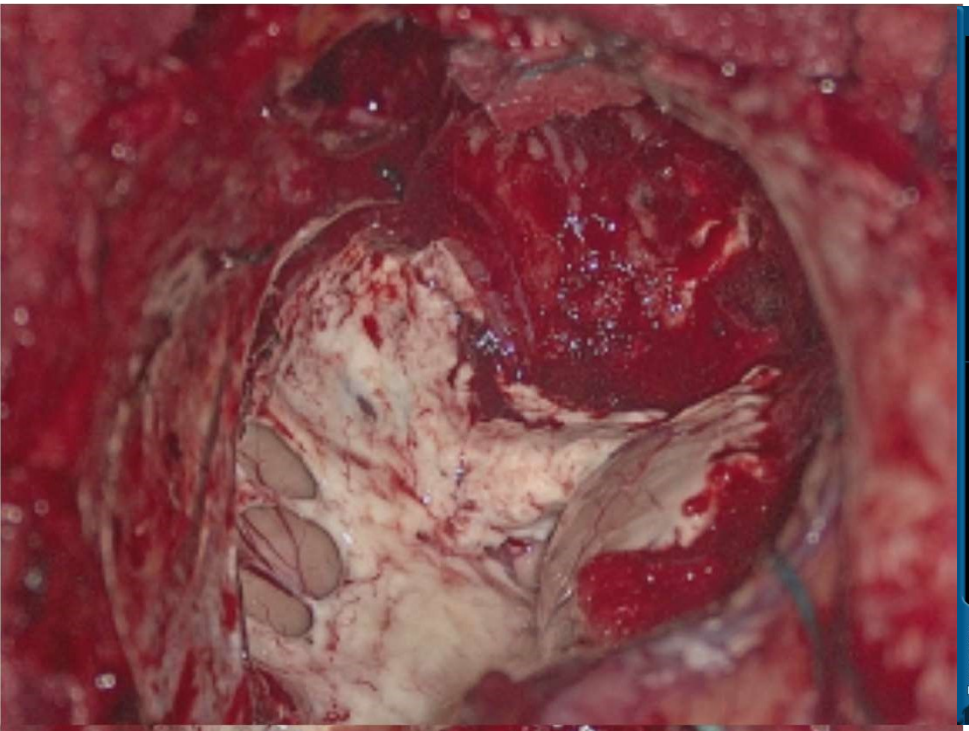

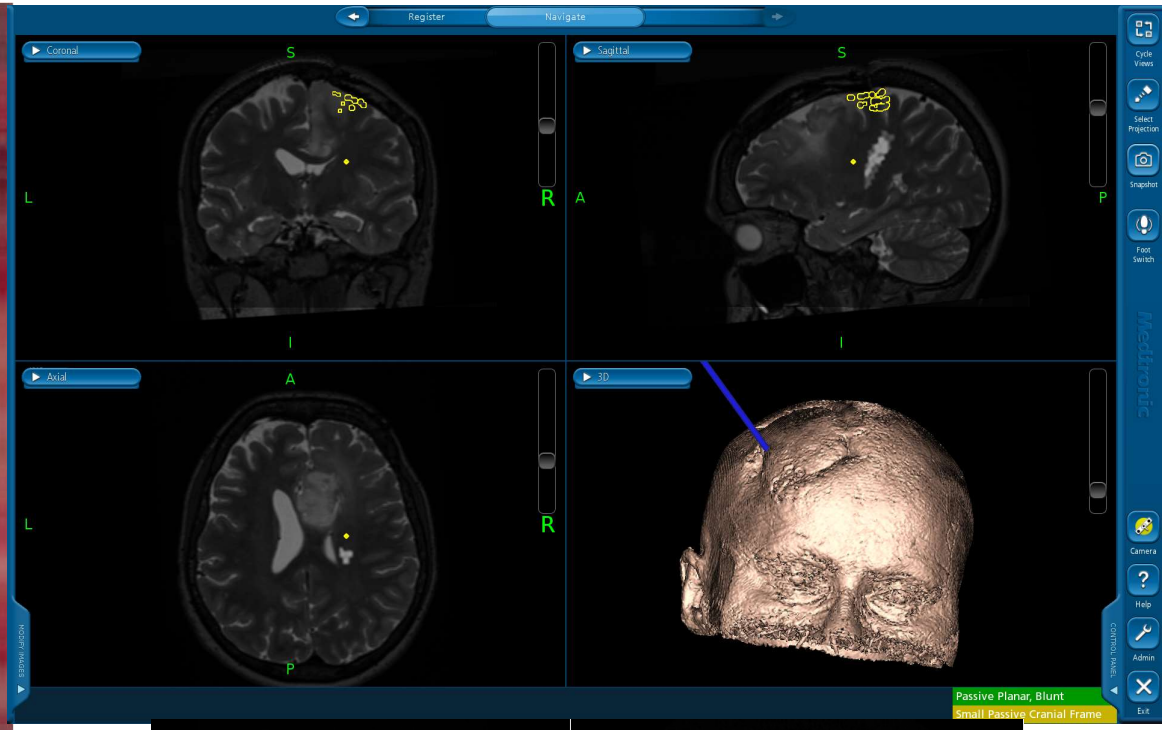
Register
Navigate
Coronal
Sagittal
Axial
3D
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L
R
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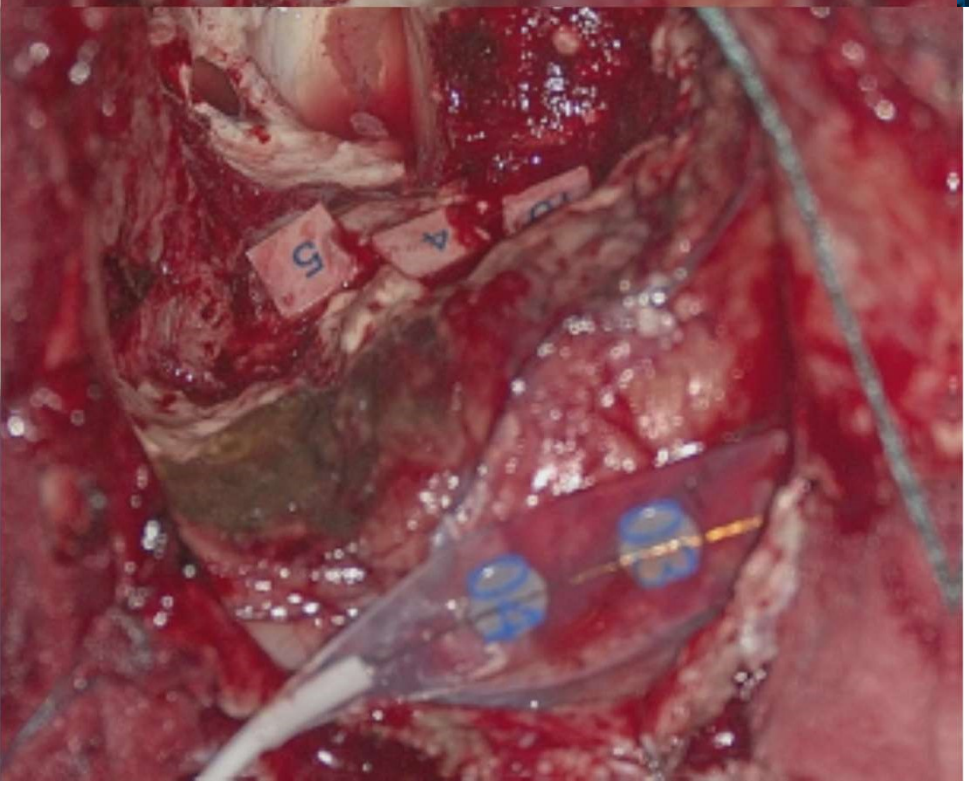
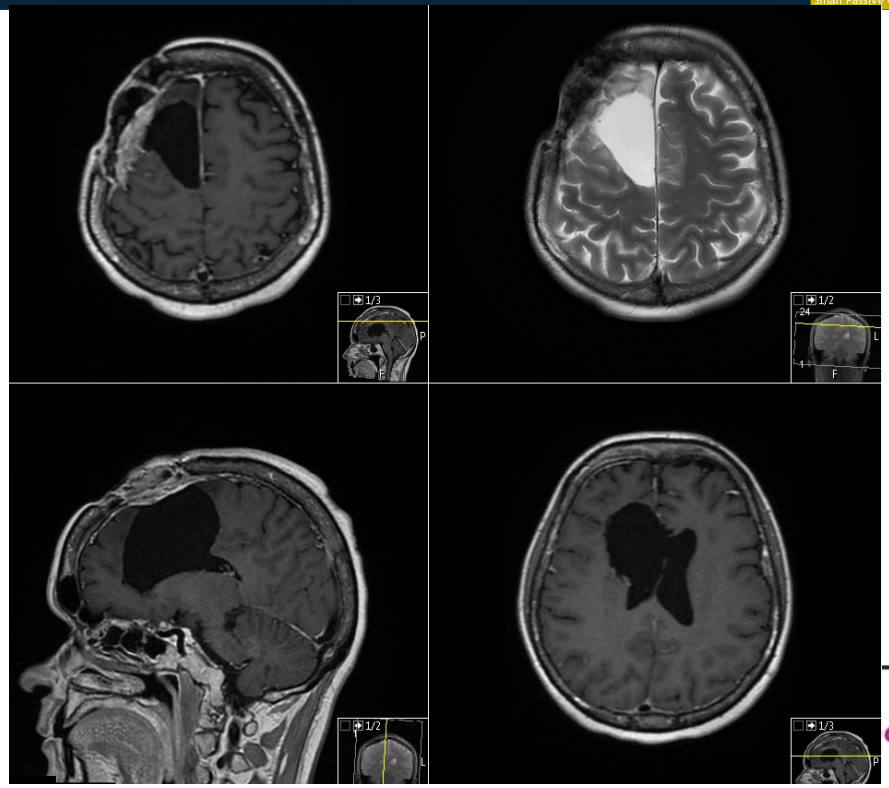
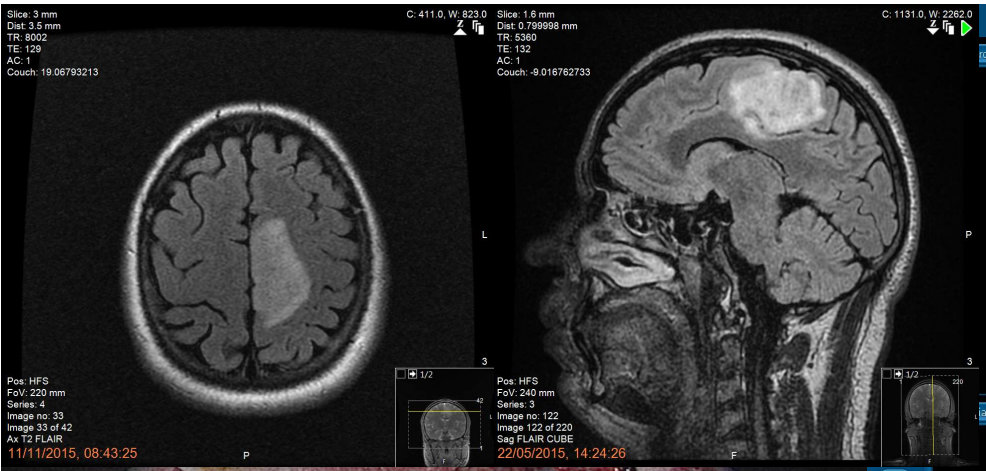
P
I
Passive Planar, Blunt
Small Passive Cranial Frame

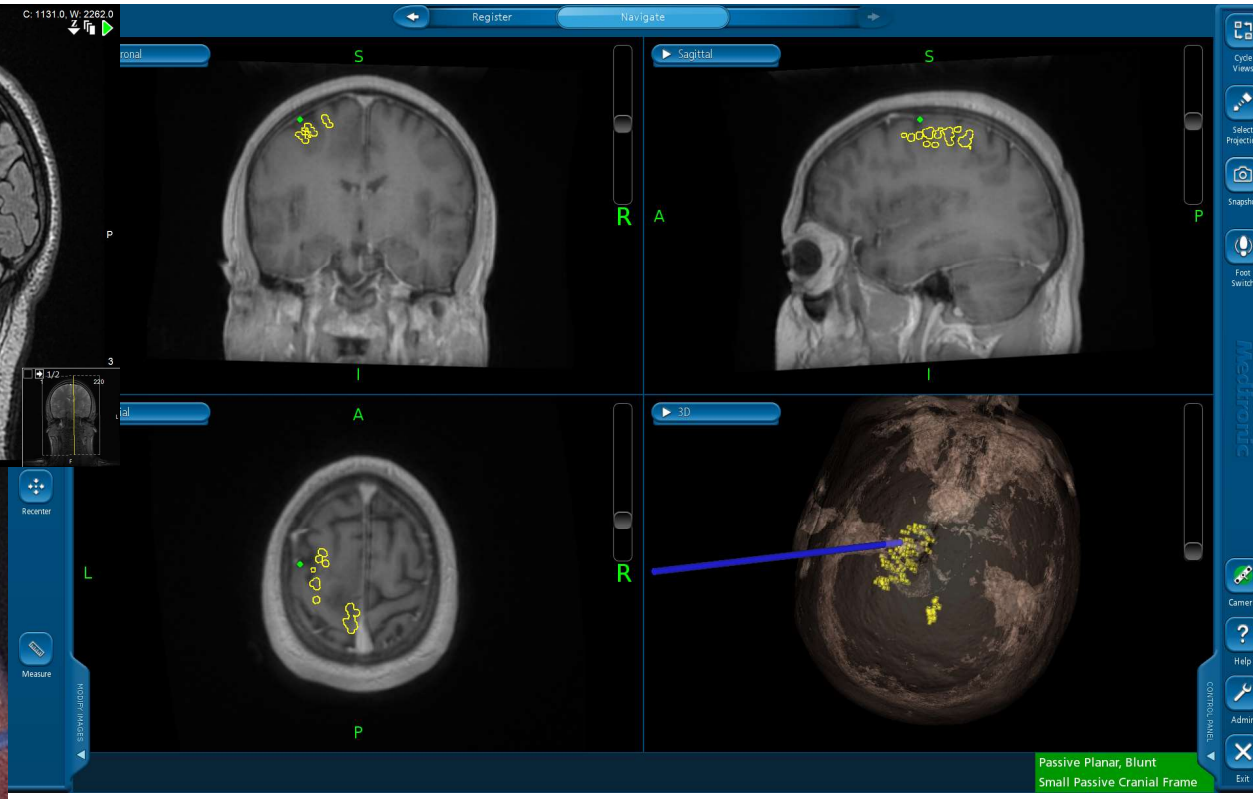


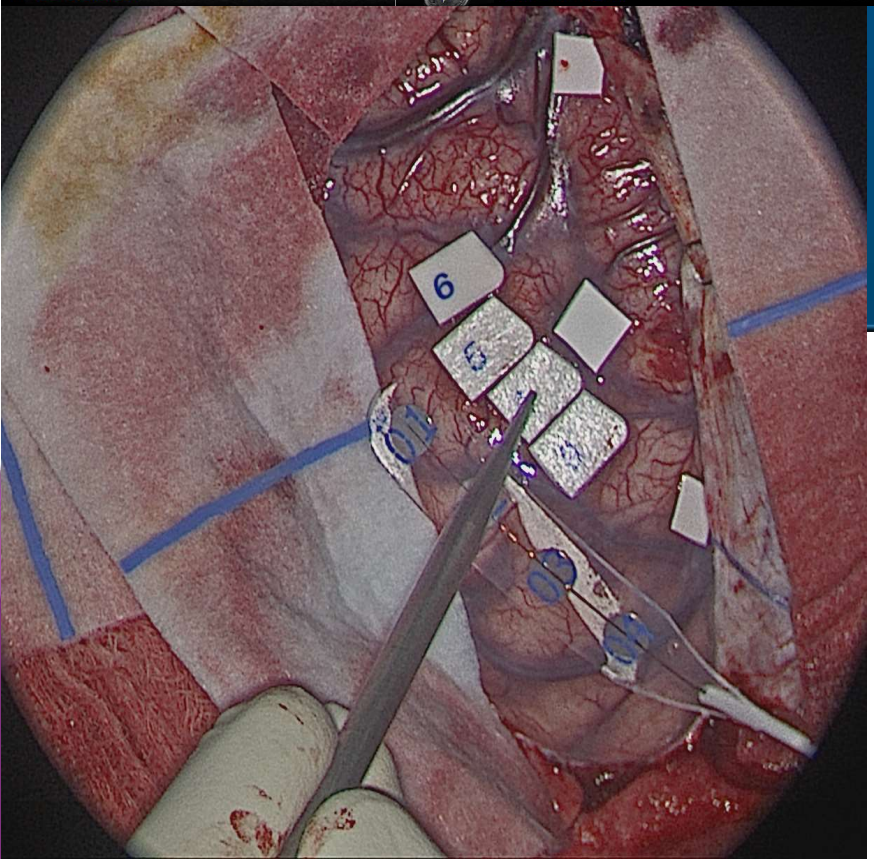


Aleep-Awake-Asleep Left SMA/Cingulum Low Grade

Anatomy – Functional networks – Mapping – Neuronav+TMS







Left: Tag 4 - cortical stimulation eliciting hand and forearm response at 8 mA
White tags: tumour boundaries

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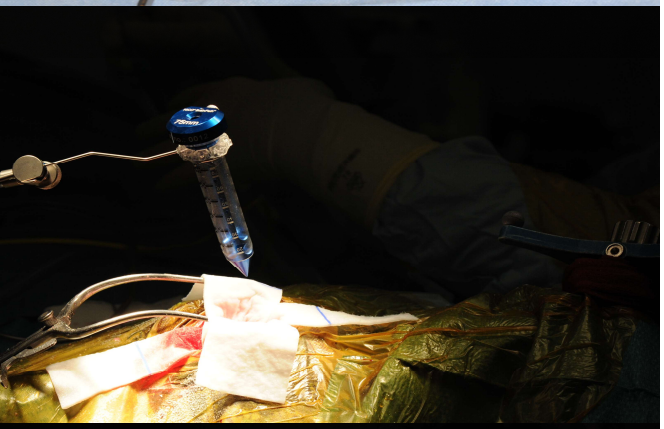
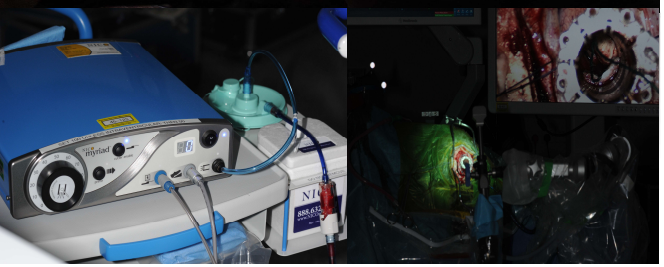
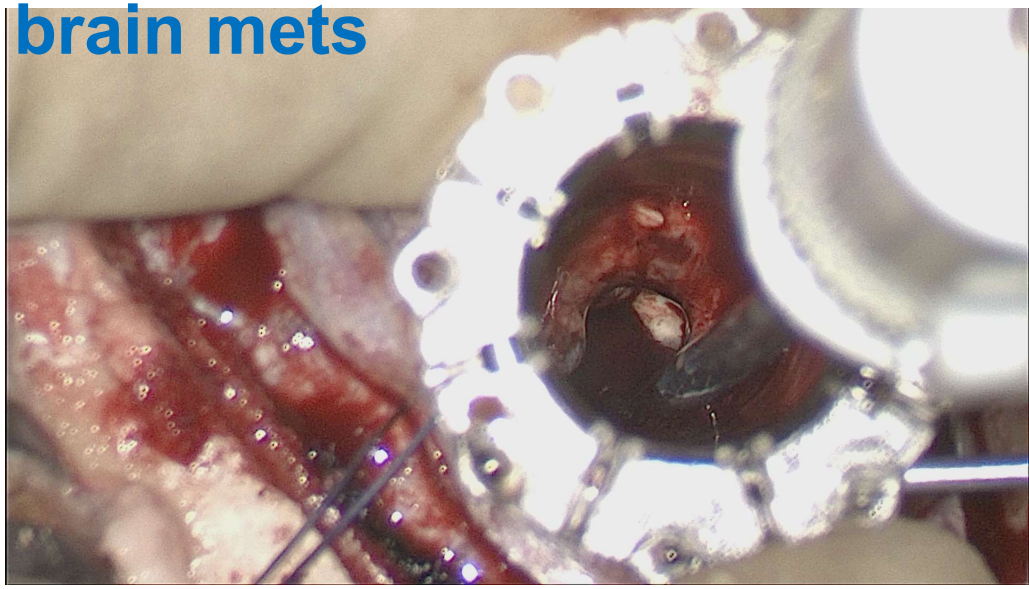
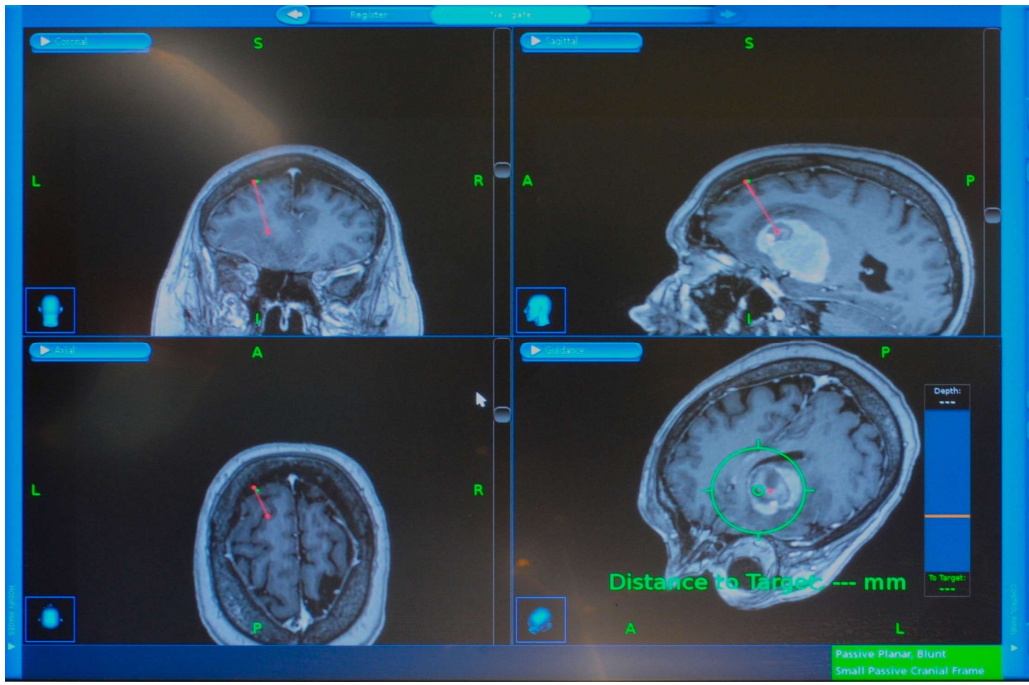
Exoscope + NICO + Brain Path

Deep seated brain mets









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King's Neuro-oncology Team

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- K Ashkan
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- V Hurwitz
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- C Kennedy
- J La

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- L Brazil
- A Swampillai
- C Cikurel
- G Finnerty

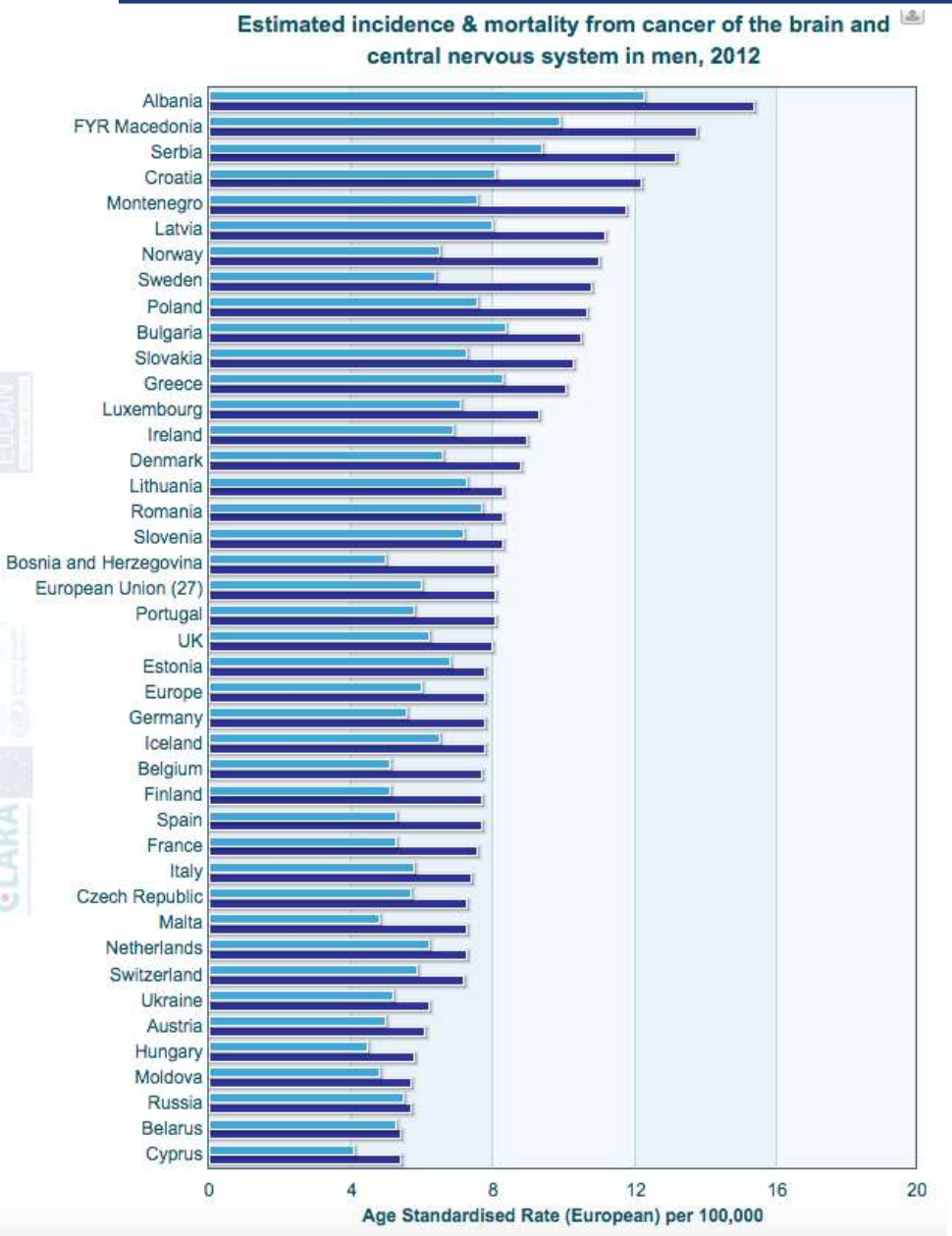
Therapists

- SLT/OT/Physio

International Agency for Research on Cancer
World Health Organization

EUCAN
http://eco.iarc.fr/eucan

Languages: Français | English



Country	Incidence		Mortality		Prevalence		
	Number	Rate	Number	Rate	1-year	3-year	5-year
Europe	30715	7.8	24551	6.0	12543	26574	34861

Brain and CNS Tumours Europe

30.715 new cases
24.551 deaths per year

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Low Grade and High Grade Gliomas

- Difficult to treat due to their propensity to infiltrate deep into surrounding parenchyma

- An increasing body of evidence suggests **that extent of surgical resection affect**
  - **both overall and progression-free survival**
  - **Time to malignant transformation**
  - **Seizure control**

- Predictive of patient outcome:
  - **Extent of resection**
  - Age
  - Tumour histology
  - Molecular Markers (1p19q Co-deletion, IDH status, MGMT Meth, ATRX Mut)

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Low Grade and High Grade Gliomas

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  - **Extent of resection**
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Low Grade

An Evidence Based Approach

- Since 1990, 25 studies are in favor of extent of resection to improve OS and PFS
- Mean survival benefit from 61.1 to 90 months with maximal resection

Table 1 Summary of literature on extent of resection in low-grade (WHO grade II) glioma

Overall survival	Non-volumetric studies	No. patients	Volumetric studies	No. patients
Benefit	North et al. [16]	77	van Veelen et al. [25]	75
	Philippon et al. [18]	179	Claus et al. [9]	156
	Rajan et al. [19]	82	Smith et al. [23]	216
	Leighton et al. [15]	167	Sanai and Berger [20]	104
	Nakamura et al. [4]	88	Incekara et al. [11]	128
	Yeh et al. [27]	93	Hollon et al. [10]	109
	McGirt et al. [53]	170	Snyder et al. [24]	93
	Ahmadi et al. [155]	130		
	Chaichana et al. [156]	191		
	Jakola et al. [28]	153		
	Lote et al. [3]	379		
	Nicolato et al. [5]	76		
	Scerrati et al. [6]	131		
	Ito et al. [12]	89		
	Karim et al. [14]	311		
	Peraud et al. [17]	75		
	Shaw et al. [21]	203		
	Shibamoto et al. [22]	178		
No benefit	Whitton and Bloom [26]	88	None to date	
	Bauman et al. [8]	401		
	Johannesen et al. [13]	993		

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Gross Total Resection impacts natural history of low-grade gliomas

- Malignant transformation ranges between 4 and 29 months
- 45% of WHO grade II undergo anaplastic tranformation in 5 years

- If resection > 90%
  - Median time to progression: 5.5 years
  - Median time to malignant transformation: 10.1 years
  - 5yy survival rates is 97% (vs 76% if extent of resection <90%)

Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, Tihan T, Vandenberg S, McDermott MW, Berger MS (2008) Role of extent of resection in the long-term outcome of low- grade hemispheric gliomas. J Clin Oncol 26:1338–1345

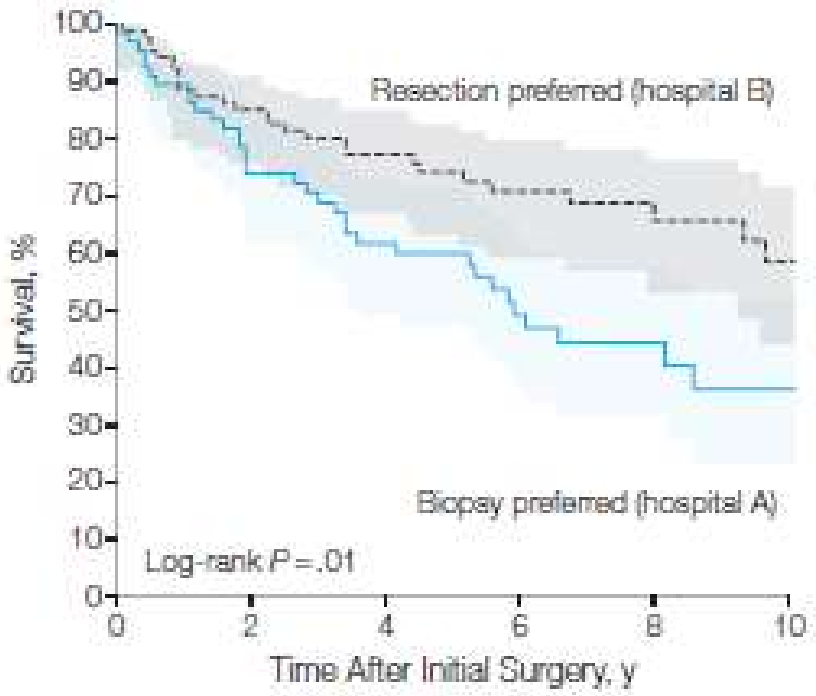
Low Grade

An Evidence Based Approach

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



- Population-based natural history study
- 153 pt, 2 hospitals serving two different regions
- Treatment dependent on residential address
- **A) Biopsy + Watchful waiting**
  - **MS 5,9 yy**
  - **5 year survival: 60%**
- **B) Maximal safe resection**
  - **No reach of MS by the end of the study**
  - **5 year survival: 74%**

Jakola et al. JAMA, 2012

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Incidentally discovered low-grade surgical resection

- In favor
  - Pallud J, Fontaine D, Duffau H, Mandonnet E, Sanai N, Tail- landier L, Peruzzi P, Guillevin R, Bauchet L, Bernier V, Baron MH, Guyotat J, Capelle L (2010) Natural history of incidental World Health Organization grade II gliomas. Ann Neurol 68:727–73330.
  - Potts MB, Smith JS, Molinaro AM, Berger MS (2012) Natural history and surgical management of incidentally discovered low- grade gliomas. J Neurosurg 116:365–372
- Due to:
  - Identifying gliomas of smaller size has a greater likelihood of gross-total resection
  - **Perioperative seizures 0-3%** de Oliveira Lima GL, Duffau H (2015) J Neurosurg 122:1397–1405

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Low Grade gliomas
Seizure control impacts quality of life

- Seizure free patients:
  - 43% Subtotal lesionectomy
  - 79% Gross-total resection
  - 87% Lesionectomy + hyppocampectomy/neocortical resection

Ruda R, Bello L, Duffau H, Soffietti R (2012) Seizures in low- grade gliomas: natural history, pathogenesis, and outcome after treatments. Neuro Oncol 14(Suppl 4):iv55–6435.

Englot DJ, Han SJ, Berger MS, Barbaro NM, Chang EF (2012) Extent of surgical resection predicts seizure freedom in low- grade temporal lobe brain tumors. Neurosurgery 70:921–928

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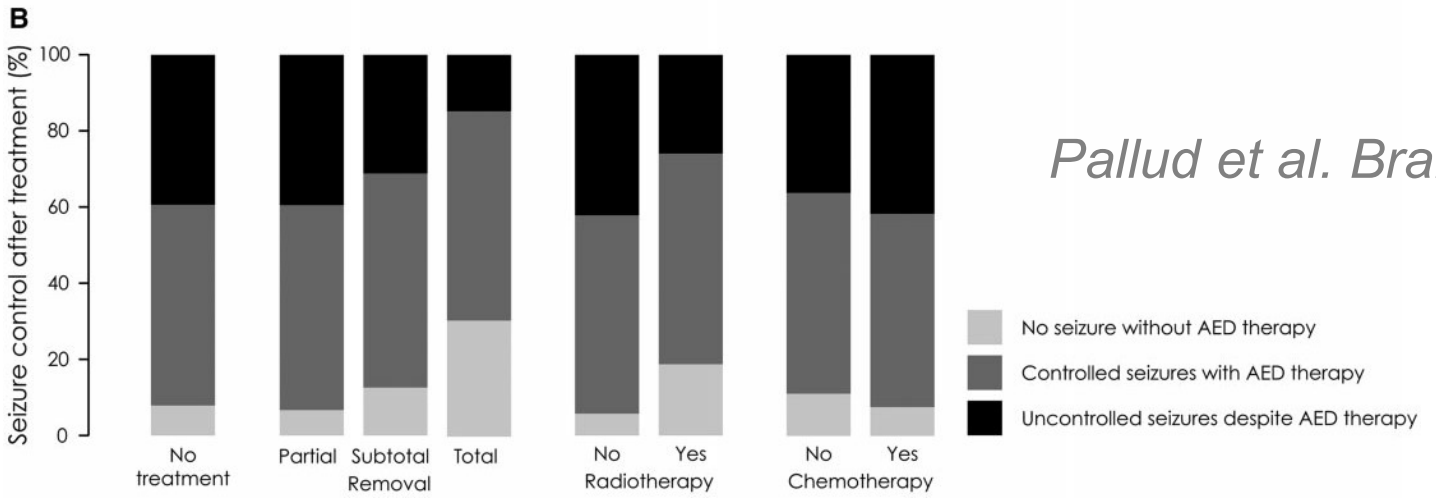
Low Grade gliomas

BRAIN
A JOURNAL OF NEUROLOGY

Epileptic seizures in diffuse low-grade gliomas in adults



Pallud et al. Brain, 2014

Patient age ($P \leq 0.001$), subtotal ($P = 0.007$) and total ($P \leq 0.001$) 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.

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High Grade gliomas

An Evidence Based Approach

J Neurooncol (2016) 130:269–282

Overall survival	Non-volumetric studies	No. patients	Volumetric studies	No. patients
Benefit	Vecht et al. [68]	243	Keles et al. [48]	107
	Shibamoto et al. [64]	135	Lacroix et al. [2]	416
	Curran et al. [41]	103	Pope et al. [59]	110
	Simpson et al. [65]	645	Keles et al. [49]	102
	Dinapoli et al. [42]	346	Sanai et al. [62]	500
	Jeremic et al. [47]	86	Oppenlander et al. [56]	170
	Nitta and Sato [54]	101		
	Barker et al. [37]	222		
	Buckner et al. [40]	275		
	Lamborn et al. [51]	832		
	Brown et al. [39]	124		
	Ushio et al. [67]	105		
	Stark et al. [66]	267		
	Nomiya et al. [55]	170		
	Stummer et al. [148]	243		
	McGirt et al. [53]	949		
	Oszvald et al. [57]	146		
No benefit	Hollerhage et al. [45]	118	None to date	
	Phillips et al. [58]	173		
	Sandberg-Wollheim et al. [63]	171		
	Prados et al. [60]	357		
	Duncan et al. [43]	235		
	Huber et al. [46]	163		
	Kowalczuk et al. [50]	75		
	Levin et al. [52]	92		
	Puduvalli et al. [61]	106		
	Tortosa et al. [157]	95		
	Oszvald et al. [57]	215		

- 33 publications
- Extent of resection improves TTP and OS

➢ After gross total resection
  - ➢ WHO grade III OS 64.9-75.2 m
  - ➢ WHO grade IV OS 11.3-18.5 m

Recurrent GBM benefits from gross total resection (selection bias)

➢ 19m total vs 15. for subtotal

Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, Berger MS, Parsa AT (2012) Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg 117:1032–1038

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Brain Metastases

An Evidence Based Approach

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	23	KPS≥70, age≥18	All	3.5	52	1.8
	WBRT + surgery	25			9.2	20	8.8
					$p<0.01$	$p<0.02$	$p<0.005$
Vecht *et al.* 1993 [8]	WBRT	31	WHO PS≤2, age≥18	Most	6	NR	3.5
	WBRT + surgery	32			10		7.5
					$p=0.04$		$p=0.06$
Mintz *et al.* 1996 [6]	WBRT	43	KPS≥50, age<80	All	6.3	NR	NR
	WBRT + surgery	41			5.6		
					$p=0.24$		

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

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

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

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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

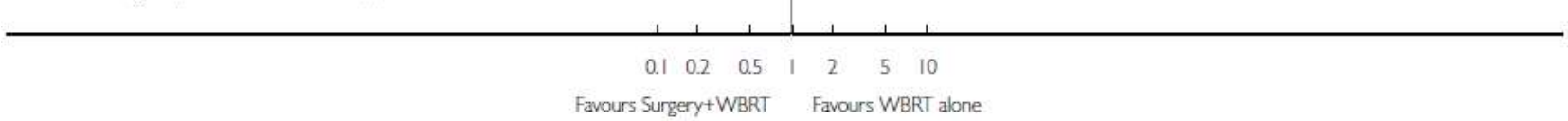
Outcome: 1 Survival

Study or subgroup	log [Survival HR] (SE)	Survival HR IV,Random,95% CI	Weight	Survival HR IV,Random,95% CI
Patchell 1990	-0.82 (0.31)		32.3 %	0.44 [0.24, 0.81]
Vecht 1993	-0.57 (0.33)		31.4 %	0.57 [0.30, 1.08]
Mintz 1996	0.33 (0.21)		36.3 %	1.39 [0.92, 2.10]
Total (95% CI)			**100.0 %**	**0.72 [0.34, 1.55]**

Heterogeneity: $Tau^2 = 0.37$; $Chi^2 = 11.52$, df = 2 (P = 0.003); $I^2 = 83\%$

Test for overall effect: Z = 0.83 (P = 0.40)

Test for subgroup differences: Not applicable



Hart MG, et al. 2014 (revised edition)

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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

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Intracranial Dermoid and Epidermoid tumours

Value of surgery

- 1-2% of all intracranial tumours. Congenital, slow-growing
- Develop between 3rd and 5th weeks of gestation from ectodermal remnants during neural tube formation
- ”Pearly tumours” (Cruveilhier)
- “The most beautiful tumours of the body (Dandy)

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Intracranial Dermoid and Epidermoid tumours

Value of surgery

Authors/years	Nº cases	MORT. (%)	GTR. (%)	REC. (%)	F/U (years)
Berguer *et al.*[3]/1985	13	0	0	7.6	4.6
Sabin *et al.*[24]/1987	20	5	5	10	6
De Souza *et al.*[7]/1989	30	3.7	18	14.8	9
Rubin *et al.*[21]/1989	7	0	57	0	4.6
Yamakawa *et al.*[33]/1989	15	6.6	47	20	8
Yasargil *et al.*[34]/1989	43	0	95.4	0	5.2
Lunardi *et al.*[16]/1990	17	12	35	17.6	9
Gormley *et al.*[10]/1994	32	5	42	26	N/A
Vinchon *et al.*[32]/1995	9	22.2	0	N/A	3
Samii *et al.*[26]/1996	40	2.5	75	7.5	5.7
Mohanty *et al.*[17]/1996	25	8	48	0	3.5
Talacchi *et al.*[29]/1998	28	3.5	57	30	8.6
Kobata *et al.*[15]/2002	30	0	56.7	6.6	11.4
Chowdhury *et al.*[4]/2013	23	4.3	73.9	N/A	3
Kato *et al.*[13]/2013	27	5	10	20	N/A

MORT: Mortality, GTR: Gross total removal, REC: Recurrence, F/U: Follow/up, N/A: Not available

Contemporary surgical series on dermoid and epidermoid tumors (IDETs)

Preventing aseptic meningitis:

- Tumor capsule excision
- Copious irrigation
- Dexamethasone

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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".

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

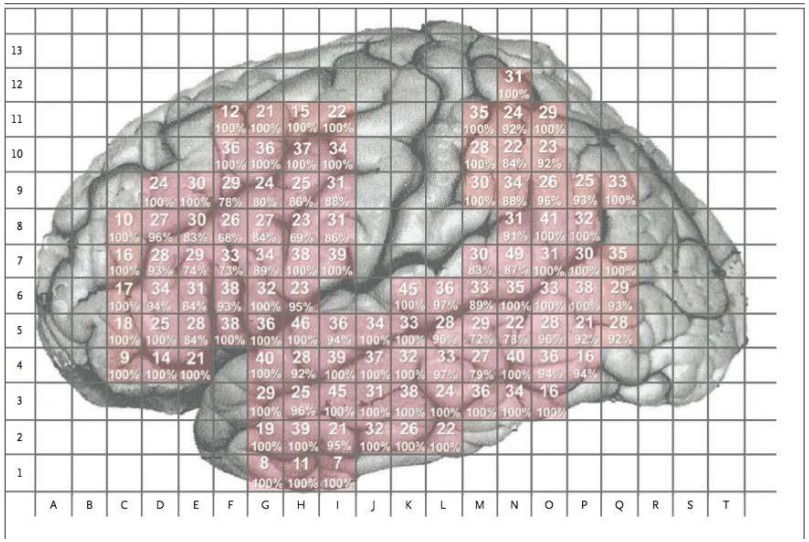
Functional Outcome after Language Mapping for Glioma Resection

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

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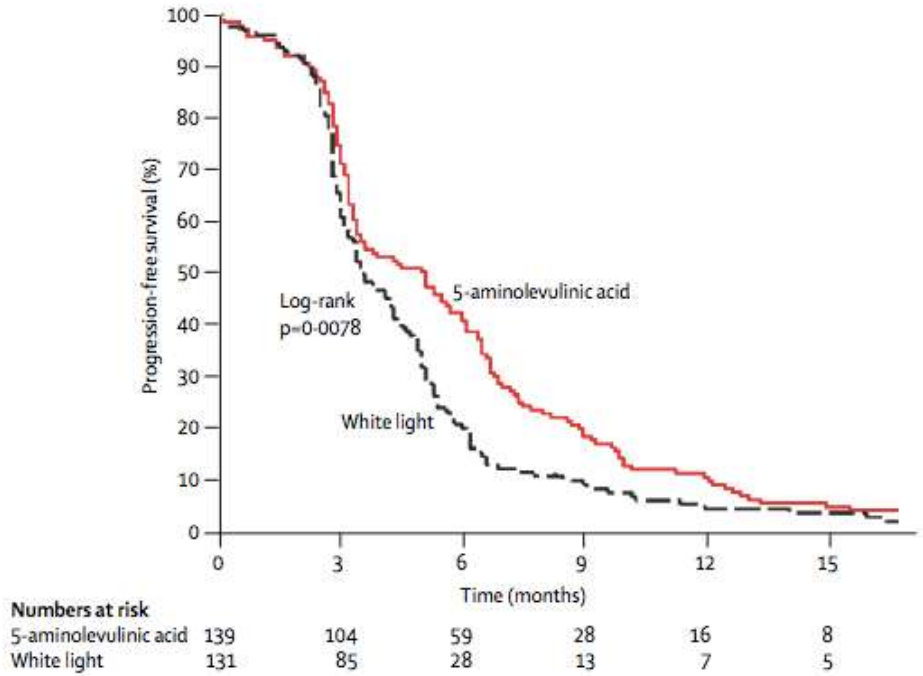
Lancet Oncol 2006; 7: 392–401

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)



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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

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

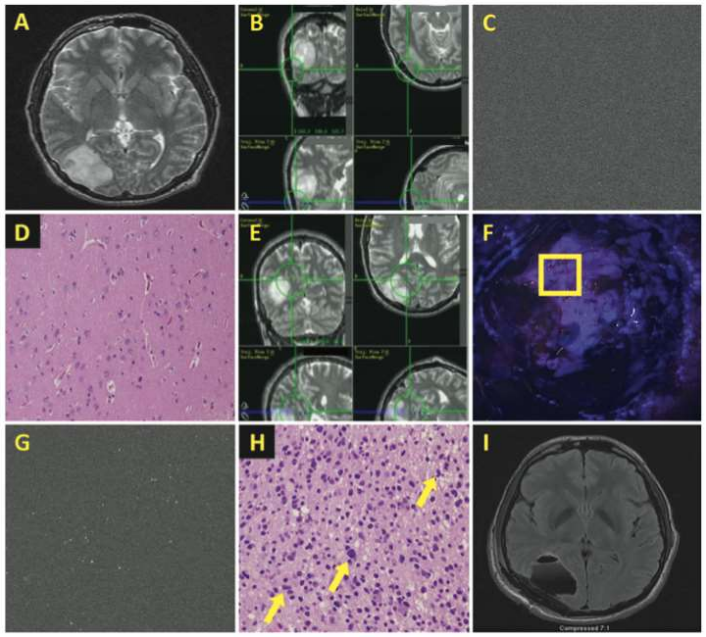
J Neurosurg 115:740–748, 2011

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.

Ongoing BALANCE trial

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Radiotherapy – Preparing the patient for treatment

G. Pesce

Radiation Oncology

Oncology Institute of Southern Switzerland

Bellinzona and Lugano - Switzerland

ESTRO Teaching Course on

Management of Brain Tumors

Vienna, October 22-24, 2017

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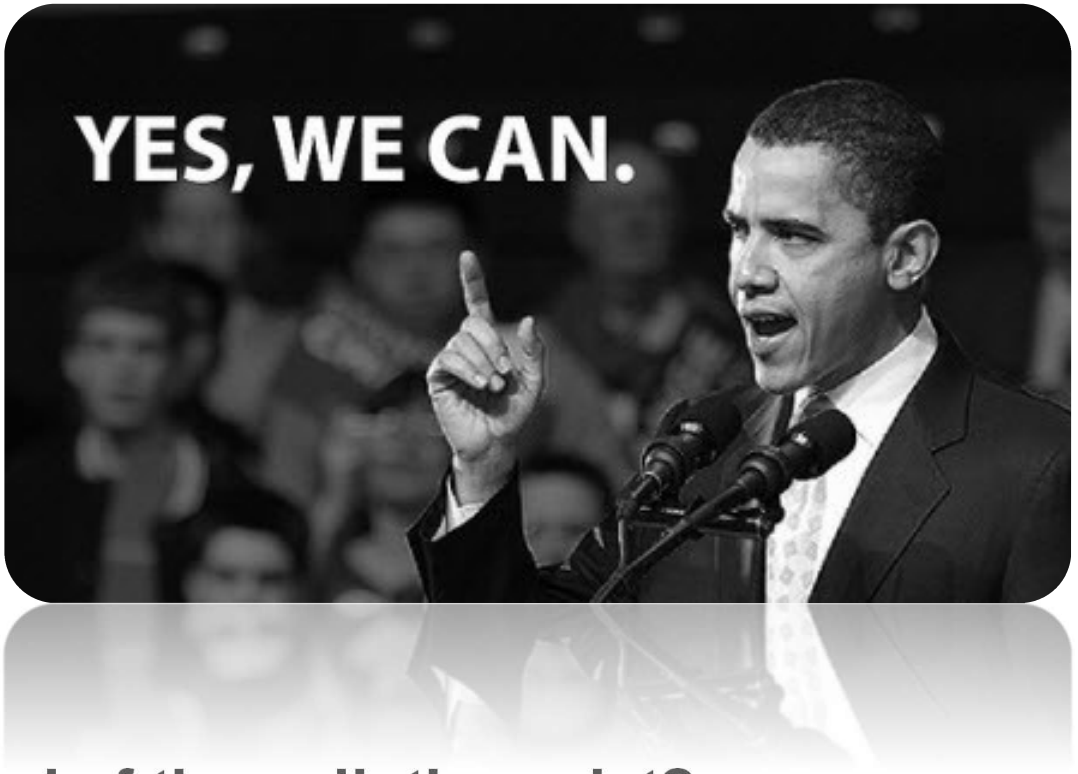

- **What is the real goal of the radiotherapist?**
  - **Achive Local Control**
  - **Reduce toxicity**
  - **Improve Survival**
  - **Maintain Quality of Life**

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Team Work in neuro-oncology

1. *Surgery: improved cure rate and reduced morbidity*
   1. *microsurgery*
   2. *intraoperative monitoring (function and tumor/healthy tissue dicrimination)*

2. *Radiotherapy: improved cure rate and reduced toxicity*
   1. *Treatment accuracy (target vs OAR)*
   2. *Curative dose increase*
   3. *Combination with drugs*
   4. *Possibility of repeated treatments*

3. *Medical therapy: better specificity,bioavailability, improved tolerance*
   1. *chemotherapy*
   2. *targeted agents*

Facing the patient

- Create a comfortable ambience
- Warrant a proficient team
- Iformed consent, take enough time for explanation of the positioning process (mask e.g.)
- Show examples, images, visit the CT simulator, and the treating room, when needed
- Many patients suffer from deficits and may need written information

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Radiotherapy – Preparing the patient for treatment

- Diagnostic accuracy
- Simulation and positioning
- Contouring
- Planning (Beam setting, Dose calculation, DVH evaluation, etc.)
- Image guidance

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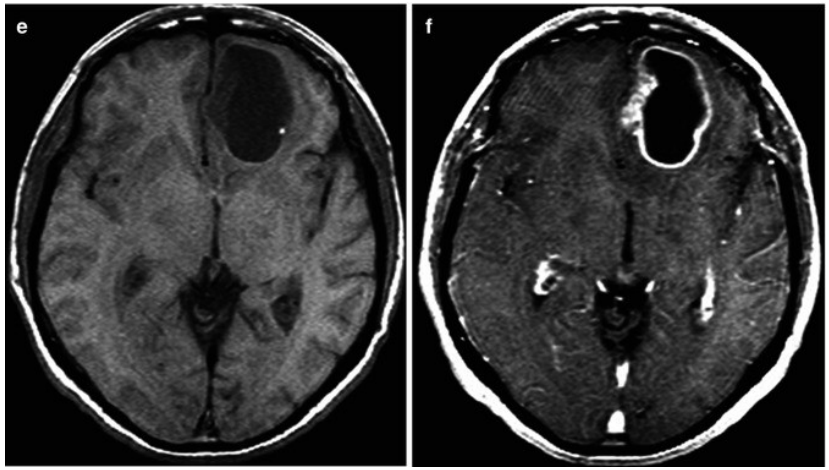
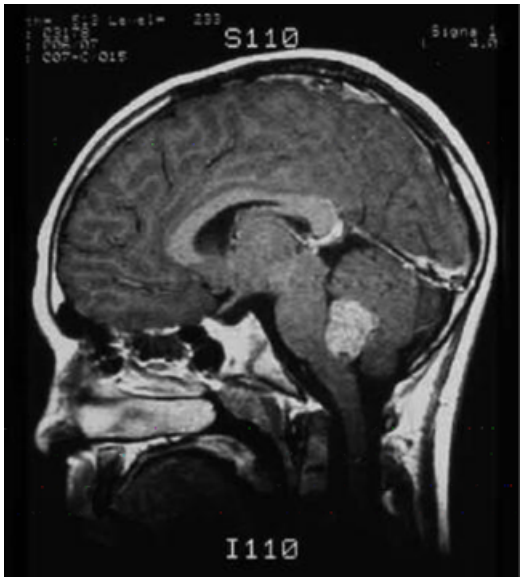
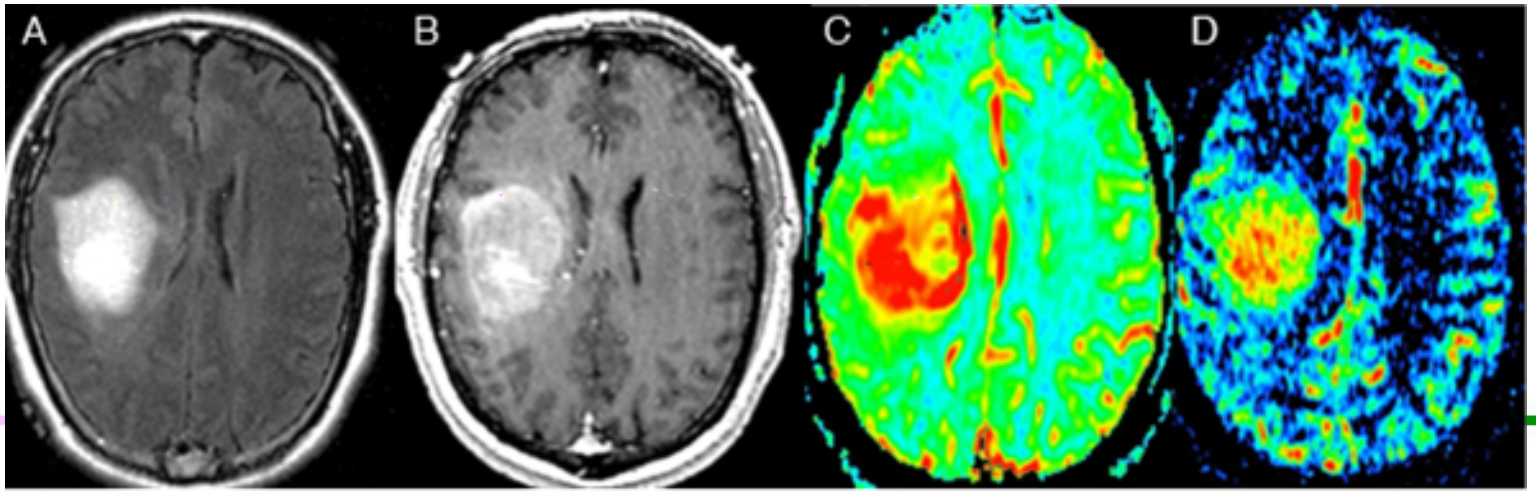
Diagnosis

- Clinical diagnosis should be appropriately tailored within the context of the patient's disease
  - Primary
  - Metastatic disease
  - Setting: is it an emergency *or may be planned*
- Relevant hystologic definition
  - Is a biopsy requested?
    Is surgery indicated before radiotherapy
- Disease extent definition
  - Imaging
  - Lab, etc.

CNS Primary tumors: imaging







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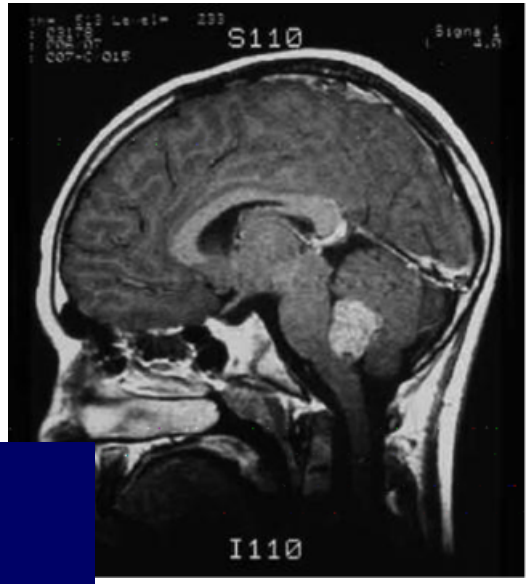
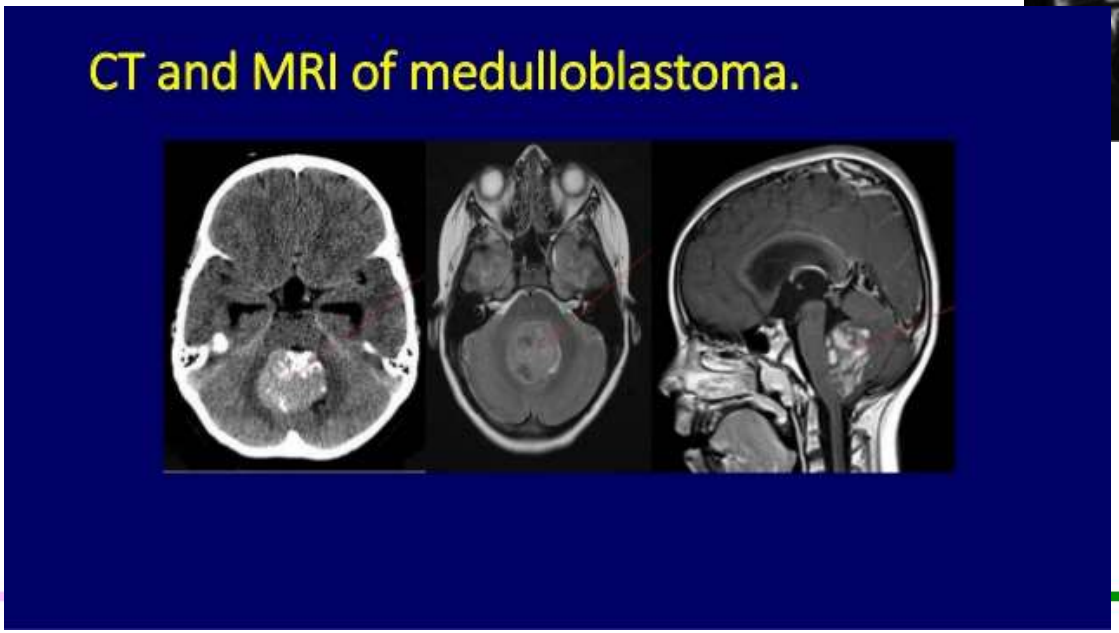
CNS Primary tumors: imaging





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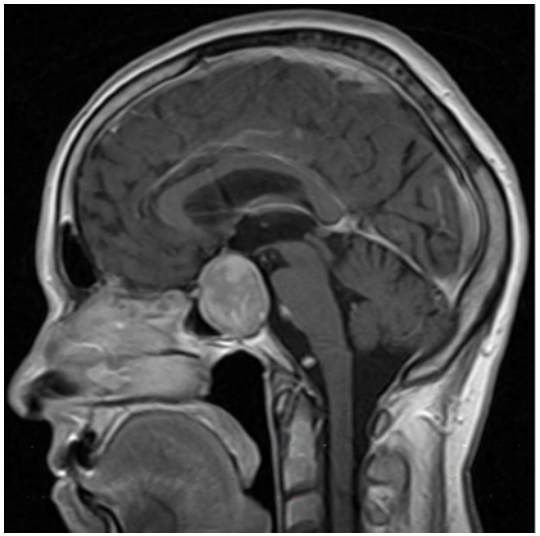
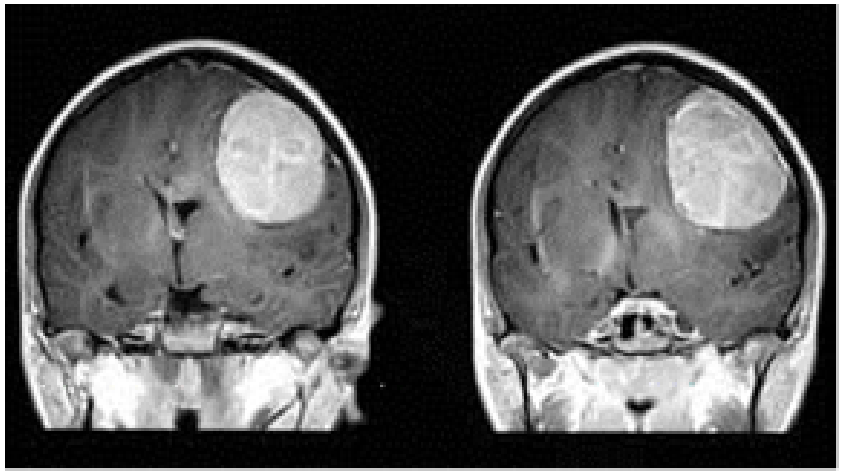
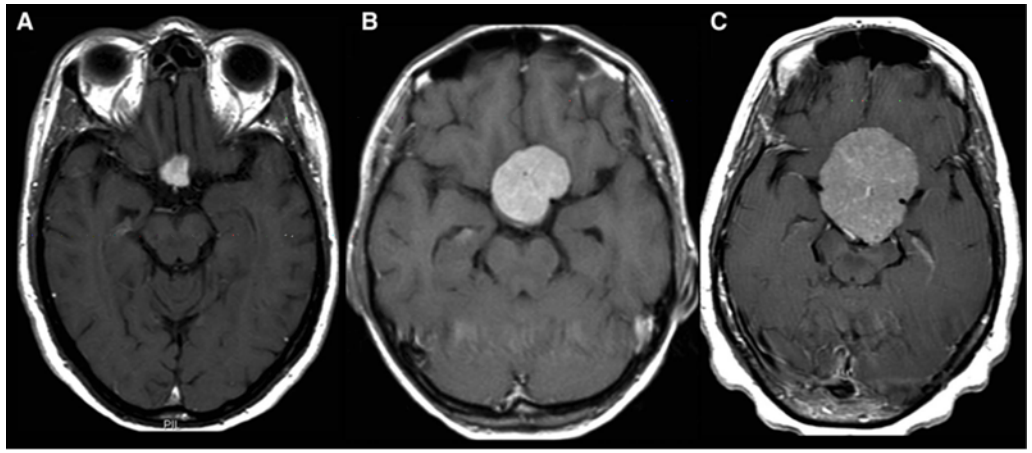
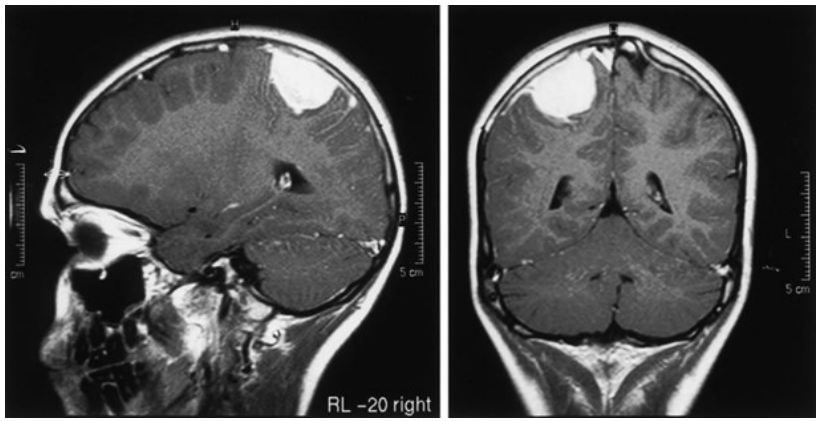
CNS Primary tumors: imaging









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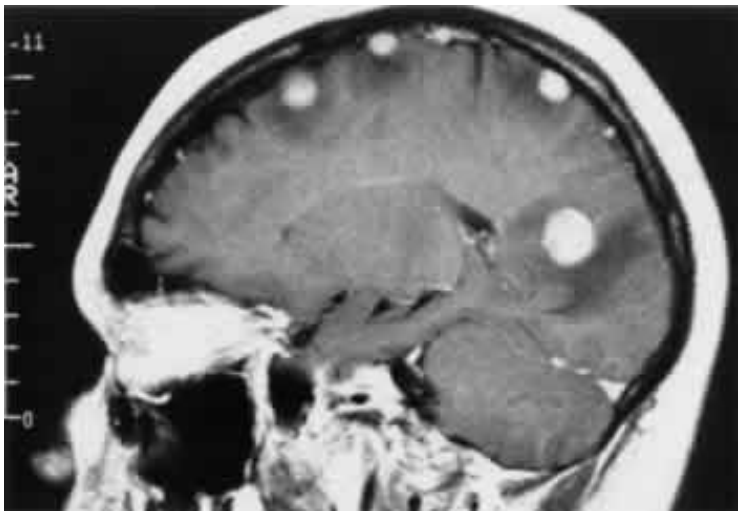
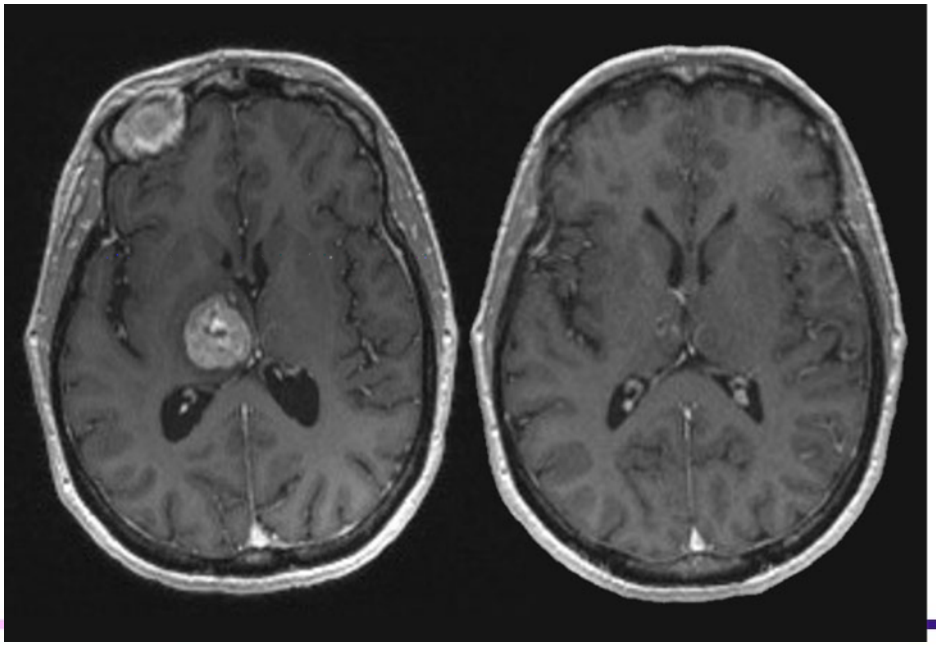
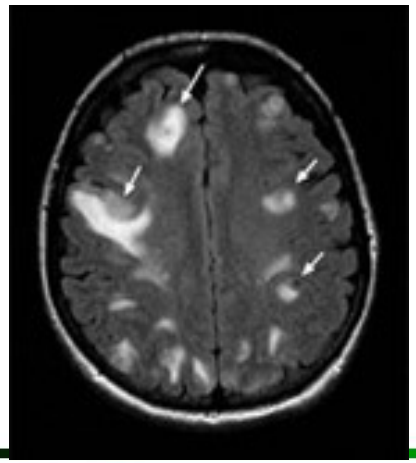
CNS Metastases: imaging







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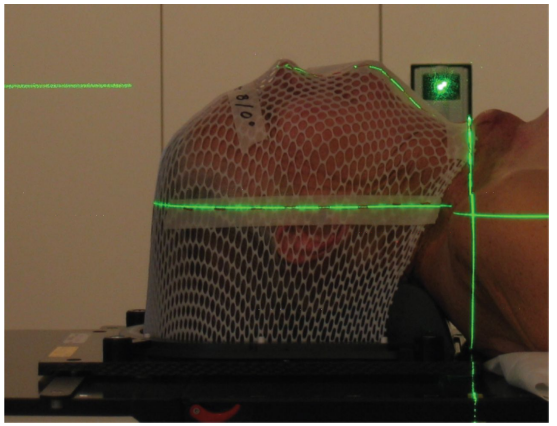
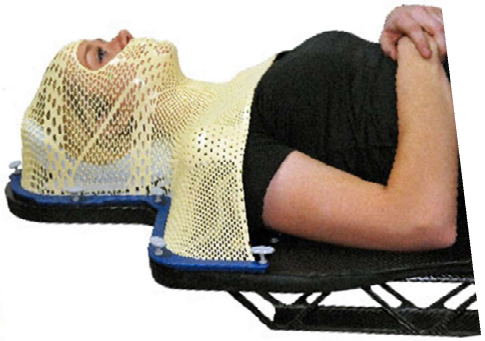
The right position

Immobilisation



- What is the intent of the treatment?
- What is the volume to treat?
- What level of precision do you need?



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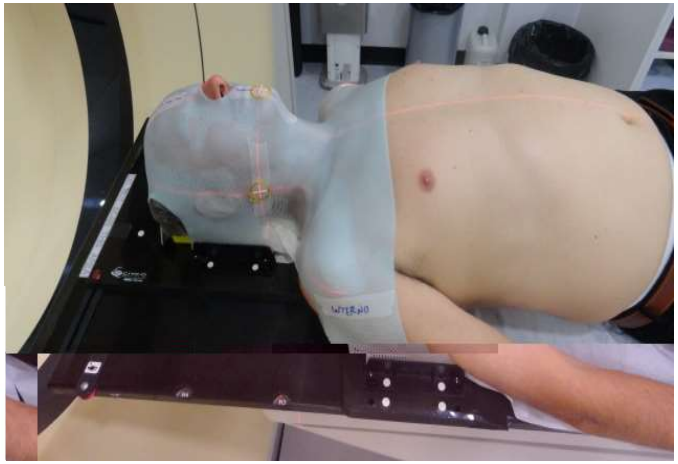
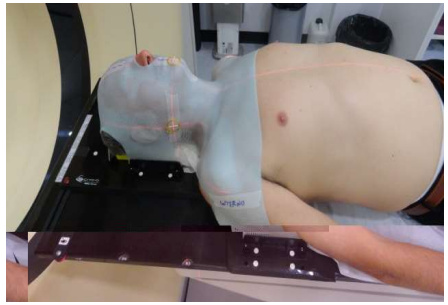
Simulation in treatment position

Virtual simulation



Virtual simulation



Strahlenther Onkol. 2002 Dec;178(12):715-21.

Simulator verification of the accuracy of patient repositioning after virtual simulation. Is physical simulation still needed?

Schüller P[1], Bruns F, Hesselmann S, Horn K, Panke JE, Schuck A, Schäfer U, Micke O, Willich N.

⊕ Author information

Abstract

PURPOSE: To evaluate the frequency and amount of displacements after repositioning a patient on the physical simulator following virtual simulation.

MATERIAL AND METHODS: After laser marking at the CT scanner and virtual simulation, patients were repositioned on the simulator. The isocenter obtained from the calculated table movements was checked by fluoroscopically measuring the distances to standardized anatomic landmarks and comparing them to the treatment plan.

RESULTS: In 86% of patients, displacements were < or = 0.5 cm. There was no significant difference between the supine and prone position, diagnosis categories or CT reconstruction indices. The use of immobilization devices and cranial versus body stem localization did make a significant difference. Rates of exact repositioning were high in brain and head and neck patients and comparatively low in abdominal tumors and breast cancer.

CONCLUSIONS: Immobilization devices play an important role for the precision of radiotherapy. Whenever precise positioning is possible (e. g. with a head mask), virtual simulation alone might be sufficient. Patients with abdominal and breast tumors, were repositioning precision is often suboptimal, might profit from an additional physical simulation.

PMID: 12491060 DOI: 10.1007/s00066-002-1037-1

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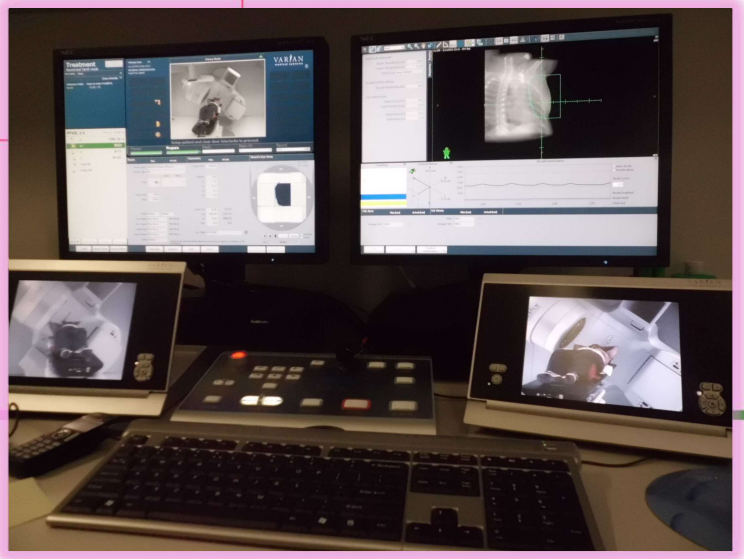
Immobilisation tools

Body

- Lining
- Laser
- Table (robotic 6D, or not)

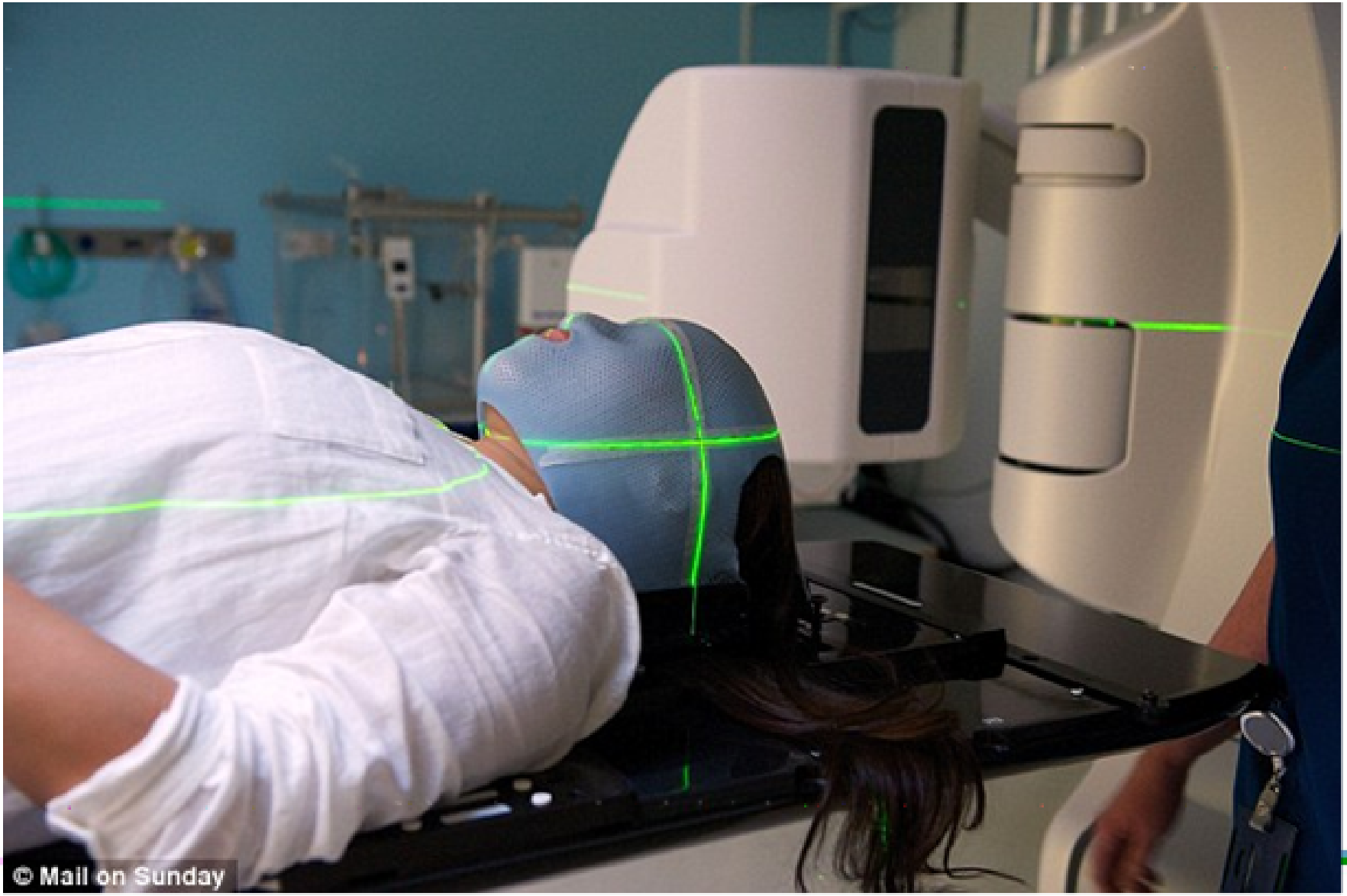
Head

- Mask
- Frame
- pillows



Do Frameless *and Don't* Frame-based

- ***Non-invasive immobilisation***
- Convincing data on Frameless techniques accuracy
- Possibility of dose fractionation
- Patient's Comfort



http://i.dailymail.co.uk/i/pix/2011/12/10/article-0-0F20AFBB00000578-489_634x422.jpg

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Planning

Icru

- Volumes
- Target(s)
- OAR

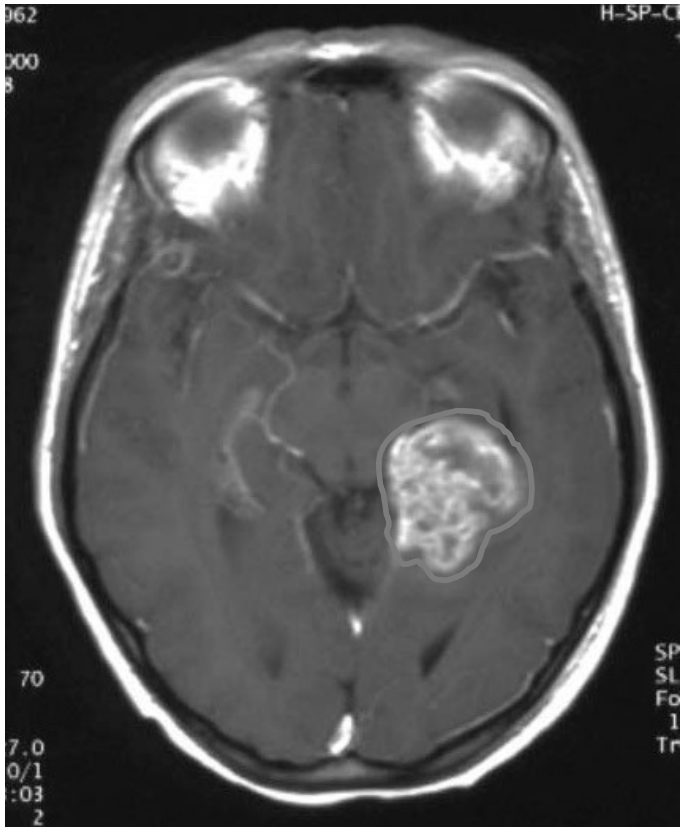
QUANTEC !

Selecting the correct imaging for planning

Disease	Imaging	Sequence, etc.
Lower grade glioma	MRI	T2, FLAIR,
High grade glioma	MRI	T2, FLAIR, T1 gado
Acoustic Neuroma	MRI	T2, FLAIR, CISS (1), DRIVE (1)
Brain Metastases	CT, MRI	c.e., T1 gado
Meningioma	MRI	T1 gado

(1): CISS and DRIVE are useful for cochlaea and other membranous structures
Aminoacid PET and fMRI are investigational

Defining the treatment volume



Conventional conformal radiotherapy of high grade glioma

Courtesy-modified from M. Brada

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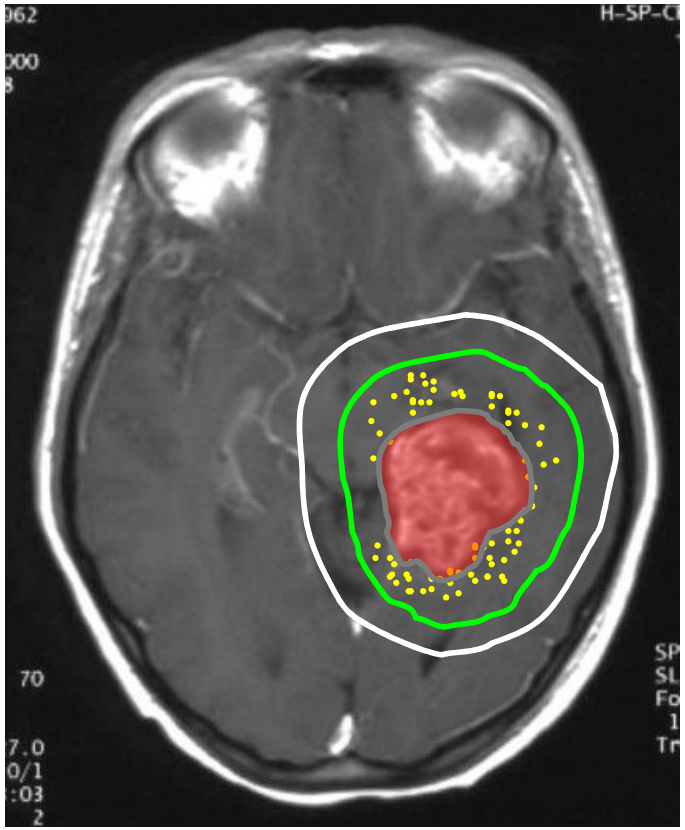
Defining the treatment volume

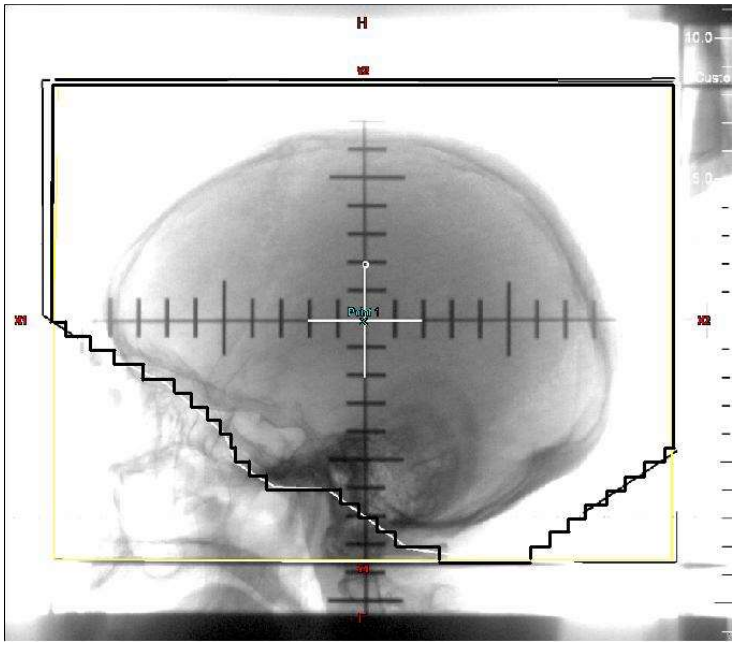


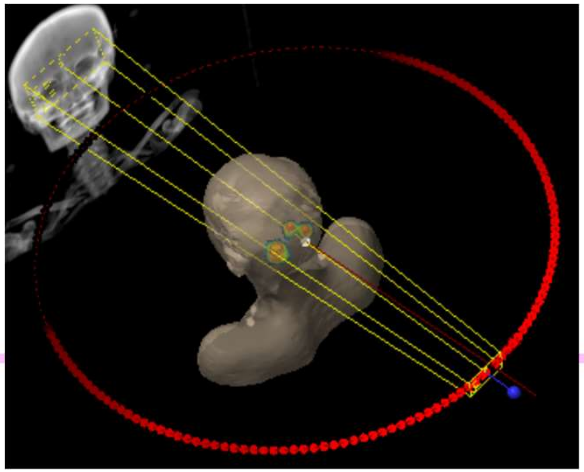
Conventional conformal radiotherapy of high grade glioma

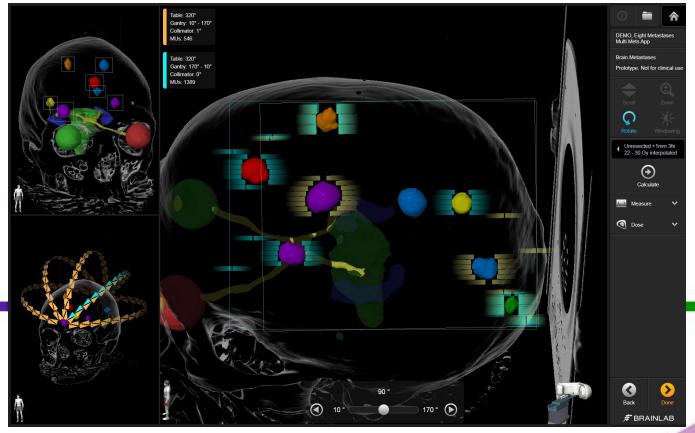
Courtesy-modified from M. Brada

Contouring for brain mets

- WBRT
- WBRT SIB
- SRS
- Multiple BM SRS
- HFSRT







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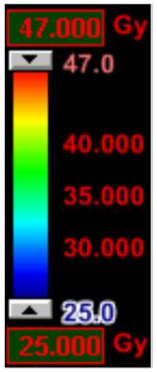
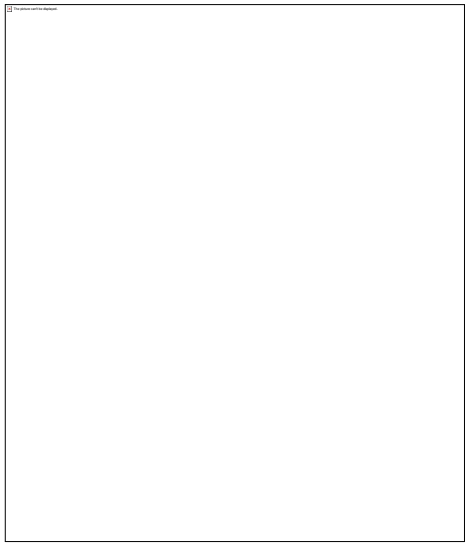
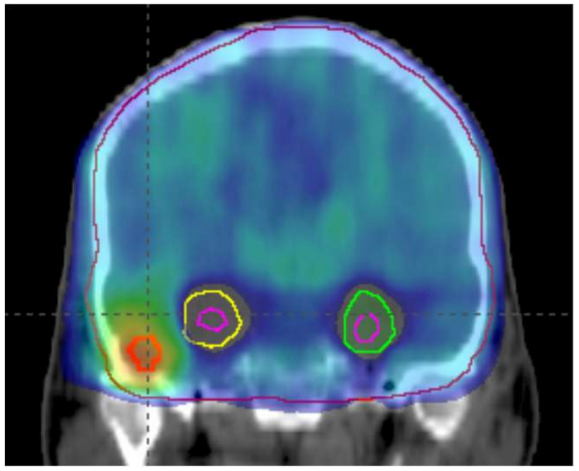
RapidArc: multiple brain mets+WB (3)

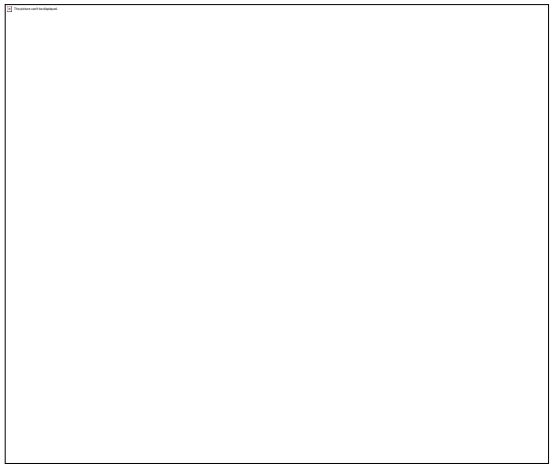
Mets: 15x 3.0 Gy = 45 Gy WB 15 x 2.0 Gy = 30 Gy

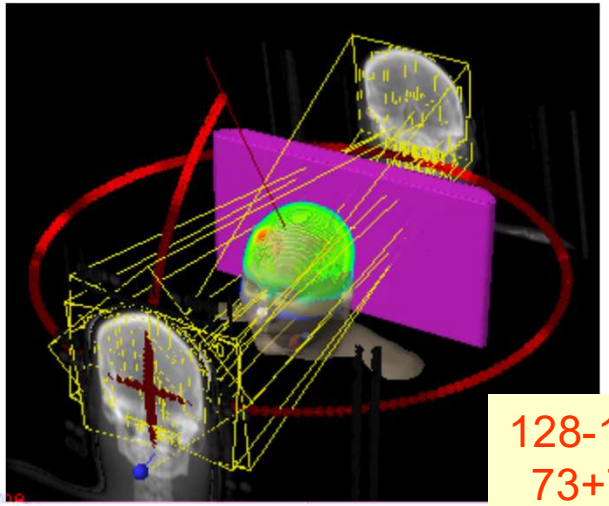
Σ3mets: 35.4 cm³ WB:1730 cm³



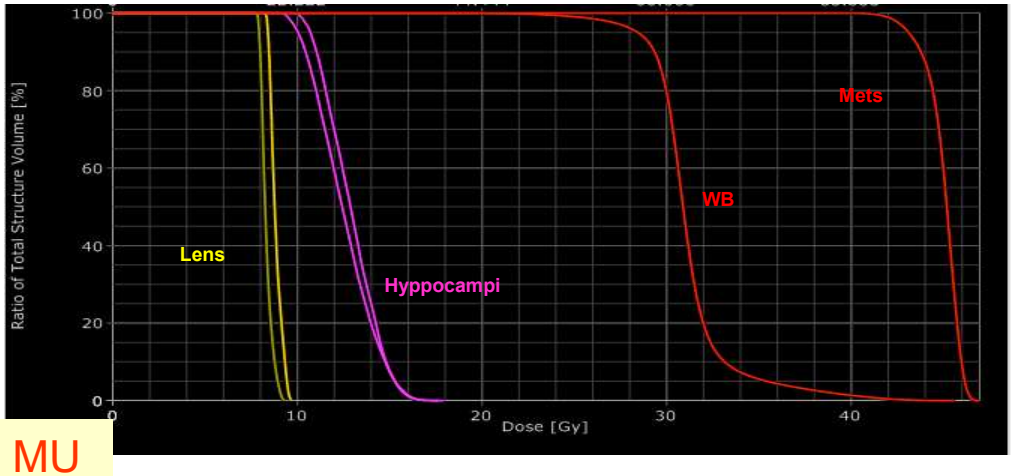








4 isocentric arcs

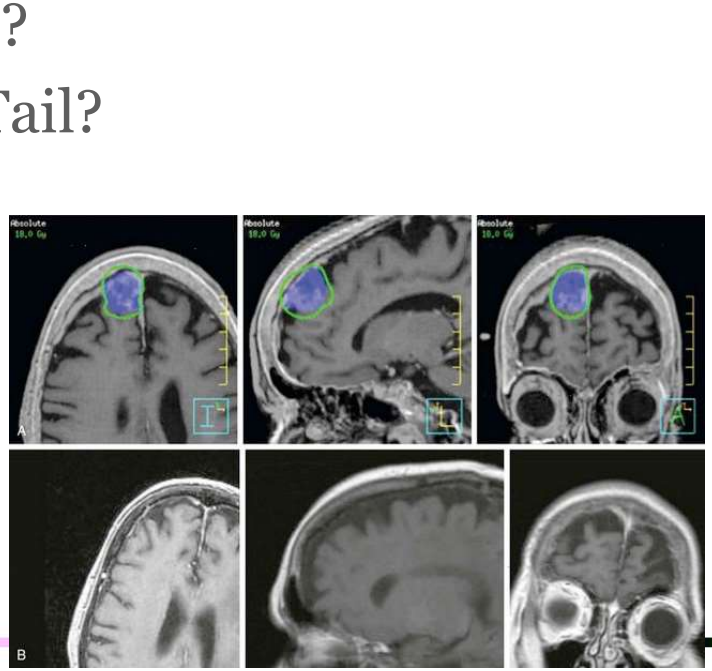


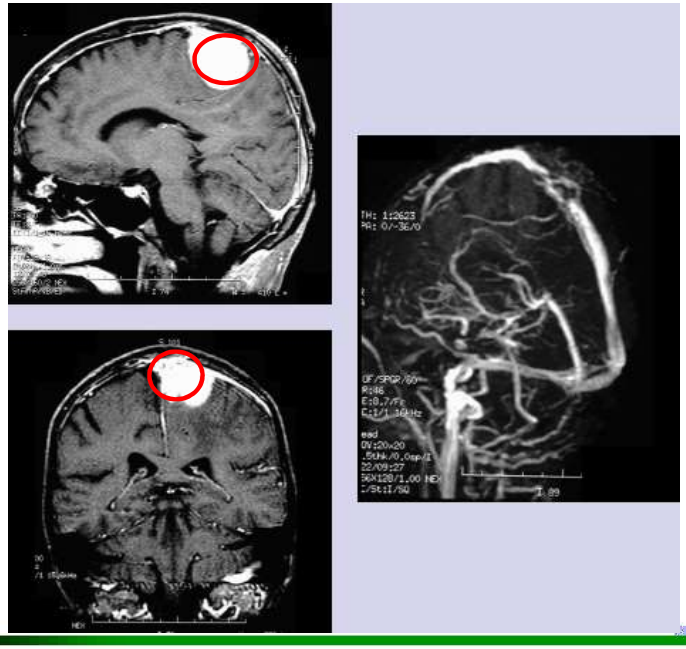
128-111-124-26 MU
73+73+73+15 sec

Left/right hIppoc. mean dose = 12.9 /12.5 Gy
Left/right lens mean dose = 8.8 / 8.3 Gy

Contouring for meningioma

- Postoperative RT (Simpson? Grade?)
- FSRT for Sin Cav meningioma
- SRS for small convexity meningioma
- Protons for base of the skull
- Margin?
- Dural Tail?





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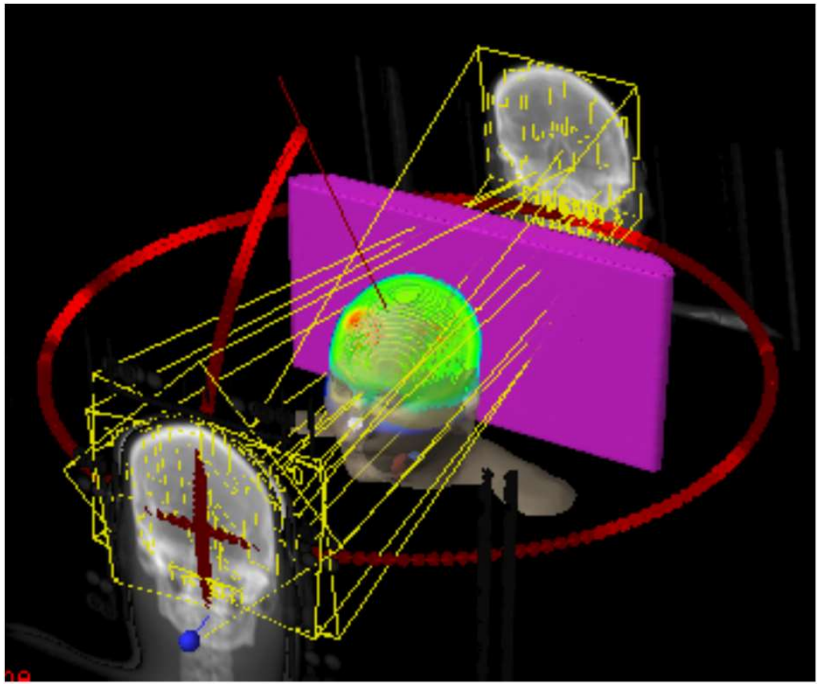
Planning

- Build the radiotherapy plan on a solid imaging acquired in a confortable, reproducible position
- The majority of plans are calculated on CT scans (without contrast)
- MRI only planning is promising, but still experimental
- The Planning CT may be fused with other enhancing techniques in order to improve accuracy
    - MRI (T1+gado, T2, FLAIR, other)
    - CT with contrast
    - Aminoacid- CT-PET

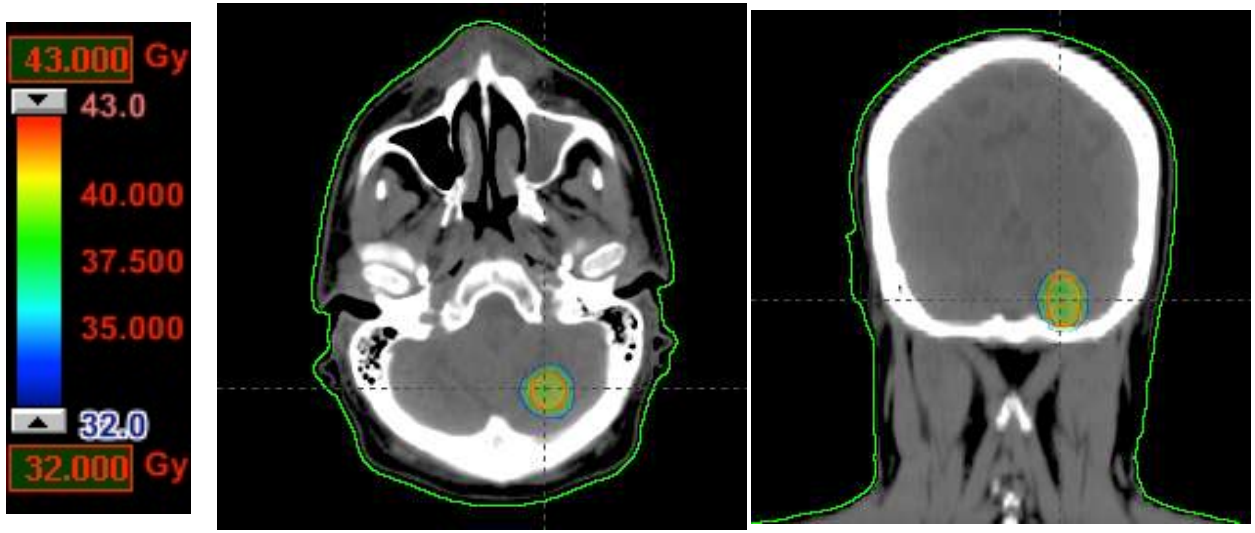
Beam shaping, geometry

- Photons, Particles (Protons, Carbon Ions)
- Energy
- Precision needed
- 3D CRT, IMRT, SRT, etc.



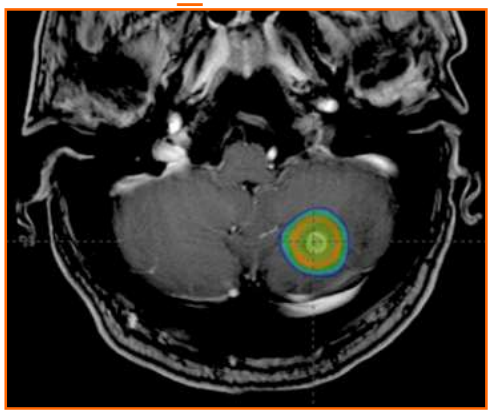
A single brain met from NSCLC

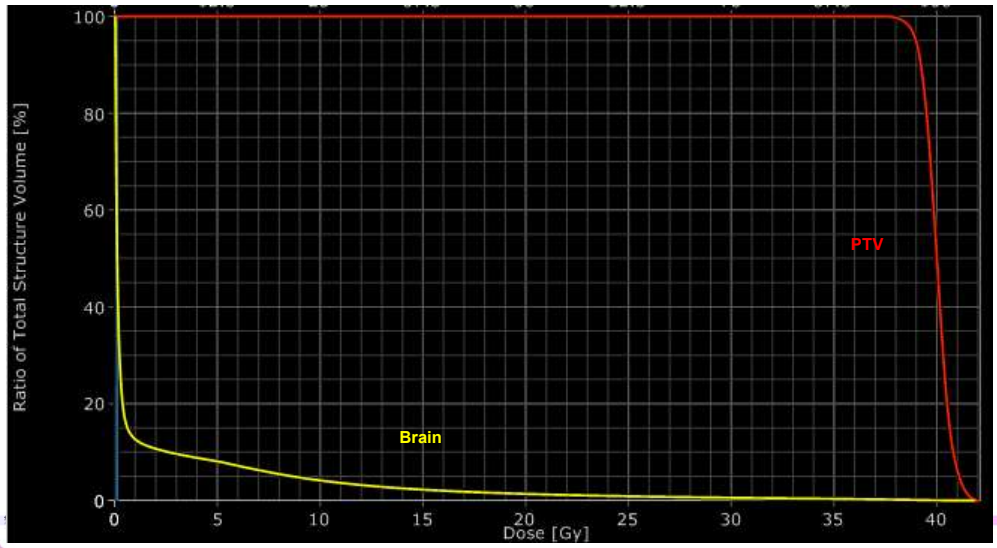
5 x 8 Gy = 40 Gy



PTV: 4.1 cm^3

MR_T1 FFE Gd



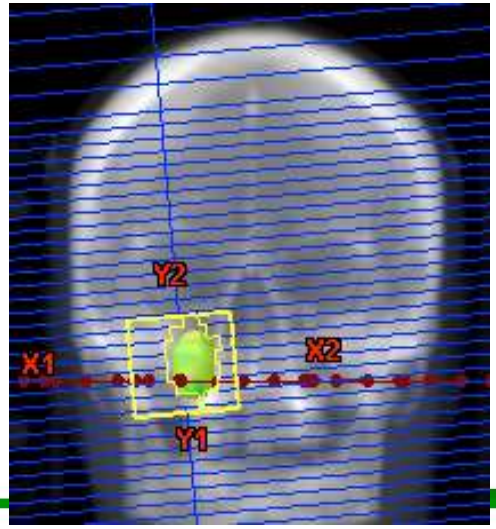


1 single arc

Dose calculation grid:

1.25mm

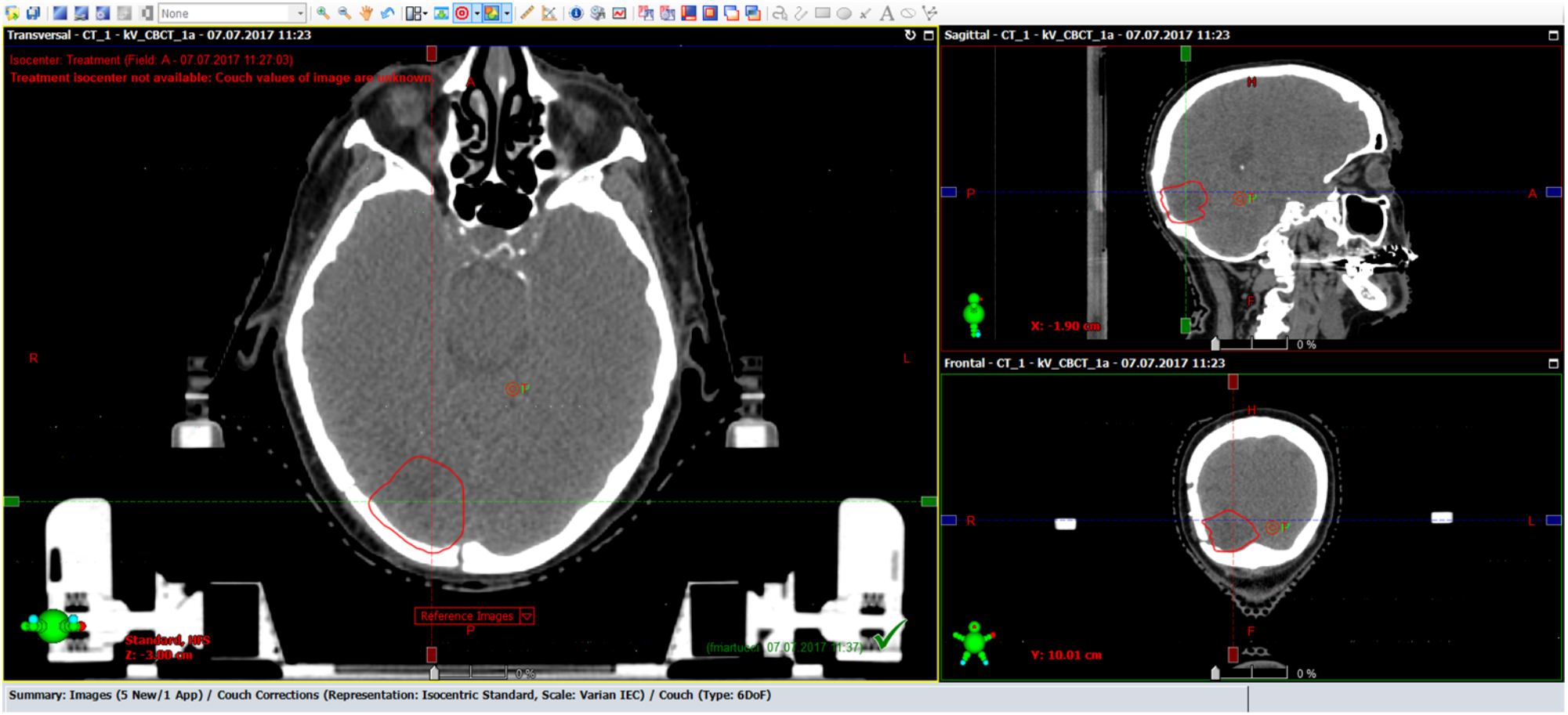
1492 MU
152 sec



Verification for Image guidance

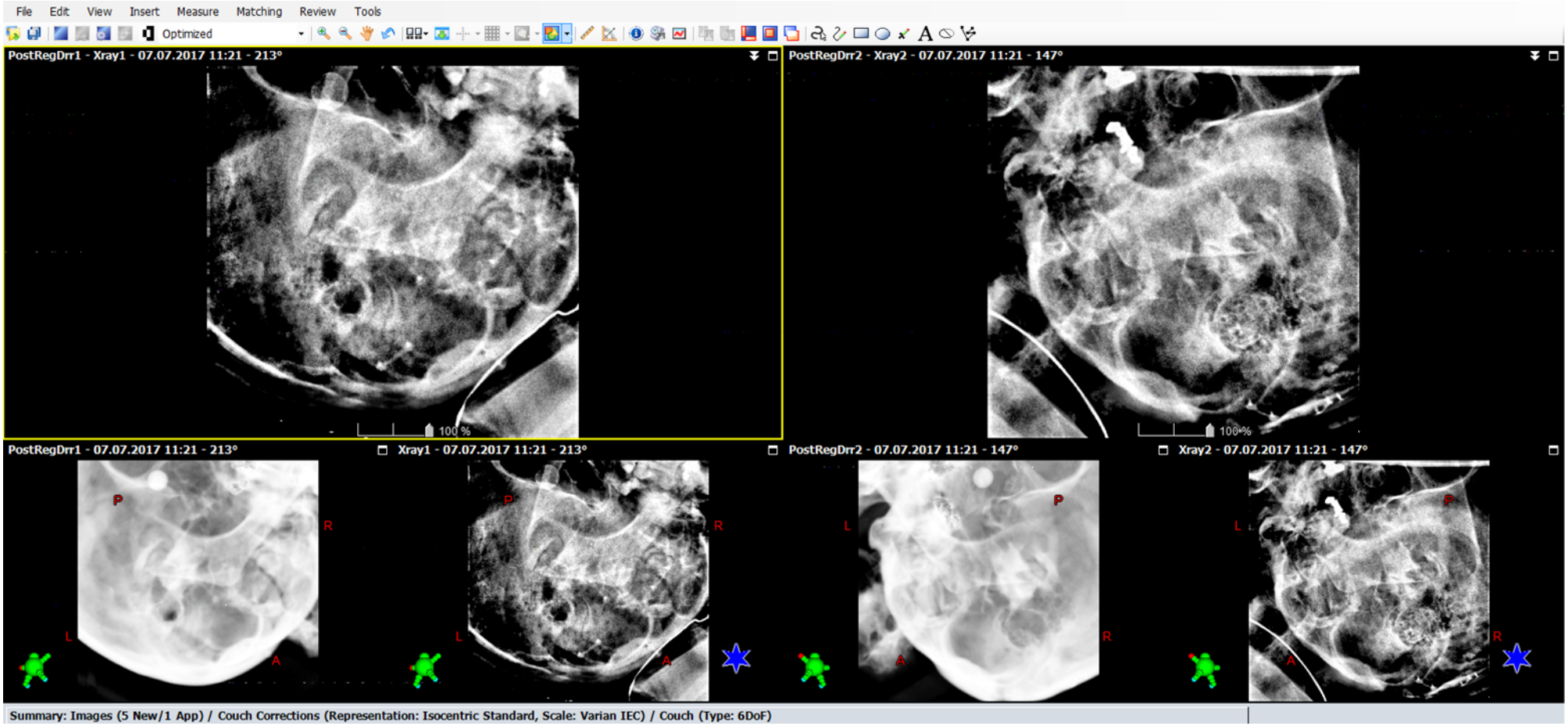
- Precision needed
- The Tools I have….
  Are they enough?
- How often?

Verification: CBCT



Verification: CBCT

Verification: ExacTrac®



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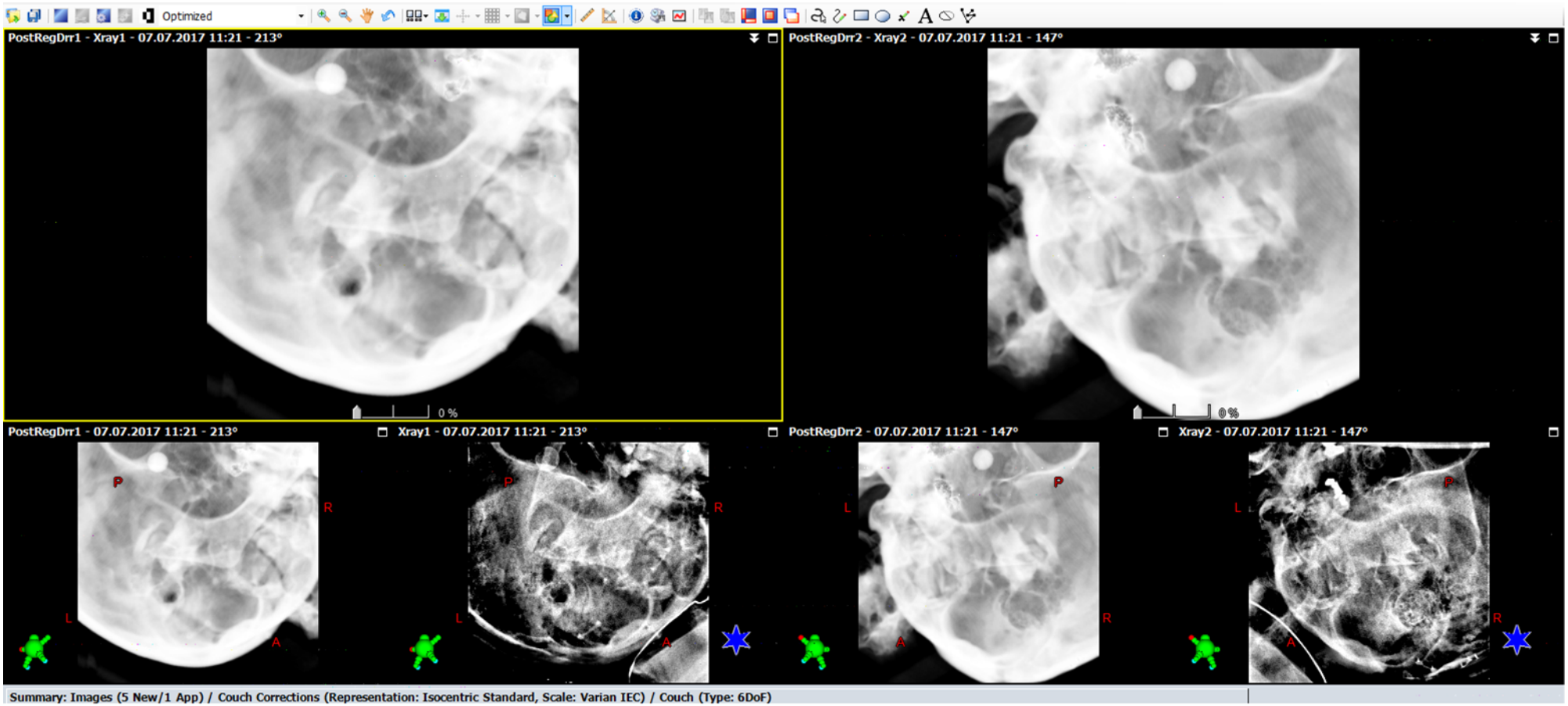
Verification: ExacTrac®



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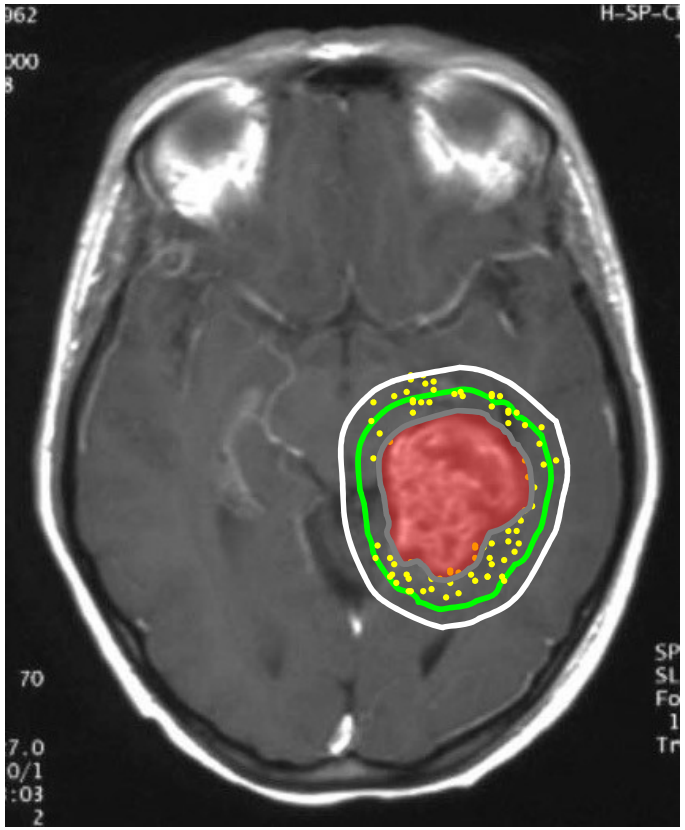
Improved accuracy of dose delivery

reducing margin for inaccuracy & microscopic spread



Courtesy-modified from M. Brada

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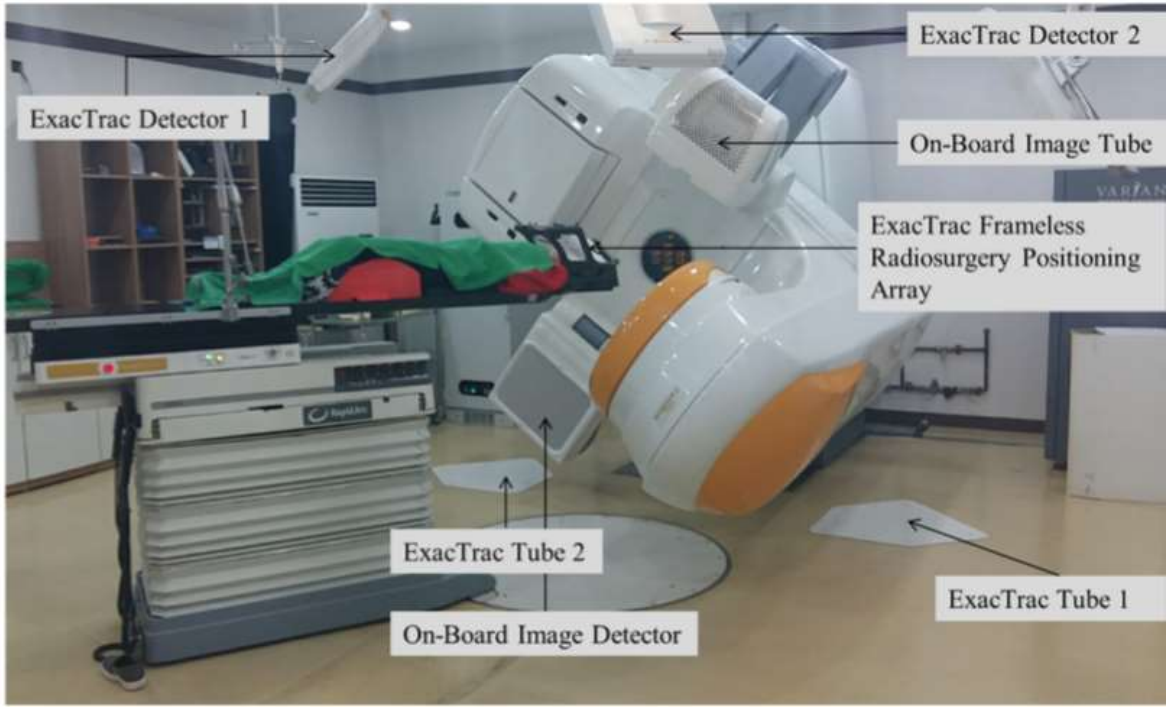
Verification

RESEARCH ARTICLE

Evaluations of the setup discrepancy between BrainLAB 6D ExacTrac and cone-beam computed tomography used with the imaging guidance system Novalis-Tx for intracranial stereotactic radiosurgery

Se An Oh[1], Jae Won Park[1,2], Ji Woon Yea[1,2], Sung Kyu Kim[1,2]*

1 Department of Radiation Oncology, Yeungnam University Medical Center, Daegu, Korea, **2** Department of Radiation Oncology, Yeungnam University College of Medicine, Daegu, Korea



- Comparison between ExacTrac, 3D CBCT and 6D CBCT
- Minor, but not negiglible variations

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Conclusions

- First requirement is the proper setting to discuss and help the patient well understand and helping him and his caregivers to take part to the decisions
- Proper explanation and preparation of the simulation/positioning will avoid, anxiety, errors and improve patient's wellbeing
- Buy the better technology you can, based on scientific evidence (tools, not toys)

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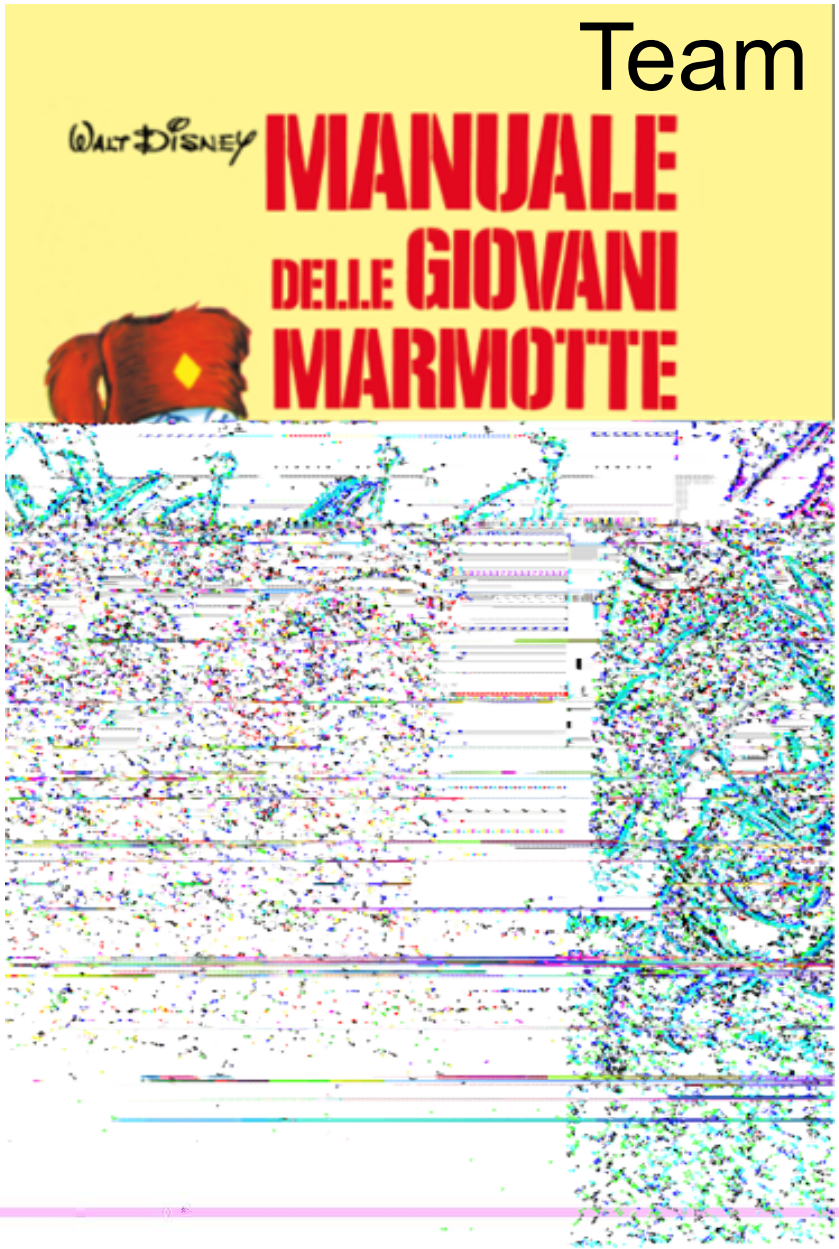
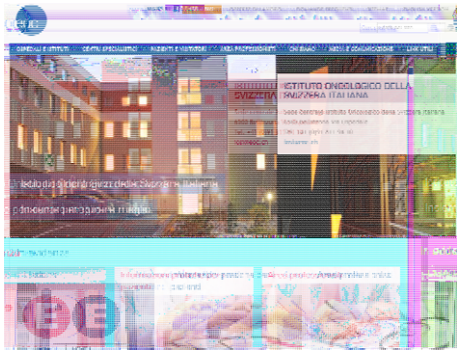
Team



Specialized Nurses
Radiation Oncology
Medical Physics EOC
Neurosurgery
Neurology
Medical Oncology
Palliative care
Psicho-oncology
Occupational and physical therapy
Neuro-Radiology
Research Branch

G. Pesce, M. Reinert,A. Cassarino, E. Tiganj, E. Bortolin, D. Bosetti, C. Prosperetti, W. Gulden-Sala, V. Espeli, T. Robert, F. Marchi, L. Valci, A. Richetti, A. Kaelin, A. Cianfoni, E. Pravatà, L. Mazzucchelli, M. Frattini, M. Ghielmini, D. Piffaretti, S. Presilla, F. Pupillo, My Family, My Patients, My Parents, My team



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MEDICAL UNIVERSITY OF VIENNA

COMPREHENSIVE CANCER CENTER VIENNA

Universitätsklinik für Strahlentherapie und Strahlenbiologie Wien

Radiotherapy- treatment techniques wide field irradiation CS and WBRT

Karin Dieckmann

Rolf Kortmann

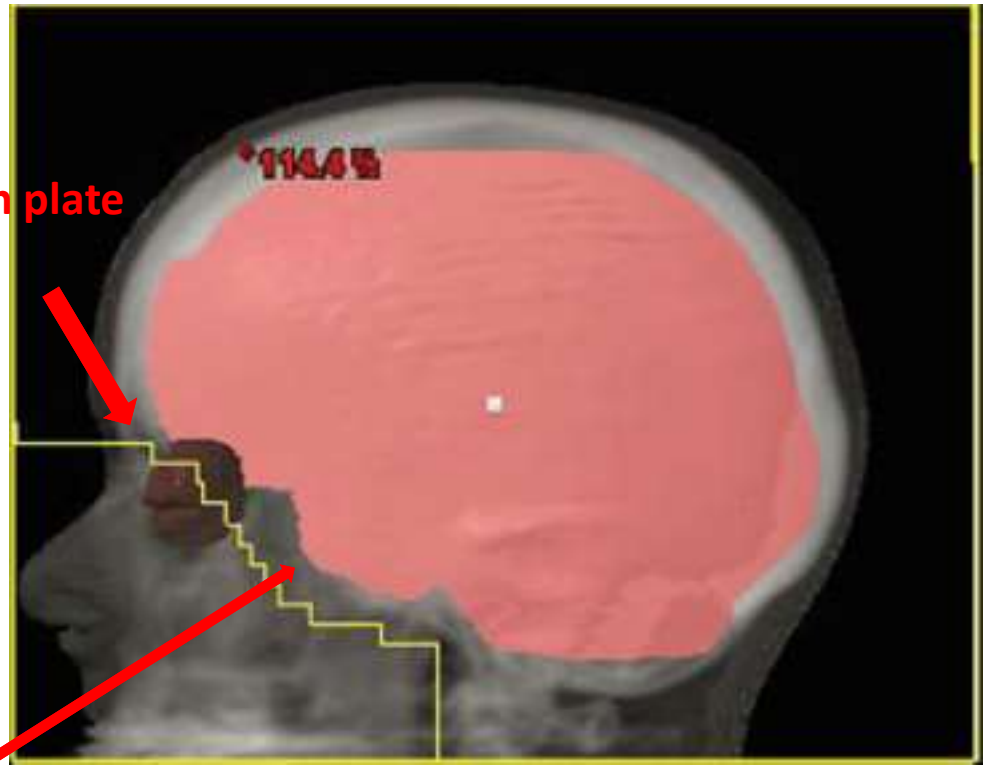
Department of Radiotherapy

Medical University of Vienne

Techniques

- Conventional technologies
  (according to simulation based technique)
- IMRT
- V-MAT technologies
- Tomotherapy
- Protontherapy (different technologies)

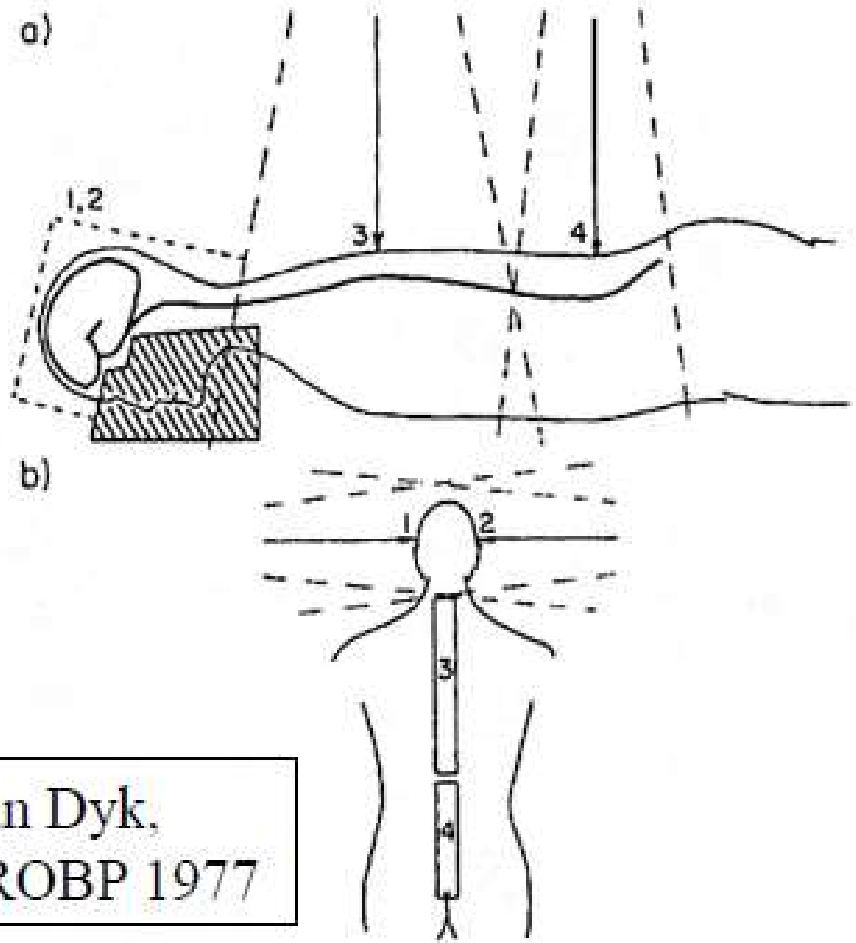
Whole Brain Radiotherapy



- Anterior cranial fossa
- Middle cranial fossa
- Posterior fossa

A margin of 1-2cm margin to the base of the brain includes the foramina which the cranial nerves exit.

Standard CSRT 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

van Dyk et al 1977 (IJROBP 2: 993-1005)

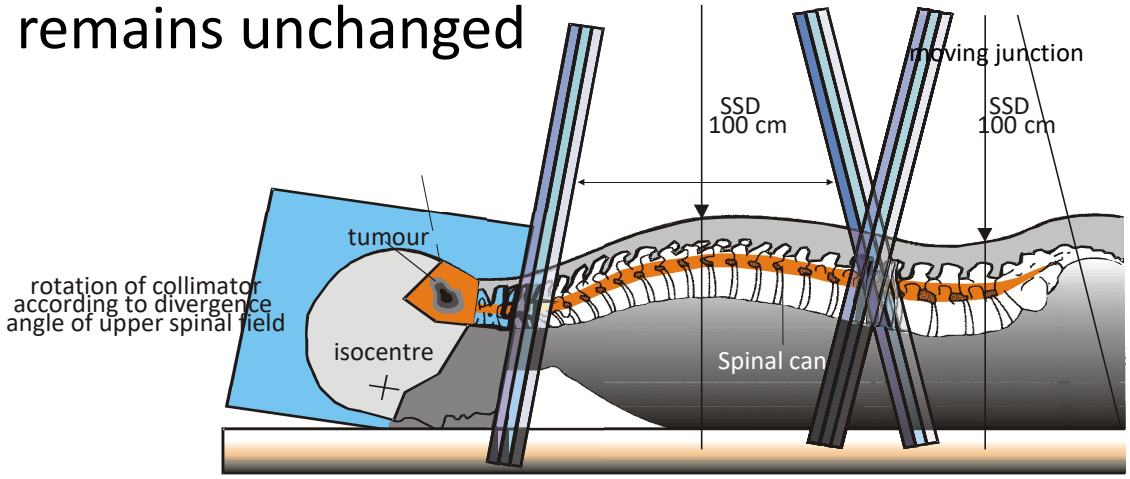
Technical Procedure

Junction lines are moved 0.5-1.0 cm every 8-12 Gy

to avoid overdosing or underdosing segments of the cord

Procedure:

1. shortening the inferior margin of the lateral cranial fields
2. Symmetrically lengthening the superior and inferior margins of the posterior spine field
3. Shortening the cranail margin of the caudal spinal field
4. The caudal spinal field remains unchanged



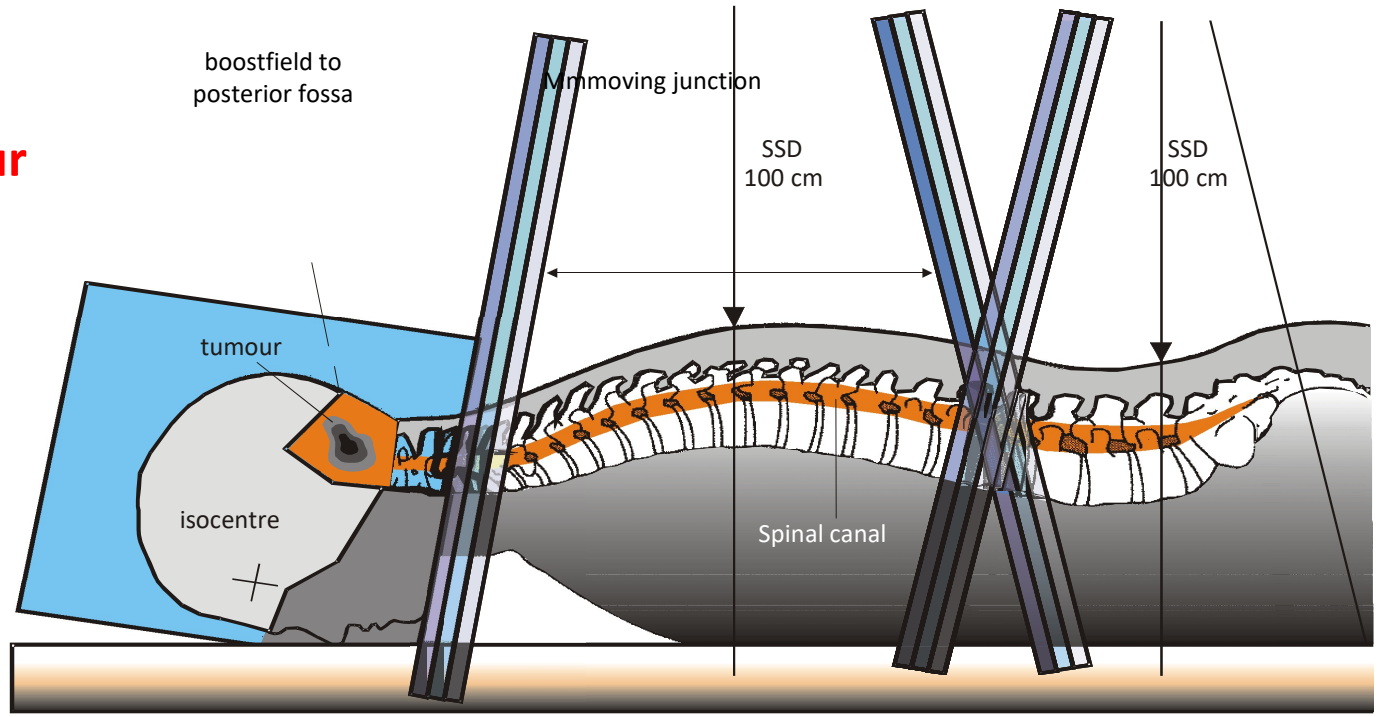
SSD : source to skin distance

Areas at Risk

1. Leptomeningeal space
(subclinical disease / „low risk“)

2. Posterior fossa
(subclinical disease
„high risk“ ?)

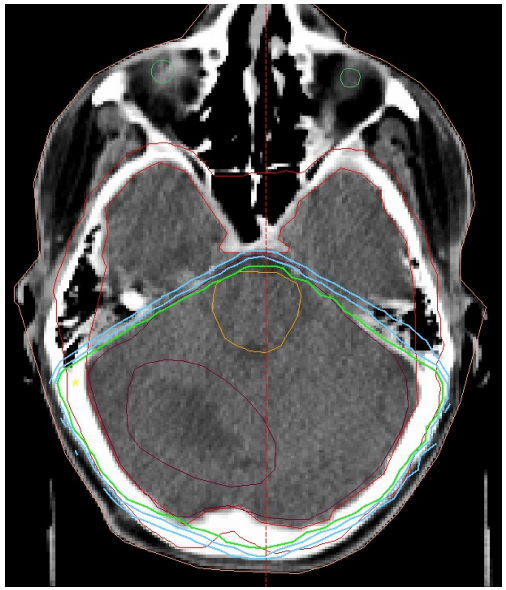
3. Tumour site
(residual tumour
R1-2)



rotation of collimator
according to divergence
angle of upper spinal field

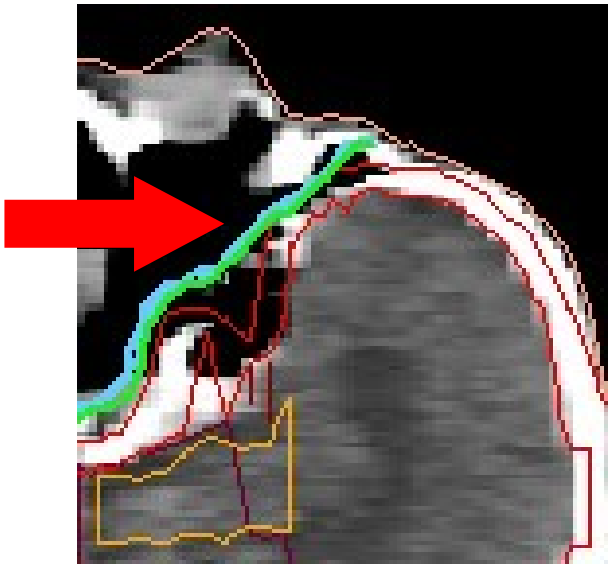
SSD : source to skin distance

Medulloblastoma

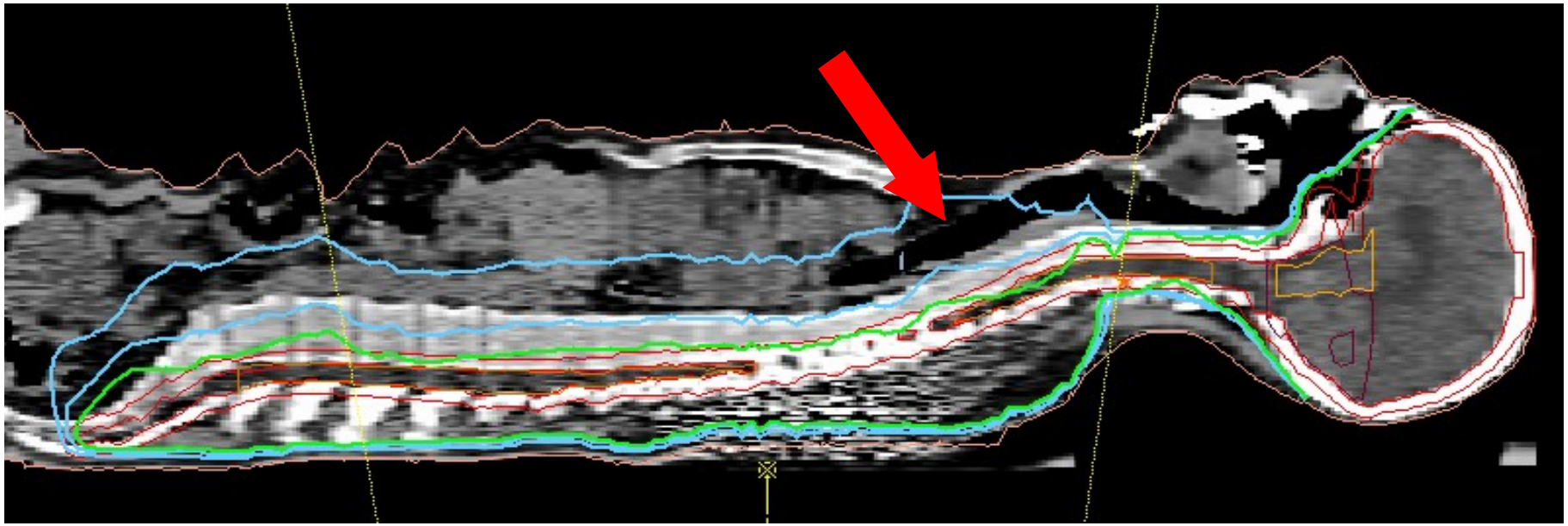


1. Coverage of target volume

2. Homogeneous dose distribution



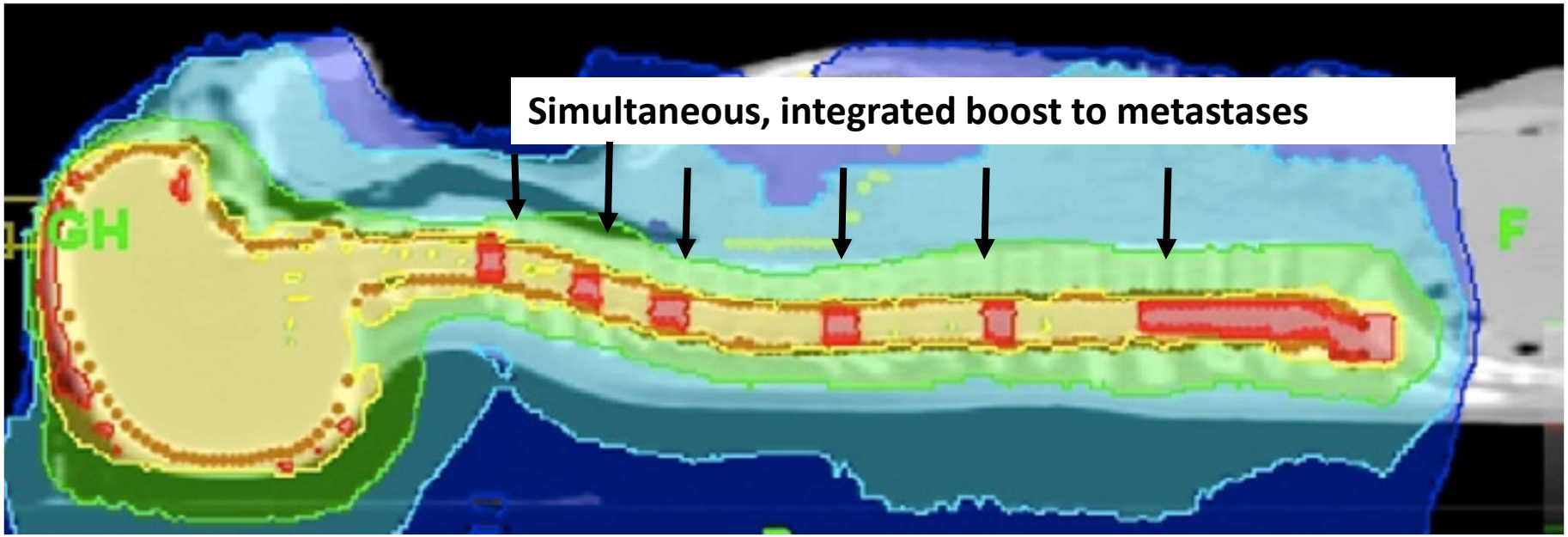
CT planning CSA



Craniospinal Irradiation Tomotherapy (IMRT)

Advantage: homogeneous dose distribution
(no field junctions)
integrated boosts possible

Disadvantage: higher dose exposure to non-target tissue

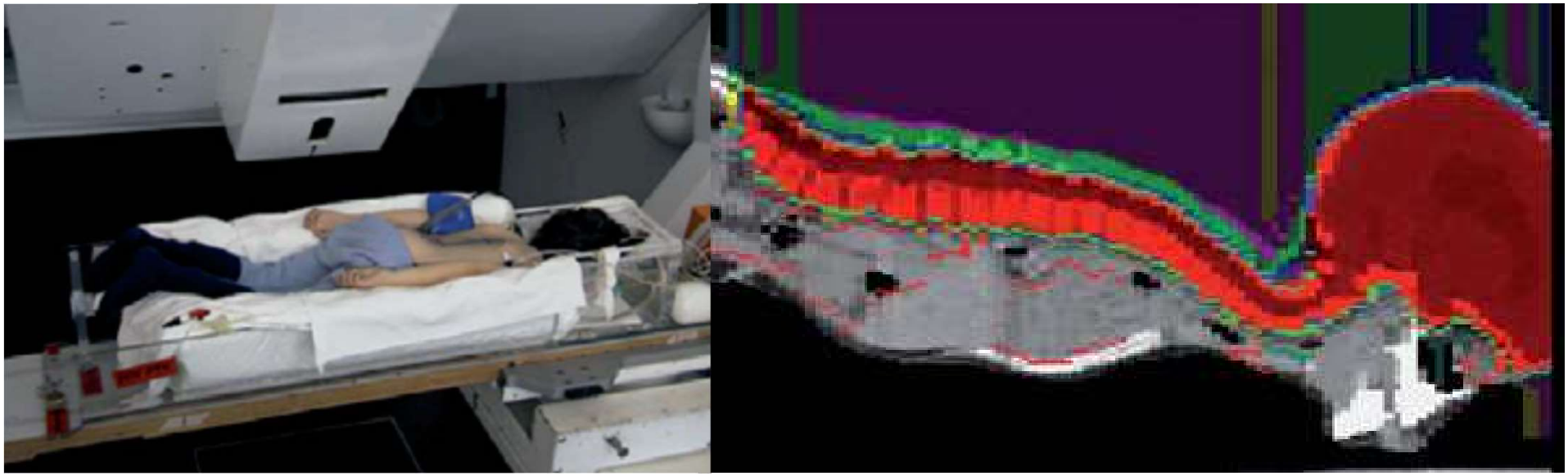


Parker et al., 2010

Craniospinal irradiation
Protons spot scanning technique

Advantage: homogeneous dose distribution (no field junctions)
lower dose to non-target tissue (reduced risk for 2nd malignancies)

Disadvantage: high costs



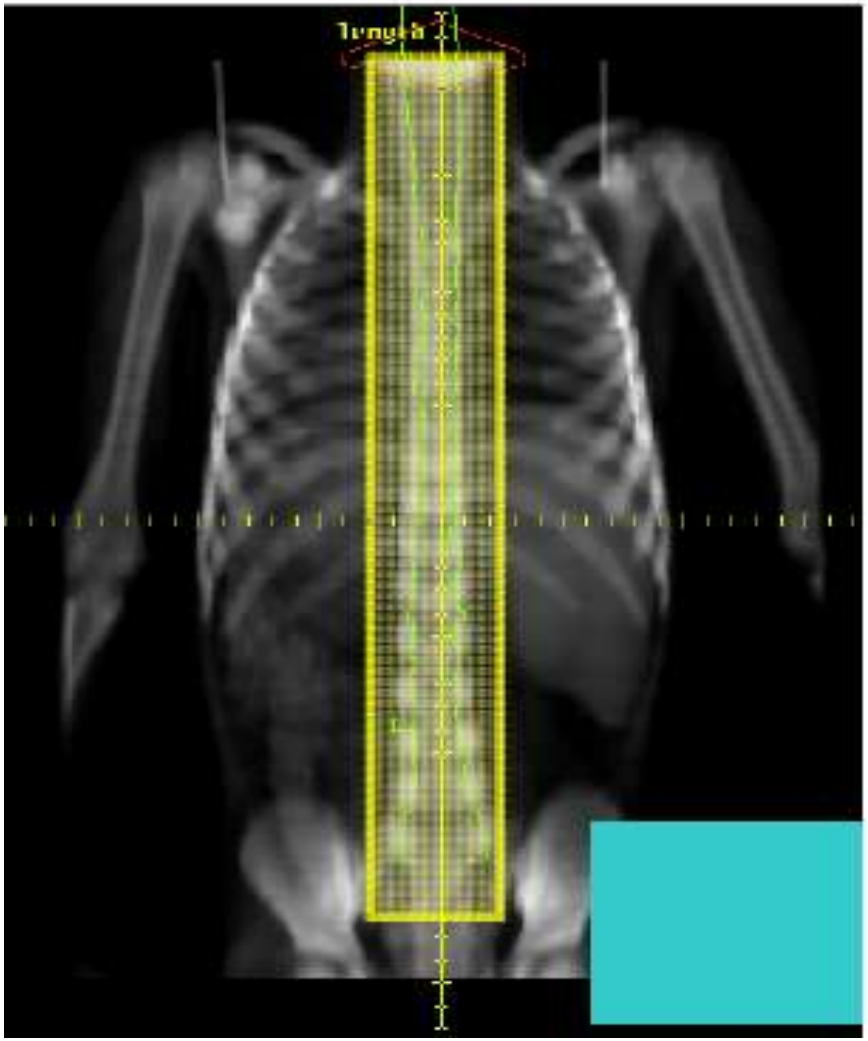
Timmermann et al., 2007

Target Volumes

Do we known how to define the targets ?

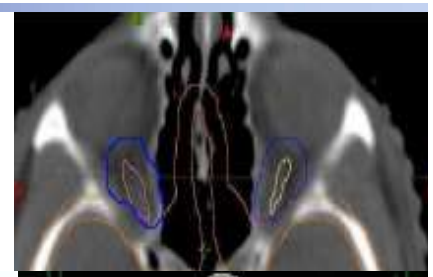
- Optic nerve
- Craniospinal Axis
- Posterior Fossa
- Tumour Bed

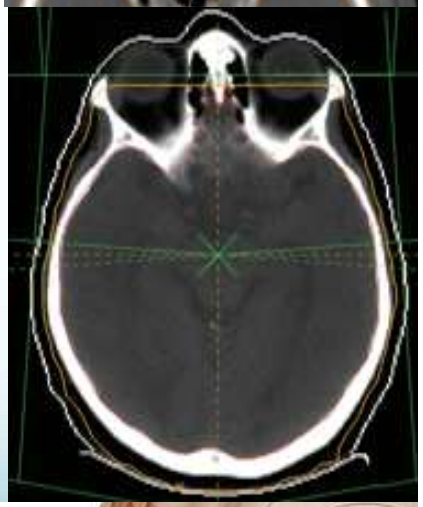
Target Volume for CSRT Spine



- ACNS0331:
  - "…laterally on both sides to cover the recesses of the entire vertebral bodies, with at least 1cm margin on either side"
  - Lower limit "…2 cm below the termination of the subdural space"…"at least to the inferior border of the 2nd sacral segment (S2/3 interspace)"

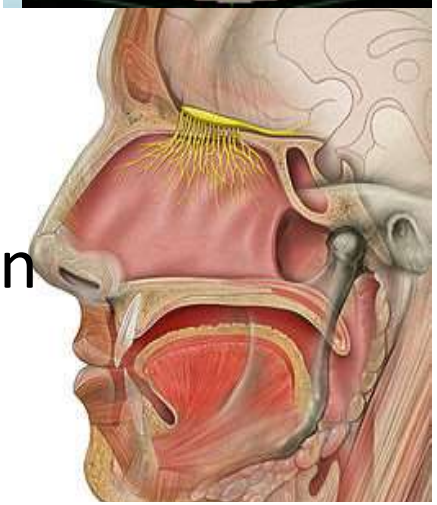
Target Volume (CTV) / Cranial Fields





- Meninges surrounding whole brain and ventricular system

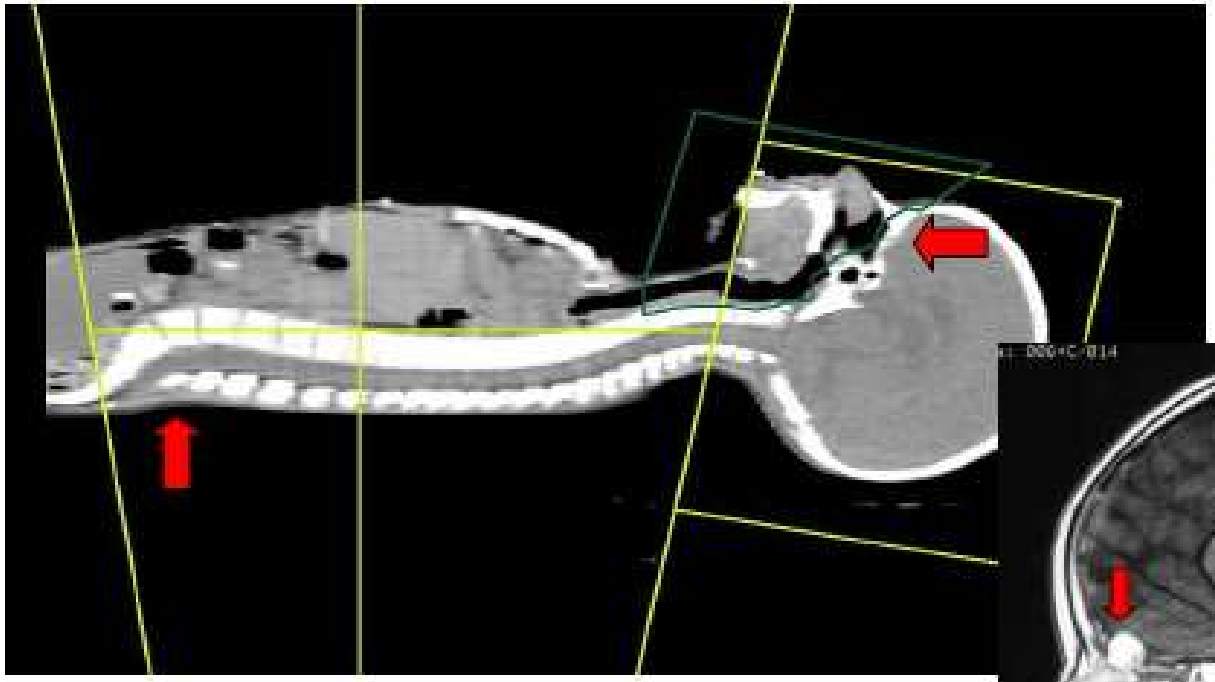
- Particular attention to cribriform fossa, temporal fossa, base of skull, Caudal extend of the tecal sac

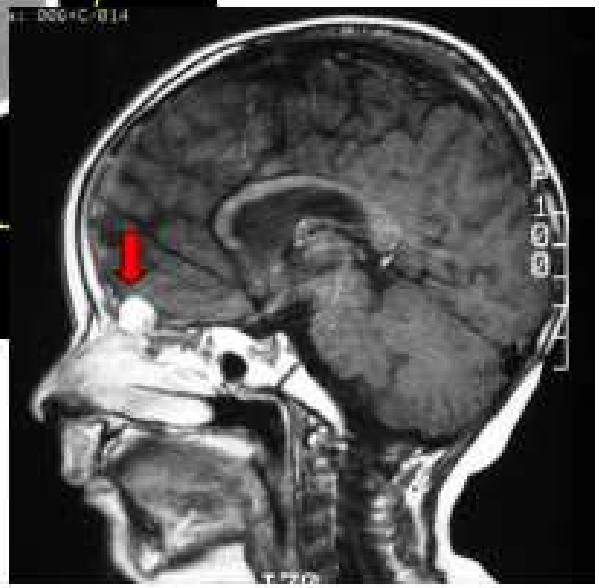


- Irradiate the full width of vertebrae for children

Target Volume for CSRT

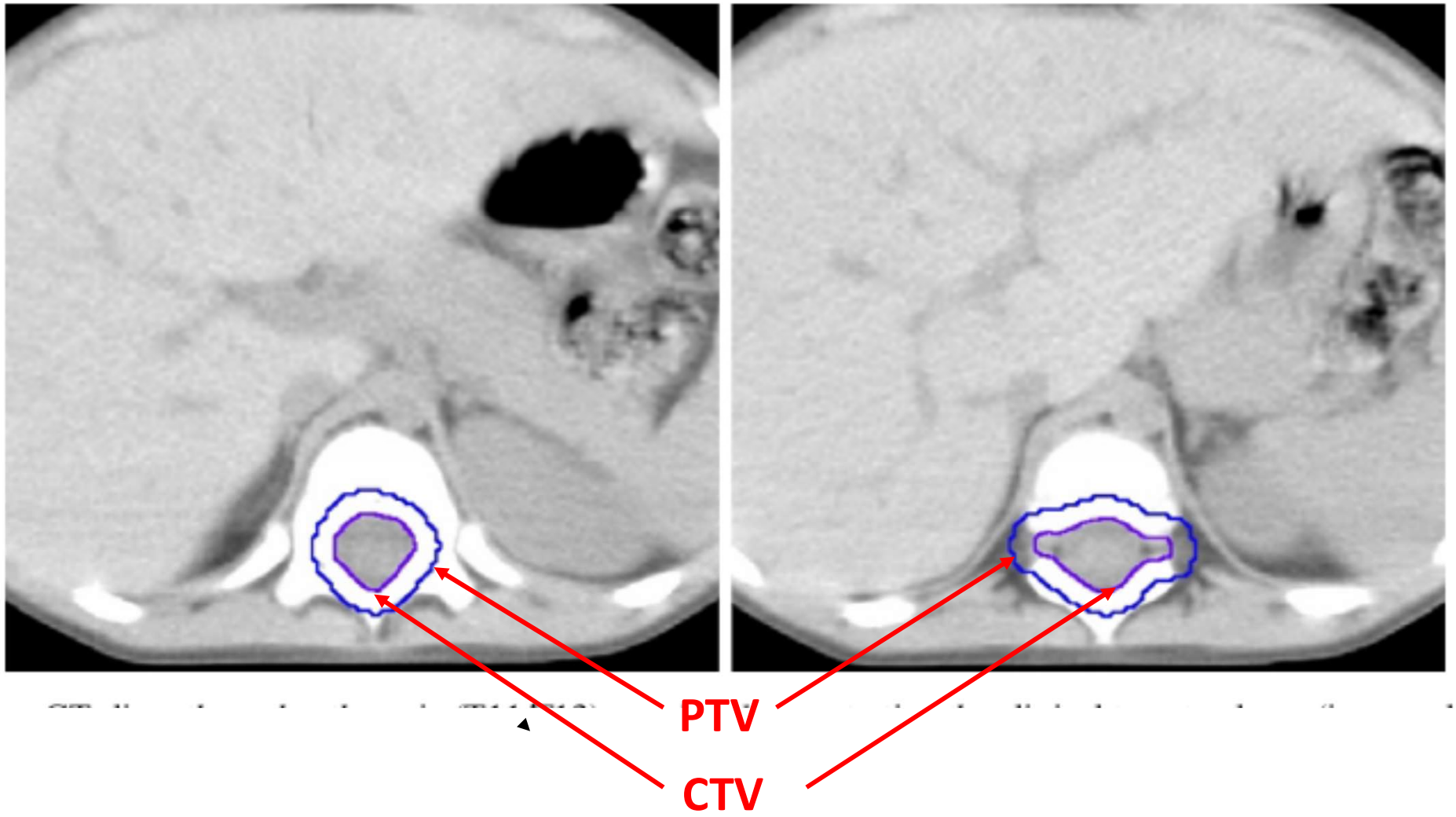
- Problem areas:
  - frontal region/ cribriform plate
  - caudal extent of thecal sac



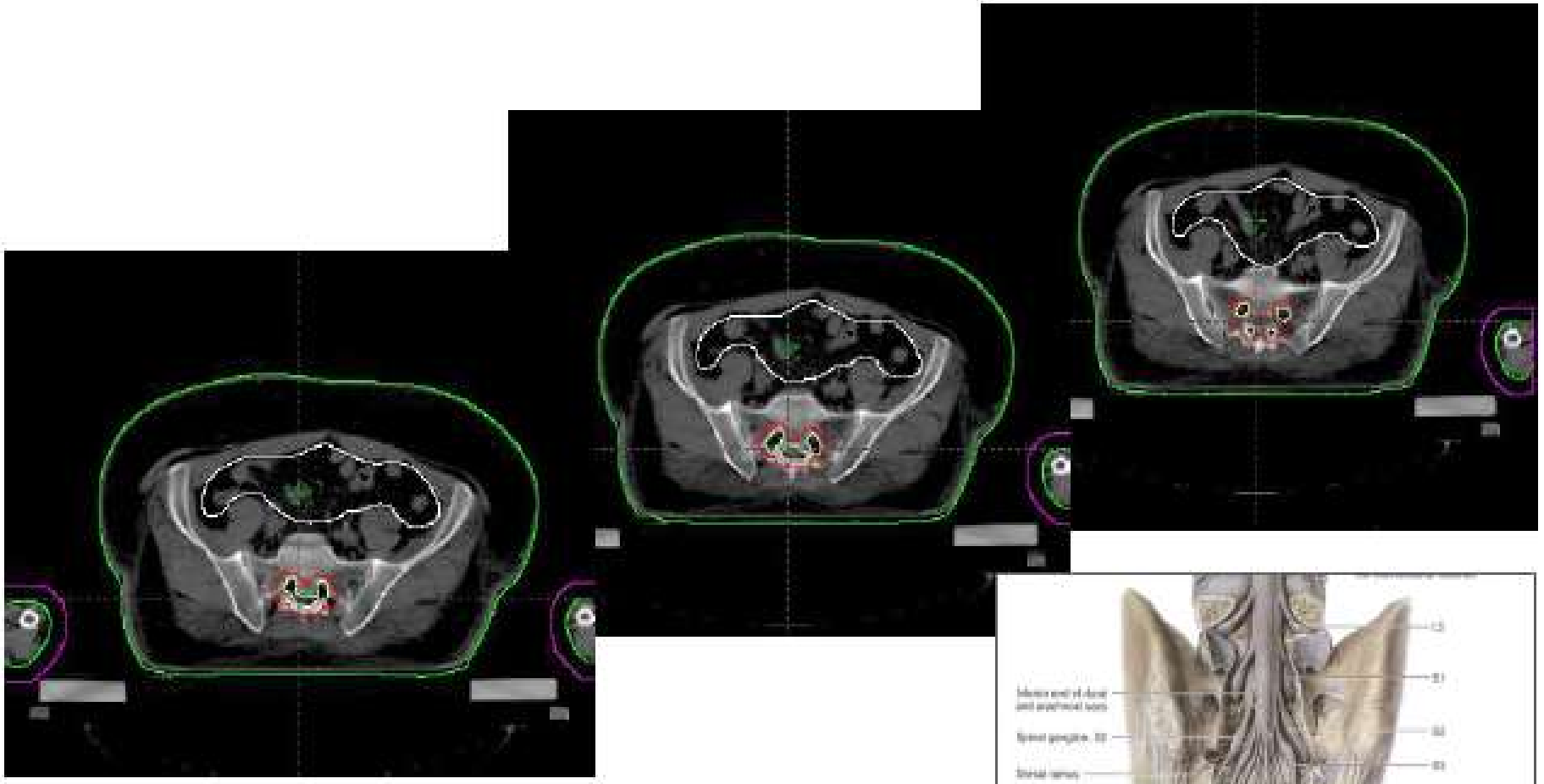


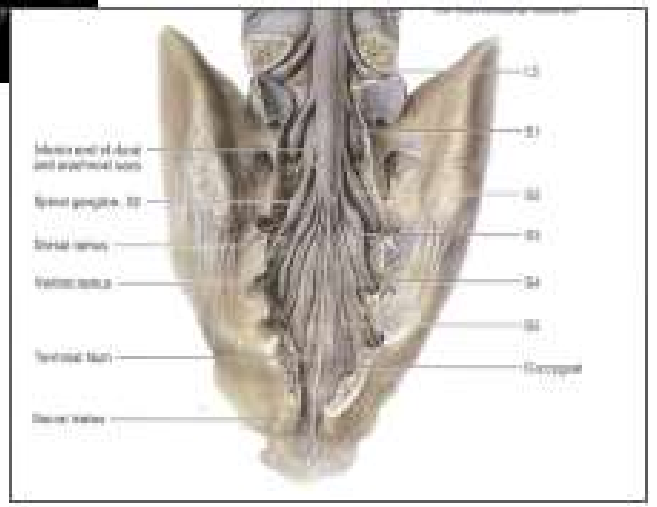
Spinal CTV and PTV

Extensions of nerve roots as far as intervertebral foramina



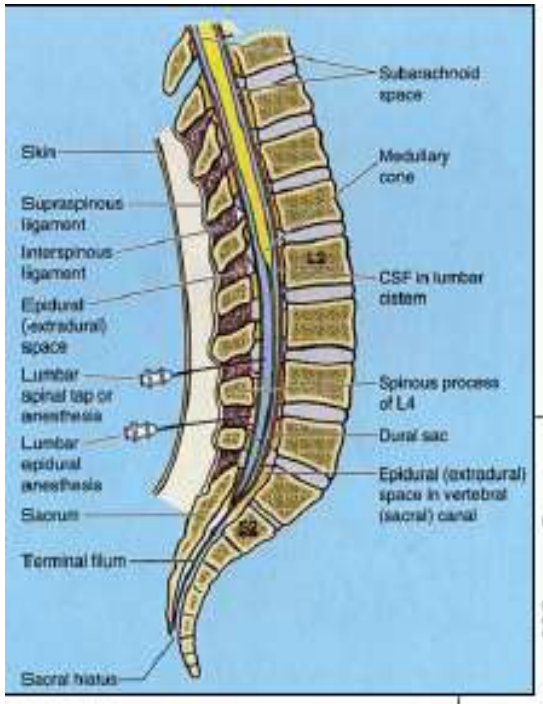
Target Volume for CSRT Sacral Roots

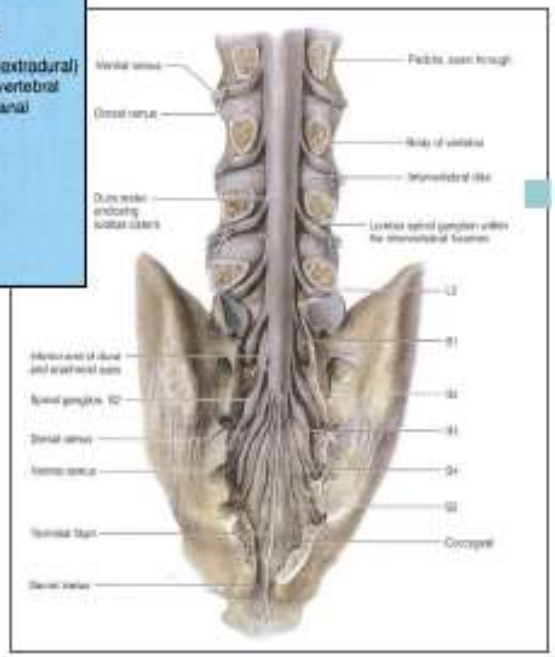




Meninges extending to the lower border of the thecal sac as determined by MR scanning

CSRT – Thecal Sac





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

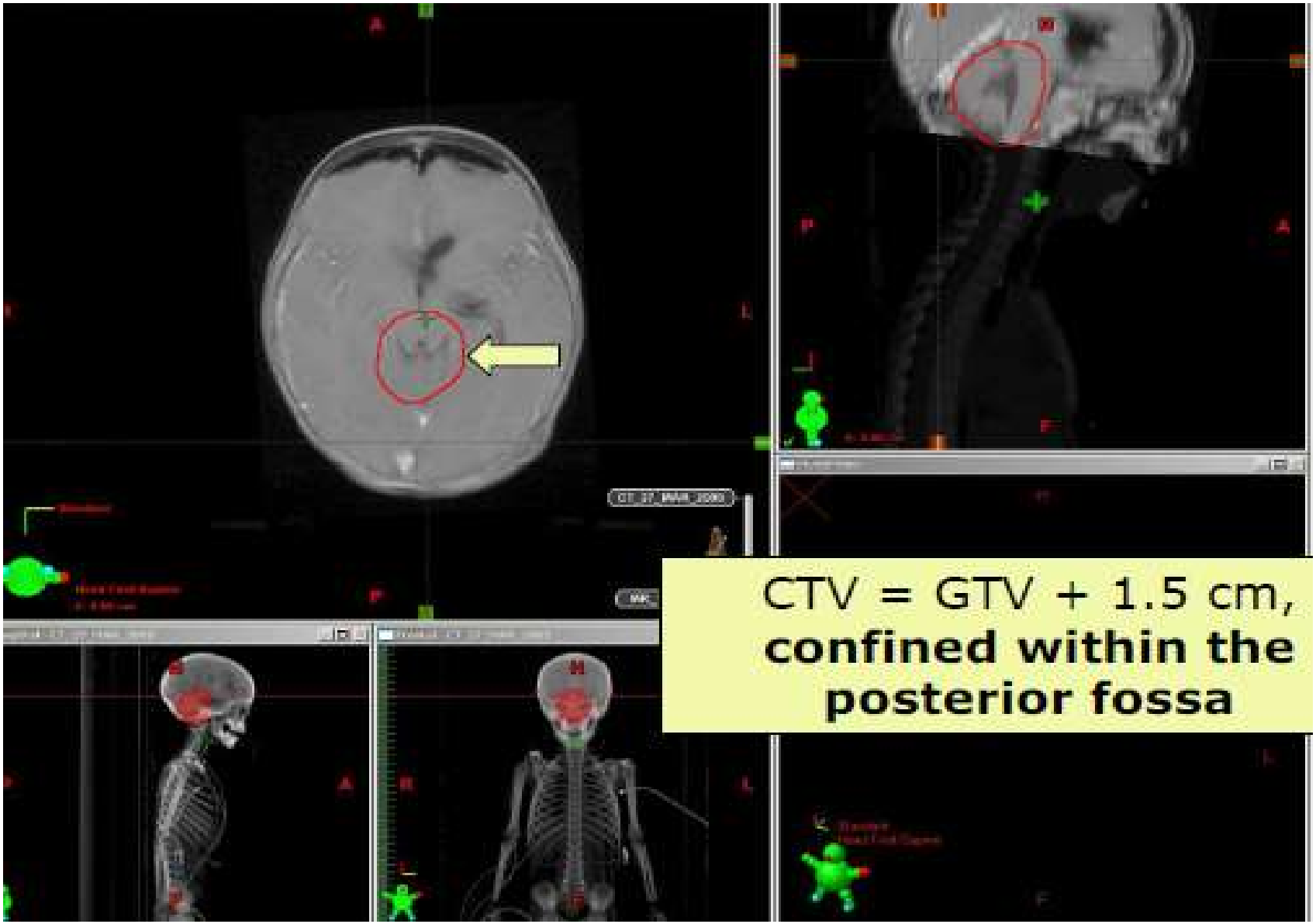
MRI is **essential** for accurate determination of the caudal extent of the thecal sac

Target Volume for Tumour Bed RT

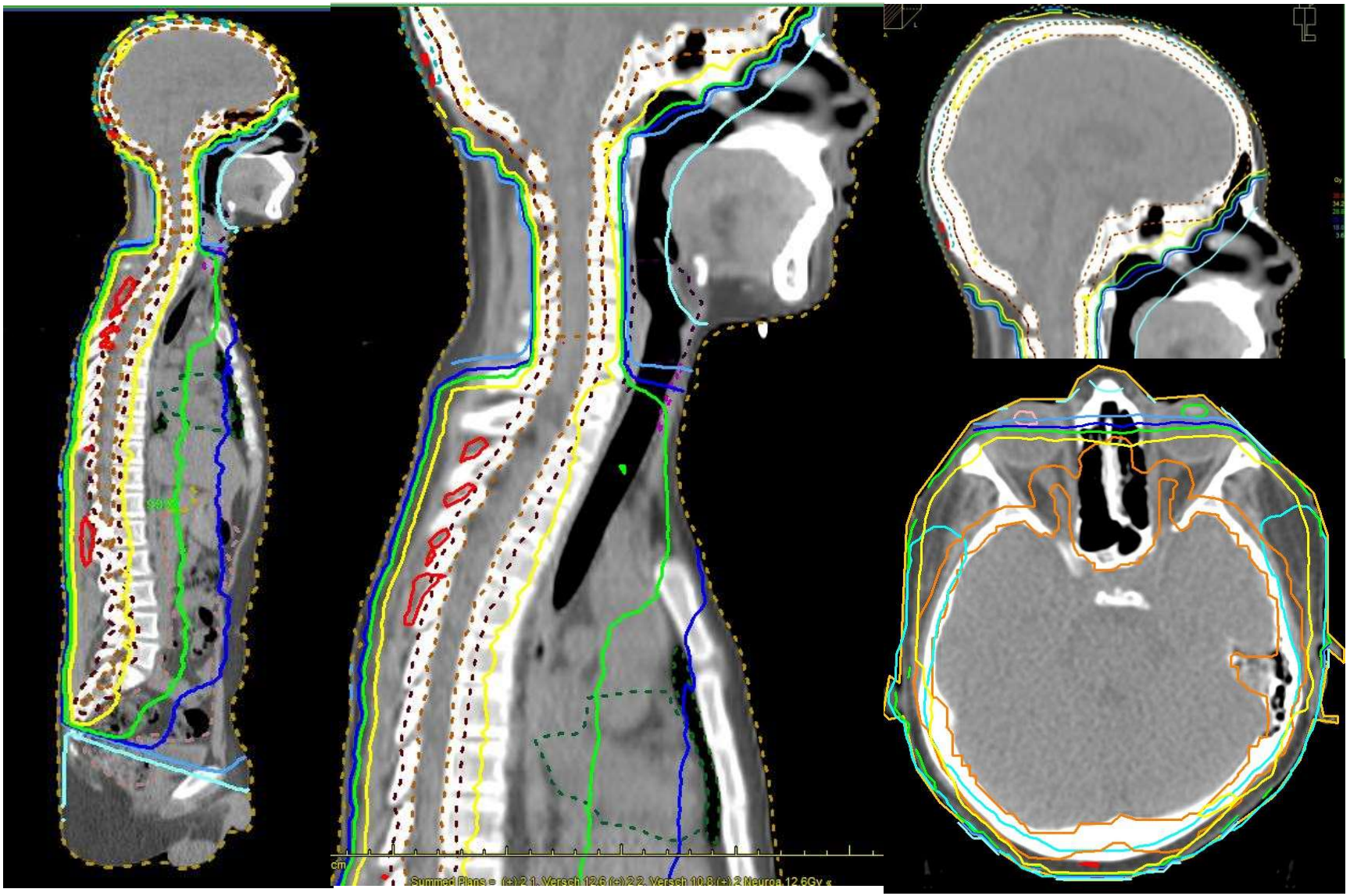
GTV:

- Any residual tumour on imaging
- Post-surgical cavity including tumour/brain interface prior to resection
- Allow for post-surgical changes to anatomy **CTV** margin
- **PTV** according to institutional policy

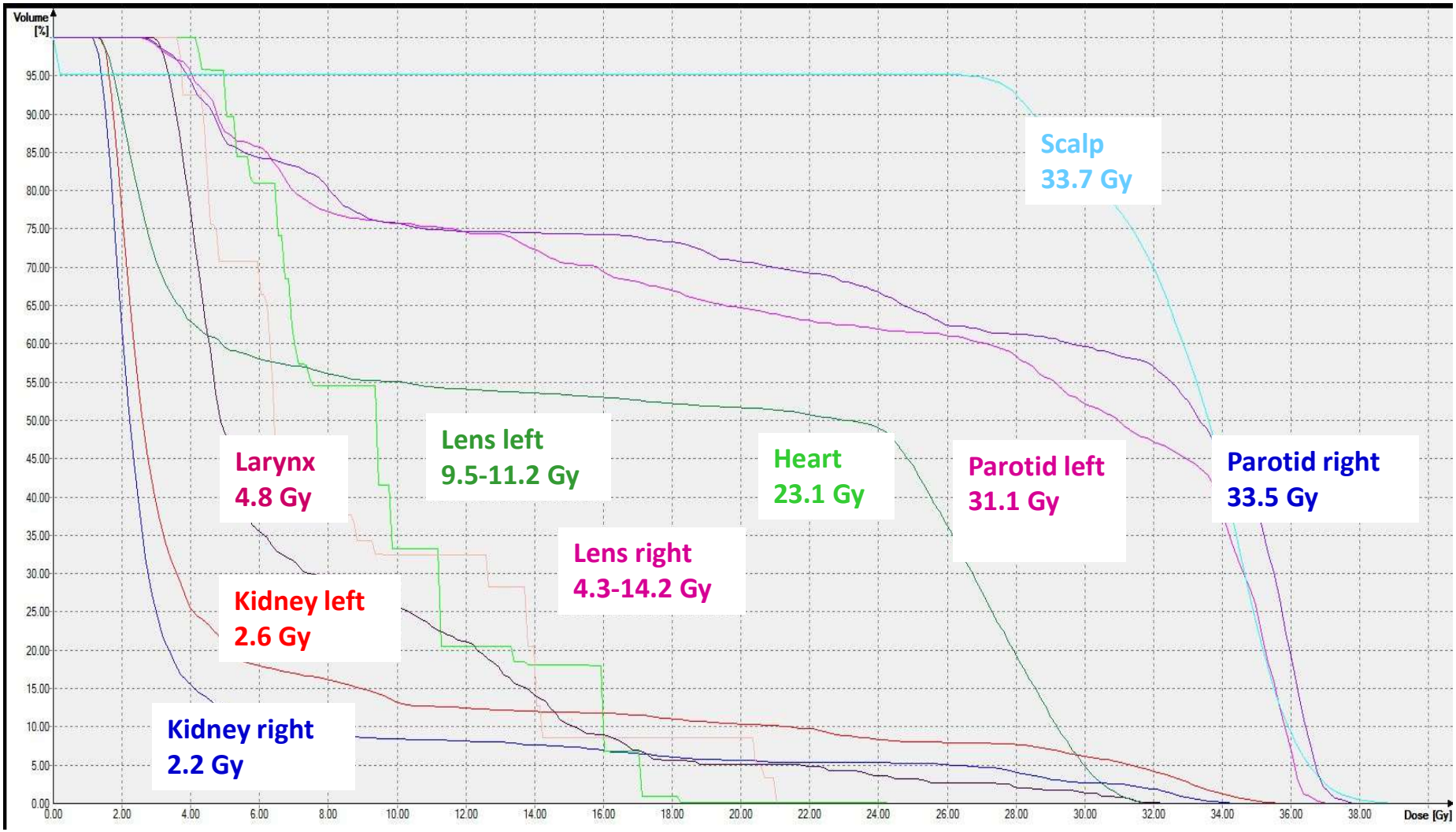
Medulloblastoma -Tumour Bed Boost



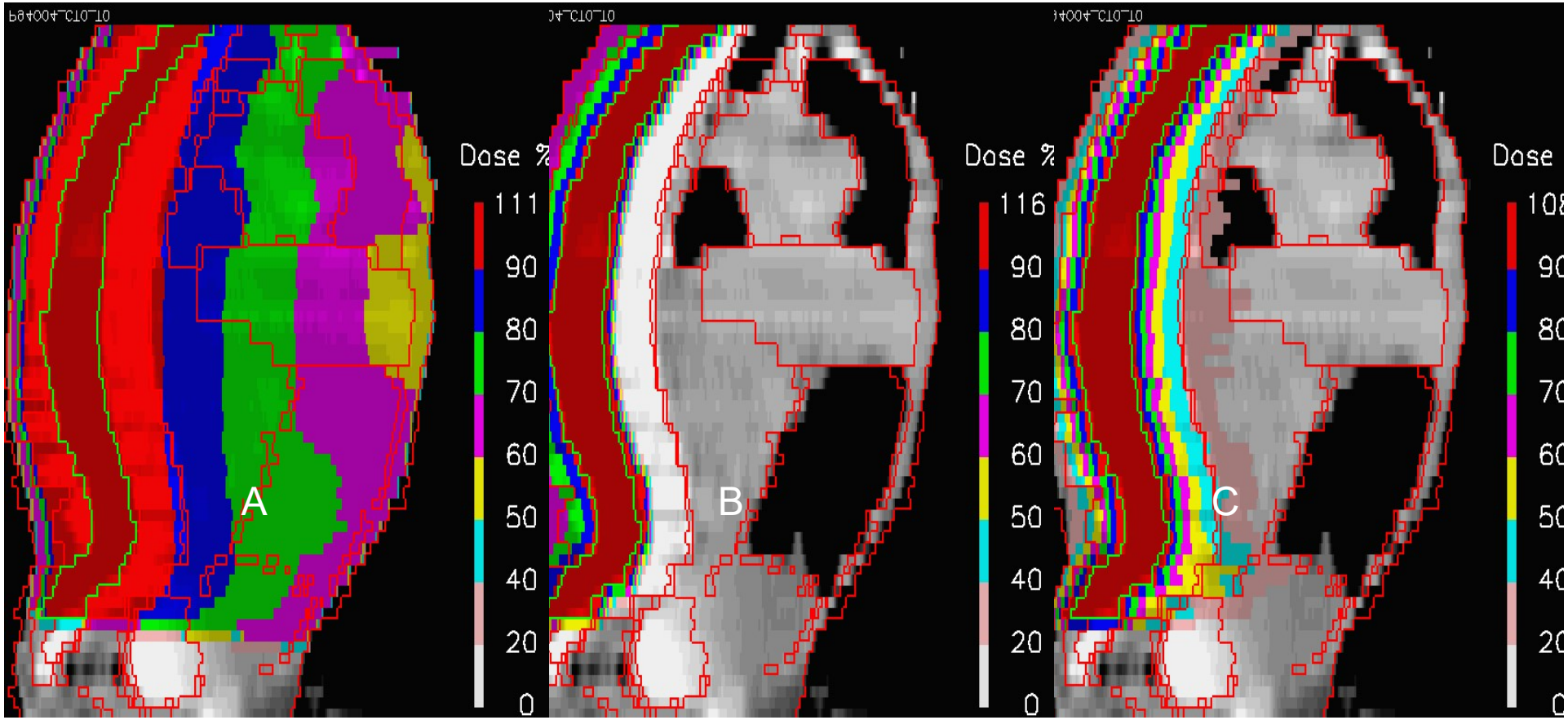
Treatment Plan / Isodose Distribution



Treatment Plan / DVH / Median Dose

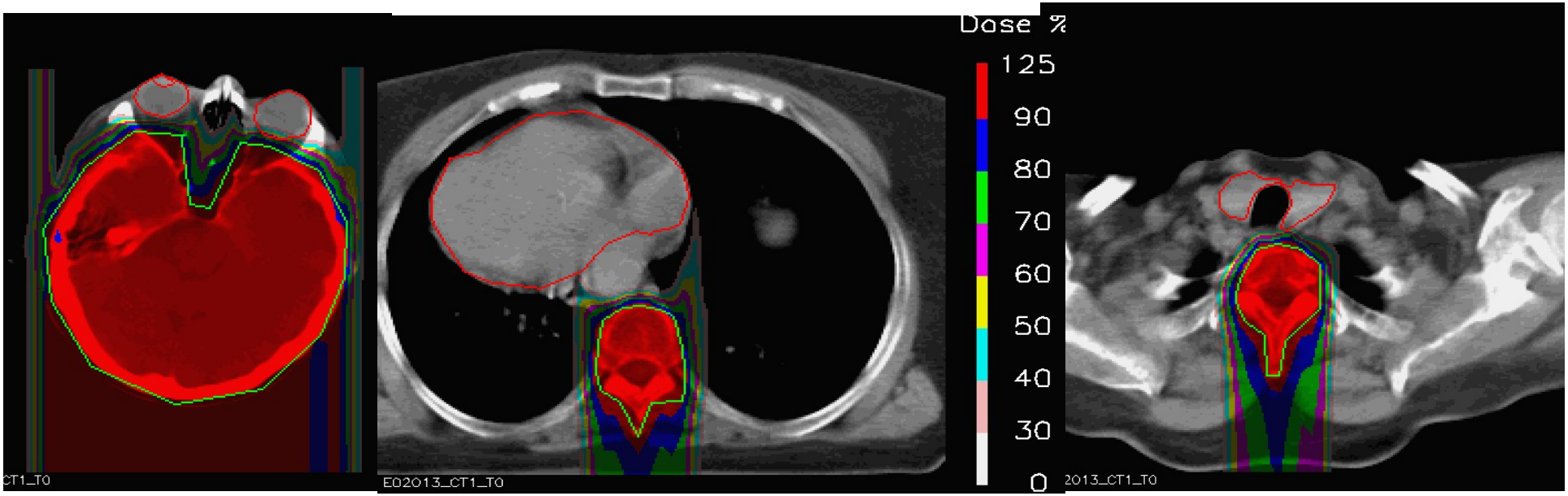


Comparative dose distributions in a sagittal plane through the center of the spinal axis



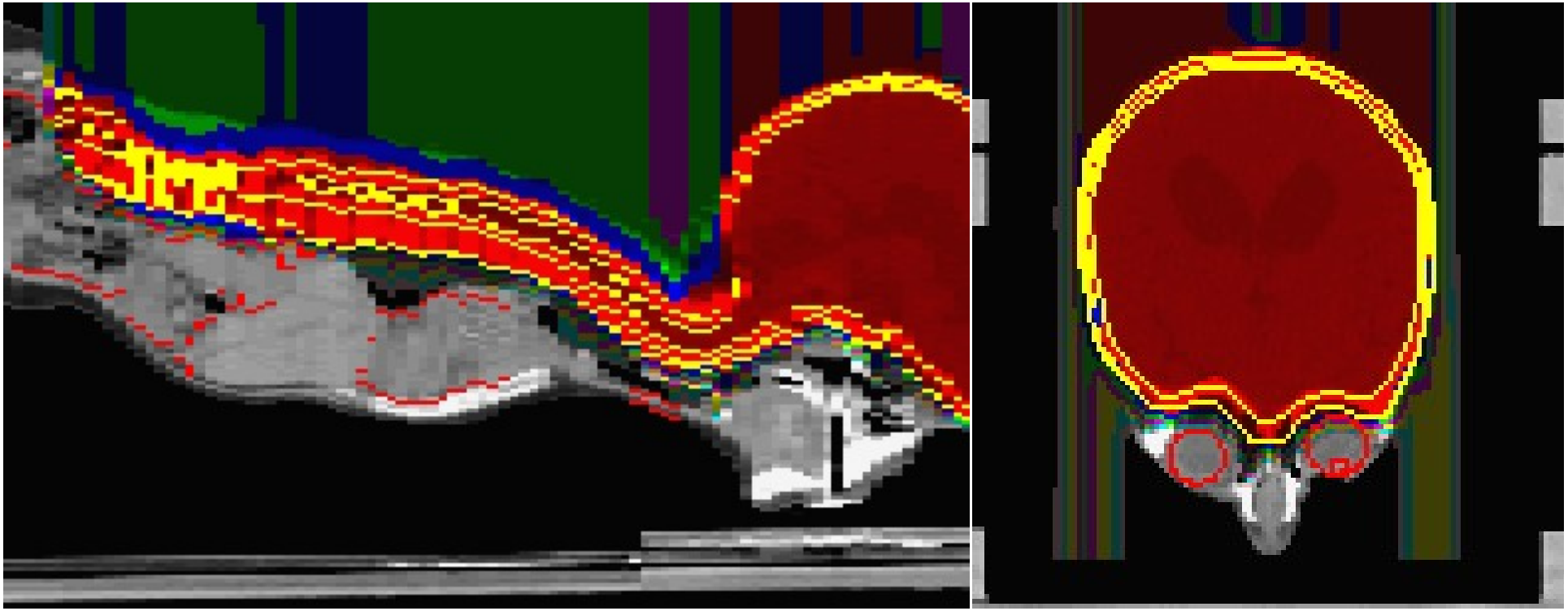
conventional photons **spot scanned protons** **IM photons**

CSI with Protons



Optimisation of the ventral dose distribution

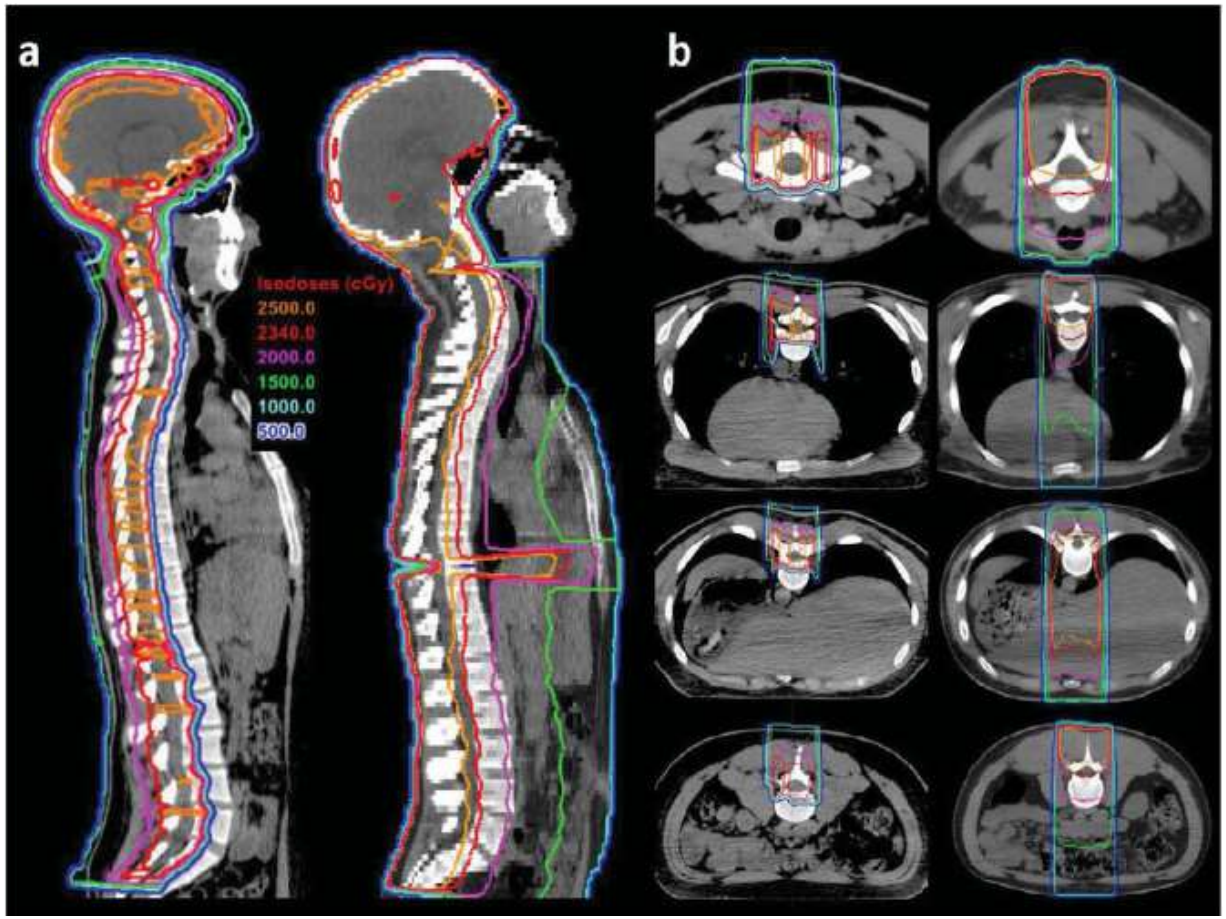
CSI with Protons in a 5 years old boy



Whole vertebras are included into the PTV

Proton Beam Craniospinal Irradiation Reduces Acute Toxicity for Adults with Medulloblastoma

Aaron P. Brown



Proton CSI Photon CSI

CSI protons: n=21

CSI photons: n=19

Dose 30.6 Gy/50.4Gy

Dose reduction

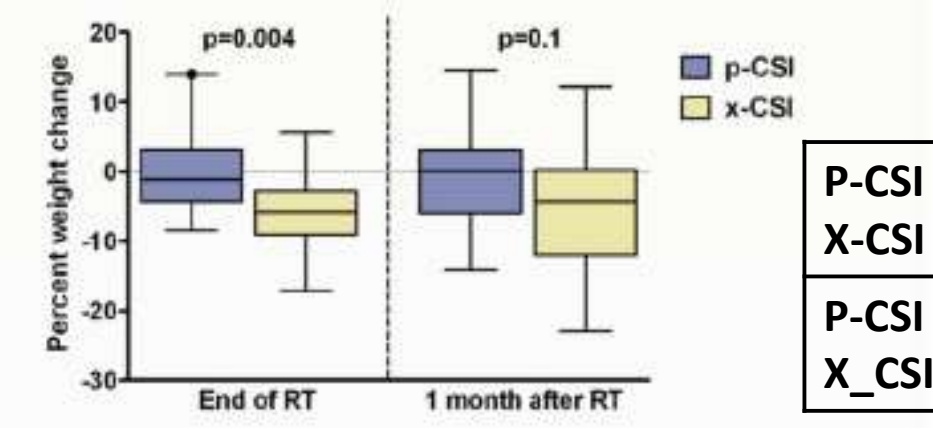
- Thyroid gland
- Esophagus
- Heart
- Lungs
- Liver
- Stomach
- Bowel
- Ant. vertebral body

Int J Radiat Oncol Biol Phys. 2013 June 1; 86(2): 277–284.

Proton Beam Craniospinal Irradiation Reduces Acute Toxicity for Adults with Medulloblastoma

Aaron P. Brown

Weight loss



P-CSI X-CSI	-1.2% (range +14 to -8.4%) -5.8% (range +5.8to -17.1%)	p=0.004
P-CSI X_CSI	+0.1% (range +14.6 to -14.2%) -4.4% (range 12.2 to-23%)	P=0.1

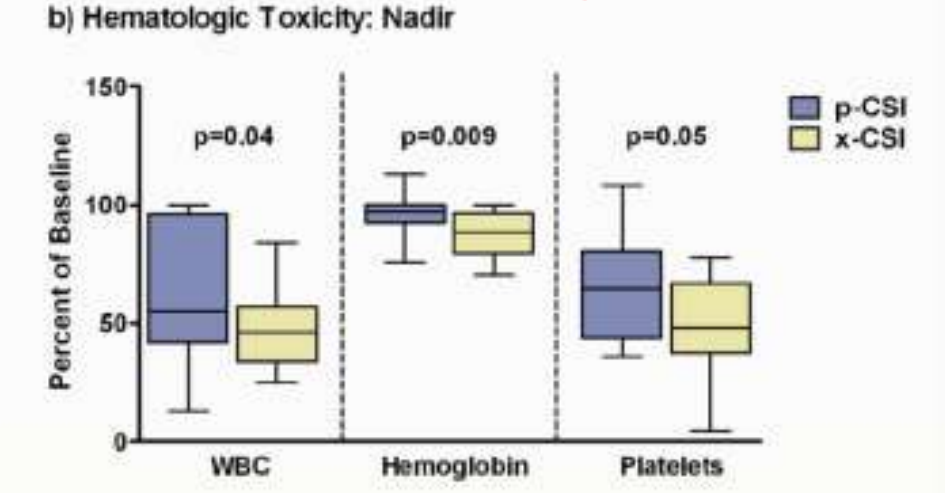
- GI toxicities (nausea, vomiting, dysphagia, anorexia and weight loss) are relatively common and can affect outcomes and quality of life.
- P-CSI had significant less weight loss and better recovery.

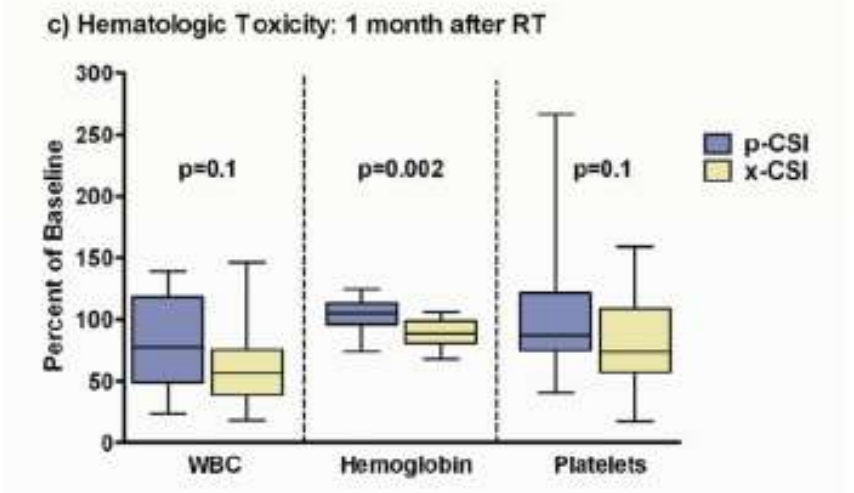
Int J Radiat Oncol Biol Phys. 2013 June 1; 86(2): 277–284.

Proton Beam Craniospinal Irradiation Reduces Acute Toxicity for Adults with Medulloblastoma

Aaron P. Brown

Median percentage of baseline WBCs, hemoglobine, platelets



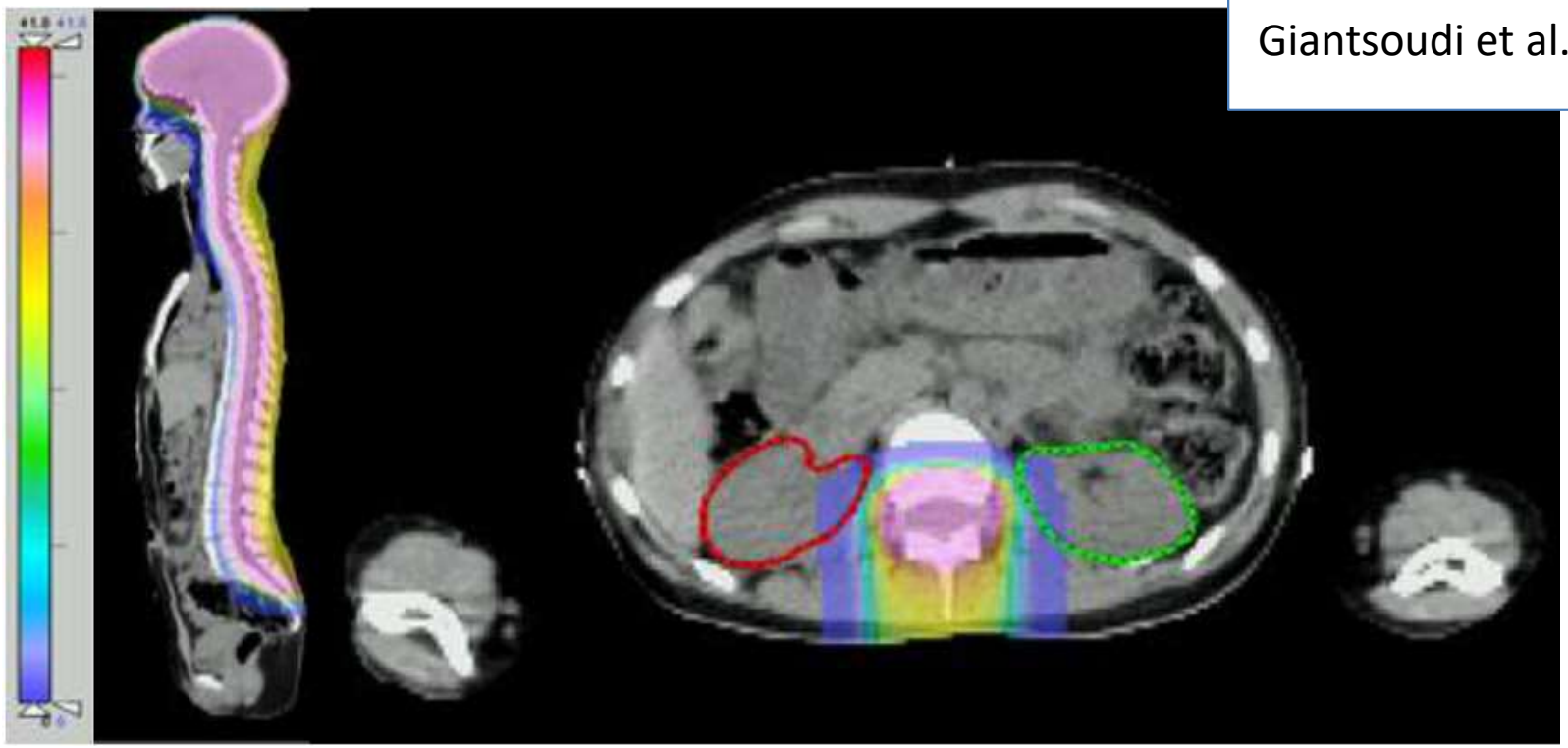


WBC	P-CSI x-CSI	55% (13-100%) 46% (25-84%)	P=0.04
Hemo-globin	P-CSI x-CSI	97% (76-113%) 88% (74-100%)	P=0.009
Platelets	P-CSI x-CSI	65% (36-108%) 48% (5-78%)	P=0.05

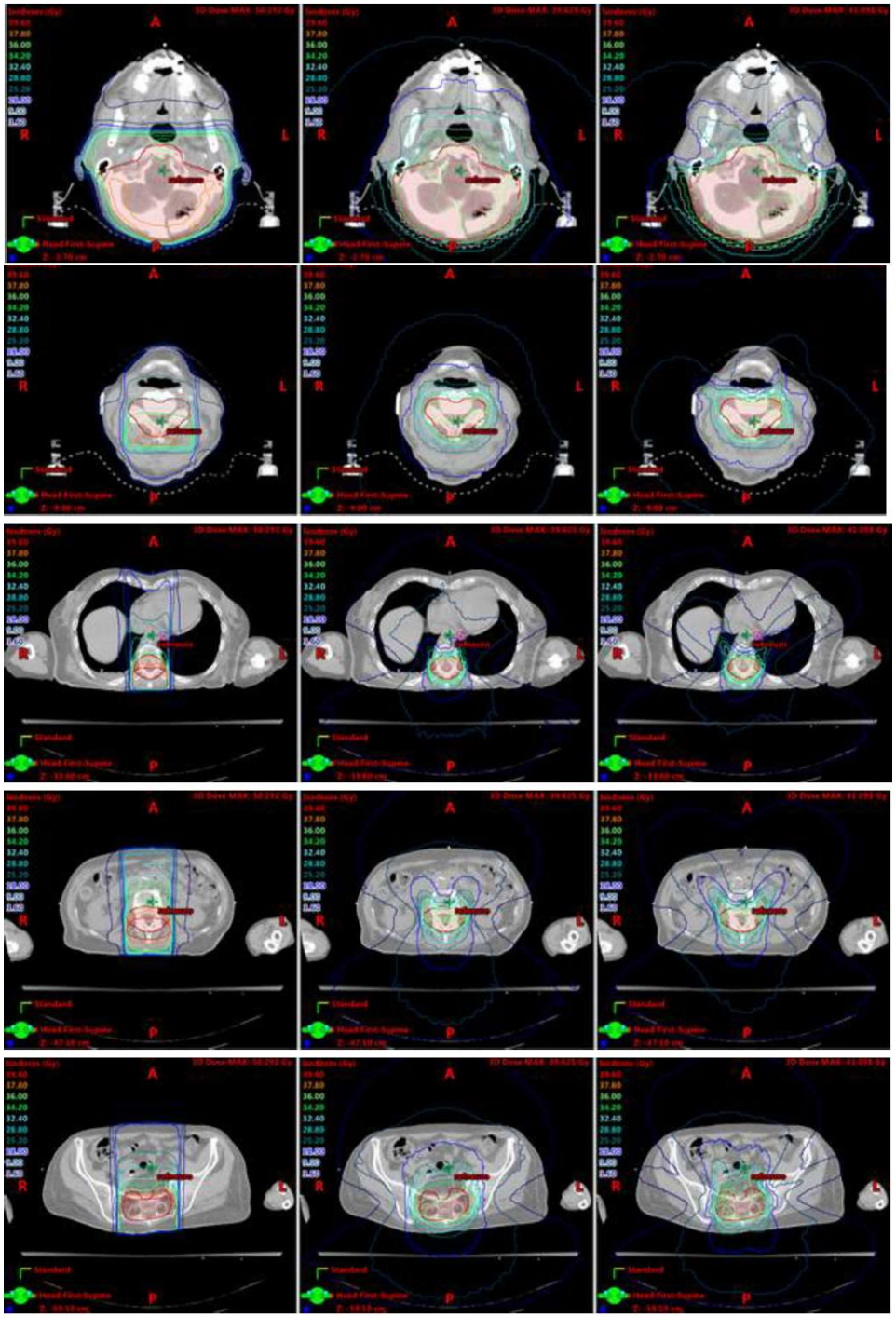
WBC	P-CSI x-CSI	78% (24-139%) 56% (18-146%)	P=0.1
Hemo-globin	P-CSI x-CSI	105% (74-124%) 88% (68-106%)	P=0.002
Platelets	P-CSI x-CSI	87% (41-266%) 73% (17-158%)	P=0.1

- P-CSI experienced significantly smaller reductions in blood counts than x-CSI
- Better recovery one month after RT in P-CSI than after x-CSI patients

Giantsoudi et al. 2017



Prescribed dose 23.4 RBE		Photons	Protons
V 10	cranial	100%	59.5%-76%
	thoracic		29.9% - 34.6%
	lumbal		20.6% - 25.1%
V20	cranial	99%	17.8% - 20 %
	thoracic		7.2% - 7.6%
	lumbal		4% -4.6%



Michal Devecka

Plan comparison:

- 3D-CRT
- Original HT
- Optimized HT

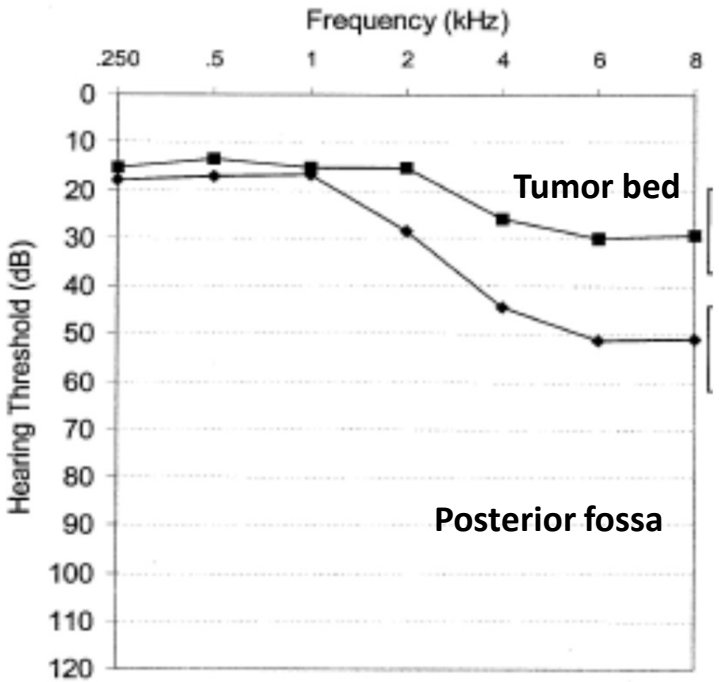
- Increasing mean vertebral dose is significantly associated with Nadir in WBC (thrombocytes,hemoglobin) after one month.
- More suff. Techniques can reduceBone marrow side effects.

Unpublished data

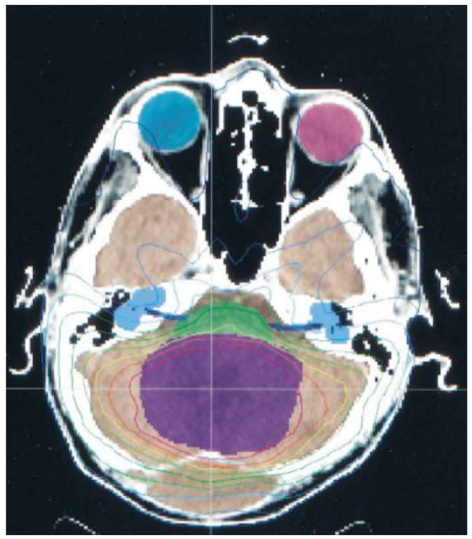
Protection of Inner the Ears /Medulloblastoma

Reduction of Ototoxicity by RT Technique

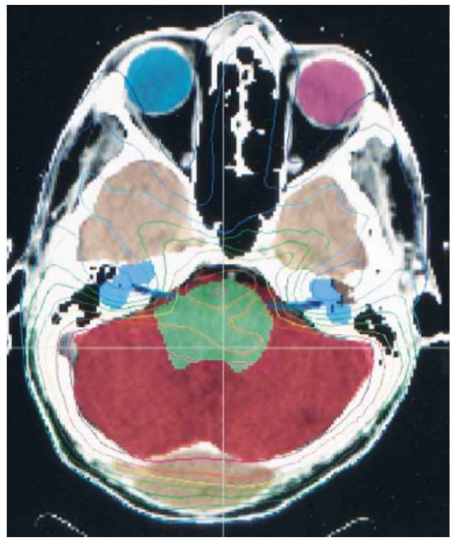
11 Pat. conv. : 23,4 Gy CSA / 54 Gy PF
15 Pat. IMRT : 23,4 Gy CSA / 36 Gy PF / 55.8 Gy tumorbed



Tumorbed / IMRT



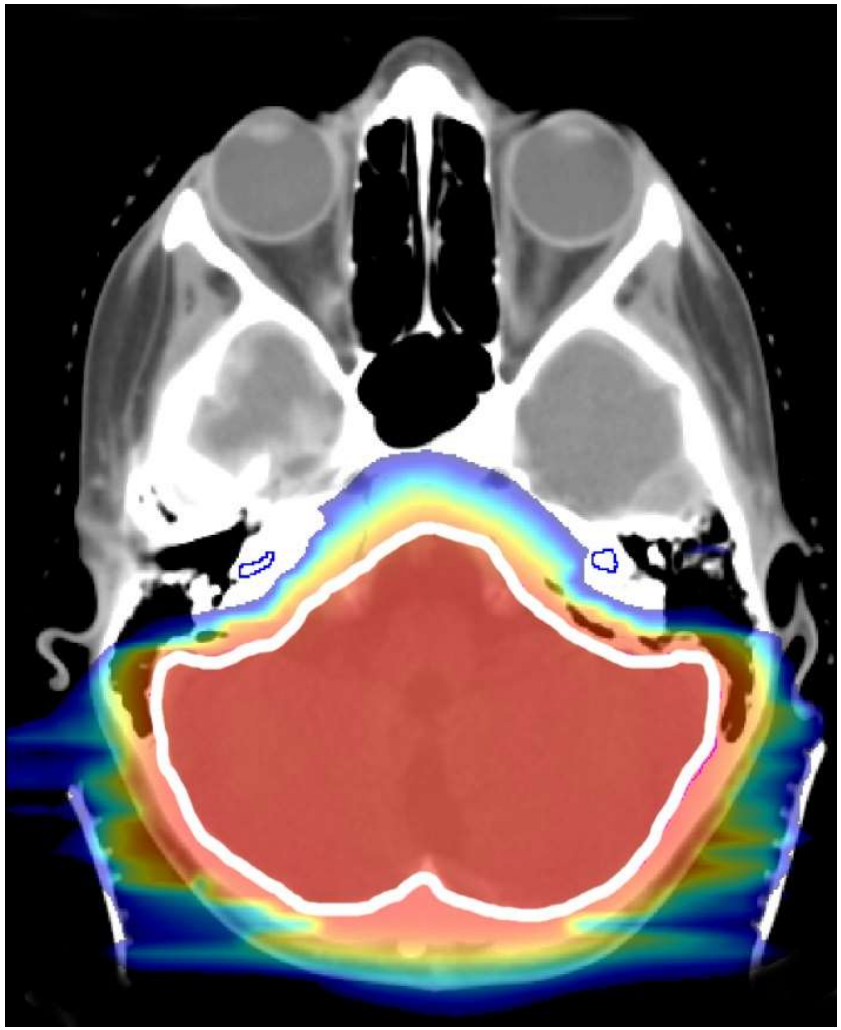
Post. Fossa / Conv.



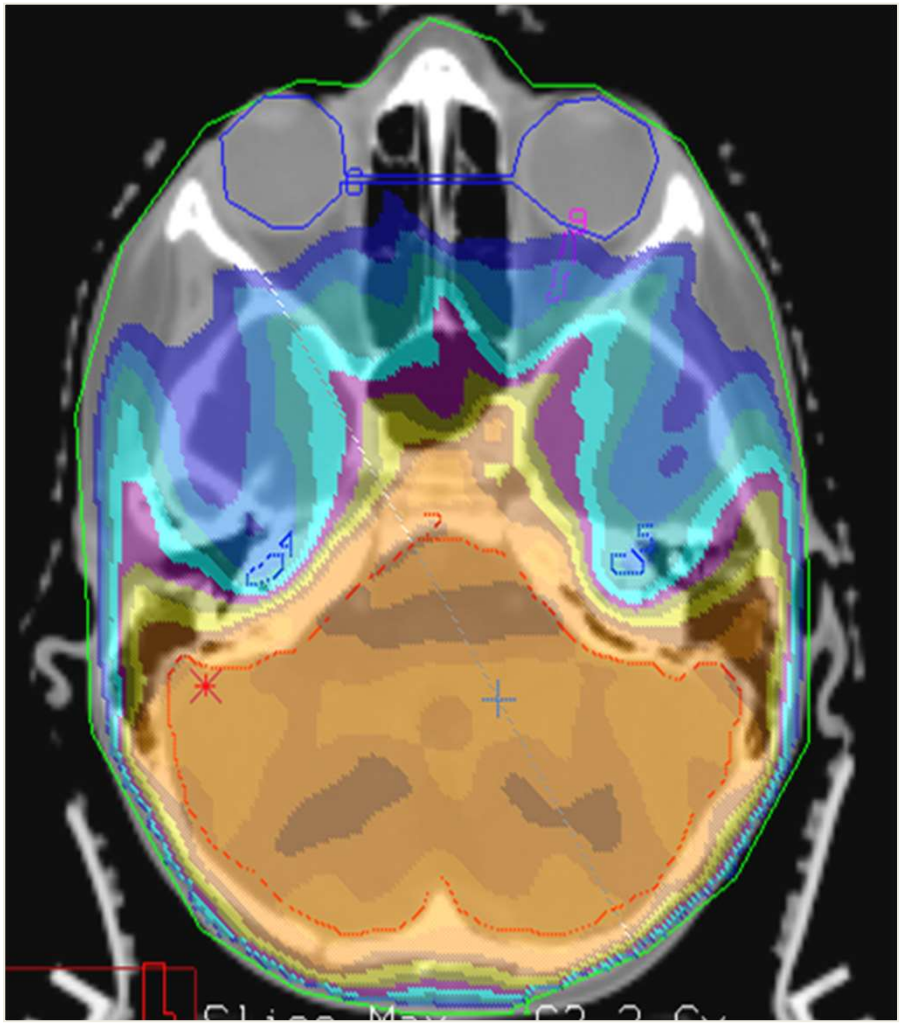
Huang et al., 2002

Protection of Inner the Ears / Protons vs IMRT

Protons



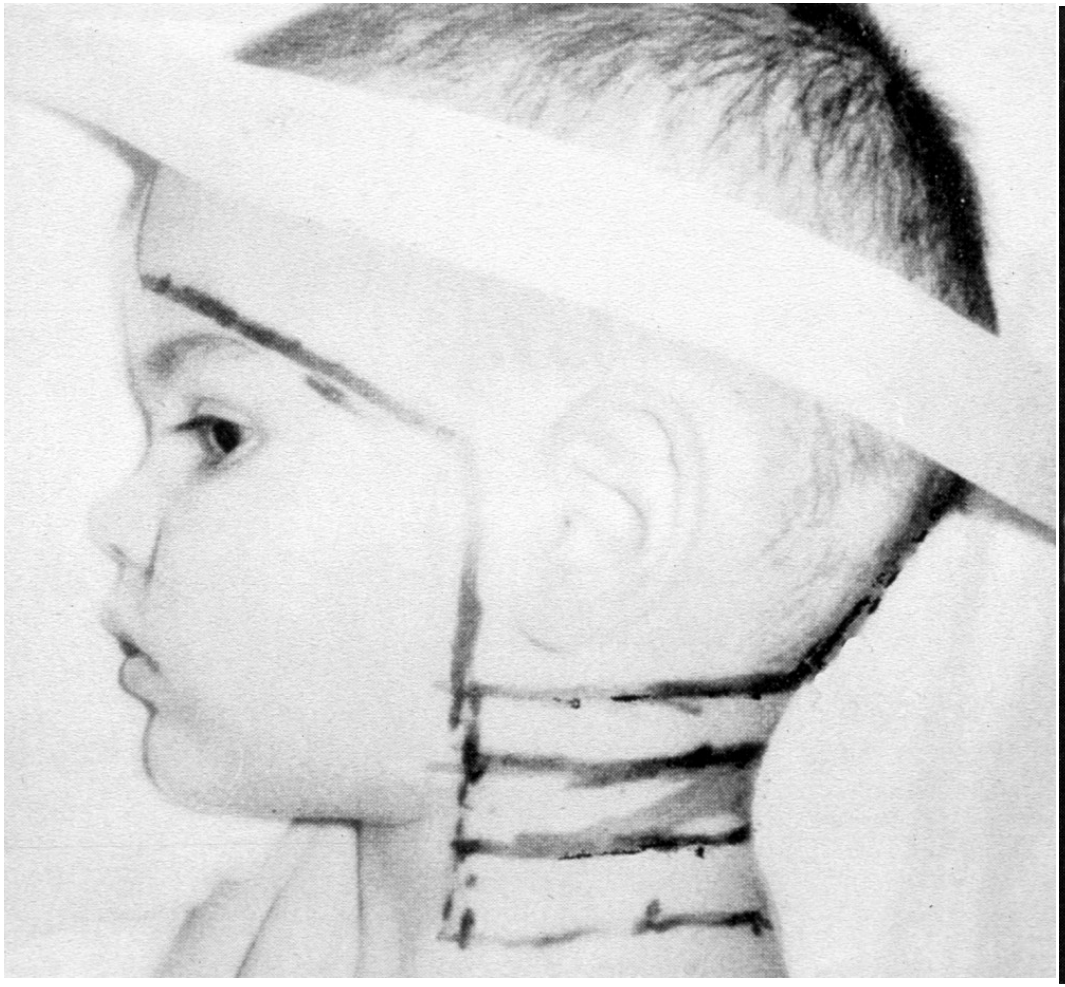
IMRT



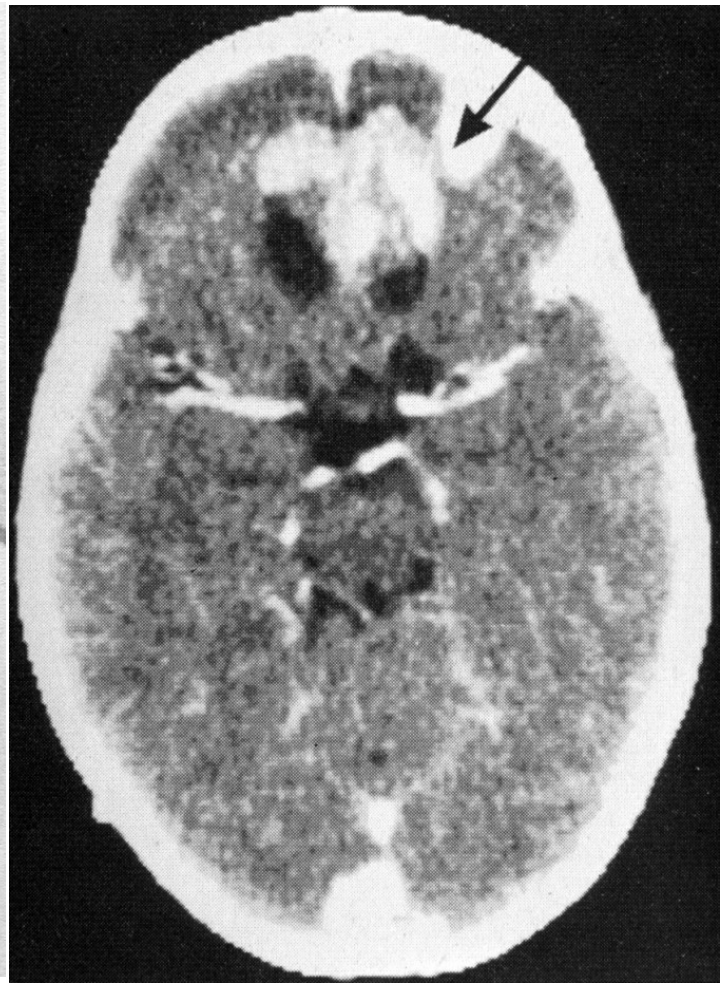
Tarbell et al., 2003

Quality of RT

„Helmet technique“



anterior cranial fossa shielded



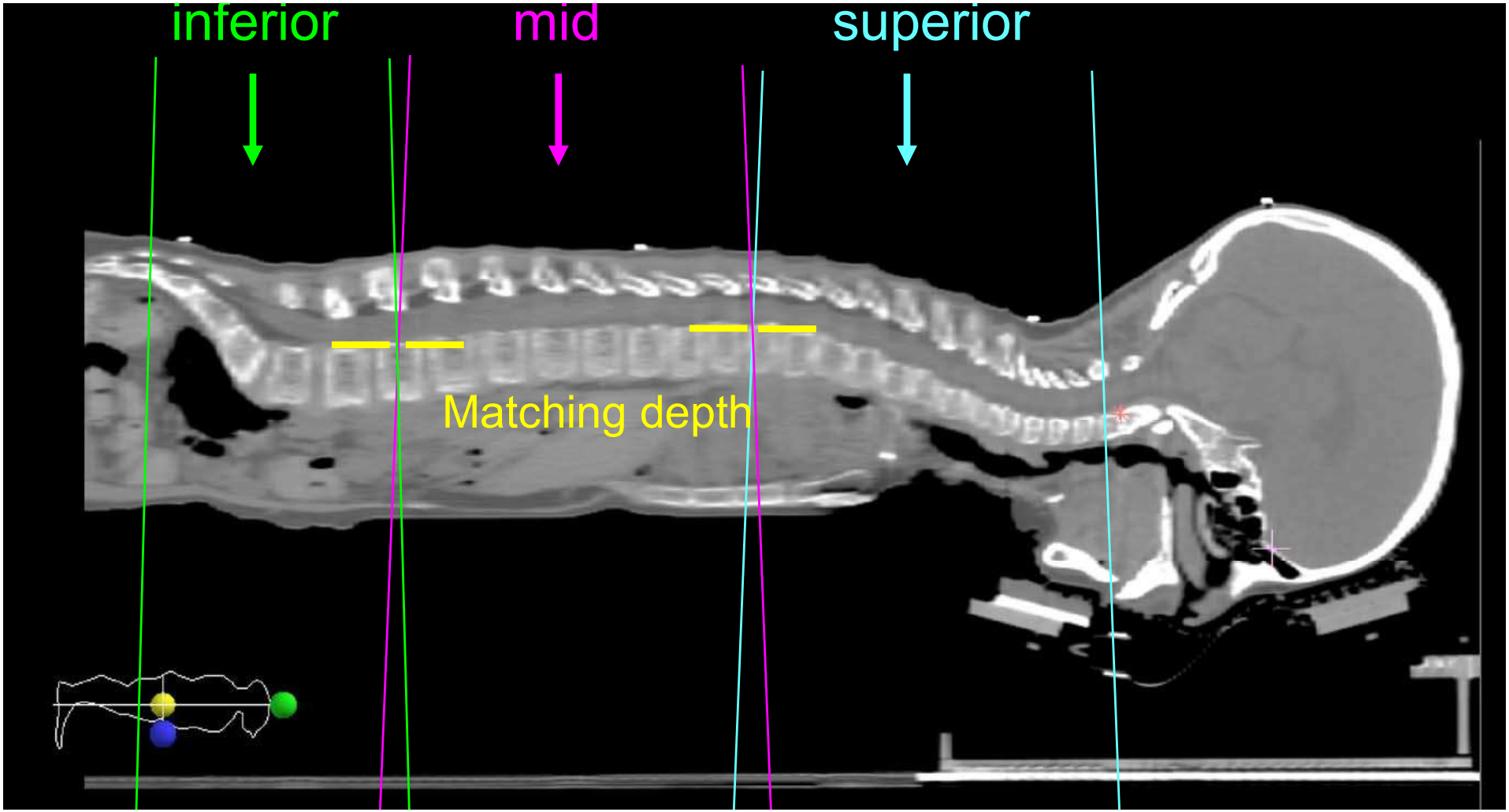
relapse

C. Carrie et al, 1994

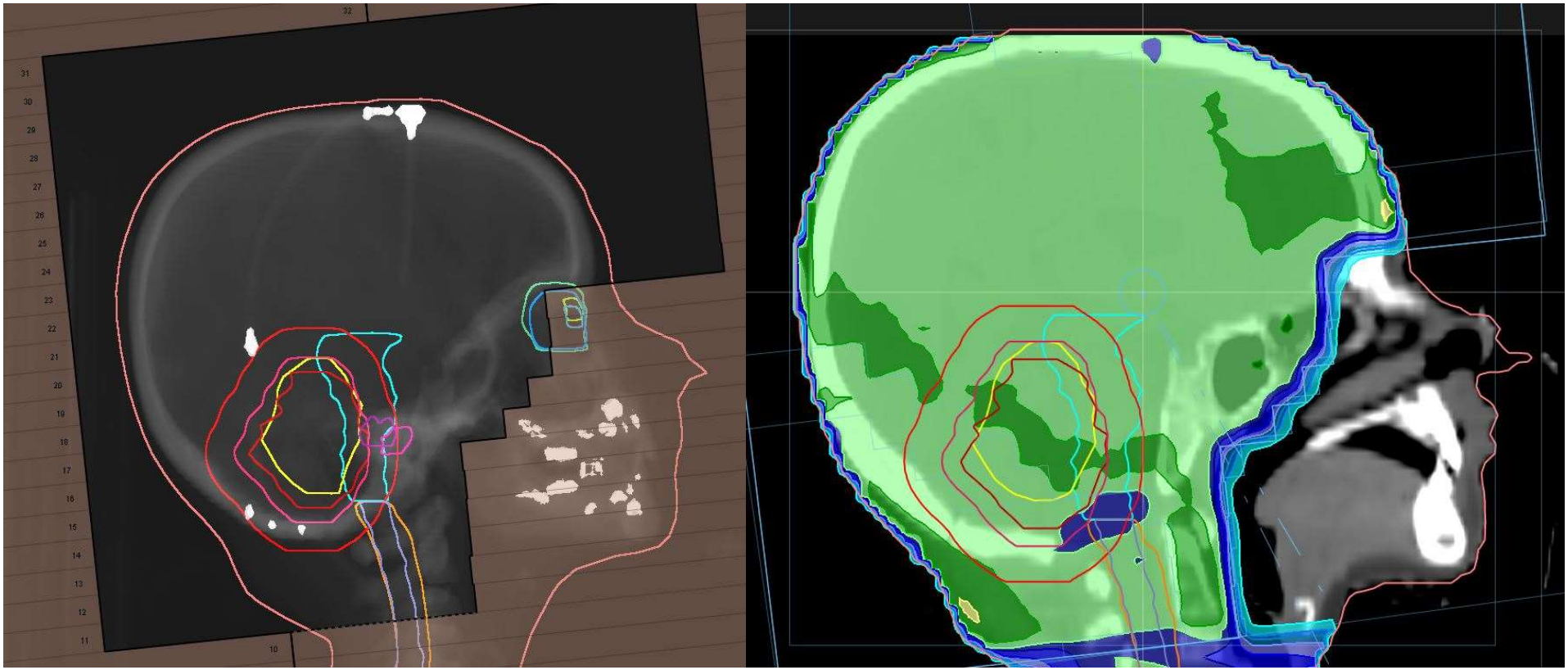
Medulloblastoma - Quality of Radiotherapy

Author/ study	*Pat.*	*"low quality"*	*"high quality"*	*Survival*	*Significance*
Packer et al., 1991	108	RT 1975 -82 n=67	RT 1983-89 n=41	49% vs.82% 5-y PFS	Significant P=0.004
Graben bauer et al., 1996	40	RT before 1980	RT after 1980	5-y overall survival 64% versus 80%	Significant p=0.02
Miralbell, et al.1997	77	36 inadequate „helmet-technique“	41 adequate „helmet-technique“	5-y PFS 94 % versus 72 %	Significant p=0.016
Carrie et al., 1999	169	Min. viol. :67 (40%) Maj. Viol. :53 (31%), Of these : 36 one maj. Viol. 11 two maj. Viol. 6 three maj.Viol.	49 (29%)	3 y. relapse rate 33% : all patients 23 % : corr. Treatment 17% : one maj. Viol. 67% : two maj. Viol. 78% : three maj. Viol.	Significant. P=0.04
Packer et al., 1999	63	Violations : 20	No viol.: 43	5-y PFS 81% vs. 70%	Not signif. P=0.42

Spinal Field Matching



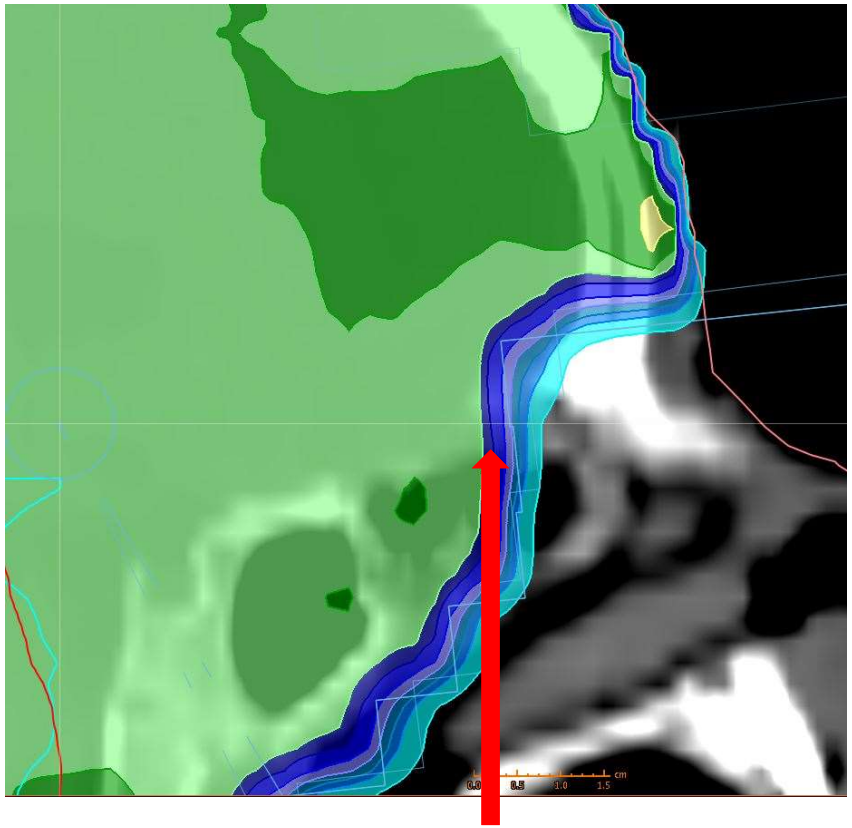
Quality Assurance



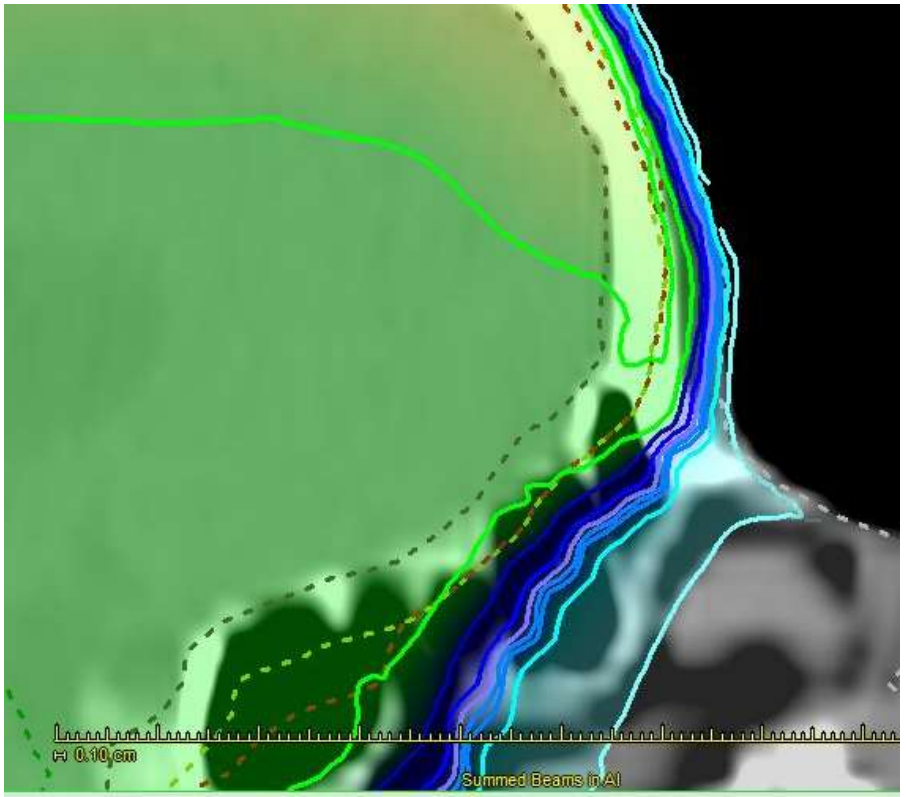
Quality Assurance

Review RT Plan / Example
Cribri Form Plate Blocked

major deviation



correct

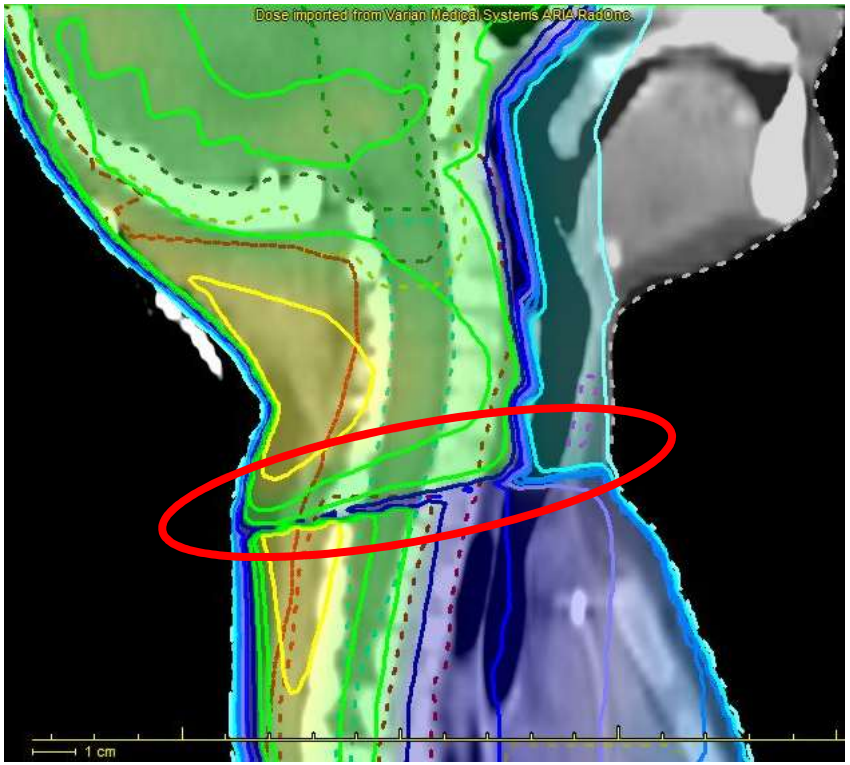


Blocked lamina Cribrosa

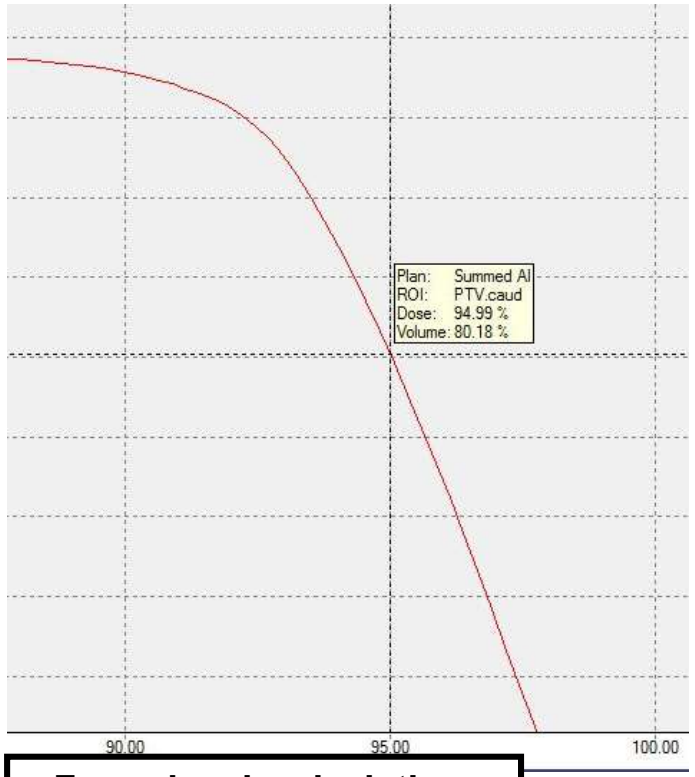
Quality Assurance Medulloblastoma

Dosis Homogeneity / Spinal Cord

Field junction, underdosage



DVH



Formal major deviation, Underdoses at other site (soft tissue and junction) clin. not relevant

Conclusion

- There will be an advantage in switching from conventional photon therapy to complex techniques and proton therapy.

- Target delineation and definition becomes more and more Important in treatment planning.

  - Cave: Lamina cribrosa
    optic nerve
    Inner ear
    Skull base

- Stable and reproducible positioning of the patient on daily imaging control is necessary adapting targets to anatomical structures.

Localised radiotherapy techniques

for intracranial tumours

Michael Brada

ESTRO BT course

Vienna 22 October 2017

Terminology of local RT delivery techniques

3D conformal radiotherapy

IMRT

stereotactic radiotherapy

stereotactic radiosurgery

volumetric arcing IMRT (VMAT/RapidArc)

tomotherapy

particle therapy

the reality of local RT terminology

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

- 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)

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

Classification of radiotherapy technologies

MRI in the radiotherapy process

Challenges to accuracy of target delineation

operator dependent	technical
visualisation	coregistration
interpretation	distortion

MRI in the radiotherapy process

Challenges to accuracy of target delineation

operator dependent	technical
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MRI in the radiotherapy process

Challenges to accuracy of target delineation

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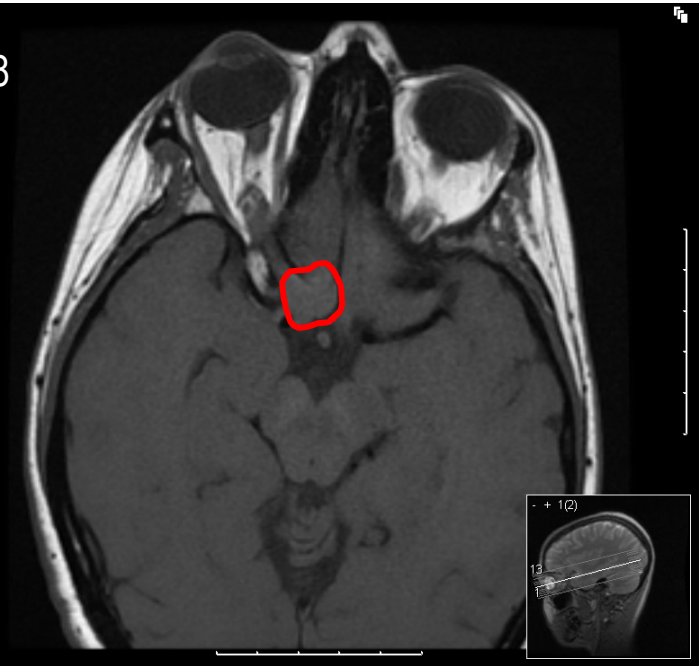
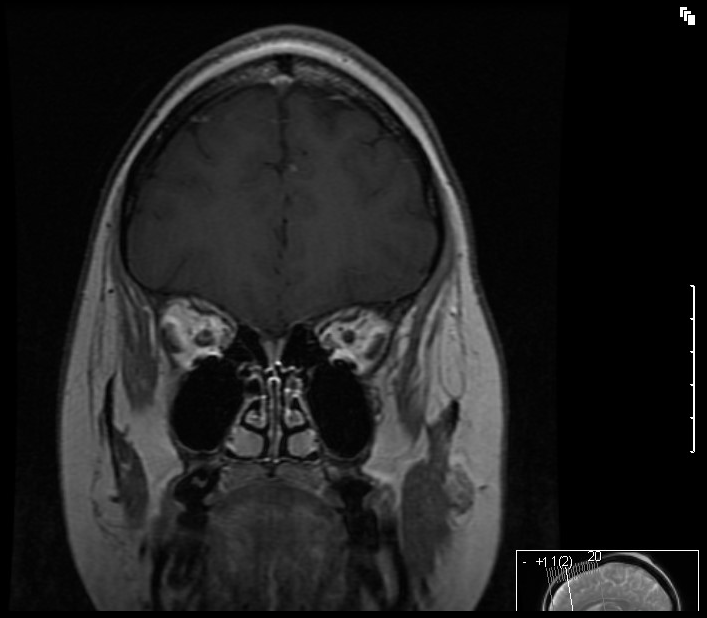
12.8.08



30.11.07



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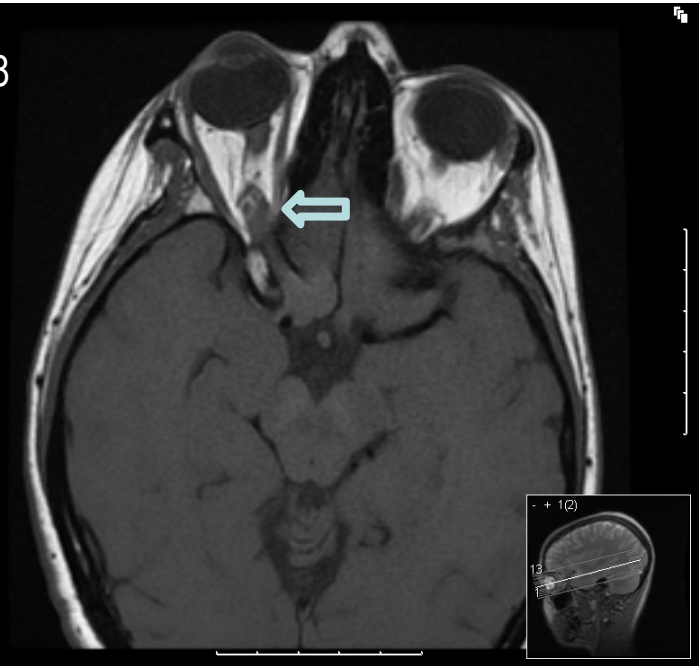

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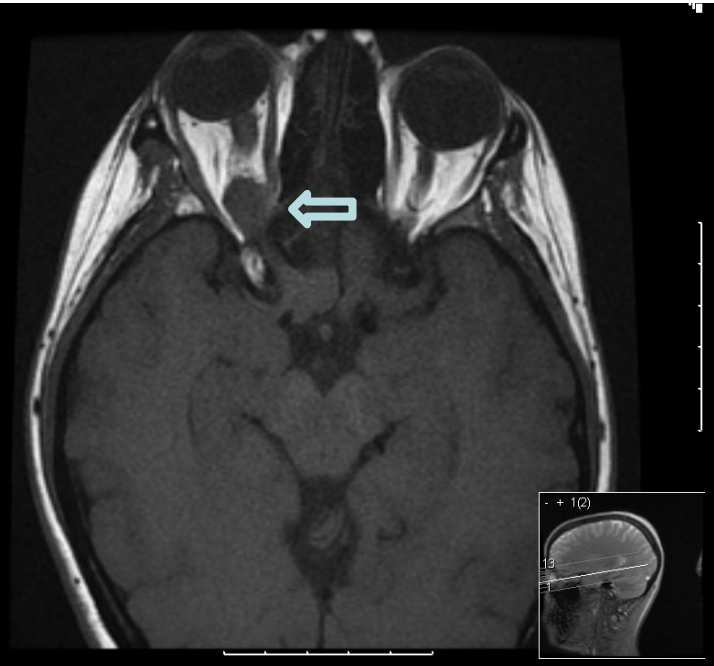

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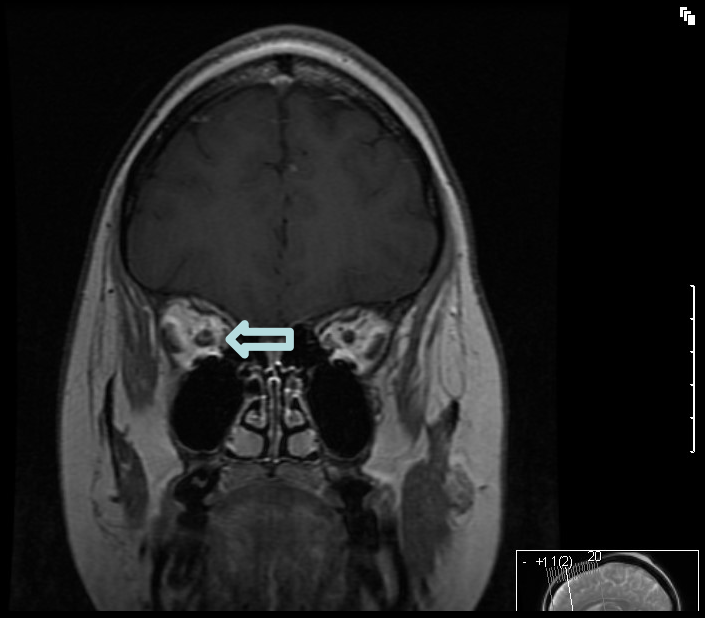

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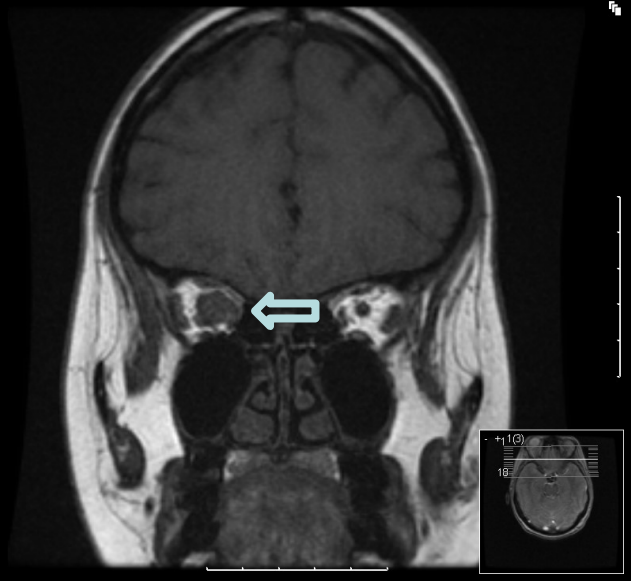
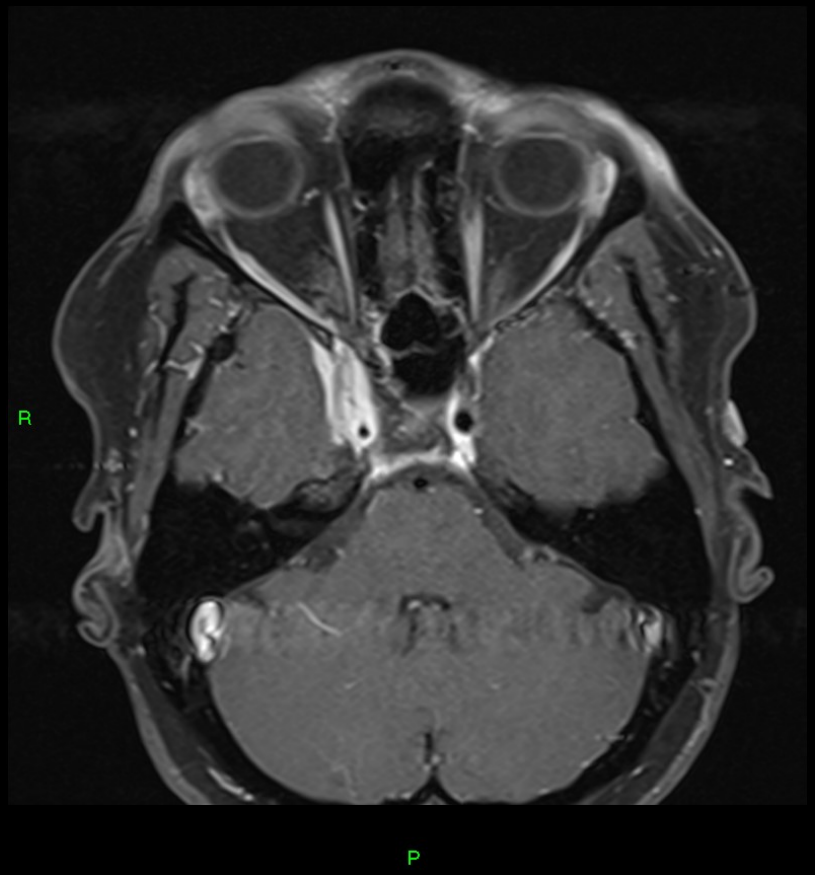
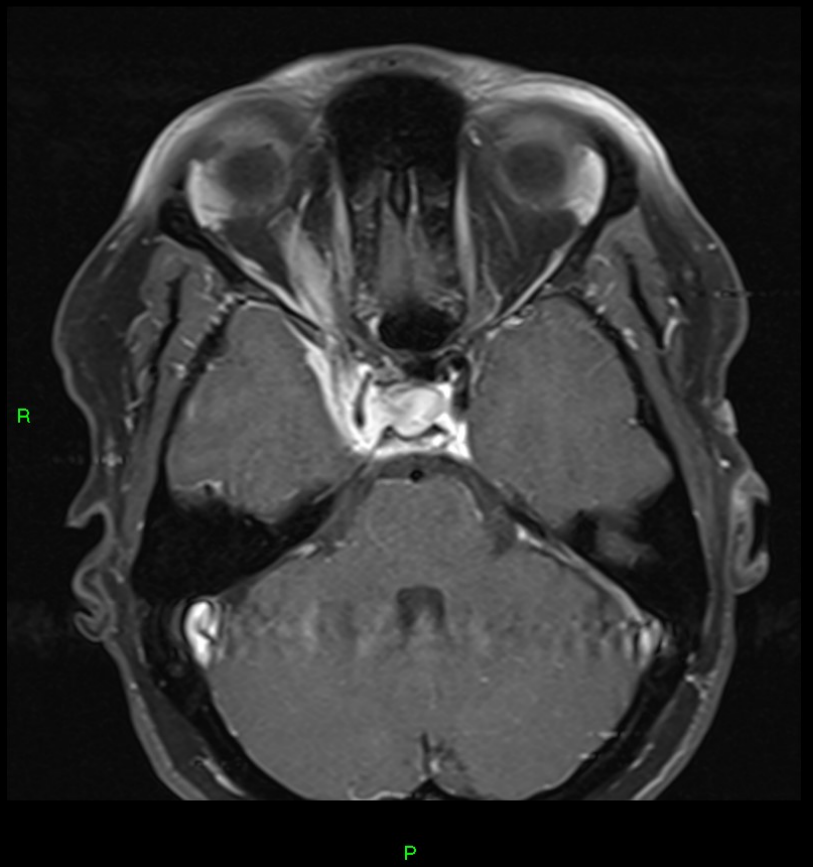
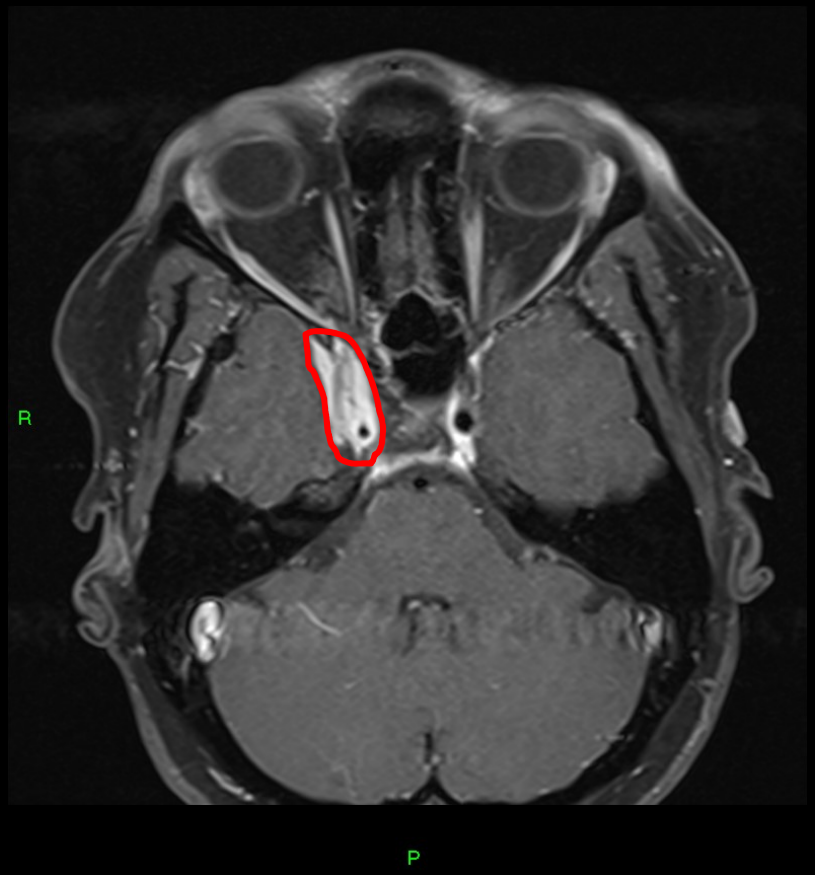


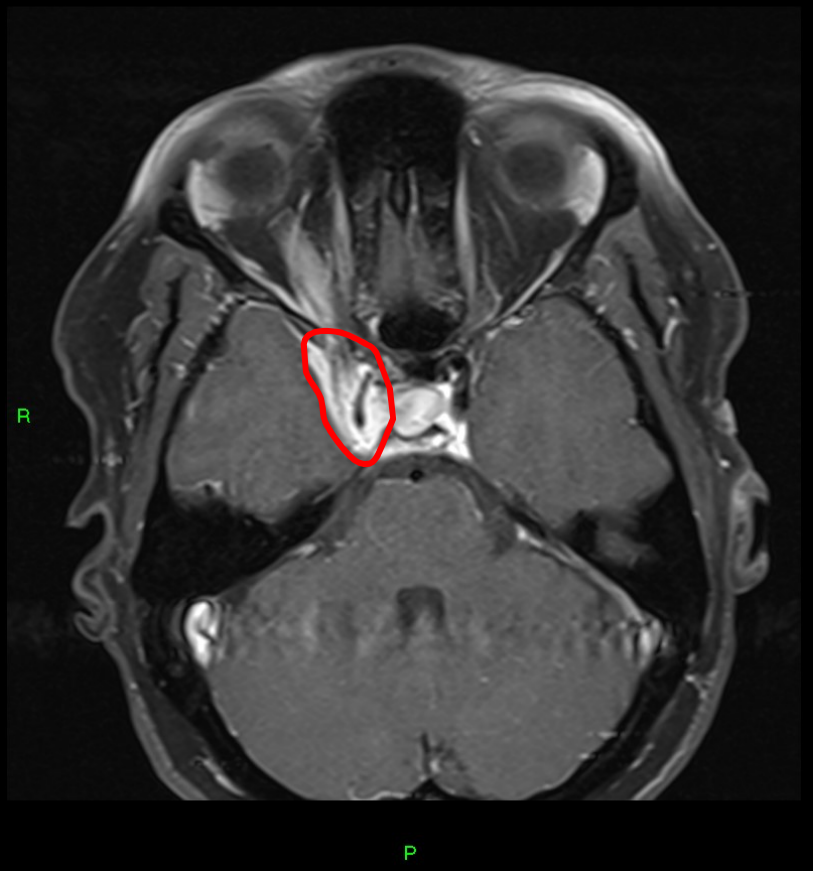
cavernous meningioma



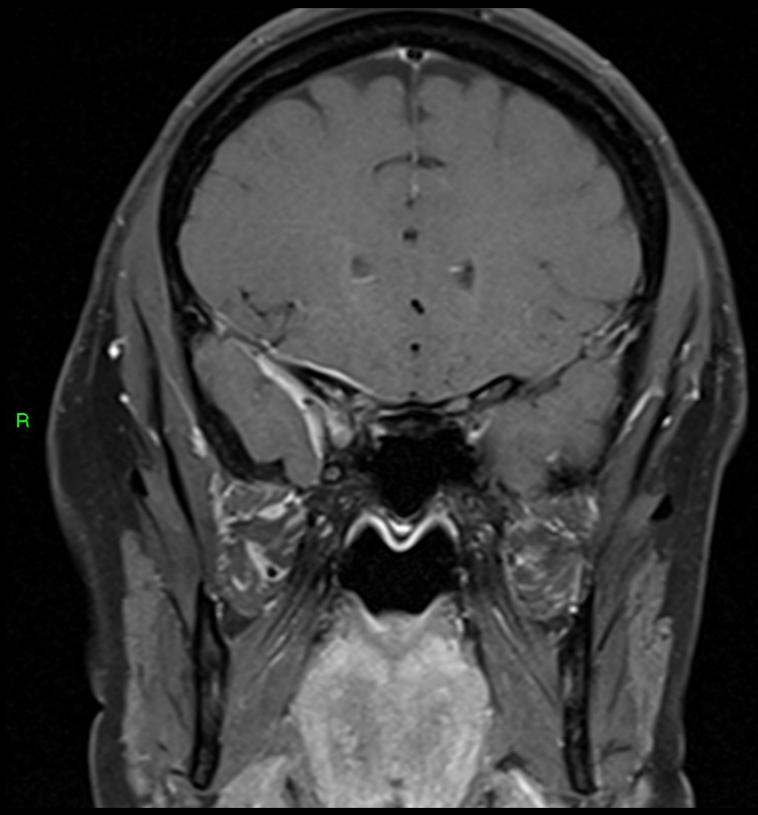


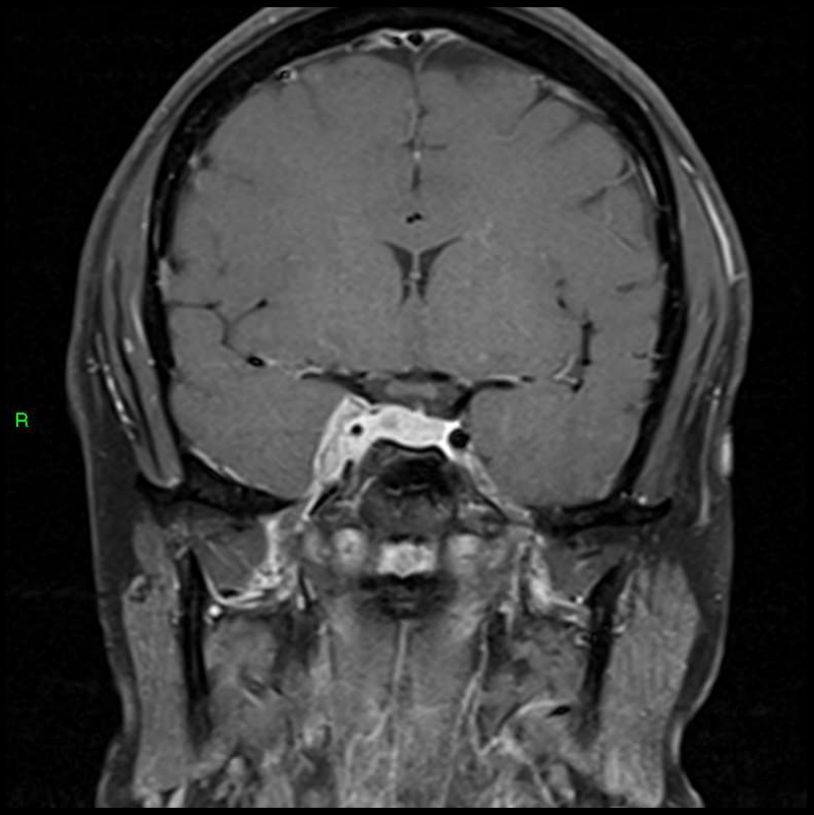
cavernous meningioma



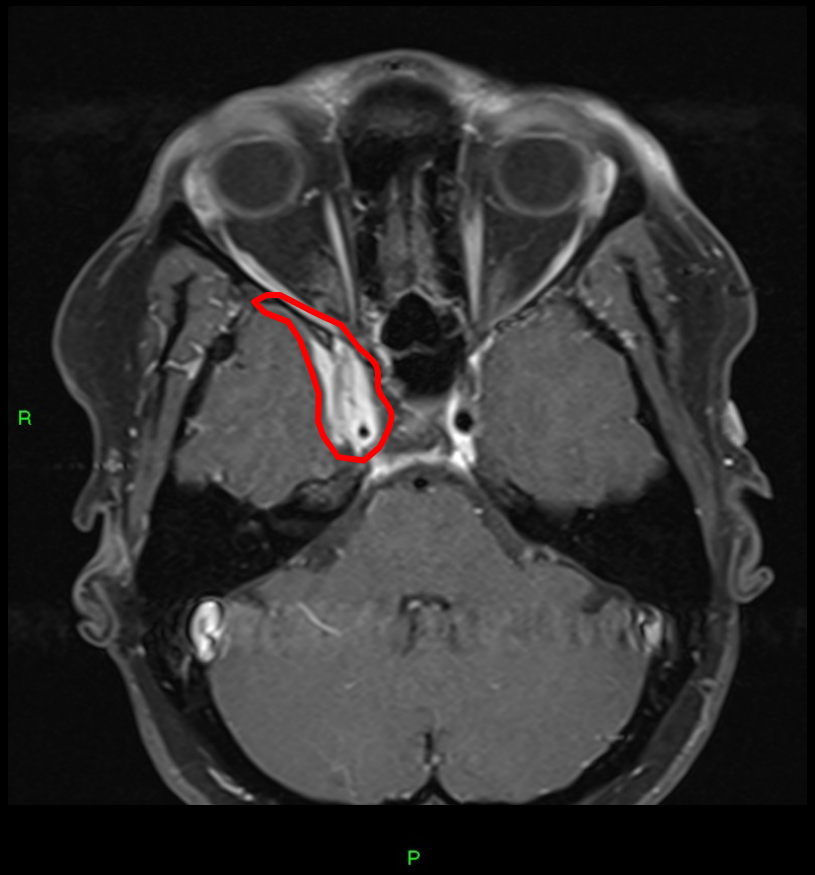


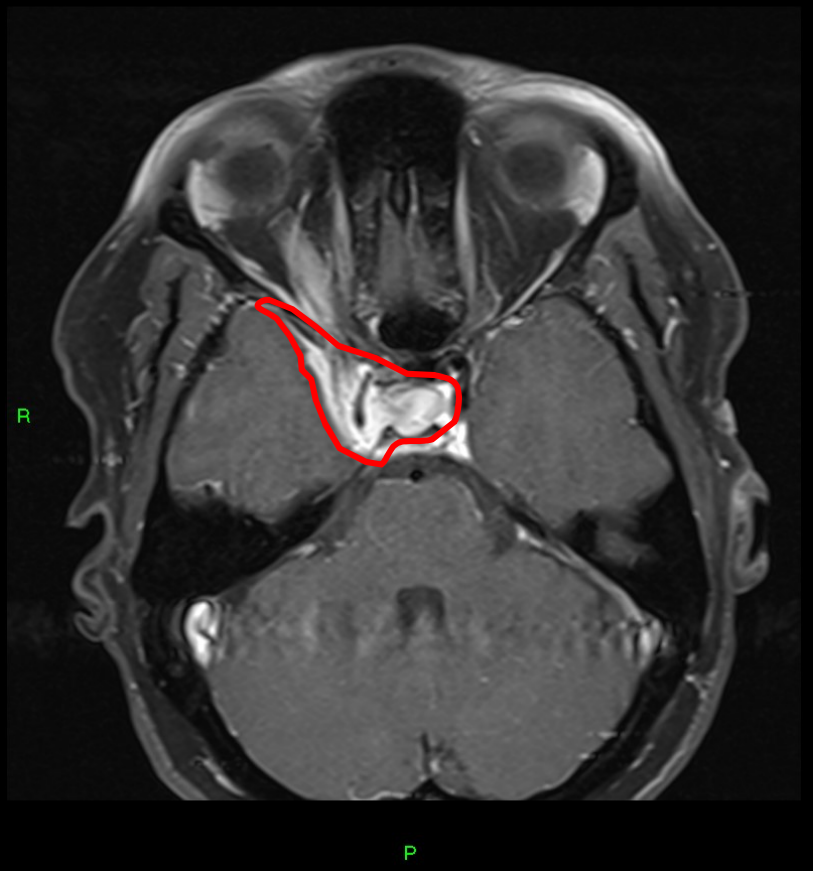
cavernous meningioma





cavernous meningioma





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

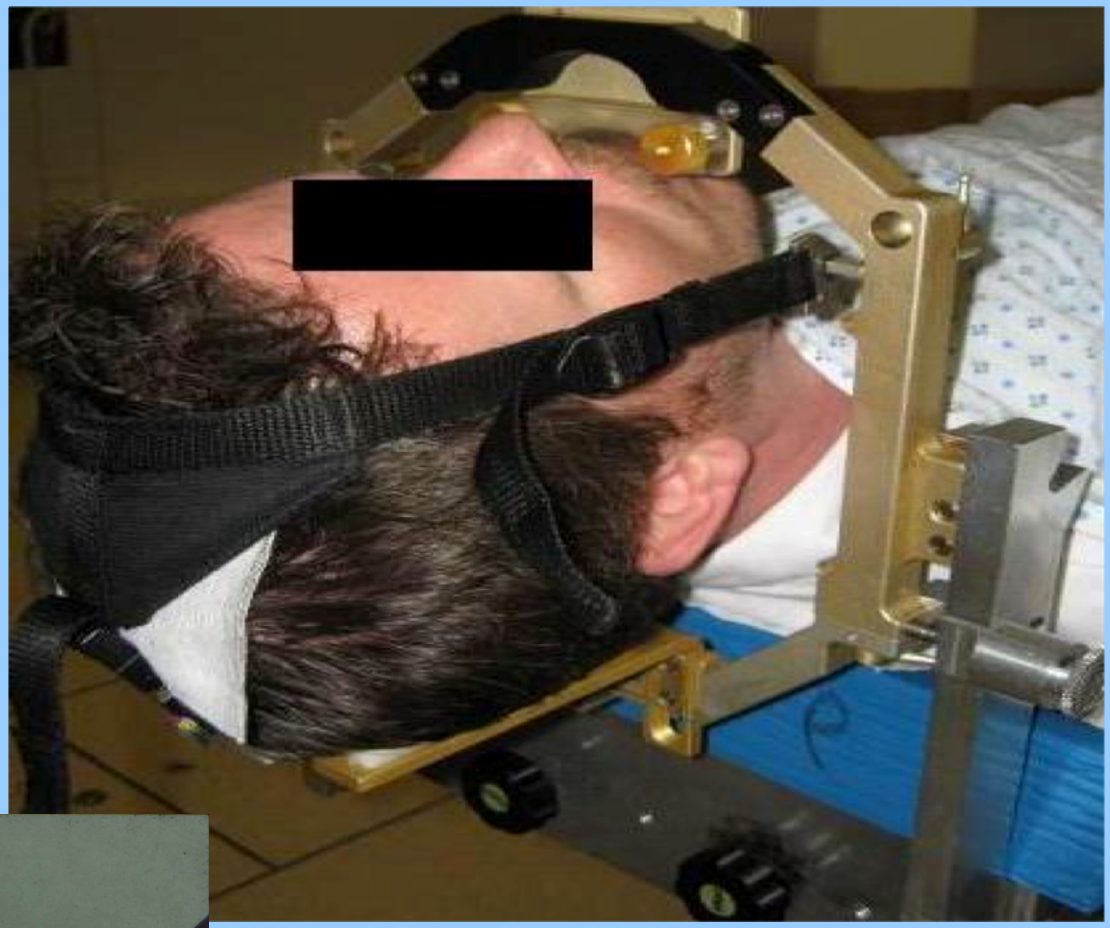
quality assurance

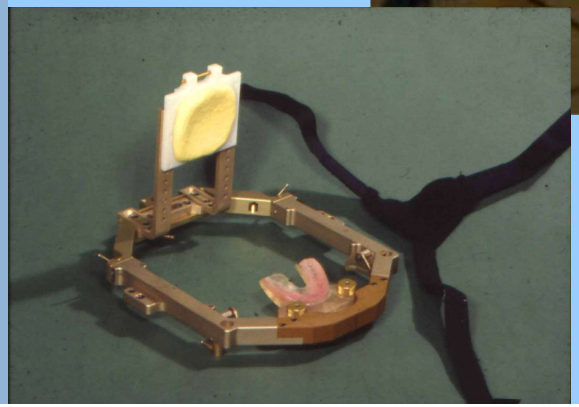
- imaging closer to treatment delivery (IGRT)

Classification of radiotherapy technologies

Frame system

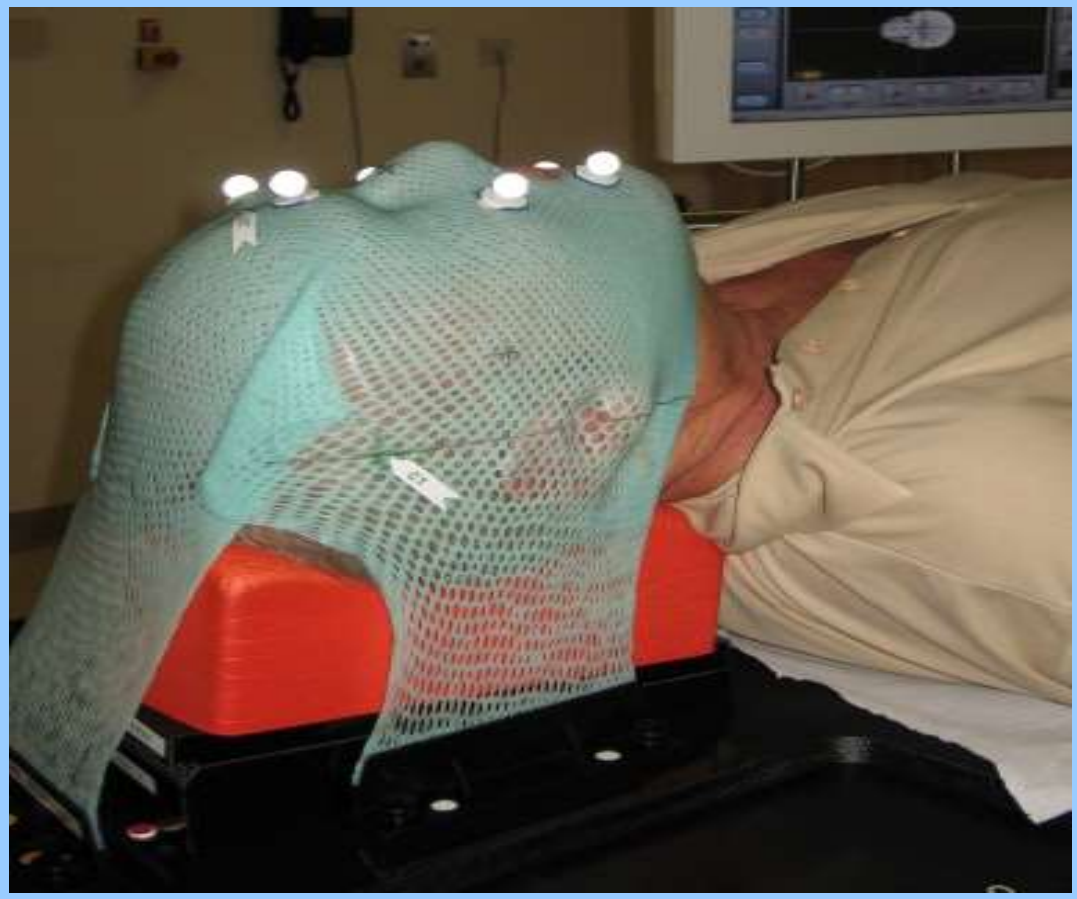
GTC relocatable frame





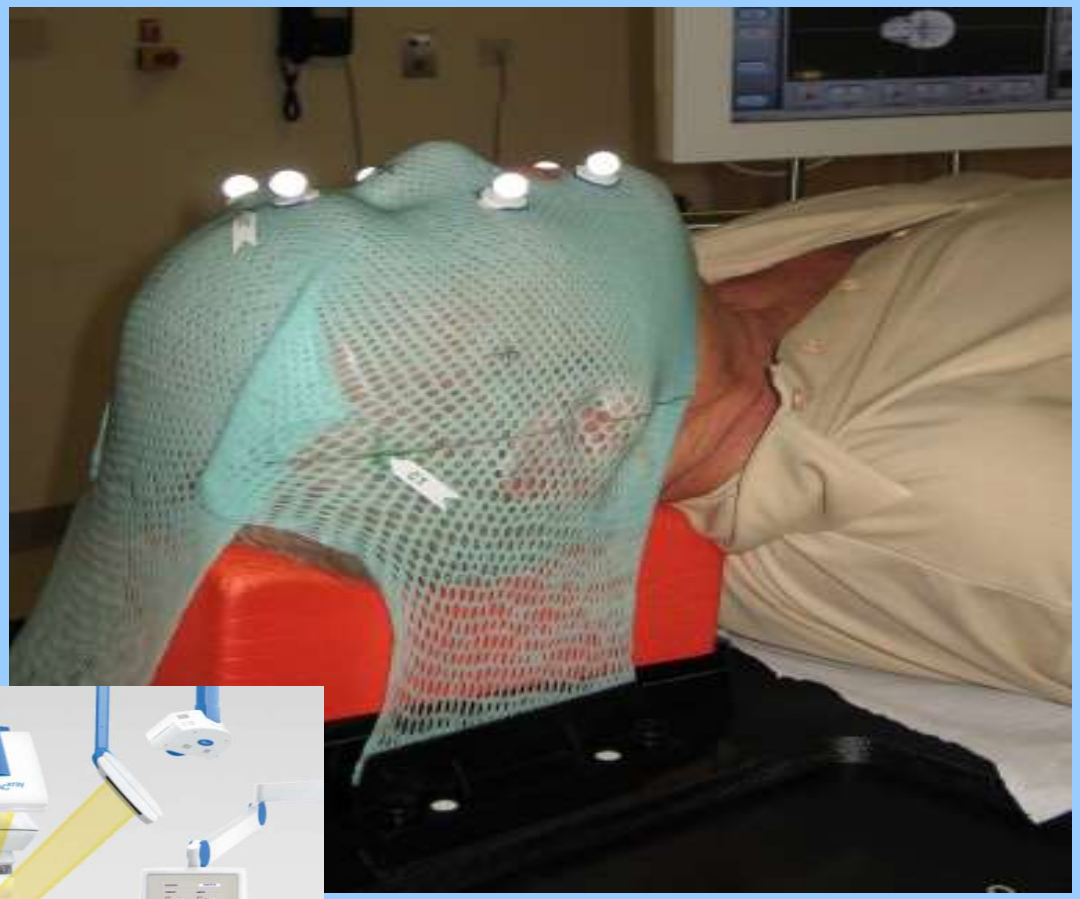
Methods of immobilization

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
Less expensive
2-3 visits for planning
Relocation accuracy 3-5 mm

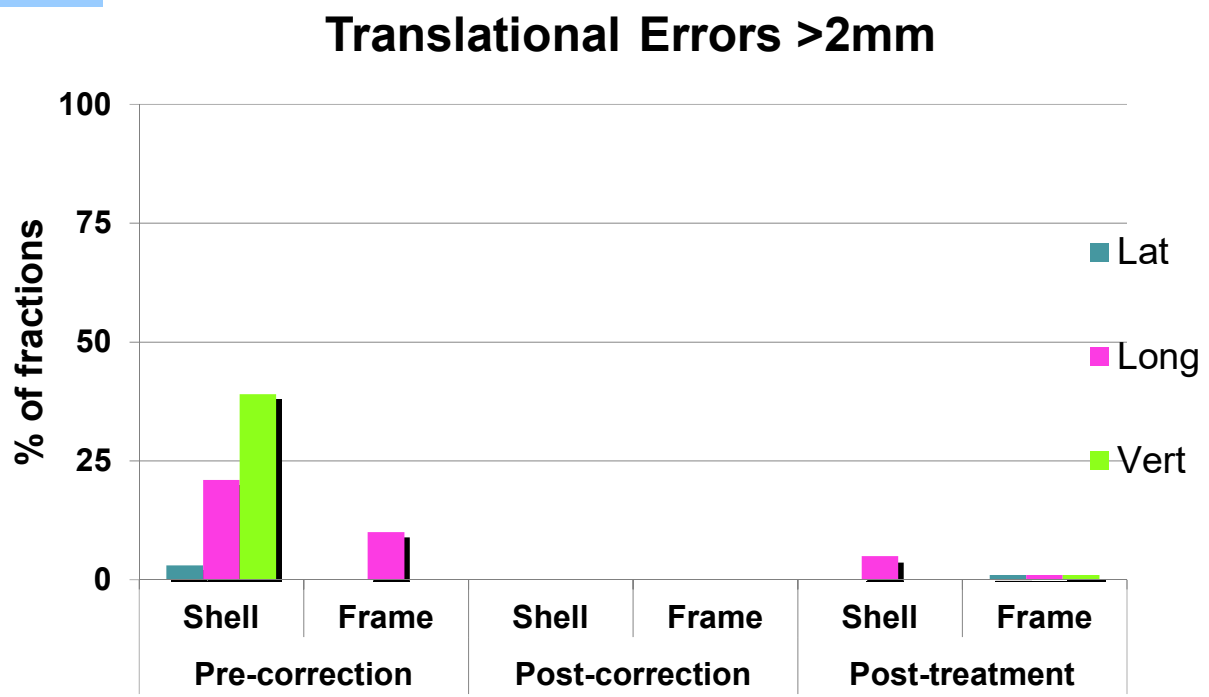
Comparison of immobilisation techniques

The ExacTrac kV stereoscopic image verification system

Comparison of immobilisation techniques

IGRT with ExacTrac kV stereoscopic image verification system

Errors



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**

target delivery
normal tissue avoidance

time factor (4D

- intrafracti
- interfraction changes in tumour & normal tissue

quality assurance

- imaging closer to treatment delivery (IGRT)

Classification of radiotherapy technologies

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- **photons**
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- intrafractio
- interfraction changes in tumour & normal tissue

quality assurance

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target delivery

normal tissue avoidance

- noncritical adjacent normal tissue
- critical OARs

Classification of radiotherapy technologies

Attributes of modern local RT delivery

refinements of conformal radiotherapy

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photons

protons

time factor (4D

intrafractio

interfraction changes in tumour & normal tissue

quality assurance

imaging closer to treatment delivery (IGRT)

Delivery equipment

linac - conventional/adapted
small linac on robotic arm (Cyberknife)
helical rotating linac (Tomotherapy)
multiheaded Cobalt unit (Gamma Knife)

Classification of radiotherapy technologies

Attributes of modern local RT delivery

refinements of conformal radiotherapy

precision

conformality

photons

protons

time factor (4D

intrafractio

interfractio

quality assurance

imaging closer to treatment delivery (IGRT)

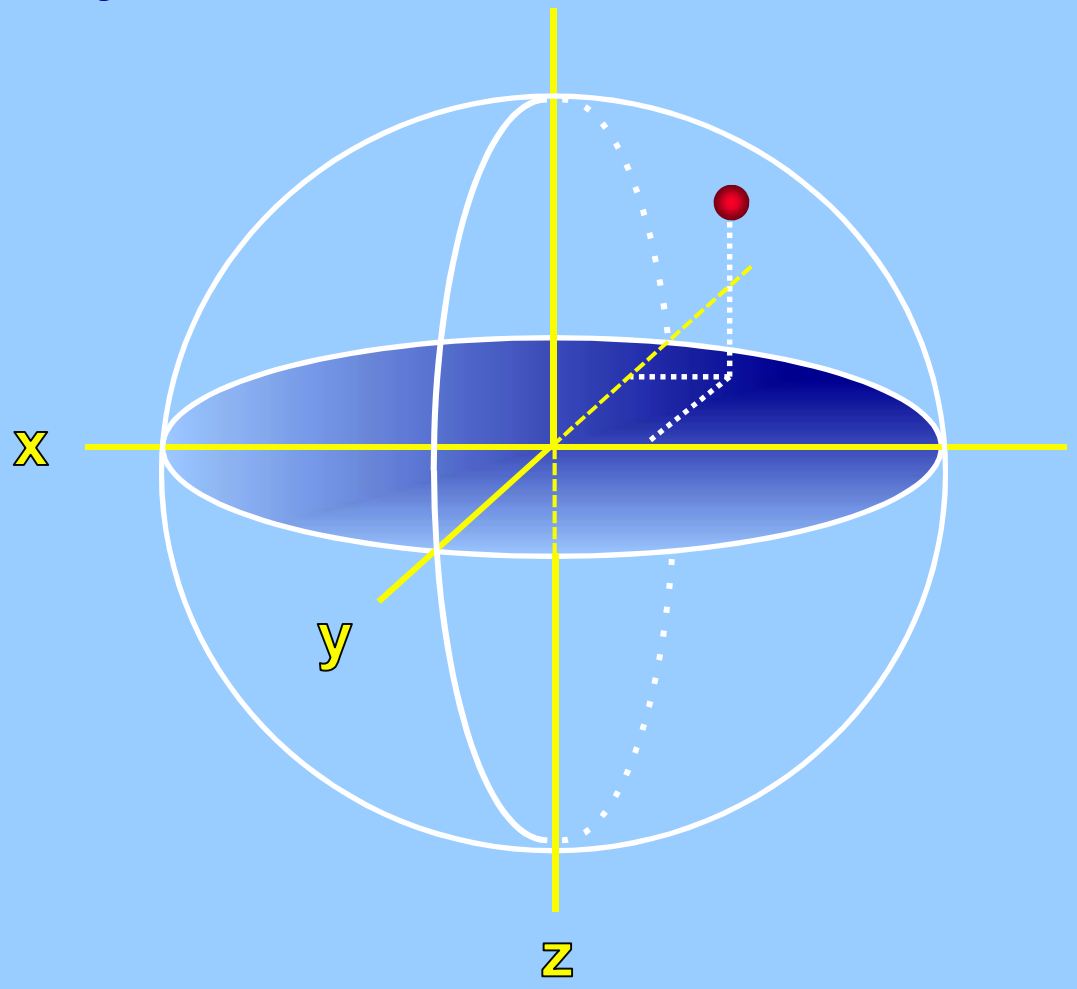
Delivery techniques

multiple conformal fixed fields
single or multiple/dynamic arcs +/- IMRT
single or multiple isocentres
multiple sources & isocentres (GK)
multiple small beams & isocentres (CK)

stereotactic

Classification of radiotherapy technologies

Stereotaxy



Classification of radiotherapy technologies

Stereotaxy

"stereotactic radiotherapy"
is marketing terminology

Classification of radiotherapy technologies

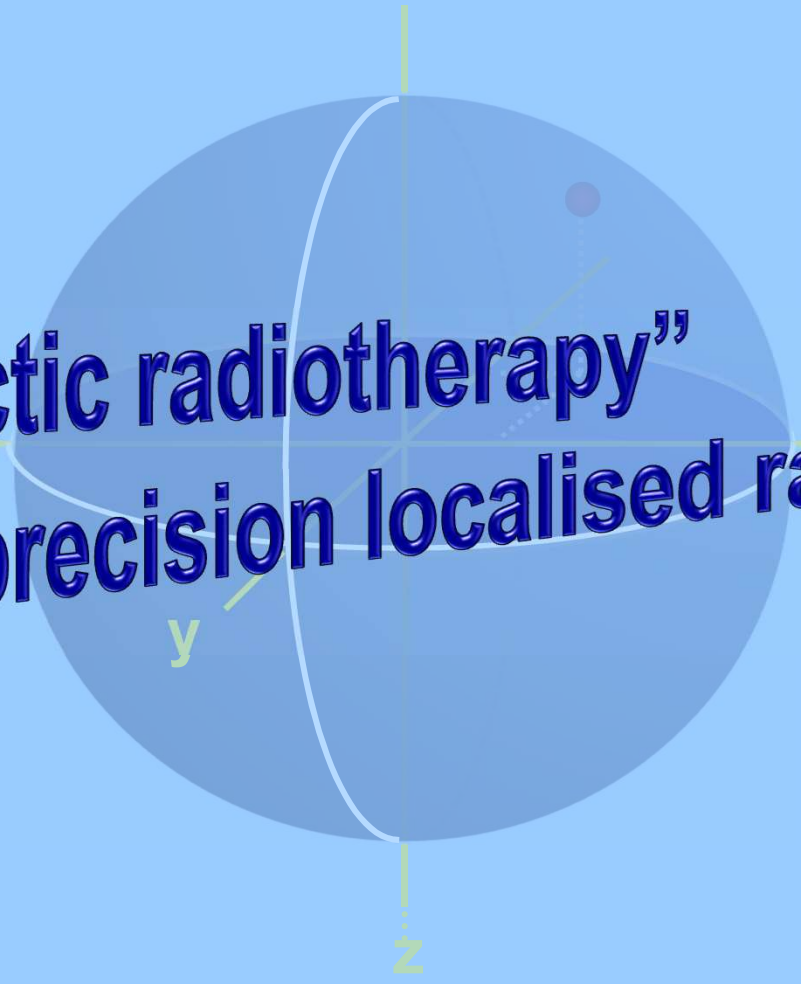
Stereotactic radiotherapy attributes

- Precision
- Conformality
- Dose
- Fractionation

High precision localised radiotherapy

Deconstructing stereotactic radiotherapy

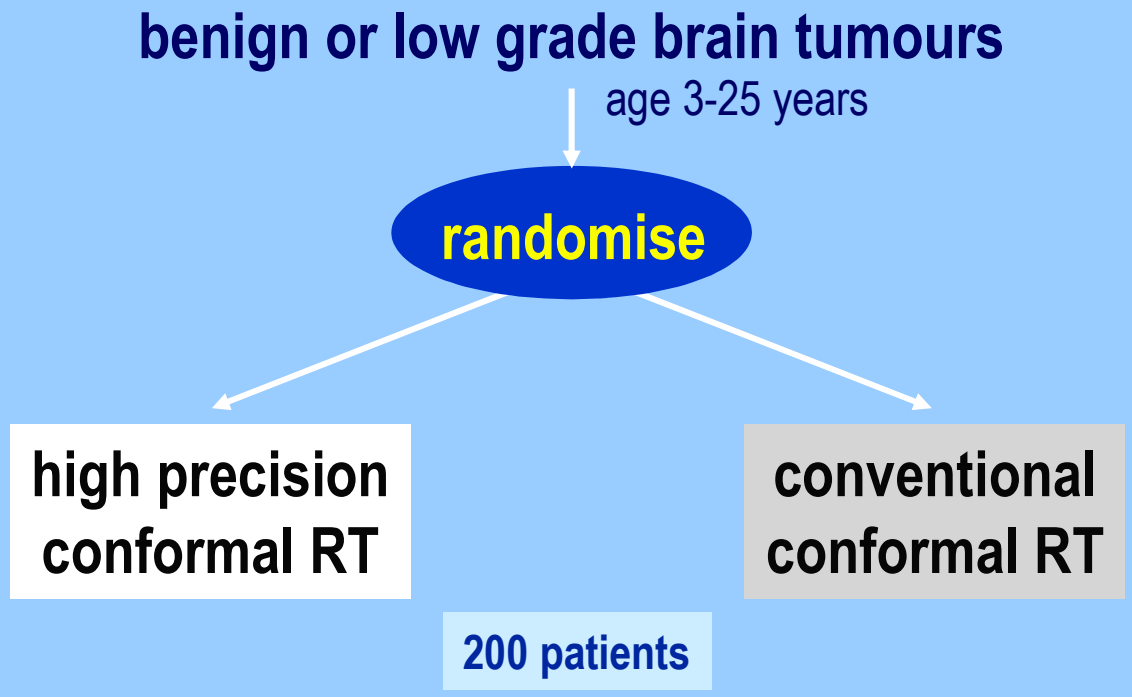
Stereotaxy



"stereotactic radiotherapy"
is a high precision localised radiotherapy

Classification of radiotherapy technologies

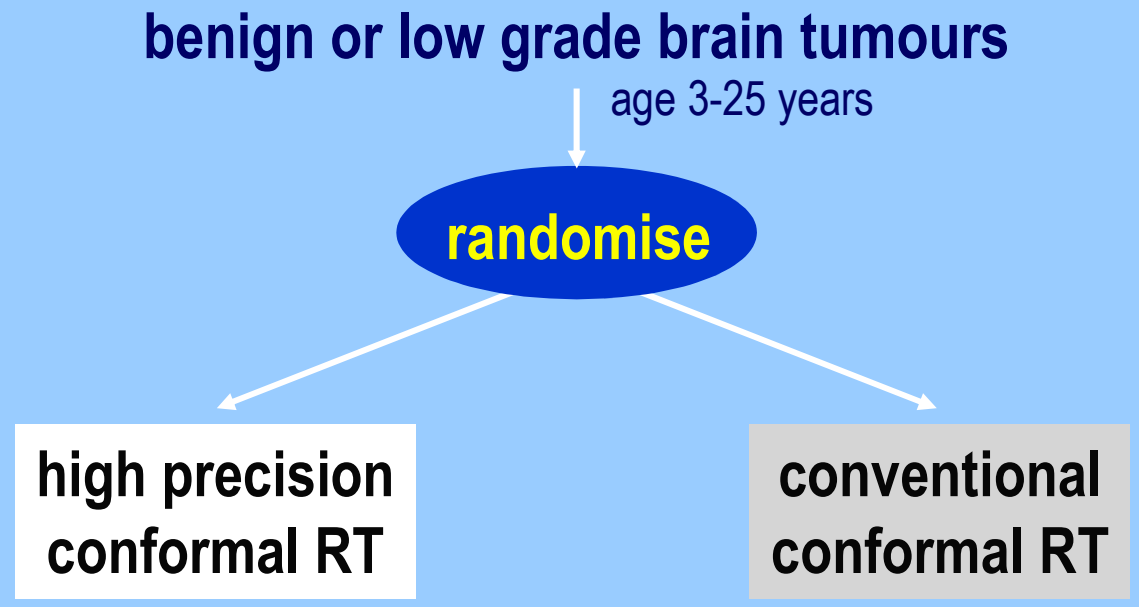
high precision vs conventional conformal RT



Benefit of high precision conformal radiotherapy

Jalali et al 2017, JAMA Oncol; 3 (10): 1368-1376

high precision vs conventional conformal RT

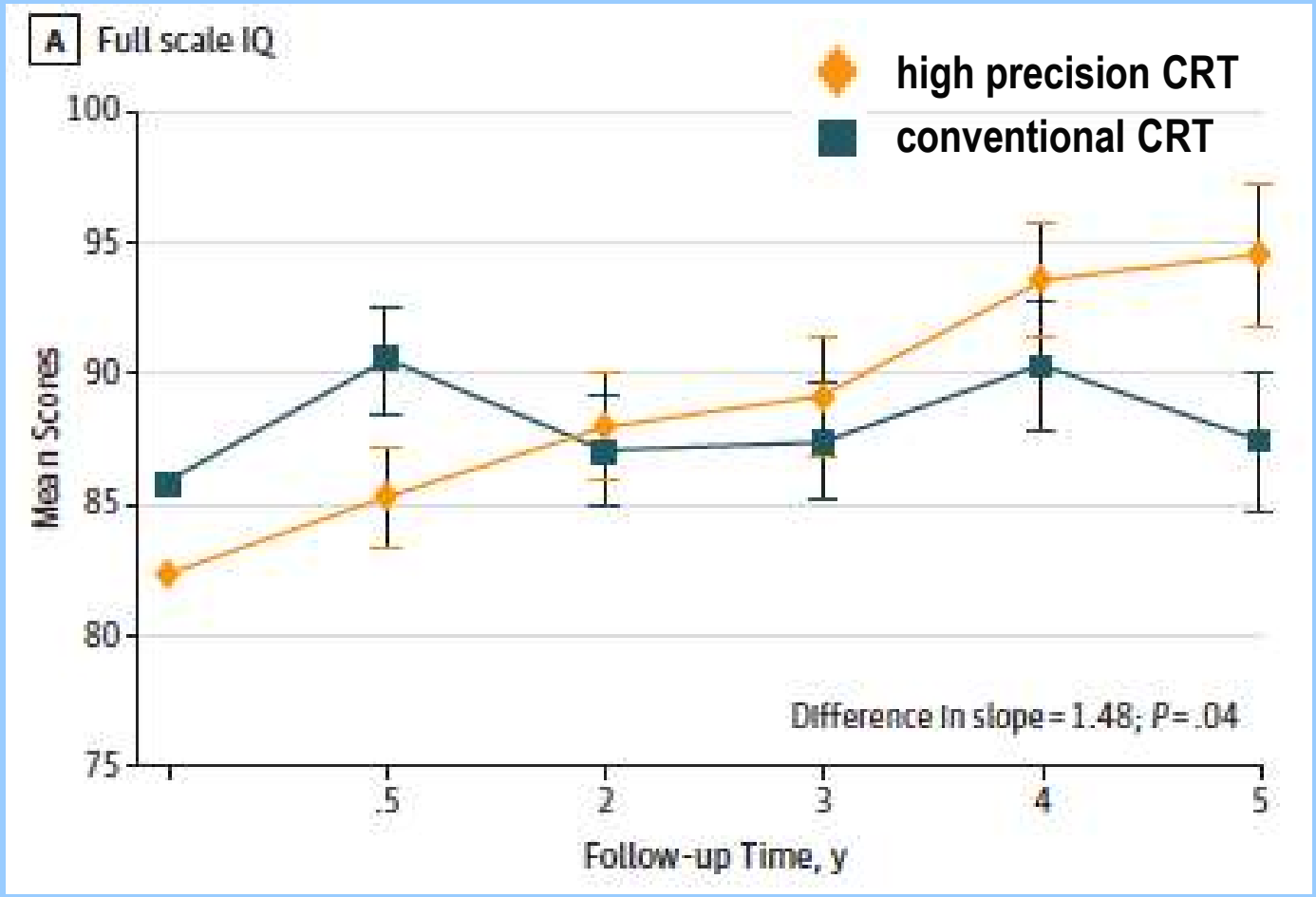


differences
MRI as well as CT
smaller margin
larger no. & noncoplanar fields

Benefit of high precision conformal radiotherapy

Jalali et al 2017, JAMA Oncol; 3 (10): 1368-1376

high precision vs conventional conformal RT



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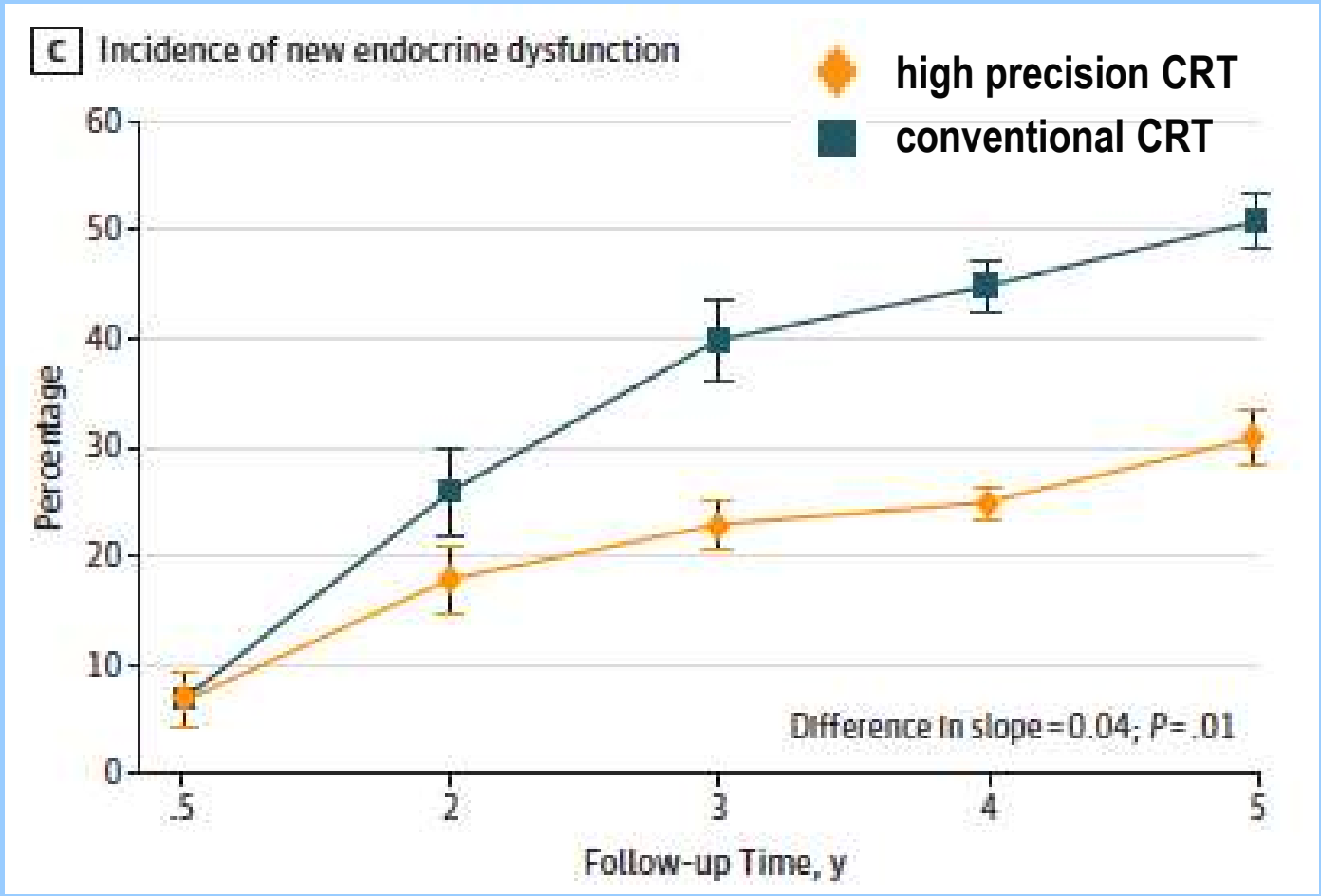
high precision vs conventional conformal RT

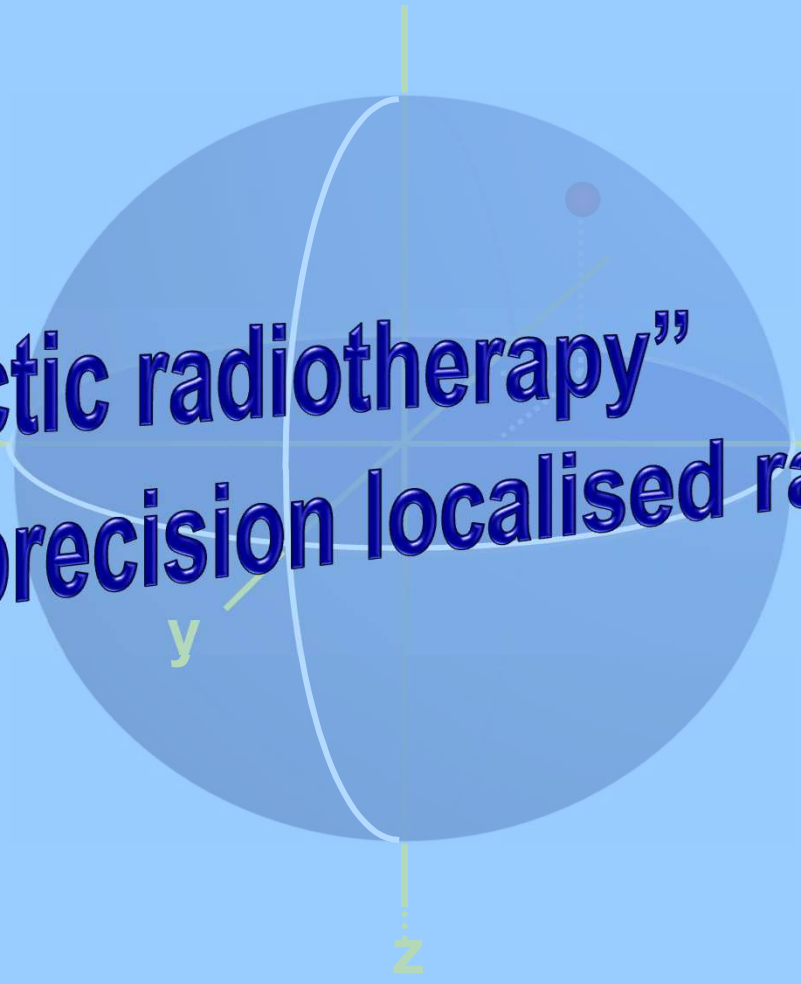


Benefit of high precision conformal radiotherapy

Jalali et al 2017, JAMA Oncol; 3 (10): 1368-1376

Stereotaxy

metrics



"stereotactic radiotherapy"
is a high precision localised radiotherapy

Metrics for high precision RT

Which of these techniques is stereotactic

multiple conformal fixed fields

single or multiple/dynamic arcs +/- IMRT

single or multiple isocentres

multiple sources & isocentres (GK)

multiple small beams & isocentres (CK)

none

all

Metric	
conformity index (RTOG)	**rCI**
conformity index (Paddick)	**pCI**
homogeneity index	**HI**
gradient index	**GI**

Metrics for high precision RT

Metric		*calculation*
conformity index (RTOG)	**rCI**	V_{Rx} / V_{PTV}
conformity index (Paddick)	**target delivery**	$V^2_{PTV,Rx} / V_{PTV} \times V_{Rx}$
homogeneity index	**HI**	D_{max} / D_{Rx}
gradient index	**GI**	$V_{50\%} / V_{100\%}$

normal tissue avoidance

noncritical adjacent normal tissue

V_{Rx} - volume covered by prescription isodose
V_{PTV} - PTV volume
$V_{PTV,Rx}$ - overlapping volume
D_{max} - maximum dose at the PTV
D_{Rx} - prescription dose in the PTV

Metrics for high precision RT

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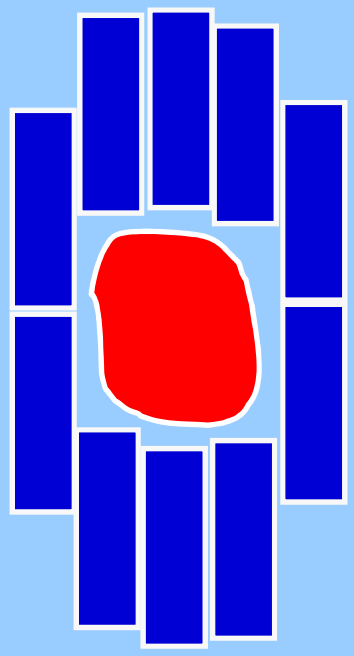
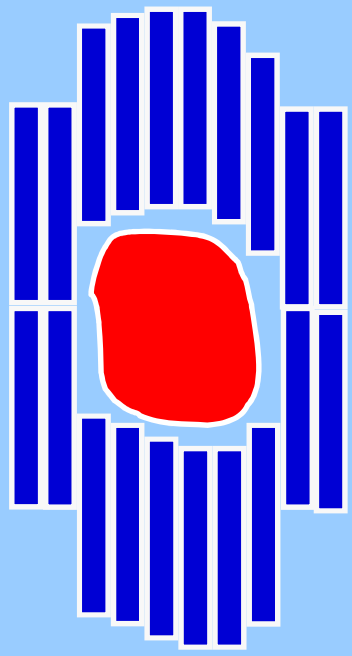
Metrics for high precision RT

conformal treatment delivery



5 mm



2.5 mm

multi-leaf collimator leaf size

Collimation

Metric		*calculation*
conformity index (RTOG)	**rCI**	V_{Rx} / V_{PTV}
conformity index (Paddick)	**target delivery**	$V^2_{PTV,Rx} / V_{PTV} \times V_{Rx}$
homogeneity index	**HI**	D_{max} / D_{Rx}
gradient index	**GI**	$V_{50\%} / V_{100\%}$

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noncritical adjacent normal tissue

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Metrics for high precision RT

Metric		*calculation*
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normal tissue avoidance

noncritical adjacent normal tissue

critical OARs

V_{Rx} - volume covered by prescription isodose

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D_{max} - maximum dose at the PTV

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Metrics for high precision RT

Metric		*calculation*
conformity index (RTOG)	**rCI**	V_{Rx} / V_{PTV}
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normal tissue volume (brain/ROIs) irradiated to Dx (DVH)		

V_{Rx} - volume covered by prescription isodose
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D_{max} - maximum dose at the PTV
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Metrics for high precision RT

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homogeneity index	**HI**	D_{max} / D_{Rx}
gradient index	**GI**	$V_{50\%} / V_{100\%}$
normal tissue volume (brain/ROIs) irradiated to Dx (DVH)		
planning time, treatment time etc.		

V_{Rx} - volume covered by prescription isodose
V_{PTV} - PTV volume
$V_{PTV,Rx}$ - overlapping volume
D_{max} - maximum dose at the PTV
D_{Rx} - prescription dose in the PTV

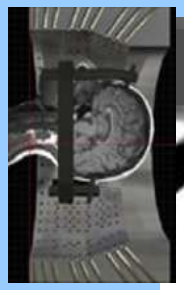
Metrics for high precision RT

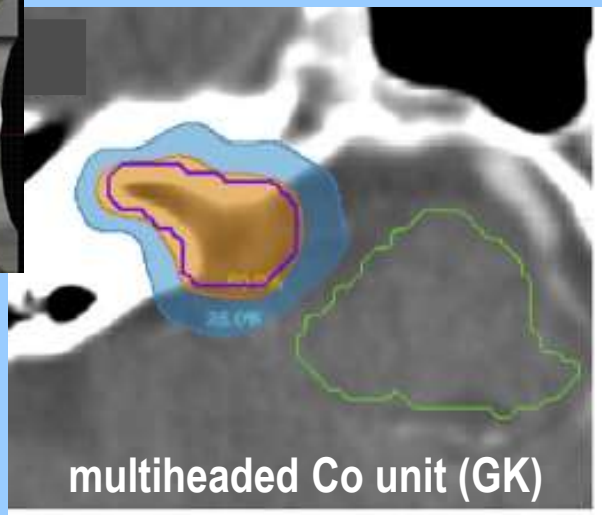
Metric		*calculation*	*worse*	*ideal value*
conformity index (RTOG)	**rCI**	V_{Rx} / V_{PTV}	low	1.0
conformity index (Paddick)	**pCI**	$V^2_{PTV,Rx} / V_{PTV} \times V_{Rx}$	low	1.0
homogeneity index	**HI**	D_{max} / D_{Rx}	high	1.0
gradient index	**GI**	$V_{50\%} / V_{100\%}$	high	1.0

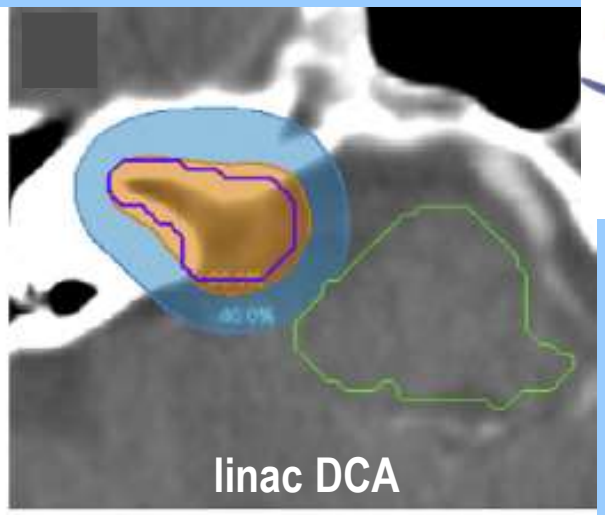
V_{Rx} - volume covered by prescription isodose
V_{PTV} - PTV volume
$V_{PTV,Rx}$ - overlapping volume
D_{max} - maximum dose in the PTV
D_{Rx} - prescription dose in the PTV

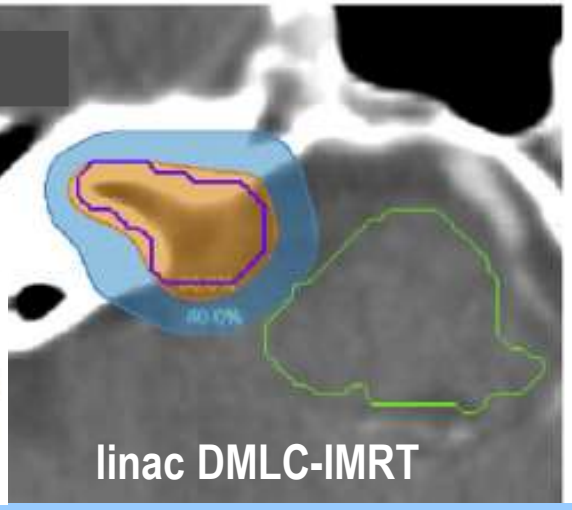
Metrics for high precision RT

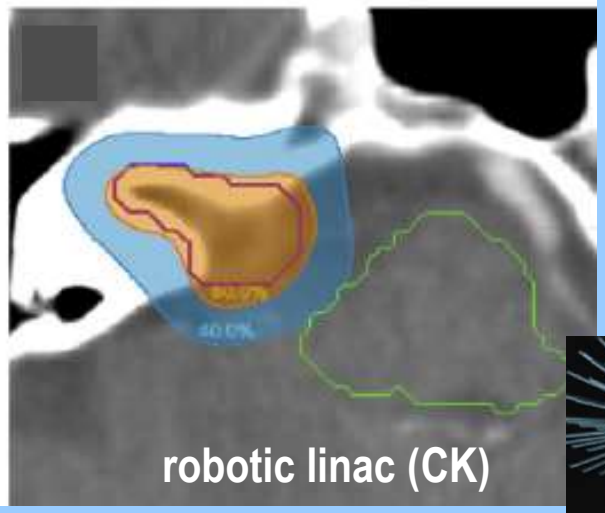
example of acoustic neuroma

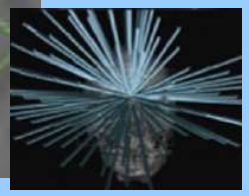












DCA - dynamic conformal arcs
DMLC - dynamic MLC
GK - gamma knife
CK - cyberknife

Comparison of techniques

Gevaert et al 2013 Radiother Oncol 106,192–197

		GK	DCA	IMRT	CK
Paddick conformity index	Mean	0.77	0.66	0.68	0.77
	SD	0.04	0.04	0.04	0.06
	Min	0.68	0.59	0.52	0.67
	Max	0.84	0.74	0.89	0.85
	Mean acoustic neuromas	0.76	0.67	0.66	0.75
	SD	0.04	0.05	0.06	0.06
	Mean arteriovenous malformation	0.80	0.65	0.70	0.80
	SD	0.04	0.03	0.06	0.04
Dose heterogeneity index	Mean	0.84	0.30	0.18	0.22
	SD	0.05	0.03	0.05	0.02
	Min	0.71	0.25	0.09	0.21
	Max	0.92	0.35	0.28	0.26
	Mean acoustic neuromas	0.83	0.29	0.18	0.22
	SD	0.05	0.03	0.06	0.02
	Mean arteriovenous malformation	0.86	0.32	0.18	0.21
	SD	0.03	0.03	0.04	0.01
Gradient index	Mean	2.59	3.16	3.94	3.48
	SD	0.10	0.55	0.92	0.47
	Min	2.47	2.48	2.74	2.81
	Max	2.81	4.45	6.00	4.54
	Mean acoustic neuromas	2.55	3.00	3.52	3.41
	SD	0.07	0.36	0.64	0.46
	Mean arteriovenous malformation	2.68	3.77	4.78	3.62

DCA - dynamic conformal arcs
DMLC - dynamic MLC (IMRT)
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Comparison of techniques

Gevaert et al 2013 Radiother Oncol 106,192–197

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	Max				
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pCI

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	Min				
	Max				

GI

	GK	DCA	IMRT	CK
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	Min	2.47	2.48	2.74	2.81
		2.81	4.45	6.00	4.54

treatment time (mins)

neuromas	GK	DCA	IMRT	CK
Mean	68.1	16.8	21.7	28.4
SD	27.5	2.2	3.4	8.1

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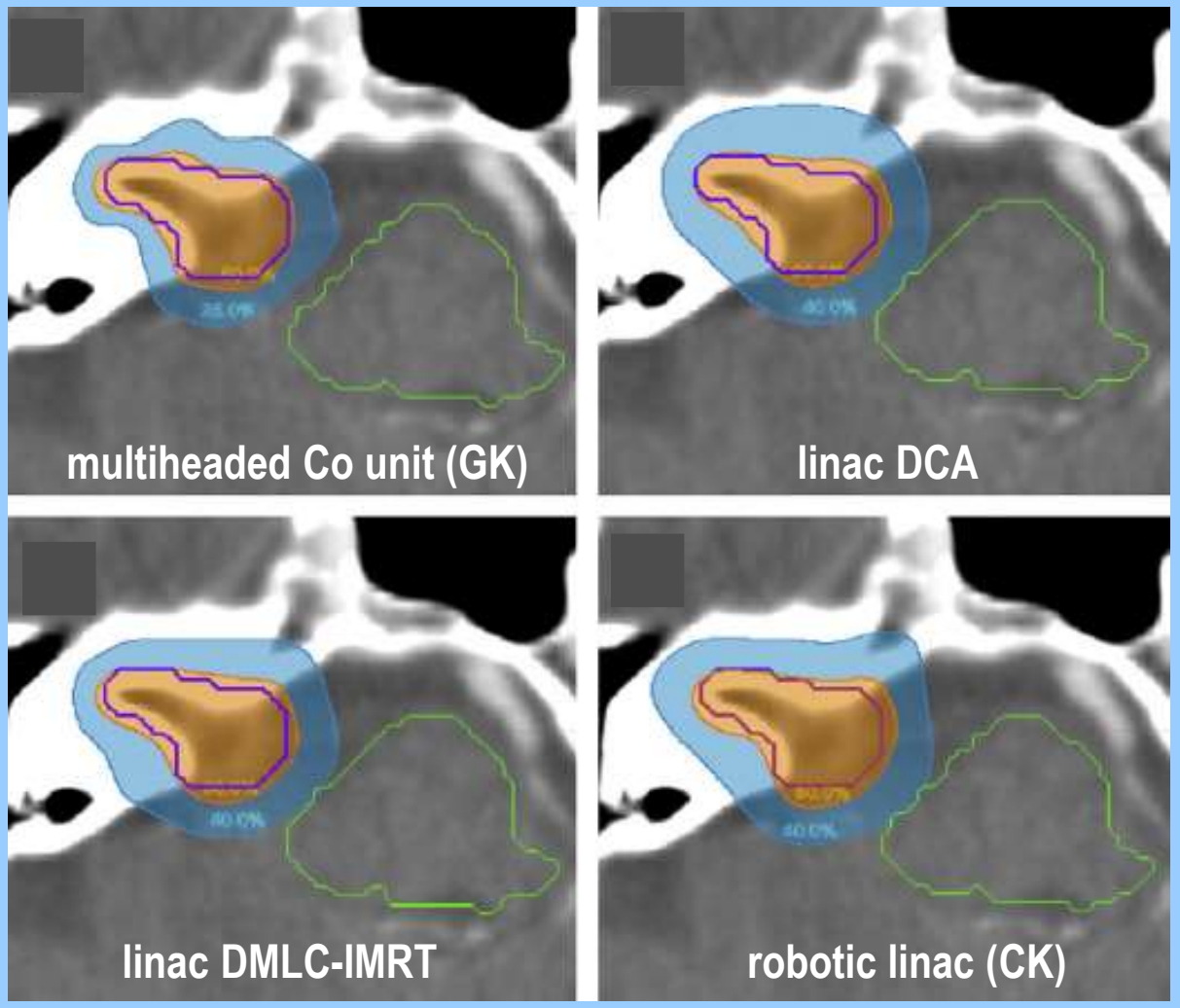
CK - cyberknife

Comparison of techniques

Gevaert et al 2013 Radiother Oncol 106,192–197

example of acoustic neuroma



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normal tissue volume (brain/ROIs) irradiated to Dx (DVH)		

V_{Rx} - volume covered by prescription isodose
V_{PTV} - PTV volume
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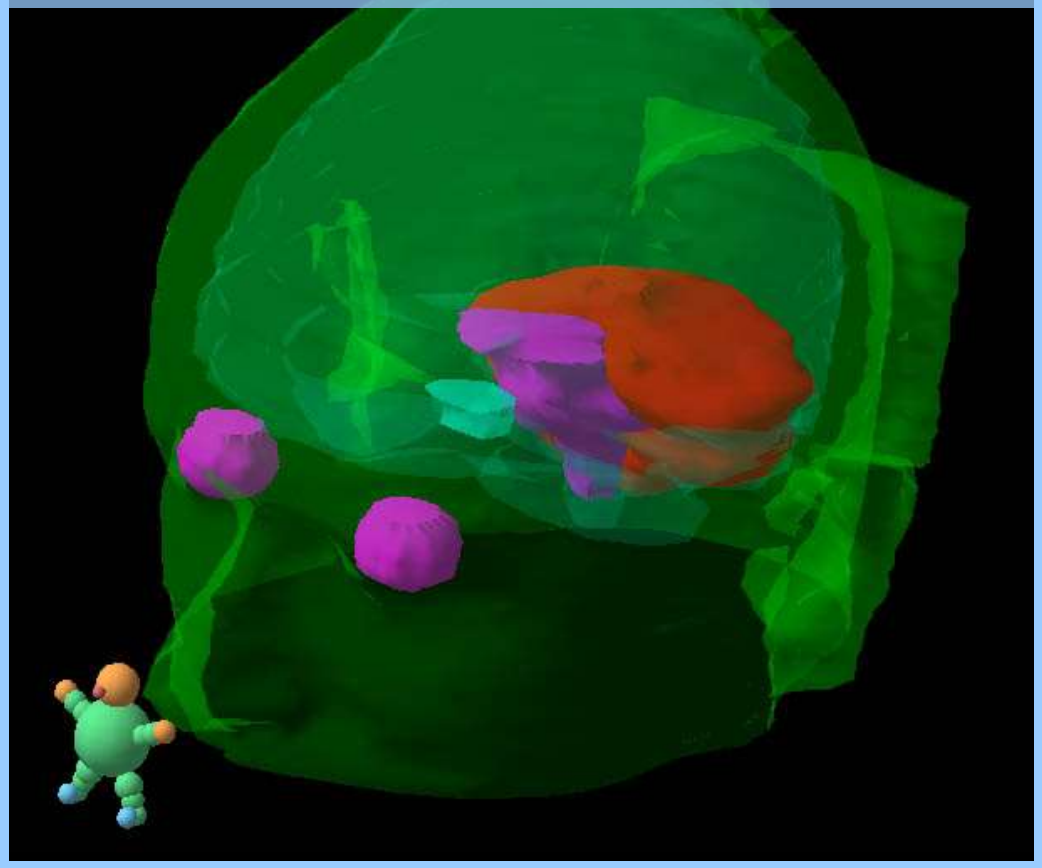
Metrics for high precision RT

Physical endpoints – normal tissue avoidance

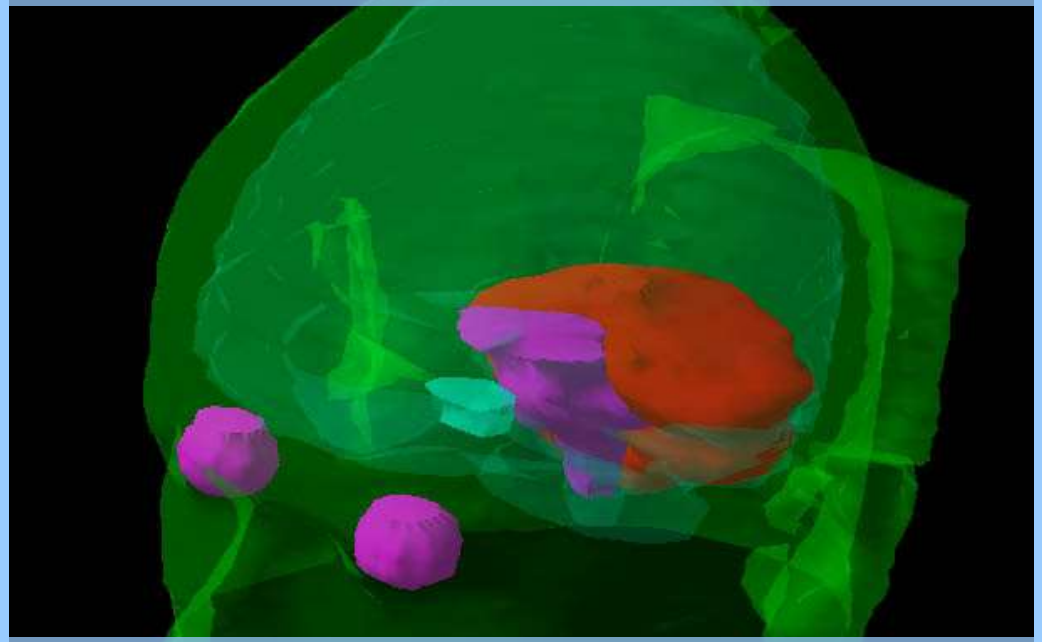
reduce normal tissue volume & dose



Evaluation of local radiotherapy techniques

Physical endpoints – normal tissue avoidance

reduce normal tissue volume & dose



central nervous system

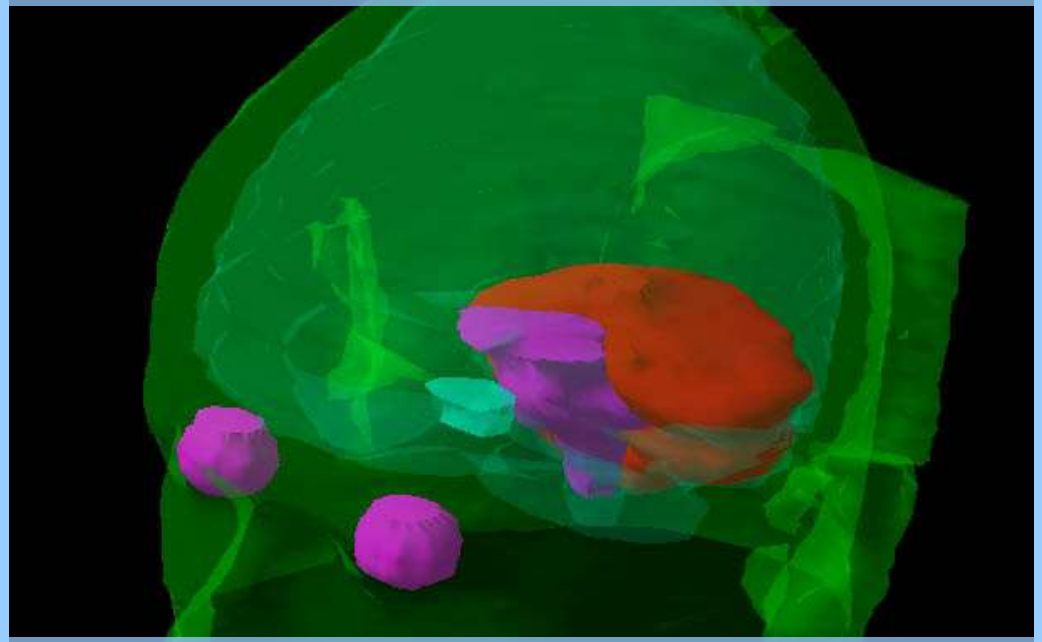
critical structures (OARs)

Evaluation of local radiotherapy techniques

OAR – organ at risk

Physical endpoints – normal tissue avoidance

reduce normal tissue volume & dose



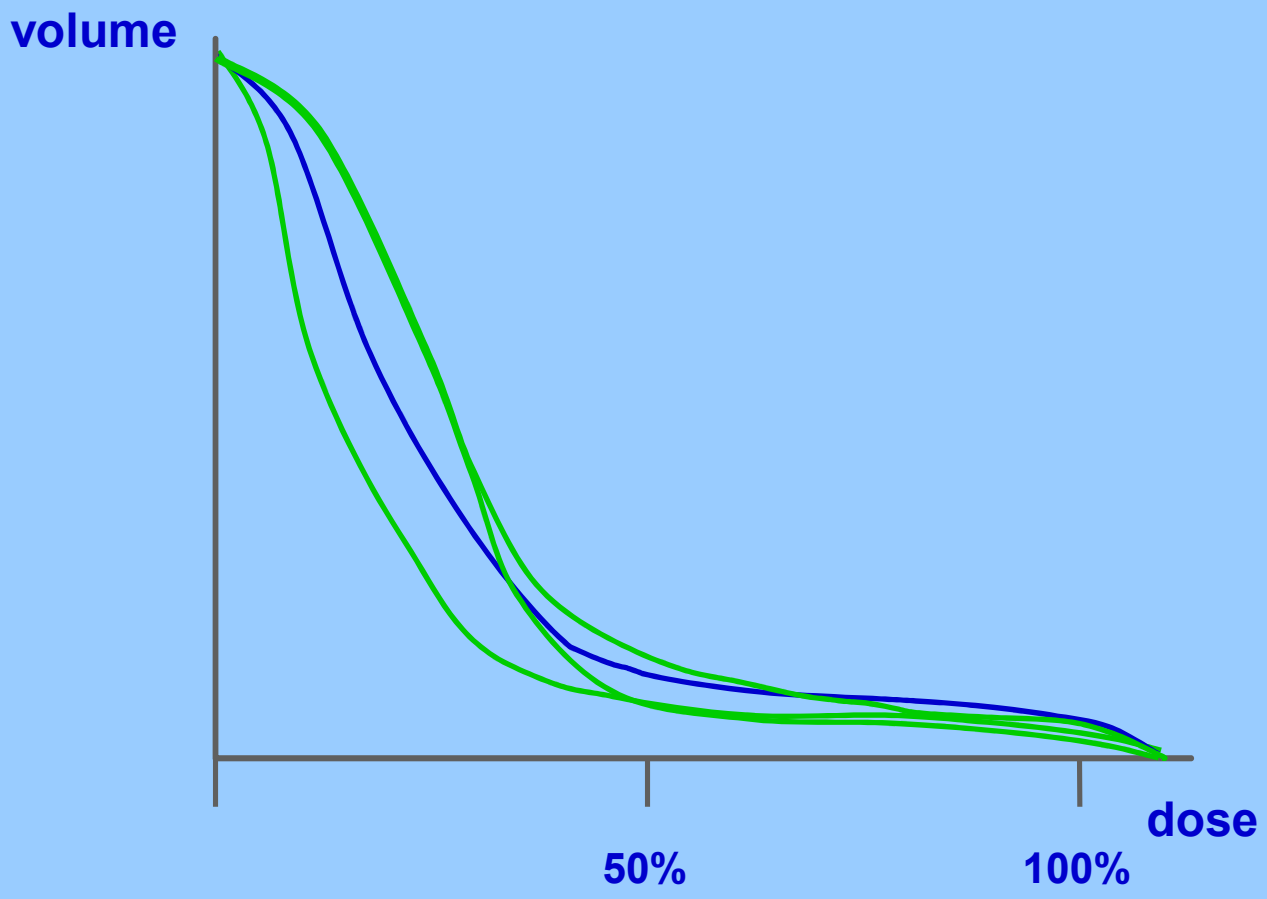
central nervous system

critical structures (OARs)

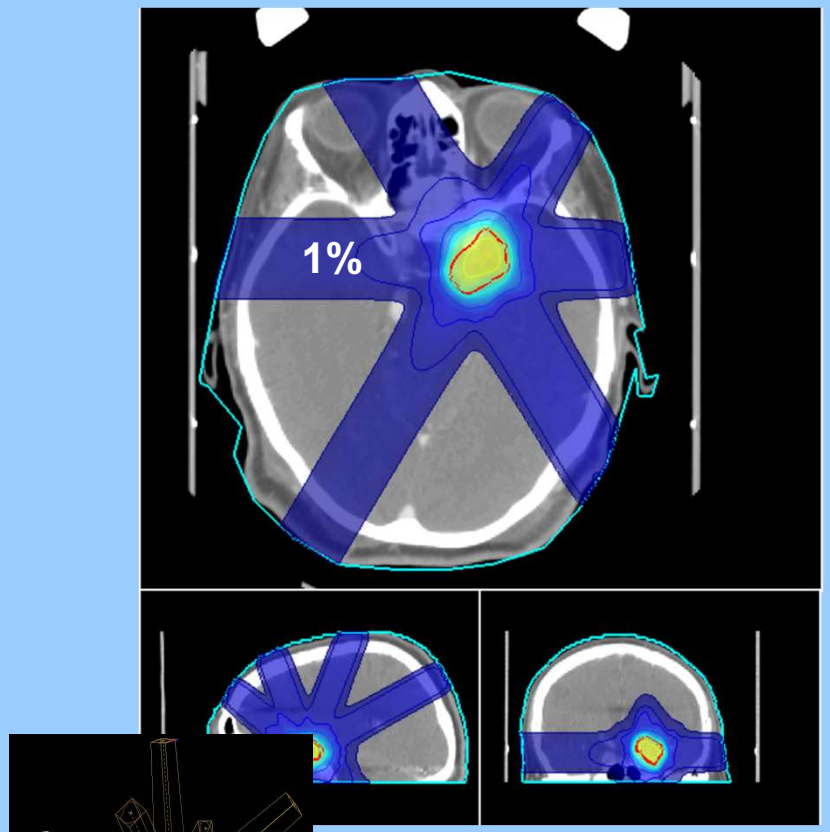
Evaluation of local radiotherapy techniques

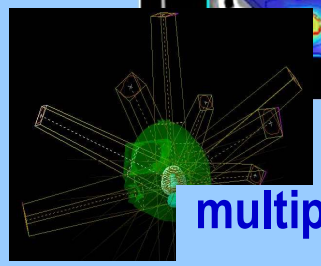
OAR – organ at risk

Physical endpoints central nervous system DVH



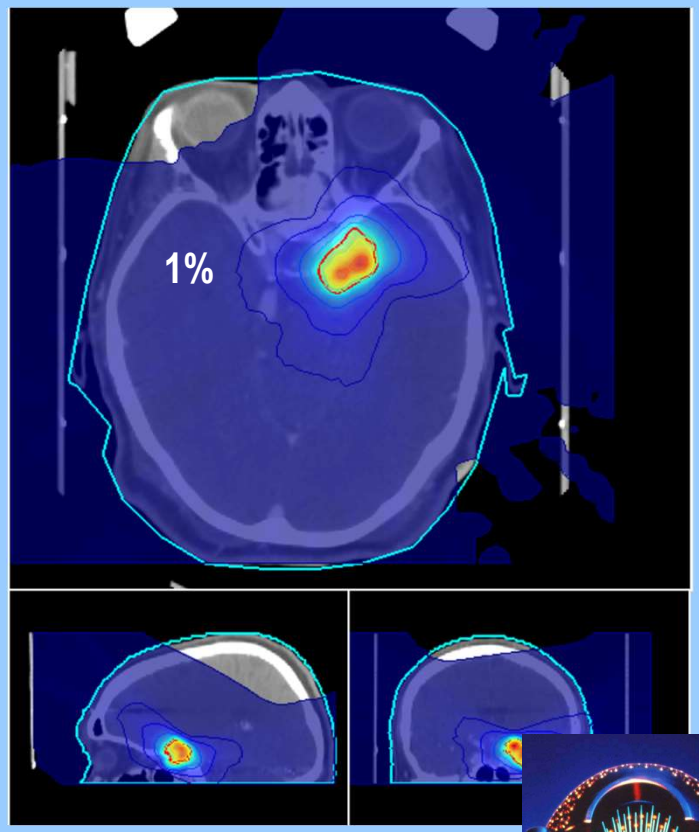
Evaluation of local radiotherapy techniques





multiple conformal fileds

linear accelerator

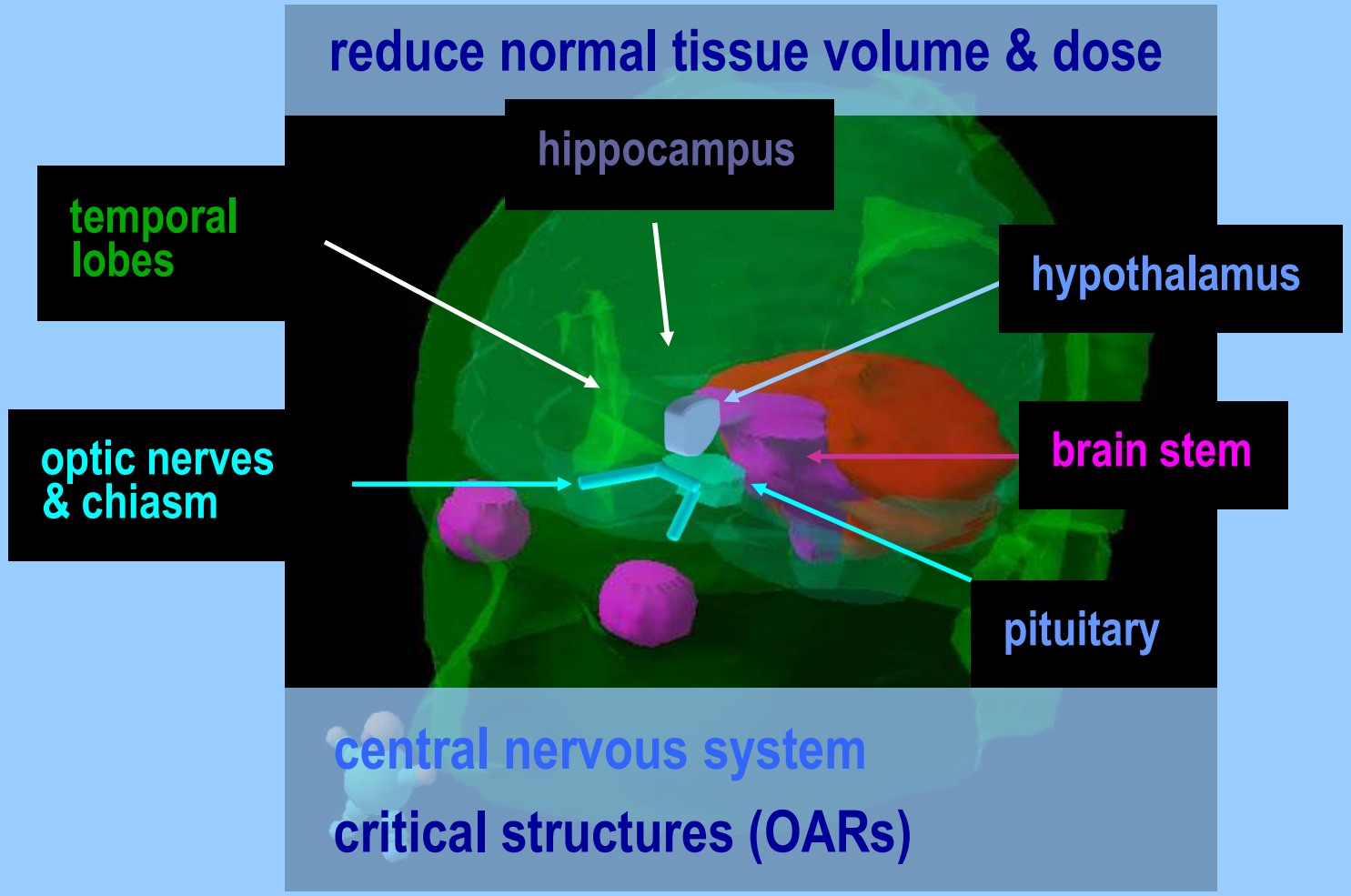


multiple isocentres

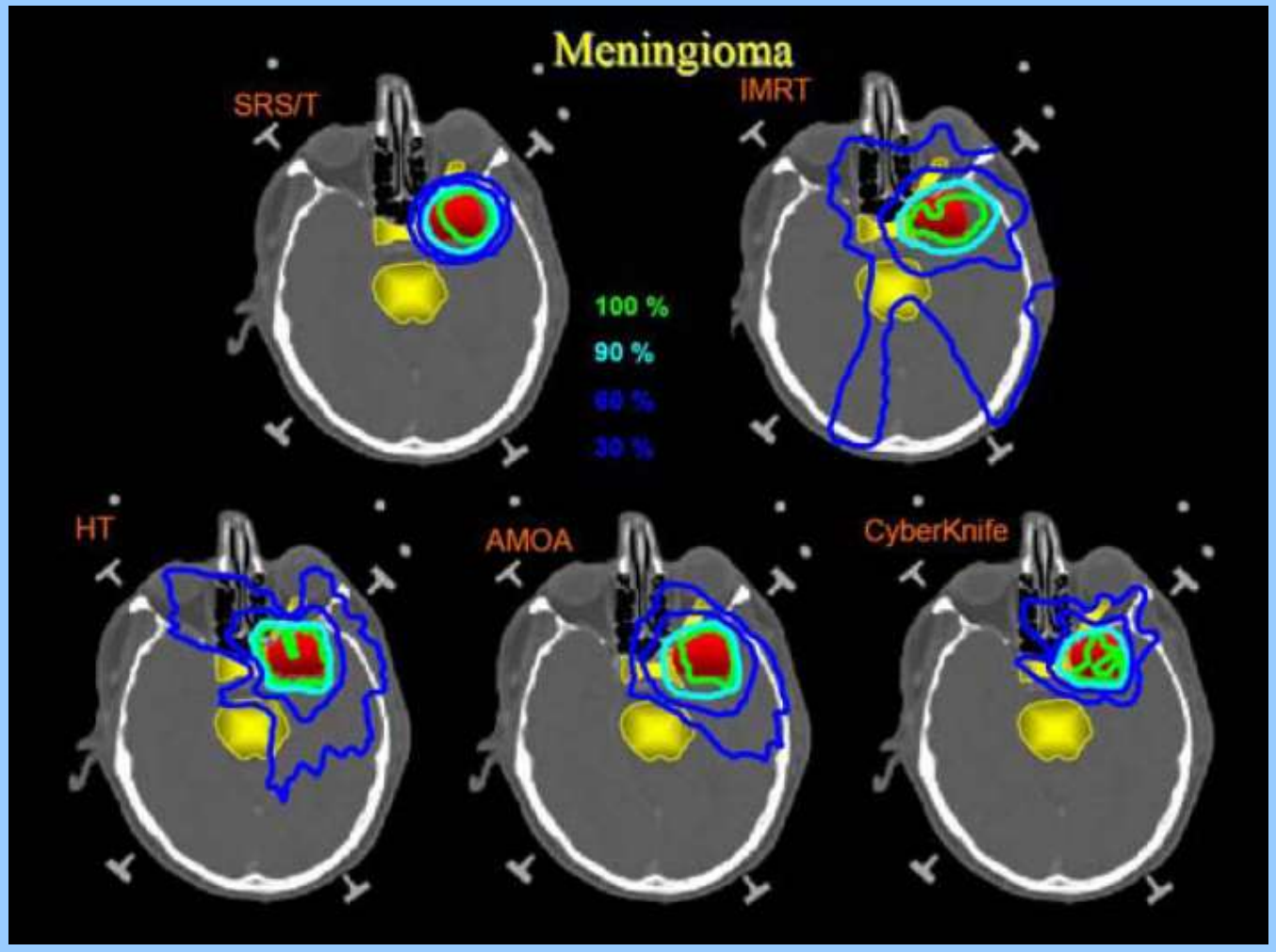
gamma knife

Comparison of conformal fixed field & multiple isocentre techniques

Avoidance in the treatment of skull base tumours



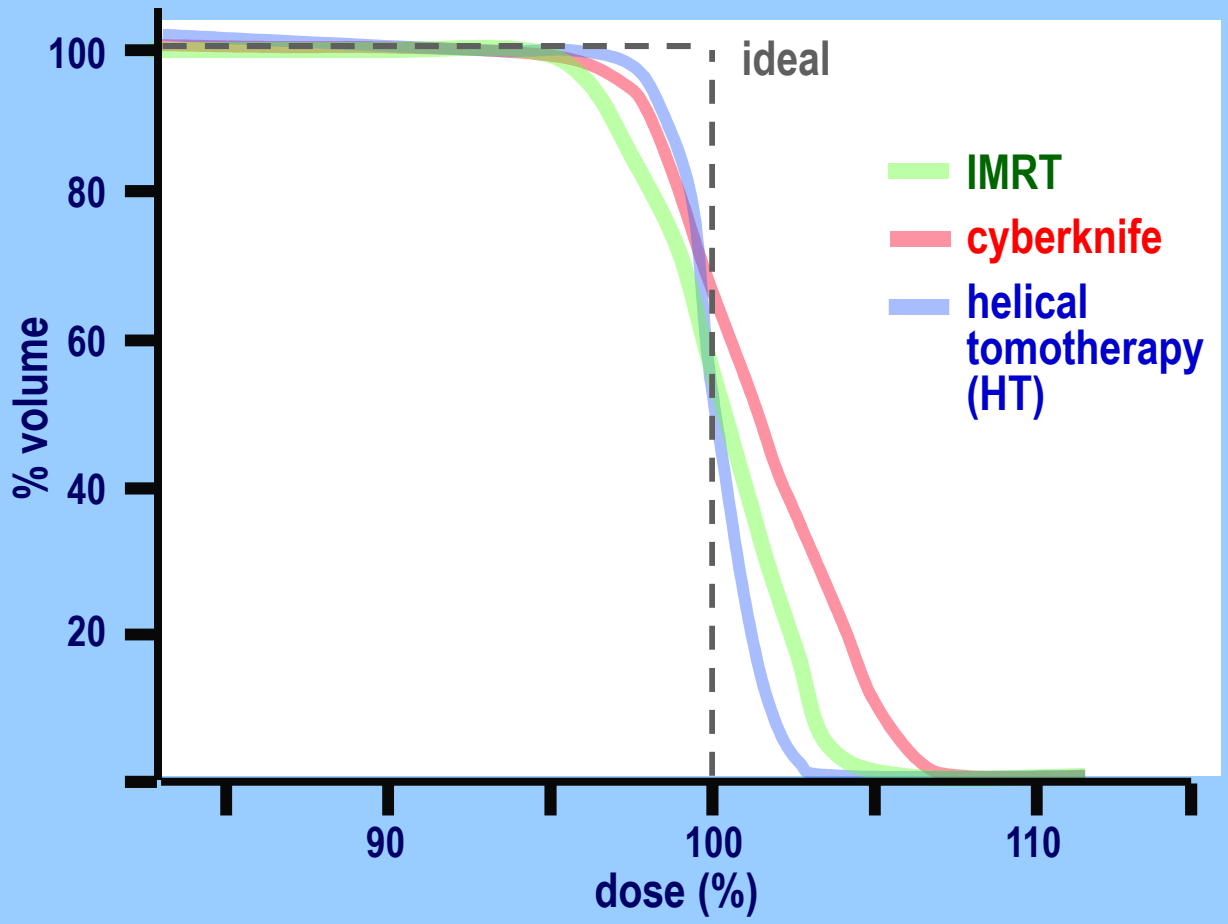
Evaluation of local radiotherapy techniques



Comparison of conformal radiotherapy techniques

Cozzi et al 2006 Radiother Oncol 80, 268–273

Planning Target Volume (PTV) dose distribution

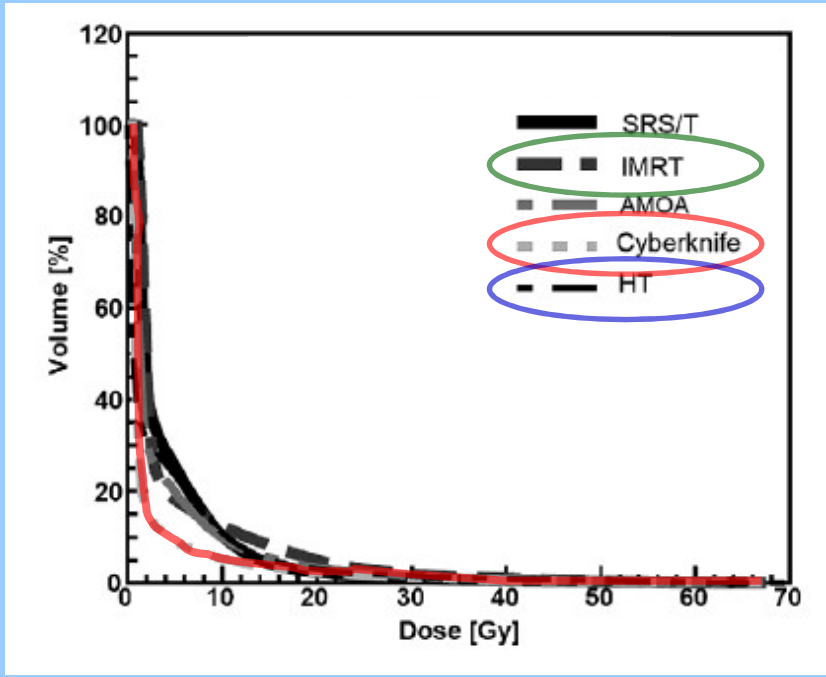


Comparison of conformal radiotherapy techniques

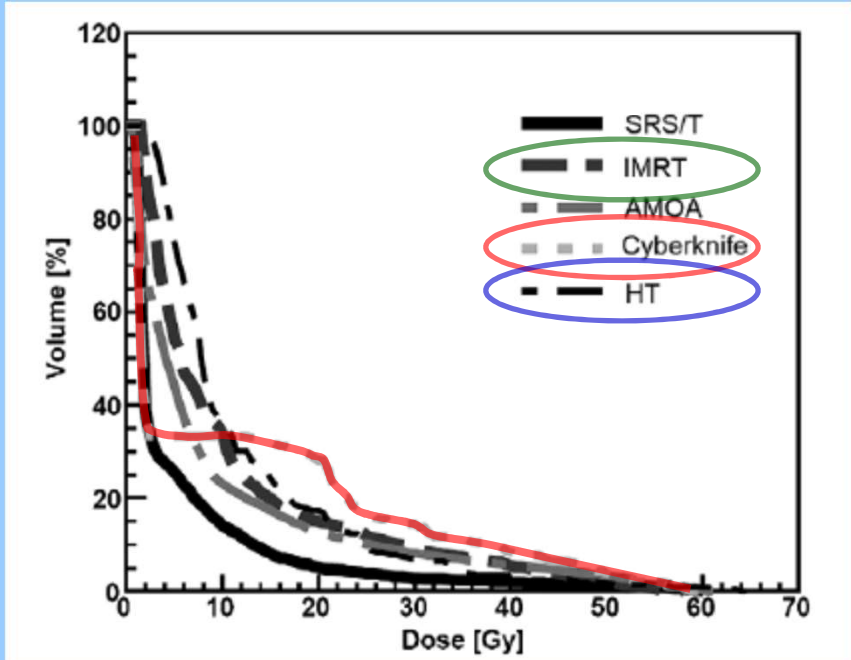
Cozzi et al 2006 Radiother Oncol 80, 268–273

Organs at risk DVH

brain stem



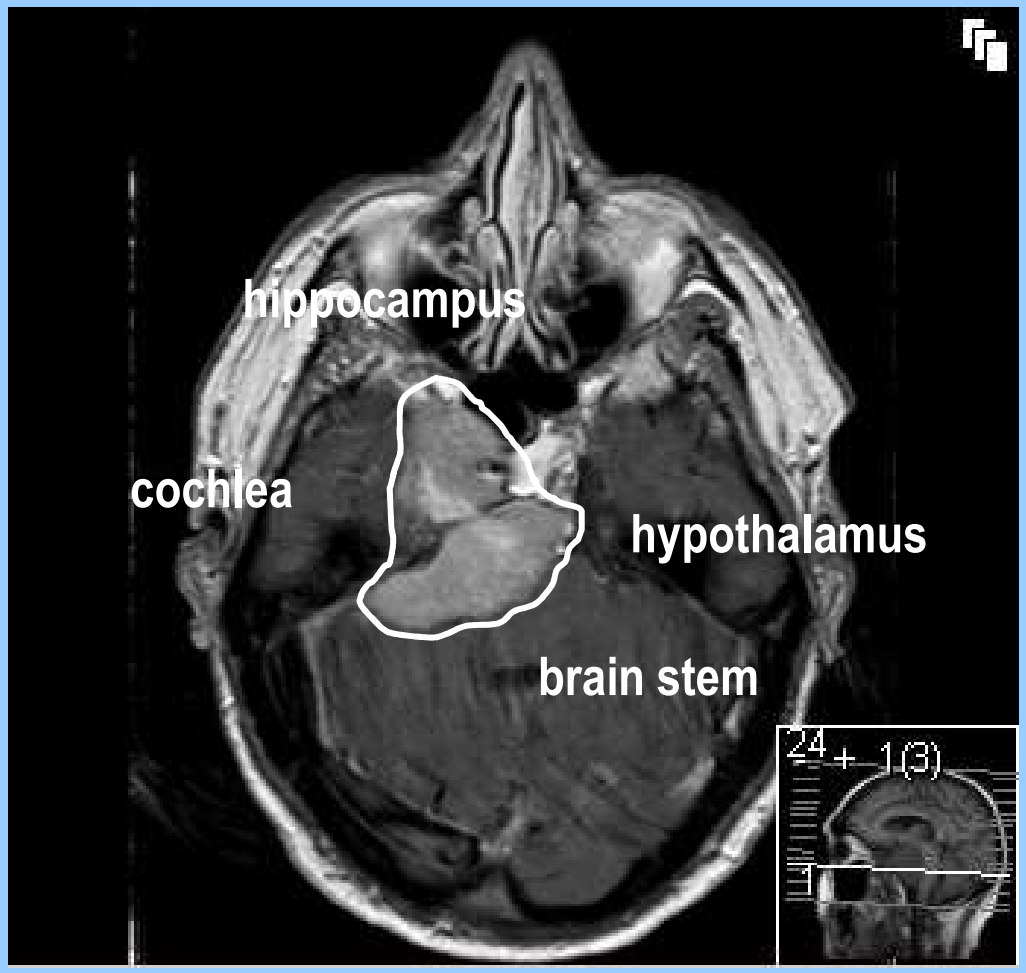
ipsilateral optic nerve



Comparison of conformal radiotherapy techniques

Cozzi et al 2006 Radiother Oncol 80, 268–273

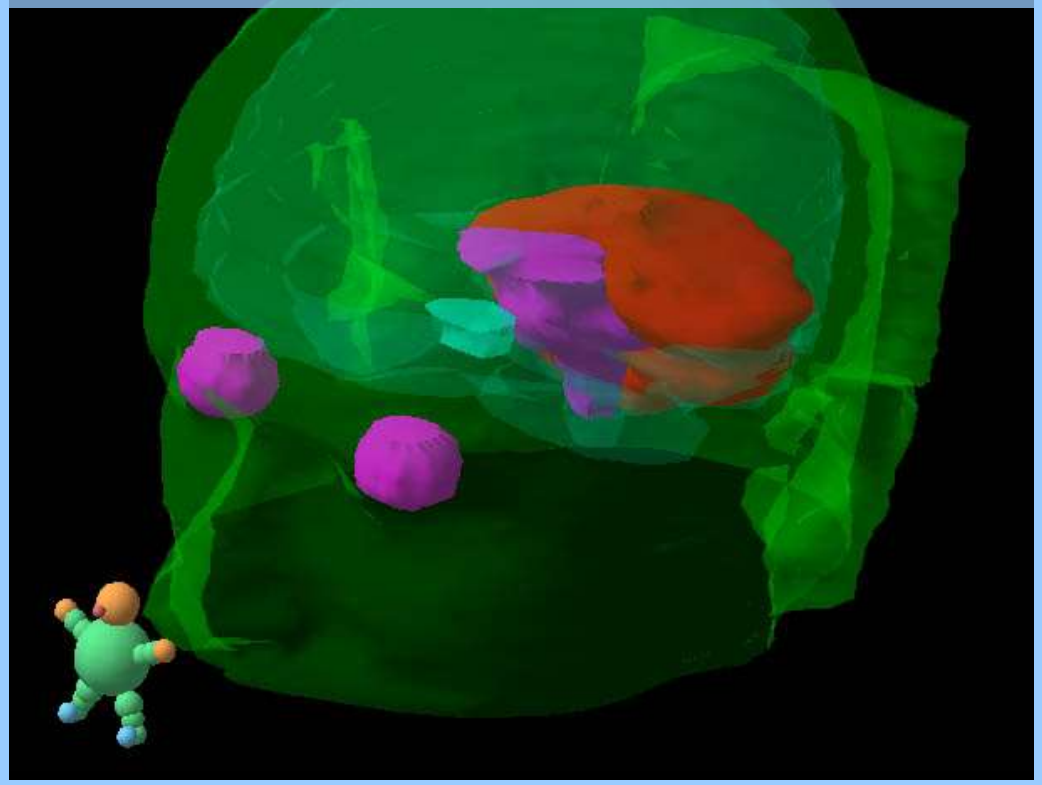
Avoidance of critical structures



High precision conformal RT for meningioma

Localised radiation delivery metrics

operator skill
clinical relevance



Evaluation of local radiotherapy techniques

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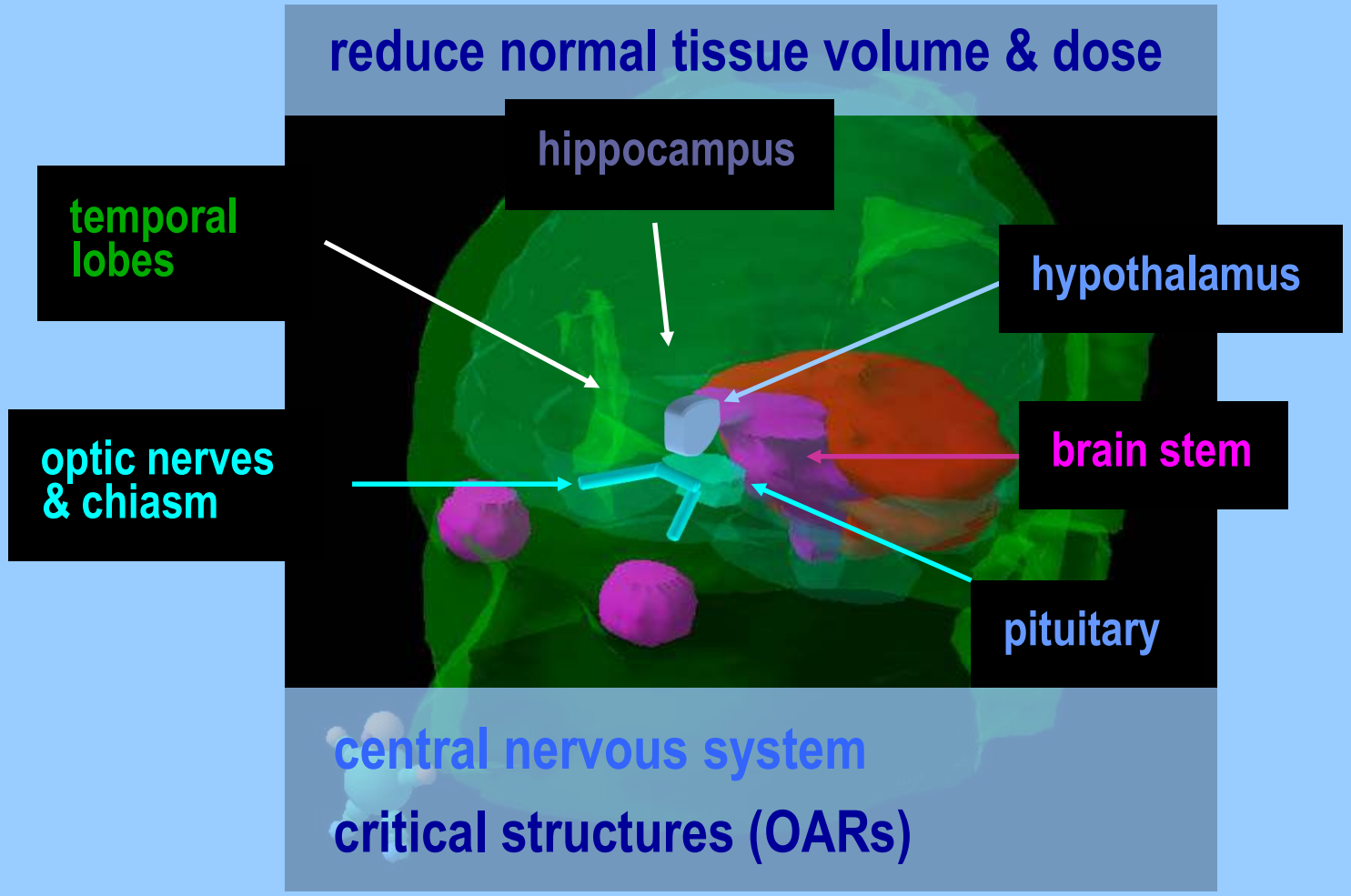


Evaluation of local radiotherapy techniques

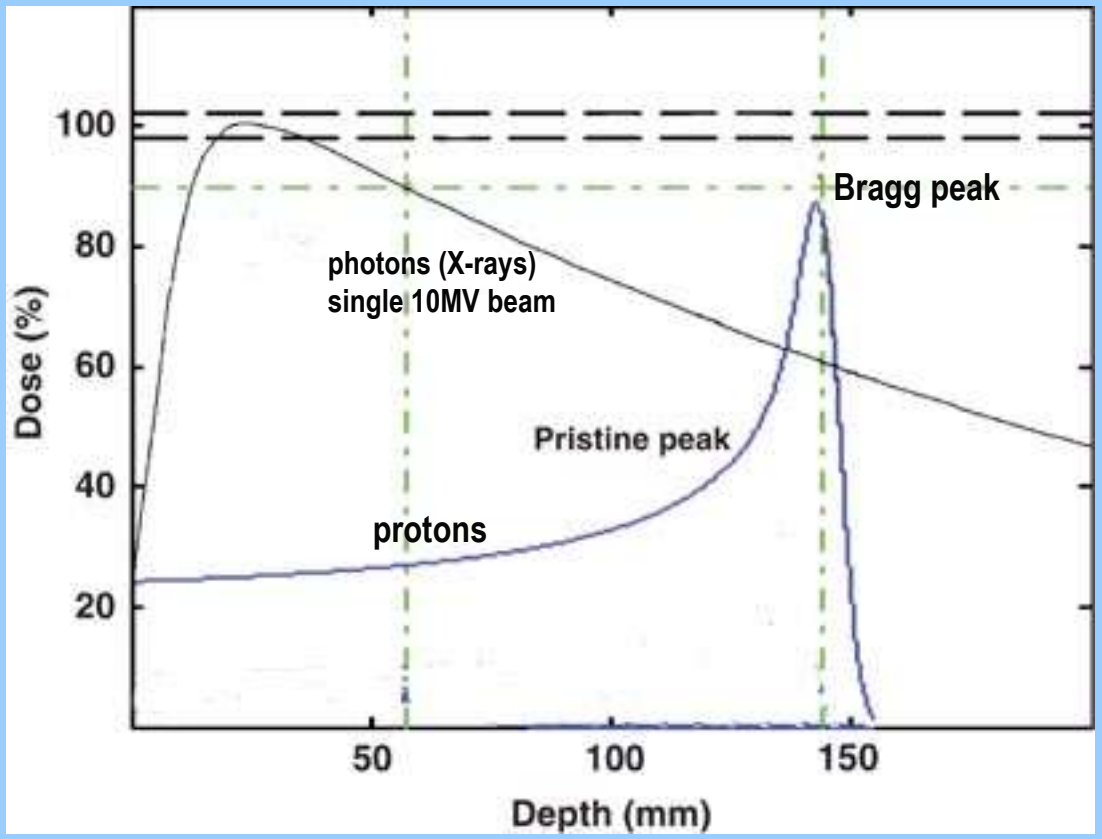
Attributes of modern local RT delivery

refinements of conformal radiotherapy

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

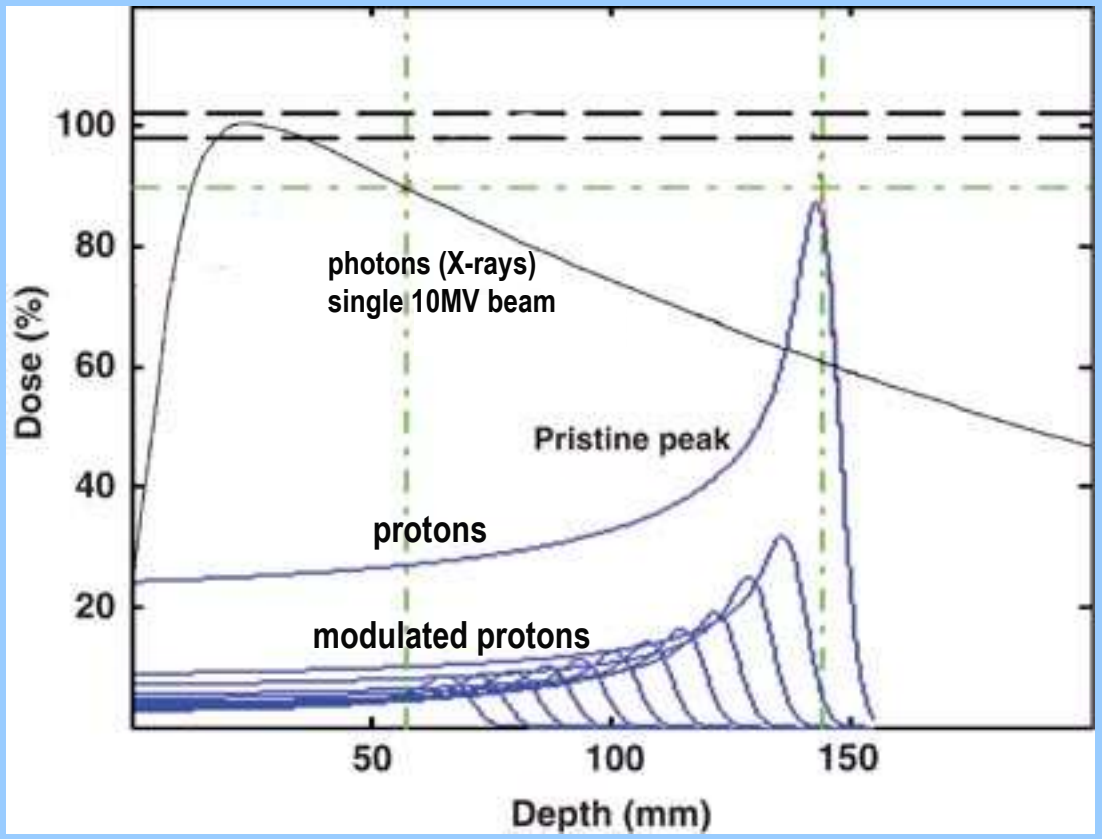
Classification of radiotherapy technologies

Theory



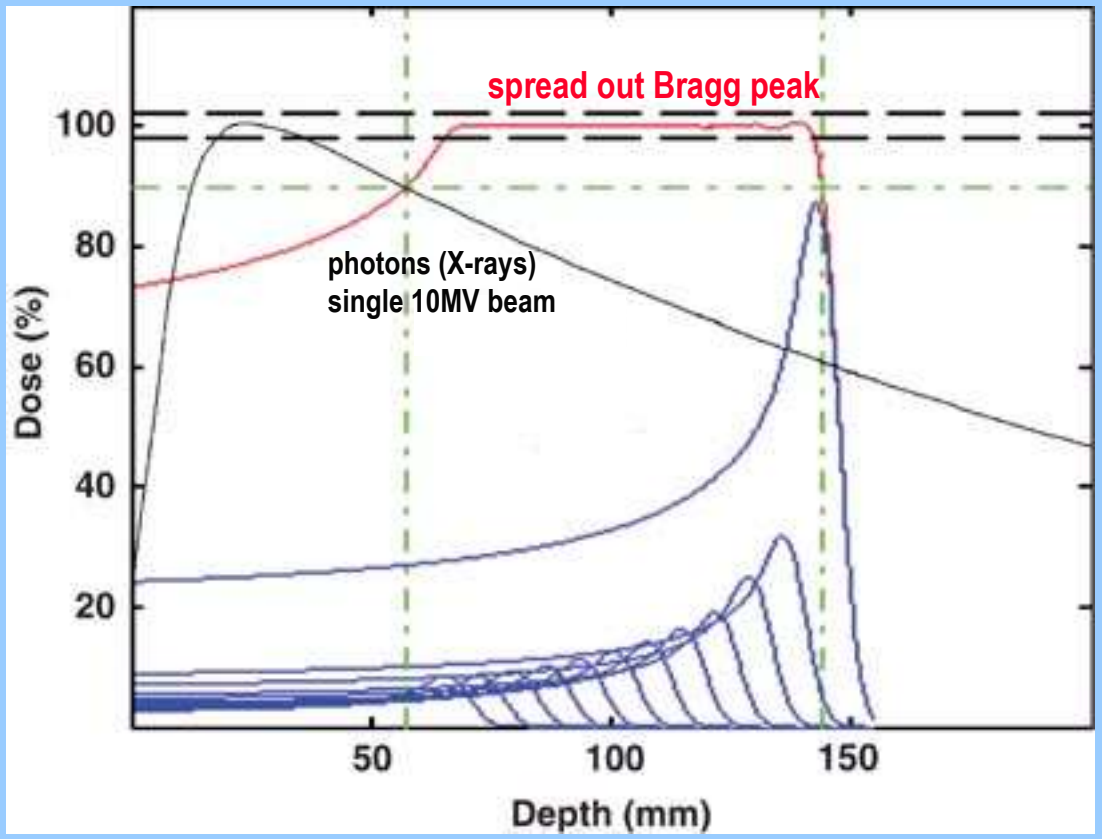
Depth dose distribution of photons and protons

Theory



Depth dose distribution of photons and protons

Reality



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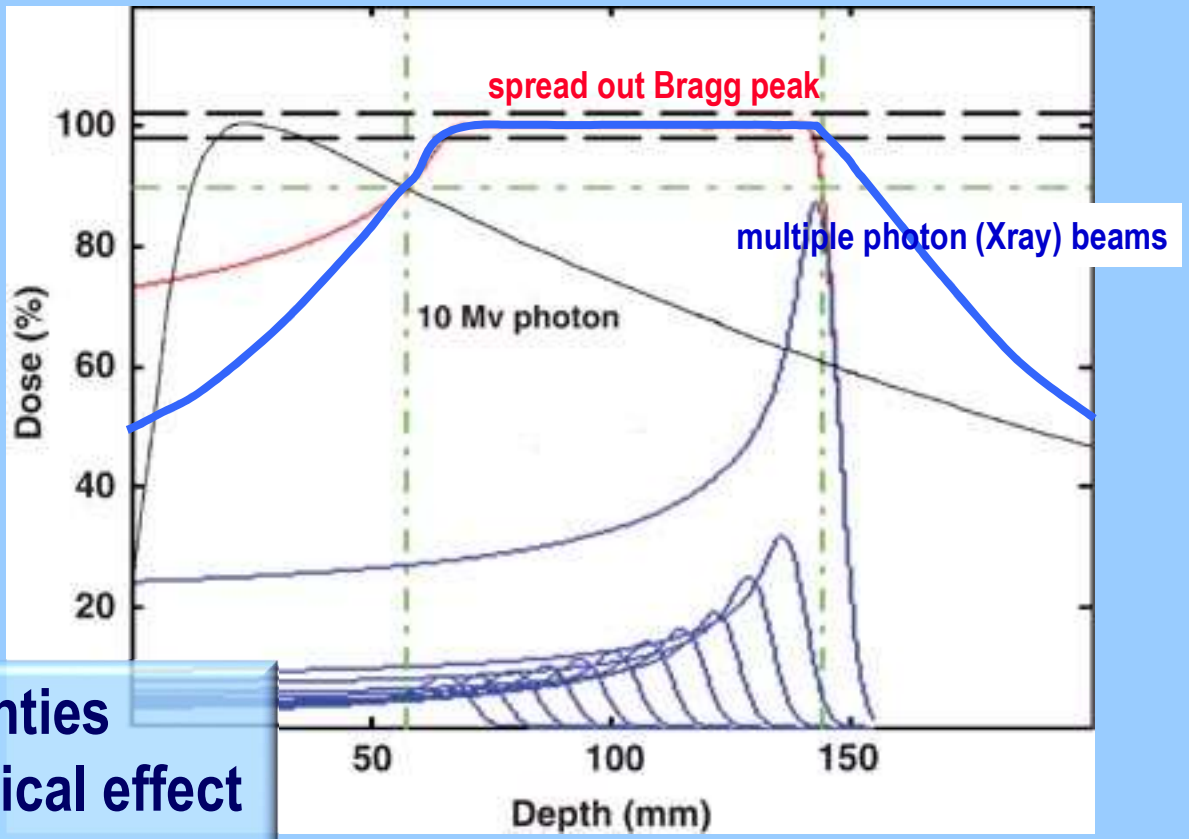
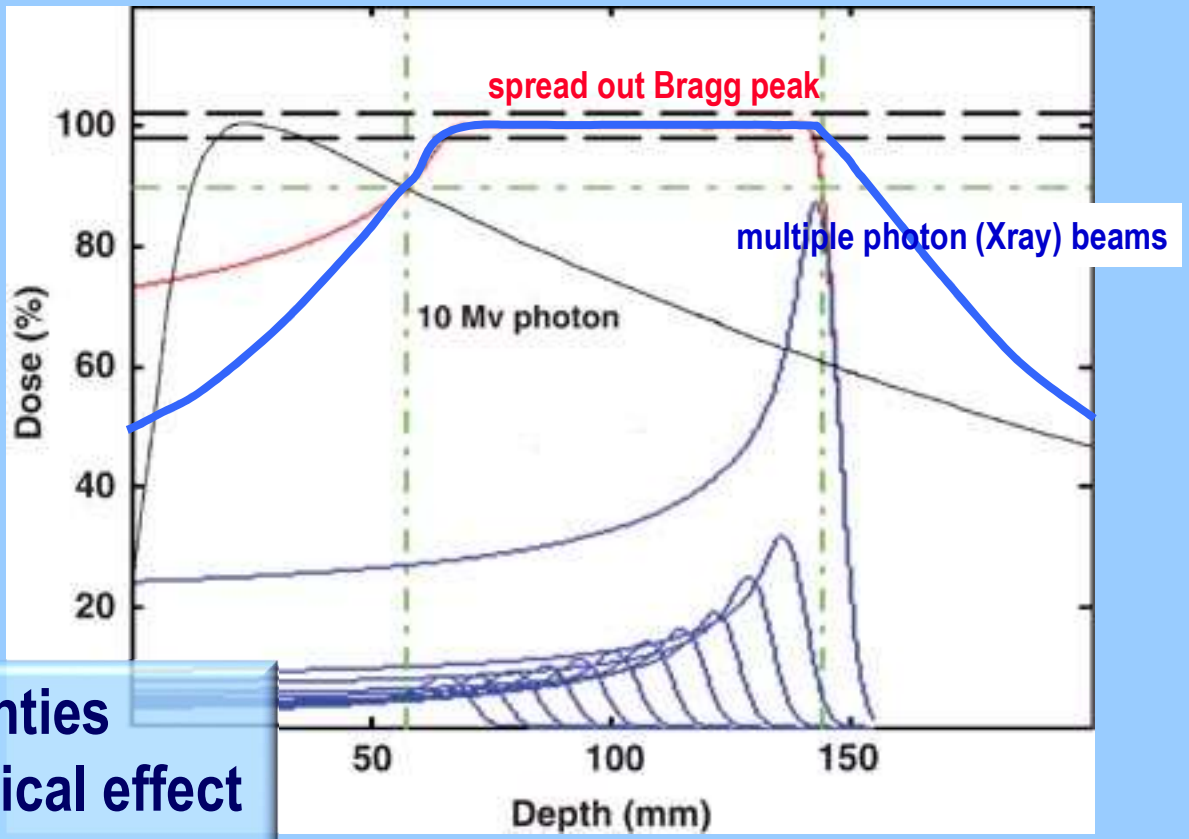


uncertainties

- **biological effect**
- **range**

Depth dose distribution of photons and protons

Reality



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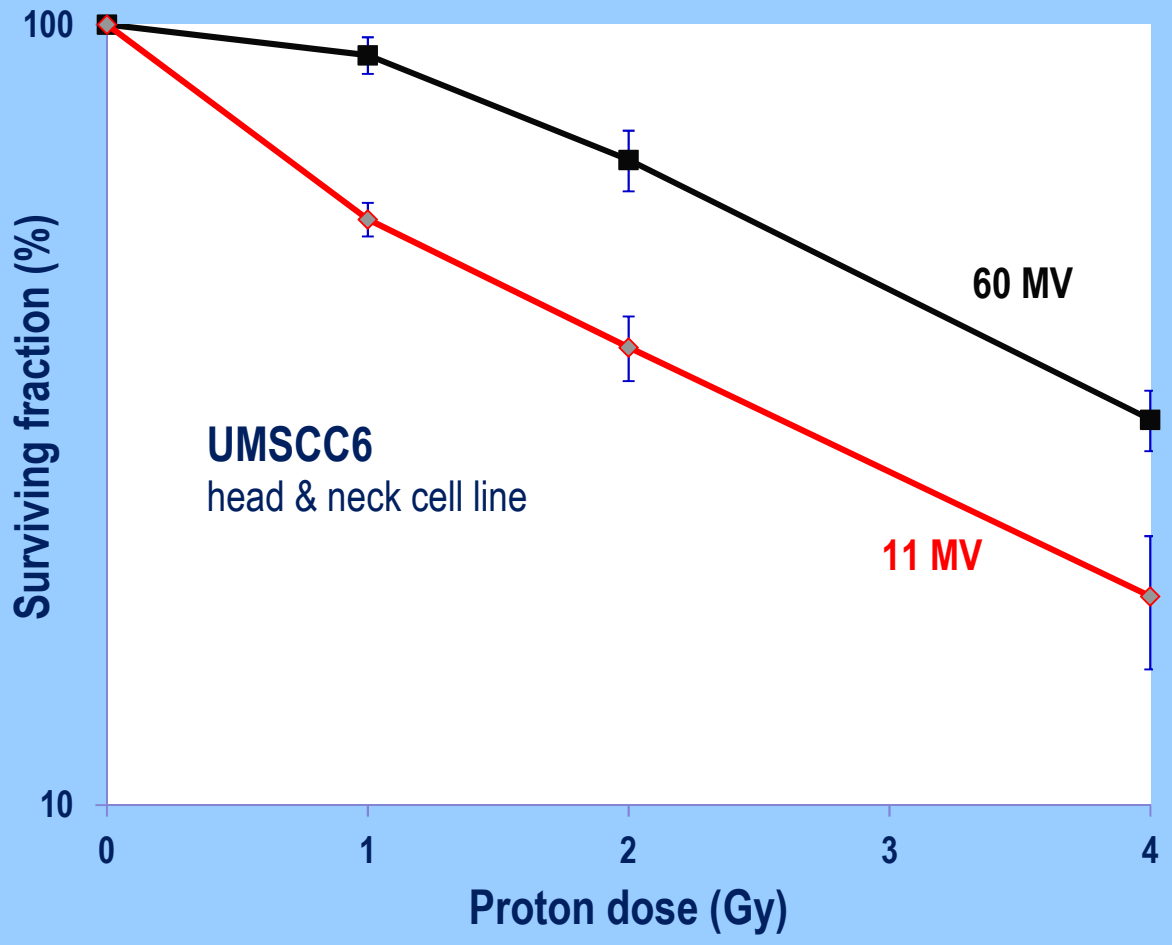
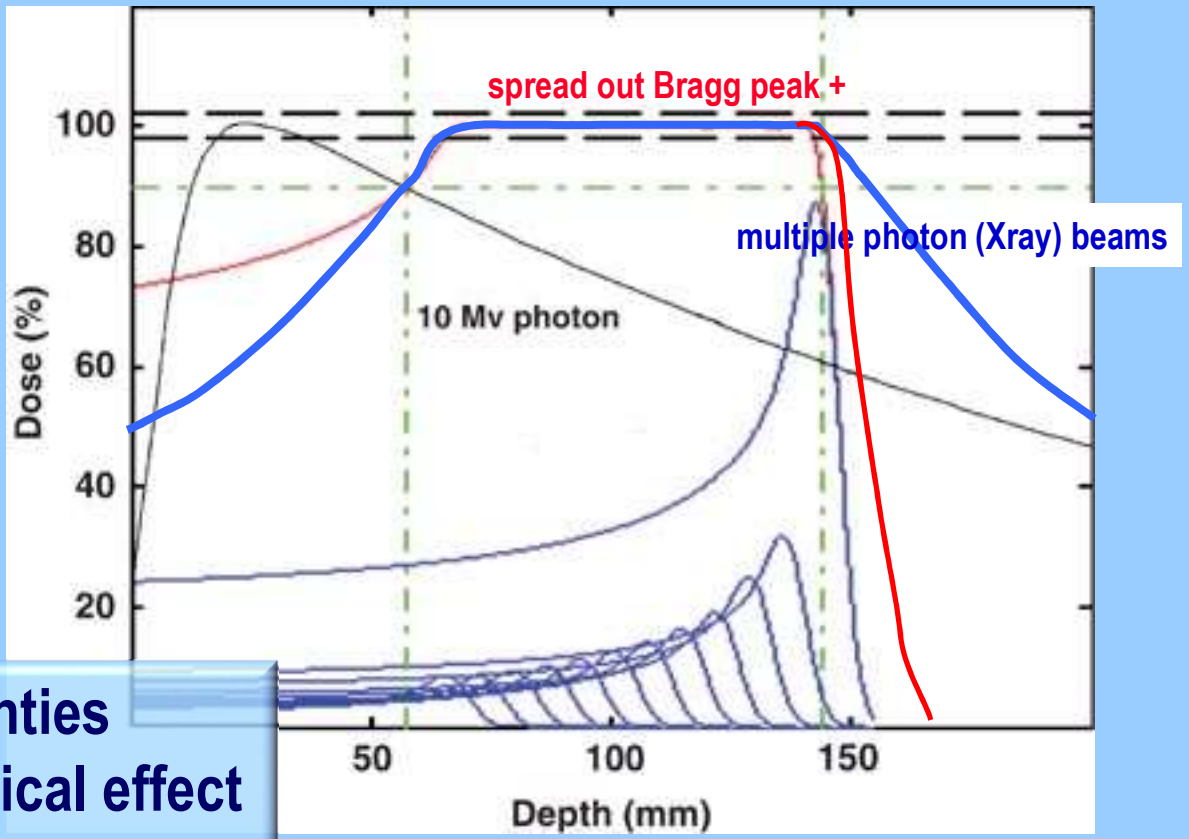


Energy dependence of radiation damage

Nickson, Kacperek & Parsons 2016

Reality



uncertainties

- **biological effect**
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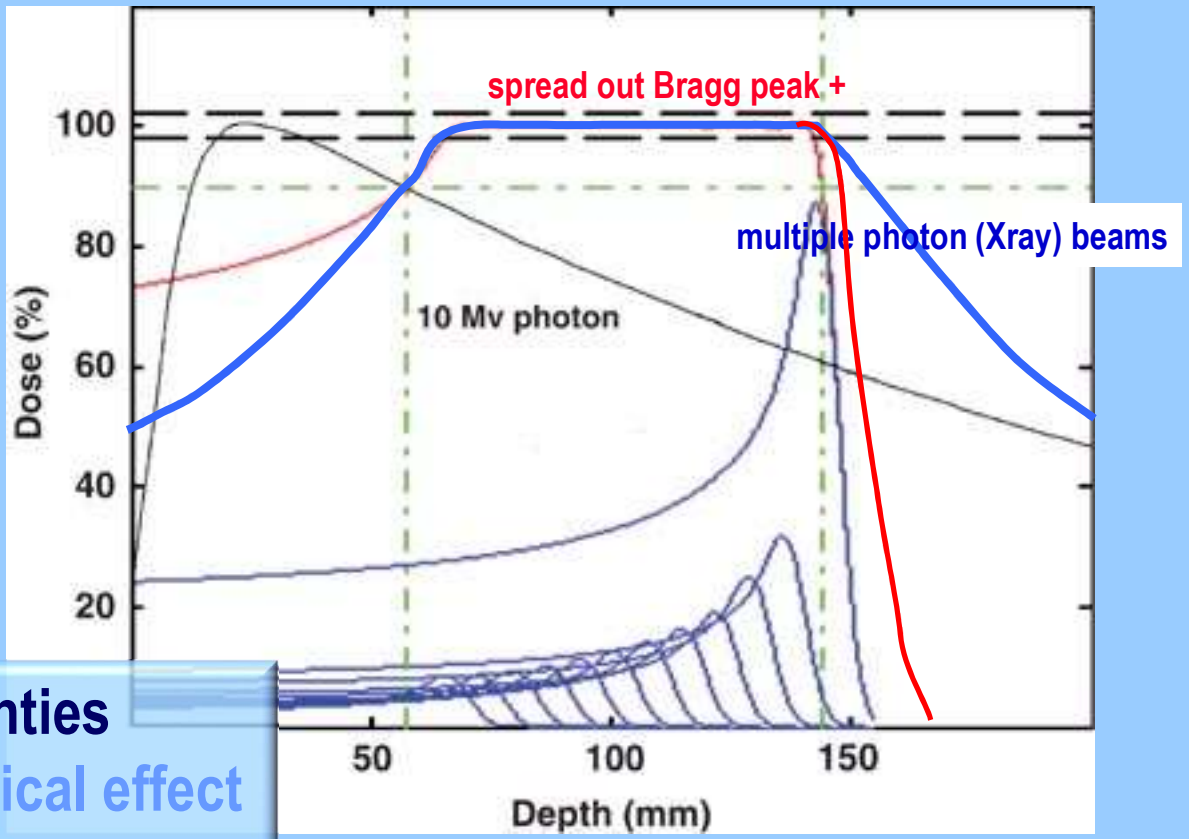
Depth dose distribution of photons and protons

Reality

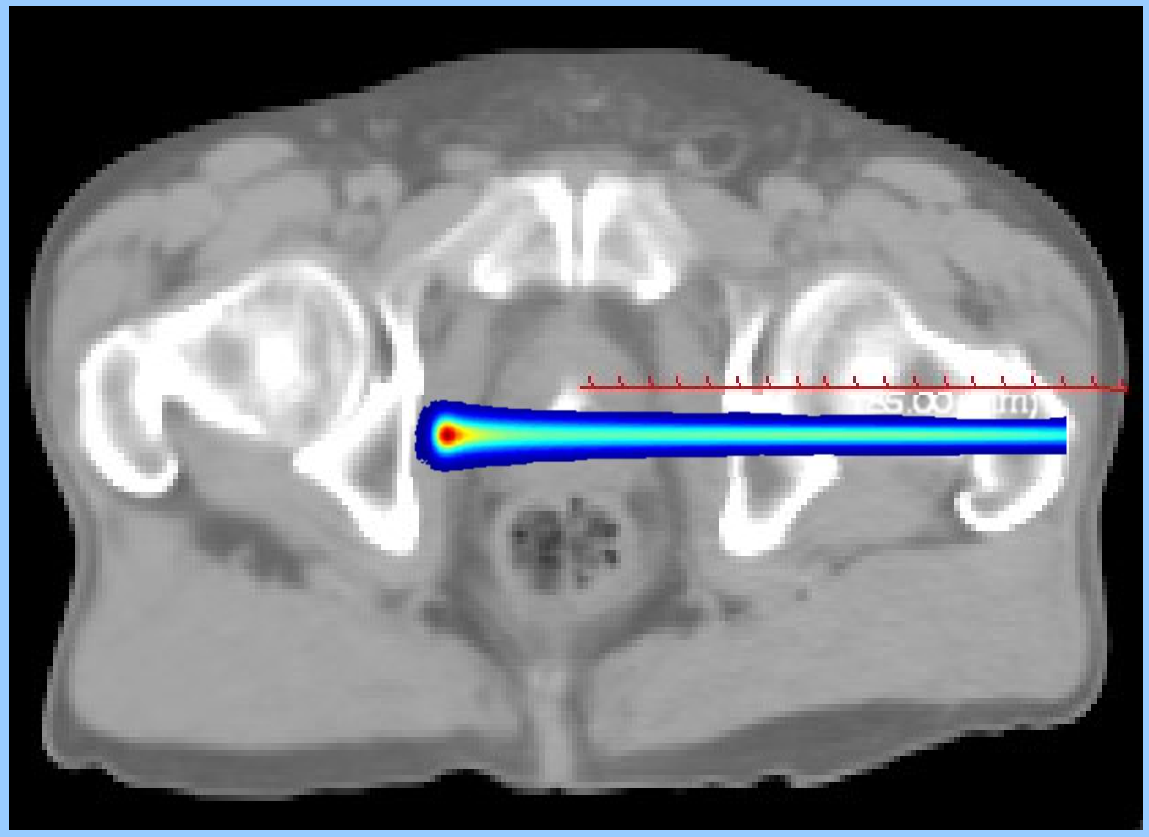


uncertainties

- biological effect
- range

Depth dose distribution of photons and protons

Range uncertainties due to setup

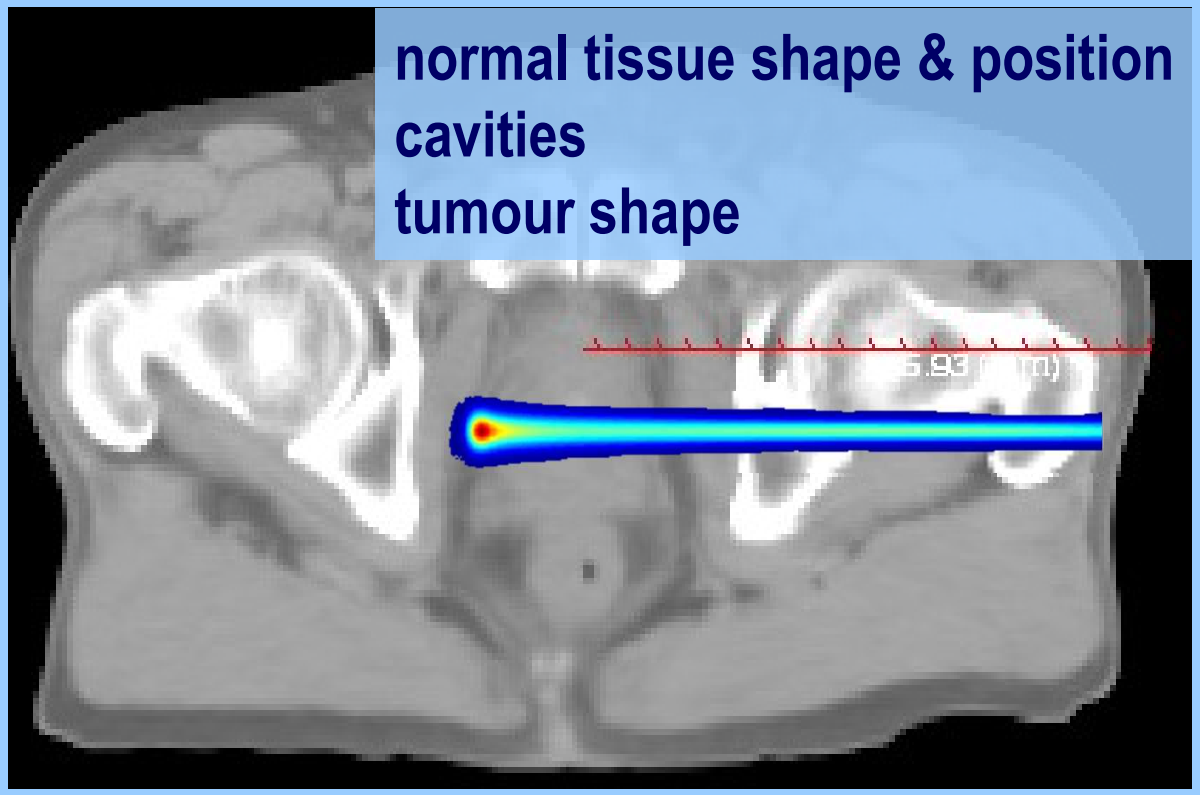


8 Jan

Proton uncertainties

Chen et al 2000, Int J Rad Oncol Biol Phys 48(3):339

Range uncertainties due to setup

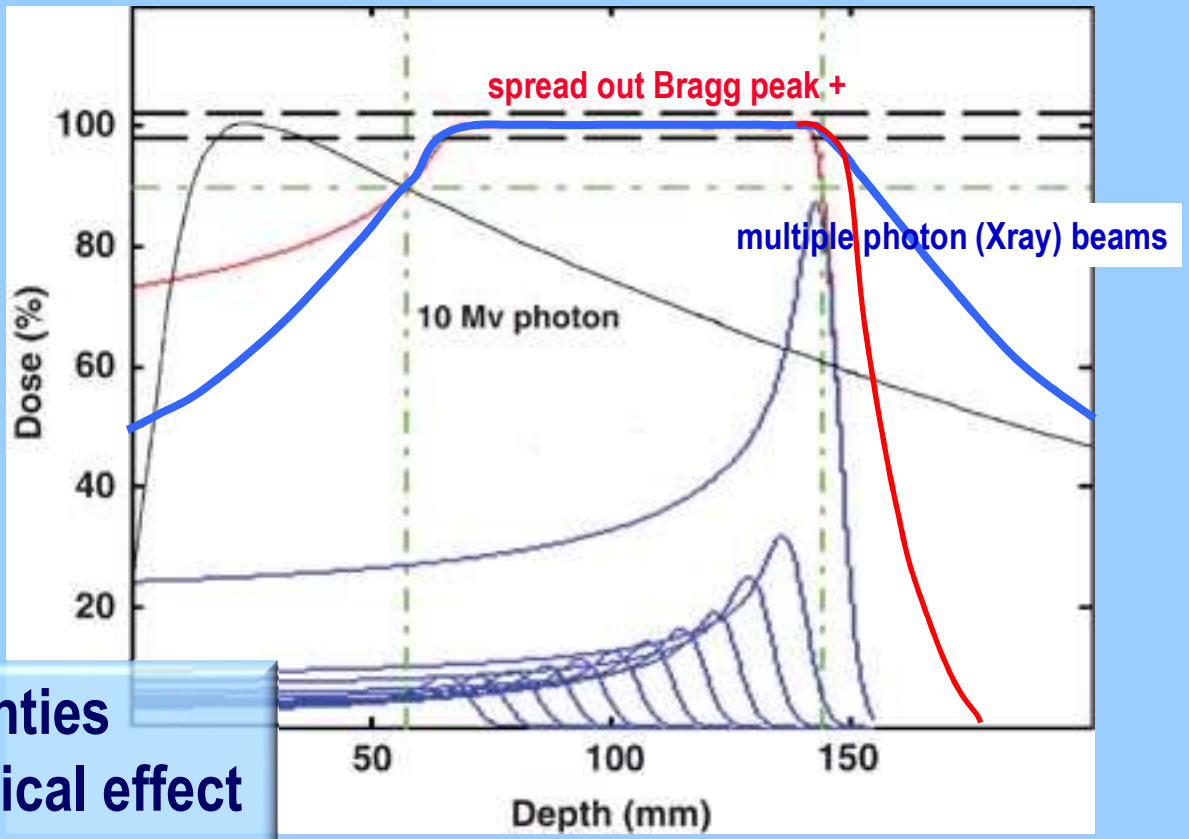


11 Jan

Proton uncertainties

Chen et al 2000, Int J Rad Oncol Biol Phys 48(3):339

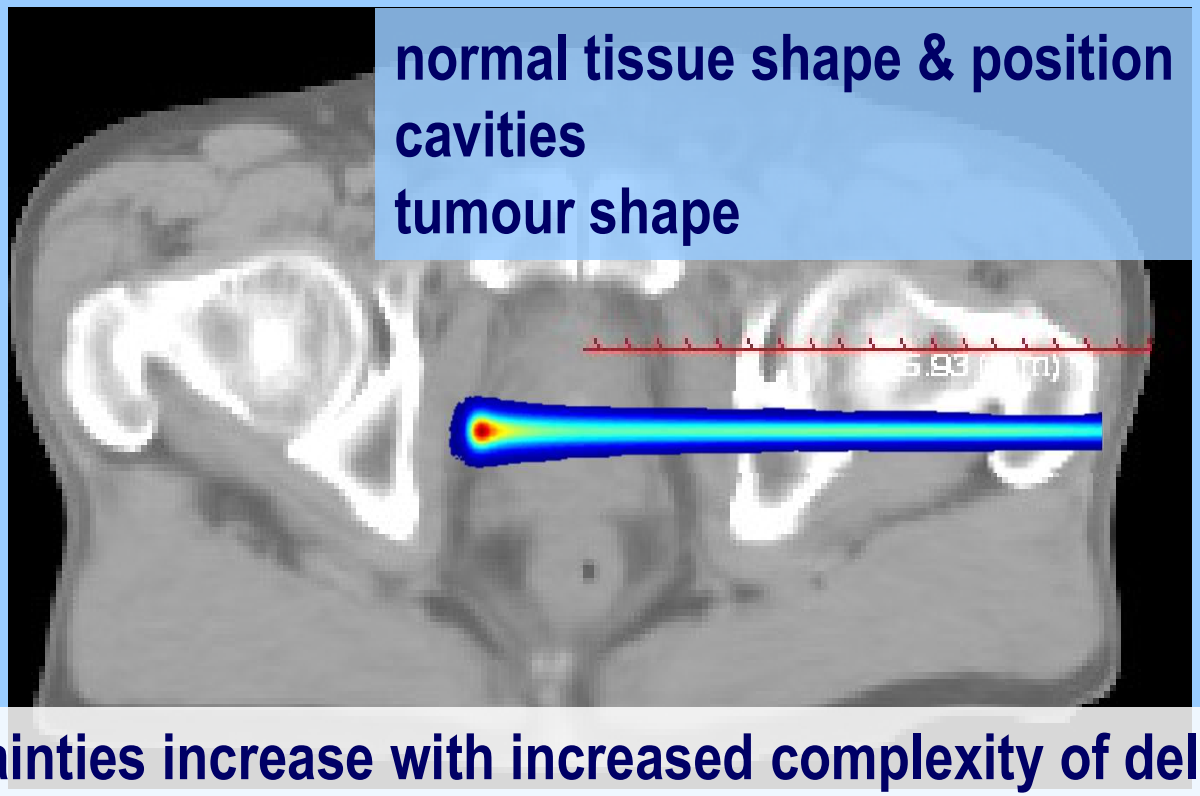
Reality



uncertainties
- biological effect
- range

Depth dose distribution of photons and protons

Range uncertainties due to setup



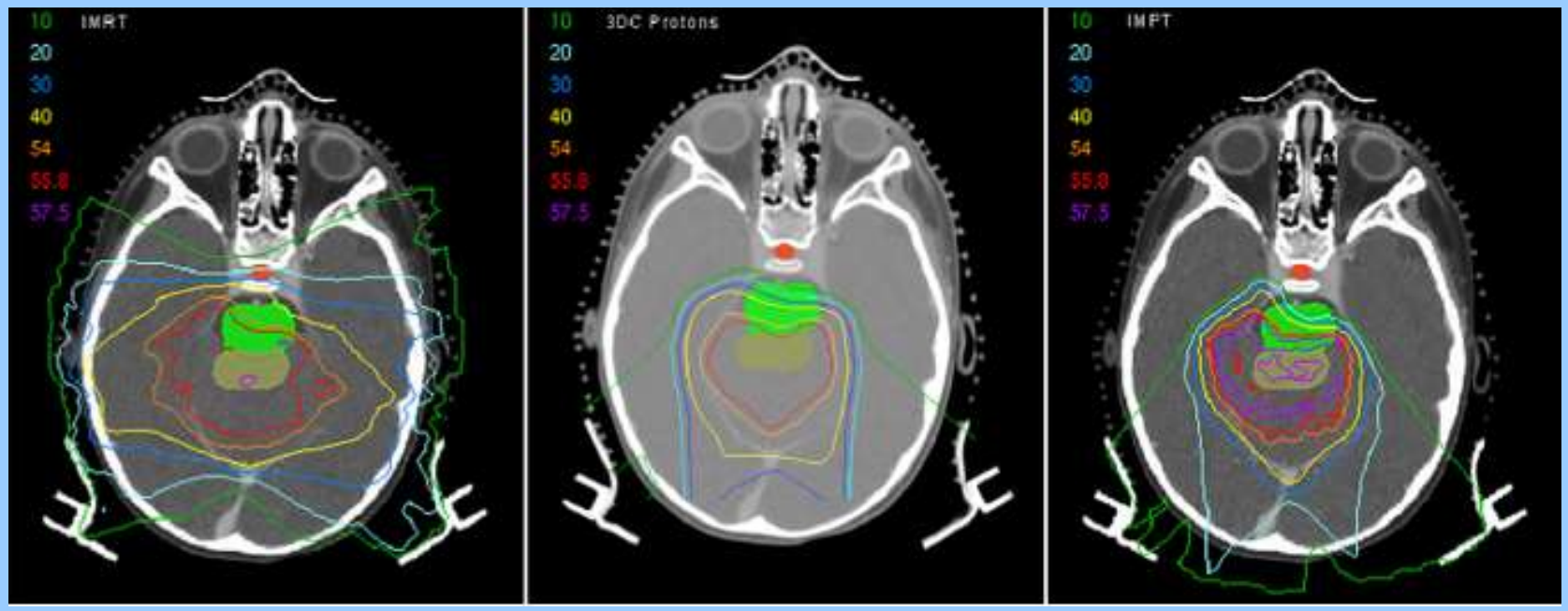
uncertainties increase with increased complexity of delivery

Proton uncertainties

Chen et al 2000, Int J Rad Oncol Biol Phys 48(3):339

Range uncertainties - with increased complexity of delivery

Ependymoma



photons IMRT **protons fixed fields** **protons IMPT**

IMRT – intensity modulated radiotherapy
IMPT – intensity modulated proton therapy

Proton uncertainties

MacDonald et al 2008, Int J Radiat Oncol Biol Phys, 71; (4), 979-986

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

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Classification of radiotherapy technologies

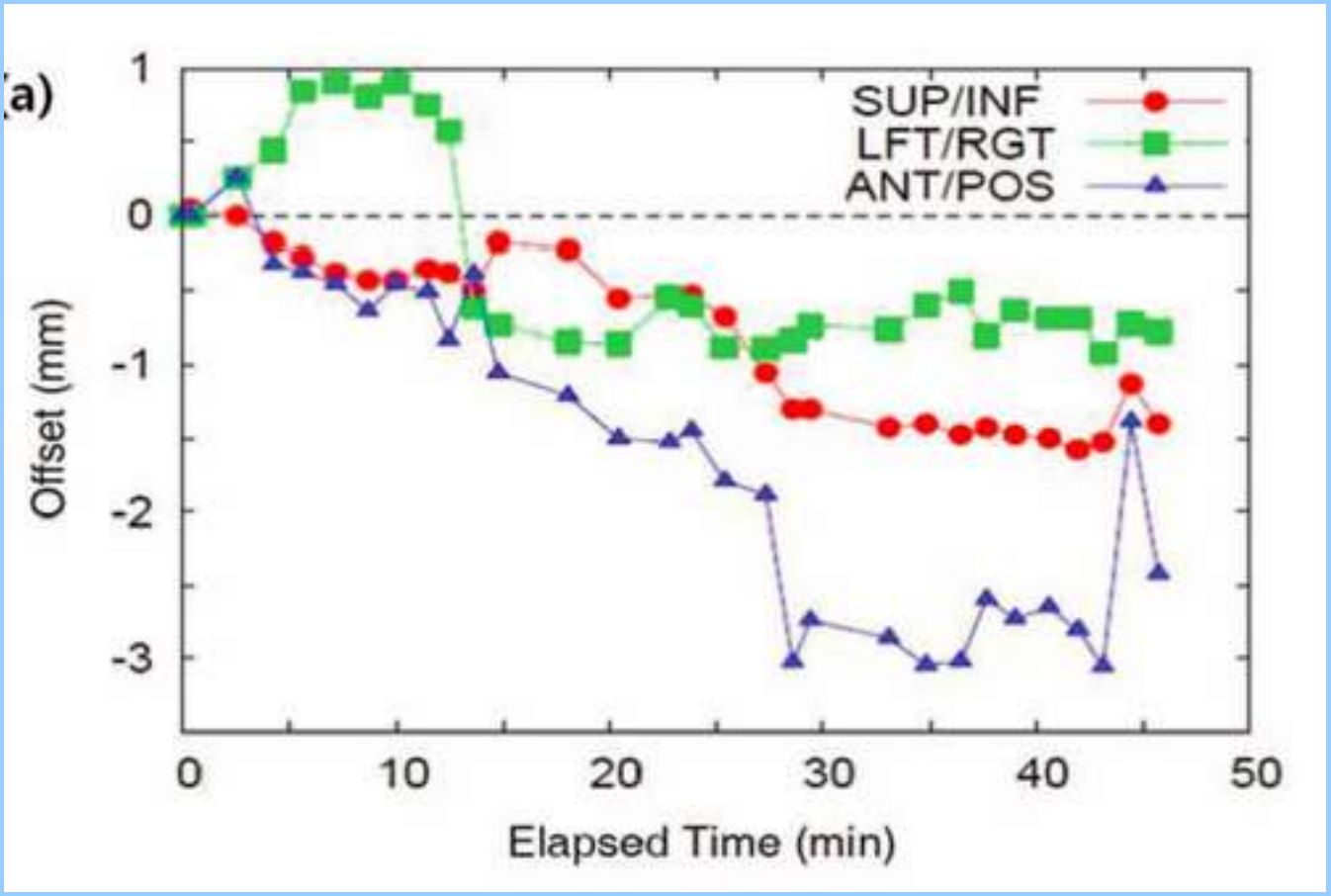
IGRT with ExacTrac kV stereoscopic image ver

Errors

ncol 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

Attributes of modern local RT delivery

refinements of conformal radiotherapy

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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

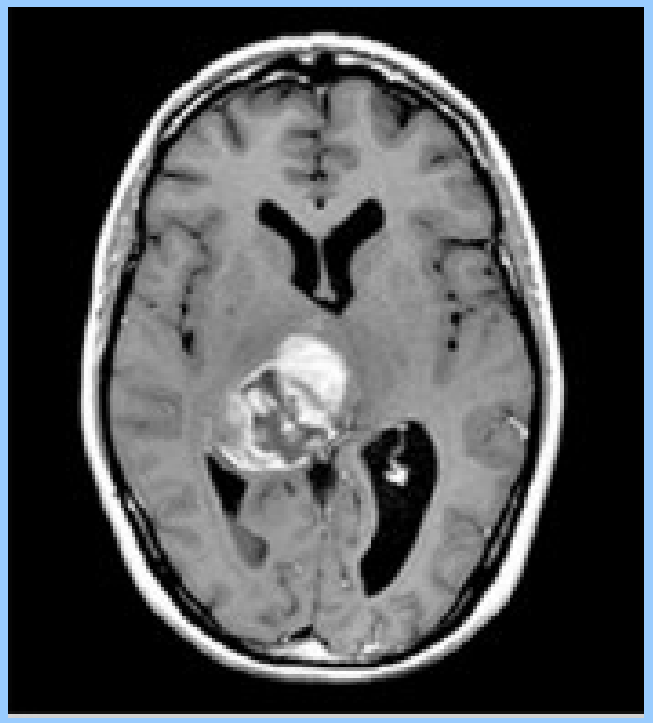
change in tumour position	change in tumour shape & volume

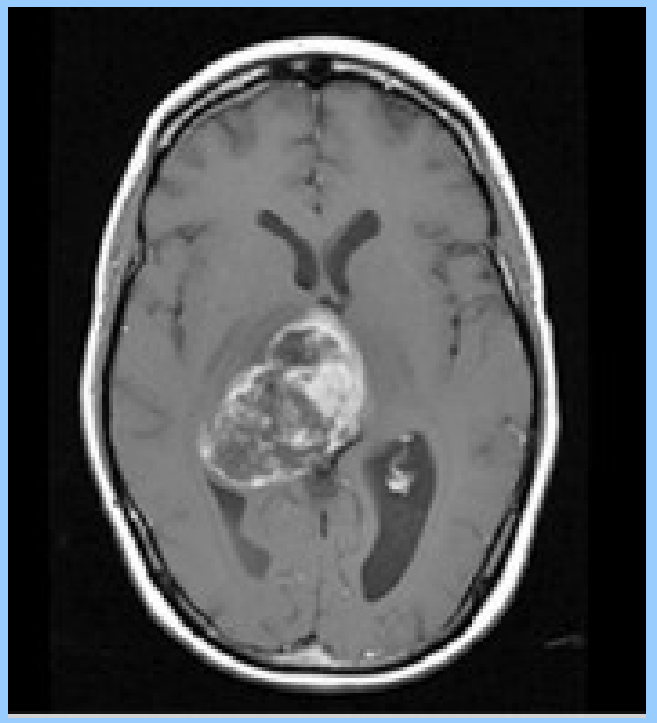
IGRT - adaptive radiotherapy
adjusting for interfraction motion

change in tumour position

change in tumour shape & volume

glioblastoma pseudoprogression

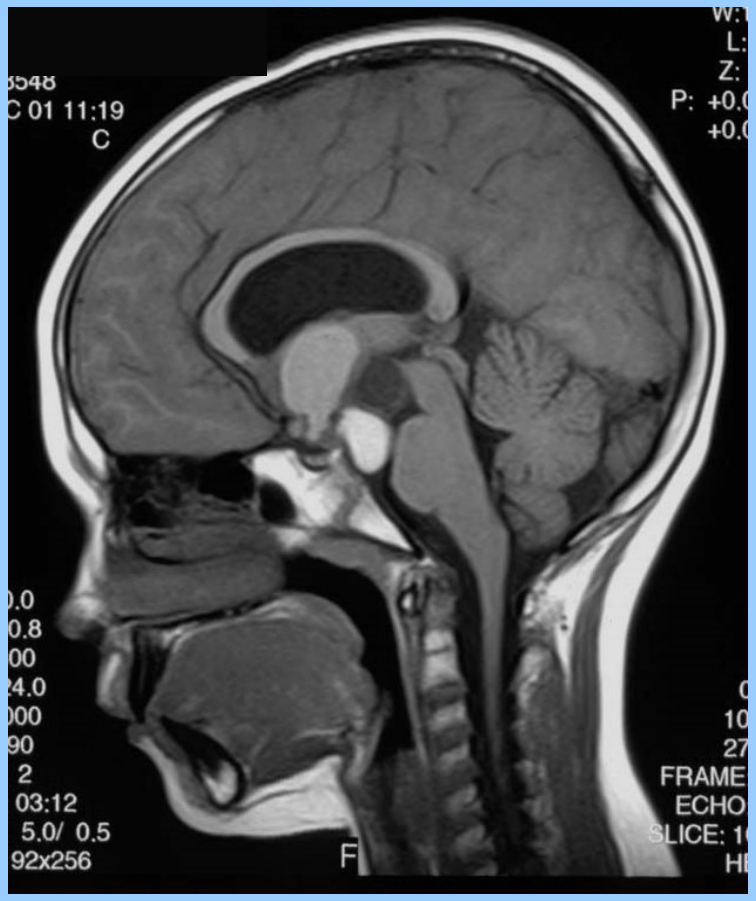




1 month post radiotherapy

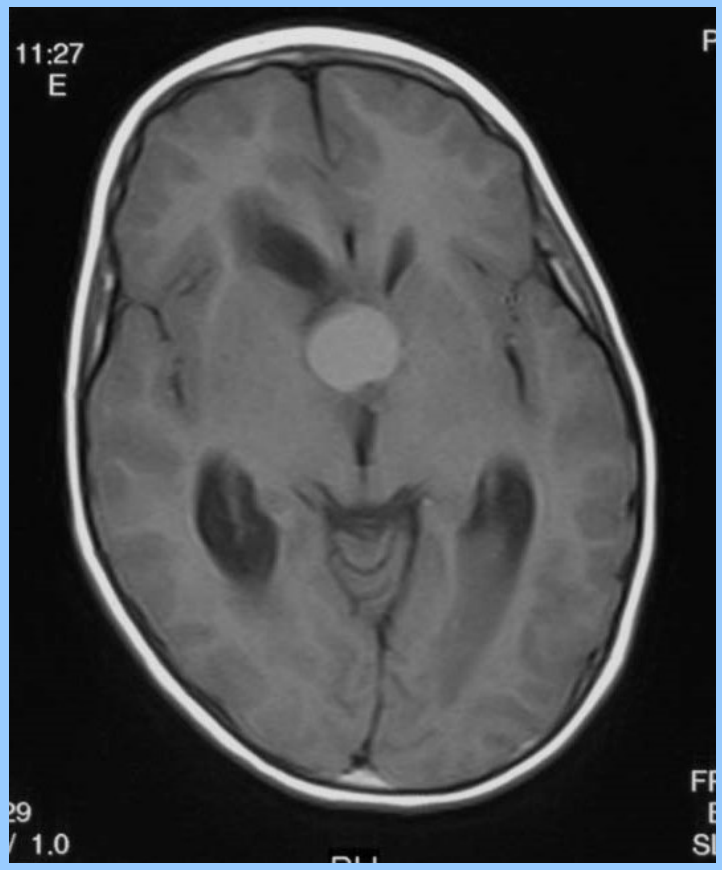
Adaptation in brain tumour radiotherapy

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



Craniopharyngioma

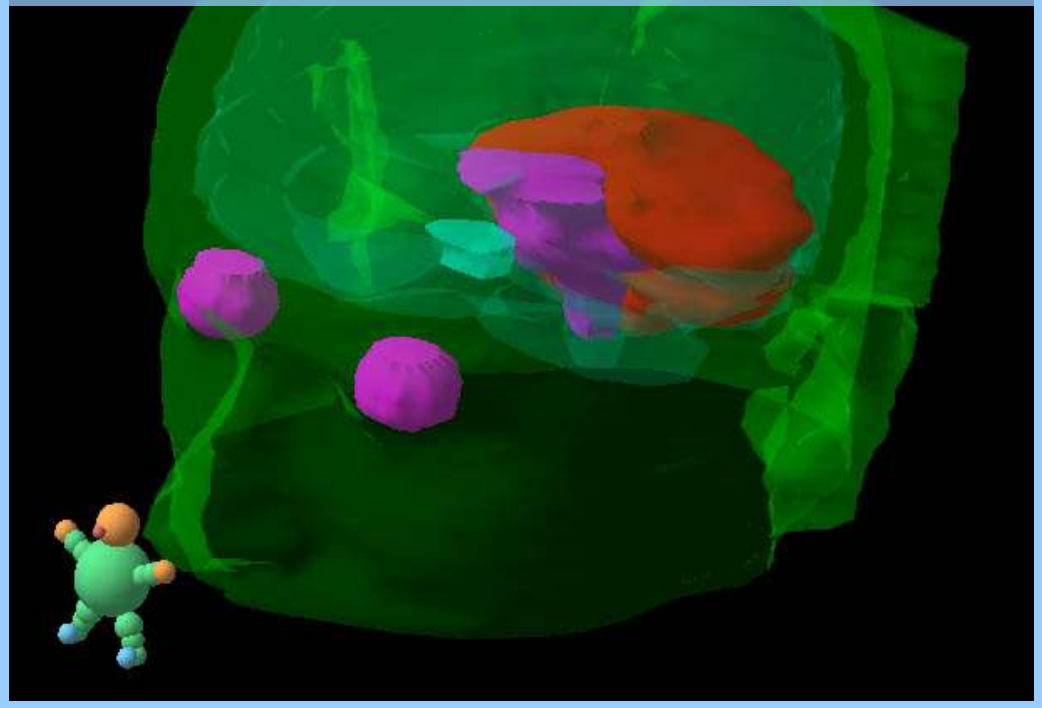
IGRT - adaptive radiotherapy
adjusting for interfraction change in size and shape



Craniopharyngioma

Localised radiation delivery

physical endpoints
standards for comparison
clinical relevance



Evaluation of local radiotherapy techniques

Attributes of modern local RT delivery

refinements of conformal radiotherapy

precision

conformality

- photons
- protons

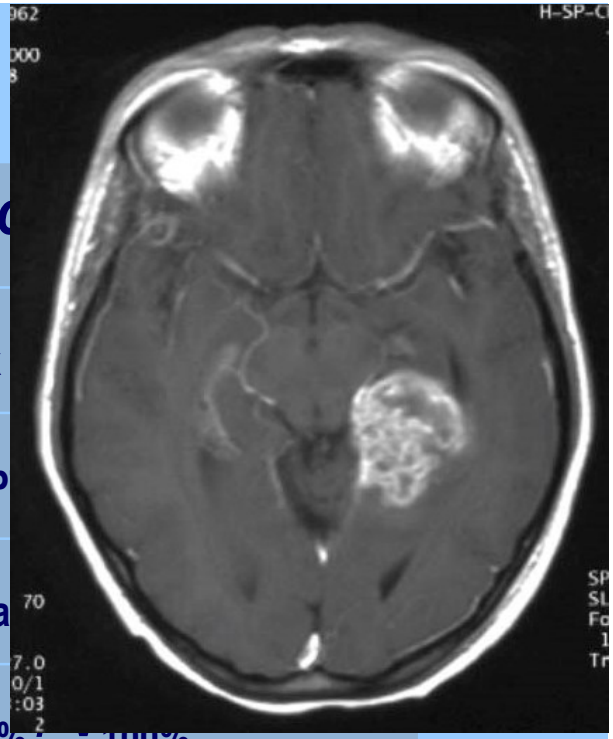
time factor (4D RT)

technical and clinical skill

quality assurance

- imaging closer to treatment delivery **(IGRT)**

Classification of radiotherapy technologies



Metric		*calc*
conformity index (RTOG)	**rCI**	V_{Rx}
conformity index (Paddick)	**pCI**	V^2_{P}
homogeneity index	**HI**	D_{ma}
gradient index	**GI**	$V_{50\%}$? - 100%
normal tissue volume (brain/ROIs) irradiated to Dx (DVH)		
planning time, treatment time etc.		

application to daily practice

V_{Rx} - volume covered by prescription isodose
V_{PTV} - PTV volume
$V_{PTV,Rx}$ - overlapping volume
D_{max} - maximum dose at the PTV
D_{Rx} - prescription dose in the PTV

Metrics for high precision RT

Localised radiotherapy techniques

for intracranial tumours

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Professor of Radiation Oncology
University of Liverpool

Department of Molecular and Clinical Cancer Medicine
& Department of Radiation Oncology
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UNIVERSITY OF LIVERPOOL

The Clatterbridge Cancer Centre NHS
NHS Foundation Trust

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Radiotherapy – Radiation Tolerance of the Brain

G. Pesce

Radiation Oncology

Oncology Institute of Southern Switzerland

Bellinzona and Lugano - Switzerland

ESTRO Teaching Course on

Management of Brain Tumors

Vienna, October 22-24, 2017

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Radiotherapy – Radiation Tolerance of the Brain

- Radiobiology of Nervous tissue
- Acute effects of radiotherapy
- Late effects of radiotherapy
- Theory turns to experiences
- Guidelines on constraints (Emami, QUANTEC and the others)
- Consequences on practice: Planning, DVH evaluation, Image guidance

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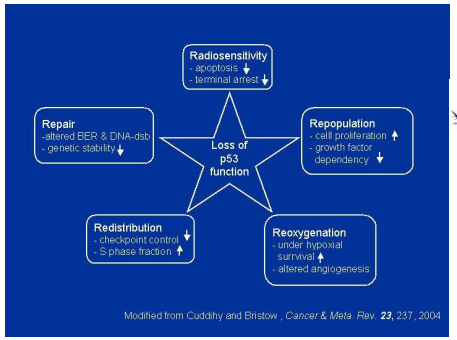
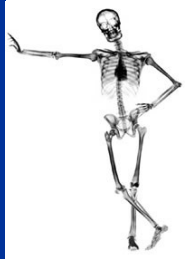
Radiobiology of RT/SRS/FSRT

- The goal of any medical intervention is to reach the highest role of *clinical success* in terms of desired effect with the minimum rate of side effects *treatment related*
- Historically radiation was delivered considering a variable safety margin to include *microscopic tumor infiltration* in normal tissue
- The relationship between time of radiation, dose and number of fractions, to influence the biological effect is based on 4Rs of ionizing radiation





A. Santacroce, et al., biomed research International, 2013

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Different tissues different responses to radiation

(1) late responding target embedded within late responding tissue: AVM,

(2) late responding target surrounded by late responding tissue: meningioma/schwannoma,

(3) early responding target embedded within late responding tissue: low grade glioma,

(4) early responding target surrounded by late responding tissue: glioblastomas/metastases.

Santacroce, et al., biomed research International, 2013
Larsson, et. al., IJROBP, 1993

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Radiobiology in the CNS: the vascular effect (SRS)

- Mainly for the case of benign lesions (AVM and meningioma, namely) large parte of the effect is determined by the combination of:
  - **Citotoxic effect** of the high dose of radiation with direct double strand DNA damage
  - **Vascular injury** with doubled number of apoptotic cells in the first 48 hours
  - Such a vascular effect is seen on tumor and AVM, but **not in normal vessels** (different vascular/endothelial radiosensitivity)
  - The probability of vascular damage is directly proportional to the fraction dose (particularly when higher than 10 Gy!!!)
  - High dose induces reduction of vascular mass and increase of vascular permeability

Park and Griffin, Rad Res., 2012

Radiotherapy – Radiation Tolerance of the Brain

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Acute effects of RT

Effect	Consequences	Comments
Alopecia Skin redness	Social appearance Itching, burning sensations	Psichologic discomfort
Edema	Nausea Blurred vision Fatigue Headache Seizures	Treatment with steroids needed (and related complications) needed?. AED needed?
Haemorrhage	Shock Focal deficit Risk of death Seizures	Emergency Steroids and AED needed?
?	Somnolence syndrome	Social discomfort, working disability

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Radiotherapy – Radiation Tolerance of the Brain

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Late effects of RT

Effect	Functional	Comments
Necrosis	Cognitive disfunction Disability, Fatigue	Defines tolerance
Vascular Effects (hyschaemia, haemorrage)	Focal deficits	Disability
Demyelinization	Cognitive disfunction	Social problems
Atrophy	Focal deficits	Disability
Neuronal Depletion	Fatigue, Cognitive disfunction	Social problems, working unability, etc.

Late effects of RT

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Supportive therapy

- Steroid treatment
  - Beware of related toxicity
- AED
  - New molecules better tolerated

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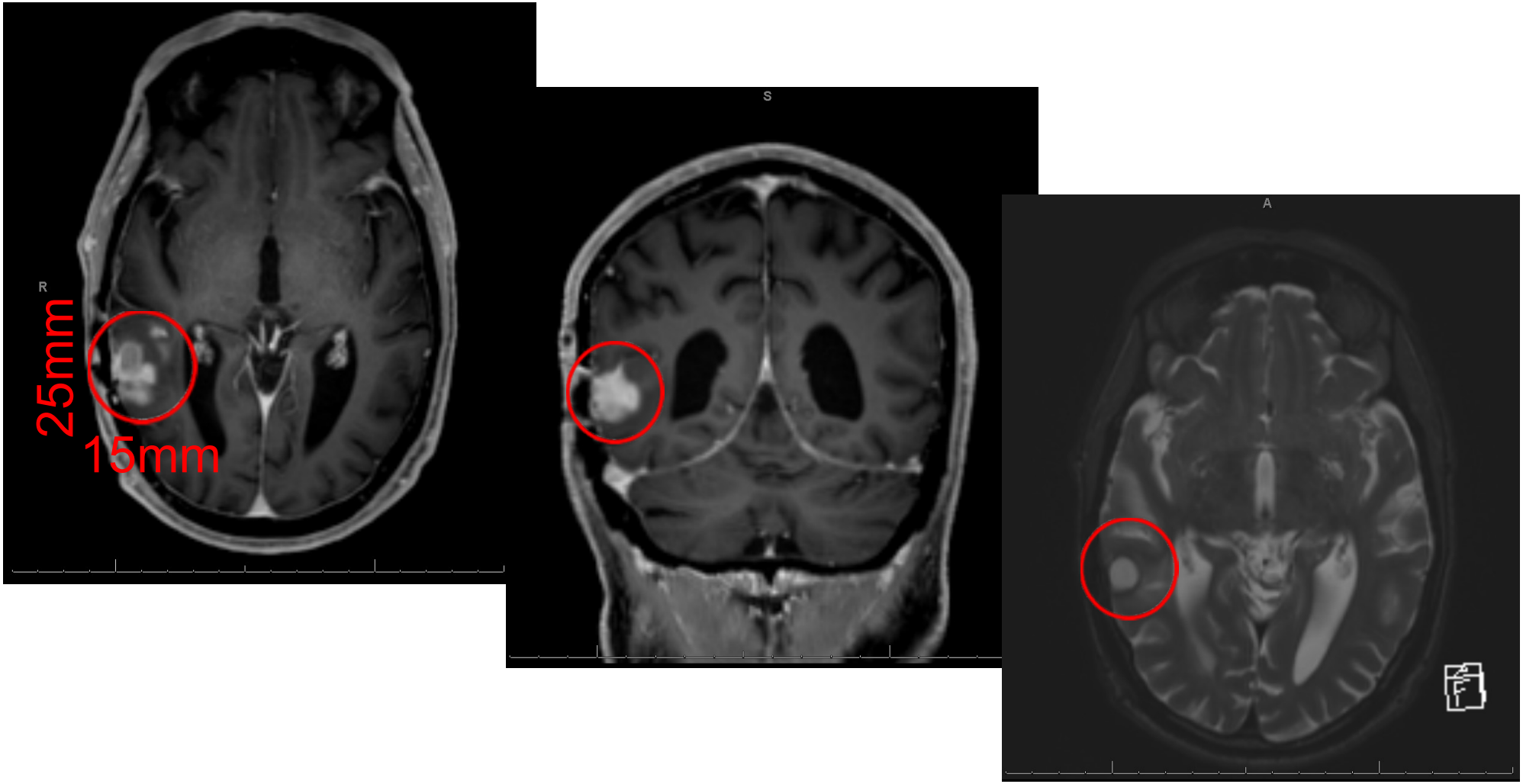
MRI June 2017 (FU 15 months)



Tumor regrowth tissue at the margin of the resection cavity, at 15 mths after 1st surgery and Cht/RT for Anaplastic IDHwt, unmethylated not deleted astrocytoma

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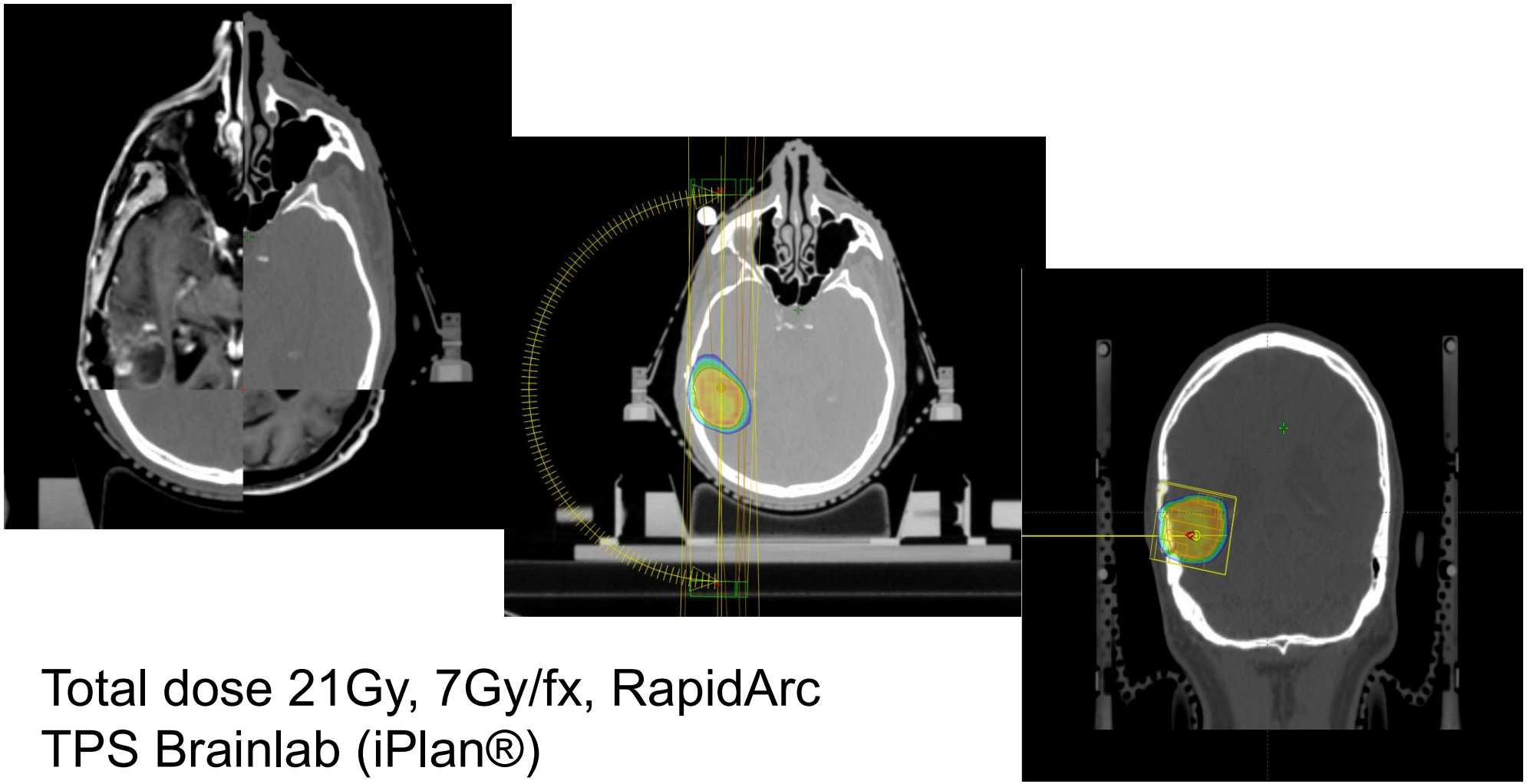
Stereotactic radiosurgery



Total dose 21Gy, 7Gy/fx, RapidArc
TPS Brainlab (iPlan®)

…Woluld you start on Steroids? AED?

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Supportive therapy

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  - Beware of related toxicity
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Supportive therapy

- Steroid treatment
  - Beware of related toxicity
  - Start on symptom
  - *Short and Strong*
- AED
  - New molecules better tolerated
  - Start on symptom

Radiotherapy – Radiation Tolerance of the Brain

- Radiobiology of Nervous tissue
- Acute effects of radiotherapy
- Late effects of radiotherapy
- Theory turns to experiences
- Guidelines on constraints (QUANTEC)
- Consequences on practice: Planning, DVH evaluation, Image guidance

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Risk of Neurocognitive impairment after RT

- The risk in patients treated for glioma is mainly related to large volume (no WB better) (1)
- The risk of dementia in long survivors after WBRT in patients treated for brain metastases is strongly related to fractionation (<3Gy better)
- Rate of Neurocog sequelae is lower than 3% for partial brain irradiation, while respecting dose constraints
- Experiences on normal NSCs department avoidance also with larger treatment volumes are promising (3)

(1) Sarkissian et al. Neurol Lett, 2005
(2) De Angelis et al. Neurology, 1989
(3) Barani et al. IJROBP, 2007

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Studies on neuro-toxicity in gliomas

Author	year	Setting	Tumor	Nr	Dose	Resp.	Tumor PD
Taylor	1998	Pro	HGG	701	60Gy	No significant Neurotoxicity	Worsening of NC
Brown	2001	Pro	LGG	203	50.4 vs 64 Gy	Worsening at 1, 2, 5 years: 8.2, 4.6, 5.3%	Significant improvement 59%, 50%, and 67% at years 1, 2, and 5,
Armstrong	2000	Pro	LGG	20	46-63 Gy	Verbal decline at 3m, recovery at 1y	-
Vigliani	1996	Pro	LGG	17	54-55.8 Gy	No tox compared to matched pairs, improvement*	-
Klein	2001	Retro	LGG	195	n.r.	No significant impairment	n.r.
Taphoorn	1994	Retro	LGG	41 (20 RT/21 Sg only)	45-63 Gy	No difference Comparison to 19 haem dis. CHT,LGG both groups with lower Cog/mood/asteni a	-

Radiotherapy – Radiation Tolerance of the Brain

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QUANTEC

- *Quantitative Analysis of Normal Tissue Effects in the Clinic*
  - Large committee of experts (n=57)
  - Convened by ASTRO / AAPM
  - Updated guidelines published in Red Journal supplement (vol 76, No. 3)
  - 16 organ-specific papers
  - Several “general principle” papers

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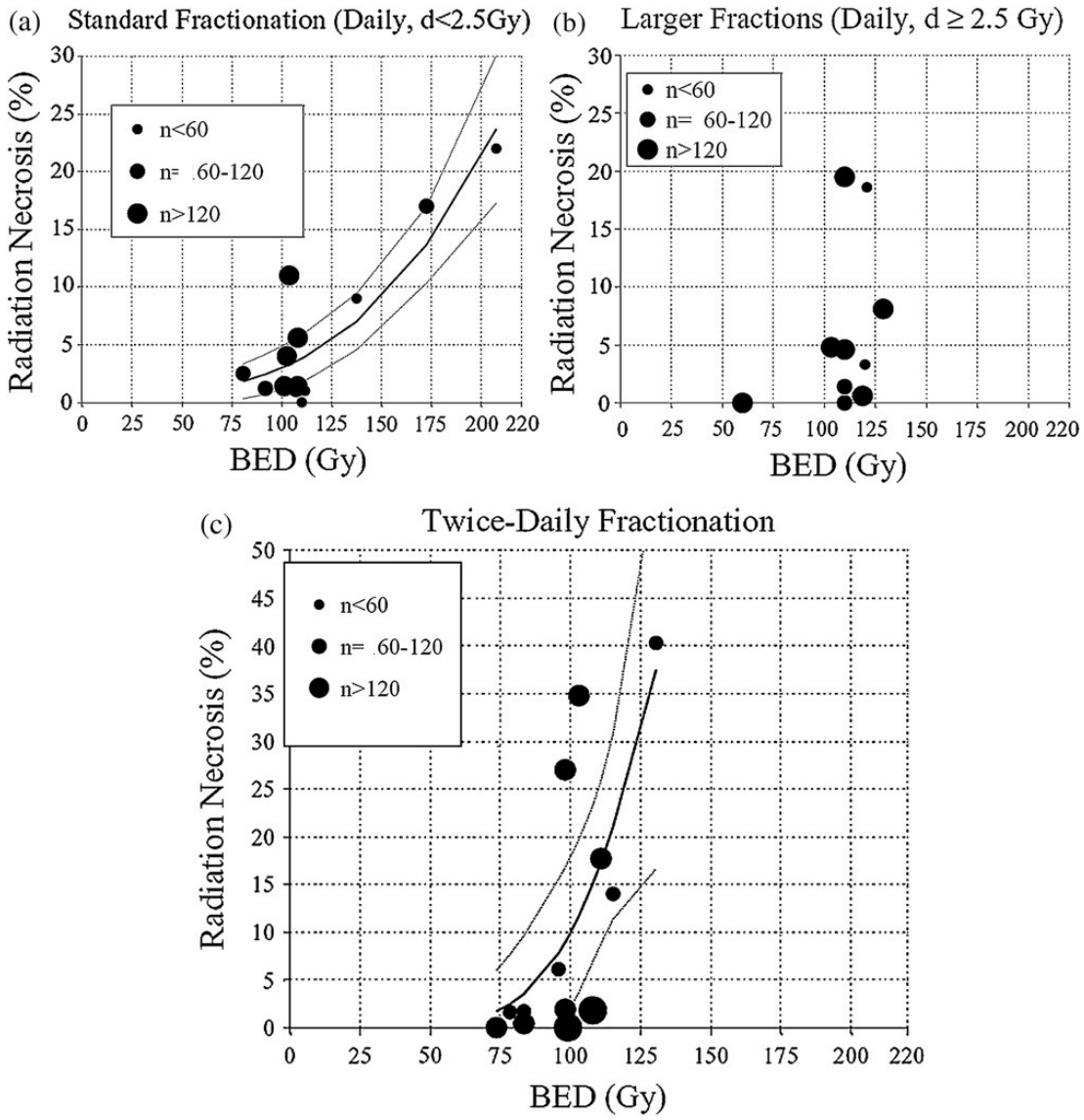
Brain – Data Summary



Brain – Proposed Constraints

- 5% risk radiation necrosis @ BED 120 Gy (**72 Gy**/2 Gy)
  - Emami: "overly conservative" (**60 Gy**/2Gy)
- 10% risk @ 150 Gy (**90 Gy**/2Gy)
- Increased risk with hypofractionation/twice daily
- 18 Gy WBRT: cognitive changes in children
- **SRS**: Increased risk if >5-10 cm^3 exposed to >**12 Gy** (proposed reporting)

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Specific normal tissue avoidance

OAR	objective
brainstem	D≤54Gy, 1-10cm^3 <59Gy (periph)
chiasm	D_{max}<55Gy
cochlea	ideally one side <45Gy
eyes - macula	<45Gy
eyes - lens	ideally <6Gy max 10Gy
lacrimal gland	D_{max}<40Gy
optic nerves	D_{max}≤54Gy, D_{max}<55Gy
pituitary	D_{max}<50Gy

Suggested dose limits in glioblastoma radiotherapy

Niyazi et al. 2016, Radiotherapy and Oncology 118 (2016) 35–42

Quantec for the brain

What are the recommended dose constraints for the following organs and clinical scenarios? *(Continued)*	
ORGAN	***CONSTRAINTS***
CNS (single fraction)	
Brain	**V12 Gy <5-10 cc** (QUANTEC)
Chiasm/optic nerves	**max 10 Gy** (QUANTEC)
Brainstem	**max 12.5 Gy** (QUANTEC)
Sacral plexus	**V18 <0.035 cc, V14.4 <5 cc** (RTOG 0631)
Cauda equina	**V16 <0.035 cc, V14 <5 cc** (RTOG 0631)

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Quantec for the brain

What are the recommended dose constraints for the following organs and clinical scenarios?	
ORGAN	***CONSTRAINTS***
CNS (1.8-2.0 Gy/fx)	
Spinal cord	**max 50 Gy** (full cord cross-section); tolerance increases by 25% 6 mos after 1st course (for re-irradiation) (QUANTEC)
Brain	**max 72 Gy** (partial brain); avoid >2 Gy/fx or hyperfractionation (QUANTEC)
Chiasm/optic nerves	**max 55 Gy** (QUANTEC)
Brainstem	**Entire brainstem <54 Gy, V59 Gy <1-10 cc** (QUANTEC)
Eyes (globe)	**Mean <35 Gy** (RTOG 0225), **max 54 Gy** (RTOG 0615)
Lens	**max 7 Gy** (RTOG 0539)
Retina	**max 50 Gy** (RTOG 0539)
Lacrimal Gland	**max 40 Gy** (Parsons)
Inner ear/cochlea	**mean ≤45 Gy** (consider constraining to ≤35 Gy with concurrent cisplatin) (QUANTEC)
Pituitary gland	**max 45 Gy** (for panhypopituitarism, lower for GH deficiency) (Emami)
Cauda equina	**Max 60 Gy** (Emami)
CNS (single fraction)	
Spinal cord	**max 13 Gy** (if 3 fxs, max 20 Gy) (QUANTEC)

Radiotherapy – Radiation Tolerance of the Brain

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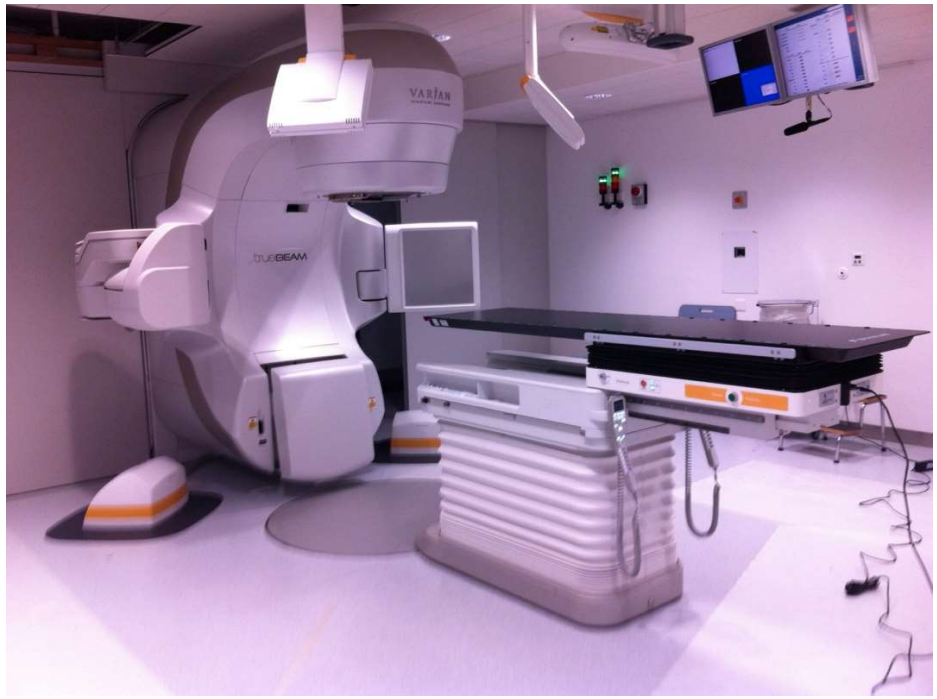
Technology Improvement

- Improved accuracy
- Improved imaging (MRI, PET, CT fusion)
  - planning/contouring
  - verification (ExacTrac®, CBCT, e.g.)
- Improved dose delivery
  - Higher dose rate, shorter treatment time



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Neural Stem Cells and RT toxicity

- NSCs exhibit exquisite in situ radiosensitivity
- Radiation can directly depopulate NSC niches, causing immediate loss of NSC-mediated repair and plasticity
- Indirect effects of radiation are inflammatory in nature, dose dependent, and capable of stunting neurogenesis even at low doses
- The scope of NSC dysfunction is age dependent, with greater effects noted in immature brains

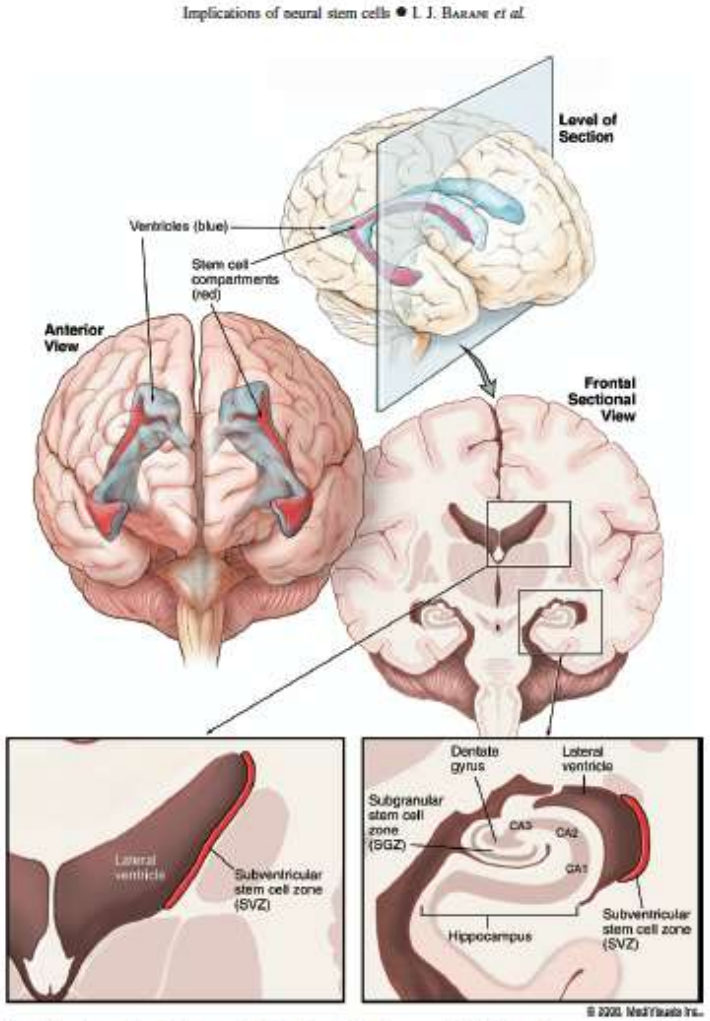

Fig. 1. Germinal regions of adult human brain. Subventricular zone (SVZ) is the largest germinal region in adult mammalian brain. The subgranular zone (SGZ) is located within dentate gyrus of hippocampus. CA1, CA2, and CA3 represent Cornu Ammonis fields of hippocampus proper and, along with dentate gyrus, constitute the hippocampal formation, primary memory center in brain.

Barani I, IJROBP 2007

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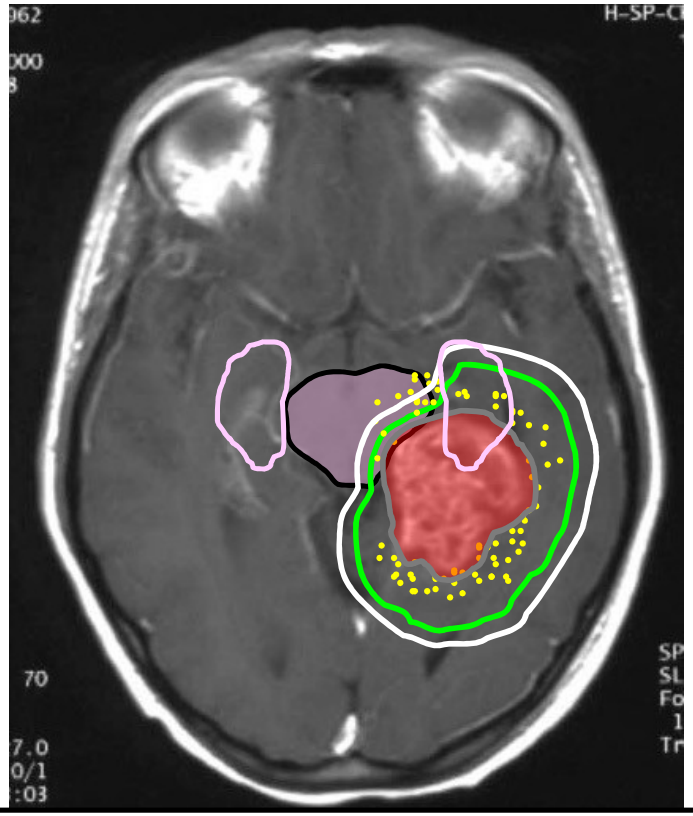
Hippocampal avoidance with IMRT*



limited clinical data showing benefit

Intensity modulated radiotherapy (IMRT) in malignant glioma

*Marsh et al 2011 J Med Imaging Radiat Oncol. 2011;55:442-449.

Courtesy-modified from M. Brada, ASCO 50°, 2014

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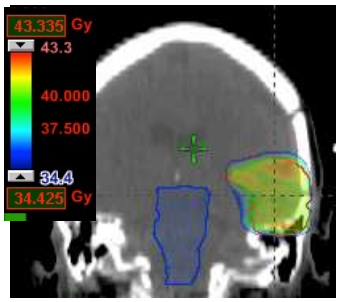
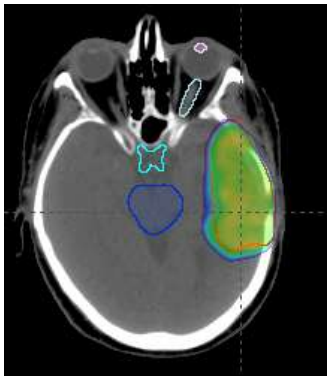
Re-irradiation for brain

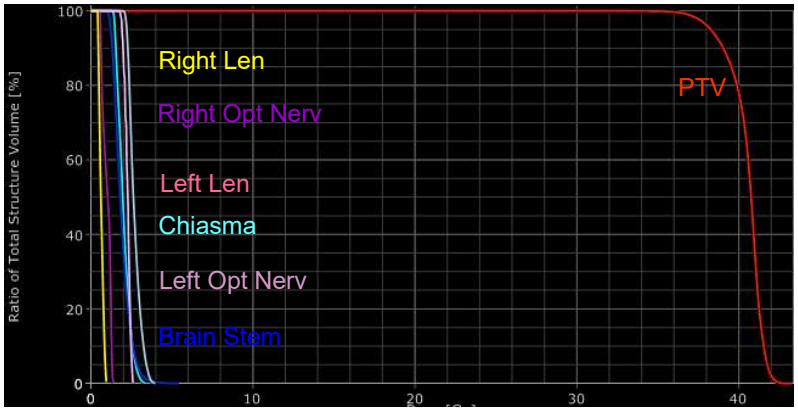
15 x 2.7 Gy = 40.5 Gy

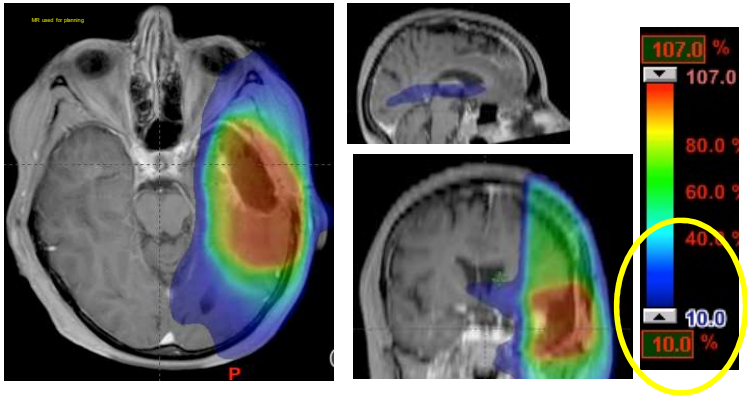
(previous treatment @60Gy [30 months], with brainstem Dmax~54Gy, LeftOptNerv & chiasma Dmax~52Gy)



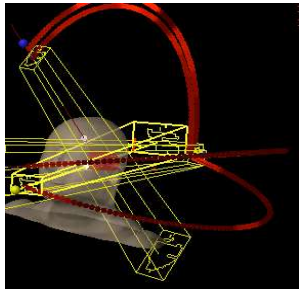


PTV : 85.5 cm3





brain stem max_{pt} dose = 5.4 Gy
chiasma max_{pt} dose = 3.4 Gy
left opt nerve max_{pt} dose = 3.9 Gy



4 isocentric arcs
partial arc

123-115-72-77 MU
28+28+34+34 sec

REIRRADIATION TOLERANCE OF THE HUMAN BRAIN

RAMONA MAYER, M.D., M.SC.,* AND PETER SMINIA, PH.D.[y]

* Department of Therapeutic Radiology and Oncology, Medical University of Graz, Graz, Austria; and [y]Department of Radiation Oncology, Division Radiobiology, VU University Medical Center, Amsterdam, The Netherlands

- Radiation-induced normal brain tissue necrosis was found to occur at $NTD_{cumulative}$ >100 Gy
- The applied reirradiation dose and $NTD_{cumulative}$ were found to increase with a change in irradiation technique from conventional to conformal techniques such as FSRT to SRS, without increasing the probability of normal brain necrosis.
- The analysis shows the applied total cumulative dose to be the most important factor with regard to the development of radionecrosis
- Reirradiation is a feasible option as palliative therapy for recurrent high grade glioma

R Mayer, et al., IJROBP, 2008

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Drugs?

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Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation (Review)

Day J, Zienius K, Gehring K, Grosshans D, Taphoorn M, Grant R, Li J, Brown PD

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Drugs for memory…

- There is supportive evidence that memantine may help prevent cognitive deficits for adults with brain metastases receiving cranialirradiation
- There is supportive evidence that donepezil may have a role in treating cognitive deficits in adults with primary or metastatic brain tumours who have been treated with cranial irradiation

ADDITIONAL TABLES

Table 1. Summary of findings: Memantine versus placebo

Cognitive functioning measure (standardised scores)	Memantine		Placebo		P
	N	Median change after 24 weeks (IQR)	*N*	Median change after 24 weeks (IQR)	
Short-term verbal memory	77	-0.23 (-1.16 to 0.70)	90	-0.415 (-1.86 to 0.46)	0.21
Long-term verbal memory (recall)	76	0 (-1.67 to 0.59)	90	-0.90 (-2.22 to 0.55)	0.06
Long-term verbal memory (recognition)	76	0 (-1.12 to 1.43)	90	-0.72 (-2.73 to 0.71)	0.01*
Verbal Fluency	78	-0.10 (-0.62 to 0.53)	90	-0.16 (-0.83 to 0.61)	0.31
Trail making test A	76	0.08 (-1.01 to 1.82)	92	-0.37 (-2.08 to 0.50)	0.02*
Trail making test B	74	-0.45 (-2.37 to 1.04)	90	-0.49 (-2.60 to 0.62)	0.30
Cognitive composite score	73	-0.03 (-0.90 to 0.72)	90	-0.41 (-1.30 to 0.12)	0.02*

* P < .05
IQR: interquartile range

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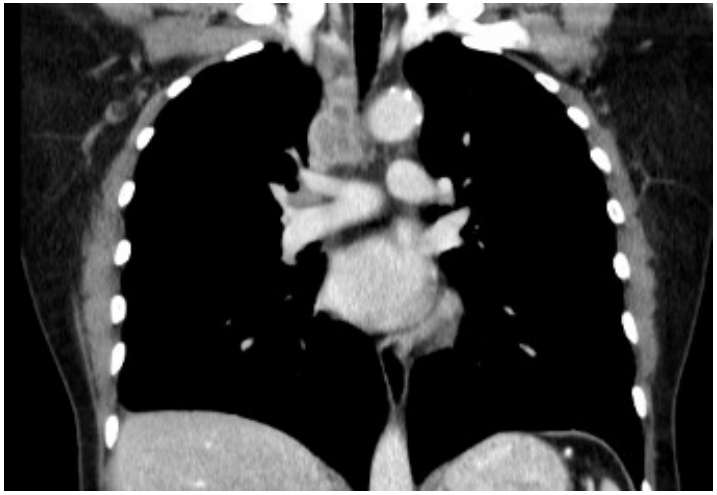
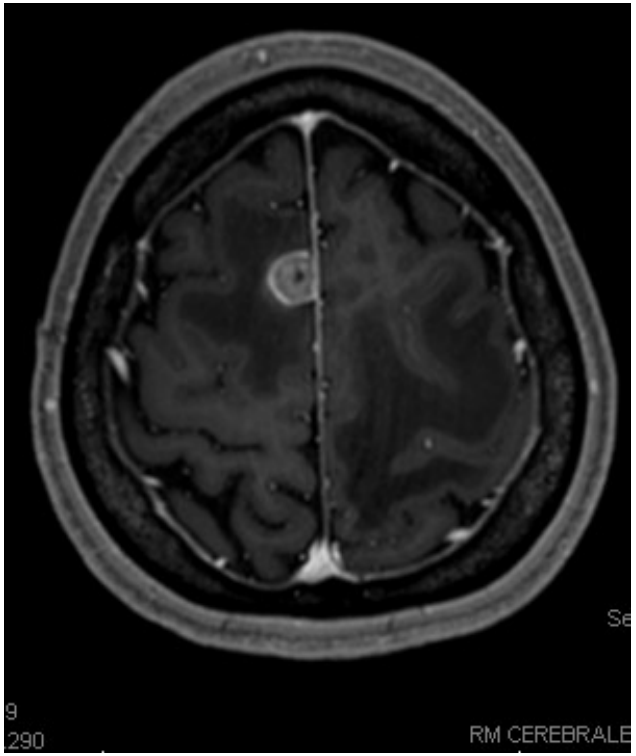
Other than drugs

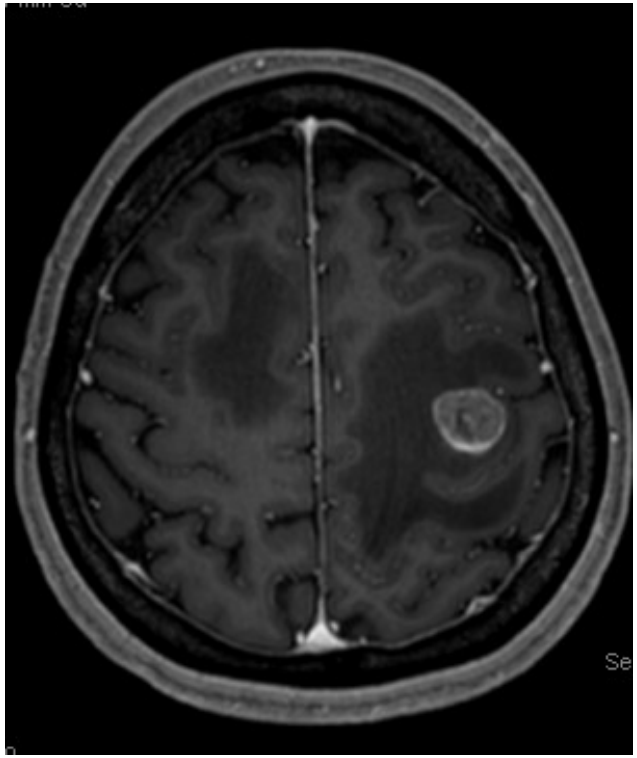
- There is no strong evidence to support any non-pharmacological interventions (medical or cognitive/behavioural) in the prevention or amelioration of cognitive deficits.
- Non-randomised studies appear promising but are as yet to be conclusive via translation into high quality evidence.
- Further research is required

Clinical case

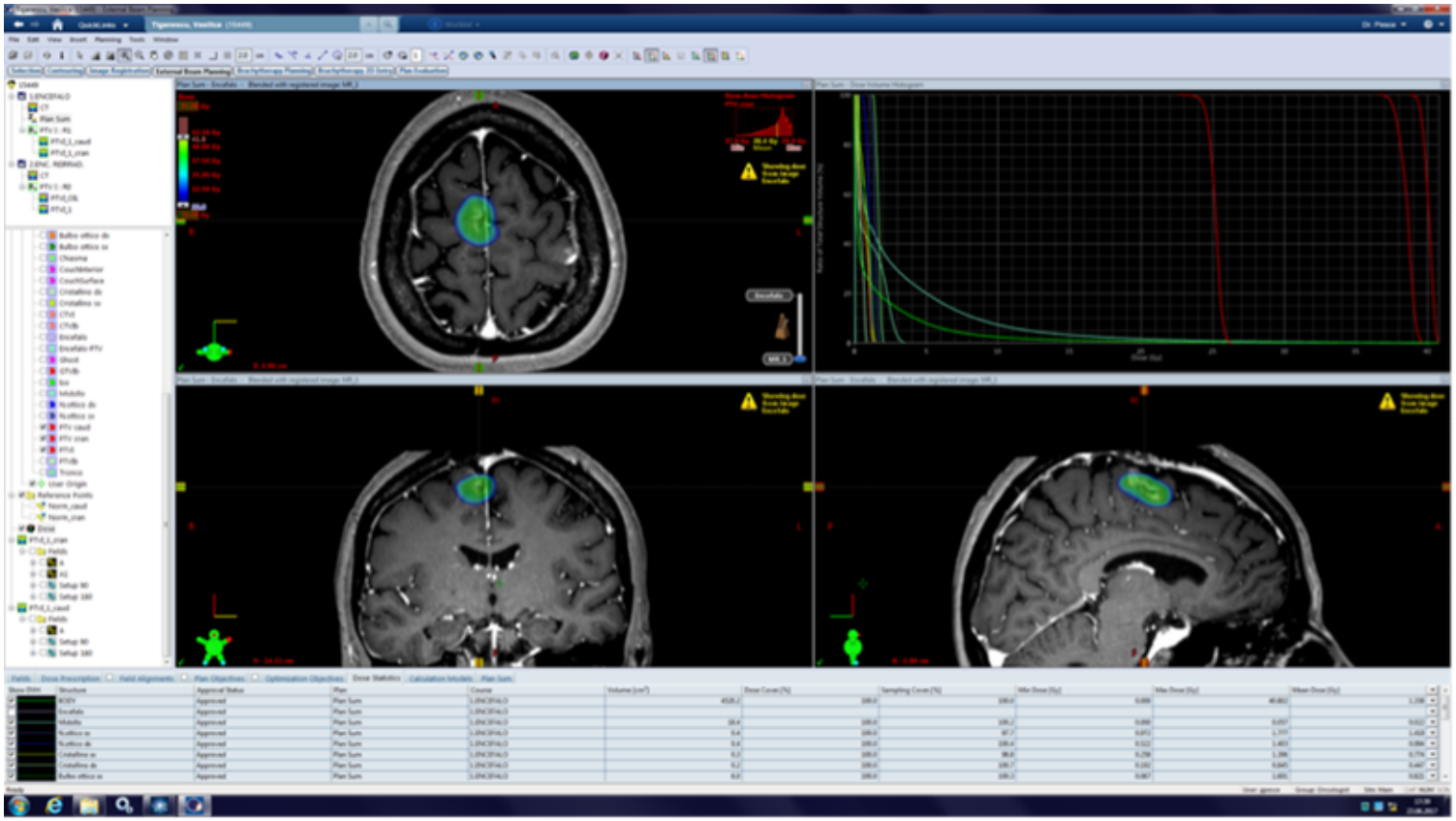
- 47 year old woman
- Partial seizures
- NSCLC



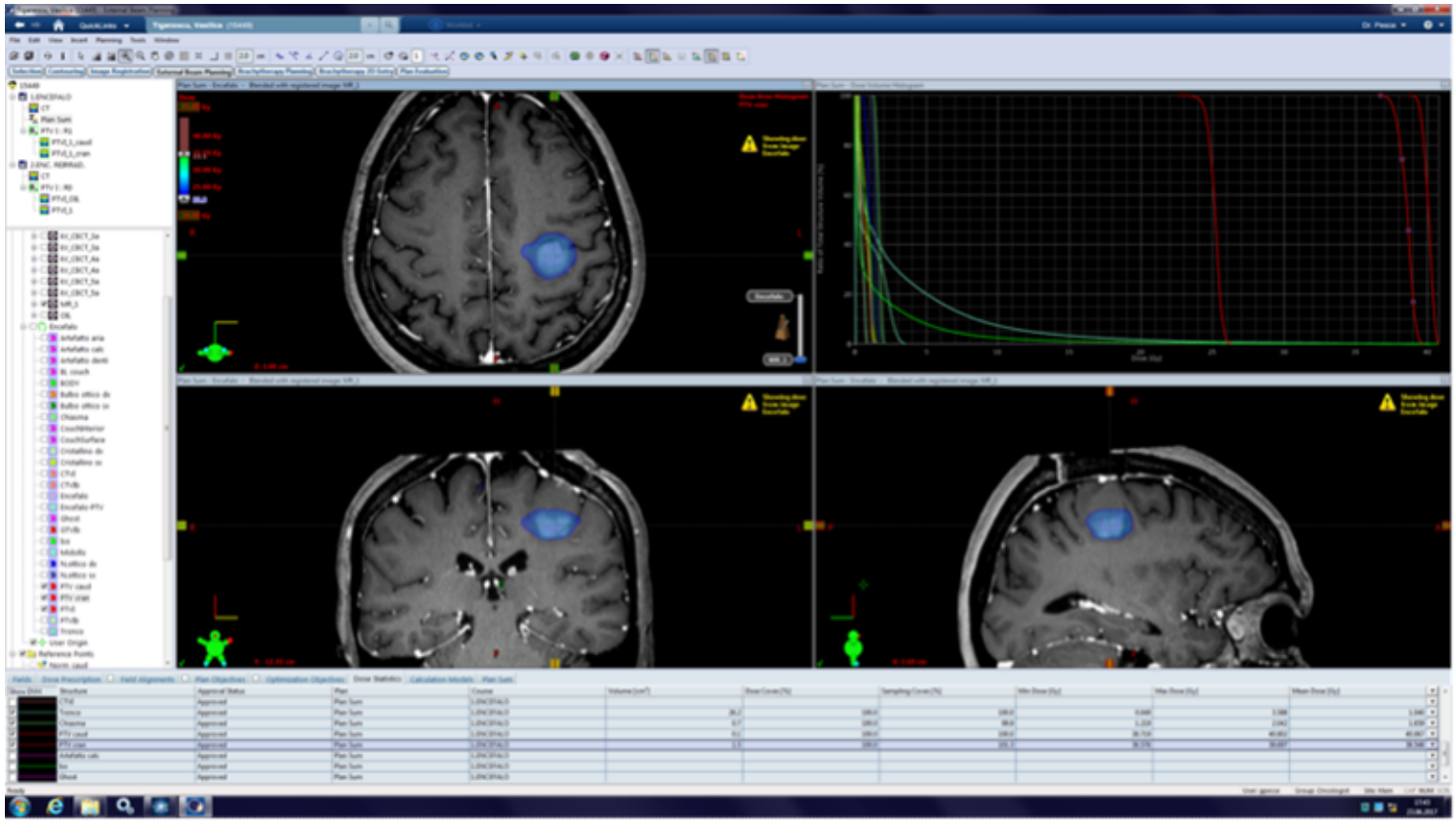




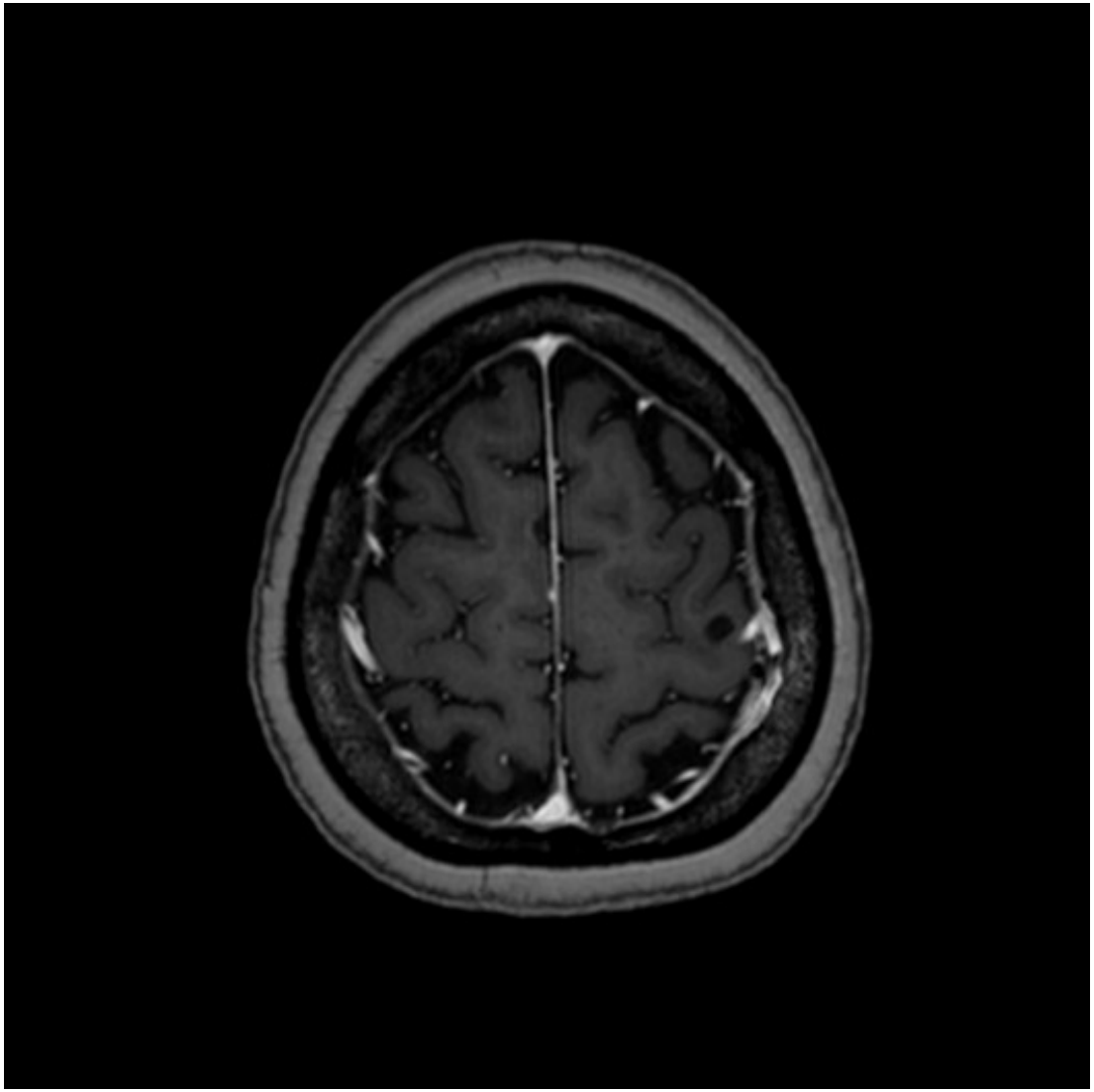
Resection cavity R front: SRS RA 5x5Gy



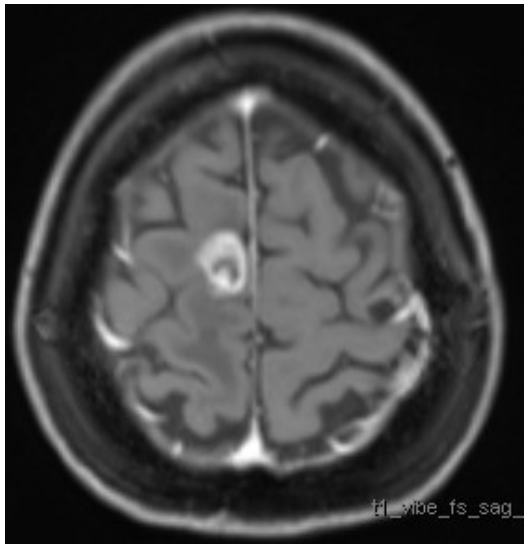
Resection cavity L par.: SRS RA 5x5Gy

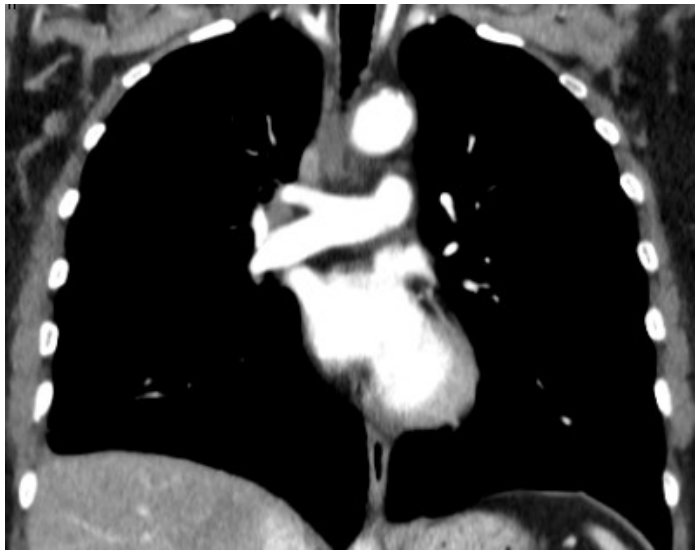


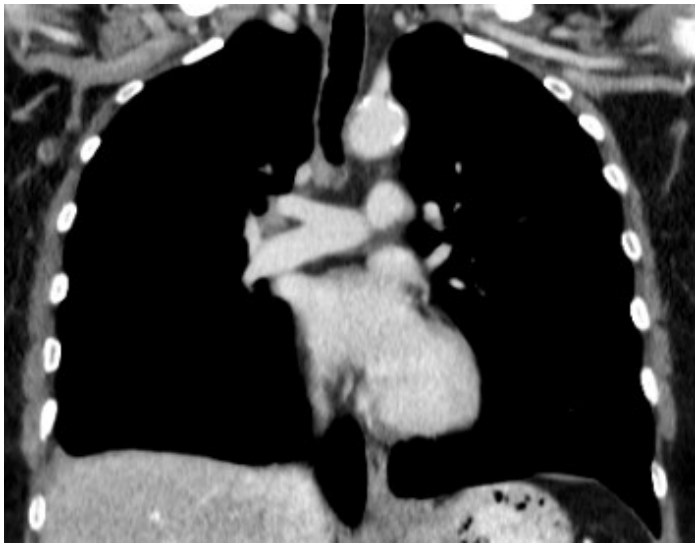
December 2015: CR



Epileptic seizures and brain PD, Systemic control on Nivolumab







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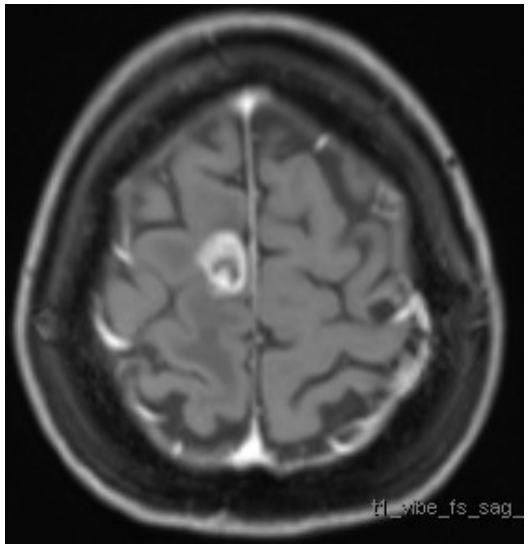
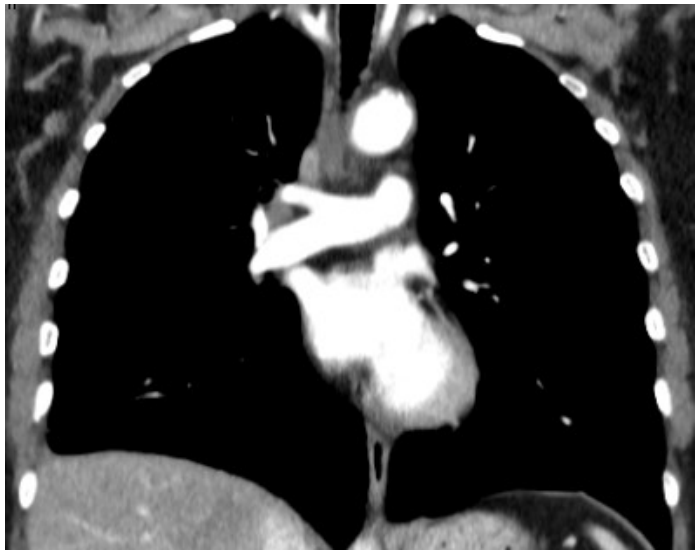
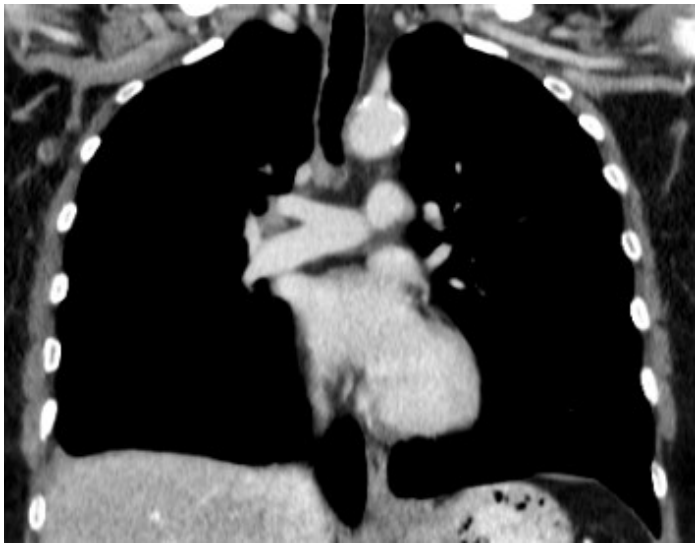
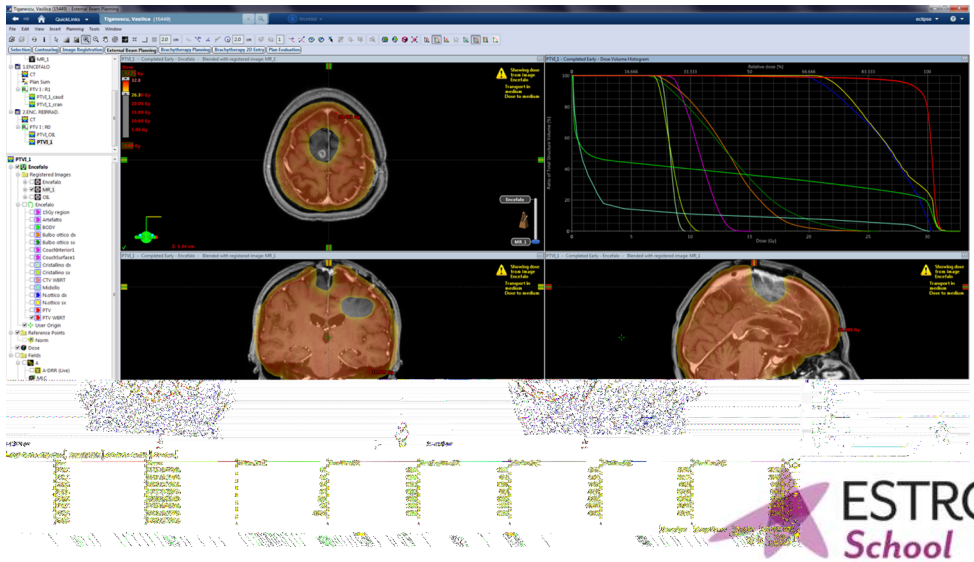






RA 30 Gy, with avoidance



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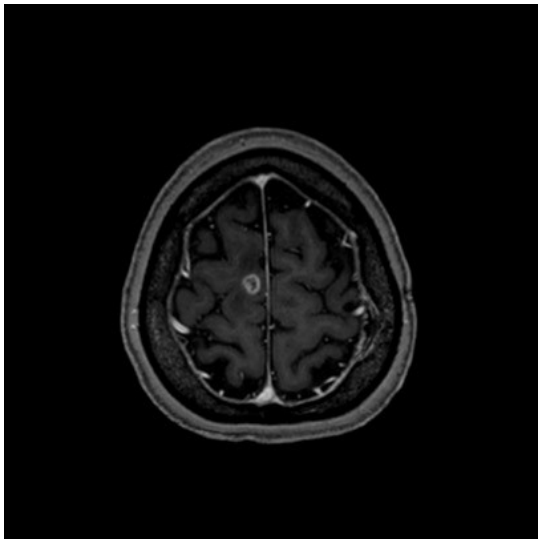

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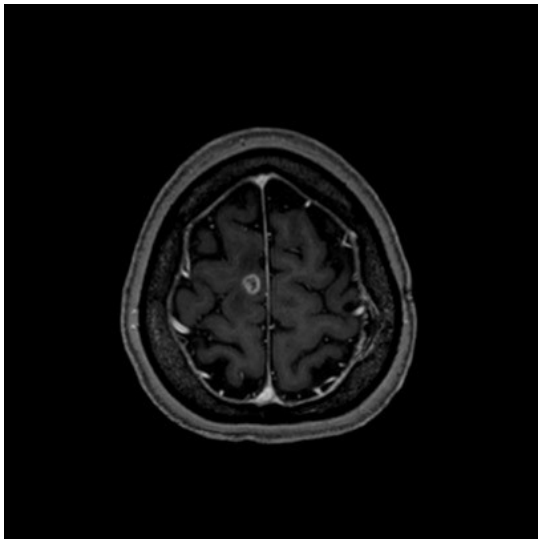

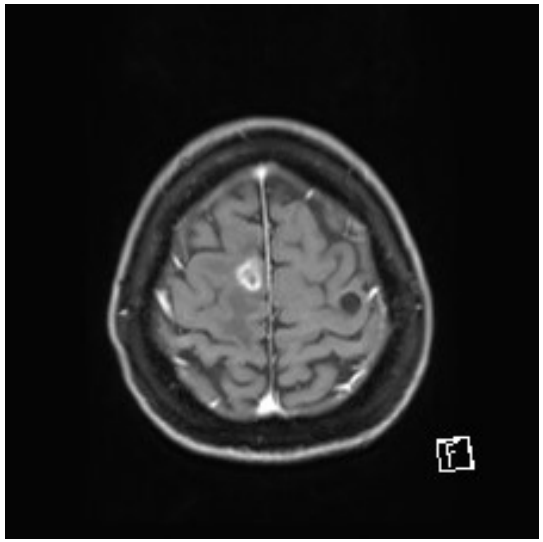

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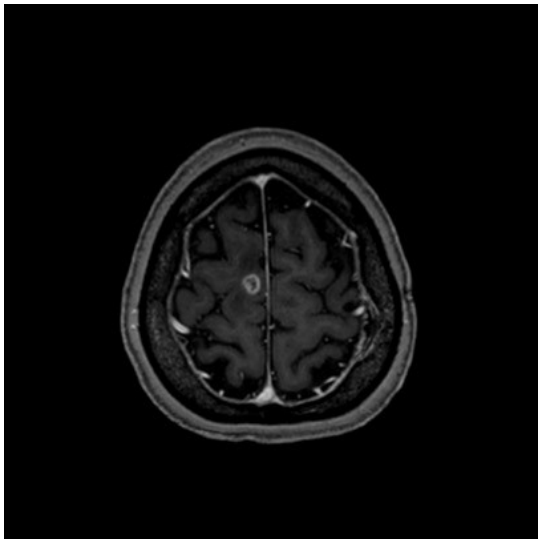

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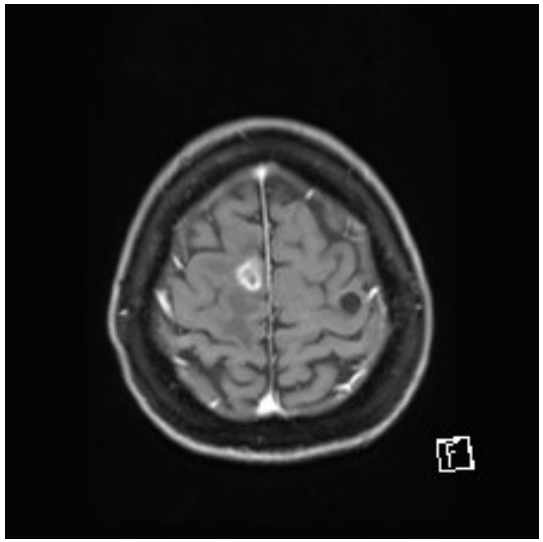
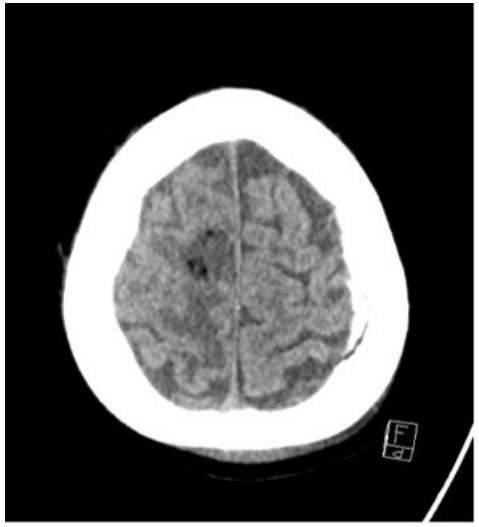


December 2016

→ resection



Postop. CT 21.2.17

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Histology: Radionecrosis

International Journal of
Radiation Oncology
biology • physics

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Clinical Investigation

Association Between Radiation Necrosis and Tumor Biology After Stereotactic Radiosurgery for Brain Metastasis

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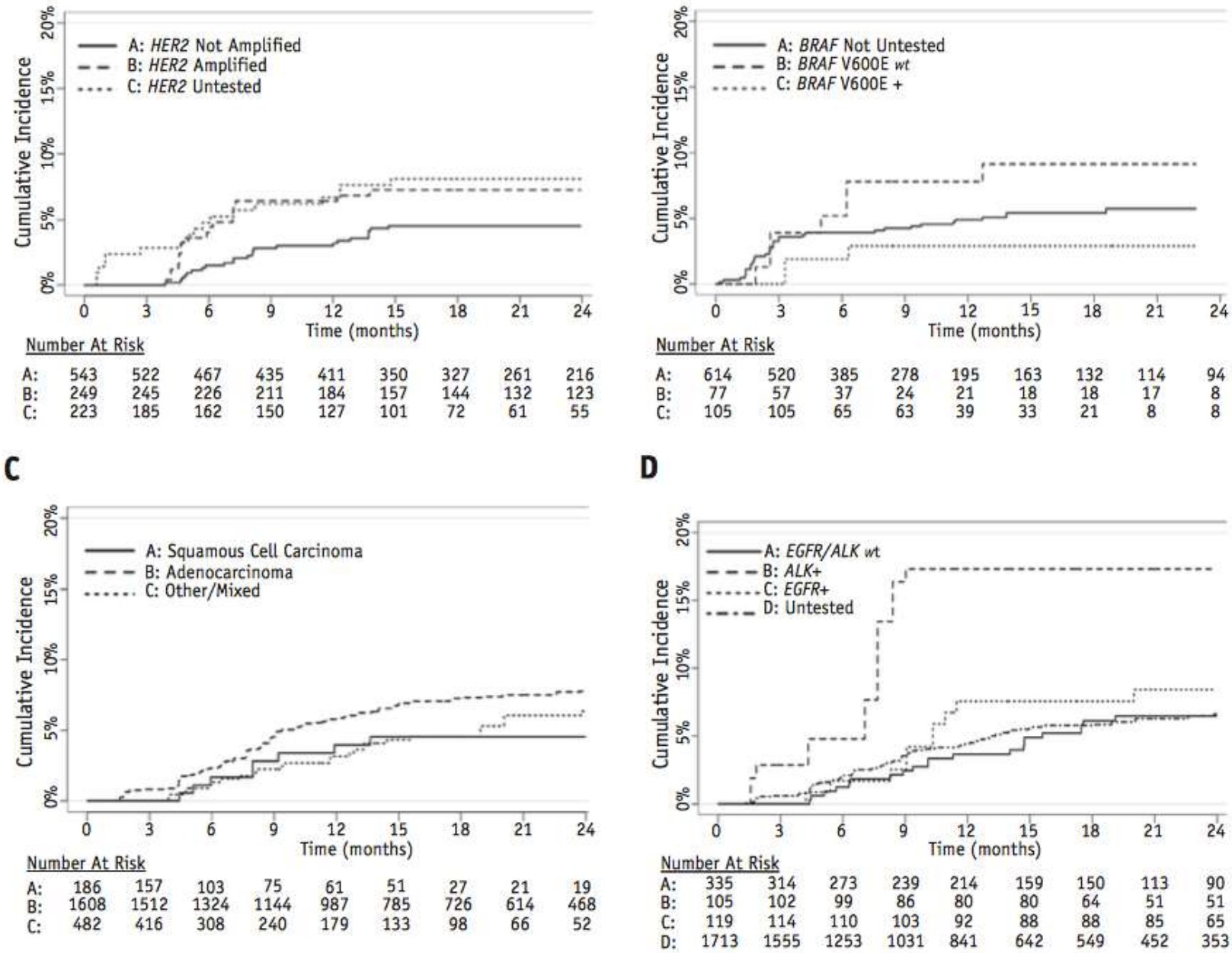
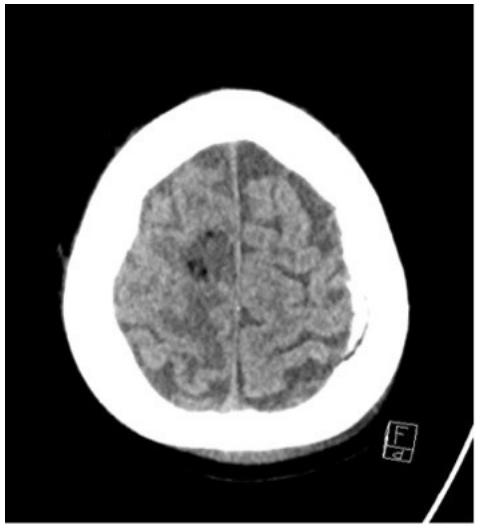


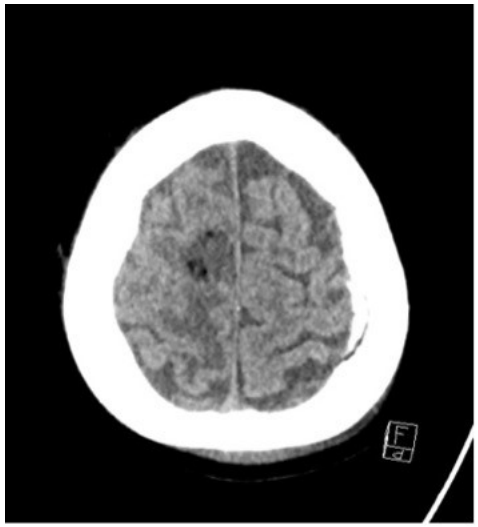
Fig. 3. Cumulative incidence of radiation necrosis stratified by (A) *HER2* amplification status among breast cancer metastases, (B) *BRAF* mutational status among melanoma metastases, (C) histology among non−small cell lung cancer metastases, and (D) *EGFR* and *ALK* mutational status among non−small cell lung cancer metastases.

Ressolved?

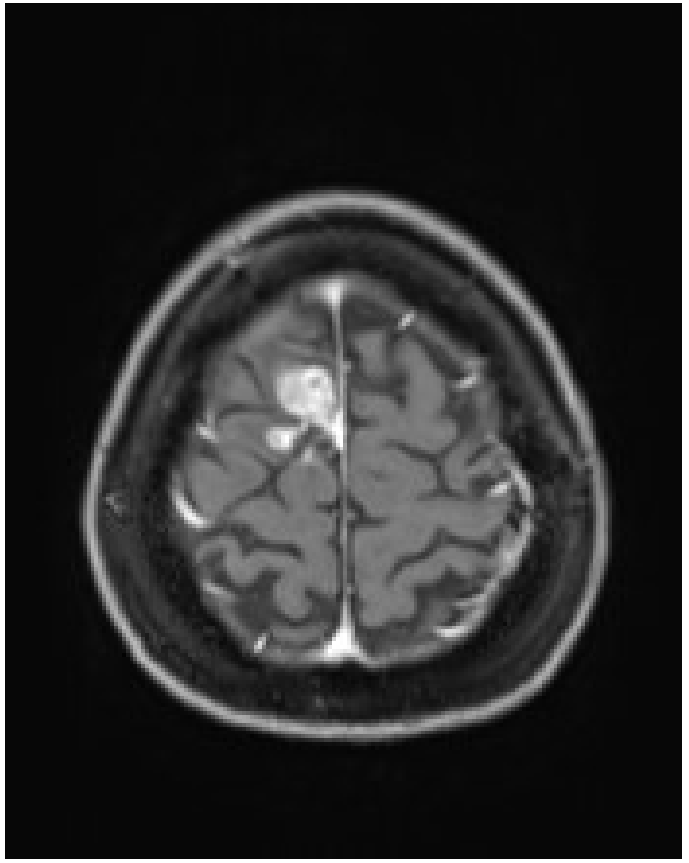


Postop. CT 21.2.17

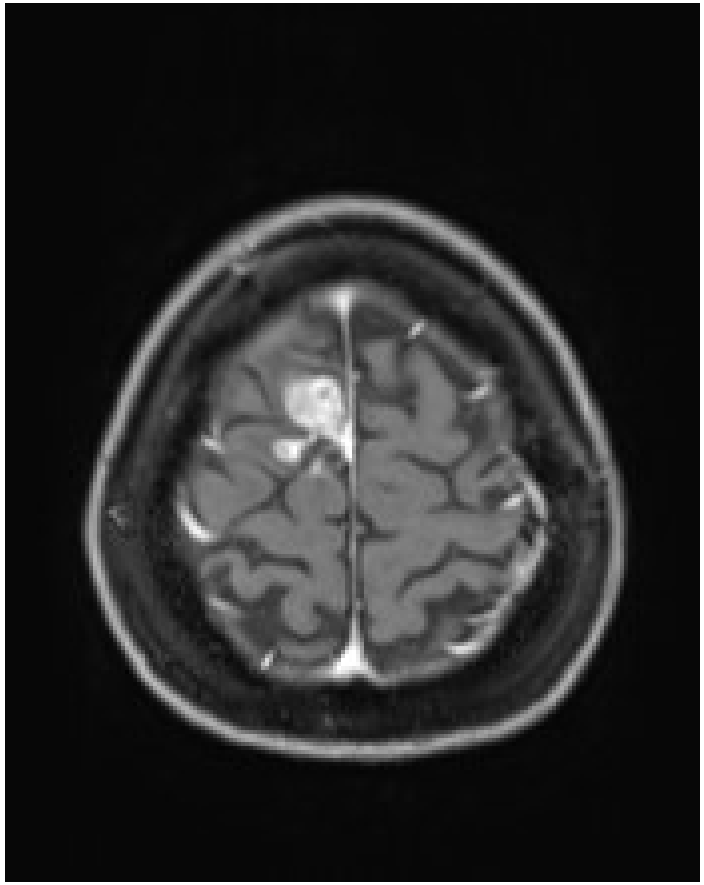
Ressolved?



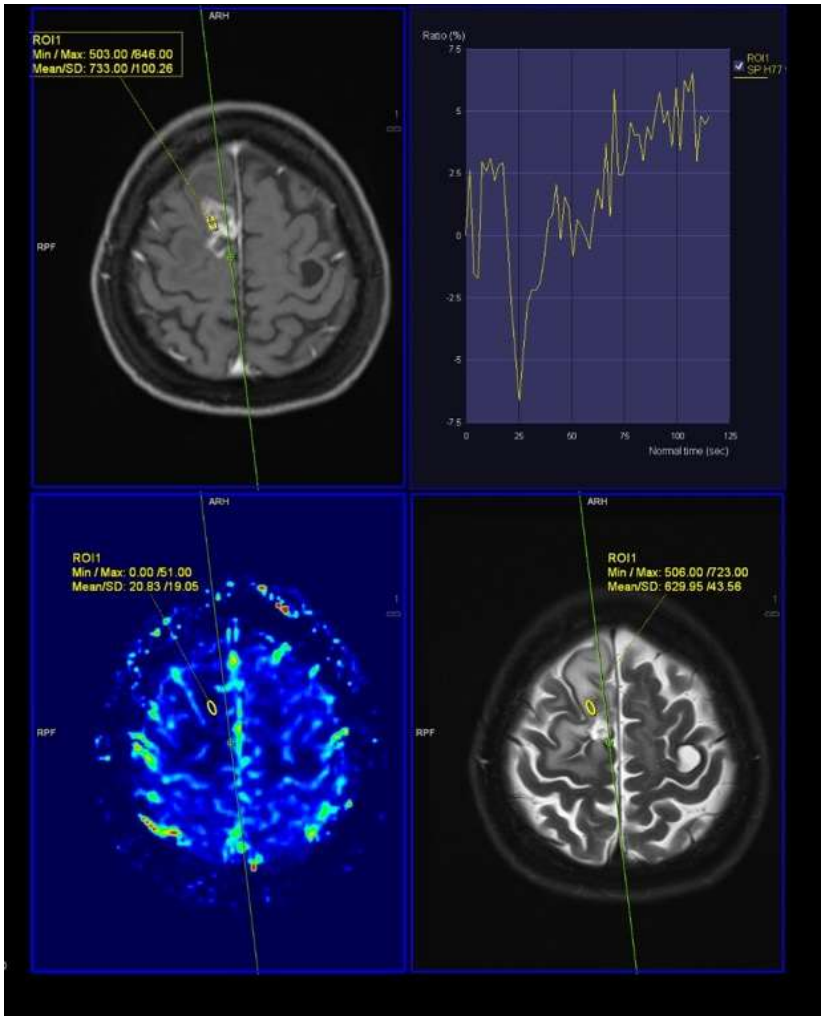
Postop. CT 21.2.17



Gado June 2017



MRI Gado
June 2017



Spectro
June 2017

CT postop 21.2.17

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And then?

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?

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Conclusions

- ✓ Improvement of radiotherapy safety, with promising efficacy in patients with brain metastases
- ✓ Well defined dose constraints (QUANTEC, ESTRO, RTOG)
- ✓ New knowledge concerning the role of Neural Stem Cells permitted to identify brain regions involved in plasticity and repair processes (Hippocampus e.g.)
- ✓ Randomized controlled trials have demonstrated significant activity of Memantine and Donepezil for neurocognitive impairment prevention, in patients treated with cranial radiotherapy for primary and metastatic brain tumors
- ✓ Even with new treatments (BEV e.g.) radiation necrosis remains a challenge; better treatment for that is prevention

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SYSTEMIC THERAPY ISSUES

ESTRO teaching course
Management of brain tumours

Patrick Roth

Department of Neurology and Brain Tumor Center
University Hospital Zurich

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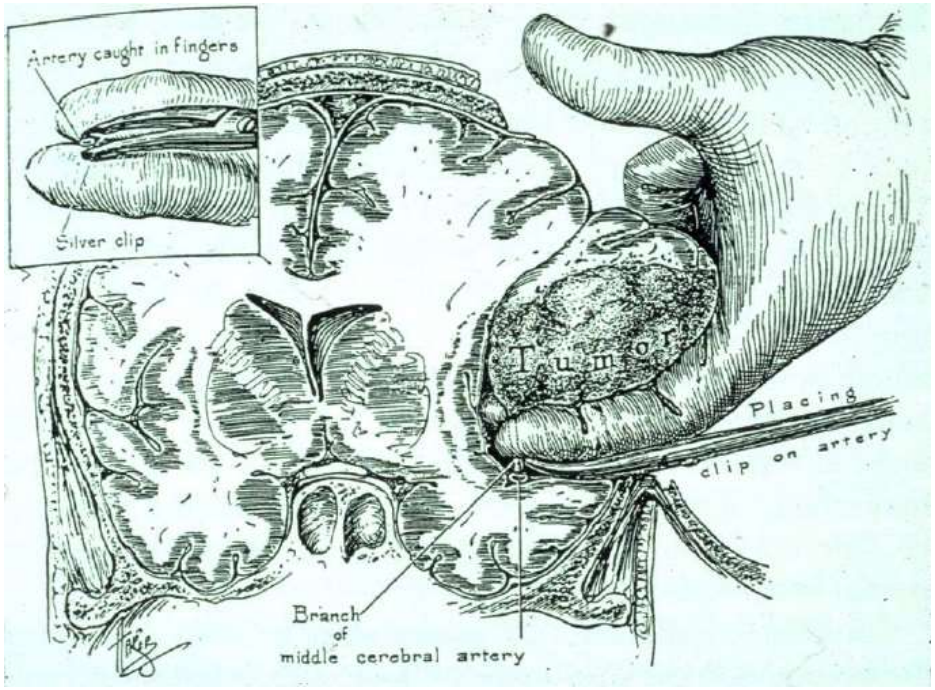
« On the treatment of brain masses »

„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

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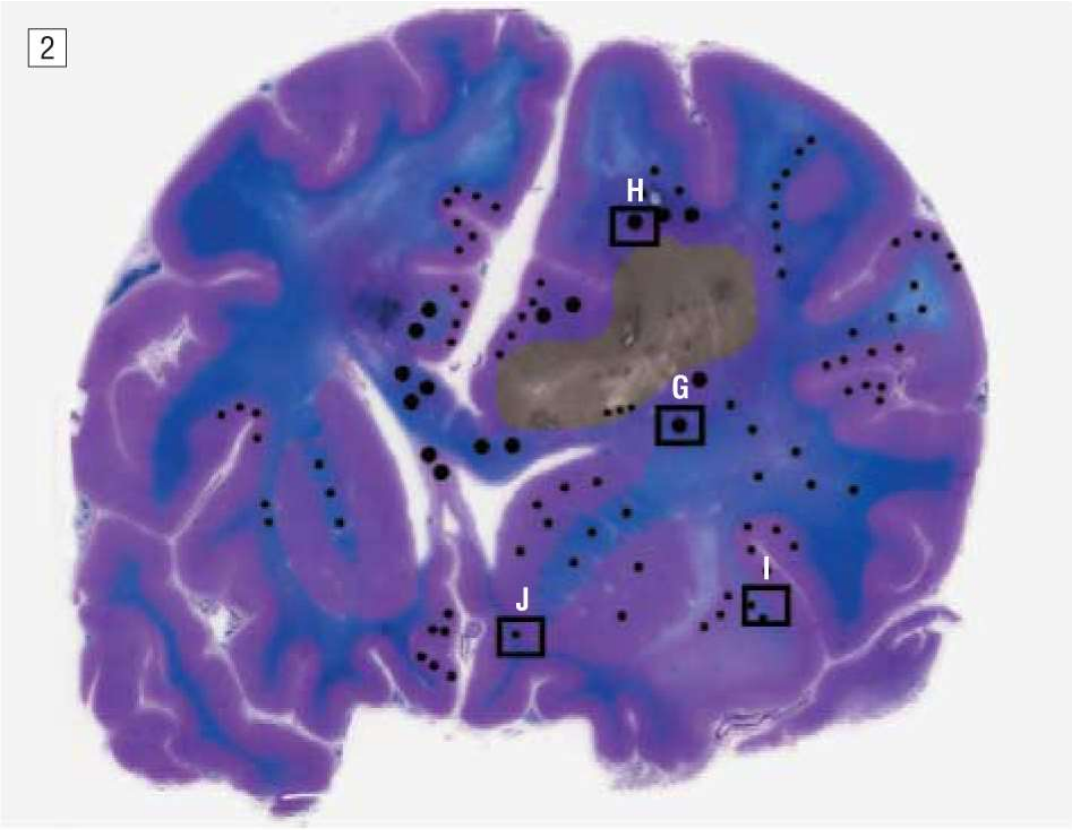
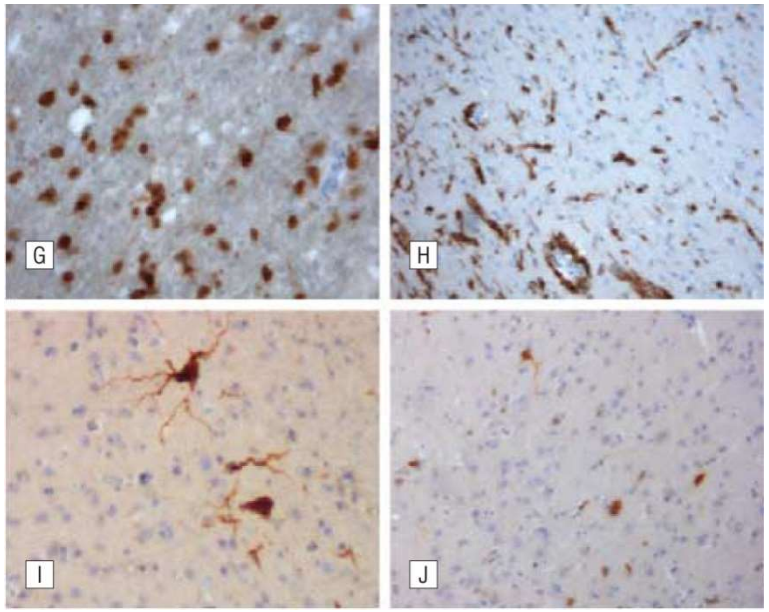
Why systemic therapy?





anti-IDH1 R132H

Sahm et al, Arch Neurol 2012

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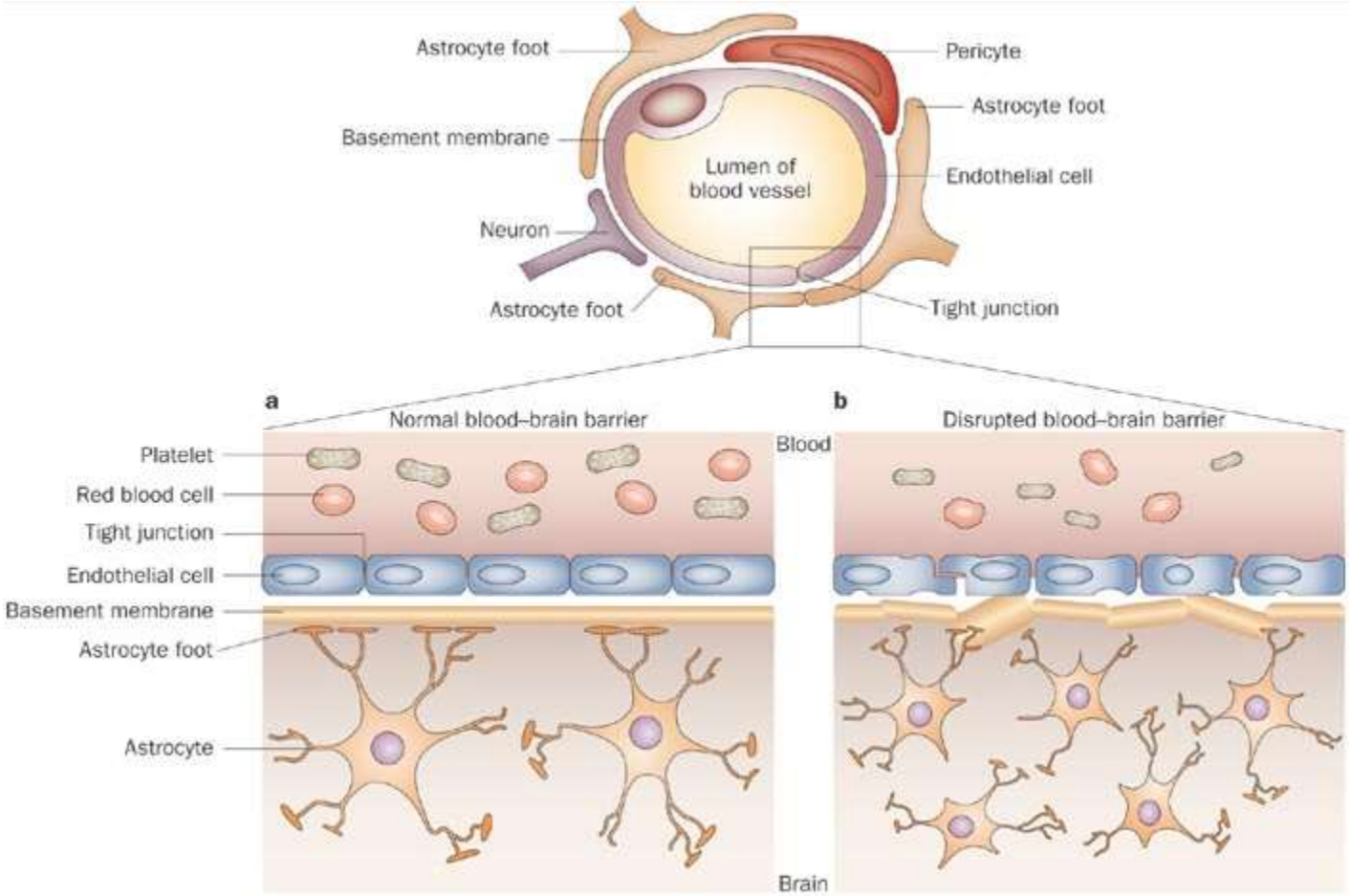
Systemic therapy: blood-brain barrier



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

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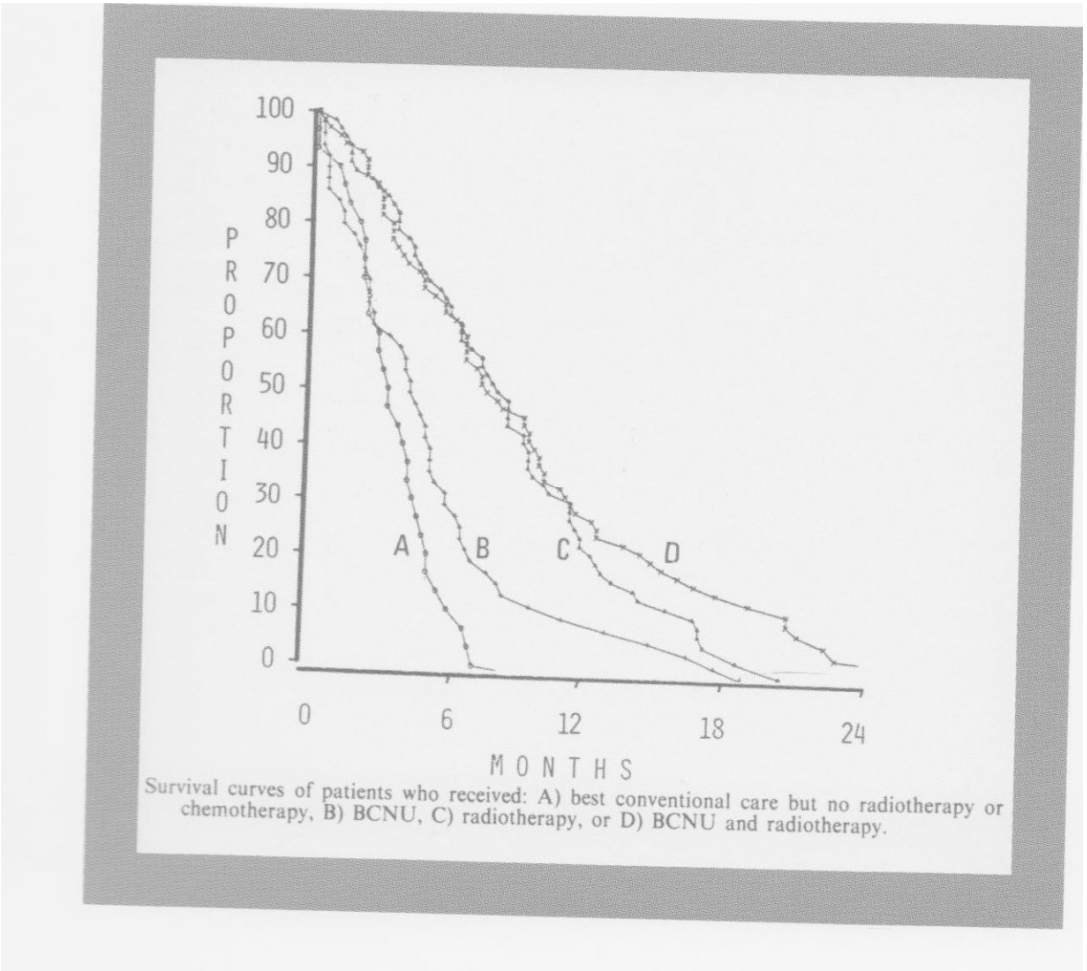
Systemic therapy for glioma: the early days



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

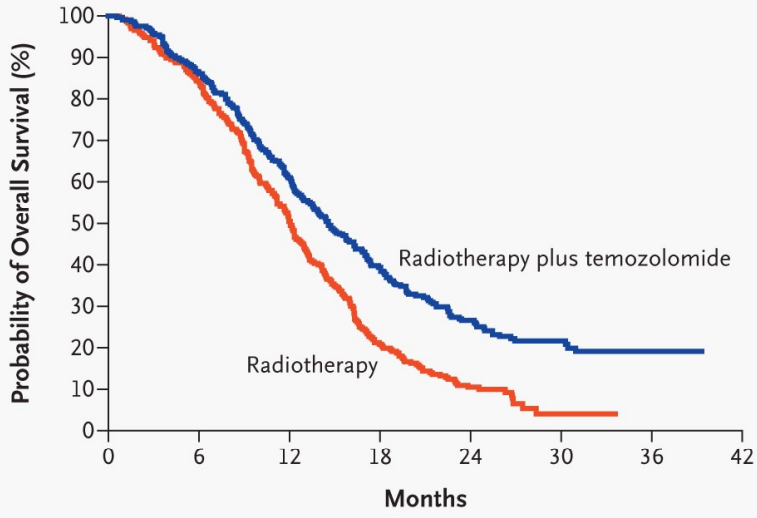
The NEW ENGLAND JOURNAL of MEDICINE

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



No. at Risk

Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

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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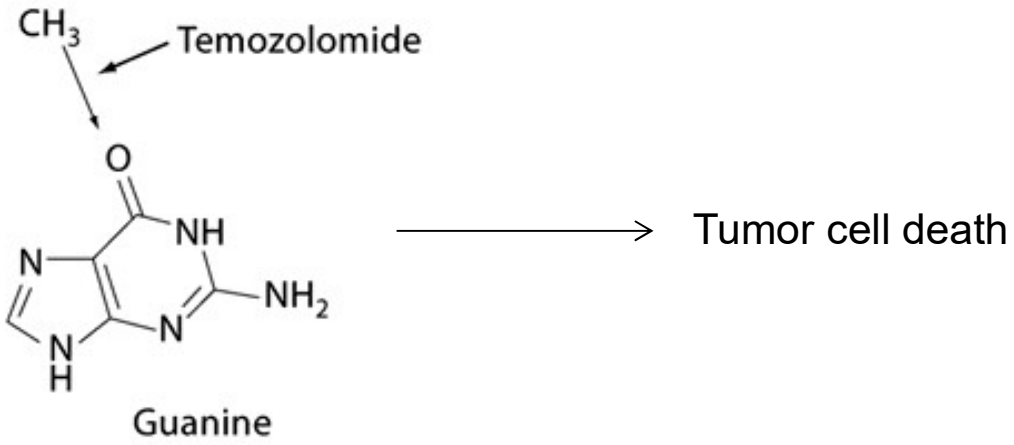
Temozolomide

- 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)

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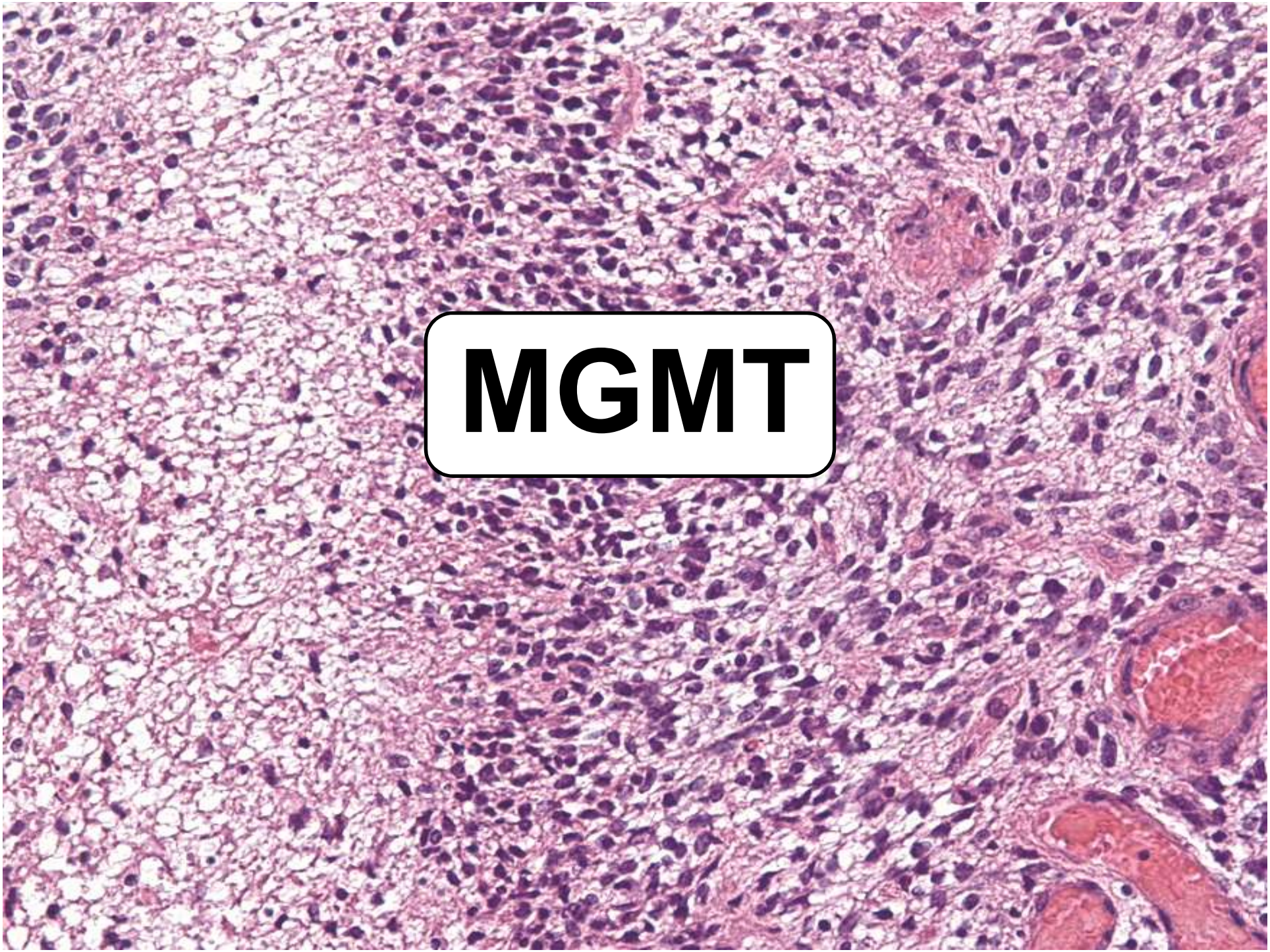
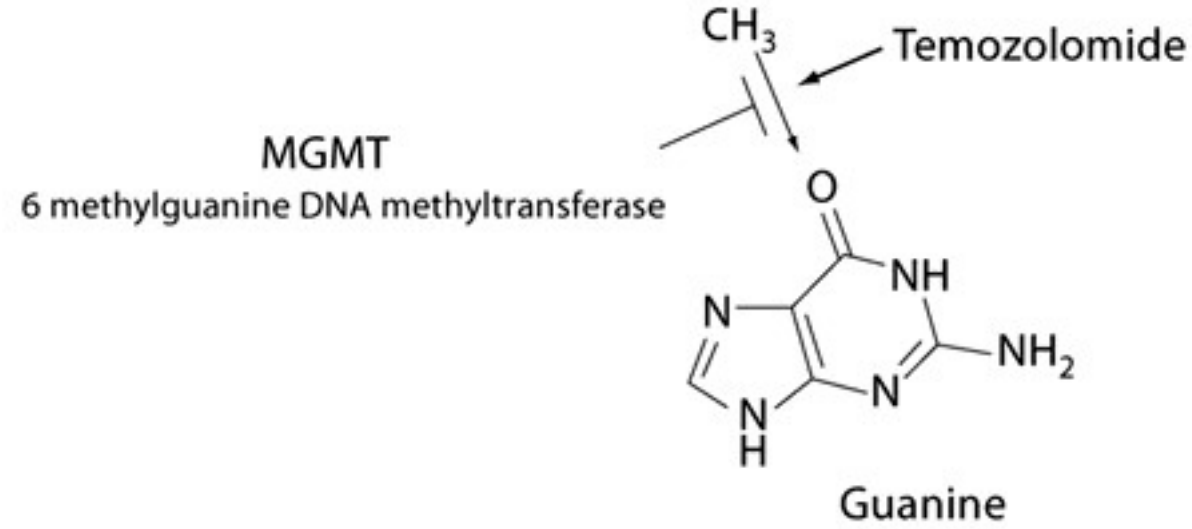

MGMT

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“)



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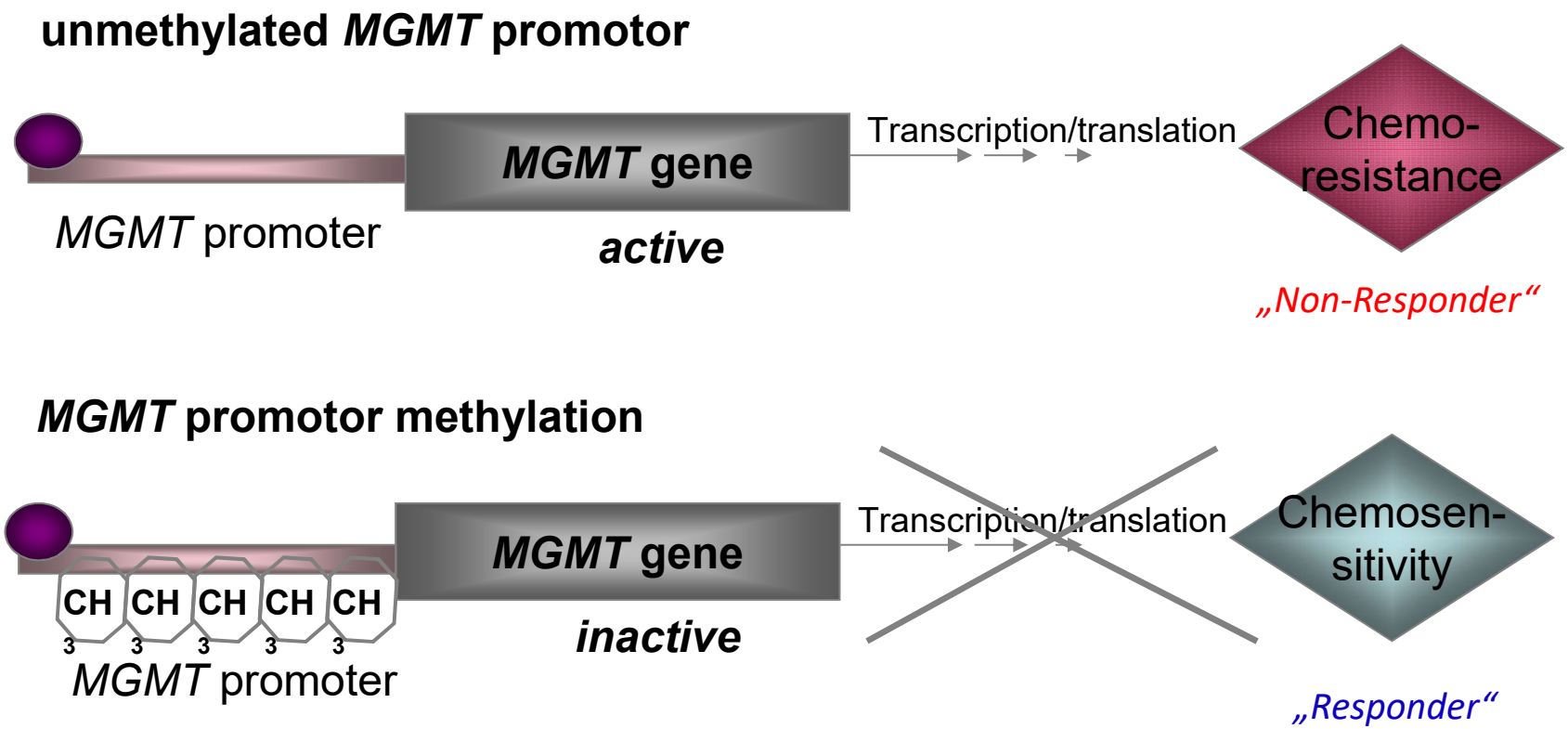
Inactivation of MGMT gene by promoter methylation



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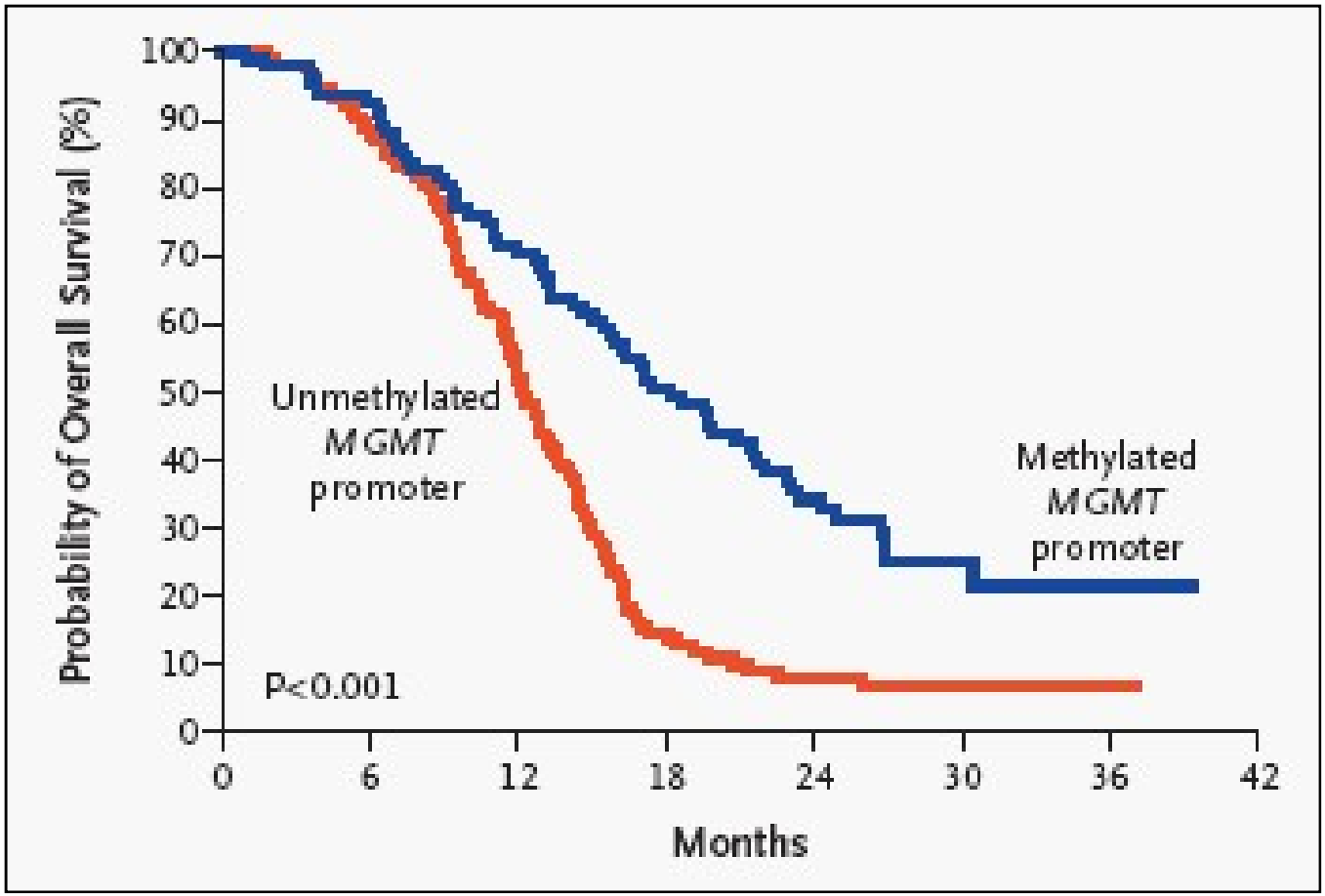
Prognostic role of MGMT



Hegi et al, NEJM 2005

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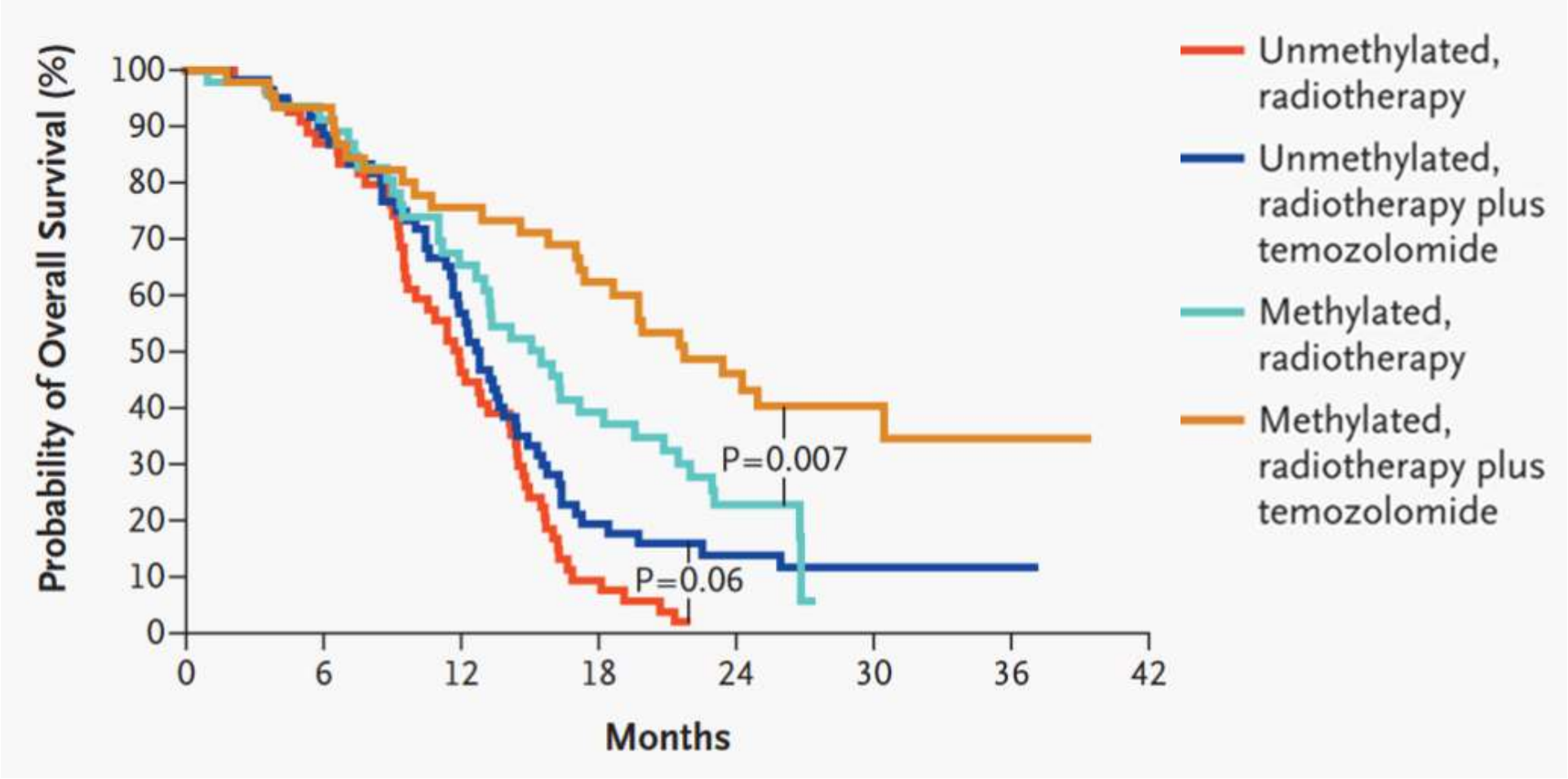
Predictive role of MGMT



Hegi et al, NEJM 2005

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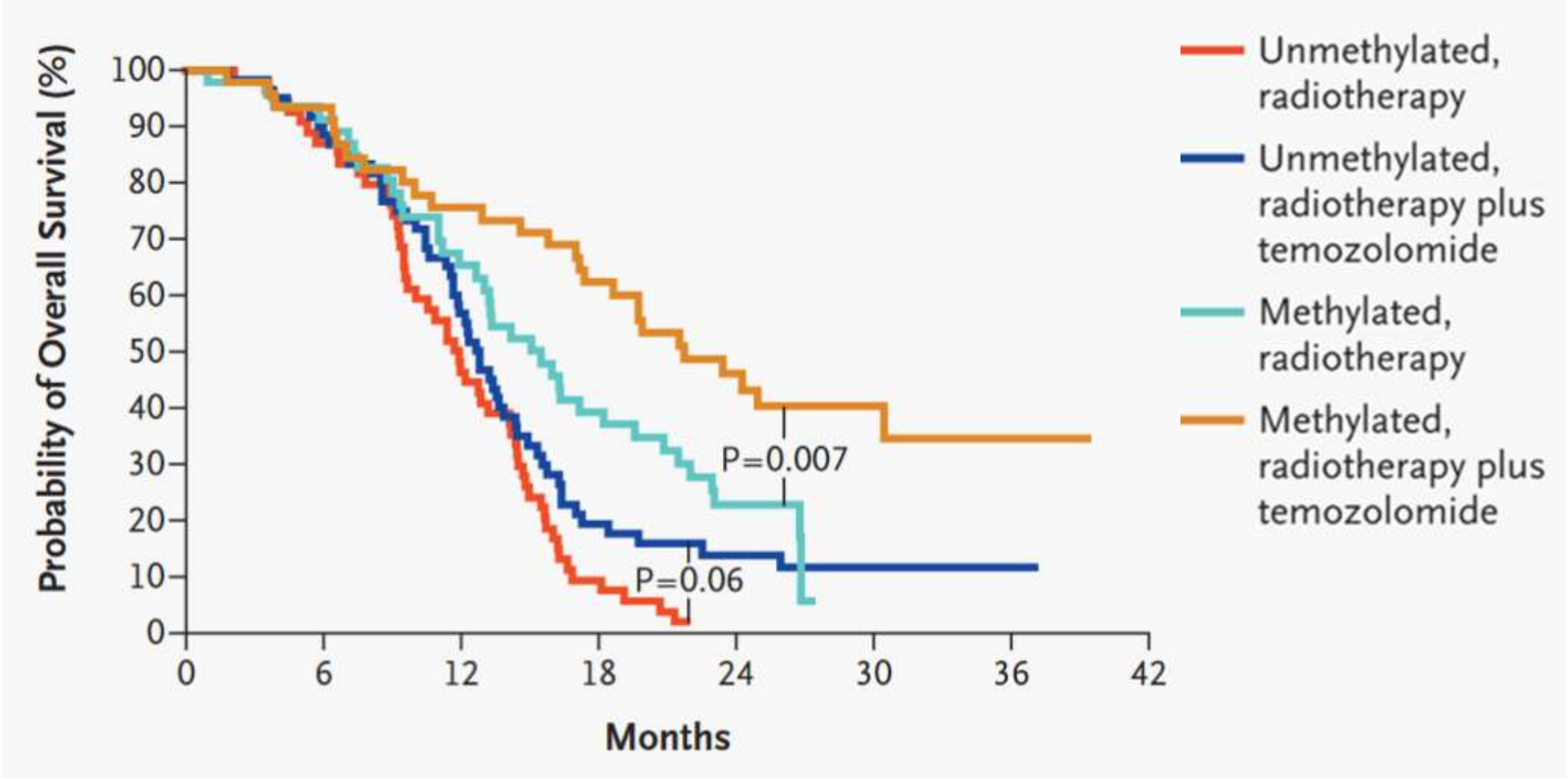
Predictive role of MGMT



Hegi et al, NEJM 2005

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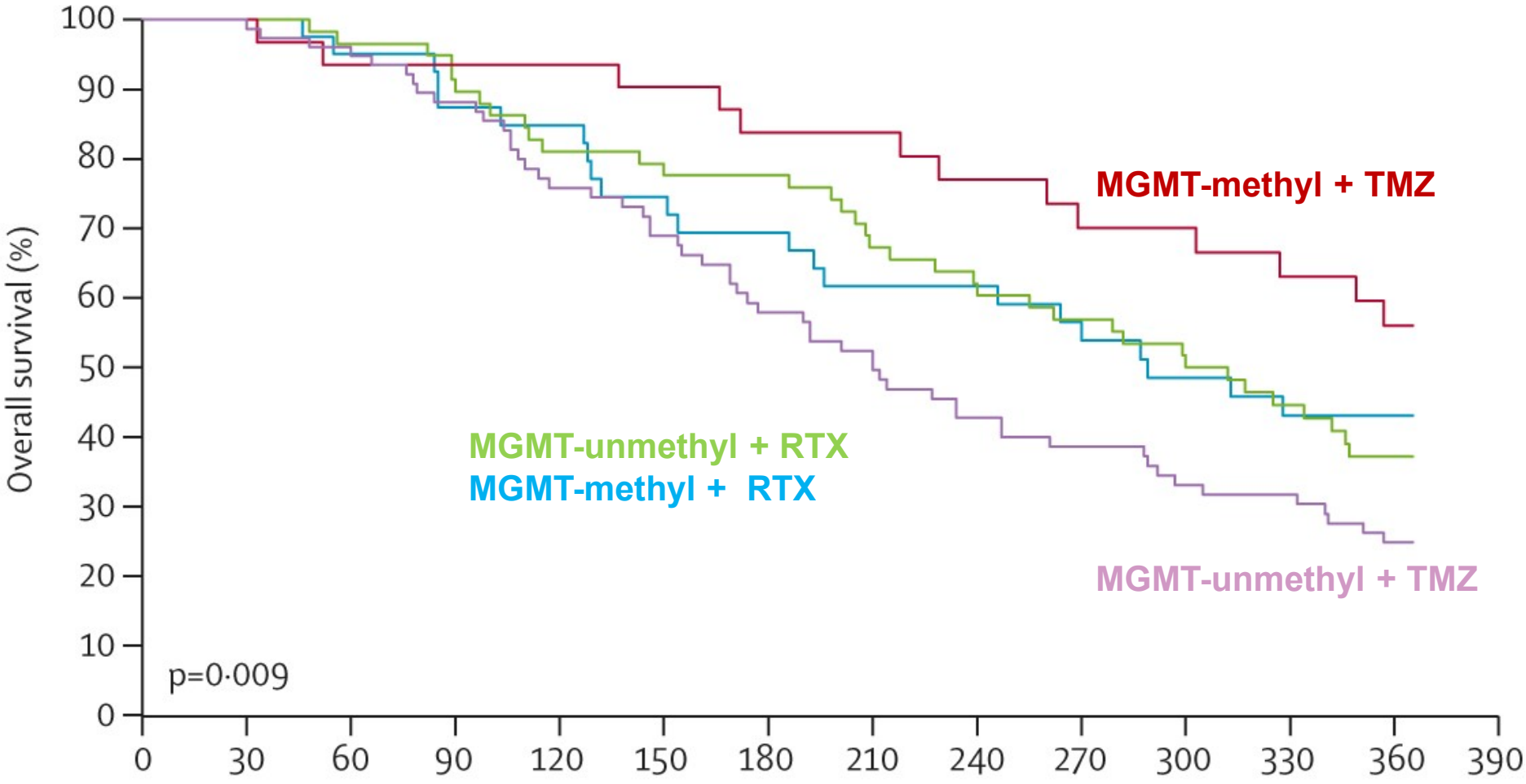
Predictive effect in elderly glioblastoma patients



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

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“

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Good old chemotherapy

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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

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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?

Kim et al. Lancet Oncol 2016

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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

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WWW.ESTRO.ORG/SCHOOL

Evidence based management of grade II and III astrocytic tumors

G. Pesce

Radiation Oncology

Oncology Institute of Southern Switzerland

Bellinzona and Lugano - Switzerland

ESTRO Teaching Course on

Management of Brain Tumors

Vienna, October 22-24, 2017

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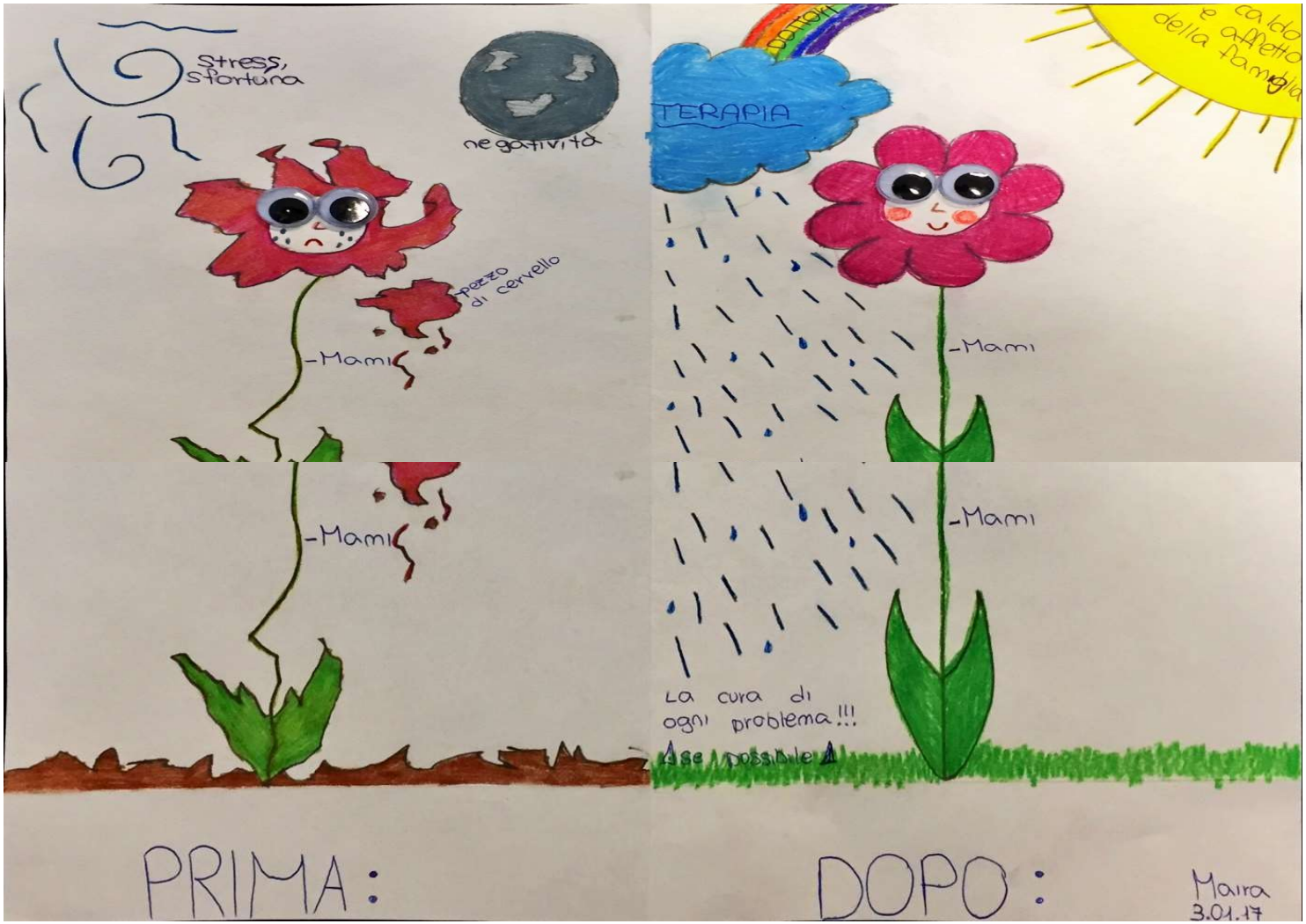
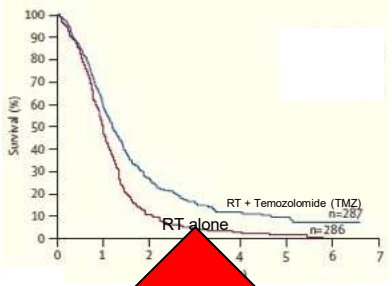
How to get there….



LIFE EXPECTANCY



SOCIAL/ECONOMICAL

SELF ESTIME

CNS TUMOR

PSYCHOLOGICAL HEALTH

MOVEMENT AND SPEECH

COUPLE/FAMILY

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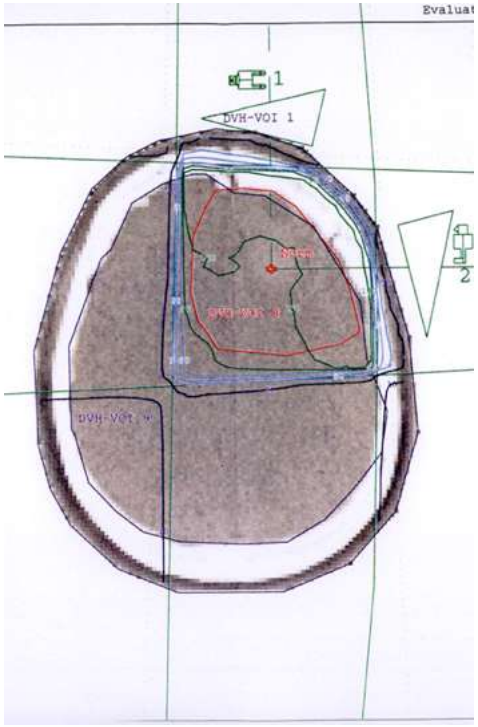
Clinical case



History of present illness:

40 year old woman

2 generalized epileptic seizures in july 2000

Past Medical History:

Several head traumas

Hypothyroidism

Migraine

Initial CT-SCAN:

Ipodense lesion in the left frontal lobe (2 cm) w/o contrast enhancement: attributed to a scar →initiate of carbamazepine

Persistence of epileptic seizure:

Minimal increase of MRI abnormality without contrast enhancement, with features of low grade glioma

Therapy

Biopsy at that time consistent with Anaplastic astrocytoma WHO III, no Molecular Biology

→GTR + RT 66Gy/2Gy daily fractions (2000) (for MRC trial)

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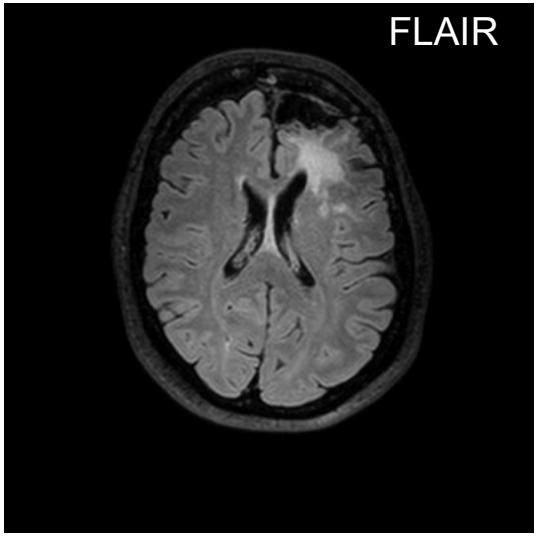
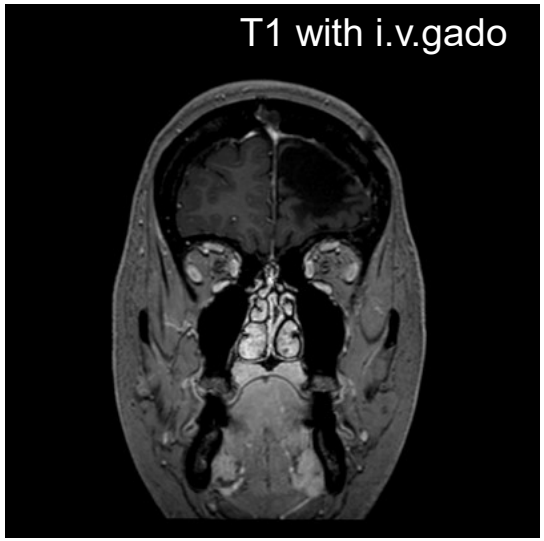
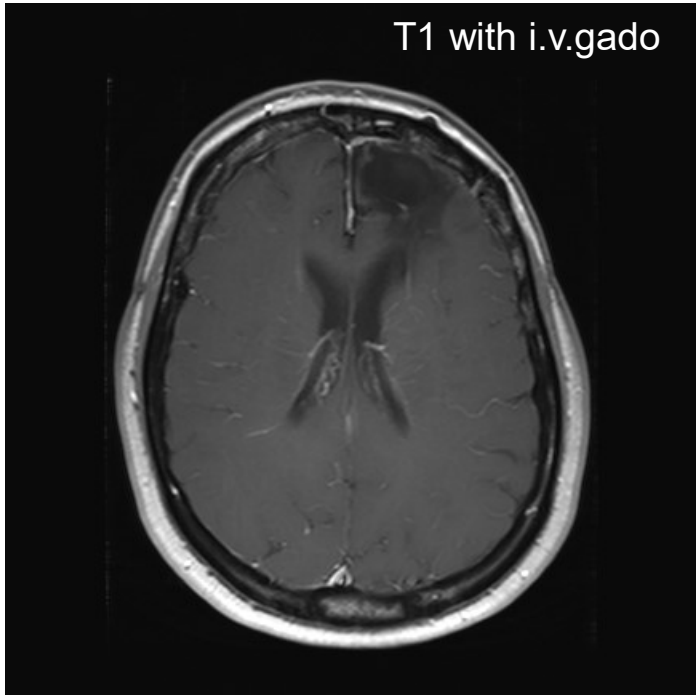
Outcome 2017

NED







Histology review 2014: Low grade astrocytoma

IDH1/2 mutated, 1p/19q codeleted

WHO grade II and III glioma

Low grade glioma?

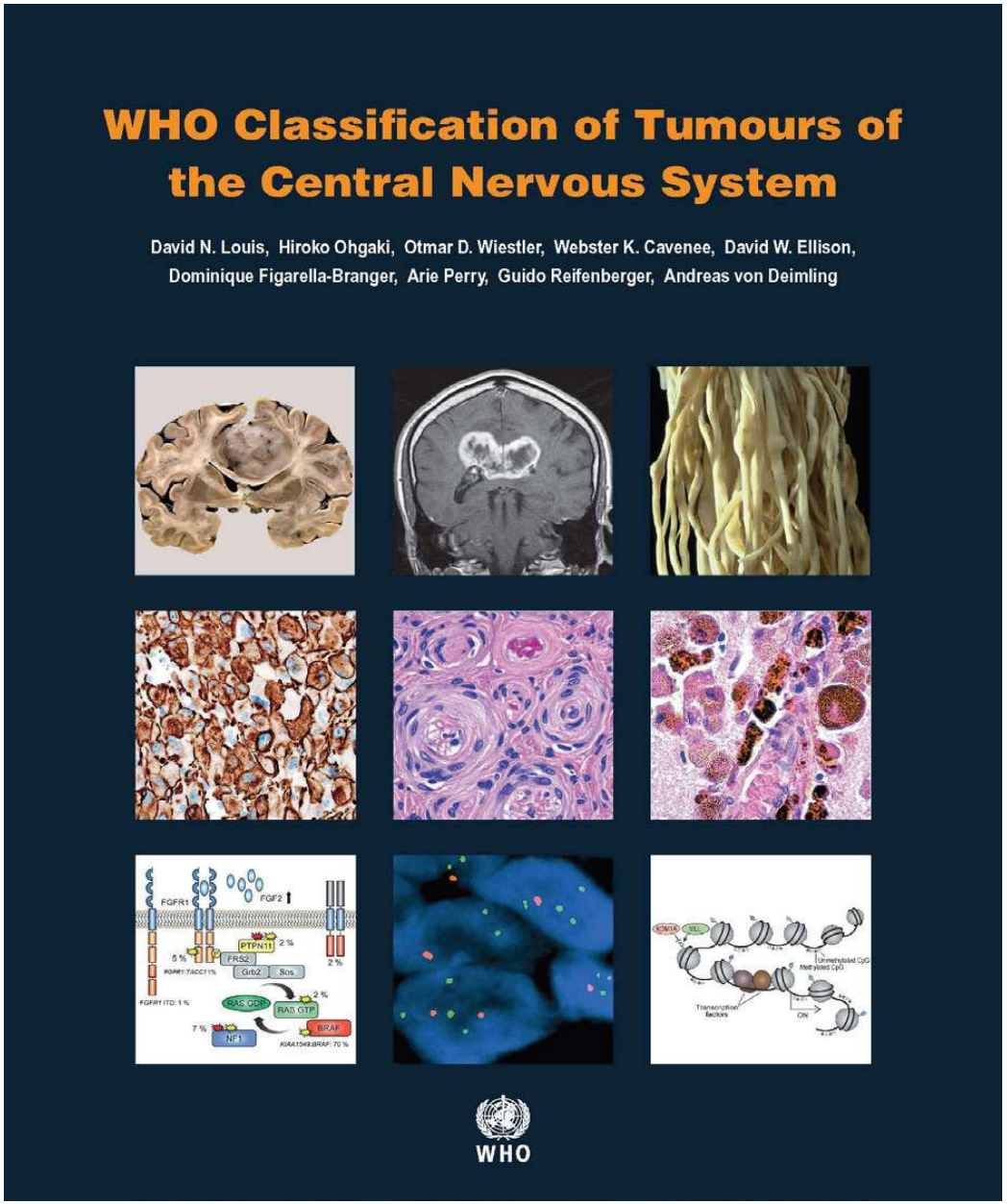
Anaplastic Astrocytoma?

Anaplastic

RT was for long the standard after surgery, but…

What is the role of biomarkers

Does chemotherapy help?



Louis, et al. 2016

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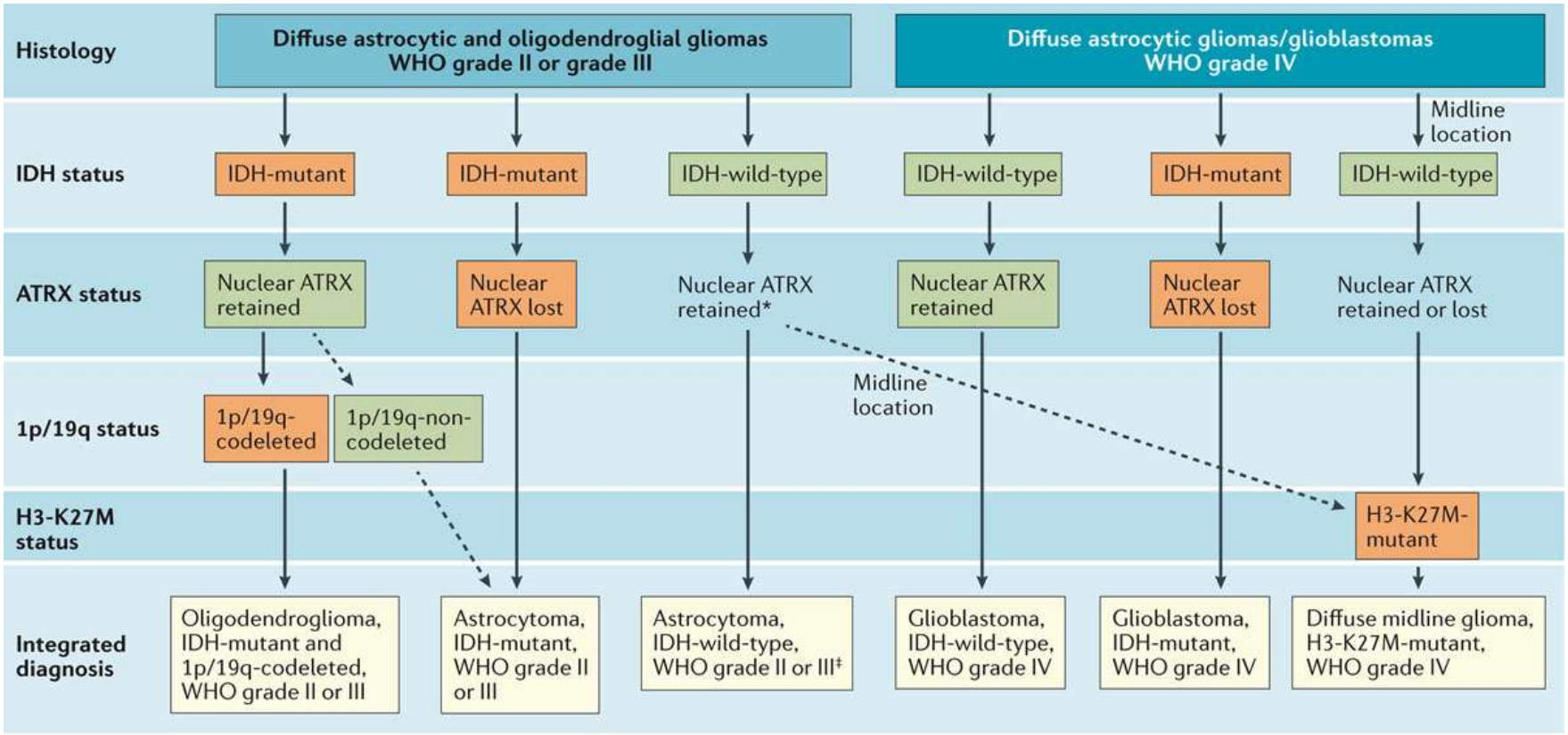
Integrated histological and molecular classification of diffuse gliomas according to the 2016 WHO Classification



Nature Reviews | Clinical Oncology

Reifenberger, G. *et al.* (2016) Advances in the molecular genetics of gliomas — implications for classification and therapy *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2016.204

Courtesy of Monika Hegi

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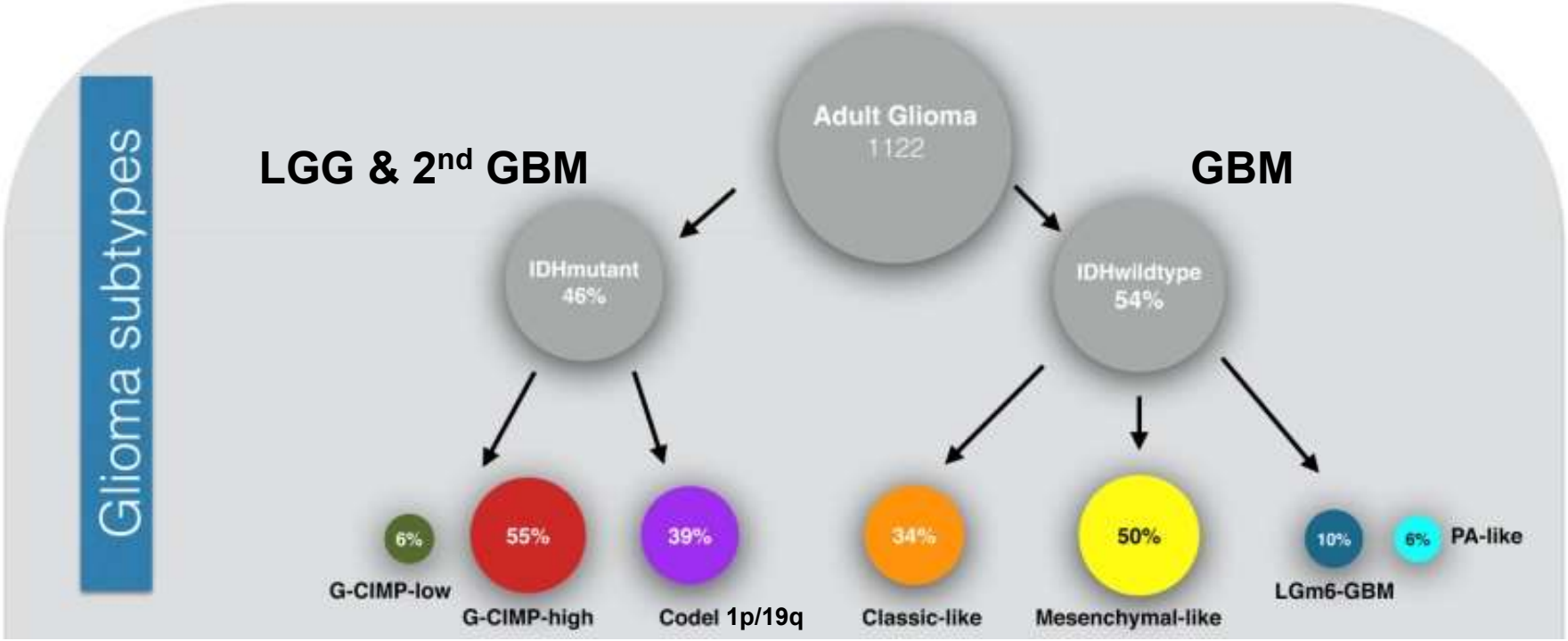
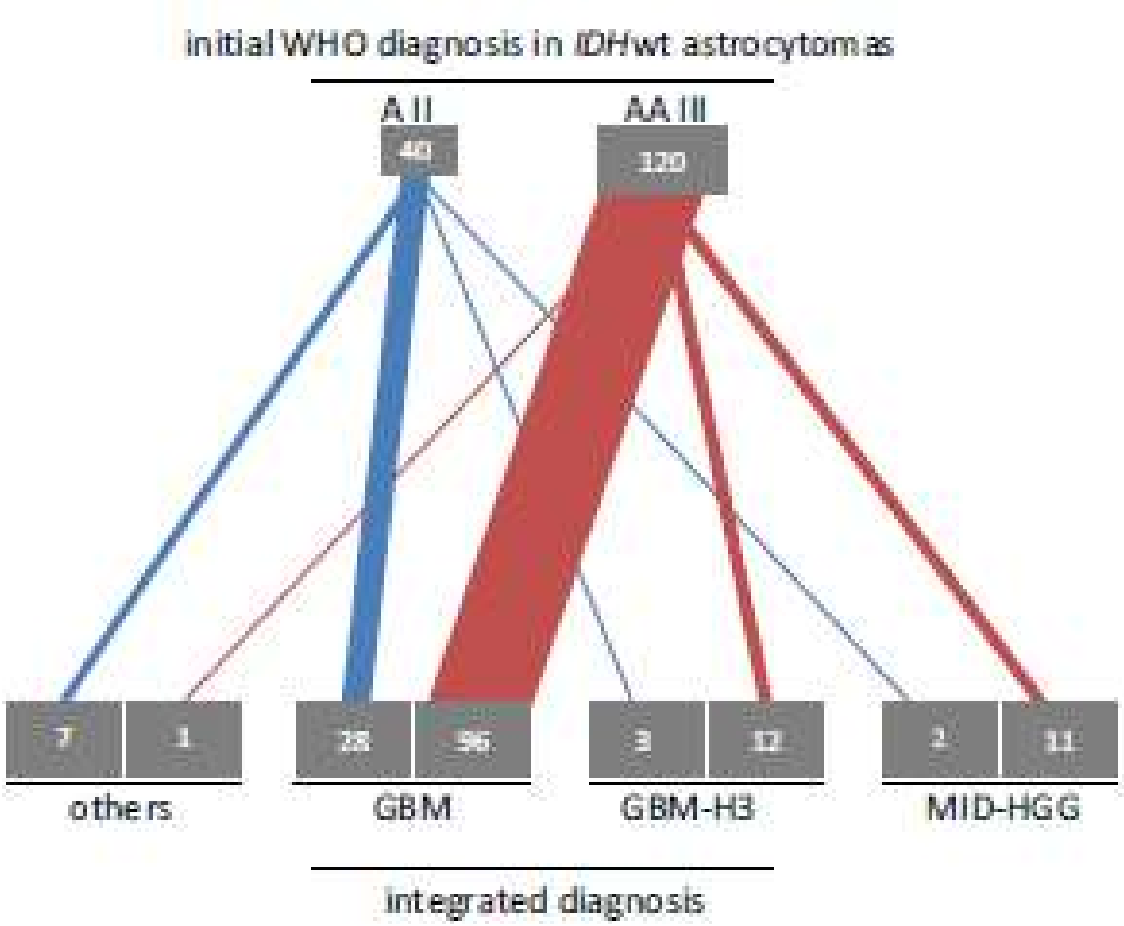
Molecular Glioma Subtypes



Adapted from Ceccarelli et al., *Cell* 2016 164, 550-563DOI: (10.1016/j.cell.2015.12.028)

Courtesy of Monika Hegi

Changes from initial WHO to integrated diagnosis in 160 patients with *IDHwt astrocytoma*



Reuss et al. Acta Neuropathol, 2015

Courtesy of Monika Hegi

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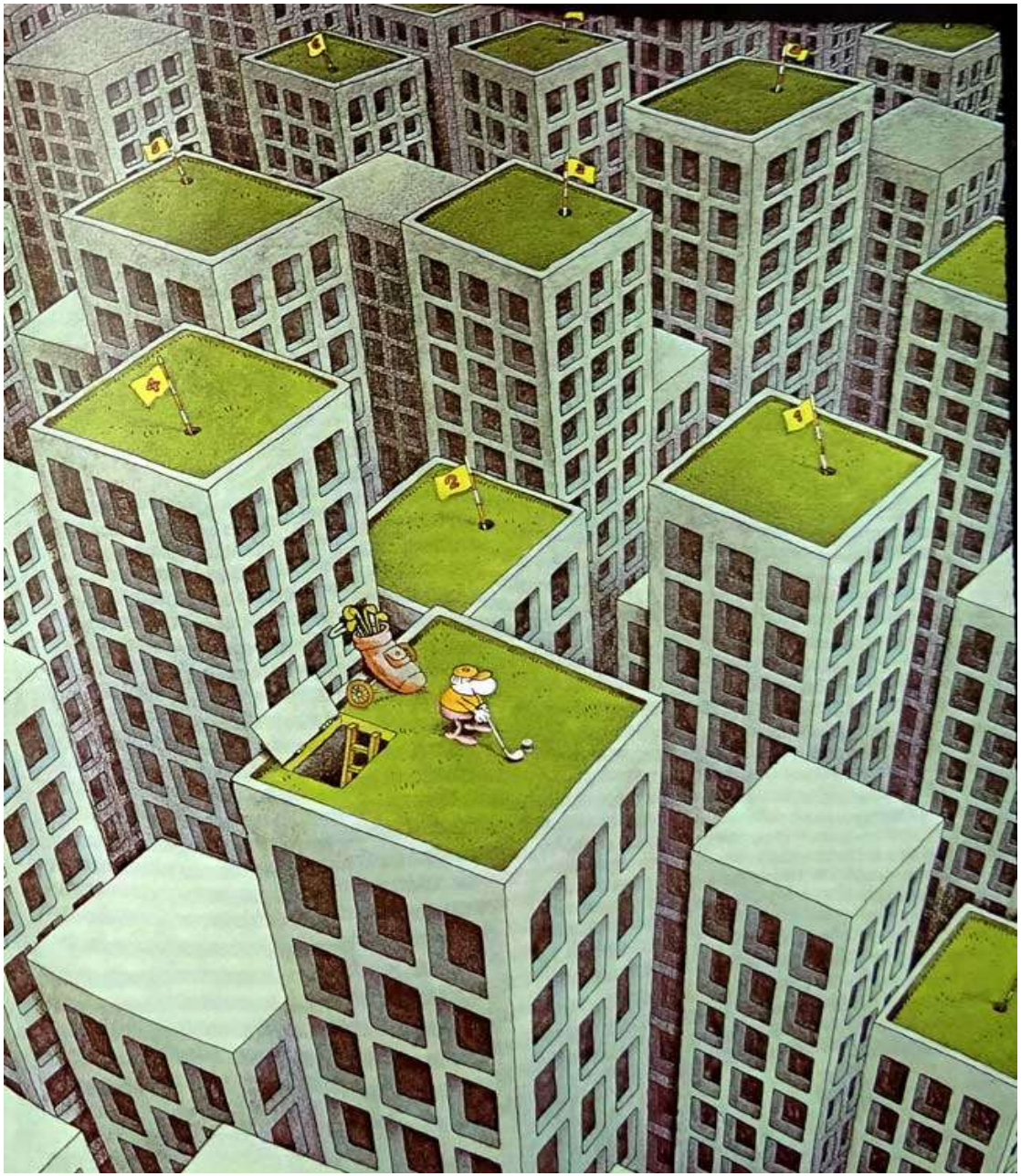
WHO grade II glioma

- Quite a demanding task
- Good resection is gold (*does the true come from France?)*
- Can RT prolong life while we preserve cognitive functioning?



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European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas

Michael Weller, Martin van den Bent, Jörg C Tonn, Roger Stupp, Matthias Preusser, Elizabeth Cohen-Jonathan-Moyal, Roger Henriksson, Emilie Le Rhun, Carmen Balana, Olivier Chinot, Martin Bendszus, Jaap C Reijneveld, Frederick Dhermain, Pim French, Christine Marosi, Colin Watts, Ingela Oberg, Geoffrey Pilkington, Brigitta G Baumert, Martin J B Taphoorn, Monika Hegi, Manfred Westphal, Guido Reifenberger, Riccardo Soffietti, Wolfgang Wick, for the European Association for Neuro-Oncology (EANO) Task Force on Gliomas

Beyond a histological diagnosis, the goal of surgery is to remove as much of the tumour as safely possible to improve neurological function

M. Weller, et al. The Lancet Oncol. Published online May 5, 2017

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Surgery of gliomas

The extent of resection is of prognostic value

(Li YM, Suki D, Hess K, Sawaya R: The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection?; J Neurosurg. 2016 Apr;124(4):977-88; Smith JS, Chang EF, Lamborn KR, et al.: Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 2008; 26: 1338–1345.

The resected tumor volume is predictive for malignant transformation in low grade glioma (Duffau H: A new philosophy in surgery for diffuse low-grade glioma (DLGG): oncological and functional outcomes. Neurochirurgie 2013; 59: 2–8)

Courtesy of W. Sala-Gulden

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European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas

Michael Weller, Martin van den Bent, Jörg C Tonn, Roger Stupp, Matthias Preusser, Elizabeth Cohen-Jonathan-Moyal, Roger Henriksson, Emilie Le Rhun, Carmen Balana, Olivier Chinot, Martin Bendszus, Jaap C Reijneveld, Frederick Dhermain, Pim French, Christine Marosi, Colin Watts, Ingela Oberg, Geoffrey Pilkington, Brigitta G Baumert, Martin J B Taphoorn, Monika Hegi, Manfred Westphal, Guido Reifenberger, Riccardo Soffietti, Wolfgang Wick, for the European Association for Neuro-Oncology (EANO) Task Force on Gliomas

- The goal of radiotherapy for patients with gliomas is to improve local control at a reasonable risk benefit ratio.
- Radiotherapy helps to preserve function and increases survival

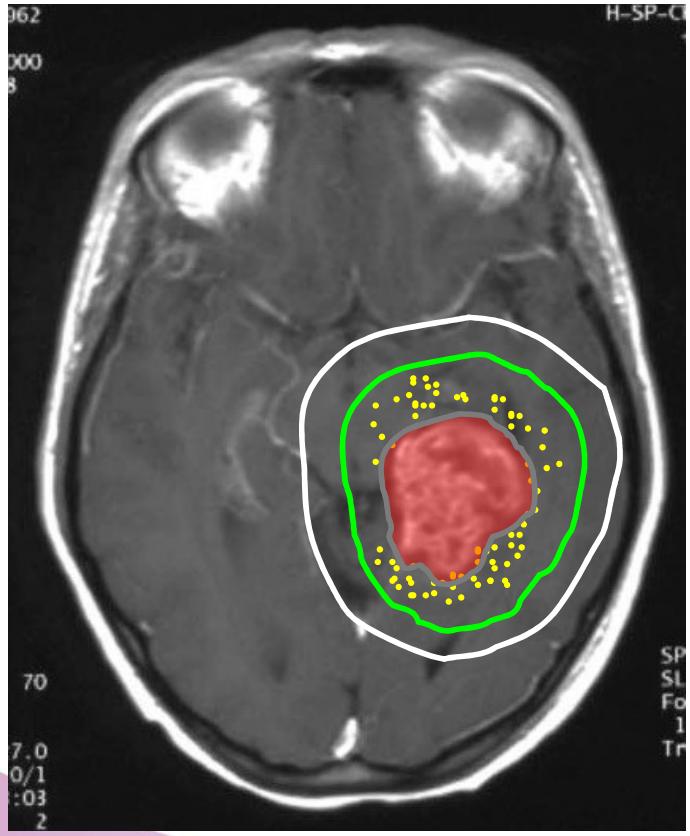
M. Weller, et al. The Lancet Oncol. Published online May 5, 2017


TECHNOLOGY IMPROVEMENT

Radiotherapy of GLIOMAS

- ICRU is still around…
- GTV to PTV
  - Enhancing
  - Abnormality in T2
  - STOP at anatomic boundaries
- Guidelines

That means 1.5-2.5 cm



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ESTRO-ACROP guidelines: Gliobastoma

ESTRO-ACROP guideline "target delineation of glioblastomas"

Maximilian Niyazi[a,*], Michael Brada[b], Anthony J. Chalmers[c], Stephanie E. Combs[d], Sara C. Erridge[e], Alba Fiorentino[f], Anca L. Grosu[g], Frank J. Lagerwaard[h], Giuseppe Minniti[i], René-Olivier Mirimanoff[j], Umberto Ricardi[k], Susan C. Short[l], Damien C. Weber[m,n], Claus Belka[a]

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Courtesy-modified from M. Brada

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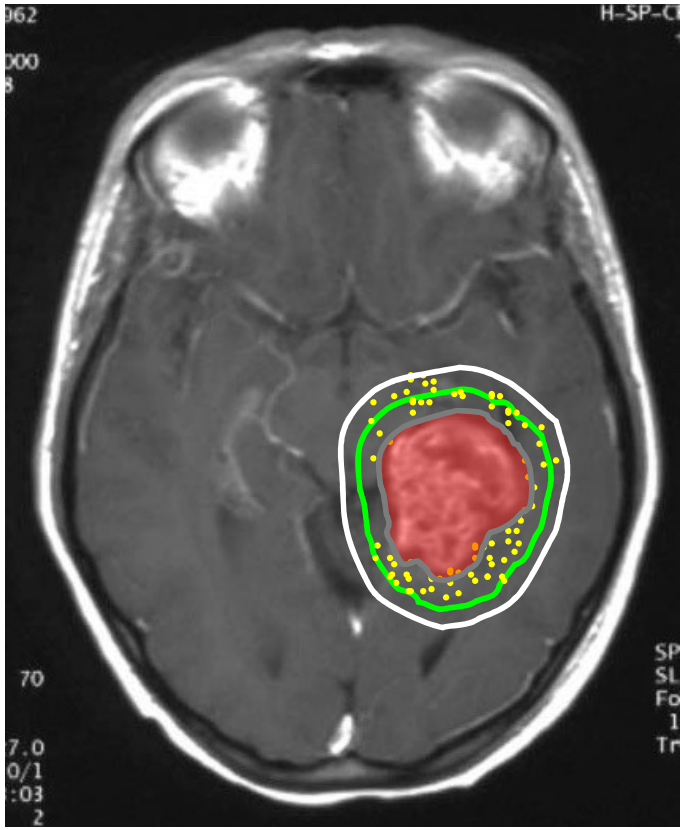
How large should be the margin? Which technique should be used?

- Several series analyzed the pattern of failure after radiotherapy for LGG
- In the NCCTG 86-72-51 trial 92% of the failures occurred in the treatment field, 3% within 2cm and 5% more than 2 cm
- Radiosurgery remains investigational but margins may be reduced
- Protons may reduce the integral dose and can result in reduction of late toxicity

Improved accuracy of dose delivery

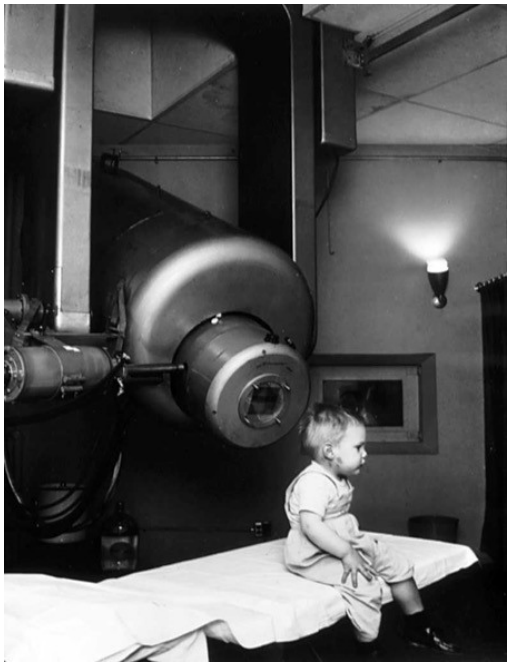
reducing margin for inaccuracy & microscopic spread



Courtesy-modified from M. Brada

Radiotherapy trials on LGG

When and How to do it



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Radiotherapy: RCT

Does dose matter?

● *Clinical Original Contribution*

A RANDOMIZED TRIAL ON DOSE–RESPONSE IN RADIATION THERAPY OF LOW-GRADE CEREBRAL GLIOMA: EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) STUDY 22844

ABUL B. M. F. KARIM, M.D., PH.D.,* BEN MAAT, M.D.,† REIDULV HATLEVOLL, M.D.,‡ JOHAN MENTEN, M.D.,§ EWALD H. J. M. RUTTEN, M.D.,‖ DAVID G. T. THOMAS, M.D., PH.D.,¶ FRANCISCO MASCARENHAS, M.D.,# JEAN C. HORIOT, M.D., PH.D.,∫ LEENA M. PARVINEN,∞ MATTHIJS VAN REIJN, M.D.,** JOS J. JAGER, M.D.,†† MARIA G. FABRINI, M.D.,‡‡ AUGUST M. VAN ALPHEN, M.D., PH.D.,§§ HAN P. HAMERS, M.D., PH.D.,‖‖ LUIS GASPAR, M.D.,¶¶ EVA NOORDMAN, M.D., PH.D.,## MARIANNE PIERART, M.SC.∫∫ AND MARTINE VAN GLABBEKE, M.SC.∫∫

*Department of Radiation Oncology, Free University Hospital, Amsterdam, The Netherlands; †Department of Radiation Oncology, BV Institute, Tilburg, The Netherlands; ‡Department of Radiation Oncology, University Radium Hospital, Oslo, Norway; §Department of Radiation Oncology, University Hospital, Leuven, Belgium; ‖Department of Radiation Oncology, University Hospital, Nijmegen, The Netherlands; ¶Department of Neurosurgery, Queens Square Neurological Institute, London, UK; #Department of Radiation Oncology, Santa Maria University Hospital, Lisbon, Portugal; ∫Department of Radiation Oncology, Dijon University Hospital, Dijon, France; ∞Department of Radiation Oncology, Turku Central Hospital, Turku, Finland; **Department of Radiation Oncology, Enschede Hospital, Enschede, The Netherlands; ††Department of Radiation Oncology, Maastricht University Hospital, Maastricht, The Netherlands; ‡‡Department of Radiation Oncology, Pisa University Hospital, Pisa, Italy; §§Department of Neurosurgery, Free University Hospital, Amsterdam, The Netherlands; ‖‖Department of Radiation Oncology, Radiotherapy Institute, Tilburg, The Netherlands; ¶¶Department of Radiation Oncology, Lisbon University Hospital, Lisbon, Portugal; ##Department of Radiation Oncology, University Hospital, Turku, Finland; and ∫∫EORTC, Brussels, Belgium

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EORTC 22844

323 adults with LGG

results

R: 45Gy/1.8 vs 54Gy/1.8

ESTRO School

EORTC 22844

results

323 adults with LGG

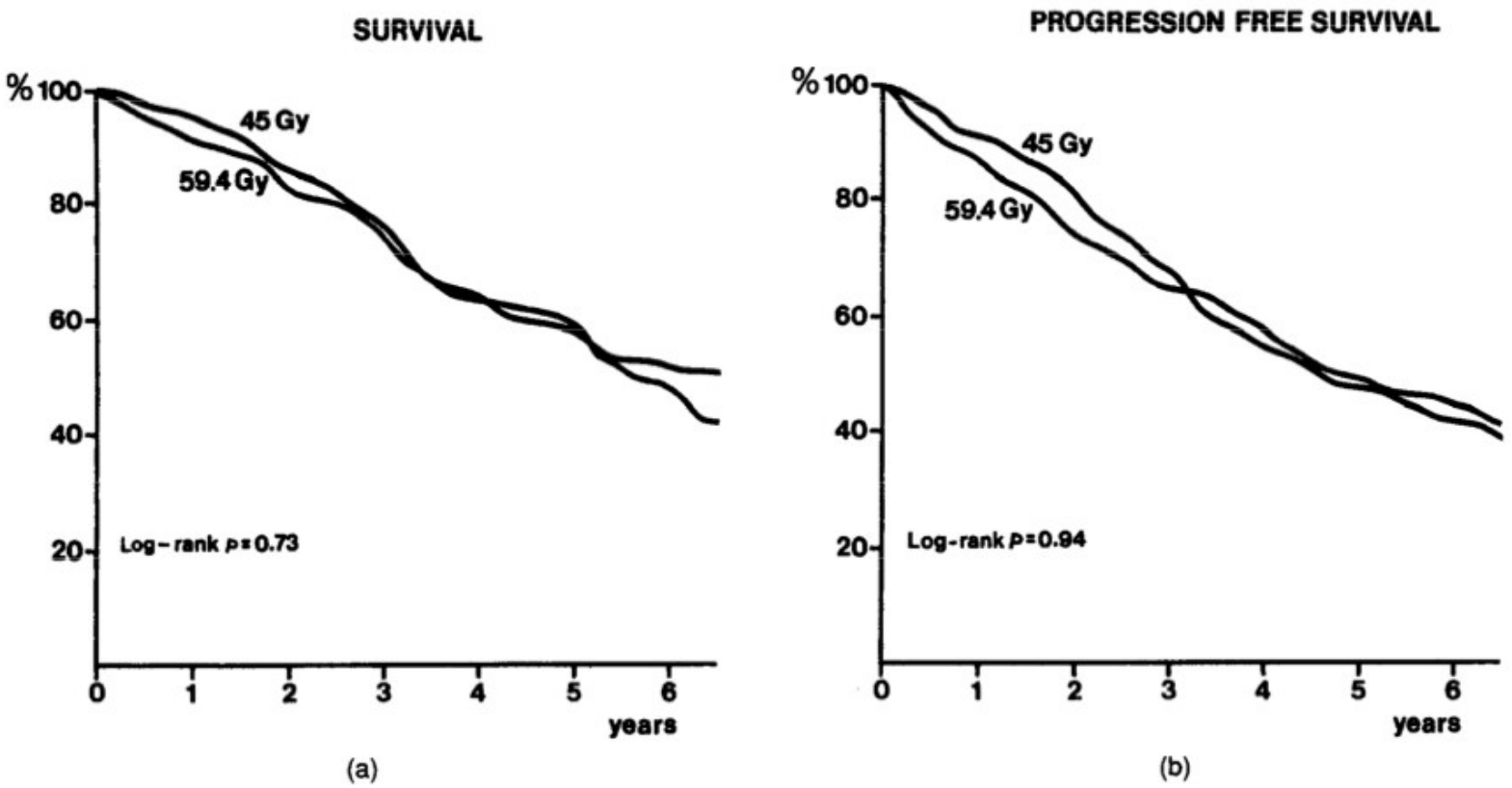

Fig. 1. (a) Survival and (b) progression-free survival (PFS) of patients treated with a low dose (45 Gy) and high dose (59.4 Gy).

1.8

NCCTG

203 adults with LGG

Prospective Randomized Trial of Low- Versus High-Dose Radiation Therapy in Adults With Supratentorial Low-Grade Glioma: Initial Report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group Study

By E. Shaw, R. Arusell, B. Scheithauer, J. O'Fallon, B. O'Neill, R. Dinapoli, D. Nelson, J. Earle, C. Jones, T. Cascino, D. Nichols, R. Ivnik, R. Hellman, W. Curran, and R. Abrams

1986-1994

R: 50.4 Gy/1.8 vs 64.8 Gy/1.8

Dose encore…

Shaw, et al. JCO 2002

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NCCTG

203 adults with LGG

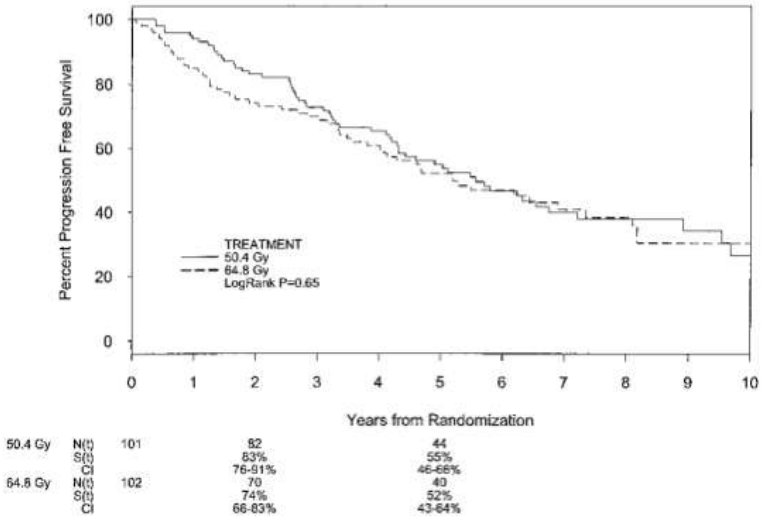

Fig 2. Kaplan-Meier (K-M) estimates of TTP by treatment arm for patients receiving low-dose (arm A) or high-dose radiation therapy (arm B). Two-sided log rank test $P = .65$. N(t), number of patients; S(t), K-M survival; CI, 95% confidence interval.

Toxicity higher dose arm was more evident (radionecrosis)
A report by the same group in 2003 did not show relevant impact of RT on cognitive function (MMSE)

Prospective Randomized Trial of Low- Versus High-Dose Radiation Therapy in Adults With Supratentorial Low-Grade Glioma: Initial Report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group Study

By E. Shaw, R. Arusell, B. Scheithauer, J. O'Fallon, B. O'Neill, R. Dinapoli, D. Nelson, J. Earle, C. Jones, T. Cascino, D. Nichols, R. Ivnik, R. Hellman, W. Curran, and R. Abrams

results

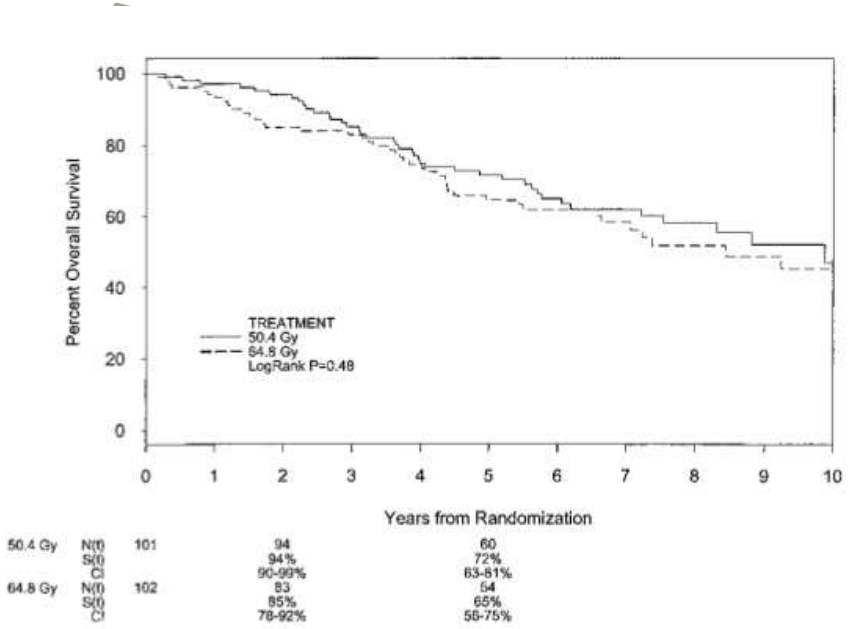

Fig 1. Kaplan-Meier (K-M) estimates of overall survival by treatment arm for patients receiving low-dose (arm A) or high-dose radiation therapy (arm B). Two-sided log rank test $P = .48$. N(t), number of patients; S(t), K-M survival; CI, 95% confidence interval.

Shaw, et al. JCO 2002

Radiotherapy at diagnosis or at relapse?

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

ABUL B. M. F. KARIM, M.D., F.R.C.R., PH.D.,* DENES AFRA, M.D.,† PHILIPPE CORNU, M.D.,‡ NORMAN BLEEHAN, M.D., F.R.C.R.,§ SIMON SCHRAUB, M.D.,‖ OLIVIER DE WITTE, M.D.,¶ FRANÇOIS DARCEL, M.D.,# SALLY STENNING, M.SC.,** MARIANNE PIERART, M.SC,†† AND MARTINE VAN GLABBEKE, IR., M.SC.††

*Department of Radiation Oncology, Vrije University Hospital, Amsterdam, The Netherlands; †National Institute of Neurosurgery, Budapest, Hungary; ‡Department of Neurosurgery, CHU Pitié-Salpetriere, Paris, France; §Department of Radiation Oncology, Addenbrooke's Hospital, Cambridge, United Kingdom; ‖Department of Neurosurgery, Hospital J. Minjoz, Besancon, France; ¶Department of Neurosurgery, Hopital Univverstaire Erasme, Brussels, Belgium; #Department of Neurosurgery, CHU Pontachaillou, Rennes, France; **Medical Research Council, Cancer Trials Office, Cambridge, United Kingdom; ††European Organization for Research and Treatment of Cancer Data Center, Brussels, Belgium

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EORTC 22845

290 eligible of 311 adults operated for LGG

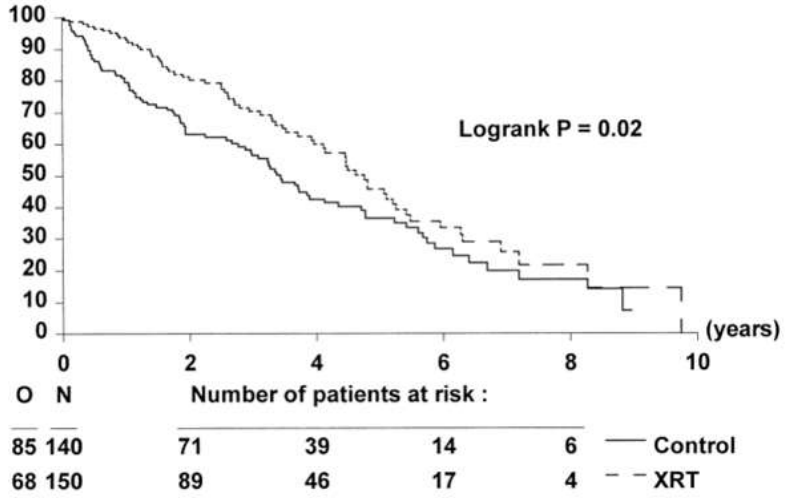


Fig. 2. TTP of patients in the two arms of the trial. The difference between the two groups was statistically significant. O = observed events; N = number of patients.

R: 54Gy after surgery or at PD

Median F-up 60m

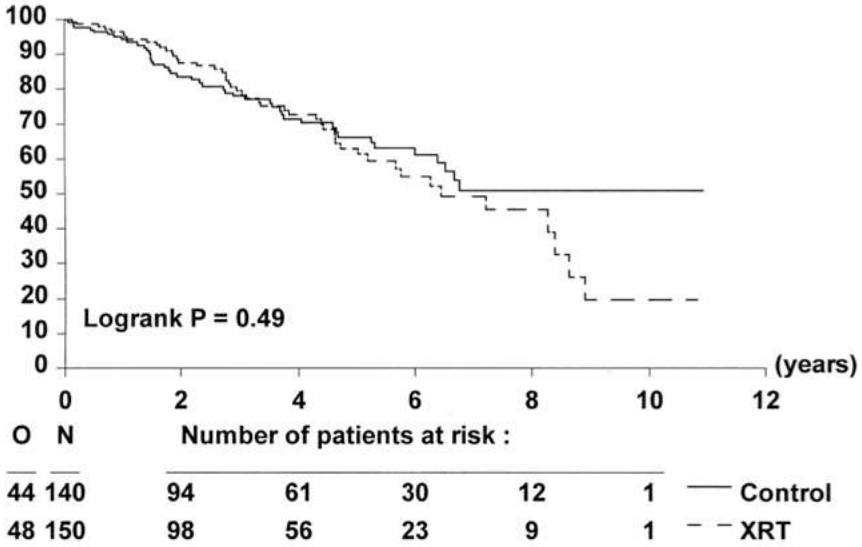


Fig. 1. OS of patients with LGG. Irradiated vs. nonirradiated groups in the two arms of the trial. O = observed events; N = number of patients.

STRO School

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

Summary

Background Postoperative policies of "wait-and-see" and radiotherapy for low-grade glioma are poorly defined. A trial in the mid 1980s established the radiation dose. In 1986 the EORTC Radiotherapy and Brain Tumor Groups initiated a prospective trial to compare early radiotherapy with delayed radiotherapy. An interim analysis has been reported. We now present the long-term results.

Methods After surgery, patients from 24 centres across Europe were randomly assigned to either early radiotherapy of 54 Gy in fractions of 1·8 Gy or deferred radiotherapy until the time of progression (control group). Patients with low-grade astrocytoma, oligodendroglioma, mixed oligoastrocytoma, and incompletely resected pilocytic astrocytoma, with a WHO performance status 0–2 were eligible. Analysis was by intention to treat, and primary endpoints were overall and progression-free survival.

Findings 157 patients were assigned early radiotherapy, and 157 control. Median progression-free survival was 5·3 years in the early radiotherapy group and 3·4 years in the control group (hazard ratio 0·59, 95% CI 0·45–0·77; $p<0·0001$). However, overall survival was similar between groups: median survival in the radiotherapy group was 7·4 years compared with 7·2 years in the control group (hazard ratio 0·97, 95% CI 0·71–1·34; $p=0·872$). In the control group, 65% of patients received radiotherapy at progression. At 1 year, seizures were better controlled in the early radiotherapy group.

Interpretation Early radiotherapy after surgery lengthens the period without progression but does not affect overall survival. Because quality of life was not studied, it is not known whether time to progression reflects clinical deterioration. Radiotherapy could be deferred for patients with low-grade glioma who are in a good condition, provided they are carefully monitored.

Lancet 2005; 366: 985–90

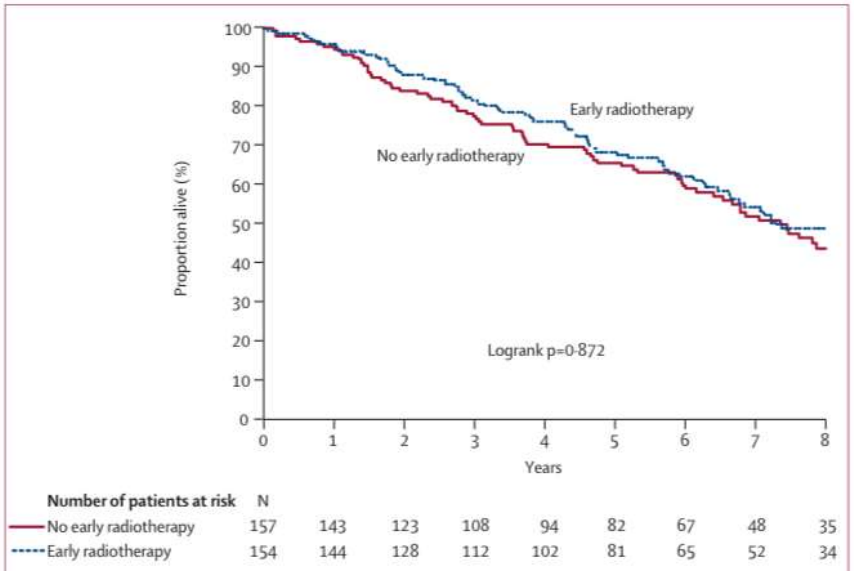
Published online August 18, 2005
DOI:10.1016/S0140-6736(05)67070-5

Erasmus Medical Centrum Daniel den Hoed Oncology Center, Rotterdam (M J van den Bent MD); National Institute of Neurosurgery, Budapest, Hungary (D Afra MD); Hopital Universitaire Erasme, Brussels (O de Witte MD); EORTC Data Center, Brussels, Belgium (L Collette MSc, M Piérart MSc); Centre Eugène Marquis, Rennes (M Ben Hassel MD); Hopital Jean Minjoz, Besançon (S Schraub MD); Centre Universitaire Pitié-Salpétrière, Paris, France (K Hoang-Xuan MD); Lund University Hospital, Lund, Sweden (P O Malmström MD); Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (R Mirimanoff MD); and Vrije

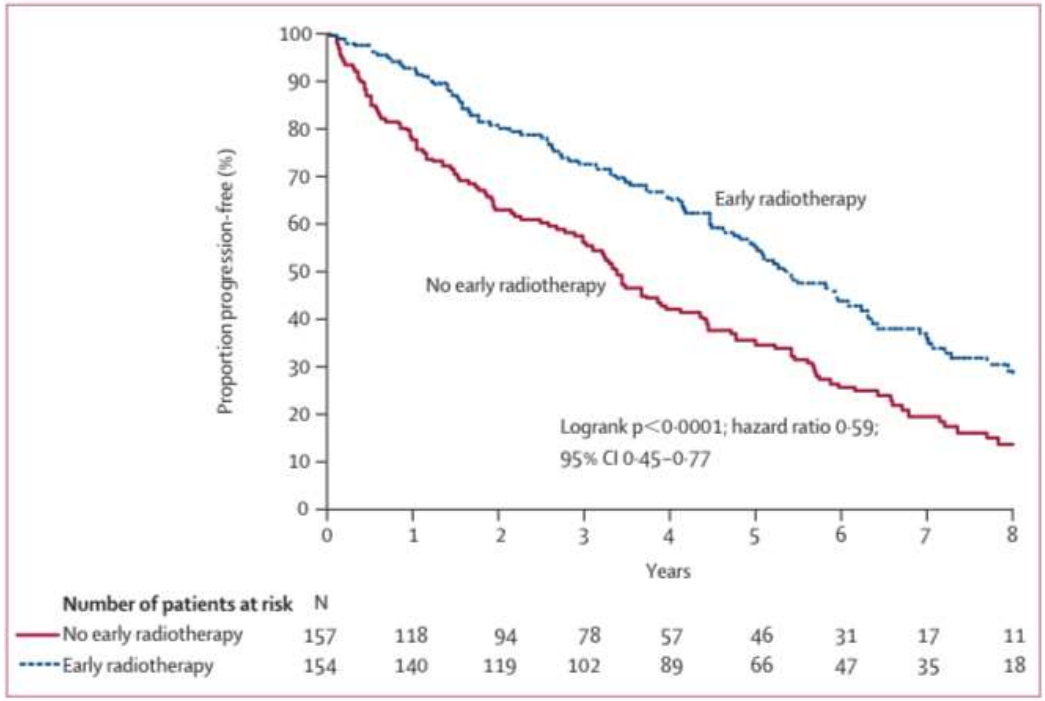
School

EORTC 22845

154 early RT, 157 obs.; adults operated for LGG



R: 54G



Median F-up 7.8 years

	No early radiotheraphy (n=157)	Early radiotherapy (n=154)	Hazard ratio (95% CI)
Overall survival			
Median years (95% CI)	7·4 (6·1–8·9)	7·2 (6·4–8·6)	0·97 (0·71–1·34)
Proportion alive at 5 years	65·7% (57·8–73·5)	68·4% (60·7–76·2)	
Progression-free survival			
Median years (95% CI)	3·4 (2·9–4·4)	5·3 (4·6–6·3)	0·59 (0·45–0·77)
Proportion free from progression at 5 years	34·6% (26·7–42·5)	55·0% (46·7–63·3)	

Table 2: Survival and progression-free survival

Van Den Bent, Lancet 2005

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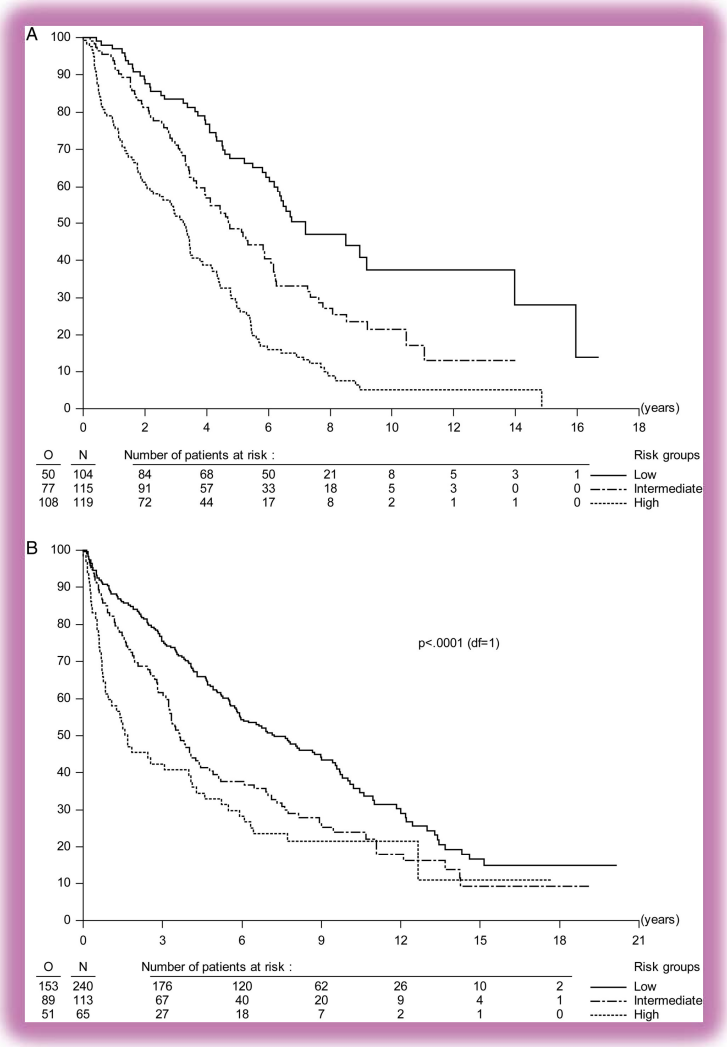
RT RCT- *summary*

- Radiotherapy is effective at a dose of 45 to 54 Gy
- Higher dose could be dangerous (late toxicity seen more often in the HD arm of the NCCTG trial)
- Early postoperative radiotherapy determined significant improvement in progression free survival from 3.4 to 5.3 years in the EORTC 22845 trial
- Deferring radiotherapy did not impact adversely on overall survival, but the effect on PFS and Freedom from seizure may substancially impact on quality of life
- *Those trials were carried out between the 80s and the 90s, with quite simple radiotherapy techniques also including Cobalt*

Favourable prognostic factors

- Age<40
- Longer duration of symptoms
- Radiation *(PFS ok; OSR n.s.)*
- Tumor size ≦5cm
- Resection *vs* Biopsy
- Histology (OD vs A)



T. Gorlia, et al. Neuro Oncol 2013

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LGG: EORTC prognostic calculator

PROGNOSTIC CALCULATORS OF PROGRESSION FREE AND OVERALL SURVIVAL FOR PATIENTS WITH LOW GRADE GLIOMA

About | Calculator | Licence and disclaimer | Kaplan Meier Survival curves

Cited in

New validated prognostic models and calculators in patients with low grade gliomas confirmed by central pathology review: a pooled analysis of EORTC/RTOG/NCCTG phase III clinical trials. Under review.

IMPORTANT: The Progression Free Survival (PFS) and Overall Survival (OS) estimates provided by this online calculator have valid accuracy for patients who satisfy to the eligibility criteria to enter the EORTC 22884 or 22845 trials or RTOG 9802 trial or NCCTG 86-72-51 trial.

By using theses calculators you agree with the following License and Disclaimer

Calculators for PFS and OS			
Diagnosis	A	Median PFS (months) (95% Confidence Interval)	41(30.62-53.06)
Time since first symptoms	>=30 weeks	PFS 3 years (%) (95% Confidence Interval)	56.31(43.18-67.52)
Presence of neurological deficit	Some	Median OS (months) (95% Confidence Interval)	106.97(88.15-N)
Tumor size	<5cm	OS 5 years (%) (95% Confidence Interval)	78.47(66.85-86.41)
Treatment	Delayed RT		
		Risk group	HIGH RISK

www.eortc.be

T. Gorlia, et al. Neuro Oncol 2013

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LGG: EORTC prognostic calculator

PROGNOSTIC CALCULATORS OF PROGRESSION FREE AND OVERALL SURVIVAL FOR PATIENTS WITH LOW GRADE GLIOMA

About | Calculator | Licence and disclaimer | Kaplan Meier Survival curves

Cited in

New validated prognostic models and calculators in patients with low grade gliomas confirmed by central pathology review: a pooled analysis of EORTC/RTOG/NCCTG phase III clinical trials. Under review.

IMPORTANT: The Progression Free Survival (PFS) and Overall Survival (OS) estimates provided by this online calculator have valid accuracy for patients who satisfy to the eligibility criteria to enter the EORTC 22884 or 22845 trials or RTOG 9802 trial or NCCTG 86-72-51 trial.

By using theses calculators you agree with the following License and Disclaimer

Calculators for PFS and OS			
Diagnosis	A	Median PFS (months) (95% Confidence Interval)	27.33(20.47-40.25)
Time since first symptoms	>=30 weeks	PFS 3 years (%) (95% Confidence Interval)	41.62(28.83-53.91)
Presence of neurological deficit	Some	Median OS (months) (95% Confidence Interval)	81.22(70.64-103.89)
Tumor size	>=5cm	OS 5 years (%) (95% Confidence Interval)	65.54(51.1-76.65)
Treatment	Delayed RT		
		Risk group	HIGH RISK

www.eortc.be

T. Gorlia, et al. Neuro Oncol 2013

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Does chemotherapy add?

Chemotherapy of LGG

EORTC 22033-26033 RTX vs. TMZ in LGG stratifying for 1p loss

Author	No	Response	Survival	Therapy	Histology
Van den Bent 1998 (Ref 19)	52	OD: 9/20 (45%) OA: (33%) RR 64%	MTP 8 months	PCV	OD, OA
Soffietti 1998 (Ref 20)	26	12% CR, 50% PR, RR 62%	MTP 24 months	PCV	17 OD, 9 OA
Van den Bent 2000 (Ref 21)	30	3 CR, 5 PR, RR 26%	MTP 14 months	TMZ	22 OD, 8 OA
Pace 2003 (Ref 22)	43	4 CR, 16 PR, 17 SD, 6 PD	6 months-PFS 76.8%, 12 mths PFS 39.6% MTP 10 mths	TMZ	29 Astro, 10 OA, 4 OD
Astro, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma, PA, pilocytic astrocytoma					

Table 3. Chemotherapy for recurrent low-grade glioma.

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Chemotherapy of LGG

Author	No	Response	Therapy	Toxicity	Histology
Mason 1996 (Ref 24)	9	6 PR, 3 SD (2 MR)	PCV/I-PCV	I-PC: high	
Soffietti 1999 (Ref 25)	13	3 PR, 10 SD (2 MR), 2/5 improved symptoms	PCV	low	OD, OA
Mason 2001 (Ref 26)	8	2 PR, 5/6 symptoms improved	Mini-PCV	moderate	6 OD, 2 OA
Buckner 2003 (Ref 27)	28	8 PR, 17 SD, 3 PD	PCV	moderate	17 OD, 11 OA
Astro, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma, PA, pilocytic astrocytoma					

Table 4: Neo-adjuvant chemotherapy for patients with a low-grade glioma

LGG chemo-radiotherapy RCT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma

Jan C. Buckner, M.D., Edward G. Shaw, M.D., Stephanie L. Pugh, Ph.D., Arnab Chakravarti, M.D., Mark R. Gilbert, M.D., Geoffrey R. Barger, M.D., Stephen Coons, M.D., Peter Ricci, M.D., Dennis Bullard, M.D., Paul D. Brown, M.D., Keith Stelzer, M.D., David Brachman, M.D., John H. Suh, M.D., Christopher J. Schultz, M.D., Jean-Paul Bahary, M.D., Barbara J. Fisher, M.D., Harold Kim, M.D., Albert D. Murtha, M.D., Erica H. Bell, Ph.D., Minhee Won, M.A., Minesh P. Mehta, M.D., and Walter J. Curran, Jr., M.D.

ABSTRACT

N Engl J Med 2016;374:1344-55.

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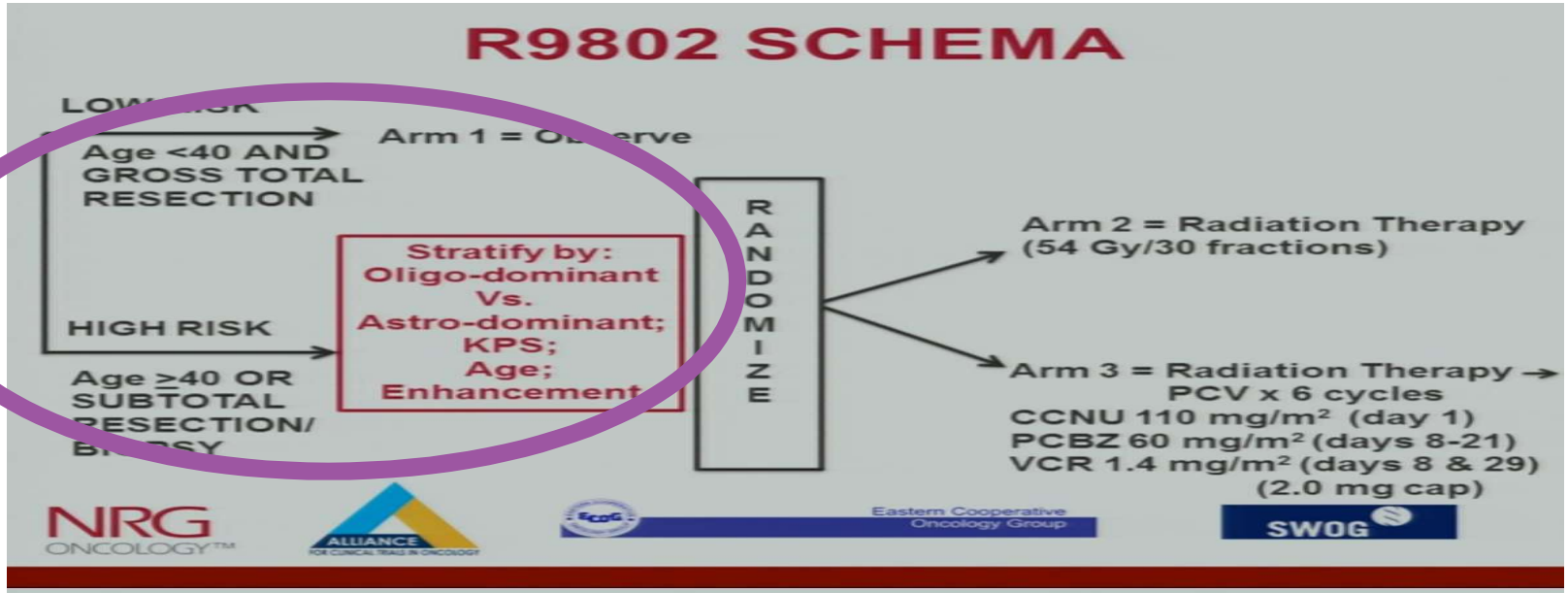

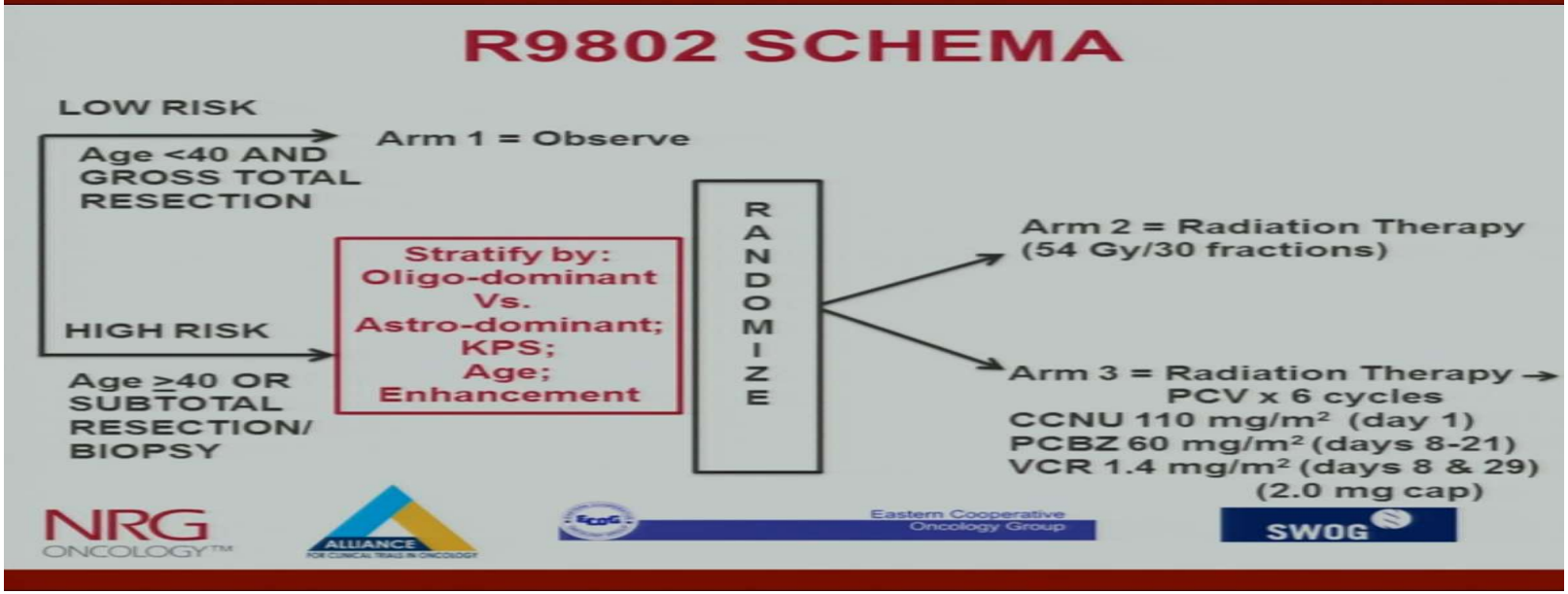

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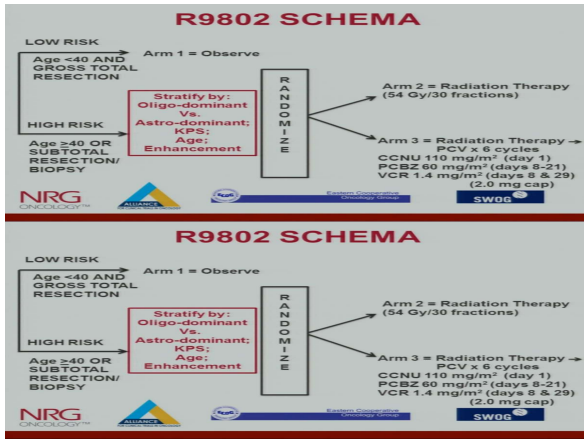
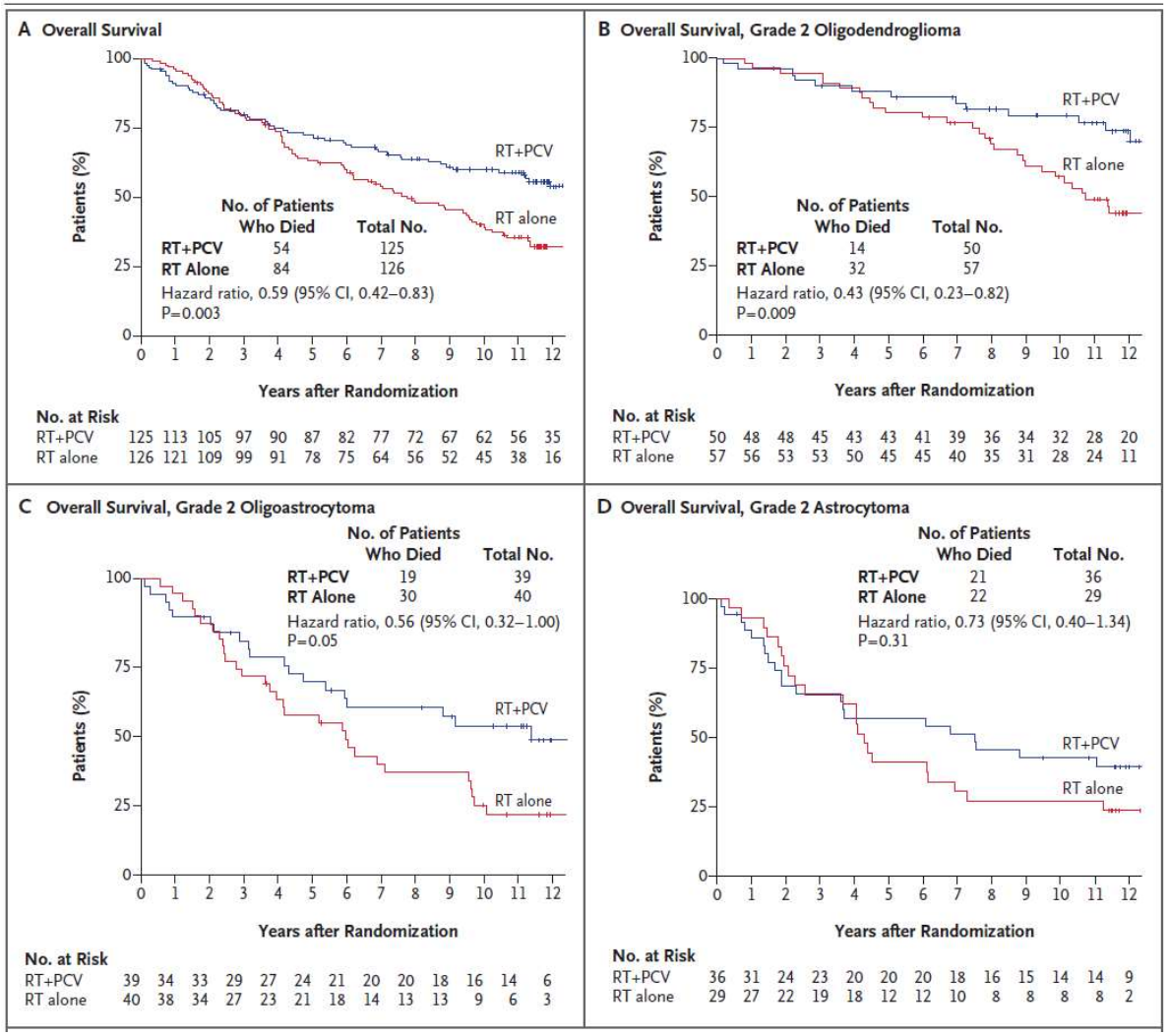
Buckner 2016



5 years



N Engl J Med 2016;374:1344-55.

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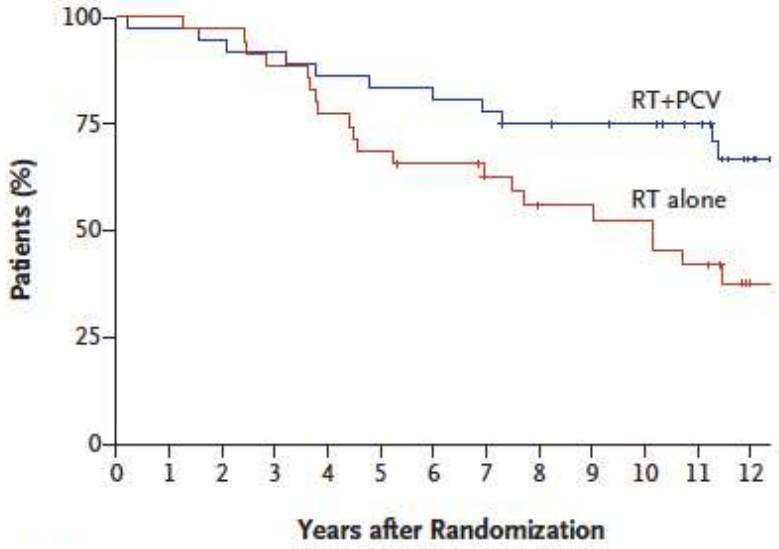
Buckner 2016

E **Overall Survival among Patients with *IDH1* R132H Mutation**



No. at Risk													
RT+PCV	36	35	34	33	31	30	29	28	26	25	24	21	12
RT alone	35	35	34	31	27	24	22	19	16	15	15	12	5

	No. of Patients Who Died	Total No.
RT+PCV	11	36
RT Alone	22	35

Hazard ratio, 0.42 (95% CI, 0.20–0.86)
P=0.02

Data are not sufficient to evaluate the role of 1p/19q codeletion

N Engl J Med 2016;374:1344-55.

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Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

Brigitta G Baumert, Monika E Hegi*, Martin J van den Bent, Andreas von Deimling, Thierry Gorlia, Khê Hoang-Xuan, Alba A Brandes, Guy Kantor, Martin J B Taphoorn, Mohamed Ben Hassel, Christian Hartmann, Gail Ryan, David Capper, Johan M Kros, Sebastian Kurscheid, Wolfgang Wick, Roelien Enting, Michele Reni, Brian Thiessen, Frederic Dhermain, Jacoline E Bromberg, Loic Feuvret, Jaap C Reijneveld, Olivier Chinot, Johanna M M Gijtenbeek, John P Rossiter, Nicolas Dif, Carmen Balana, Jose Bravo-Marques, Paul M Clement, Christine Marosi, Tzahala Tzuk-Shina, Robert A Nordal, Jeremy Rees, Denis Lacombe, Warren P Mason, Roger Stupp**

Summary

Background Outcome of low-grade glioma (WHO grade II) is highly variable, reflecting molecular heterogeneity of the disease. We compared two different, single-modality treatment strategies of standard radiotherapy versus primary temozolomide chemotherapy in patients with low-grade glioma, and assessed progression-free survival outcomes and identified predictive molecular factors.

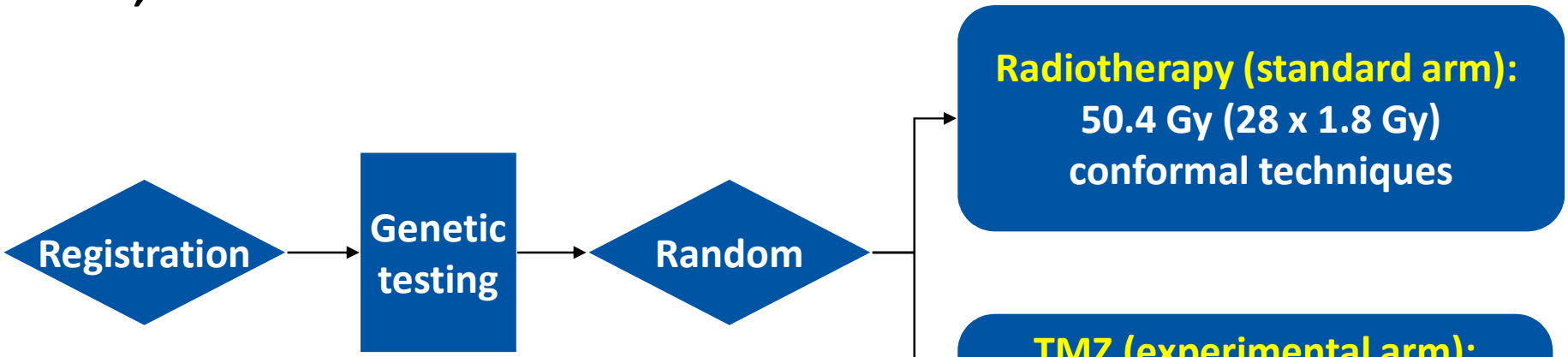
Lancet Oncol 2016; 17: 1521–32
Published Online
September 26, 2016
http://dx.doi.org/10.1016/S1470-2045(16)30313-8

B. Baumert, et al. Lancet Oncol, 2016

EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033) in patients with a high risk low-grade glioma

Participating groups: EORTC ROG and BTG, NCI-CTG,

TROG, MRC-CTU

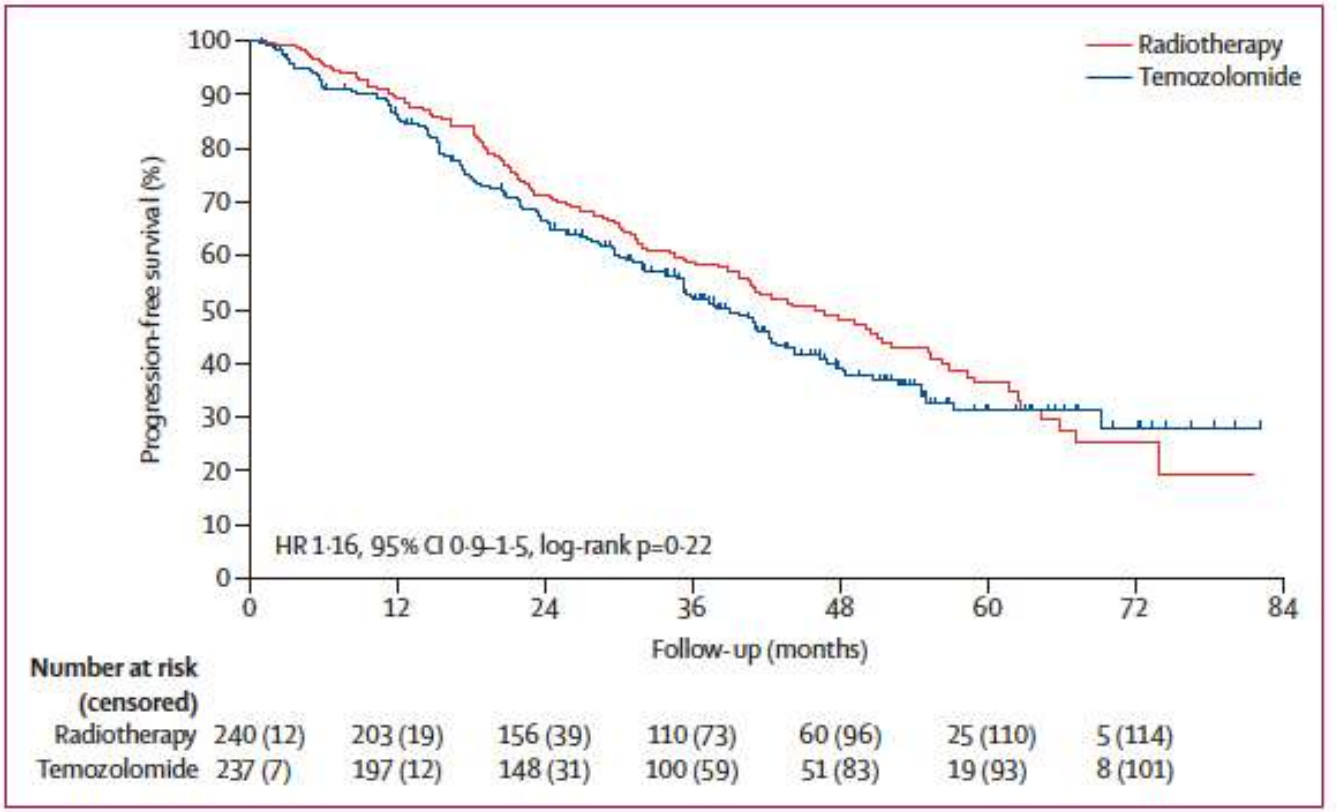


Stratification: **1p deletion**
contrast on MRI, age and PS, institute,
contrast enhancement MRI, age: <40
vs ≥ 40 yrs, WHO PS 0 /1 versus 2

Accrual: **2005 – 2012**
707 patients registered
477 randomized

Baumert, Hegi,…Stupp, Lancet Oncol 17, 1521–1532, 2016

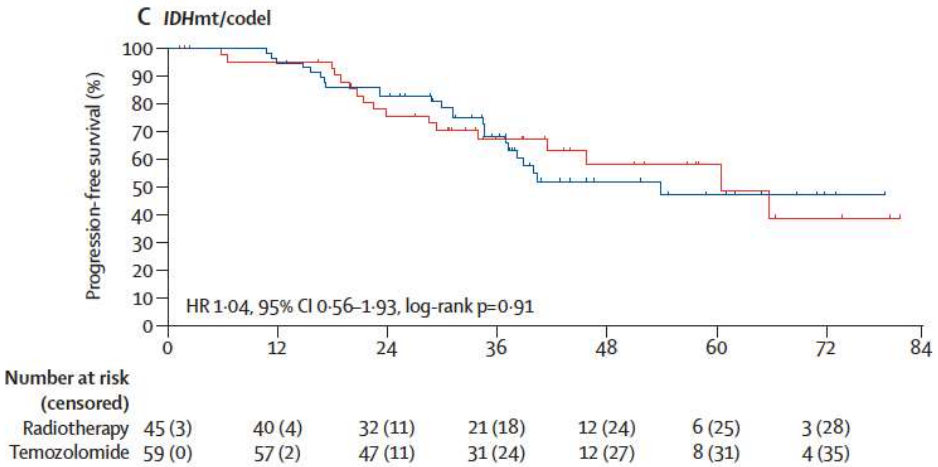
EORTC 22033 trial
PFS

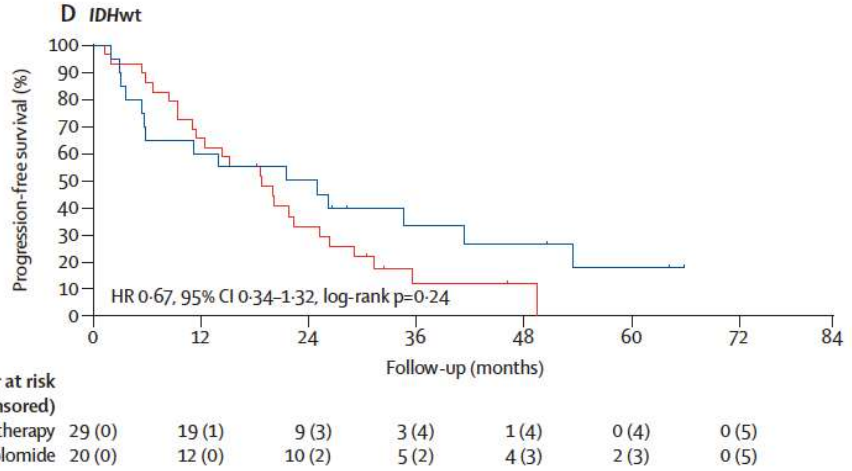


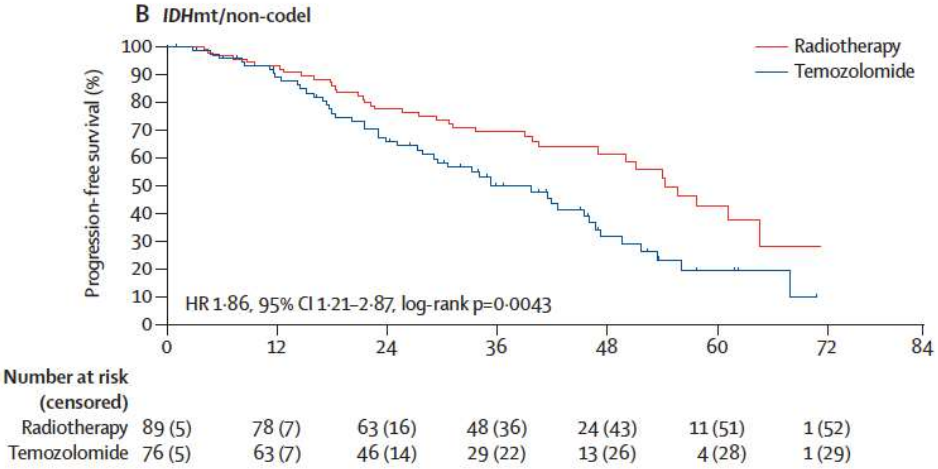
Median Survival not reached

B. Baumert, et al. Lancet Oncol, 2016

EORTC 22033





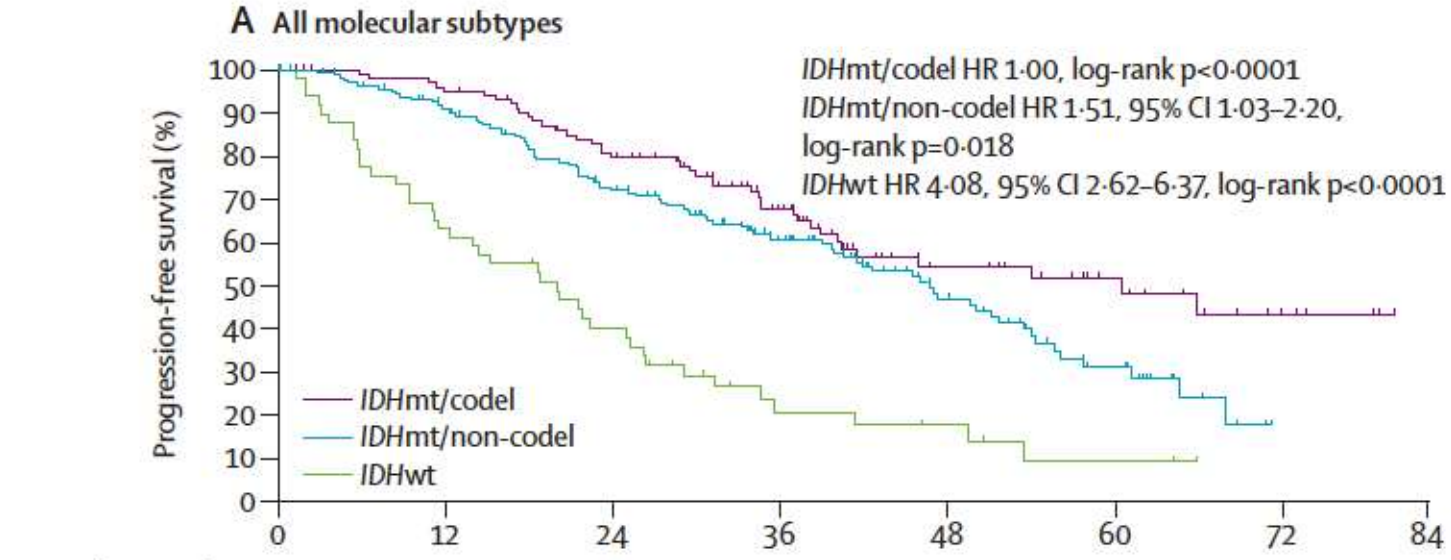


Median Survival not reached

B. Baumert, et al. Lancet Oncol, 2016

EORTC 22033

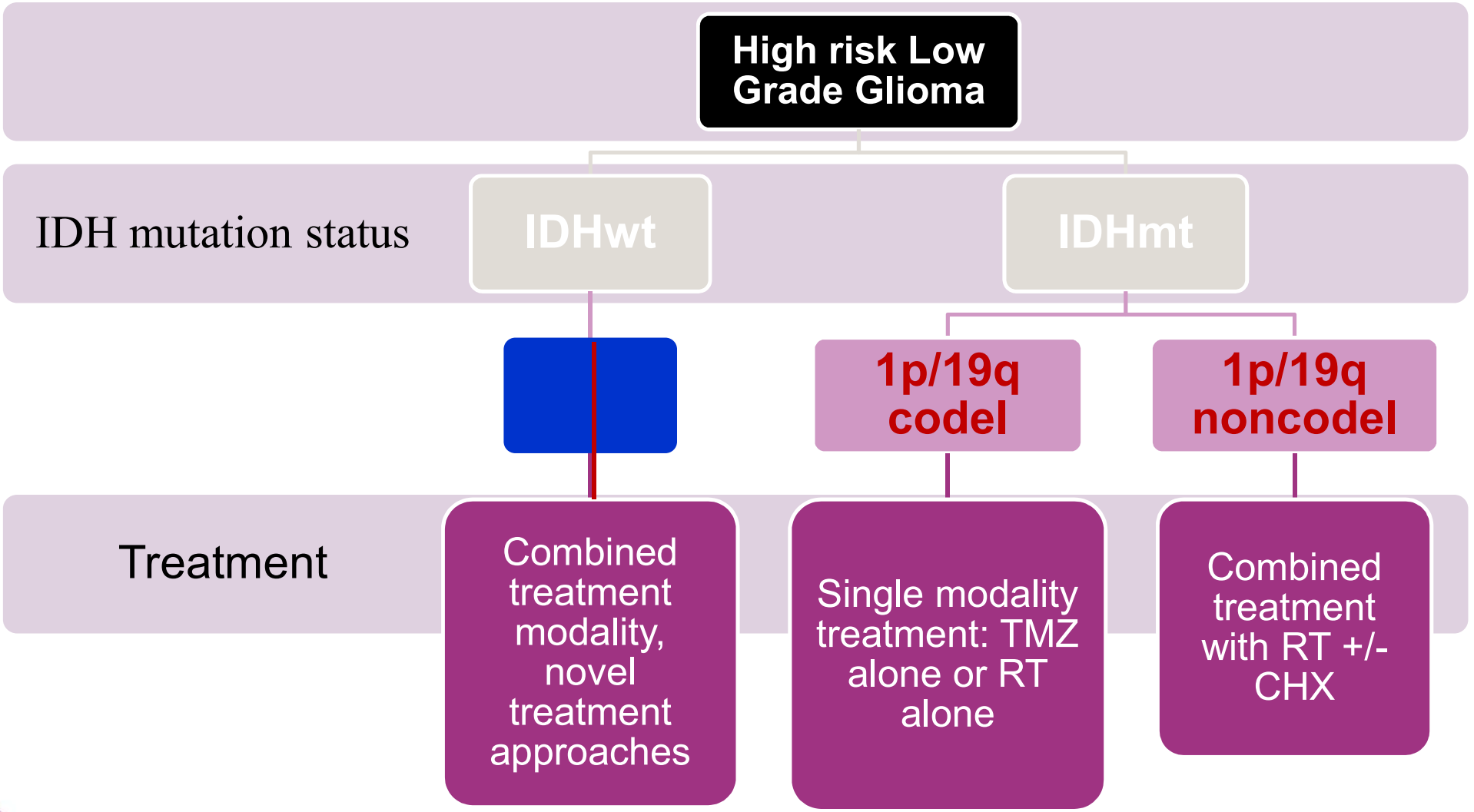
All molecular subtypes



Number at risk (censored)							
*IDH*mt/codel	104 (3)	97 (6)	79 (22)	52 (42)	24 (51)	14 (56)	7 (63)
*IDH*mt/non-codel	165 (10)	141 (14)	109 (30)	77 (58)	37 (69)	15 (79)	2 (81)
*IDH*wt	49 (0)	31 (1)	19 (5)	8 (6)	5 (7)	2 (9)	0 (0)

B. Baumert, et al. Lancet Oncol, 2016

Treatment algorithm based on molecular marker



Courtesy of B. Baumert

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Low grade astrocytoma

- Chemotherapy can be a therapeutic option to defer, or an alternative to RT at progression, but, deferring RT must be balanced with the lower control of seizures and shorter PFS [1,2]
- Long term results of athe RTOG 9802 trial showed a survival advantage of 5.5 years by addition of chemotherapy to RT in patients with adverse prognostic factors[2]
- The same experience indicates that treatment of LGG patients, immediately after surgery or at progression, should be tailored according to specific prognostic factors [1-5]
- Patients' subgroups should be treated and trials should be designed according to specific biomarkers, being IDH mutation and 1p/19q codeletion the most relevant[1-5]

1. *Baumert, et al. Lancet Oncol 2016*
2. *Buckner, et al., NEJM 2016*
3. *Soffietti, et al. EJN 2010*
4. *Gorlia, et al. Neuro-Oncol 2013*
5. *Weller, et al, Lancet Oncol, 2017*

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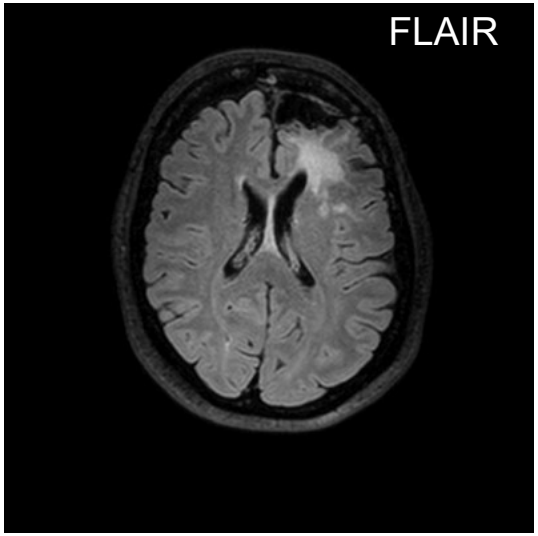
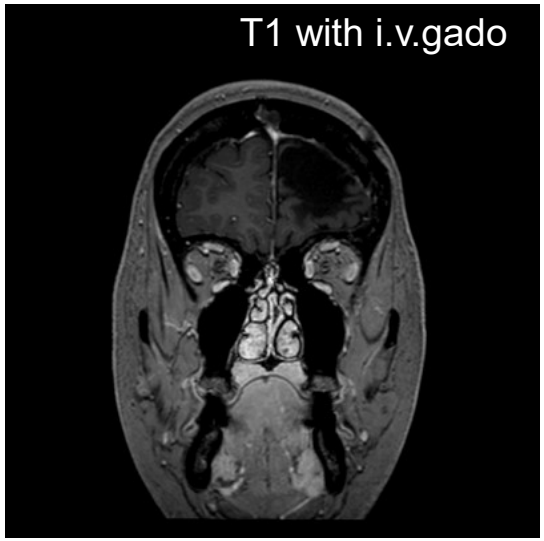
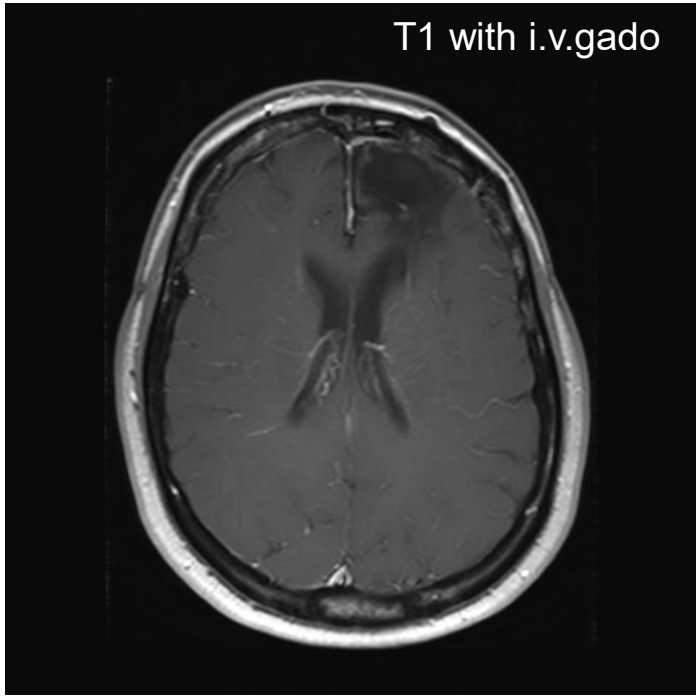
Outcome 2017

NED







Histology review 2014: Low grade astrocytoma

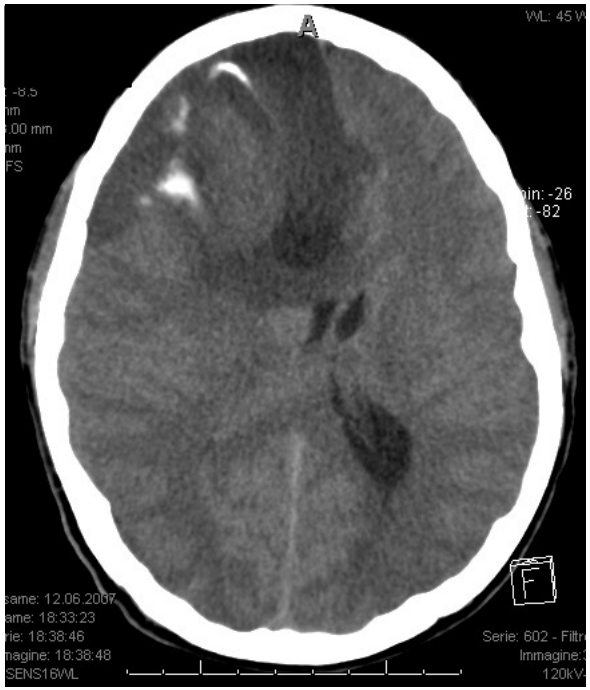
IDH1/2 mutated, 1p/19q codeleted

What are the evidences

HIGHER GRADE GLIOMA

Clinical case 2

- 33 years old woman
- Worsening Headache and vomiting



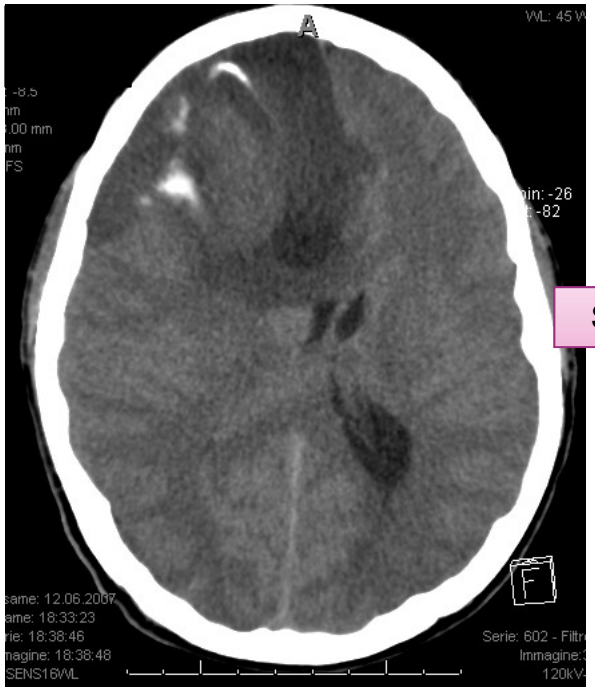
June 2007

Clinical case 2

33 years old woman

Worsening Headache and vomiting

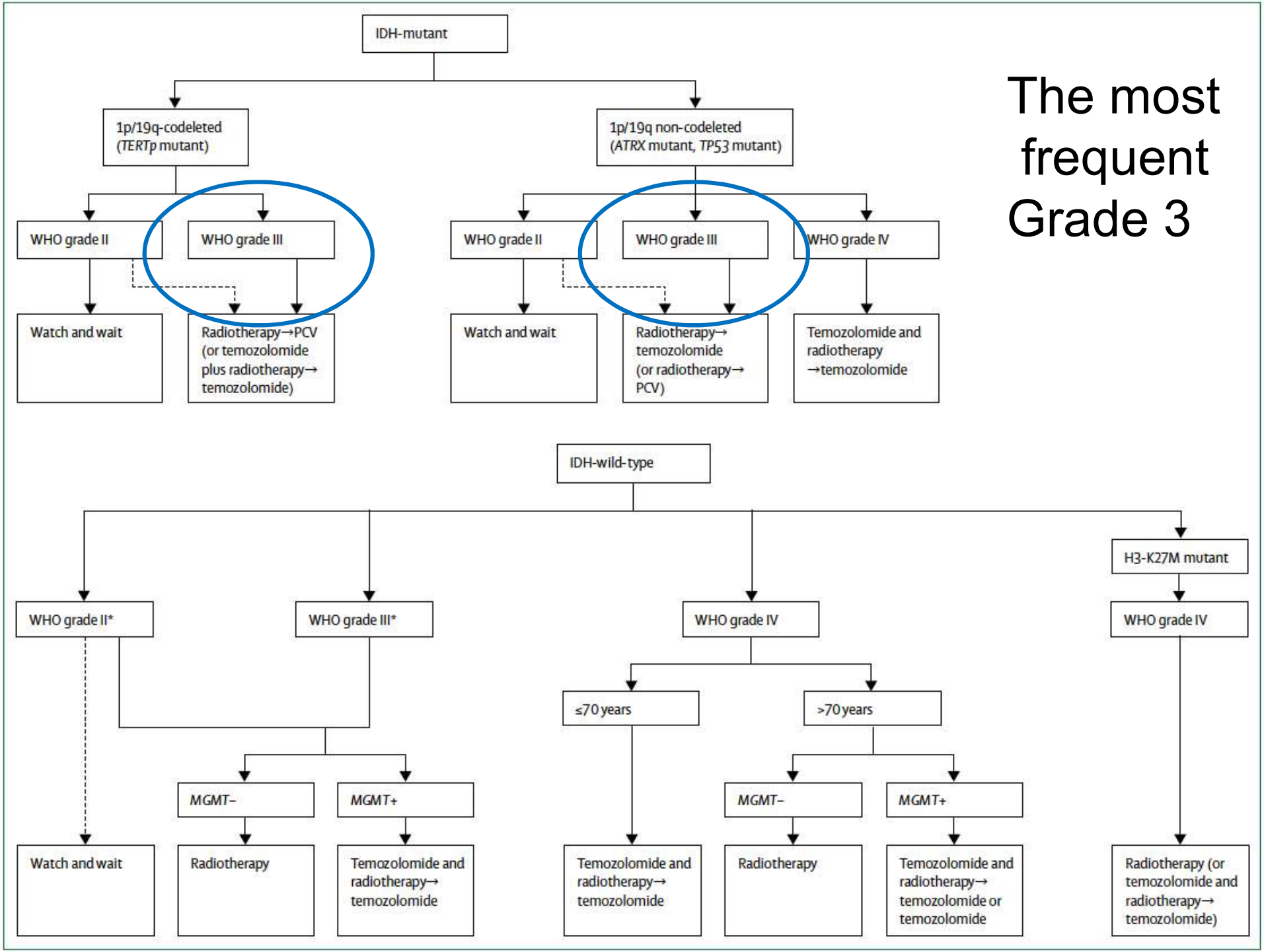
Histology: Oligodendroglioma WHO III, 1p/19q co-deletion



June 2007

Surgery

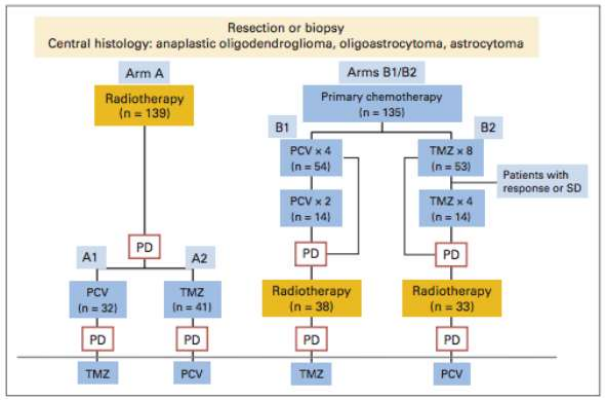
July-August 2007

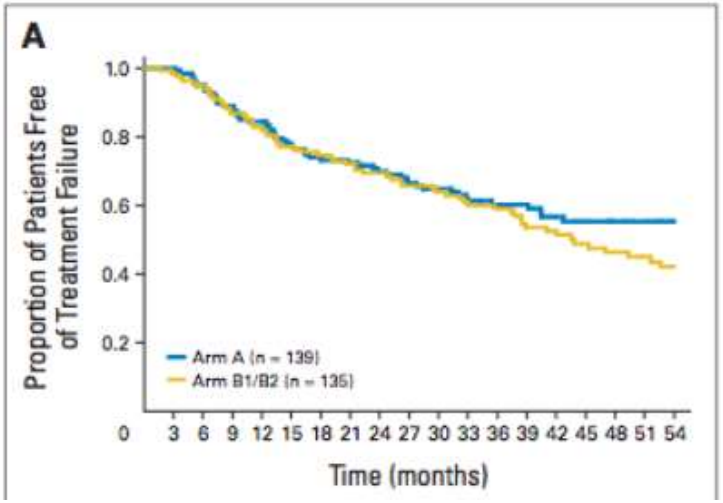


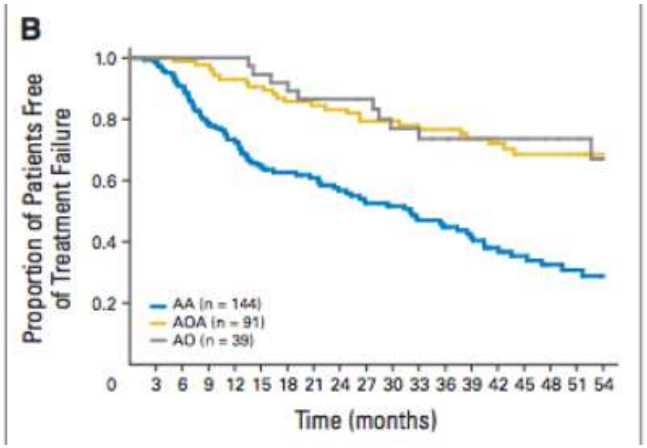
The most frequent Grade 3

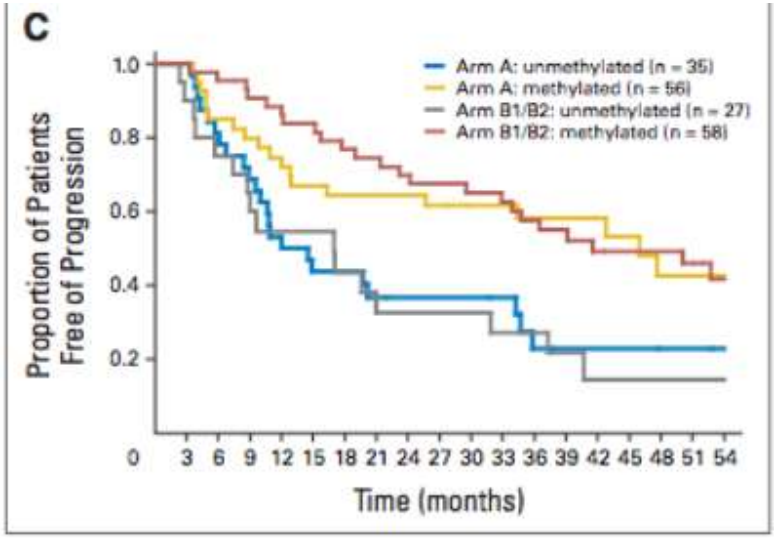
M. Weller, et al. The Lancet Oncol. Published online May 5, 2017

NOA-4 trial









- Equal response to RT or chemotherapy (PCV or TMZ) as single modality
- Better prognosis for patients showing oligodendroglial component (1p/19q co-deletion) and MGMT methylation[1]
- A retrospective analysis of the same trial revealed that the addition of chemotherapy was beneficial for IDH1/2 mutated, or IDH1/2 wild type and MGMT methylated[2]

1. *Wick, et al. JCO, 2009*
2. *Wick, et al. Neurol, 2013*

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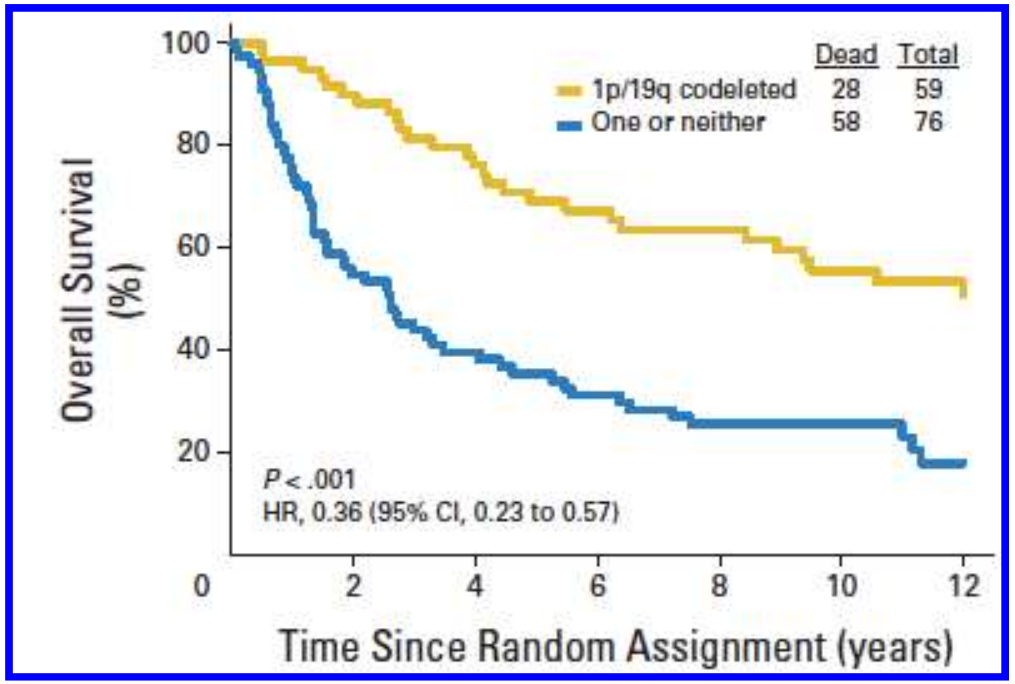
Modified from A. Chalmers

PCV - RT

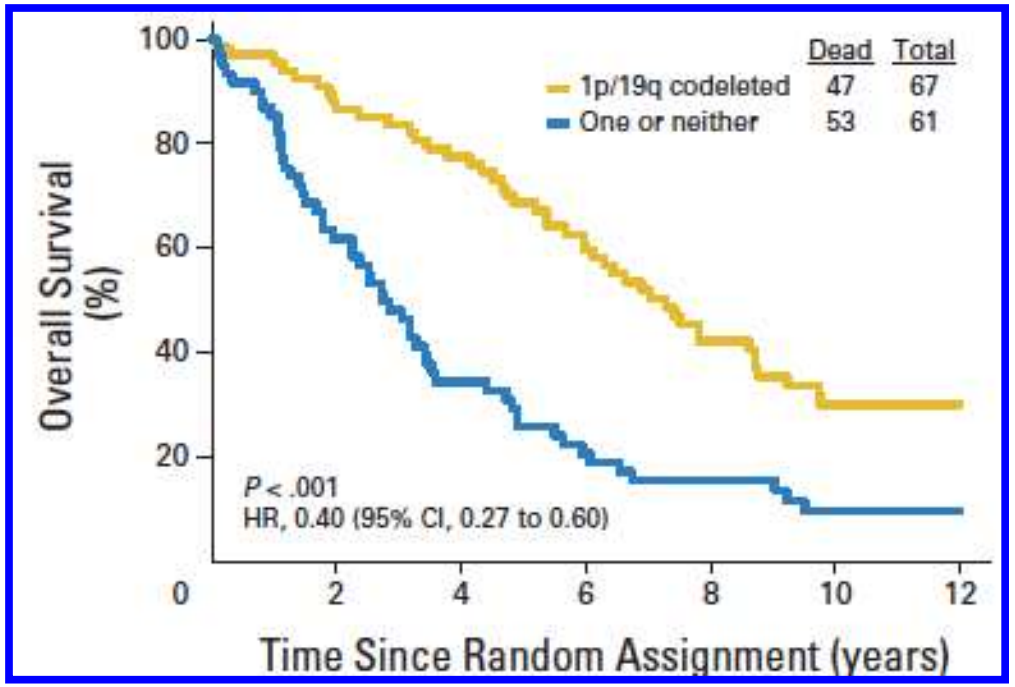


1p19q codeleted

1p19q intact

Grade 3 glioma

RT



1p19q codeleted

1p19q intact

Cairncross, J Clin Onc 2014

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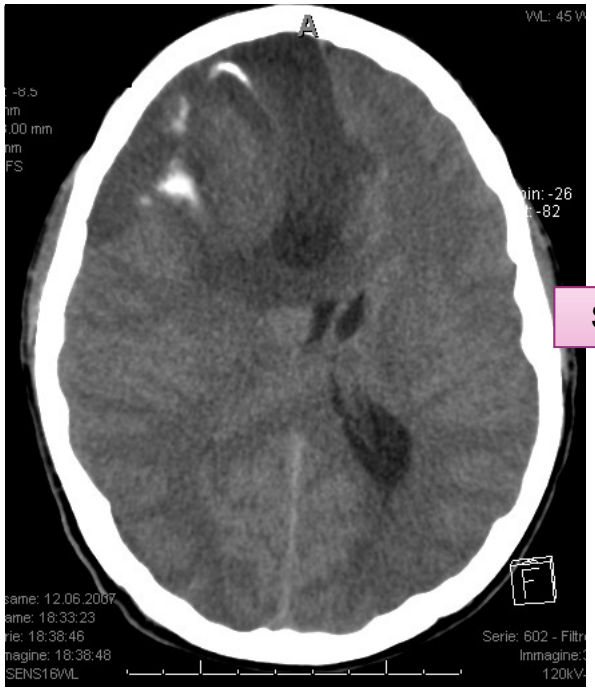
Clinical case 2

33 years old woman

Worsening Headache and vomiting

Histology: Oligodendroglioma WHO III, 1p/19q co-deletion



June 2007

Surgery

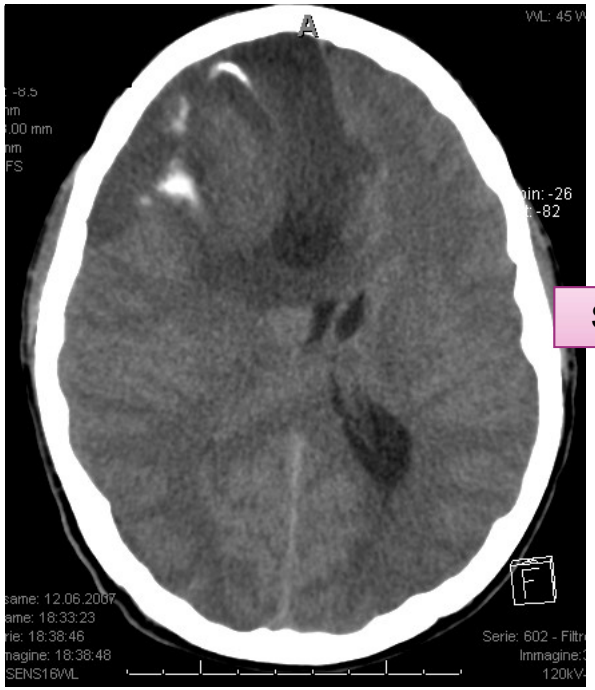
July-August 2007

Clinical case 2

33 years old woman

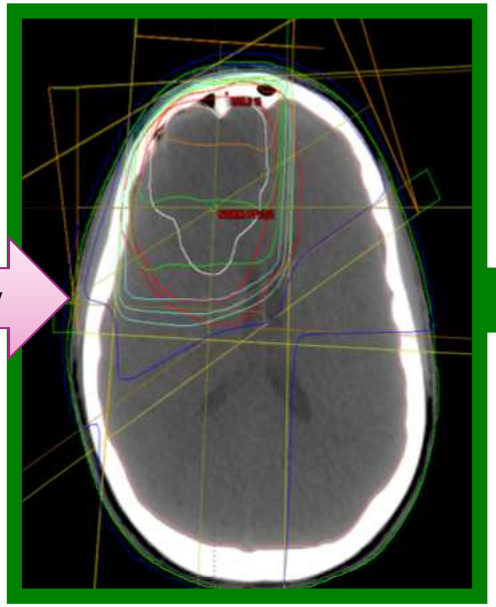
Worsening Headache and vomiting

Histology: Oligodendroglioma WHO III, 1p/19q co-deletion



June 2007

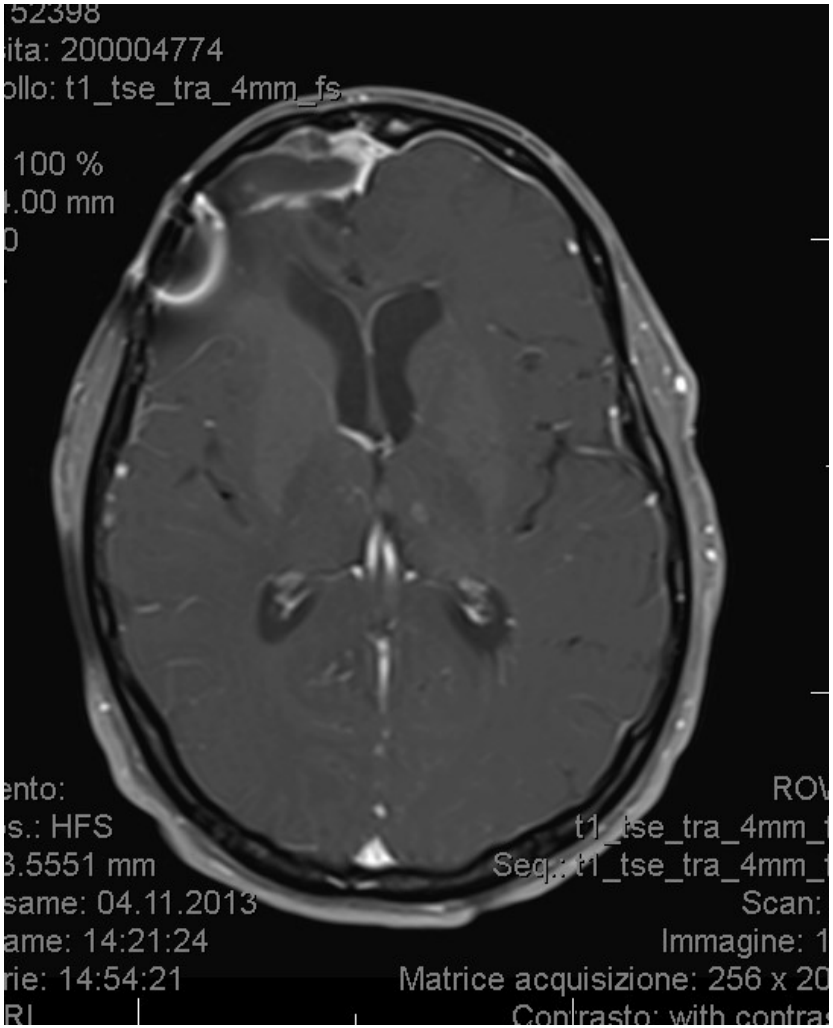
Surgery

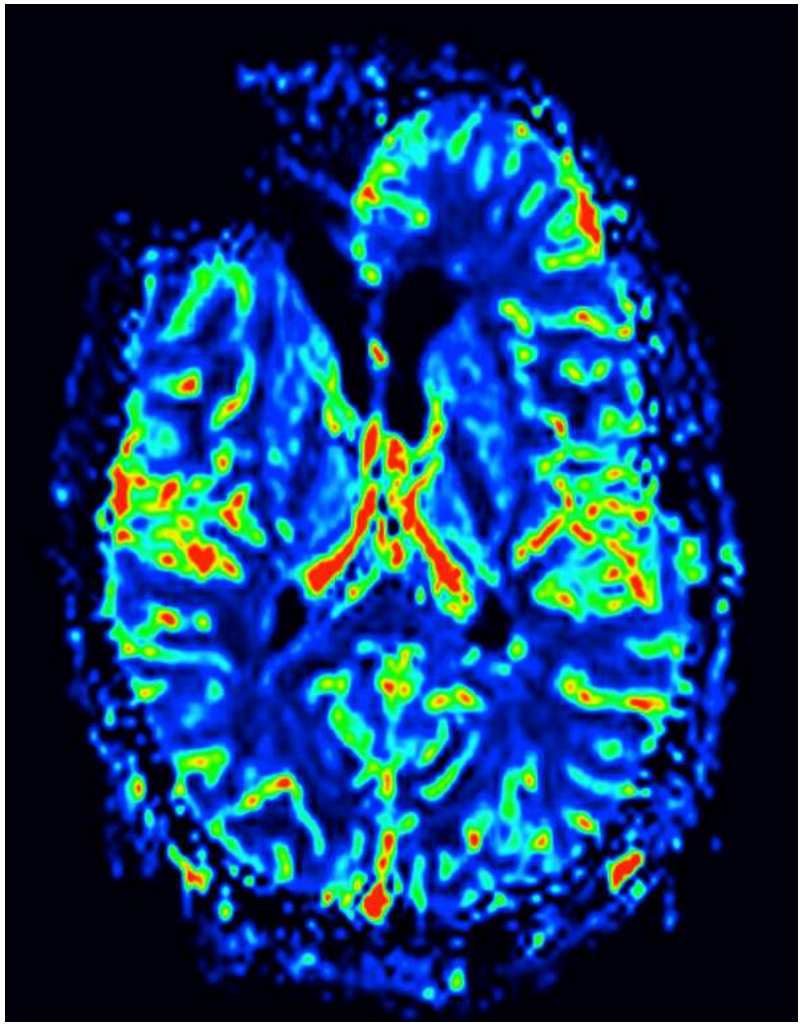


Concomitant and adjuvant TMZ

July-August 2007

Patient 2 outcome, 2017





What for non Codeleted?

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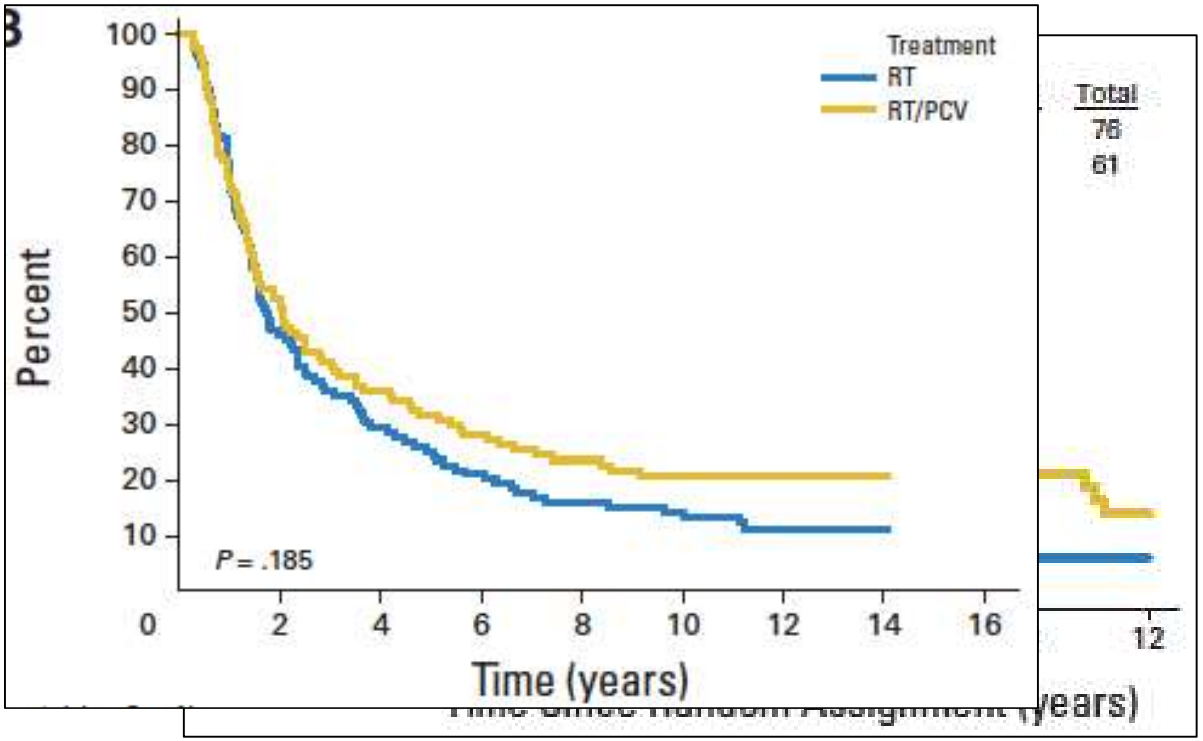

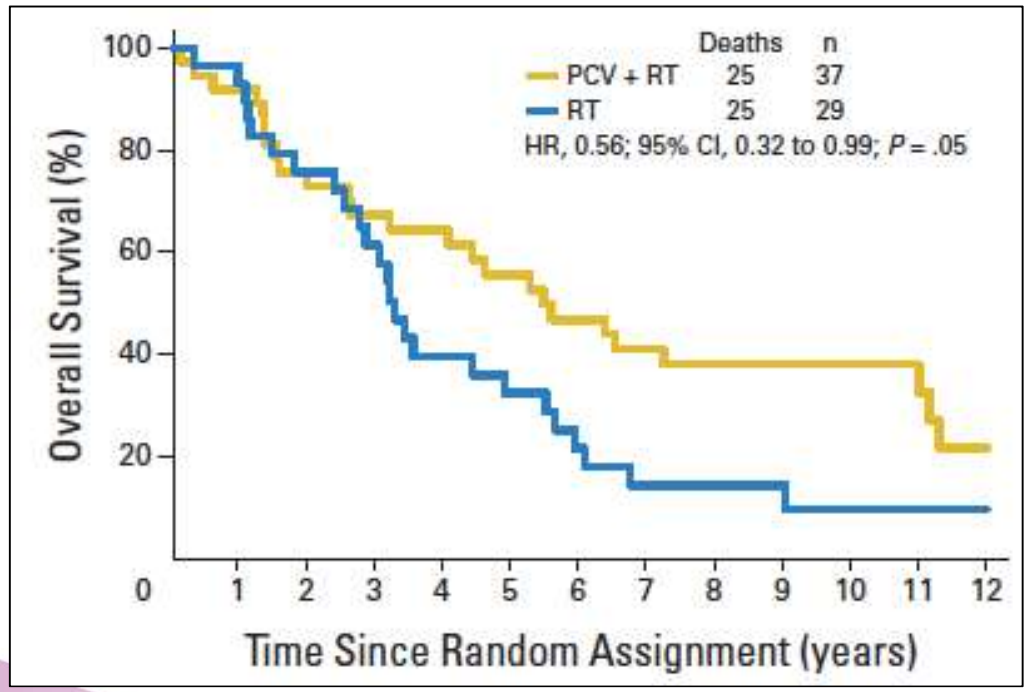

Courtesy of A. Chalmers

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

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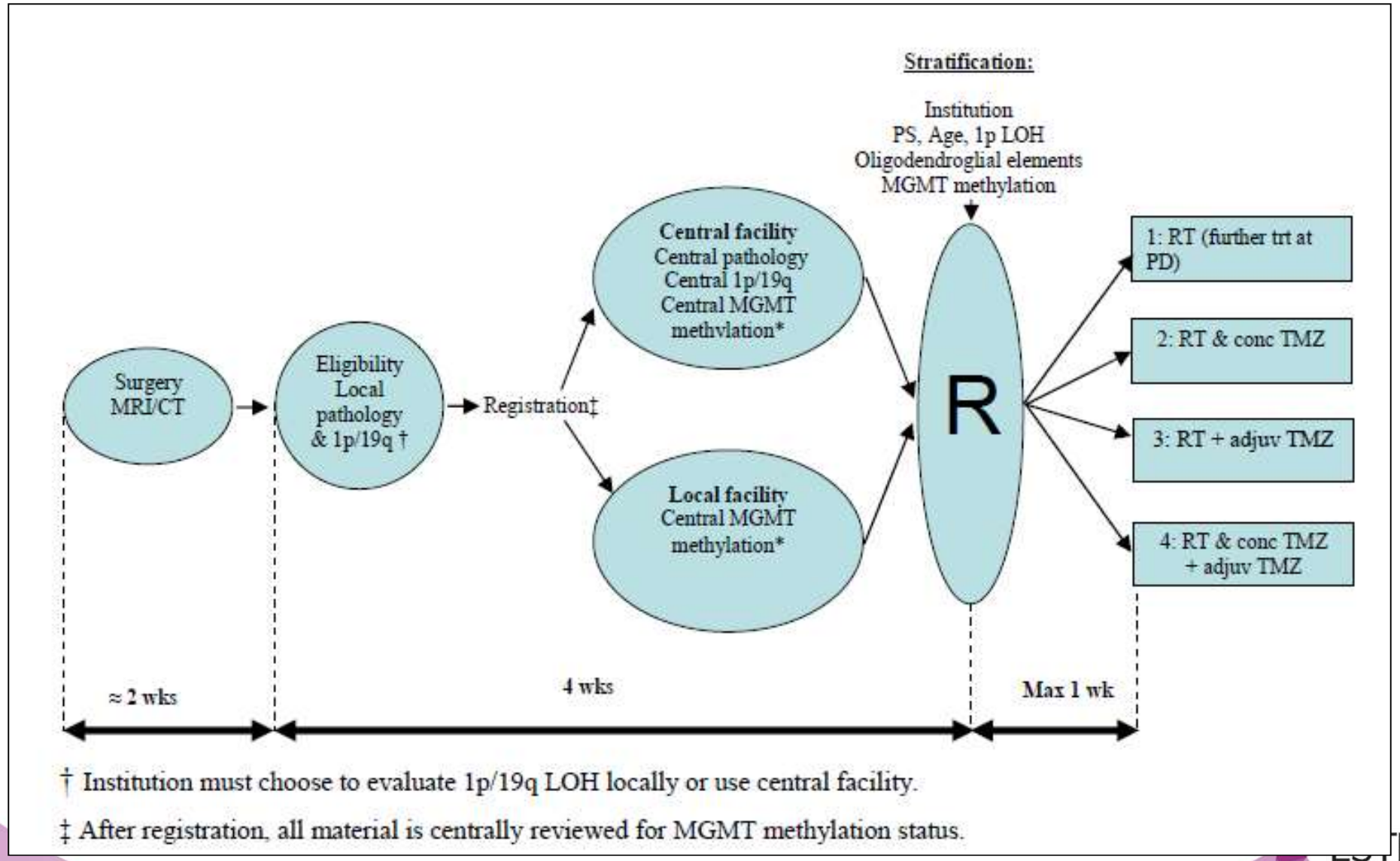
CATNON

Courtesy of A. Chalmers

grade 3 gliomas WITHOUT co-deletion of 1p19q



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Interim analysis is ready…

Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study

Martin J van den Bent, Brigitta Baumert, Sara C Erridge, Michael A Vogelbaum, Anna K Nowak, Marc Sanson, Alba Ariela Brandes, Paul M Clement, Jean Francais Baurain, Warren P Mason, Helen Wheeler, Olivier L Chinot, Sanjeev Gill, Matthew Griffin, David G Brachman, Walter Taal, Roberta Rudà, Michael Weller, Catherine McBain, Jaap Reijneveld, Roelien H Enting, Damien C Weber, Thierry Lesimple, Susan Clenton, Anja Gijtenbeek, Sarah Pascoe, Ulrich Herrlinger, Peter Hau, Frederic Dhermain, Irene van Heuvel, Roger Stupp, Ken Aldape, Robert B Jenkins, Hendrikus Jan Dubbink, Winand N M Dinjens, Pieter Wesseling, Sarah Nuyens, Vassilis Golfinopoulos, Thierry Gorlia, Wolfgang Wick, Johan M Kros

Summary

Background The role of temozolomide chemotherapy in newly diagnosed 1p/19q non-co-deleted anaplastic gliomas, which are associated with lower sensitivity to chemotherapy and worse prognosis than 1p/19q co-deleted tumours, is unclear. We assessed the use of radiotherapy with concurrent and adjuvant temozolomide in adults with non-co-deleted anaplastic gliomas.

Lancet 2017; 390: 1645–53
Published Online
August 8, 2017
http://dx.doi.org/10.1016/S0140-6736(17)31442-3

	Overall survival			Progression-free survival		
	Number of deaths	Median (95% CI) survival (months)	5-year survival (95% CI)	Number of patients with disease progression	Median (95% CI) survival (months)	5-year survival (95% CI)
Received adjuvant temozolomide	92	Not reached	55·9% (47·2–63·8)	144	42·8 (28·6–60·6)	43·1% (35·0–50·9)
Did not receive adjuvant temozolomide	129	41·1 (36·6–60·7)	44·1% (36·3–51·6)	200	19·0 (14·4–24·6)	24·3% (17·7–31·6)

Table 3: **Median and 5-year overall and progression-free survival**

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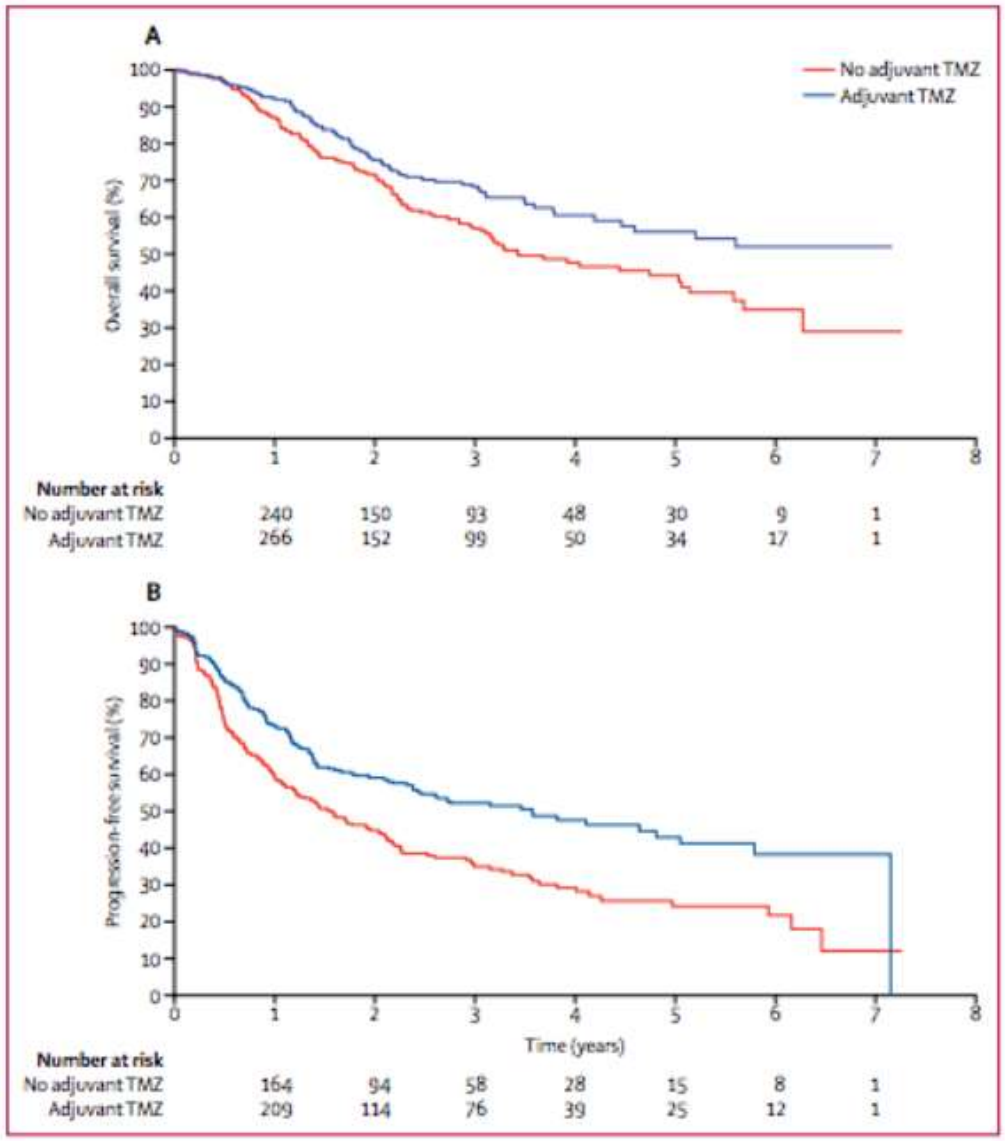
12 cycles of adjuvant TMZ are better



Van Den Bent, et al, The Lancet 2017

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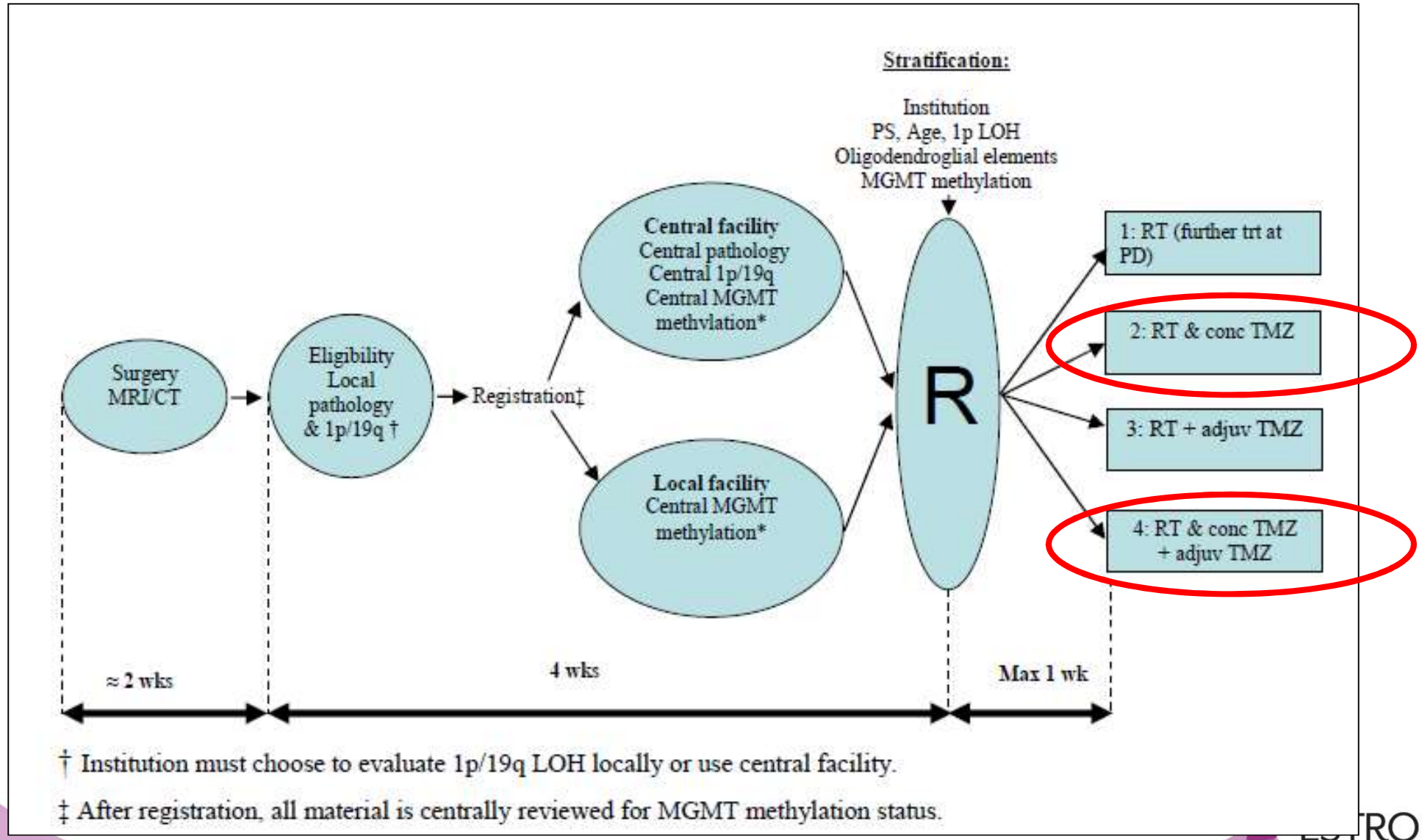
CATNON

grade 3 gliomas WITHOUT co-deletion of 1p19q



Courtesy of A. Chalmers

Summary for Anaplastic Astrocytoma

- Upfront chemotherapy with PCV resulted in improved survival in patients treated for oligodendroglioma and oligoastrocytoma, with 1p/19q co-deletion[1,2]
- Interim results from EORTC 26053-22054 demonstrated a signigicant survival benefit in patients with non co-deleted anaplastic astrocytoma adding adjuvant TMZ to RT[3]
- The question of concomitant RT/TMZ remains open until the final analysis of the CATNON trial
- Repeated surgery and Re-irradiation is still an option for recurrent disease in combination with systemic therapy (CHT and BEV)

1. *Van den Bent, et al. JCO, 2013*
2. *Cairncross, et al. JCO, 2014*
3. *Van den Bent, et al. The Lancet, 2017*

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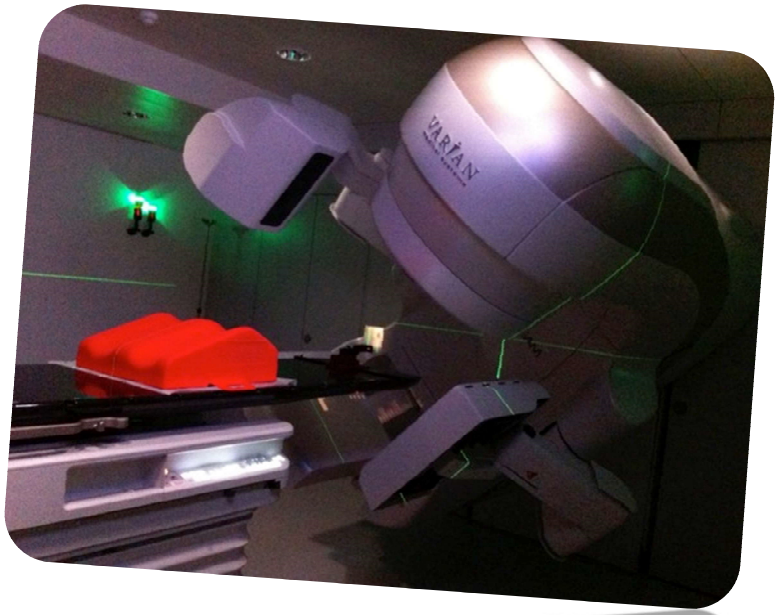
10 COMMANDMENTS LIST
SO4J.com
SO4J-TV & VIDEO

Radiotherapy Bible for CNS gliomas

I. You won't have belief other than ICRU
II. GO for Niyazi, Brada, Chalmers & friends for guidelines
III. Adapt the dose according to histology
IV. OAR: never forget GP yesterday (QUANTEC)
V. Best conformity, IMRT, VMAT
VI. Don't forget to properly verify (IGRT)
VII. Combine RT with proper systemic therapy for high risk (St. Patrick's rule)
VIII. Don't underestimate molecular biology
IX. Retreat needed according to OAR tolerance
X. Stay updated and take part to clinical research



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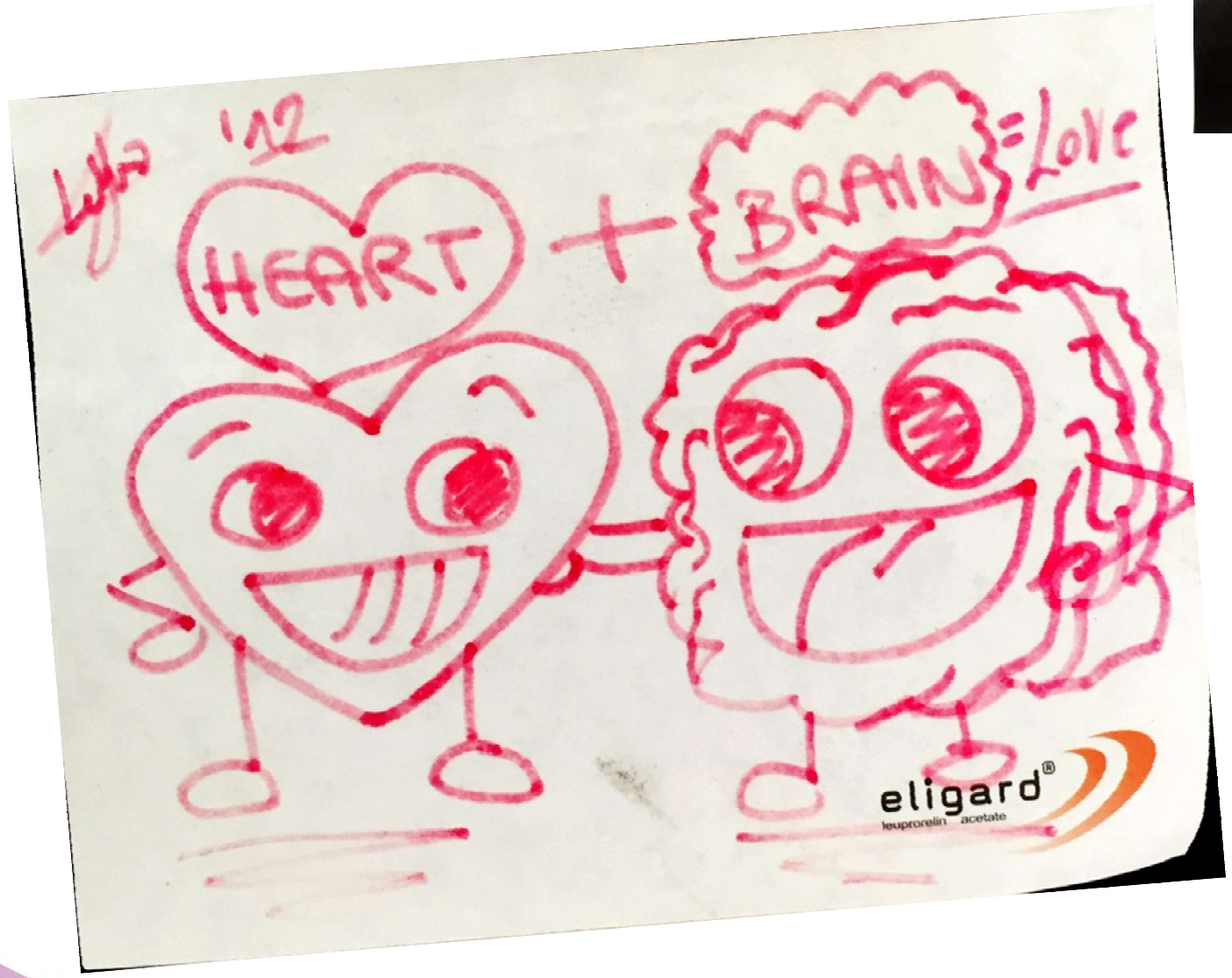
Conclusions

- Brain gliomas still represent a major challenge due to the complexity of the medical management and impact on patients' life
- The use of surgery, radiotherapy and chemotherapy need to be tailored according to histology and molecular biology as well as the clinical situation
- Trials are ongoing in the attempt to answer relevant open questions, as are the correct sequence/combination of chemo-radiotherapy in some particular tumor subtypes and the role of biologic targeted agents

What to do?



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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

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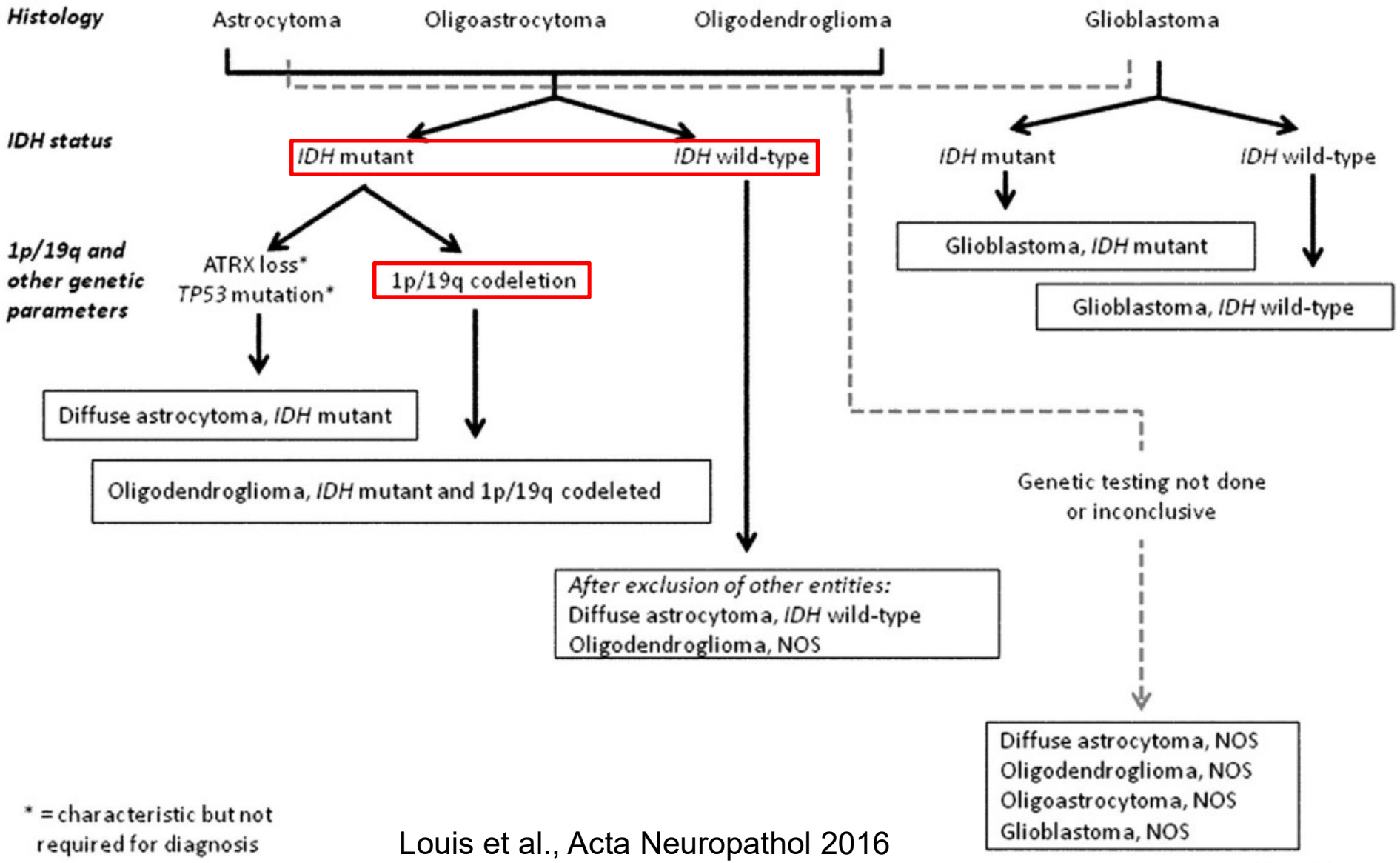
1p/19q in the WHO classification

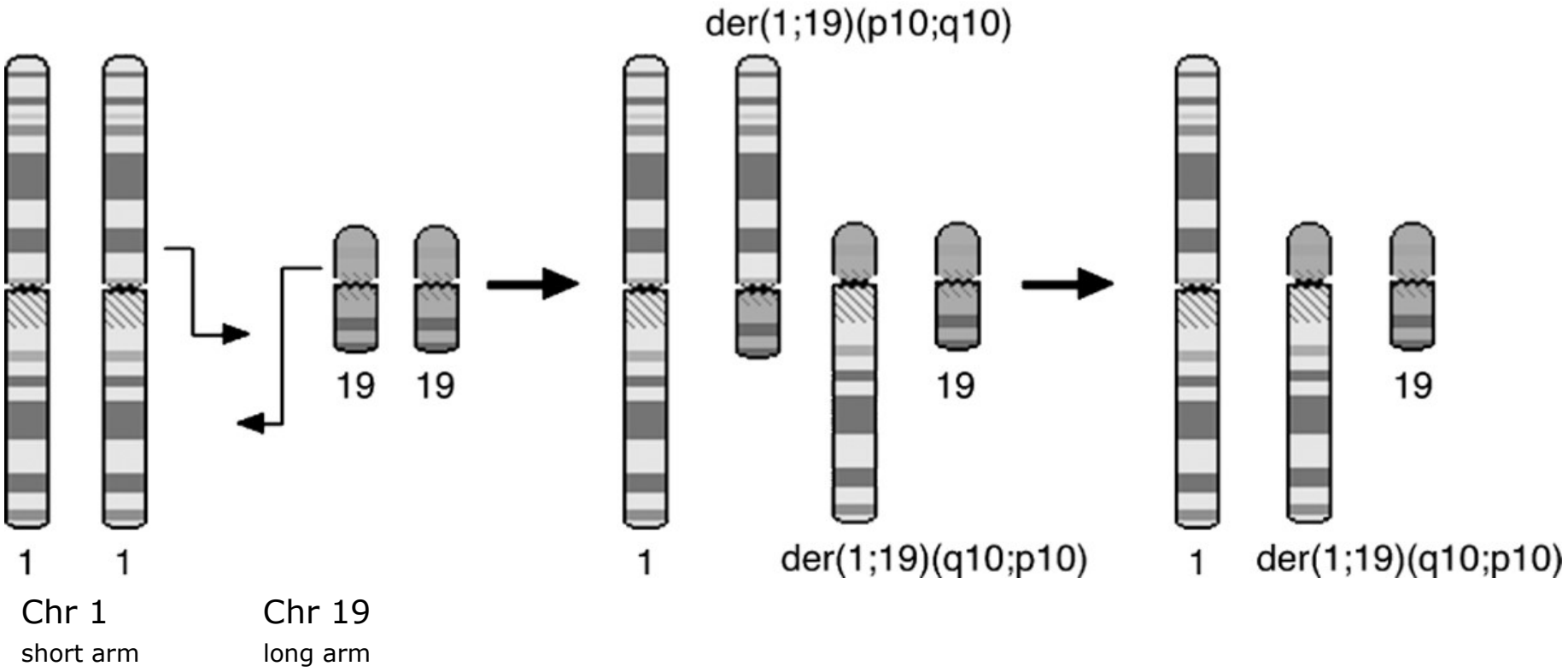


* = characteristic but not required for diagnosis

Louis et al., Acta Neuropathol 2016

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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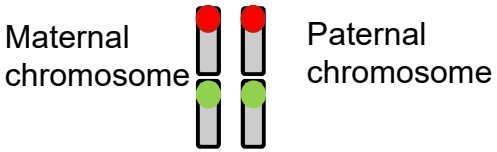
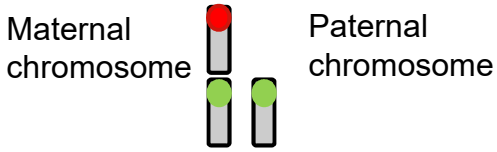
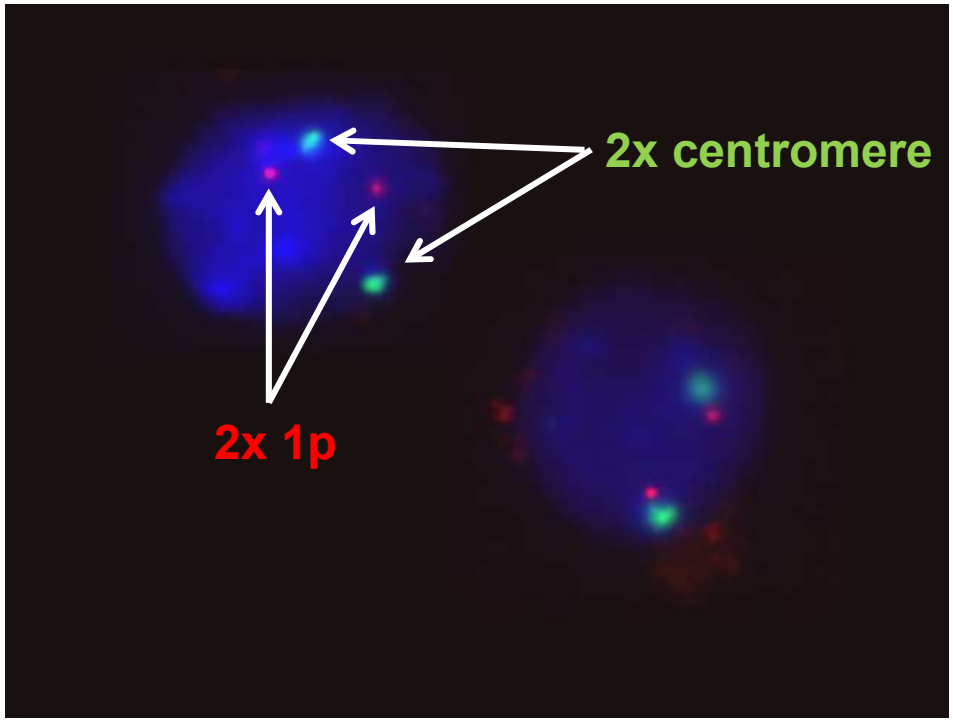
FISH (fluorescent in situ hybridization)

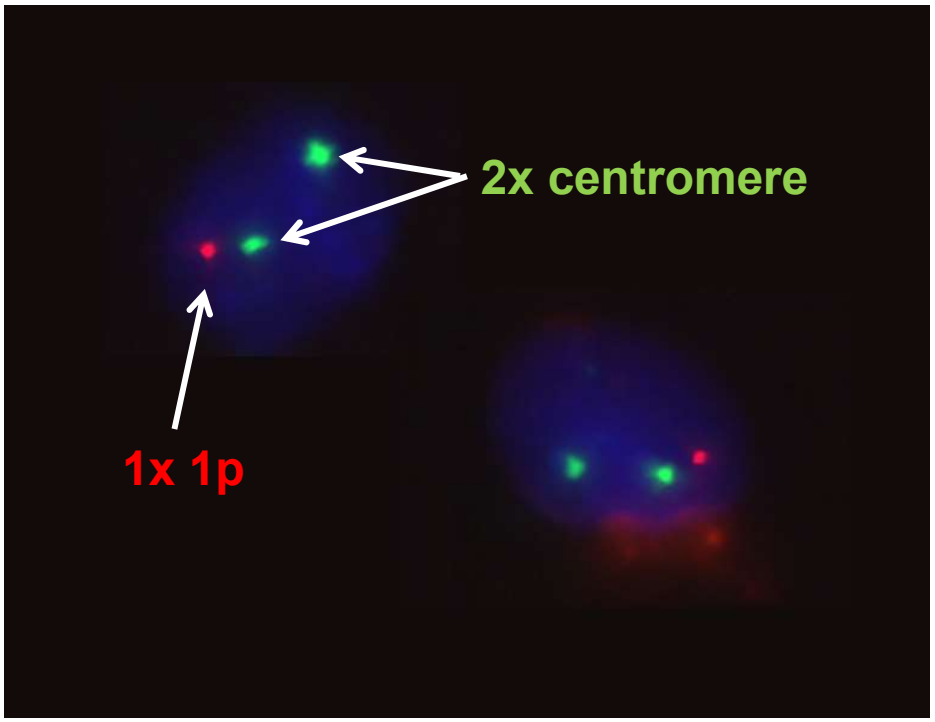




1p non-deleted



1p deletion



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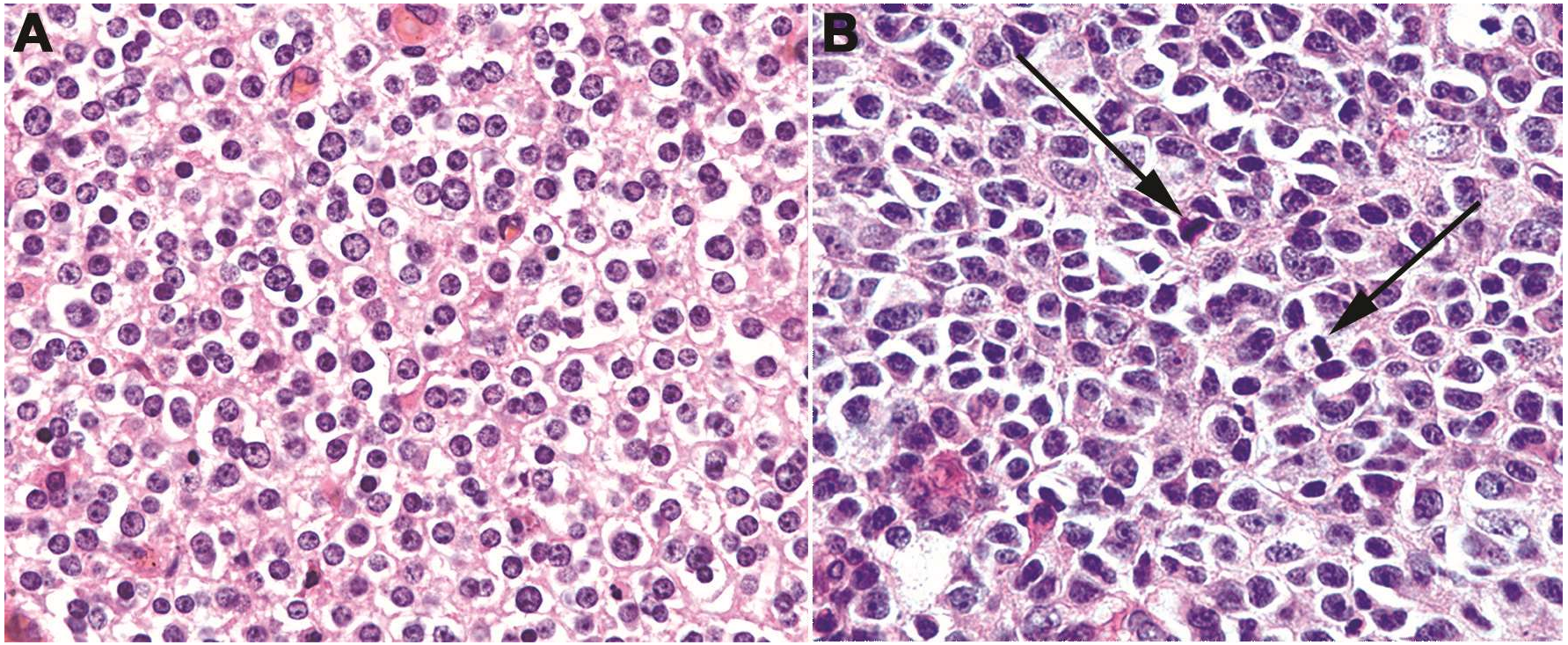
Where do we find 1p/19q co-deletion?



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

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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

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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

PCV

- Established in 1980s
- 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

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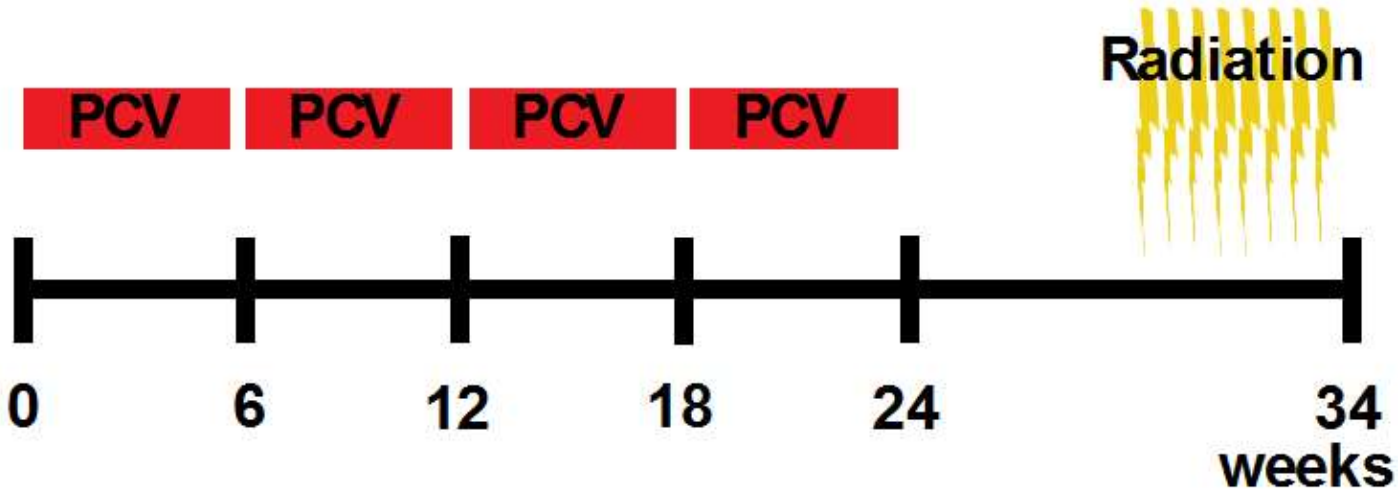
RTOG 9402



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

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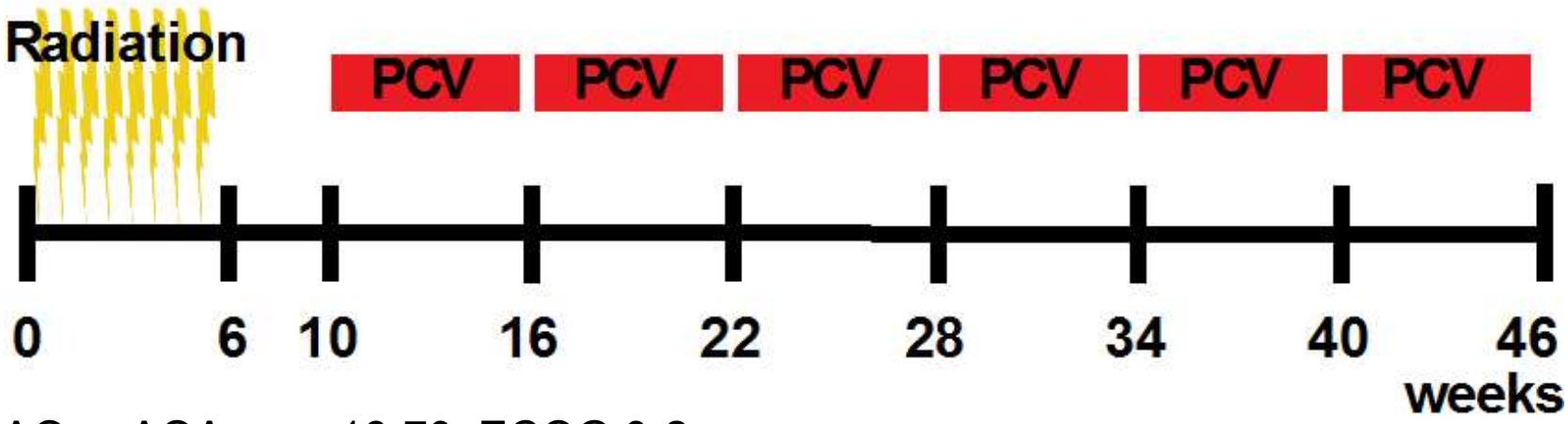
EORTC 26951



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

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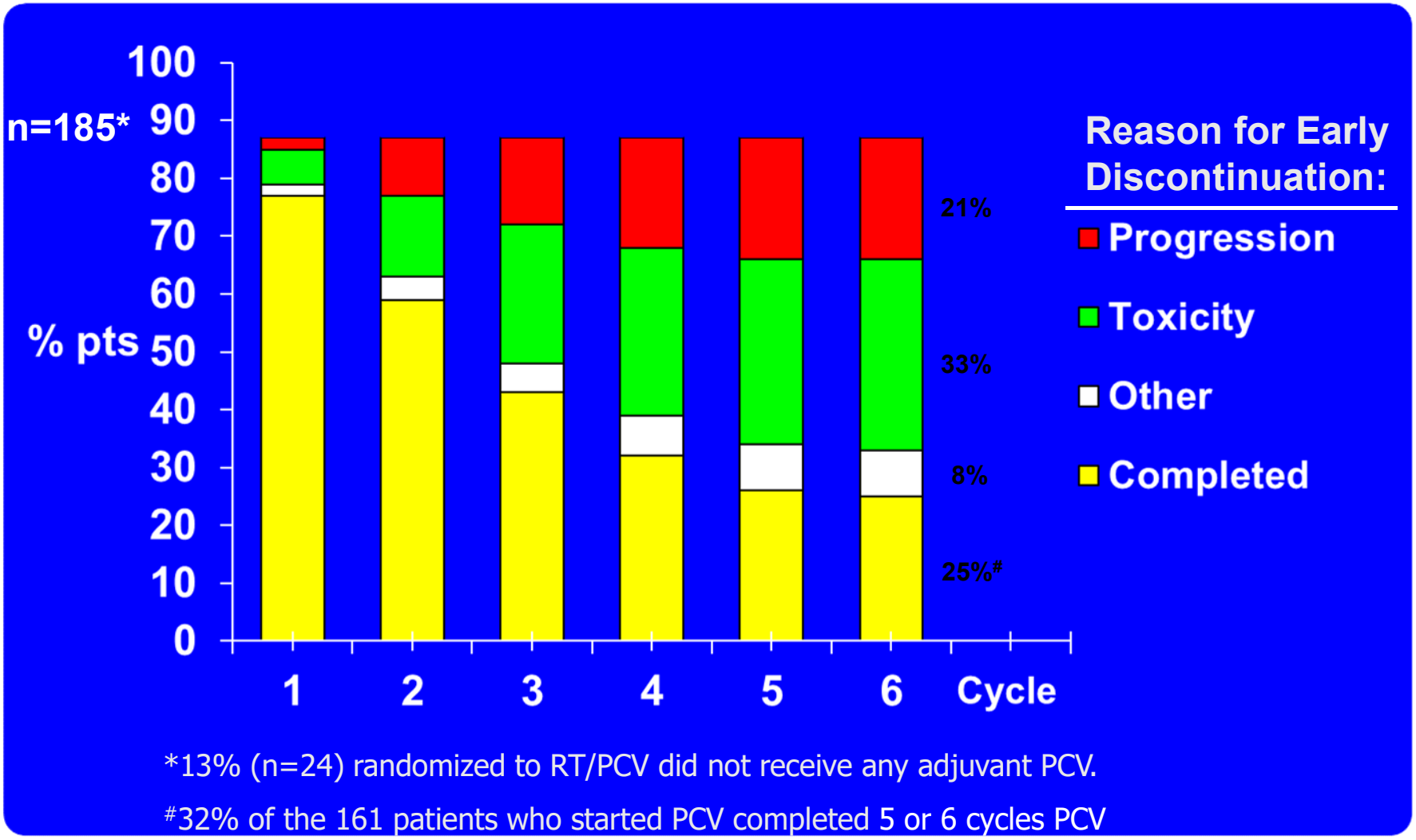
PCV toxicities EORTC 26951 vs RTOG 9402

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 treatment stop	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

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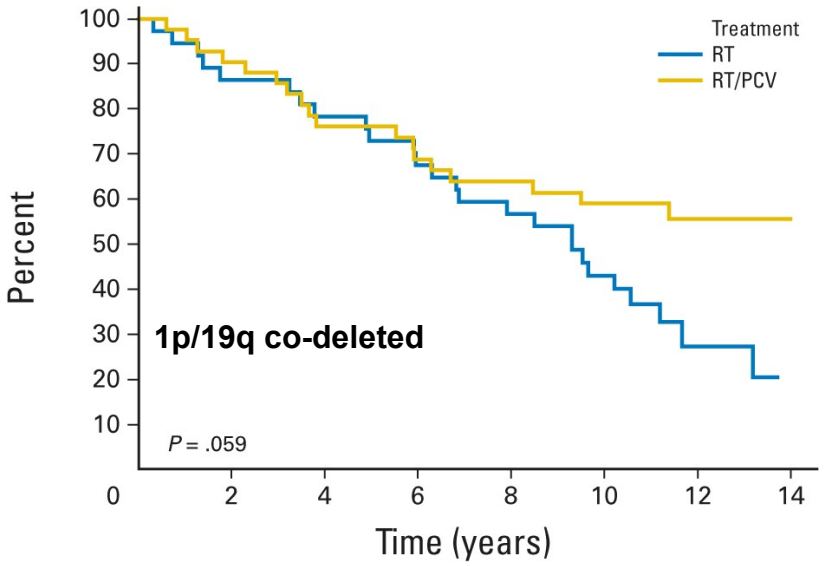
OS in patients with 1p/19q co-deleted tumors

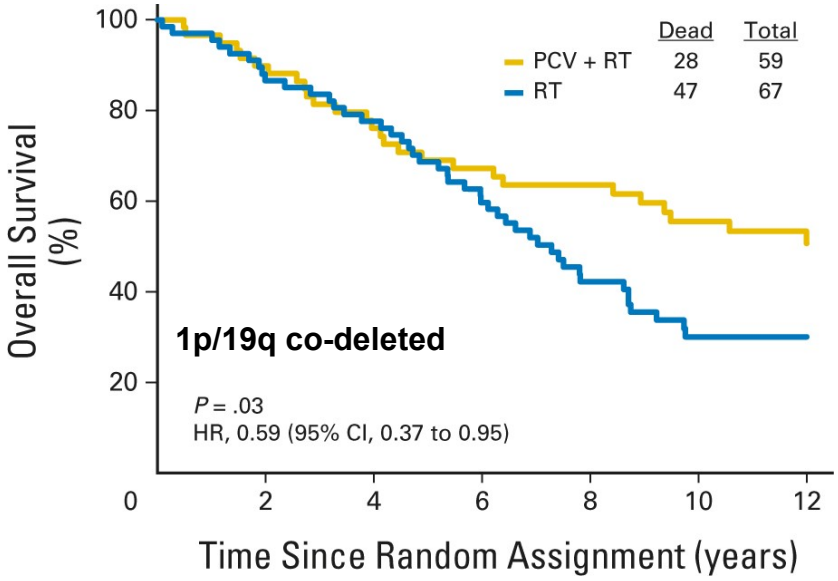
Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

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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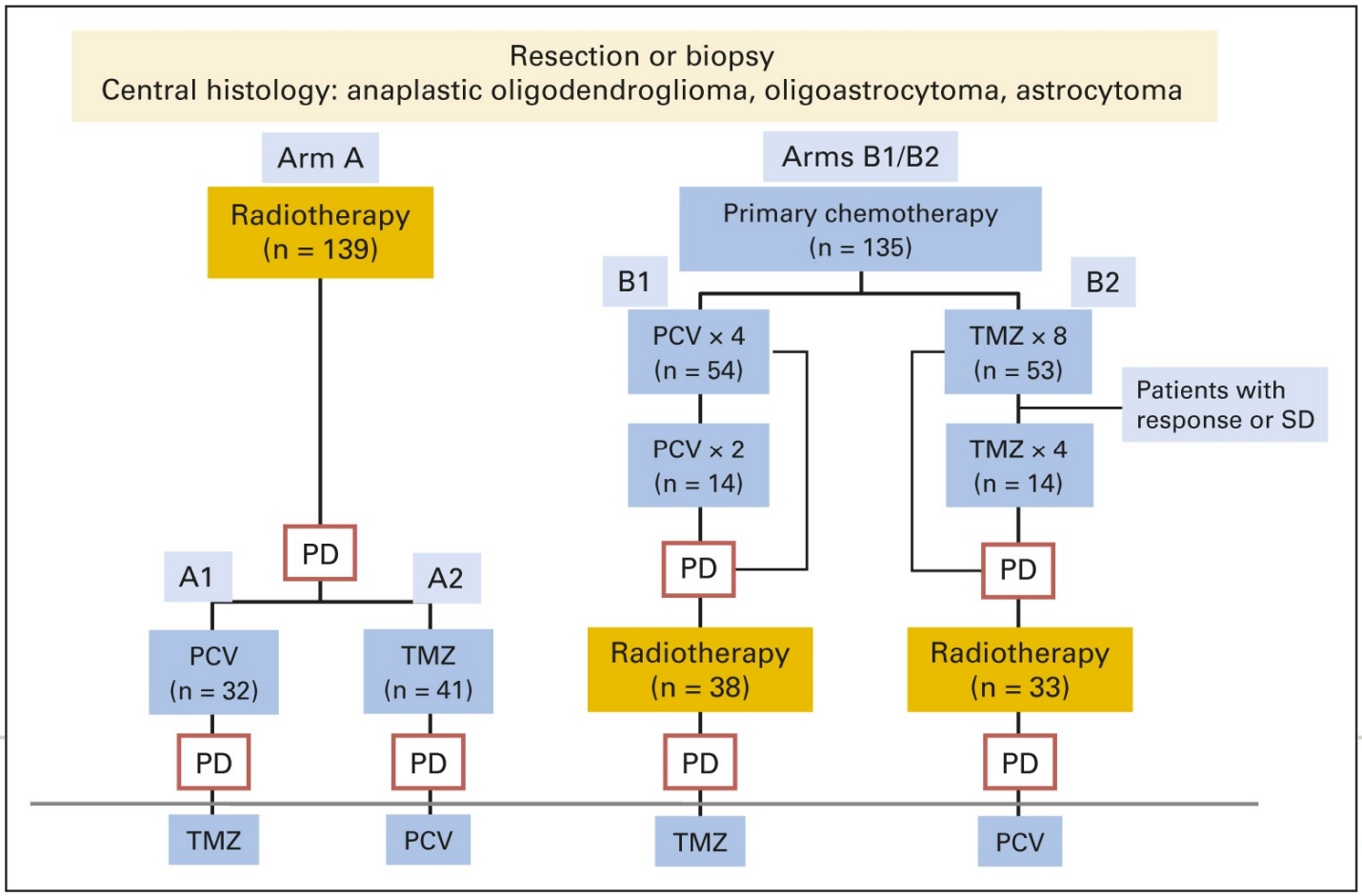
Can we avoid RT and use chemotherapy alone?

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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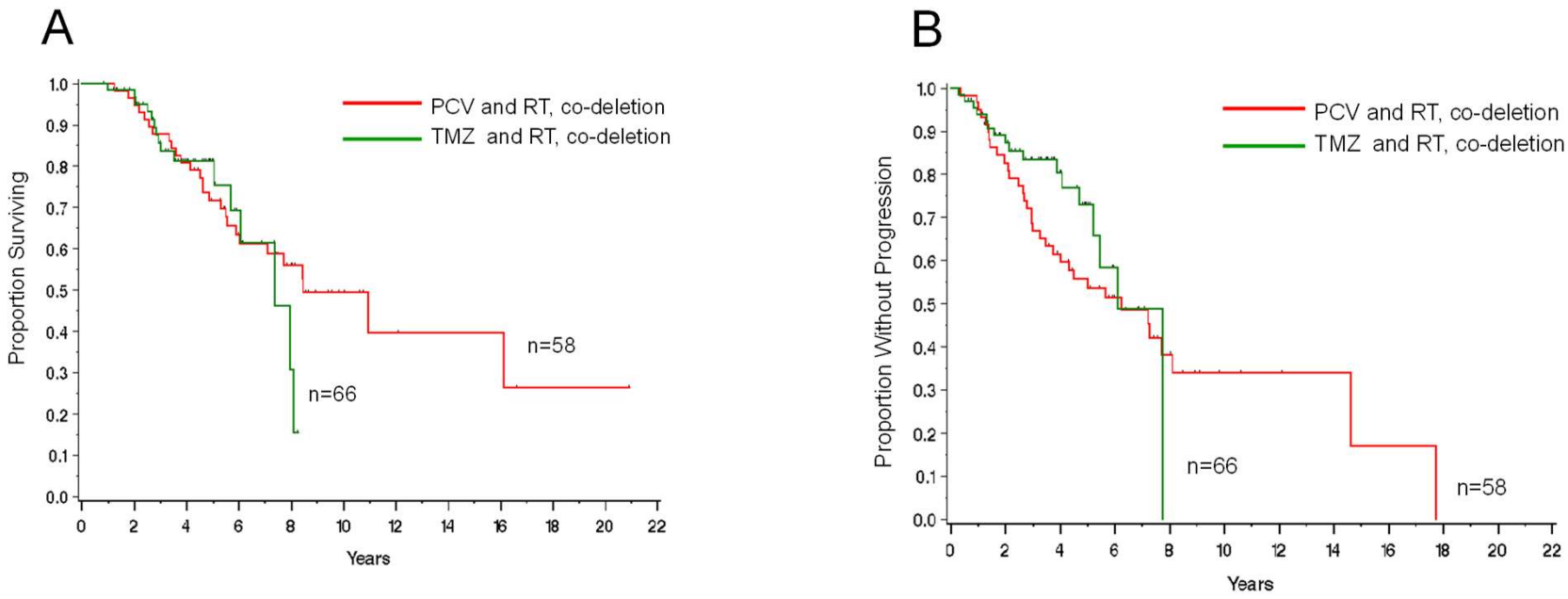
PCV or TMZ?



Kaplan-Meier estimates of overall survival (A) and time to progression (B) by treatment (PCV and RT or TMZ and RT) and deletion status.

Lassmann et al. International retrospective study of over 1000 adults with anaplastic oligodendroglial tumors. Neurooncol 2011.

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1p/19q non co-deleted

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

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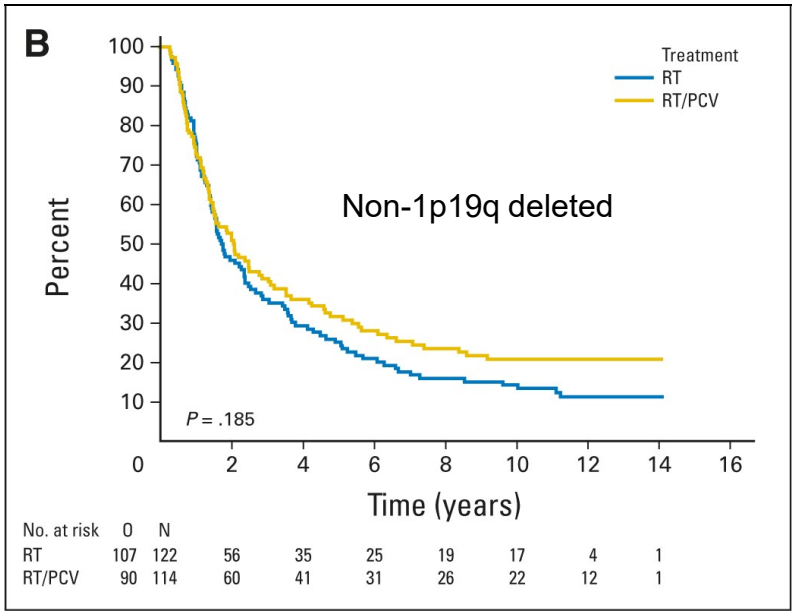
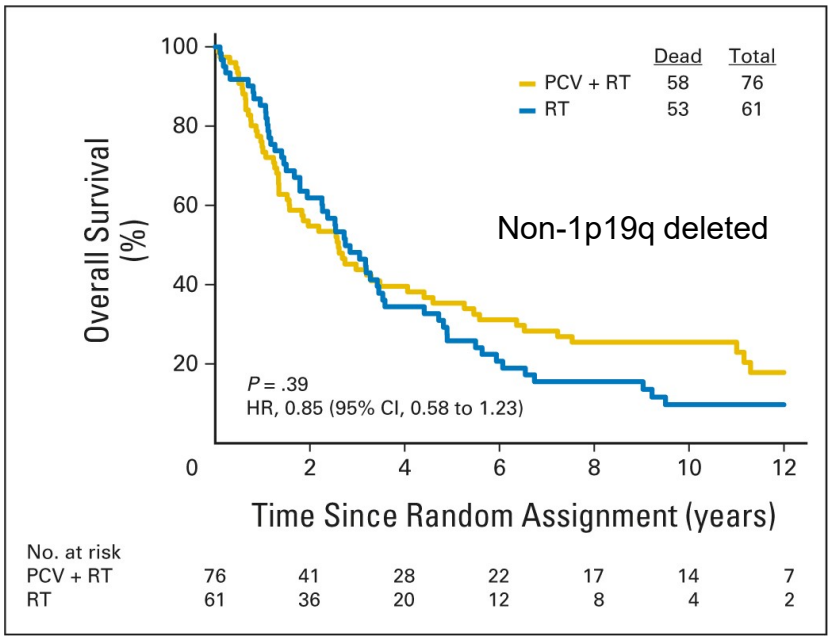


Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402

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



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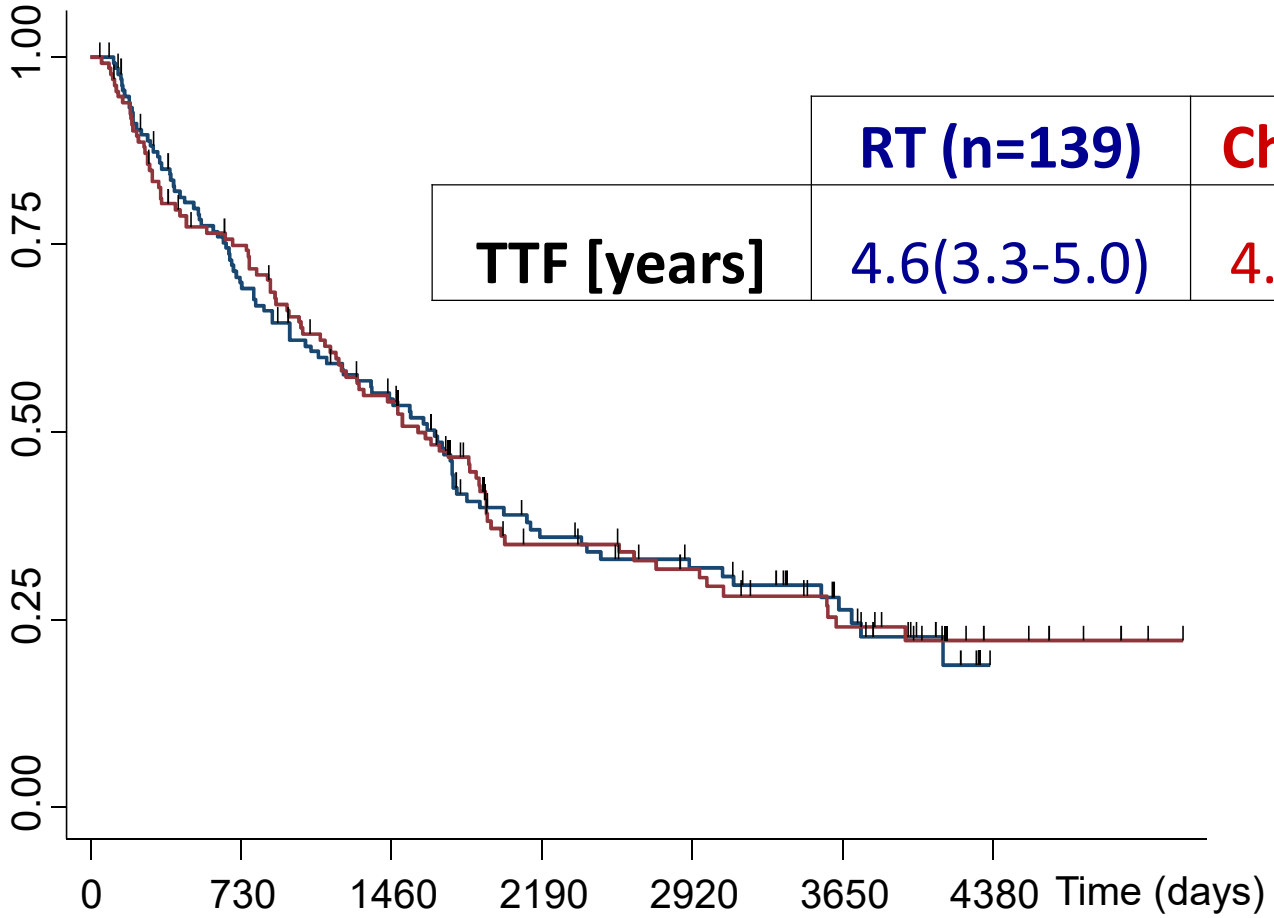
Time to treatment failure – by therapy



	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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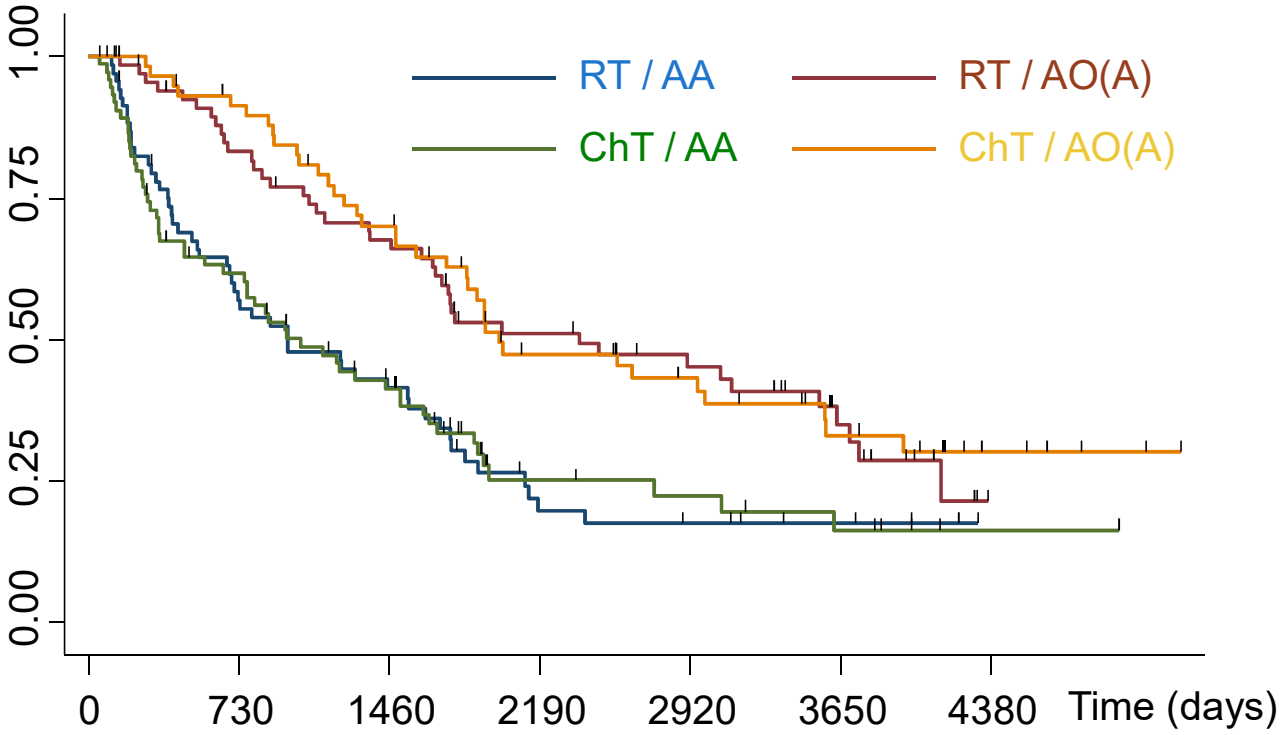
Time to treatment failure – by therapy/histology



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

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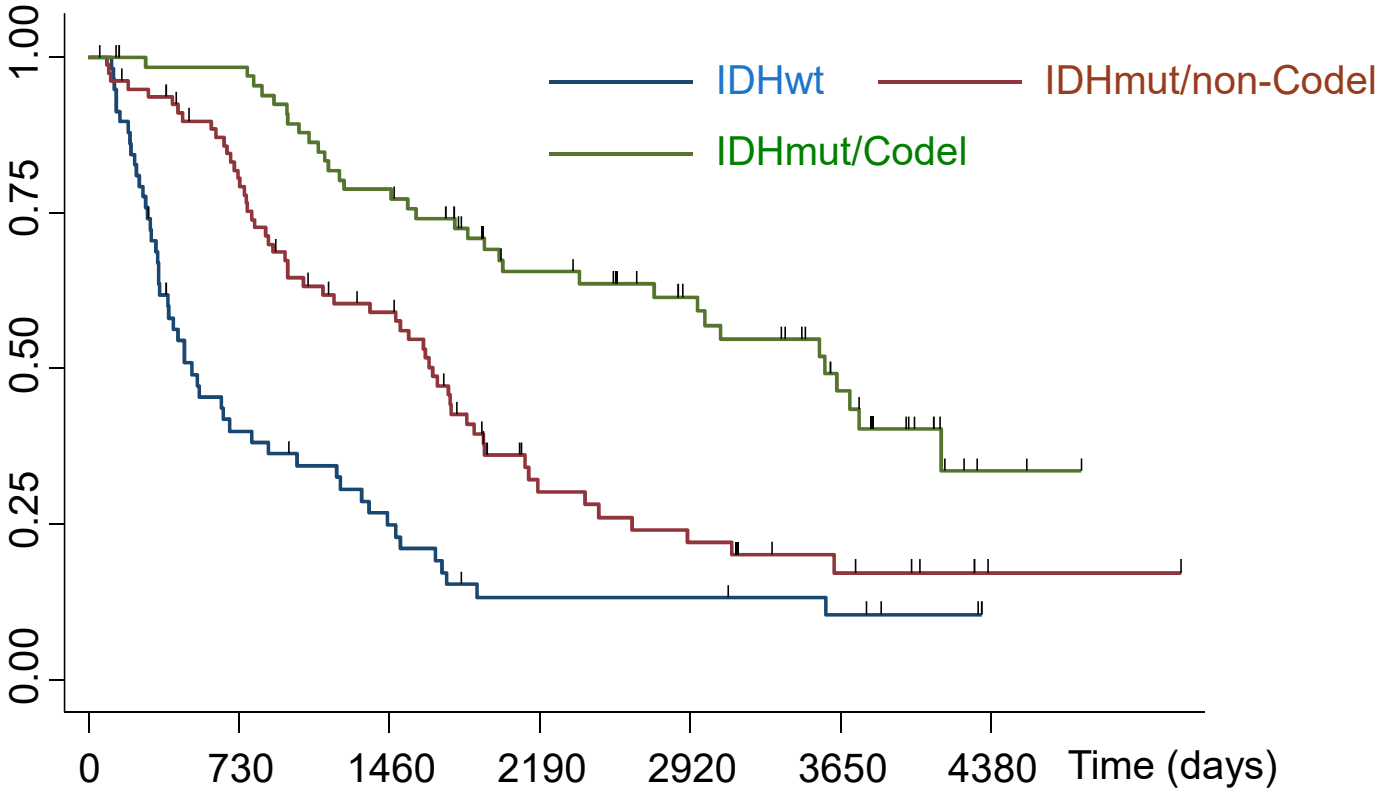
Time to treatment failure – by molecular diagnosis



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

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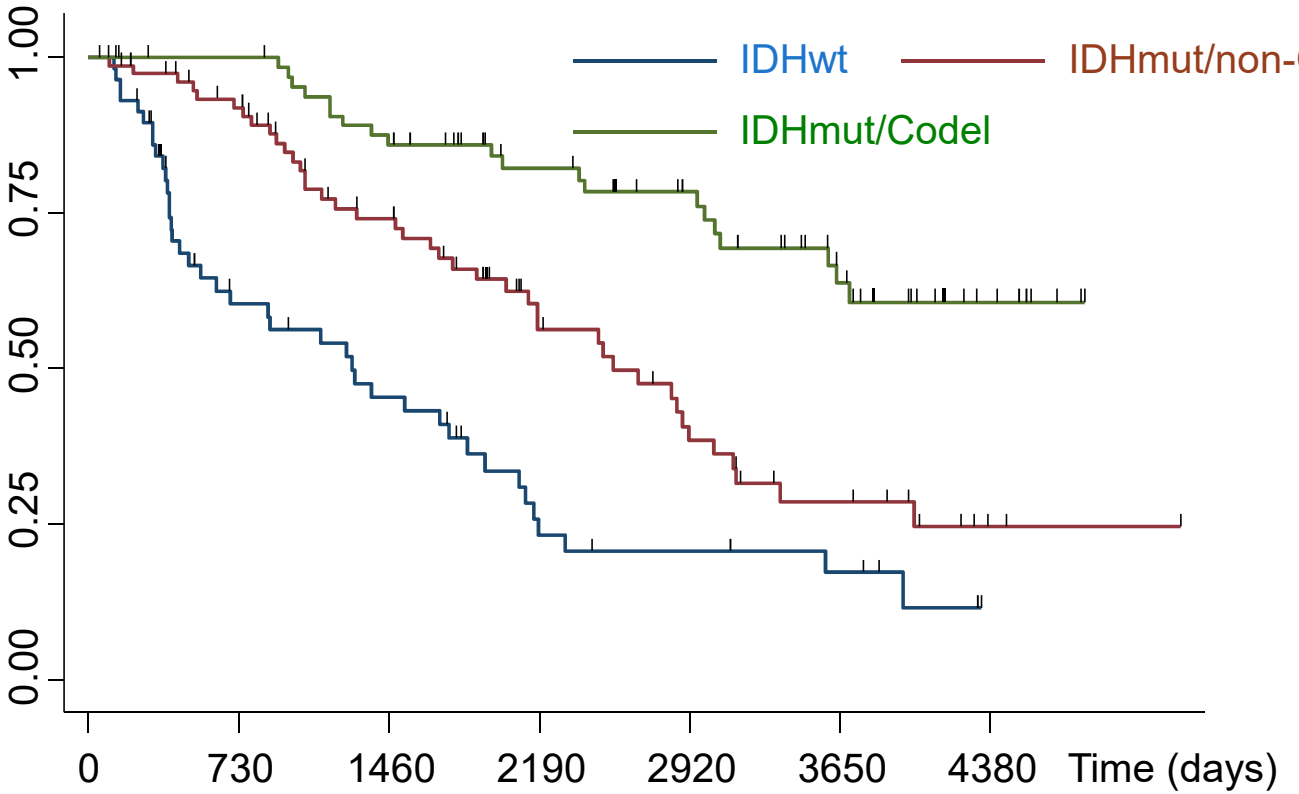
Overall survival – by molecular diagnosis



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

Wick et al., Neuro Oncol 2016

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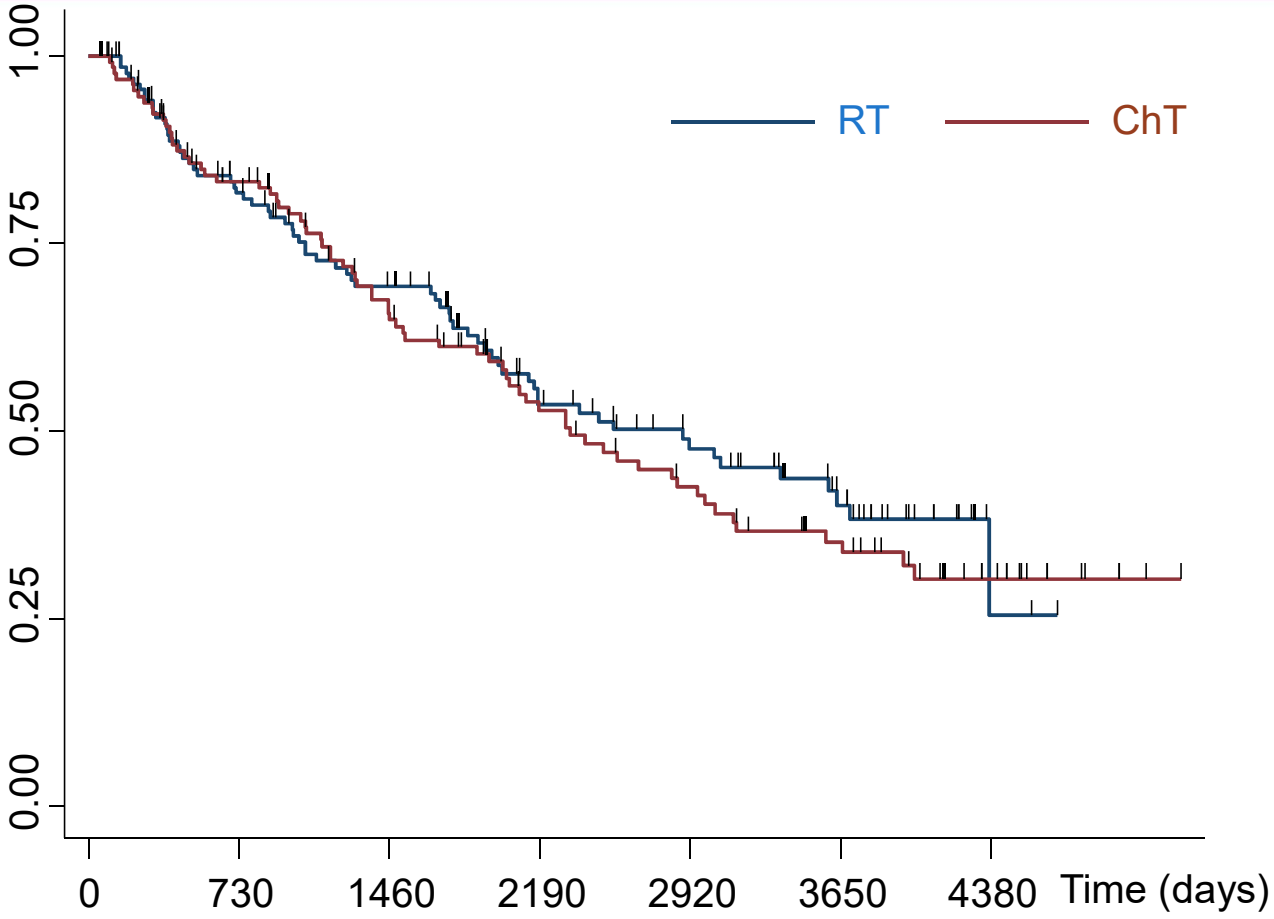
Overall survival – by therapy



Number at risk

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

Wick et al., Neuro Oncol 2016

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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)

Wick et al., Neuro Oncol 2016

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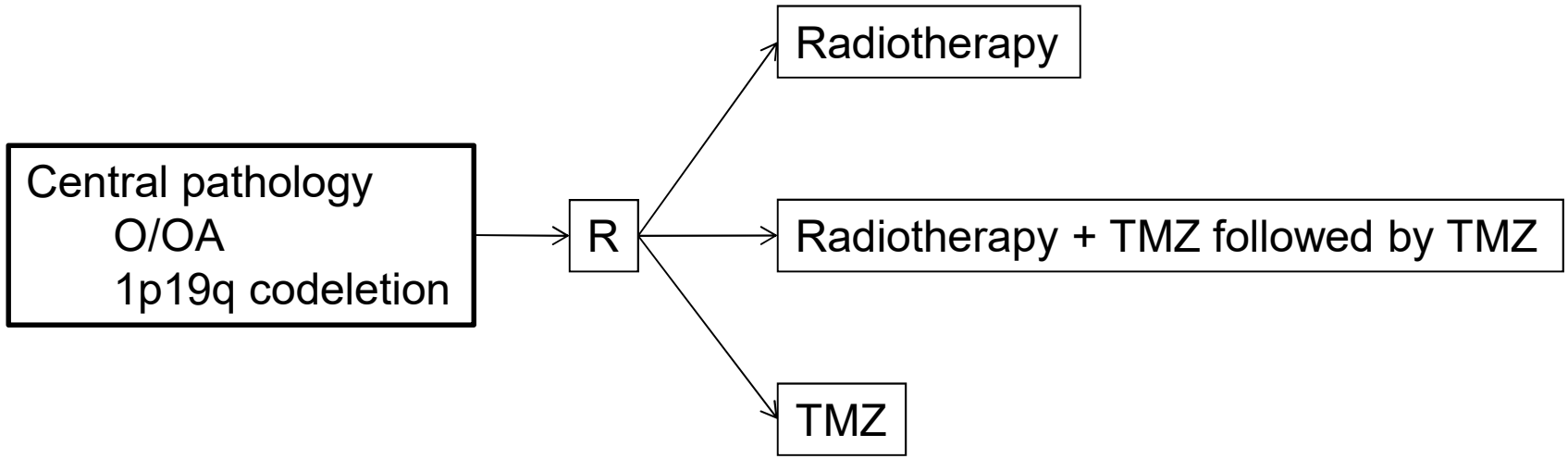
Efficacy outcomes – across trial

	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

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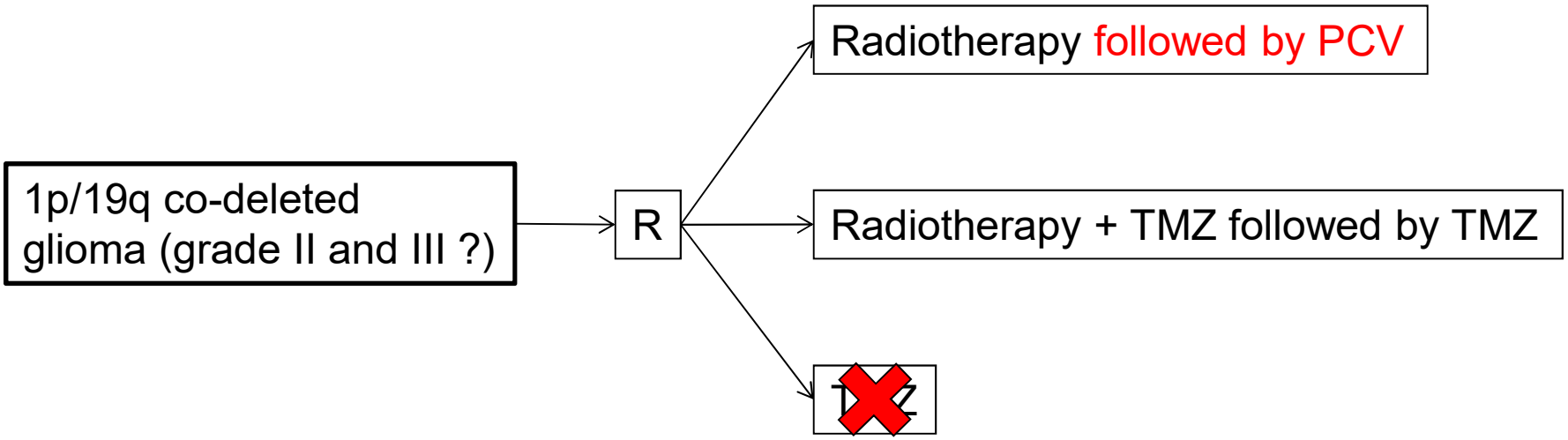
CODEL trial: updated design

Proposed design of revitalized CODEL trial



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Conclusions: 1p/19q co-deleted anaplastic gliomas

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

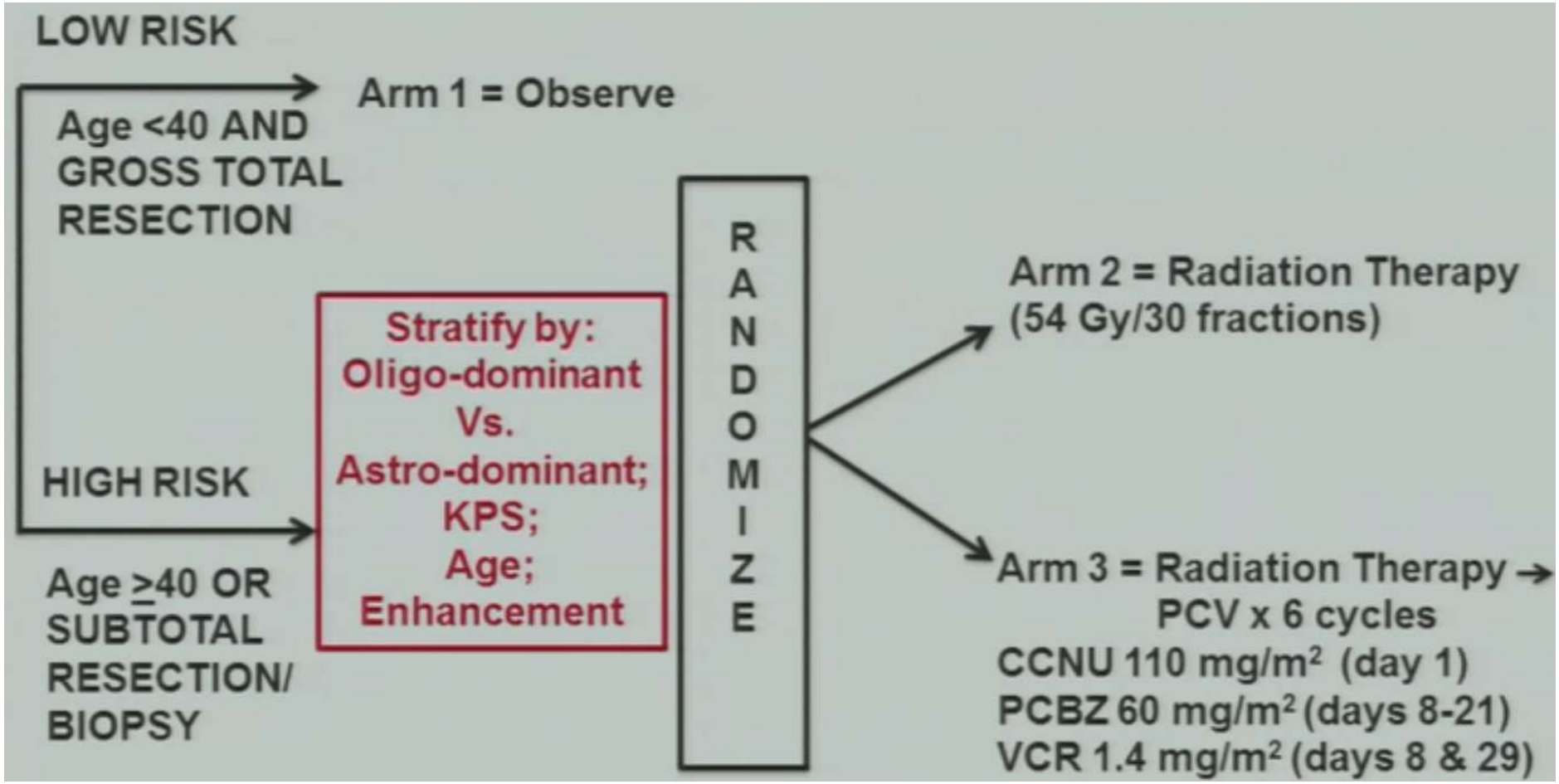
And in patients with low-grade gliomas…?

Feasible options:

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

And in patients with low-grade gliomas…?

RTOG 9802



Buckner et al., N Engl J Med 2014

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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 et al., N Engl J Med 2014

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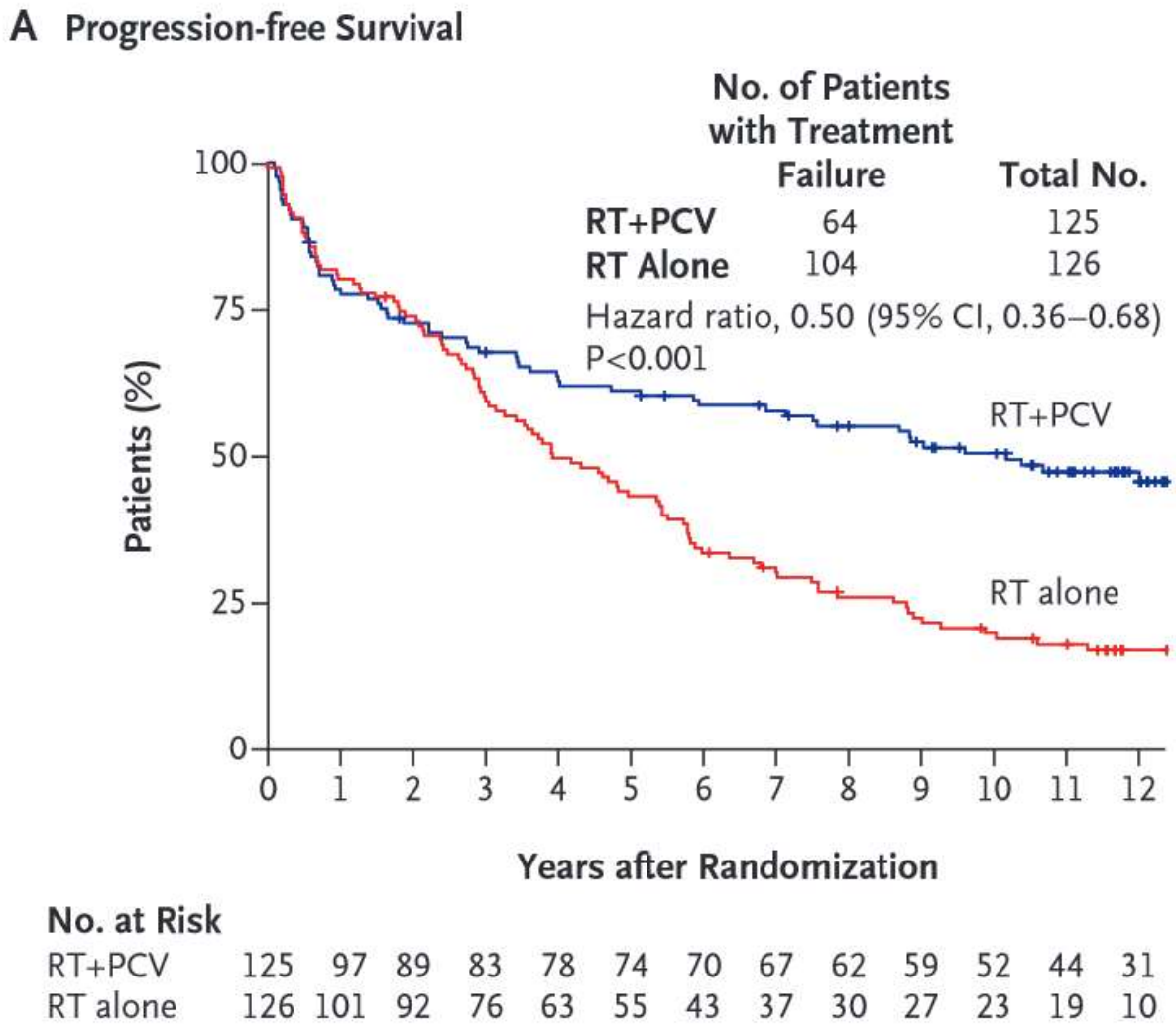
RTOG 9802: PFS long-term follow-up



Buckner et al., N Engl J Med 2016

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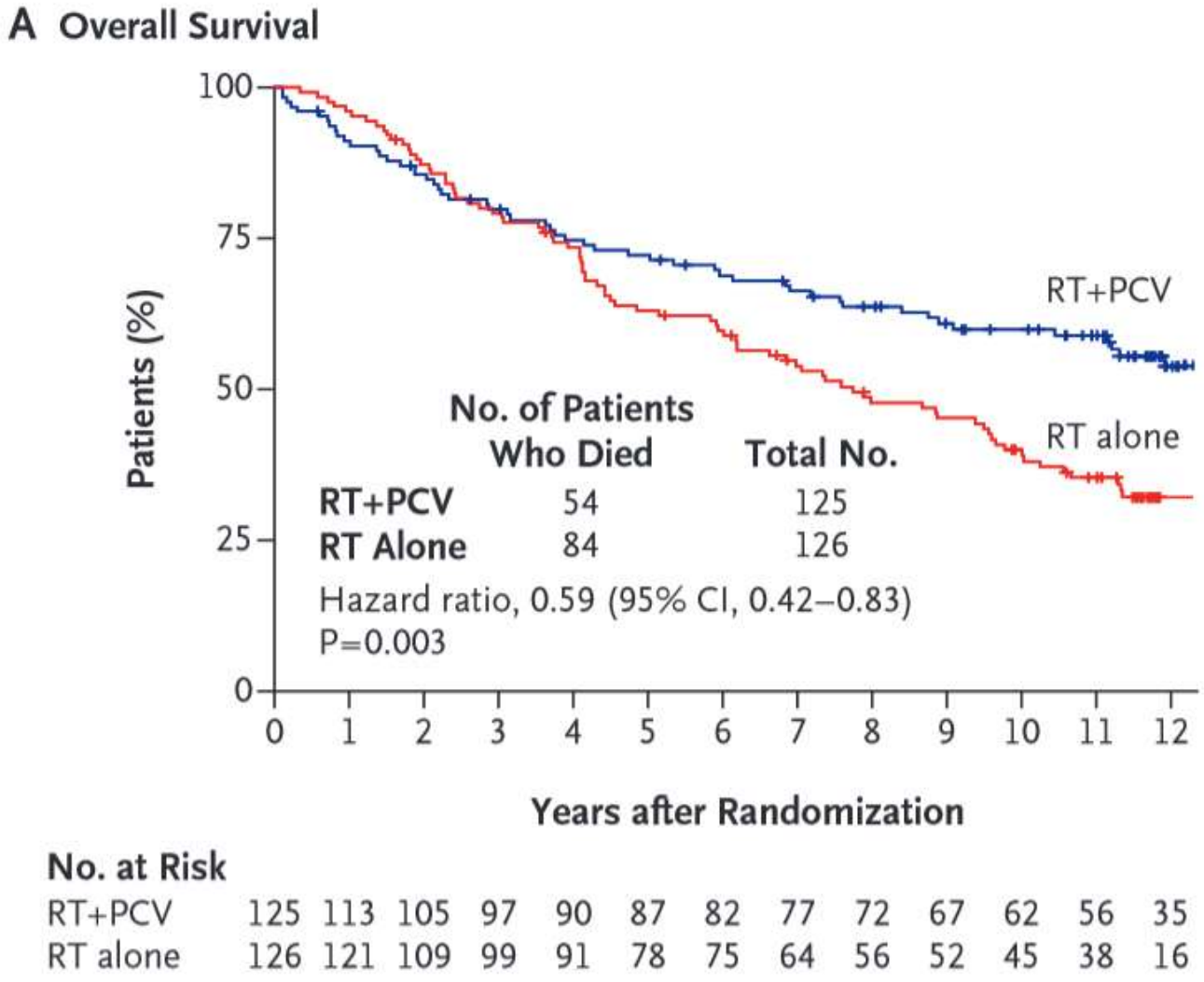
RTOG 9802: OS long-term follow-up



Buckner et al., N Engl J Med 2016

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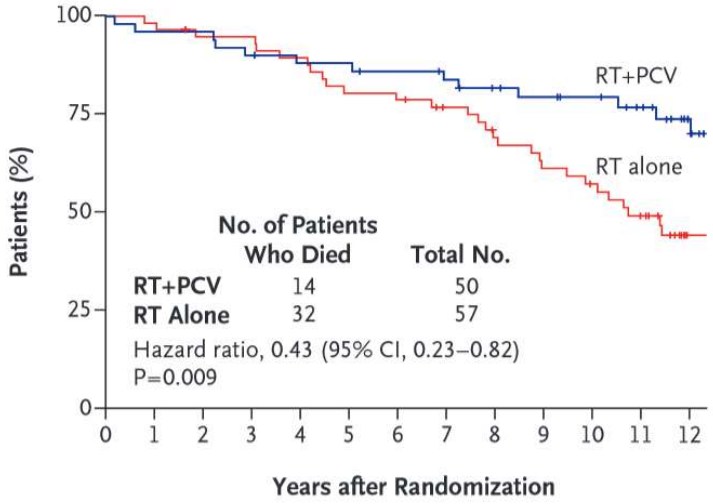
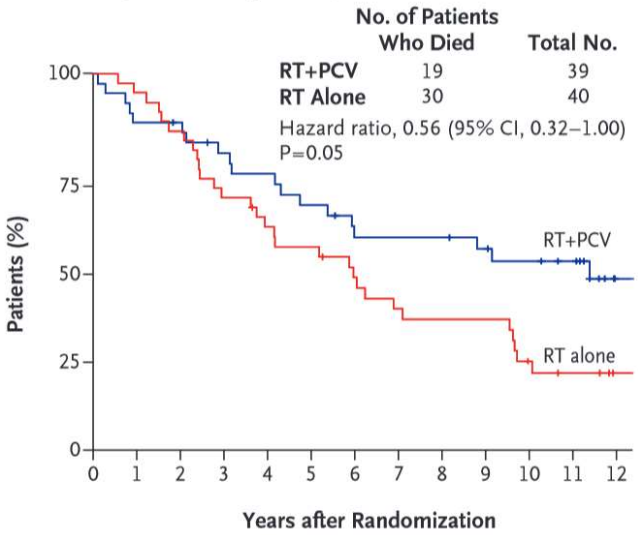
B Overall Survival, Grade 2 Oligodendroglioma



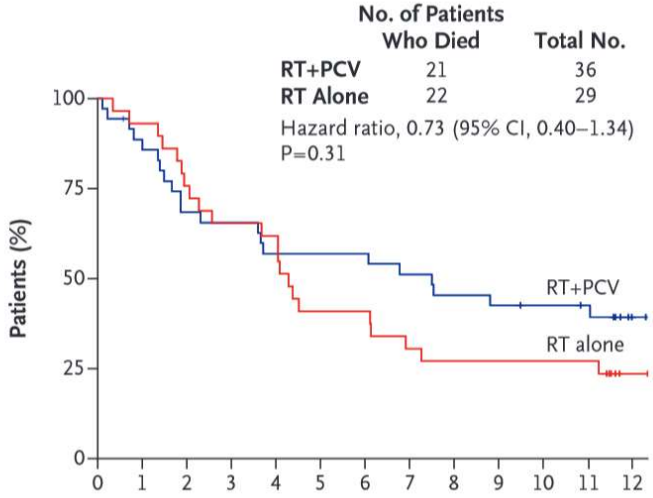
No. at Risk													
RT+PCV	50	48	48	45	43	43	41	39	36	34	32	28	20
RT alone	57	56	53	53	50	45	45	40	35	31	28	24	11

C Overall Survival, Grade 2 Oligoastrocytoma



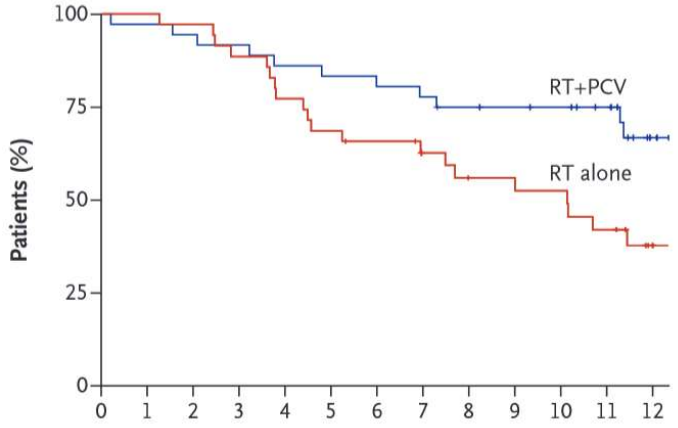
No. at Risk													
RT+PCV	39	34	33	29	27	24	21	20	20	18	16	14	6
RT alone	40	38	34	27	23	21	18	14	13	13	9	6	3

D Overall Survival, Grade 2 Astrocytoma



No. at Risk													
RT+PCV	36	31	24	23	20	20	20	18	16	15	14	14	9
RT alone	29	27	22	19	18	12	12	10	8	8	8	8	2

E Overall Survival among Patients with *IDH1* R132H Mutation



No. at Risk													
RT+PCV	36	35	34	33	31	30	29	28	26	25	24	21	12
RT alone	35	35	34	31	27	24	22	19	16	15	15	12	5

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 glioblastoma

Anthony Chalmers

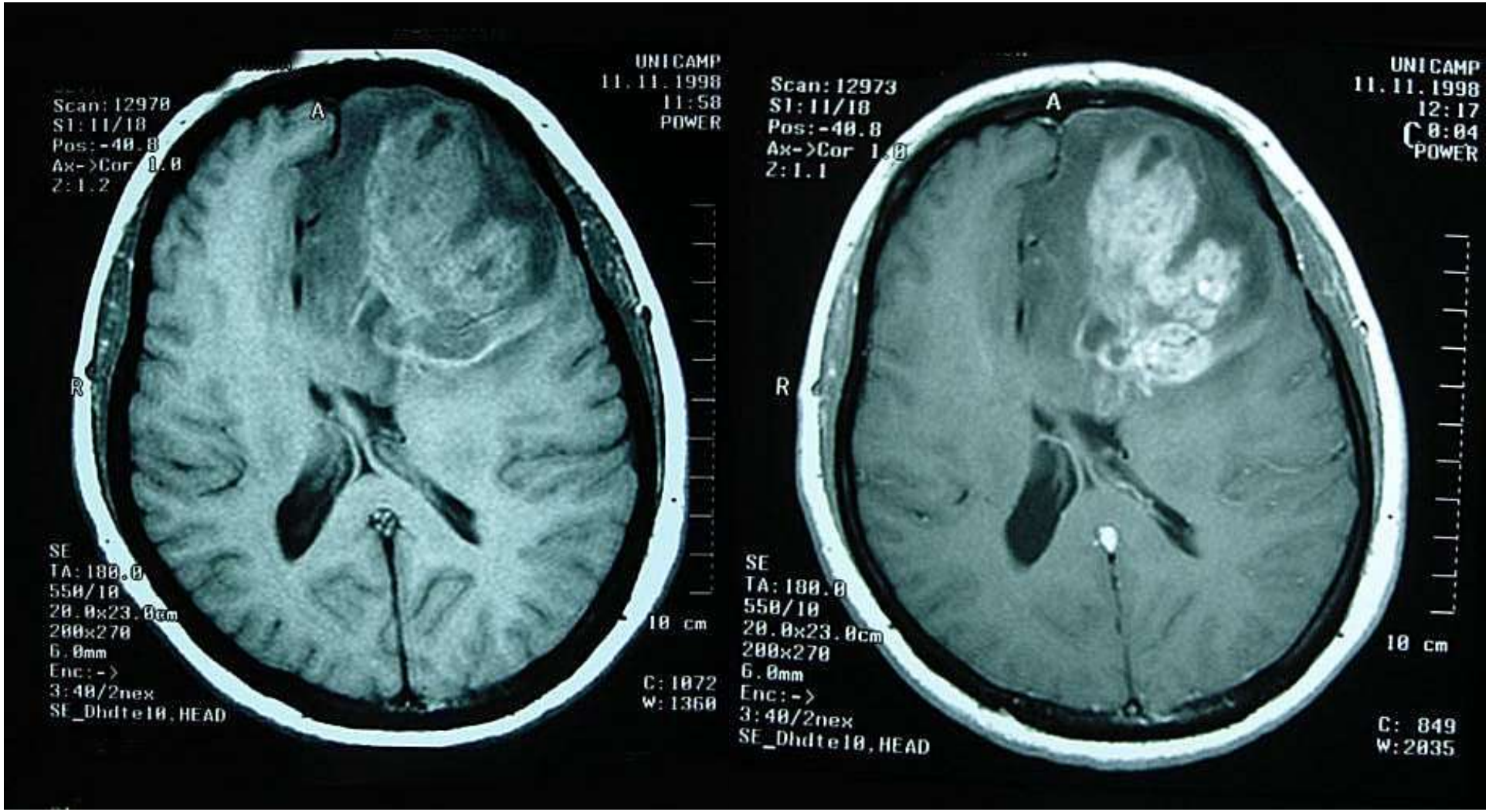
ESTRO Brain Tumour Course

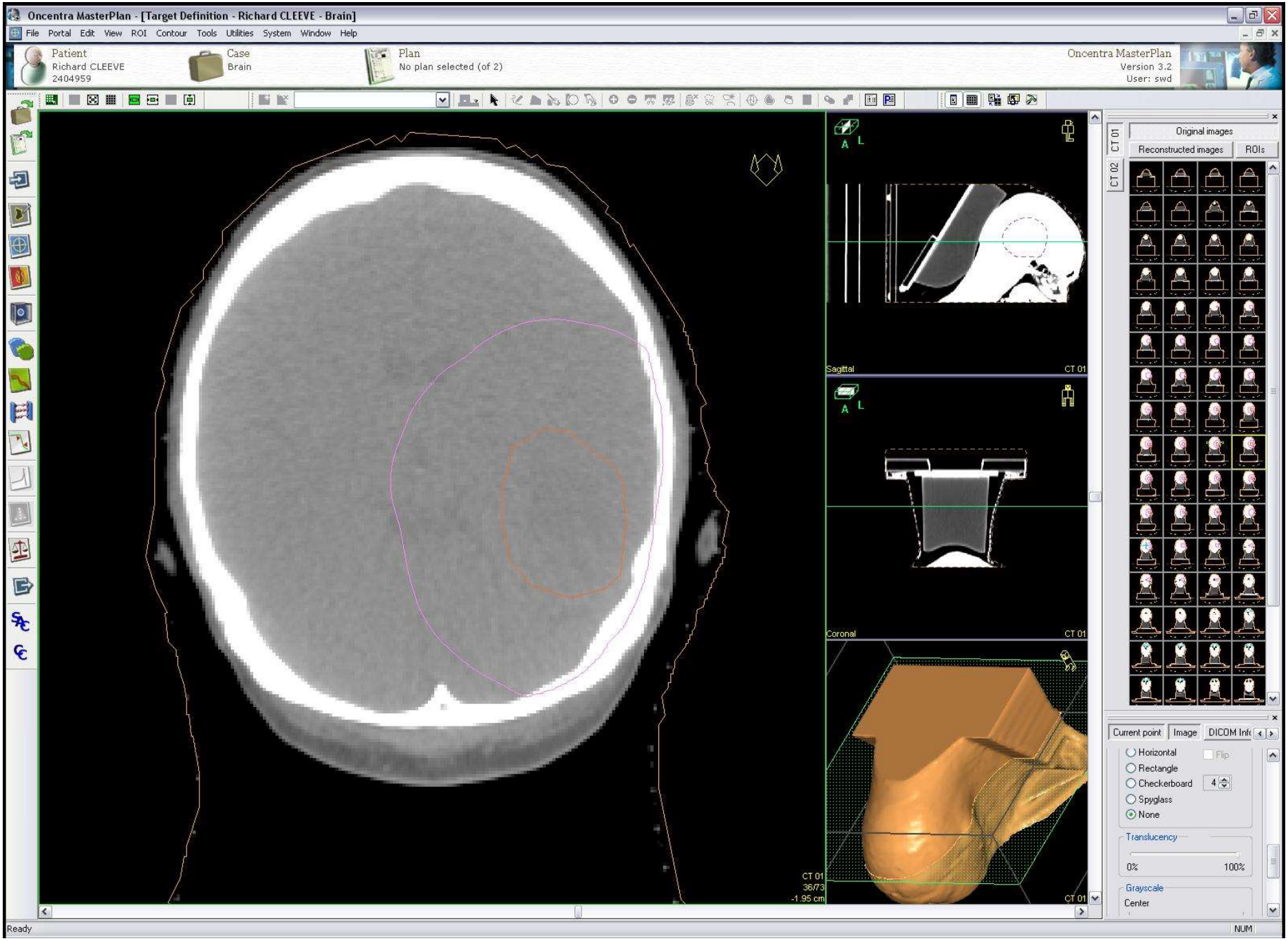
2017

Prognostic factors

- age
- performance status
- molecular markers:
  - 1p19q co-deletion; MGMT promoter methylation; IDH1 mutation
- extent of surgical resection

Glioblastoma

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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
Sagittal
CT 01
Coronal
CT 01
CT 01
36/73
-1.95 cm
CT 01
CT 02
Original images
Reconstructed images
ROIs
Current point
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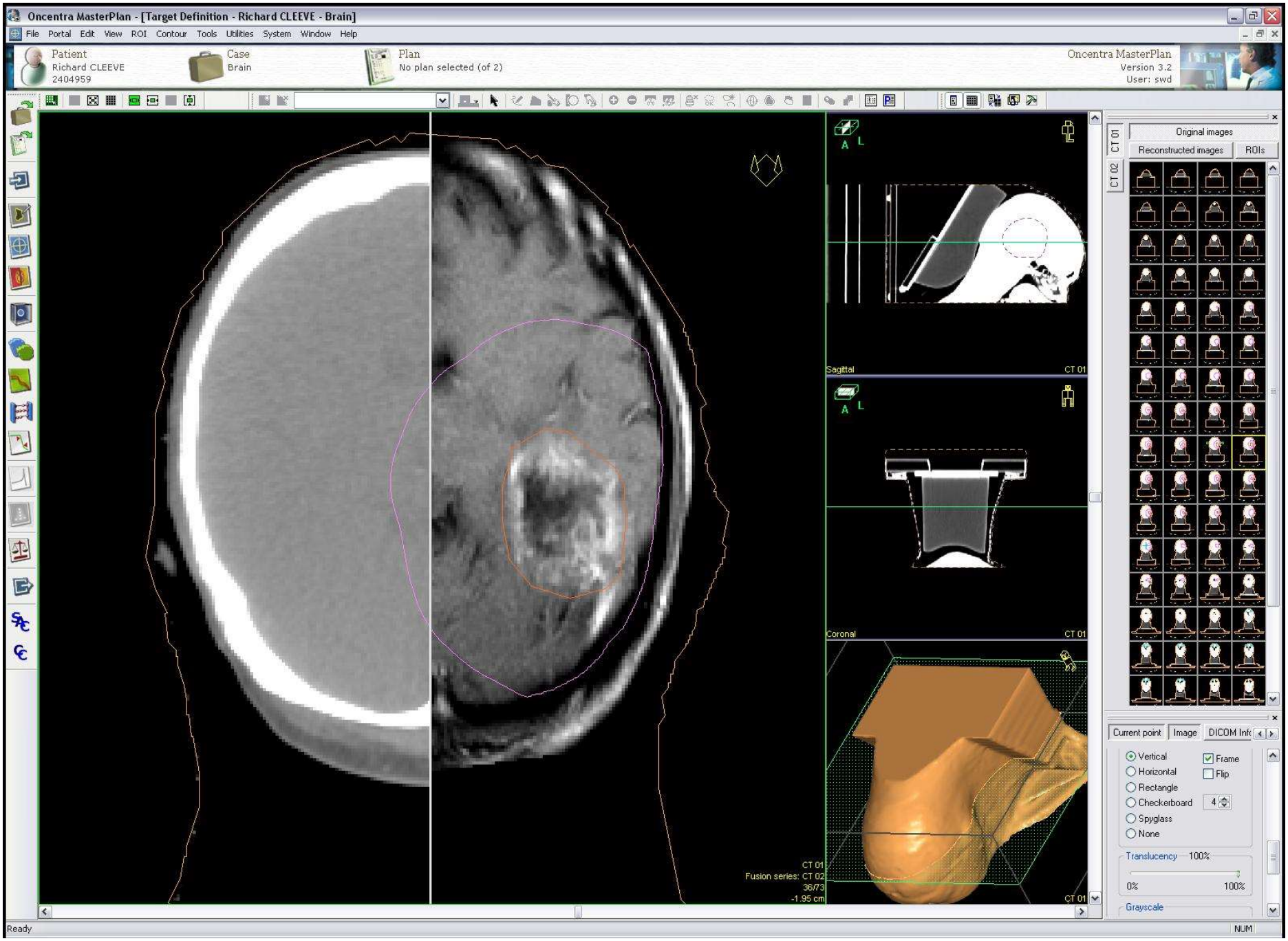
Oncentra MasterPlan - [Target Definition - Richard CLEEVE - Brain]
File Portal Edit View ROI Contour Tools Utilities System Window Help
Patient
Richard CLEEVE
2404959
Case
Brain
Plan
No plan selected (of 2)
Oncentra MasterPlan
Version 3.2
User: swd
Sagittal
CT 01
Coronal
CT 01
CT 01
Fusion series: CT 02
36/73
-1.95 cm
CT 01
Original images
Reconstructed images
ROIs
CT 01
CT 02
Current point
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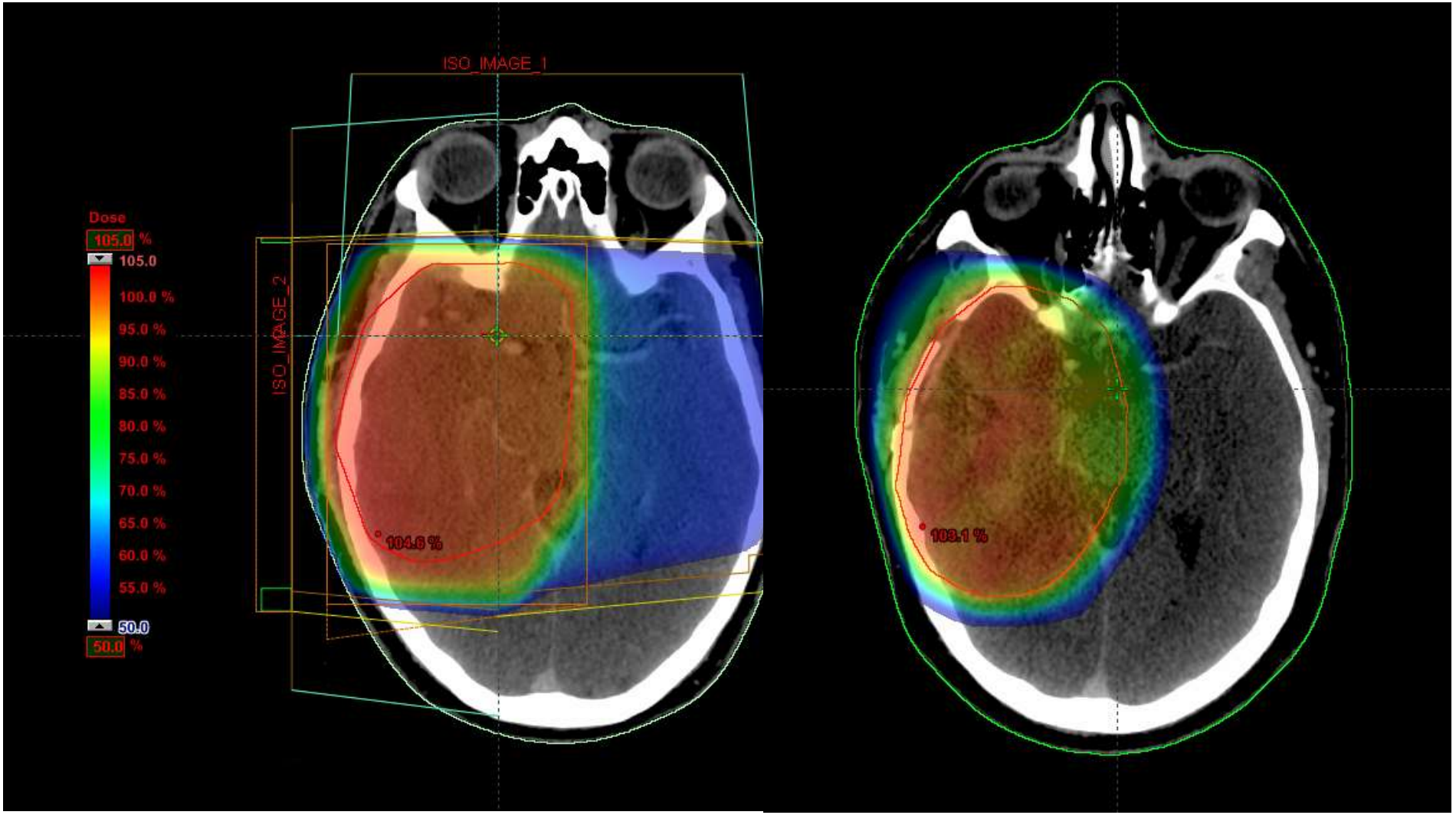
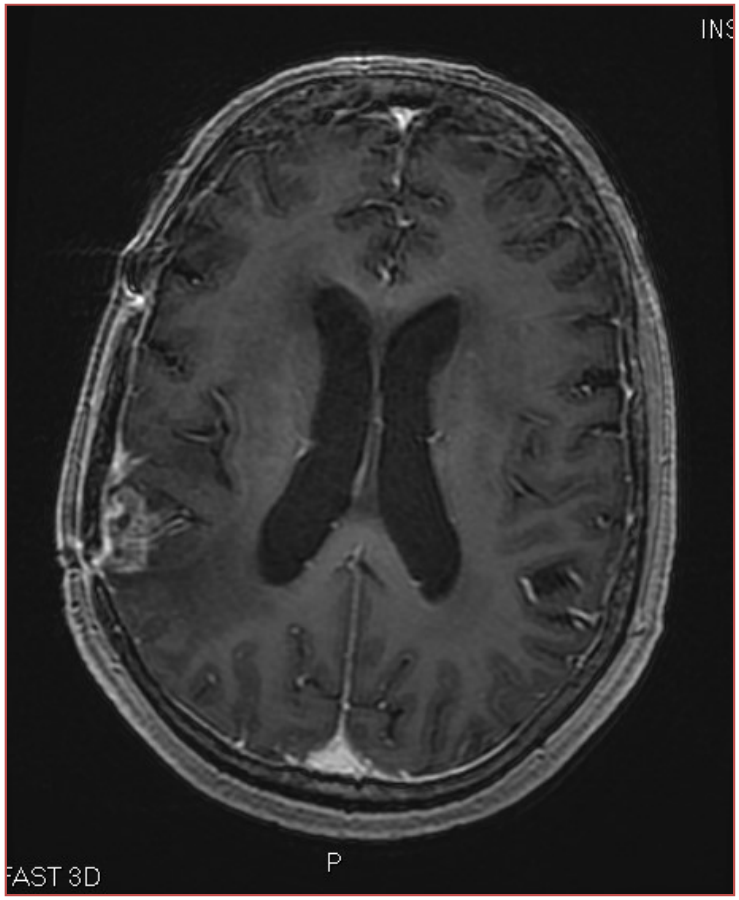
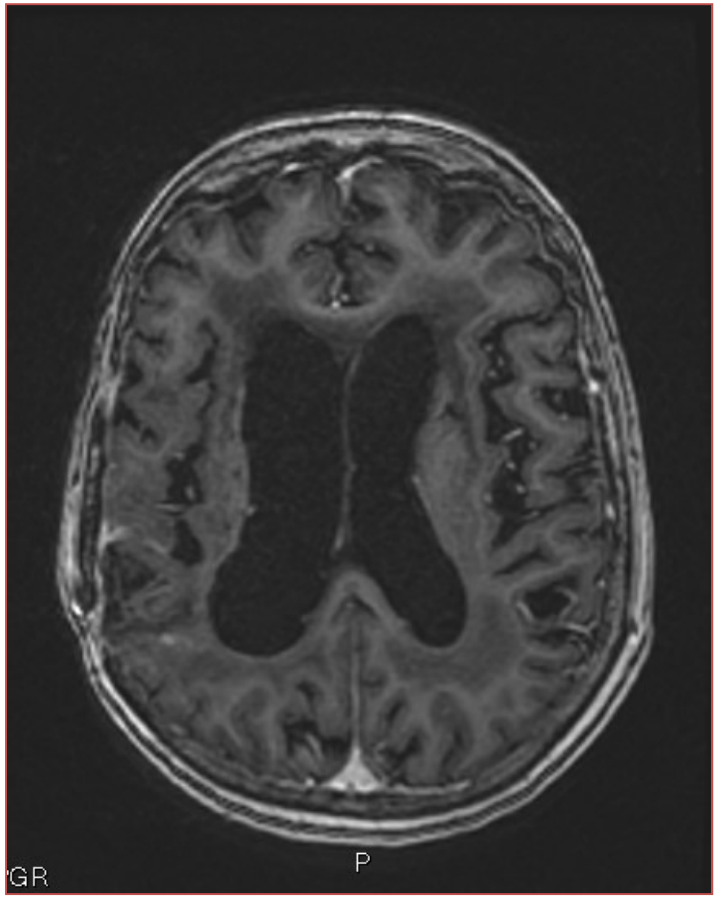
Conformal RT

IMRT

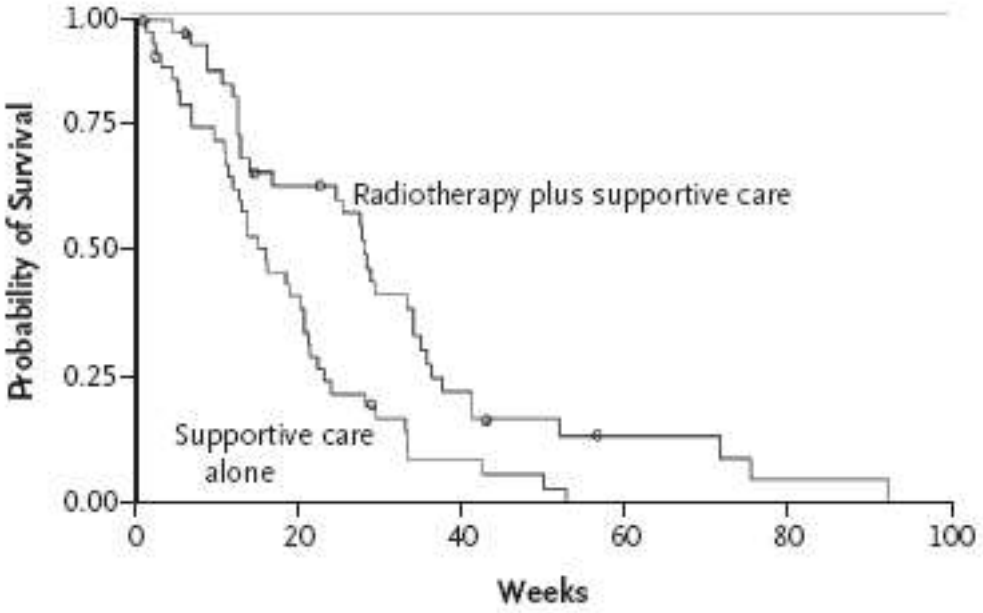




Pre-radiation



18 months
post-radiation



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

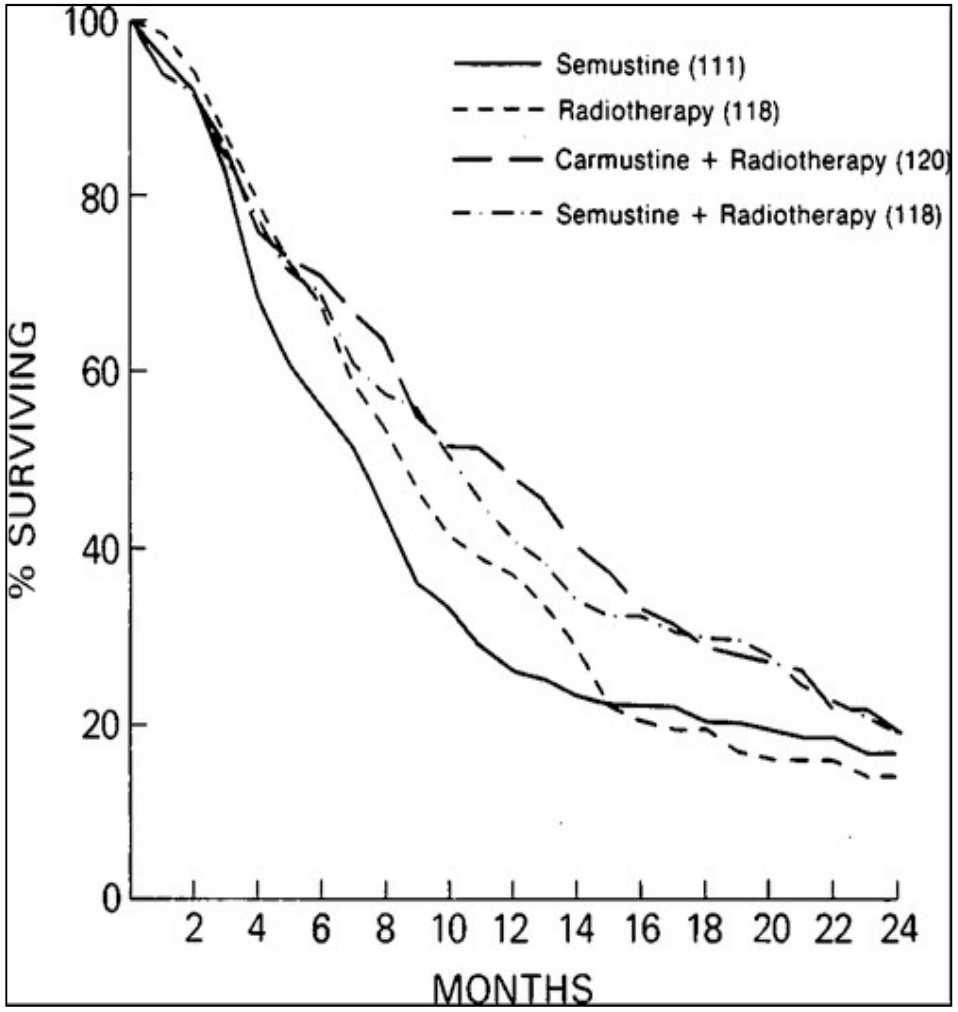
Figure 2. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

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

Discussion tomorrow…

Keime-Guibert NEJM 2007



Walker NEJM 1978

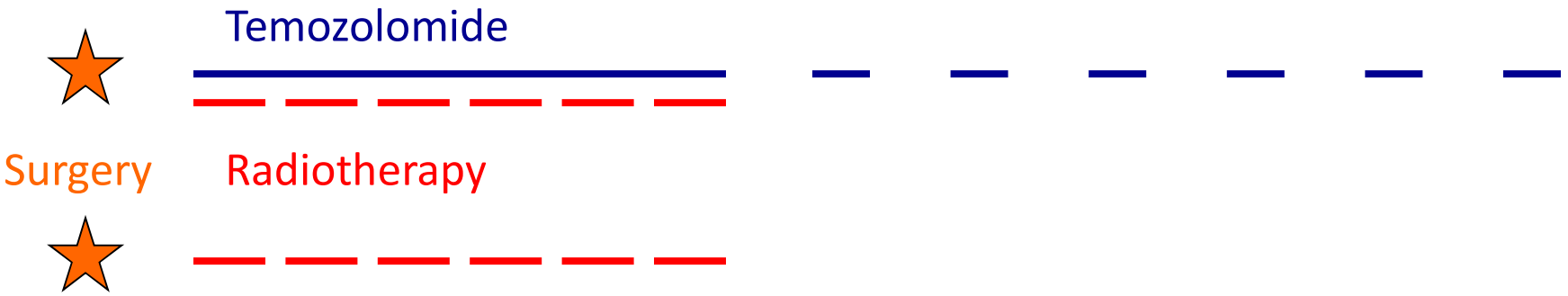
Survival of GBM patients did not improve between 1978 and 2005....

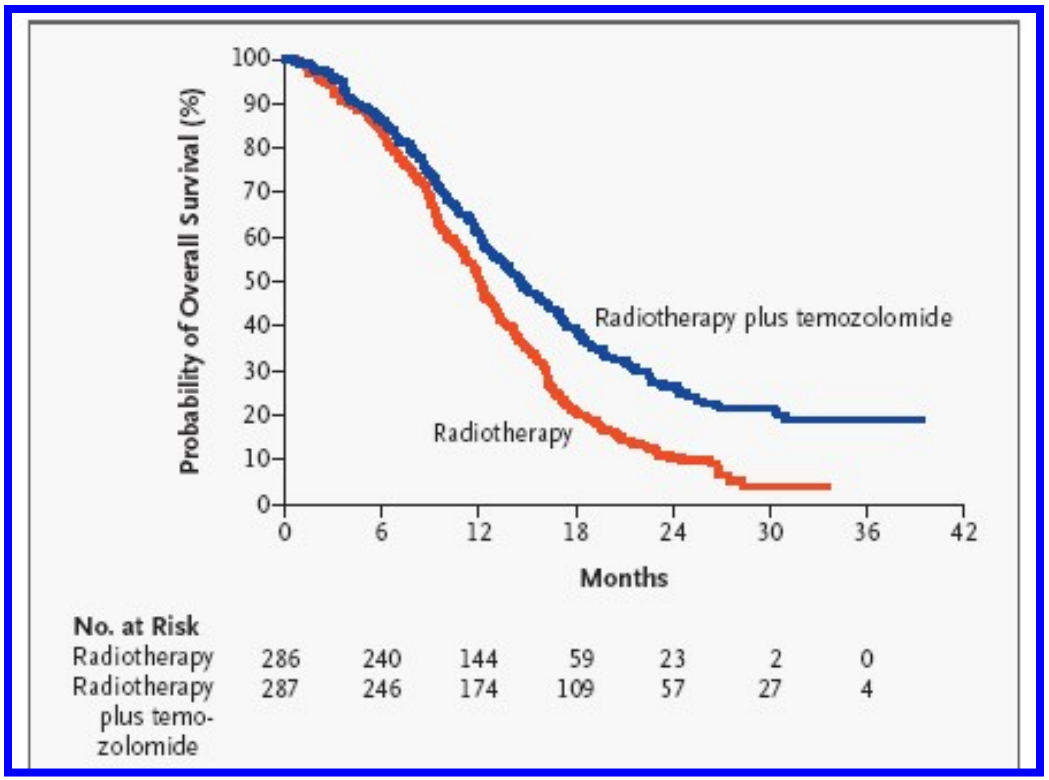
The NEW ENGLAND JOURNAL of MEDICINE

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*





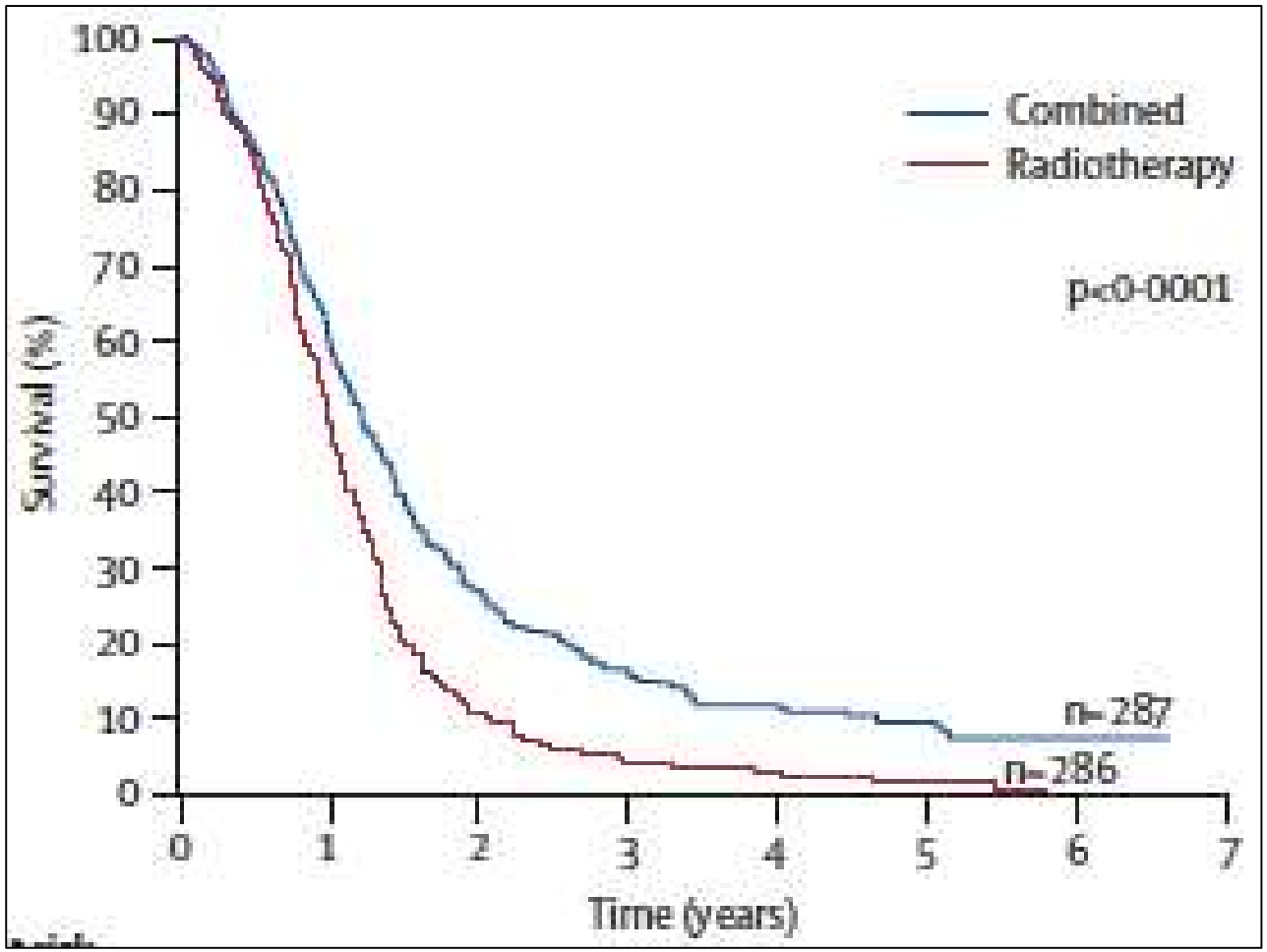
Glioblastoma patients aged < 70 yrs

Stupp NEJM 2005

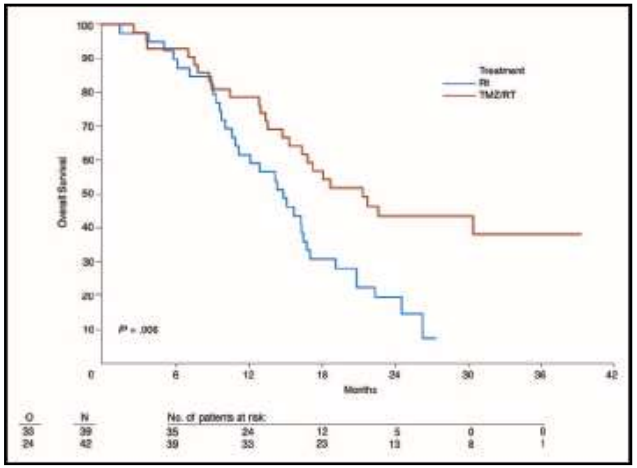
‘Stupp’ regime

- 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

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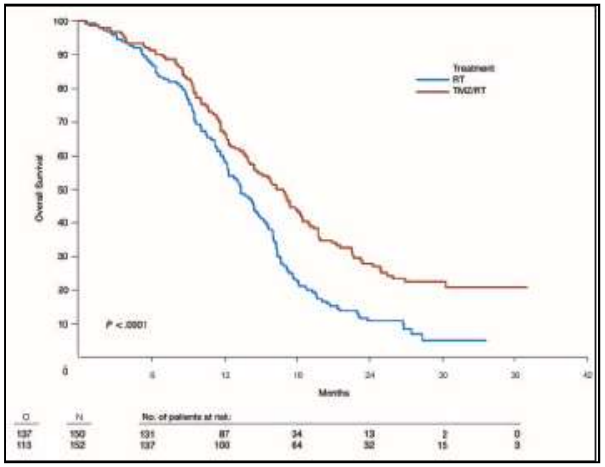

RPA IV

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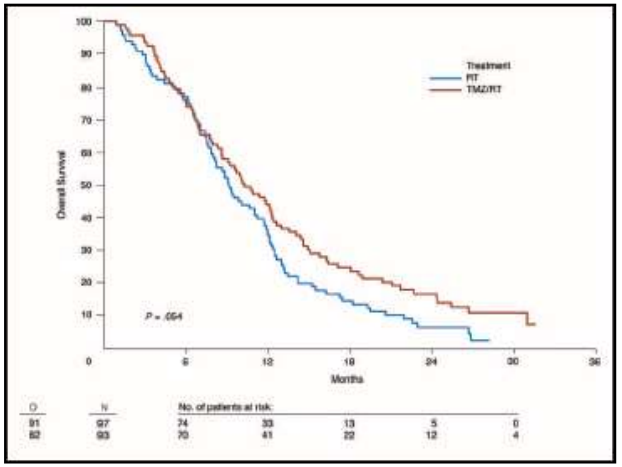


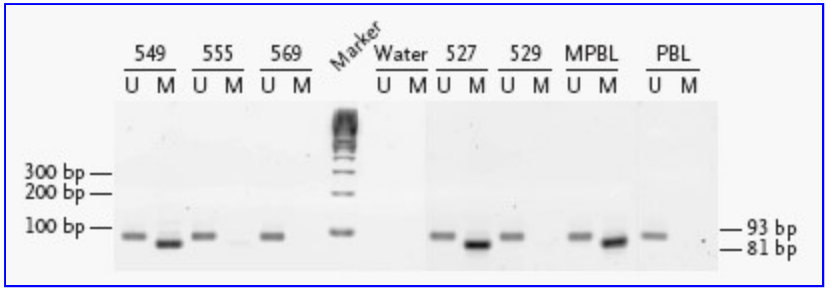
RPA V

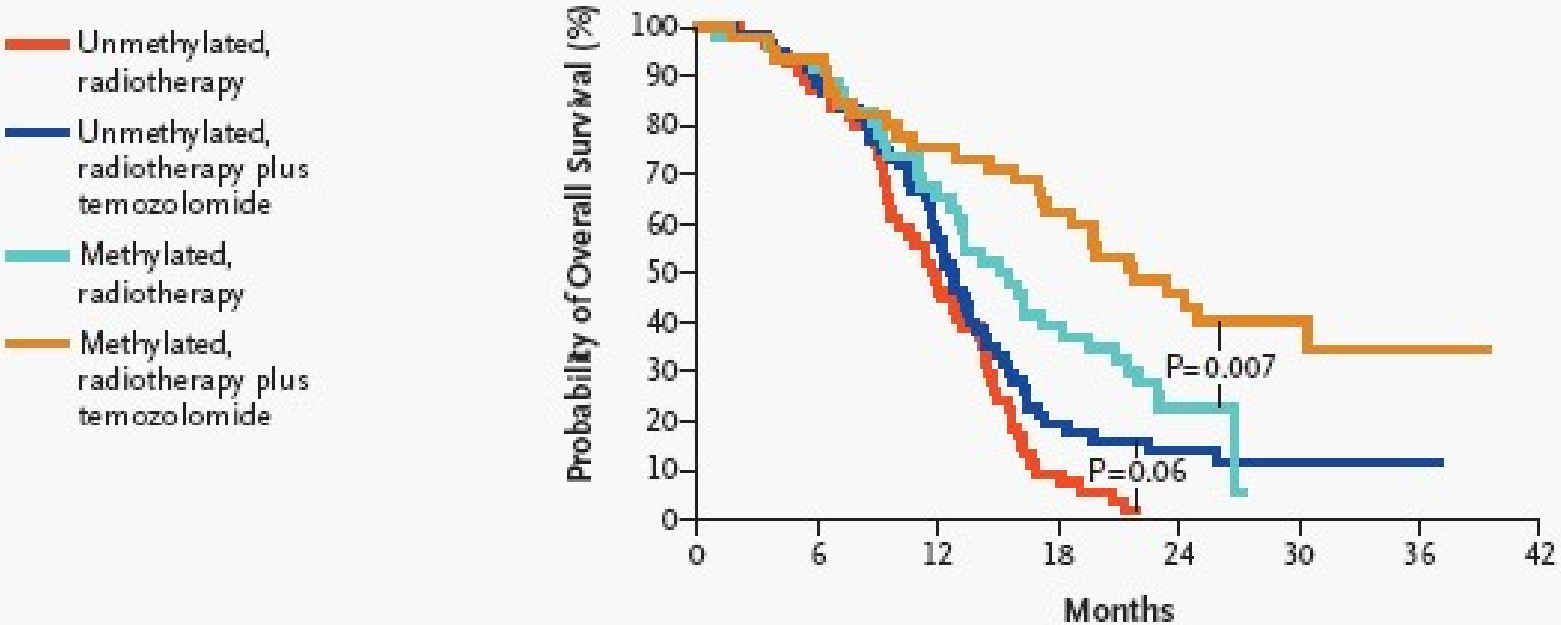
p=0.054

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

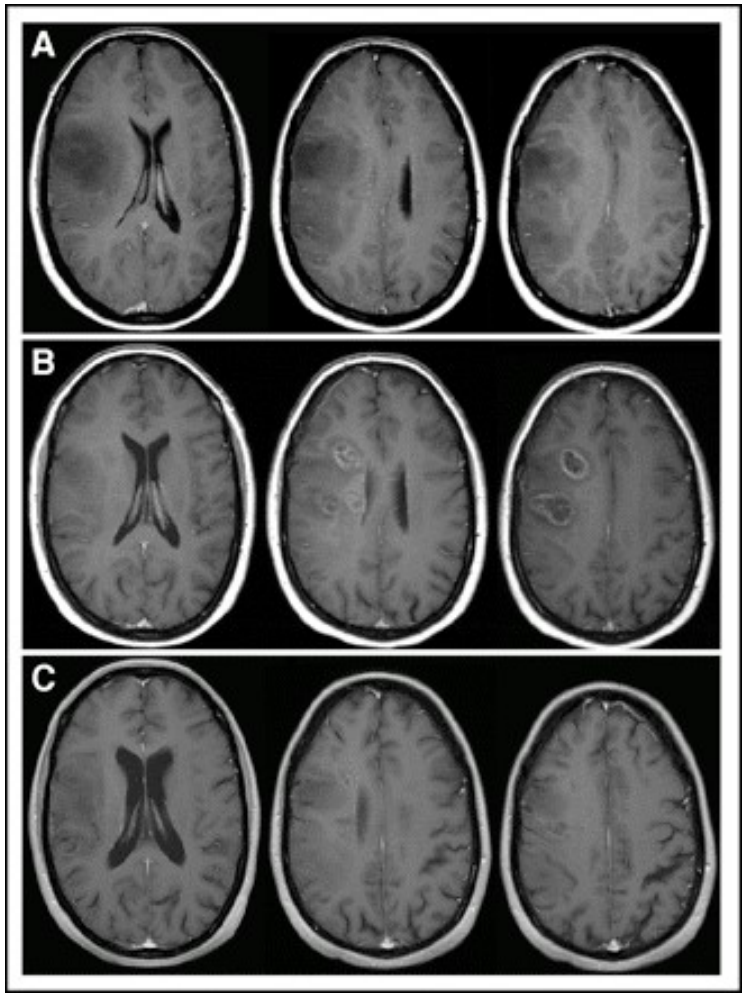
Chemoradiation for GBM: common issues

- continuous temozolomide associated with **lymphopenia**
  - exacerbated by prior and concomitant steroid treatment
  - prophylactic co-trimoxazole or pentamidine recommended if lymphocyte count <0.5
- occasional patients experience pancytopenia during concomitant treatment
- adjuvant temozolomide associated with **neutropenia, thrombocytopenia and fatigue**
- 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



Lesion enlargement, evidenced at the first MRI scan in 50 of 103 patients, was subsequently classified as psPD in 32 patients and early disease progression in 18 patients.

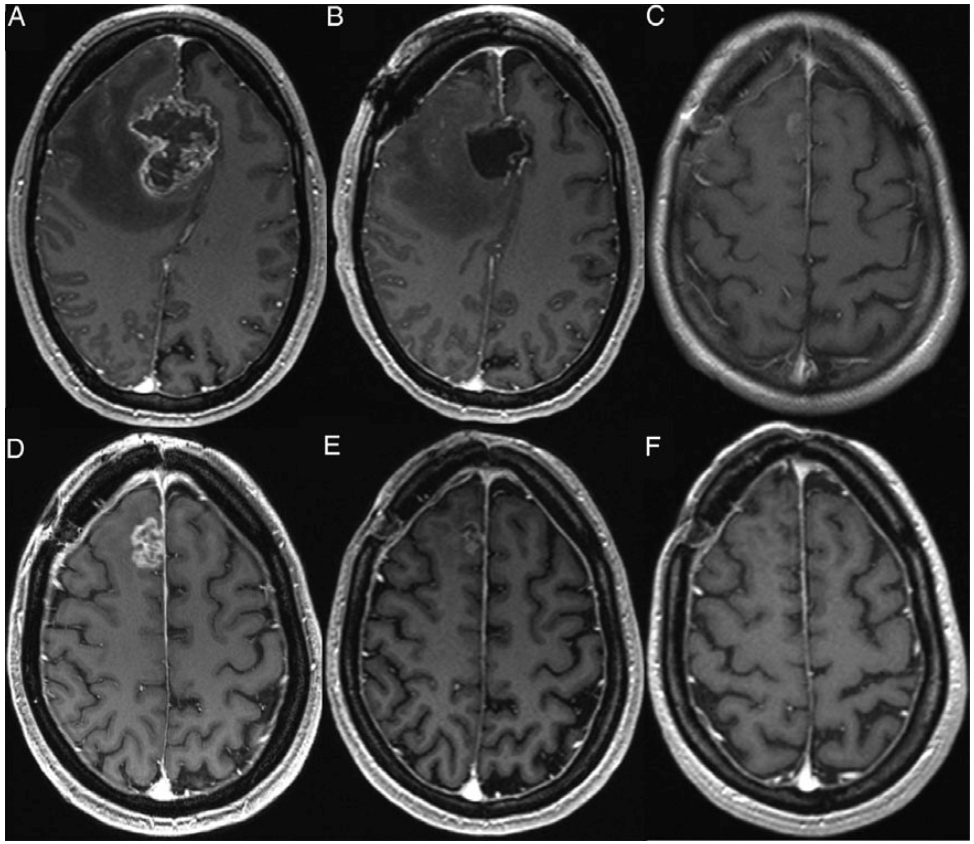
Brandes et al, J Clin Oncol 2008

Pseudoprogression in patients with glioblastoma: clinical relevance despite low incidence

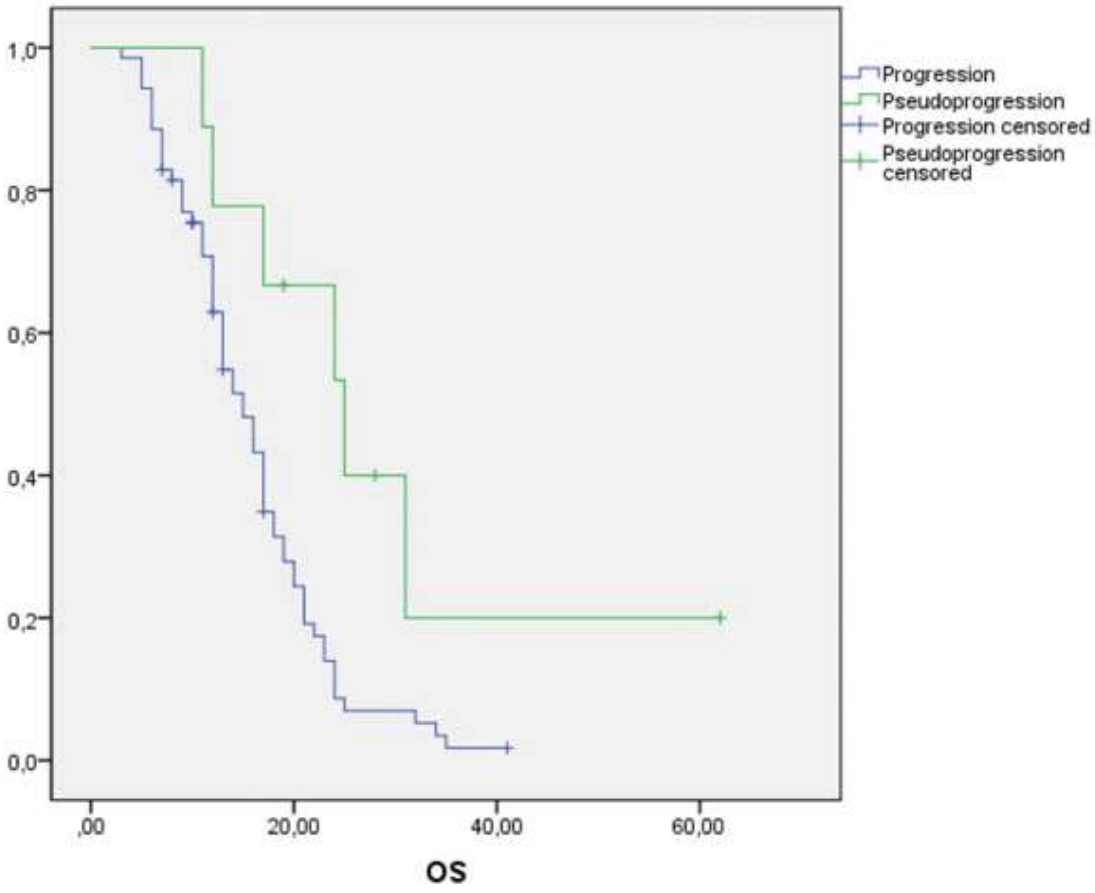
Alexander Radbruch, Joachim Fladt, Philipp Kickingereder, Benedikt Wiestler, Martha Nowosielski, Philipp Bäumer, Heinz-Peter Schlemmer, Antje Wick, Sabine Heiland, Wolfgang Wick, and Martin Bendszus

To qualify for true progression or PsP, patients had to present an enhancement increase of at least 25% of an original lesion with ≥10 mm of perpendicular diameters or a new nodular component ≥10 mm within the radiation field in the first, second, third, or fourth f/u compared with the baseline

Neuro-Oncology 17(1), 151–159, 2015
doi:10.1093/neuonc/nou129



- 548 patients
- 79 fulfilled inclusion criteria
- Only 9 cases of pseudoprogression (11.4%)
- PsP detected at 1, 4 and 7 months

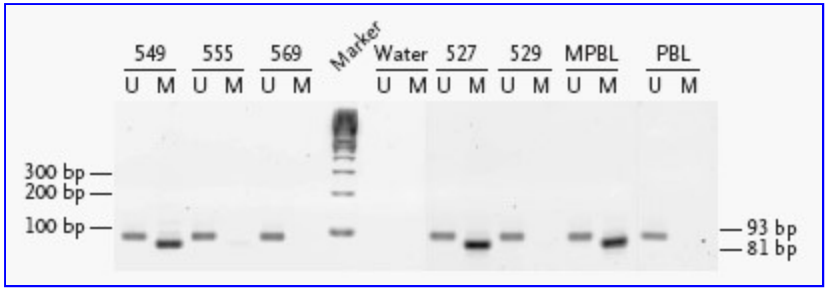


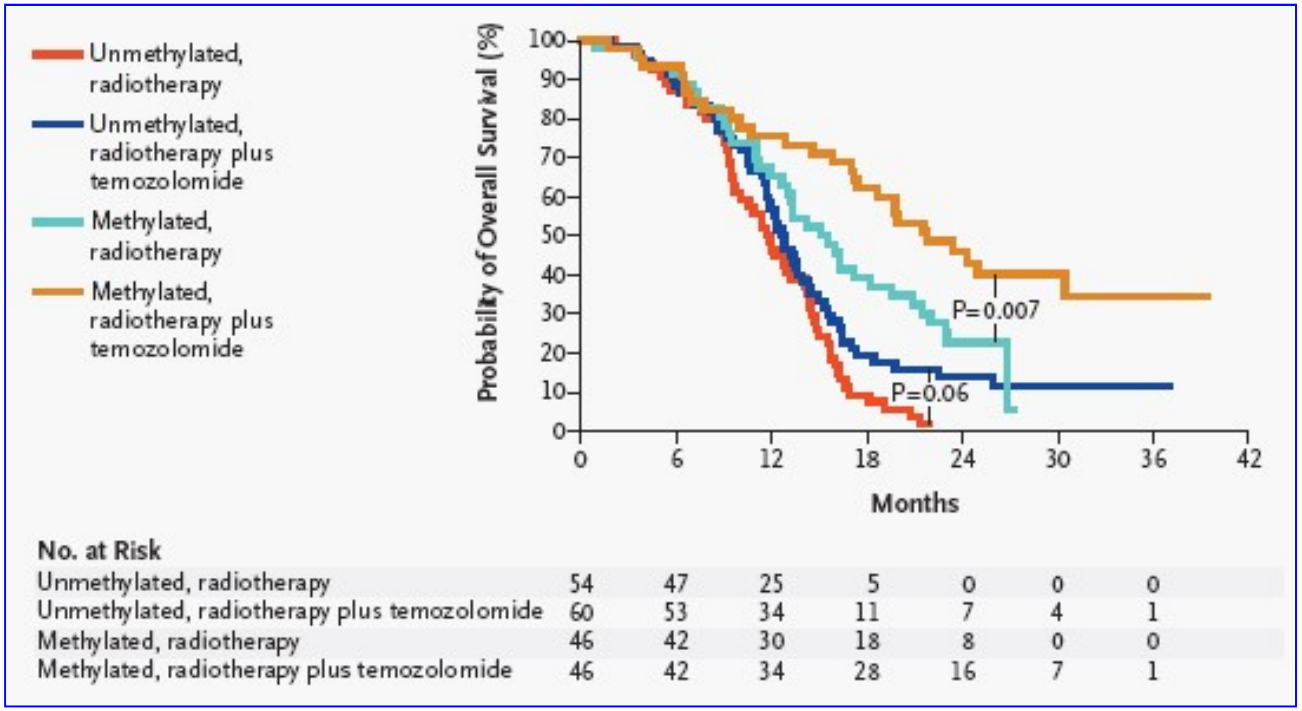
Neuro-Oncology 17(1), 151–159, 2015
doi:10.1093/neuonc/nou129

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.,





- Can we overcome TMZ resistance by increasing dose intensity?

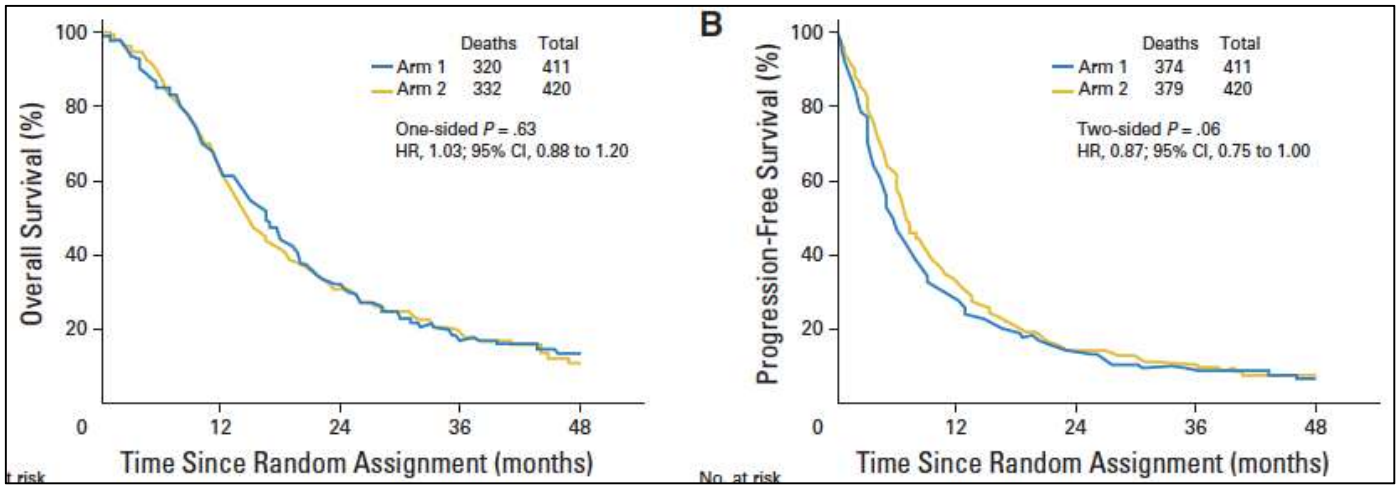
VOLUME 31 · NUMBER 32 · NOVEMBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

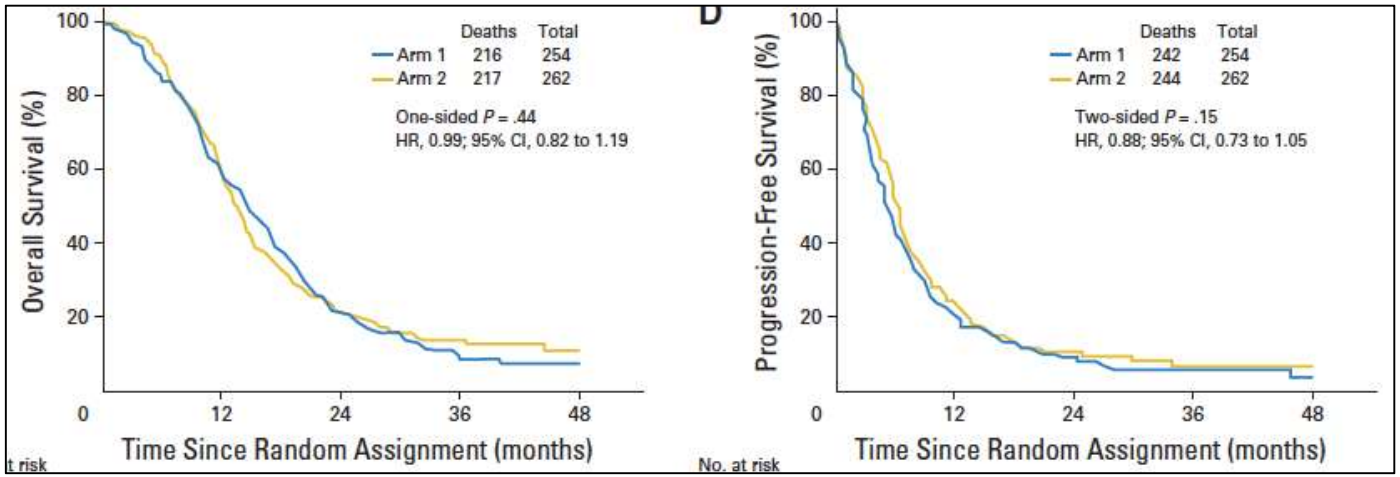
ORIGINAL REPORT

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



All patients



MGMT unmethylated only

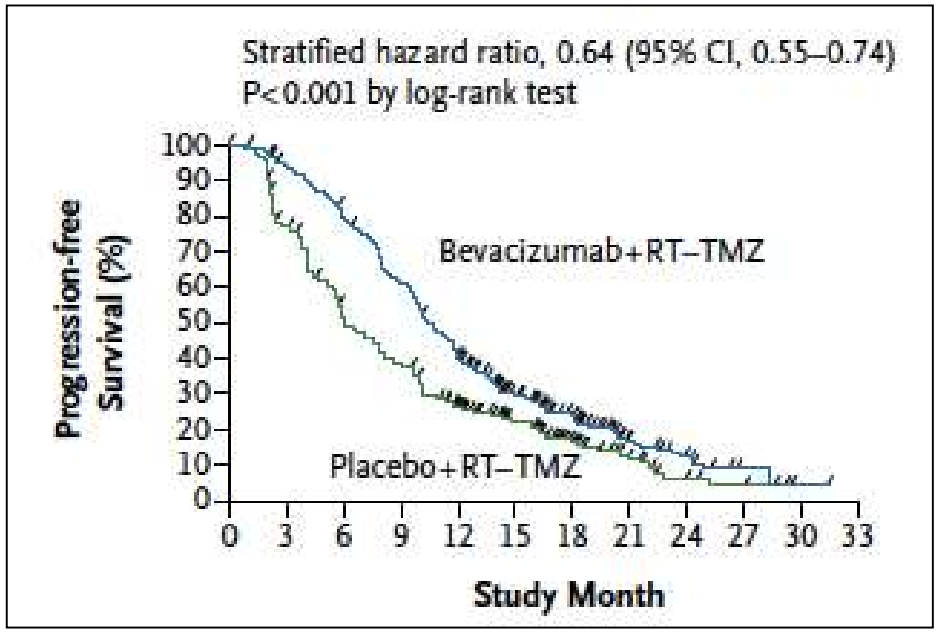
The NEW ENGLAND JOURNAL of MEDICINE

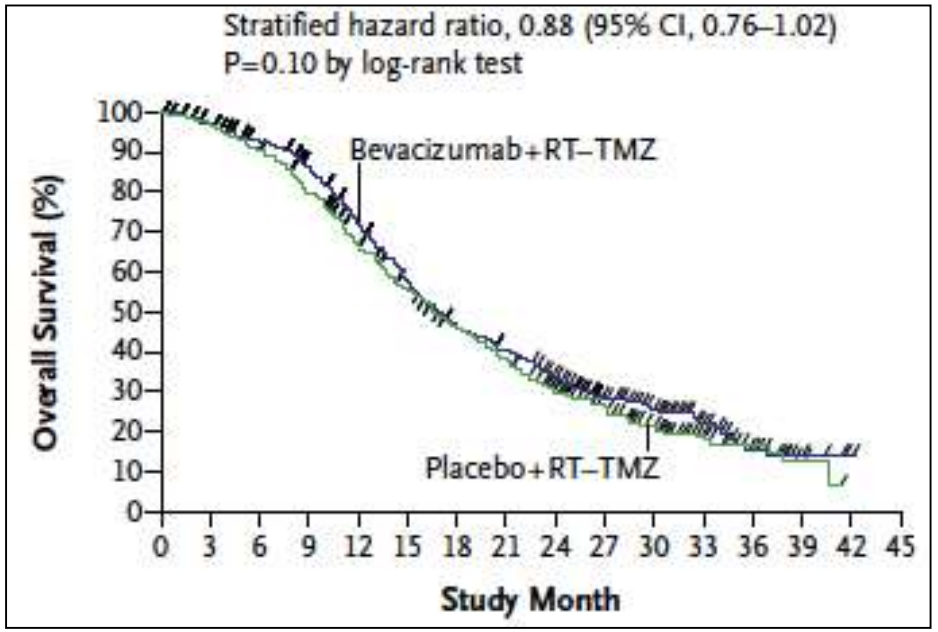
ORIGINAL ARTICLE

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





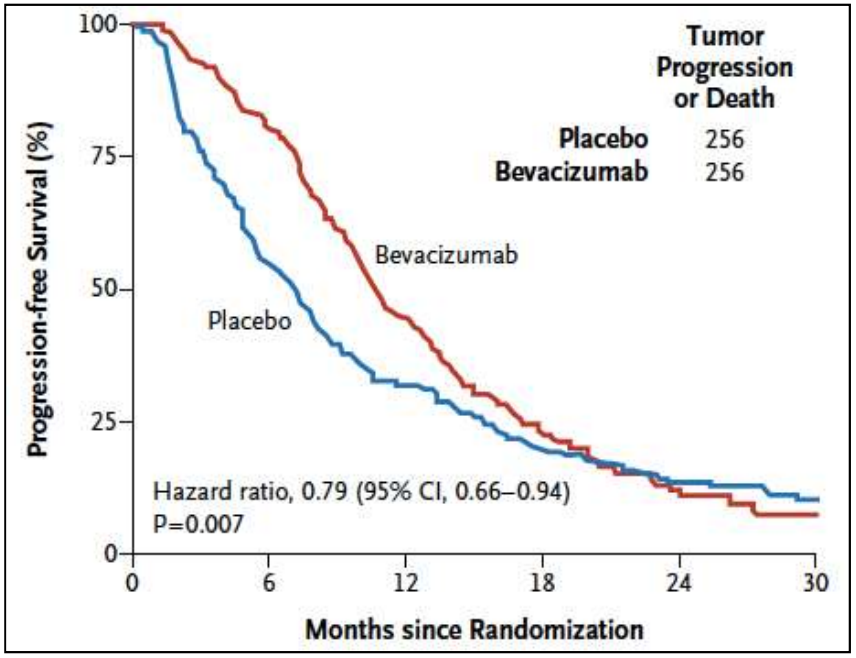
The NEW ENGLAND JOURNAL of MEDICINE

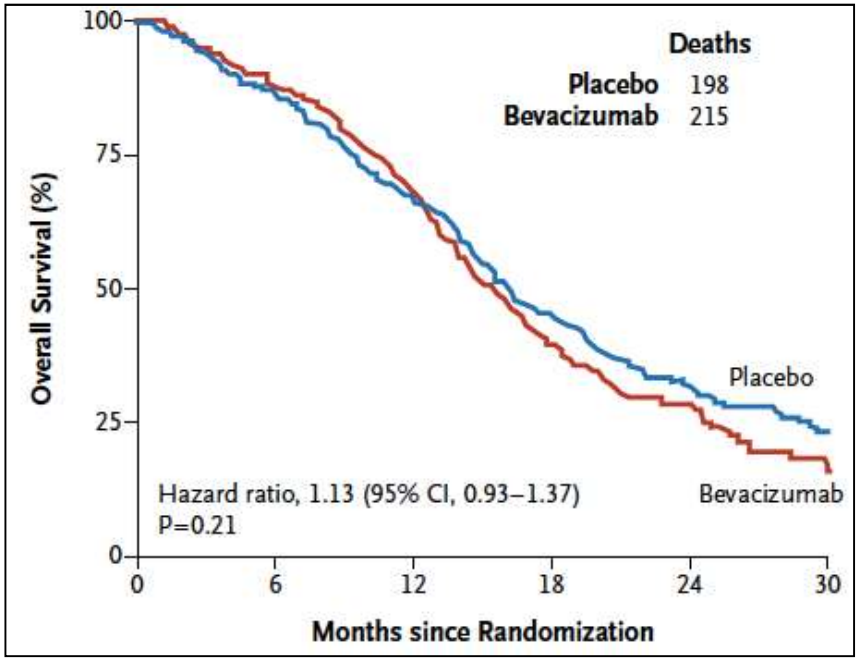
ESTABLISHED IN 1812 FEBRUARY 20, 2014 VOL. 370 NO. 8

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

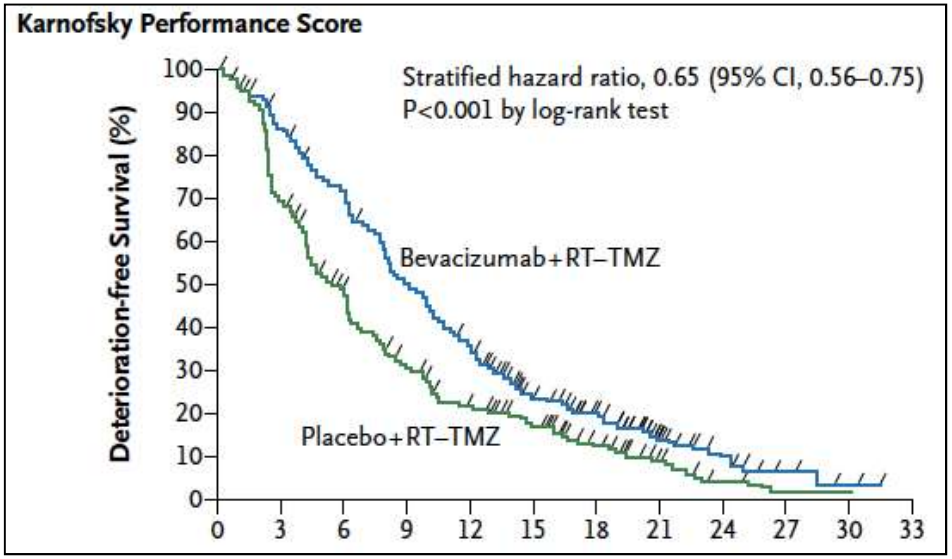
Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.A., Robert Jeraj, Ph.D., Paul D. Brown, 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.

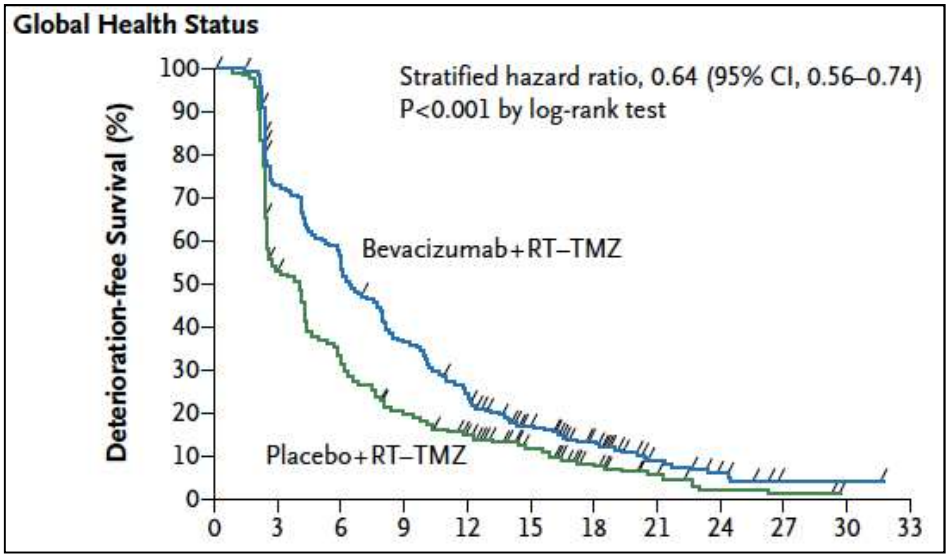
RTOG 0825





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

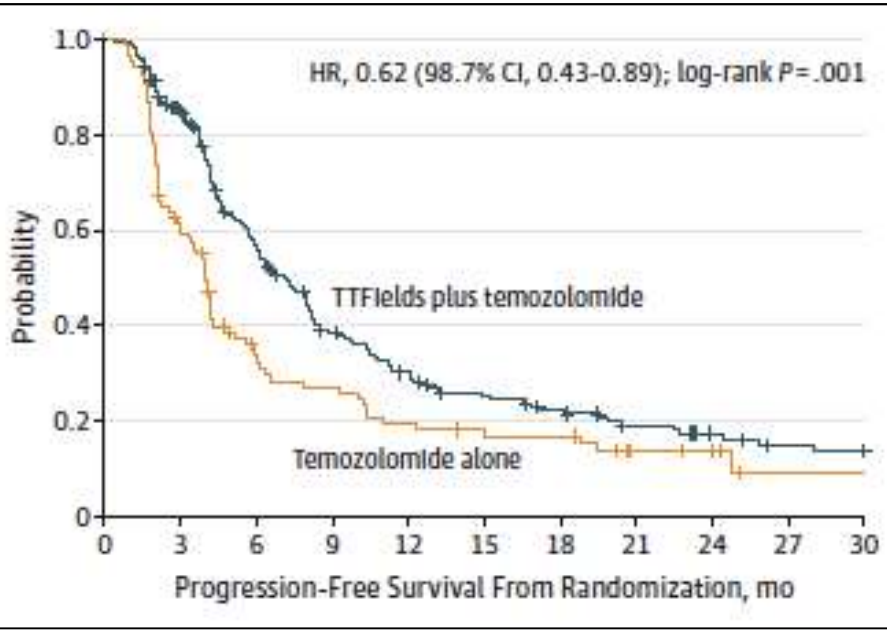
During the maintenance phase, serious adverse events were more prevalent in the bevacizumab group than in the placebo group, including hypertension (4.2% vs. 0.9%), thromboembolic disease (7.7% vs. 4.7%), wound dehiscence (1.5% vs. 0.9%), fatigue (13.1% vs. 9.0%), visceral perforation (1.2% vs. 0.4%),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

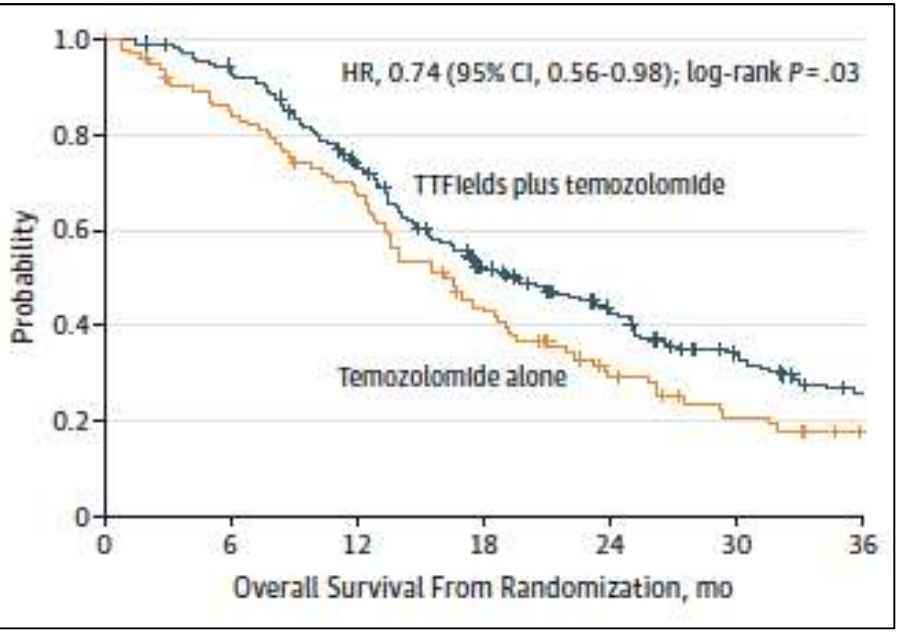
Preliminary Communication

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma

A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew A. Kanner, MD; Santosh Kesari, MD, PhD; David M. Steinberg, PhD; Steven A. Toms, MD, FACS, MPH; Lynne P. Taylor, MD, FAAN; Frank Lieberman, MD; Antonio Silvani, MD; Karen L. Fink, MD, PhD; Gene H. Barnett, MD, MBA; Jay-Jiguang Zhu, MD, PhD; John W. Henson, MD, MBA, FAAN; Herbert H. Engelhard, MD, PhD; Thomas C. Chen, MD, PhD; David D. Tran, MD, PhD; Jan Sroubek, MD; Nam D. Tran, MD, PhD; Andreas F. Hottinger, MD, PhD; Joseph Landolfi, DO; Rajiv Desai, MD; Manuela Caroli, MD; Yvonne Kew, MD, PhD; Jerome Honnorat, MD, PhD; Ahmed Idbaih, MD, PhD; Eilon D. Kirson, MD, PhD; Uri Weinberg, MD, PhD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD





JAMA. 2015;314(23):2535-2543.

Tumor Treating Fields; updated data

Treatment Characteristics

	TTFields/TMZ (n=466)	**TMZ alone** (n=229)
Completed standard radiation therapy (57-63 Gy) [%]	92%	94%
Median time from GBM diagnosis - randomization	3.8 mo	3.7 mo
Median no. of adj. TMZ cycles	6	5
range	*0 – 51*	*0 – 33*
Median no. of TTFields cycles (1 mo = 1 cy)	8.2	NA
range	*0 – 82*	
TTFields Treatment Adherence † (>75%)	75%	
Region: US / Rest of the world	47% / 53%	52% / 48%

† during first 3 mo of treatment

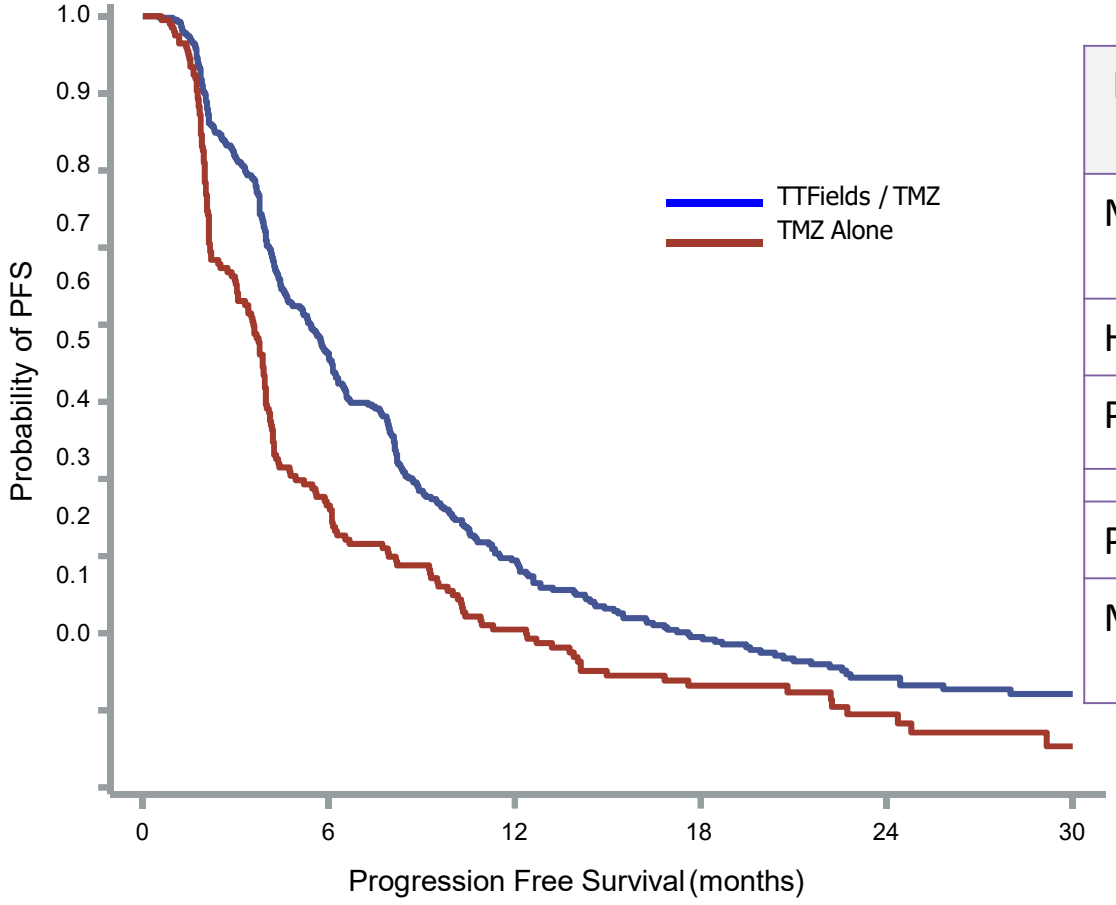
Safety (Grade 3-4 AEs)

	TTFields / TMZ		TMZ Alone	
	(N=456)		(N=216)	
System Organ Class \ Preferred Term	Grade 3	Grade 4	Grade 3	Grade 4
Number of Patients with >=1 AE	37%	14%	36%	12%
Blood and lymphatic system disorders	9%	4%	9%	2%
Leukopenia	2%	0	<1%	0
Lymphopenia	3%	1%	3%	0
Neutropenia	2%	1%	1%	<1%
Thrombocytopenia	6%	3%	4%	1%
Gastrointestinal disorders	5%	<1%	3%	<1%
General disorders + administration site conditions	9%	<1%	6%	0
Asthenia	3%	0	1%	0
Fatigue	4%	0	3%	0
Gait disturbance	2%	0	1%	0
Infections and infestations	7%	<1%	4%	1%
Injury, poisoning and procedural complications	5%	0	3%	0
Fall	2%	0	1%	0
Medical device site reaction	2%†	0	0	0

†Grade 1+2 skin irritations in 52% of patients

Progression Free Survival - ITT

(n = 695)

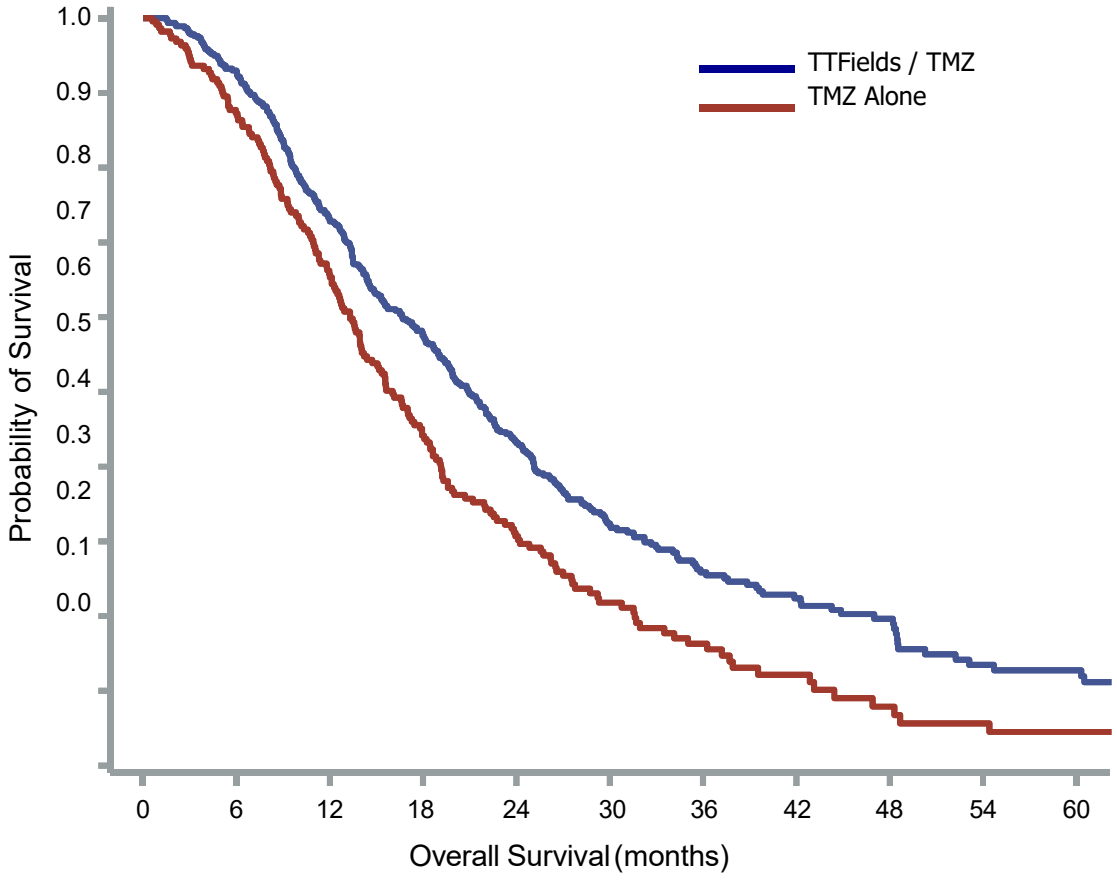


TTFields	466	229	100	62	30	18
TMZ	229	66	35	18	9	2

Progression free	TTFields/TMZ	TMZ
Median	6.7 mo 6.1 – 8.1	4.0mo 3.8 – 4.4
Hazard ratio	0.63 (CI 0.52 – 0.76)	
P-value	0.00005	
PFS from diagnosis:		
Median	11.2 mo 10.0 – 11.8	7.8mo 7.3 – 8.2

Overall Survival - ITT

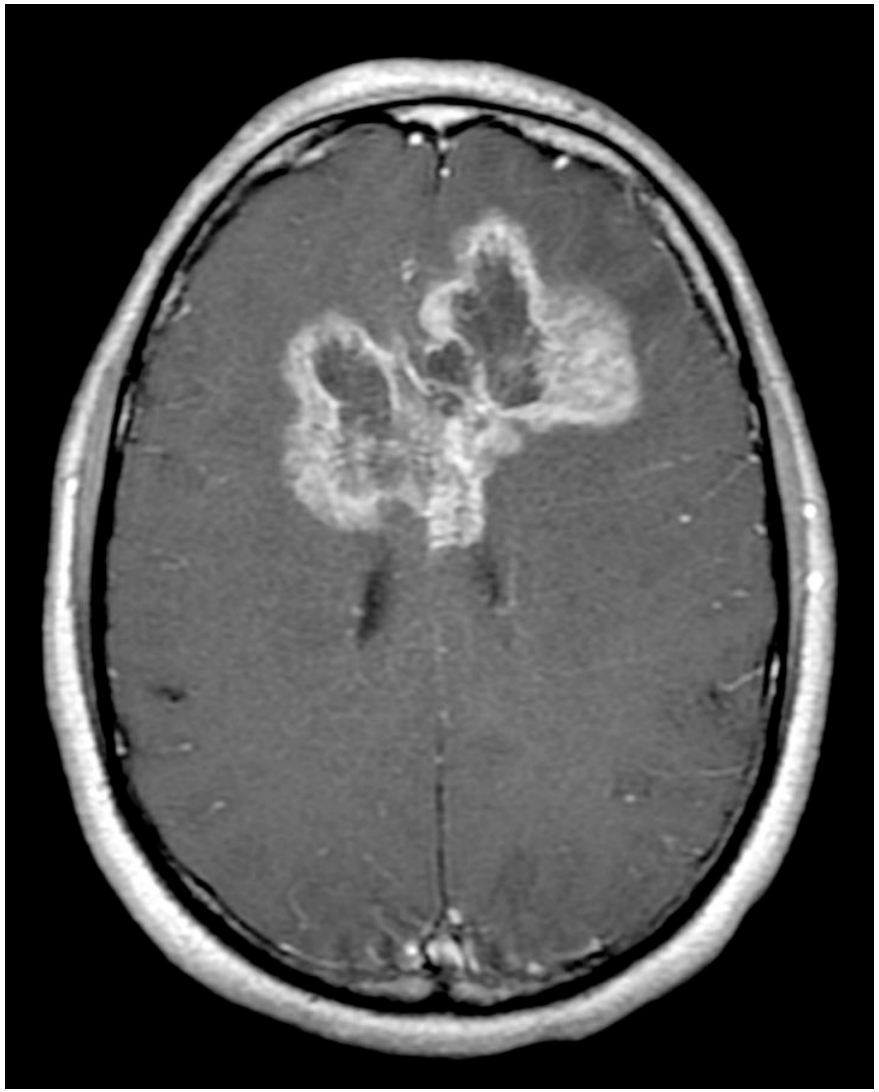
(n = 695)



TTFields	466 424 333 256 174 107 65 45 30 19 16	
TMZ	229 191 144 95 60 33 22 13 7 5 2	

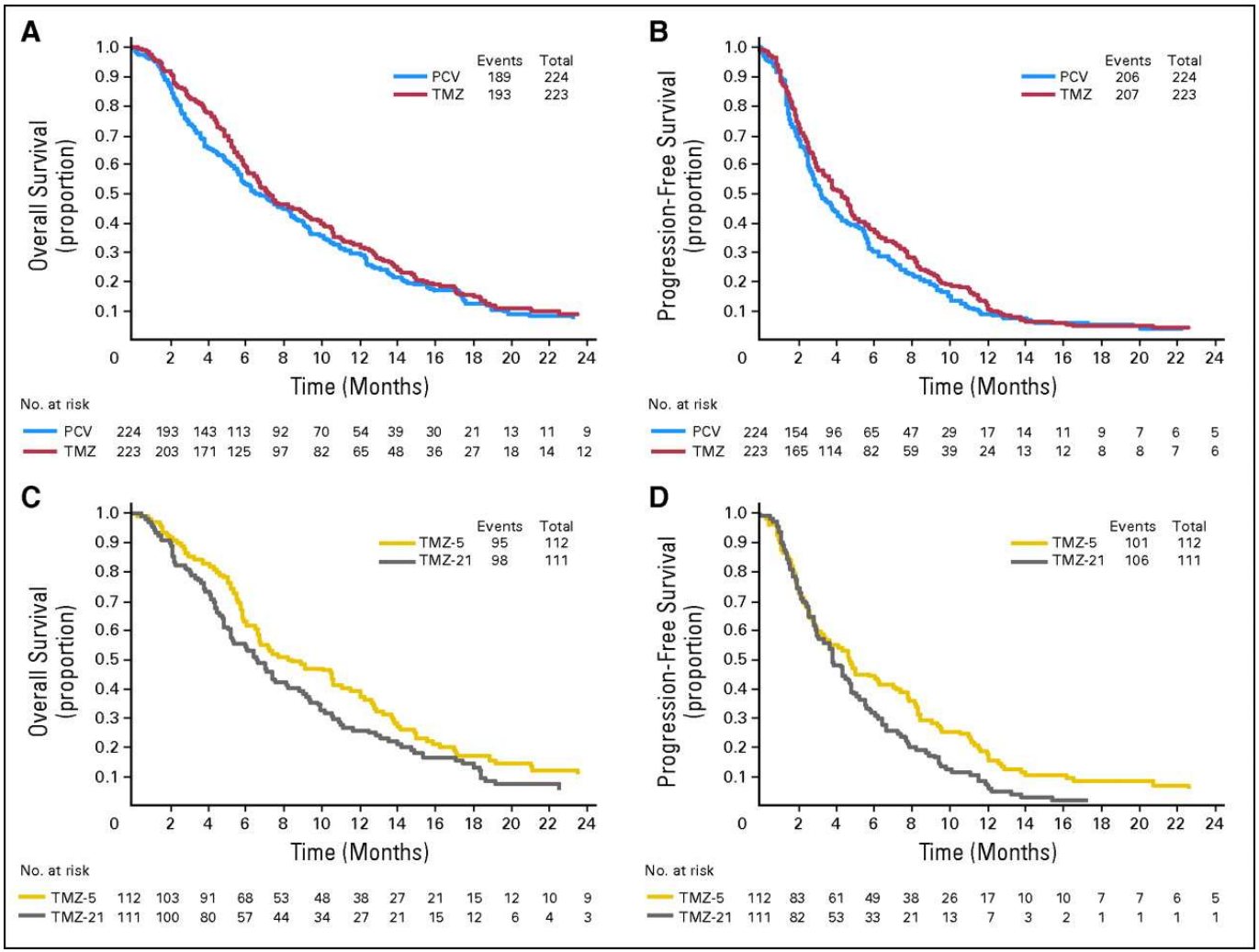
Survival (from random)	**TTFields/TMZ**	**TMZ**
Median 95% CI	20.9 mo 19 .3 – 22.7	16.0 mo 14.0 – 18.4
2-year 95% CI	43.1 % (38.7 – 48.0)	30.7 % (25.1 – 37.5)
Hazard ratio	0.63 (CI 0.53 – 0.76)	
P-value	0.00006	
Survival from diagnosis:		
Median 95% CI	24.5 mo 22.8 – 26.3	19.8 mo 17.6 22.1

Recurrent GBM



Recurrent GBM:

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



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

JOURNAL OF CLINICAL ONCOLOGY ASCO

Relapsed GBM after RT-TMZ

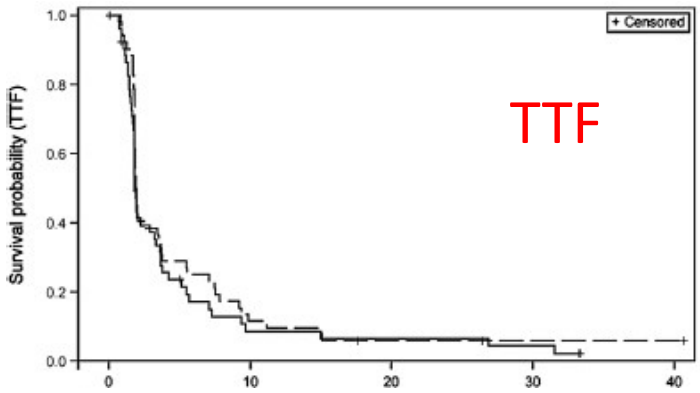
- **No widely accepted standard**
  - Re-resection +/- carmustine wafers?
  - PCV?
  - VEGF inhibition +/- CCNU:
    - various regimes containing bevacizumab
    - cediranib negative
  - EGFR TK inhibitors
    - erlotinib associated with *reduced* PFS (van den Bent JCO 2009)
  - TMZ rechallenge +/- altered temozolomide scheduling?
  - Immune checkpoint inhibition

Opportunity to test novel agents

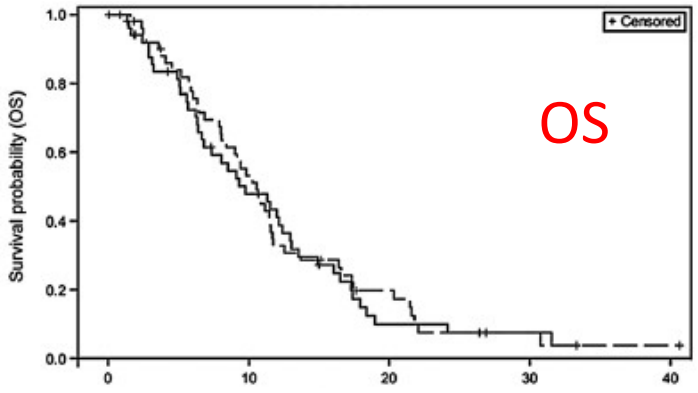
Personalized Medicine and Imaging

Clinical Cancer Research

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



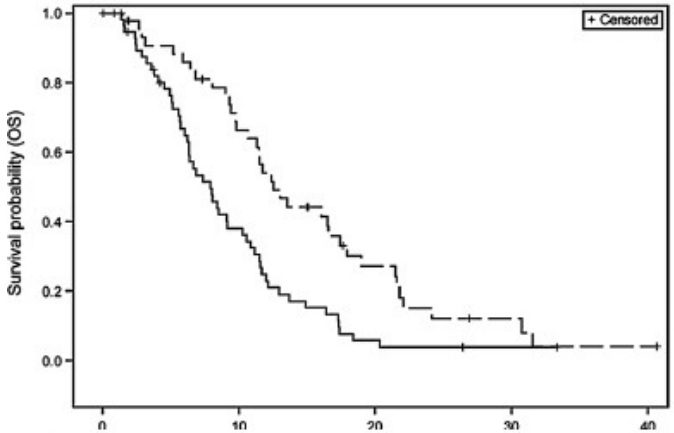
TTF



OS

TMZ 7/14 days
v. 21/28 days

PFS-6: 21%



Improved OS in MGMT methylated with either regime

Weller et al, Clin Can Res 2015

VOLUME 25 · NUMBER 30 · OCTOBER 20 2007

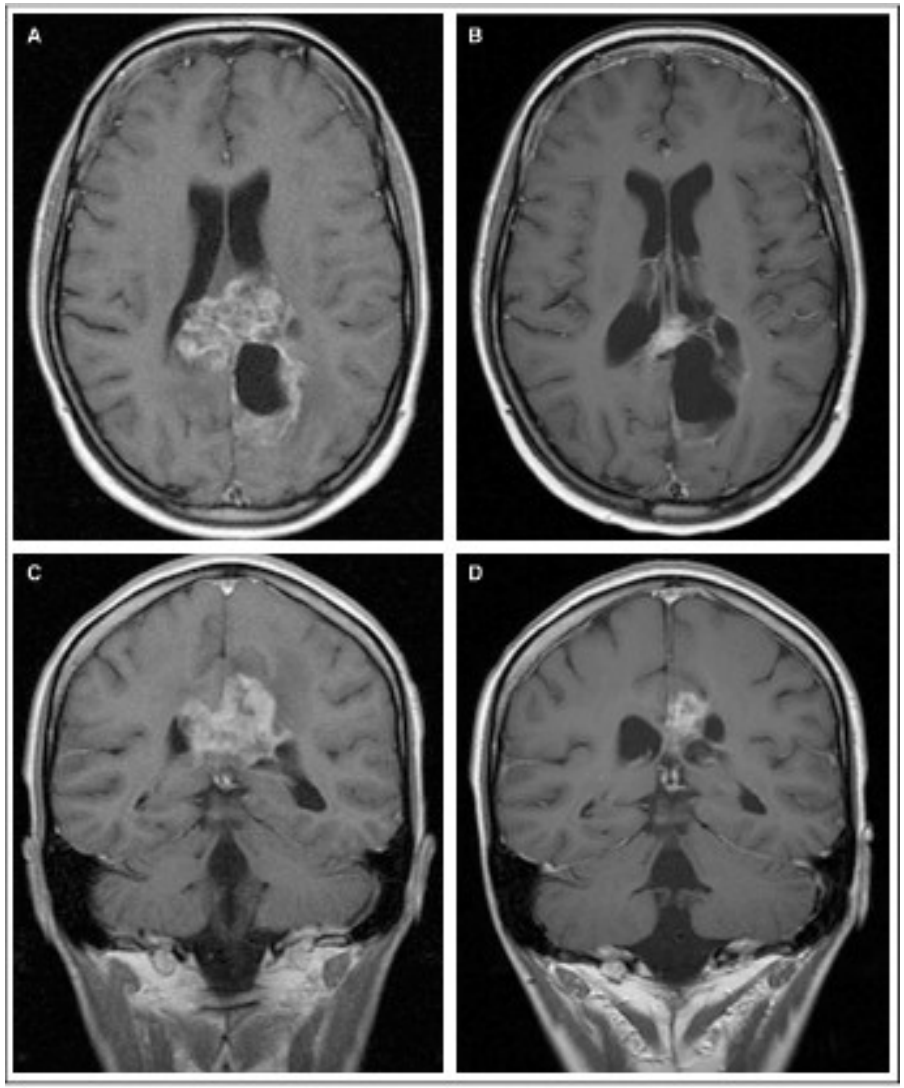
JOURNAL OF CLINICAL ONCOLOGY

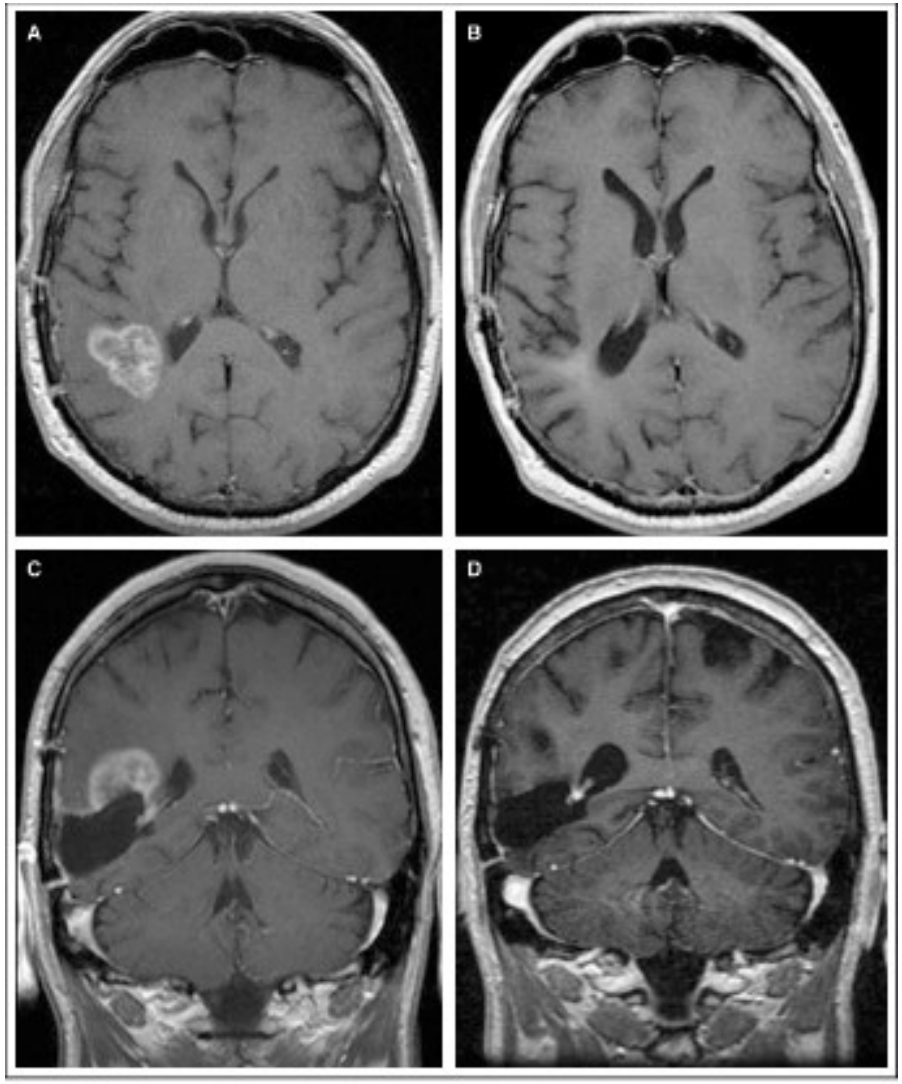
ORIGINAL REPORT

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

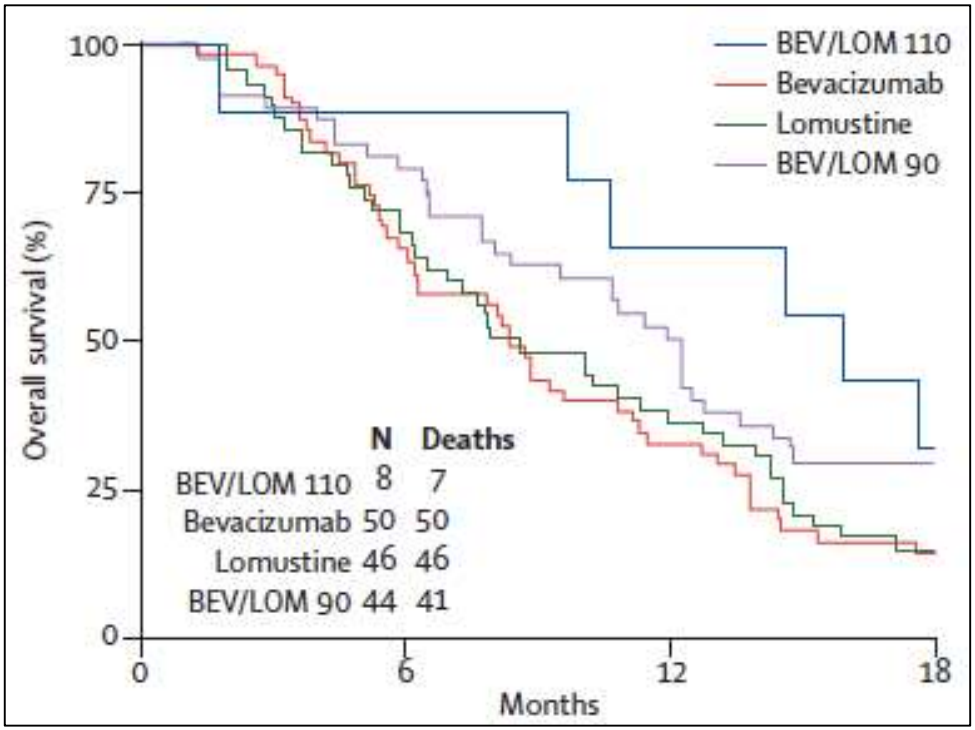




Response v. pseudoresponse?

Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial

Walter Taal, Hendrika M Oosterkamp, Annemiek M E Walenkamp*, Hendrikus J Dubbink*, Laurens V Beerepoot, Monique C J Hanse, Jan Buter, Aafke H Honkoop, Dolf Boerman, Filip Y F de Vos, Winand N M Dinjens, Roelien H Enting, Martin J B Taphoorn, Franchette W P J van den Berkmortel, Rob L H Jansen, Dieta Brandsma, Jacoline E C Bromberg, Irene van Heuvel, René M Vernhout, Bronno van der Holt, Martin J van den Bent*



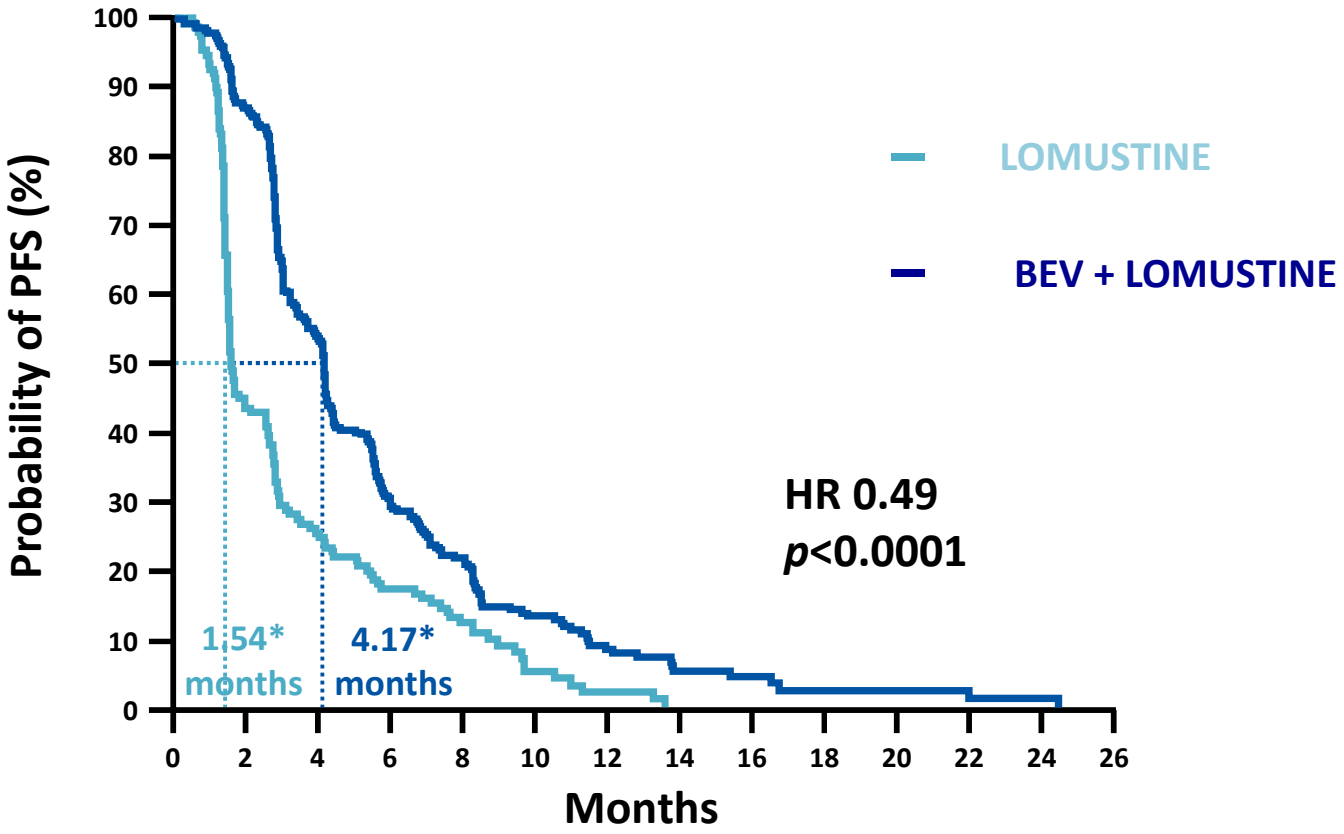
PFS-6: 11% MGMT unmethylated
40% MGMT methylated

Taal et al, Lancet Oncol 2014

EORTC 26101
A Phase III Trial Exploring the Combination of Bevacizumab and Lomustine in Patients with First Recurrence of a Glioblastoma

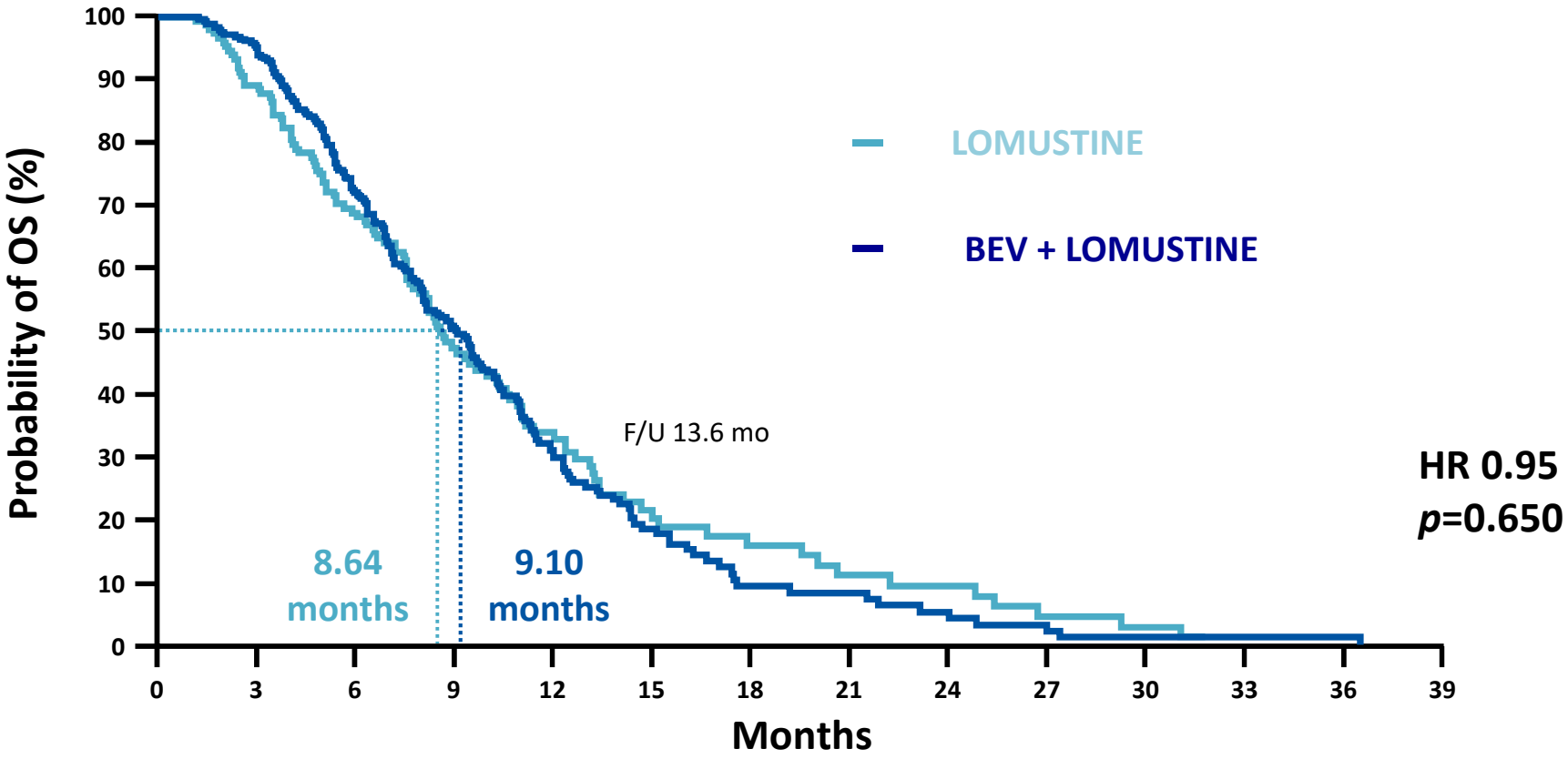
Wolfgang Wick
on behalf of the EORTC Brain Tumor Group Investigators

26101: Progression-Free Survival



*Stratified analysis

26101: Overall Survival



	O	N	Patients at risk, N											
LOM	113	149	132	102	55	32	17	11	7	6	3	2	0	0
Bv+LOM	216	288	273	207	122	58	25	10	9	6	4	1	1	1

Immune checkpoint inhibition

"Bristol-Myers Squibb today announced that CheckMate -143, a randomized Phase 3 clinical trial evaluating the efficacy and safety of *Opdivo* (nivolumab) in patients with first recurrence of glioblastoma multiforme (GBM), did not meet its primary endpoint of improved overall survival over bevacizumab monotherapy."

Sativex (GW Pharma)

- Cannabinoid mix
  - 1:1 THC + CBD
  - From *Cannabis sativa*
  - (≠ cannabis)
  - Oromucosal spray
  - Individual dose titration
  - Widely used in MS, cancer pain, nausea, epilepsy

Mechanisms

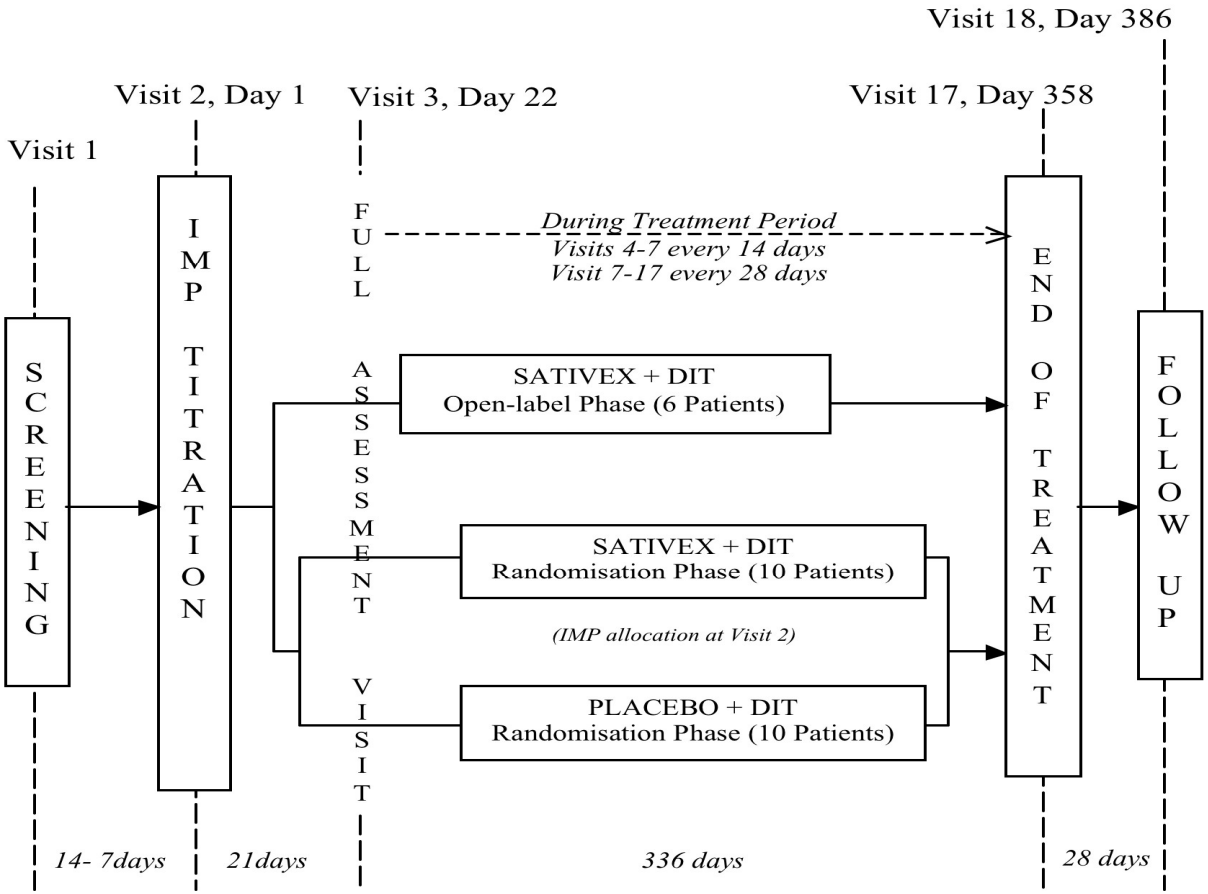
- Pro-apoptotic
- Via ER stress (autophagy) pathways

  - In vitro data in established cell lines
    - GBM stem-like lines
    - Additive/synergism w TMZ and XR

  - In vivo data in standard orthotopic models
    - Enhanced growth delay w TMZ and XR

Study overview

- Open label PhI, run in to randomised, placebo controlled Ph Ib



Dose Intense TMZ: 85mg/m^2 21 q28.

Self titrate Sativex after 7d TMZ: Min 3 max 12 sprays/day

Sativex study – preliminary data

1 year OS 83% vs 44%
PFS-6: 42% vs 33%

PFS-6 from DIRECTOR trial: 21%

Any questions?

Management of ependymoma of the brain and spinal cord

Sarah Jefferies

Overview

- Excellent update on surgery and the recent molecular advances
- Overview of evidence for adjuvant treatment in children
- Overview of evidence for adjuvant treatment in adults

Treatment

- **Surgery**
  - Gross total resection
  - Re-resection for recurrence

- **Adjuvant Treatments**
  - Radiotherapy
  - (+re-irradiation)

  - Chemotherapy

Evidence for surgery

Is gross-total resection sufficient treatment for posterior fossa ependymomas?

LELAND ROGERS, M.D., JEANETTE PUESCHEL, M.D., ROBERT SPETZLER, M.D., WILLIAM SHAPIRO, M.D., STEPHEN COONS, M.D., TERRY THOMAS, M.S., AND BURTON SPEISER, M.D., M.S.

J Neurosurg 102:629–636, 2005

ESTRO School

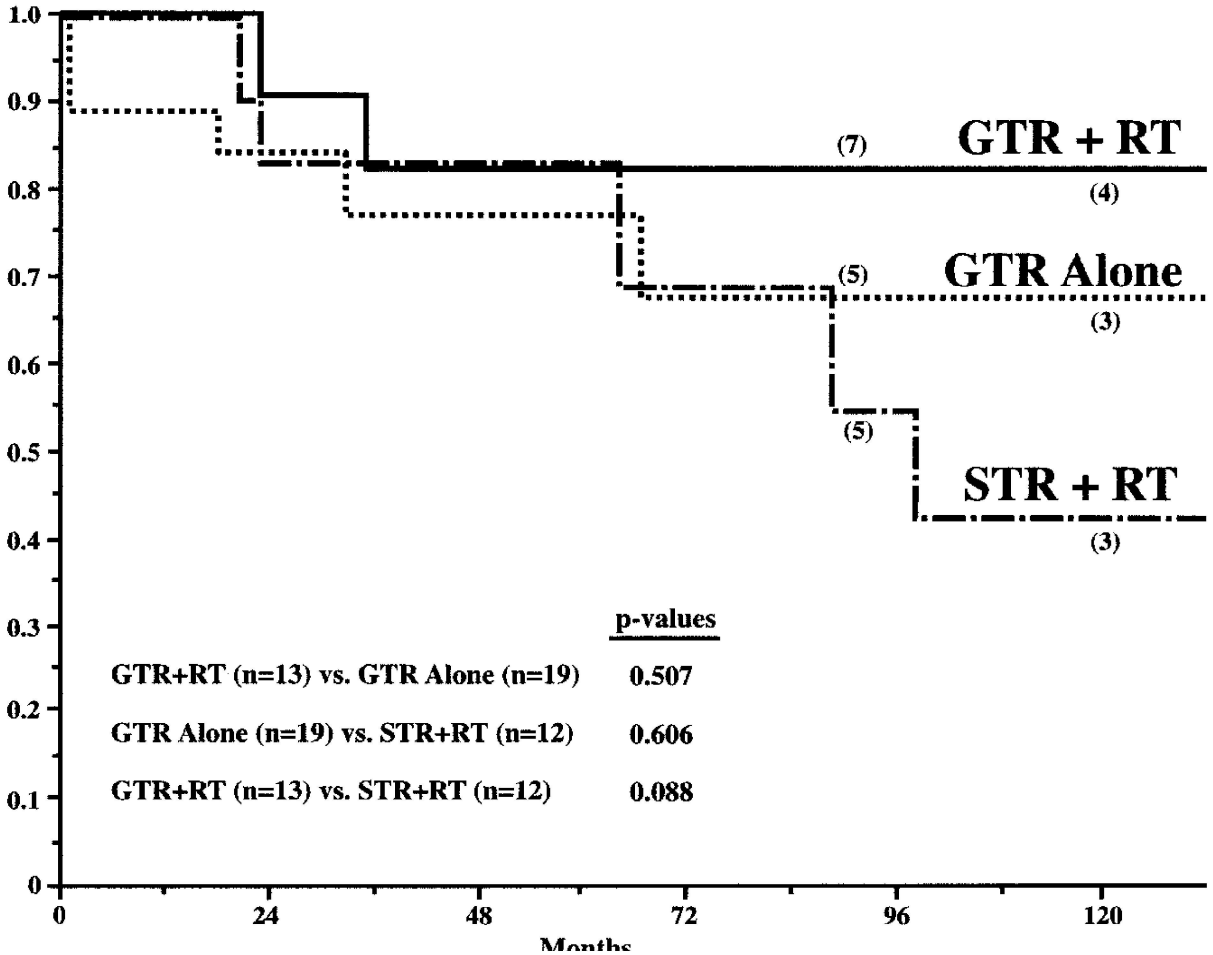
Evidence for surgery

Characteristics of patients with posterior fossa ependymomas

Characteristic	No. of Patients (%)
total no. of patients	45 (100)
sex	
male	29 (64)
female	16 (36)
age at diagnosis (yrs)	
<18	12 (27)
≥18	33 (73)
median	36.9
range	1.3–84.5
location of lesion	
floor of 4th ventricle	27 (60)
roof of 4th ventricle	5 (11)
cerebellopontine angle	8 (18)
brainstem	5 (11)
grade of lesion	
low grade	43 (96)
anaplastic	2 (4)

J Neurosurg 102:629–636, 2005

Evidence for surgery



J Neurosurg 102:629–636, 2005

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Evidence for radiotherapy

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

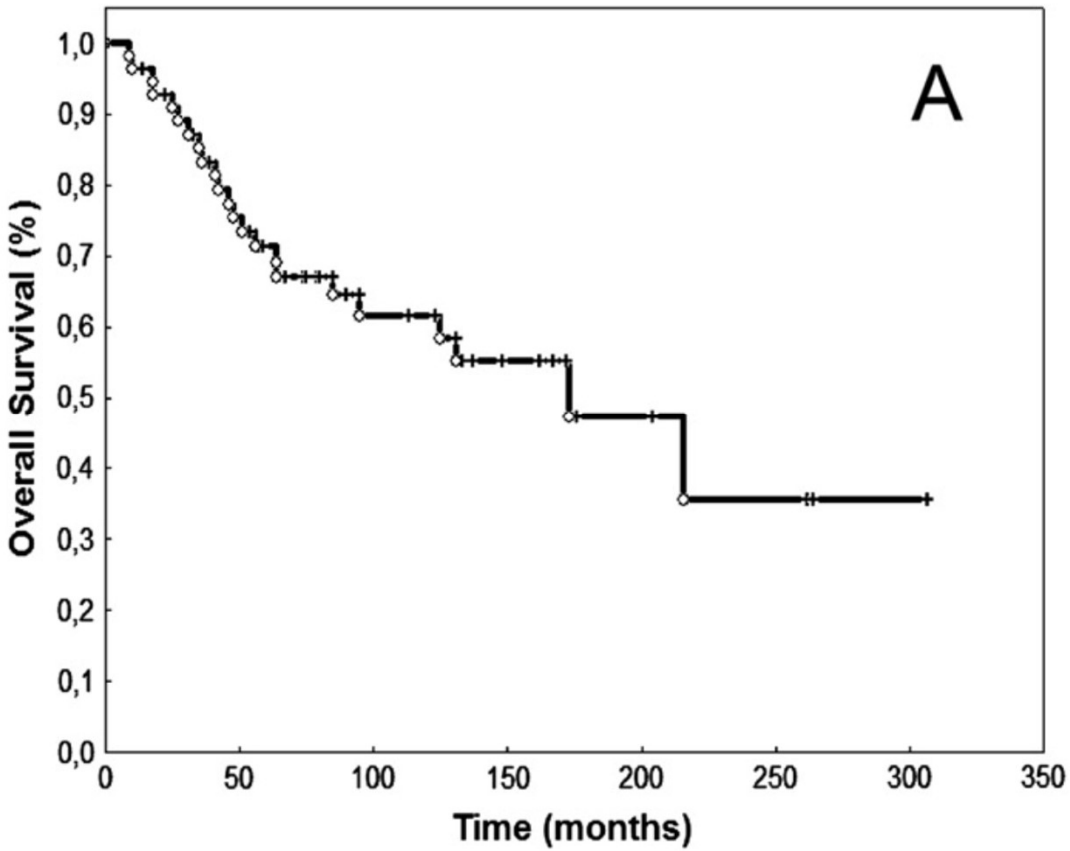
STEPHANIE E. COMBS, M.D.,* VERENA KELTER,* THOMAS WELZEL, M.D.,* WOLFGANG BEHNISCH, M.D.,[y]
ANDREAS E. KULOZIK, M.D., PH.D.,[y] MARC BISCHOF, M.D.,* HOLGER HOF, M.D.,*
JÜRGEN DEBUS, M.D., PH.D.,* AND DANIELA SCHULZ-ERTNER, M.D.*

Table 2. Summary of surgical resection and radiotherapy in 57 patients treated for histologically confirmed ependymoma

	Surgery			Radiotherapy	
Histology	Biopsy	Subtotal resection	Complete resection	Local	Craniospinal axis
Myxopapillary ependymoma (n = 4; 7%)	0	4	0	4	0
Ependymoma (n = 23; 40%)	6	14	3	20	3
Anaplastic ependymoma (n = 28; 53%)	2	17	11	17	13

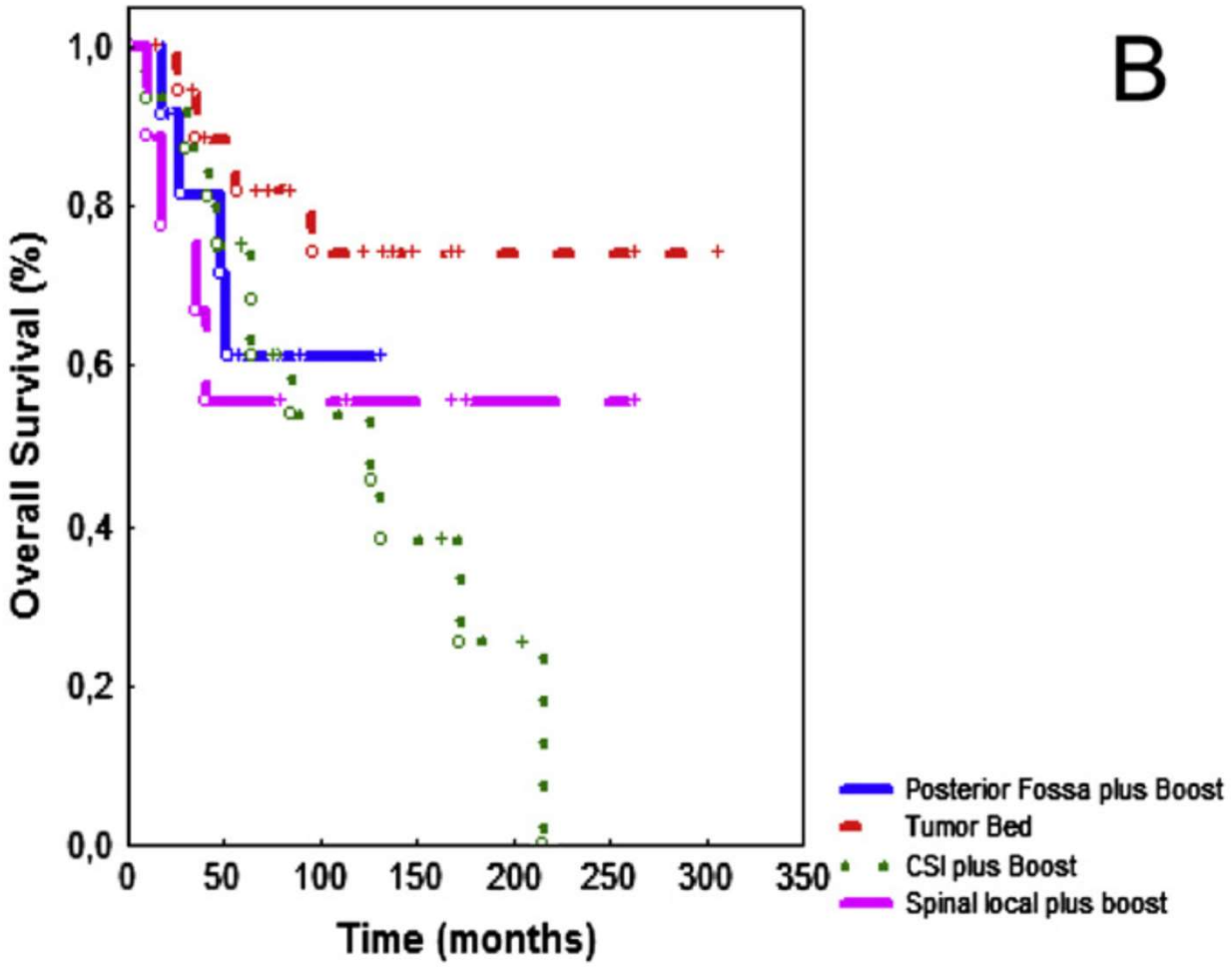
Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 972–978, 2008

Overall Survival



Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 972–978, 2008

Localised RT not CSI



Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 972–978, 2008

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THE SIGNIFICANCE OF RADIOTHERAPY TREATMENT DURATION IN INTRACRANIAL EPENDYMOMA

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

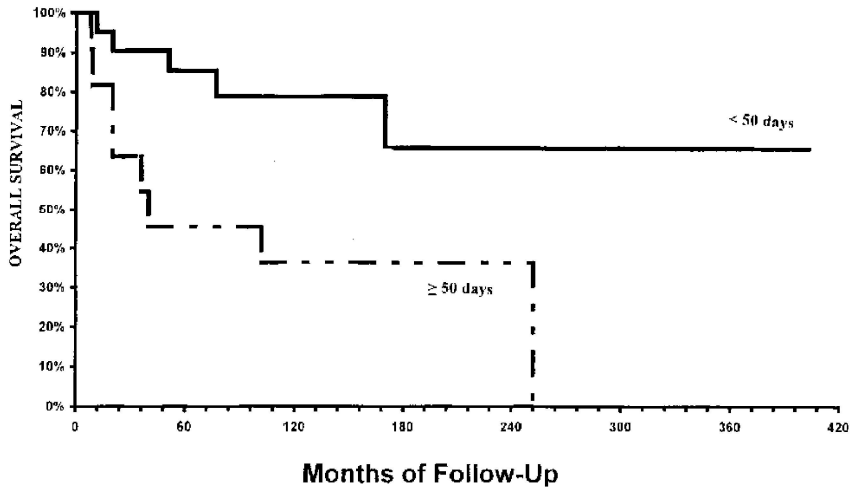


Fig. 2. Comparison of overall survival rates for patients with radiotherapy treatment duration <50 days vs. ≥50 days (p = 0.01, log-rank test).

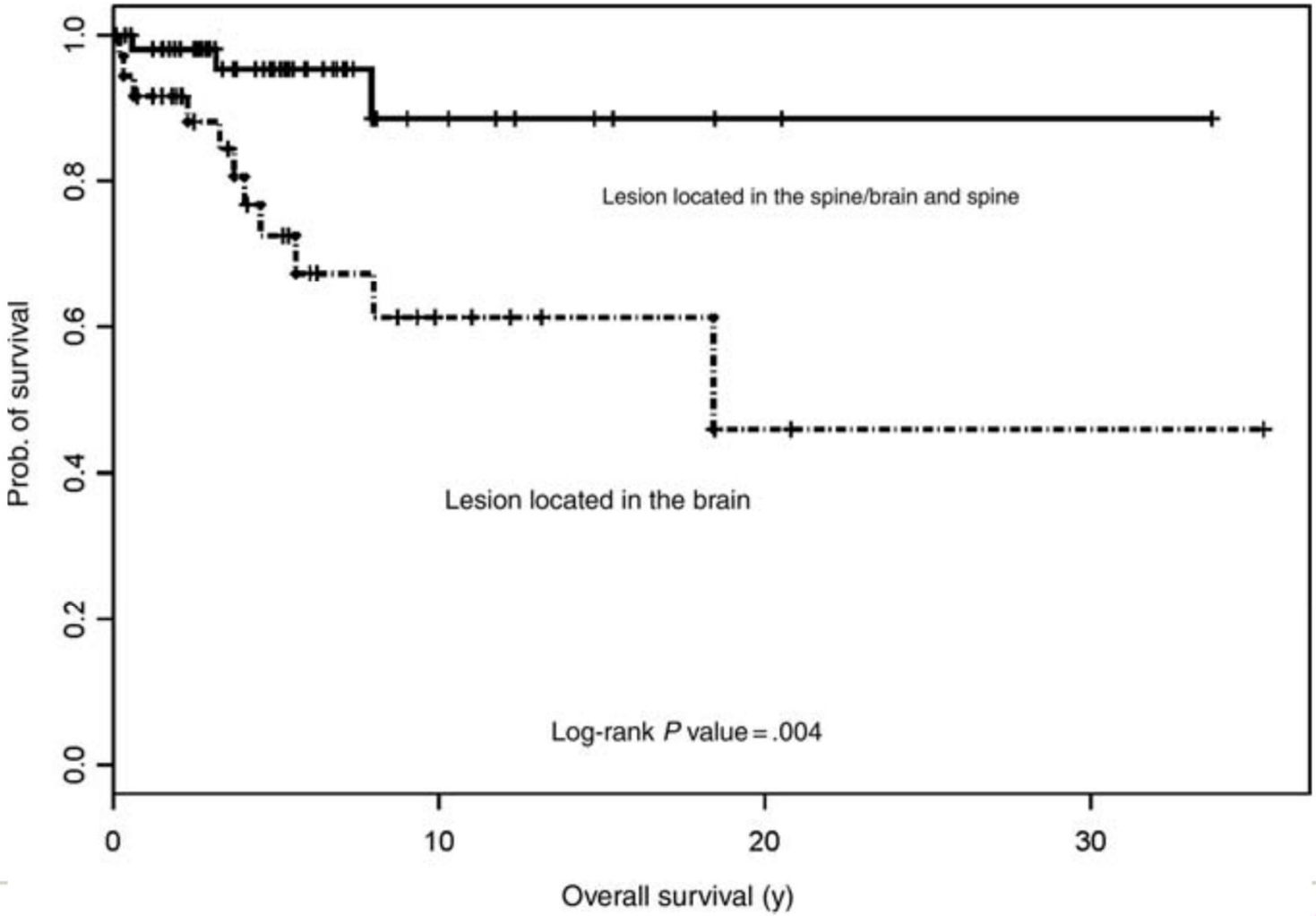
Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 3, pp. 585–589, 2000

Prognostic Features in adults

	All	Brain	Spine
Total	123	40	80
Gender			
Male	63 (51%)	20 (50%)	42 (53%)
Female	60 (49%)	20 (50%)	38 (47%)
Age			
Range	18–72	19–72	18–69
Mean/median	40/39	40/38	42/40
Location			
Supratentorial		16 (40%)	
Infratentorial		23 (58%)	
Malignancy			
Grade II	112 (91%)	30 (75%)	79 (99%)
Grade III	11 (9%)	10 (25%)	1 (0.01%)
Grade III at recurrence	15	13	2

Neuro-Oncology 12(8):862–870, 2010.

Prognostic Features in adults



Neuro-Oncology 12(8):862–870, 2010.

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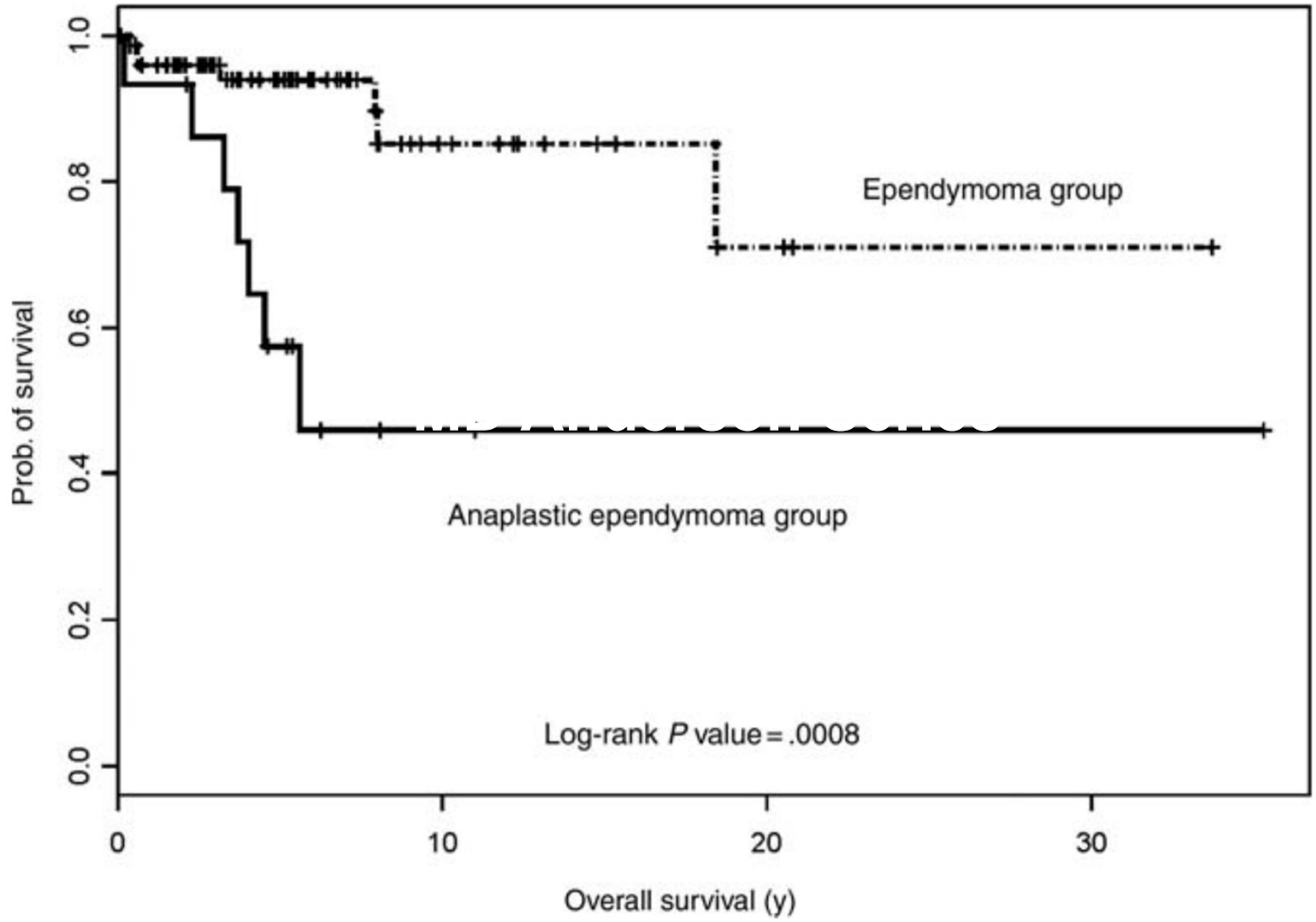
Prognostic Features in adults



Neuro-Oncology 12(8):862–870, 2010.

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Evidence for chemotherapy

- (or lack of……)

Evidence for chemotherapy

- Sensitivity of ependymoma to chemotherapy agents is low

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

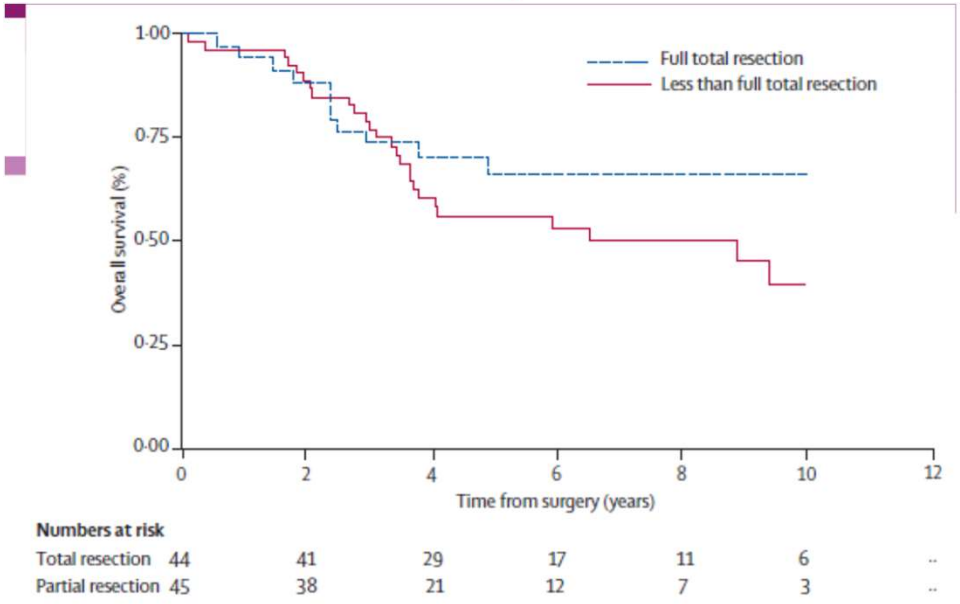
Agent	CR+PR/patients	CR	Reference
Cisplatin	11/33	6	[2–5]
Carboplatin	4/31		[6, 7]
AZQ	2/29	2	[18–22]
Ifosfamide	1/20		[11, 12]
Idarubicin	0/13		[27]
thio-TEPA	0/12		[13, 14]
Dibromodulcitol	0/12		[23]
PCNU	1/11	1	[8, 9]
Etoposide	2/9	1	[16, 17]
Iproplatin	0/7		[7]
Topotecan	0/4		[15]
Procarbazine	0/3		[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%)	

Chemotherapy

	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



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Chemotherapy

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

Lancet Oncol 2007; 8: 696–705

	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.

VOLUME 34 · NUMBER 21 · JULY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Therapeutic Impact of Cytoreductive Surgery and Irradiation of Posterior Fossa Ependymoma in the Molecular Era: A Retrospective Multicohort Analysis

4 retrospective cohorts of posterior fossa ependymoma n= 820

Assessed molecular variants EPN_PFA and EPN_ PFB

Assessed role of surgery and radiotherapy

Variable	Hazard Ratio	95% CI	*P*
Progression-free survival (n = 777)			
Age	0.99	0.98 to 1.00	.13
Male	1.25	1.02 to 1.54	.03
Incomplete resection	1.84	1.49 to 2.28	< .001
Adjuvant first-line radiation	0.63	0.49 to 0.79	< .001
Chemotherapy	1.04	0.81 to 1.34	.76
EPN_PFA subgroup	2.14	1.31 to 3.49	.002
Overall survival (n = 778)			
Age	0.98	0.96 to 1.00	.12
Male	1.41	1.97 to 1.85	01
Incomplete resection	2.13	1.60 to 2.82	< .001
Adjuvant first-line radiation	0.52	0.38 to 0.72	< .001
Chemotherapy	0.90	0.65 to 1.26	54
EPN_PFA subgroup	4.30	1.88 to 9.87	< .001

INTERNATIONAL SOCIETY
OF PAEDIATRIC ONCOLOGY

SIOP EPENDYMOMA II

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

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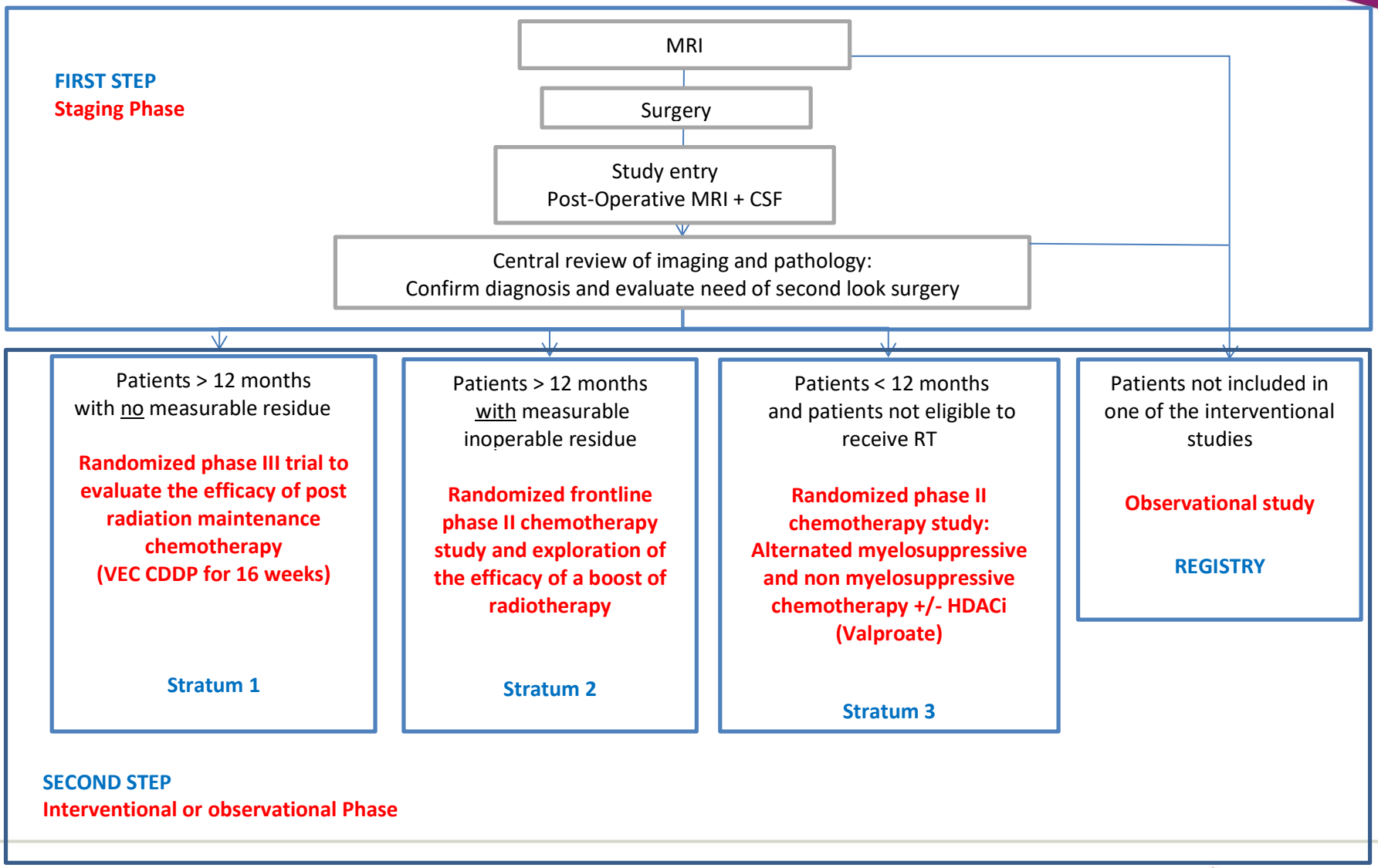

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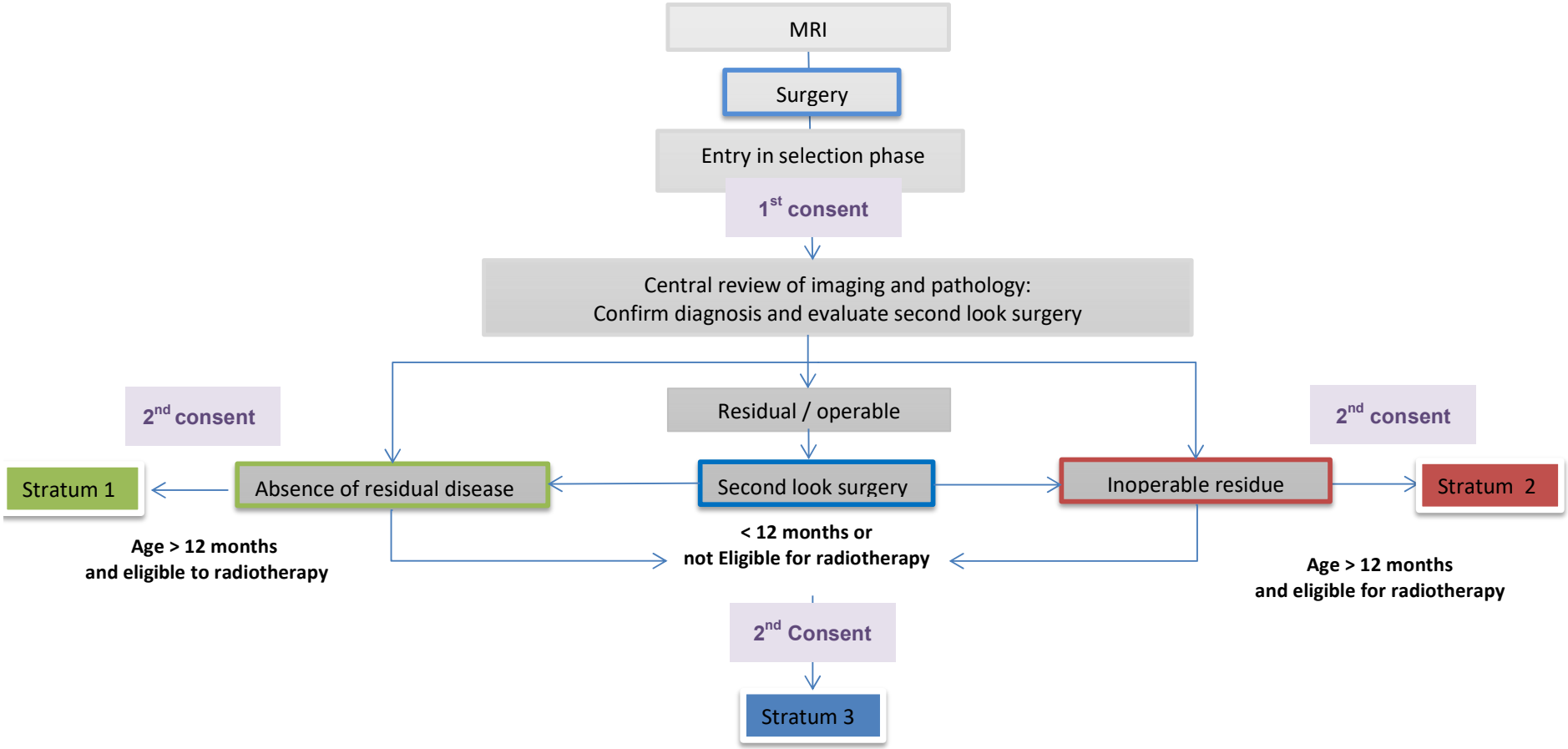
FLOW SHEETS OF PATIENTS INCLUSION



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AT-23. A PHASE II STUDY OF LAPATINIB AND DOSE-DENSE TEMOZOLOMIDE (TMZ) FOR ADULTS WITH RECURRENT EPENDYMOMA: A CERN CLINICAL TRIAL

- First randomised study in adult ependymoma
- Patient related outcomes
- Molecular information collected
- 50 patients enrolled
- Await further follow-up

Neuro-Oncology 16:v8–v22, 2014.

So what to do in adults?

Myxopapillary ependymoma

- Gross total resection
  - no need for further treatment
  - imaging follow-up
- Sub-total/recurrence
  - Radiotherapy
- Further recurrence
  - No standard chemotherapy

So what to do in adults?

Grade II Ependymoma

- Gross Total Resection – observation

Grade II subtotal/Grade III

- radiotherapy

Recurrence

- no proven role for chemotherapy
- ? Re-irradiation

Radiation Doses

Radiotherapy Dose

- Children:
  - 54 Gy/30#
  - High risk 59.4 Gy/33#*
- Adult:
  - 54Gy -60GY/30-33#

* Netson KL, Conklin HM, Wu S, Xiong X, Merchant TE. A 5-year investigation of children's adaptive functioning following conformal radiation therapy for localized ependymoma. Int J Radiat Oncol Biol Phys 2012;84:217-23.

Re-irradiation?

Ependymoma recurrence:

~ 40% local

~ 40% metastatic

~ 20% local and metastatic

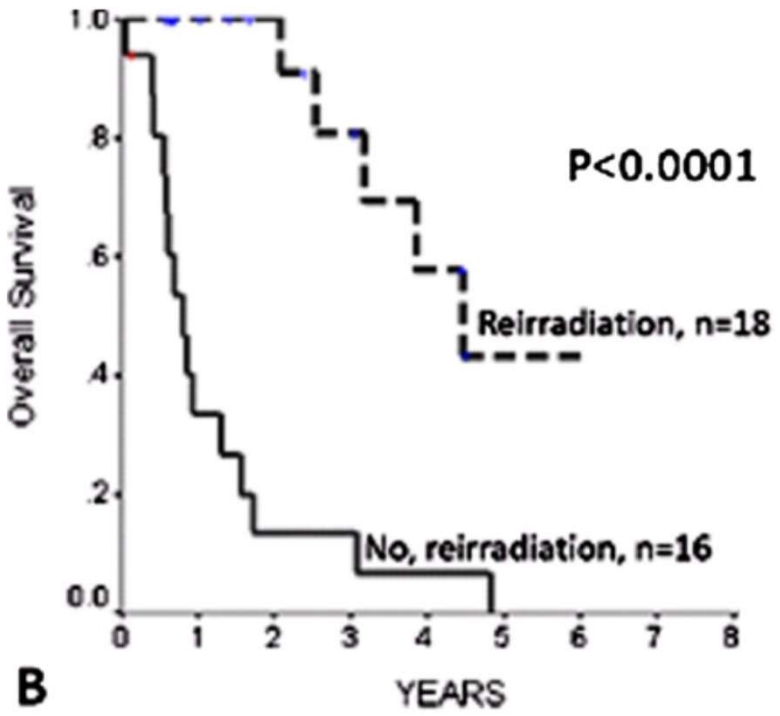
Survival Benefit for Pediatric Patients With Recurrent Ependymoma Treated With Reirradiation

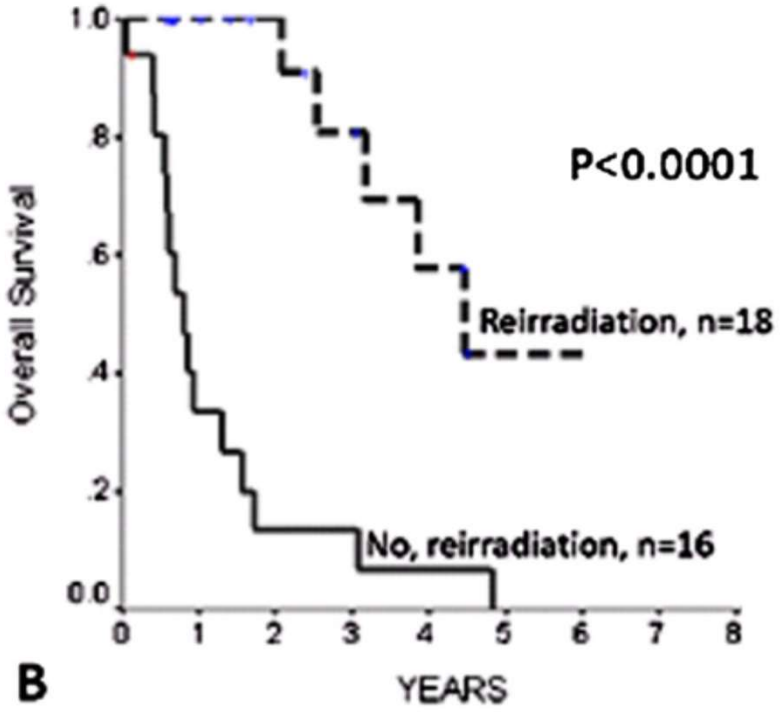
Eric Bouffet, M.D.,* Cynthia E. Hawkins, M.D., Ph.D.,† Walid Ballourah, M.D.,* Michael D. Taylor, M.D., Ph.D.,‡ Ute K. Bartels, M.D.,* Nicholas Schoenhoff,§ Elena Tsangaris,* Annie Huang, M.D., Ph.D.,* Abhaya Kulkarni, M.D., Ph.D.,‡ Donald J. Mabbot, Ph.D.,§ Normand Laperriere, M.D.,¶ and Uri Tabori, M.D.*

- Retrospective series 1986-2010
- 113 patients 47 relapsed
  - 13 – no RT at diagnosis
  - 18 – re-irradiated FSRT or CSI (54GY to brain/36Gy to spine)
  - 16 – no re-irradiation
- Median time to relapse 2.2 years (1.1-9.4)

Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, pp. 1541–1548, 2012

Re-irradiation





- No acute toxicity
- Report some neurocognitive change between pre and post radiotherapy*

Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, pp. 1541–1548, 2012

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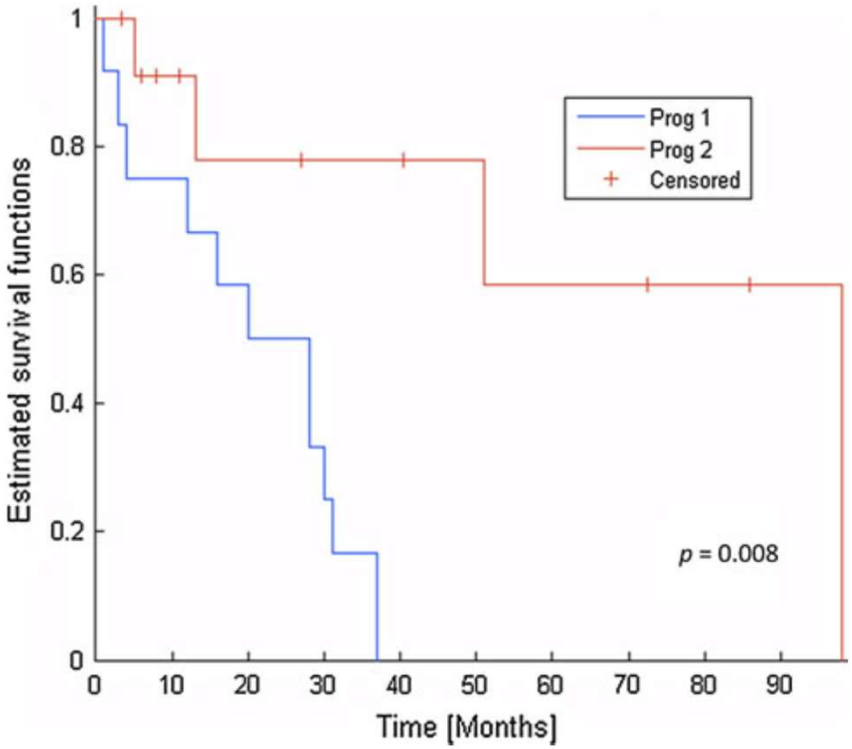
Fractionated stereotactic radiosurgery for recurrent ependymoma in children

Lindsey M. Hoffman · S. Reed Plimpton · Nicholas K. Foreman · Nicholas V. Stence · Todd C. Hankinson · Michael H. Handler · Molly S. Hemenway · Rajeev Vibhakar · Arthur K. Liu

- Retrospective series 1995-2012
- N=12
- Mean time to recurrence 24 months (1-37)
- Treated with fractionated SRS (24Gy/3# or 30/3#)

J Neurooncol (2014) 116:107–111

Re-irradiation



*6/12 patients radionecrosis
3 required treatment

J Neurooncol (2014) 116:107–111

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Recent Advances in the Classification and Treatment of Ependymomas

Heather Leeper, MD[1]
Michelle M. Felicella, MD[2]
Tobias Walbert, MD[3,*]

Curr. Treat. Options in Oncol. (2017) 18: 55
DOI 10.1007/s11864-017-0496-7

Neuro-oncology (GJ Lesser, Section Editor)

ESTRO School


23/10/2017

Cranial germ cell tumours

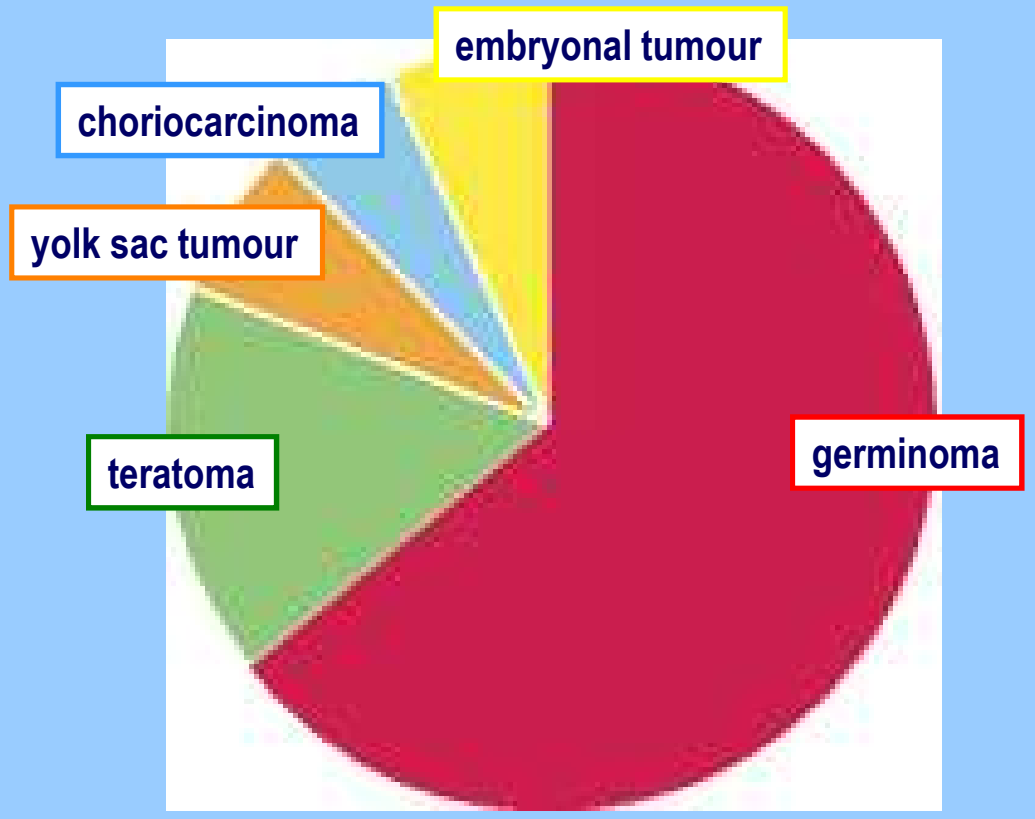
Michael Brada

Vienna

24 October 2017

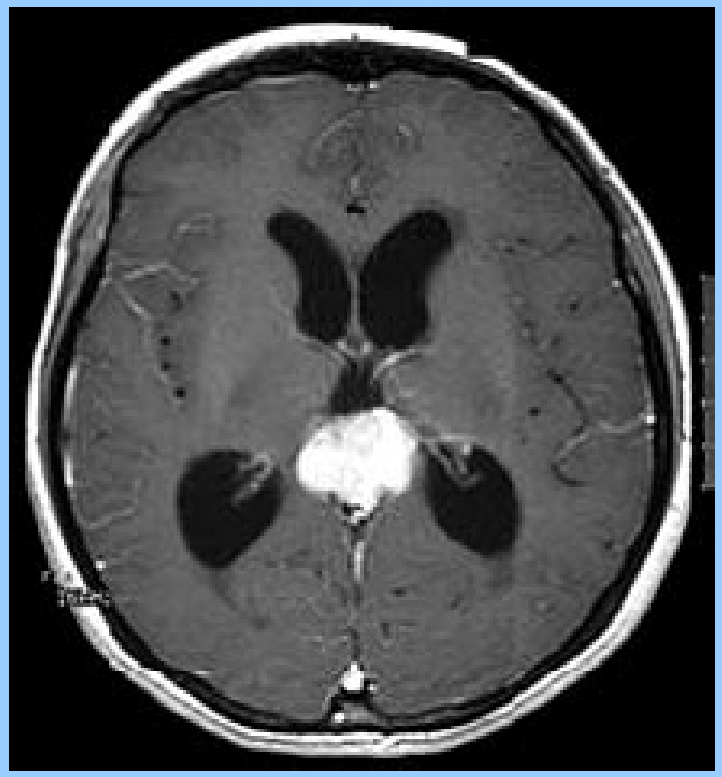
UNIVERSITY OF LIVERPOOL

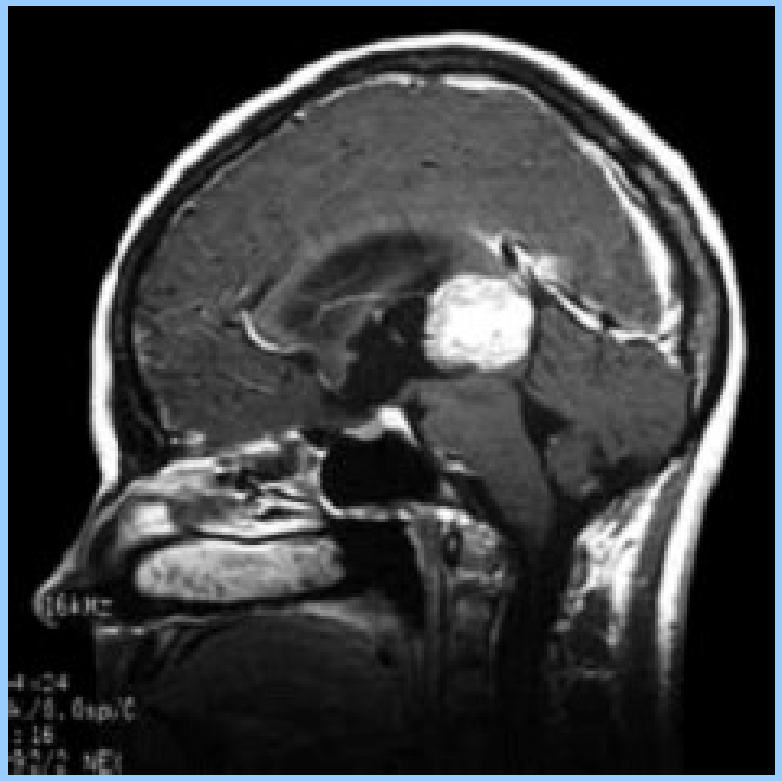
The Clatterbridge Cancer Centre NHS
NHS Foundation Trust



Cranial germ cell tumours

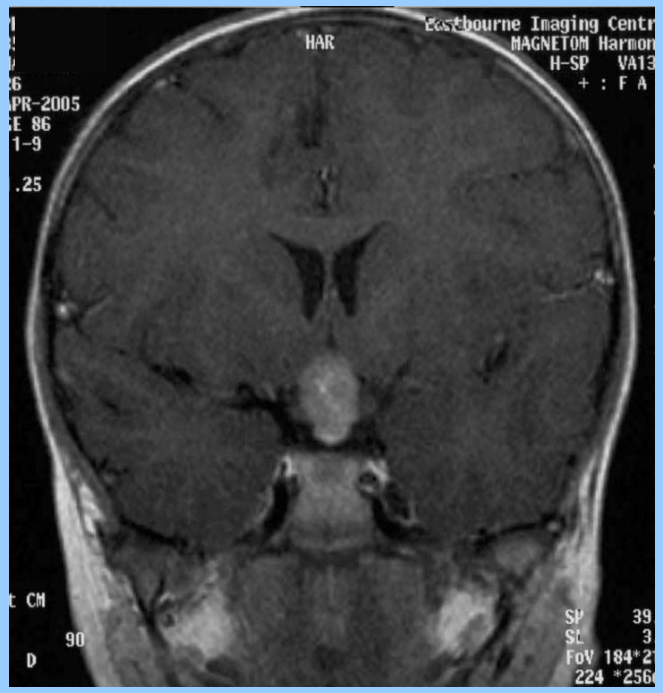
Pineal

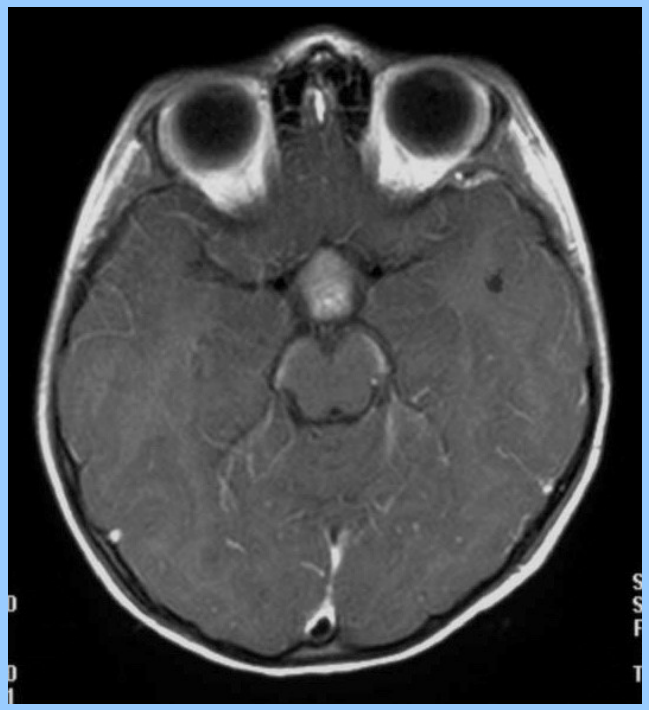




Cranial germinoma

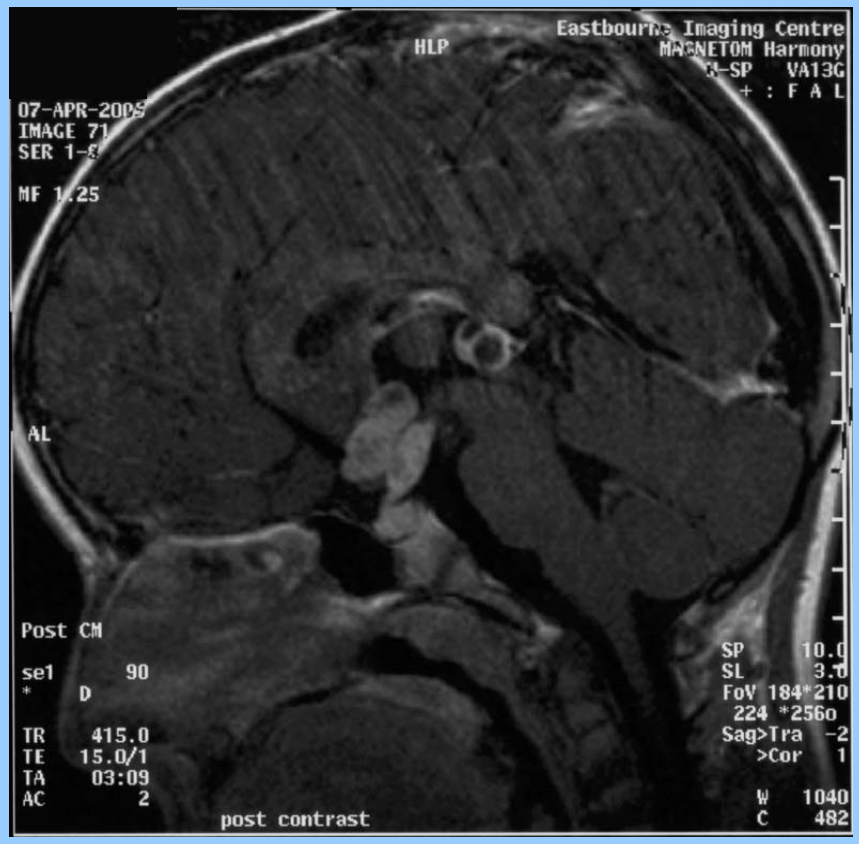
Suprasellar





Cranial germinoma

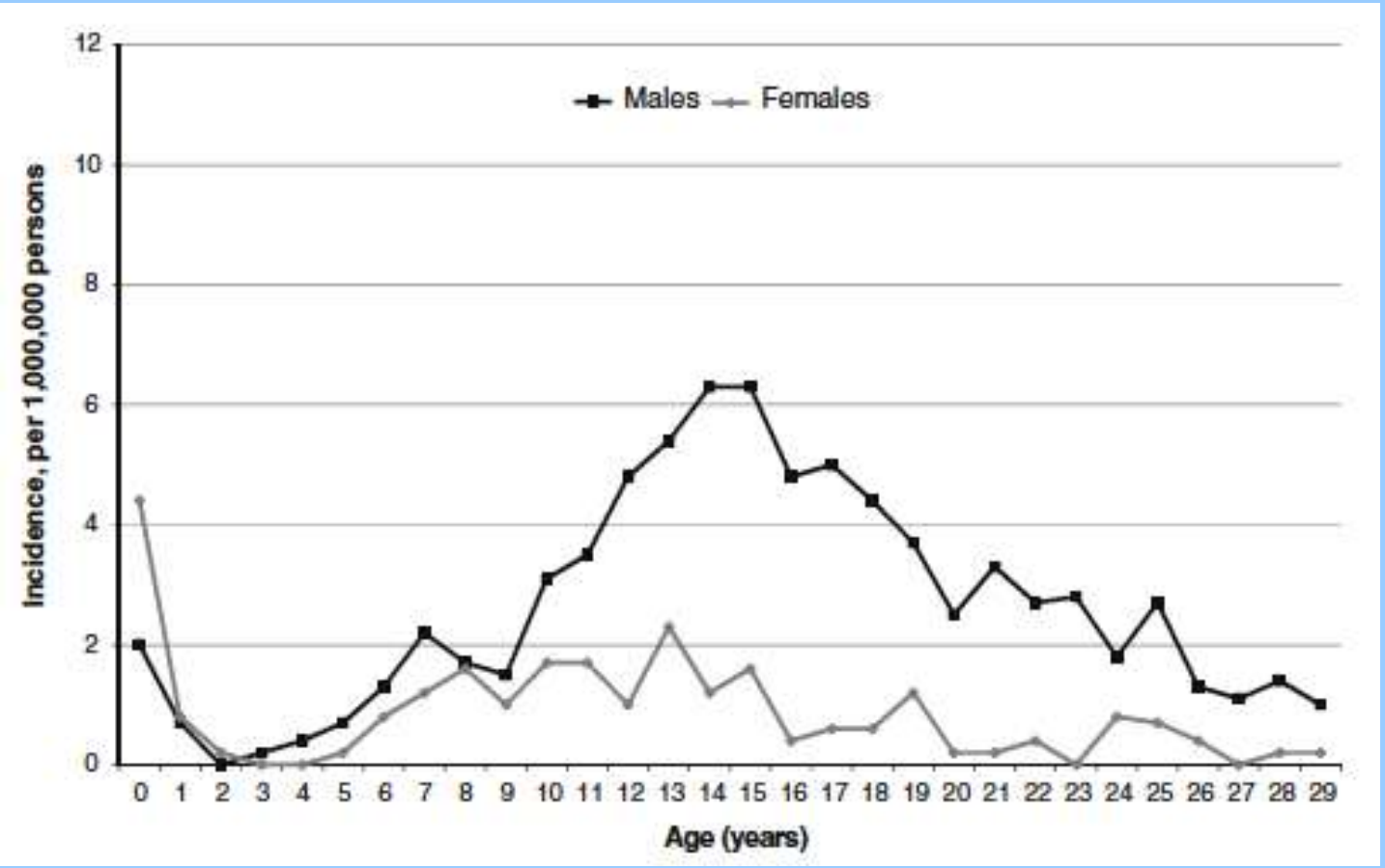
Pineal & suprasellar



Cranial germinoma

SEERS registry 1992-2010
males & females 0 – 29 years

incidence & gender

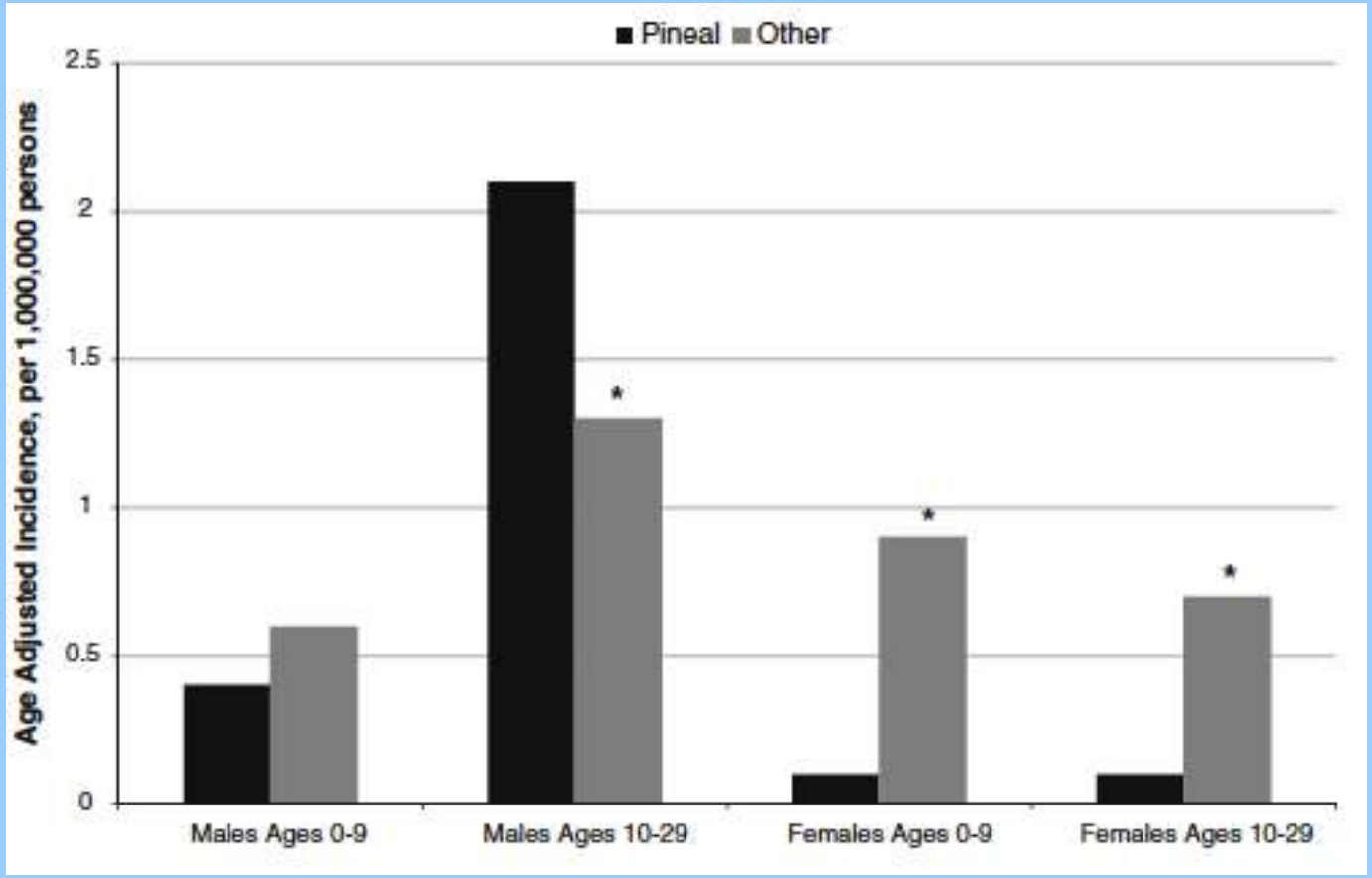


Cranial germ cell tumours

Poynter et al 2014 J Neuro-oncology;120: 381-388

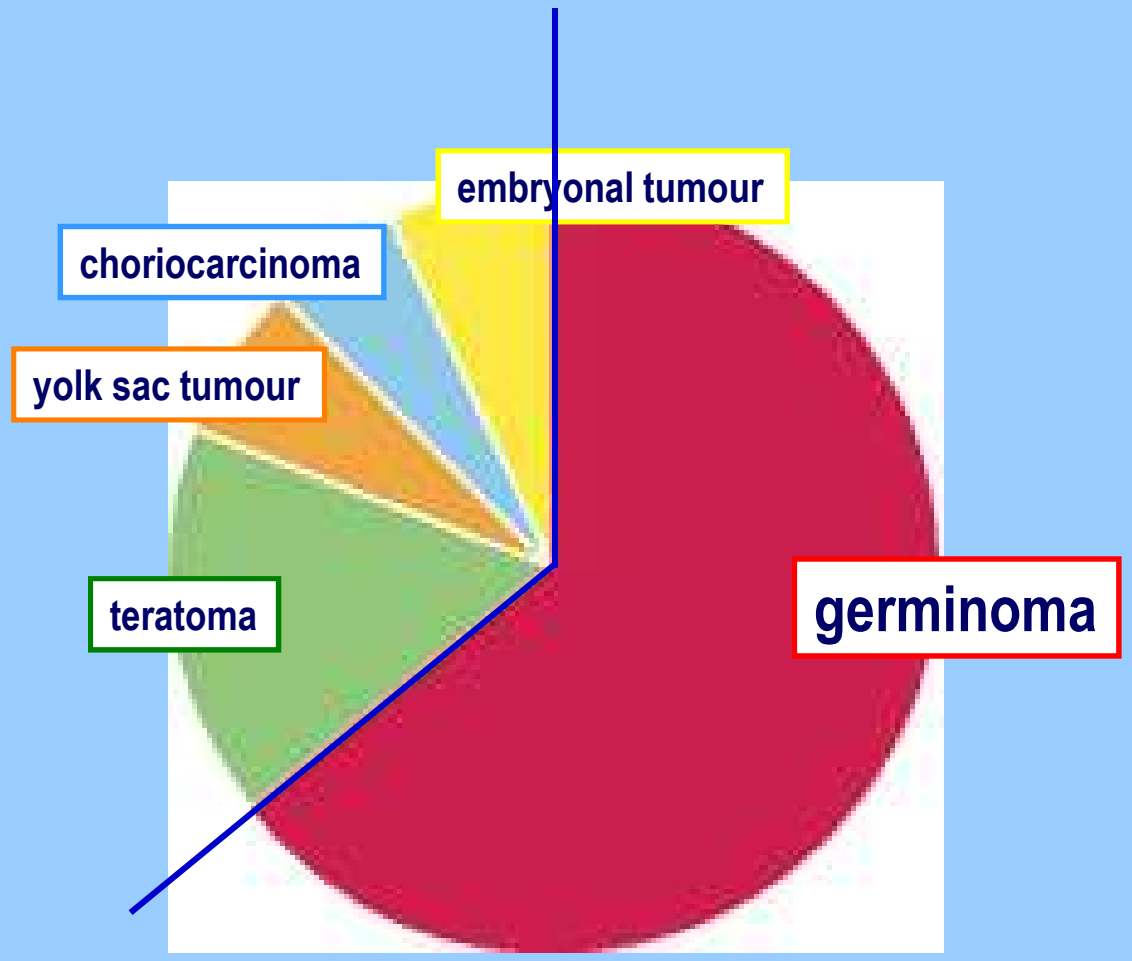
SEERS registry 1992-2010
males & females 0 – 29 years

incidence by tumour location & gender

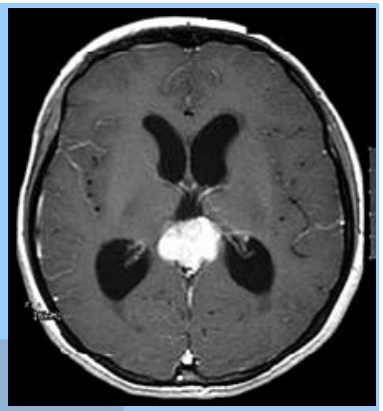


Cranial germ cell tumours

Poynter et al 2014 J Neuro-oncology;120: 381-388



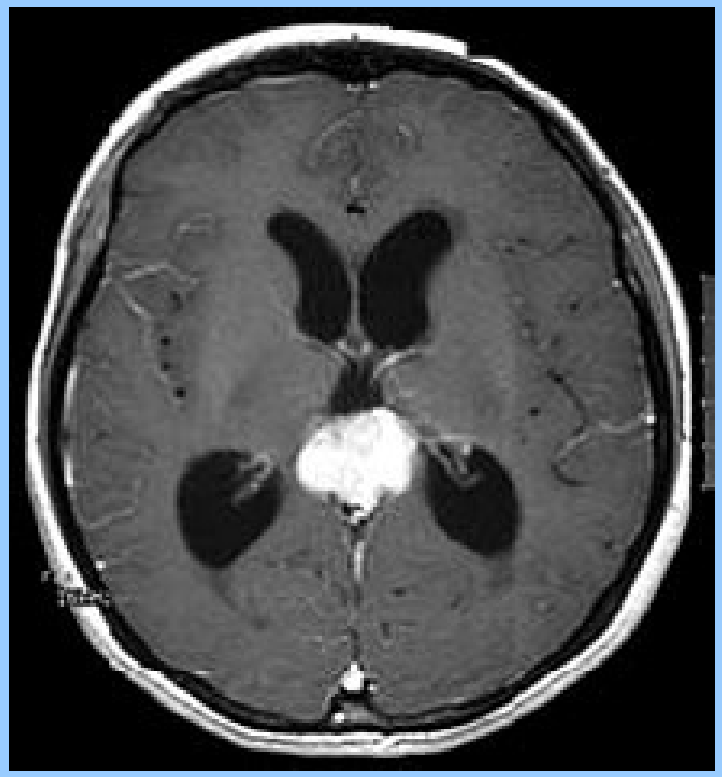
Cranial germ cell tumours

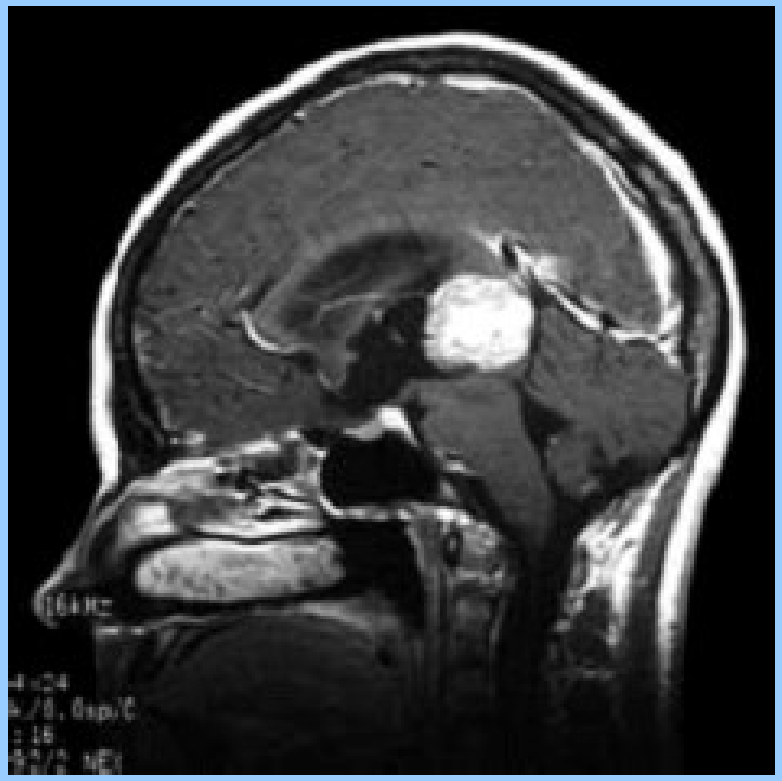


- diagnosis
  - serum and CSF markers
  - histology
- staging
  - CSF cytology
  - craniospinal MRI

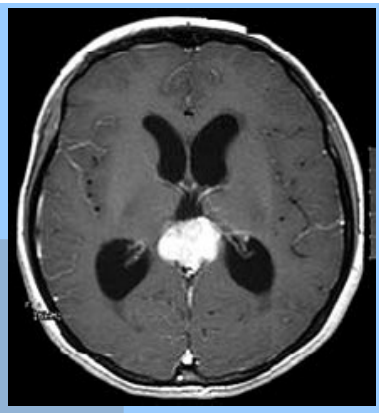
Cranial germinoma

Acute management of hydrocephalus



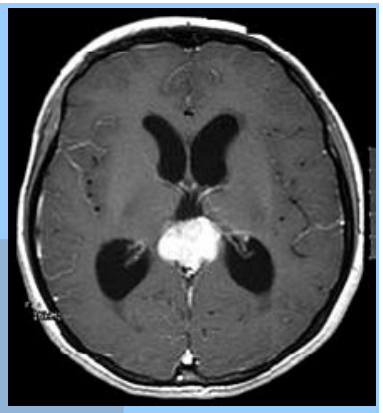


Cranial germ cell tumor



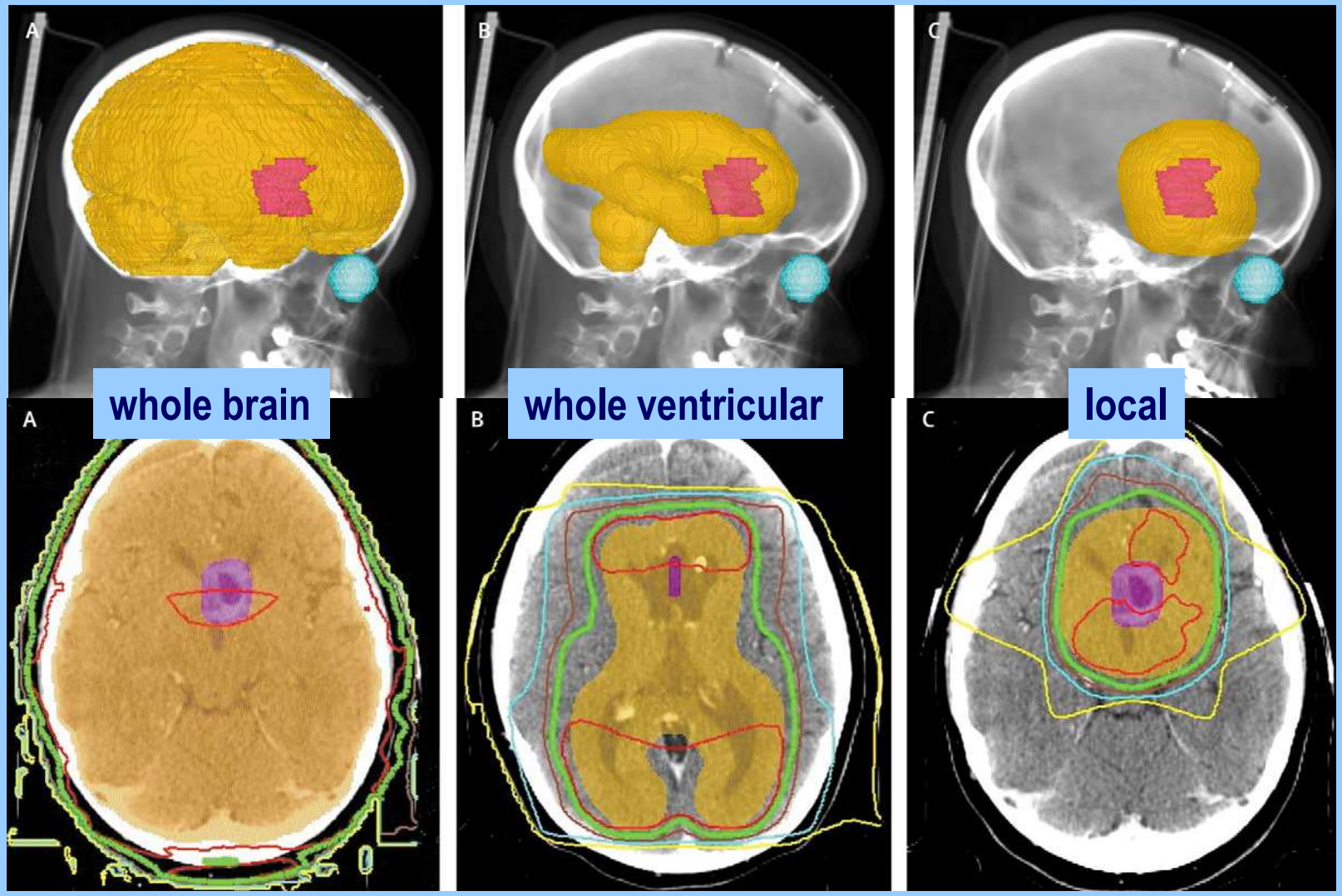
- surgery
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - cranio-spinal axis
- chemotherapy
  - alone
  - adjuvant

Cranial germinoma



- surgery
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - cranio-spinal axis
- chemotherapy
  - alone
  - adjuvant

Cranial germinoma



brain radiotherapy

Cranial germinoma

Rogers et al 2005 Lancet Oncol; 6: 509–19

Evolution of germinoma therapy

radiotherapy

cranio-spinal axis RT 36 Gy + boost to tumour site 14Gy
(total tumour dose 50Gy)

dose reduction

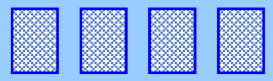
cranio-spinal axis RT 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

volume reduction

whole brain or whole ventricular RT 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

chemotherapy & volume reduction

chemotherapy



Carboplatin
Etoposide
Ifosfamide

radiotherapy

whole ventricular or tumour site RT
(total tumour dose 40Gy)

Cranial germinoma

Evolution of germinoma therapy

German MAKEI studies

radiotherapy

cranio-spinal axis RT 36 Gy + boost to tumour site 14Gy
(total tumour dose 50Gy)

dose reduction

cranio-spinal axis RT 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

volume reduction

whole brain or whole ventricular RT 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

chemotherapy & volume reduction

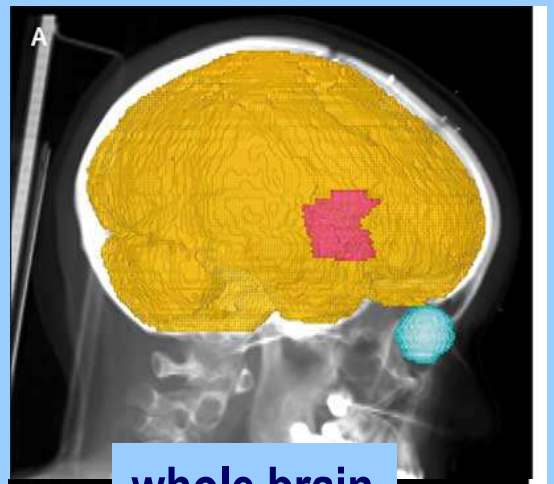
chemotherapy

Carboplatin
Etoposide
Ifosfamide

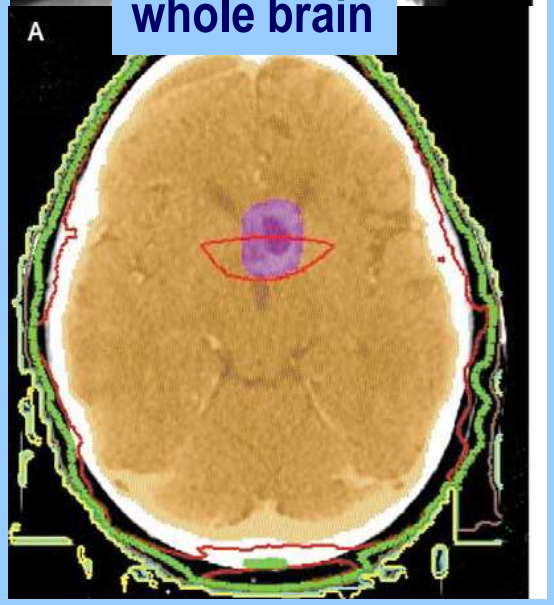
radiotherapy

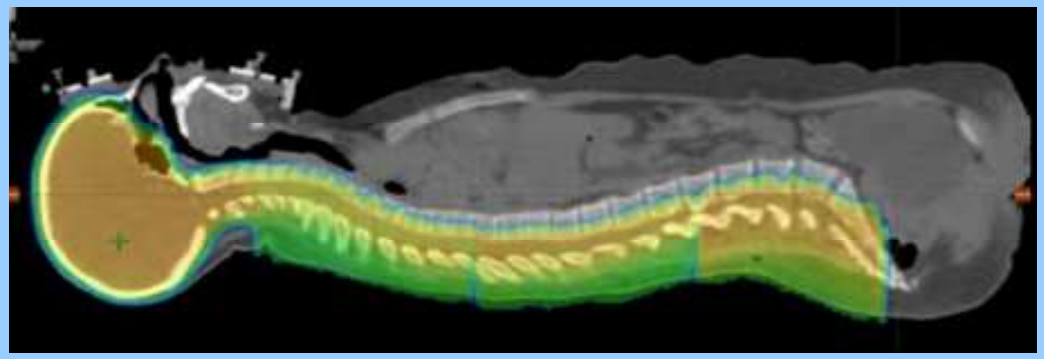
whole ventricular or tumour site RT
(total tumour dose 40Gy)

Cranial germinoma



whole brain

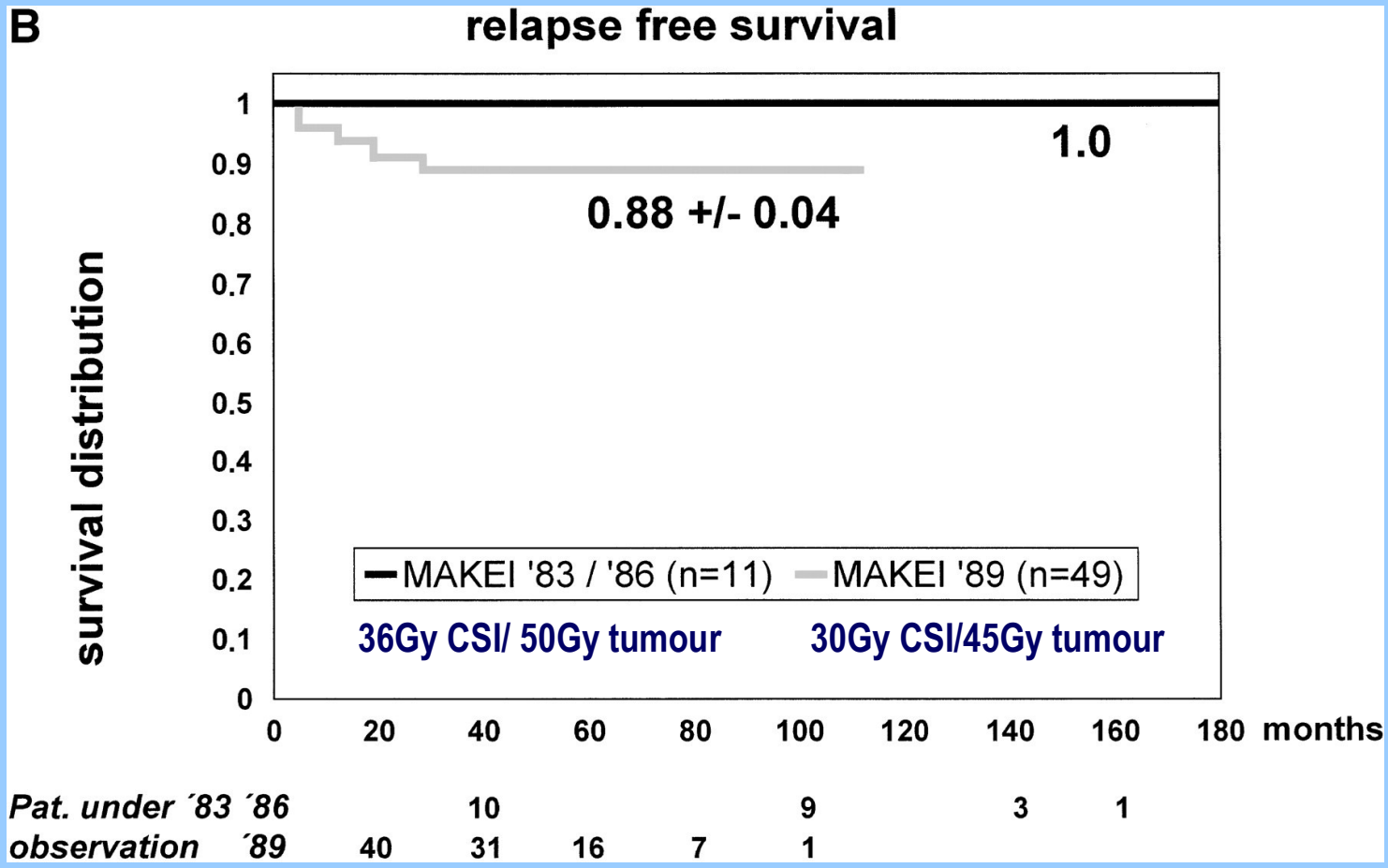




cranio-spinal brain radiotherapy + boost

Cranial germinoma

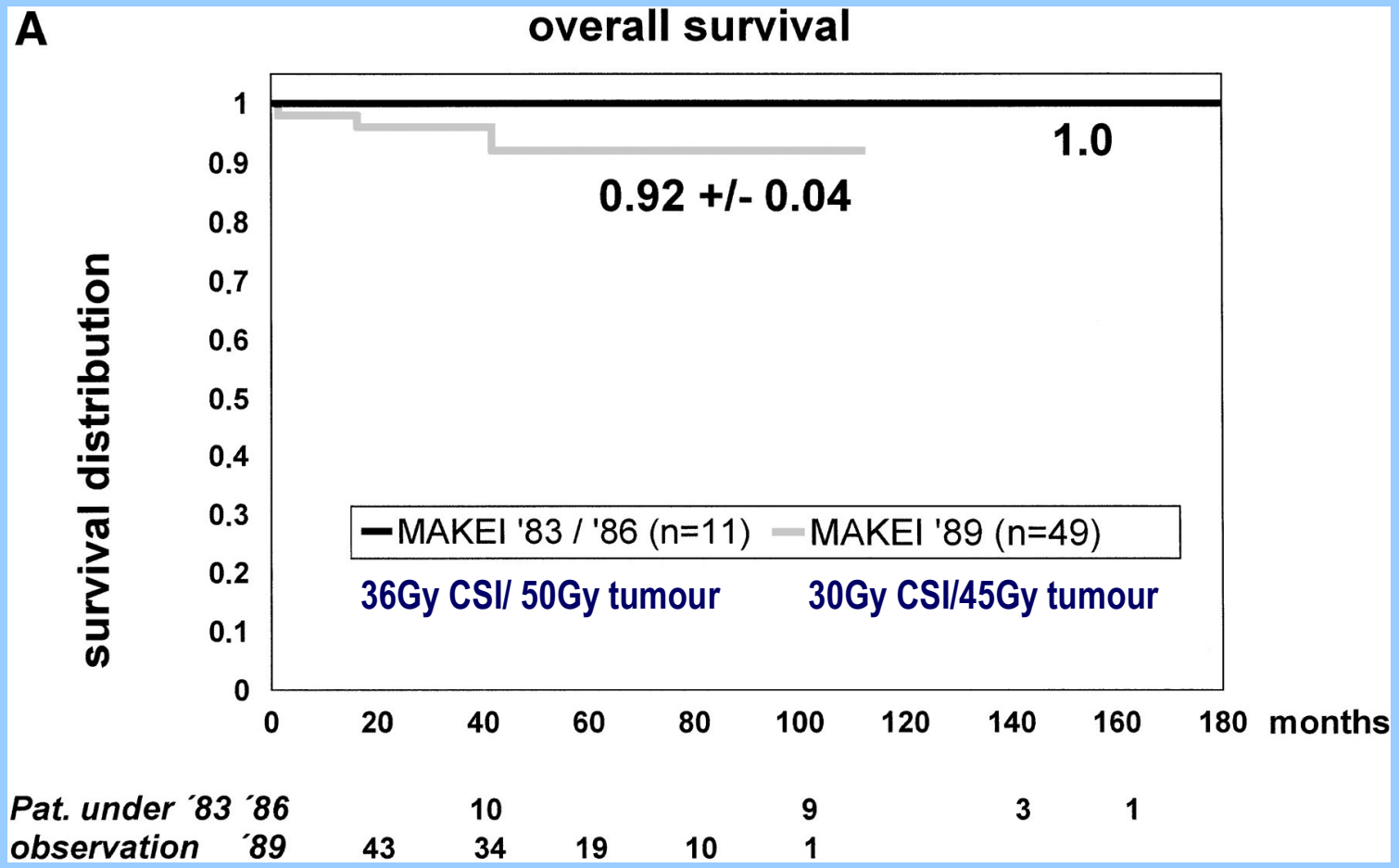
German MAKEI studies - radiotherapy alone



Cranial germinoma

Bamberg et al 1999, J Clin Oncol; 17:2585

German MAKEI studies - radiotherapy alone



Cranial germinoma

Bamberg et al 1999, J Clin Oncol; 17:2585

Evolution of germinoma therapy

SIOP study

radiotherapy

cranio-spinal axis RT 36 Gy + boost to tumour site 14Gy
(total tumour dose 50Gy)

dose reduction

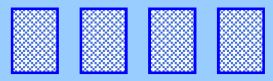
cranio-spinal axis RT 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

volume reduction

whole brain or whole ventricular RT 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

chemotherapy & volume reduction

chemotherapy

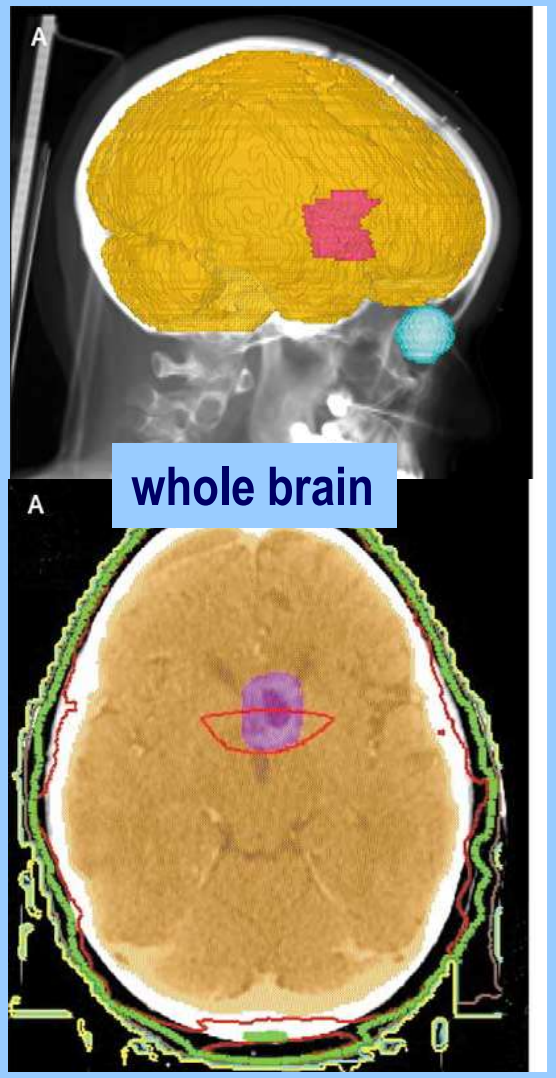


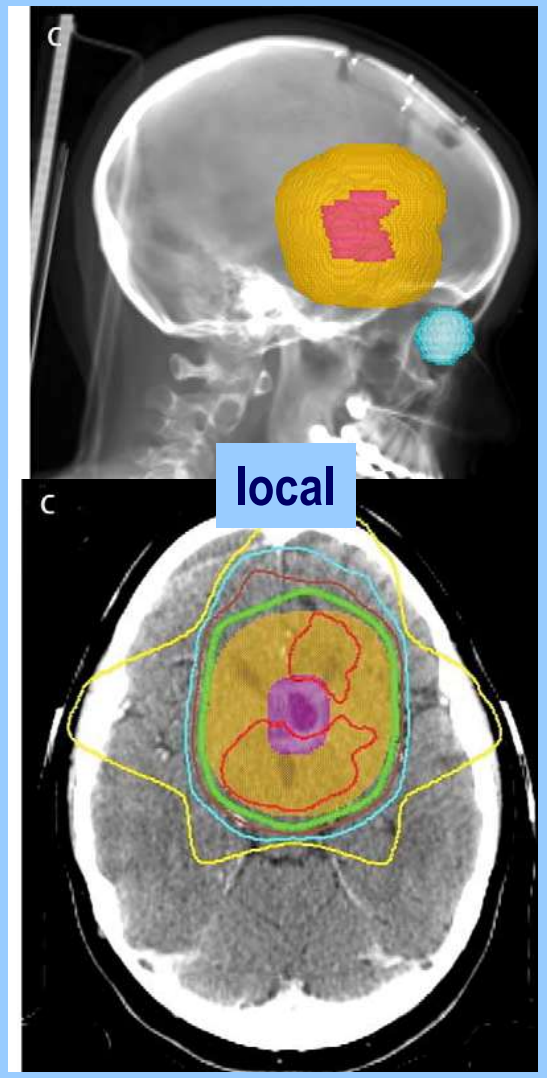
Carboplatin
Etoposide
Ifosfamide

radiotherapy

whole ventricular or tumour site RT
(total tumour dose 40Gy)

Cranial germinoma





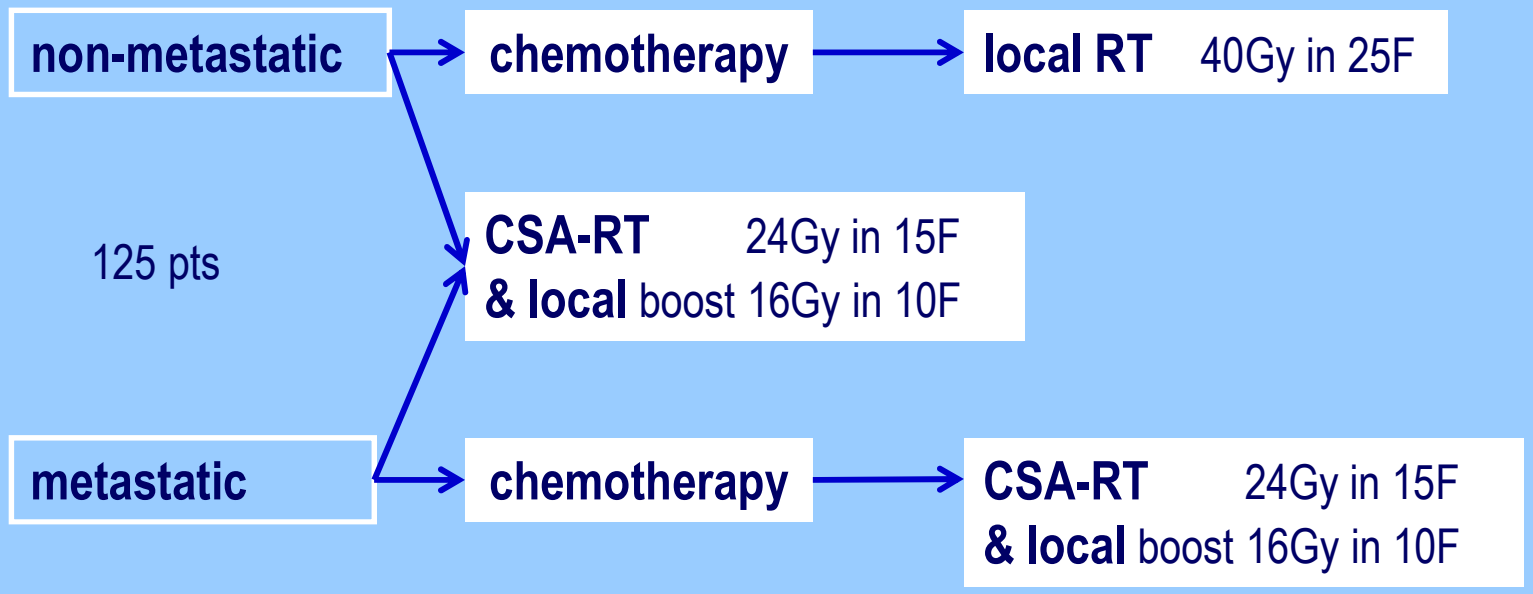
brain radiotherapy

Cranial germinoma

Rogers et al 2005 Lancet Oncol; 6: 509–19

SIOP CNS GCT 96 - germinoma

investigator choice



CSA-RT - craniospinal axis radiotherapy

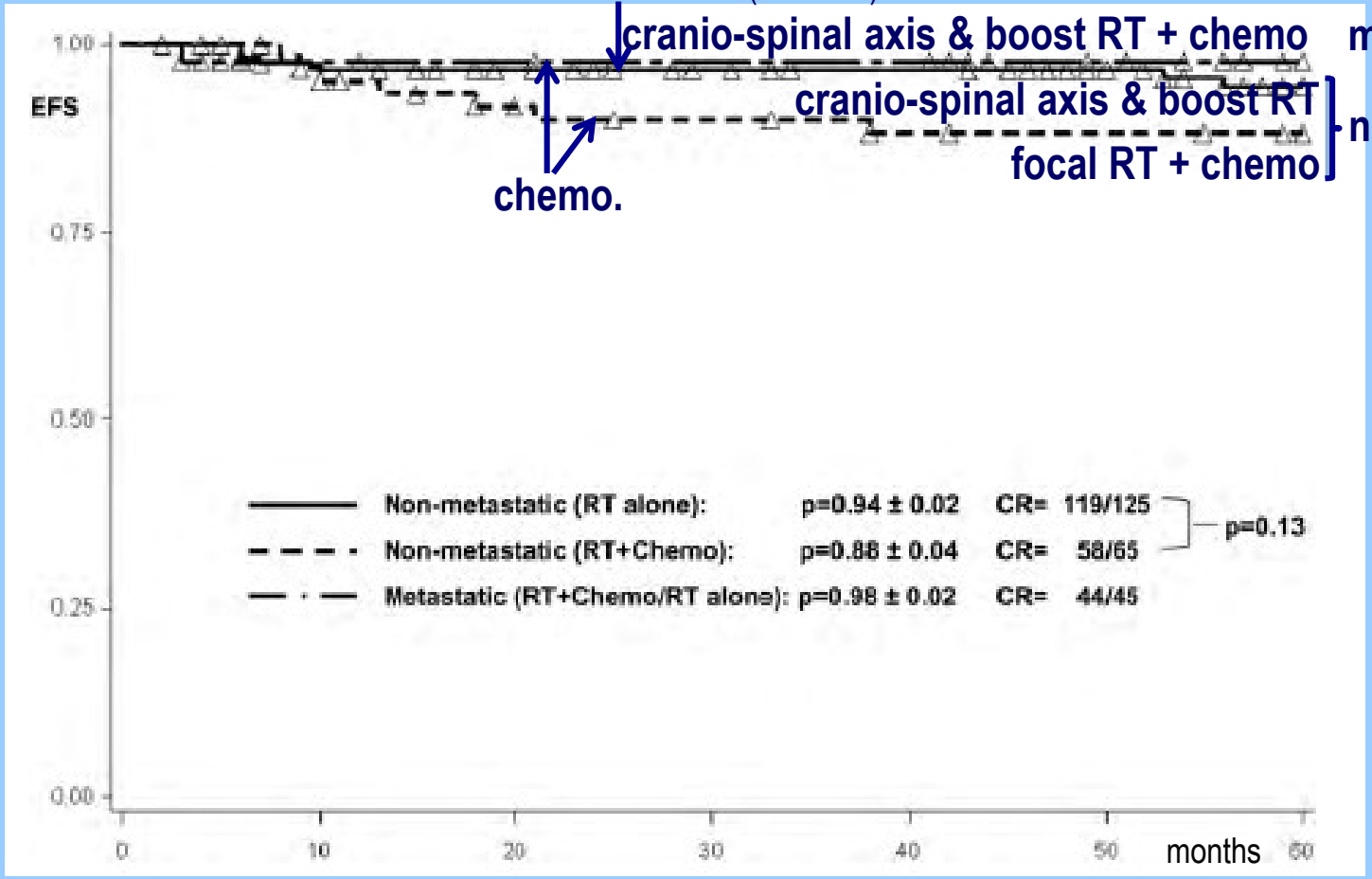
chemotherapy alternating Carboplatin/Etoposide and Carboplatin/Ifosfamide

Cranial germinoma

Calaminus et al 2013 Neuro-oncology;15(6):788-96

SIOP CNS GCT 96

event free survival

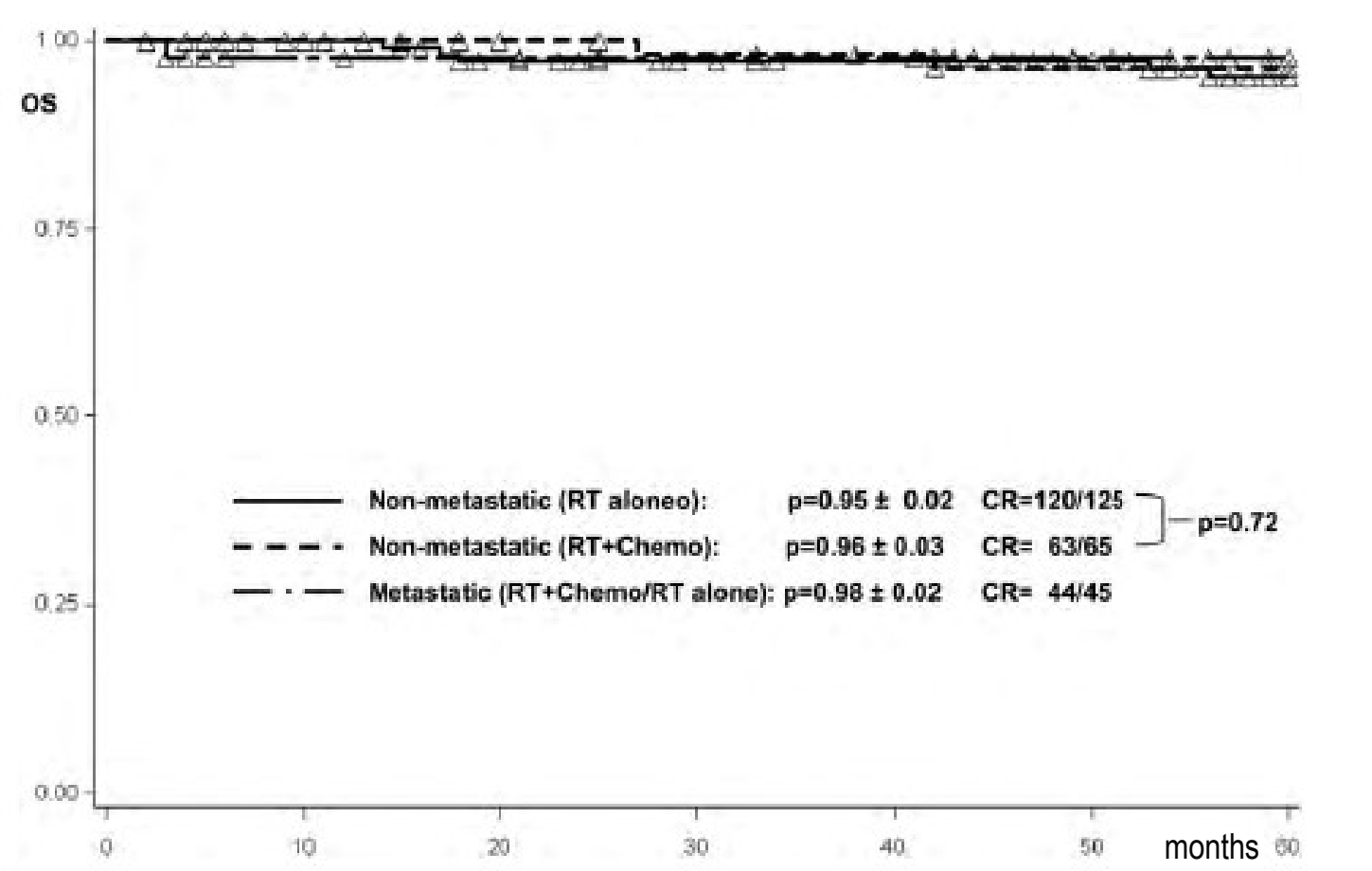


Cranial germinoma

Calaminus et al 2013 Neuro-oncology;15(6):788-96

SIOP CNS GCT 96

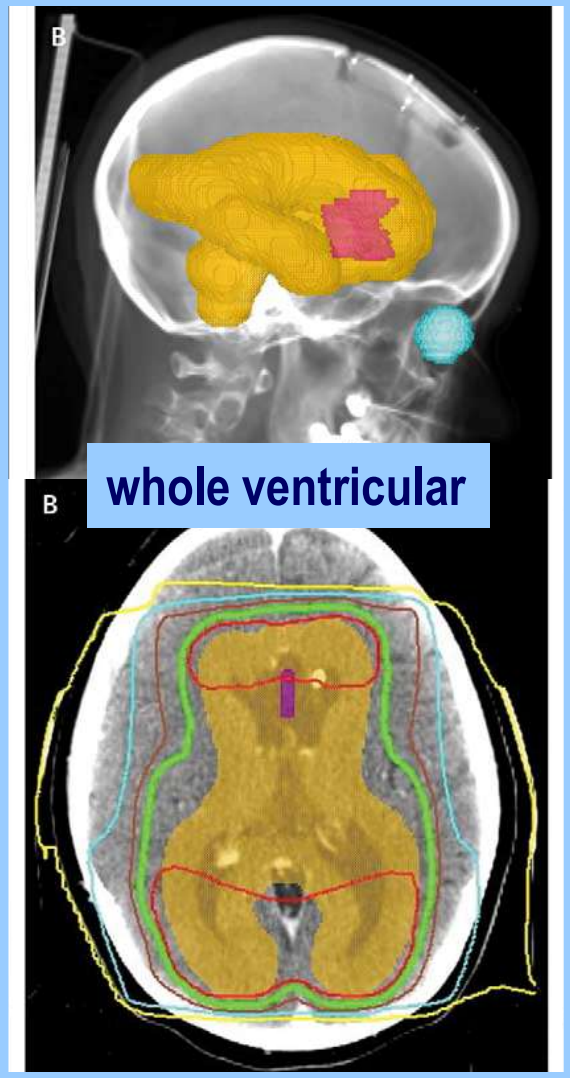
survival



Cranial germinoma

Calaminus et al 2013 Neuro-oncology;15(6):788-96

rationale



whole ventricular

brain radiotherapy

Cranial germinoma

Rogers et al 2005 Lancet Oncol; 6: 509–19

recurrence rate and extent of irradiation

volume of RT	**recurrences** (% all sites)	recurrences (% spine)	no. pts
local only	**24%**	10%	130
whole ventricular +	**6%**	2%	54
whole brain +	**7%**	3%	91
cranio-spinal axis +	**5%**	1%	287

+ boost

Radiotherapy in cranial germinoma

Aoyama et al 2009, Prog Neurol Surg: 23, 96-105

Evolution of germinoma therapy

SFOP-TMG-90 French study

radiotherapy

cranio-spinal axis 36 Gy + boost to tumour site 14Gy
(total tumour dose 50Gy)

dose reduction

cranio-spinal axis 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

volume reduction

whole brain or whole ventricular RT 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

chemotherapy & volume reduction

chemotherapy

Carboplatin
Etoposide
Ifosfamide

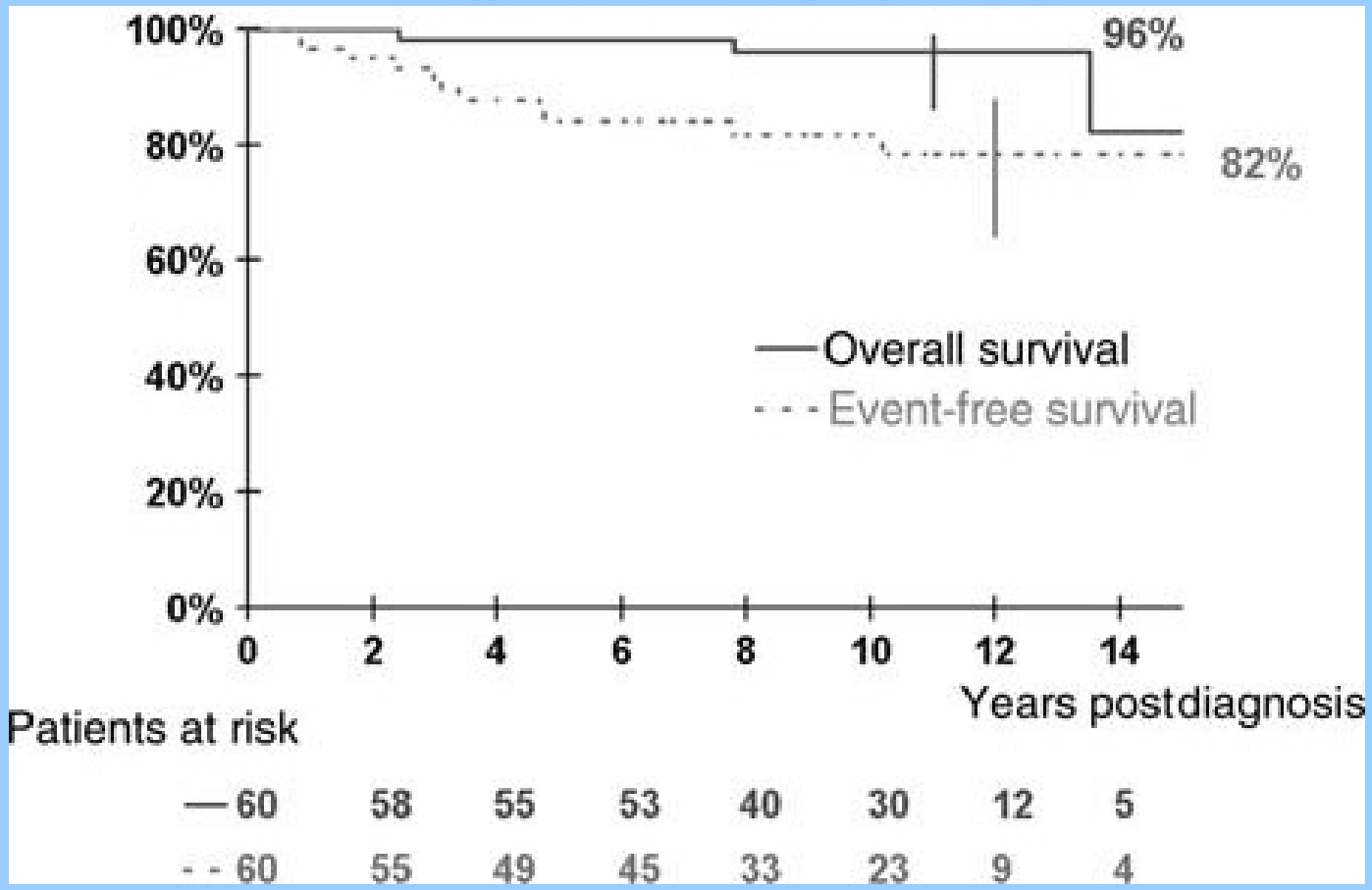
radiotherapy

tumour site alone
(total tumour dose 40Gy)

Cranial germinoma

SFOP-TMG-90

survival & event free survival

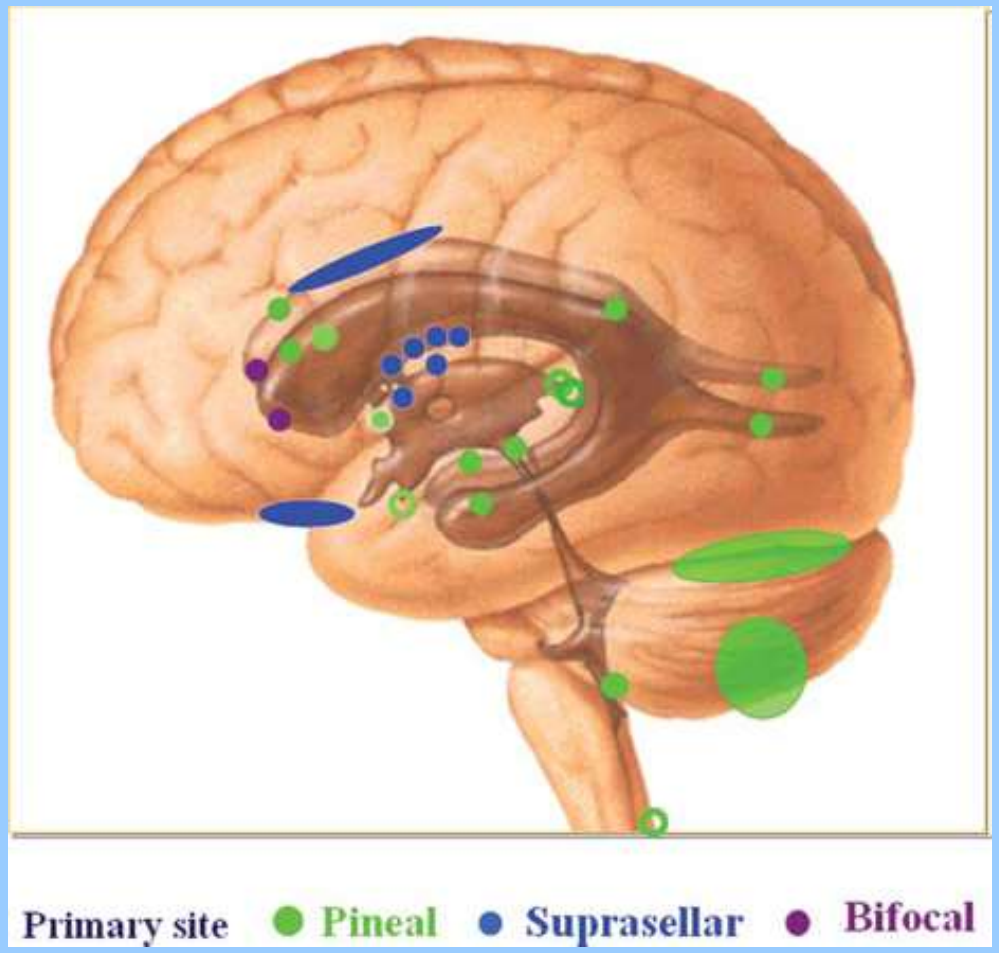


Cranial germinoma

Alapetite et al 2010 Neuro-oncology. 12(12):1318-25

SFOP-TMG-90

sites of relapse

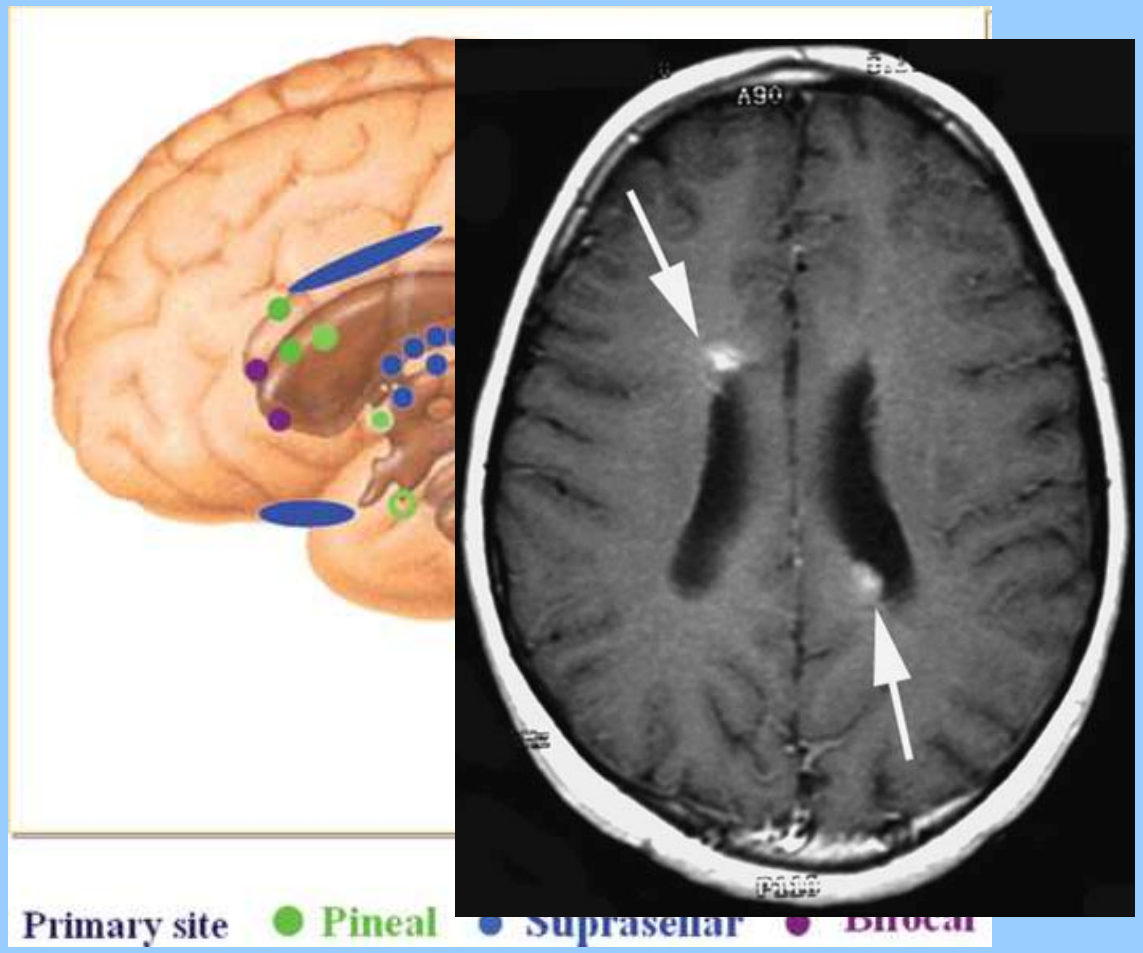


Cranial germinoma

Alapetite et al 2010 Neuro-oncology. 12(12):1318-25

SFOP-TMG-90

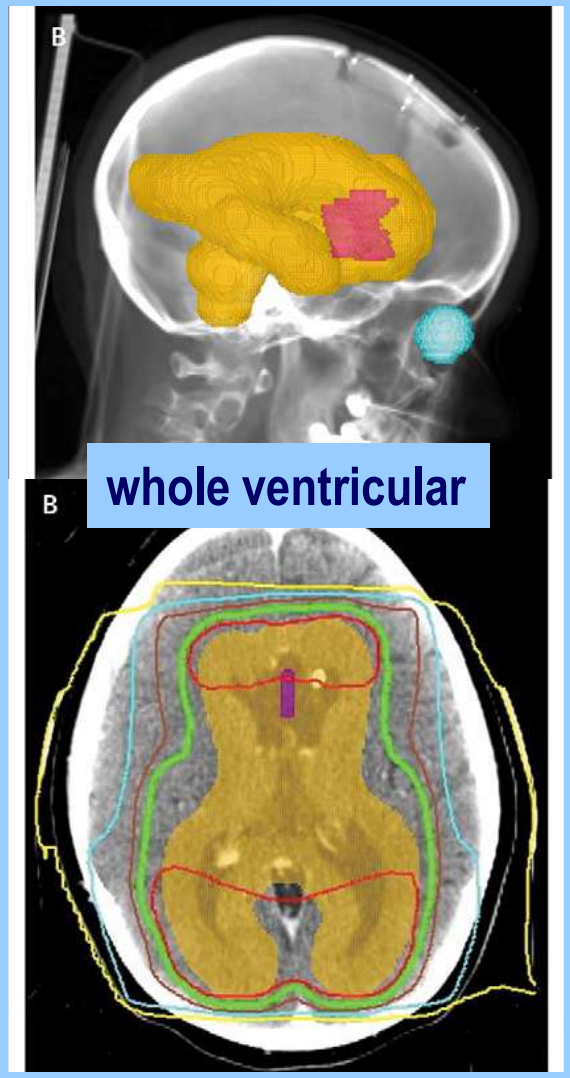
sites of relapse



Cranial germinoma

Alapetite et al 2010 Neuro-oncology. 12(12):1318-25

rationale

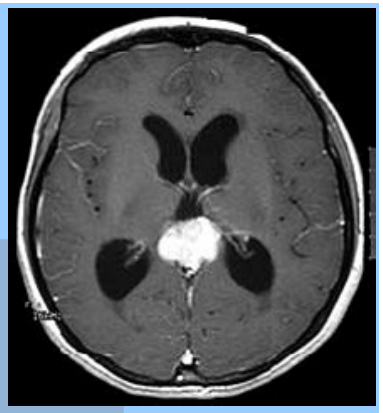


whole ventricular

brain radiotherapy

Cranial germinoma

Rogers et al 2005 Lancet Oncol; 6: 509–19



- surgery
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - cranio-spinal axis
- **chemotherapy**
  - **alone**
  - adjuvant

Cranial germinoma

Evolution of germinoma therapy

International multicentre study
(consortium)

radiotherapy

cranio-spinal axis 36 Gy + boost to tumour site 14Gy
(total tumour dose 50Gy)

dose reduction

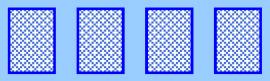
cranio-spinal axis 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

volume reduction

whole brain or whole ventricular RT 24Gy + boost to tumour site 16Gy
(total tumour dose 40Gy)

***chemotherapy** & volume reduction*

chemotherapy



Carboplatin
Etoposide
Bleomycin

radiotherapy

tumour site alone
(total tumour dose 40Gy)

Cranial germinoma

Balmaceda et al 1996, J Clin Oncol, 14: 2908-2915

tumour control following chemotherapy

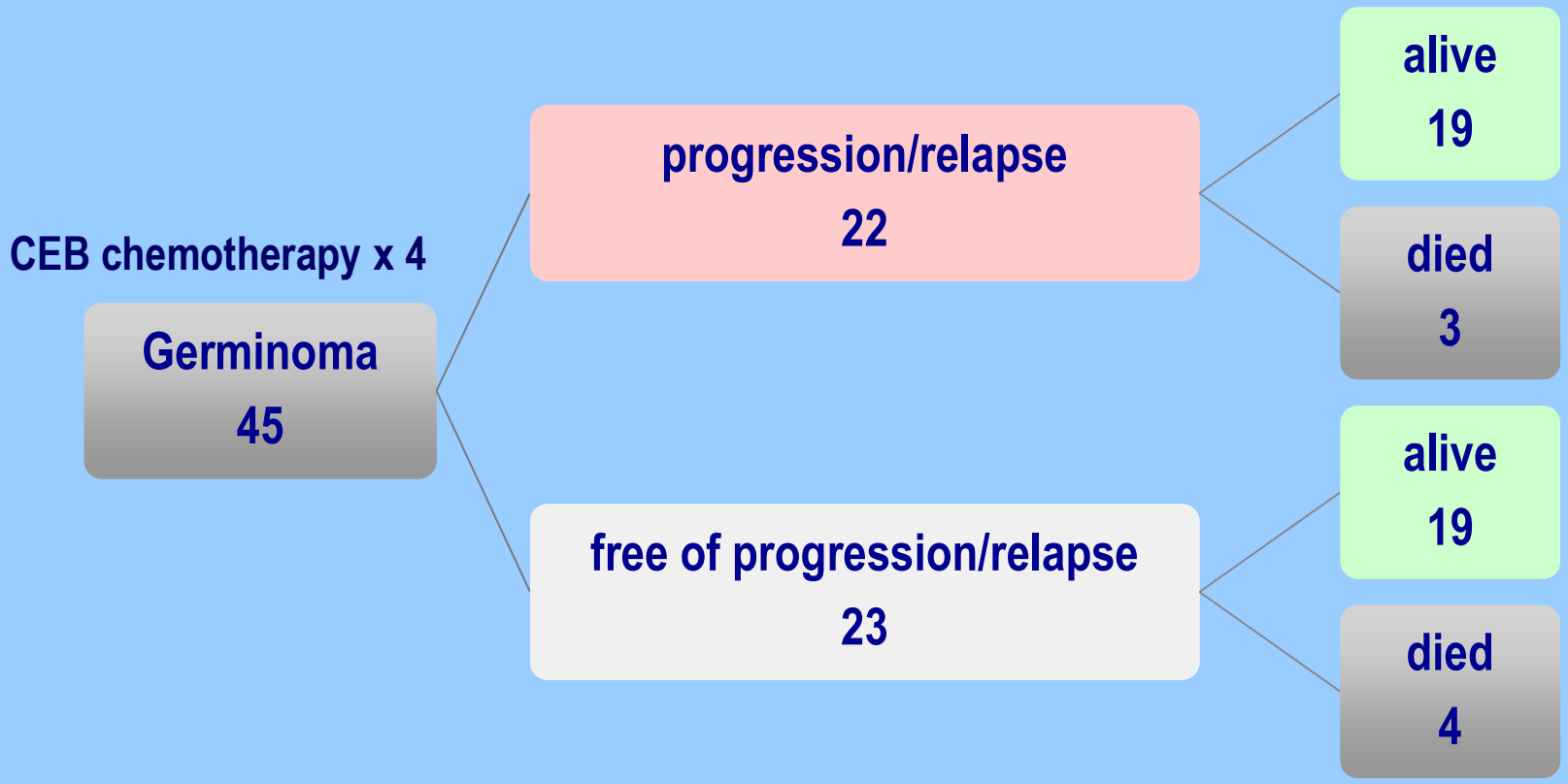
CEB chemotherapy x 4

Germinoma
45

Chemotherapy alone in cranial germinoma

Balmaceda et al 1996, J Clin Oncol, 14: 2908-2915

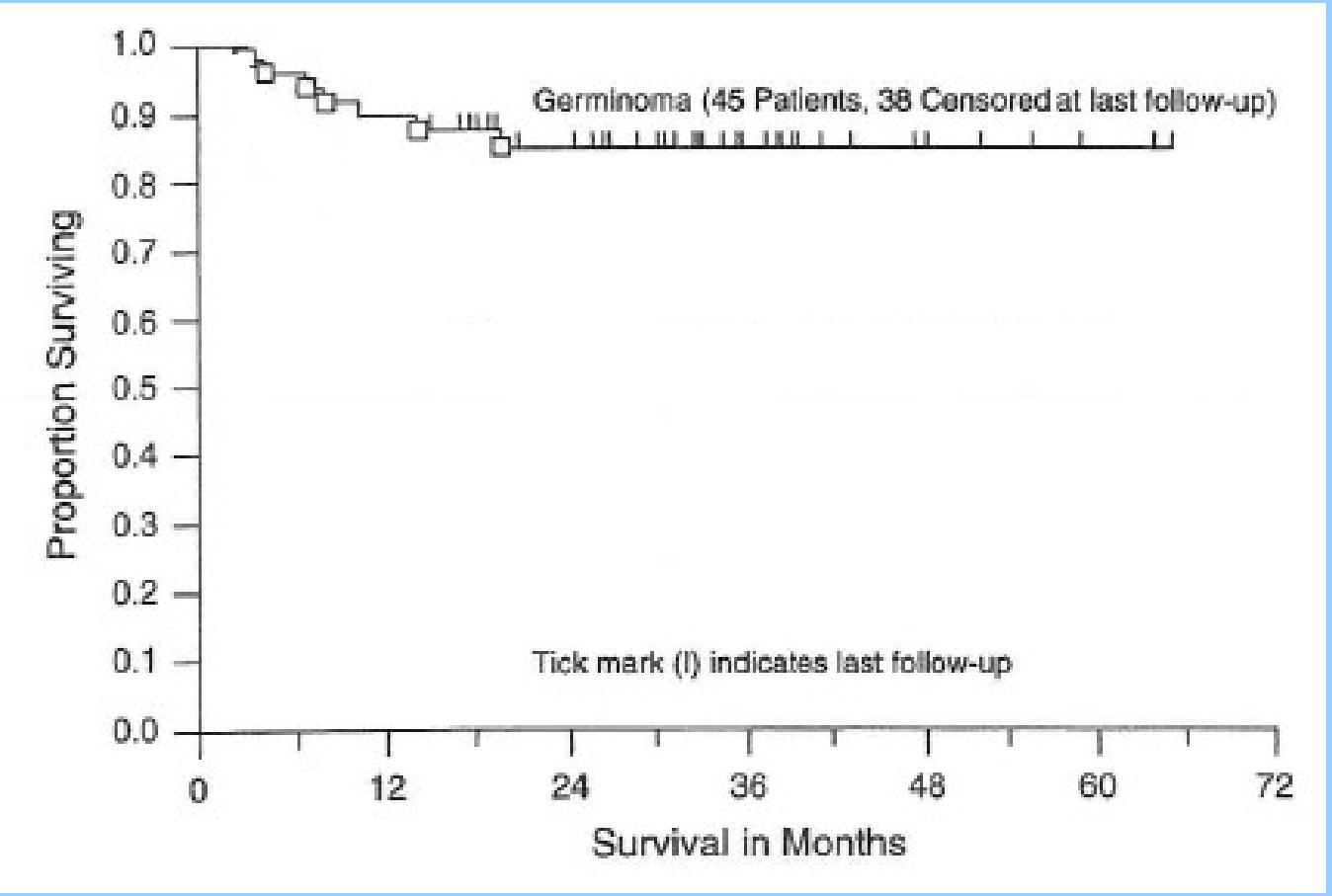
tumour control following chemotherapy



Chemotherapy alone in cranial germinoma

Balmaceda et al 1996, J Clin Oncol, 14: 2908-2915

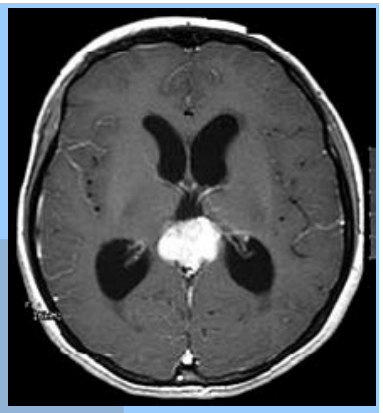
overall survival



Chemotherapy alone in cranial germinoma

Balmaceda et al 1996, J Clin Oncol, 14: 2908-2915

Conclusion



- surgery
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - cranio-spinal axis
- chemotherapy
  - alone
  - adjuvant

Cranial germinoma

SIOP CNS GCT II

localised (& 2 sites)

2 x CarboPEI

CR → **24 Gy whole ventricular RT**

PR → **24 Gy whole ventricular RT + 16Gy boost**

disseminated

24 Gy cranio-spinal RT + 16Gy boost

Cranial germinoma

SIOP CNS GCT II

Alternative approach

localised (& 2 sites)

2 x CarboPEI

CR → **24 Gy whole ventricular RT**

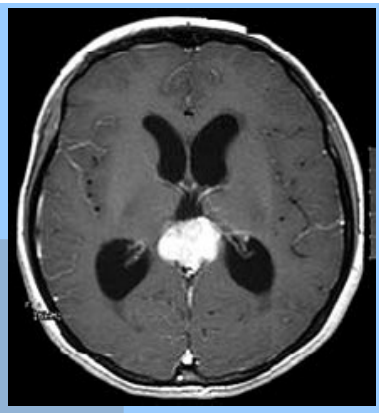
PR → **24 Gy whole ventricular RT + 16Gy boost**

disseminated

24 Gy cranio-spinal RT + 16Gy boost

Cranial germinoma

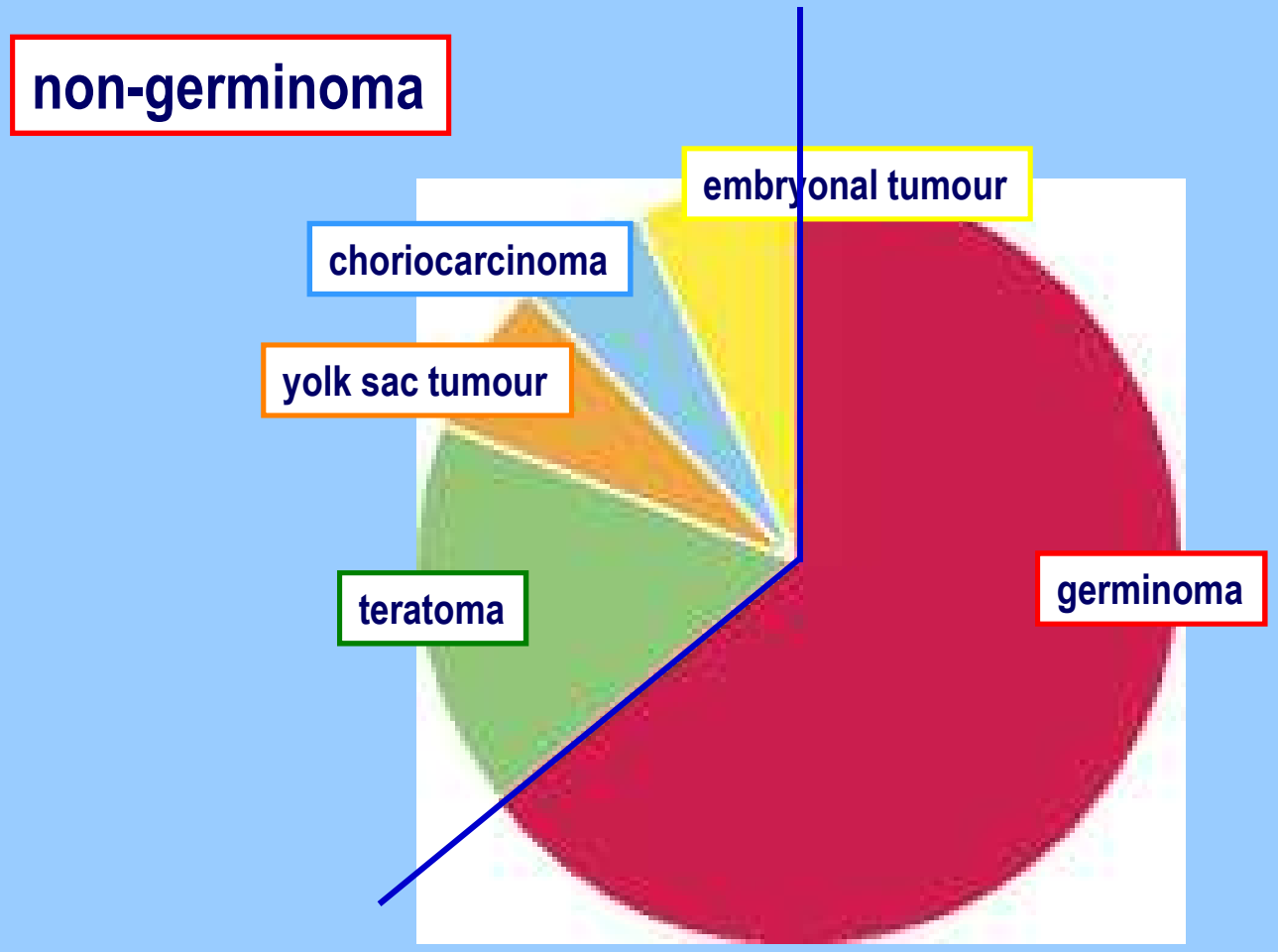
Conclusion



- surgery
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - cranio-spinal axis
- chemotherapy
  - alone
  - adjuvant

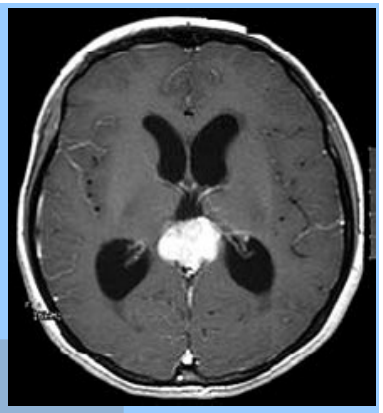
rare highly curable tumour
treatment in specialised centres

Cranial germinoma



Cranial germ cell tumours

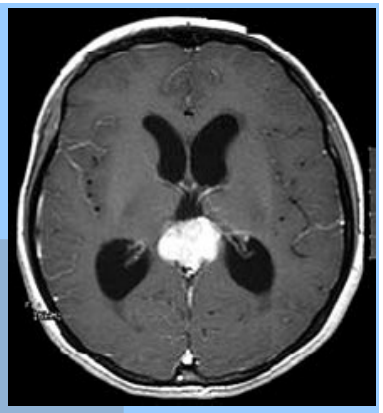
cranial NGGCT



- diagnosis
  - serum and CSF markers
  - histology
- staging
  - CSF cytology
  - craniospinal MRI

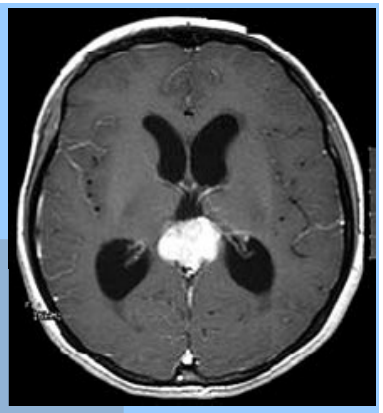
Cranial non-germinomatous germ cell tumours (NGGCT)

cranial NGGCT - management options



- surgery
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - cranio-spinal axis
- chemotherapy
  - alone
  - adjuvant

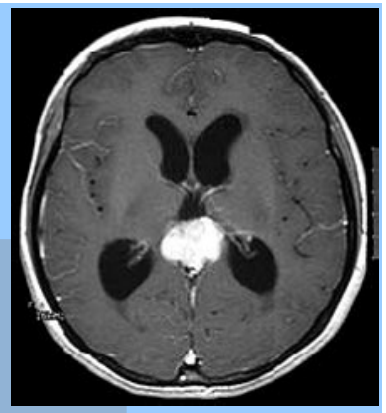
cranial NGGCT - no malignant component/mature



- **surgery**
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - cranio-spinal axis
- chemotherapy
  - alone
  - adjuvant

- mature teratoma
- immature teratoma without malignant component

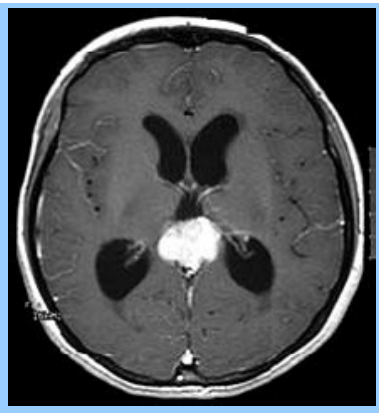
cranial NGGCT - malignant

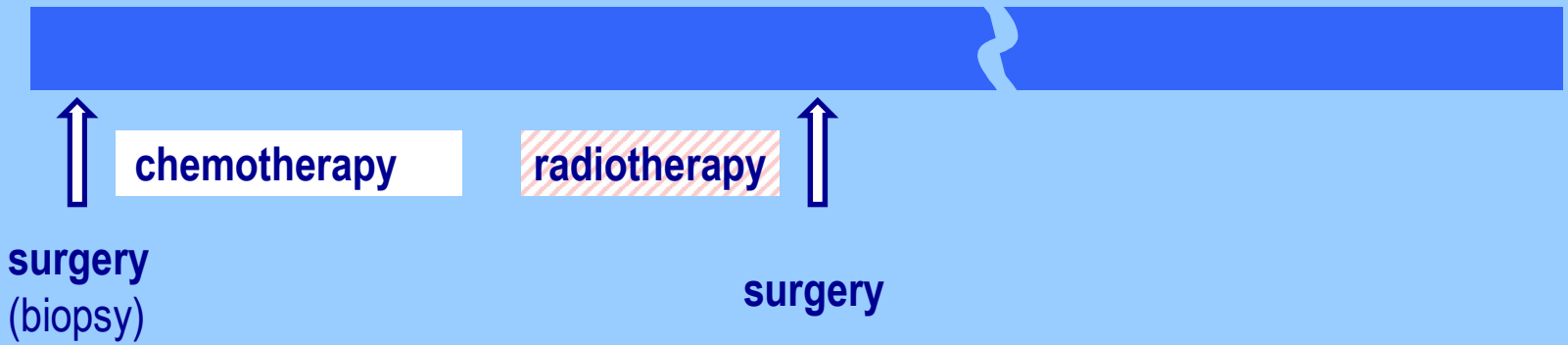


- surgery
- chemotherapy
  - alone
  - adjuvant
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - cranio-spinal axis

management of malignant cranial NGGCT

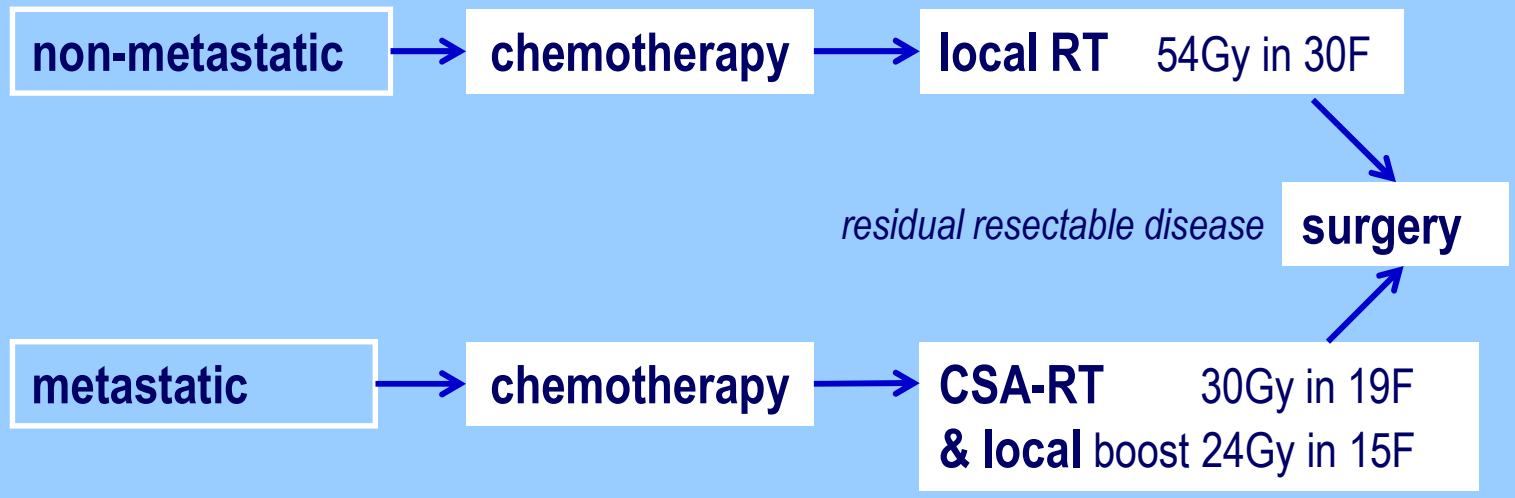
conventional approach





Cranial non-germinomatous germ cell tumours (NGGCT)

SIOP CNS GCT 96 - non-germinoma



CSA-RT - craniospinal axis radiotherapy

chemotherapy

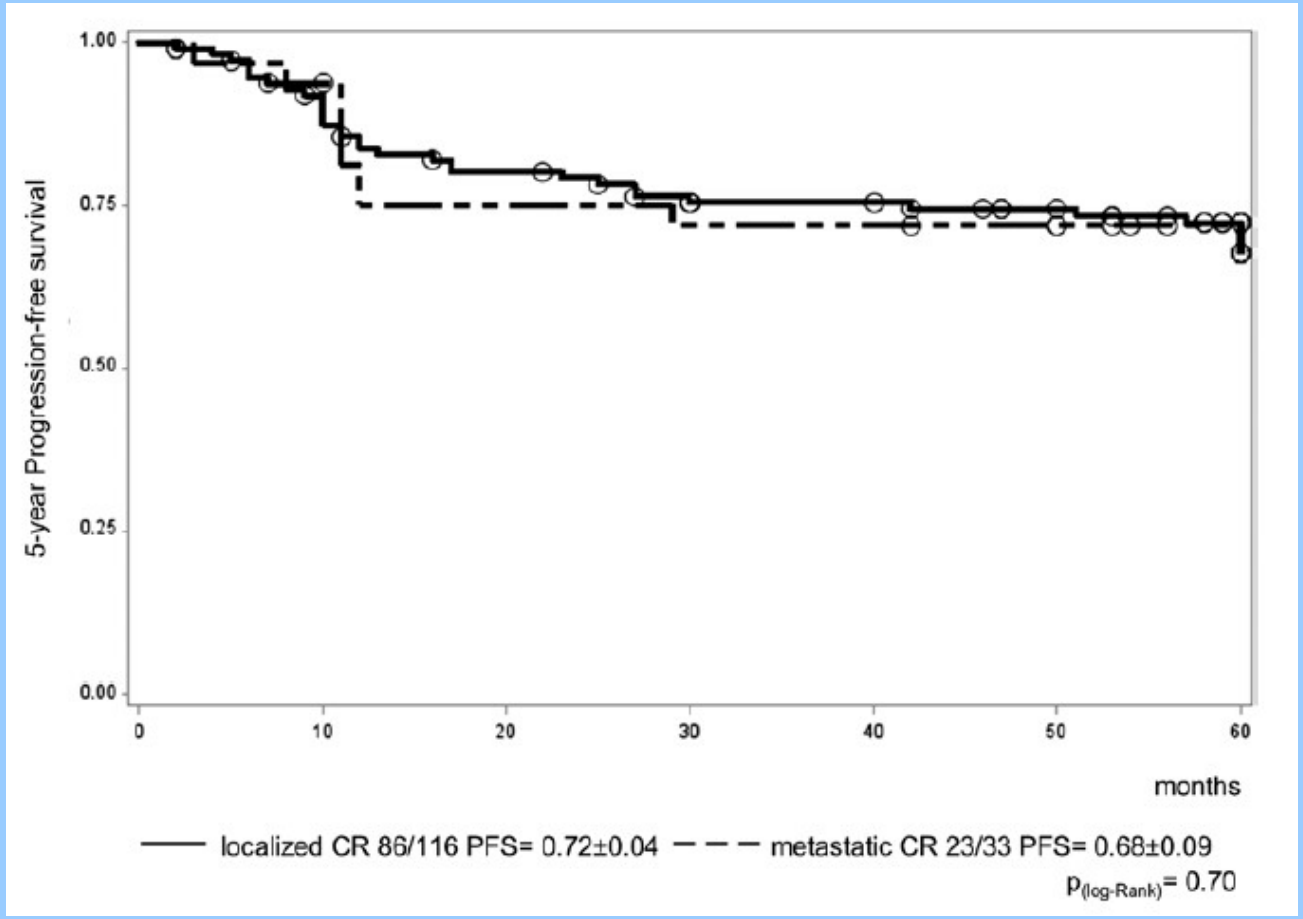
Carboplatin/Etoposide/Ifosfamide

Cranial non-germinomatous germ cell tumours (NGGCT)

Calaminus et al 2017 Neuro-oncology; e-publ July2017

SIOP CNS GCT 96 - non-germinoma

progression free survival

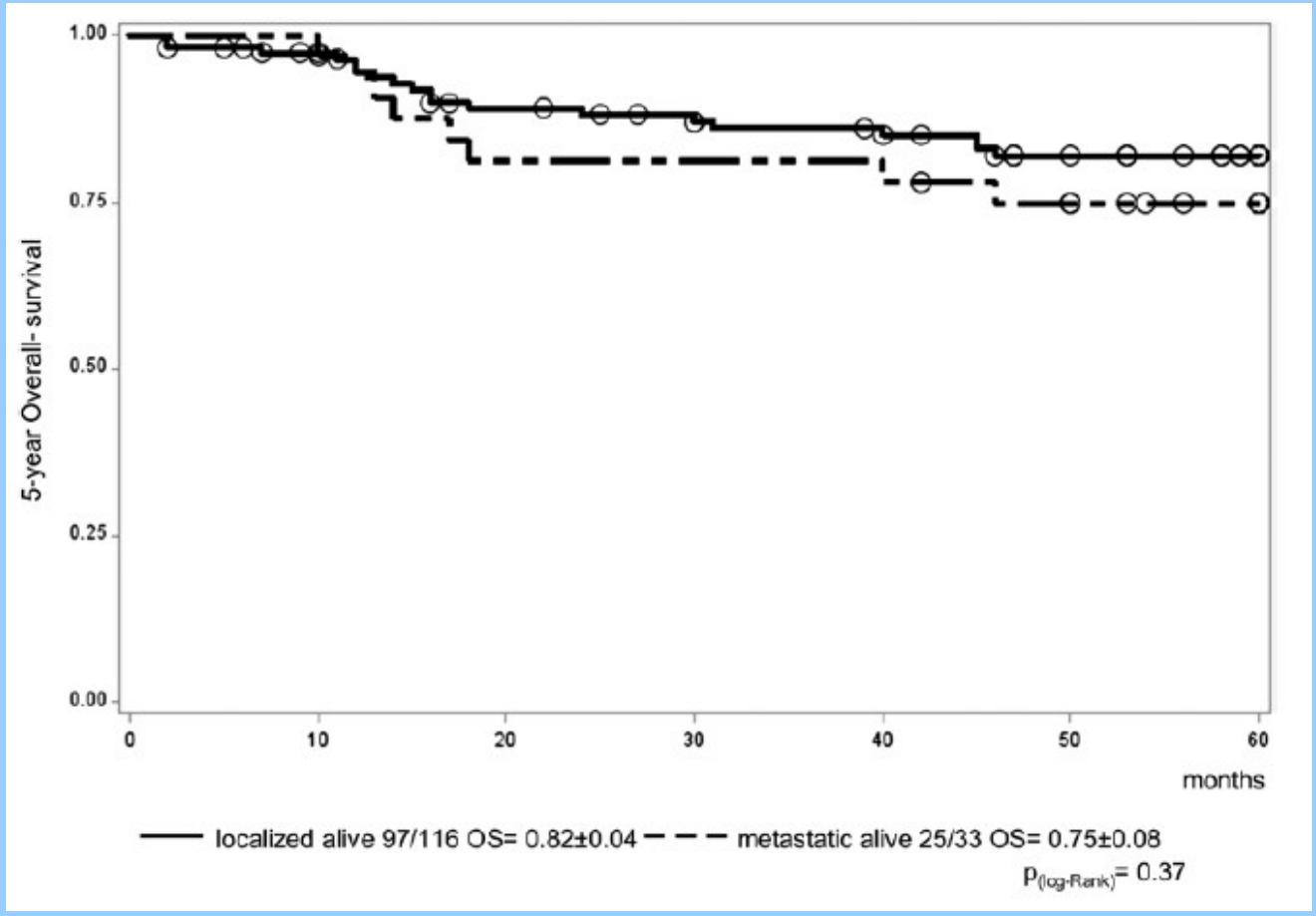


Cranial non-germinomatous germ cell tumours (NGGCT)

Calaminus et al 2017 Neuro-oncology; e-publ July2017

SIOP CNS GCT 96 - non-germinoma

survival



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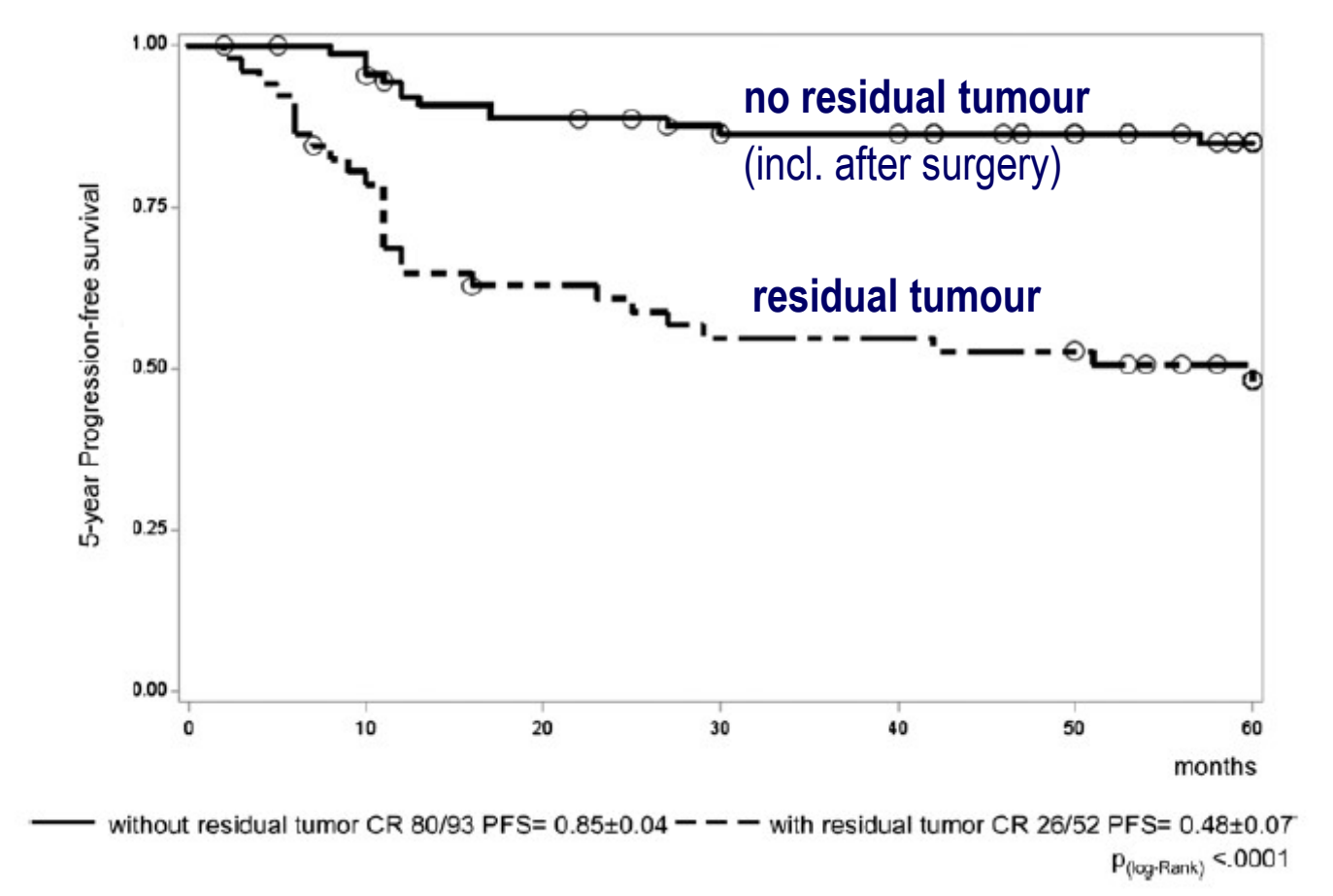
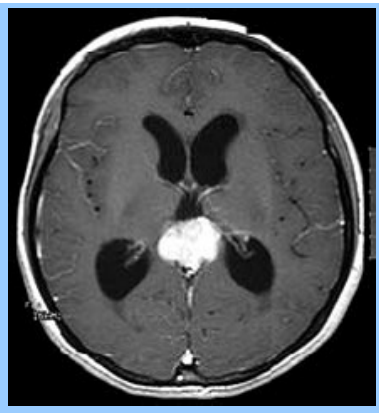


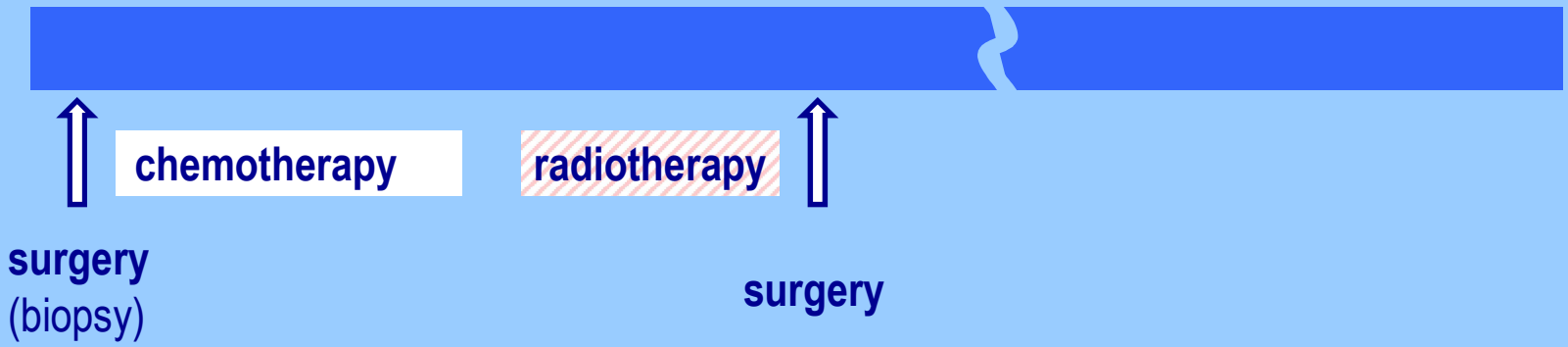
Cranial non-germinomatous germ cell tumours (NGGCT)

Calaminus et al 2017 Neuro-oncology; e-publ July2017

management of malignant cranial NGGCT

SIOP - CNS GCT 96

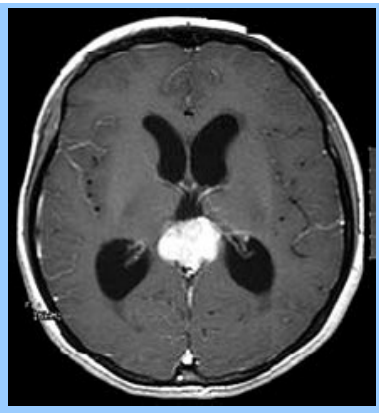


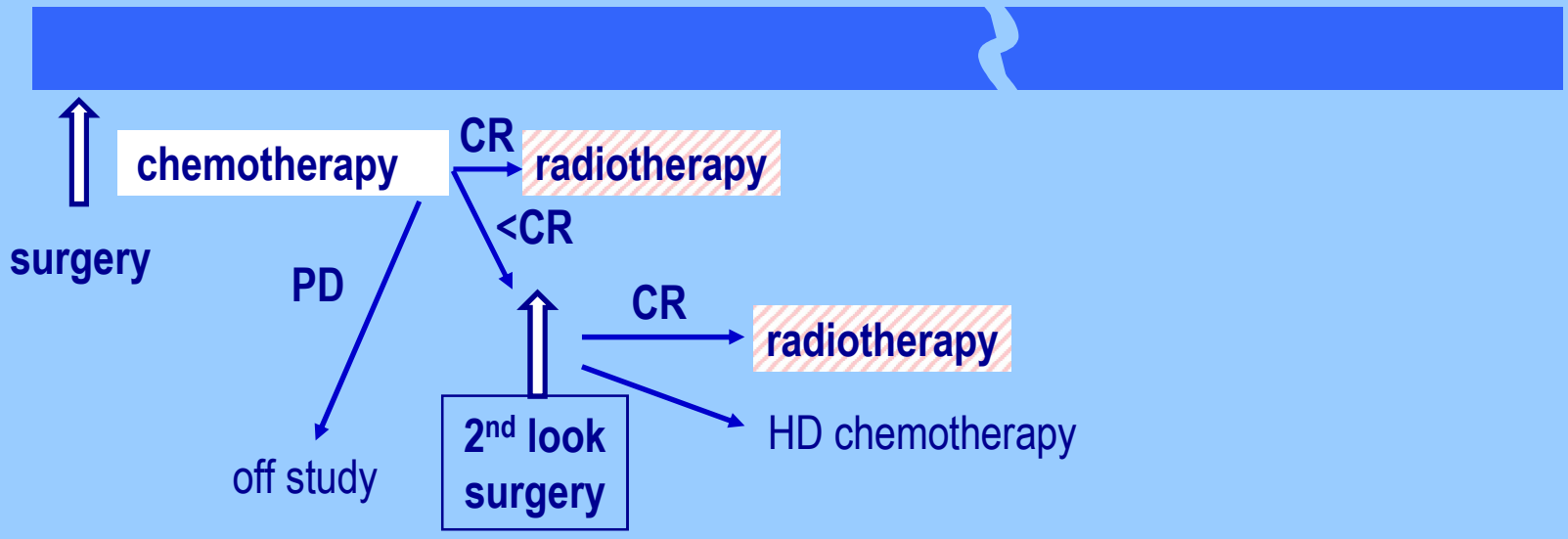


Cranial non-germinomatous germ cell tumours (NGGCT)

management of malignant cranial NGGCT

POG study

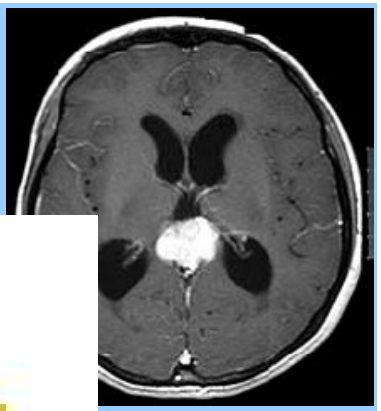


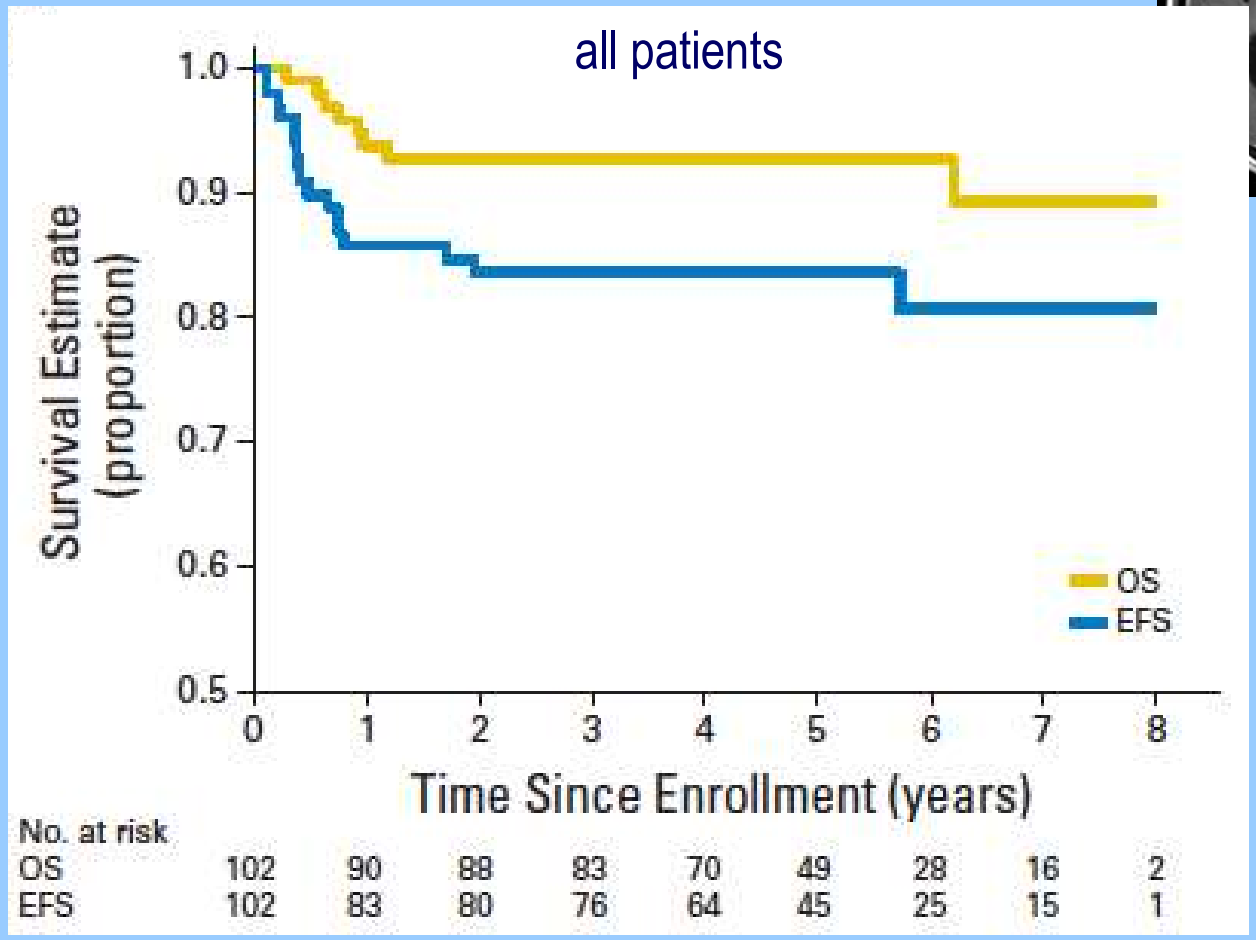


Cranial non-germinomatous germ cell tumours (NGGCT)

Goldman et al 2015 J Clin Oncol 33:2464-2471

POG study in malignant cranial NGGCT





Cranial non-germinomatous germ cell tumours (NGGCT)

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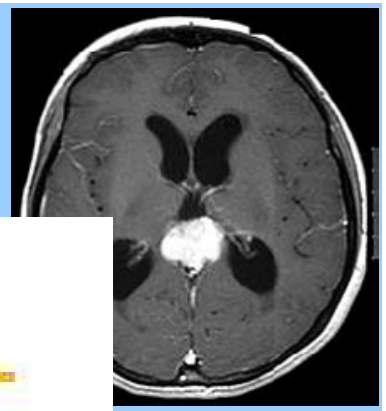
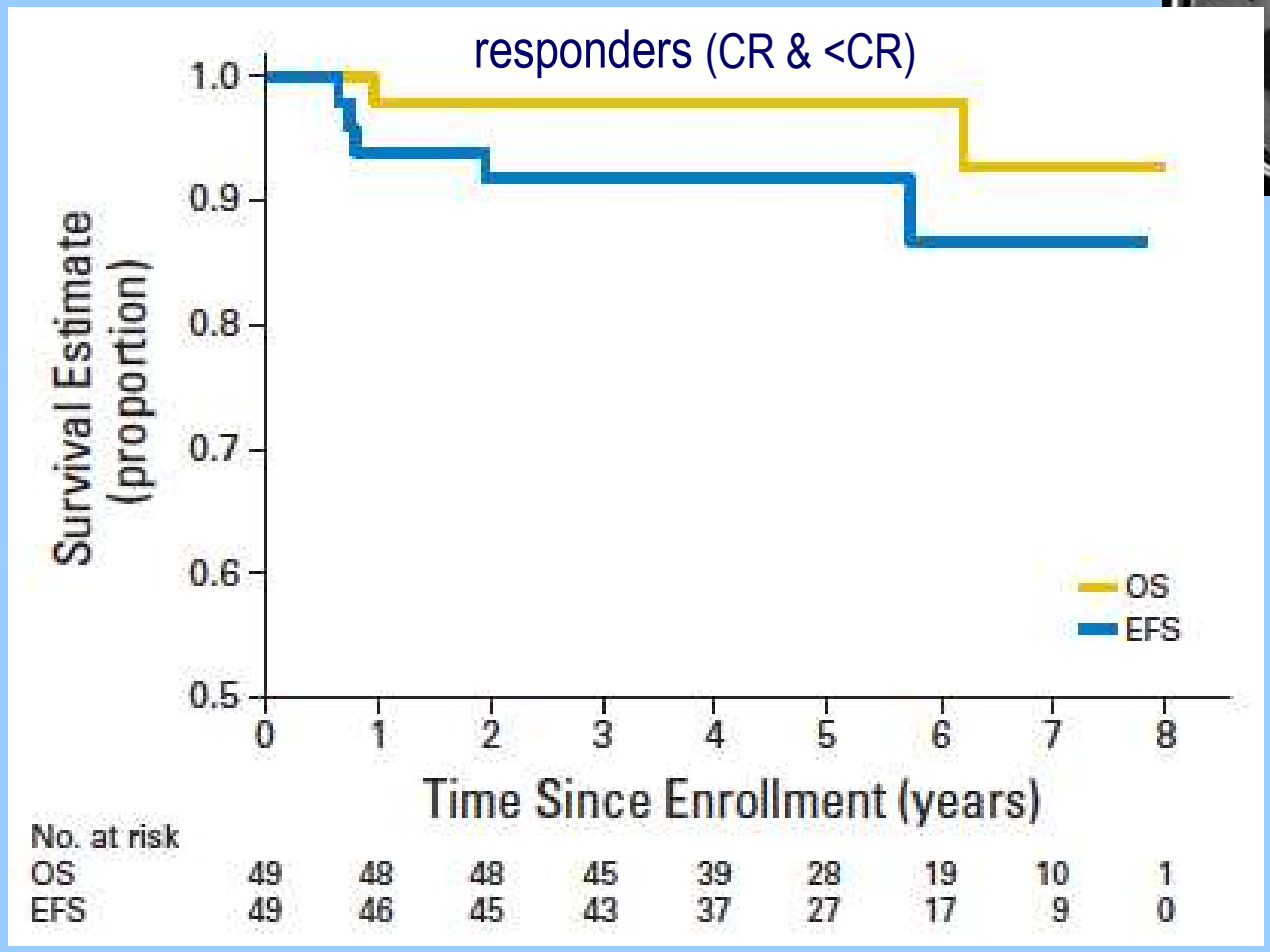
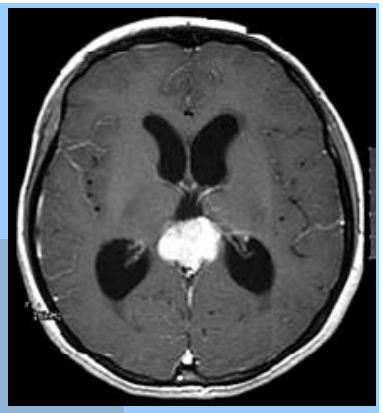




Cranial non-germinomatous germ cell tumours (NGGCT)

Goldman et al 2015 J Clin Oncol 33:2464-2471

Conclusion



- surgery
- chemotherapy
  - alone
  - adjuvant
- radiotherapy
  - localised
  - whole ventricular/whole brain
  - whole spinal axis

rare curable tumours
treatment in specialised centres

Cranial non-germinomatous germ cell tumours (NGGCT)

Cranial germ cell tumours

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The Clatterbridge Cancer Centre NHS
NHS Foundation Trust

Primary CNS lymphoma

ESTRO teaching course
Management of brain tumours

Patrick Roth

Department of Neurology and Brain Tumor Center
University Hospital Zurich

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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

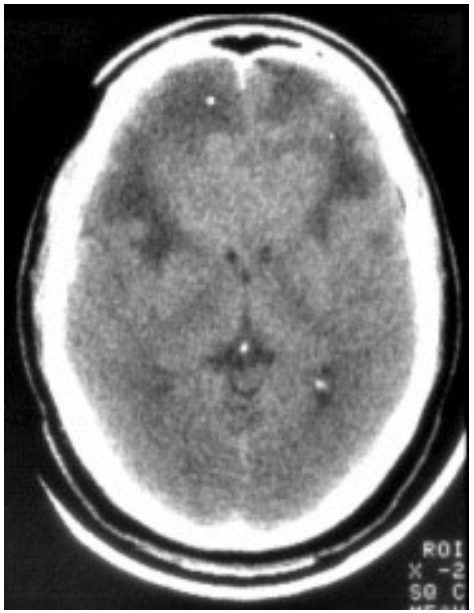
  => incidence decreasing since introduction of HAART
- Unclear pathogenesis => specific CNS tropism?

Clincal presentation

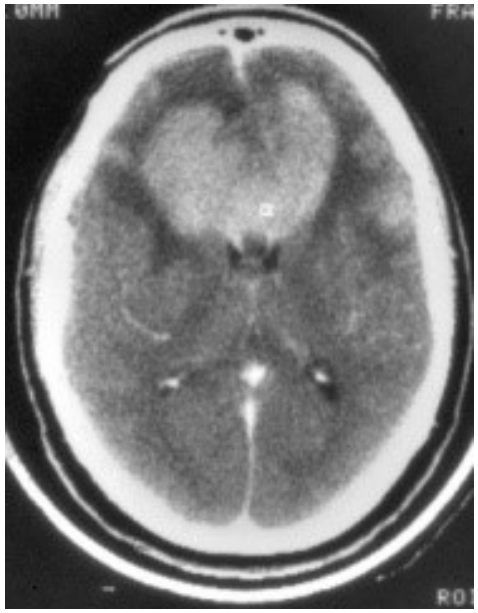
- Personality changes
- Symptoms associated with increased intracranial pressure
- Motor and sensory deficits
- Cranial nerve palsies
- Seizures (rare)
- Cerebellar symptoms

Imaging: CT

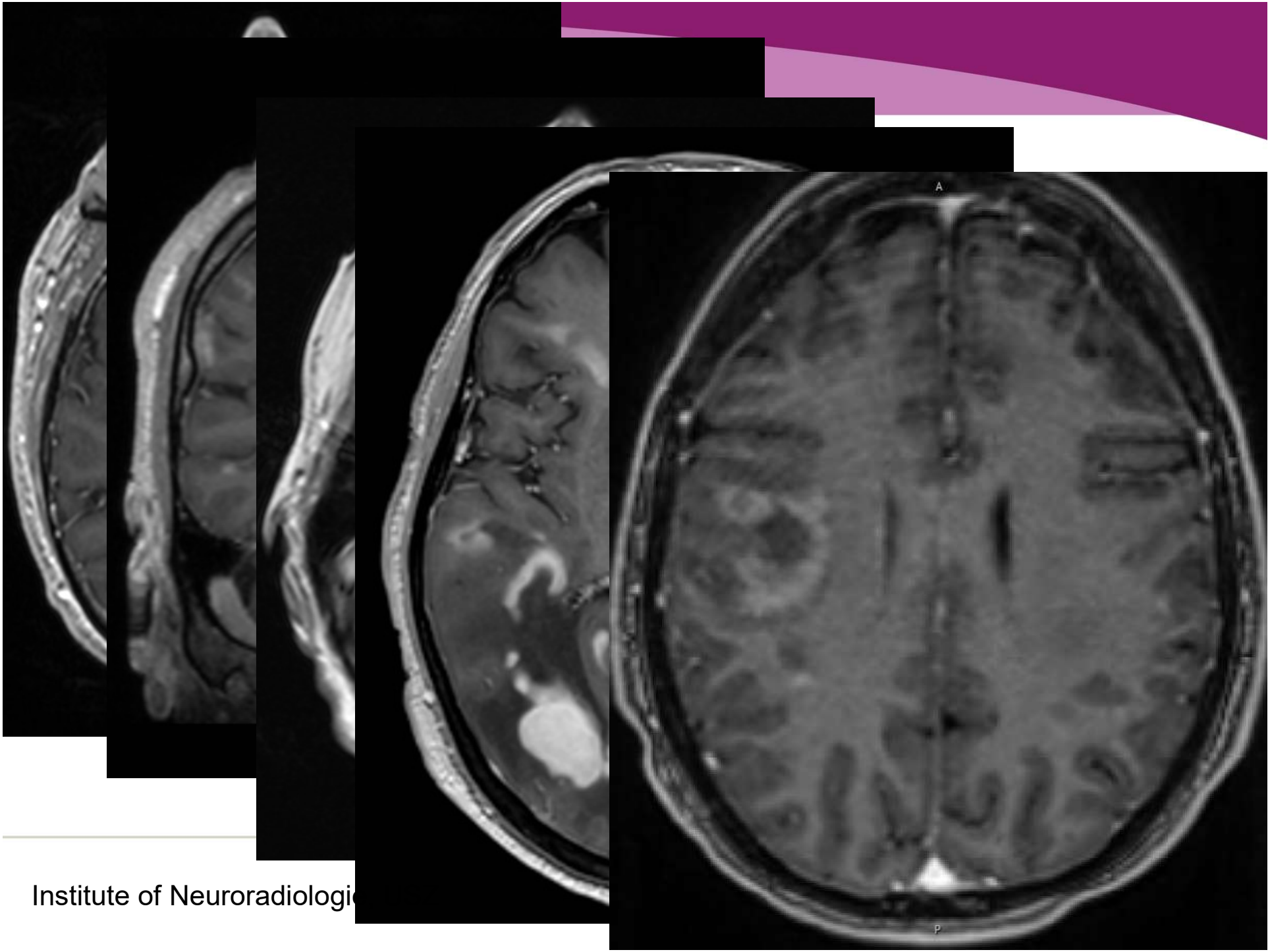
- Iso- or hyperdense mass
- Multiple lesions in about 30-40% of all patients



native



contrast


A
P

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

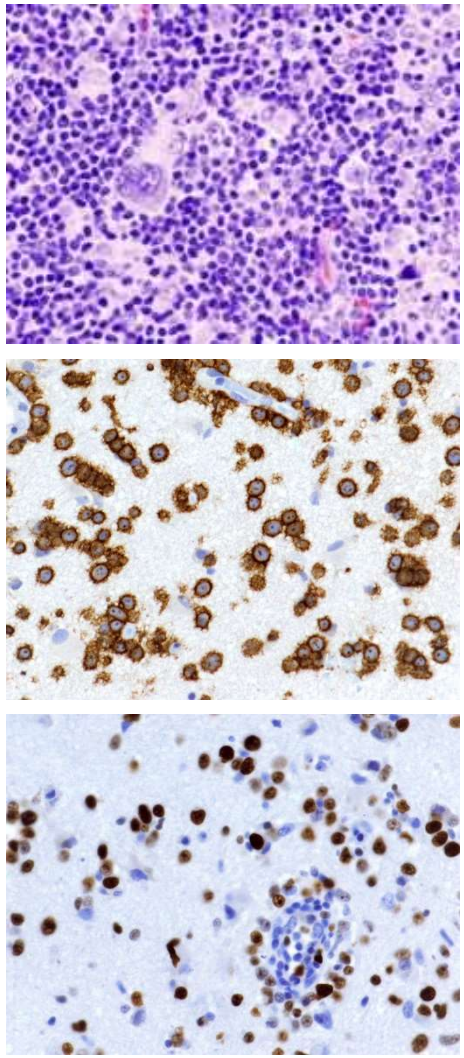
- Stereotactic biopsy: do not administer steroids before!
- Tumor resection does not affect survival – really…?

Staging:

- Slit lamp examination (ocular involvement in 10-15%)
- CT scan chest and abdomen, bone marrow biopsy
- HIV testing

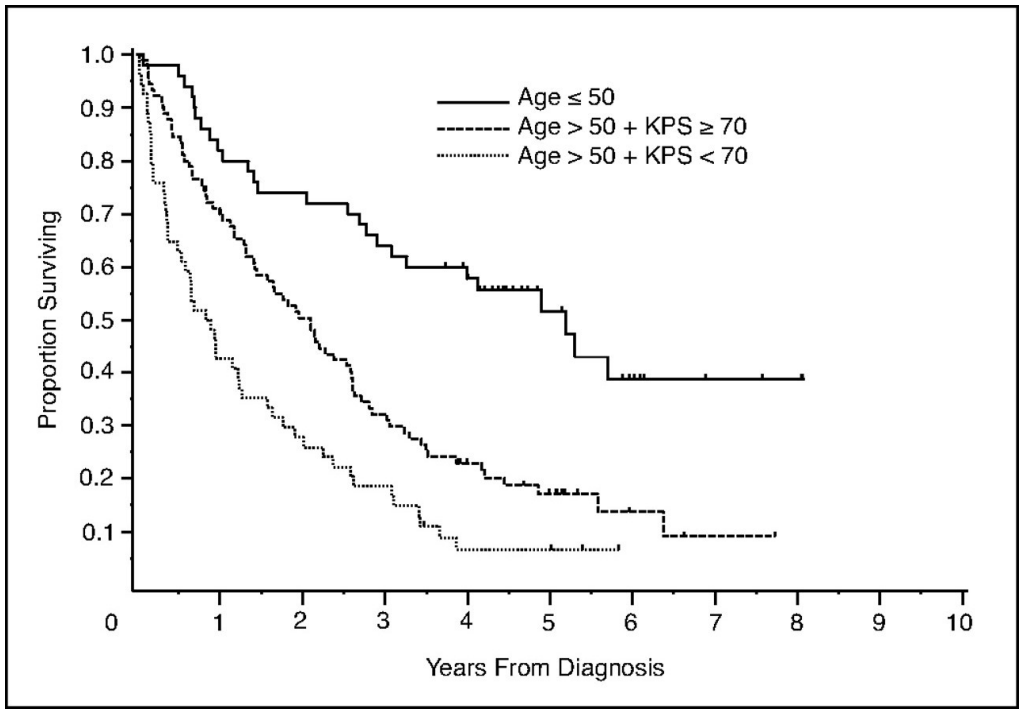
Histology

- 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: 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

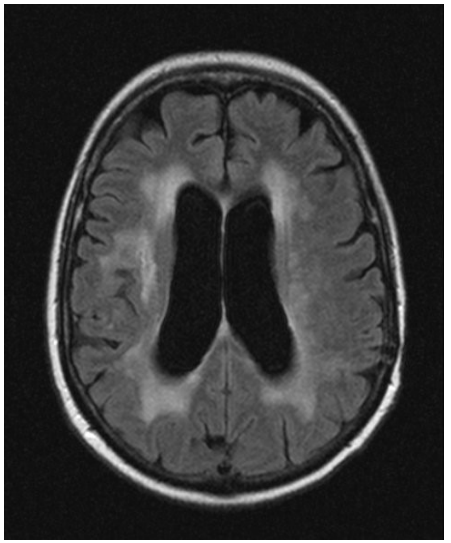
  ~25% surviving 5 years or more (Herrlinger et al., 2005)

- 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



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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

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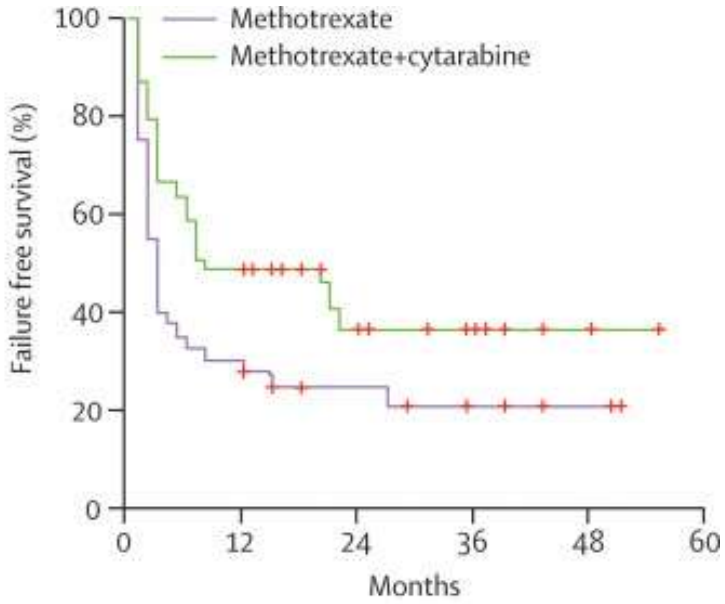
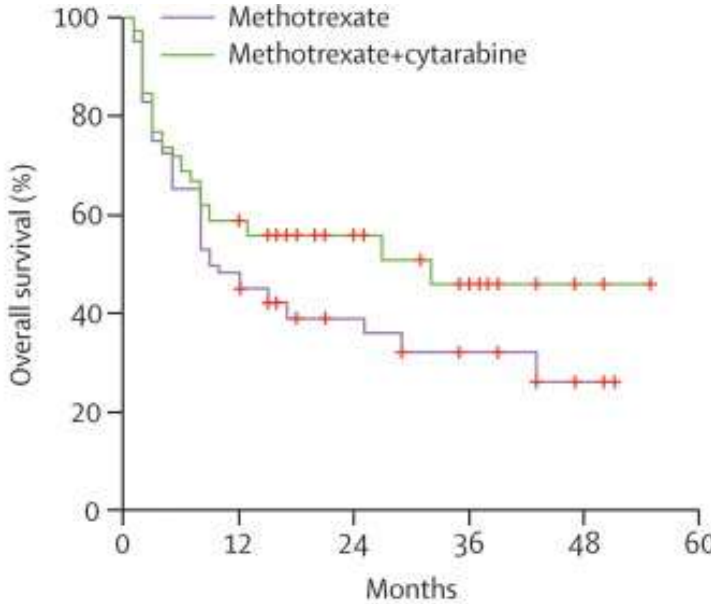
IELSG-20: MTX vs. MTX/Ara-C

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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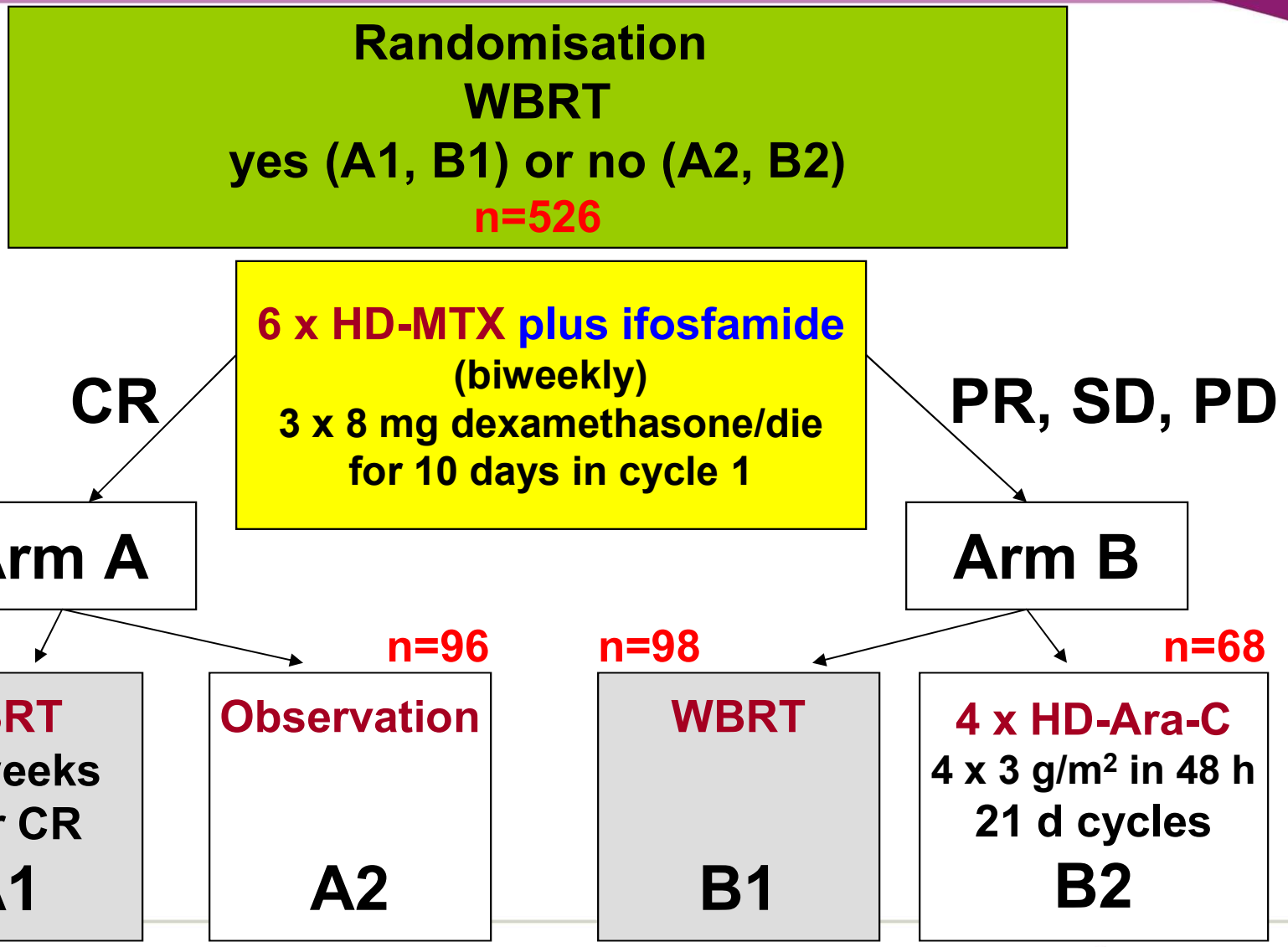
The G-PCNSL-SG1 trial



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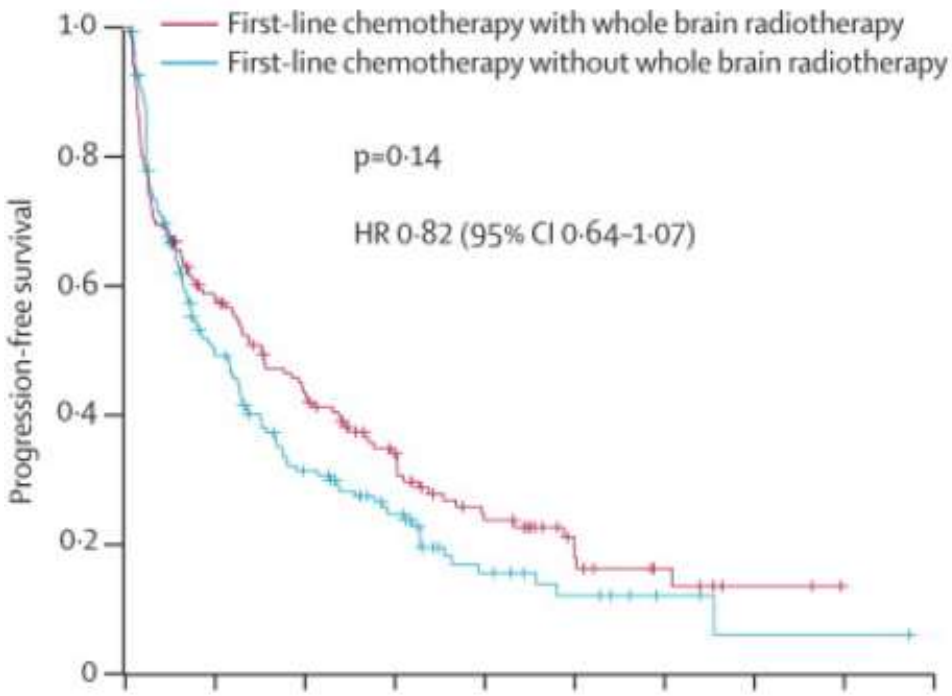
The G-PCNSL-SG1 trial

PFS



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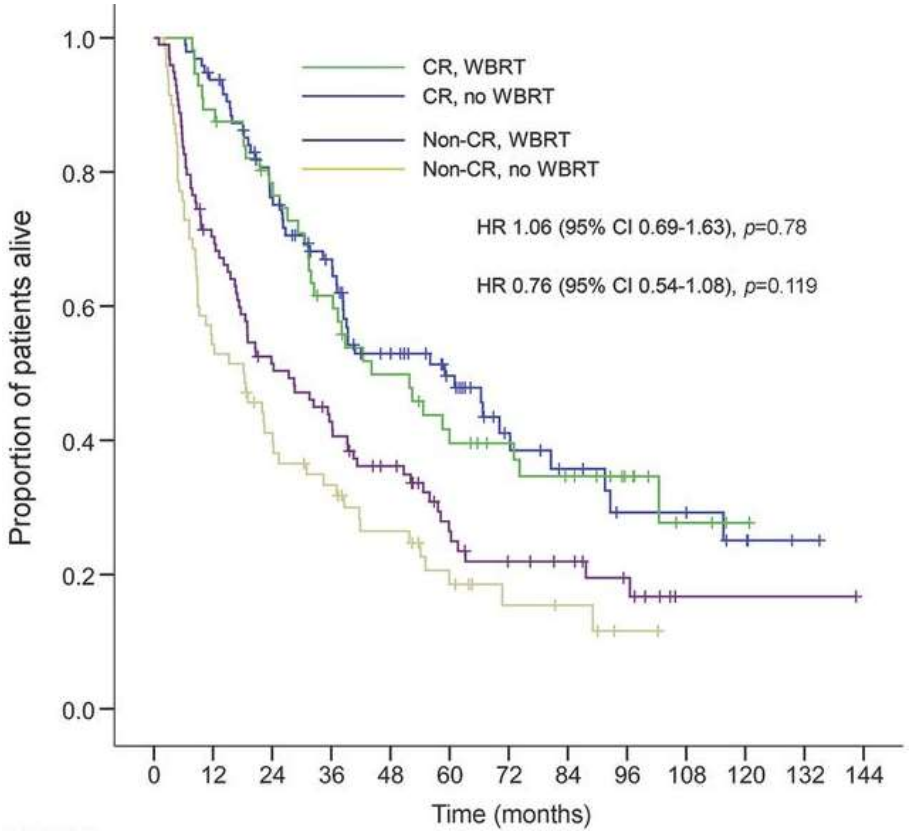

=> early WBRT does not prolong overall survival

Thiel et al., Lancet Oncol 2009
Korfel et al. Neurology 2015

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No role for resection – for 4 decades

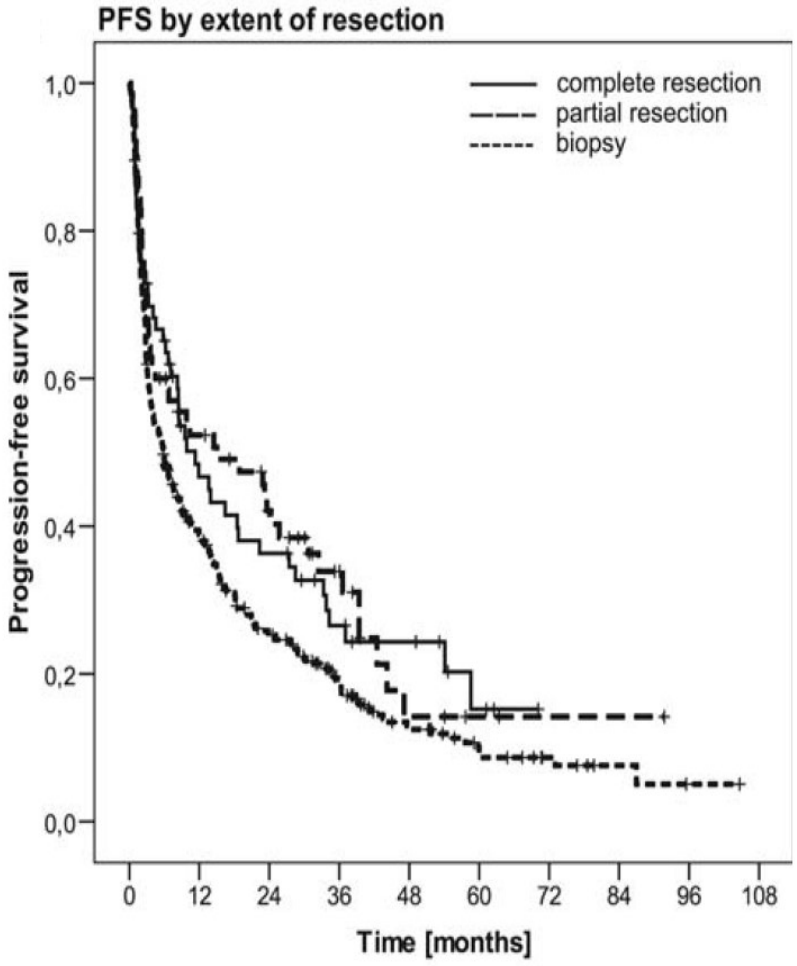
PRIMARY MALIGNANT LYMPHOMAS OF THE CENTRAL NERVOUS SYSTEM

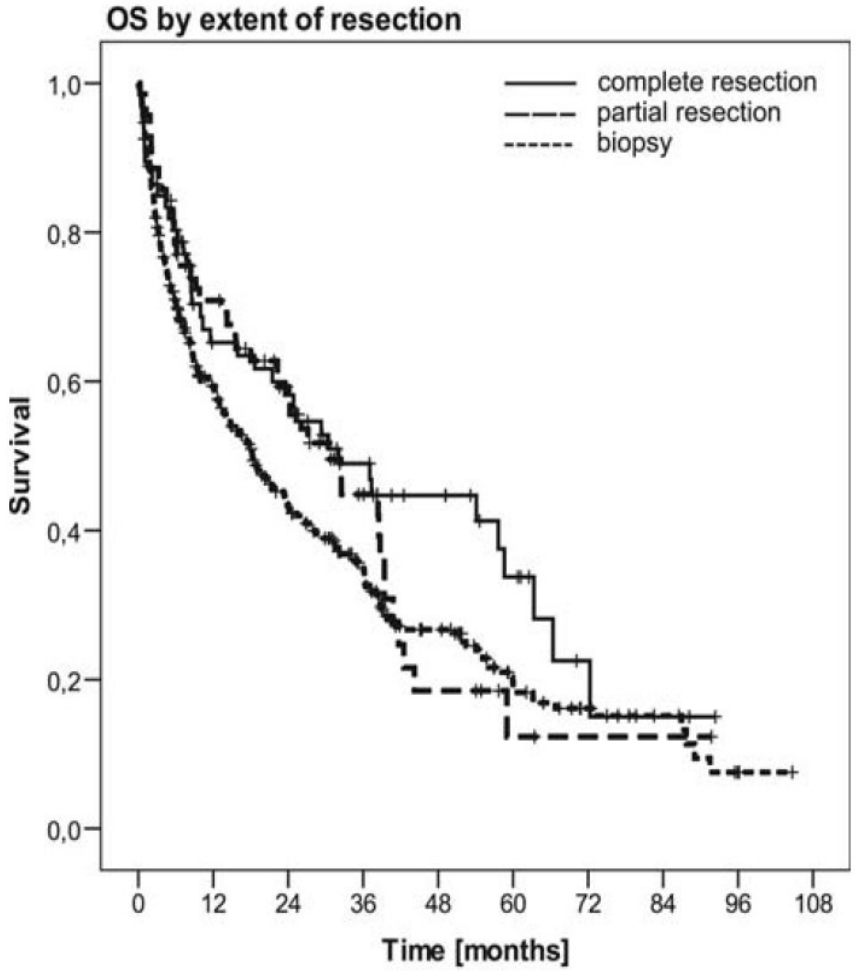
JAMES M. HENRY, MAJ, MC, USA, REID R. HEFFNER, JR, MD,
SAMUEL H. DILLARD, MAJ, MC, USA, KENNETH M. EARLE, MD,*
AND RICHARD L. DAVIS, MD†

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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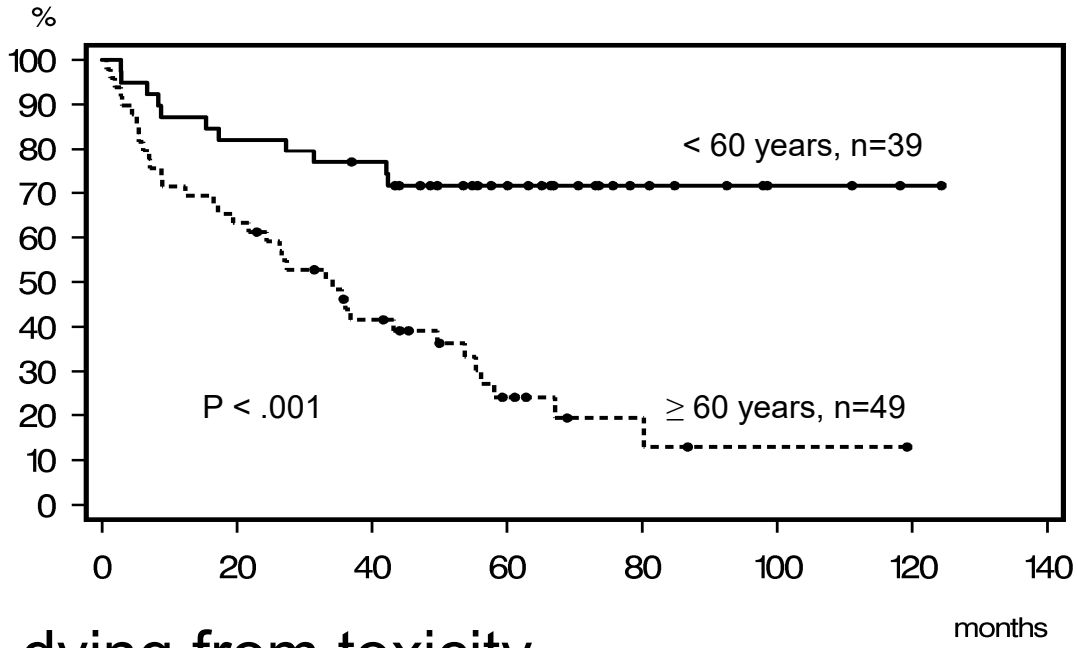
Bonn protocol - polychemotherapy

- 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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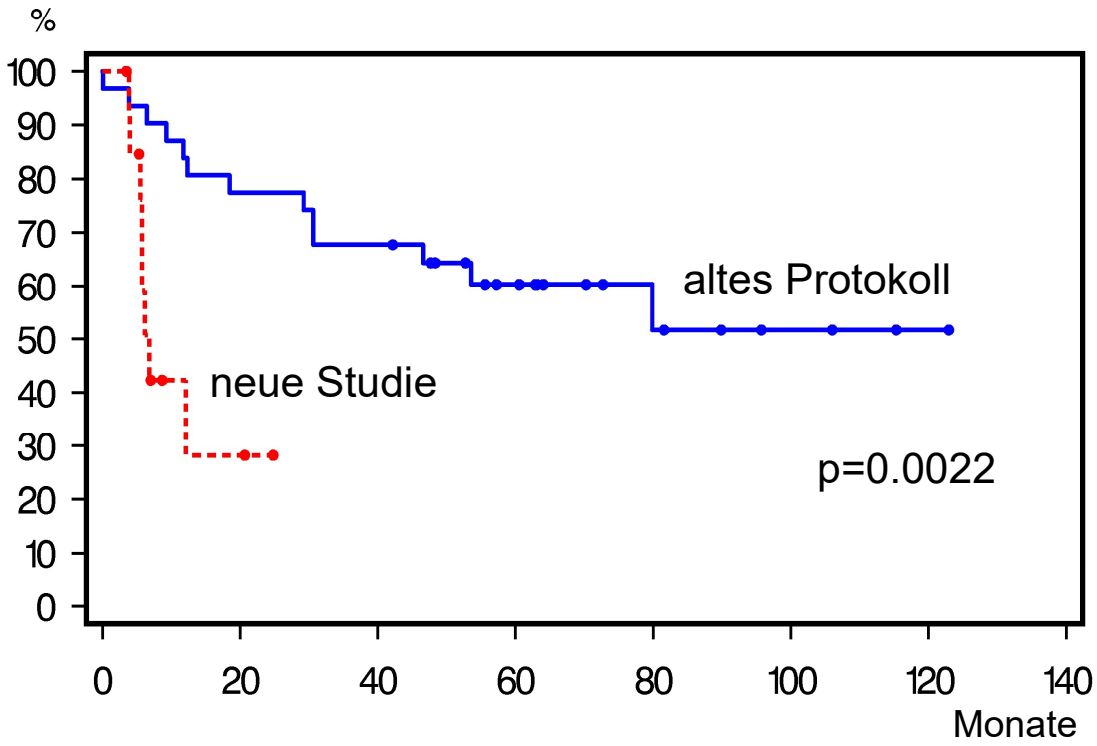
Bonn-Bochumer Protokoll 2

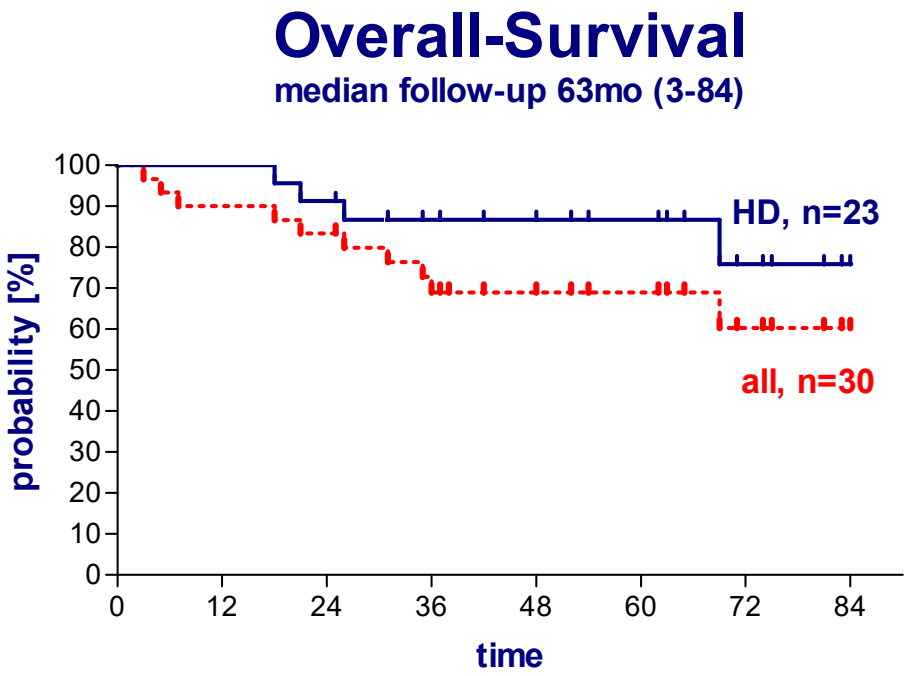
- Ohne intrathekale Chemotherapie (n=18):
- CR-Rate etwas schlechter als in der Vorstudie (53%)
- PFS deutlich reduziert



Pels et al., 2009

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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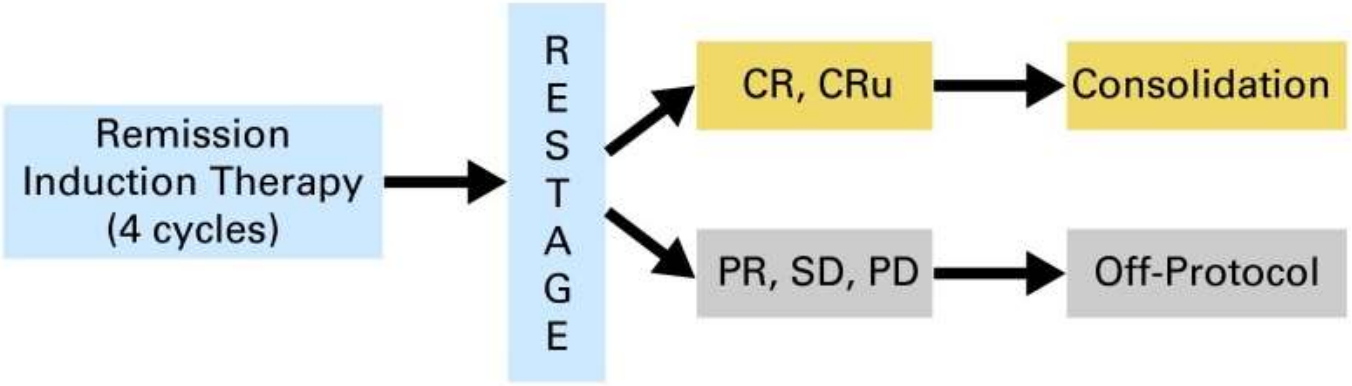
CALGB 50202: intensive chemotherapy + rituximab



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

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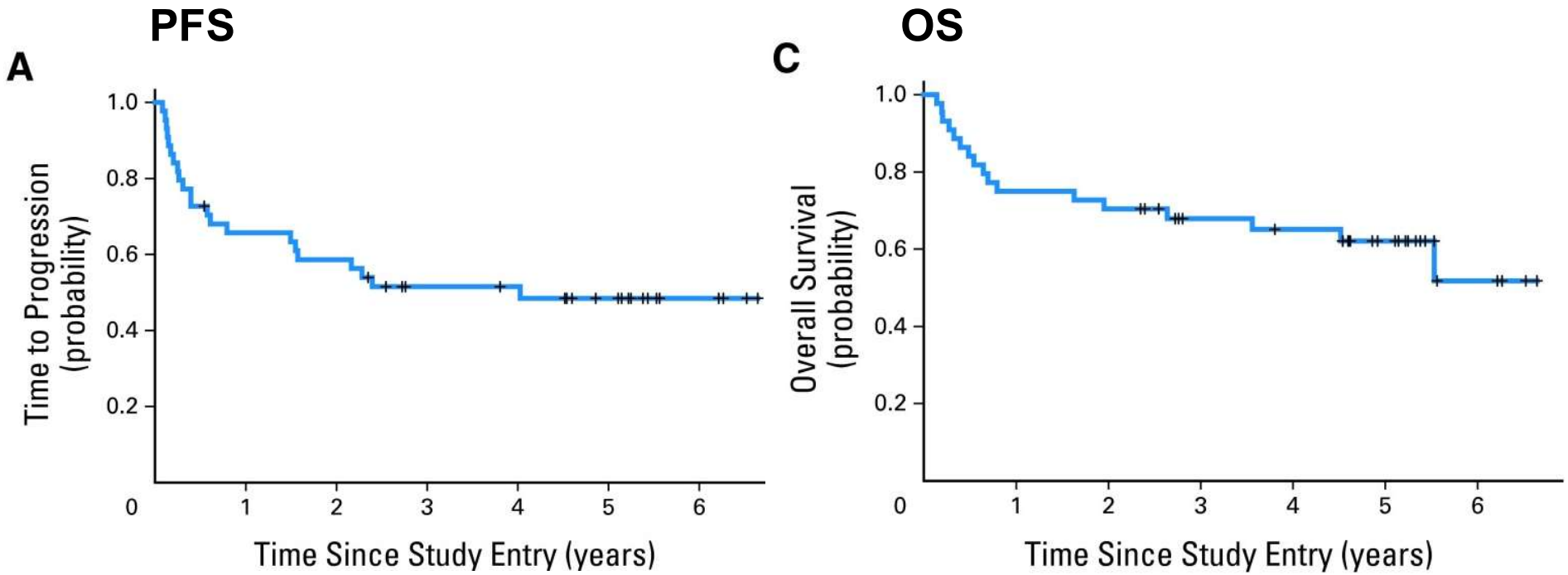
CALGB 50202: intensive chemotherapy + rituximab



Rubenstein et al., J Clin Oncol 2013

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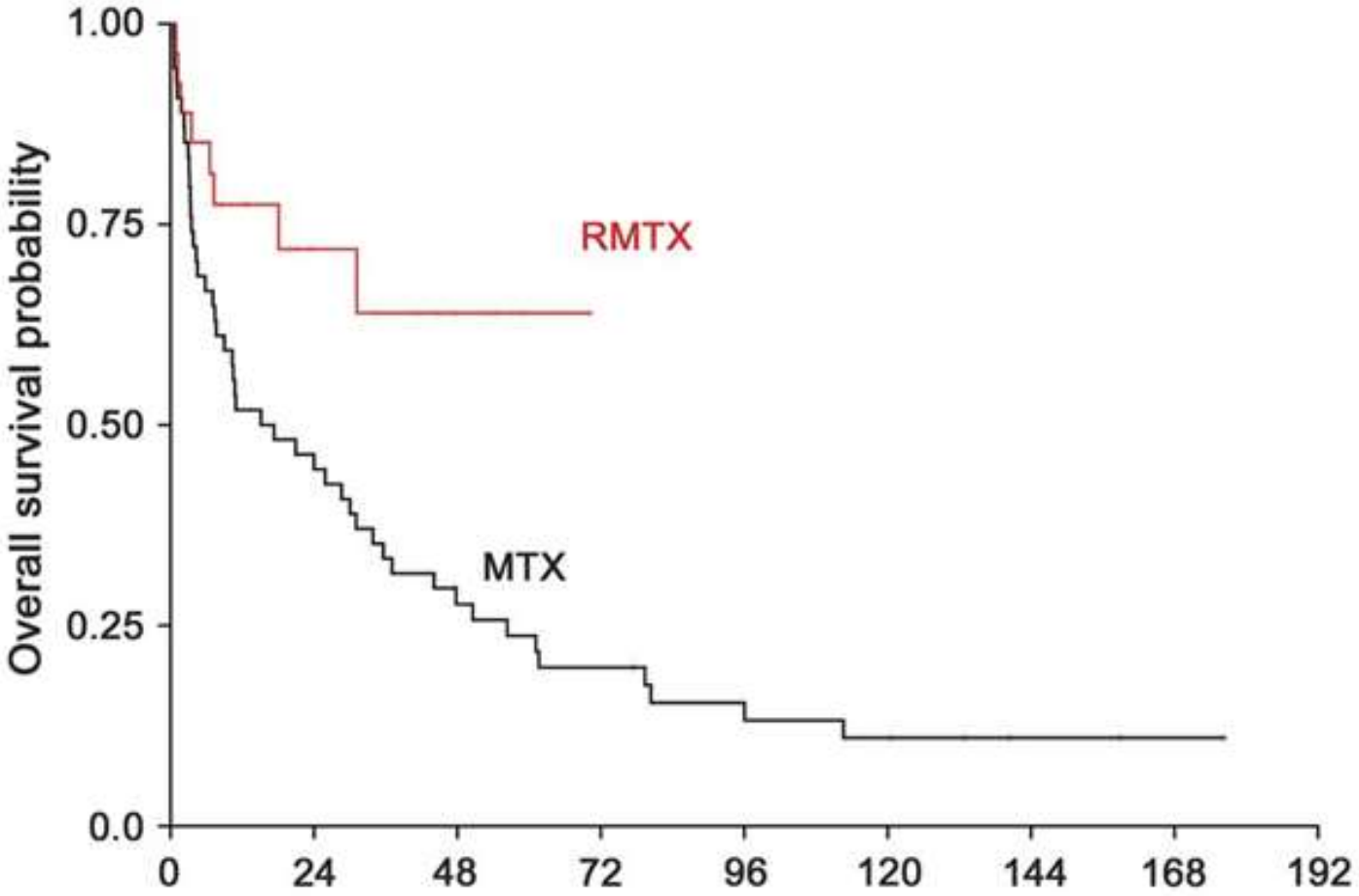
What is the role for rituximab in PCNSL?



Holdhoff et al., Neurology 2014

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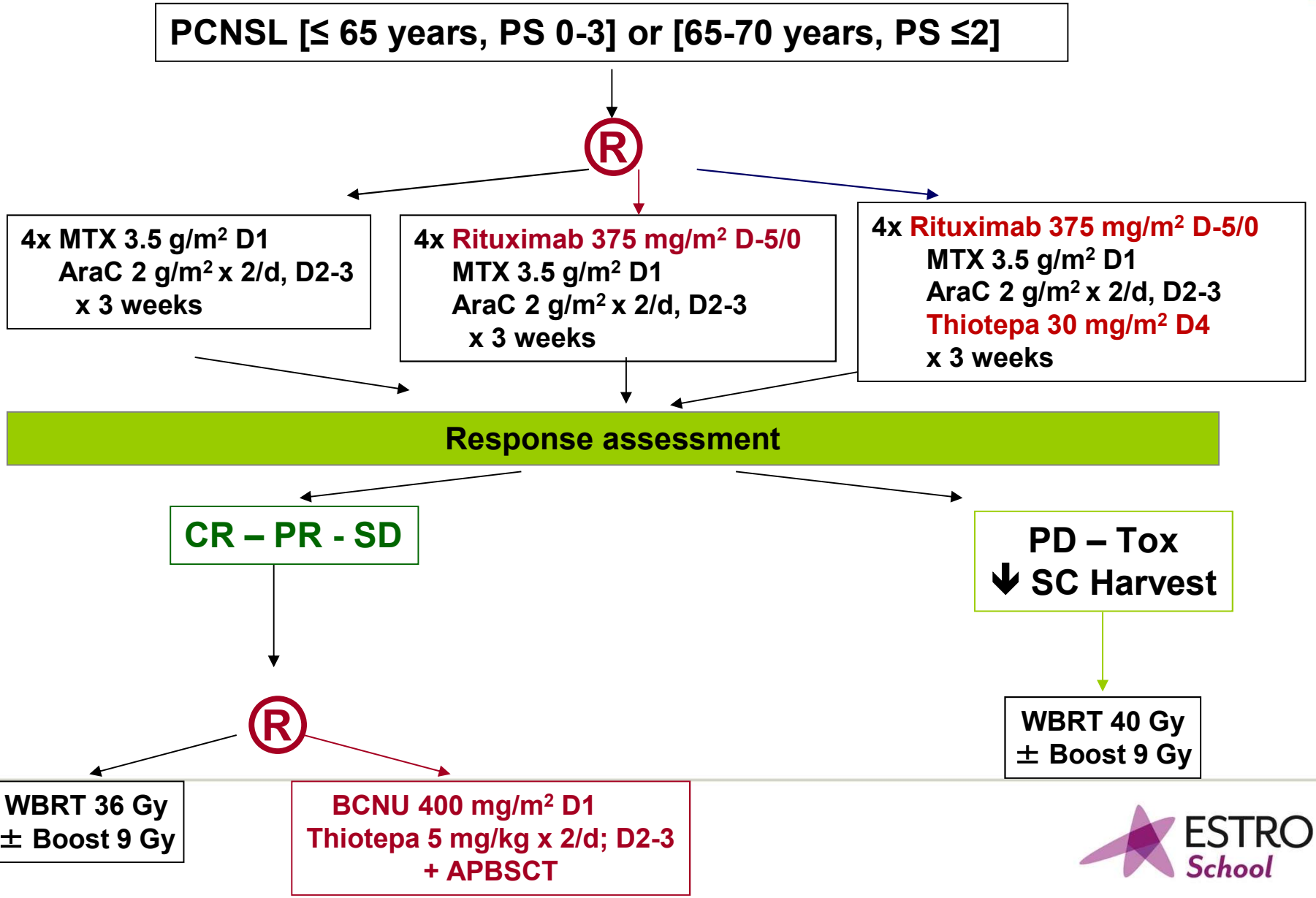
IELSG-32 trial



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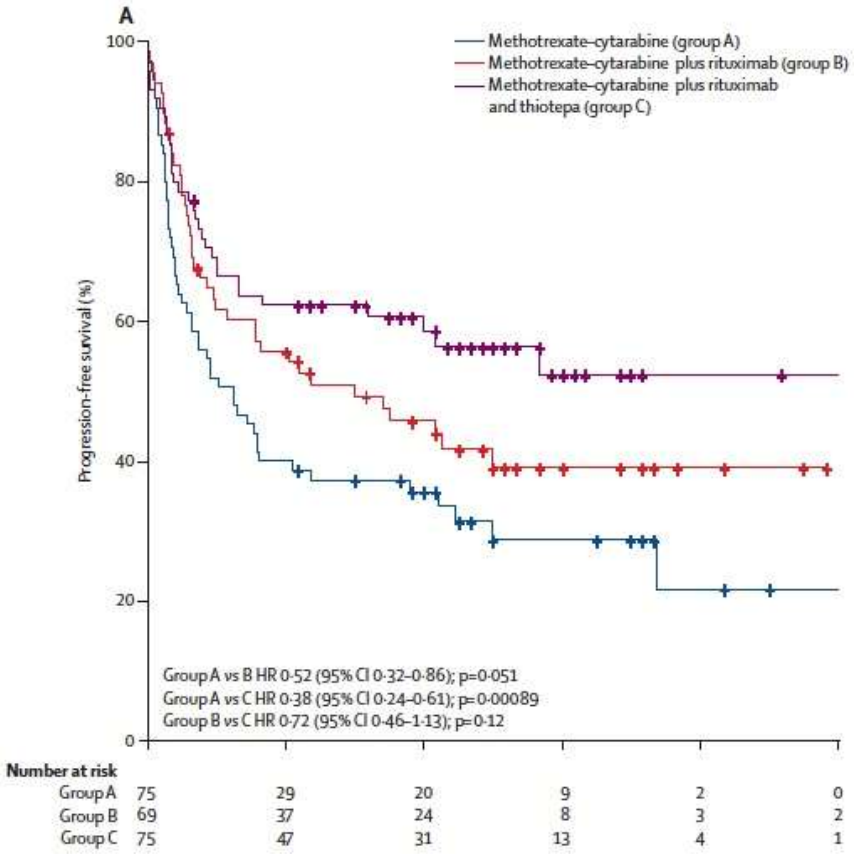
IELSG-32 trial

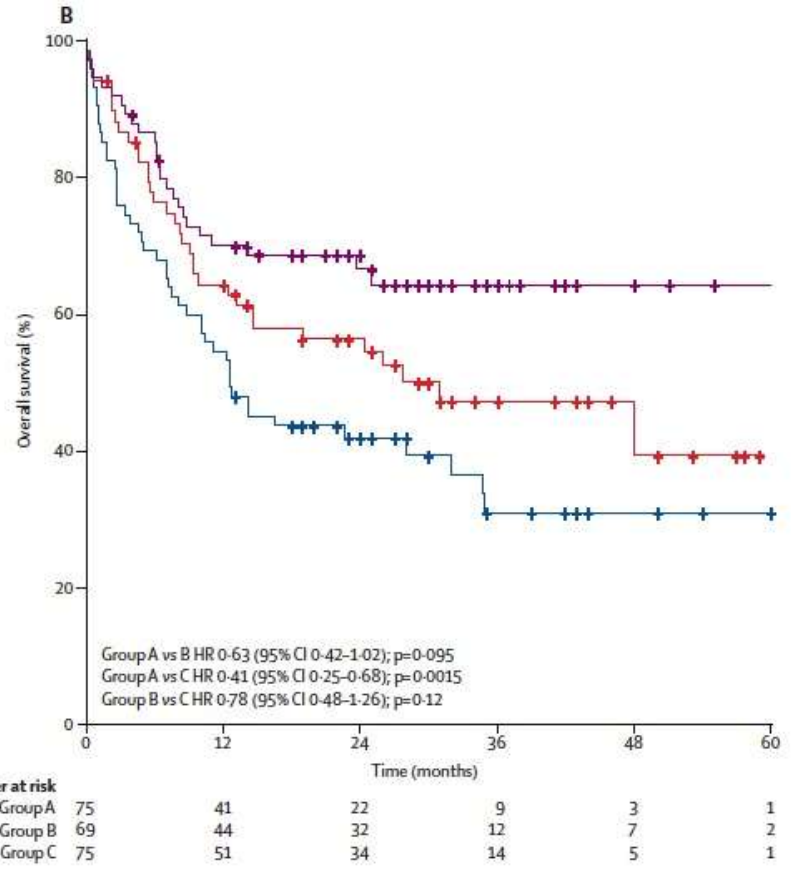
Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial

Andrés J M Ferreri, Kate Cwynarski, Elisa Pulczynski, Maurilio Ponzoni, Martina Deckert, Letterio S Politi, Valter Torri, Christopher P Fox, Paul La Rosée, Elisabeth Schorb, Achille Ambrosetti, Alexander Roth, Claire Hemmaway, Angela Ferrari, Kim M Linton, Roberta Rudà, Mascha Binder, Tobias Pukrop, Monica Balzarotti, Alberto Fabbri, Peter Johnson, Jette Sønderskov Gørløv, Georg Hess, Jens Panse, Francesco Pisani, Alessandra Tucci, Stephan Stilgenbauer, Bernd Hertenstein, Ulrich Keller, Stefan W Krause, Alessandro Levis, Hans J Schmoll, Franco Cavalli, Jürgen Finke, Michele Reni, Emanuele Zucca, Gerald Illerhaus, for the International Extranodal Lymphoma Study Group (IELSG)*

PFS



OS



Ferreri et al., Lancet Haematol 2016

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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

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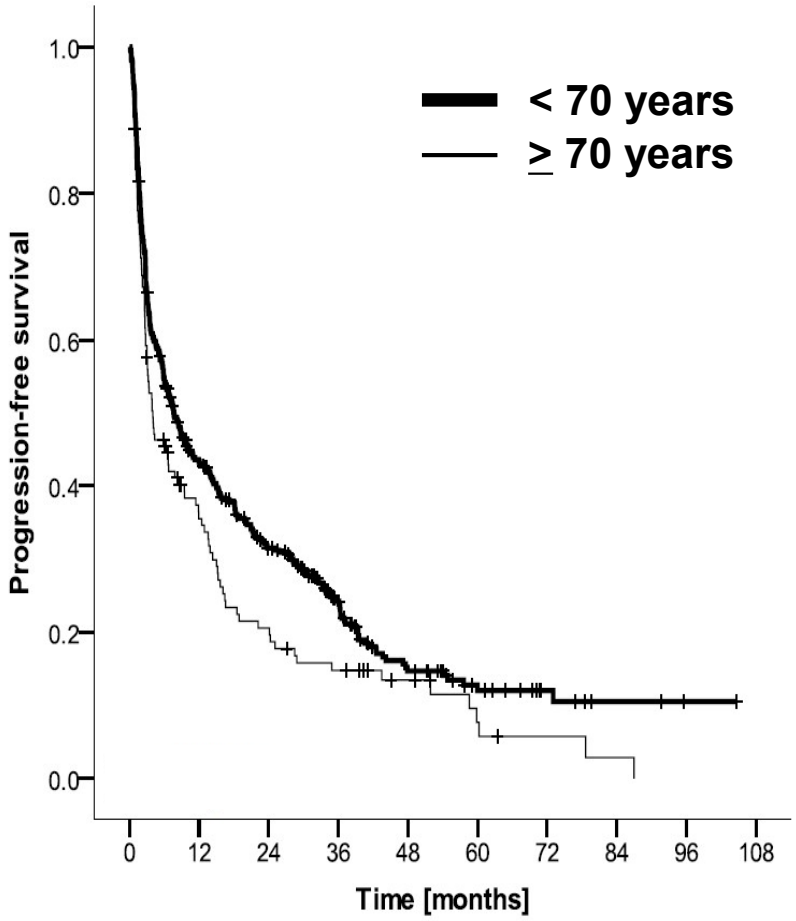
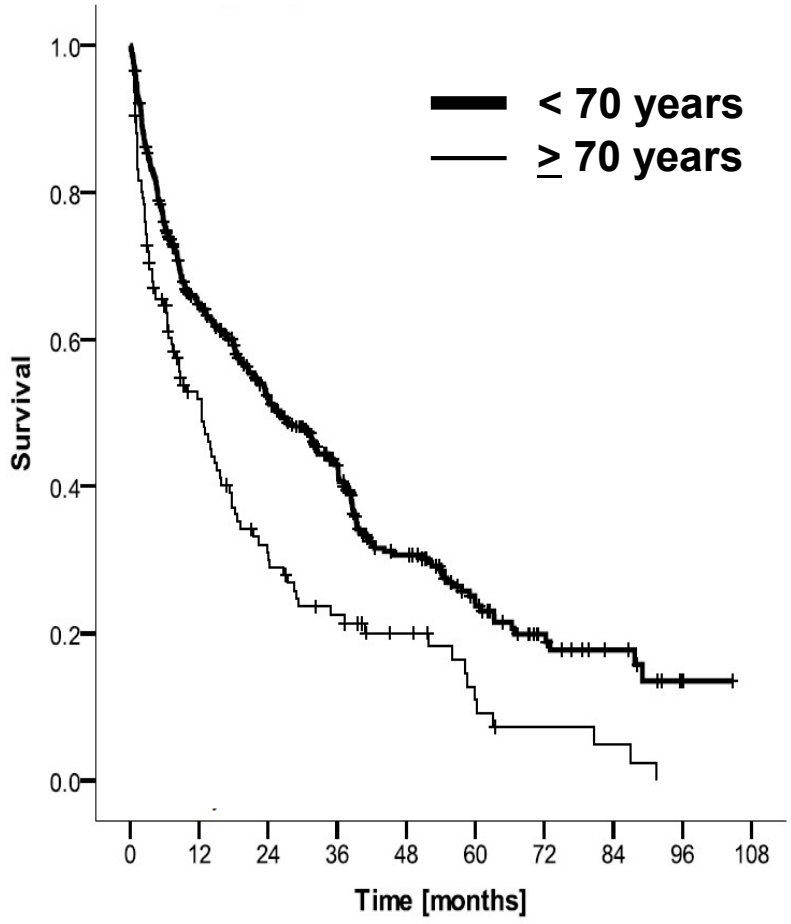
Elderly PCNSL patients in G-PCNSL-SG1

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

ESTRO School

MTX/TMZ vs. MPV-A in elderly patients

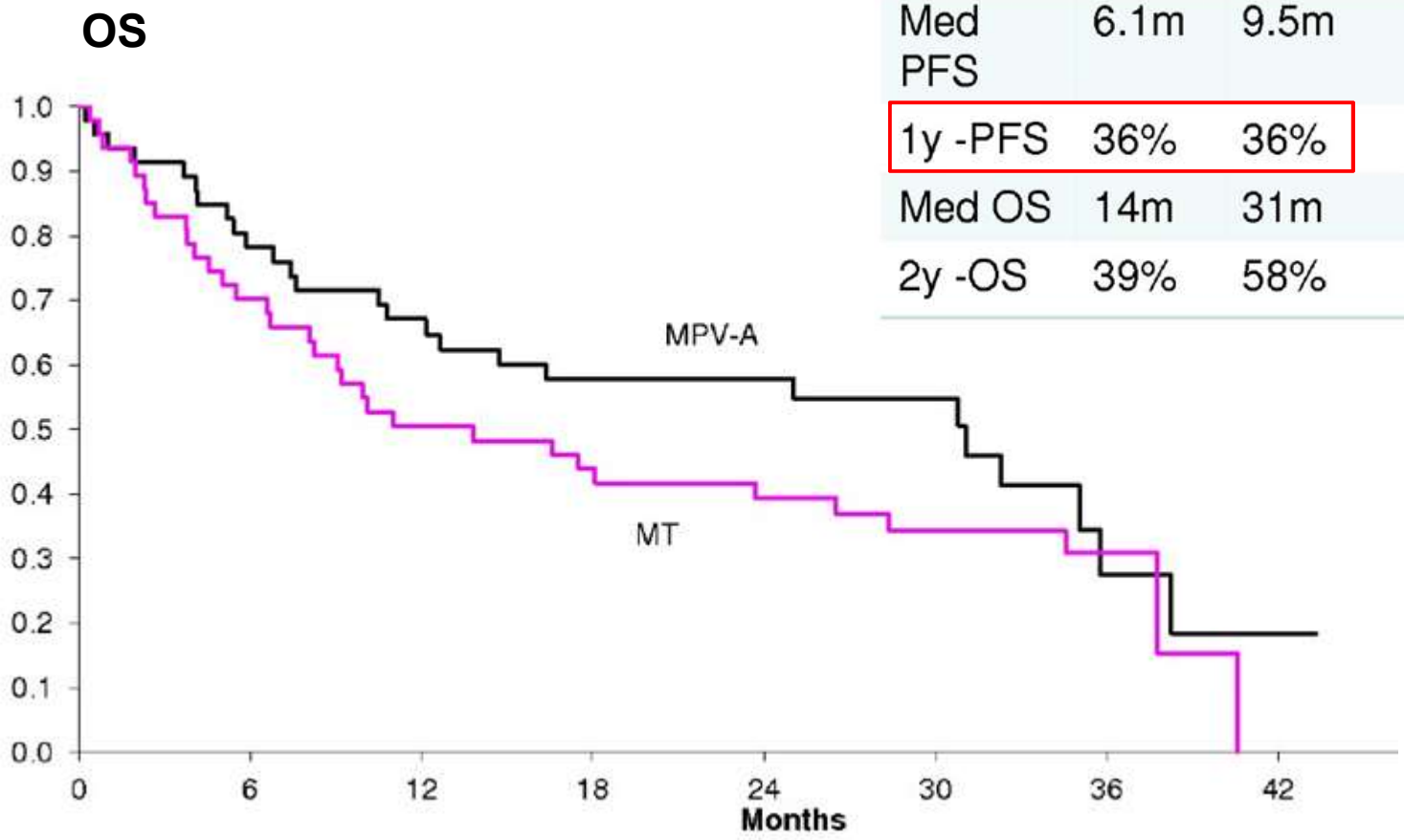
- **Randomized phase II trial**
- **95 patients, median age 72 years (60–85)**
- **Treatment arms:**
  - **MTX 3.5 g/m^2 + Temozolomide**
  - **MTX 3.5 g/m^2 + Procarbazine, Vincristine, AraC**
- **Primary einpoint: PFS at 1 year (PFS-1)**
- **Toxicity (Grad 3/4): no difference**
- **CR rate: 45% (MT) vs. 62% (MPV-A)**

Omuro et al., Lancet Hematol 2015

ESTRO School

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 MTX, TMZ	62% 45%	26% 20%	9.5 6.1	31 14

ESTRO School

Novel agents: Ibrutinib

- Bruton tyrosine kinase (BTK) inhibitor

  → BTK links the B-cell antigen receptor (BCR) and Toll-like receptors with the NF-κB pathway

- Monotreatment or in combination with other drugs
- Increased aspergillosis as a particular side effect
- Retrospective series of 13 patients with recurrent PCNSL

  → Overall response rate: 50%

Chamoun et al., Neurology 2017

Novel agents: Ibrutinib

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Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma

Christian Grommes, Alessandro Pastore, Nicolaos Palaskas, Sarah S Tang, Carl Campos, Derrek Schartz, Paolo Codega, Donna Nichol, Owen Clark, Wan-Ying Hsieh, Daniel Rohle, Marc K. Rosenblum, Agnes Viale, Viviane Tabar, Cameron W Brennan, Igor T Gavrilovic, Thomas J Kaley, Craig Nolan, Antonio M. P. Omuro, Elena Pentsova, Alissa A Thomas, Elina Tsyvkin, Ariela Noy, M. Lia Palomba, Paul A. Hamlin, Craig Sauter, Craig H Moskowitz, Julia Wolfe, Ahmet Dogan, Minhee Won, Jon Glass, Scott Peak, Enrico C Lallana, Vaios Hatzoglou, Anne S. Reiner, Philip Gutin, Jason T Huse, Katherine Panageas, Thomas G. Graeber, Nikolaus Schultz, Lisa M DeAngelis, and Ingo K. Mellinghoff

DOI: 10.1158/2159-8290.CD-17-0613 Published January 2017 Check for updates

Article Figures & Data Info & Metrics PDF

Published OnlineFirst June 22, 2017
doi: 10.1158/2159-8290.CD-17-0613

ESTRO School

Novel agents: PD-1 inhibitors

PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma

Lakshmi Nayak,[1,2] Fabio M. Iwamoto,[3] Ann LaCasce,[1,2] Srinivasan Mukundan,[1,2] Margaretha G. M. Roemer,[1] Bjoern Chapuy,[1] Philippe Armand,[1,2] Scott J. Rodig,[1,2] and Margaret A. Shipp[1,2]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; and [3]New York Presbyterian Hospital, New York, NY

Key Points

- Genetic analysis reveals frequent 9p24.1/PD-L1/PD-L2 copy-number alterations and increased expression of the PD-1 ligands in PCNSL and PTL.
- PD-1 blockade with nivolumab demonstrated activity in patients with relapsed/refractory PCNSL and PTL.

Primary central nervous system (CNS) lymphoma (PCNSL) and primary testicular lymphoma (PTL) are rare extranodal large B-cell lymphomas with similar genetic signatures. There are no standard-of-care treatment options for patients with relapsed and refractory PCNSL and PTL, and the overall prognosis is poor. PCNSLs and PTLs exhibit frequent 9p24.1 copy-number alterations and infrequent translocations of 9p24.1 and associated increased expression of the programmed cell death protein 1 (PD-1) ligands, PD-L1 and PD-L2. The activity of PD-1 blockade in other lymphomas with 9p24.1 alterations prompted us to test the efficacy of the anti–PD1 antibody, nivolumab, in 4 patients with relapsed/refractory PCNSL and 1 patient with CNS relapse of PTL. All 5 patients had clinical and radiographic responses to PD-1 blockade, and 3 patients remain progression-free at 13^+ to 17^+ months. Our data suggest that nivolumab is active in relapsed/refractory PCNSL and PTL and support further investigation of PD-1 blockade in these diseases. (*Blood*. 2017;129(23):3071-3073)

blood

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Take home messages

- Cure is probably restricted to younger patients
- Standard of care is only poorly defined

  => further trials are urgently needed

- HD-MTX as the therapeutic backbone / rituximab increasingly used
- WBRT should be avoided in the first-line setting

- Open questions:
  - Role for new drugs, e.g. immune checkpoint inhibitors, ibrutinib…?
  - Optimal treatment for elderly/frail patients?

MEDICAL UNIVERSITY OF VIENNA

COMPREHENSIVE CANCER CENTER VIENNA

Universitätsklinik für Strahlentherapie und Strahlenbiologie Wien

Evidence based management of „childhood“ tumours in adults

Management of medulloblastoma

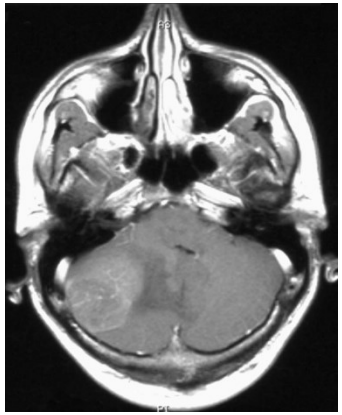
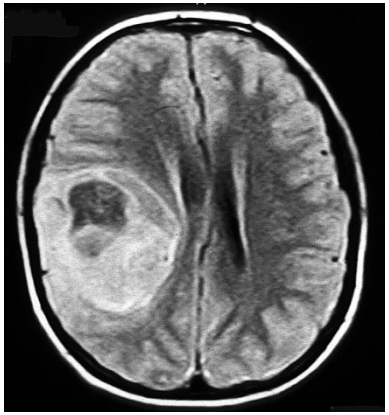
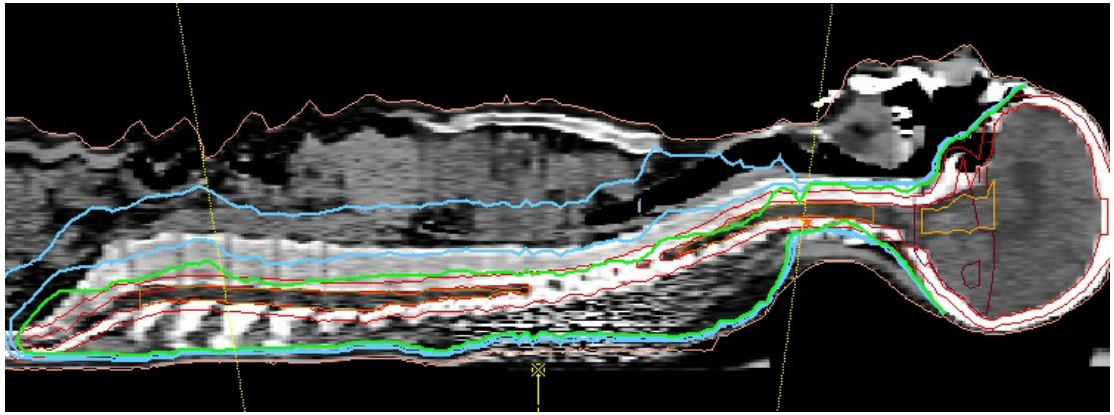
Karin Dieckmann

Department of Radiotherapy

Medical University of Vienne

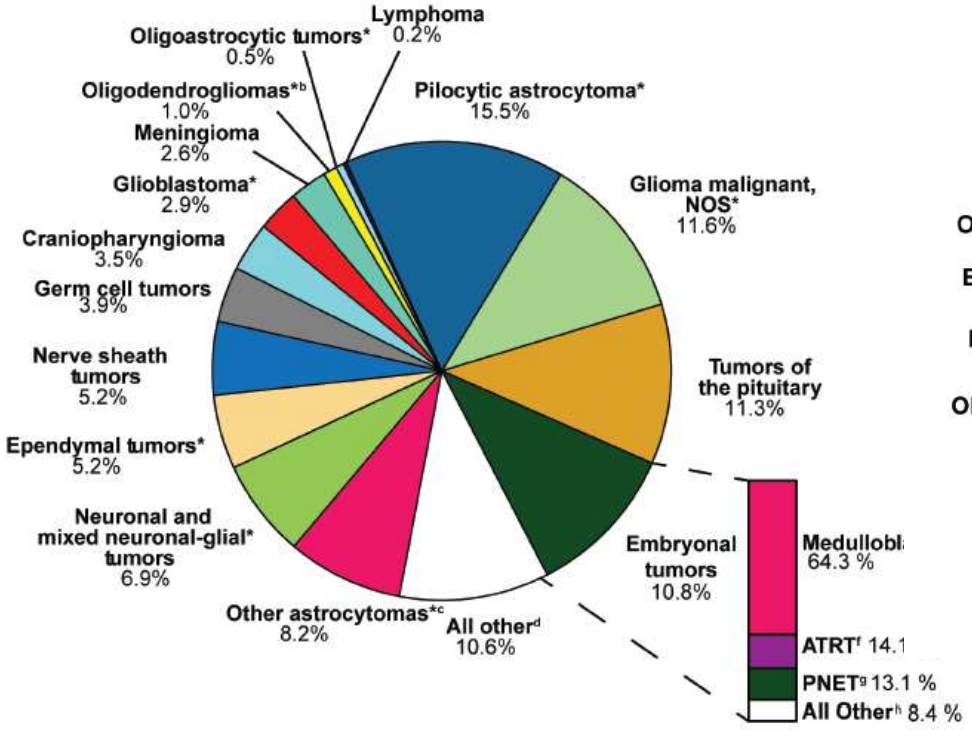
Medulloblastoma Epidemiology

- Incidence 2.6-5.4 per 100,000 children aged <19
- 5 y. Progression free survival < 60%
- Survival rate around 65% overall
- Survivors have significant long-term-health issues
- **Incidence 0.5 per 100,000 adults per year**
- **Survival rate around 80% after 5 years**

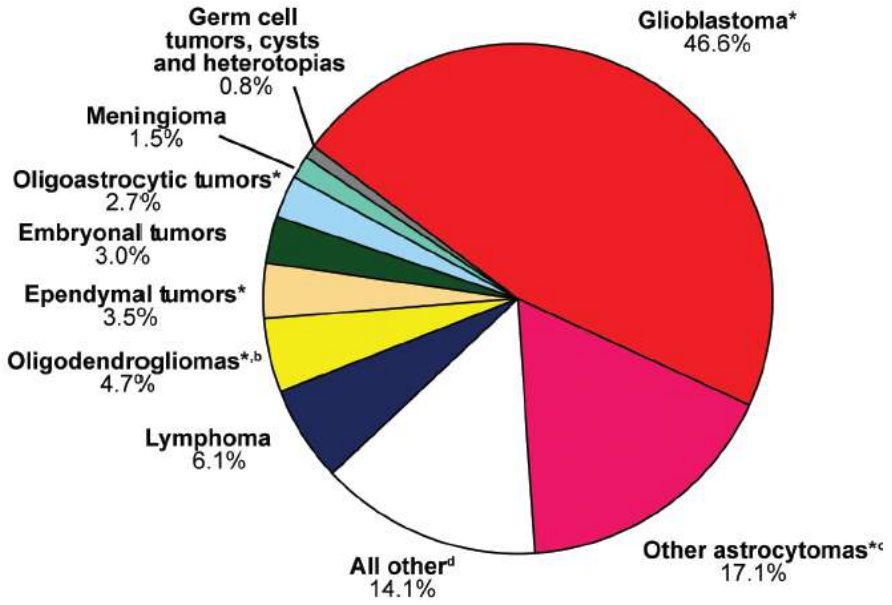




CBTRUS Statistical Report United States 2009-2013

Children



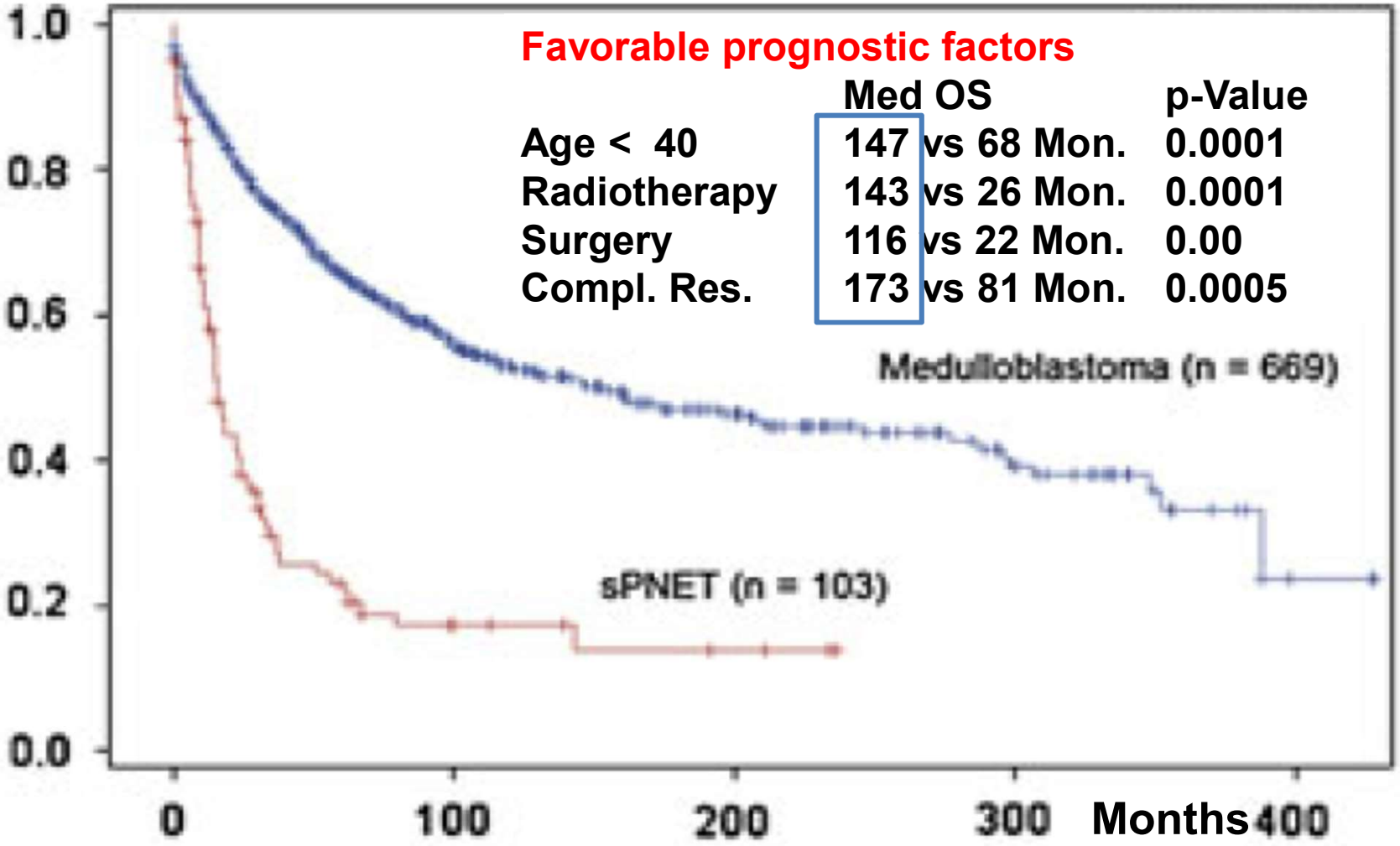
Adults



Less than 3% of all brain tumors in adults are Medullo-blastoma or PNET

OS of Adults with Medulloblastoma and stPNET

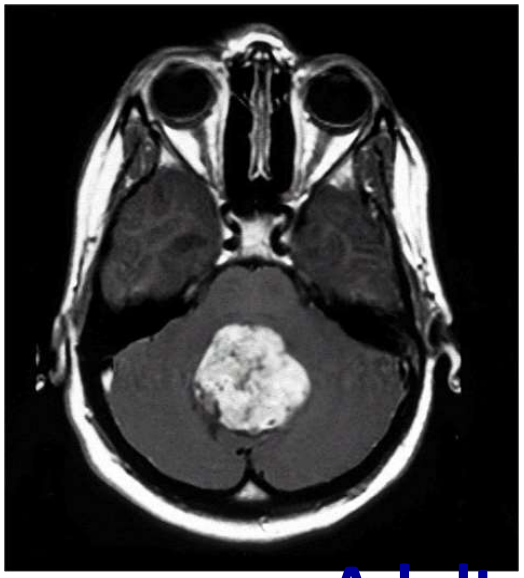
OS / SEER 18 Register, 669 MB, 103 stPNET,
Med. Age at time of diagnosis, 32ys MB; 30 ys srPNET, 1973-2009



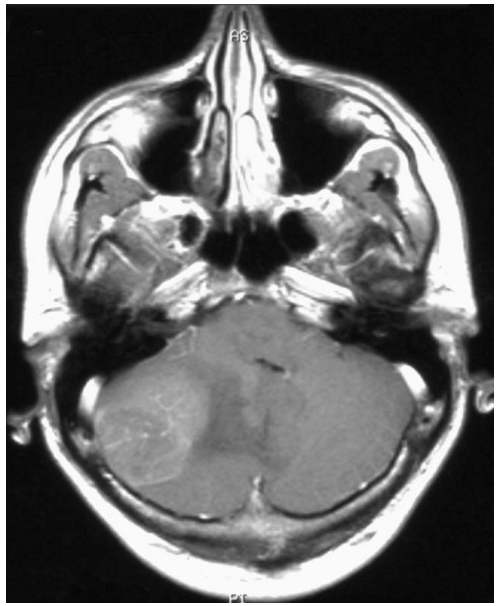
Gandhi et al., 2013

Medulloblastoma Differences

Child



Adult



Discrepancies in childhood and adult MB :

- **cell of origin**
- **tumor cell differentiation**
- **pathologic features**
- **localisation**
- **response to therapy**

Staging according to Chang

Variable	Tumor dimension	Variable	Tumor dimension
Tumor classification		Metastasis classification	
T1	<3 cm	M0	No evidence of gross subarachnoid or hemato. metastasis
T2	>3cm	M1	Microscopic tumor cell in CSF
T3a	>3 with Tu into the aqueduct/foramen Luschkae, cerebral subarachnoid space, third or lateral ventricles	M2	Gross nodular seeding in cerebellum
T3b	>3 cm with unequivocal spread into the brainstem; for T3b surgical staging may be used in the absence of involvement at imaging	M3	Gross nodular seeding in spinal subarachnoid space
T4	>3cm with spread beyond the aqueduct of Sylvius and Foramen magnum	M4	Metastasis beyond cerebrospinal axis

Medulloblastoma Different Studies

Autor	n	RT	Chx	Age	Results
Greenberg et al.,2001	**17**	**CSI + local boost**	**Packer (n=10) POG (n=7)**	**Median: 23 (18-47)**	EFS – (median)/ *(MST)*: Packer-Gr. : 26 Mon./ *(36 Mon.)* POG-Gr. : 48 Mon./ *(57 Mon.)*
Coulbois et al., 2001	**22**	**n.A.**	**n.A.**	**n.A.**	5- y PFS: 63.1% 5- y OS : 81.3%
Brandes et al., 2003	**36**	**CSI + boost (36,0 Gy / 54.8 Gy)**	**Chx. only "high risk"**	**≥ 18 years**	PFS 5 – J.: M0 75% vs. M+ 45% PFS 5 – J. "standard risk" 76% vs."high risk" 61%
Louis et al., 2002	**24**	**CSI +local boost**	**Chx. in 6 Pat. after relapse**	**≥ 16 years**	5 – y. OS: 82%
Spreafico et al., 2005	**23**	**A : 36 /55 Gy B : HART 39,1 / 60 Gy**	**Sandwich**	**Med. 26 y (18-41 y.)**	5 – J. DFS : 65% OS: 73% HART all pts. med 39 Mon. OS
Padovani et al., 2007	**253**	**CSI <30/> 30 Gy PF<50/>50 Gy**	**Sandwich**	**Med. 26 y (18-41 y.)**	5 – J. DFS : 65% OS : 73% HART all pts. med 39 Mon. OS
Friedrich et al., 2013	**70**	**CSI 35,2 PF : 55 Gy**	**Packer-Chx. 49 Pts.**	**Med. 28,5y (21-50 y.)**	4 – J. EFS : 68% (only M 0) OS : 89%

Medulloblastoma Different Prospective Studies

Autor	n	RT	Chx	Age	Results
Brandes et al., 2007	36	CSI + boost (36,0 Gy / 54.8 Gy)	Chx. only "high risk"	≥ 18 years	PFS 5 – y.: M0 78% vs. M+ 61% PFS 5 – y. "standard risk" 80% vs."high risk" 69% OS 5 –y.: 80% low risk vs.73%high risk

N=36 pts. 10 low risk **Radiotherapy alone**

26 high risk **Upfront CT + RT + adjuvant CT**

22/26 upfront chemotherapy: 26 MOPP based

6 cisplatin based

RT Posterior Fossa 54.8Gy / CSI 36 Gy

Maintenance CT since 1995: cisplatin 25 mg/m2 day 1-4

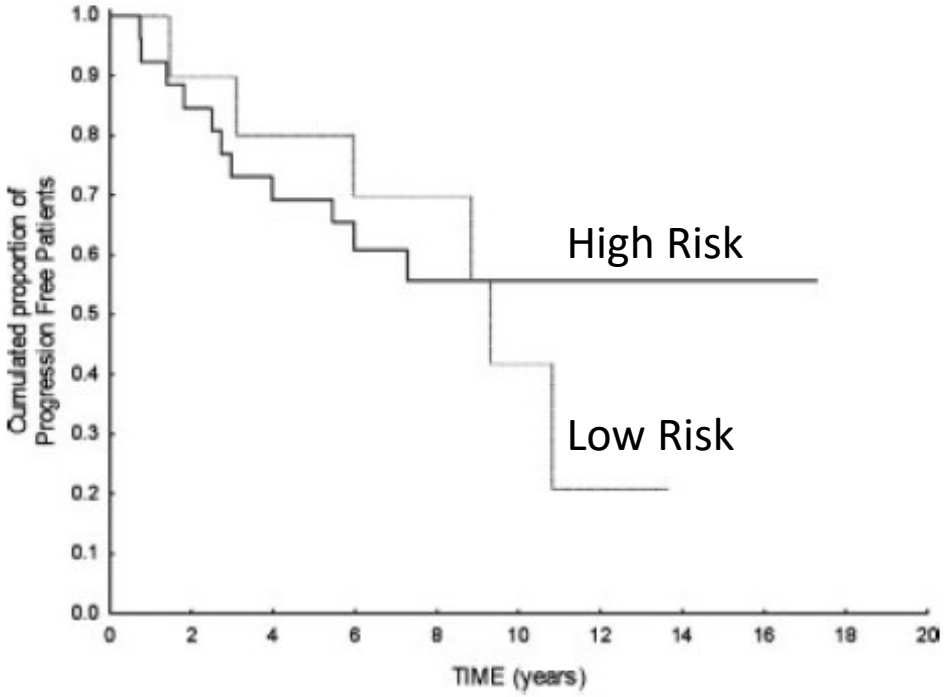
Etoposide 40 mg/m2 day 1-4

Cyclophosphamide 1000 mg/m2 day 4

Long-term Results of a Prospective Study on the Treatment of Medulloblastoma in Adults

Alba A. Brandes, MD[1]

Progression free survival



5 y PFS low risk: 80%; (59% CI, 59-100%)

5 y PFS high risk: 69%; (95% CI, 54-89%)

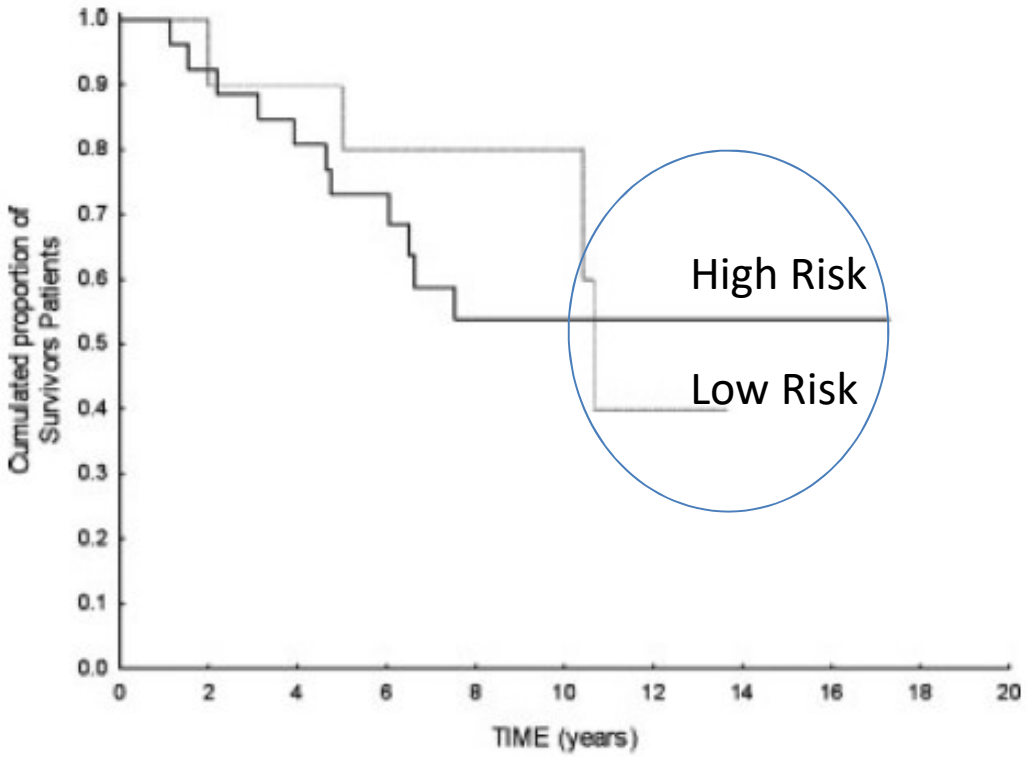
- No influence of metastatic status; presence of residual disease after surgery had a significant effect on 5 year PFS.
- Longer follow up High risk patients have a better outcome.

CANCER November 1, 2007 / Volume 110 / Number 9

Long-term Results of a Prospective Study on the Treatment of Medulloblastoma in Adults

Alba A. Brandes, MD[1]

Overall Survival



Median follow up 7.6 years

Median OS 10.7 years low risk pts

5 y OS low risk: 80%; (95% CI, 58-100%)

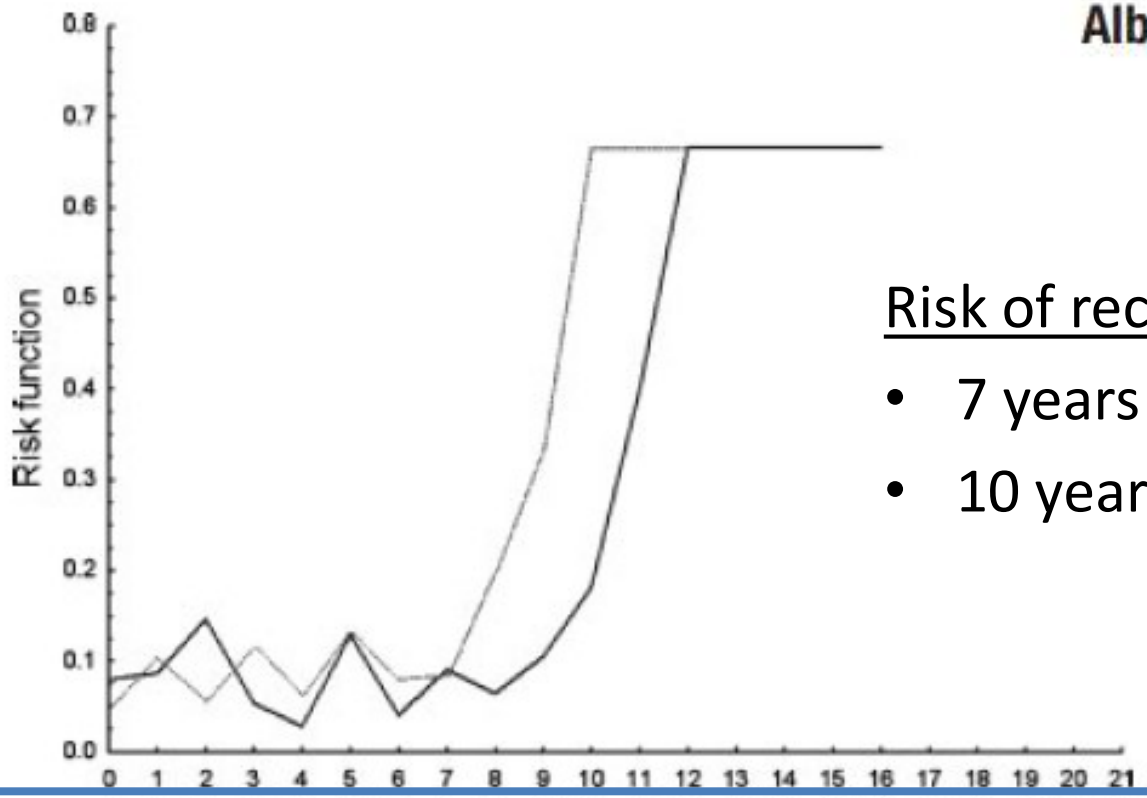
5 y OS high risk: 73%; (95% CI, 58-92%)

- 5 years OS was not influenced by metastatic status at time of Diagnosis; Presence of residual disease after surgery.

CANCER November 1, 2007 / Volume 110 / Number 9

Long-term Results of a Prospective Study on the Treatment of Medulloblastoma in Adults

Alba A. Brandes, MD[1]



Risk of recurrence:

- 7 years for low risk
- 10 years for high risk

Open question:

- Can low risk patients with MB profit from CT as children and increase the OS
- Can RT of the CSI be reduced in l low risk patients

CANCER November 1, 2007 / Volume 110 / Number 9

Medulloblastoma

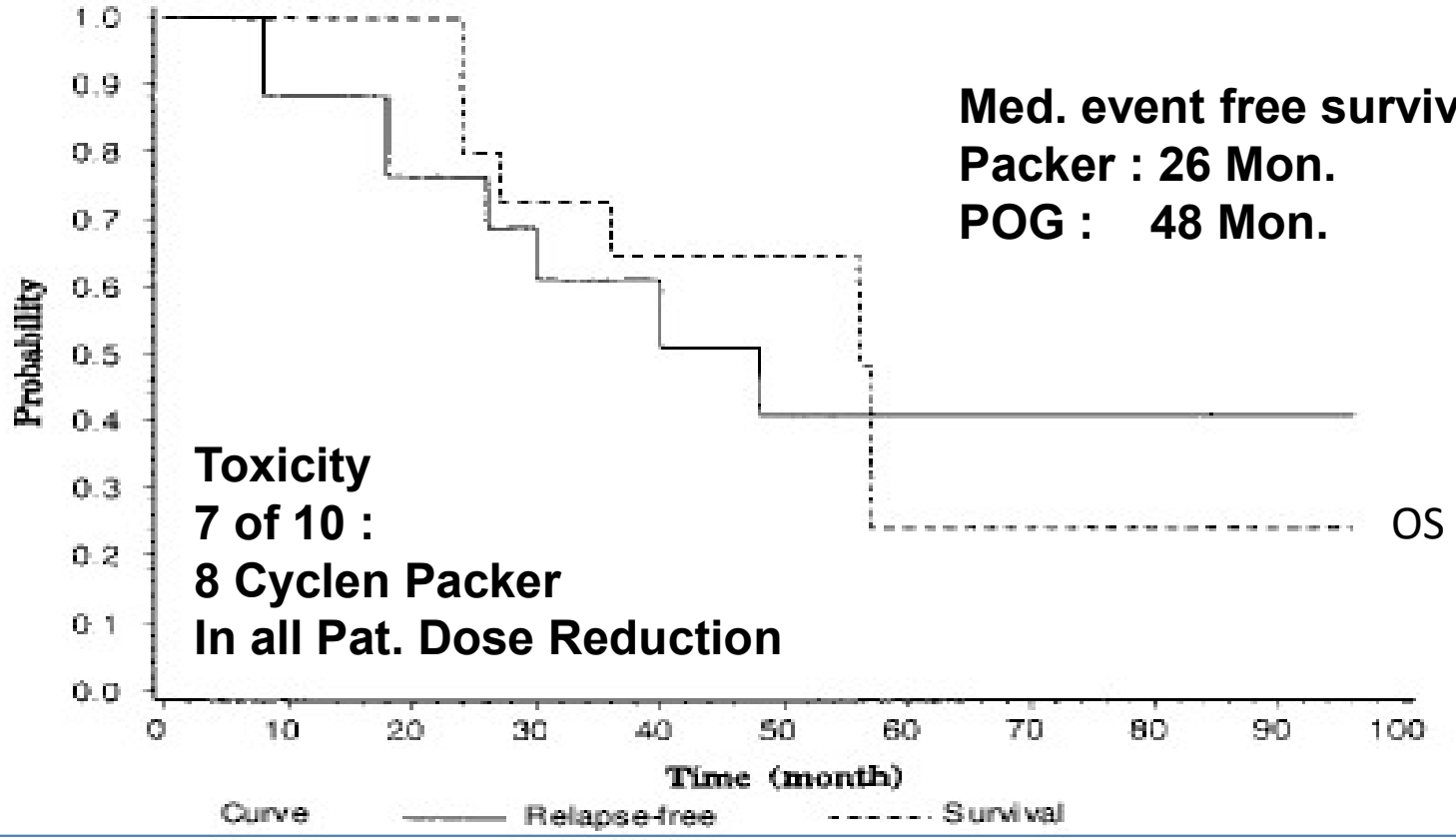
Additional Chemotherapy?

(Standard in case of Children (M0-3))

Medulloblastoma in adults

Greenberg, 2001

Medulloblastoma, postop. RT plus Chemo (n = 17 (10 „Packer“, 7 POG))



Med. event free survival
Packer : 26 Mon.
POG : 48 Mon.

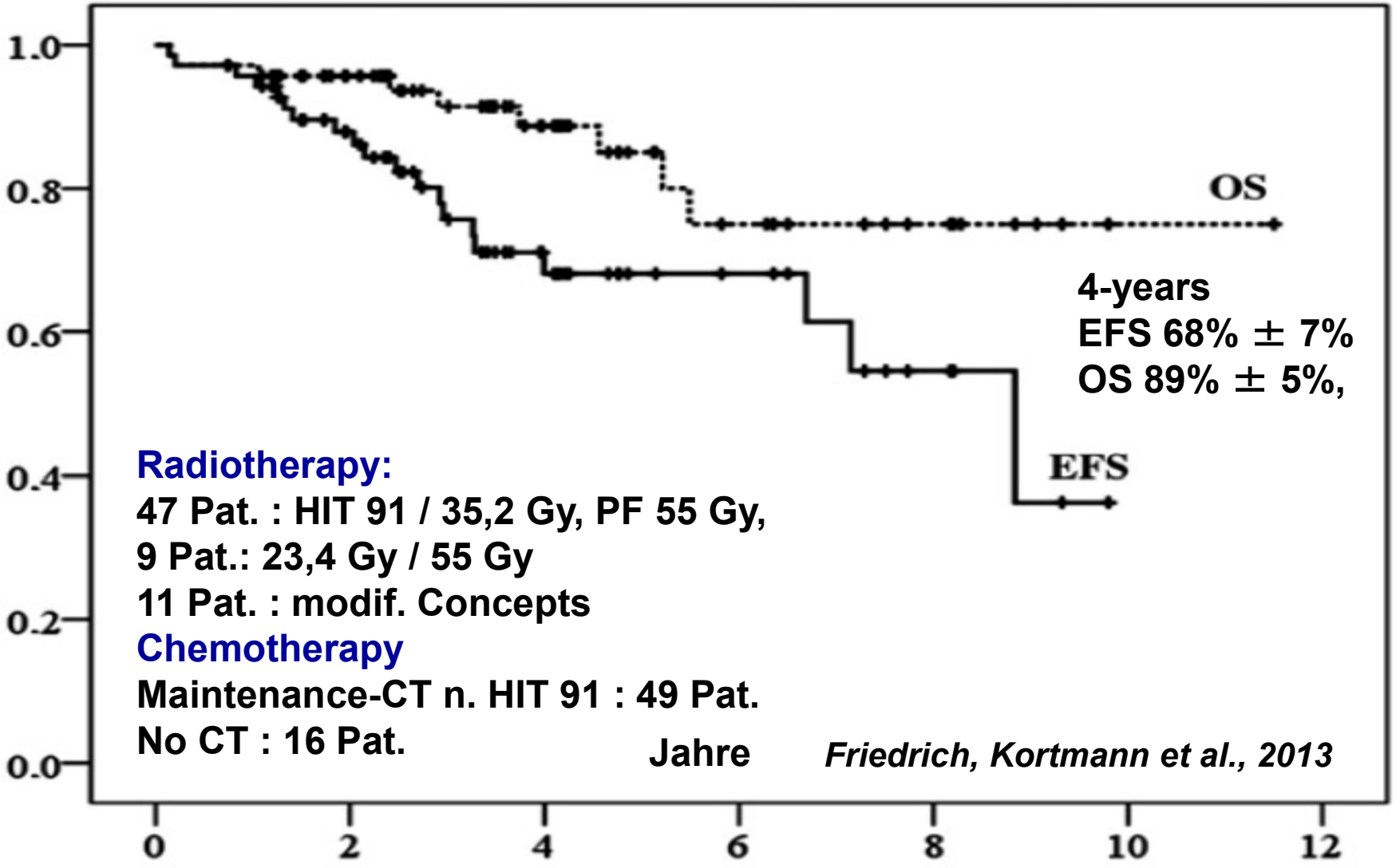
OS

Toxicity
7 of 10 :
8 Cyclen Packer
In all Pat. Dose Reduction

Additional CT intensifies toxcicity without improvement of the prognosis. Survival can be worse due to chemo in MB in adults

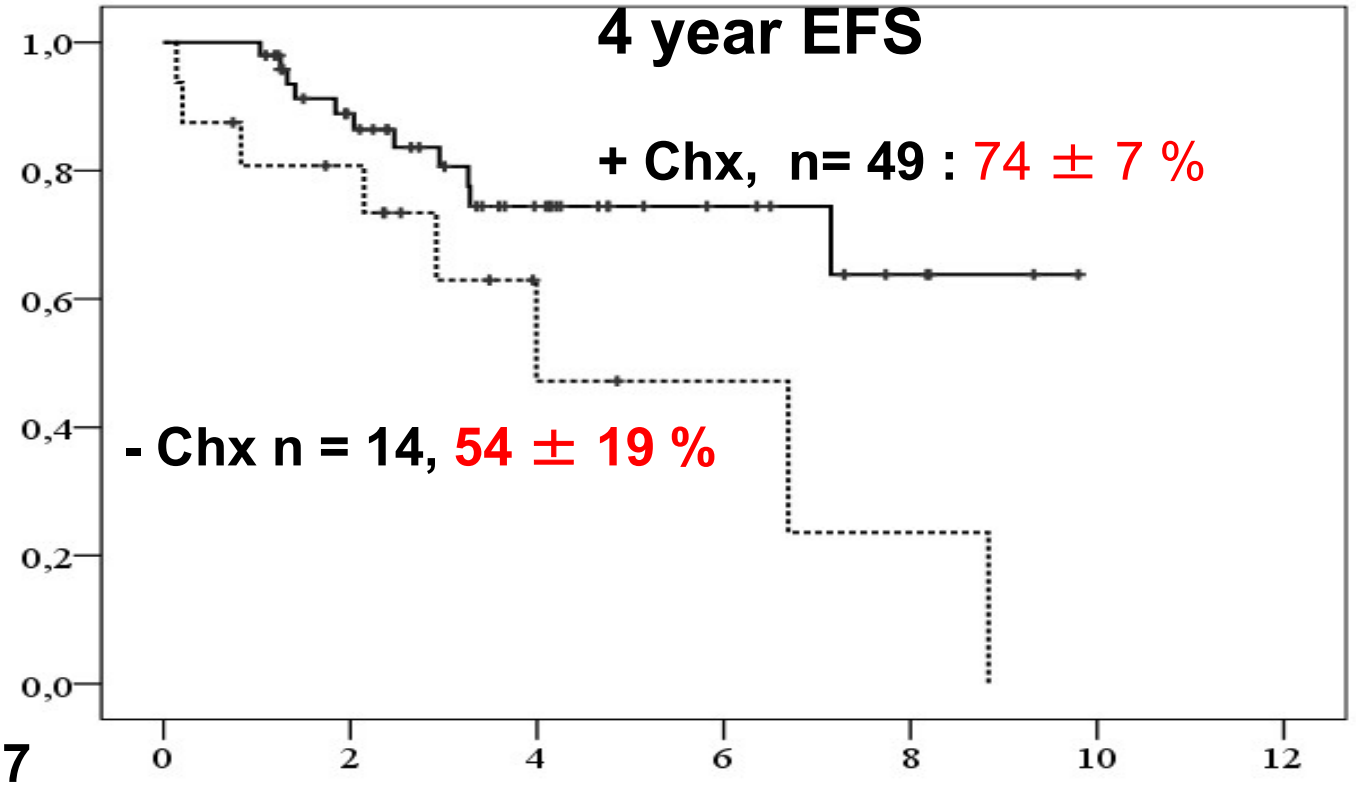
Medulloblastoma in Adults

HIT Register : Tübingen / Leipzig – Würzburg / Hamburg, Age : > 21 years, 70 Pat. / M0



Medulloblastoma in Adults

HIT Register : Tübingen / Leipzig – Würzburg / Hamburg, Alter : > 21 years., 70 Pat. / M0



p=0.027

Friedrich, Kortmann et al., 2013

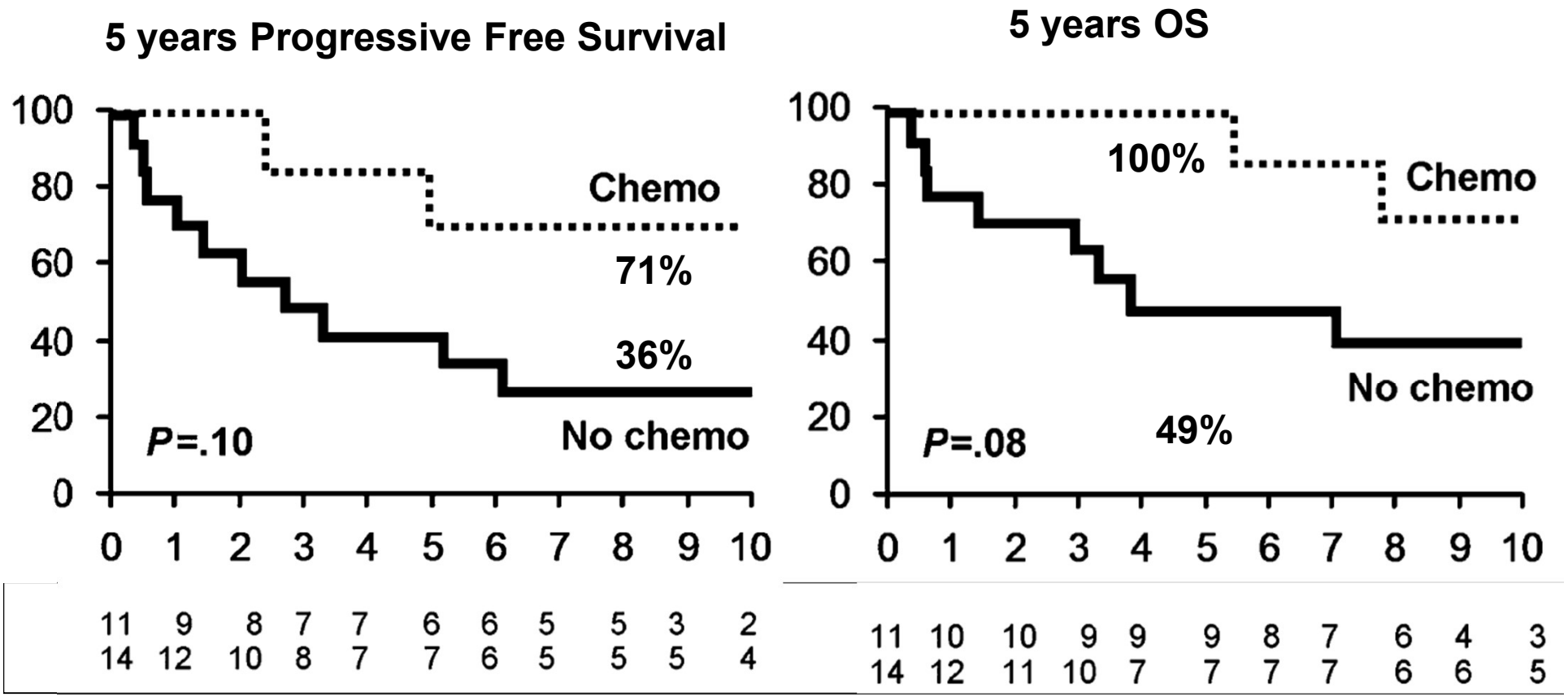
- Improvement of EFS in **low risk** patients by chemotherapy

Medulloblastoma in Adults

Mayo / Rochester / 66 Pat. Alter : > 18 years, med.age 33 years (1969-2008)

High risk and classical Subtyp / n = 25 Pat.

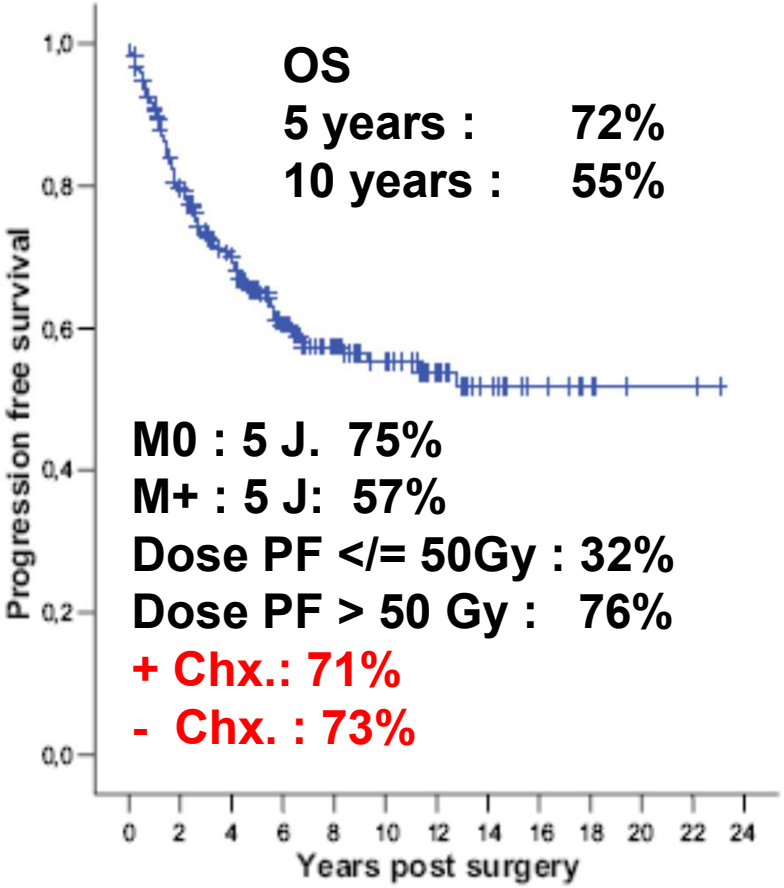
Role of Chemotherapy (different Protocols)



Call, Laack et al., 2014

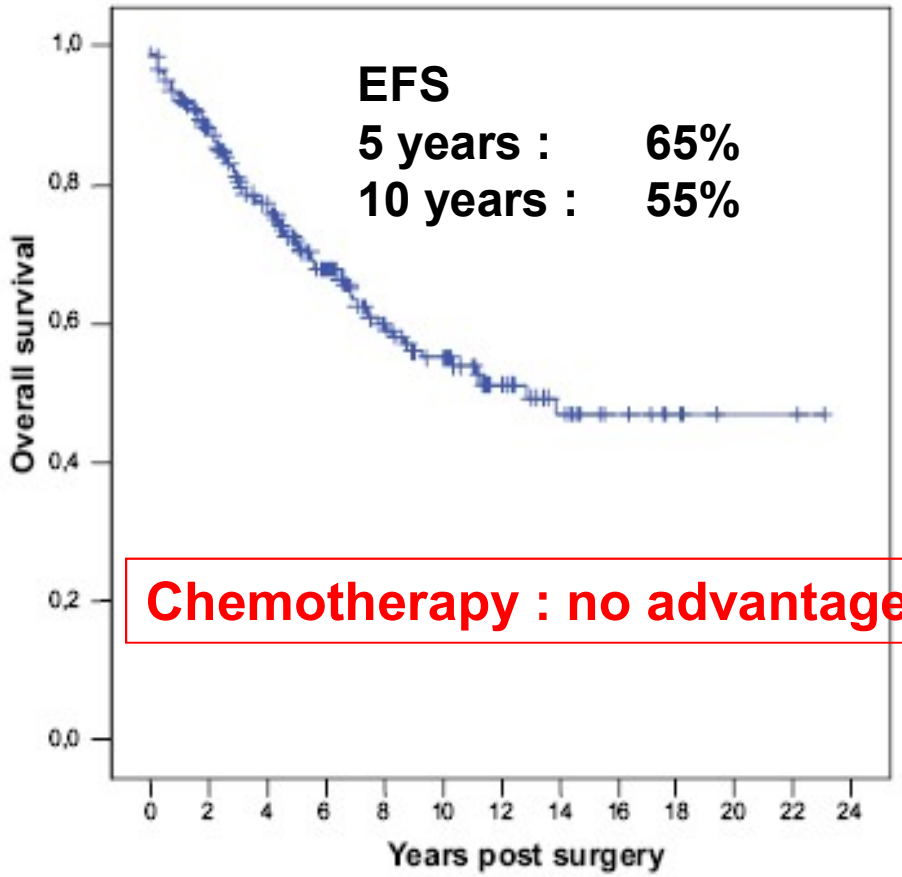
Medulloblastoma in Adults

Medulloblastoma, retrospective Analysis, 253 Pat. (1975 – 2004)



OS
5 years : 72%
10 years : 55%

M0 : 5 J. 75%
M+ : 5 J: 57%
Dose PF </= 50Gy : 32%
Dose PF > 50 Gy : 76%
+ Chx.: 71%
- Chx. : 73%



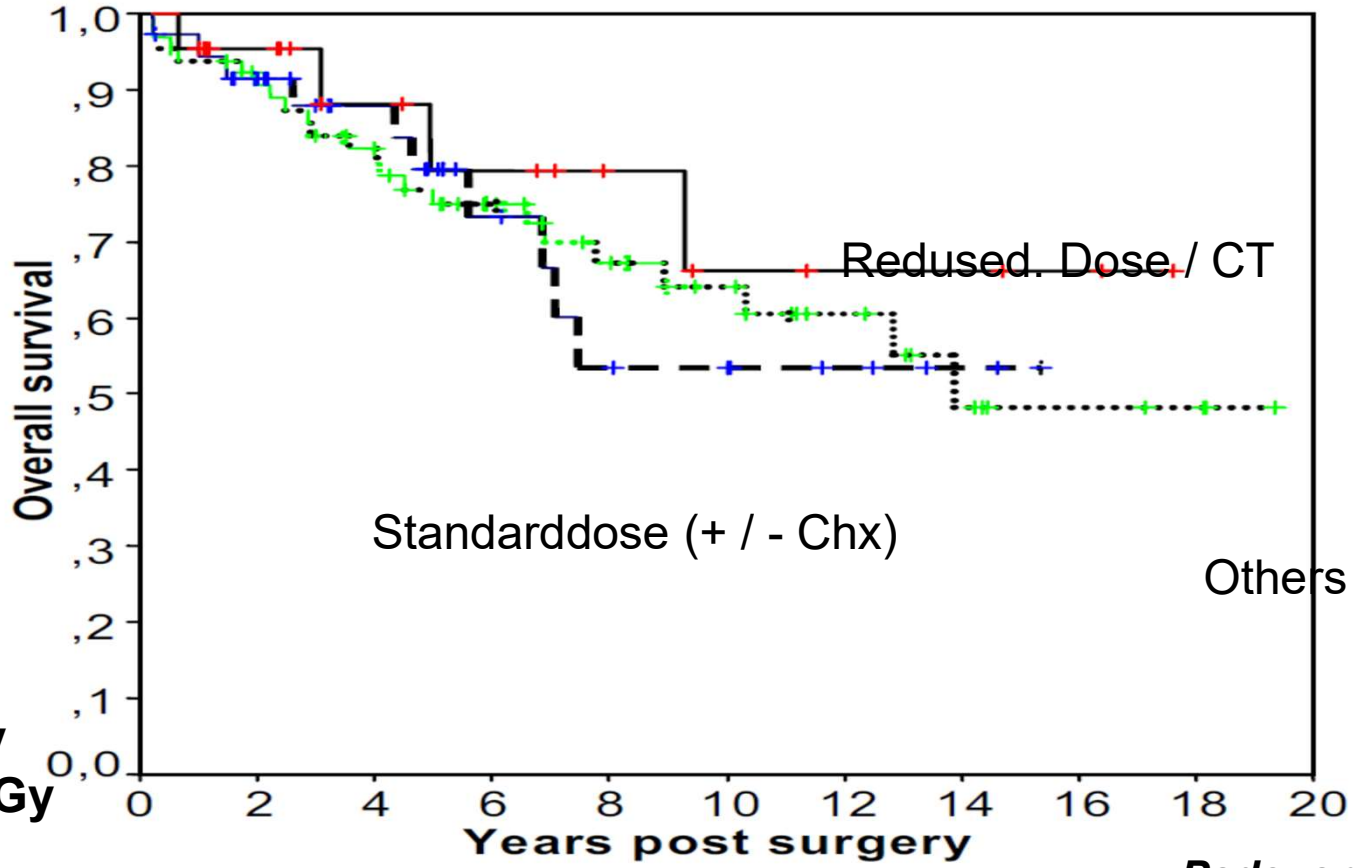
EFS
5 years : 65%
10 years : 55%

Chemotherapy : no advantage

Padovani et al., 2007

Medulloblastoma in adults

France / retrospective Analysis
Dose / Dose relation ship / Rolle of CT M0



CSI
<30/> 30 Gy
PF<50/>50 Gy

Padovani et al., 2007

- No lost of OS in case of redused RT dose and Chemotherapy
- Toxicity

Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07)

Dagmar Beier

- prospective descriptive multicenter single-arm phase II trial to evaluate feasibility and toxicity of radio-polychemotherapy.
- **The NOA-07 trial combined CSI with vincristine**
  Maintenance CT 8 cycles of cisplatin, lomustine, and vincristine.
- Primary endpoint was the rate of toxicity-related treatment terminations after 4 chemotherapy cycles, and the toxicity profile.
- The feasibility goal was reached if at least 45% of patients received at least 4 cycles of maintenance chemotherapy.

Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07)

Dagmar Beier

Results N=30 pts ; 50% showed classic and desmoplastic/nodular histology. 67% were classified into SHH subgroup without *TP53* alterations, 13% in WNT, 17% in non-WNT/non-SHH.

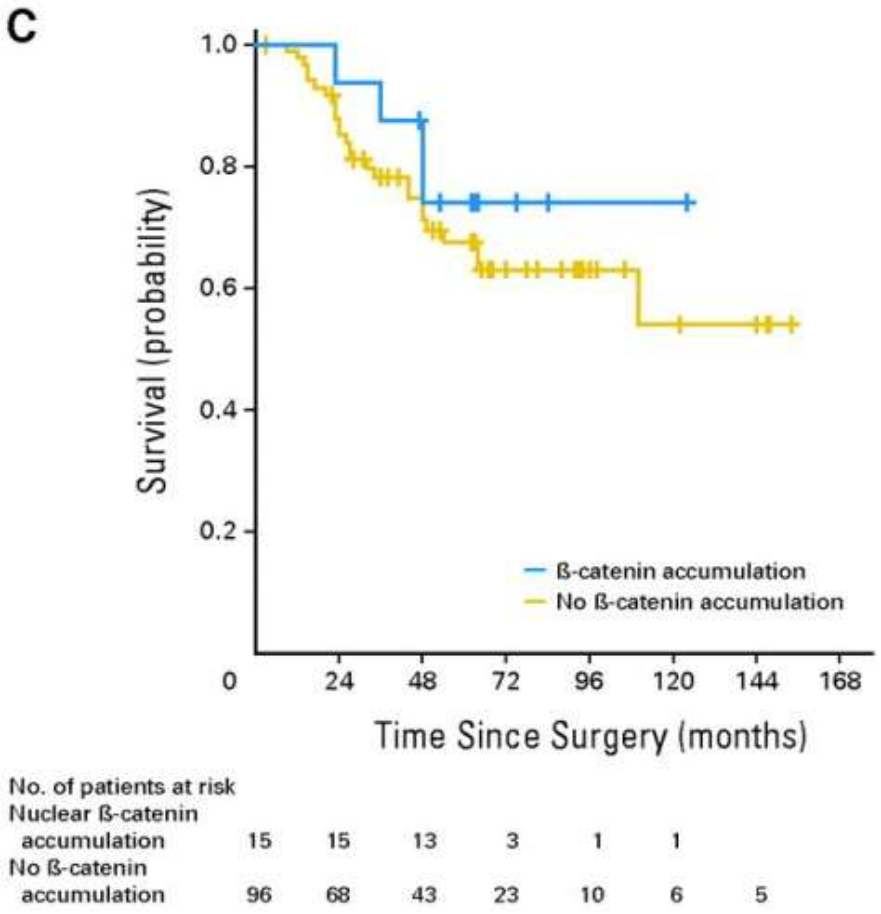
- Four cycles of CT were feasible in the majority (*n* = 21; 70.0%).
- *Hematological side effects and polyneuropathy were prevalent toxicities.*
- The 3-year event-free survival rate was 66.6% at the time of databank lock.

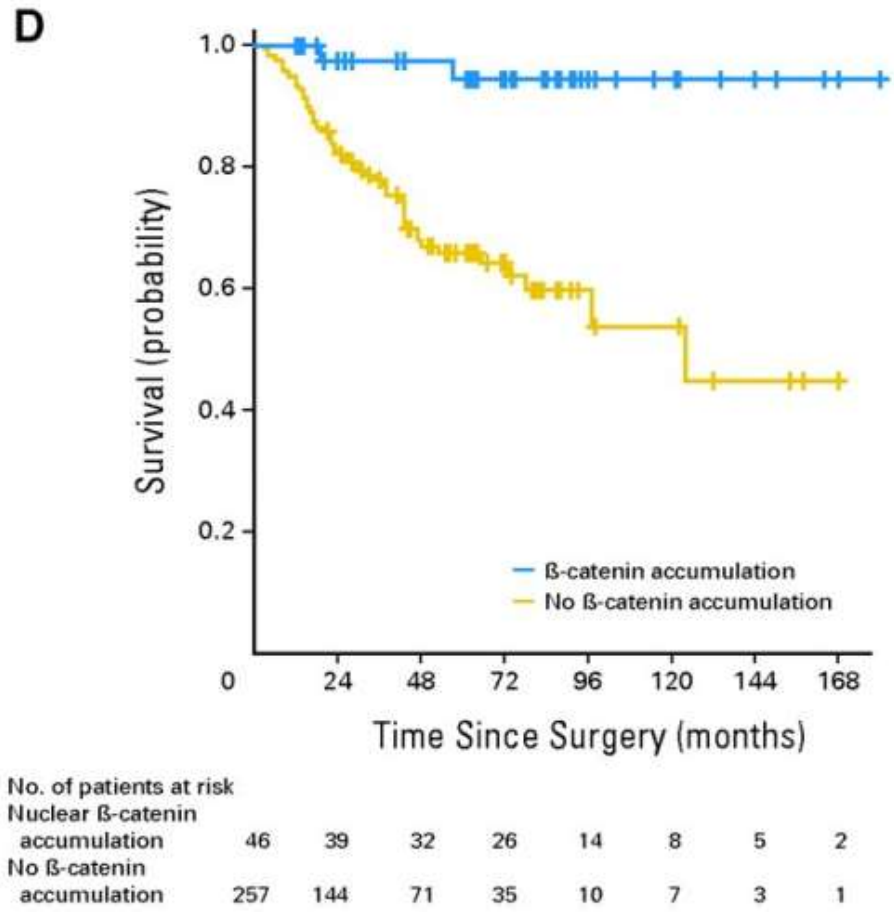
- RT/CT did lead to considerable toxicity in adults, dose reductions through out the first 4 CT cycles
- Modifications on CT have to be performed

Medulloblastom in adults

Wingless (WNT) Signalling
Beta catenin / impact of age

>18 Jahre **<18 Jahre**





Korshunov et al., 2010

Medulloblastoma in adults

Medulloblastoma

Arguments for additional Chemotherapy

⇨ Additional adjuvant CT improves the prognosis in „Standard „ and „High Risk“ Patients

⇨ Additional adjuvant CT allows to reduce the RT-Dose in CSI? (36 Gy to 23.4 Gy) (Reduction of Neurotoxicity)

⇨ Additional adjuvant CT prevent late relapses and the Risk for metastasis outside the craniospinal region.

Medulloblastom in Adults

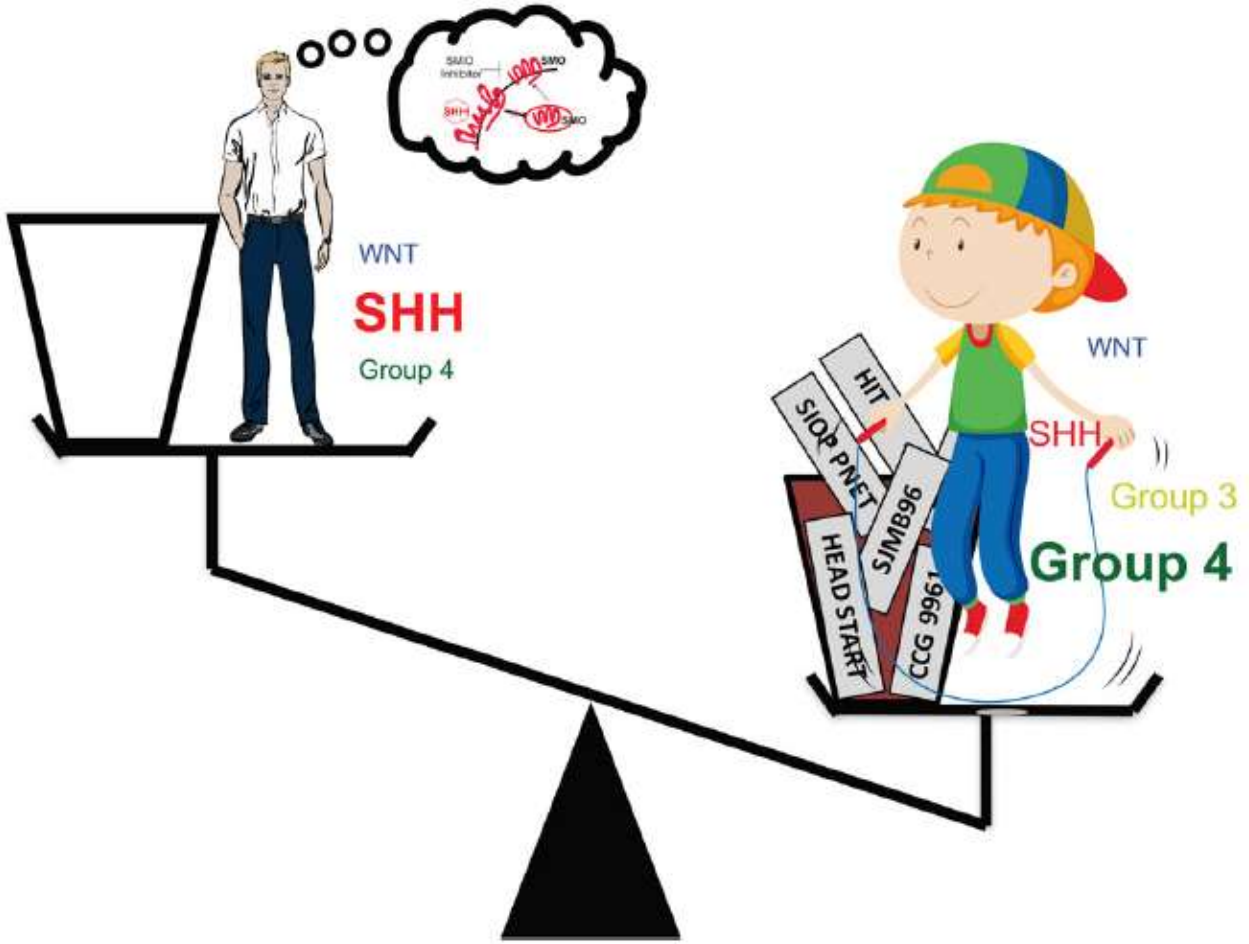
Medulloblastoma
Arguments *against* additional Chemotherapy

⇨ **The additional adjuvant CT is not practible with Standard protokoll („Packer“) for „standard risk „ Patients . Therefore a dose reduction in the spinal axis (von 36 auf 23.4 Gy) should be taken into account. Data Padovani ?**

⇨ **Additional adjuvant CT increases Toxicity without improving the prognosis (Greenberg et al., 2001).**

⇨ **All hyperfractionated RTs for „standard risk“ patients result in identical OS with only minor neurocognitive dysfunction. (M-SFOP 98, Mumbai) im Vergleich mit reduz. kon. RT mit Chx.. eine zusätzl. Chx.ist daher verzichtbar.**

Medulloblastoma in adults: they're not just big kids



Molecular characterisation will be done in Adults and is the Base for individual Treatment

Medulloblastoma in Adults
Conclusion

Actual Standard

postop. RT CSI 36 Gy / 54 Gy boost PF

(Boost only to the Tumor ?)

Dose reduction is not possible at the moment

Chemotherapy for „Standard risk „ ?

Feasibility and effectiveness?

New Concepts ? RT- CT ?

CT- Protocol for „High risk“ ?

Molecular markers for choosing individual MB Therapy

Molecular markers and the concept of biological Risk Profile will Influence MB Therapy .

Treatment concepts of the children cannot be adopted one by one for adults, studies are needed.

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Management of medulloblastoma in children

Darren Hargrave

Consultant Paediatric Oncologist,

Neuro-oncology & Experimental Therapeutics

Great Ormond Street Hospital. London, UK.

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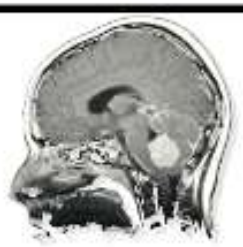
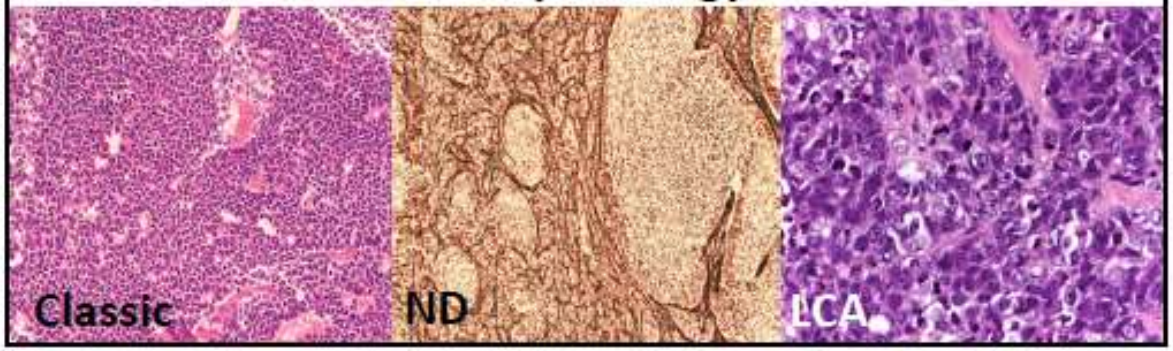
Medulloblastoma: an aggressive and complex brain tumor



Posterior Fossa Location
20% of all pediatric brain tumors

Metastasis

Histopathology



School

Medulloblastoma

- Most common malignant CNS tumour in children
- Tremendous progress over last 20 years
  - Treatment
  - Biology >>> several distinct subtypes

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 - Aetiology

- Unknown for most patients
- Familial cases
    - SIR 4.1 for siblings

- Genetic susceptibility

Genetic susceptibility
-Seen in several familiar cancer predisposition syndromes (Gorlin syndrome, Turcot syndrome, Li-Fraumeni syndrome, Fragile X syndrome,….)
-Frequency 10% overall, 30% of pts < 3 years
-Genetic counselling/screening of family members

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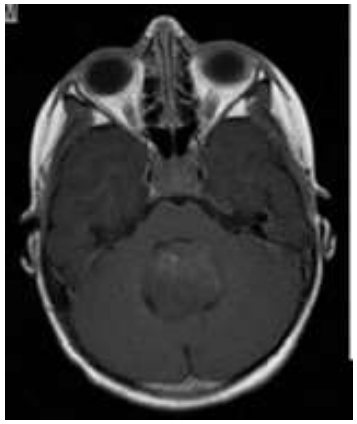
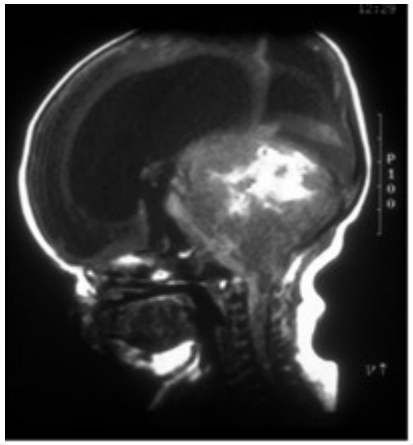
Medulloblastoma - Clinical presentation

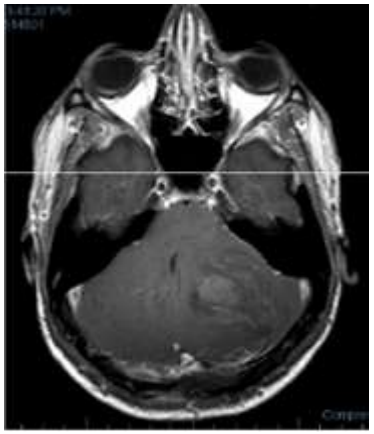
- Typical midline location, arising in the vermis, causing IVth ventricle compression (symptoms and signs of raised intracranial pressure)

- In infants increase in head circumference, bulging of the fontanelles

- Hemispheric location more common in very young children and adults (lateralising difficulties with coordination: ataxia and dysmetria)

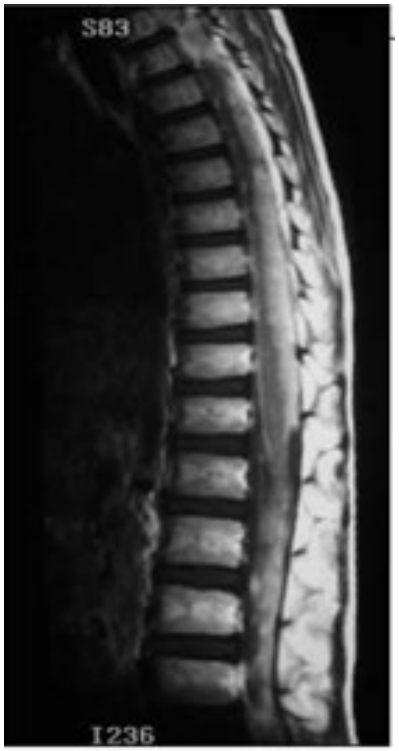






Medulloblastoma - Spread

- Frequency of leptomeningeal seeding at diagnosis 30-35%
- Greater in infants and very young children
- Extra CNS metastases very uncommon (<5%) [lymph nodes, bone, bone marrow]



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Medulloblastoma - Work-up

- Pre-op craniospinal MR imaging
- Post-op cranial MR 24-48 hours after surgery
- MRI of spine pre or post-op > 14 d
- 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 tumor/completeness of surgical resection

-Presence or absence of leptomeningeal seeding

Medulloblastoma - Prognosis

Risk groups for management

- Standard risk
  - GTR/residual tumour <1.5 cm² 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

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Medulloblastoma - Prognosis

Prognosis depends on…

- Extent of primary tumour/ completeness of surgical resection
- Presence or absence of leptomeningeal seeding

Also…

- Pathologic/molecular subtype

Medulloblastoma
Pathologic subtypes (WHO 2007)

- Medulloblastoma («classic») 70-80% all
- Desmoplastic/nodular medulloblastoma Good
- Medulloblastoma with extensive nodularity (MBEN) Good
- Anaplastic medulloblastoma Bad
- Large cell medulloblastoma Bad

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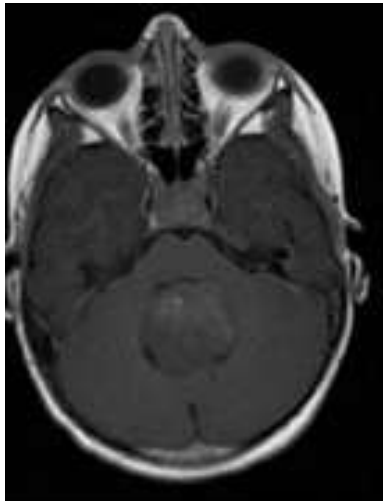
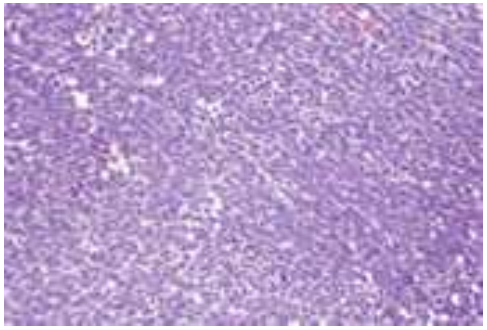
Classic Medulloblastoma

- 70-80% all
- Prototypical small blue cell tumor
- Densely packed undifferentiated cells



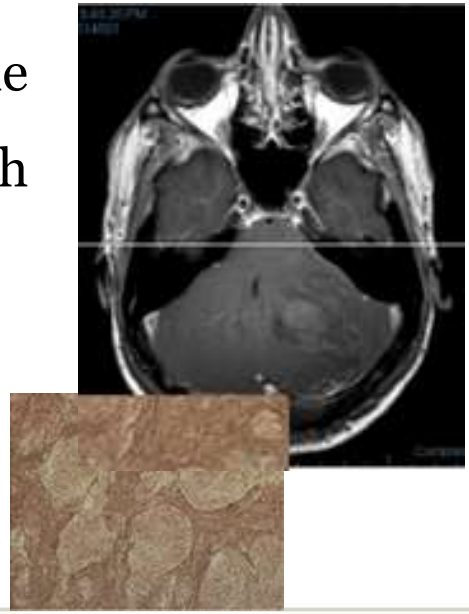


Desmoplastic Medulloblastoma

- Mostly in hemispheres
- Very young children and adults
- Biphasic architecture

Nodules showing neuronal differentiation («pale islands») surrounded by more cellular areas with prominent desmoplasia

- More favourable



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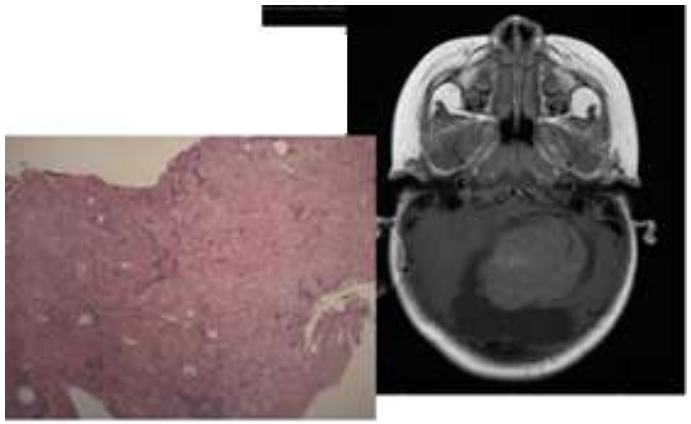
Medulloblastoma with extensive nodularity (MBEN)

- Overlaps with desmoplastic MB (10-15% of young children)
- Pronounced nodularity (macroscopic)
- Greatly expanded «pale islands» with more advanced neuronal differentiation (neurocytes): previously called “cerebellar neuroblastoma”

MBEN
- Infants (<3 years)
- Strong association with Gorlin syndrome
- Better prognosis than other subtypes (lower frequency of mts, more sensitive to CT and RT)



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Large cell medulloblastoma

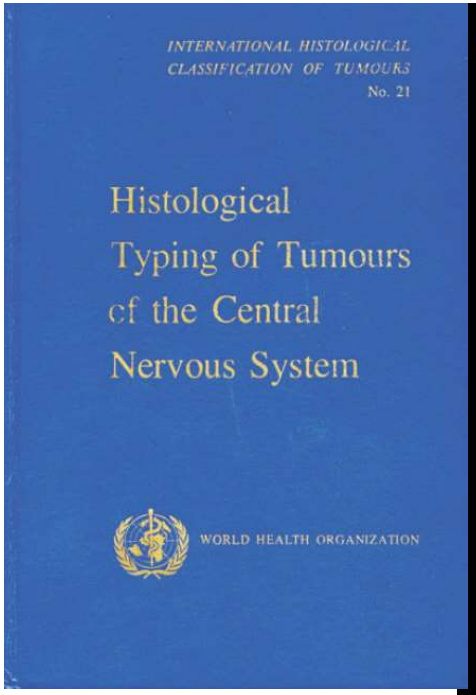
- Rare (2-4% of MB)
- Significantly more aggressive
- Large monomorphic cells
- High mitotic rate, extensive apoptosis
- Overlap with anaplastic subtypes

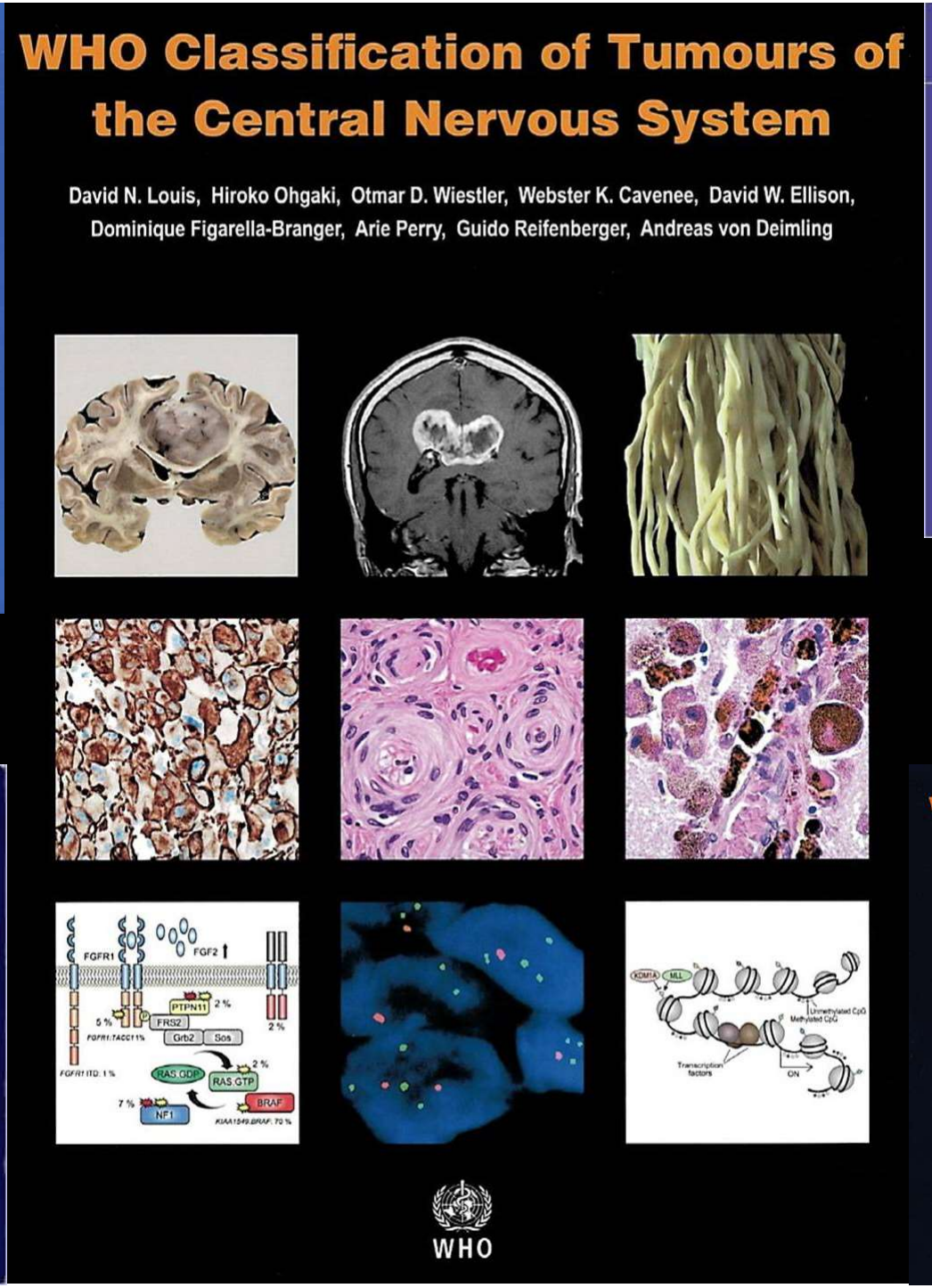
Anaplastic medulloblastoma

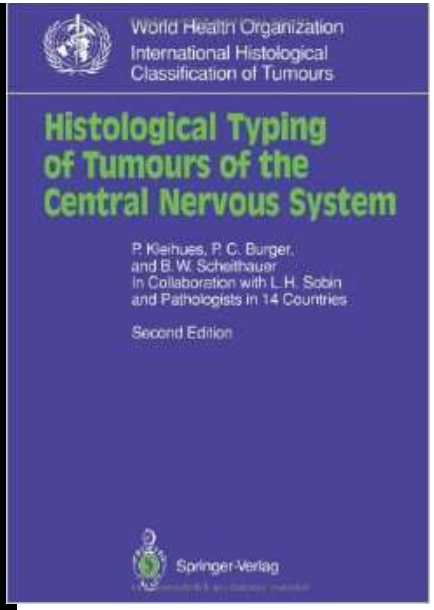
- Recently introduced concept

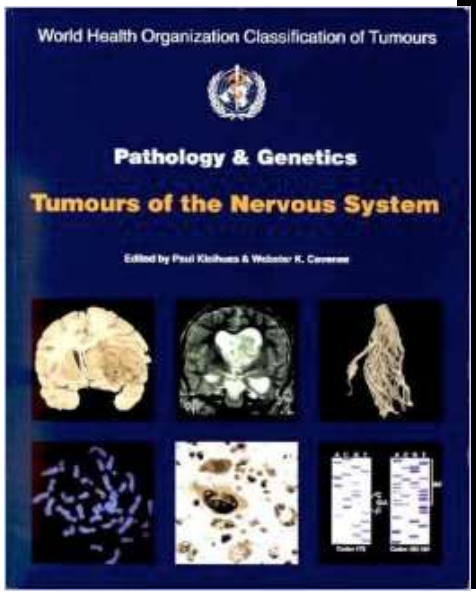
- Problem: many MBs show varying degrees of anaplasia

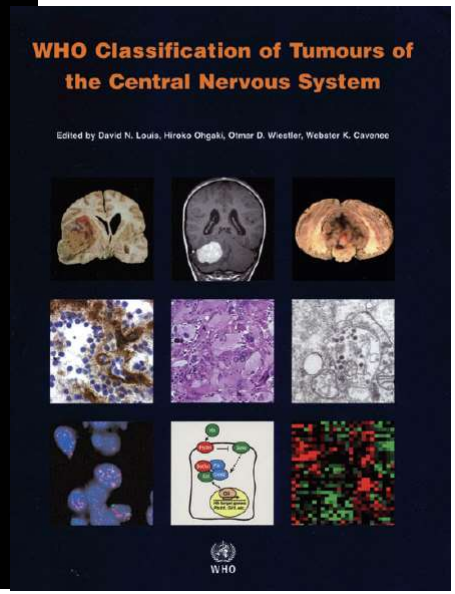
    - Anaplasia only a significant prognostic factor if severe and diffuse
    - May not be an independent factor….


INTERNATIONAL HISTOLOGICAL CLASSIFICATION OF TUMOURS
No. 21
Histological Typing of Tumours of the Central Nervous System
WORLD HEALTH ORGANIZATION

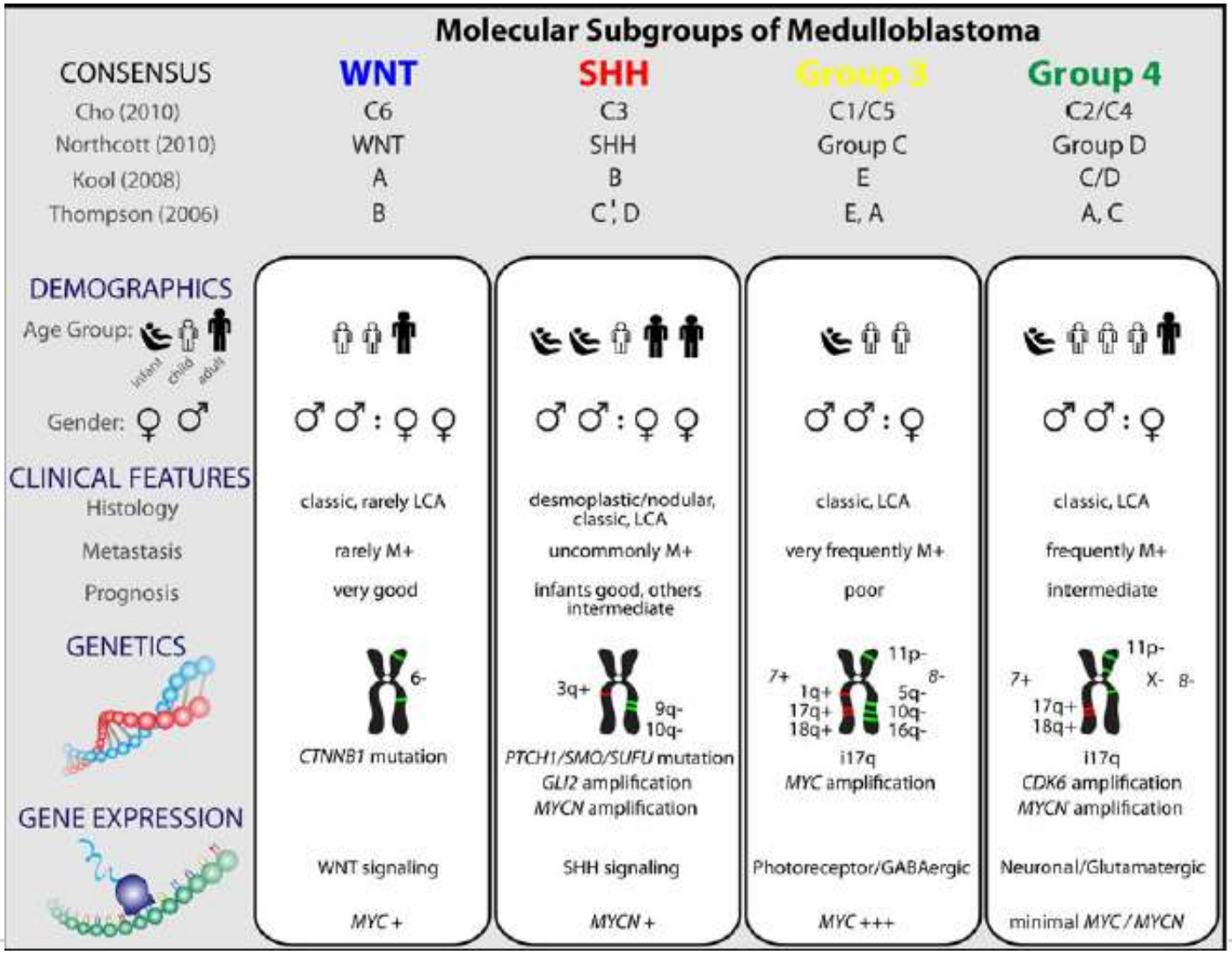

WHO Classification of Tumours of the Central Nervous System
David N. Louis, Hiroko Ohgaki, Otmar D. Wiestler, Webster K. Cavenee, David W. Ellison, Dominique Figarella-Branger, Arie Perry, Guido Reifenberger, Andreas von Deimling
FGFR1
FGF2
PTPN11
FRS2
Grb2
Sos
RAS GDP
RAS GTP
BRAF
NF1
KIAA1549:BRAF: 70 %
KDM1A
MLL
Transcription factors
ON
WHO


World Health Organization
International Histological Classification of Tumours
Histological Typing of Tumours of the Central Nervous System
P. Kleihues, P. C. Burger, and B. W. Scheithauer
In Collaboration with L. H. Sobin and Pathologists in 14 Countries
Second Edition
Springer-Verlag


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


WHO Classification of Tumours of the Central Nervous System
Edited by David N. Louis, Hiroko Ohgaki, Otmar D. Wiestler, Webster K. Cavenee
WHO

Comparison of the various subgroups of medulloblastoma including their affiliations with previously published papers on medulloblastoma molecular subgrouping



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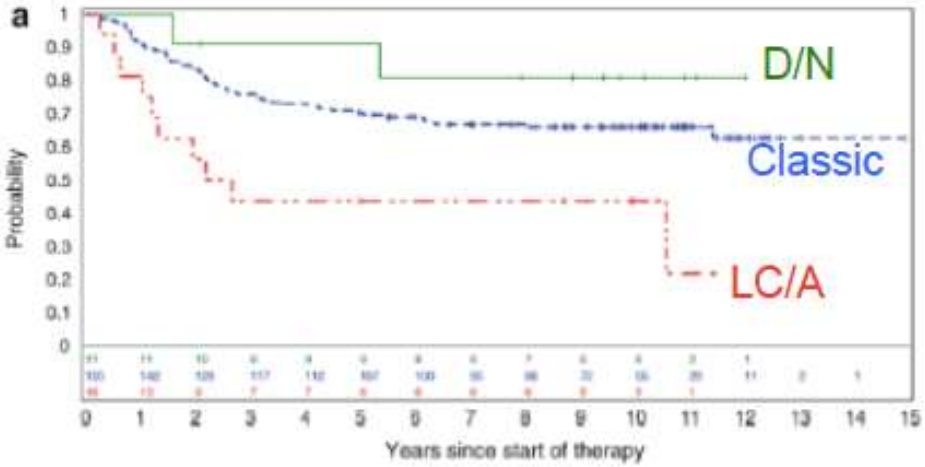
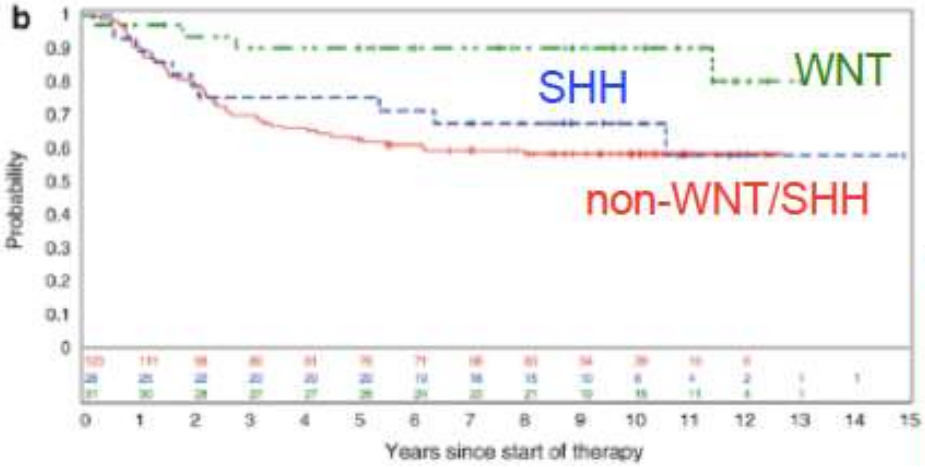
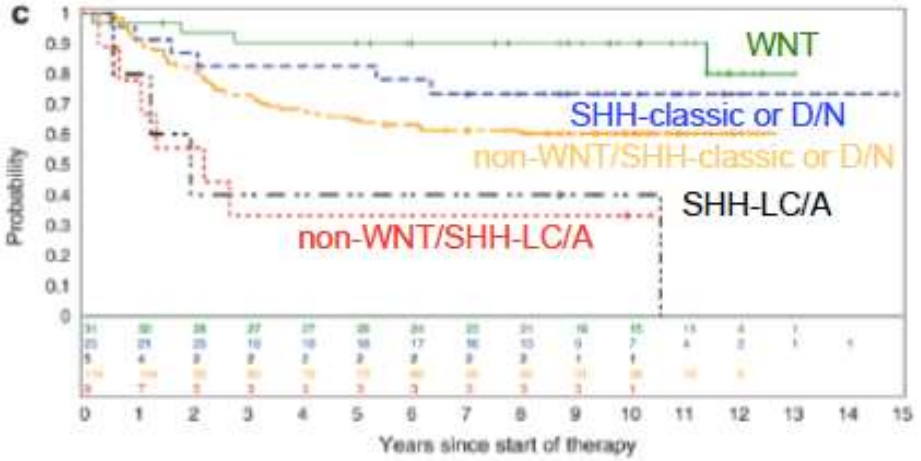
Medulloblastoma

- Both the histologic and molecular subgroups have prognostic and therapeutic value



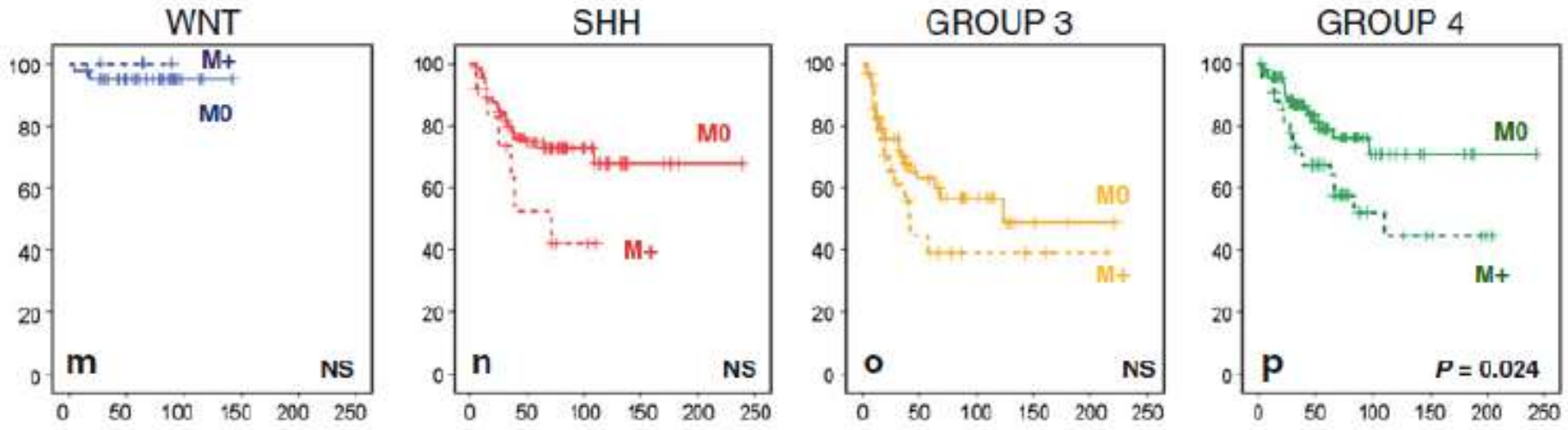




Outcome analyses among patients aged 3-16 years on the CNS9102/PNET3 trial. Progression-free survival curves.

Ellison et al. *Acta Neuropathol* 2011

Molecular subgroups of Medulloblastoma



Extent of resection in medulloblastoma: time to reconsider?

THE LANCET Oncology

Volume 17, Issue 4, April 2016, Pages 409–410

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Redefining subsets

Group A (WNT)

-15%
-Older children
-All had β catenin mutation (not found in other groups)
-Classic histology
-No metastasis
-Prognosis very good

Group B (SHH)

-25%
-Mostly desmoplastic
-Rarely metastatic
-Infants and adults
-Good prognosis for infants, intermediate for adults

Redefining subsets (cont'd)

Group C,D (Group 4), E (Group 3)

-60%
-Young children
-Markers of neuronal and/or photoreceptor differentiation
-Hystology classic or LCA
-Propensity to CSF spread
-Prognosis poor for group E, intermediate for group C,D

Medulloblastoma: the management

- **Standard risk Medulloblastoma**
- High risk medulloblastoma
- Infant medulloblastoma

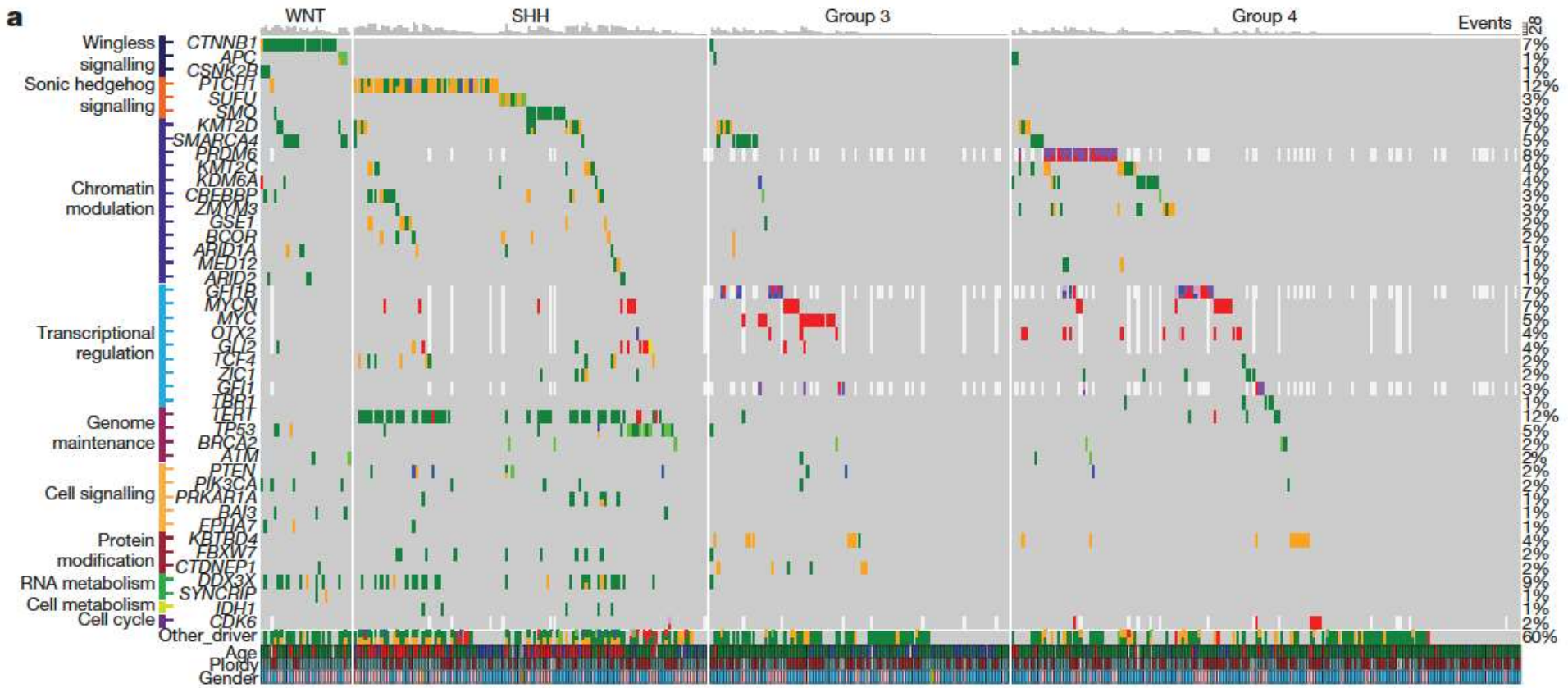
ARTICLE

OPEN

doi:10.1038/nature22973

The whole-genome landscape of medulloblastoma subtypes

Paul A. Northcott[1,2]*, Ivo Buchhalter[3,4,5]*, A. Sorana Morrissy[6]*, Volker Hovestadt[7], Joachim Weischenfeldt[8], Tobias Ehrenberger[9], Susanne Gröbner[1,10], Maia Segura-Wang[11], Thomas Zichner[11], Vasilisa A. Rudneva[11,2], Hans-Jörg Warnatz[12], Nikos Sidiropoulos[8], Aaron H. Phillips[13], Steven Schumacher[14], Kortine Kleinheinz[3], Sebastian M. Waszak[11], Serap Erkek[1,11], David T. W. Jones[1,10], Barbara C. Worst[1,10], Marcel Kool[1,10], Marc Zapatka[7], Natalie Jäger[3], Lukas Chavez[1,10], Barbara Hutter[4], Matthias Bieg[3,15], Nagarajan Paramasivam[3,16], Michael Heinold[3,5], Zuguang Gu[3,15], Naveed Ishaque[3,15], Christina Jäger-Schmidt[3], Charles D. Imbusch[4], Alke Jugold[3], Daniel Hübschmann[3,5,17], Thomas Risch[12], Vyacheslav Amstislavskiy[12], Francisco German Rodriguez Gonzalez[8], Ursula D. Weber[7], Stephan Wolf[18], Giles W. Robinson[19], Xin Zhou[20], Gang Wu[20], David Finkelstein[20], Yanling Liu[20], Florence M. G. Cavalli[6], Betty Luu[6], Vijay Ramaswamy[6], Xiaochong Wu[6], Jan Koster[21], Marina Ryzhova[22], Yoon-Jae Cho[23], Scott L. Pomeroy[24], Christel Herold-Mende[25], Martin Schuhmann[26], Martin Ebinger[27], Linda M. Liau[28], Jaume Mora[29], Roger E. McLendon[30], Nada Jabado[31], Toshihiro Kumabe[32], Eric Chuah[33], Yussanne Ma[33], Richard A. Moore[33], Andrew J. Mungall[33], Karen L. Mungall[33], Nina Thiessen[33], Kane Tse[33], Tina Wong[33], Steven J. M. Jones[33], Olaf Witt[17], Till Milde[17], Andreas Von Deimling[34], David Capper[34], Andrey Korshunov[34], Marie-Laure Yaspo[12], Richard Kriwacki[13], Amar Gajjar[19], Jinghui Zhang[20], Rameen Beroukhim[14], Ernest Fraenkel[9], Jan O. Korbel[11], Benedikt Brors[3,4,10], Matthias Schlesner[3], Roland Eils[3,5,10]§, Marco A. Marra[33]§, Stefan M. Pfister[1,10,17]§, Michael D. Taylor[6,35]§ & Peter Lichter[7,10]§



Alterations
- Amplification
- Deletion
- SNV
- Indel
- High expression
- Germline
- Translocation
- Inversion

Ploidy
- Diploid
- Hyperploid

Age
- Infant
- Child
- Adult

Gender
- Male
- Female
- Klinefelter (47, XXY)
- Turner (45, X)

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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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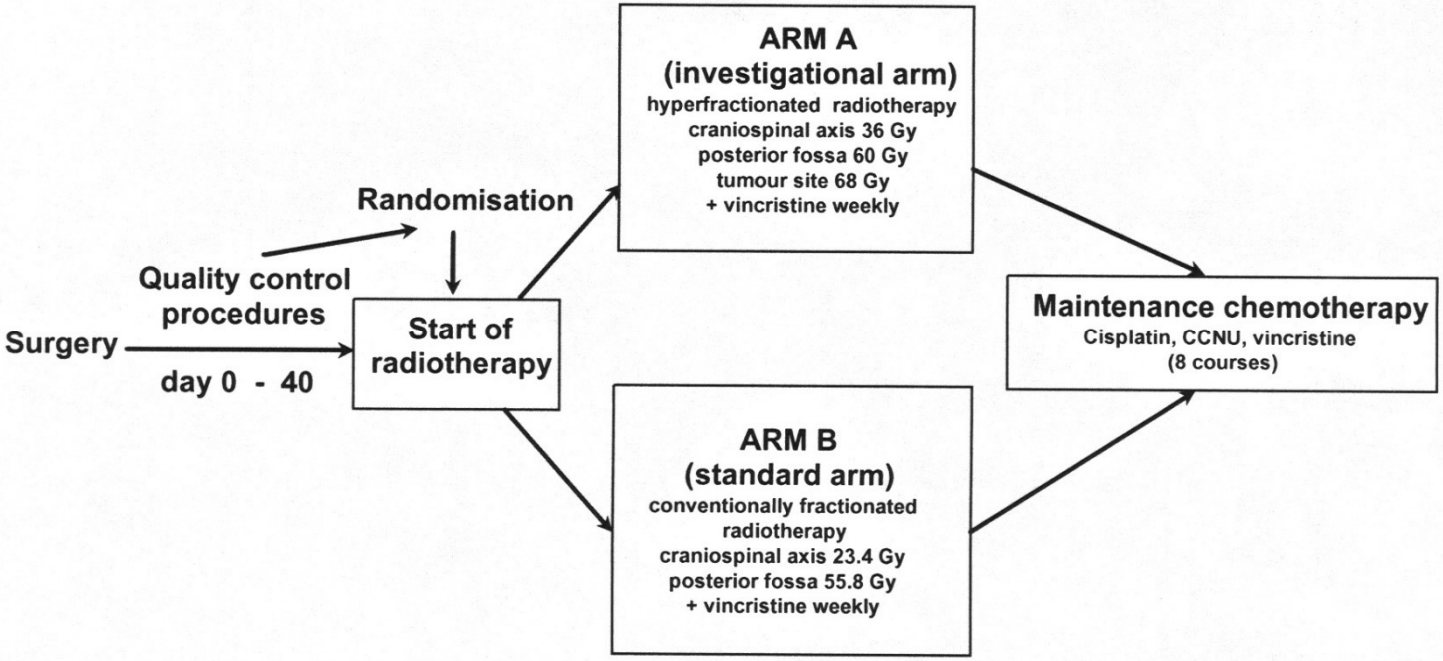
VOLUME 30 · NUMBER 26 · SEPTEMBER 10 2012

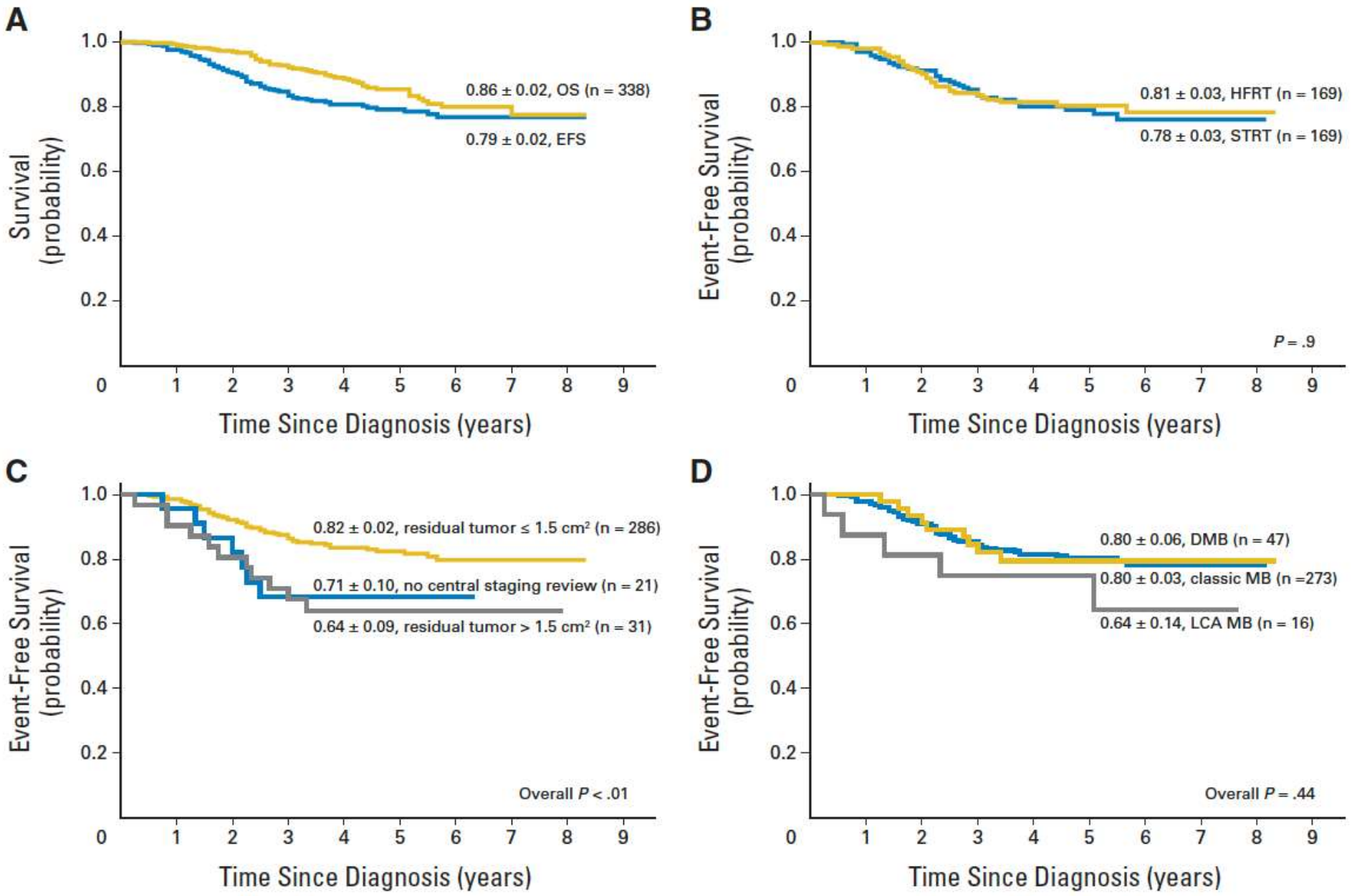
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hyperfractionated Versus Conventional Radiotherapy Followed by Chemotherapy in Standard-Risk Medulloblastoma: Results From the Randomized Multicenter HIT-SIOP PNET 4 Trial

Birgitta Lannering, Stefan Rutkowski, Francois Doz, Barry Pizer, Göran Gustafsson, Aurora Navajas, Maura Massimino, Roel Reddingius, Martin Benesch, Christian Carrie, Roger Taylor, Lorenza Gandola, Thomas Björk-Eriksson, Jordi Giralt, Foppe Oldenburger, Torsten Pietsch, Dominique Figarella-Branger, Keith Robson, Marco Forni, Steven C. Clifford, Monica Warmuth-Metz, Katja von Hoff, Andreas Faldum, Véronique Mosseri, and Rolf Kortmann




A
1.0
0.8
0.6
0.4
0.2
0
Survival (probability)
0.86 ± 0.02, OS (n = 338)
0.79 ± 0.02, EFS
1 2 3 4 5 6 7 8 9
Time Since Diagnosis (years)
B
1.0
0.8
0.6
0.4
0.2
0
Event-Free Survival (probability)
0.81 ± 0.03, HFRT (n = 169)
0.78 ± 0.03, STRT (n = 169)
P = .9
1 2 3 4 5 6 7 8 9
Time Since Diagnosis (years)
C
1.0
0.8
0.6
0.4
0.2
0
Event-Free Survival (probability)
0.82 ± 0.02, residual tumor ≤ 1.5 cm² (n = 286)
0.71 ± 0.10, no central staging review (n = 21)
0.64 ± 0.09, residual tumor > 1.5 cm² (n = 31)
Overall P < .01
1 2 3 4 5 6 7 8 9
Time Since Diagnosis (years)
D
1.0
0.8
0.6
0.4
0.2
0
Event-Free Survival (probability)
0.80 ± 0.06, DMB (n = 47)
0.80 ± 0.03, classic MB (n =273)
0.64 ± 0.14, LCA MB (n = 16)
Overall P = .44
1 2 3 4 5 6 7 8 9
Time Since Diagnosis (years)

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Clinical Investigation

Neuropsychological Outcome of Children Treated for Standard Risk Medulloblastoma in the PNET4 European Randomized Controlled Trial of Hyperfractionated Versus Standard Radiation Therapy and Maintenance Chemotherapy

Hugo Câmara-Costa, PhD,* Anika Resch, MSc,† Virginie Kieffer, MSc,‡ Clémence Lalande, MSc,§ Geraldina Poggi, MD,‖ Colin Kennedy, MBBS, MD,¶ Kim Bull, PhD,¶ Gabriele Calaminus, MD,# Jacques Grill, MD, PhD,§ François Doz, MD,** Stefan Rutkowski, MD,† Maura Massimino, MD,†† Rolf-Dieter Kortmann, MD,‡‡ Birgitta Lannering, MD,§§ Georges Dellatolas, MD, PhD,* and Mathilde Chevignard, MD, PhD‖‖, on behalf of the Quality of Survival Working Group of the Brain Tumour Group of SIOP-Europe

Table 2 Mean differences in cognitive outcomes according to treatment allocation and age at diagnosis

	HFRT				STRT				
Outcome	N	M	SD	Range	N	M	SD	Range	P^*
FSIQ	71	90.3	19.7	40-137	66	86.4	18.9	40-122	.24
FSIQ (age >8)	40	90.7	21.8	40-137	41	87.6	19.3	40-118	.49
FSIQ (age <8)	31	89.7	16.8	65.5-128.5	25	84.5	18.6	40-122	.27
VIQ	58	96.3	17.1	55-128	55	92.4	20.6	43-145	.28
VIQ (age >8)	31	95.8	17.4	55-128	34	97.1	22.1	47-145	.79
VIQ (age <8)	27	96.8	17.1	60-126	21	84.8	15.7	43-112	.02
PIQ	70	89.7	21	40-140	66	87.1	17.1	40-122	.43
PIQ (age >8)	39	90.4	24.6	40-140	41	88.3	16.8	40-118	.66
PIQ (age <8)	31	88.9	15.8	65-128.5	25	85.1	17.7	41-122	.40
WMI	68	92.3	13.8	55-124	61	89.1	15.3	55-120	.21
WMI (age >8)	38	90	14.8	55-124	39	88.6	16.1	56-120	.69
WMI (age <8)	30	95.2	11.9	65-118	22	90	14.2	55-110	.16
PSI	29	83.3	14.7	50-112	28	75.4	15.5	50-100	.05
PSI (age >8)	18	81.1	15.6	50-112	17	75.1	16.3	50-100	.27
PSI (age <8)	11	86.8	13.1	62-103	11	75.9	14.8	50-96	.08

Abbreviations: FSIQ = full scale intelligence quotient; PIQ = performance intelligence quotient; PSI = processing speed index; VIQ = verbal intelligence quotient; WMI = working memory index. Other abbreviations as in Table 1.

* Student *t* test.

Conclusions: HFRT was associated with marginally higher VIQ in children <8 years of age at diagnosis, consistent with a previous report using questionnaire-based data. However, overall cognitive ability was not significantly different.

SIOP PNET5 MB

EudraCT-Nr. 2011-004868-30

European study (16 countries) for children older than 3 to 5 years

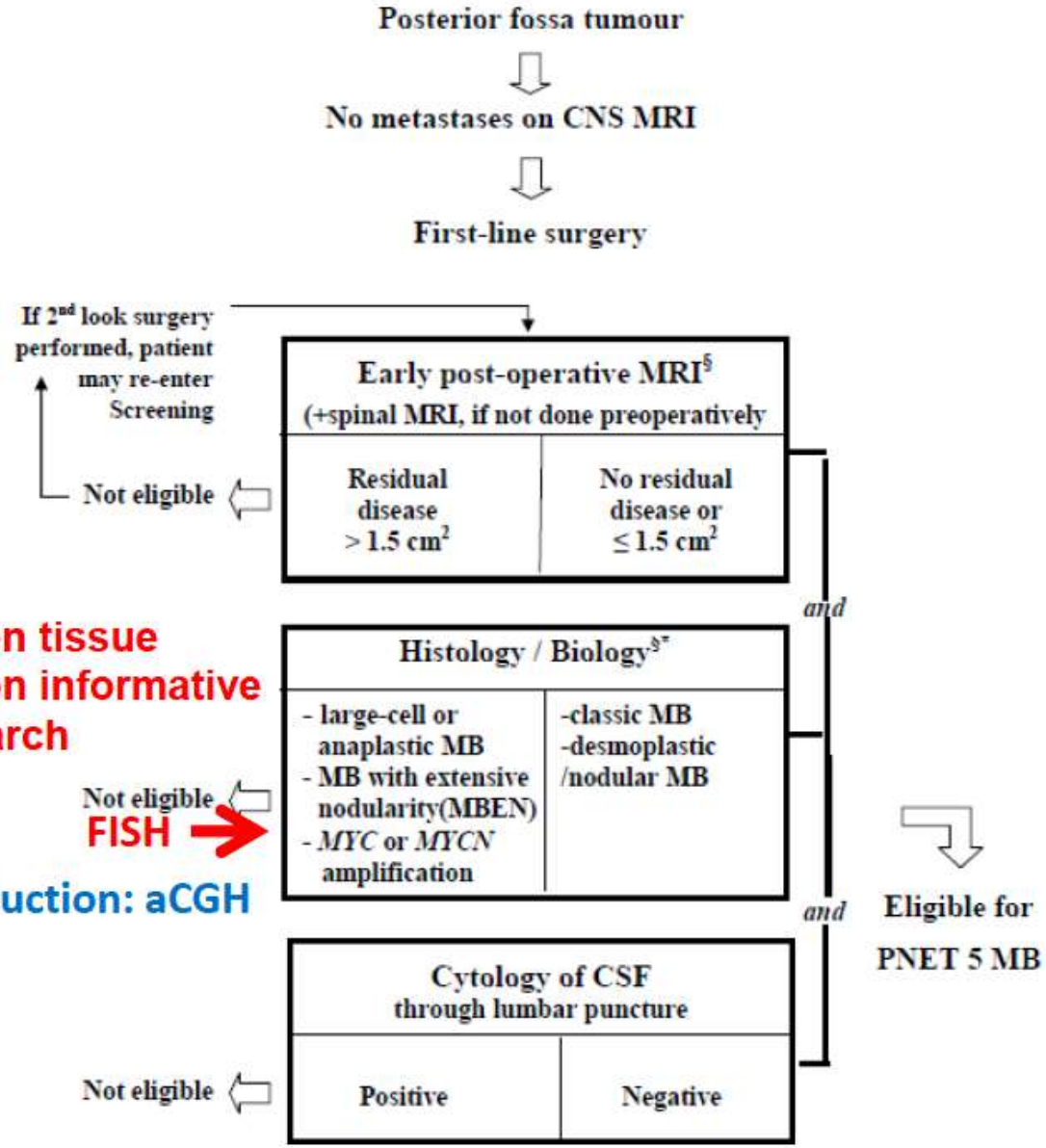
Stratification according to clinical and biological criteria

- LR: Low-risk medulloblastoma (Phase II; Co-PI: F. Doz)
- SR: Standard-risk medulloblastoma (Phase III)

PNET 5 MB substantial amendment

- New definition WNT subgroup
  - ß-catenin mutation analysis mandatory
  - monosomy 6 analysis optional
  - WNT positive patients ≥ 16 years ⟶ PNET 5 MB-SR
- Reduction of CSI dose from 23.4 Gy to 18 Gy in PNET 5 MB-LR
- 40 days period for radiotherapy starts after 1st surgery, even if 2nd surgery was performed.
- Foreseeable inability to start RT within 40 days renders patients ineligible
- Particular per-protocol analysis in LR- arm excluding patients with RT > 40days
- Possibility to add new countries
- Implementation of study board and definition function of study committee
- Use of Health Tracker only for QoS assessments

PNET 5 MB substantial amendment

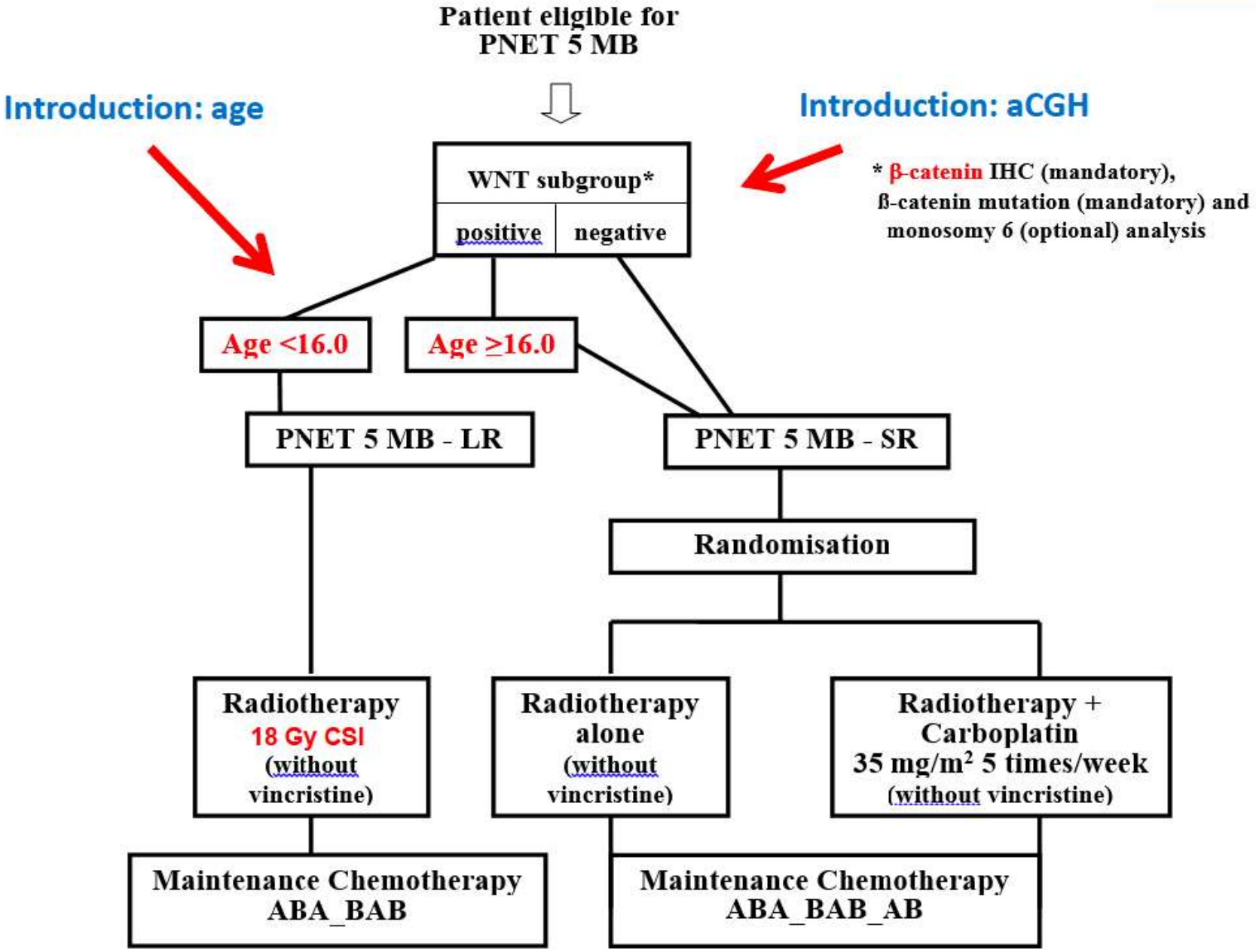


Mandatory frozen tissue

- **20% FFPE non informative**
- **Further research**

Introduction: aCGH

PNET 5 MB substantial amendment



Medulloblastoma: the management

- Standard risk Medulloblastoma
- **High risk medulloblastoma**
- Infant medulloblastoma

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

High risk MB – Approaches

COG: *Daily Carboplatin with RT* (99701)

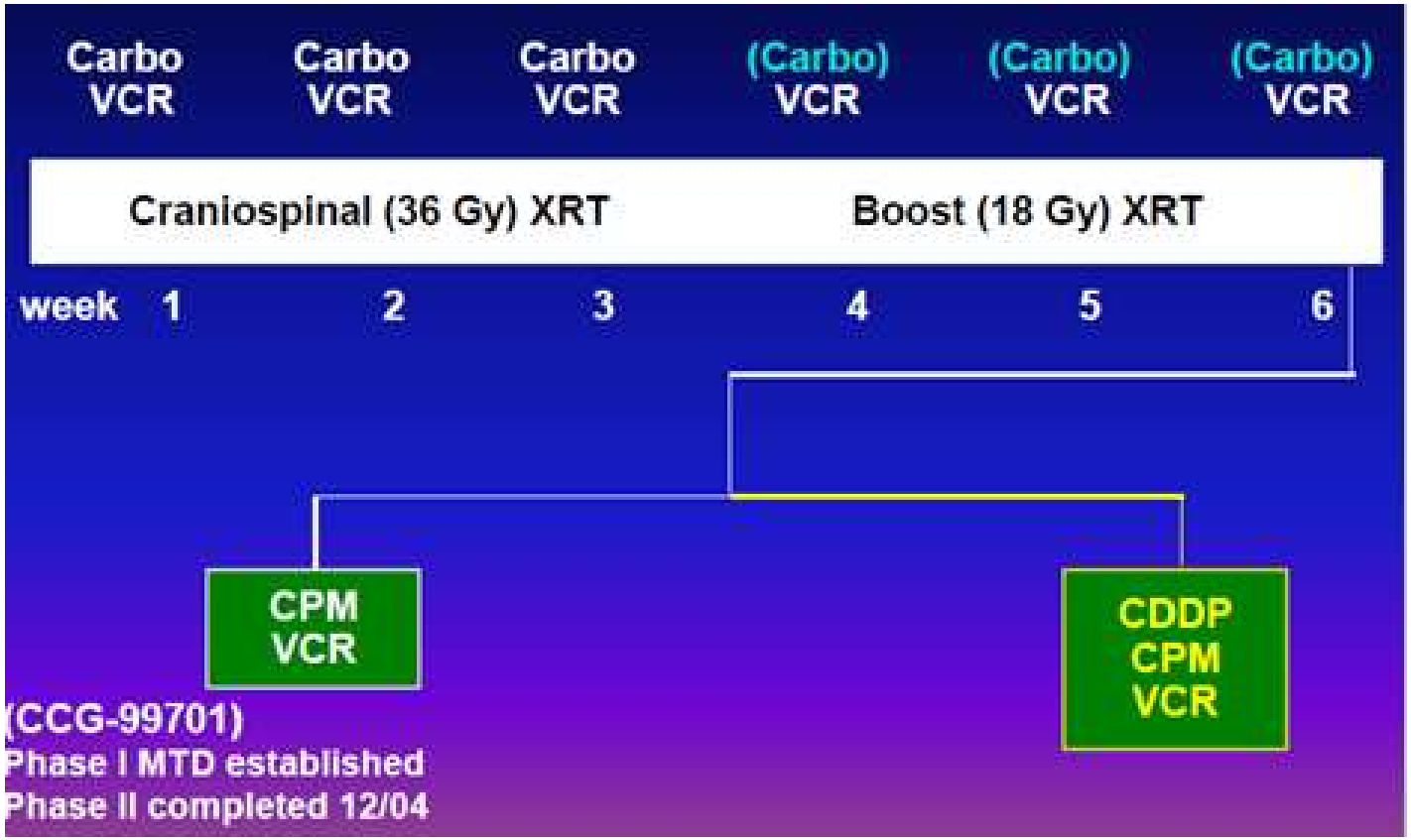
MILAN: *HFRT with HD chemotherapy*

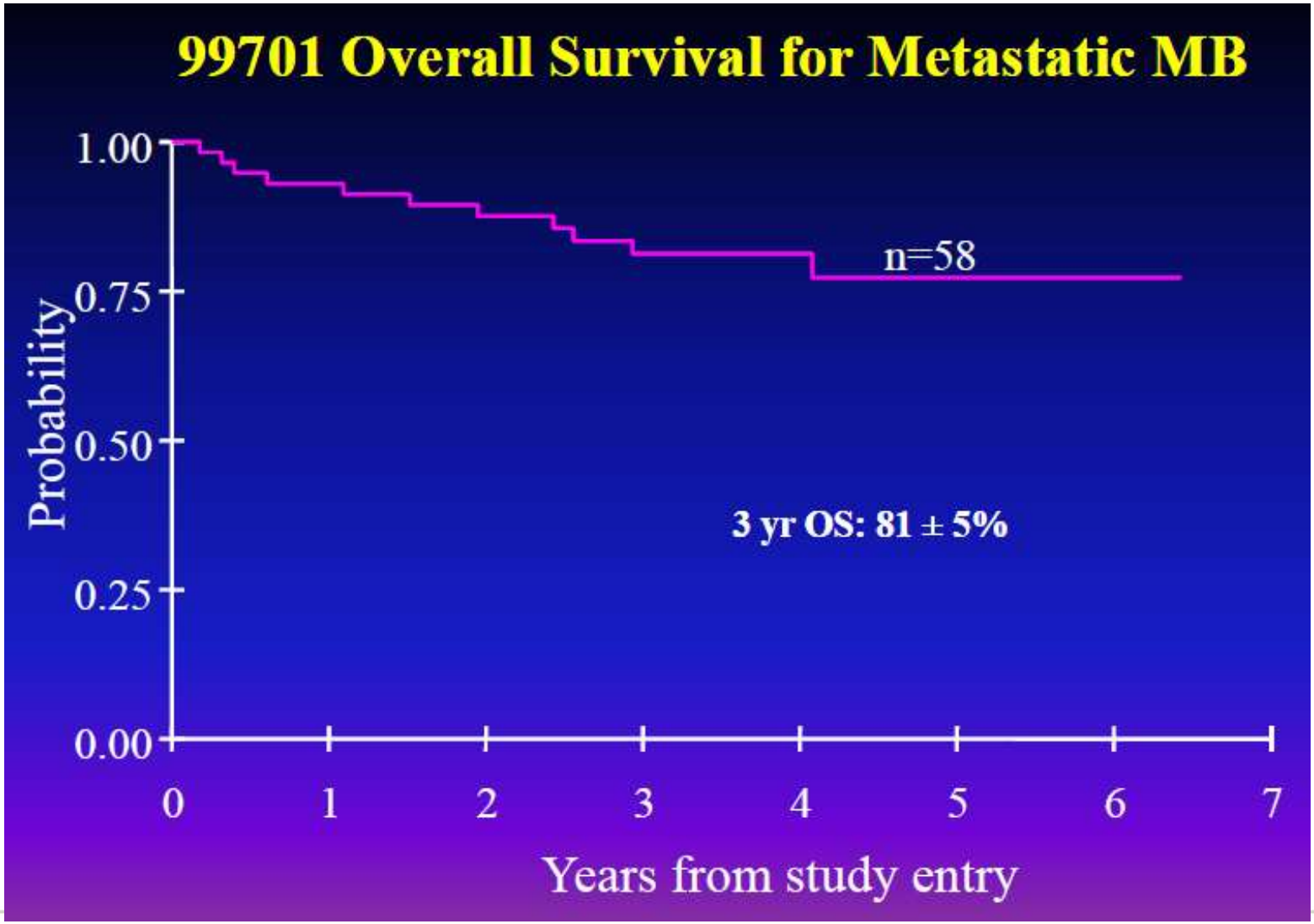
Milan HART Study

- 1998-2007
- 33 pts (M1 9, M2 6, M3 17, M4 1)
- HART: CSI (39 Gy; 1.3 Gy/fraction bid)
  posterior fossa boost up to 60 Gy (1.5 Gy/fraction 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%

COG High Risk Study
Radiosensitisation study





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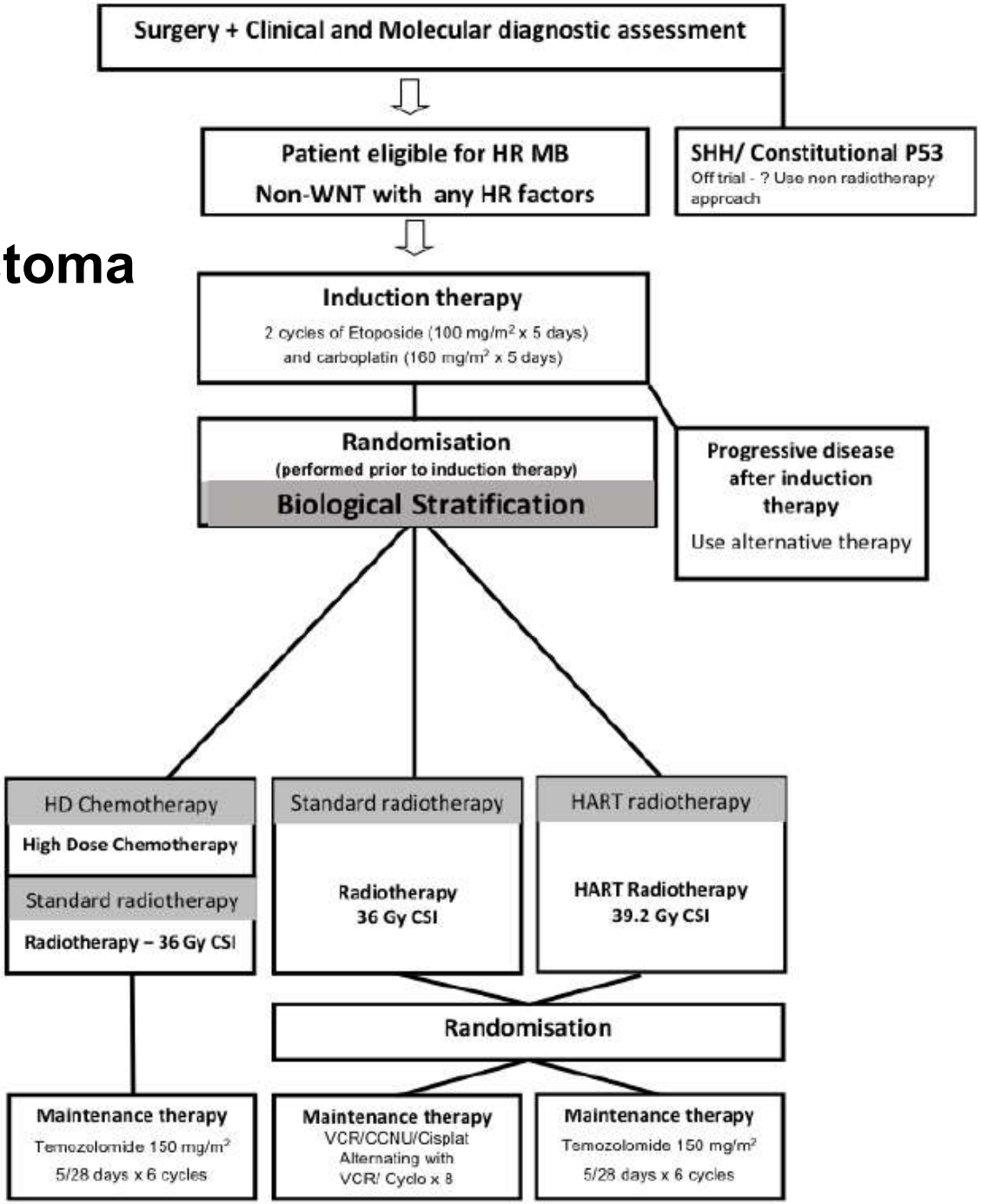
SIOP HR Medulloblastoma Trial



Medulloblastoma: the management

- Standard risk Medulloblastoma
- High risk medulloblastoma
- **Infant medulloblastoma**

Infant Medulloblastoma

- Management problematic
- Most protocols involve avoidance (or 1-2 yrs post-poning) of routine CSRT
- Most protocols have accepted impaired outcome and need for RT as salvage, when treatment is more difficult
- Lack of data on long-term quality of life outcome

ACNS1221
A Phase II Study for the Treatment of Non Metastatic Desmoplastic Medulloblastoma in Children Less Than 4 years of Age

Lucie Lafay-Cousin, Eric Bouffet, Arzu Onar-Thomas, Catherine Billups, Cynthia Hawkins, Charles Eberhart, Craig Horbinski, Giles Robinson, Douglas Strother, Linda Heier, Mark Souweidane, Maryam Fouladi, Amar Gajjar

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Background/Rational

- Nodular desmoplastic medulloblastoma and medulloblastoma with extensive nodularity (ND/MBEN) have been associated with a more favorable outcome in younger children
- Can be cured without using radiation or consolidation with high dose chemotherapy strategy
- Different toxicity /efficacy profile of regimens used
  - Fertility (CPM, Thiotepa); Ototoxicity (CDDP)
  - Neurocognitive Methotrexate (Intrathecal MTX)

Background/Rational

- Best survival outcome observed with the German HIT SKK regimen: 5y PFS of 95% ± 5%
  - No adjuvant radiotherapy
  - Conventional chemotherapy
  - **With serial intraventricular injections of Methotrexate**
- Can we replicate similar outcome using a modified HIT SKK regimen WITHOUT the IT MTX?

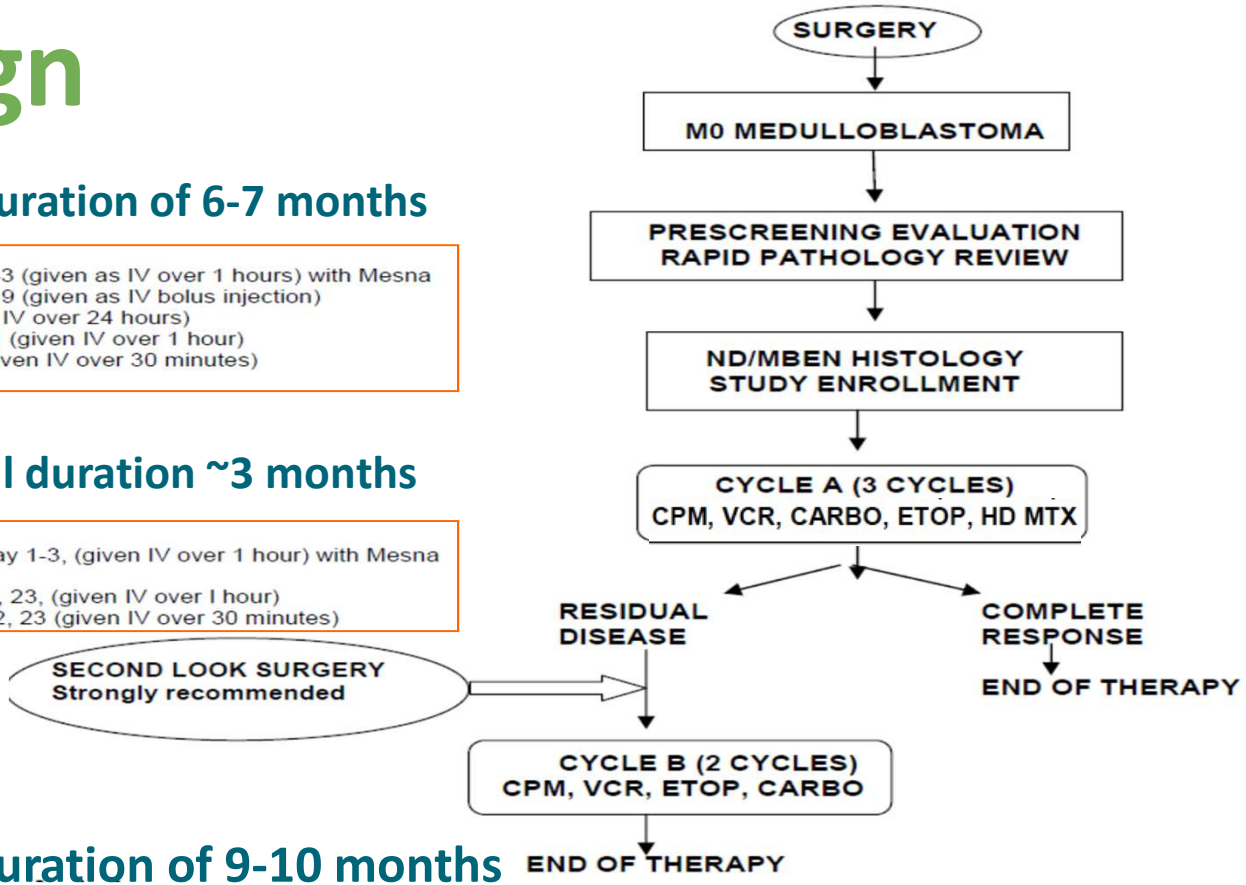
Study Design

Induction (Cycle A) total duration of 6-7 months

Cycle A
Cyclophosphamide (CPM): 800 mg/m^2 on Day 1-3 (given as IV over 1 hours) with Mesna
Vincristine (VCR): 1.5 mg/ m^2 on Day 1, 21, 35, 49 (given as IV bolus injection)
Methotrexate (MTX): 5g/m^2 on Day 21, 35 (given IV over 24 hours)
Carboplatin (CARBO): 200 mg/ m^2 on Day 49-51 (given IV over 1 hour)
Etoposide (ETOP): 150 mg/m^2 on Day 49-51 (given IV over 30 minutes)

Continuation (Cycle B) total duration ~3 months

Cycle B
Cyclophosphamide (CPM): 800 mg/m^2/day on Day 1-3, (given IV over 1 hour) with Mesna
Vincristine (VCR): 1.5 mg/m^2 on Day 1.
Carboplatin (CARBO): 200 mg/m^2 on Day 21, 22, 23, (given IV over I hour)
Etoposide (ETOP): 150 mg/m^2/day on Day 21, 22, 23 (given IV over 30 minutes)



Total planned therapy duration of 9-10 months

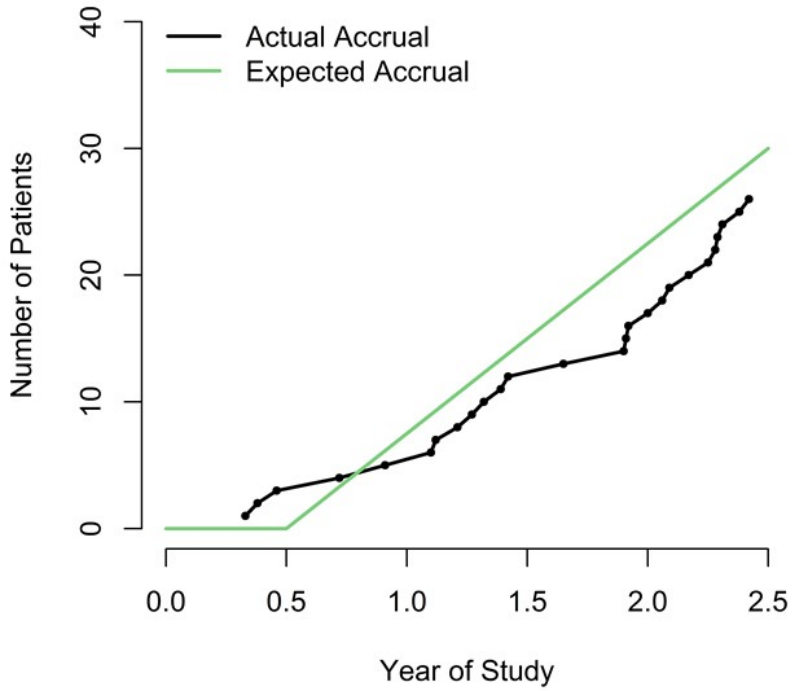
Lucie Lafay-Cousin – ASCO Meeting Chicago June 03rd 2017

Primary Objective

- Estimation of PFS for patients under 4 years of age, with M0 ND/MBEN treated with a modified HIT SKK 2000 regimen (excluding the use of intraventricular MTX)

2-year PFS rate ≥ 90% both desirable for patient and relatively comparable to HIT SKK 2000

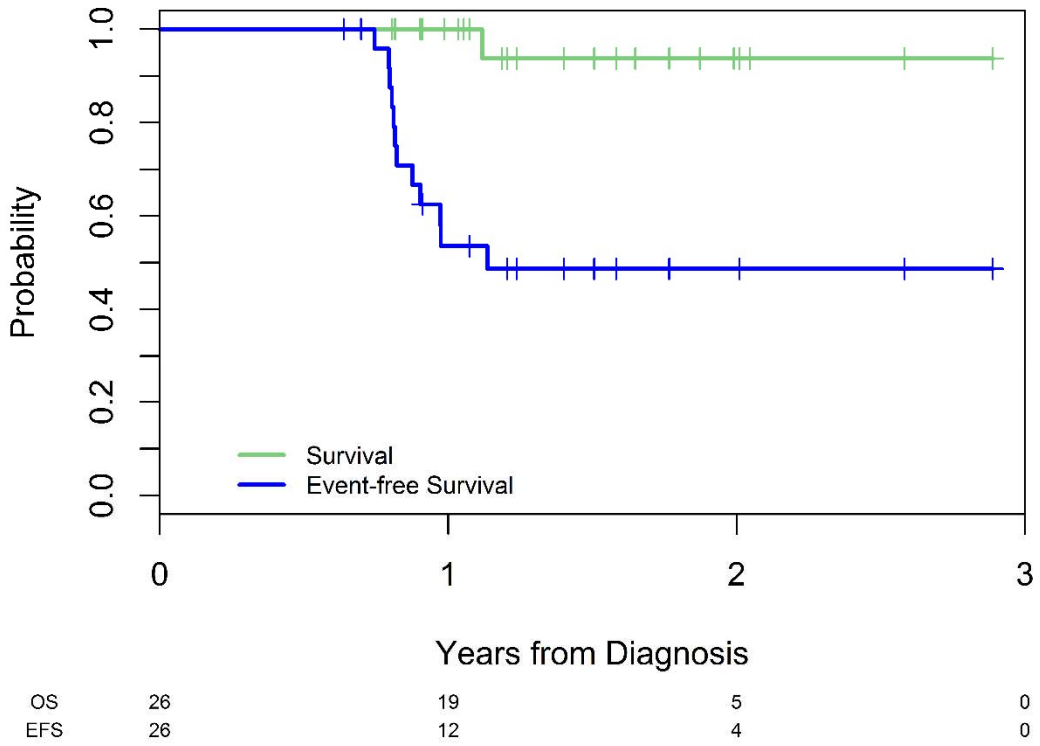
Accrual



- Study opened
  December 23rd, 2013
- Permanently closed
  July 27th, 2016
- 26 patients enrolled out of 37 needed

Lucie Lafay-Cousin – ASCO Meeting Chicago June 03rd 2017

Survival



- Study permanently closed for excess of relapse at interim analysis
- **Estimated 1 y PFS of 53.6% (SE, 10.1%)**
- Median follow up for the 25 survivors was 1.2 years (0.6 to 2.9 y)

Lucie Lafay-Cousin ASCO meeting Chicago June 03rd 2017

Relapses

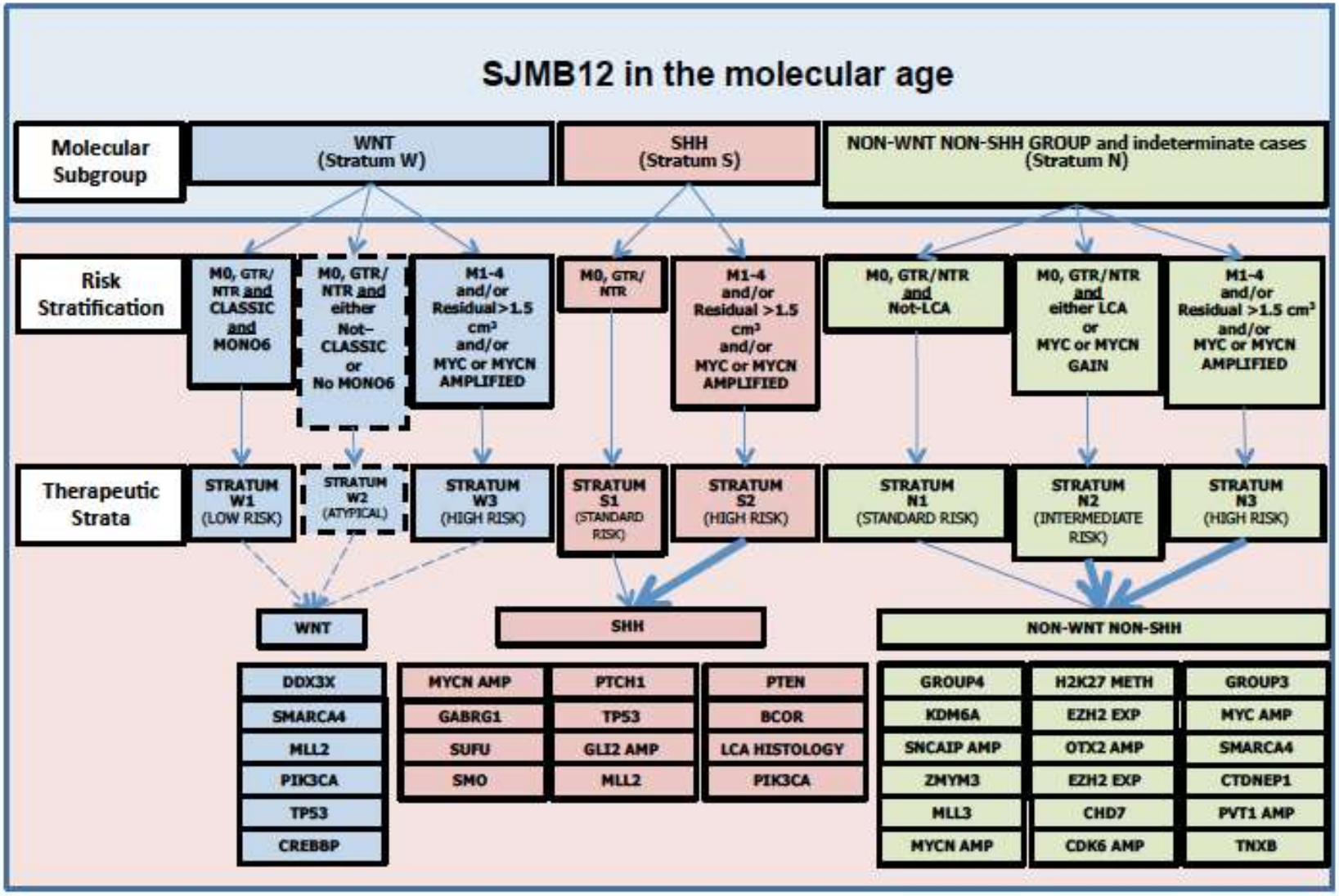
N	Sex/Age at diagnosis (months)	Residual disease	Time of relapse from diagnosis	Site of relapse	Outcome (months from relapse)	Subsequent treatment
1	M (31.1)	-	9.5	Local	Alive (14.4)	Surgery, CT, SCT
2	M (31.9)	+	9.7	Distant	Alive (14.9)	CT, RT
3	F (32.0)	-	10.5	Distant	DOD (2.9)	na
4	M(21.3)	-	13.7	Local	Alive (8.8)	na
5	F(31.4)	-	9.9	Combined	Alive (9.9)	CT
6	M(27.2)	+	8.9	Combined	Alive (5.3)	CT
7	M(20.8)	-	11.7	Distant	Alive (0.2)	na
8	M(17.2)	-	9.6	Combined	Alive (0.1)	na
9	M(24.4)	-	9.7	Local	Alive (2.9)	CT
10	M(26.7)	-	11.7	Local	Alive (0.7)	na
11	M(26.9)	-	10.9	Local	Alive (at time of relapse)	na
12	M(15.8)	-	9.8	Local	Alive (at time of relapse)	na

Lucie Lafay-Cousin ASCO meeting Chicago June 03rd 2017

Conclusion

- The ACNS1221 regimen without IT MTX failed to achieve the desirable 2y PFS of 90%, leading to premature closure of the study
- None of the MBEN and of the patients under 12 months relapsed
- The molecular characterization of this ND/MBEN cohort is currently been investigated and may help uncover patients who may still benefit from this regimen

The FUTURE



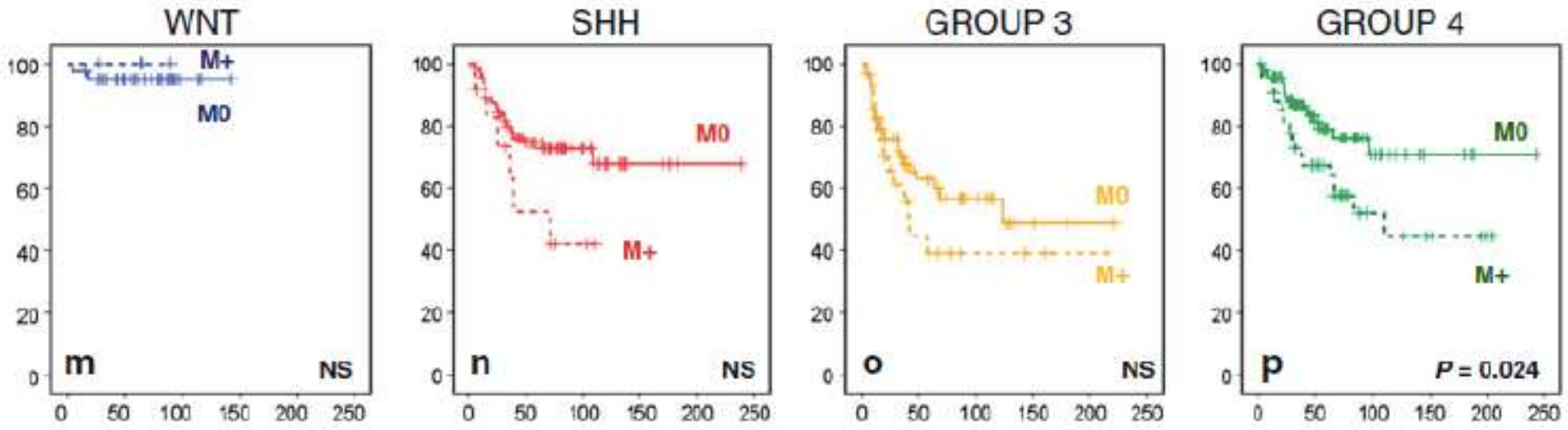
School

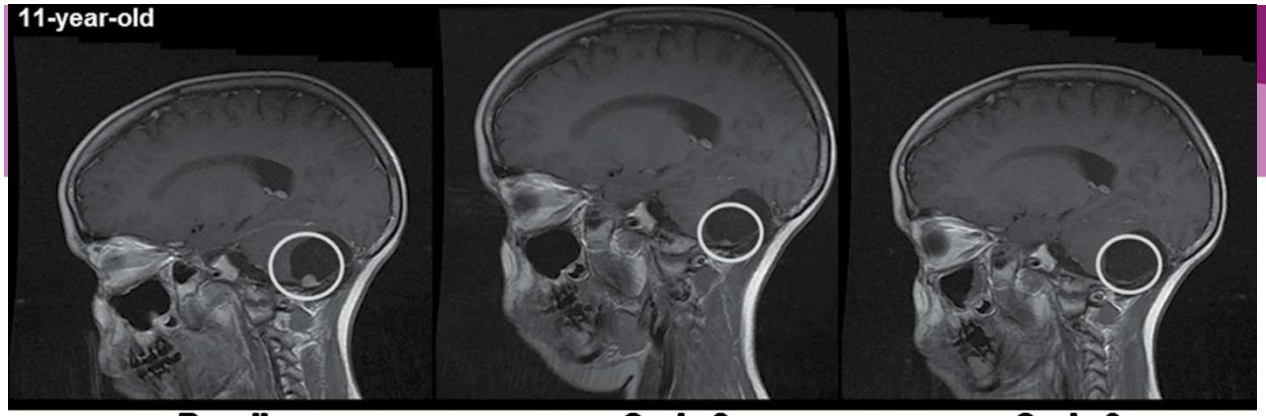
Neuro-Oncology

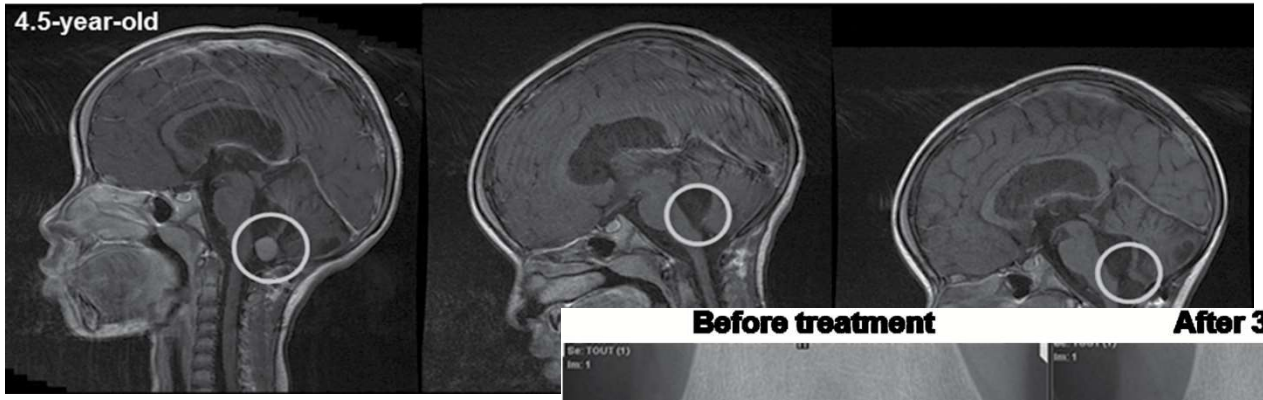
XX(XX), 1–11, 2017 | doi:10.1093/neuonc/nox109 | Advance Access date 9 June 2017

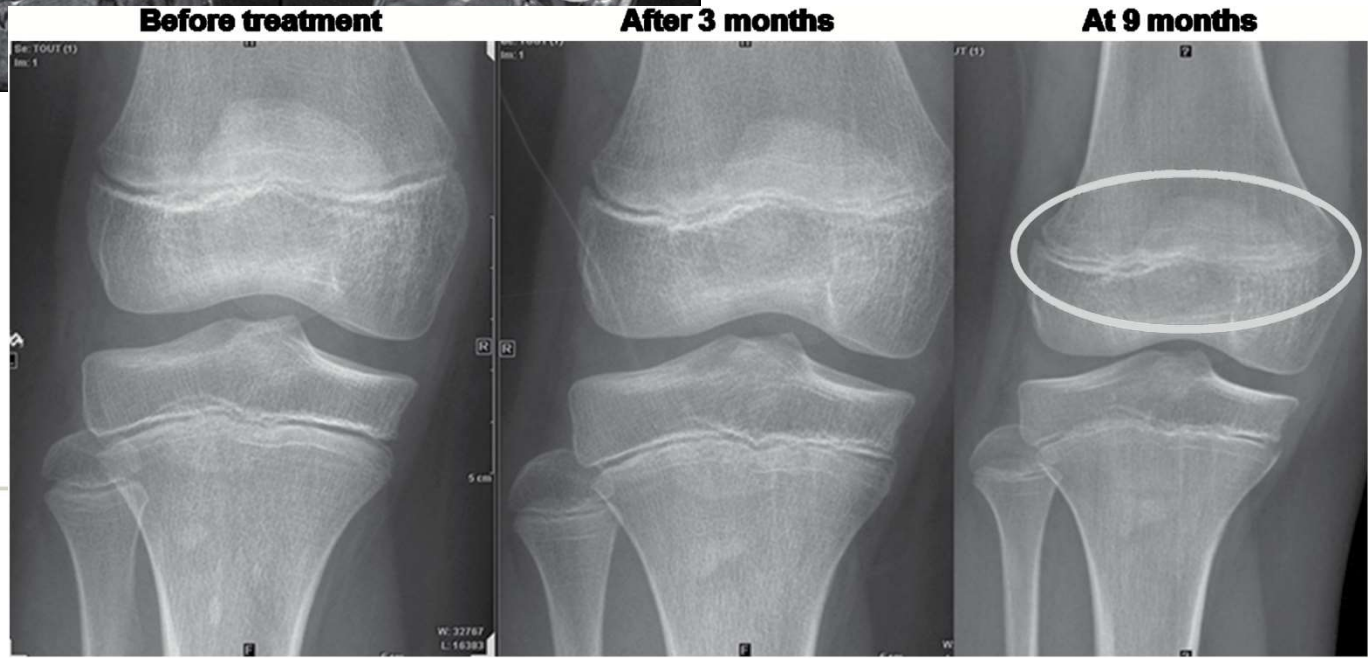
Phase I study of oral sonidegib (LDE225) in pediatric brain and solid tumors and a phase II study in children and adults with relapsed medulloblastoma

Mark W. Kieran, Julia Chisholm, Michela Casanova, Alba A. Brandes, Isabelle Aerts, Eric Bouffet, Simon Bailey, Sarah Leary, Tobey J. MacDonald, Francoise Mechinaud, Kenneth J. Cohen, Riccardo Riccardi, Warren Mason, Darren Hargrave, Stacey Kalambakas,* Priya Deshpande, Feng Tai, Eunju Hurh,* and Birgit Geoerger




11-year-old
Baseline
Cycle 2
Cycle 3


4.5-year-old


Before treatment
After 3 months
At 9 months

Management of medulloblastoma in children

Thanks!

ESTRO School

Management of pilocytic astrocytoma in children

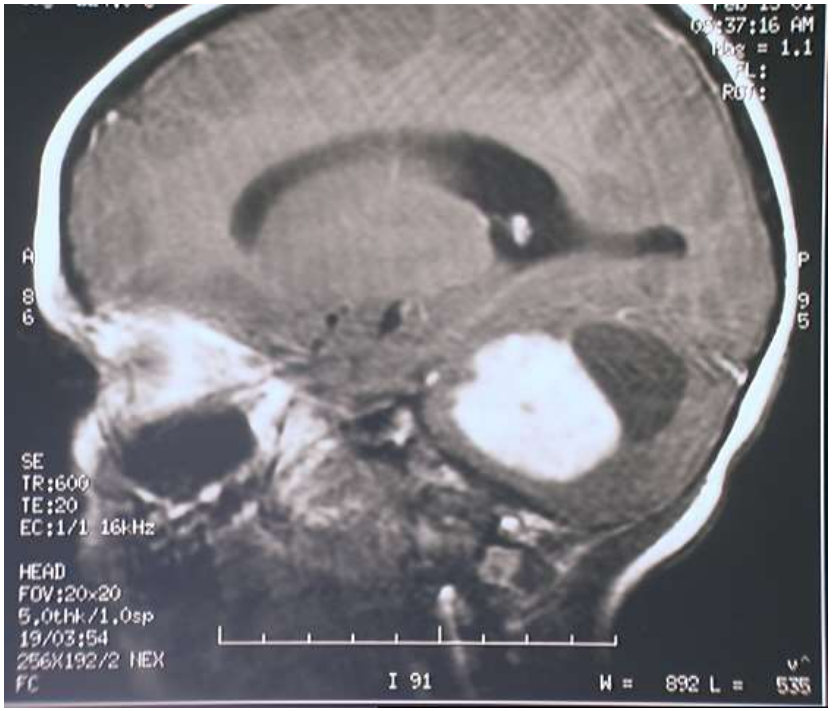
Darren Hargrave

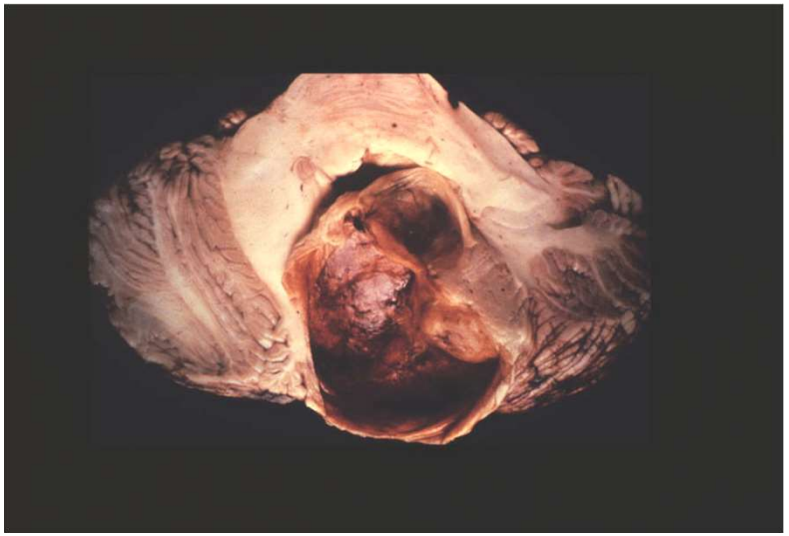
Consultant Paediatric Oncologist,

Neuro-oncology & Experimental Therapeutics

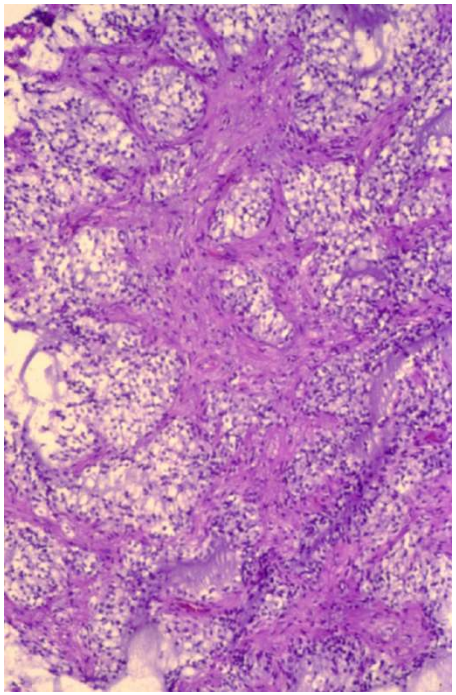
Great Ormond Street Hospital. London, UK.

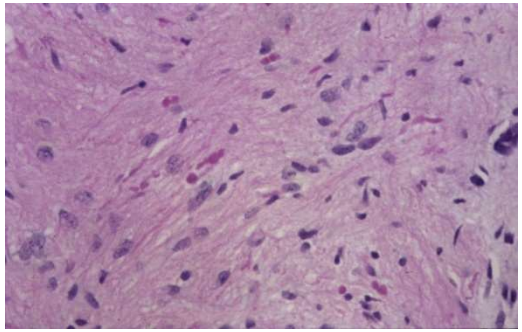
Low Grade Glioma

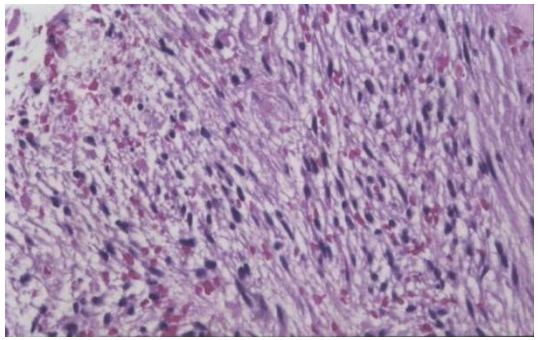




Pilocytic astrocytoma

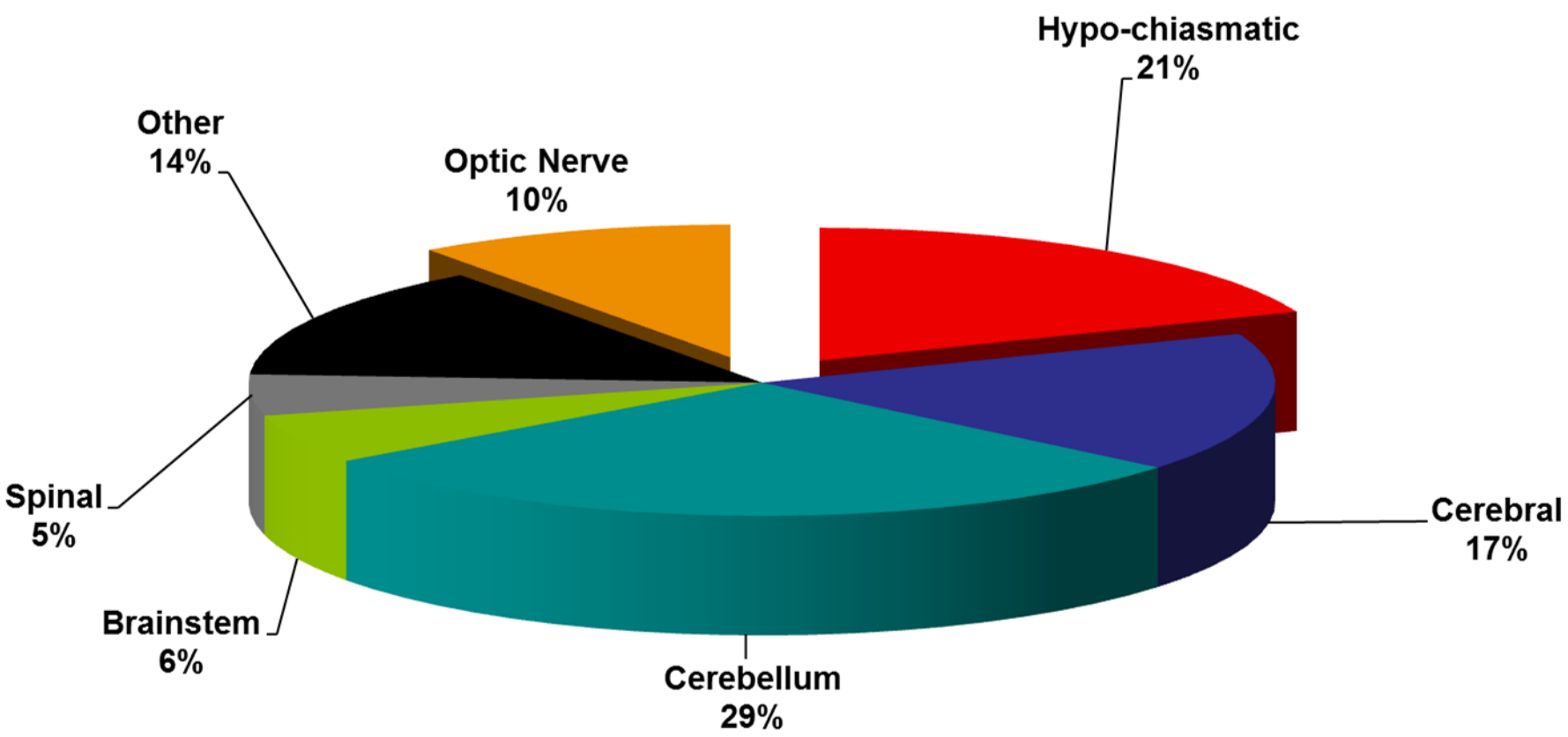






Tumor of cerebellum, often with cyst, biphasic, Rosenthal fibers, piloid cells

Primary Site of Low Grade Glioma



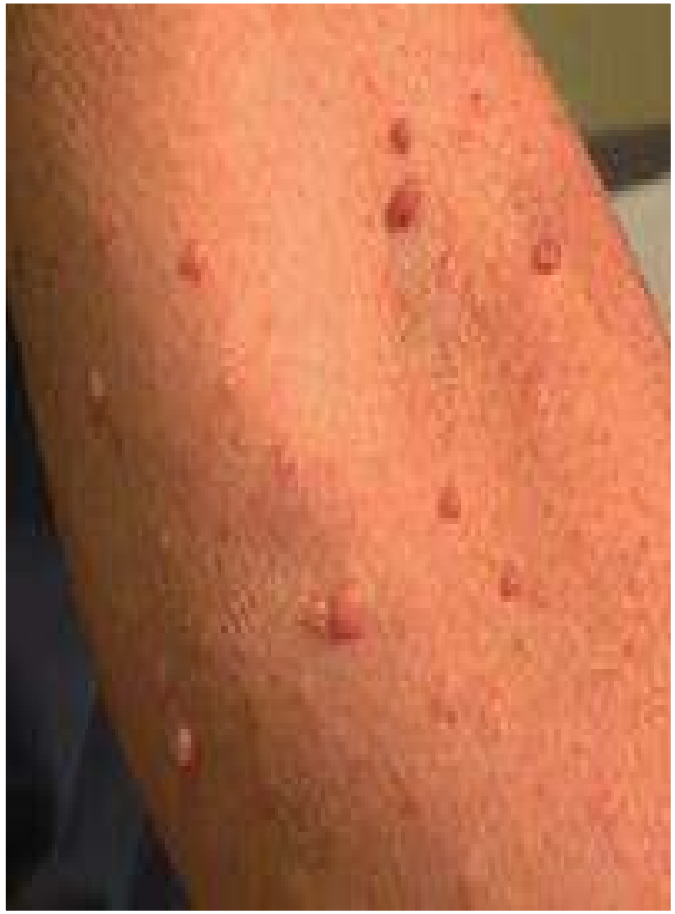
Juvenile Pilocytic Astrocytoma

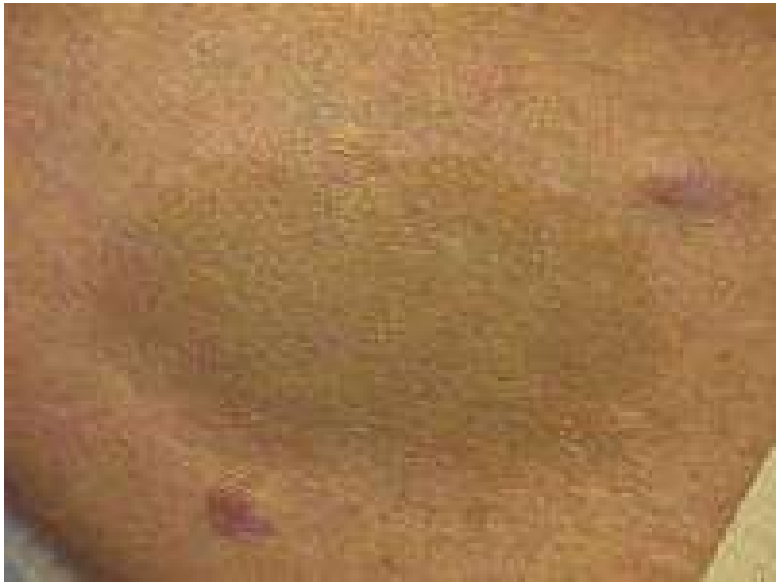
- Most common type in children
- Seen predominantly in younger children (median ~ 4 years)
- Usually well circumscribed, often partially cystic, with little oedema, no mass effect
- Enhance brightly and uniformly with contrast material
- Gross total resection often possible

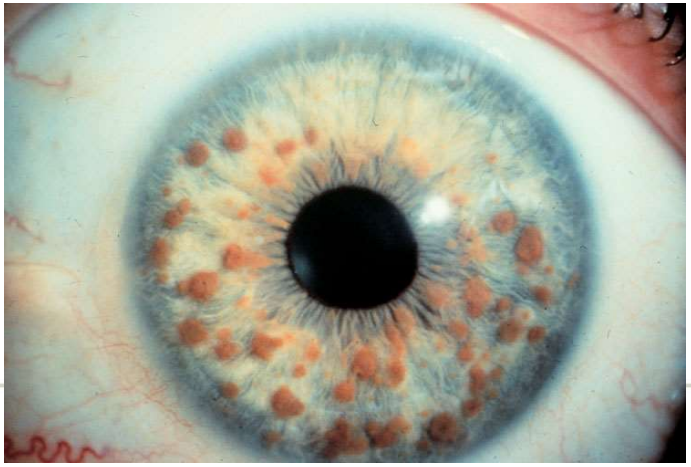
Low Grade Glioma in Children

- 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

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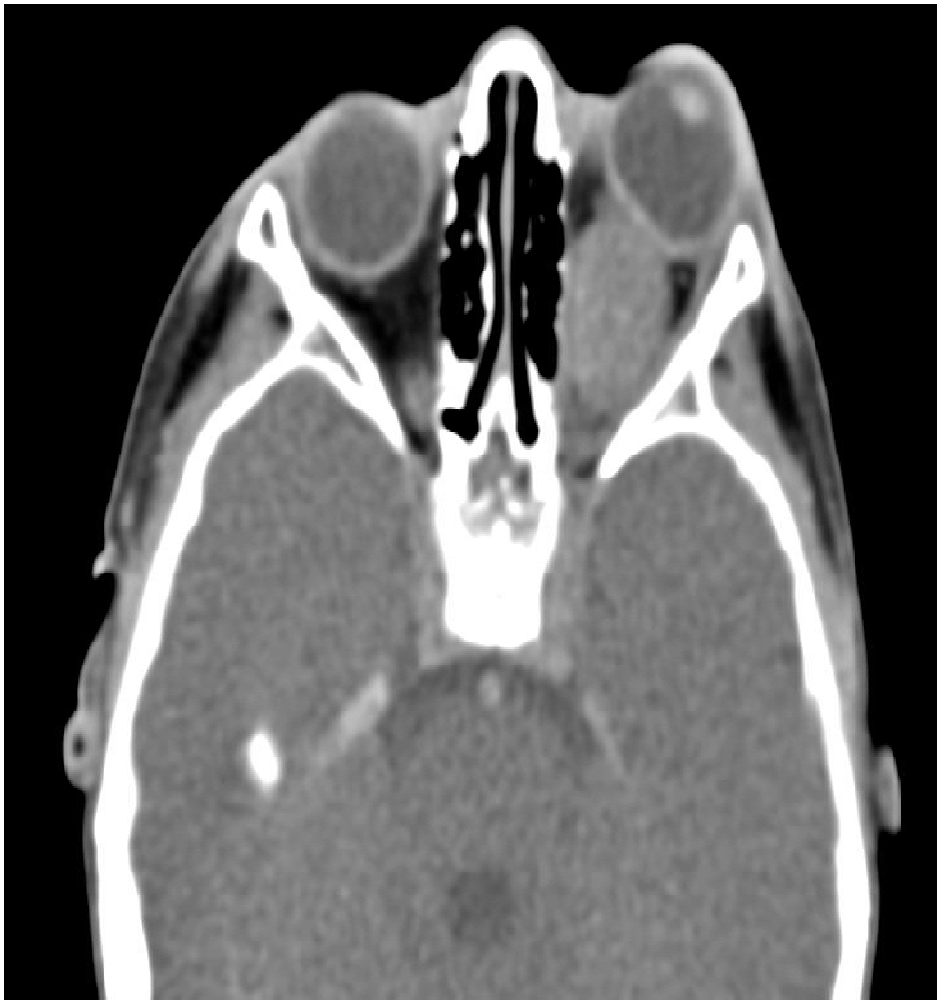
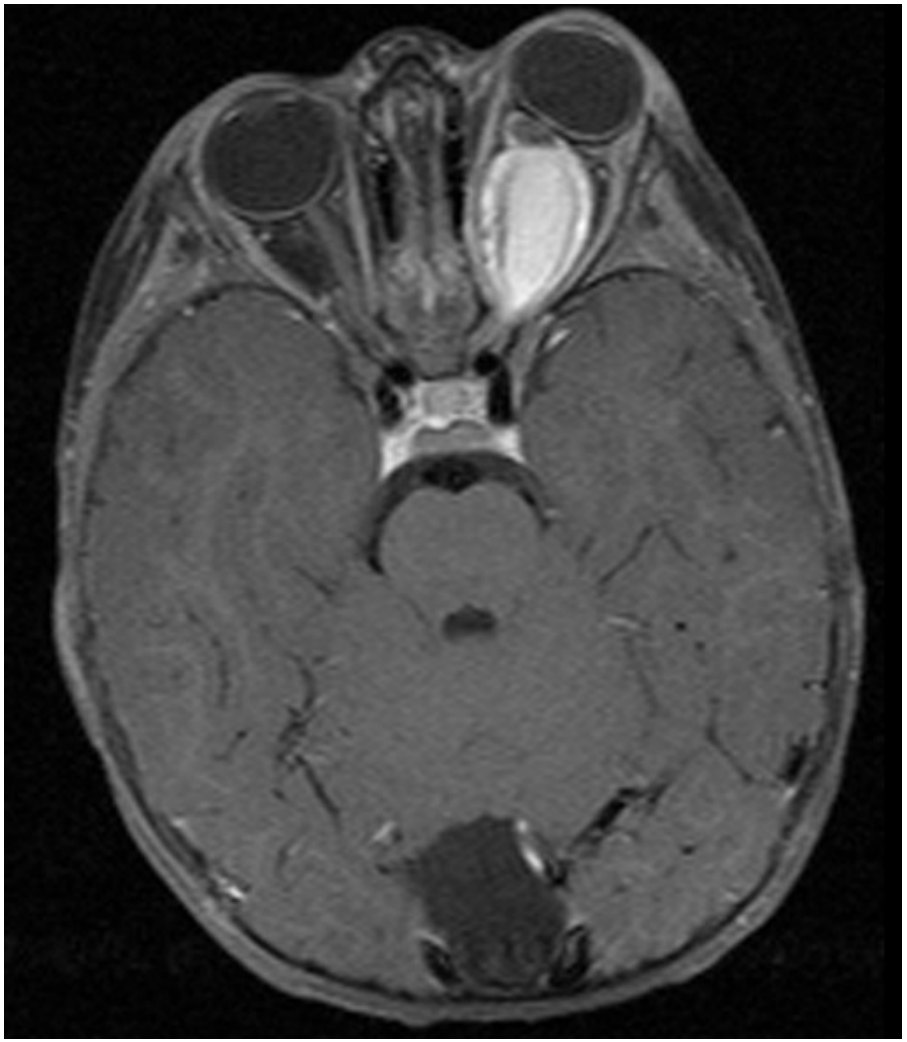
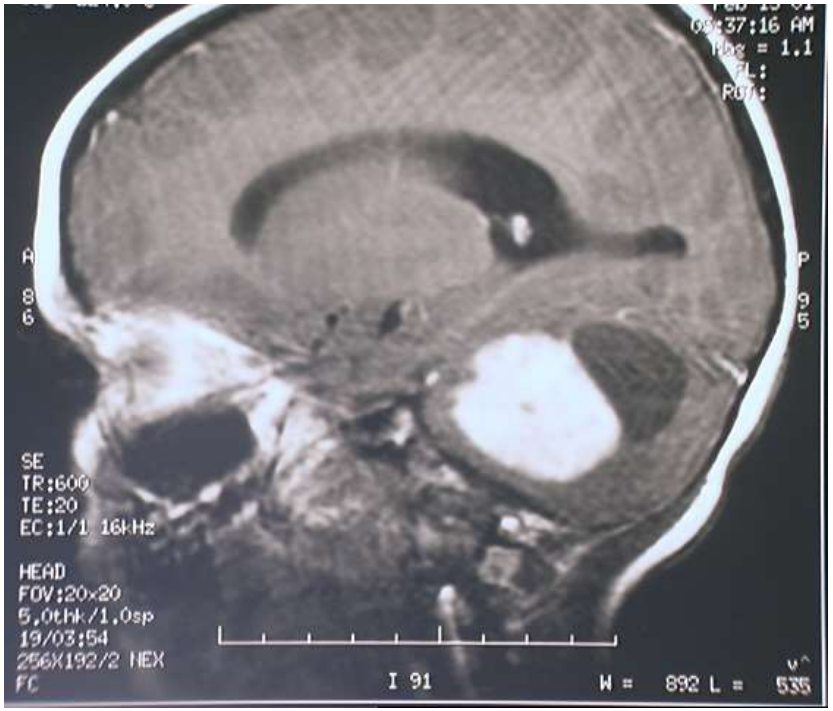
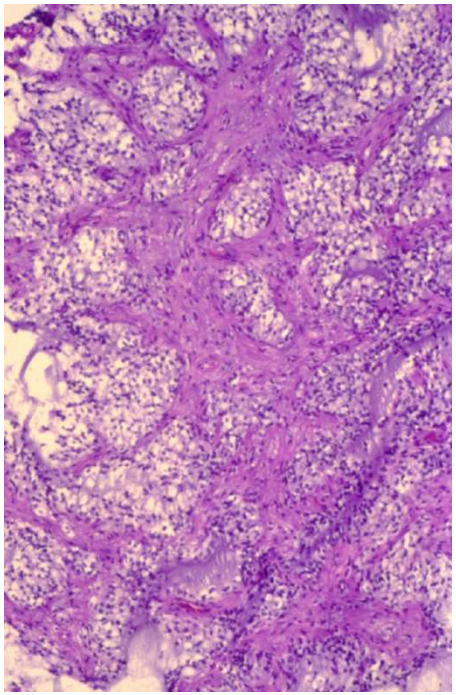
Optic Pathway Glioma

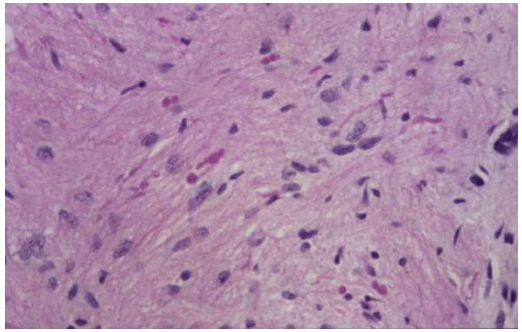


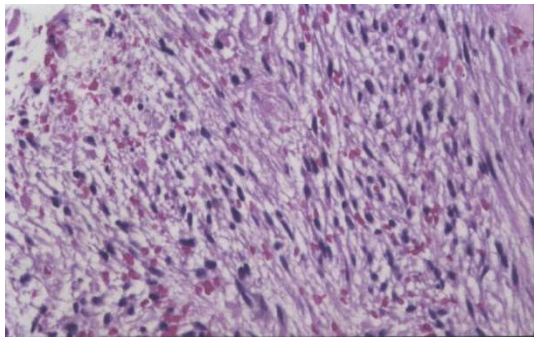


MAPK in pLGG

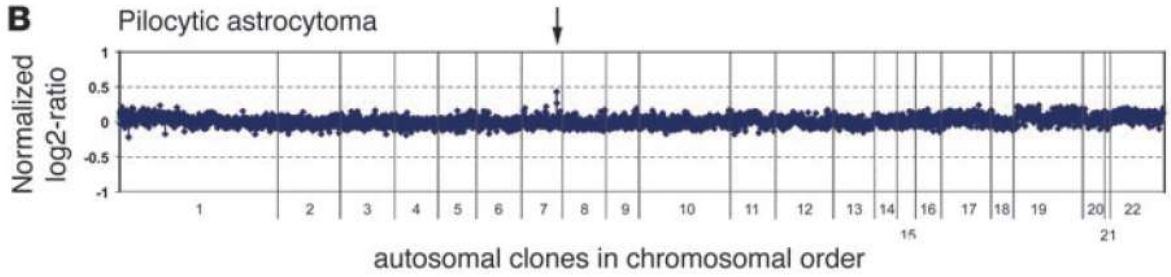

SE
TR:600
TE:20
EC:1/1 16kHz
HEAD
FOV:20x20
5.0thk/1.0sp
19/03:54
256X192/2 NEX
FC
I 91
W = 892 L = 535

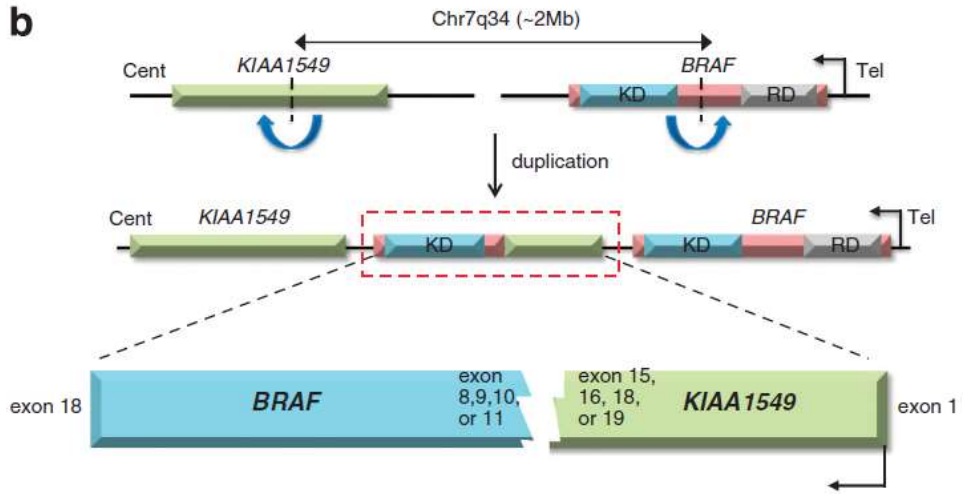


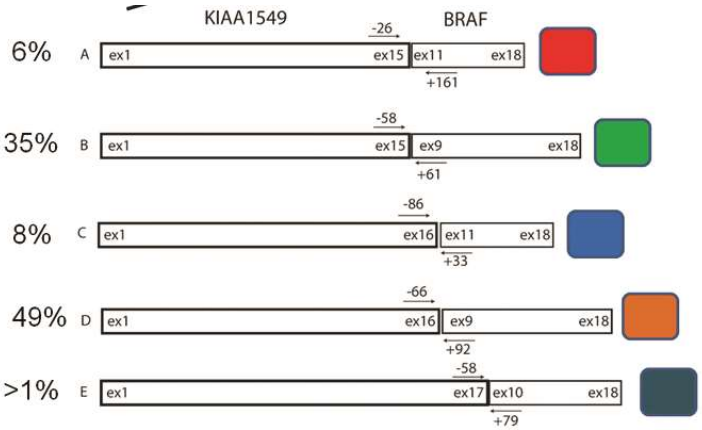


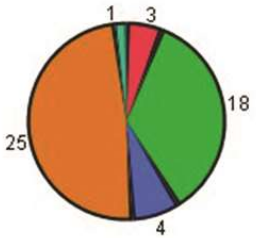


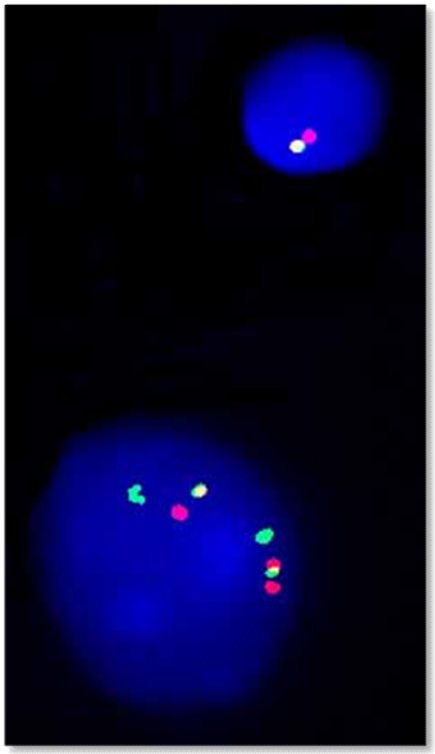
BRAF abnormalities – hallmark signature for PA











Pfister *et al.*, JCI 2008

Chen and Guttmann, Oncogene 2013

Lin *et al.*, J Neuropathol Exp Neurol 71, 2012

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

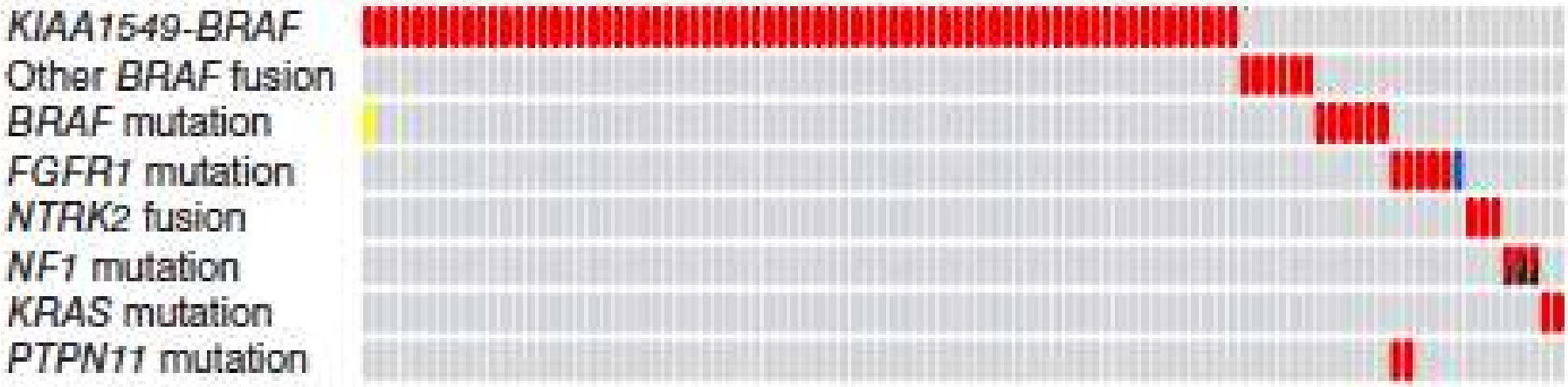


Figure 4 Summary of MAPK pathway alterations in pilocytic astrocytoma.

Brain Pathology ISSN 1015–6305

RESEARCH ARTICLE

Genetic alterations related to BRAF-FGFR genes and dysregulated MAPK/ERK/mTOR signaling in adult pilocytic astrocytoma

Pankaj Pathak[1], Anupam Kumar[2], Prerana Jha[1], Suvendu Purkait[1], Mohammed Faruq[3], Ashish Suri[2], Vaishali Suri[1], Mehar C. Sharma[1], Chitra Sarkar[1]

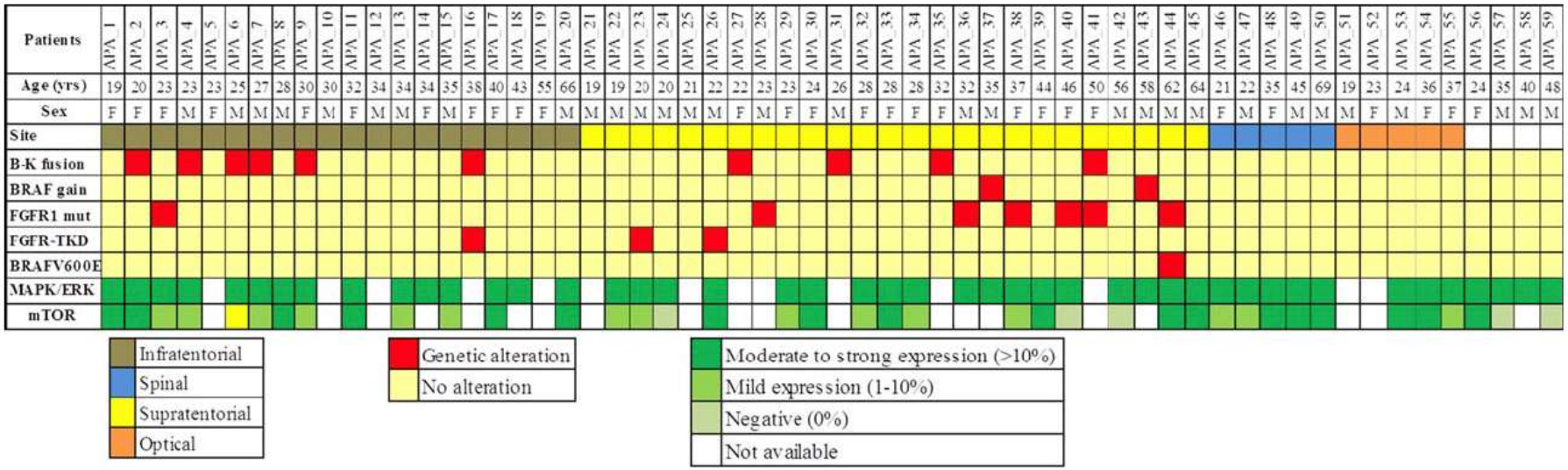


Figure 1. Clinicopathological and molecular genetic features for the 59 adult pilocytic astrocytoma cases with the different genetic and immunohistochemical analyses. (B-K fusion: BRAF-KIAA fusion).

- 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

Criteria for non-intervention in LGA

- Asymptomatic and non-progressive lesions in patients with neurofibromatosis

- Lesions in the tectal region

European Journal of Cancer 81 (2017) 206–225

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (≤16 years) low grade glioma – A final report

Astrid K. Gnekow [a,1], David A. Walker [b,*,1], Daniela Kandels [b], Susan Picton [c], Giorgio Perilongo [d,1], Jacques Grill [e], Tore Stokland [f], Per Eric Sandstrom [g], Monika Warmuth-Metz [h], Torsten Pietsch [i], Felice Giangaspero [j,k], René Schmidt [l], Andreas Faldum [l], Denise Kilmartin [m], Angela De Paoli [m], Gian Luca De Salvo [m], on behalf of the Low Grade Glioma Consortium and the participating centers[2]

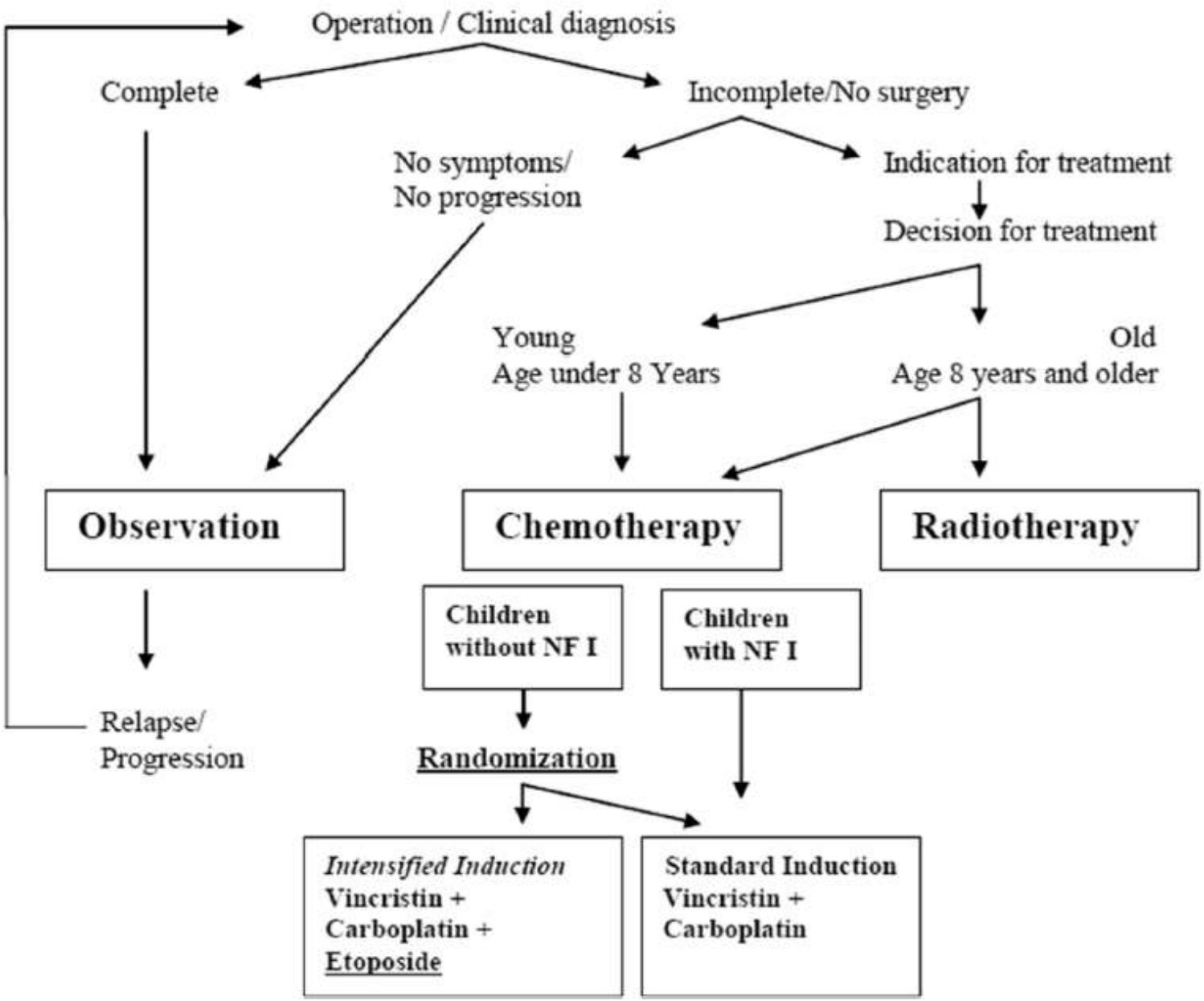
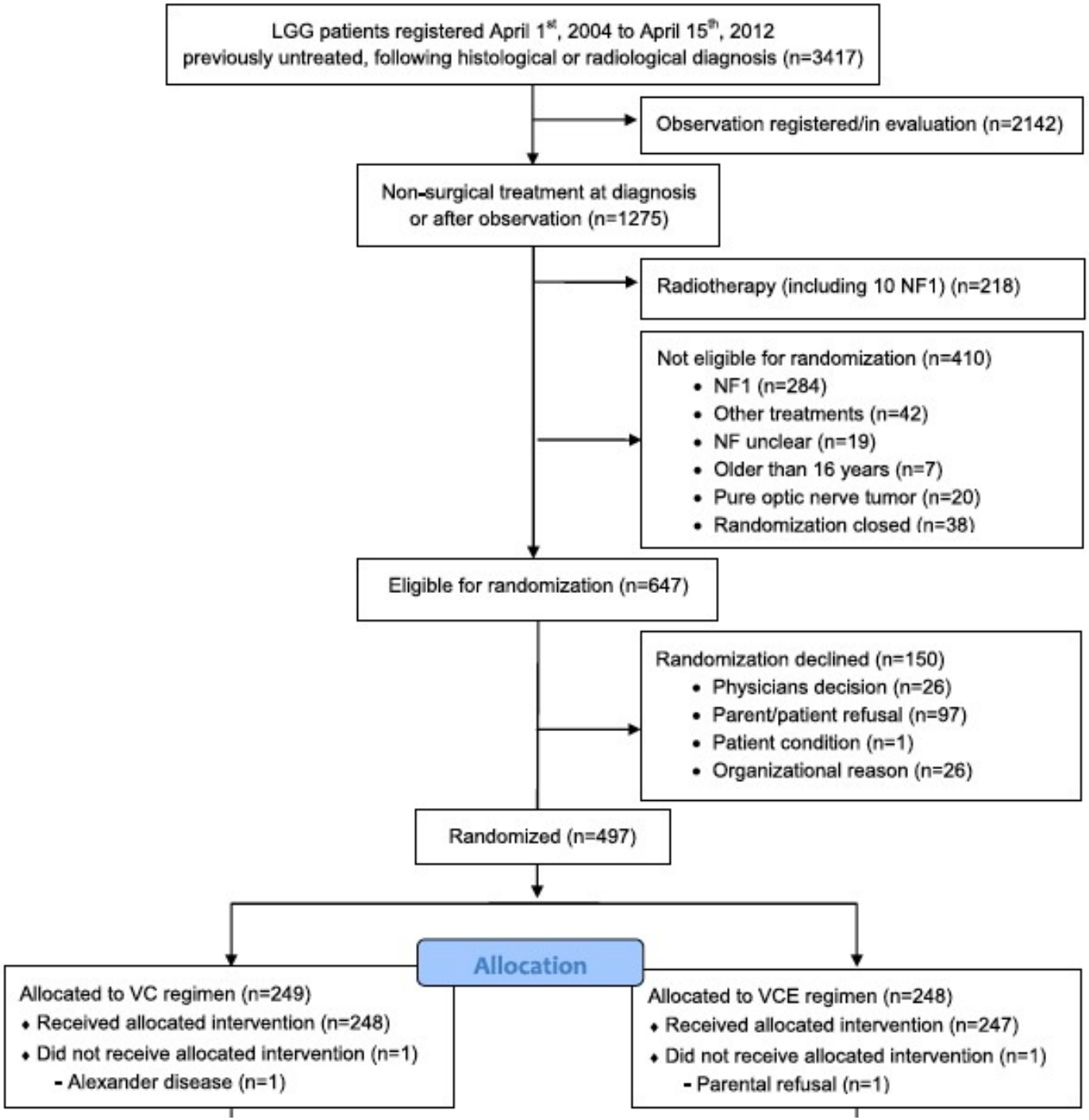
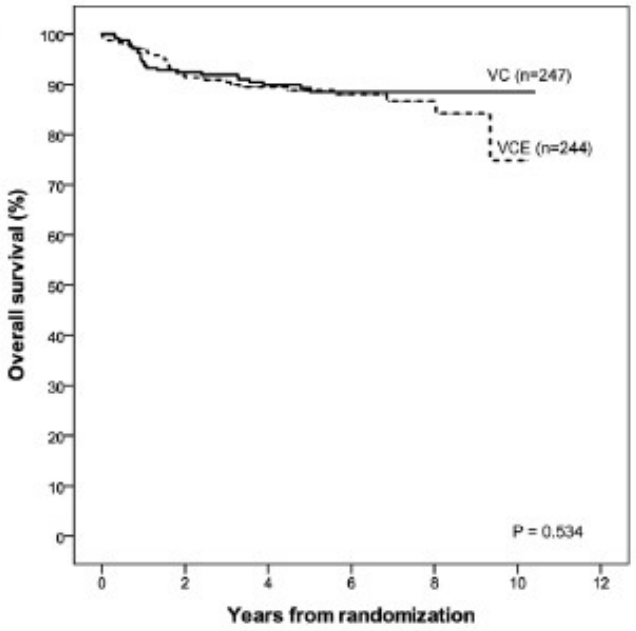


Fig. 1. Flow diagram of the study.

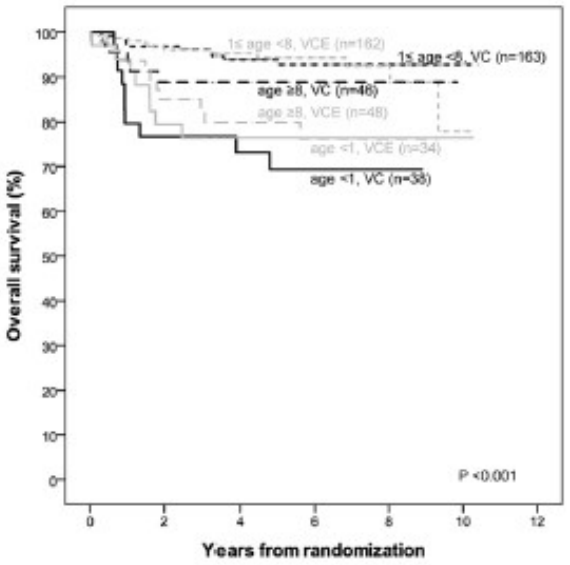

LGG patients registered April 1st, 2004 to April 15th, 2012
previously untreated, following histological or radiological diagnosis (n=3417)
Observation registered/in evaluation (n=2142)
Non-surgical treatment at diagnosis
or after observation (n=1275)
Radiotherapy (including 10 NF1) (n=218)
Not eligible for randomization (n=410)
NF1 (n=284)
Other treatments (n=42)
NF unclear (n=19)
Older than 16 years (n=7)
Pure optic nerve tumor (n=20)
Randomization closed (n=38)
Eligible for randomization (n=647)
Randomization declined (n=150)
Physicians decision (n=26)
Parent/patient refusal (n=97)
Patient condition (n=1)
Organizational reason (n=26)
Randomized (n=497)
Allocation
Allocated to VC regimen (n=249)
Received allocated intervention (n=248)
Did not receive allocated intervention (n=1)
- Alexander disease (n=1)
Allocated to VCE regimen (n=248)
Received allocated intervention (n=247)
Did not receive allocated intervention (n=1)
- Parental refusal (n=1)

a



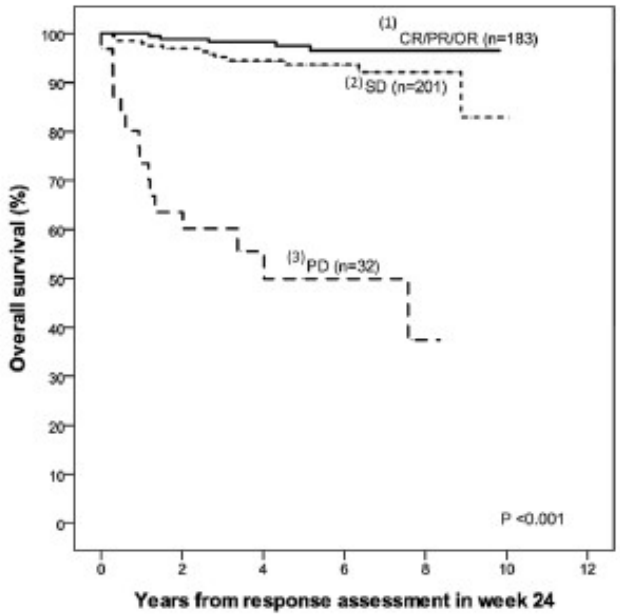
Number at risk							
VC	247	212	153	97	45	1	0
VCE	244	208	151	90	35	4	0

b

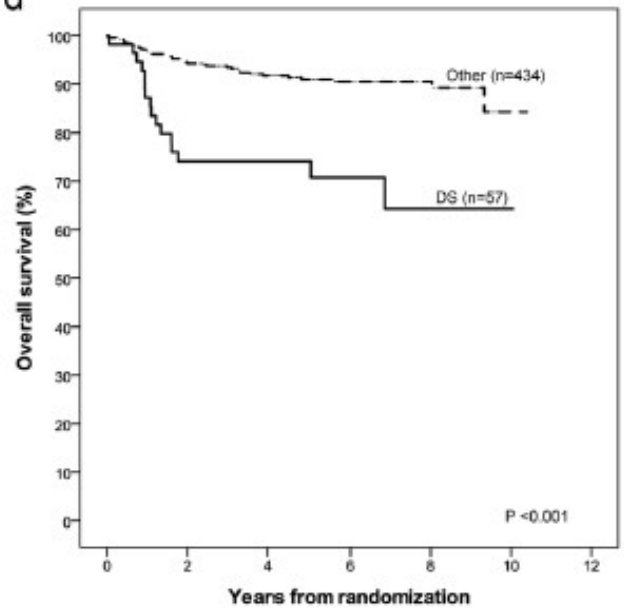


Number at risk							
age <1, VC	38	26	20	8	3	0	0
age <1, VCE	34	27	17	9	4	1	0
1≤ age <8, VC	163	147	103	64	33	1	0
1≤ age <8, VCE	162	143	107	64	26	3	0
age ≥8, VC	46	39	30	25	9	0	0
age ≥8, VCE	48	38	27	17	5	0	0

c



d



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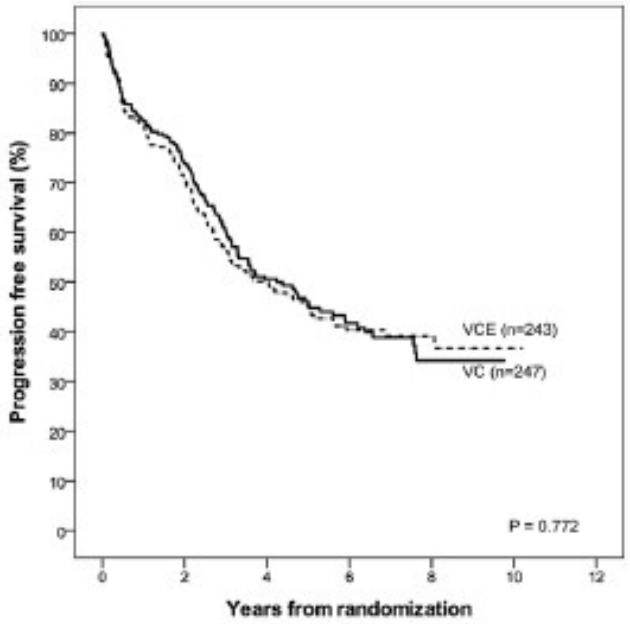
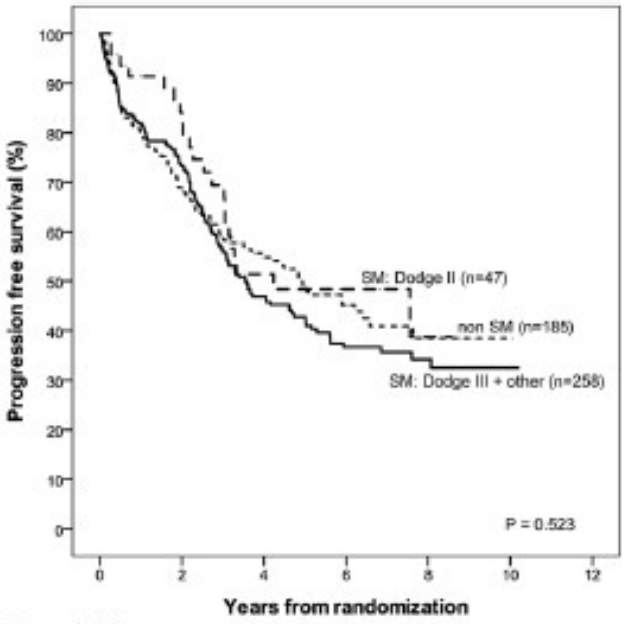


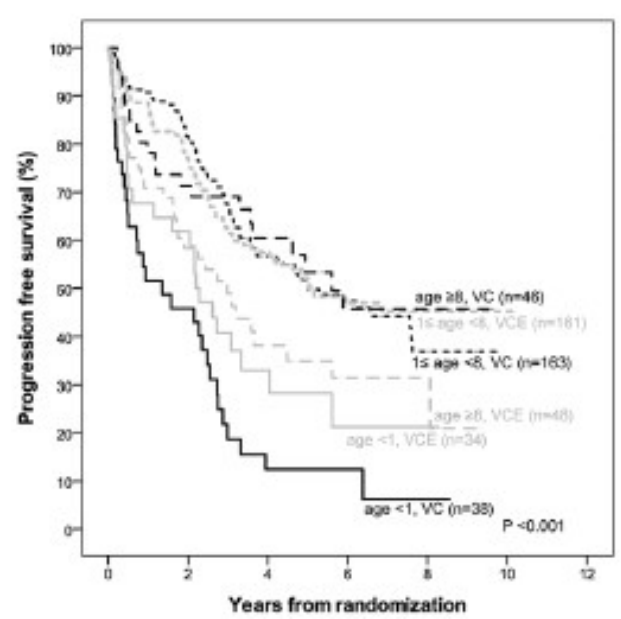
Number at risk							
VC	247	171	87	48	19	0	0
VCE	243	162	88	45	16	3	0

b



Number at risk							
SM: Dodge II	47	34	18	9	3	0	0
SM: Dodge III + other	258	178	87	44	20	2	0
non SM	185	121	70	40	12	1	0

c



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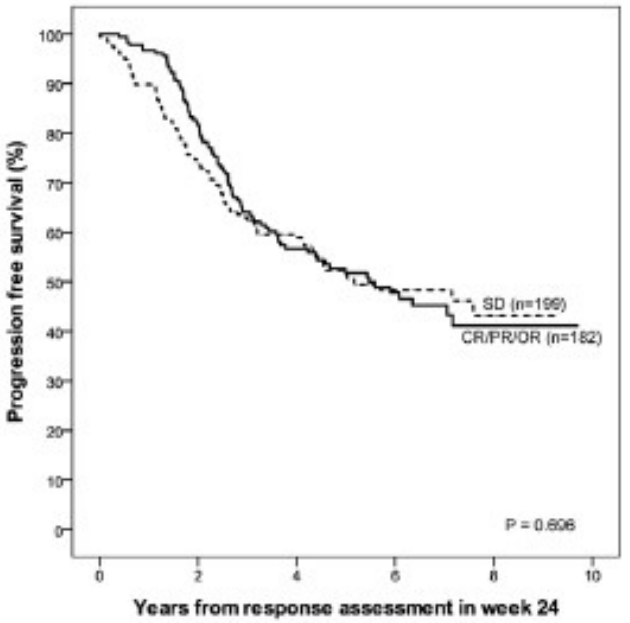


VOLUME 27 · NUMBER 22 · AUGUST 1 2009

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

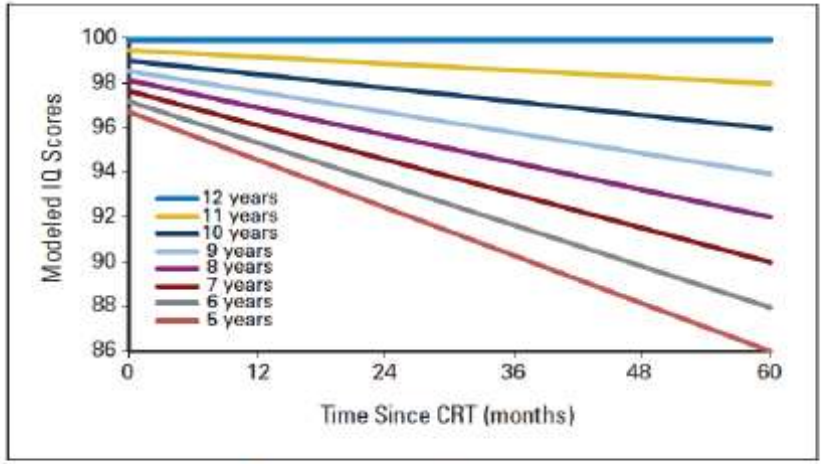


Fig 1. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age for pediatric low-grade glioma. Age is measured in years, and time is measured in months after the start of CRT.

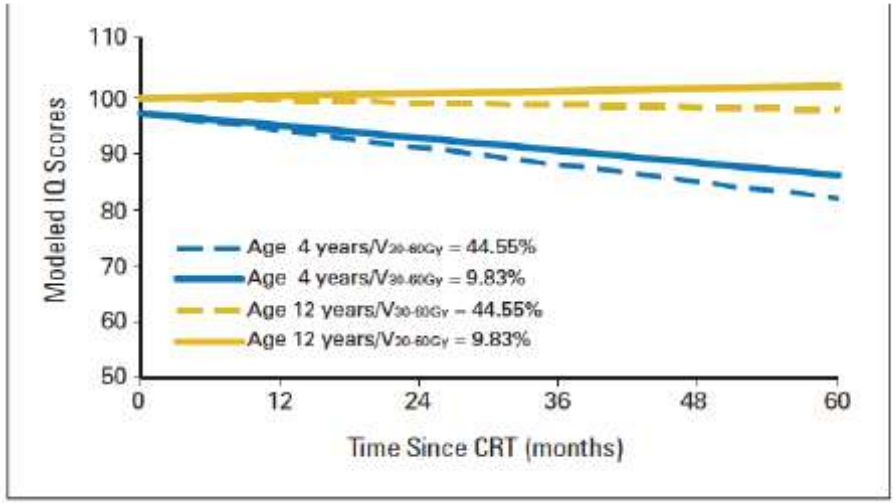


Fig 2. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age and supratentorial brain dose-volume intervals for pediatric low-grade glioma. Age is measured in years, and time is measured in months after CRT. The dose-volume intervals $V_{0\text{-}30Gy}$ and $V_{30\text{-}60Gy}$ 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

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

ESTRO School

Low Grade Glioma in Children

Alternative Chemotherapy

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

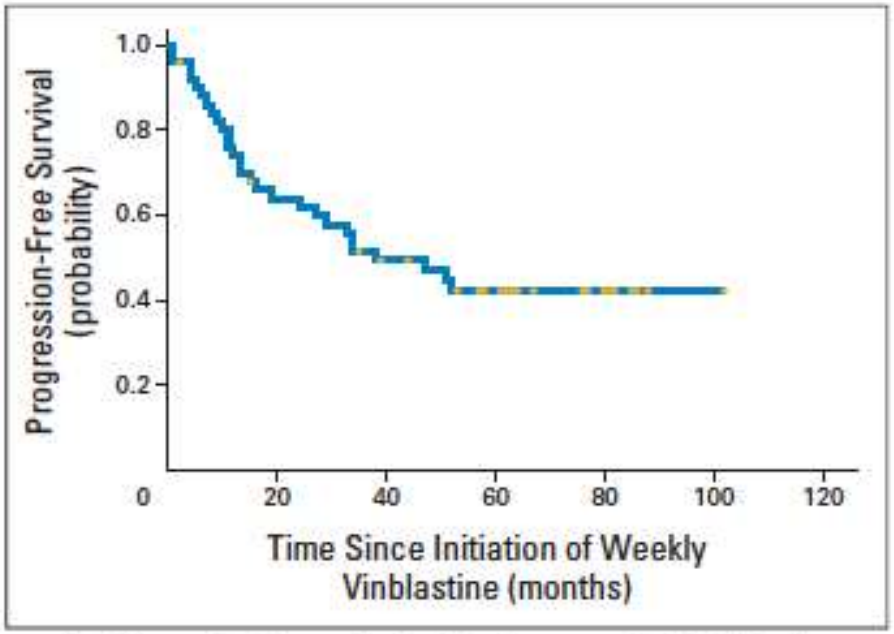


Fig 2. Progression-free survival in 51 patients treated with vinblastine.

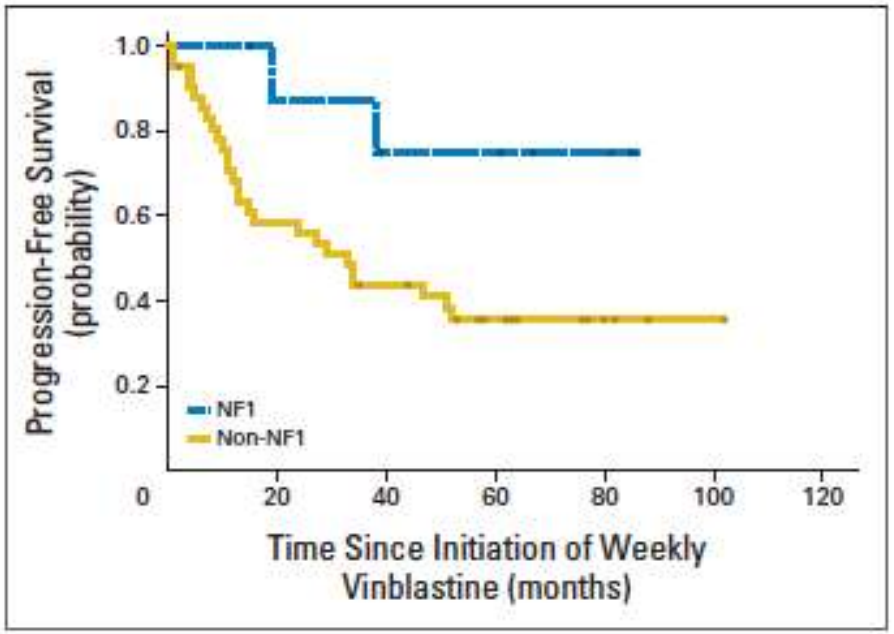


Fig 3. Progression-free survival in patients with and without neurofibromatosis type 1 (NF1; $P = .04$).

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
Published online November 14, 2013.

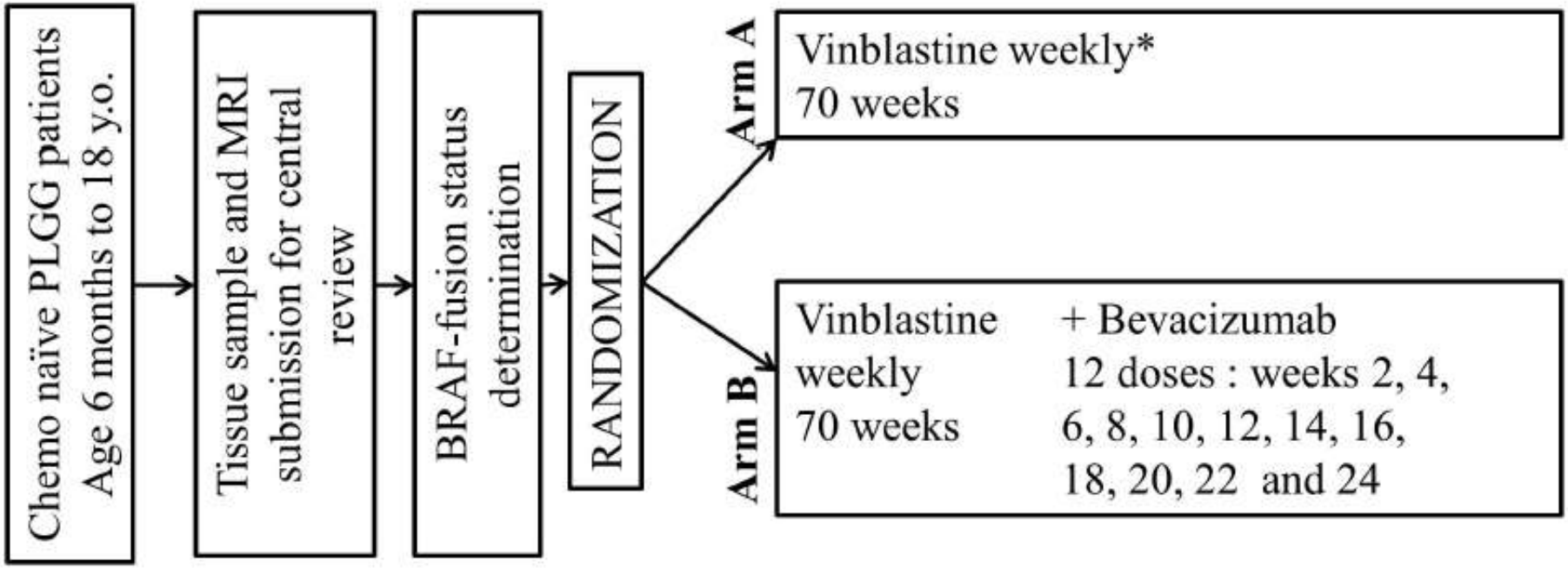
Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Robert A. Avery, DO, MSCE, Neuro-Ophthalmology Service, Department of Neurology, Children's National Medical Center, 111 Michigan Ave NW, Washington, DC 20010 (ravery@childrensnational.org).

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

FUTURE MANAGEMENT OF LGG

Neuro-Oncology

XX(XX), 1–14, 2017 | doi:10.1093/neuonc/nox141 | Advance Access date 2 August 2017

Pediatric low-grade gliomas: next biologically driven steps

David T. W. Jones,* Mark W. Kieran,* Eric Bouffet,* Sanda Alexandrescu, Pratiti Bandopadhayay, Miriam Bornhorst, David Ellison, Jason Fangusaro, Michael I. Fisher, Nicholas Foreman, Maryam Fouladi, Darren Hargrave, Cynthia Hawkins, Nada Jabado, Maura Massimino, Sabine Mueller, Giorgio Perilongo, Antoinette Y. N. Schouten van Meeteren, Uri Tabori, Katherine Warren, Angela J. Waanders, David Walker, William Weiss, Olaf Witt, Karen Wright, Yuan Zhu, Daniel C. Bowers,* Stefan M. Pfister,* and Roger J. Packer*

First Generation BRAFi pLGG

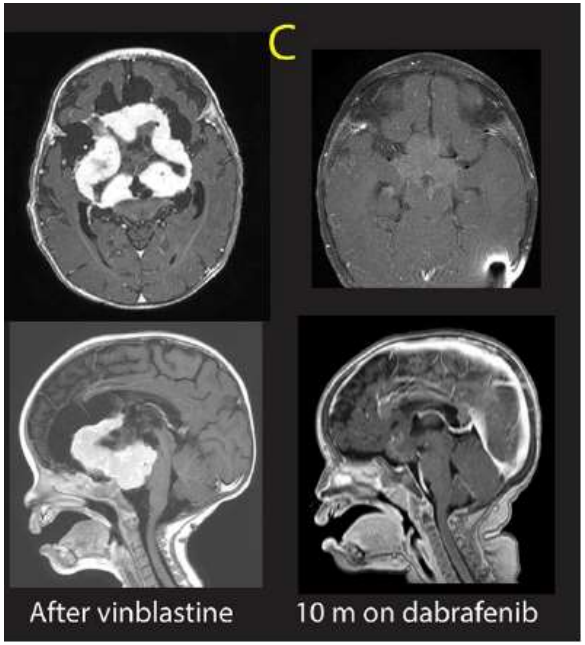
Pediatric Blood & Cancer

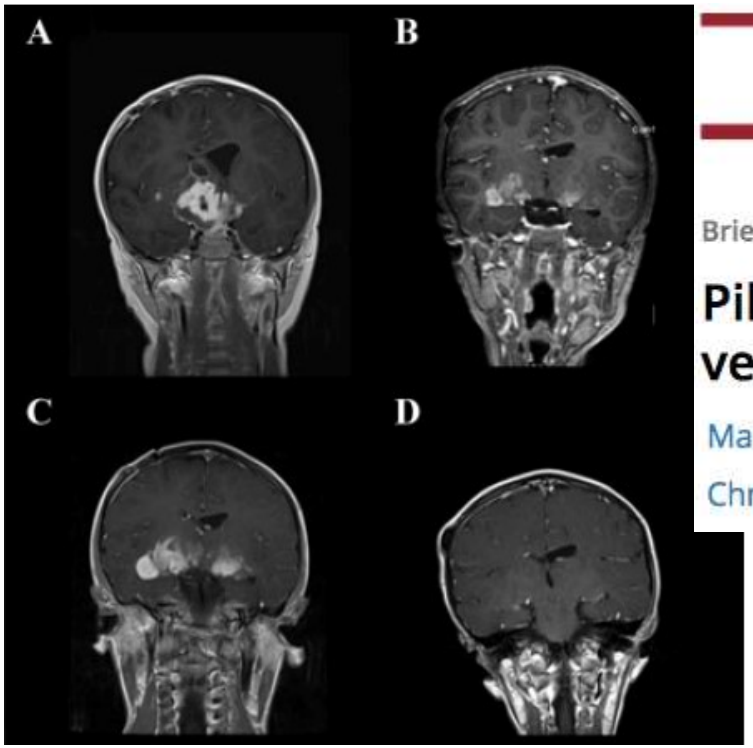
Explore this journal >

Brief Report

Profound clinical and radiological response to BRAF inhibition in a 2-month-old diencephalic child with hypothalamic/chiasmatic glioma

Alvaro Lassaletta, Ana Guerreiro Stucklin, Vijay Ramaswamy, Michal Zapotocky, Tara McKeown, Cynthia Hawkins, Eric Bouffet, Uri Tabori ✉





Pediatric Blood & Cancer

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Brief Report

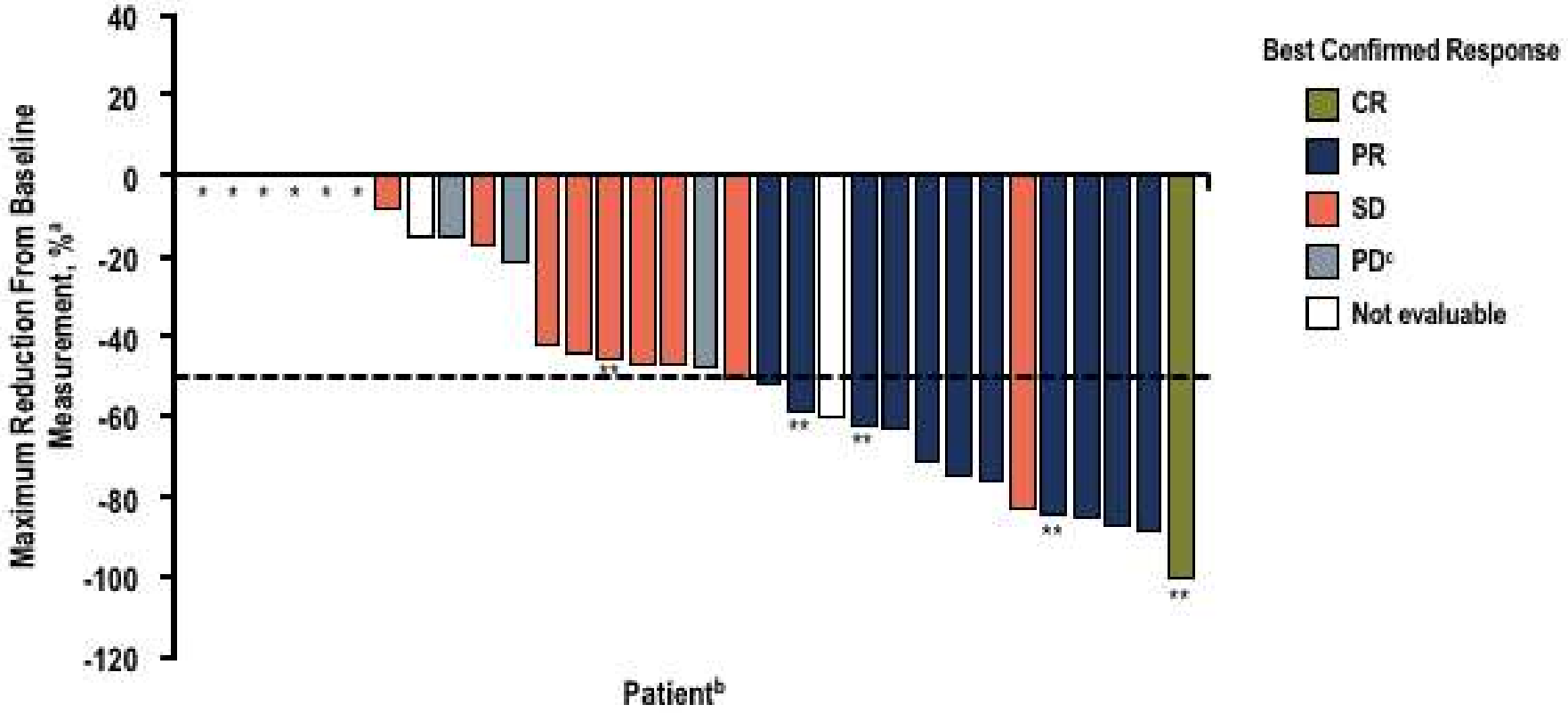
Pilomyxoid astrocytoma treated successfully with vemurafenib

Mary Skrypek MD ✉, Nicholas Foreman MD, Daniel Guillaume MD, Christopher Moertel MD

The first study of dabrafenib in pediatric patients with BRAF V600-mutant relapsed or refractory low-grade gliomas

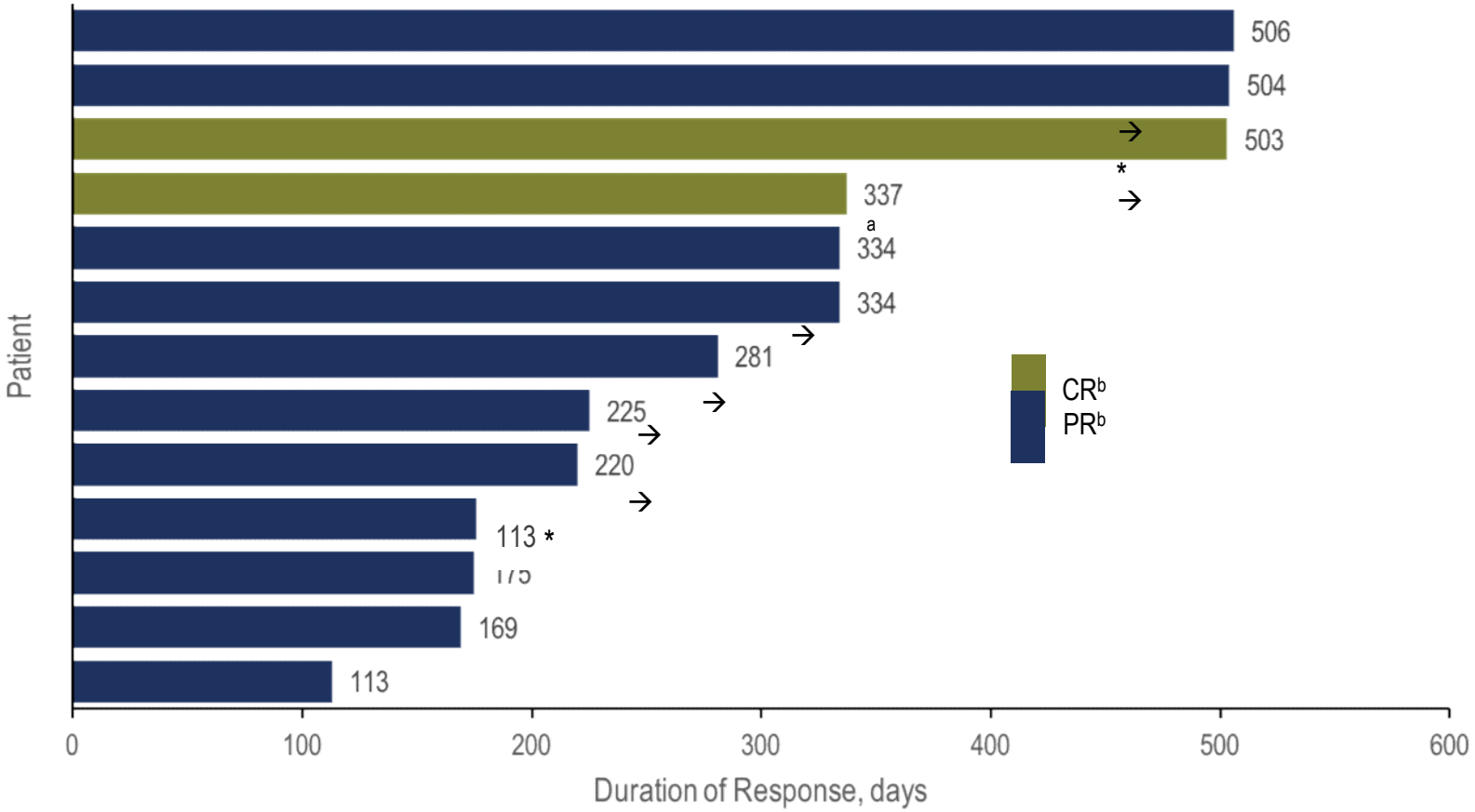
Mark Kieran, Eric Bouffet, Uri Tabori, Alberto Broniscer, Kenneth Cohen, Jordan R. Hansford, Birgit Geoerger, Pooja Hingorani, Ira Dunkel, Mark Russo, Lillian Tseng, Qing Liu, Noelia Nebot, Jim Whitlock, Darren Hargrave

Best response to dabrafenib (independent review)



* Missing patients (SD, n = 4; CR, n = 1 [patient recategorized as SD]; not evaluable, n = 1). ** Patients with no RP2D assigned dose. [a] Percentage change from baseline in sum of products will be of perpendicular diameter of target lesions. [b] Includes all patients with measurable disease and ≥ 1 post-baseline evaluation. [c] Plot shows maximum reduction on study (2 patients with PD previously had SD; 1 PD was due to a new lesion).

DURATION OF RESPONSE (INDEPENDENT REVIEW)



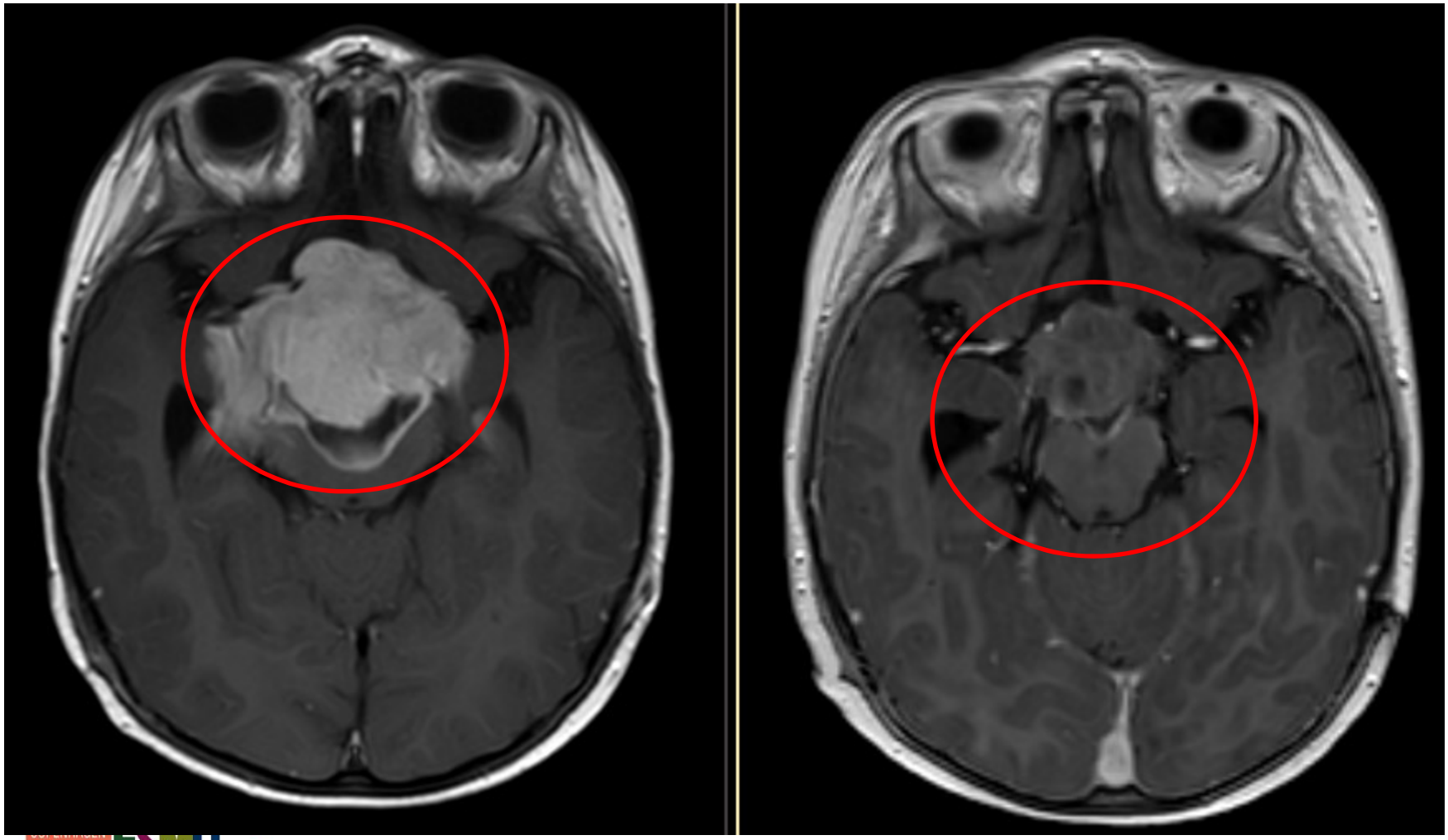
* Censored when discontinued study and patient in response at that time. → Response ongoing as of the data cutoff date (April 1, 2016).
[a] Patient initially assessed as CR and recategorized as SD. [b] Response categorization based on best overall response.

As of the data cutoff, median duration of response and median PFS have not been met

GOSH BRF 1

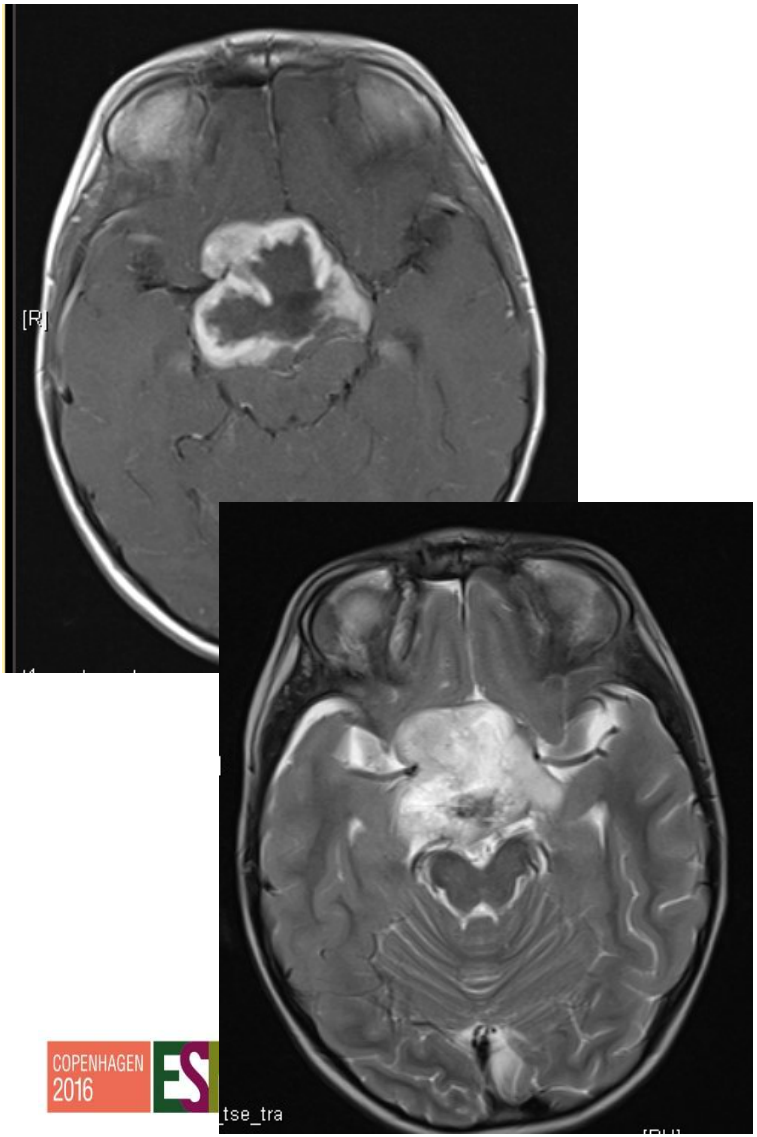
Pre Treatment

Following 10 months of treatment

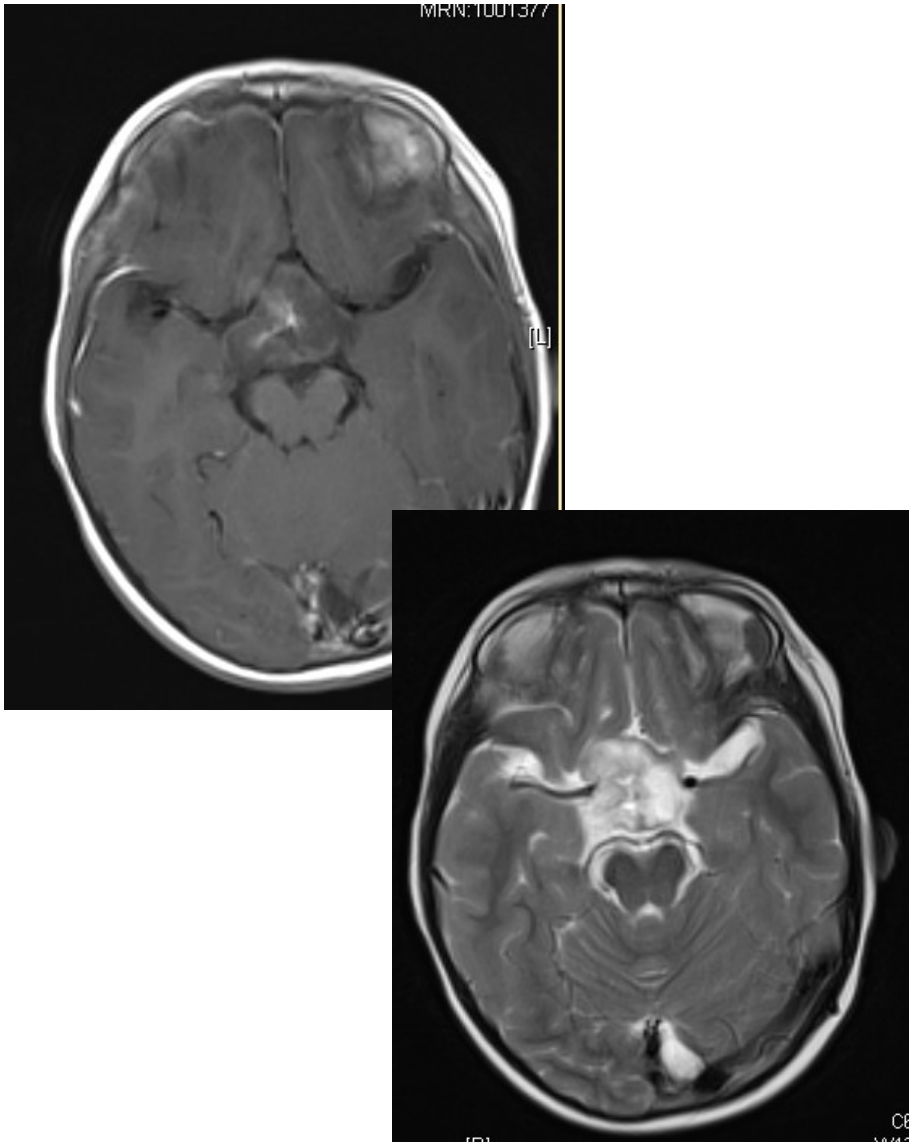


GOSH BRF6

Pre treatment



After 8 weeks of treatment

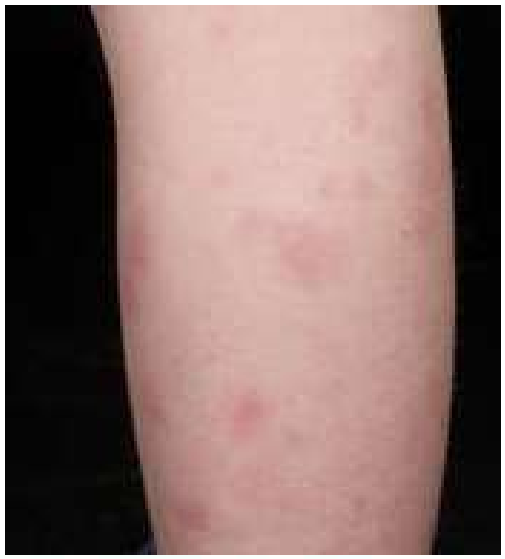


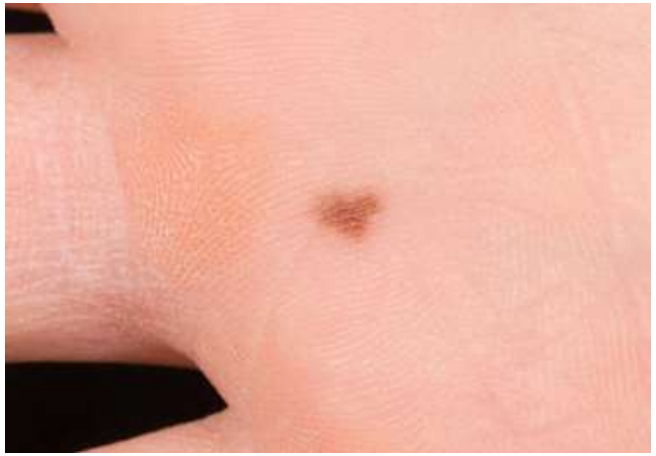
COPENHAGEN 2016

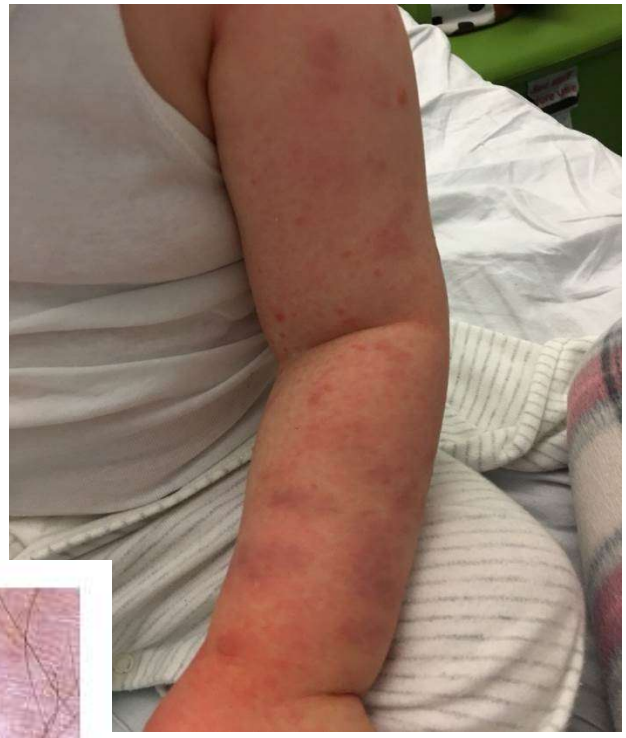
Adverse Events

- 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)

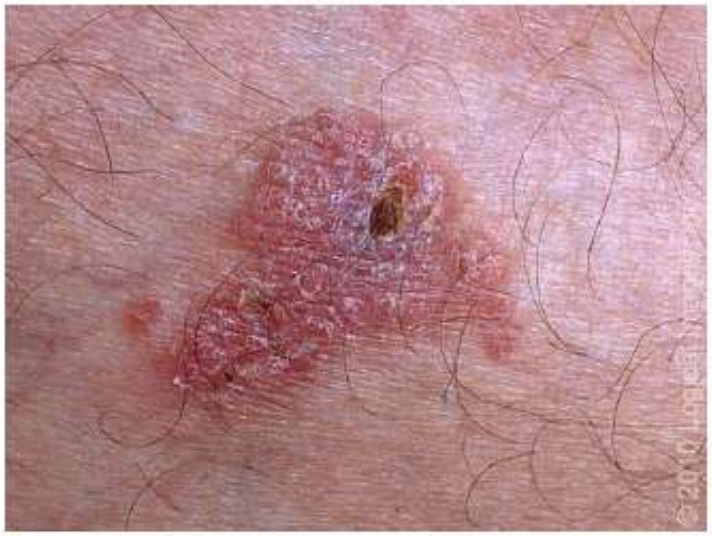
BRAFi: Toxicity







Keratoacanthoma induced by BRAFi



Squamous cell carcinoma induced by BRAFi

First Generation MEKi pLGG

ASCO 2017: Abstract #182373

A Phase II Prospective Study of Selumetinib in Children with Recurrent or Refractory Low-grade Glioma (LGG): A Pediatric Brain Tumor Consortium (PBTC) Study

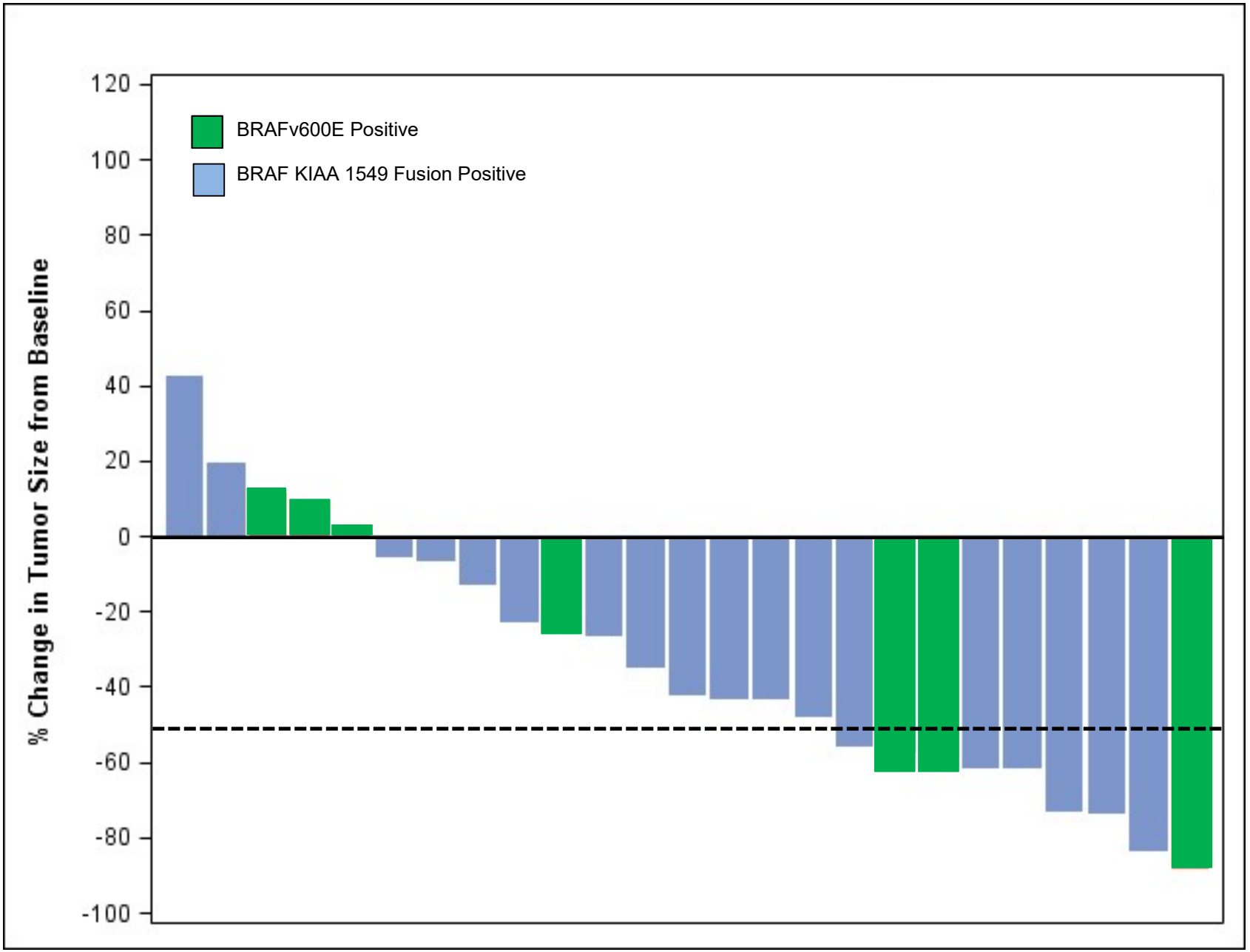
Jason Fangusaro, MD
Pediatric Brain Tumor Consortium (PBTC)
Ann & Robert H. Lurie Children's Hospital of Chicago
Associate Professor of Pediatrics
Northwestern University Feinberg School of Medicine

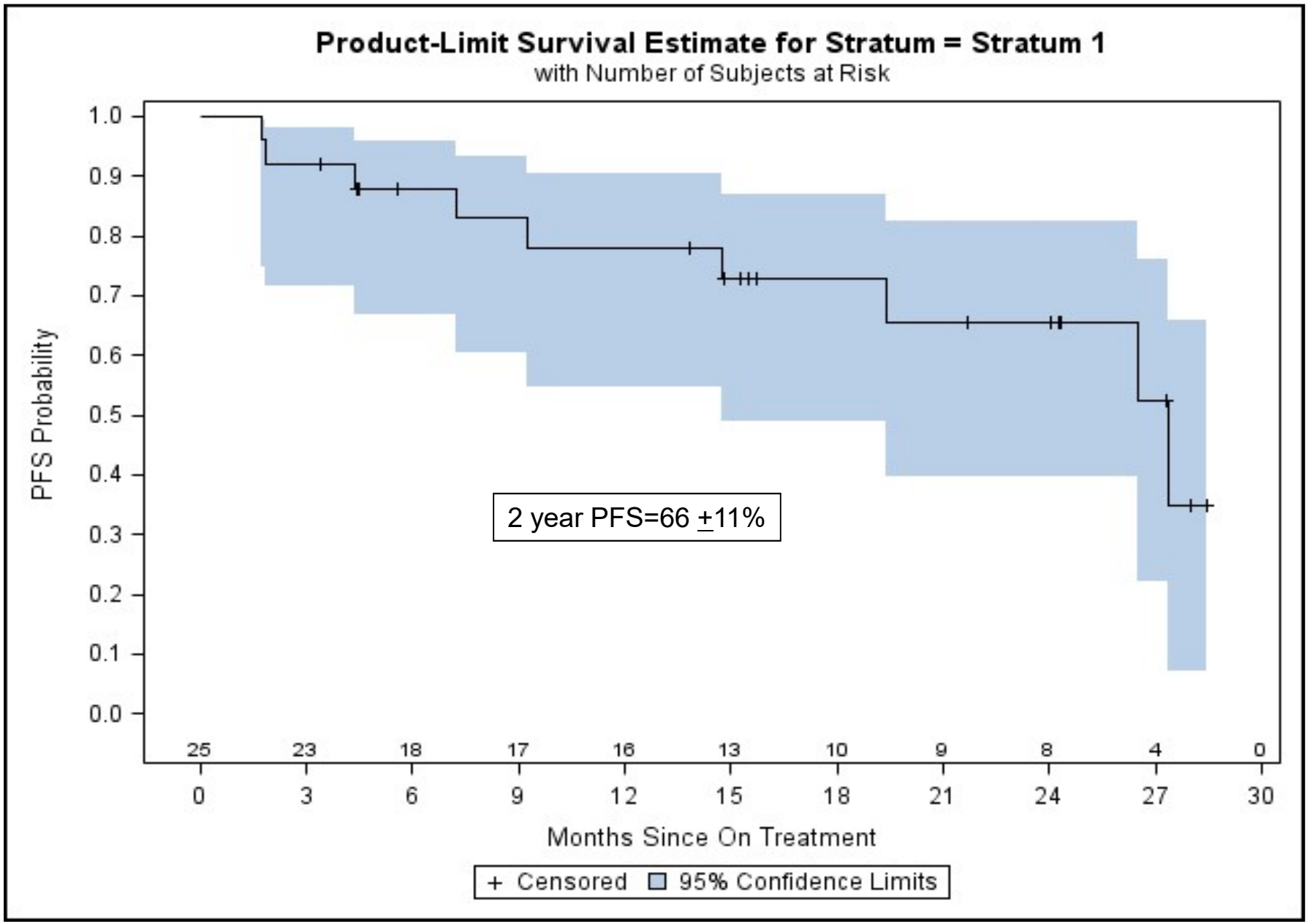
PBTC29 – Phase II study

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

Stratum 1: Recurrent/Refractory BRAF Aberrant Pilocytic Astrocytoma

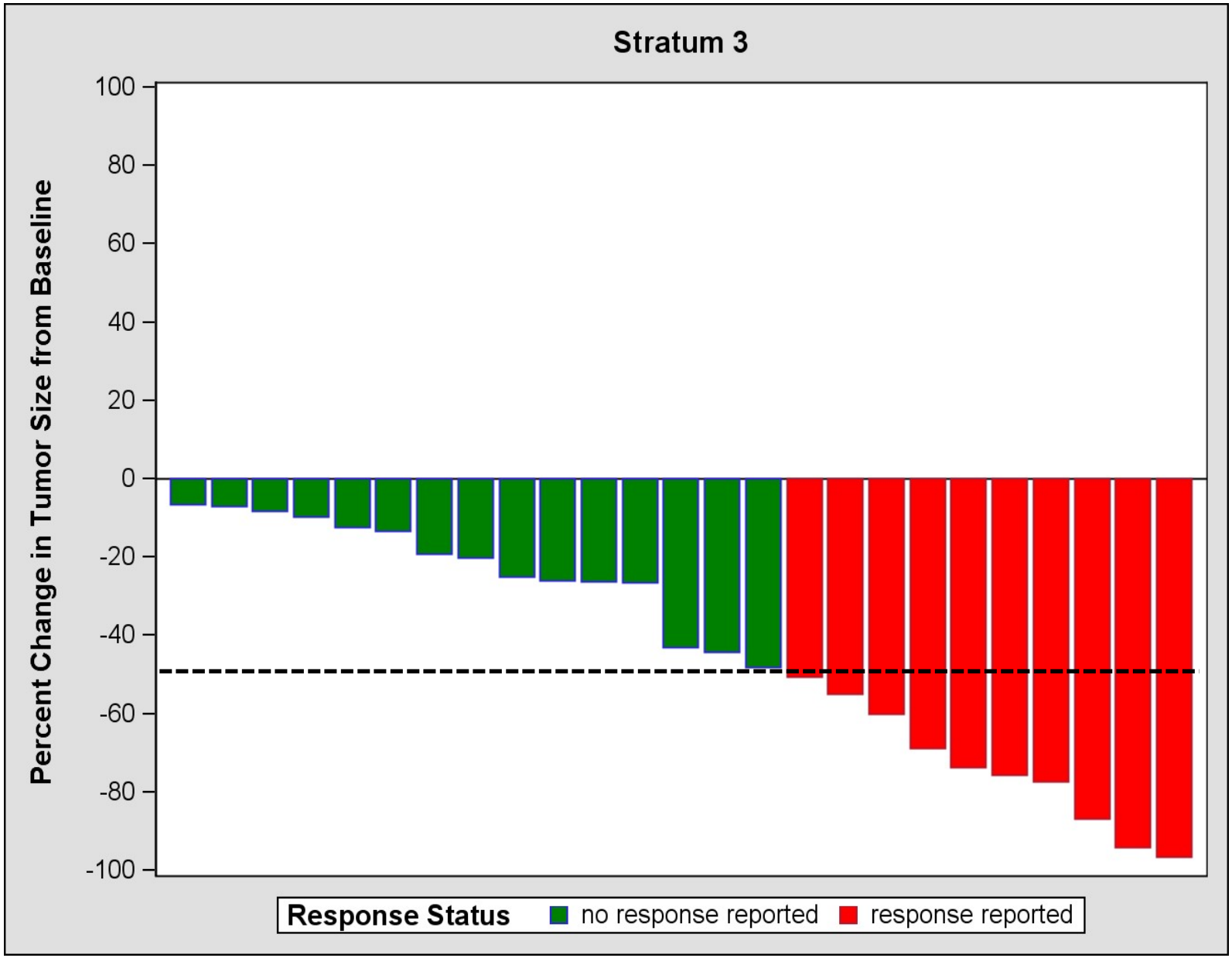
- N=25 eligible and evaluable.
  - Expansion beyond first 16 justified based on response and statistical design
  - 18 BRAF duplications and 7 BRAF V600e mutations
- Best response (regardless of timeframe):
  - 8 PR, 10 SD, 7 PD during treatment
  - Of the 8 PRs, 6 had BRAF duplication and 2 had BRAF V600e mutation
- 5 patients still on treatment.
- 5 patients progressed while off treatment and after completing all 26 courses.

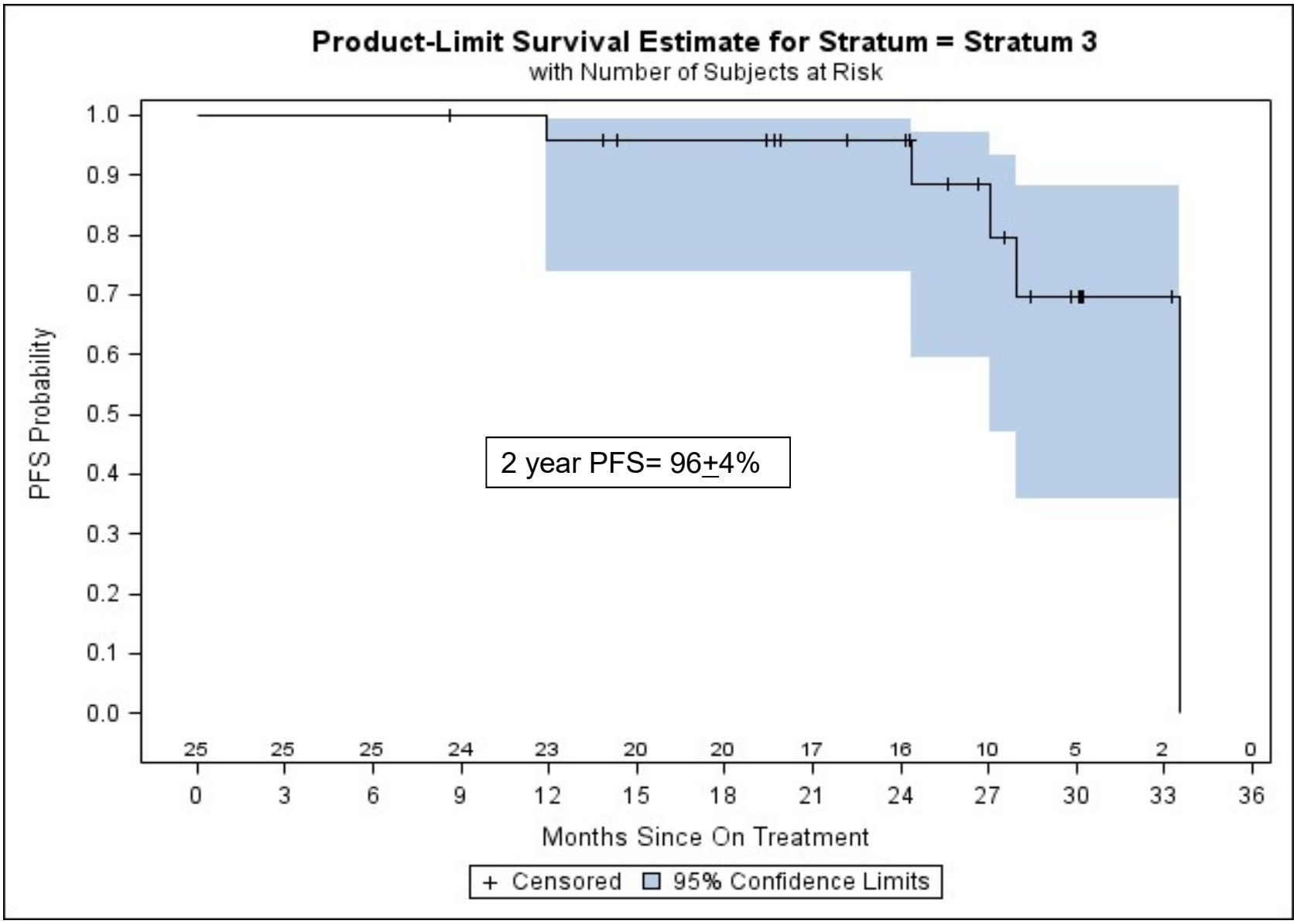

BRAFv600E Positive
BRAF KIAA 1549 Fusion Positive
% Change in Tumor Size from Baseline
120
100
80
60
40
20
0
-20
-40
-60
-80
-100


Product-Limit Survival Estimate for Stratum = Stratum 1
with Number of Subjects at Risk
PFS Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
2 year PFS=66 ±11%
25 23 18 17 16 13 10 9 8 4 0
0 3 6 9 12 15 18 21 24 27 30
Months Since On Treatment
+ Censored
95% Confidence Limits

Stratum 3: NF-1 associated Low Grade Glioma

- N=25 eligible and evaluable
  - Expansion beyond first 16 was justified on imaging based on statistical design
  - Only 3 with tissue and all negative for both BRAF alterations tested
- Best response (regardless of timeframe):
  - 10 PR, 14 SD, only 1 PD during treatment
  - 18 patients completed all 26 courses
  - 4 patients progressed while off treatment
    - 3 completed 26 course and 1 completed 24 courses (came off due to toxicity)
    - All patient completed therapy

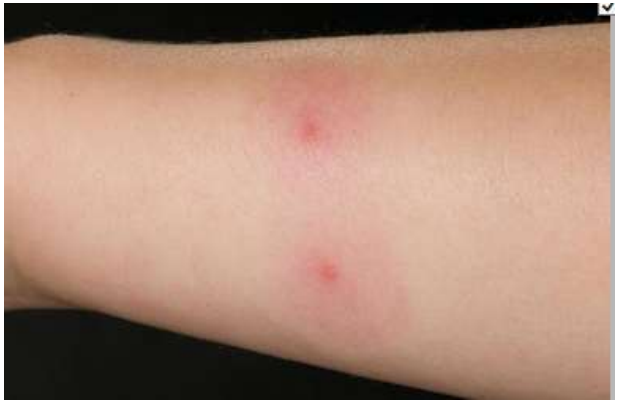

Stratum 3
Percent Change in Tumor Size from Baseline
100
80
60
40
20
0
-20
-40
-60
-80
-100
Response Status
no response reported
response reported

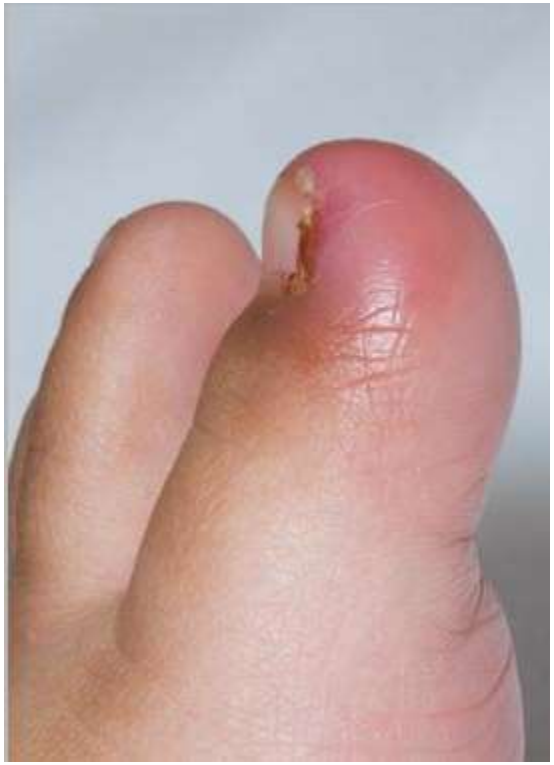

Product-Limit Survival Estimate for Stratum = Stratum 3
with Number of Subjects at Risk
PFS Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
2 year PFS= 96±4%
25 25 25 24 23 20 20 17 16 10 5 2 0
0 3 6 9 12 15 18 21 24 27 30 33 36
Months Since On Treatment
+ Censored
95% Confidence Limits

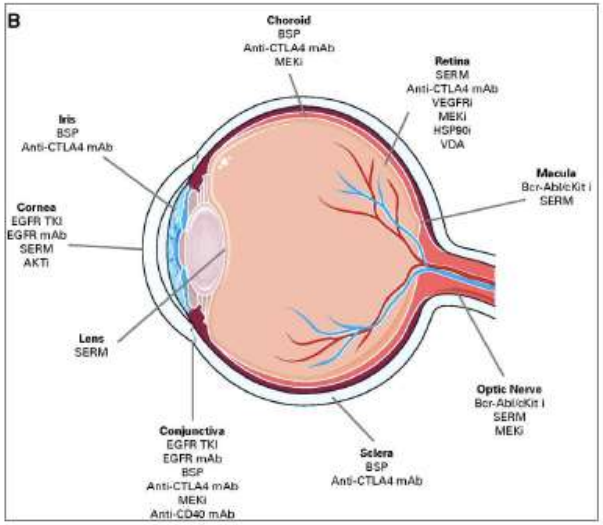
Toxicity

- Most common toxicities were Grade 1/2 CPK elevation, diarrhea, hypoalbuminemia, elevated AST and rash.
- Rare Grade 3/4 toxicities included aymptommatic elevated CPK, rash, neutropenia, emesis and paronychia.

MEKi: Toxicity







Serous retinopathy /
Retinal detachment

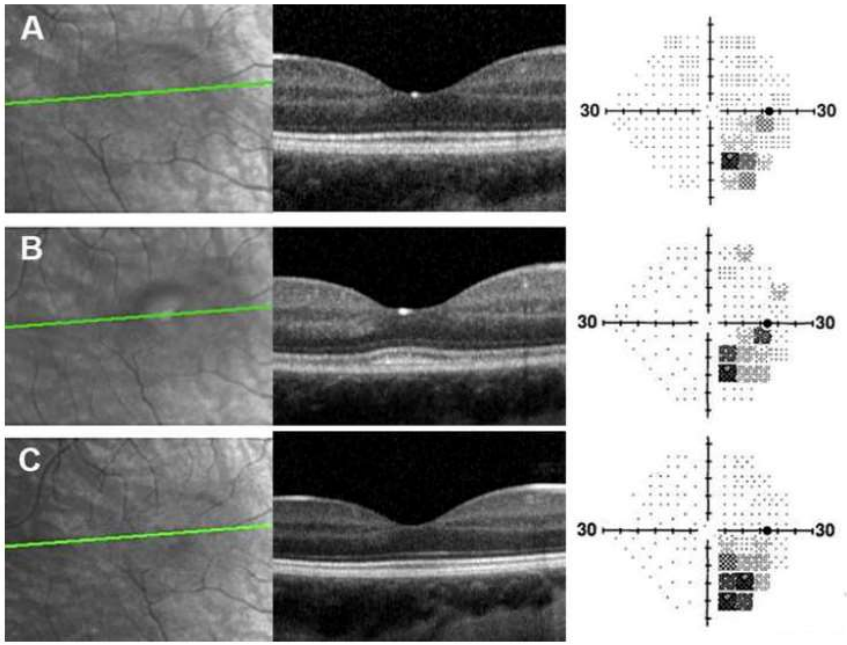
- **Cobimetinib** (GDC-0973)
- Trametinib
- Selumetinib (AZD6244)

Retinal vein occlusion

- PD0325901

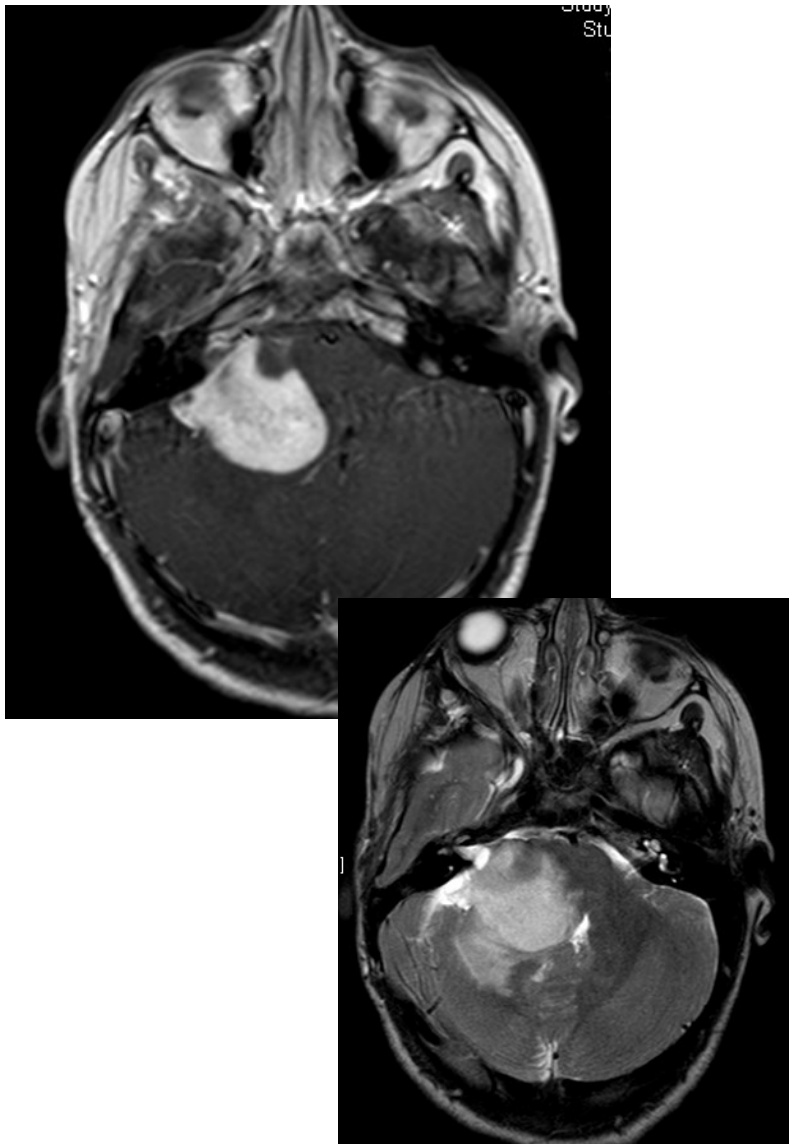
Subconjunctival hemorrhage

- Trametinib
- Selumetinib (AZD6244)

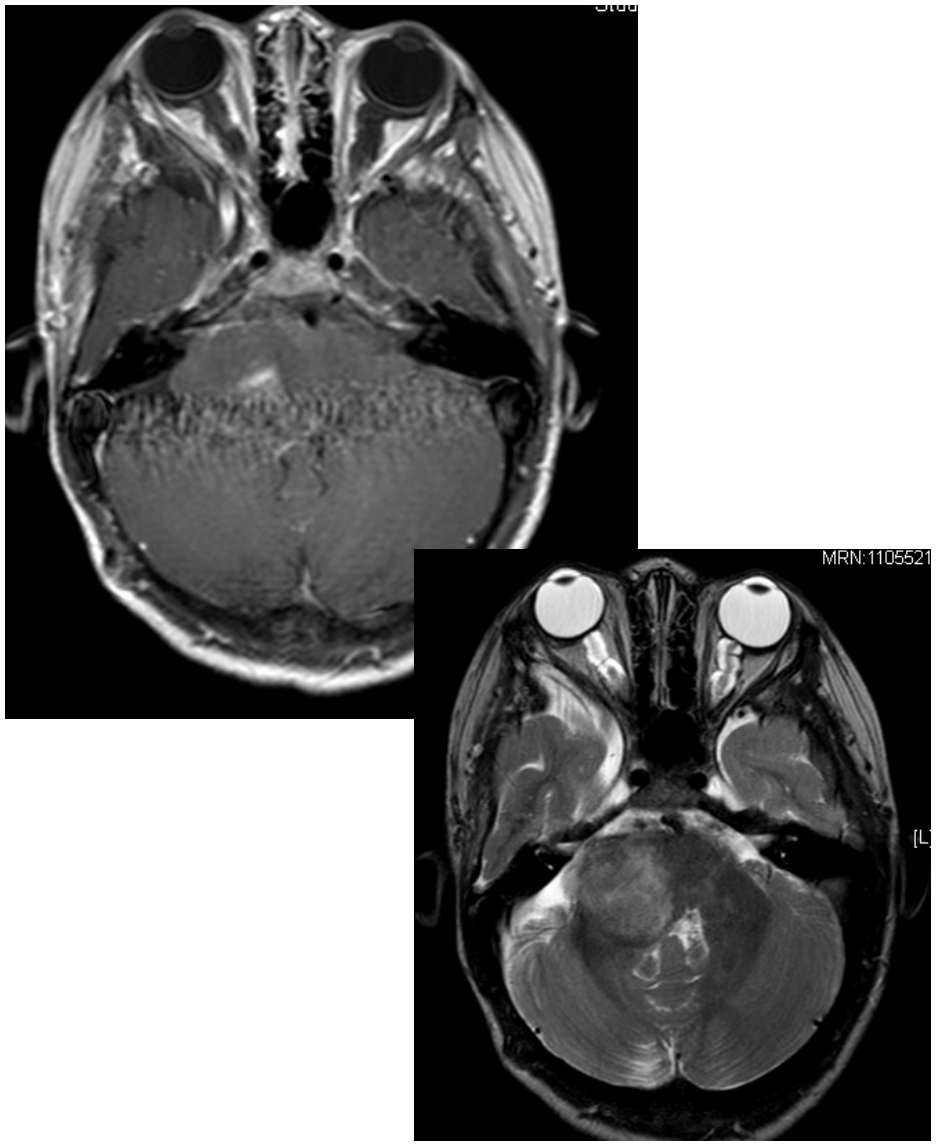


GOSH MEK 1

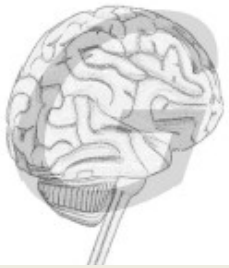
Pre treatment



After 6mnths of treatment



LO GIC



… because function & biology matters

EUROPE

LOw Grade Glioma In Children

Aims of the Trial

LO GIC
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

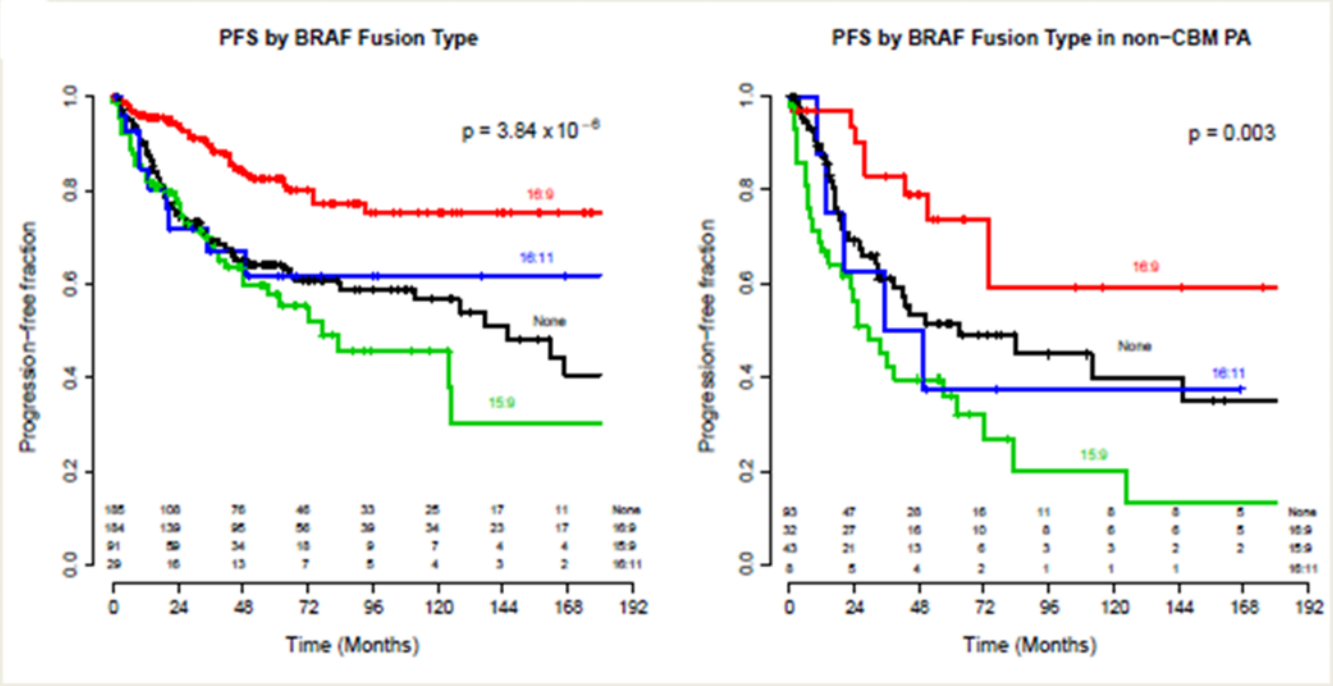
Why (biopsy) molecular biomarkers?

LO GIC
EUROPE

Meta-analysis SIOP LGG pre-clinical working group:

⇒ BRAF KIAA fusions type independent prognostics factor
(multivariate analysis: age, location, histology, extend of resection)

⇒ Stratify for relevant targeted therapies e.g. BRAF/ MEK inhibitors

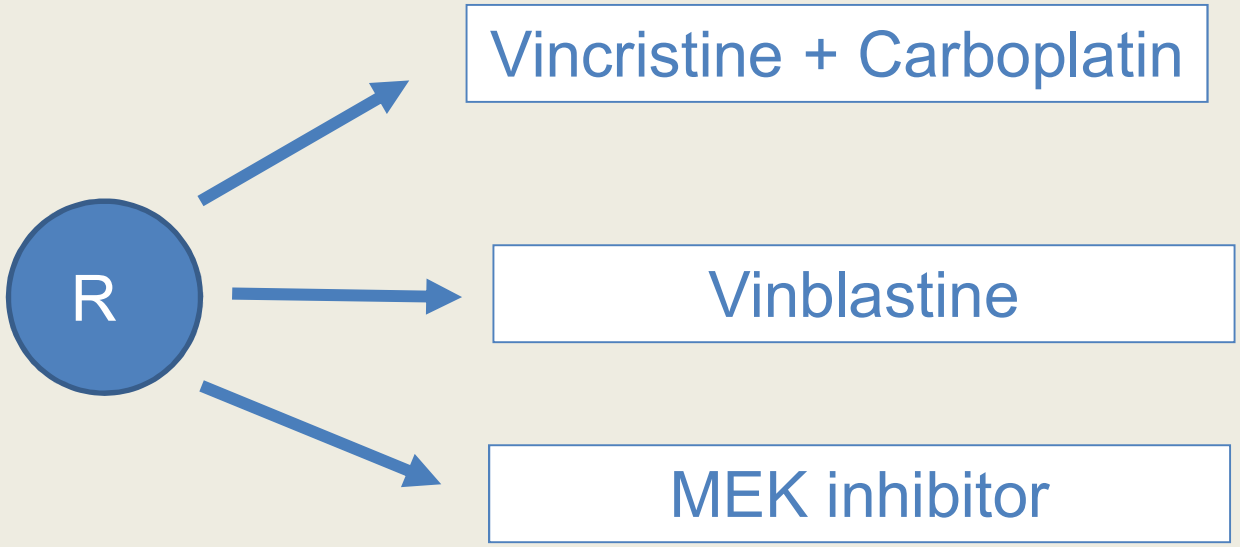


KIAA1549:BRAF breakpoint:
15_9
16_9
16_11
None

SIOP LGG Preclinical Working Group: Manuscript in preparation

Trial Design

LO GIC
EUROPE



Inclusion Criteria

LOGIC 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 

Thanks!

Childhood Tumours in Adults

pilocytic astrocytoma /optic nerve glioma

Dr Sarah Jefferies

ESTRO School

Outline

- Review management in children
- Evidence for recommended treatment of adults
- Present some clinical cases

PA in children

- Most common CNS tumour diagnosis – 5-14 years of age
- Sporadic – mainly cerebellar (NFI – optic pathways)
- Well defined tumours
- Lack of invasiveness
- Malignant transformation in <5%

Treatment in children

- Neurosurgical excision:
  - complete **10-year survival > 90%**
  - incomplete **10-year survival ~ 74%***

  *some residual tumours regress after surgery

- Recurrence
  - consider further surgical resection

Chemotherapy – in children

- Chemotherapy often first treatment if progression confirmed and no further surgery feasible
  - Carboplatin/vincristine
  - CCNU/vincristine/procarbazine combinations

Radiotherapy – in children

- Dose and fractionation: 54GY/30#
- Concerns around cognitive deficit and 2nd malignancy
- Minimize with protons?

Radiotherapy – in children

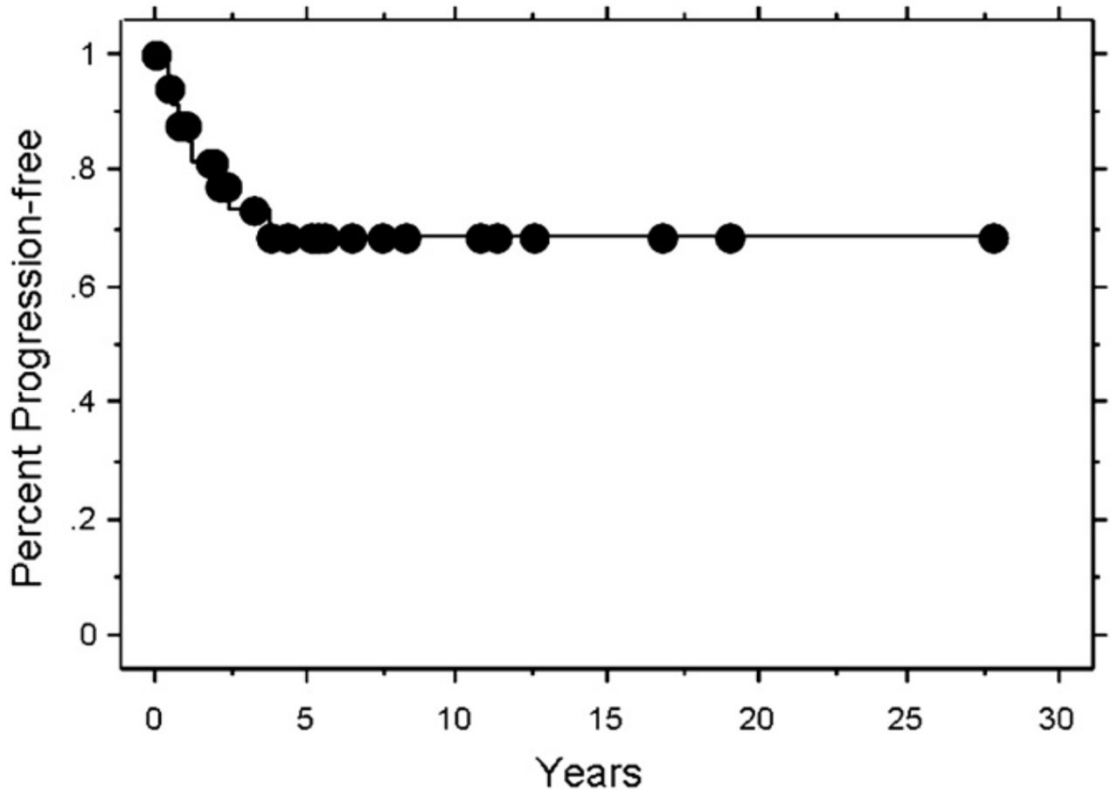
- Mansur et al.,
  - Retrospective review of PA who had received RT
- Median age at diagnosis 10 (3-18)
- Median age for RT 11 (4-25)

Table 1. Patient characteristics

	n
Total patients	35
Gender	
Male	19
Female	16
Race	
Caucasian	31
African-American	4
Central nervous system site	
Supratentorial	20
Optic pathway	3
Infratentorial	11
Spinal cord	1
Surgery extent	
Biopsy only	12
Subtotal	23
Radiotherapy timing	
Immediate	16
Delayed (after progression after observation, or chemotherapy)	19
Radiotherapy modality	
External beam only	29
Radiosurgery only	5
External beam and radiosurgery	1

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 3, pp. 829–834, 2011

Radiotherapy – in children



Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 3, pp. 829–834, 2011

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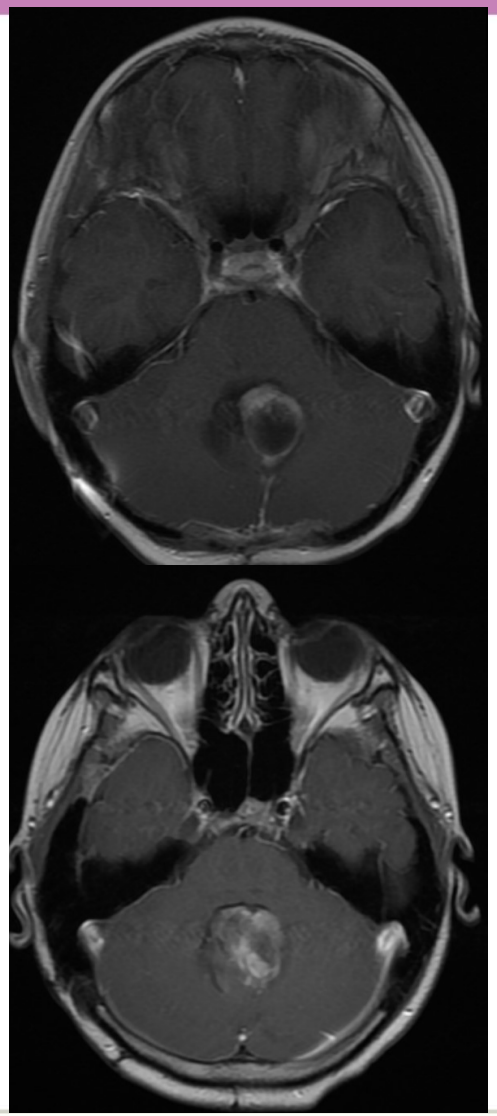
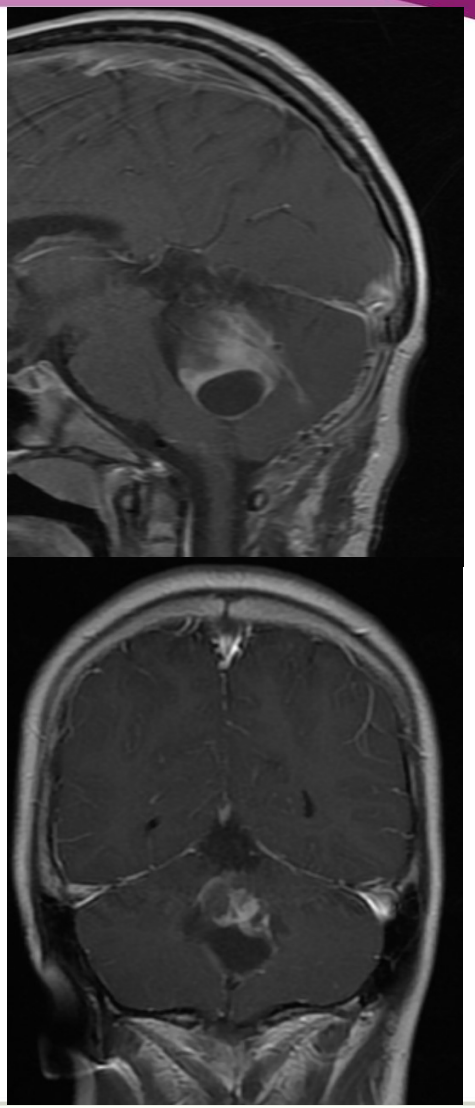
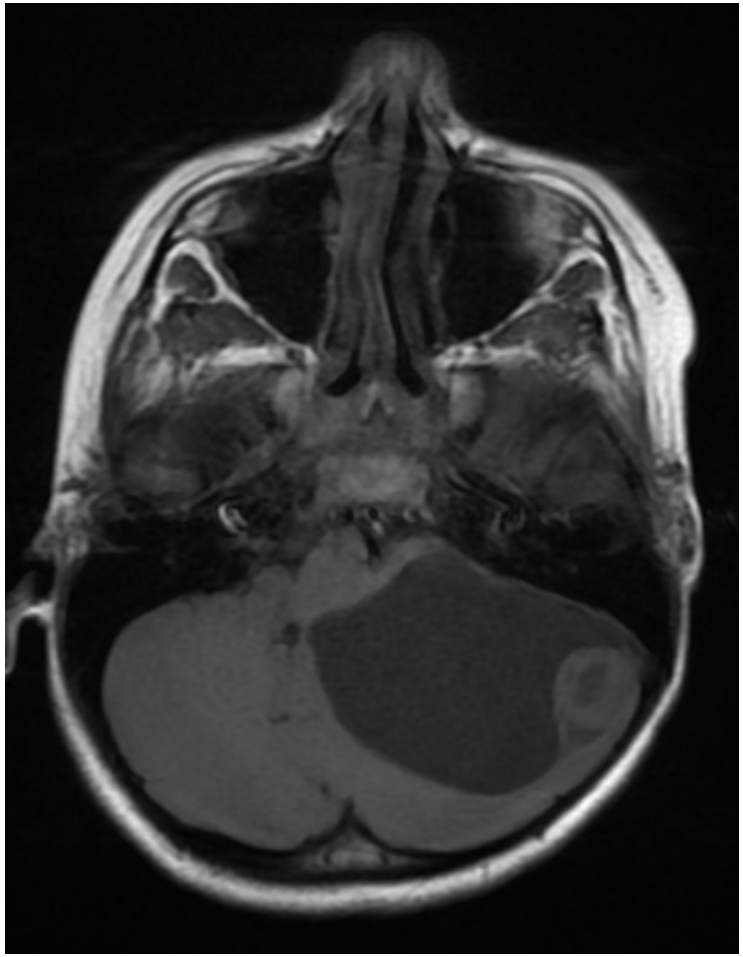
PA in childhood

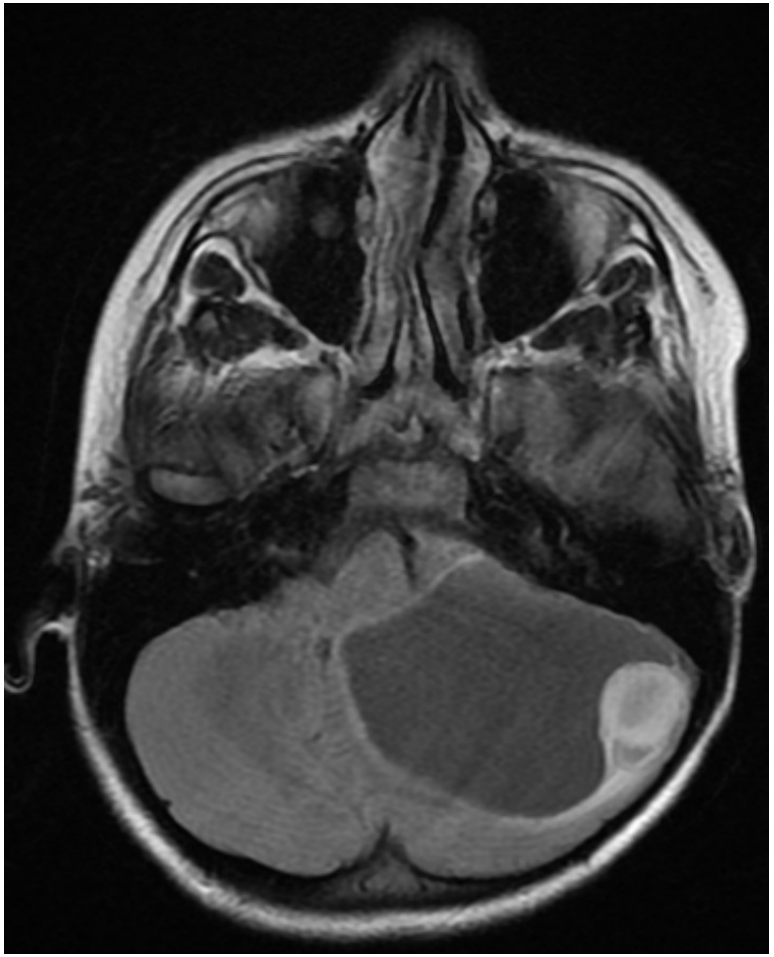


Classical appearance of PA in an 8 year old



PA in childhood





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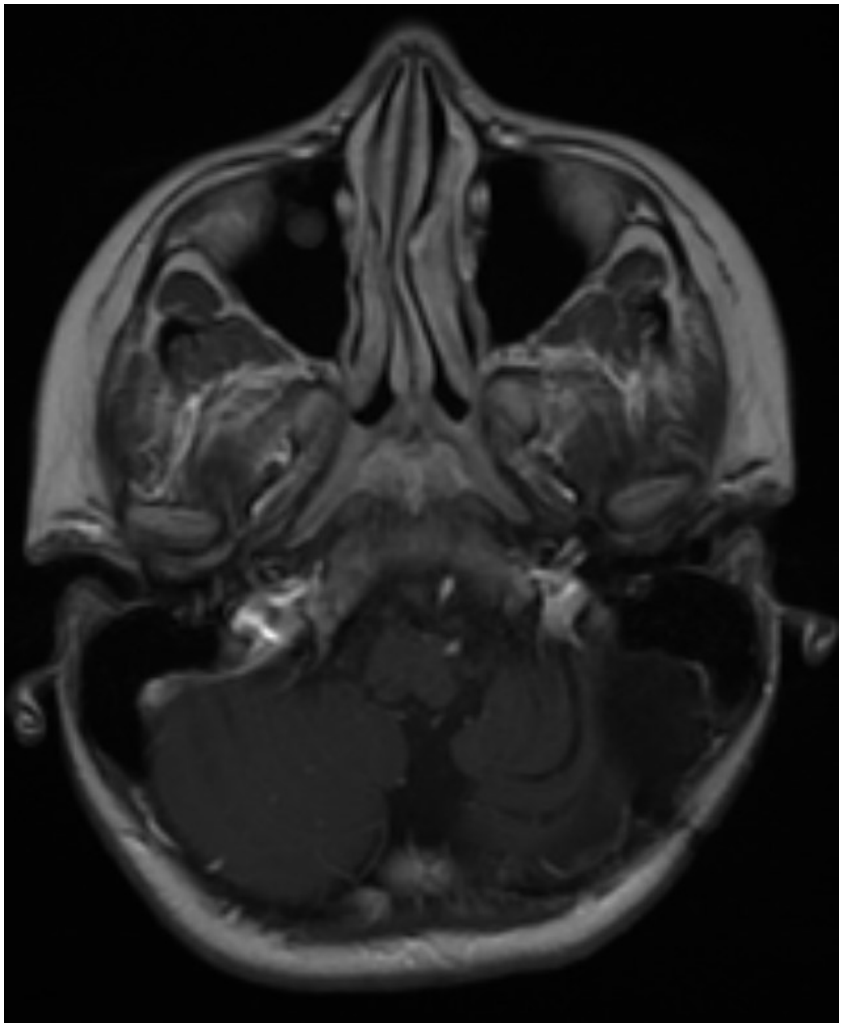
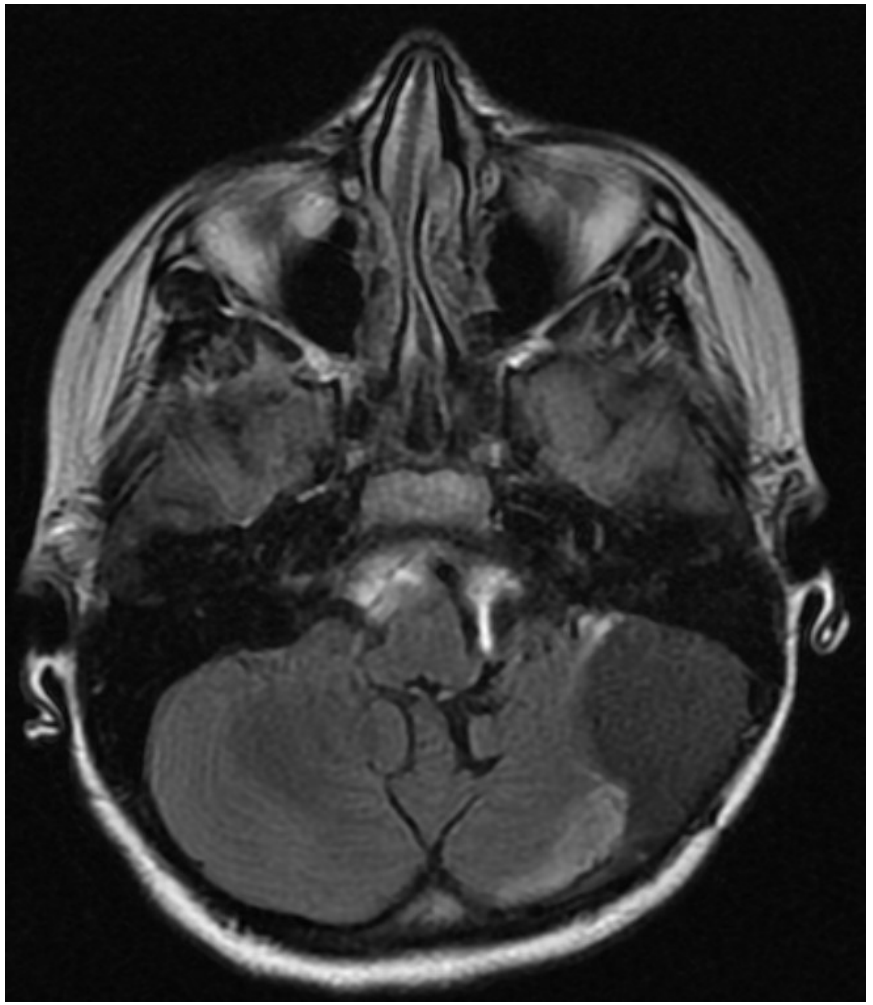
PA in childhood





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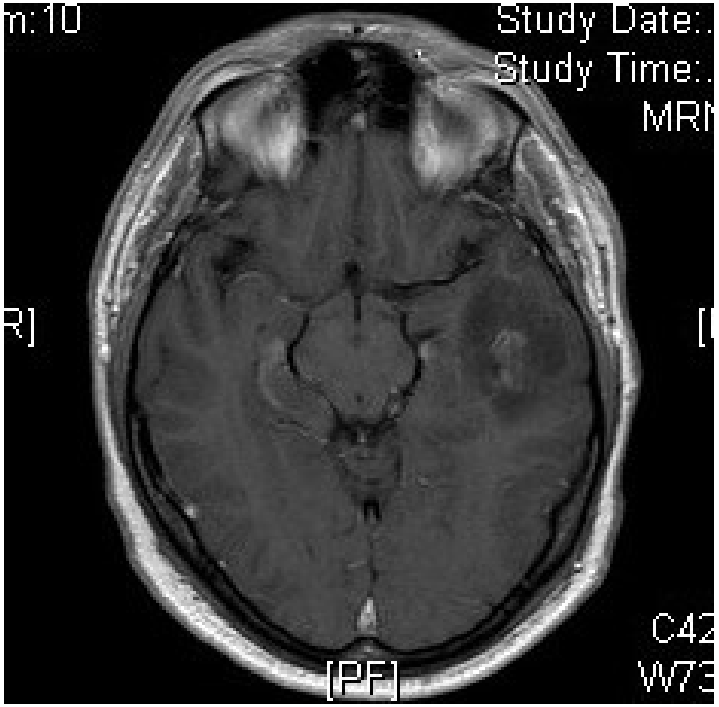
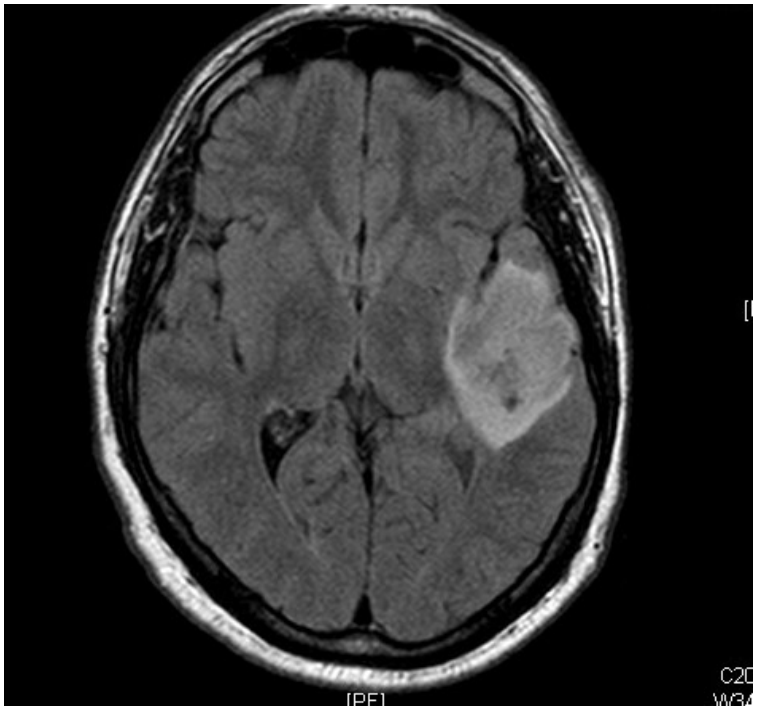
PA in Adults

- Presentation
  - Recurrence after treatment as a child
  - De novo PA in an adult

  - Important to be confident of the diagnosis

2008





Referred urgently as a GBM for ChemoRT after biopsy

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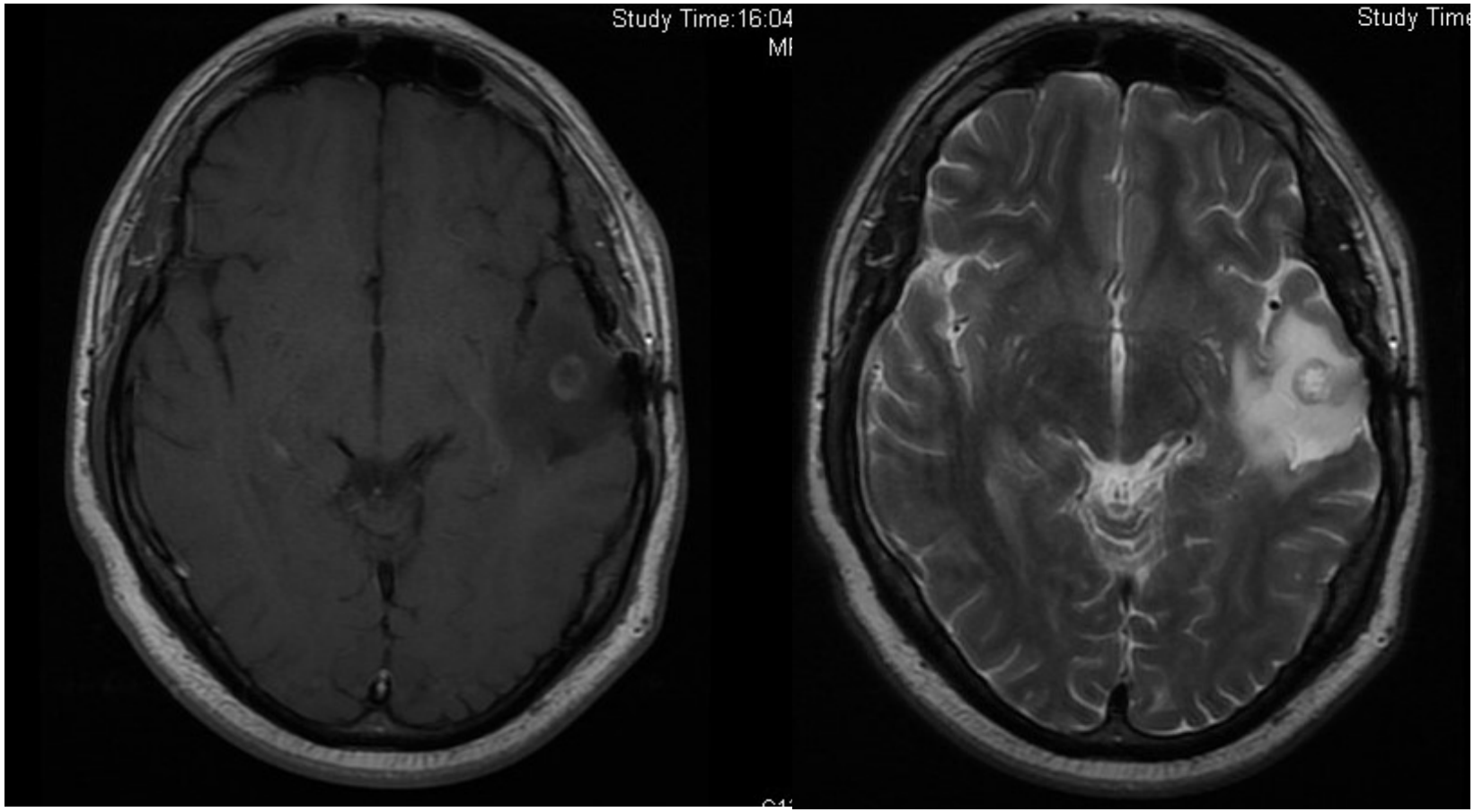
PA in adults

- 15/08/08 – underwent surgical resection
- Genome-wide copy number analysis
  - does not show the pattern of a highly malignant astrocytoma
  - does not show the common pattern of a pilocytic astrocytoma either

  - **Probable Pilocytic Astrocytoma WHO grade I**

2010



Increasing seizure frequency

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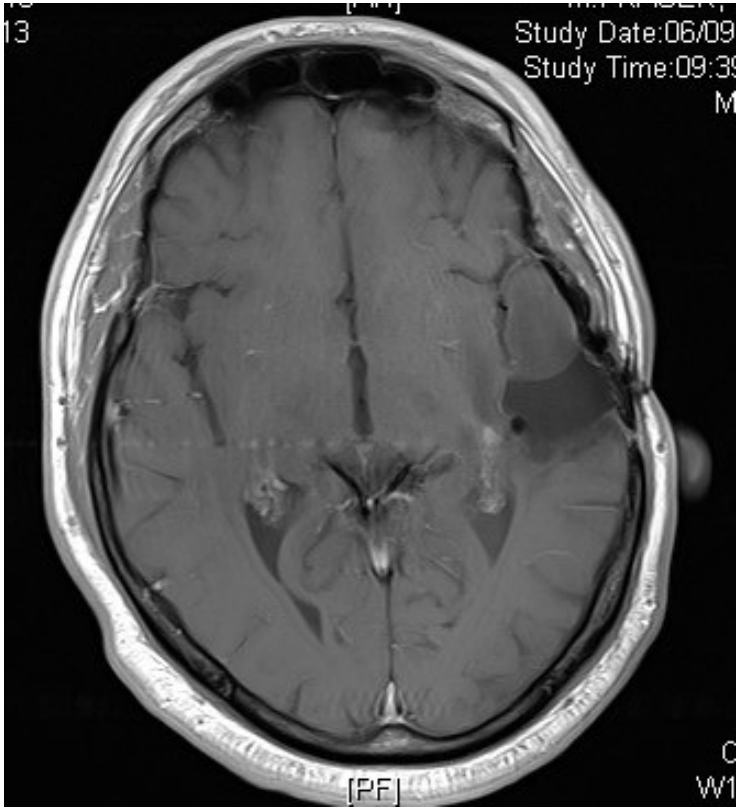
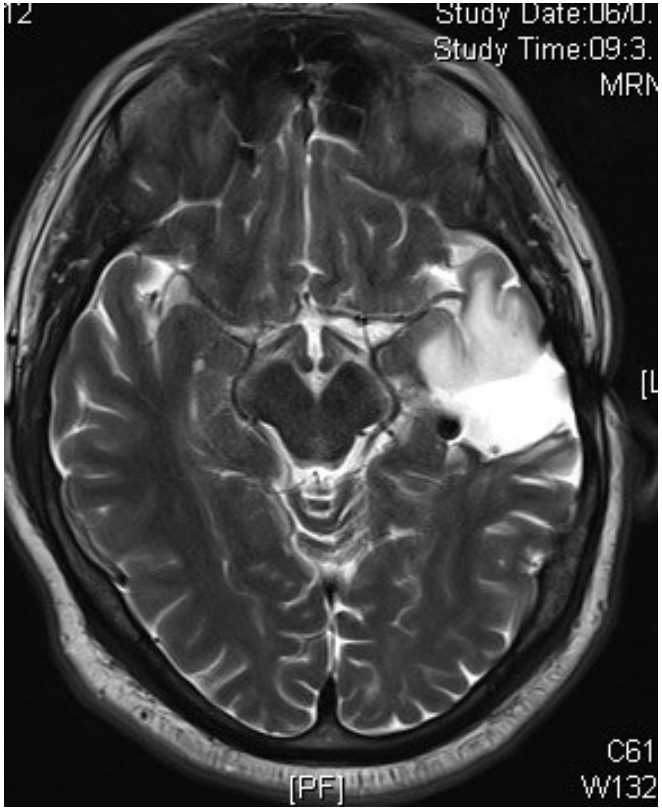
2010

- 12/02/10 – further neurosurgical resection
- Histopathology
  - Slight increase in Mib – still features of grade I pilocytic astrocytoma
- Offered post-operative radiotherapy
  - 54Gy/30#
  - Conformal technique

2017





Clinically well BRAF V600E negative, BRAF fusion negative

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Adult pilocytic astrocytomas: clinical features and molecular analysis FREE

Brett J. Theeler ✉ ✉, Benjamin Ellezam, Zsila S. Sadighi, Vidya Mehta, M. Diep Tran, Adekunle M. Adesina, Janet M. Bruner, Vinay K. Puduvalli

Clinical characteristics of adults with pilocytic astrocytomas

Total	127
Males (%)	54 (43)
Females (%)	73 (57)
Median age (years)	29
Age 18–39, *n* (%)	95 (75)
Age 40–59, *n* (%)	29 (23)
Age 60 and over *n* (%)	3 (2)
Median follow-up	61 months
Cerebrum/lobar, *n* (%)	29 (23)
Brainstem, *n* (%)	30 (24)
Optic pathway/hypothalamus, *n* (%)	21 (17)
Ventricular, *n* (%)	17 (13)
Cerebellum, *n* (%)	17 (13)
Spinal cord, *n* (%)	13 (10)

Neuro-Oncology, Volume 16, Issue 6, 1 June 2014, Pages 841–847,

ESTRO School

Adult PA

	Stable Disease	Progression	Median PFS (mo)
Overall, *n* (%)	74 (58)	53 (42)	>178.8
Biopsy, *n* (%)	16 (64)	9 (46)	>190.0
Subtotal resection, *n* (%)	32 (52)	29 (48)	>79.0*
Gross total resection, *n* (%)	26 (63)	15 (37)	>178.8
Adjuvant radiotherapy, *n* (%)	16 (39)	22 (61)	37.5
No adjuvant radiotherapy, *n* (%)	57 (70)	25 (30)	>105.5**

Neuro-Oncology, Volume 16, Issue 6, 1 June 2014, Pages 841–847,

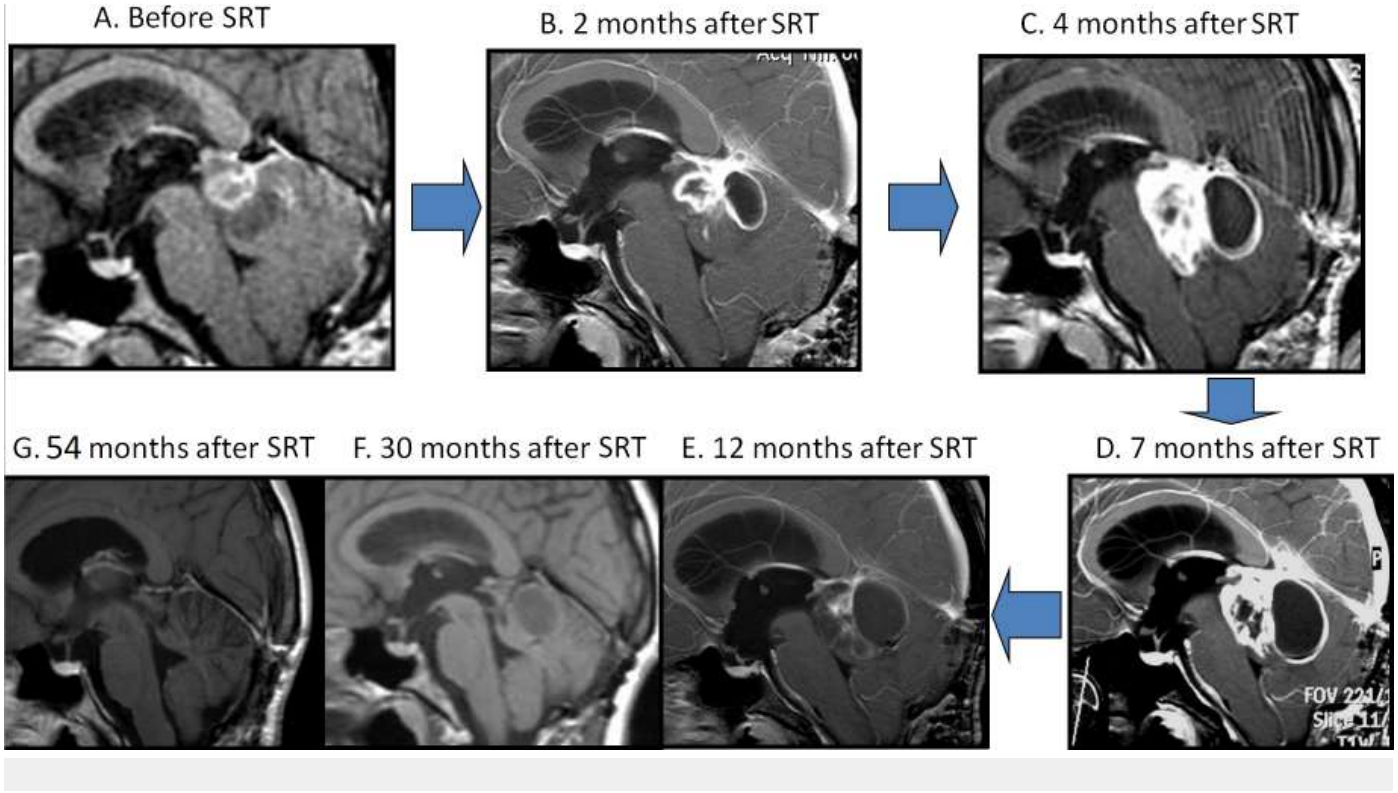
Clinical characteristics of patients treated with surgical resection plus or minus adjuvant radiotherapy

	Resection Alone	Resection Plus Adj RT	*P* value
Total, *n*	68	28	–
Males/Females, *n*	29/39	10/18	NS
Median age (years)	29	29	–
Age 18–39, *n* (%)	52 (76)	21 (75)	–
Age 40–59, *n* (%)	16 (24)	6 (21)	–
Age 60 and over, *n* (%)	0	1 (4)	–
Median KPS	90	90	–
Discordant pathology *n* (%)	10 (15)	14 (50)	*P* < .001
B–K fusion positive, *n* (% tested in sub-group)	4 (17)	5 (42)	NS*

Adult PA

- Largest retrospective series of adult PA
- Confirms:
  - Very rare > 60
  - Importance of neuropathology review
  - BRAF mutation and fusion – rare
  - Observation after surgery feasible especially if GTR

Pseudoprogression



20 year old, 54Gy/30# SRT (5mm CTV/2mm PTV)

Trunin Y, Golanov A V., Kostjuchenko V V, et al. (February 21, 2017) Pilocytic Astrocytoma Enlargement Following Irradiation: Relapse or Pseudoprogression?. Cureus 9(2): e1045. DOI 10.7759/cureus.1045

ESTRO School

ESTRO School

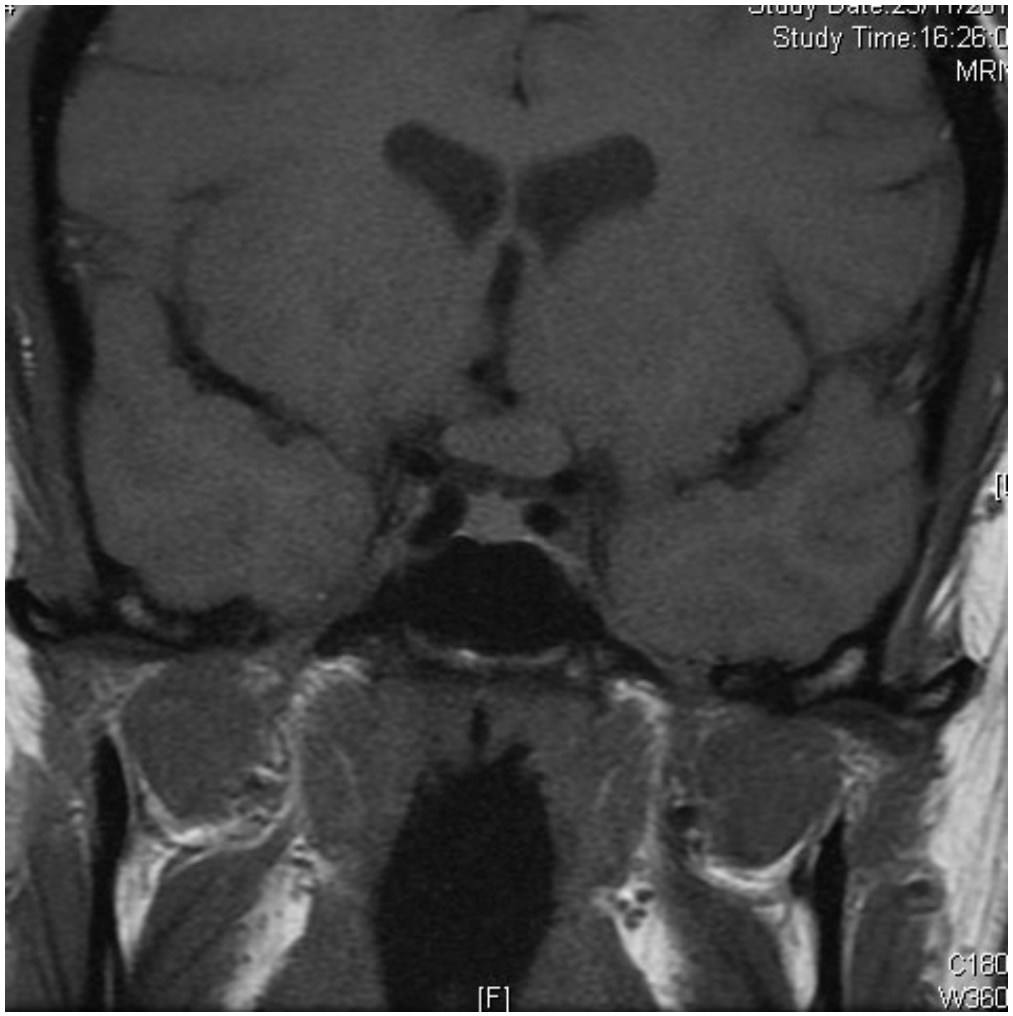
Optic Nerve Glioma

- Rare tumours
- Most commonly associated with NF2

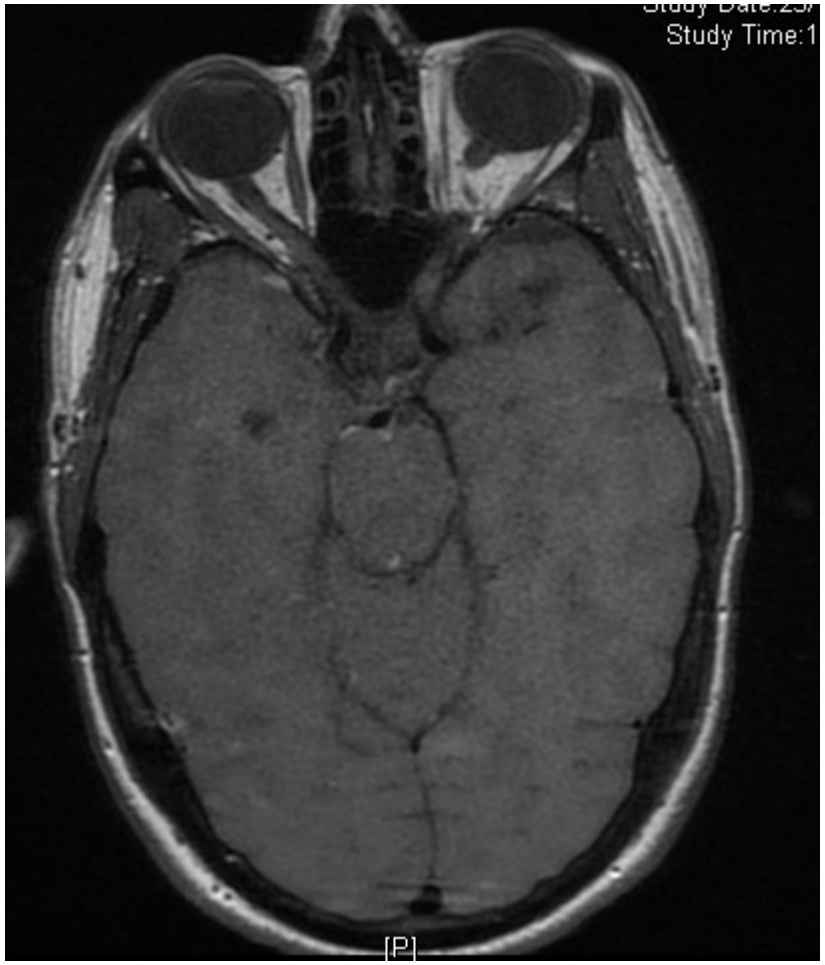
Optic nerve glioma

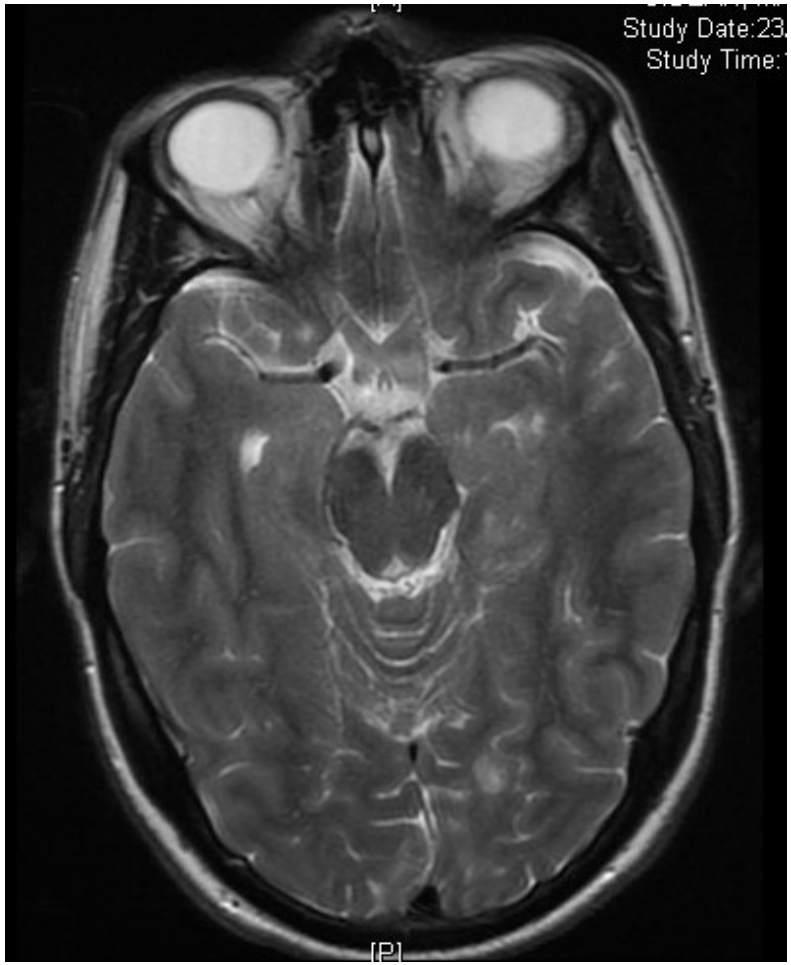
- Clinical and radiological diagnosis

- 26 year old male
  - Initially thought to have optic neuropathy
  - Managed by neurologists
  - Had oligoclonal bands in CSF
  - MRI - diagnosis


Study Time:16:26:0
[F]

Optic nerve glioma





Optic nerve glioma

- Treated with 54Gy/30# IMRT/IGRT
- Vision has stabilised
- Had some new neurological symptoms and MRI confirmed new T2 high signal changes in keeping with demyelination

Management of Adult ON Glioma

- Consider biopsy/surgery if feasible
- Always balanced with potential loss of function
- Consider if patient has neurofibromatosis

Role of Radiotherapy

- No randomised data
- Number of series – small over several decades

Retrospective Series

Patient number	Follow-up (yr)	Dose (Gy)	Progression-free survival 10 yr (%)	Overall survival 10 yr (%)	Visual Improvement (%)	Endocrine Dysfunction (%)
57	7.5	51.7	80	83.5	55	37
29	10	54	100	89	81	72
30	10	45-50	90	93	43	33
38		50	73	79	13	nr
24	6	54	88	100	30	73
43	>5	35-60	79	56	49.5	11
24	9.4	48	55	87	35	8
10	5	52.4	90	100	30	1
28	10	50	62	75	15	52
15	8	52.2	72	90	40	7
25	9	45-60	69	94	36	48

J Nucl Med Radiat Ther 3:134 2012

Radiotherapy

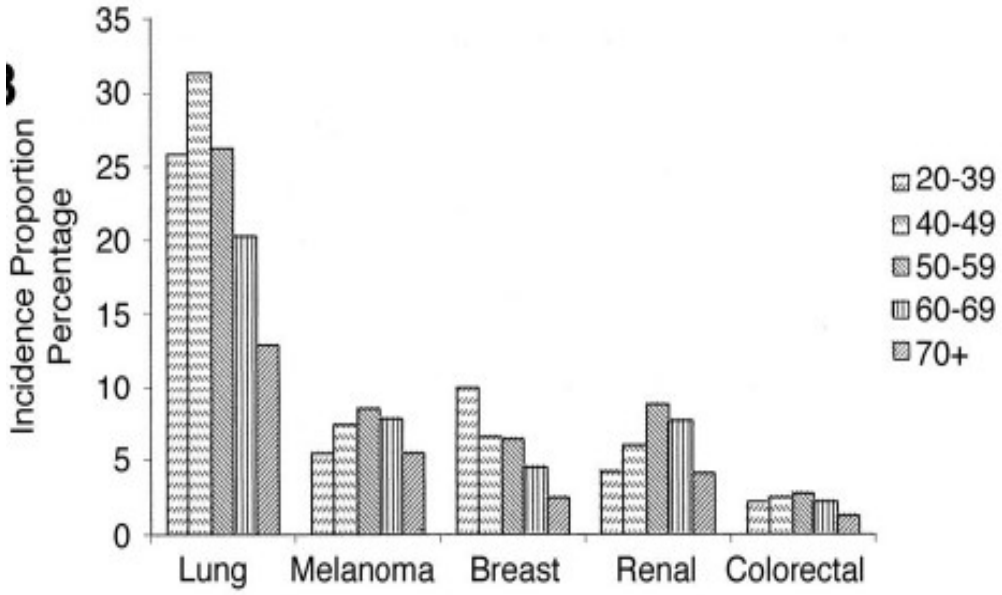
- 54Gy/30#
- Use RT technique to minimise normal tissue toxicity
- Posterior ON pathway lesions – tend to do less well

Impact of molecular understanding of brain metastases on clinical practice

Assoc. Prof. Dr. Matthias Preusser
Department of Medicine I
Comprehensive Cancer Center Vienna
Medical University of Vienna

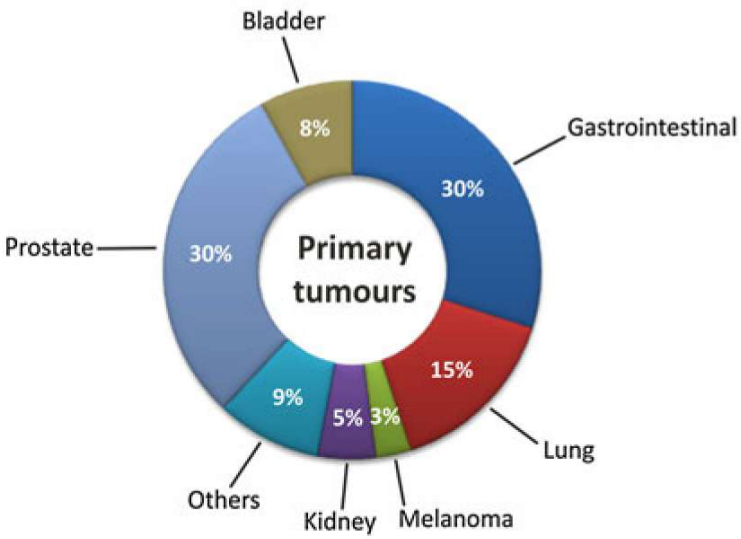
Incidence of brain metastases

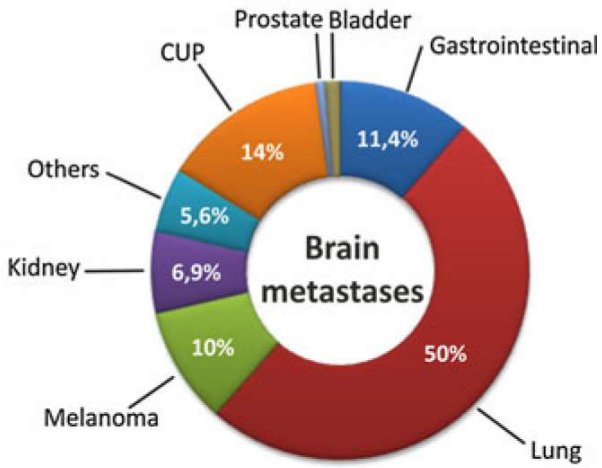
- Occur in 10-30% of all adult cancers
- Approx. 10 times more frequent than primary brain tumors
- Relative incidence increasing, due to
  - Effective systemic treatments → with longer survival
  - Improved imaging techniques and their increased availability
- Approx. half of all brain mets due to NSCLC, others:
  - Breast cancer
  - Melanoma
  - Unknown primary
  - Renal cell carcinoma



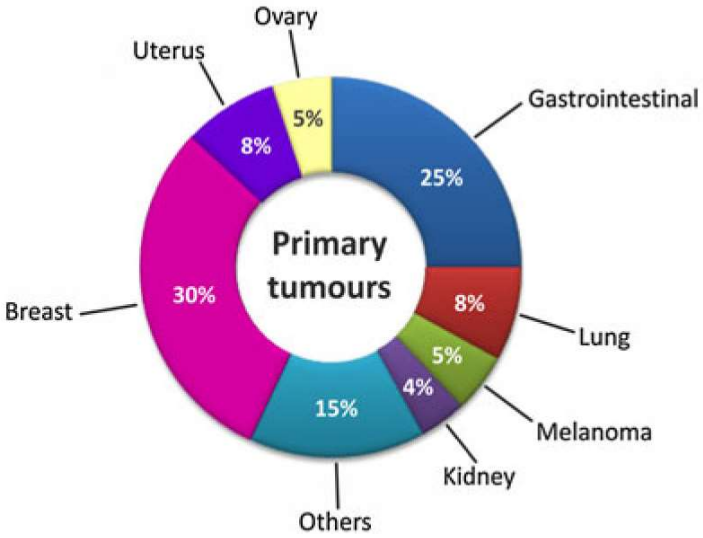
Barnholtz-Sloan… Sawaya RE.
J Clin Oncol 22:2865-72, 2004

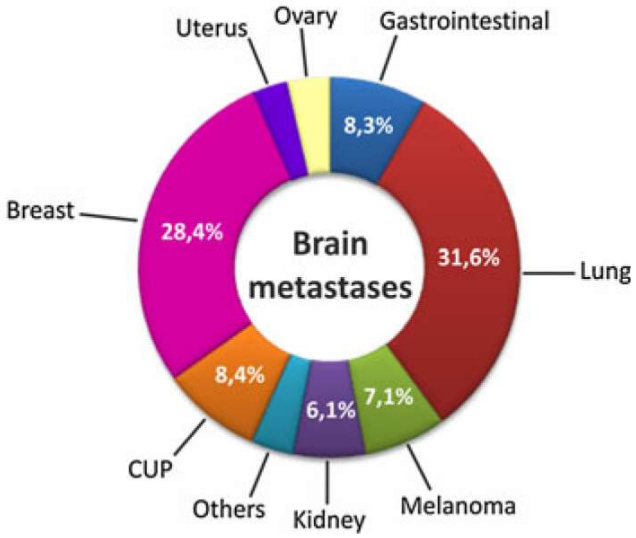
Relative frequencies of tumour types in males





Relative frequencies of tumour types in females



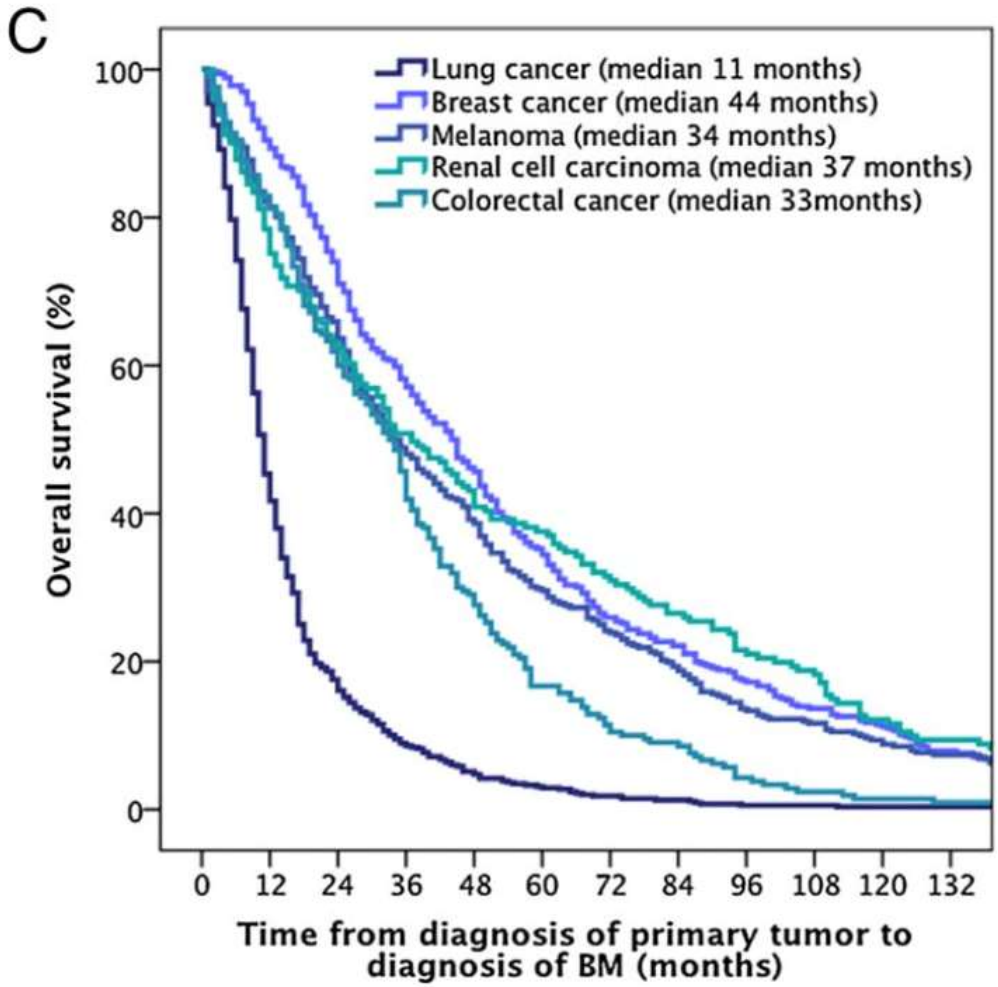


Preusser et al, Acta Neuropathol 2011

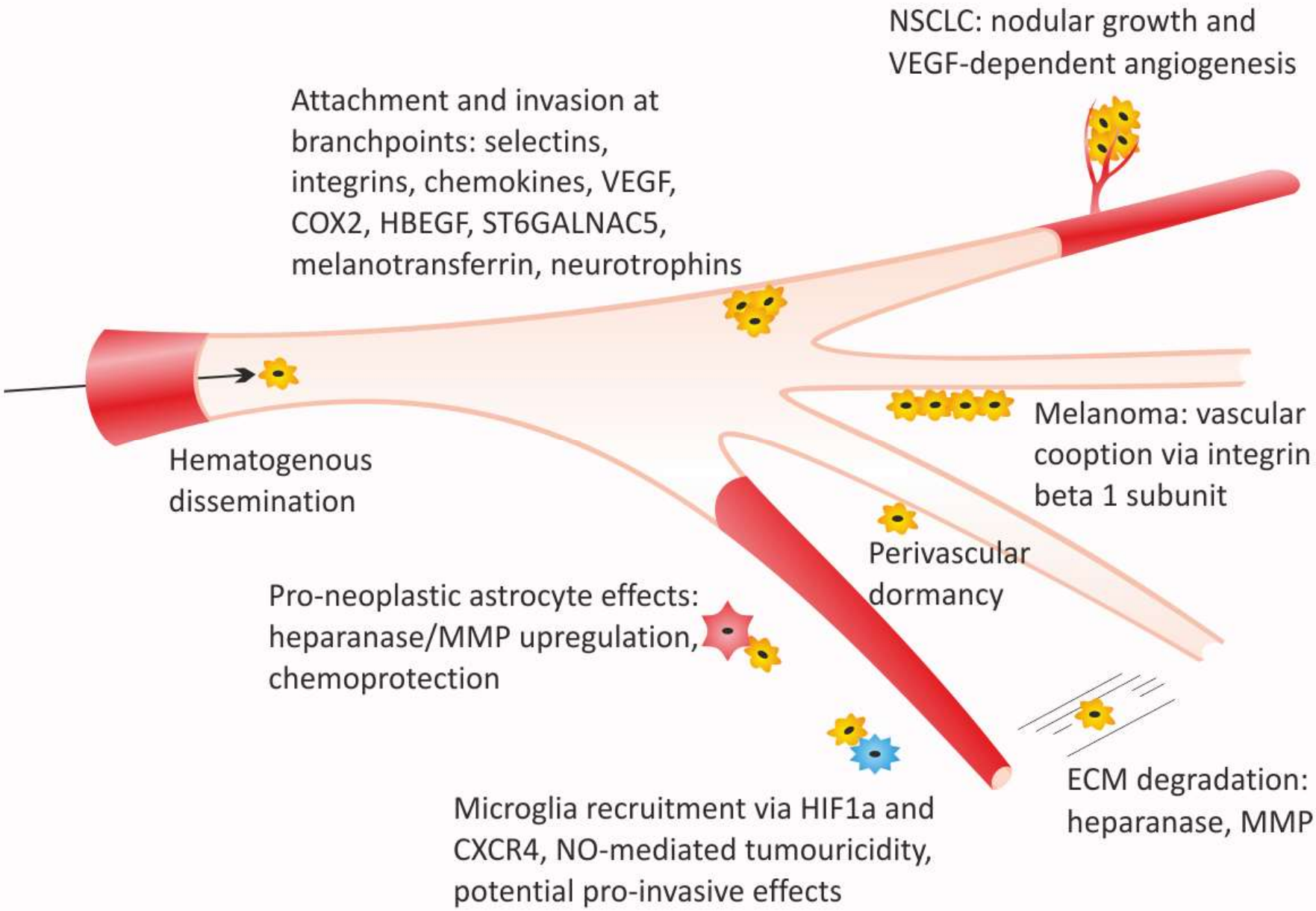
ESMO Open
Cancer Horizons

Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers

Anna S Berghoff,[1,2] Sophie Schur,[1,2] Lisa M Füreder,[1,2] Brigitte Gatterbauer,[2,3] Karin Dieckmann,[2,4] Georg Widhalm,[2,3] Johannes Hainfellner,[2,5] Christoph C Zielinski,[1,2] Peter Birner,[2,6] Rupert Bartsch,[1,2] Matthias Preusser[1,2]



Brain-metastatic cascade



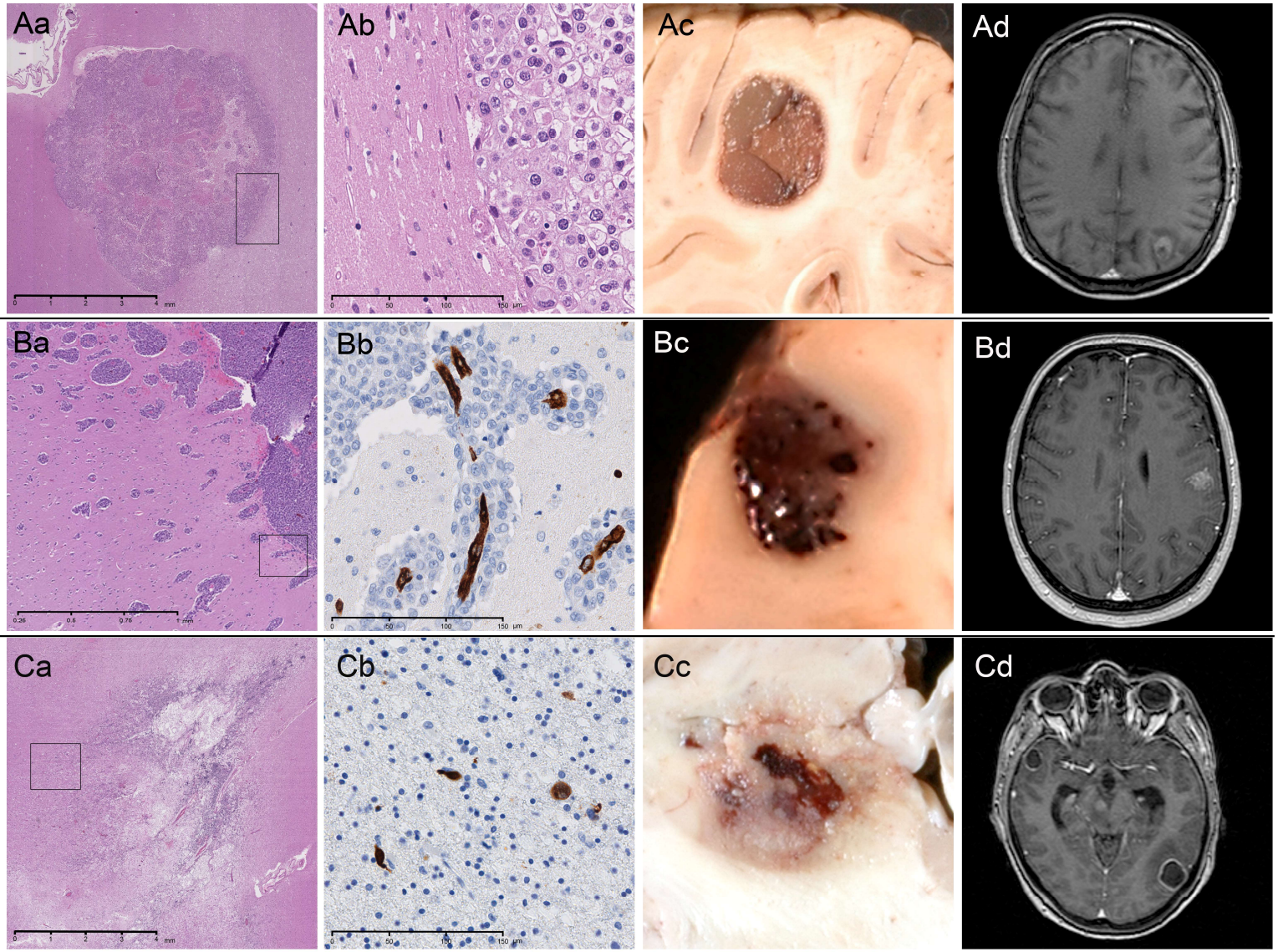
Preusser et al, Acta Neuropathol 2012

Growth patterns of brain metastases

Delineated
51%

Perivascular
18%

Diffuse
32%



Berghoff A (...) Preusser M. Neuro-Oncol 2013

Treatment approaches

- Neurosurgery
- Radiotherapy
  - Whole brain radiotherapy (WBRT)
  - Stereotactic radiosurgery/radiotherapy (SRS/SRT)
- Systemic therapy
  - Chemotherapy
  - **Targeted therapies, e.g. tyrosine kinase inhibitors, antibodies**
- Supportive therapy
  - Edema control
  - Anticonvulsants
  - Pain

Preusser et al, Oxford University Press 2015

Neurosurgery

Typical indications:

- Patients with surgically accessible single brain metastases, no or controlled extracranial tumor burden and good performance status
- Acute decompression on patients with significant mass effect from one or more brain metastases
- **Patients with an unknown primary tumor to obtain tissue for histopathological and molecular tumor (sub-)typing**

Note: unresolved issue of whether or not perform adjuvant irradiation after neurosurgical resection; possible strategies:

- WBRT
- SRS
- Wait and see

Preusser et al, Oxford University Press 2015

Are there druggable targets brain mets?

EGFR

ALK

ROS1

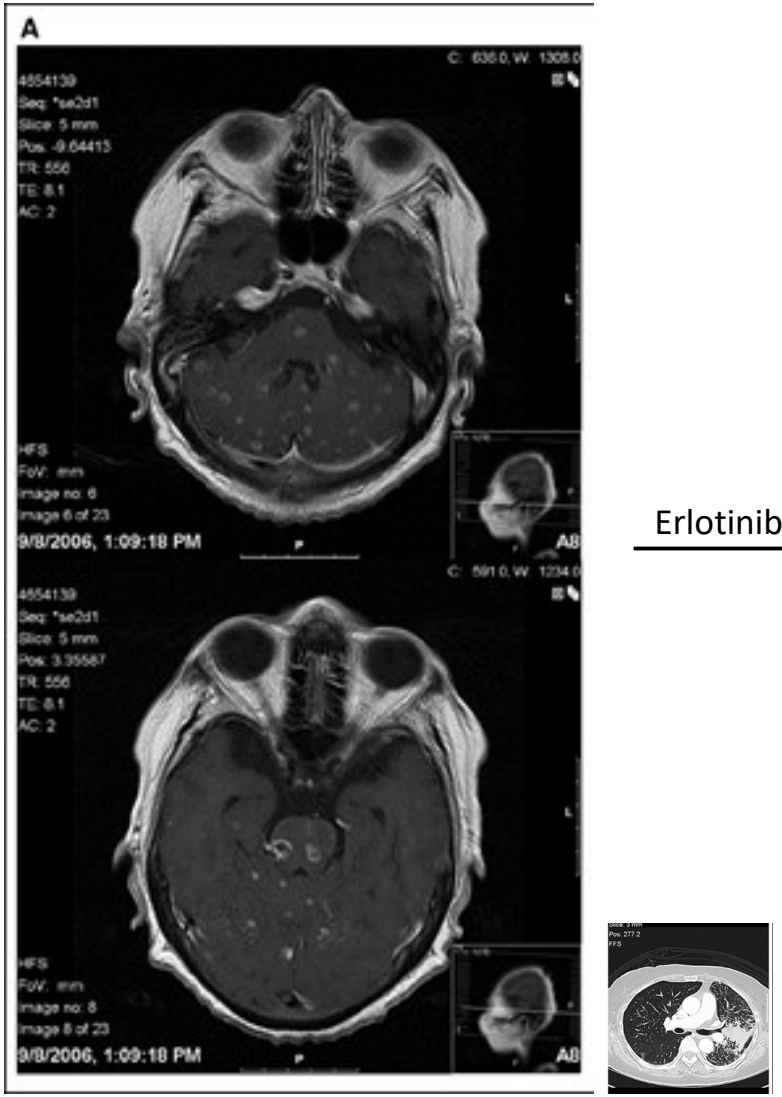
BRAF V600E

PD1/PD-L1

Angiogenesis

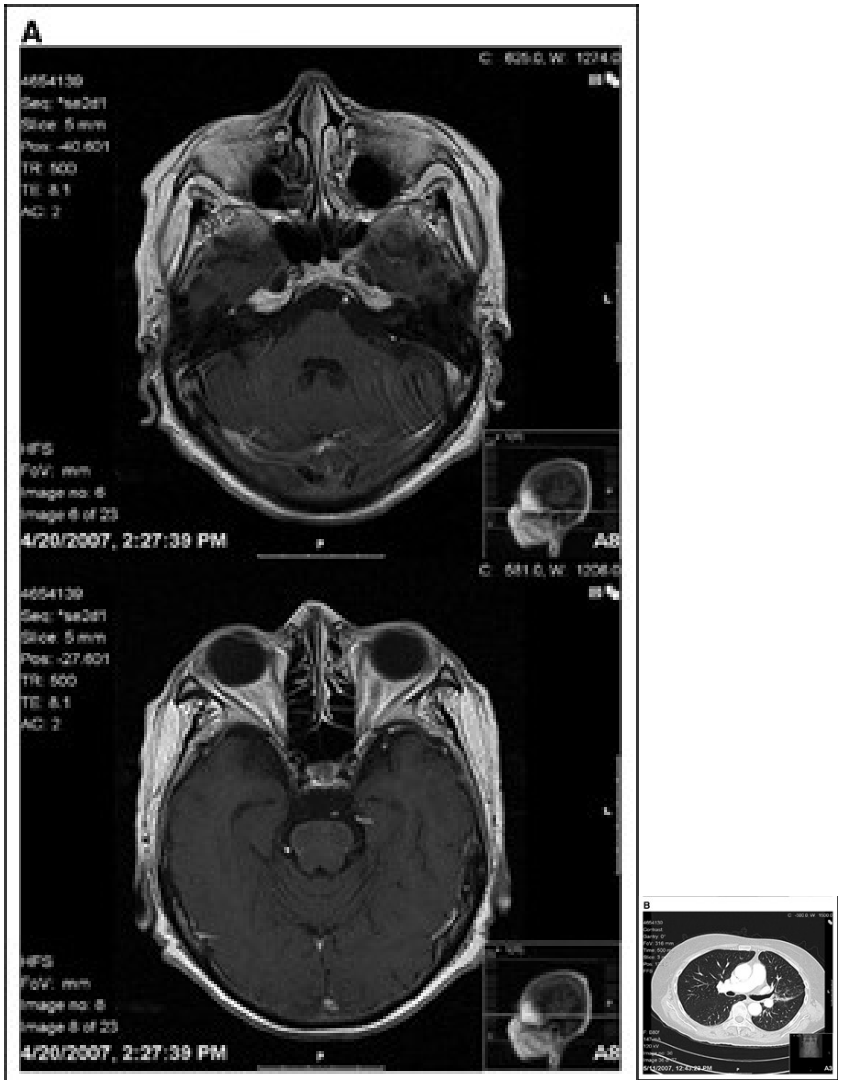
EGFR inhibitors in NSCLC

3 months after WBRT (30 Gy):



Erlotinib 150 mg

8 months later



60y, f, NSCLC IV, multiple BM

Fekrazad M H et al. JCO 2007;25:5024-5026

Neuro-Oncology 13(12):1364–1369, 2011.
doi:10.1093/neuonc/nor121
Advance Access publication August 24, 2011

"Pulsatile" high-dose weekly erlotinib for CNS metastases from *EGFR* mutant non-small cell lung cancer

Christian Grommes, Geoffrey R. Oxnard, Mark G. Kris, Vincent A. Miller, William Pao, Andrei I. Holodny, Jennifer L. Clarke, and Andrew B. Lassman

Table 2. Response, time to progression, and survival following pulsatile therapy

Patient	Best CNS response	Best response outside CNS	CNS TTP (mo)	OS (mo)	Major toxicity during Pulsatile Erlotinib (grade)	Treatment(s) after Pulsatile Erlotinib
1	SD	SD	3.2	5.9	Rash (2), CNS hemorrhage (1)	Pemetrexed, paclitaxel
2	PR	NE	2.7	2.9	None	None
3	PR[a]	SD	14.5	>25.4	None	WBRT, daily erlotinib
4	PR[a]	NE	1.8	15.3	Diarrhea (1)	WBRT, cetuximab, daily erlotinib, gemcitabine, everolimus
5	PD	PD	0.8	6.2	Fatigue (1)	Daily erlotinib
6	PR	NE	9.5	12.0	CNS hemorrhage (1)	None
7	PR	SD	7.6	17.5	Rash (1)	Added bevacizumab, pemetrexed
8	PR	NE	2.4	>11.3	CNS hemorrhage (1), nausea (1), hair thinning (1)	Pemetrexed
9	PD	PD	1.2	3.4	Fatigue (1)	Cetuximab, afatinib

Abbreviations: TTP, time to progression; OS, overall survival; SD, stable disease, PR, partial response; CR, complete response; NE, not evaluable; PD, progressive disease; >, patient alive (censored for survival) at time of analysis.
[a]Patient had clear partial response of isolated leptomeningeal metastases, designated by RECIST as non-CR/non-PD.

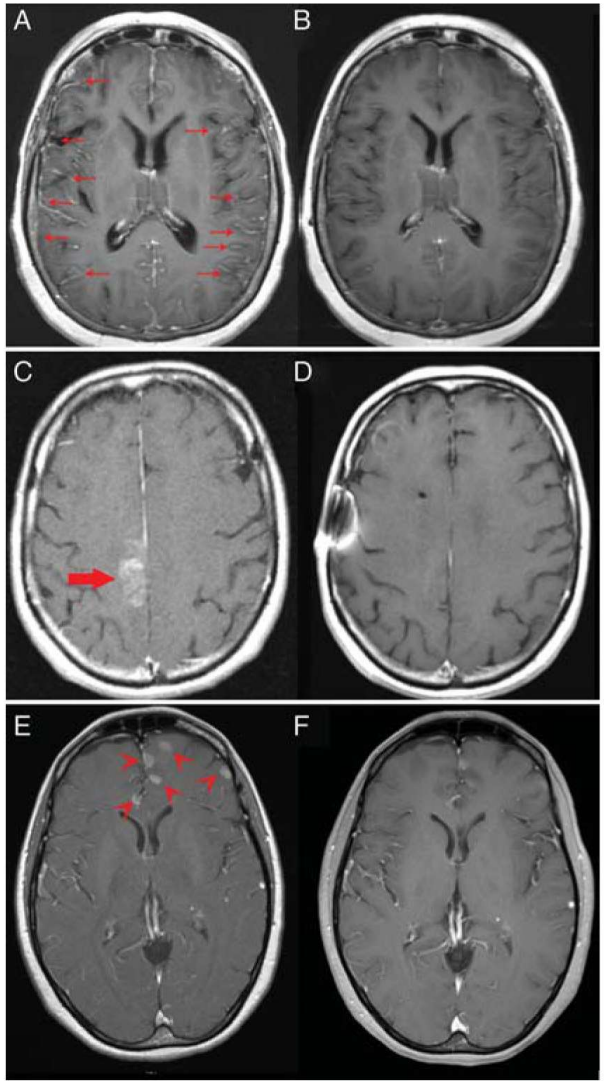
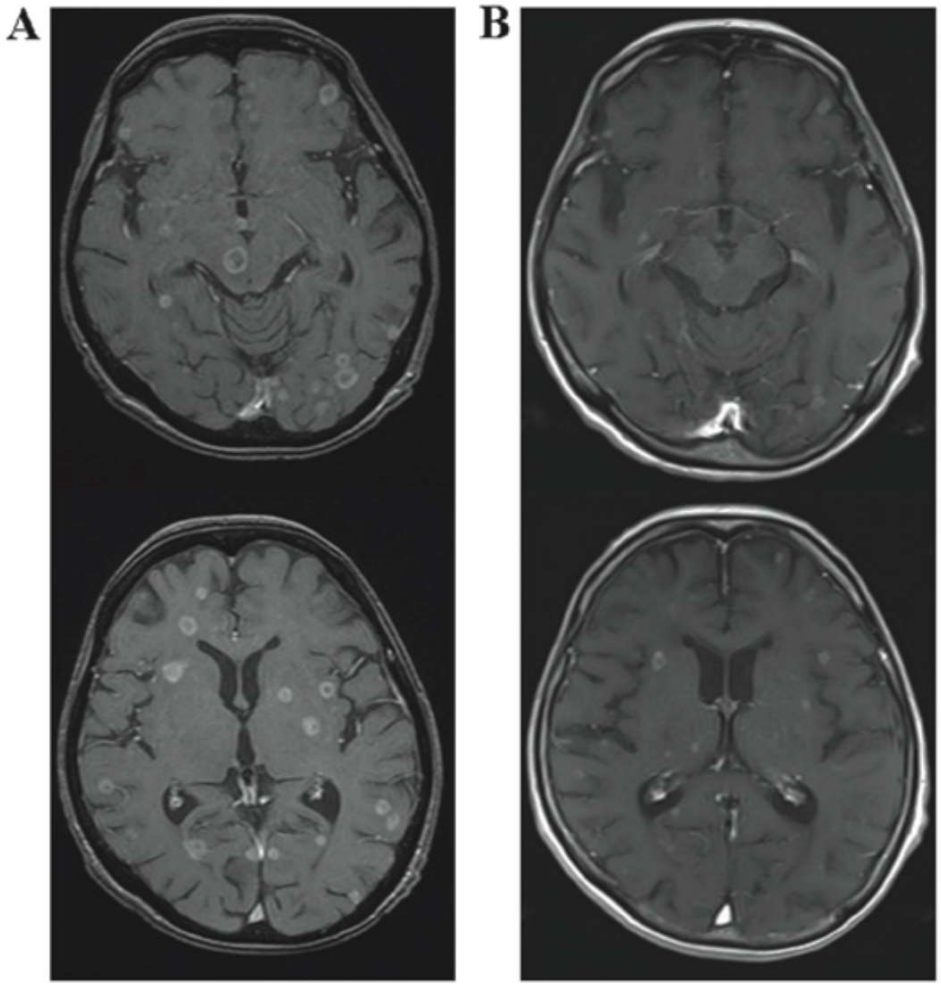


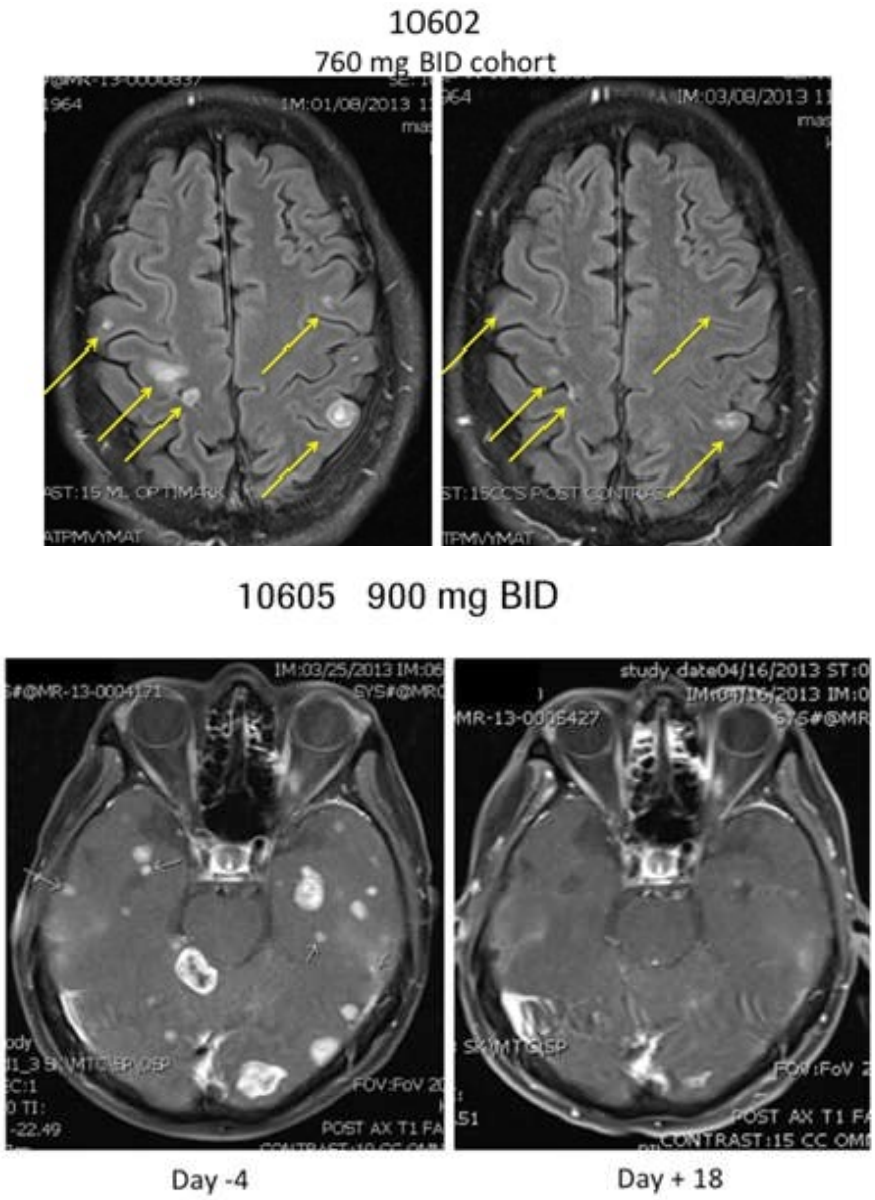
Fig. 1. Response of CNS metastases to pulsatile erlotinib in 3 patients. Contrast (gadolinium)-enhanced axial T1 MRI sequences in patient #3 with leptomeningeal metastases (arrows) before (A) and after (B) 6 months of therapy. Patient #6 with coexistent brain (large arrow) and leptomeningeal metastases (not shown) before (C) and after (D) 5 months of therapy. Patient #8 with coexistent brain (arrow heads) and leptomeningeal metastases (not shown) before (E) and after (F) 2 months of therapy.

Dramatic intracranial response to osimertinib in a poor performance status patient with lung adenocarcinoma harboring the epidermal growth factor receptor T790M mutation: A case report

MOLECULAR AND CLINICAL ONCOLOGY 6: 525-528, 2017



Phase I study of alectinib in crizotinib-resistant ALK-positive NSCLC



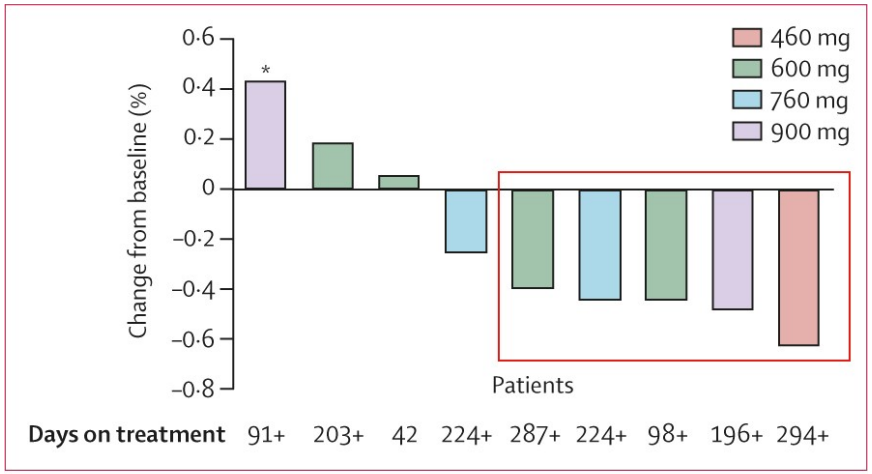
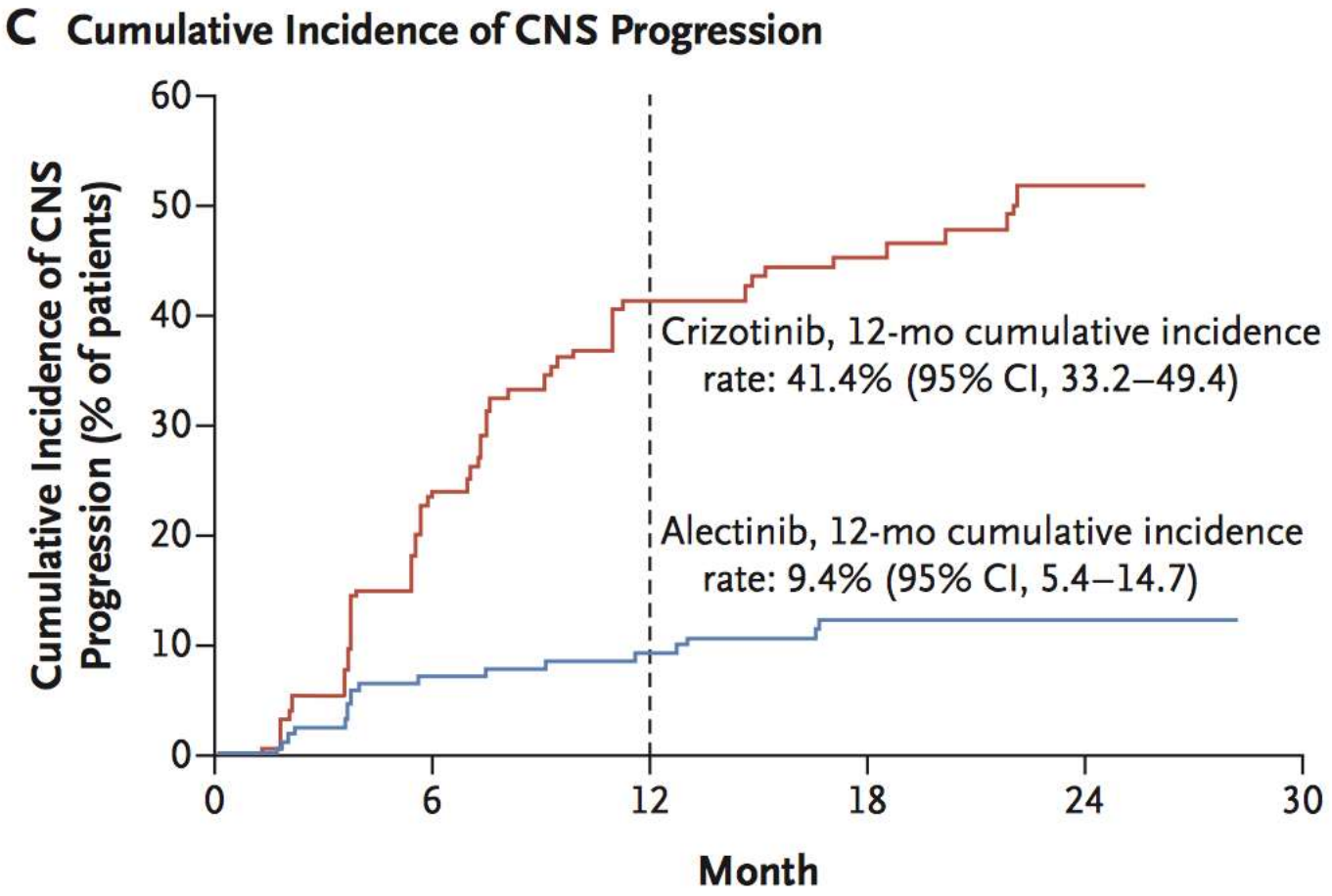


Figure 4: **Waterfall plot of best CNS response**
Bars indicate the change from baseline in the size of CNS tumours, for every assessable patient with measurable CNS lesions at baseline (n=9). Red box indicates patients who had a partial response as their best CNS response. + symbols indicate patients still on treatment. *Radiation necrosis.

Ou et al, Lancet Oncol 2014

CNS protection by alectinib



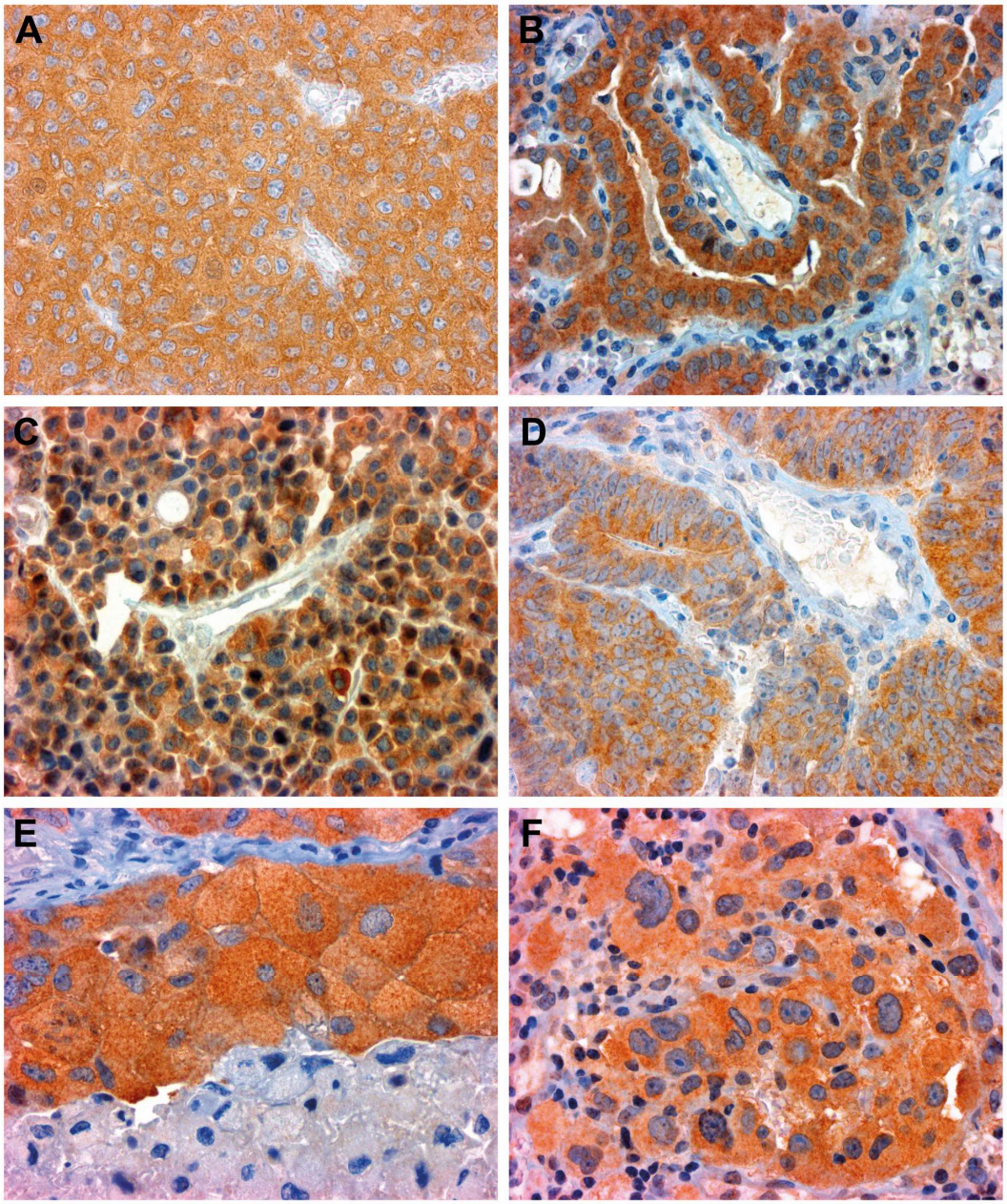
Peters et al, NEJM 2017

BRAF V600E in brain mets

Melanoma
42/76 (55.3%)

Ovarian cancer
1/15 (6.7%)

Lung cancer
1/355 (0.3%)



Thyroid cancer
2/6

Colorectal cancer
4/72 (5.5%)

Chorioncarcinoma
1/2

Acta Neuropathol 2012

Capper et al, Acta Neuropathol 2011

BRAF inhibitor active in brain metastases of V600E mutant melanoma

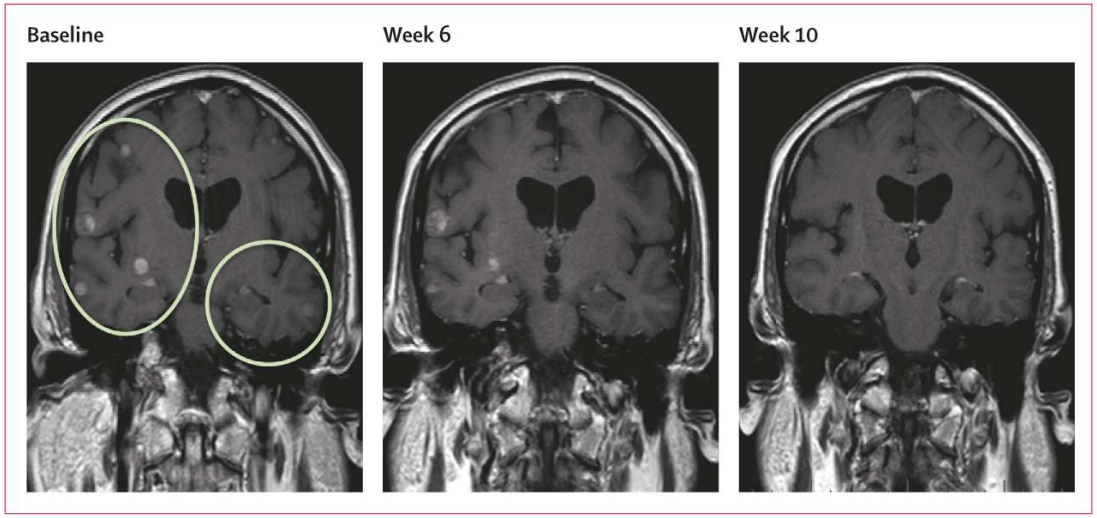


***Figure 6*: MRI images from one patient with Val600Glu BRAF-mutant melanoma and untreated brain metastases given the recommended phase 2 dose**
Image from baseline (left), week 6 (middle), and week 10 (right). Circles indicate locations of lesions. Best response was a 71% decrease in tumour size, and the best intracranial decrease was 68%.

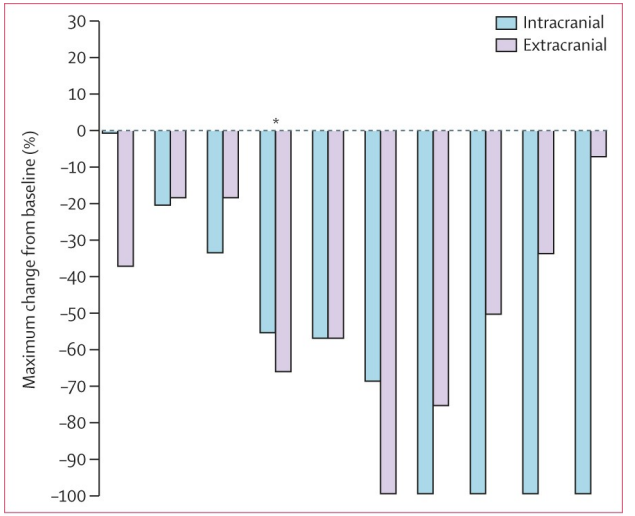
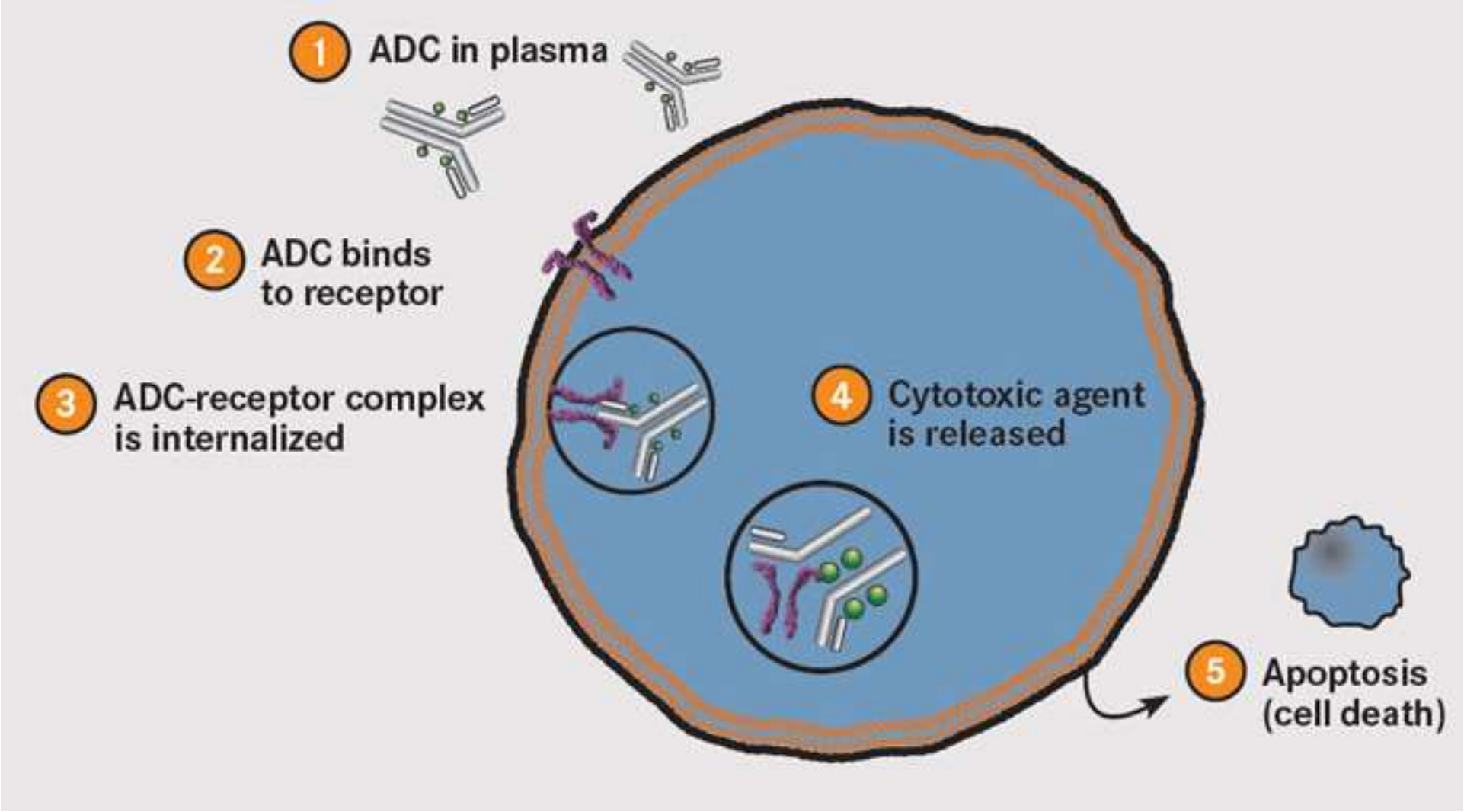


***Figure 5*: Change in intracranial and extracranial tumour size in the ten patients with Val600 BRAF-mutant melanoma and untreated brain metastases given the recommended phase 2 dose**
*Patient with Val600Lys mutation.

Falchook et al, Lancet 2012

Antibody-Drug Conjugate (ADC)

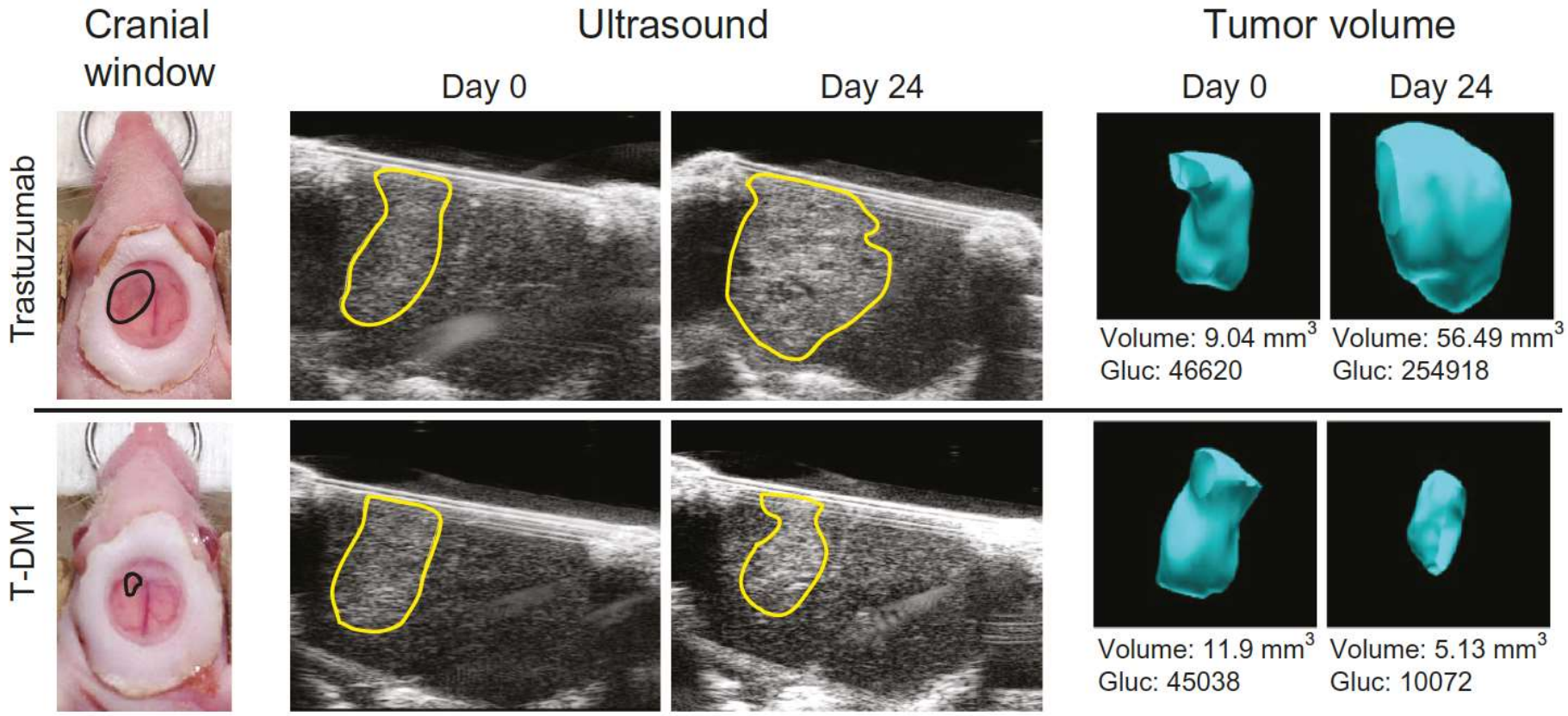
Antibody-Drug Conjugate (ADC)



Preclinical Efficacy of Ado-trastuzumab Emtansine in the Brain Microenvironment

JNCI J Natl Cancer Inst (2016) 108(2): djv313

Vasileios Askoxylakis*, Gino B. Ferraro*, David P. Kodack*, Mark Badeaux, Ram C. Shankaraiah, Giorgio Seano, Jonas Kloepper, Trupti Vardam, John D. Martin, Kamila Naxerova, Divya Bezwada, Xiaolong Qi, Martin K. Selig, Elena Brachtel, Dan G. Duda, Peigen Huang, Dai Fukumura, Jeffrey A. Engelman, Rakesh K. Jain



Activity of T-DM1 in Her2-positive breast cancer brain metastases

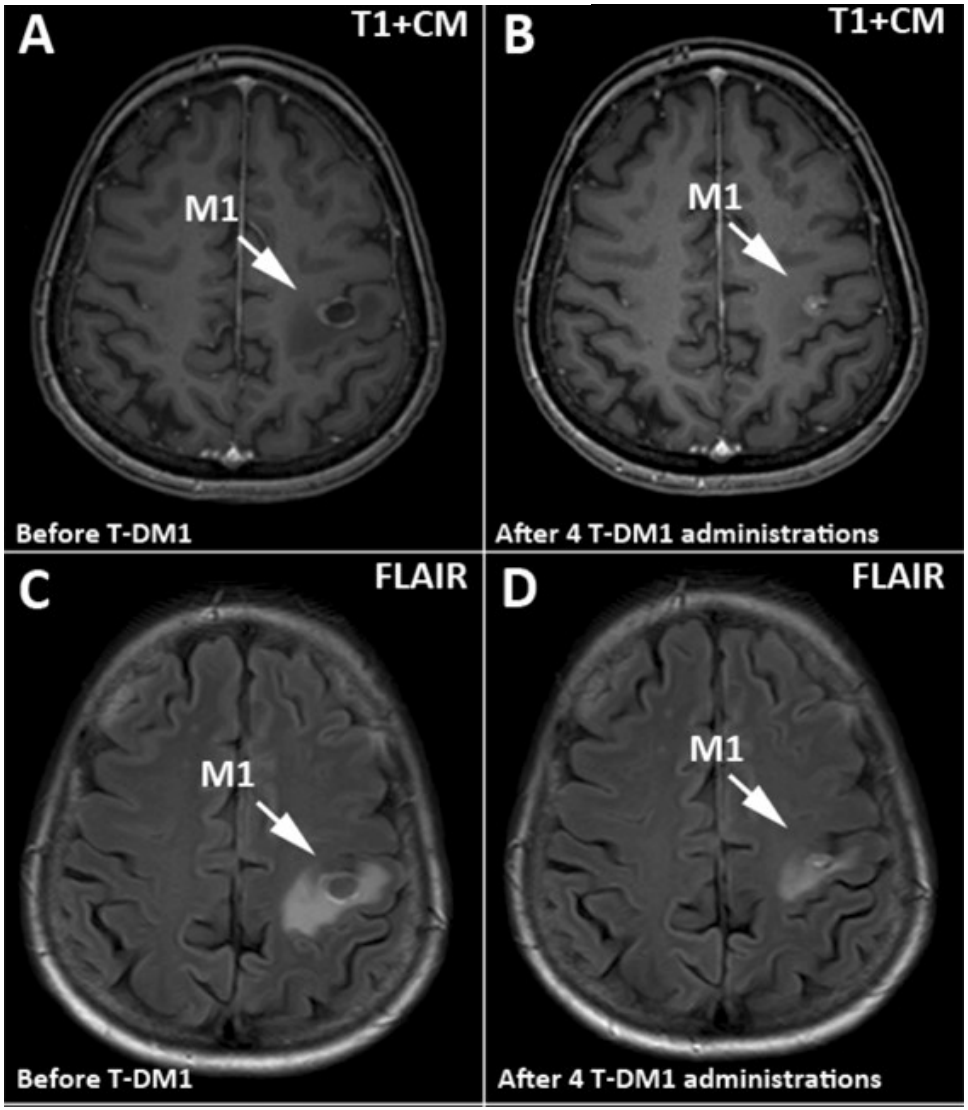
Rupert Bartsch[1,2] · Anna S. Berghoff[1,2] · Ursula Vogl[3] · Margaretha Rudas[1,4] · Elisabeth Bergen[1,2] · Peter Dubsky[1,5] · Karin Dieckmann[1,6] · Katja Pinker[1,7] · Zsuzsanna Bago-Horvath[1,4] · Arik Galid[8] · Leopold Oehler[3] · Christoph C. Zielinski[1,2] · Michael Gnant[1,5] · Guenther G. Steger[1,2] · Matthias Preusser[1,2]

10 patients

30% CNS-Response

50% clinical benefit rate

Median CNS-PFS: 5 months

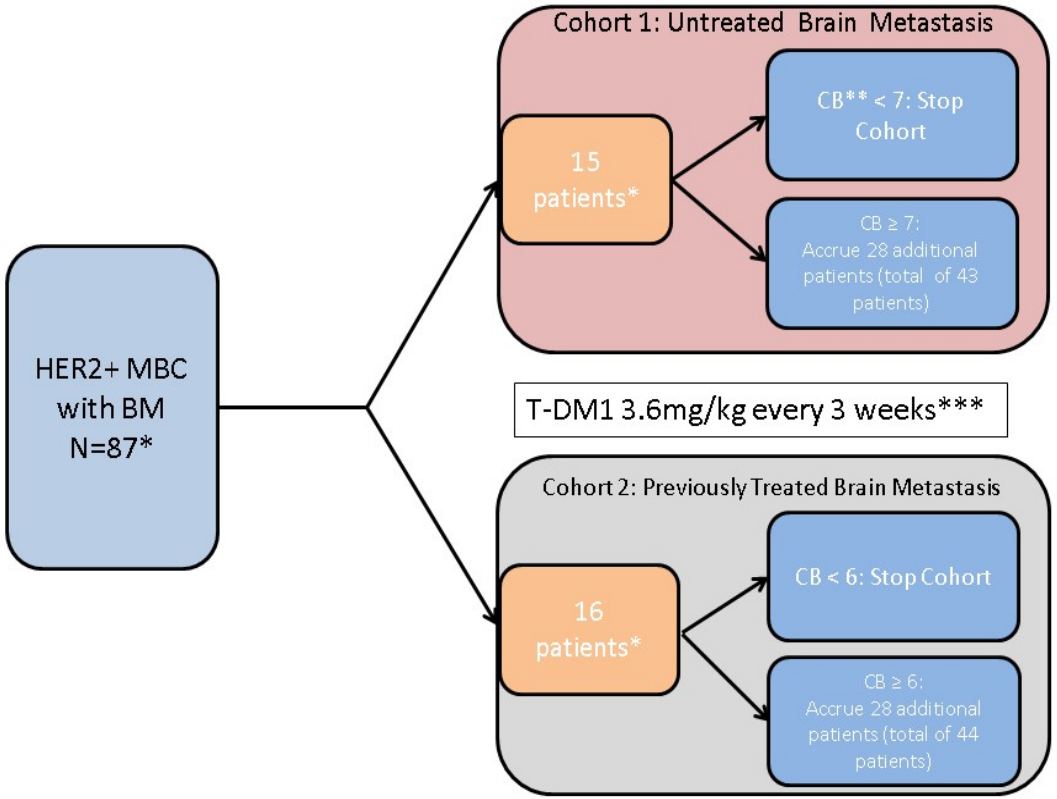


Clin Exp Metastasis
DOI 10.1007/s10585-015-9740-3

KIARA trial

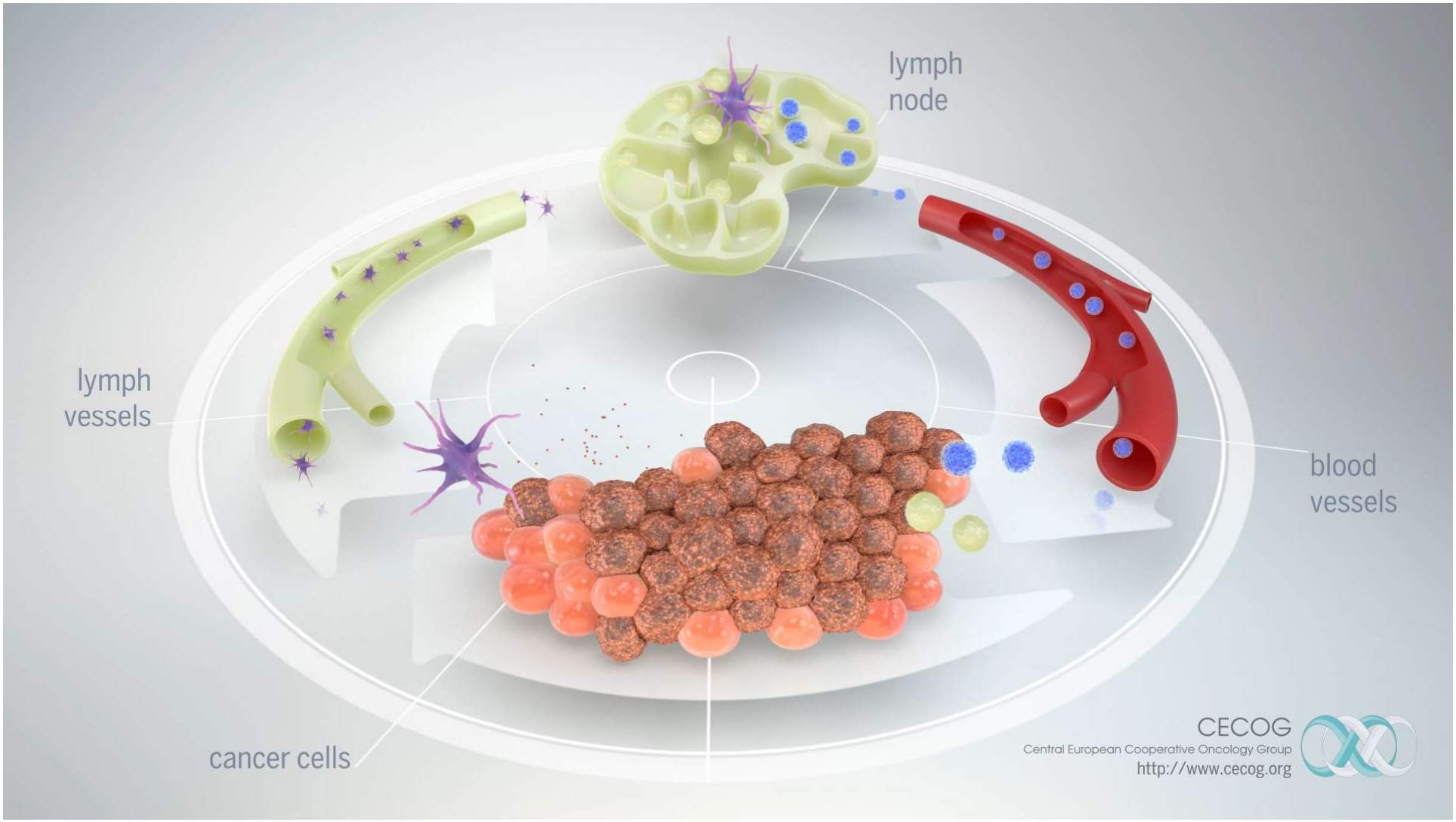
Multicenter, non-randomised, open-label, single agent, phase II study to determine the clinical benefit of T-DM1 in HER2-positive metastatic breast cancer patients with brain metastasis

PIs: M. Preusser & E. de Azambuja

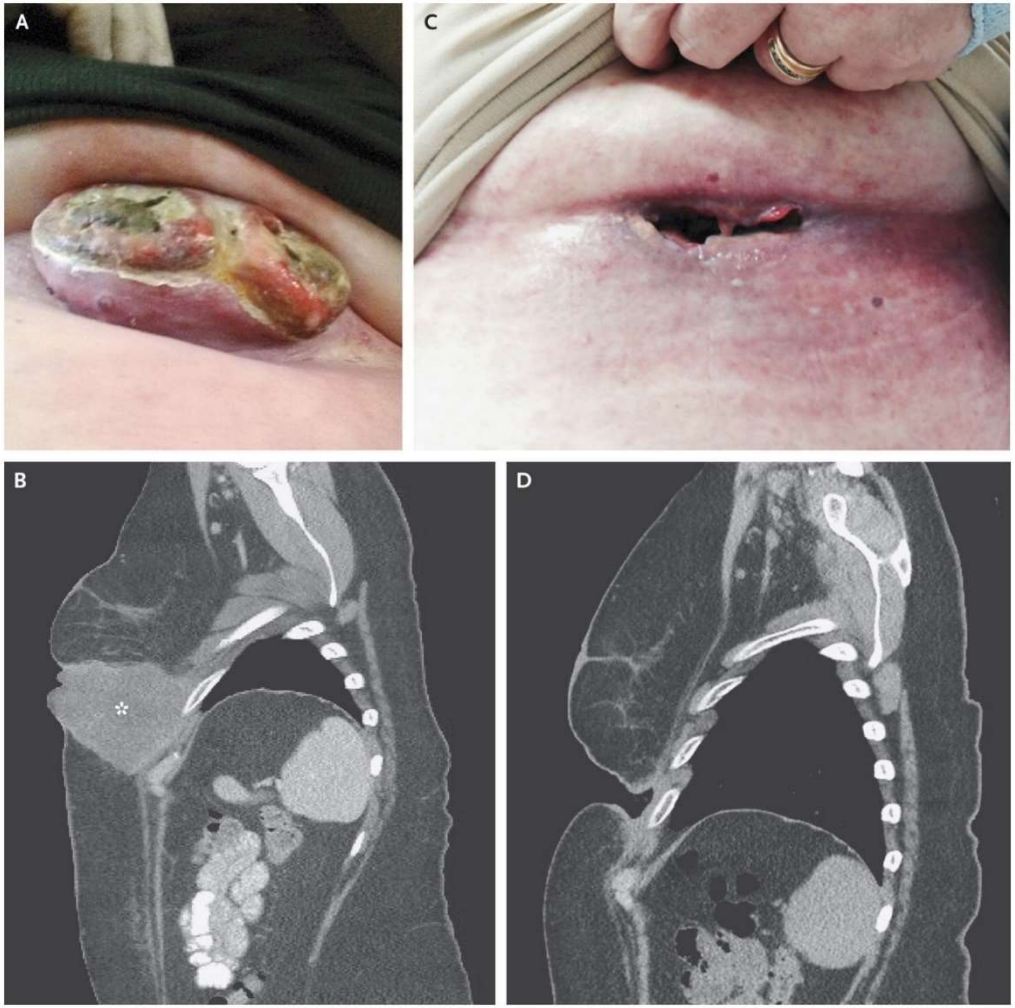


** Evaluable patients only. 5% drop-out and 5% inevaluability are expected*
***CB= Clinical benefit (CR+PR+SD)*
****Until PD, unacceptable toxicity or voluntary withdrawal*

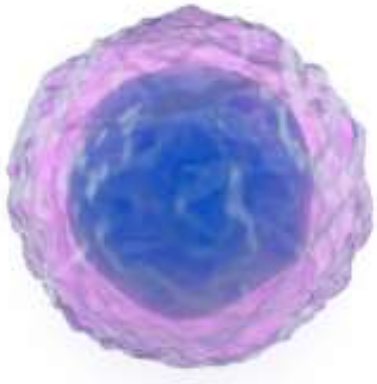
Immunotherapy

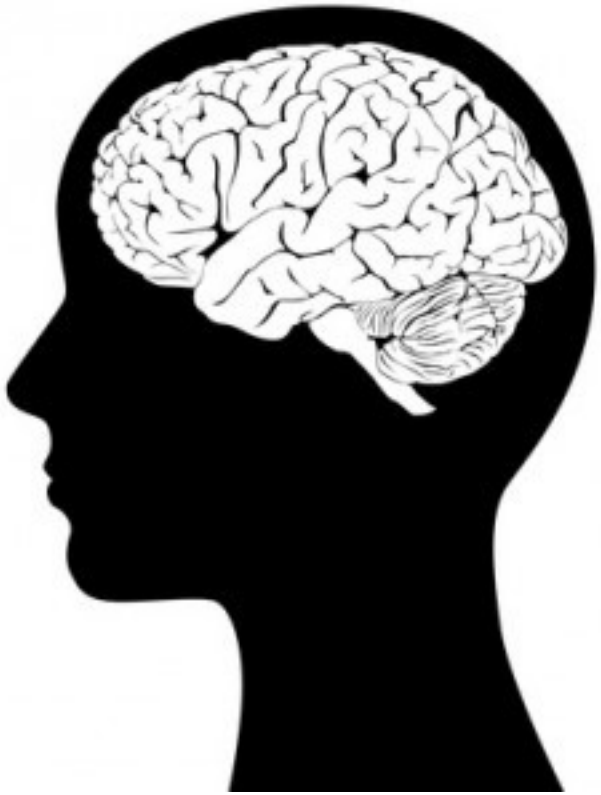


Immune-checkpoint inhibition

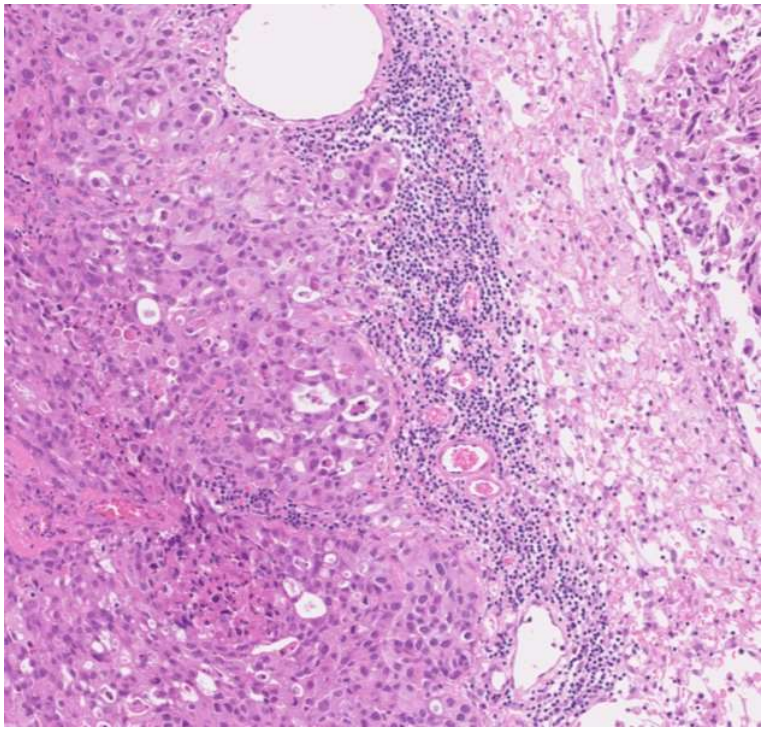


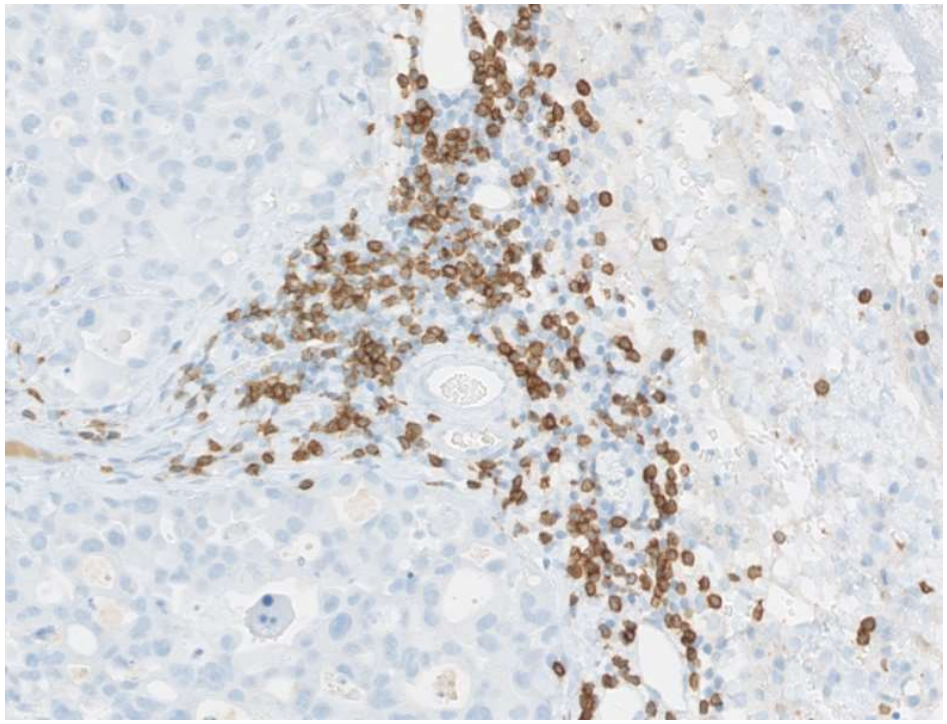
Chapman PB et al. New Engl J Med 2015



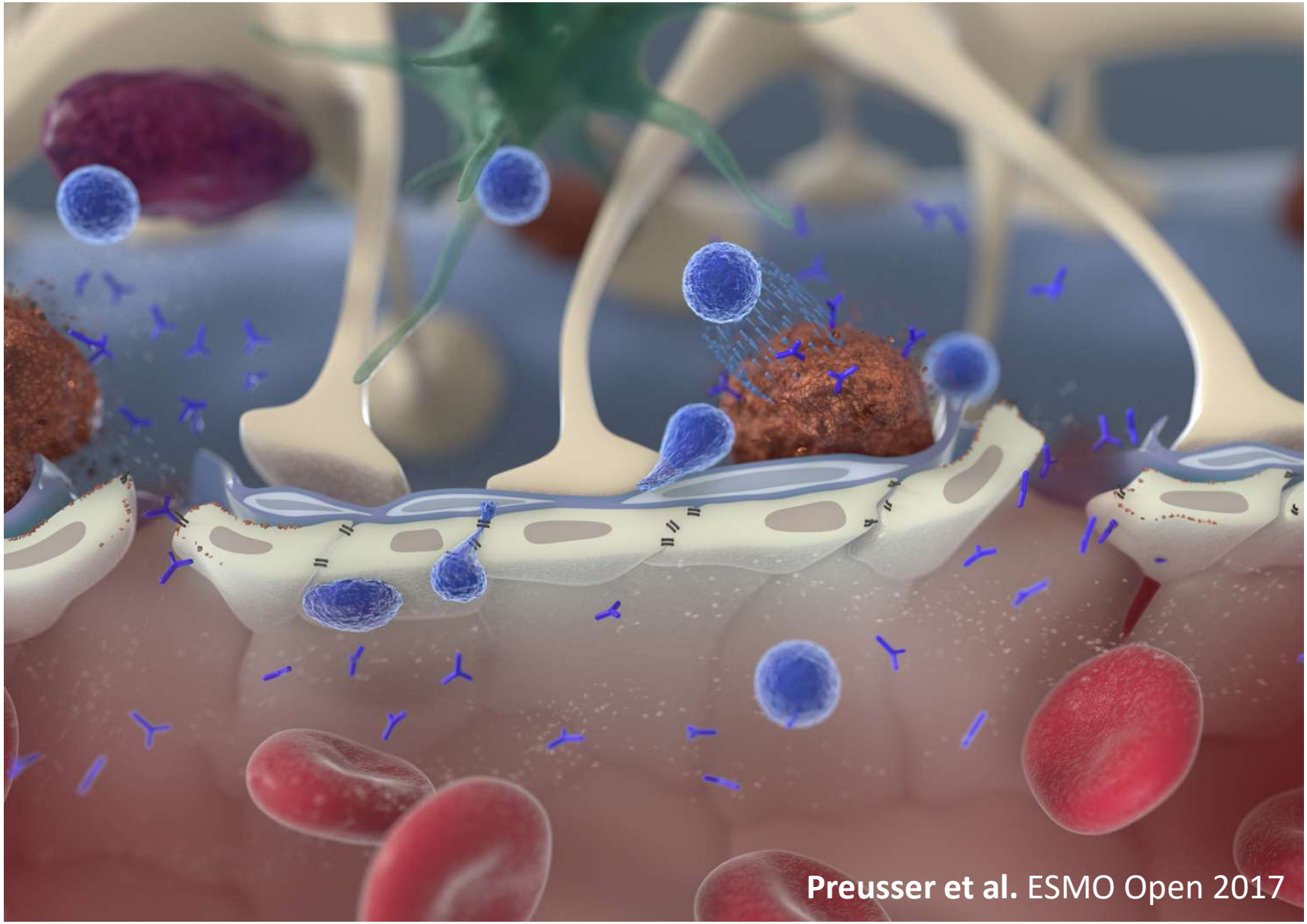


Inflammation in brain mets





Blood-brain barrier



Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

Lancet Oncol 2012; 13: 459–65

	Cohort A (n=51)		Cohort B (n=21)	
	mWHO	irRC	mWHO	irRC
Global disease control	9 (18%, 8–31)	13 (25%, 14–40)	1 (5%, 0·1–24)	2 (10%, 1–30)
CNS disease control	12 (24%, 13–38)	13 (25%, 14–40)	2 (10%, 1–30)	2 (10%, 1–30)
Non-CNS disease control	14 (27%, 16–42)	17 (33%, 21–48)	1 (5%, 0·1–24)	2 (10%, 1–30)
Global objective response	5 (10%, 3–21)	5 (10%, 3–21)	1 (5%, 0·1–24)	1 (5%, 0·1–24)
CNS objective response	8 (16%, 7–29)	8 (16%, 7–29)	1 (5%, 0·1–24)	1 (5%, 0·1–24)
Non-CNS objective response	7 (14%, 6–26)	7 (14%, 6–26)	1 (5%, 0·1–24)	1 (5%, 0·1–24)

Data are n (%, 95% CI). mWHO=modified WHO criteria. irRC=immune-related response criteria.

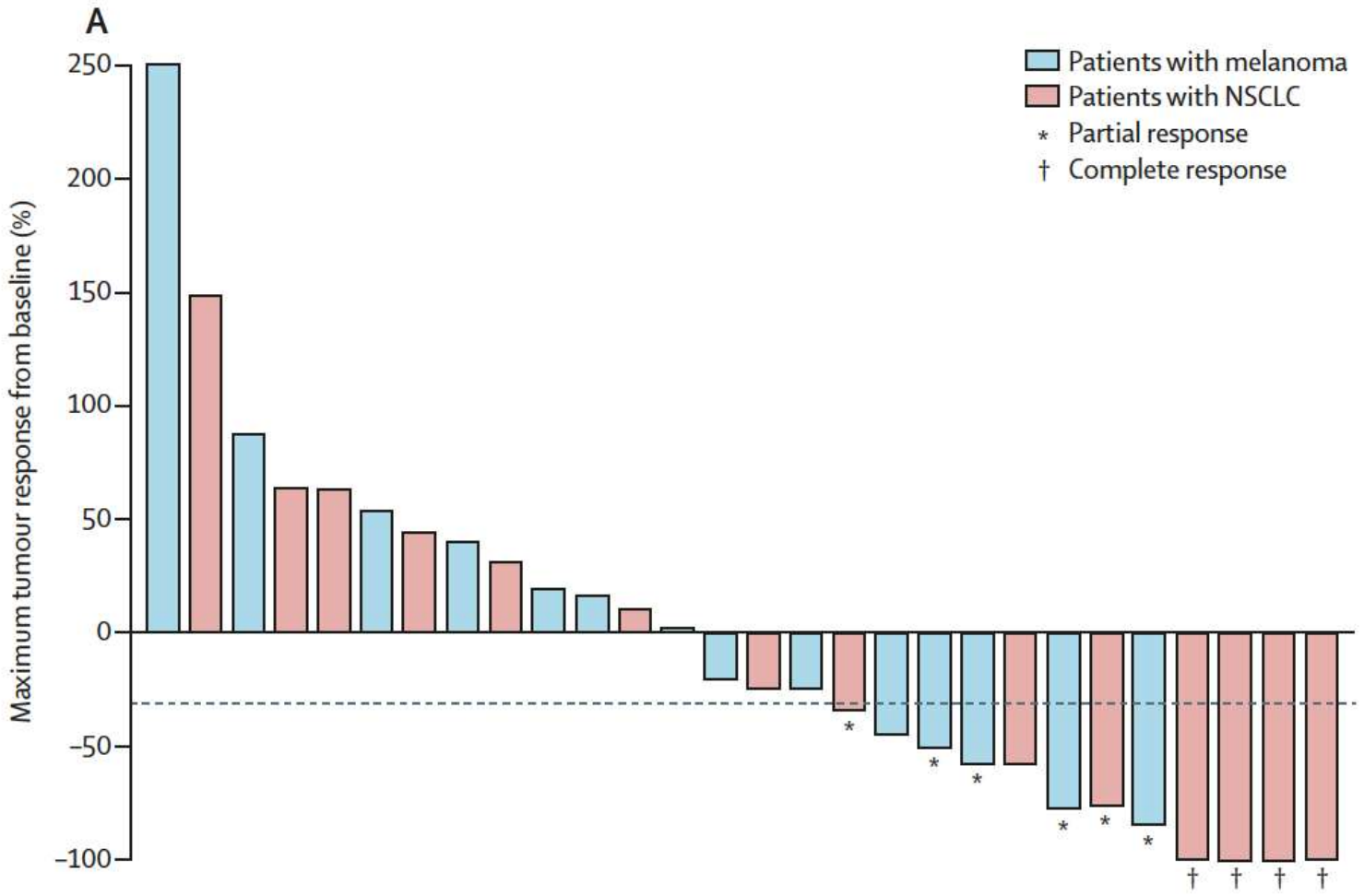
Table 3: **Disease control and objective response after 12 weeks**

Cohort A: asymtomatic, no corticosteroids (n=51)
Cohort B: symptomatic, stable dose of corticosteroids (n=21)

4x Ipi 10 mg/kg every 3 weeks, then maintenance every 12 weeks

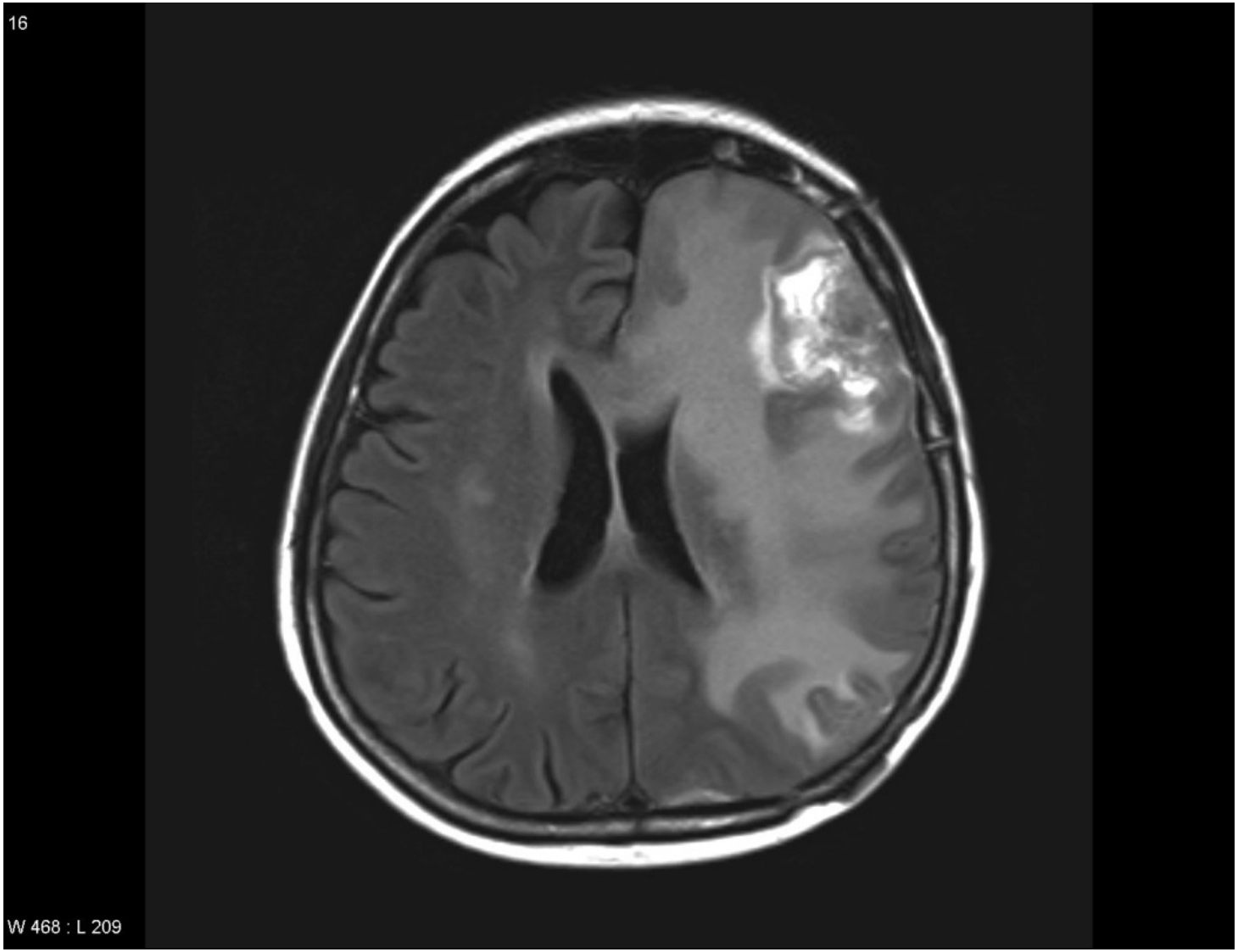
PD-1 Inhibitor Pembrolizumab

NSCLC and melanoma brain metastases



Goldberg S. Lancet Oncol 2016

Brain edema

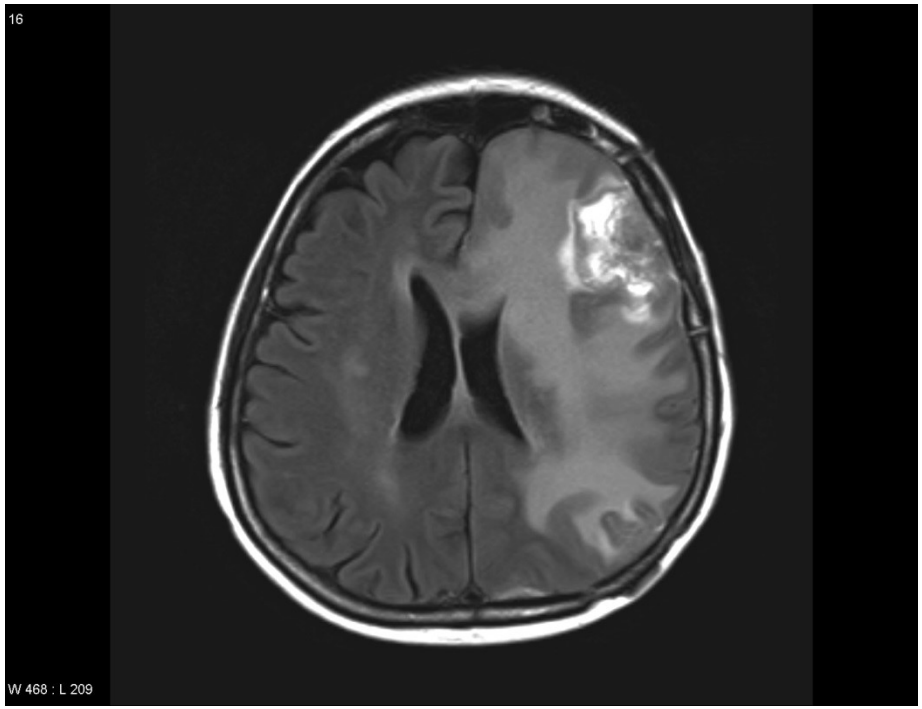


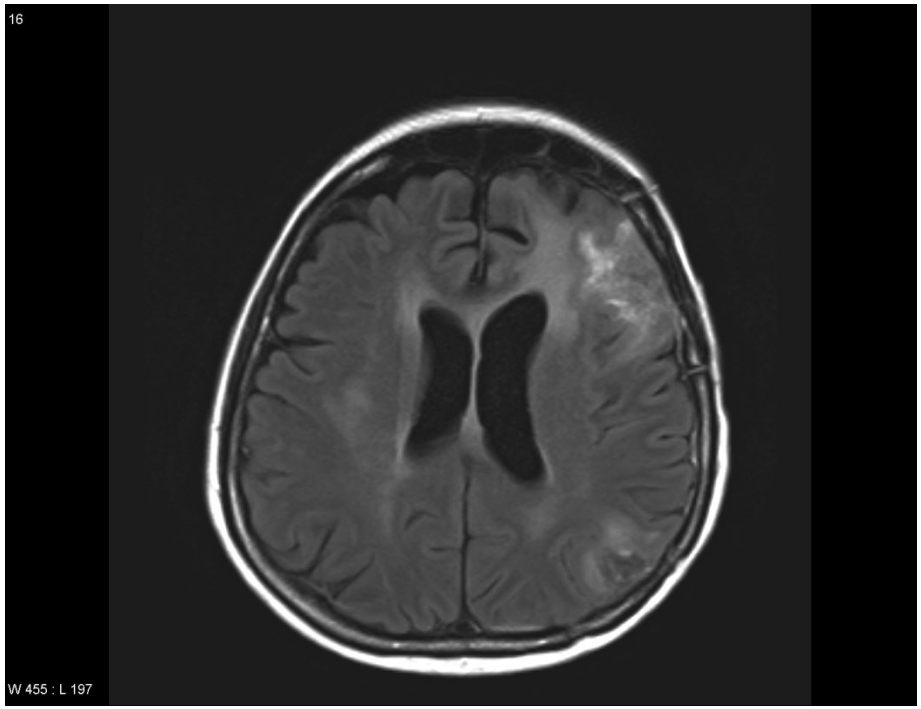
Anti-oedema therapy

- Results from leakage of plasma into the tissue through disrupted BBB
- Detectable of T2-weighted and FLAIR MRI images
- Increased intracranial pressure with headache, vertigo, nausea/vomiting
- May lead to life-threatening brainstem compression and herniation
- Drug of choice: Dexamethasone
  - Initial daily dose usually 12-16 mg
  - Steroid dose should be rapidly reduced and tapered to individual need (“as much as needed, as little as possible”)
  - Withhold corticosteroid in asymptomatic patients and when lymphoma or inflammatory lesion can not be ruled out
- Dexamethasone may be combined with osmotic agents such as mannitol or glycerol
- Obstructive hydrocephalus may be treated with CSF shunt
- Bevacizumab may reduce brain oedema and is associated with decreased corticosteroid need

Bevacizumab for brain edema and radionecrosis

FLAIR





01.12.2012
Before bevacizumab

01.03.2013
After 4x bevacizumab

Conclusions

- Brain metastases are common and a clinical challenge
- Radiotherapy/SRS and surgery are established treatment options
- Brain mets are a promising target for prophylactic and therapeutic intervention based on molecular insights, some mechanisms and drug targets identified and treatmens emerging
- Many open questions that require specifically designed trials (e.g. sequencing/combination strategies)

DANKE!

Clinical trials in neurooncology

ESTRO teaching course
Management of brain tumours

Patrick Roth

Department of Neurology and Brain Tumor Center
University Hospital Zurich

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Classification of clinical trials

- **Phase 0** Biological proof of concept / biodistribution
- **Phase I** Determination of safety, tolerability and maximum tolerated dose
- **Phase II** Suggestion of efficacy
- **Phase III** Proof of efficacy
- **Phase IV** Optimization of therapy and new patient populations (children, elderly patients)

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Clinical trial endpoints

- Survival
- Survival specified for quality, e.g., “in independence”
- Time to event
- Imaging
- Toxicity
- Quality of life
- Biological endpoints: target inhibition

Typical mistakes of clinical trial designs

- Wrong endpoints
- Inclusion criteria too narrow
- Unrealistic assumptions of effect size
- Sample size too small
- Unrealistic assumptions on accrual

Essentials for planning a clinical trial

- What is my question?
- What are my eligibility criteria?
- What is my primary endpoint?
- What effect size do I expect?
- Which quality measures do I need?
- What is the budget and who will pay?

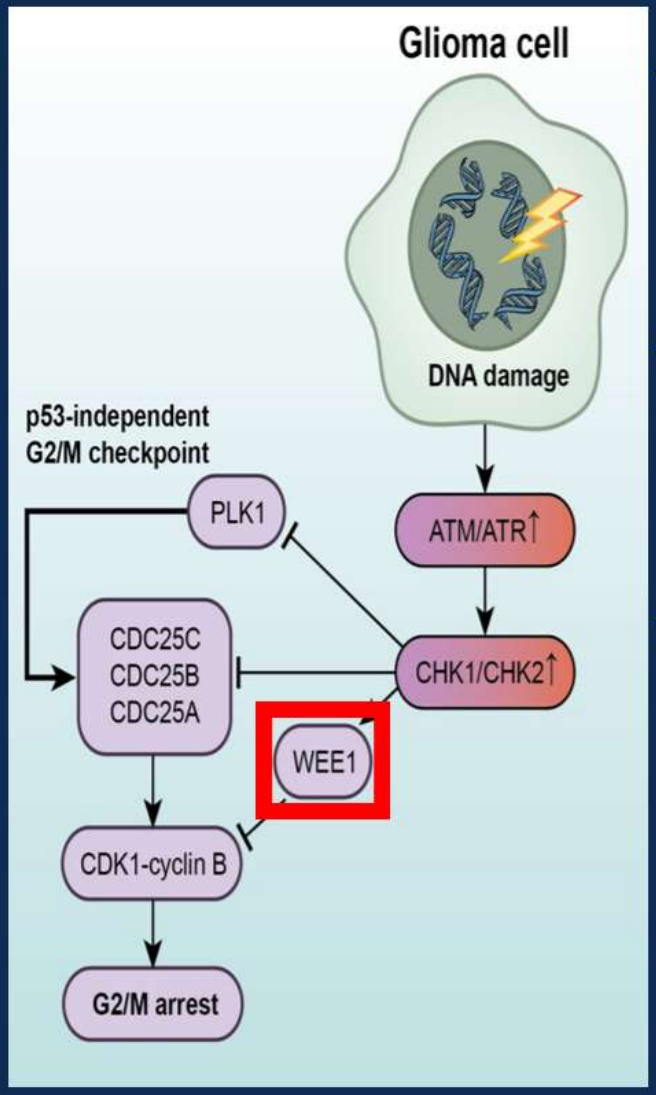
Phase 0 Trial of AZD1775 in Patients with First-Recurrence Glioblastoma

Nader Sanai, Jing Li, Julie Boerner, Harshil Dhruv, Michael Berens, and Patricia LoRusso

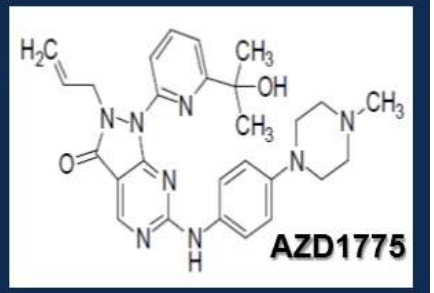
Barrow Neurological Institute, AZ; Translational Genomic Research Institute (TGen), AZ; Karmanos Cancer Institute, MI; Yale University Cancer Center, CT

PRESENTED AT: ASCO ANNUAL MEETING '16

Wee1 Inhibition for Glioblastoma

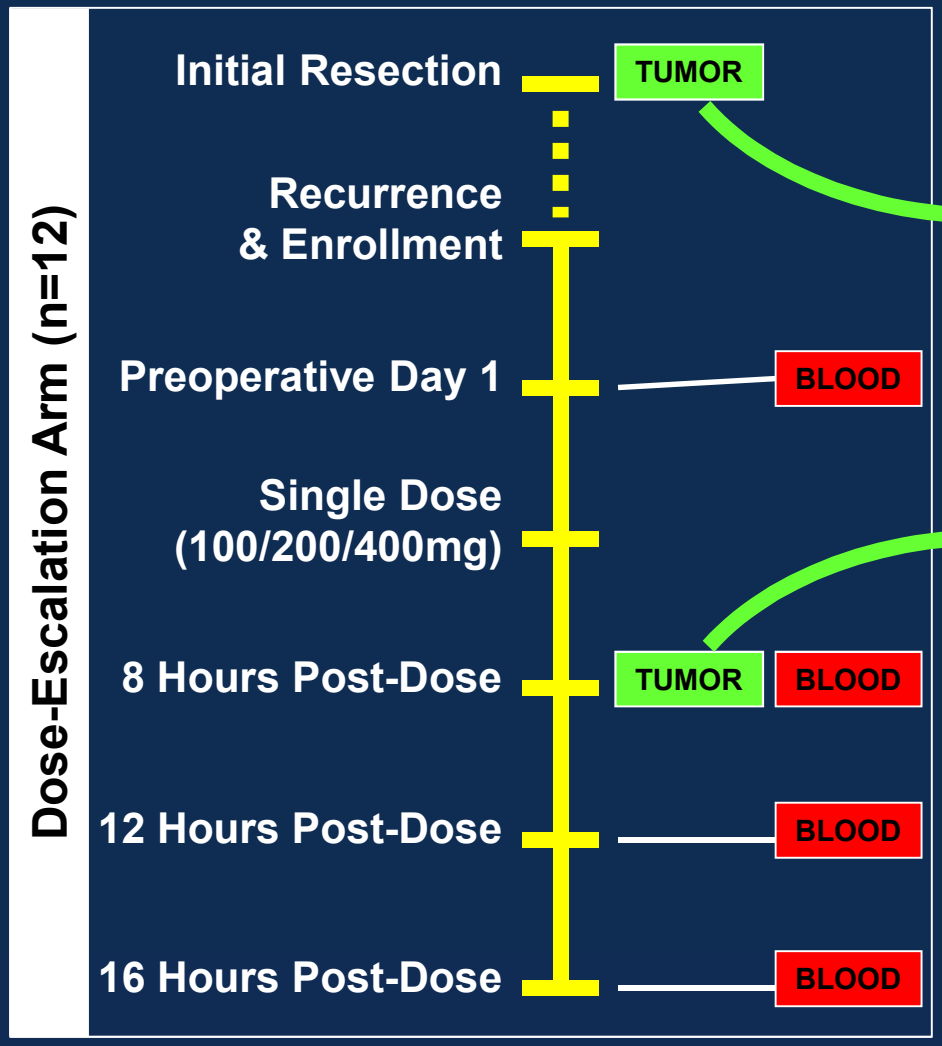


- **Wee1 overexpression in GBM inversely correlates with survival**
- **Wee1 inhibition abrogates G2 arrest and prematurely ends DNA repair**
- **AZD1775 is a potent and selective inhibitor of the Wee1-kinase**



Music *et al. J Neurooncol* 2016 Apr; 127(2): 381-9
Mir *et al. Cancer Cell* 2010 Sep 14; 18(3): 244-57

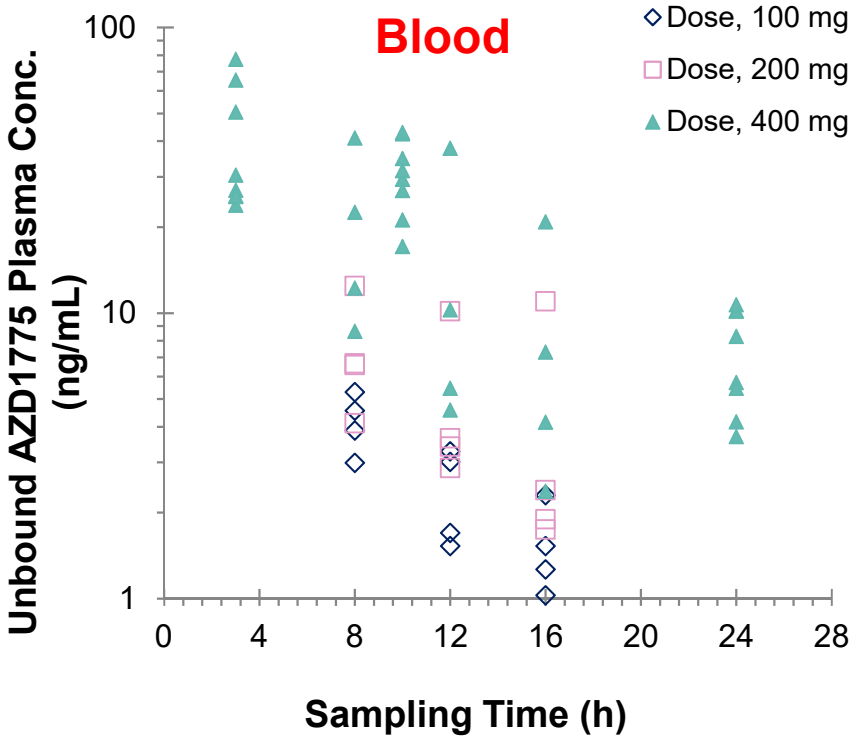
AZD1775 Phase 0 Study for GBM

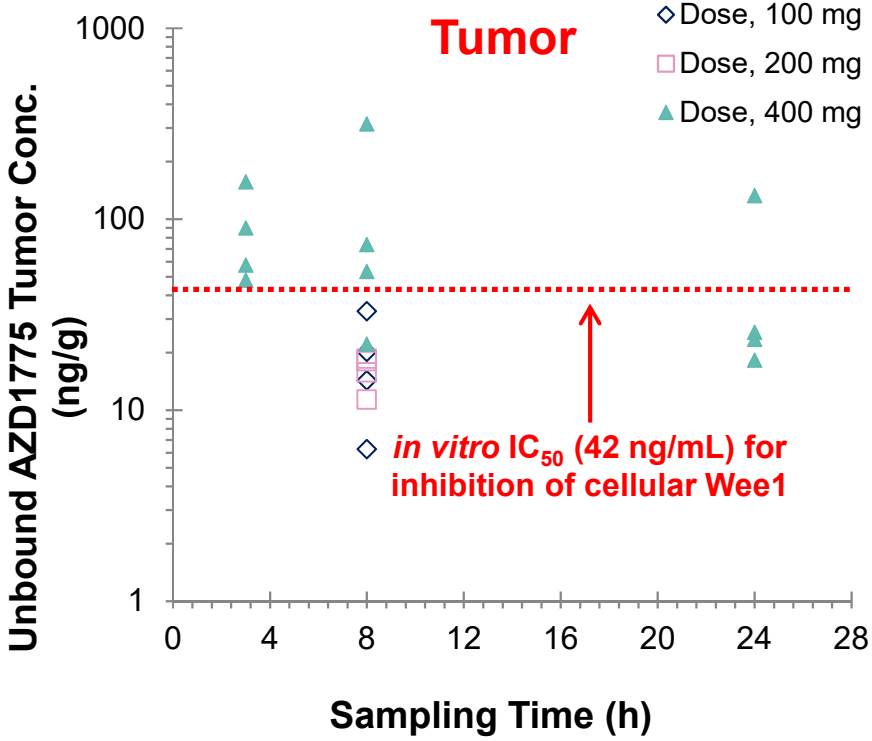


- Phosphorylated H2AX
- Phosphohistone-3
- Cleaved Caspase-3
- Cyclin E
- Phospho-Cdk1
- p53-Status
- Checkpoint Regulators
- Transport Proteins

BARROW Neurological Institute

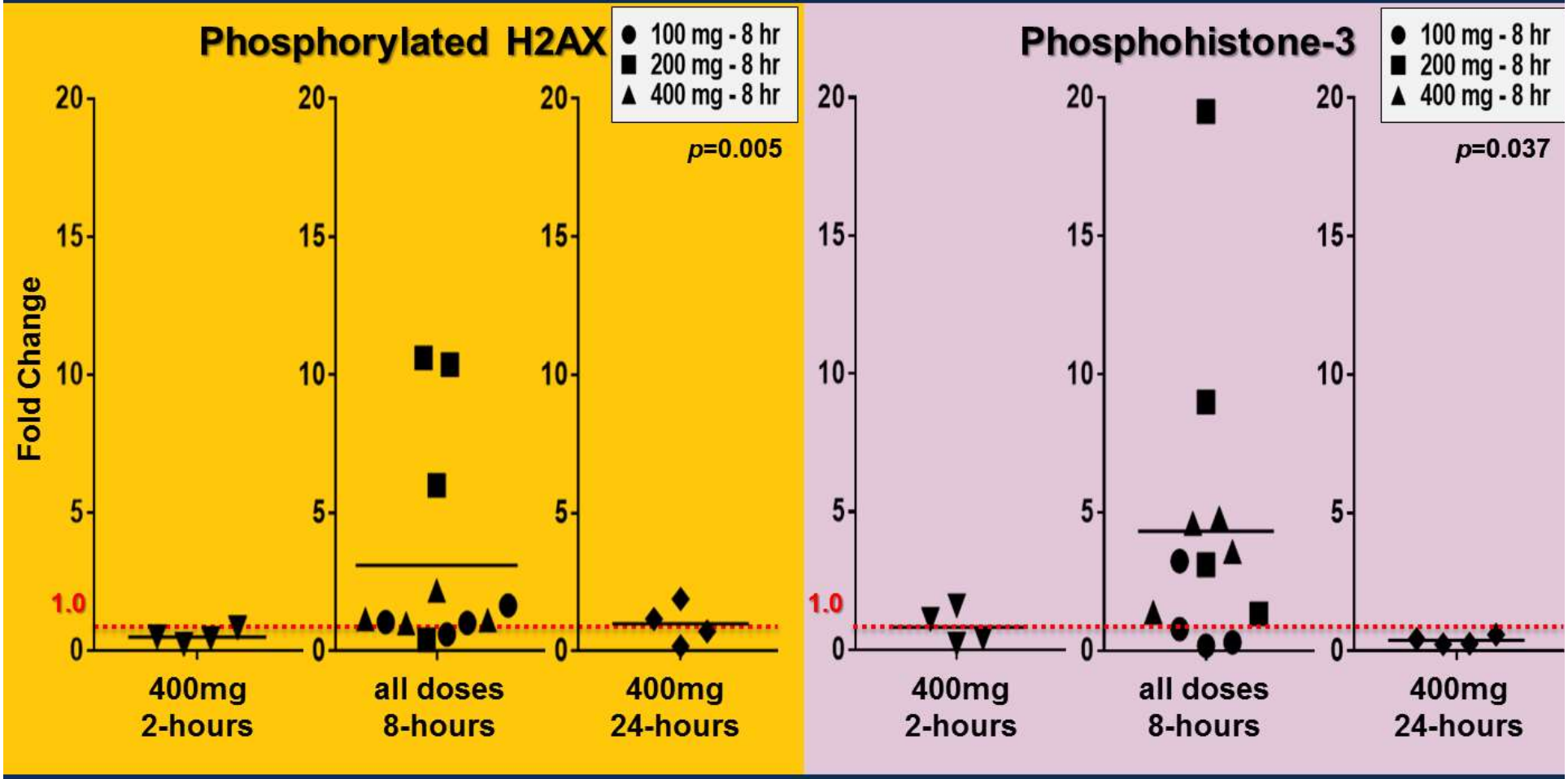
AZD1775 Pharmacokinetics in GBM



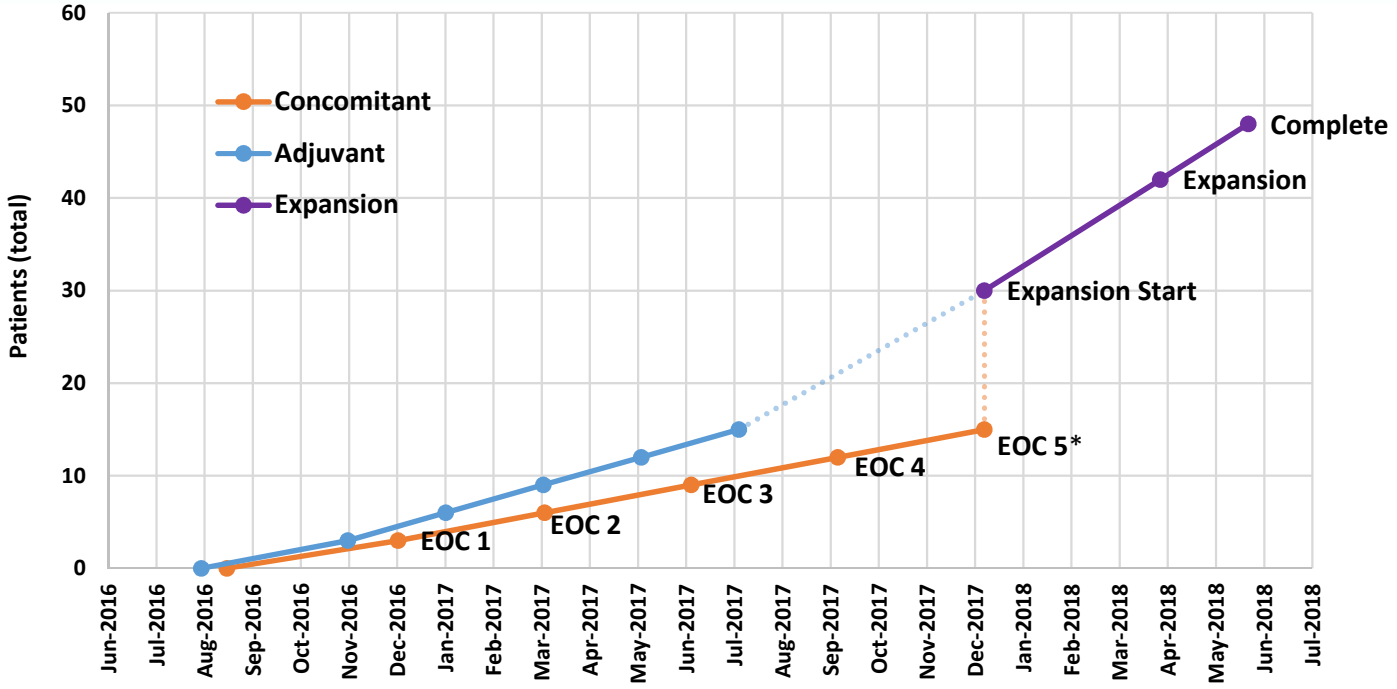


- AZD1775 plasma exposure increased with the increase of dose
- 2 to 24 h after 400mg dose, unbound (pharmacologically-active) drug concentrations in tumor ranged from 18 – 315 ng/g, with mean concentration (85 ng/g) > *in vitro* IC_{50} (42 ng/mL) for inhibition of cellular Wee1 activity

AZD1775 Pharmacodynamics in GBM



RT/TMZ→TMZ + marizomib in newly diagnosed glioblastoma



CONCOMITANT TREATMENT (MRZ+RT+TMZ 6 wks, BREAK 4 wks)				
Cohort	Dose (mg/m^2)	N*	Safety Evaluation	Timing - First Pt Dose to Safety Evaluation
1	0.55	3	8 wks	14 wks
2	0.7	3	8 wks	14 wks
3	0.8	3	8 wks	14 wks
4	1.0**	3	8 wks	14 wks
5	1.2	3	8 wks	14 wks

ADJUVANT TREATMENT (MRZ+TMZ 28-day cycle)				
Cohort	Dose (mg/m^2)	N	Safety Evaluation	Timing - First Pt Dose to Safety Evaluation
1	0.55	3	4 wks	10 wks
2	0.7	3	4 wks	10 wks
3	0.8	3	4 wks	10 wks
4	1.0**	3	4 wks	10 wks
5	1.2	3	4 wks	10 wks

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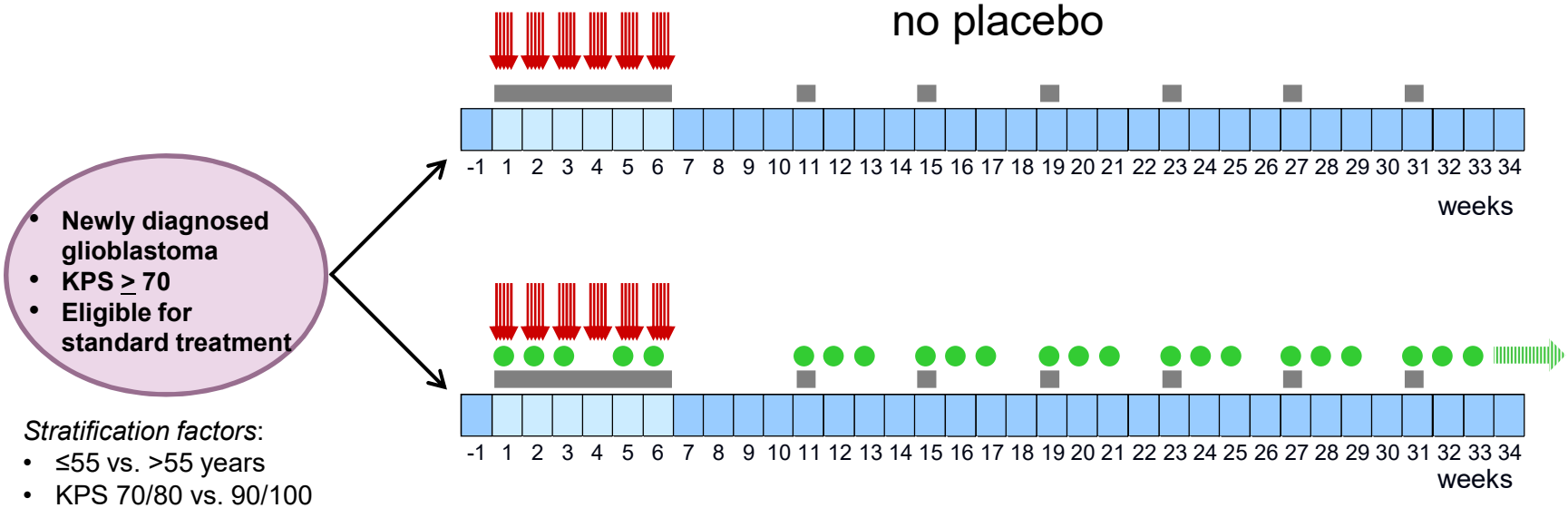
MRZ-112 trial: 3+3 design

- If none of the first 3 evaluable patients in a dose cohort experience a DLT, then enrollment into the next higher dose cohort can be initiated.
- If 1 of the first 3 evaluable patients in a dose cohort experiences a DLT, then an additional 3 patients will be enrolled into the same cohort.
- If 1/6 evaluable patients in the expanded 6-patient cohort experiences a DLT, then the next higher dose cohort can be tested and enrollment of the next 3 patients at the next higher dose level can be initiated.
- If ≥ 2/6 evaluable patients in the expanded 6-patient cohort experience a DLT, then the MTD has been exceeded and no further dose-escalation will occur.

MRZ-112: cohorts / extent of surgery

MRZ	Concomitant Patients			Adjuvant Patients		
mg/m^2	Pt ID	Surgical Notes	Category	Pt ID	Surgical Notes	Category
0.55	101-C101	Subtotal resection	Partial	101-A101	Subtotal resection	Partial
	101-C102	Subtotal resection	Partial	101-A102	Subtotal resection	Partial
	101-C103	Subtotal resection	Partial	101-A103	Subtotal resection	Partial
0.7	301-C201	Partial resection	Partial	105-A201	Sub total resection	Partial
	301-C202	Left frontal craniotomy	Unknown	301-A202	Partial resection	Partial
	101-C203	Subtotal resection	Partial	101-A203	Subtotal resection	Partial
				104-A204	Partial resection	Partial
				105-A206	Grand total resection	Complete
				301-A207	Complete lobectomy	Complete
0.8	301-C301	Right frontal lobectomy	Partial	104-A301	Subtotal resection	Partial
	104-C302	Gross total resection	Complete	301-A302	Partial craniotomy	Partial*
	104-C303	Gross total resection	Complete	101-A303	Subtotal resection	Partial
1.0	105-C402	Laser ablation, micro dissection	Partial	101-A401	Subtotal resection	Partial
	101-C403	Subtotal resection	Partial	106-A402	Partial resection	Partial
	104-C404	Gross total craniotomy	Complete*	301-A403	Partial craniotomy	Partial*
	101-C405	Gross total resection	Complete	301-A404	Left brain tumor biopsy	Biopsy
	105-C406	Gross total resection	Complete	301-A405	Subtotal resection	Partial
	401-C407	Gross total resection	Complete	101-A406	Subtotal resection	Partial

EORTC 1709



- **Newly diagnosed glioblastoma**
- **KPS ≥ 70**
- **Eligible for standard treatment**

Stratification factors:
- ≤55 vs. >55 years
- KPS 70/80 vs. 90/100
- Biopsy/partial vs. complete resection
- Institution

Radiotherapy 5x per week (total dose of 60 Gy in 30 fractions)

Temozolomide 75 mg/m^2 p.o. for 6 weeks (during radiotherapy), followed (after a 4 weeks' interval) by up to 6 cycles of maintenance TMZ chemotherapy 150-200 mg/m^2 p.o., days 1-5 out of 28 days

Marizomib 0.8 mg/m2 .v. at days 1, 8, 15, 29 and 36 during radiotherapy, followed (after a 4 weeks' interval) by adjuvant treatment at days days 1, 8, and 15 of a 28 day cycle until disease progression, unacceptable toxicity or withdrawal of consent

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NEWS FOCUS | BRAIN CANCER

A Viral Link to Glioblastoma?

Greg Miller
+ See all authors and affiliations

Science 02 Jan 2009:
Vol. 323, Issue 5910, pp. 30-31
DOI: 10.1126/science.323.5910.30

Circumstantial evidence hints that cytomegalovirus, a common herpesvirus, may play a role in the aggressive brain cancer, but big questions remain.

VIGAS study: design

IJC
International Journal of Cancer

Effects of valganciclovir as an add-on therapy in patients with cytomegalovirus-positive glioblastoma: A randomized, double-blind, hypothesis-generating study

Giuseppe Stragliotto[1], Afsar Rahbar[2*], Nina Wolmer Solberg[2*], Anders Lilja[3], Chato Taher[2], Abiel Orrego[4], Birgitta Bjurman[5], Charlotte Tammik[2], Petra Skarman[2], Inti Peredo[2,6] and Cecilia Söderberg-Nauclér[2]

- 42 patients with newly diagnosed glioblastoma with > 90% tumor resection
- Histologically verified “CMV infection” in the tumor
- Radiotherapy plus concomitant TMZ (no adjuvant TMZ?)
- Addition of valganciclovir or placebo in this trial

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Valganciclovir

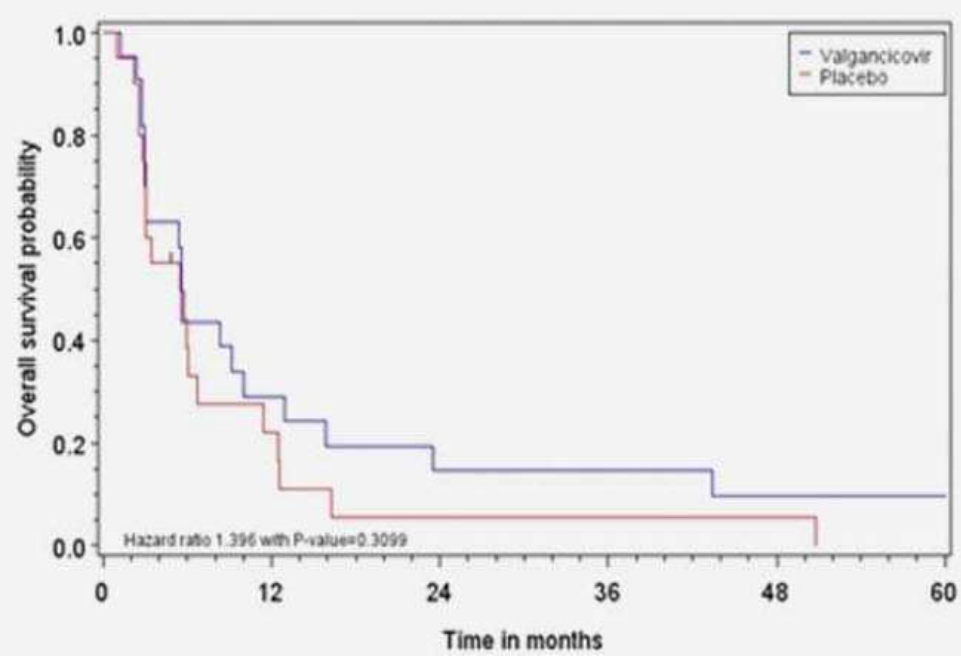
- Approved for the treatment of CMV retinitis in HIV-positive patients or for prophylaxis in immunocompromised subjects
- Side effects: nausea, diarrhea, headache, myelosuppression, fetal toxicity…
- Metabolized to ganciclovir by a CMV-encoded thymidine kinase → concentrates in CMV-infected cells
- Inhibitor of dGTP: incorporated into viral DNA → inhibits viral DNA polymerases which results in chain termination

VIGAS study: outcome

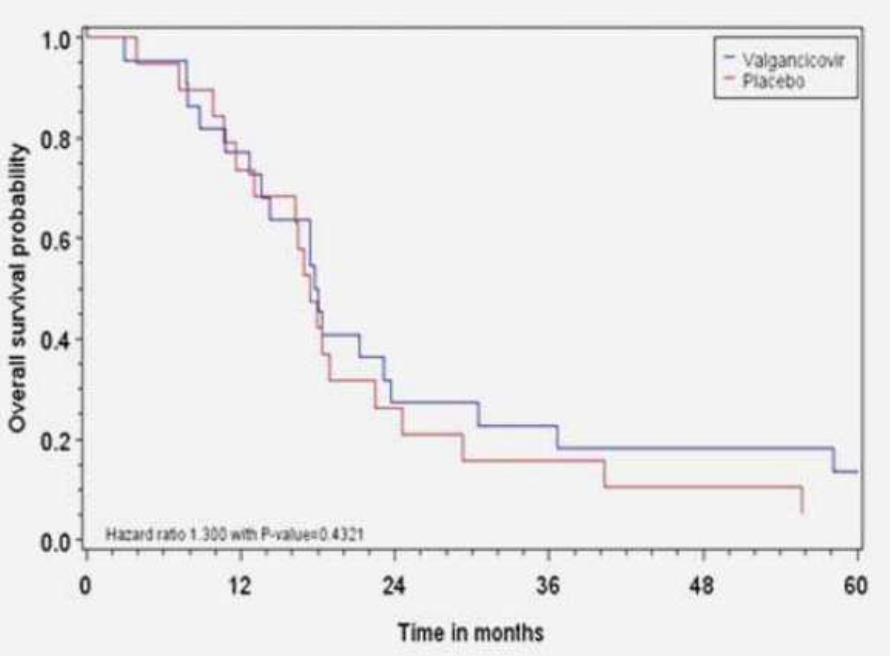
Primary endpoint: tumor size at 3 and 6 months after surgery:

→ **no difference between study arms**

Progression-free survival



Overall survival



Stragliotto et al., Int J Cancer 2013

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Valganciclovir for glioblastoma: surprise!

Survival in Patients with Glioblastoma Receiving Valganciclovir

Cecilia Söderberg-Nauclér, M.D., Ph.D.
Afsar Rahbar, Ph.D.
Giuseppe Stragliotto, M.D., Ph.D.
Karolinska Institutet
Stockholm, Sweden

N ENGL J MED 369;10 NEJM.ORG SEPTEMBER 5, 2013

The NEW ENGLAND JOURNAL of MEDICINE

- In exploratory analyses, 22 patients receiving at least 6 months of antiviral therapy, as compared with contemporary controls, had an increased OS at 2 years

- Owing to the promising results of this study, 28 patients at our hospital have received anti-CMV therapy for compassionate use in addition to their standard therapy

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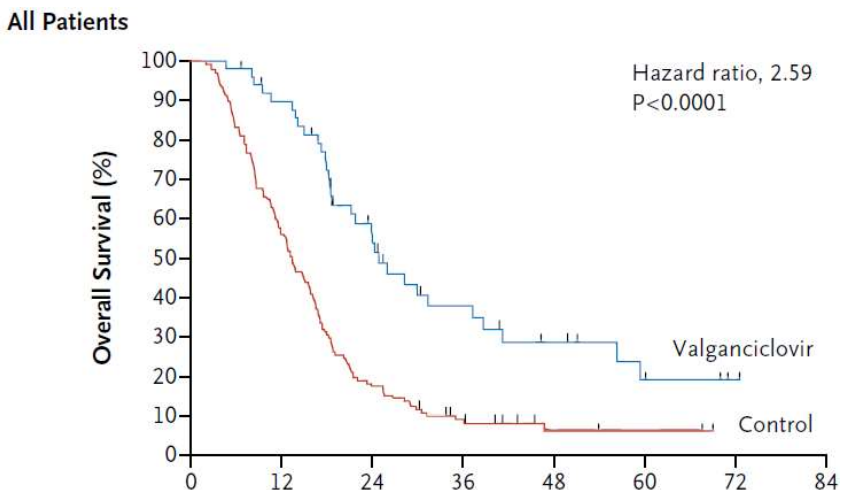
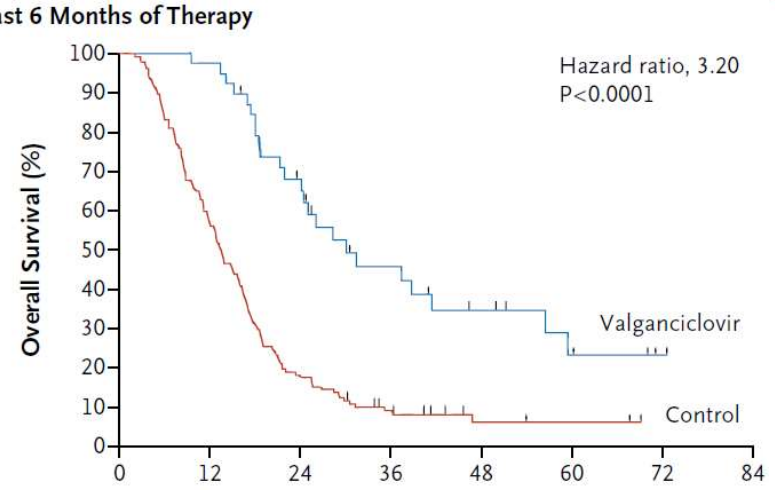
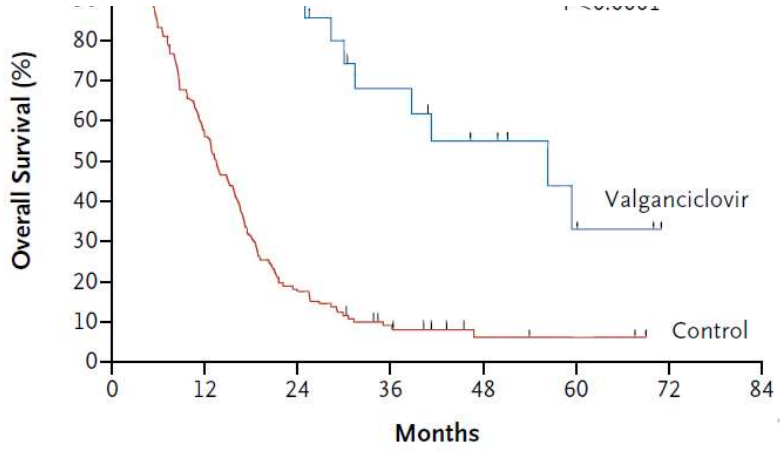
Valganciclovir-treated patients *vs.* contemporary controls





It is unlikely that any bias in patient selection could have resulted in these high rates of survival



No. at Risk								
Valganciclovir	25	24	18	11	7	3	0	0
Control	137	79	25	10	3	2	0	0

Valganciclovir-treated patients *vs.* contemporary controls

	Valganciclovir treatment			Contemporary controls 2006–2009 (n=137)
	≥1 day (n = 50)	>6 months (n = 40)	>6 months and then maintenance therapy (n = 25)	
Mean age (years) at diagnosis (range)	57 (18–77)	55 (33–75)	56 (33–75)	48.3 (32–83)
Estimated 2-year survival	62% (p<0.0001)	70% (p<0.0001)	90% (p<0.0001)	18%
Median overall survival (months)	25.0 (CI 18.7–37.4, p<0.0001)	30.1 (CI 24.1–56.4, p<0.0001)	56.4 (CI 30.0–, upper 95% limit not reached, p<0.0001)	13.5 (CI 11.8–15.9)

	median OS	2-year OS
Stupp et al., NEJM 2005 (RT/TMZ→TMZ)	14.6 months	27%
Chinot et al., NEJM 2014 (RT/TMZ→TMZ)	16.7 months	30%

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Valganciclovir-treated patients *vs.* contemporary controls

- Heterogeneous cohorts with respect to standard treatment and timing of valganciclovir
- Valganciclovir was given only "**when there was no evidence of progression**"

  → Selection of patients with valganciclovir exposure of 6 months after surgery or after 6 months of standard treatment

  → Enrichment for favorable outcome

  → Creation of a new long-term benefitting sub-group of patients

- No documentation of factors associated with longer survival, e.g. extent of resection, IDH, MGMT etc.

Journal of Clinical Neuroscience 16 (2009) 748–754

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

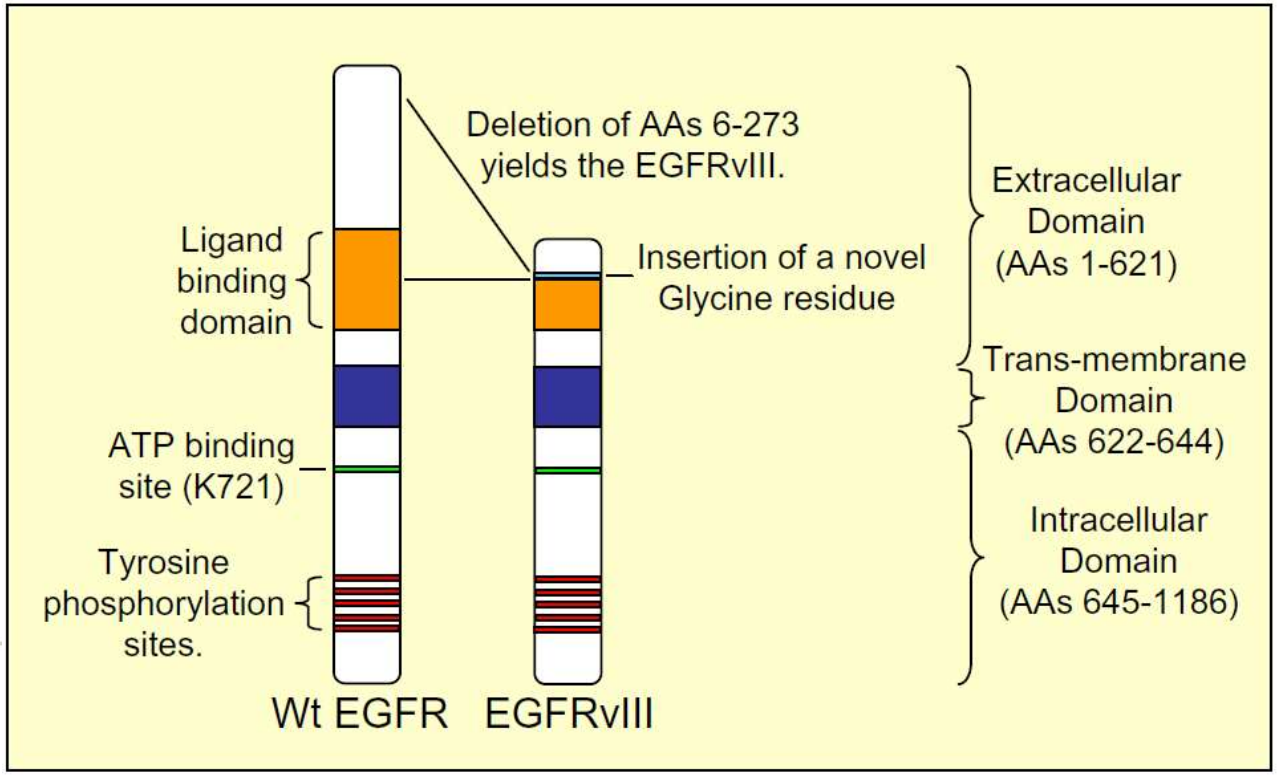
journal homepage: www.elsevier.com/locate/jocn

Review

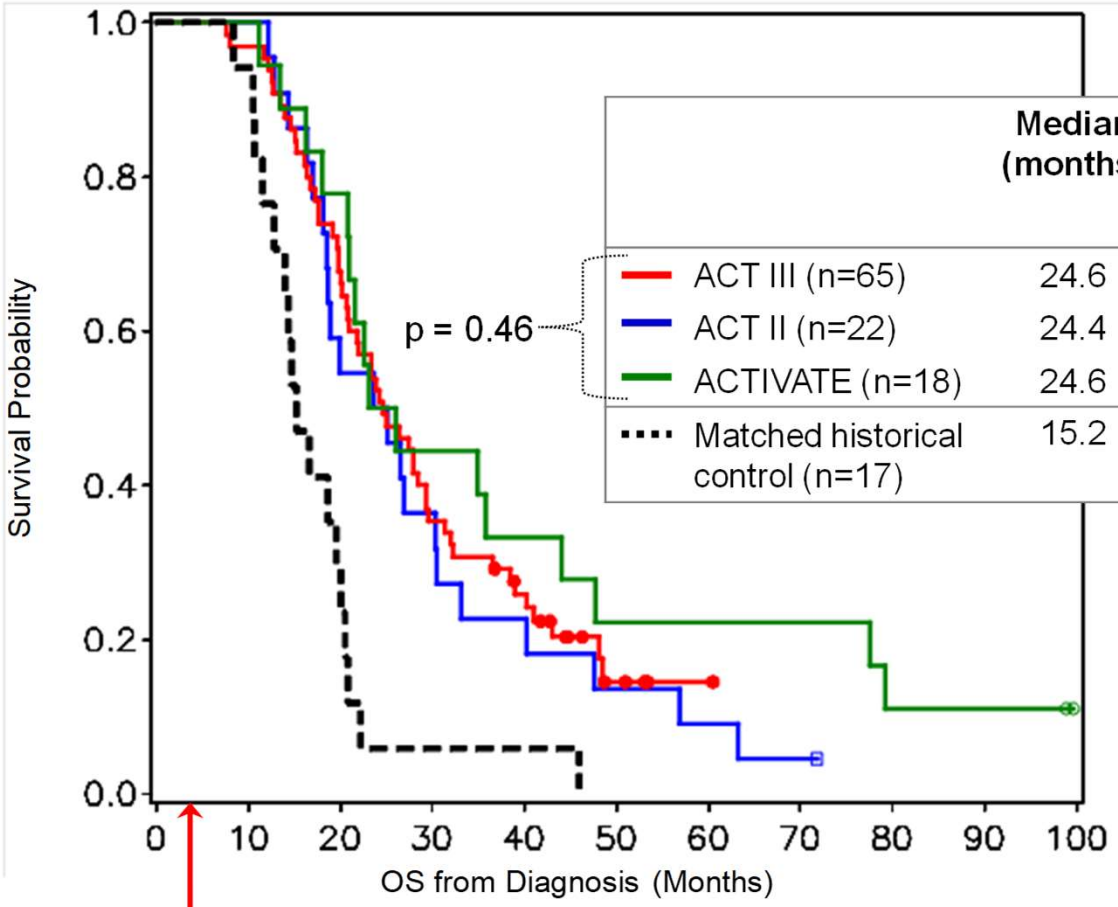
The EGFRvIII variant in glioblastoma multiforme

Hui K. Gan [a], Andrew H. Kaye [b,c], Rodney B. Luwor [b,*]

[a] Department of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, Canada
[b] Department of Surgery, Level 6, Clinical Sciences Building, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia
[c] Department of Neurosurgery, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia



Rindopepimut
Peptide vaccine targeting EGFRvIII



	Median (months)	OS at 24 Months	OS at 36 Months	Comparison to Historical Control
ACT III (n=65)	24.6	52%	31%	p = <0.0001
ACT II (n=22)	24.4	50%	23%	p = 0.0034
ACTIVATE (n=18)	24.6	50%	33%	p = 0.0003
Matched historical control (n=17)	15.2	6%	6%	

Vaccinations begin approximately 3 months after diagnosis

Median duration of follow-up:
ACT III: 48.7 months
ACT II: 71.8 months
ACTIVATE: 99.3 months

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ACT-IV: trial design

Newly diagnosed glioblastoma

- **RT/TMZ completed**
- **EGFRvIII mutation**

Adjuvant TMZ/Placebo ▸P maintenance

Adjuvant TMZ/Rindopepimut ▸ R maintenance

- Blinded study vaccine (rindopepimut/GM-CSF or KLH as control)
- ***Priming*: 2 injections, 2 weeks after RT/TMZ**
- During adjuvant TMZ: 1 injection on day 22 of every cycle
- Maintenance: 1 injection per month

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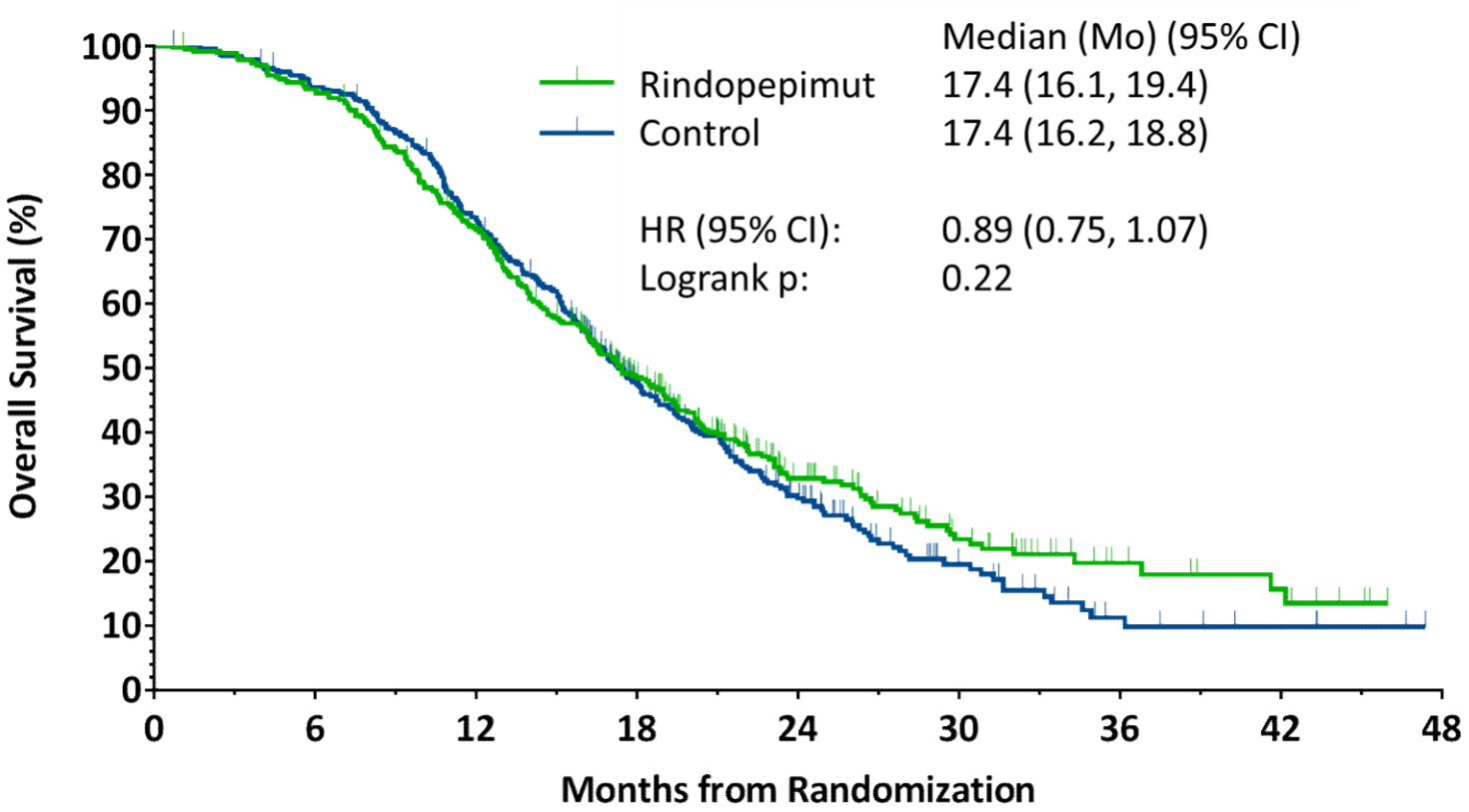
ACT-IV outcome

Overall surival



Number at Risk									
Rindopepimut	371	345	261	159	72	32	12	7	0
Control	374	347	268	149	73	25	8	4	0

Weller et al., Lancet Oncol 2017

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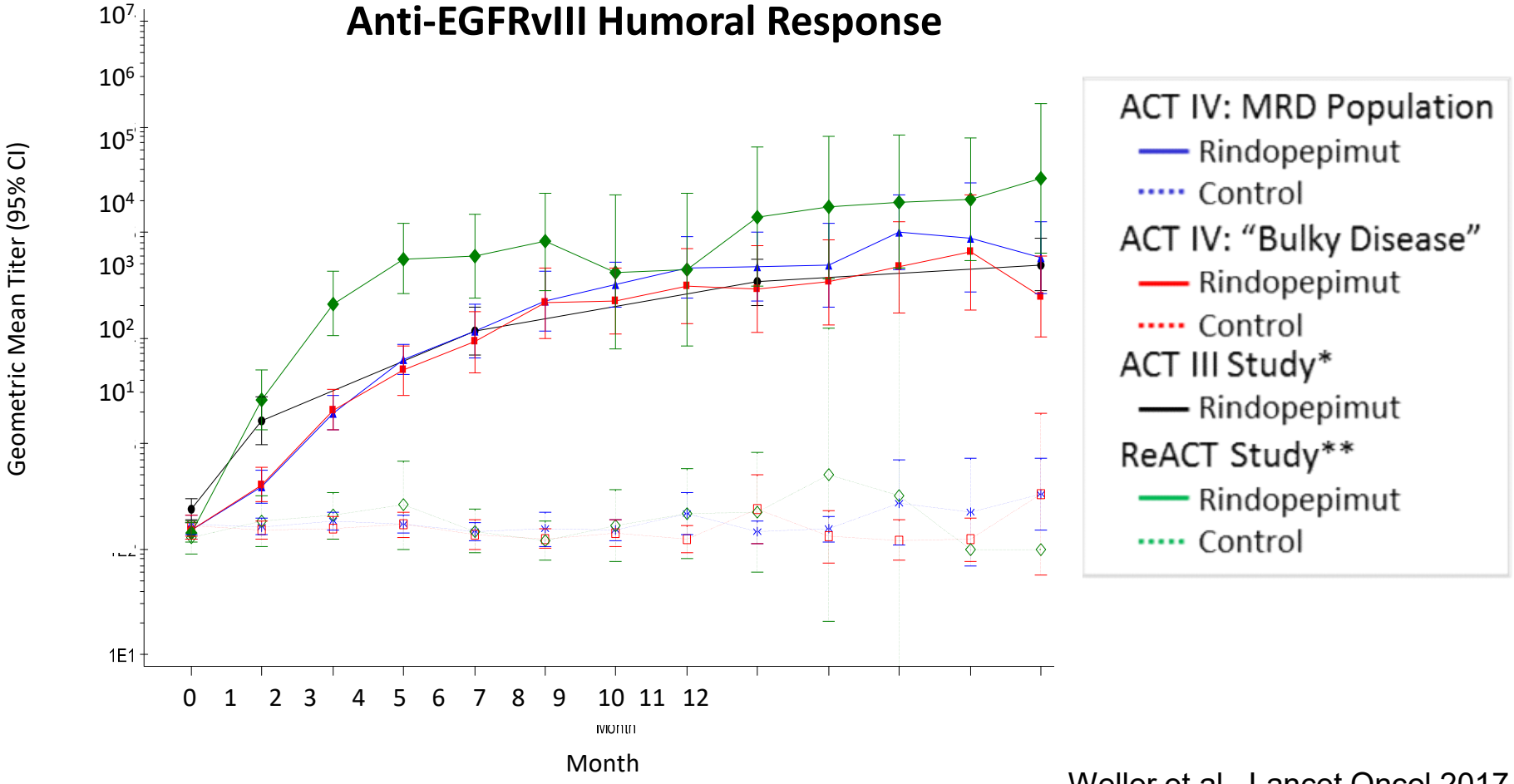
ACT-IV outcome
Humoral immune response



Weller et al., Lancet Oncol 2017

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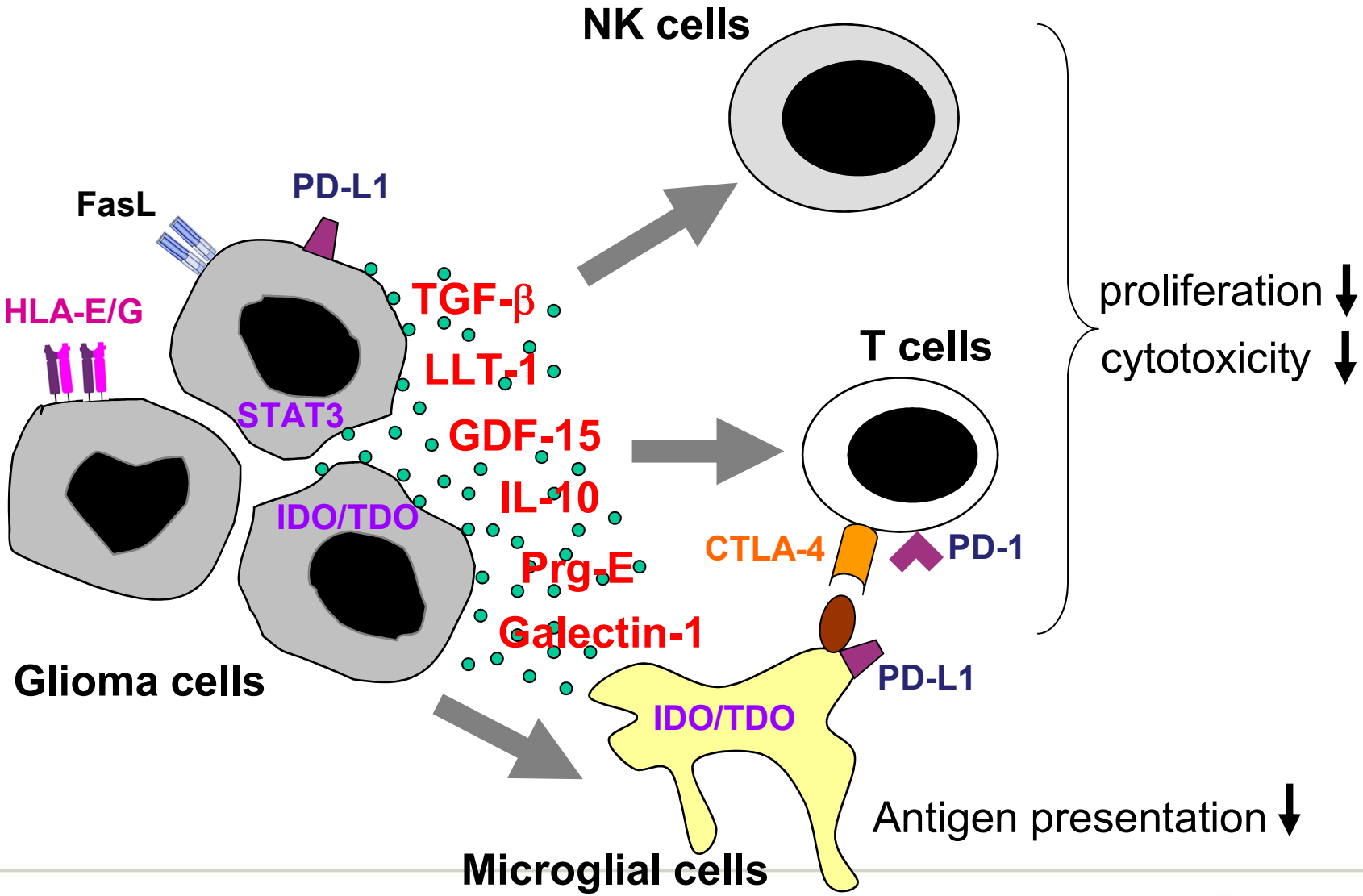
Glioma immunobiology

Multiple immunosuppressive mechanims



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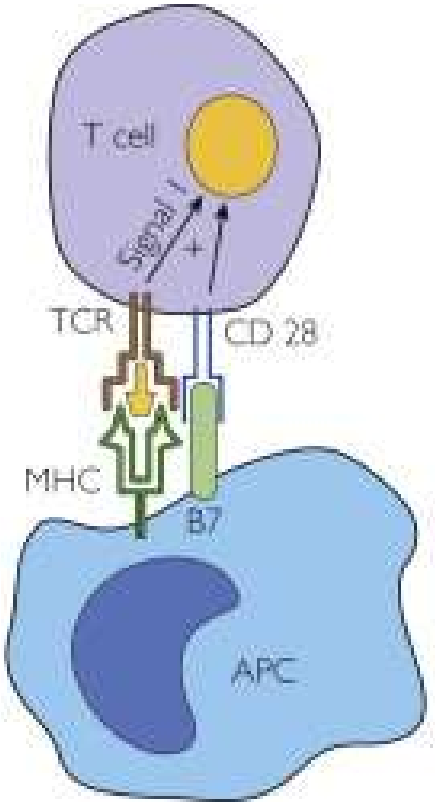
Function of CTLA-4 and PD-1



Engagement of CTLA-4 or PD-1 inhibits T cell activity

=> Inhibition of these «checkpoint» molecules may boost immune reponses against a tumor

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Immune checkpoint inhibitors

- **Immune checkpoint inhibitors may exert strong anti-tumor activity:**

  => Melanoma: anti-CTLA-4 alone vs. anti-PD-1 alone vs. combined treatment

  => Pembrolizumab and nivolumab have been approved for advanced melanoma and other tumor entities

- **May these drugs also mount anti-tumor immune responses against neoplasms in the CNS?**

Checkpoint inhibitors are active against brain metastases

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

Sarah B Goldberg, Scott N Gettinger, Amit Mahajan, Anne C Chiang, Roy S Herbst, Mario Sznol, Apostolos John Tsiouris, Justine Cohen, Alexander Vortmeyer, Lucia Jilaveanu, James Yu, Upendra Hegde, Stephanie Speaker, Matthew Madura, Amanda Ralabate, Angel Rivera, Elin Rowen, Heather Gerrish, Xiaopan Yao, Veronica Chiang, Harriet M Kluger

Lancet Oncol **2016; 17: 976–83**

BJC

British Journal of Cancer (2017), 1–6 | doi: 10.1038/bjc.2017.142

Keywords: metastatic melanoma; brain metastases; anti-PD1 therapy; corticosteroids; pembrolizumab; nivolumab

Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases

Sagun Parakh[1,2,3,11], John J Park[4,5,11], Shehara Mendis[6], Rajat Rai[5,7], Wen Xu[8], Serigne Lo[5,7], Martin Drummond[5,7], Catherine Rowe[8], Annie Wong[8], Grant McArthur[8], Andrew Haydon[6], Miles C Andrews[1,2], Jonathan Cebon[1,2], Alex Guminski[5,7,9], Richard F Kefford[4,7,10], Georgina V Long[5,7,9], Alexander M Menzies[5,7,9], Oliver Klein[1,2,12] and Matteo S Carlino*[,4,5,7,12]

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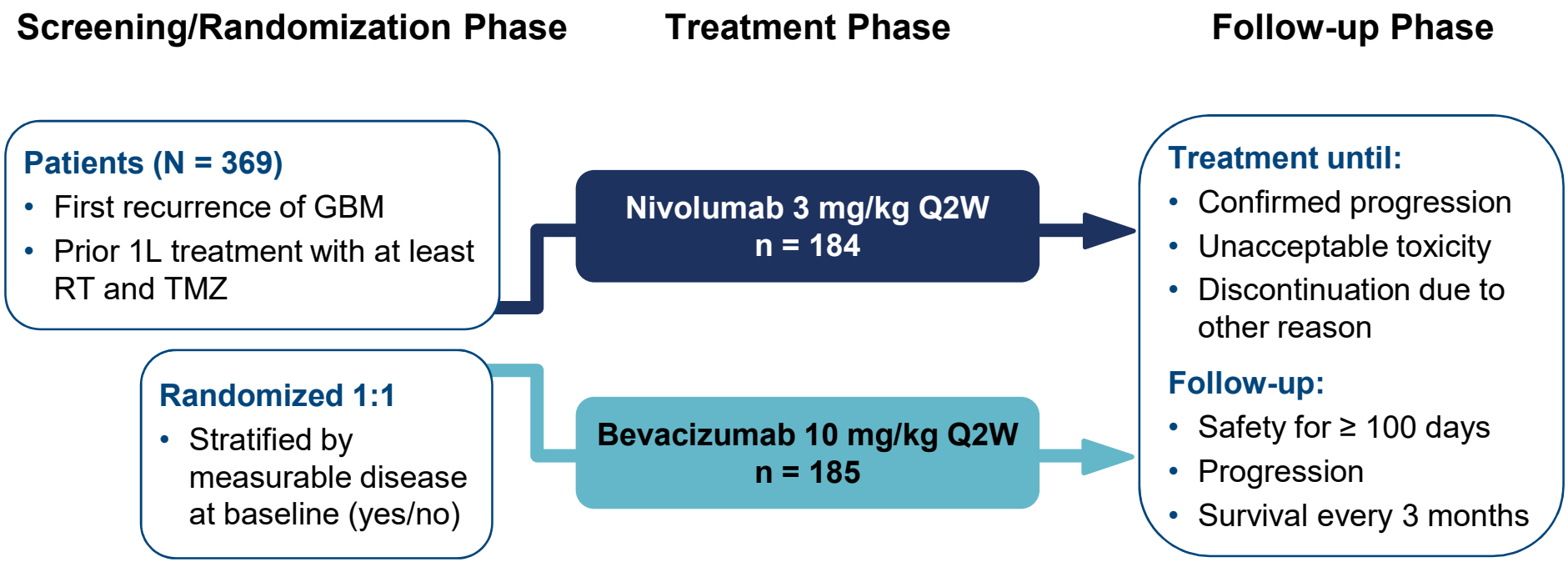
CheckMate 143
Randomized phase III trial



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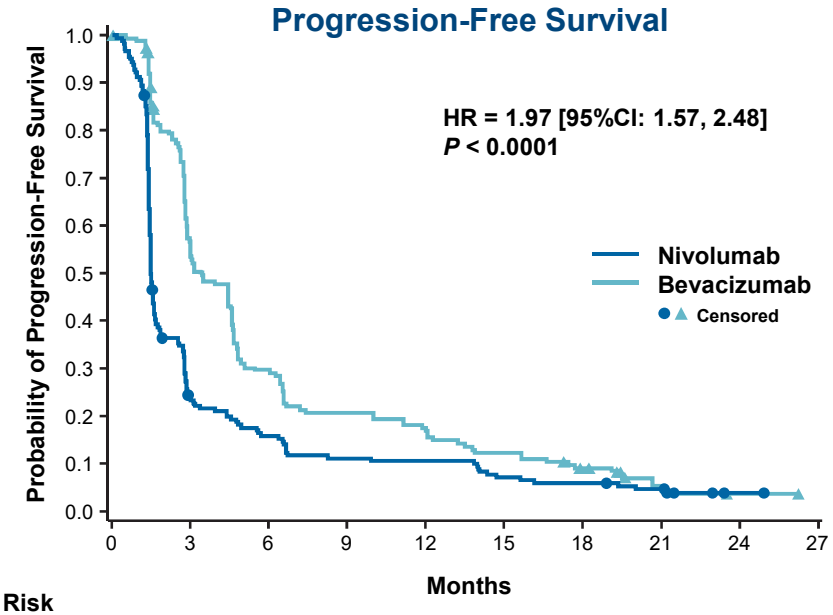
CheckMate 143
Progression-free and overall survival

PFS

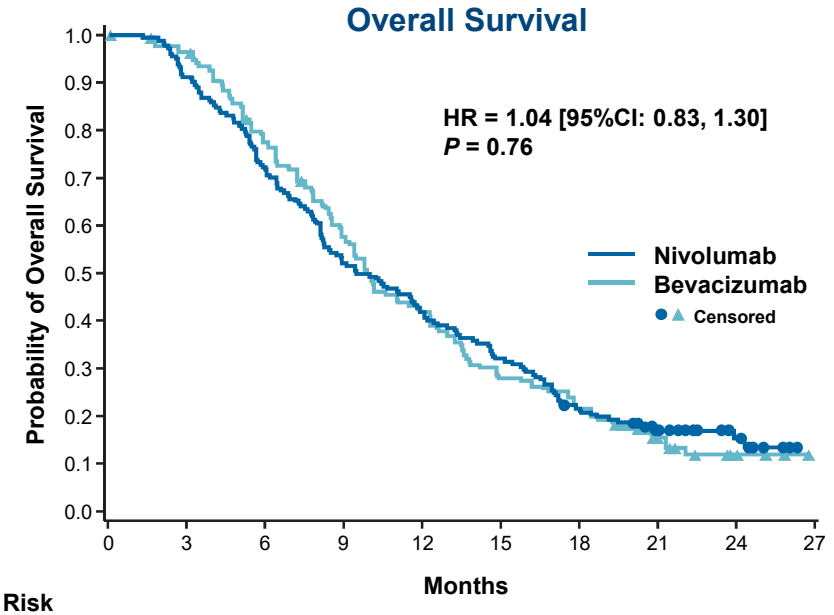
	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], months
Nivolumab	171	1.5 [1.5, 1.6]	10.5 [6.5, 15.5]
Bevacizumab	146	3.5 [2.9, 4.6]	17.4 [11.9, 23.7]



No. at Risk										
Nivolumab	184	41	27	19	18	12	10	7	1	0
Bevacizumab	185	88	46	32	27	19	12	3	1	0

OS

	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], months
Nivolumab	154	9.8 [8.2, 11.8]	41.8 [34.7, 48.8]
Bevacizumab	147	10.0 [9.0, 11.8]	42.0 [34.6, 49.3]



No. at Risk										
Nivolumab	184	168	133	96	77	59	39	24	9	0
Bevacizumab	185	169	135	99	72	48	37	14	5	0

Reardon et al., WFNOS meeting 2017

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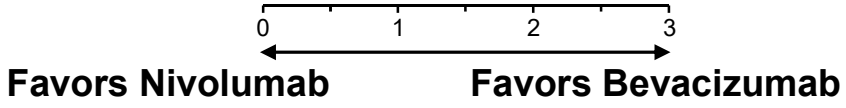
CheckMate 143
OS in prespecified patient subsets

	No. Events/No. Patients		Unstratified HR [95% CI]
	Nivolumab	Bevacizumab	
All patients	154/184	147/185	0.99 [0.79, 1.24]
KPS			
> 80%	91/113	82/103	0.94 [0.70, 1.27]
≤ 80%	63/71	64/81	1.13 [0.80, 1.60]
Measurable target lesion			
Yes	135/153	130/156	0.99 [0.78, 1.27]
No	19/31	17/29	1.01 [0.52, 1.94]
***MGMT* promoter status**			
Methylated	33/43	31/42	0.92 [0.56, 1.51]
Unmethylated	56/59	53/67	1.34 [0.92, 1.96]
Not reported/unknown	65/82	63/76	0.87 [0.62, 1.23]
Tumor PD-L1 expression			
≥ 1%	40/48	28/35	1.35 [0.83, 2.19]
< 1%	89/107	92/114	0.97 [0.72, 1.30]
Dexamethasone equivalent at baseline			
Yes	69/73	68/79	1.41 [1.01, 1.97]
No	85/111	79/106	0.84 [0.62, 1.15]



Reardon et al., WFNOS meeting 2017

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Analyses of responses

	Nivolumab n = 153[a]	Bevacizumab n = 156[a]
ORR, n (%) [95% CI]	12 (7.8) [4.1, 13.3]	36 (23.1) [16.7, 30.5]
BOR, n (%)		
CR	2 (1.3)	4 (2.6)
PR	10 (6.5)	32 (20.5)
SD	33 (21.6)	73 (46.8)
PD	107 (69.9)	26 (16.7)
Unable to determine	1 (0.7)	21 (13.5)
Not treated	1 (0.7)	16 (10.3)
Discontinued early due to toxicity	0	3 (1.9)
Other	0	2 (1.3)
Median TTR (range), months	3.0 (1.4–12.0)	1.5 (1.2–6.5)
Median DOR (range), months	11.1 (0.6–18.7)	5.3 (3.1–24.9)
PFS rate [95% CI], %		
6-months	15.7 [10.8, 21.5]	29.6 [22.7, 36.9]
12-months	10.5 [6.5, 15.5]	17.4 [11.9, 23.7]

Reardon et al., WFNOS meeting 2017

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Challenges associated with the use of immune checkpoint inhibitors

Pseudoprogression vs. (true) progression
61 yo man, recurrent glioblastoma

9/2016

THE LANCET
Oncology

Review

Immunotherapy response assessment in neuro-oncology: a report of the RANO working group

Prof Hideho Okada, MD[†], Prof Michael Weller, MD, Raymond Huang, MD, Gaetano Finocchiaro, MD, Mark R Gilbert, MD, Prof Wolfgang Wick, MD, Benjamin M Ellingson, PhD, Naoya Hashimoto, MD, Prof Ian F Pollack, MD, Alba A Brandes, MD, Enrico Franceschi, MD, Prof Christel Herold-Mende, PhD, Lakshmi Nayak, MD, Ashok Panigrahy, MD, Whitney B Pope, MD, Robert Prins, PhD, Prof John H Sampson, MD, Prof Patrick Y Wen, MD, David A Reardon, MD[†]

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Molecular profile predicts response from checkpoint inhibition

VOLUME 34 · NUMBER 19 · JULY 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency

Eric Bouffet, Valérie Larouche, Brittany B. Campbell, Daniele Merico, Richard de Borja, Melyssa Aronson, Carol Durno, Joerg Krueger, Vanja Cabric, Vijay Ramaswamy, Nataliya Zhukova, Gary Mason, Roula Farah, Samina Afzal, Michal Yalon, Gideon Rechavi, Vanan Magimairajan, Michael F. Walsh, Shlomi Constantini, Rina Dvir, Ronit Elhasid, Alyssa Reddy, Michael Osborn, Michael Sullivan, Jordan Hansford, Andrew Dodgshun, Nancy Klauber-Demore, Lindsay Peterson, Sunil Patel, Scott Lindhorst, Jeffrey Atkinson, Zane Cohen, Rachel Laframboise, Peter Dirks, Michael Taylor, David Malkin, Steffen Albrecht, Roy W.R. Dudley, Nada Jabado, Cynthia E. Hawkins, Adam Shlien, and Uri Tabori

M.D., Ph.D., Nathan Cuka, M.D., Drew M. Pardoll, M.D., Ph.D., Nickolas Papadopoulos, Ph.D., Kenneth W. Kinzler, Ph.D., Shibin Zhou, M.D., Ph.D., Toby C. Cornish, M.D., Ph.D., Janis M. Taube, M.D., Robert A. Anders, M.D., Ph.D., James R. Eshleman, M.D., Ph.D., Bert Vogelstein, M.D., and Luis A. Diaz, Jr., M.D.

N Engl J Med 2015; 372:2509-2520 | June 25, 2015 | DOI: 10.1056/NEJMoa1500596

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Conclusions

For a successful clincial trial, you need…:

- A timely question
- An appropriate endpoint
- Sufficient (financial) ressources
- Access to patients and/or a network of collaborators
- Statistical advice

Management of skull base tumours

Dr Sarah Jefferies

Cambridge University Hospitals NHS
NHS Foundation Trust

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Pre-requisites

- Excellent Imaging
- Excellent Surgery
- Anatomical knowledge
- Access to appropriate radiotherapy techniques when needed

Which tumours?

- Primary:
  - **Chordoma/chondrosarcoma**

- Secondary infiltration or involvement:

Intracranial:

Meningioma

Craniopharyngioma

Head and Neck Tumours:

Olfactory neuroblastoma

Adenoid cystic carcinoma

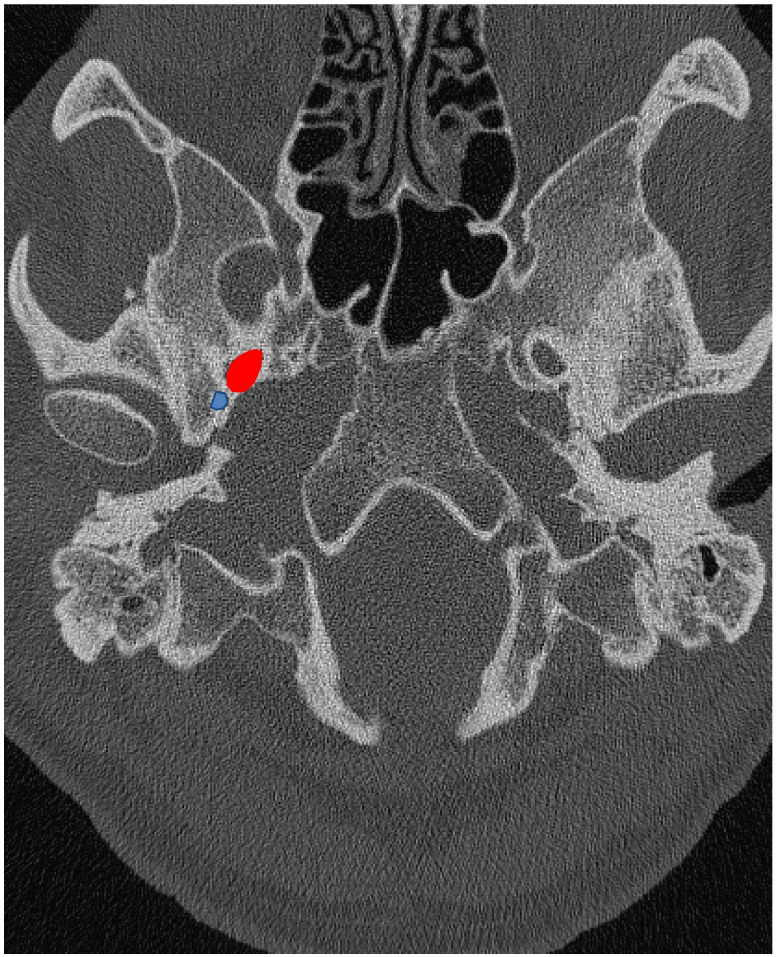
Nasopharyngeal carcinoma

Nasal cavity and paranasal sinus

Sarcoma

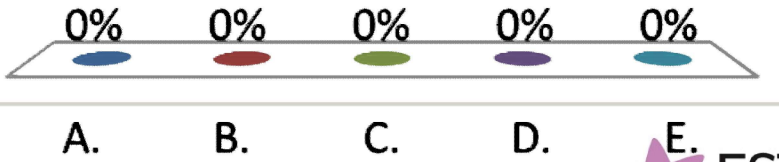
Needs anatomical knowledge

Which Foramen?



The red shape is overlying:

A. Foramen spinosum
B. Foramen lacerum
C. Jugular foramen
D. Foramen ovale
E. Foramen rotundum



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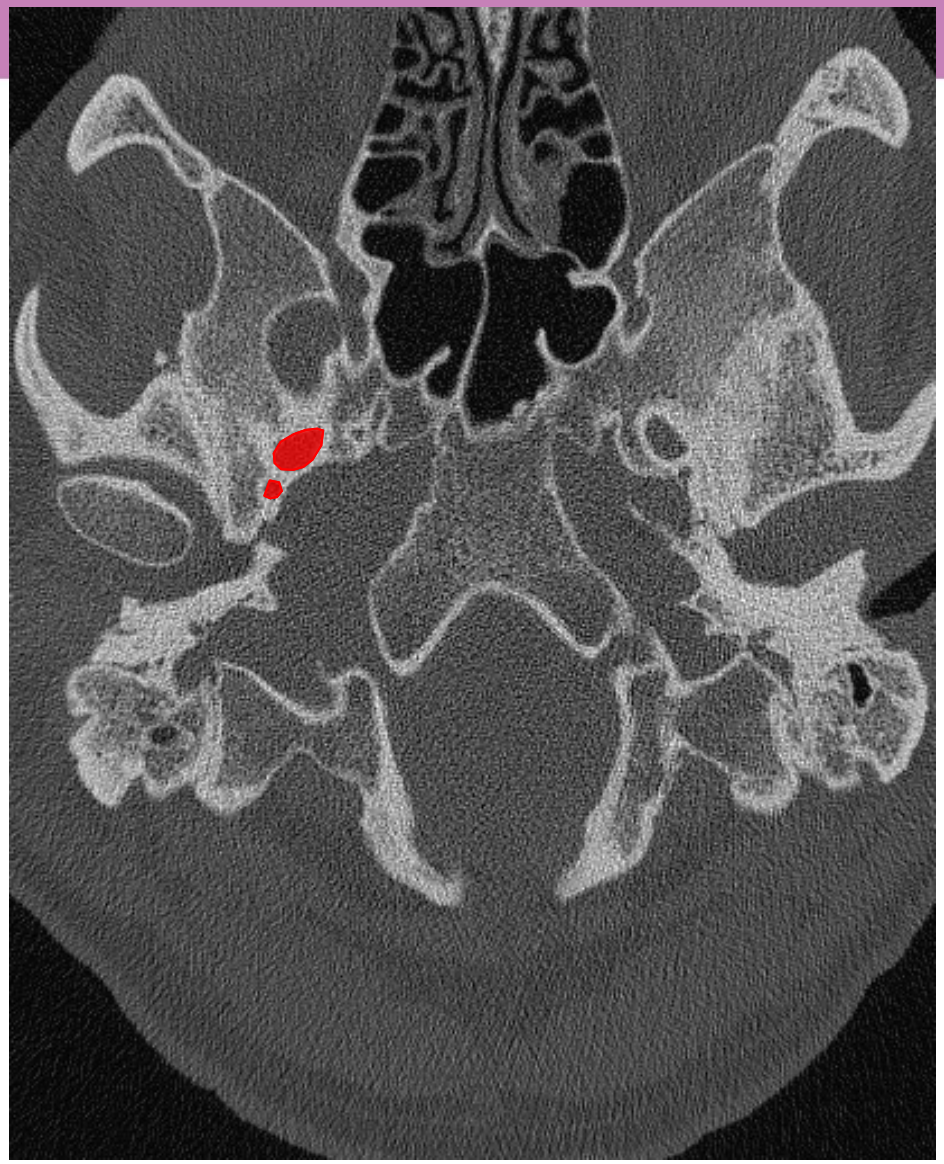
The high-heel footprint sign . . . . .



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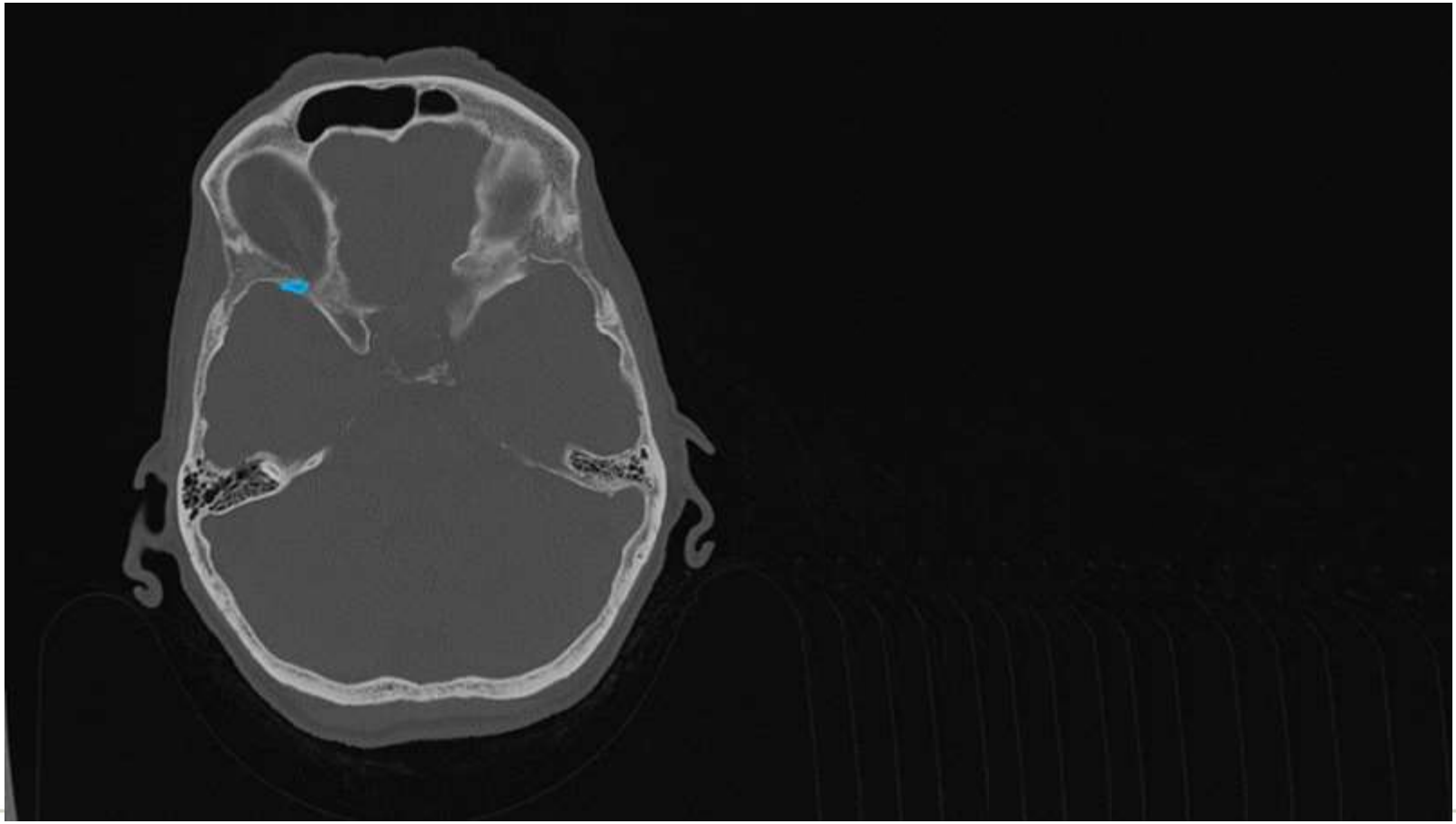
RADIOLOGICAL ANATOMY – SKULL BASE FORAMINA

- SUPERIOR ORBITAL
- OPTIC CANAL
- OLFACTORY BULB
- INTERNAL ACOUSTIC
- FORAMEN LACERUM
- CAROTID CANAL
- FORAMEN ROTUNDUM
- JUGULAR FORAMEN
- FORAMEN OVALE
- FORAMEN SPINOSUM
- HYPOGLOSSAL CANAL
- PTERYGOPALATINE FOSSA



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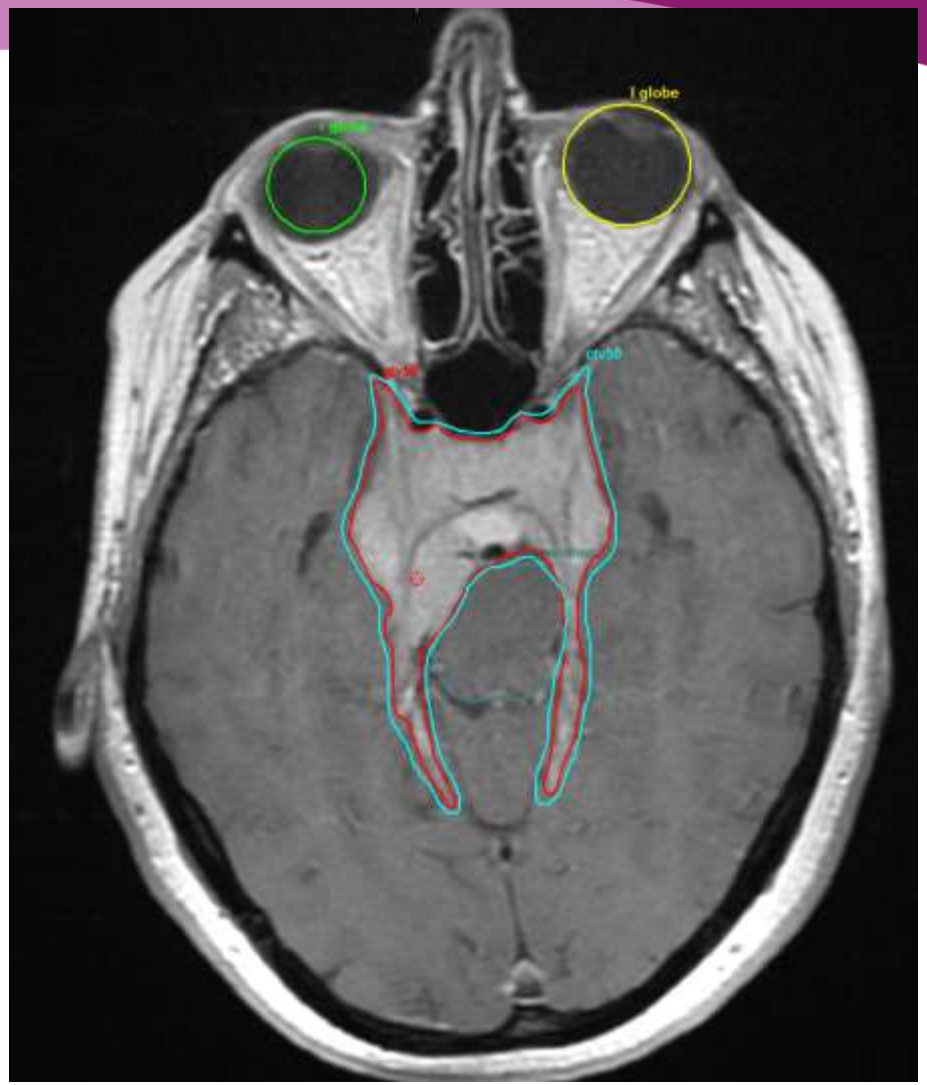
AN EXAMPLE CASE
DEMONSTRATING (MOST OF!)

55 year old lady.

- Presented with a history of gradually worsening left ptosis. No other symptoms
- O/E:
  - left III palsy (ptosis, dilated pupil)
  - left IV palsy
- Otherwise fit and well.



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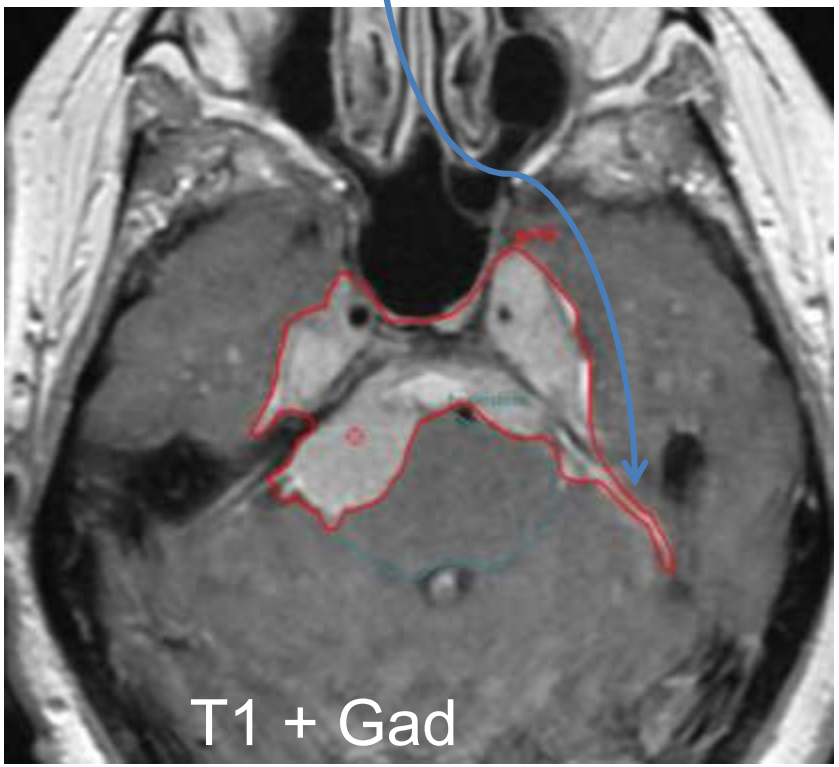
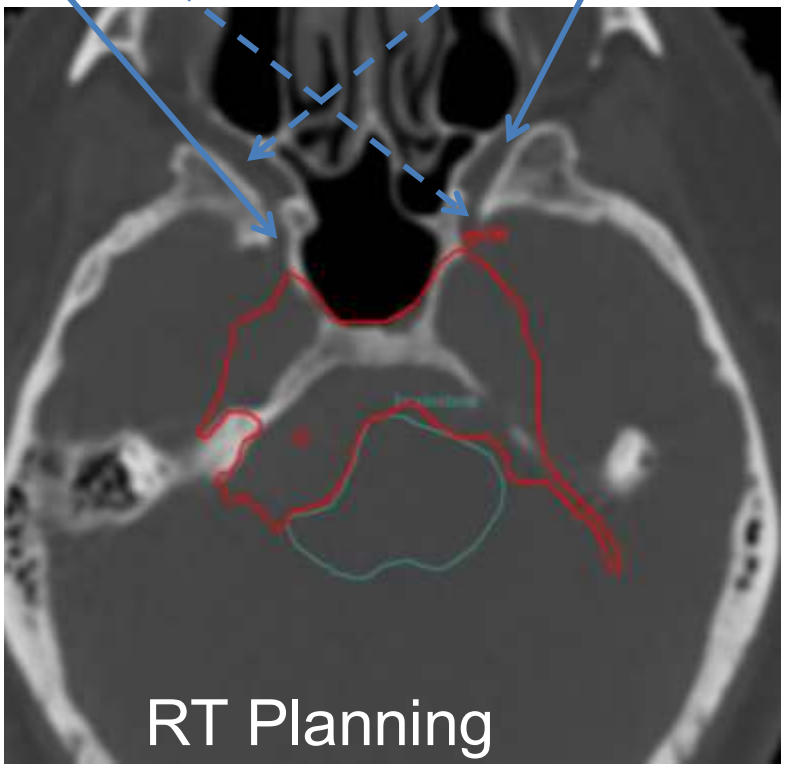
Example case - meningioma

LONG DURAL TAIL ALONG THE PETROUS TEMPORAL BONE CLEARLY VISIBLE ON MRI



FORAMEN ROTUNDUM

PTERYGOPALATINE FOSSA



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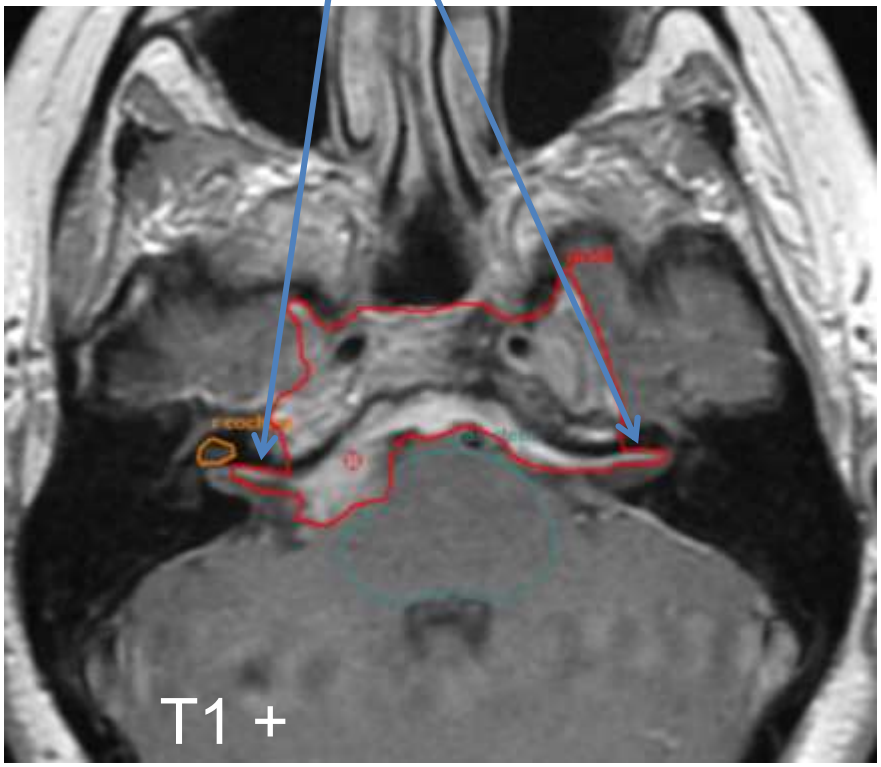
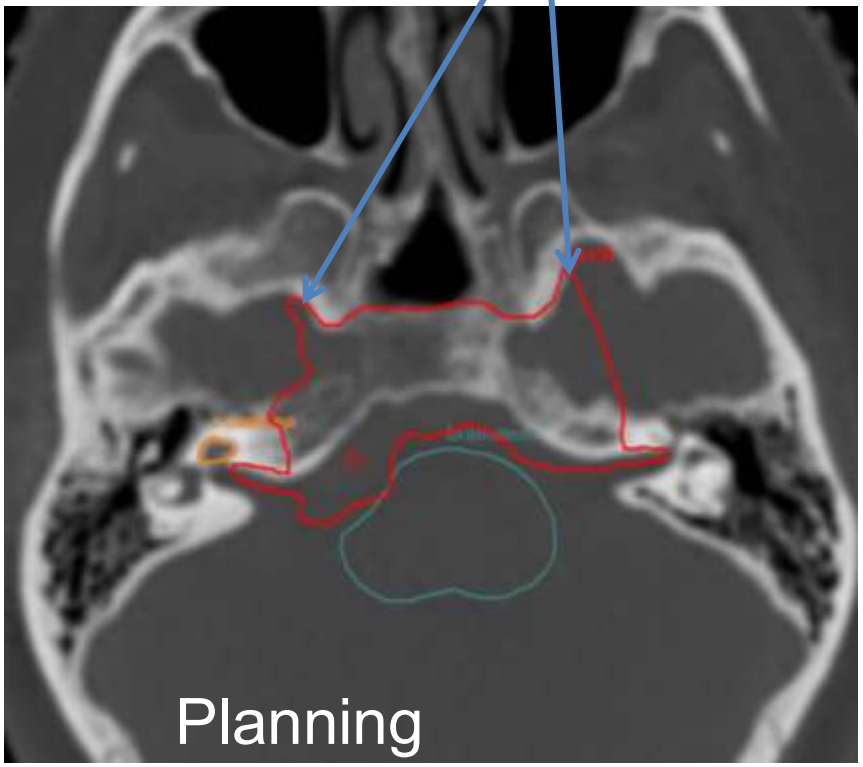
Example case - meningioma

VISIBALE DURAL TAIL INTO BOTH INTERNAL ACOUSTIC CANALS



DURAL TAIL EXTENIDNG ANTERIORLY AND INFERIORLY TOWARDS FORAMEN OVALE



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Example case - meningioma

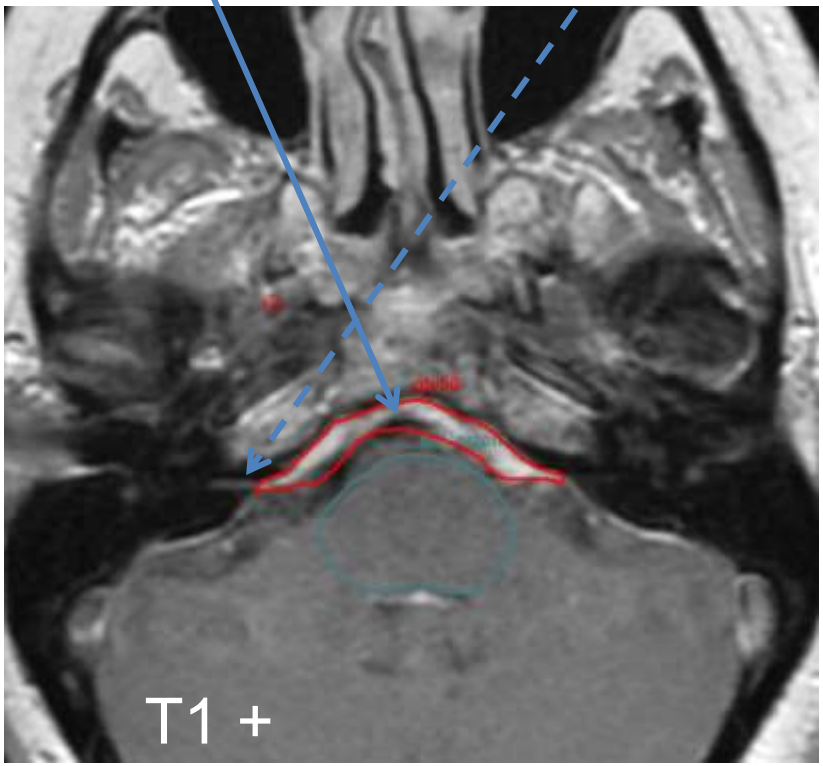
DURAL TAIL EXTENDING INFERIORLY DOWN THE CLIVUS

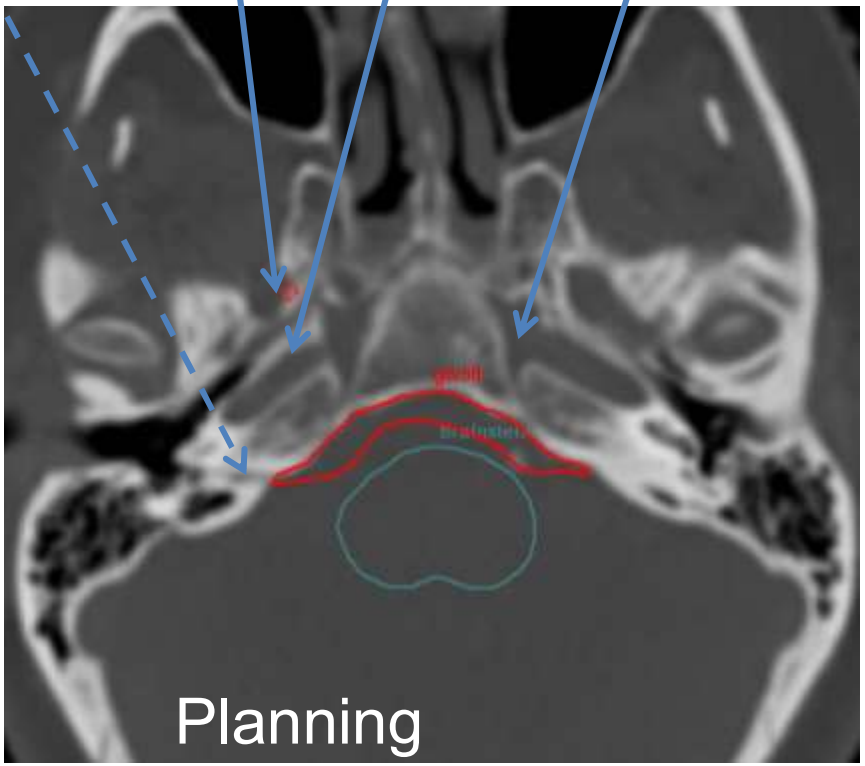
JUGULAR FORAMEN (PARS NERVOSA)

FORAMEN OVALE

CAROTID CANAL

FORAMEN LACERUM





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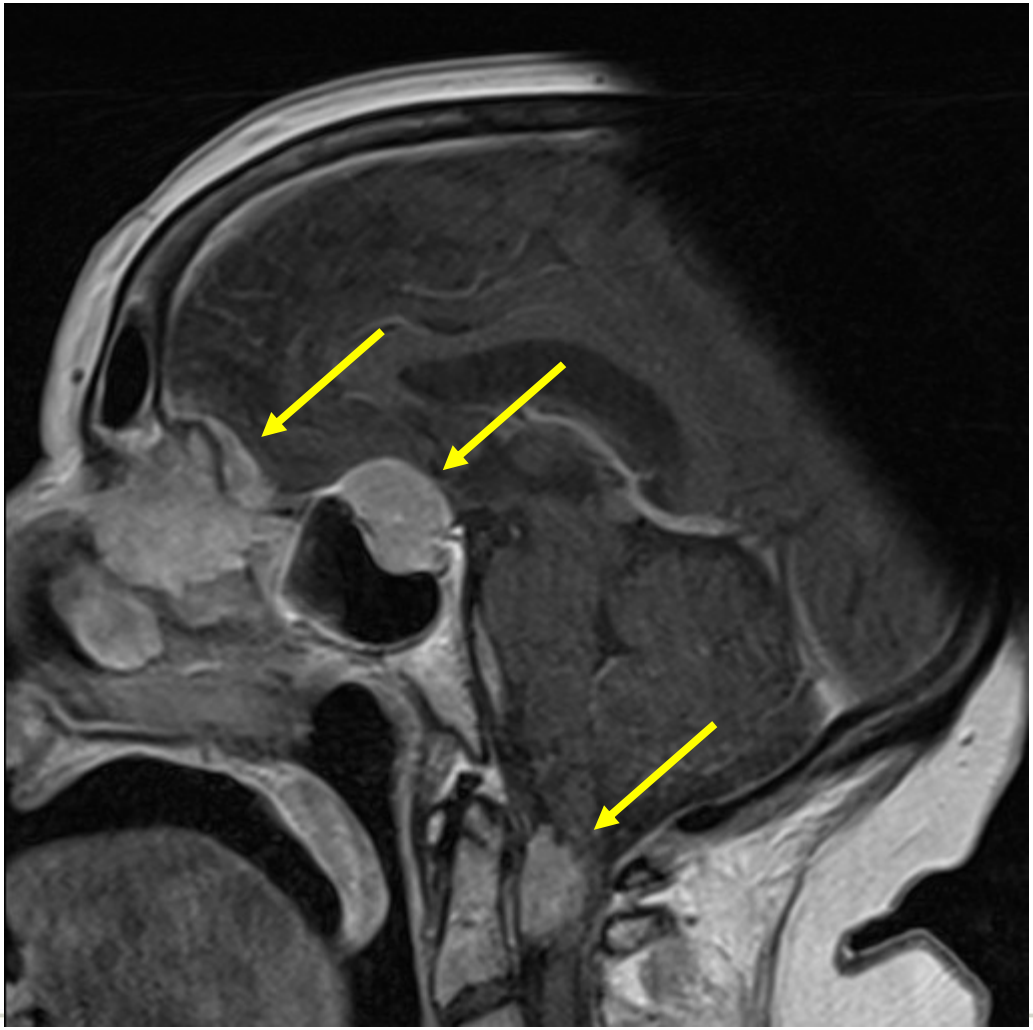
Imaging

Imaging

- Imaging is also an essential prerequisite
  - To show target better
  - For co-registered use in planning

Skull base meningioma

- Note 3 areas of disease
  - 2 areas probably contiguous
  - 3rd at cranio-cervical junction
- Partial resection of suprasellar mass, & biopsy of ethmoid mass



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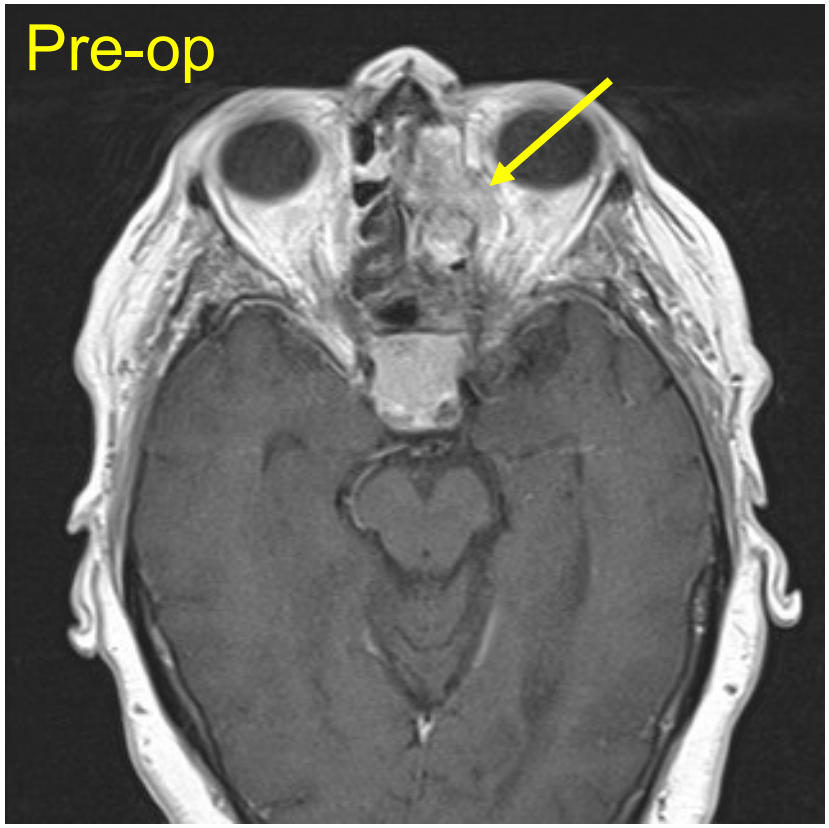
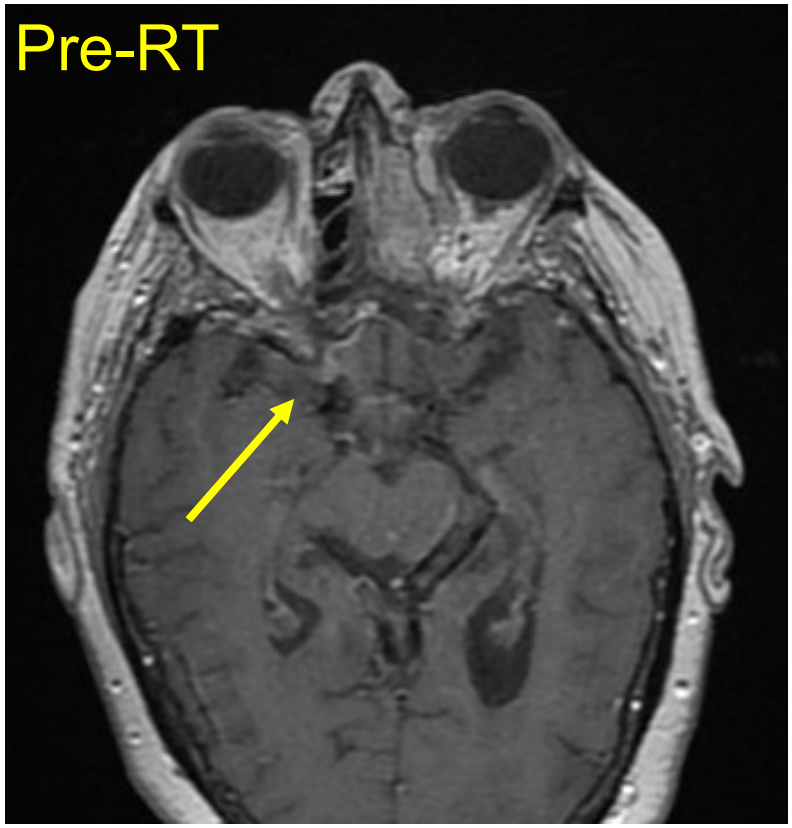
Skull base meningioma





- Definite involvement of L orbit
- Uncertain lesion at R optic foramen

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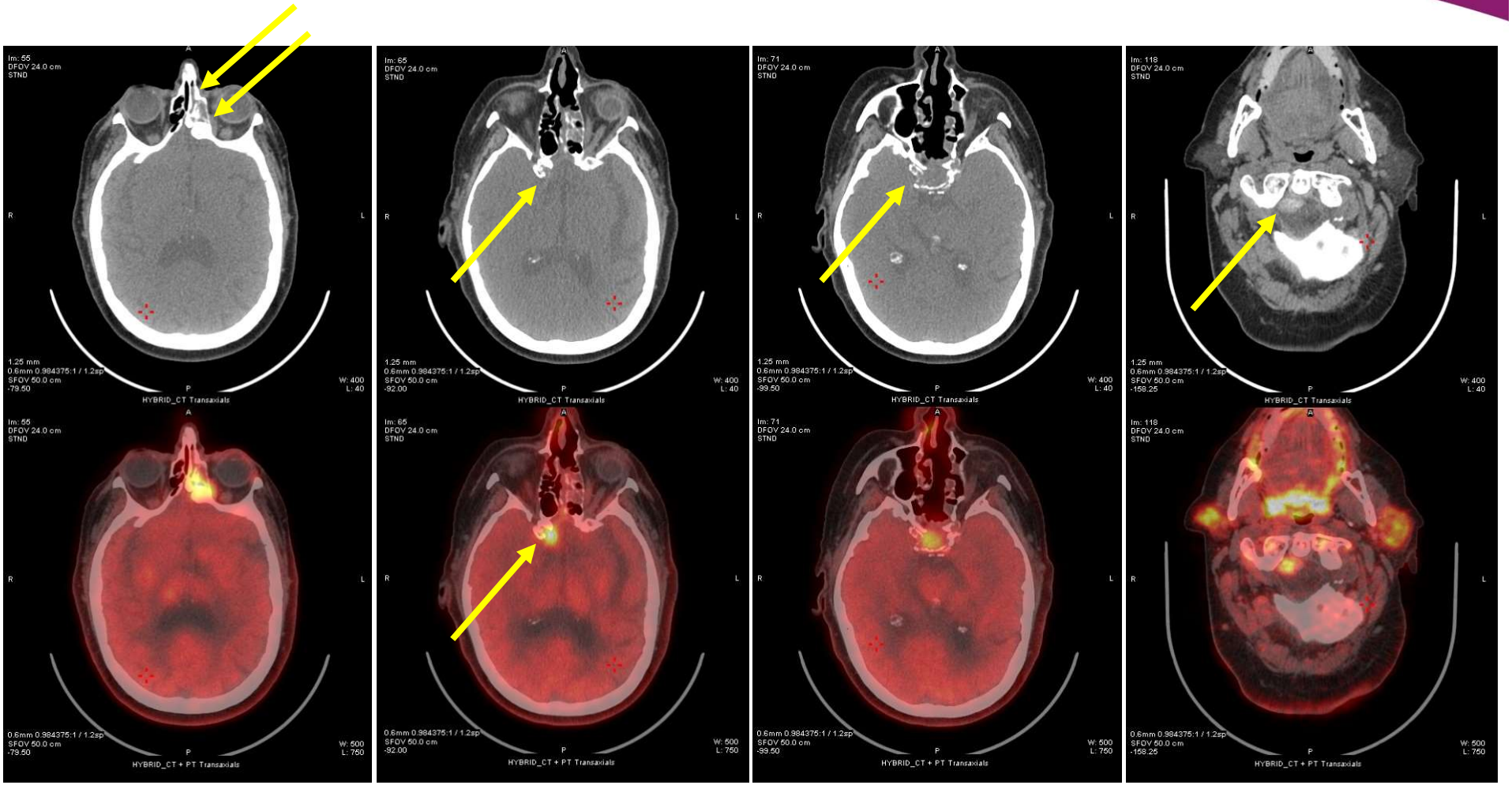
Skull base meningioma



- Methionine PET clarified area at R optic foramen

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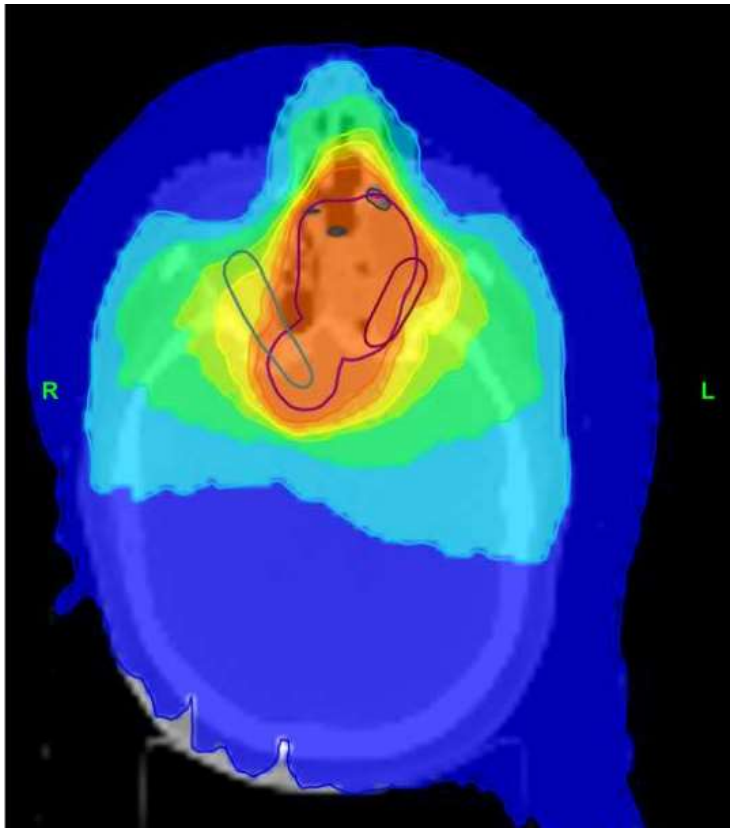
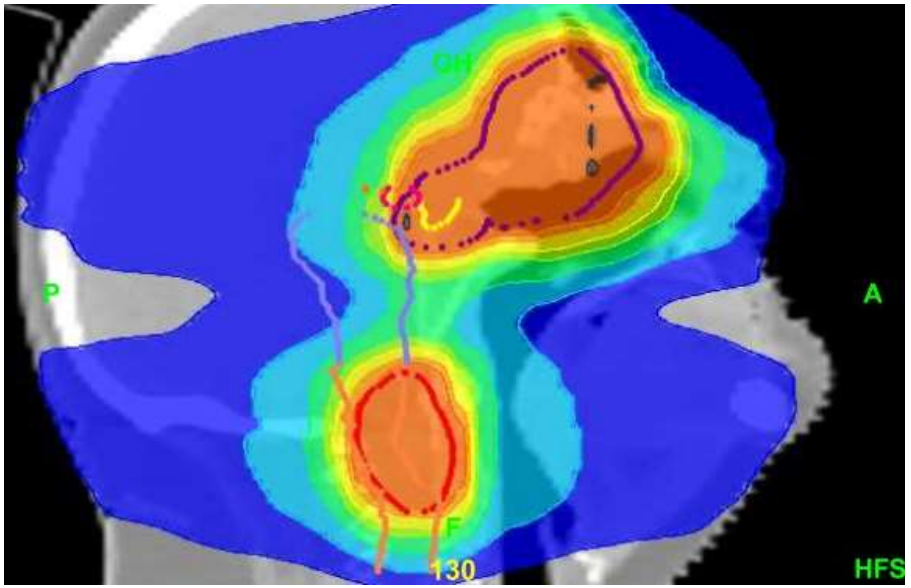
Skull base meningioma





- IMRT plan for all areas
- 50 Gy / 30#

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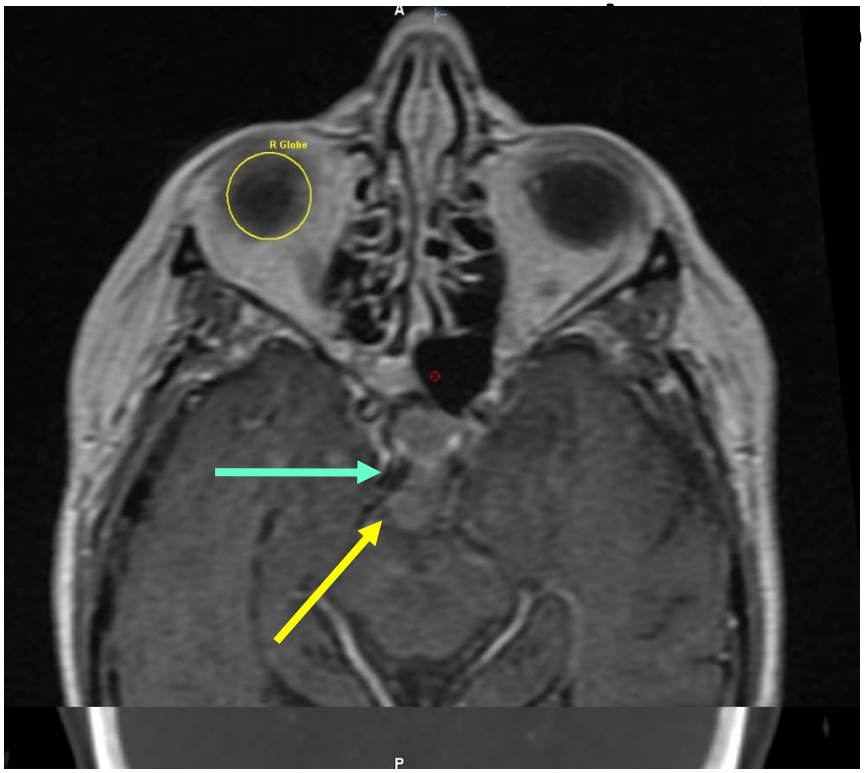
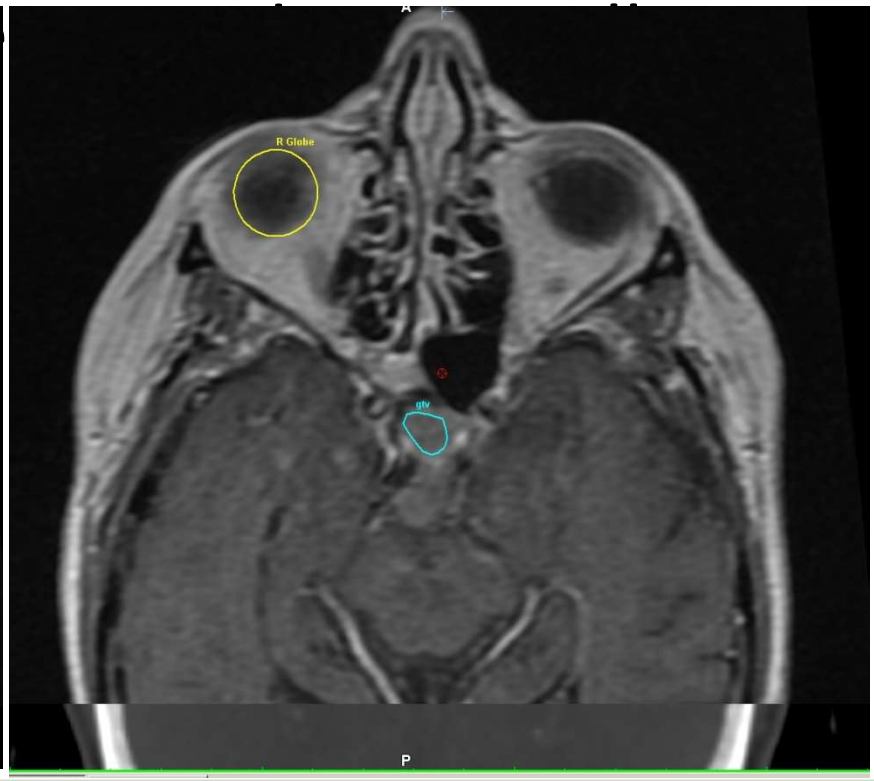
Imaging for RT planning

- Planning MR for pituitary adenoma





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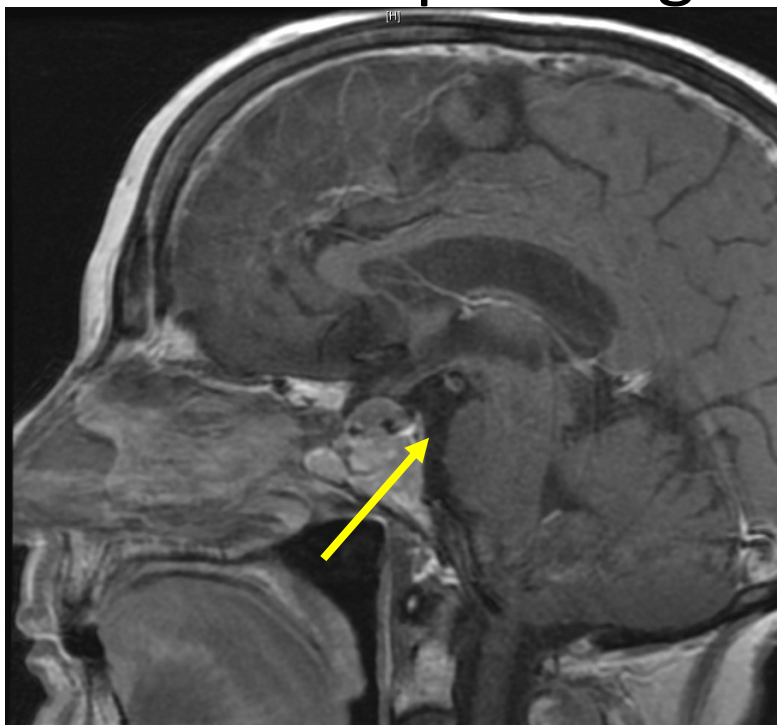
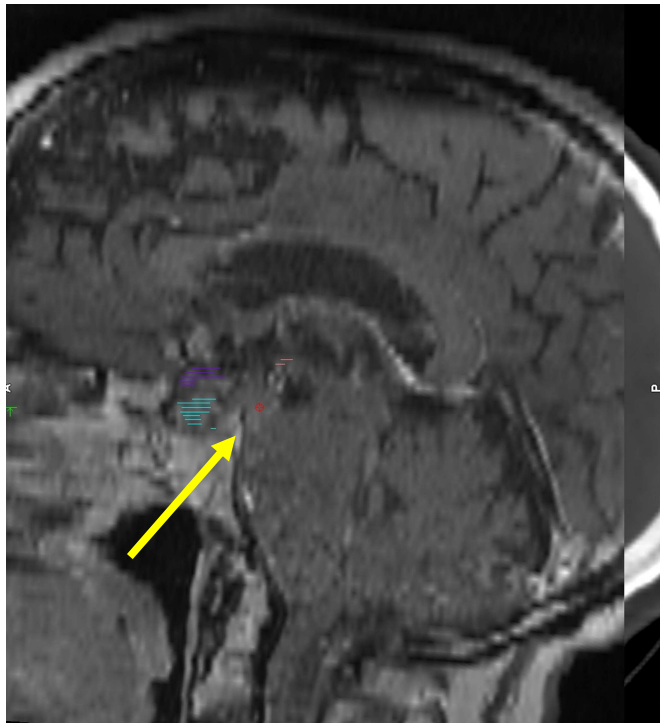
Imaging for RT planning

- Artefact on planning sequence !



Sagittal T1 + Gd



Axial T1 + Gd planning sequence

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Imaging

- The best possible imaging is needed for us to make the best of IMRT or PBT
- There is still *much* further to go for diagnostics
- We can still do better with planning imaging

Surgery

Surgery

- Excellent surgery is essential
- Includes
  - Cyto-reduction
  - Decompression
  - Provision of ‘space’
  - Stabilisation
- Needs access endoscopic techniques

Surgery

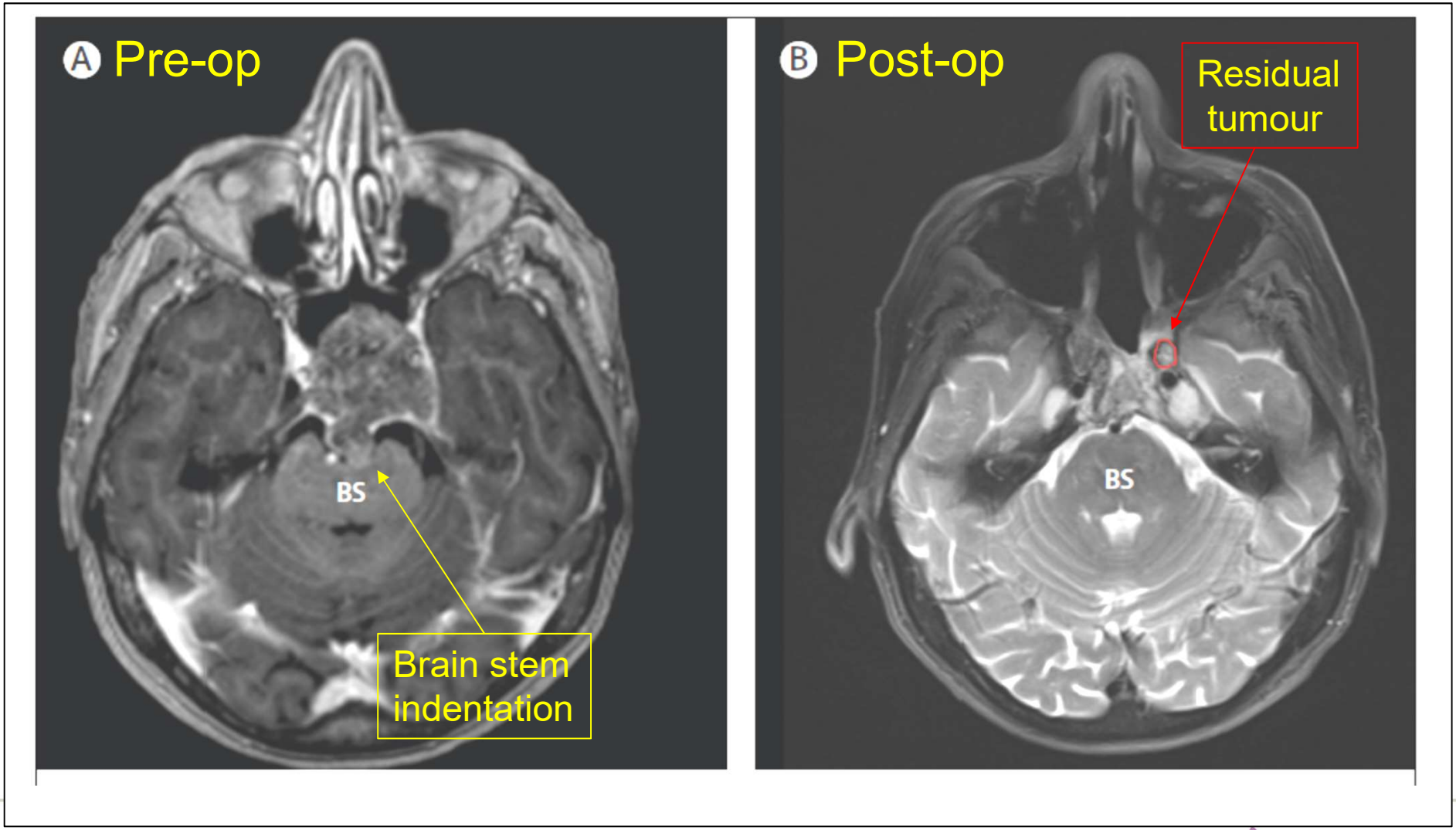

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Image guidance

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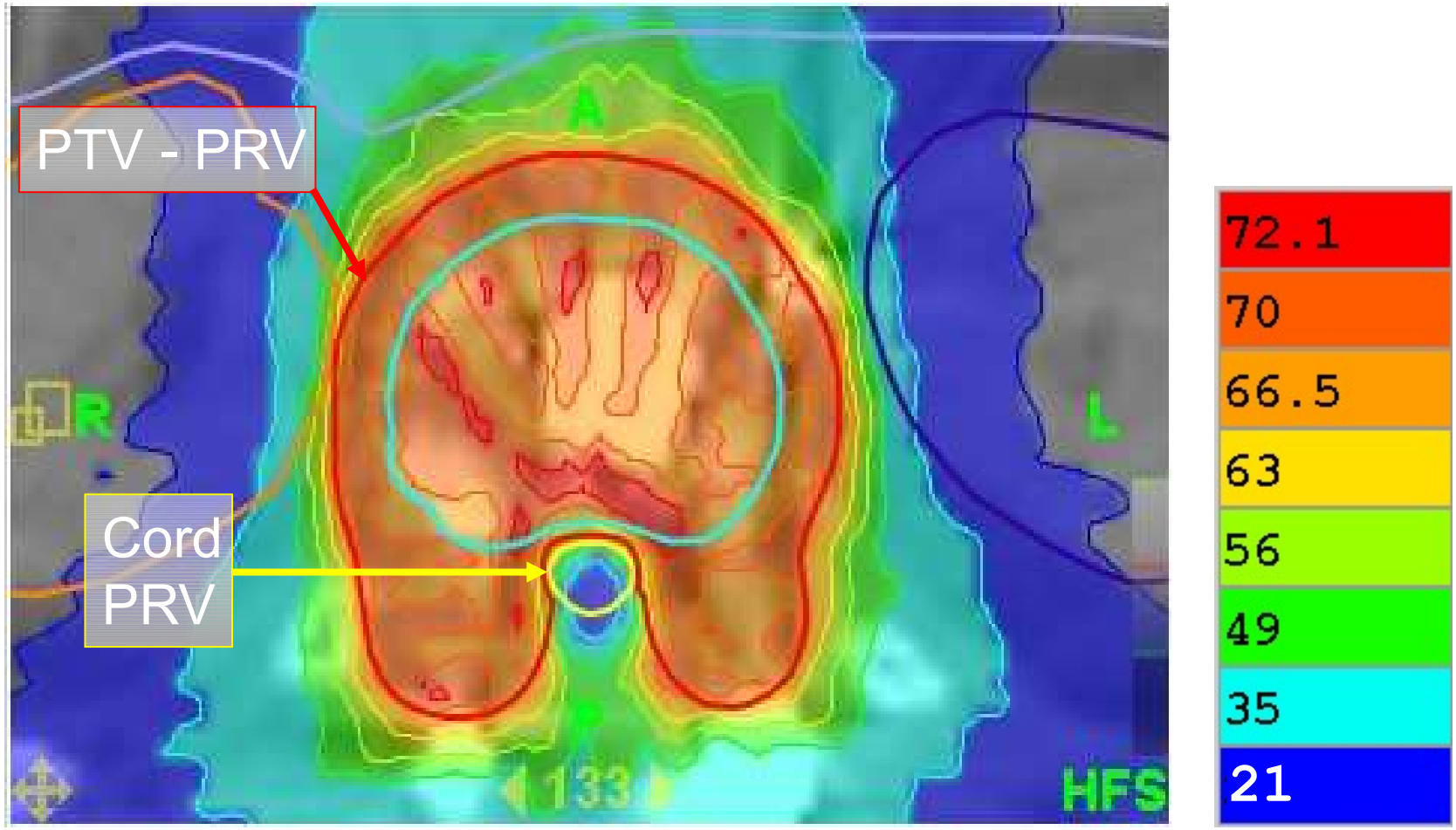
Chordoma T12



- 70 Gy median PTV dose. Well at 54 months

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Image guidance for chordoma

- Daily positional corrections moves – lateral direction

- *All* fractions had significant lateral displacement

- Note *all* positive – and large

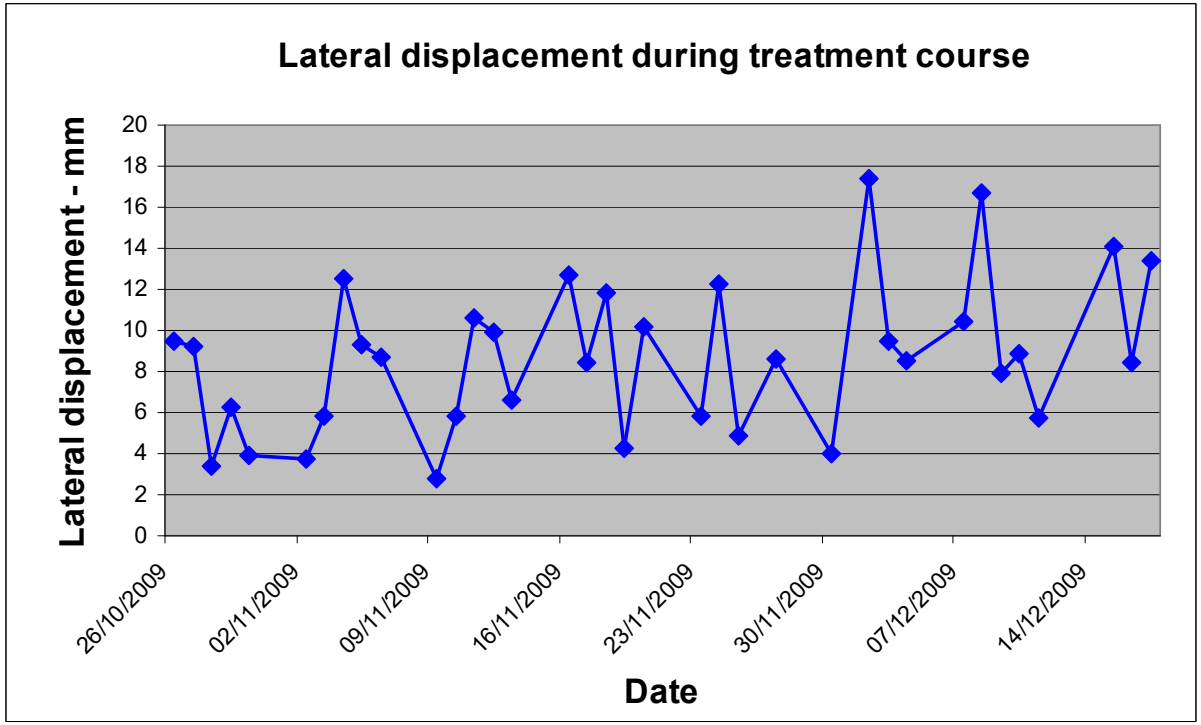

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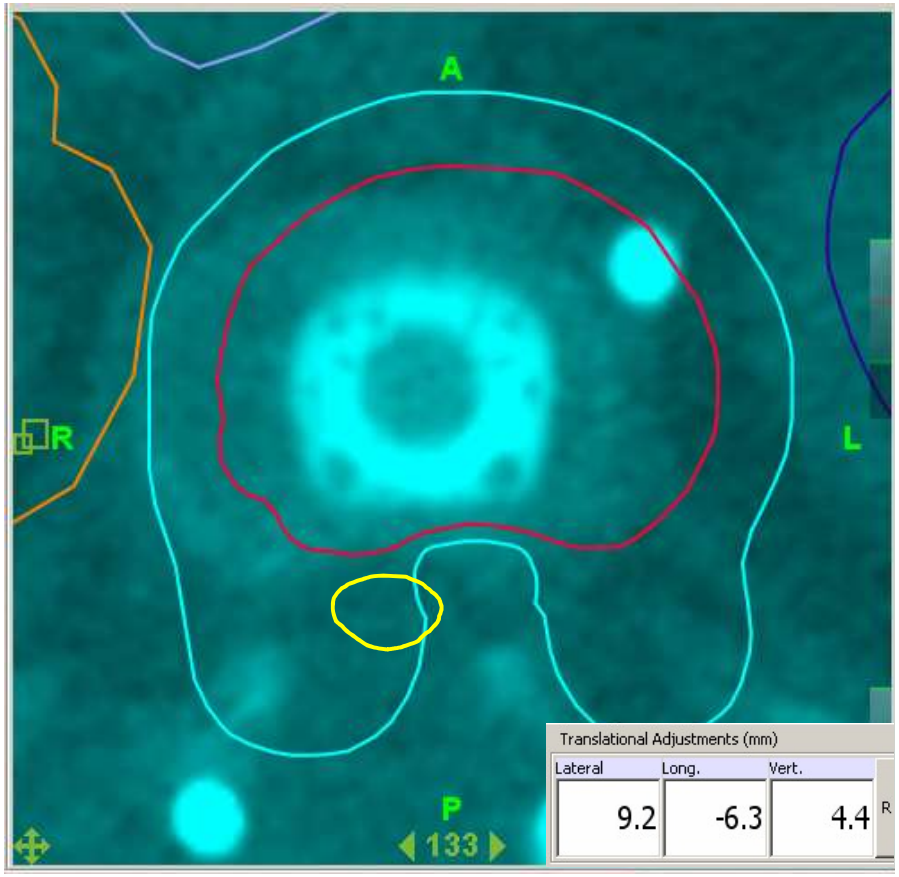
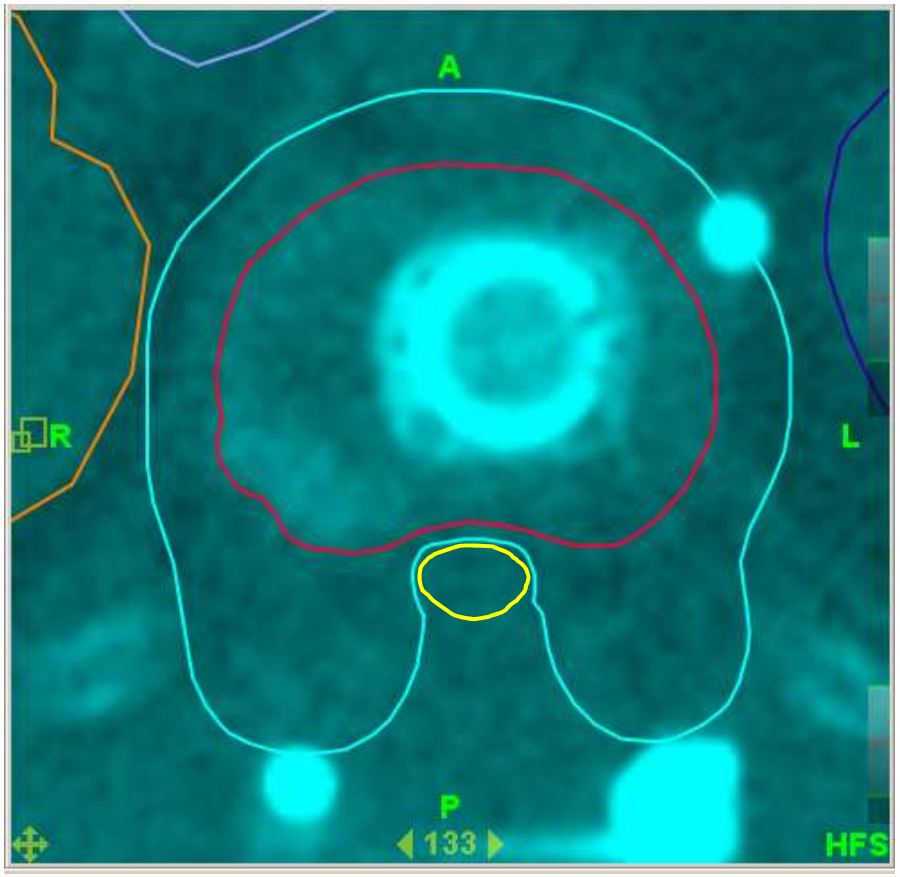
Image guidance for chordoma





- Imperfect positioning corrected by daily imaging
- 3D positional error 11.1mm

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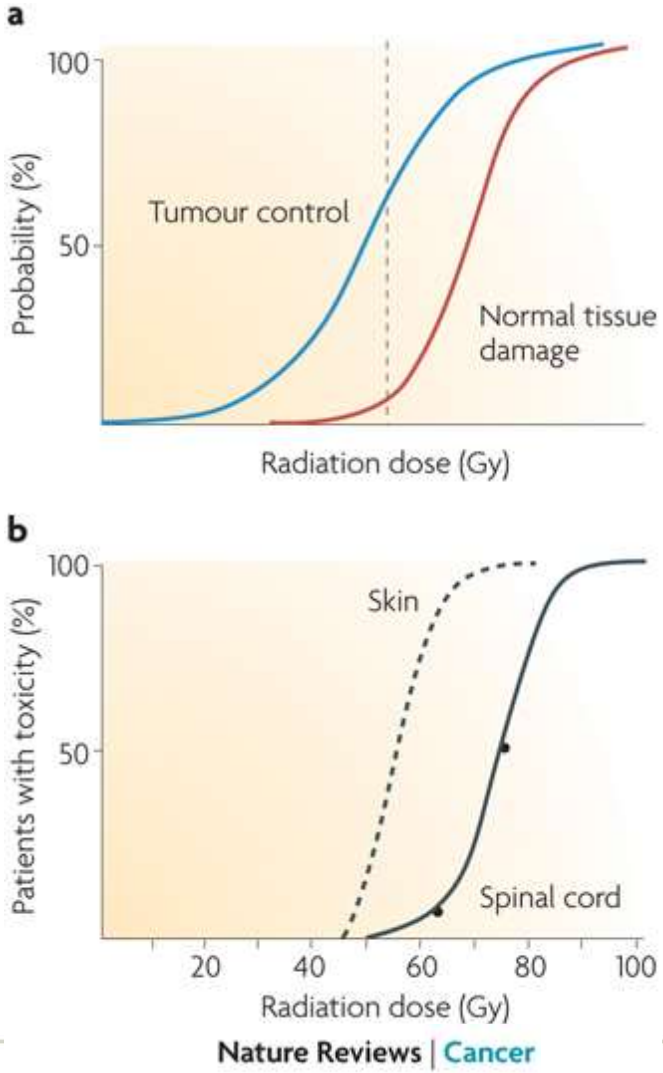
Radiotherapy

- What we do makes a difference
- Dose response curves are steep
  - Gamma-50 (γ_{50})
    - Tumour 1 - 2
    - Normal tissue 1 – 5
    - Spinal cord ~ 4.2
- Tumour
  - Dose difference of 5%
  - TCP difference 5% – 10%



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Radiotherapy

- Dose matters!
- Dose is an effective biomarker of response
  - Applies to both tumours and normal tissues
  - Current knowledge not very detailed in some tissues
  - This includes CNS tissues and endpoints
- Better conformation delivers better outcome
  - Applies to tumours
  - Applies to normal tissues

IMRT vs CRT

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 2, pp. 580–592, 2003

0360-3016/03/$–see front matter

doi:10.1016/S0360-3016(03)00587-X

PHYSICS CONTRIBUTION

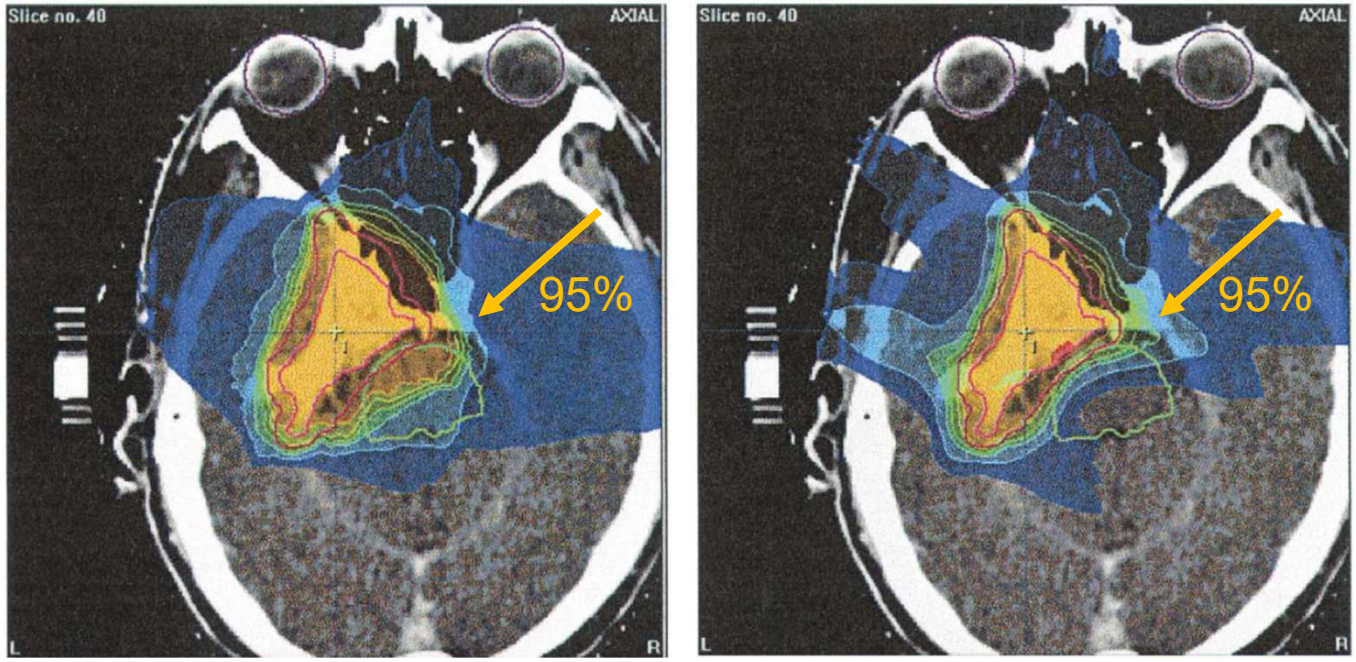
INTENSITY-MODULATED STEREOTACTIC RADIOTHERAPY VS. STEREOTACTIC CONFORMAL RADIOTHERAPY FOR THE TREATMENT OF MENINGIOMA LOCATED PREDOMINANTLY IN THE SKULL BASE

BRIGITTA G. BAUMERT, M.D., IAN A. NORTON, B.SC., AND J. BERNARD DAVIS, PH.D.

- With IMRT, PTV coverage better, esp. for complex shapes
- Lower dose to OARs

IMRT vs CRT

- Dose
  54 Gy/30#
- 95% =
  51.3 Gy



- Reduced dose to brainstem

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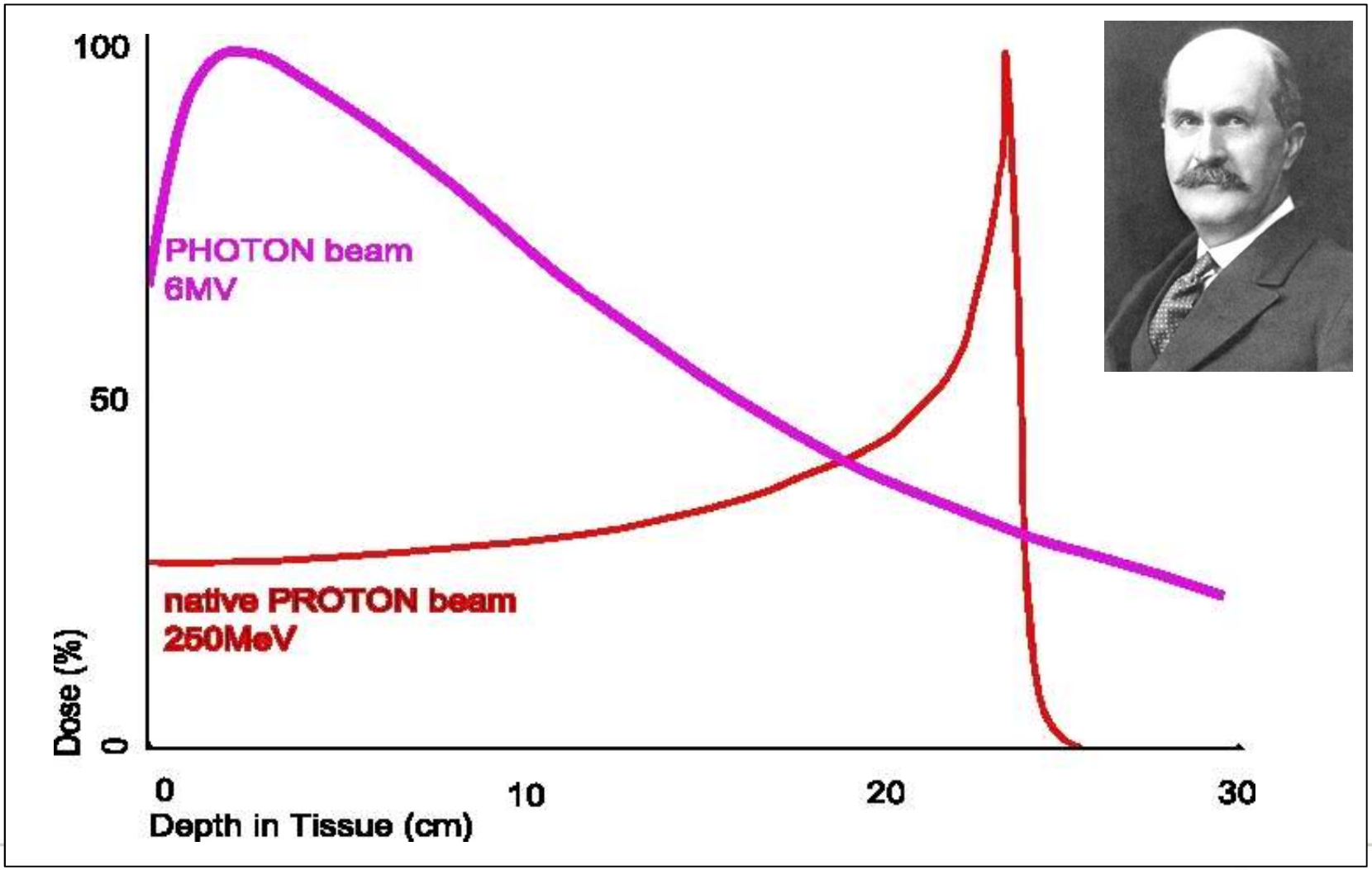
Proton beam therapy - PBT

Proton Bragg peak



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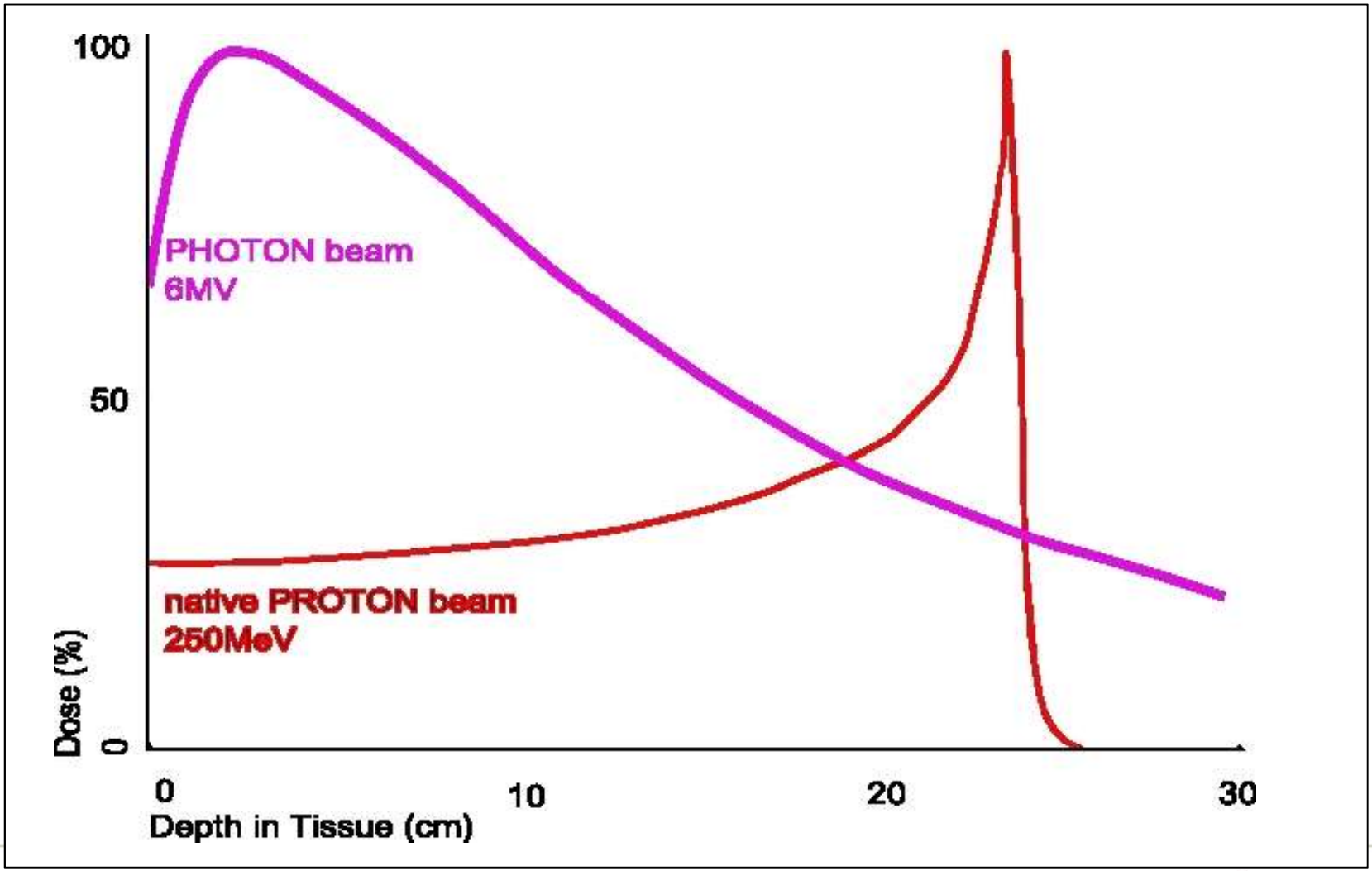
Proton Bragg peak



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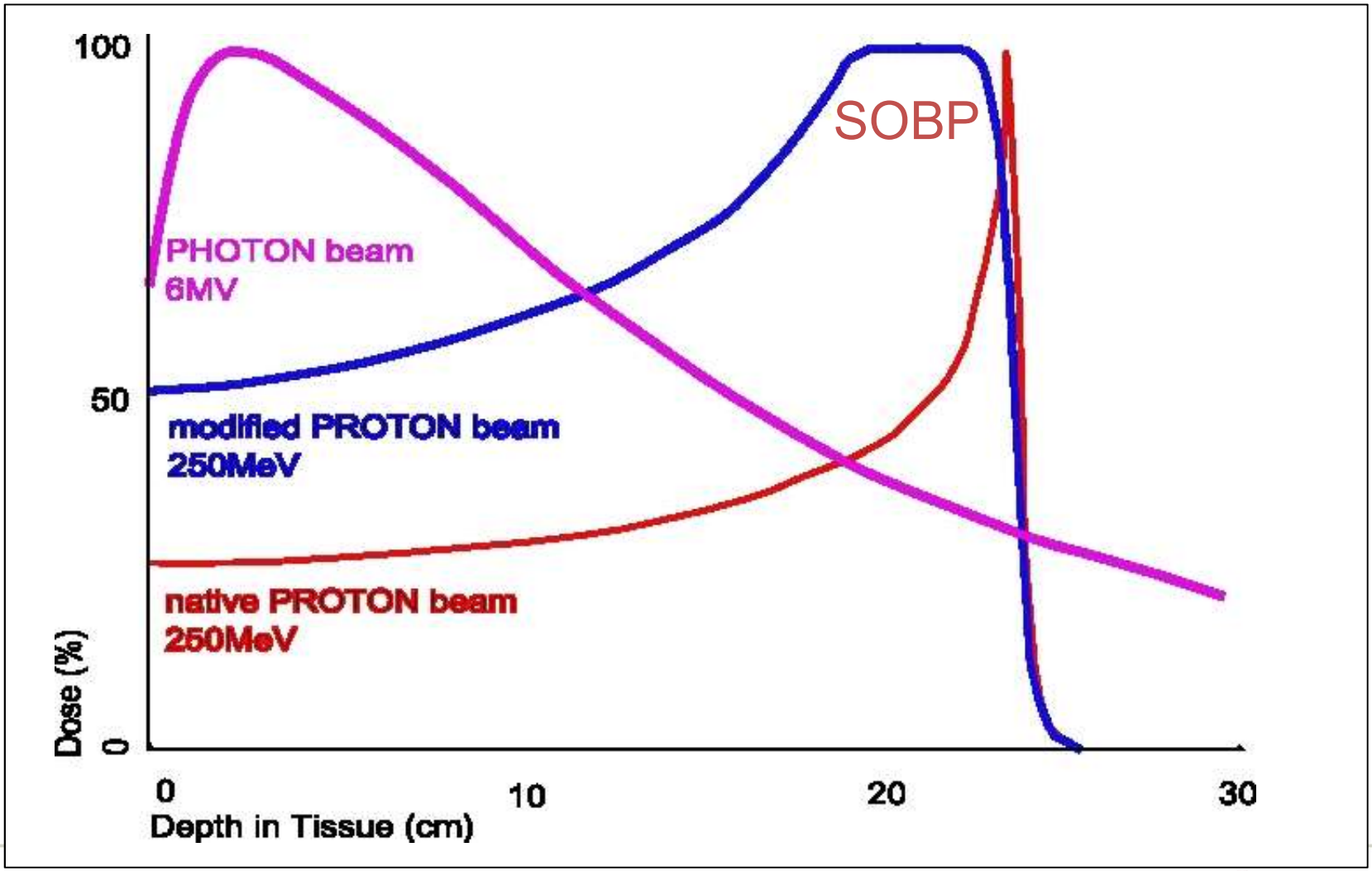
Proton Bragg peak



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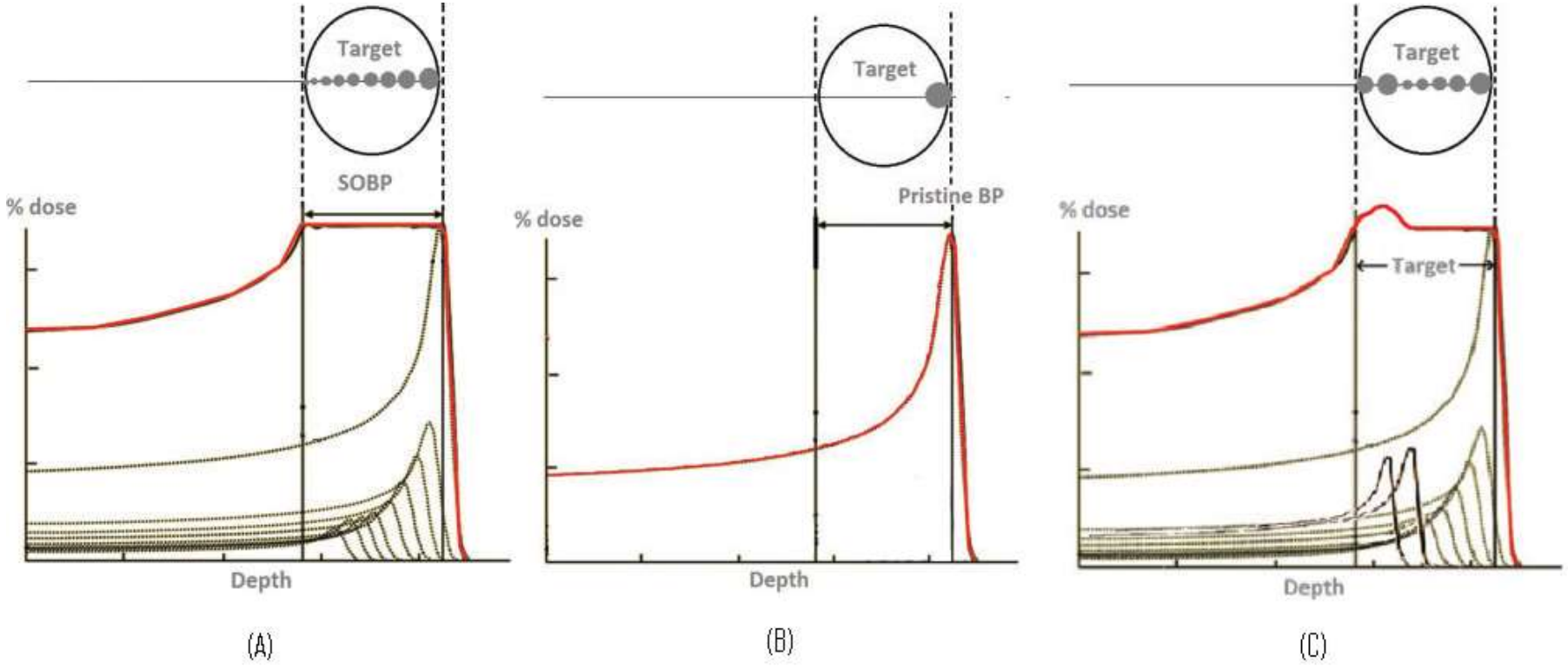
Proton delivery



Active scanning – (a)SFUD, (b)DET IMPT & (c) 3D IMPT

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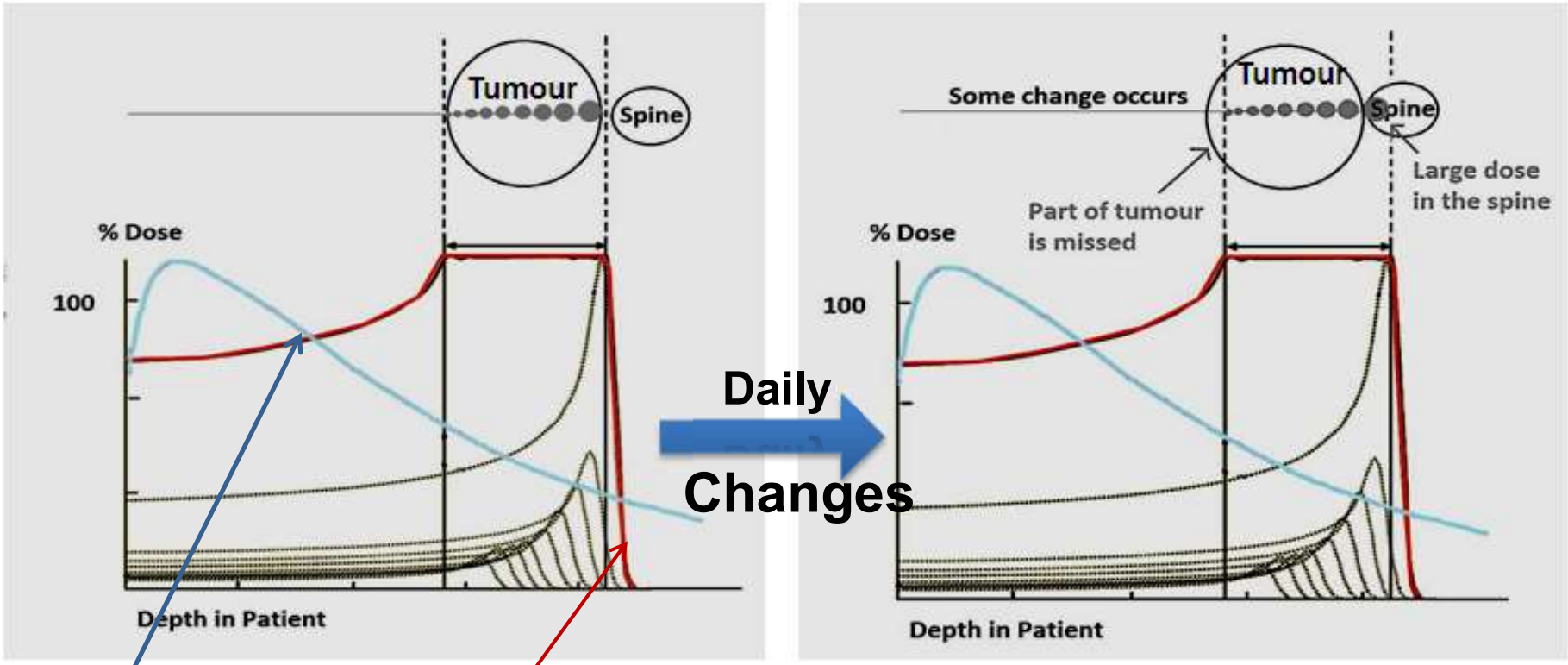
What are the issues? Range uncertainty



Infinite X-ray fall off

Finite proton range = greater conformity

BUT…
more sensitive to uncertainties

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Skull base meningioma

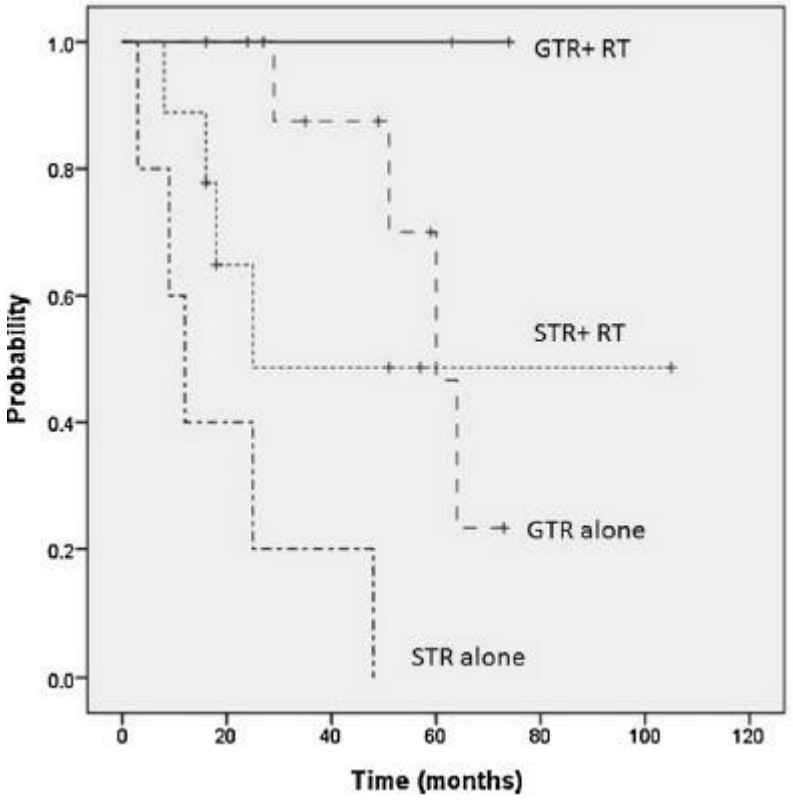
- Common
- 90% are WHO grade I
- In the skull base – complete resection rarely possible
- Adjuvant treatment should be considered

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,*]



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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]

[a] *University Hospital of Heidelberg, Germany;* [b] *German Cancer Research Center (dkfz), Heidelberg, Germany*

Radiotherapy and Oncology 106 (2013) 186–191

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1985-2010
632 meningioma cases
507 – skull base

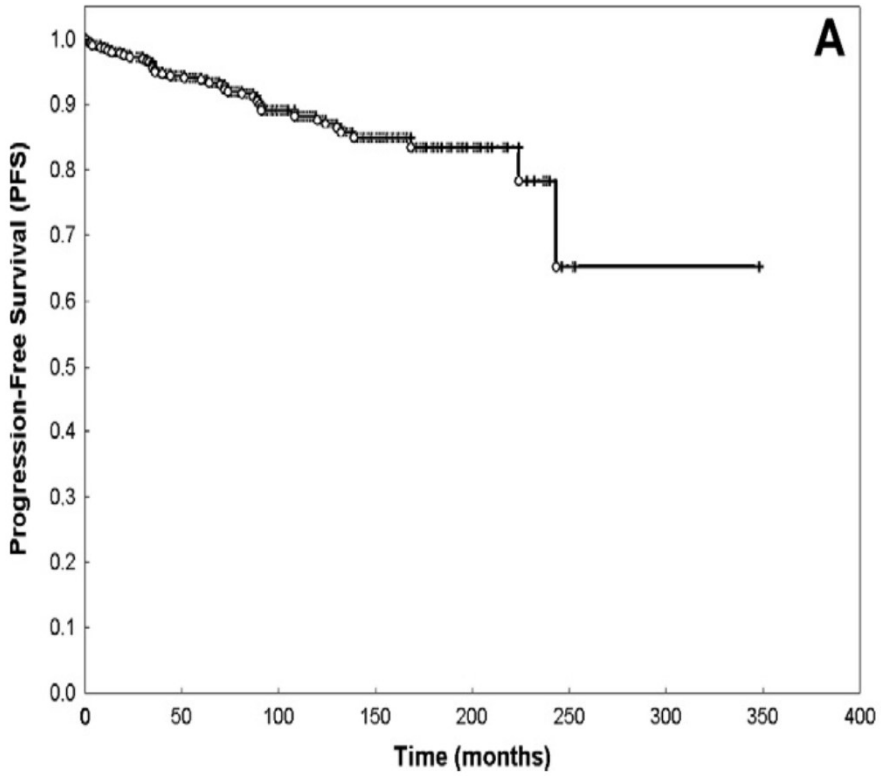
FSRT 74%
IMRT 26%
Median Dose 57.8Gy (25-68)

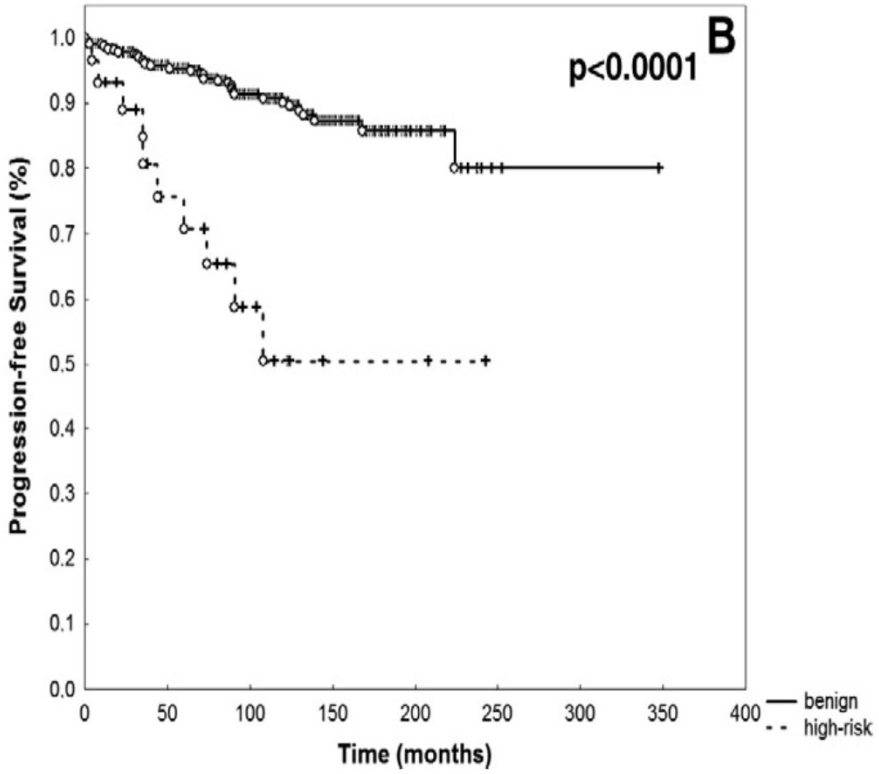
Patient characteristics of 507 patients treated with FSRT or IMRT for skull base meningiomas.

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)

Radiotherapy and Oncology 106 (2013) 186–191

Progression-Free Survival





95% PFS @ five years

88% PFS @ ten years

Radiotherapy and Oncology 106 (2013) 186–191

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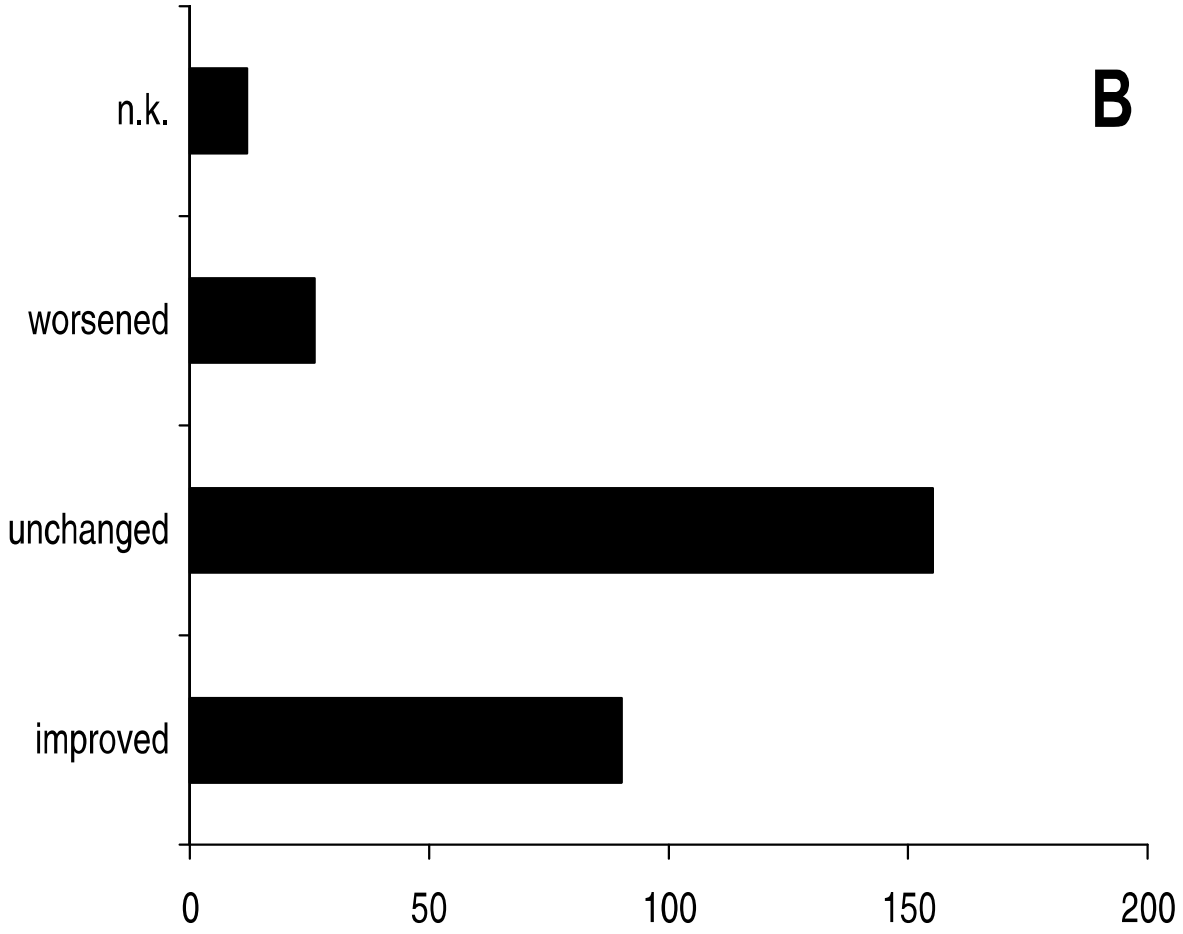
Quality of Life



340/507 patients

Radiotherapy and Oncology 106 (2013) 186–191

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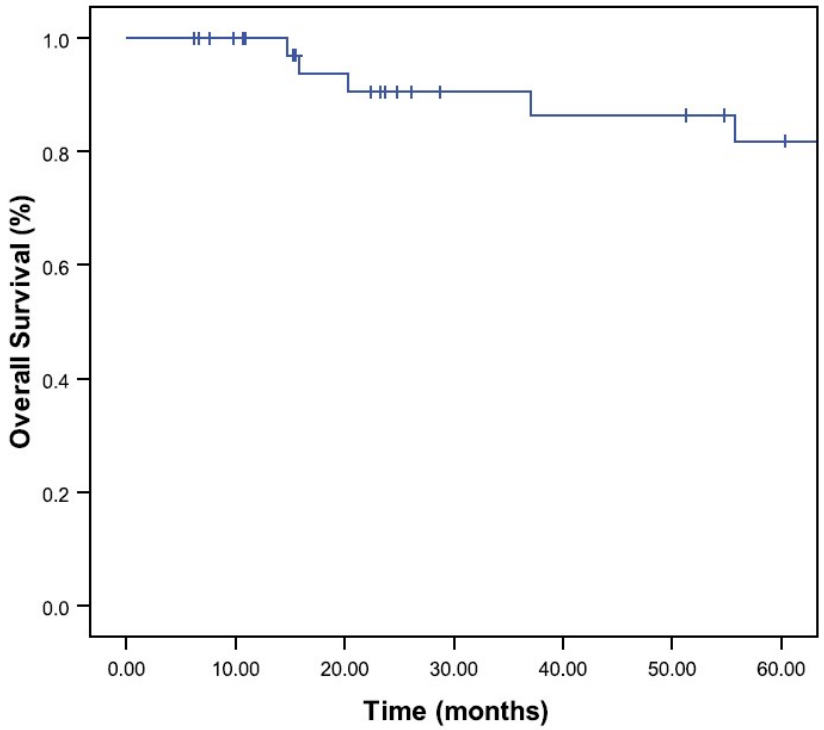
Skull base meningioma - results

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.,†

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How to treat?

- Asymptomatic – need to assess if growing
- Symptomatic – is surgery relevant or indicated
  - Can observe post surgery
- Radiotherapy dose – 50-55Gy/33#
- SRS – only for very specific cases

Complications

- Hypopituitism
- Cranial Nerve Palsies
- Cerebrovascular events
- Neurocognitive decline
- Second Malignancy

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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
- 0.84 per 1 000 000 (M>F)
- Median age 58 (3 - 95)
- **Typically Midline**

CHONDROSARCOMA

- Arise from embryonal rests of cartilaginous matrix that escape reabsorption during endochondral ossification
- 5 per 1 000 000 (M>F)
- Median age 51 (1 – 102)
- Appendicular > axial > soft tissue
- **Typically Off Midline**

Natural History

- **CHORDOMA**
  - 5 yr and 10 yr DFS **70% and 45%**
  - Recurrences may be noted many years after treatment
  - Distant metastasis rare (6% - 22%)
  - Metastasis higher in the presence of recurrent disease
  - At recurrence, 3-yr and 5-yr OS ~ **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 tumour 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

Treatment - surgery

Tai et al, Cancer, 1995:
159 patients with cranial chordomas:

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

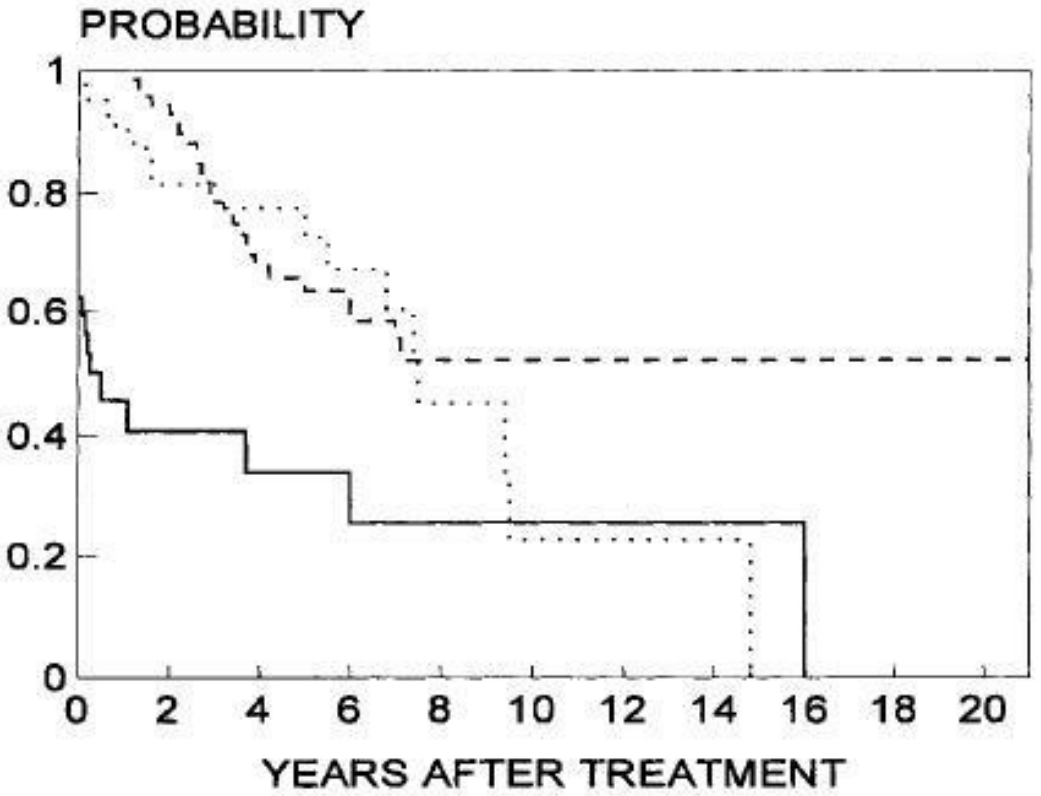

Figure 3. Overall survival according to the three treatments: ——, surgery alone, · · · ·, radiation alone; and – – – –, combined surgery and postoperative radiation.

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Treatment - radiotherapy

Chordoma:

- 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

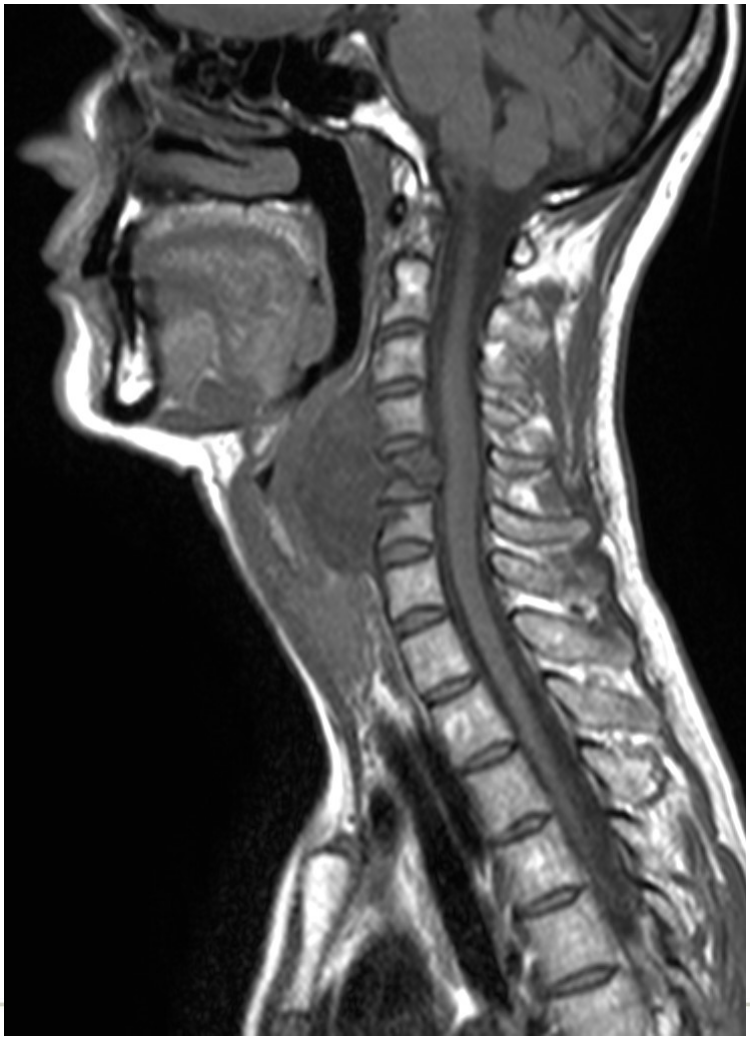
- In **1970** Pearlman and Friedman: Decrease in local failure with ↑ dose

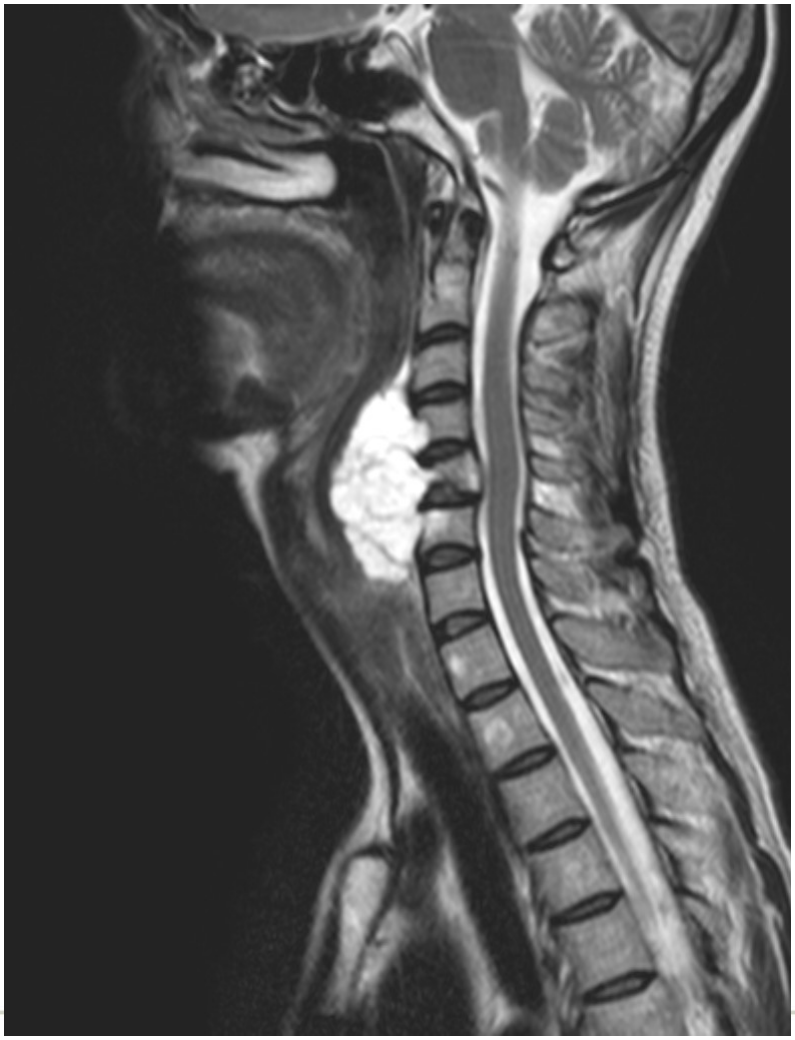
Dose versus Relapse

<40 Gy (n=47)	85%
40 – 60 Gy (n=18)	60%
60-80 Gy (n=8)	43%
>80 Gy (n=2)	0%

Chordoma

Chordoma - 1





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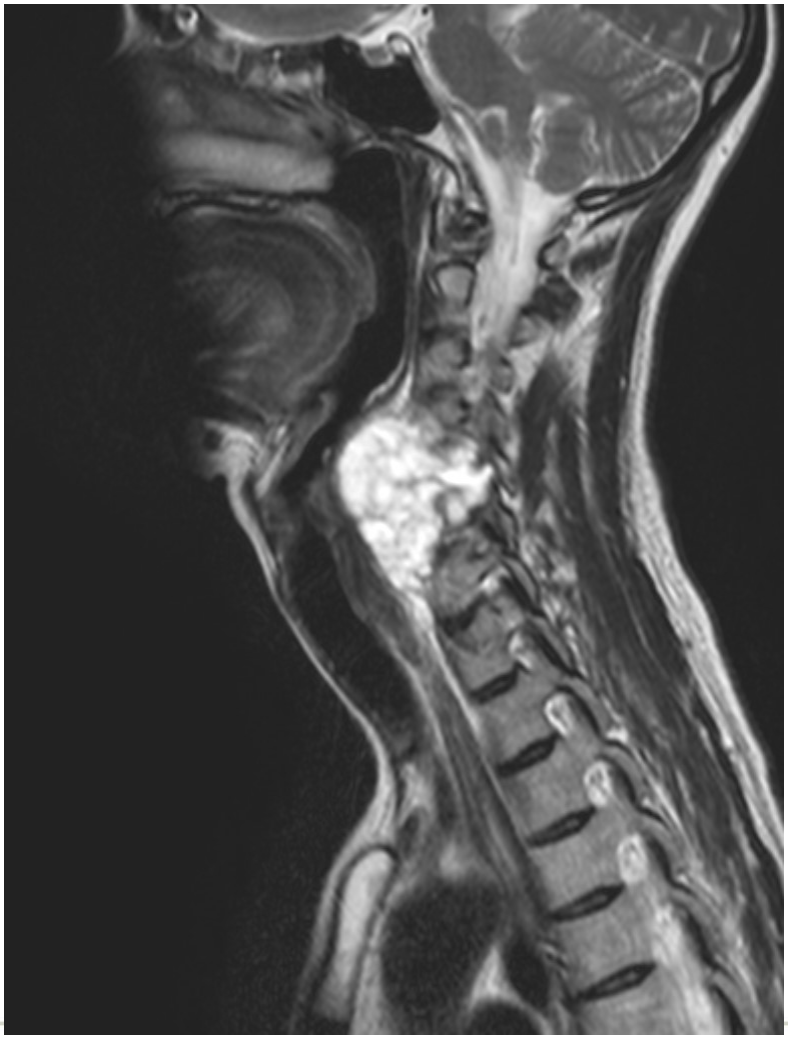
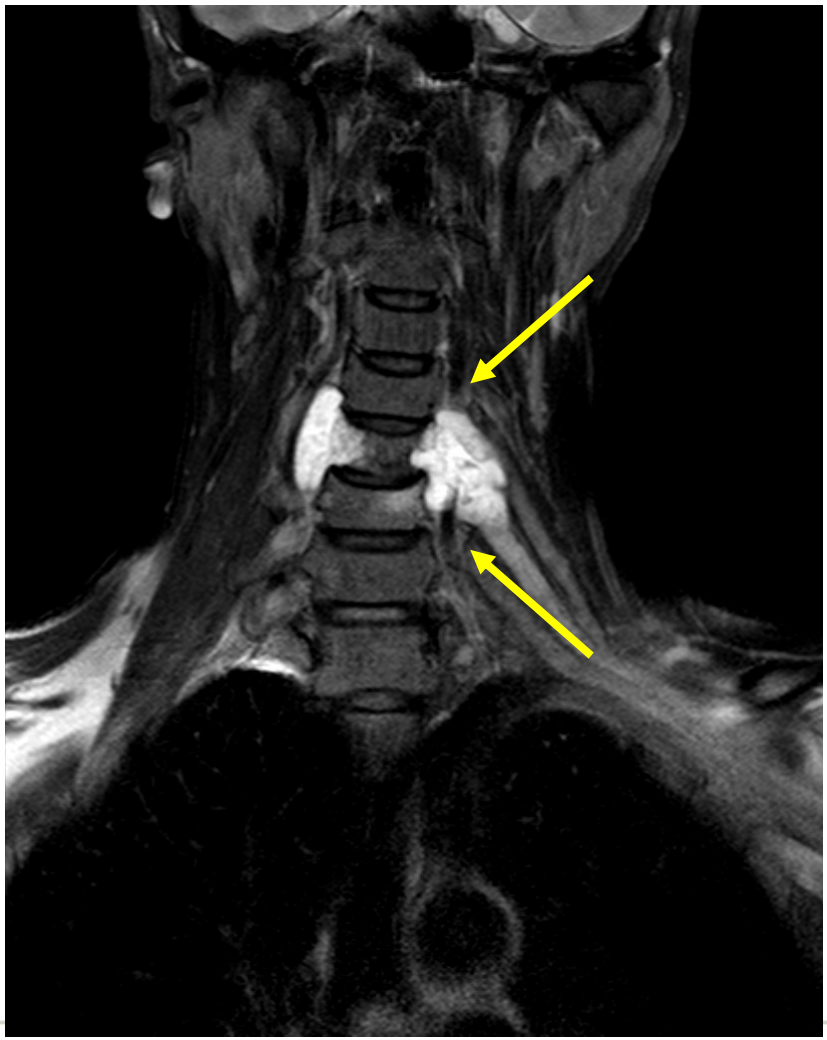
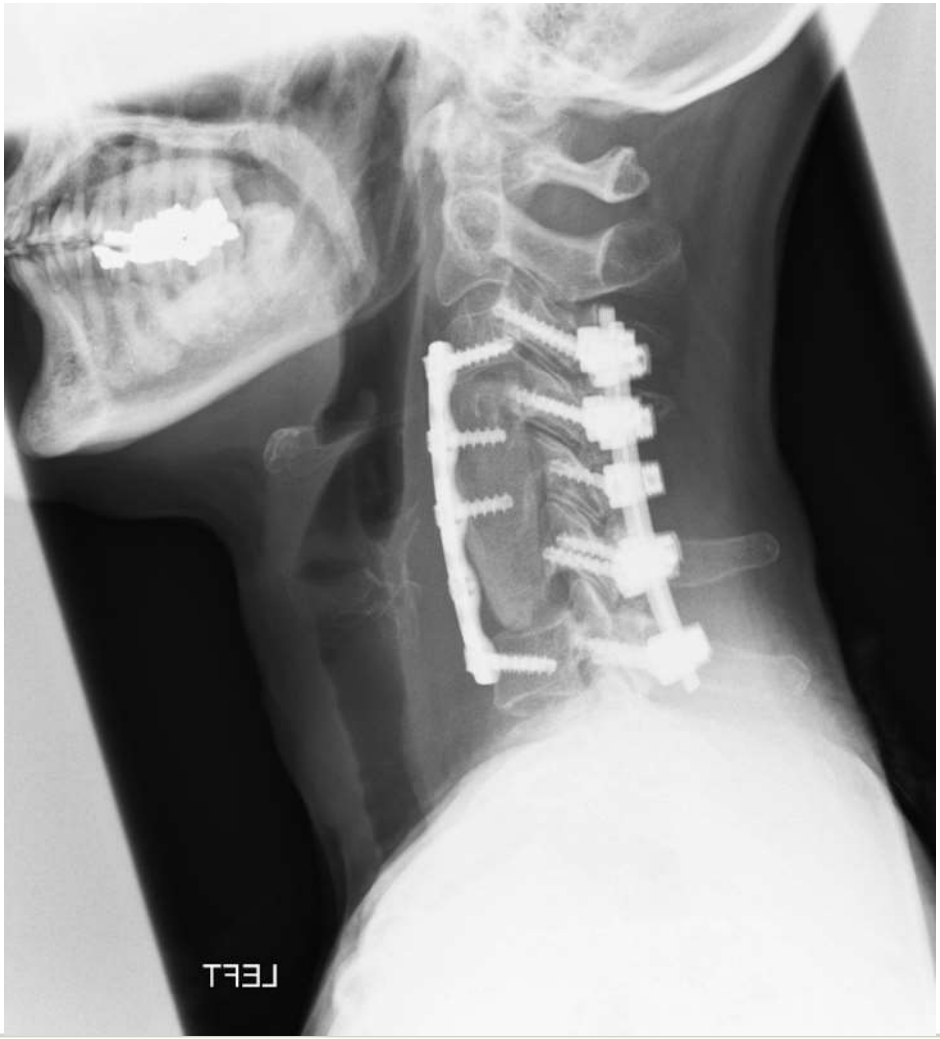
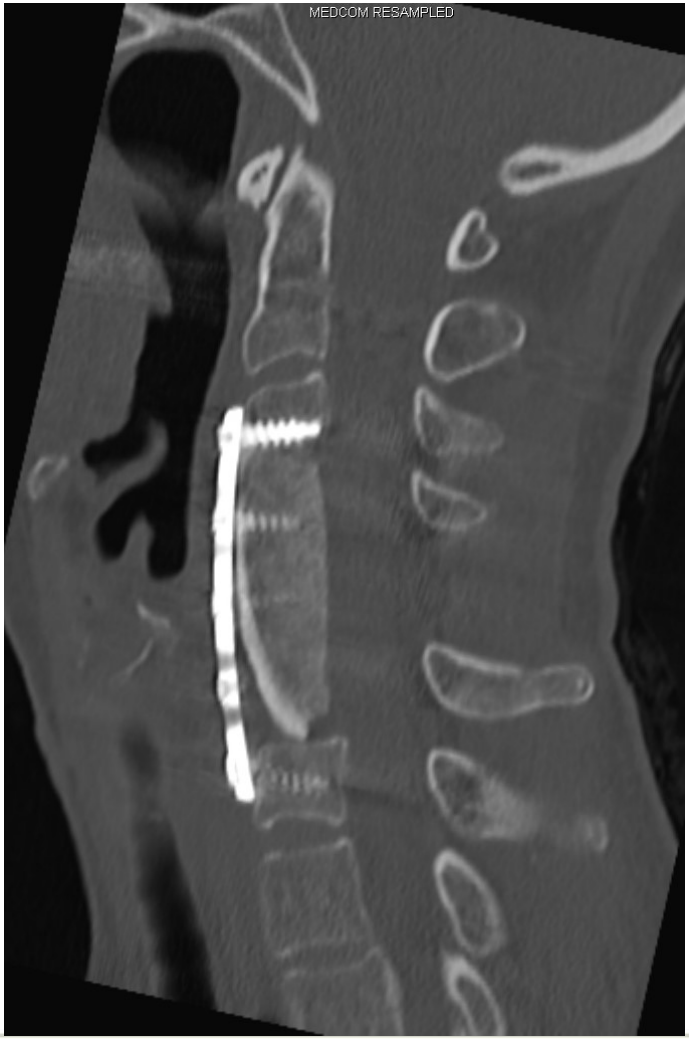
Chordoma - 1





Chordoma - 1





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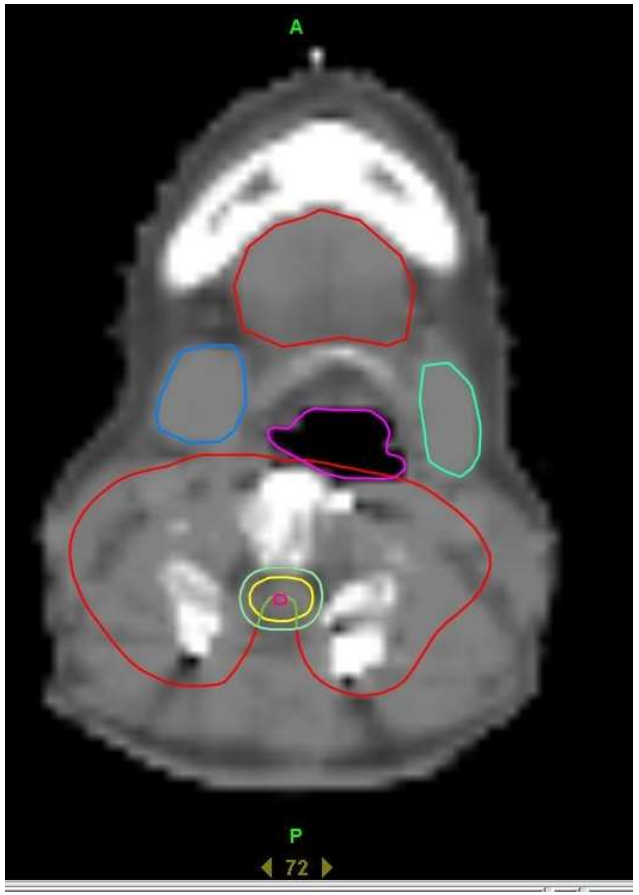
Chordoma - 1

- Many normal tissue structures to be considered
- Spinal cord especially important !
- Not suitable for PBT because of metalwork



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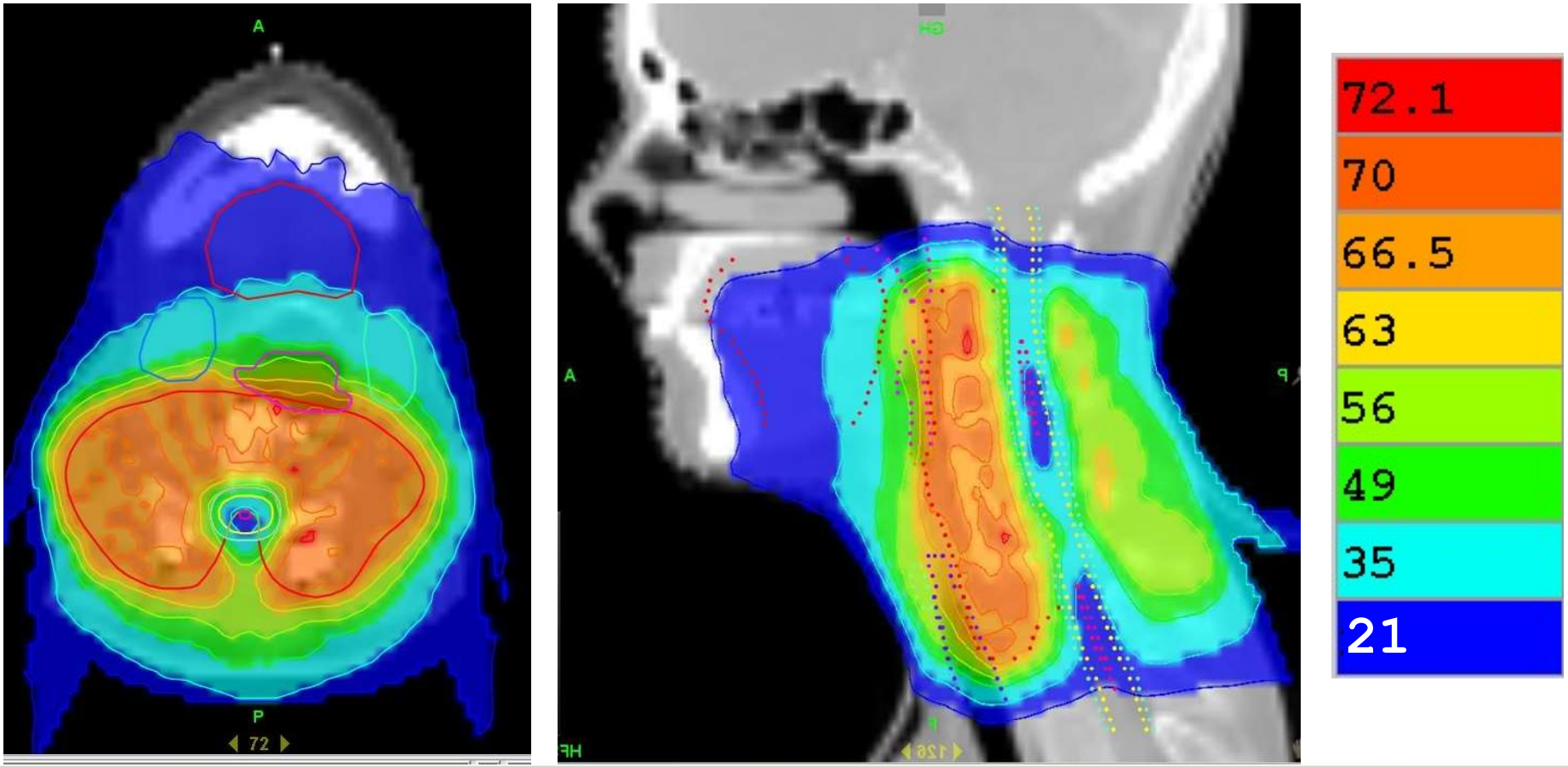
Chordoma - 1



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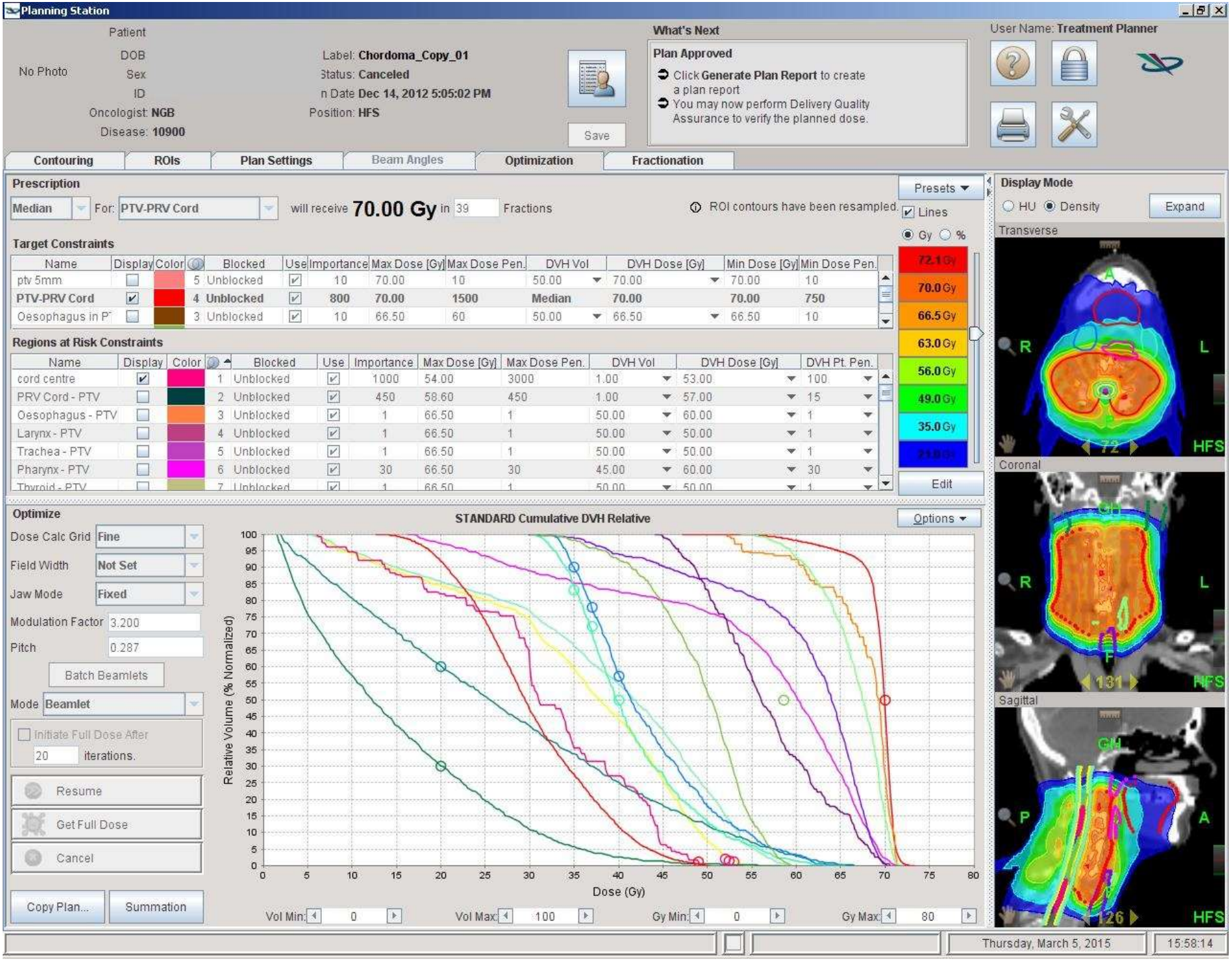
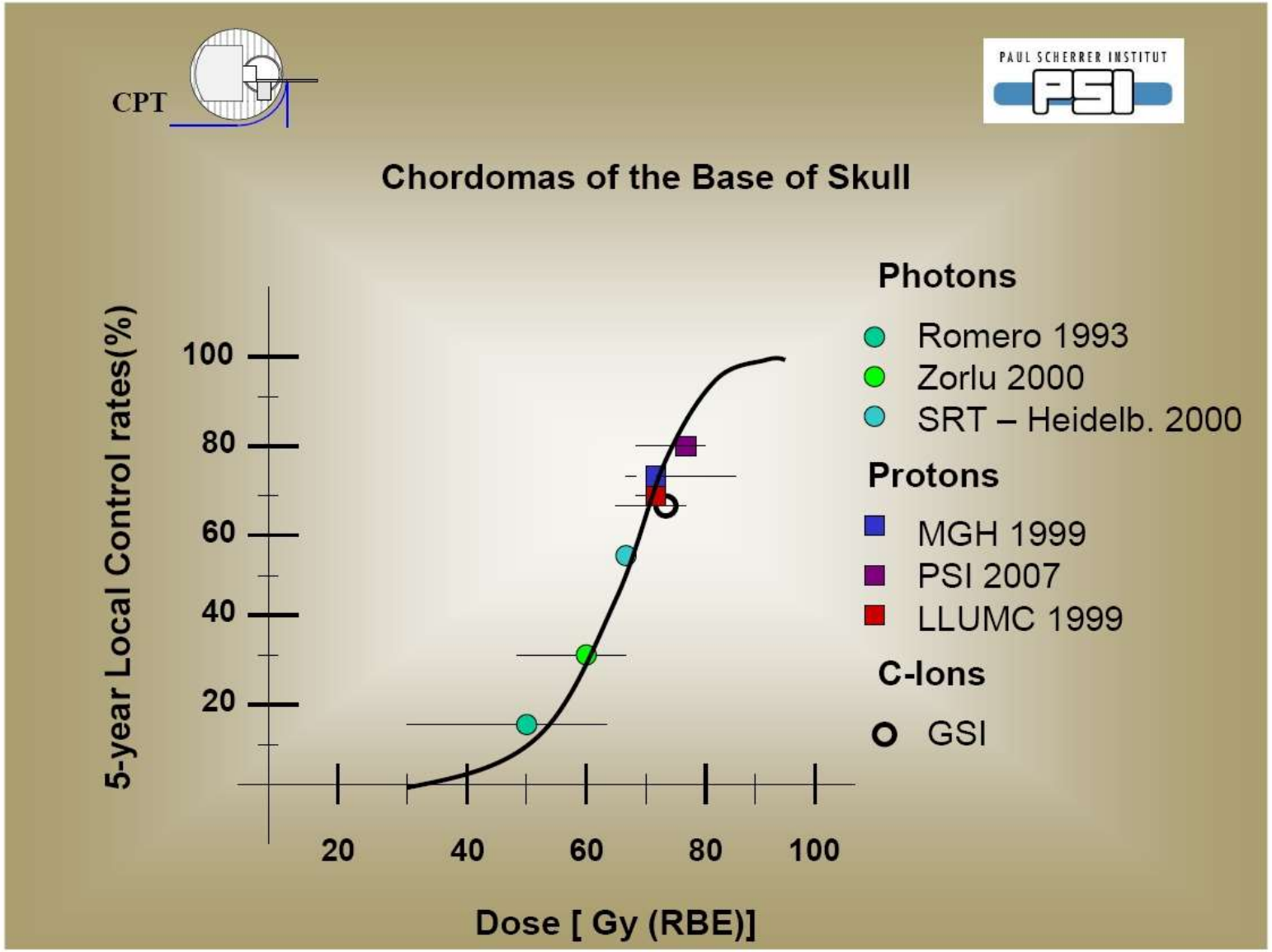
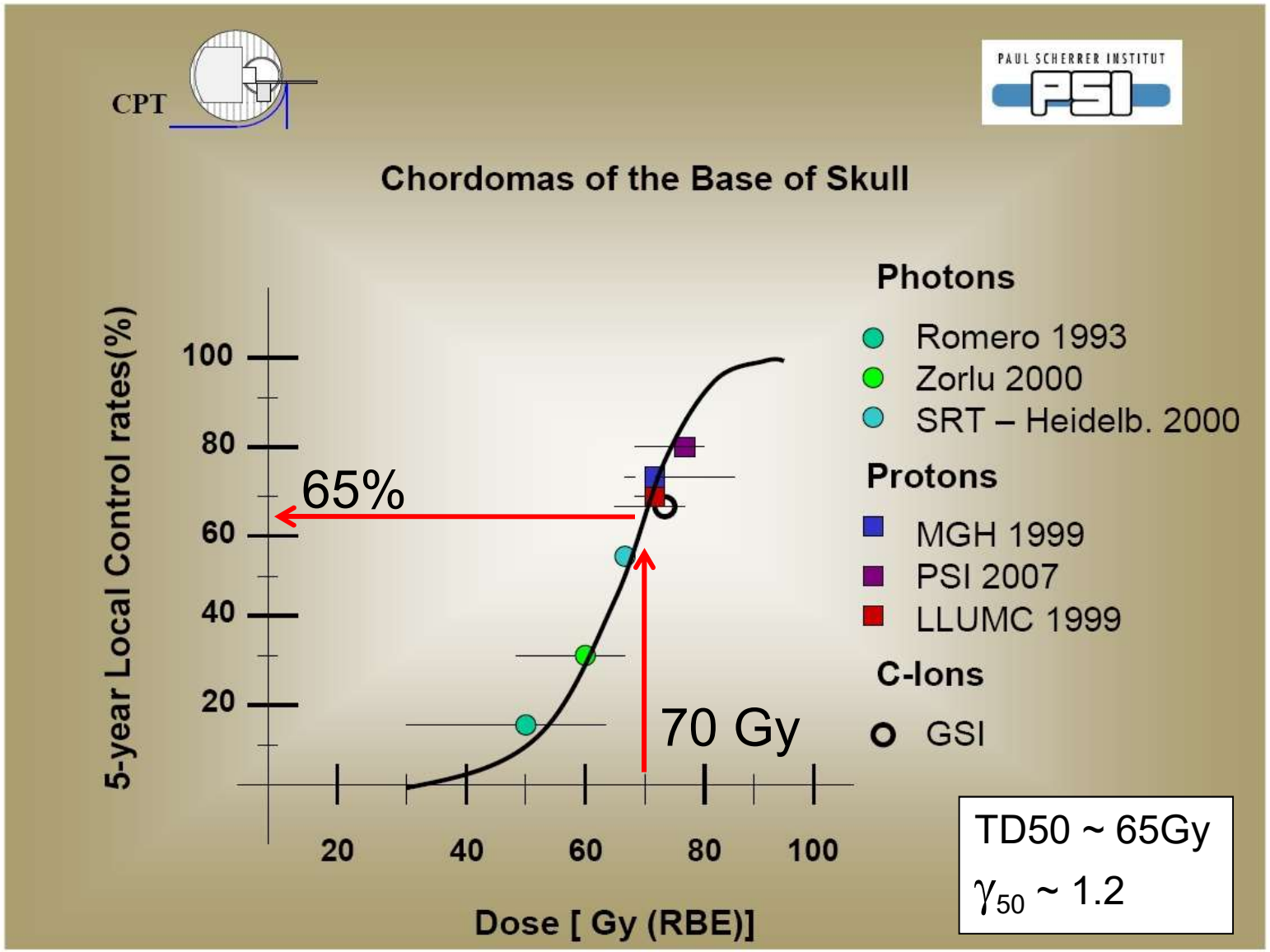

Planning Station
Patient
DOB
No Photo
Sex
ID
Oncologist: NGB
Disease: 10900
Label: Chordoma_Copy_01
Status: Canceled
n Date Dec 14, 2012 5:05:02 PM
Position: HFS
Save
What's Next
Plan Approved
Click Generate Plan Report to create a plan report
You may now perform Delivery Quality Assurance to verify the planned dose.
User Name: Treatment Planner
Contouring
ROIs
Plan Settings
Beam Angles
Optimization
Fractionation
Prescription
Median
For: PTV-PRV Cord
will receive 70.00 Gy in 39 Fractions
ROI contours have been resampled.
Presets
Lines
Gy
%
Target Constraints
Name | Display | Color | Blocked | Use | Importance | Max Dose [Gy] | Max Dose Pen. | DVH Vol | DVH Dose [Gy] | Min Dose [Gy] | Min Dose Pen.
ptv 5mm | 5 Unblocked | 10 | 70.00 | 10 | 50.00 | 70.00 | 70.00 | 10
PTV-PRV Cord | 4 Unblocked | 800 | 70.00 | 1500 | Median | 70.00 | 70.00 | 750
Oesophagus in P | 3 Unblocked | 10 | 66.50 | 60 | 50.00 | 66.50 | 66.50 | 10
72.1 Gy
70.0 Gy
66.5 Gy
63.0 Gy
56.0 Gy
49.0 Gy
35.0 Gy
Edit
Regions at Risk Constraints
Name | Display | Color | Blocked | Use | Importance | Max Dose [Gy] | Max Dose Pen. | DVH Vol | DVH Dose [Gy] | DVH Pt. Pen.
cord centre | 1 Unblocked | 1000 | 54.00 | 3000 | 1.00 | 53.00 | 100
PRV Cord - PTV | 2 Unblocked | 450 | 58.60 | 450 | 1.00 | 57.00 | 15
Oesophagus - PTV | 3 Unblocked | 1 | 66.50 | 1 | 50.00 | 60.00 | 1
Larynx - PTV | 4 Unblocked | 1 | 66.50 | 1 | 50.00 | 50.00 | 1
Trachea - PTV | 5 Unblocked | 1 | 66.50 | 1 | 50.00 | 50.00 | 1
Pharynx - PTV | 6 Unblocked | 30 | 66.50 | 30 | 45.00 | 60.00 | 30
Thyroid - PTV | 7 Unblocked | 1 | 66.50 | 1 | 50.00 | 50.00 | 1
Display Mode
HU
Density
Expand
Transverse
Coronal
Sagittal
Optimize
Dose Calc Grid: Fine
Field Width: Not Set
Jaw Mode: Fixed
Modulation Factor: 3.200
Pitch: 0.287
Batch Beamlets
Mode: Beamlet
Initiate Full Dose After
20 iterations.
Resume
Get Full Dose
Cancel
Copy Plan...
Summation
STANDARD Cumulative DVH Relative
Options
Relative Volume (% Normalized)
Dose (Gy)
Vol Min: 0
Vol Max: 100
Gy Min: 0
Gy Max: 80
Thursday, March 5, 2015
15:58:14



Courtesy of Prof Eugen Hug


CPT
PAUL SCHERRER INSTITUT
PSI
Chordomas of the Base of Skull
5-year Local Control rates(%)
100
80
60
40
20
65%
70 Gy
20
40
60
80
100
Dose [Gy (RBE)]
Photons
Romero 1993
Zorlu 2000
SRT – Heidelb. 2000
Protons
MGH 1999
PSI 2007
LLUMC 1999
C-Ions
GSI
TD50 ~ 65Gy
γ_{50} ~ 1.2

Neuro-Oncology 17(6), 889–894, 2015
doi:10.1093/neuonc/nou347
Advance Access date 27 December 2014

Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes

Arjun Sahgal, Michael W. Chan, Eshetu G. Atenafu, Laurence Masson-Cote, Gaurav Bahl, Eugene Yu, Barbara-Ann Millar, Caroline Chung, Charles Catton, Brian O'Sullivan, Jonathan C. Irish, Ralph Gilbert, Gelareh Zadeh, Michael Cusimano, Fred Gentili, and Normand J. Laperriere

5-year overall survival and local control rates were 85.6% and 87.8% (n=24)

Residual Postoperative Tumour Volume Predicts Outcome after High-dose Radiotherapy for Chordoma and Chondrosarcoma of the Skull Base and Spine

S. Potluri [*], S.J. Jefferies [*], R. Jena [*], F. Harris [*], K.E. Burton [*], A.T. Prevost [†], N.G. Burnet [‡]

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Clinical Oncology 23 (2011) 199–208

5 year cause-specific survival for radically treated patients with chordomas was 92% and the 5 year local control rate was 83% (n=13)

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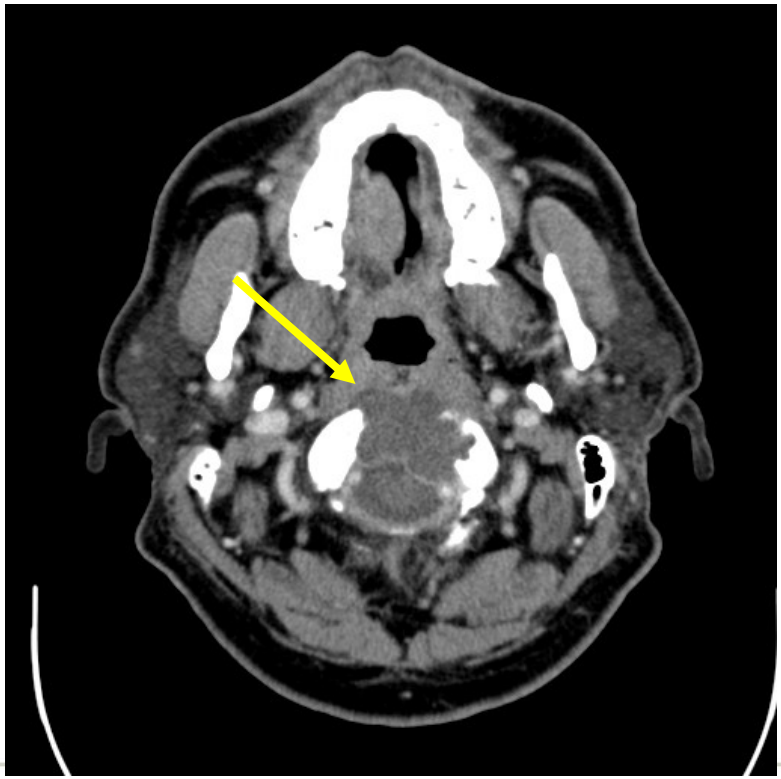
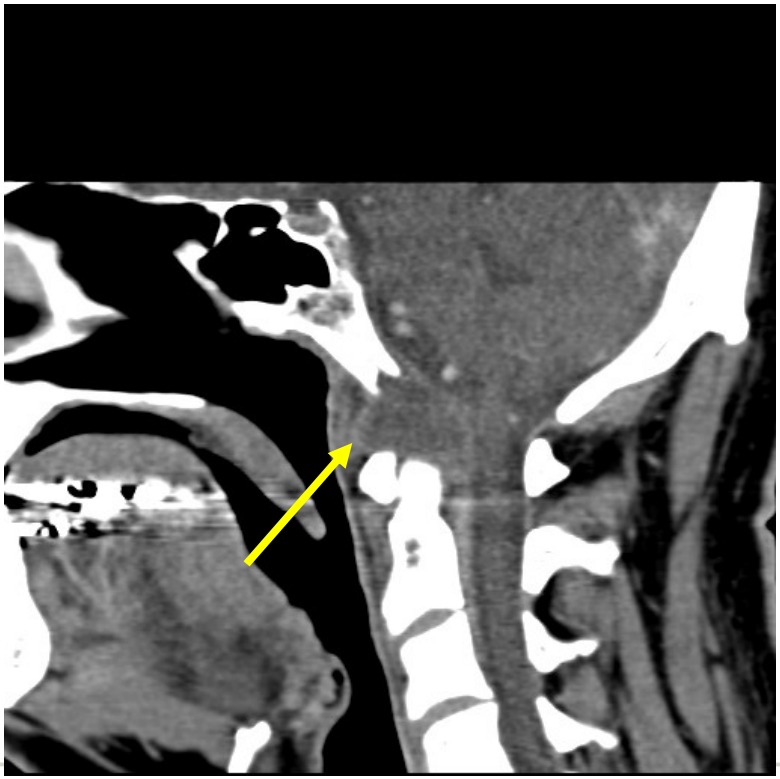
Chordoma - 2

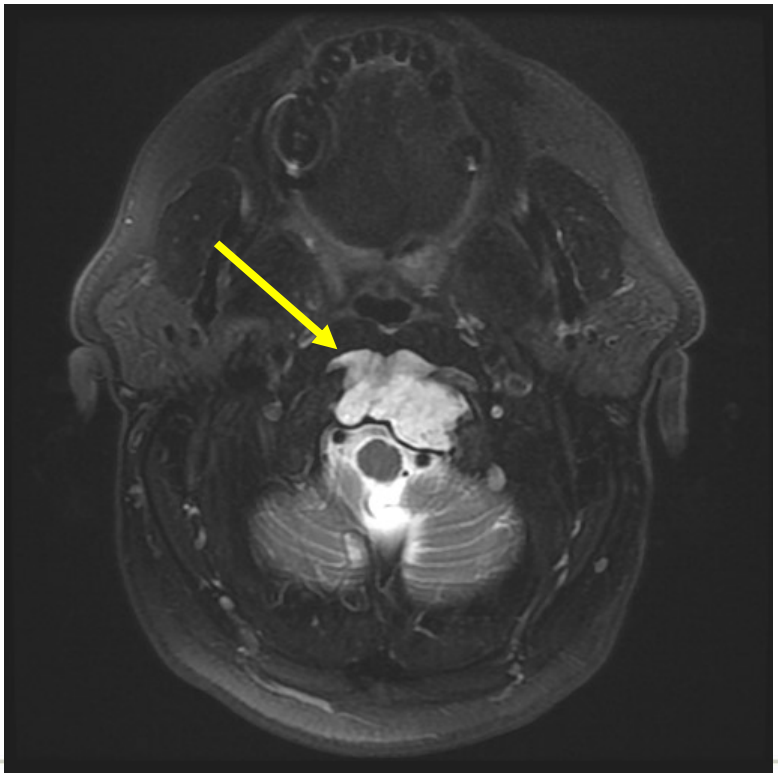
- Chordoma of clivus with bone destruction

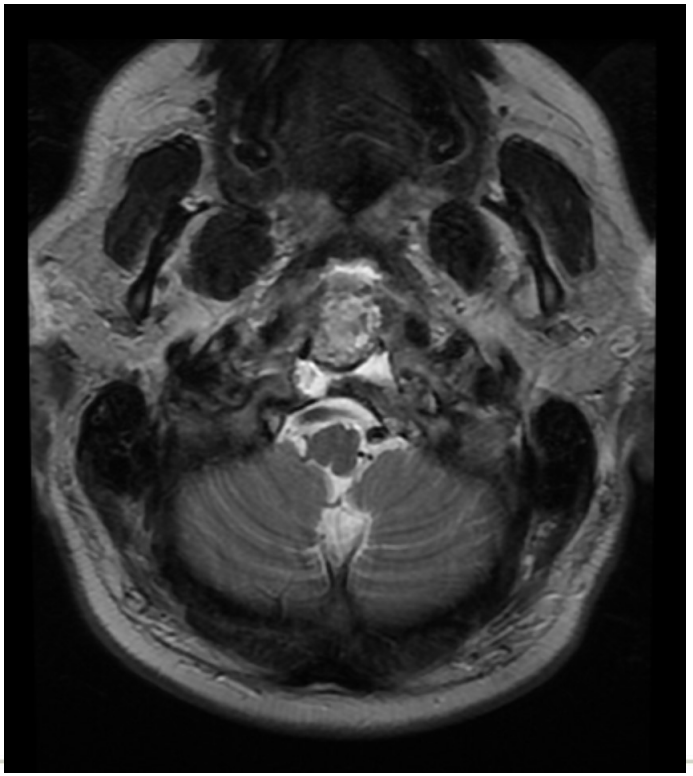




Chordoma - 2

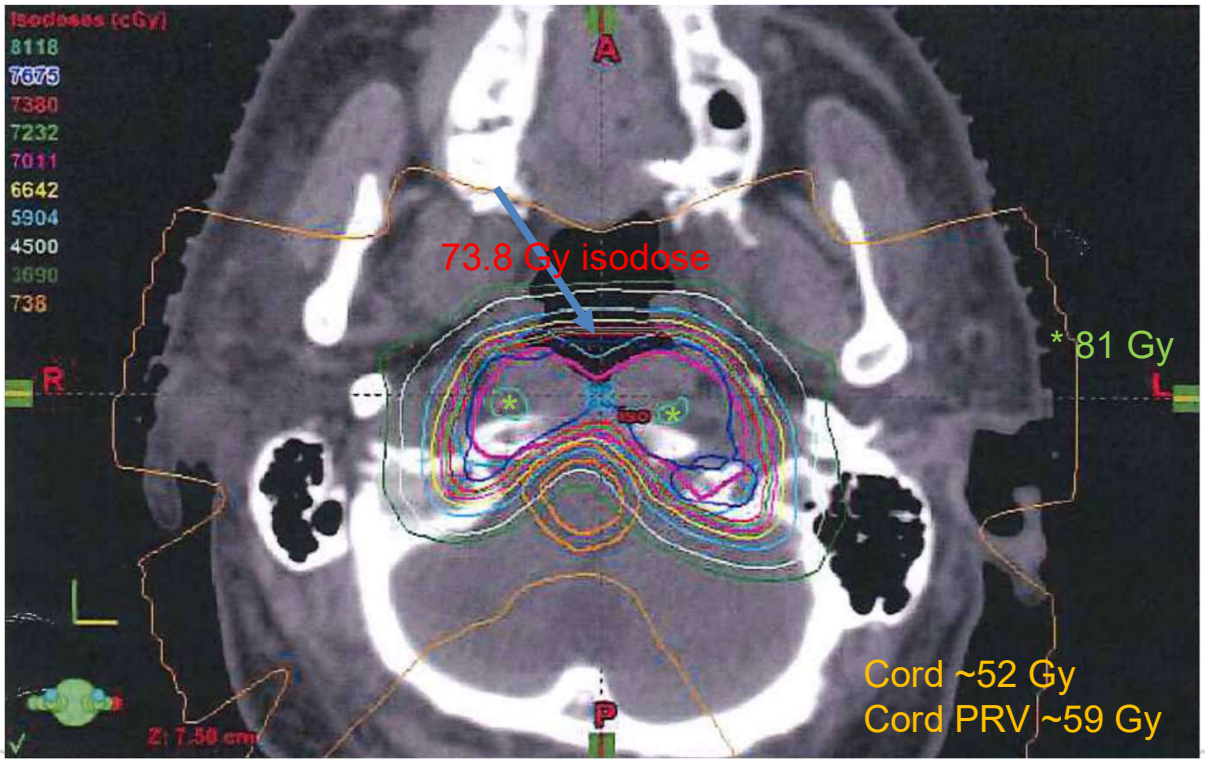
- Chordoma of clivus with bone destruction
- Complete resection. Referred for PBT

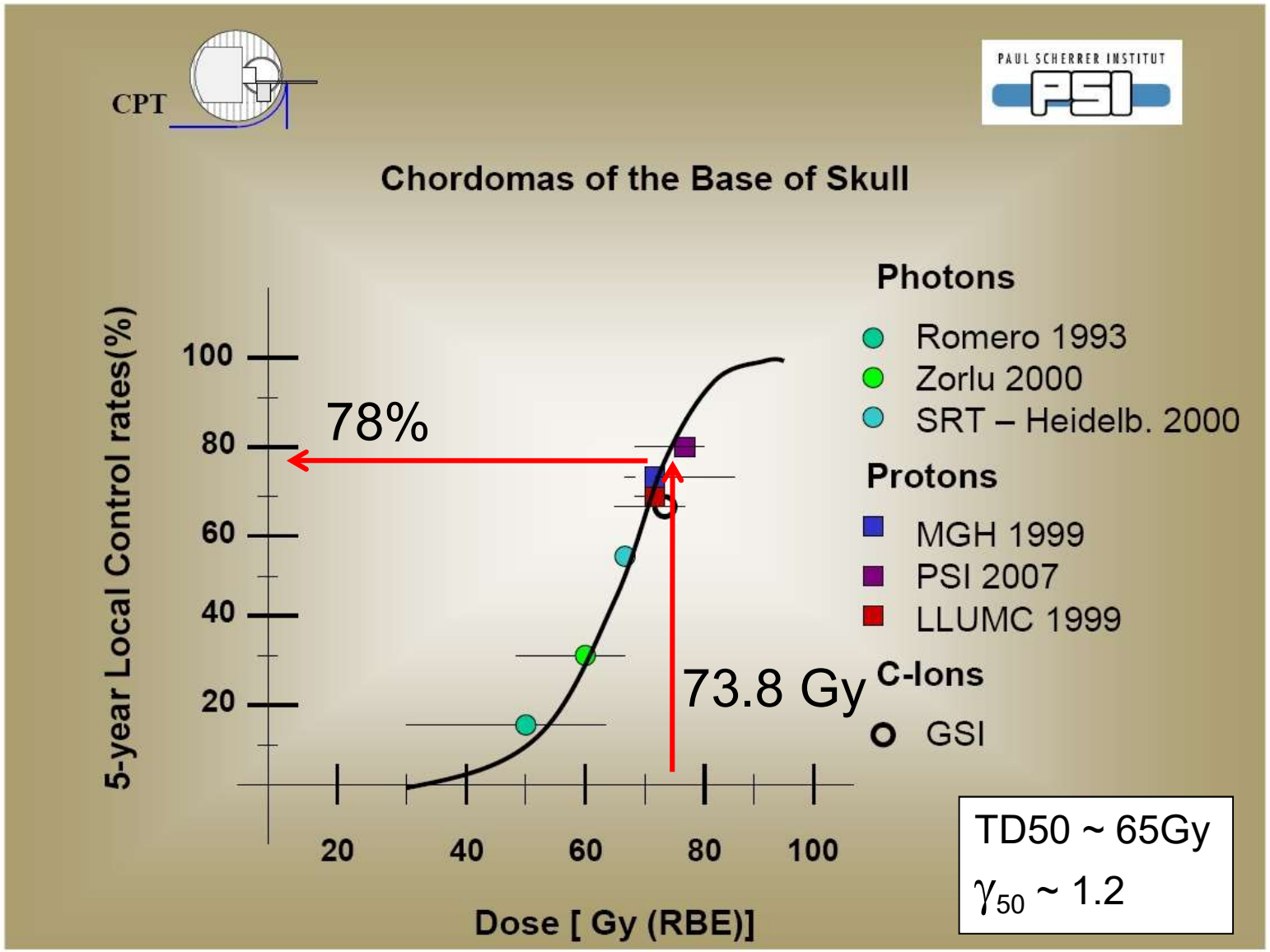




Chordoma - 2

- PBT – 2 phases (Jacksonville, passive scattering)
- 73.8 Gy / 41# @ 1.8 Gy (45/25 + 28.8/16)



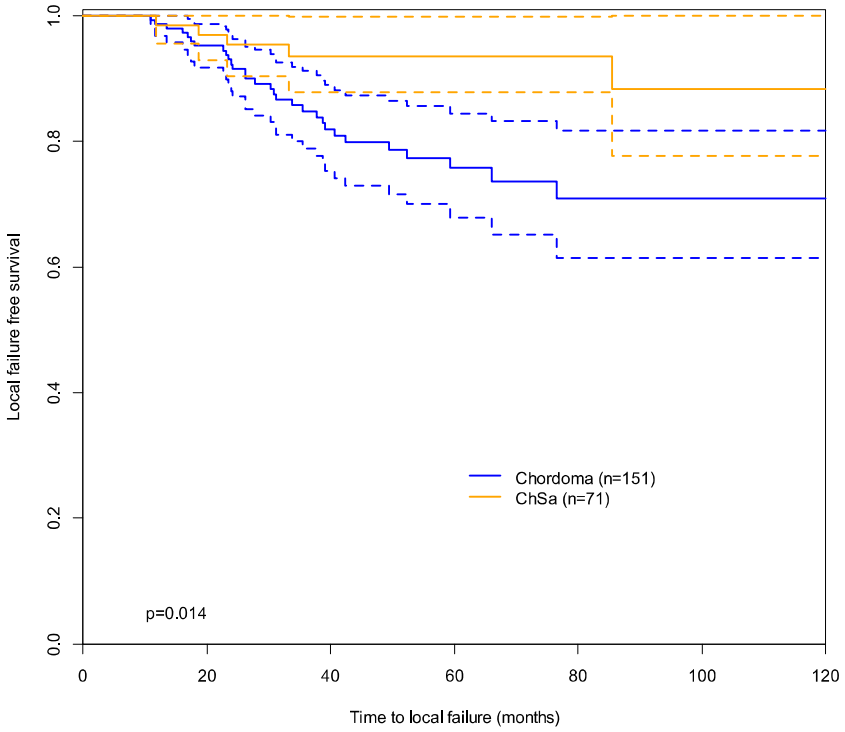

CPT
PAUL SCHERRER INSTITUT
PSI
Chordomas of the Base of Skull
5-year Local Control rates(%)
100
80
60
40
20
78%
73.8 Gy
20
40
60
80
100
Dose [Gy (RBE)]
Photons
Romero 1993
Zorlu 2000
SRT – Heidelb. 2000
Protons
MGH 1999
PSI 2007
LLUMC 1999
C-Ions
GSI
TD50 ~ 65Gy
γ_{50} ~ 1.2

Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy

Damien C. Weber [a,b,c,*], Robert Malyapa [a], Francesca Albertini [a], Alessandra Bolsi [a], Ulrike Kliebsch [a], Marc Walser [a], Alessia Pica [a], Christophe Combescure [d], Antony J. Lomax [a,e], Ralf Schneider [a]

Chordoma N= 151
Mean follow-up of 50 months (4–176) months
Estimated 7-year LC rate for chordoma 70.9% (95% 61.5–81.8)

Radiotherapy and Oncology 120 (2016) 169–174



Toxicity:

5 patients with grade 3 unilateral optic neuropathy

2 patients with grade 4 bilateral optic neuropathy

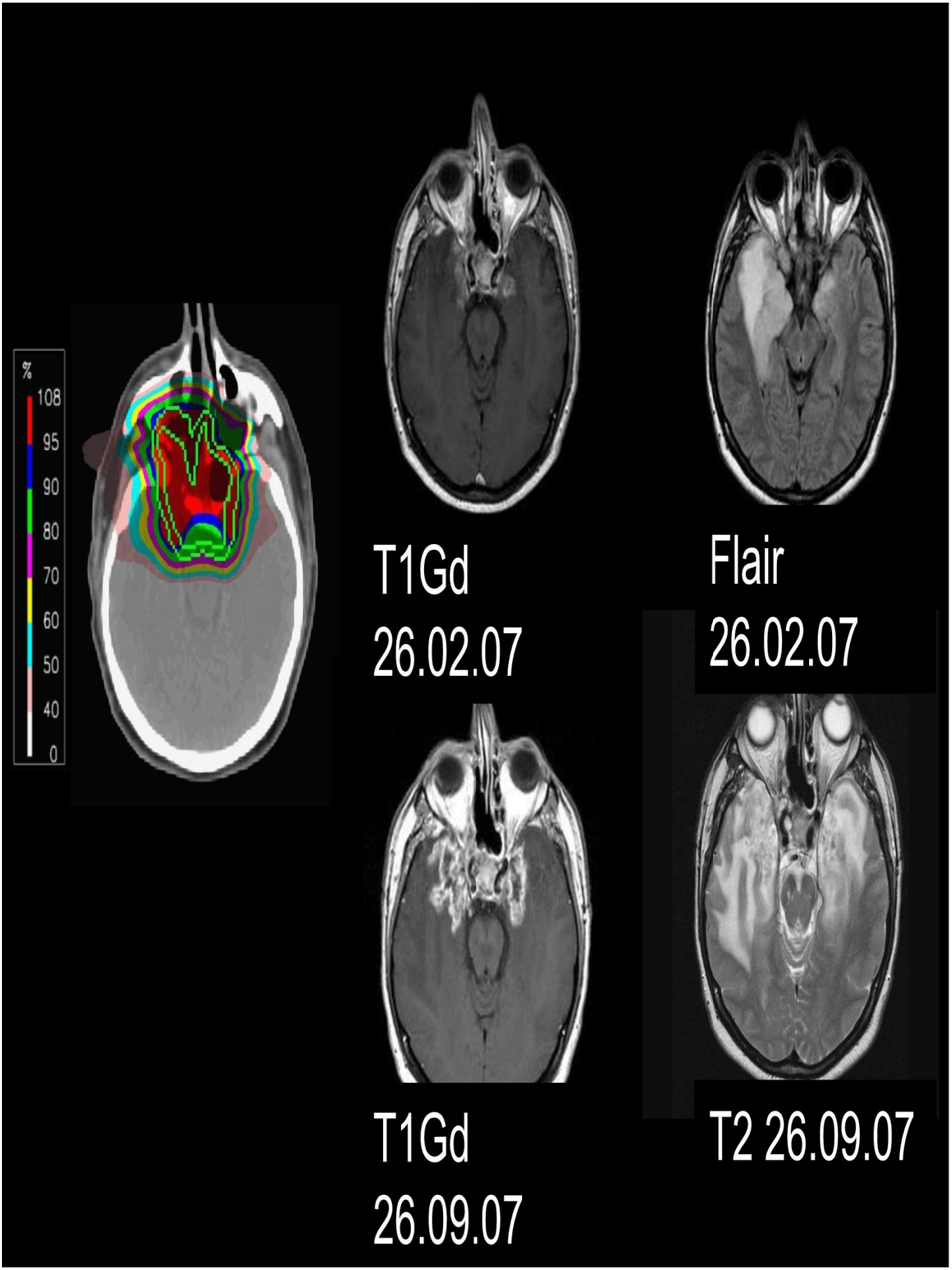
13 patients with Grade 3 temporal lobe necrosis

1 with cerebellar necrosis

1 grade 4 spinal cord necrosis

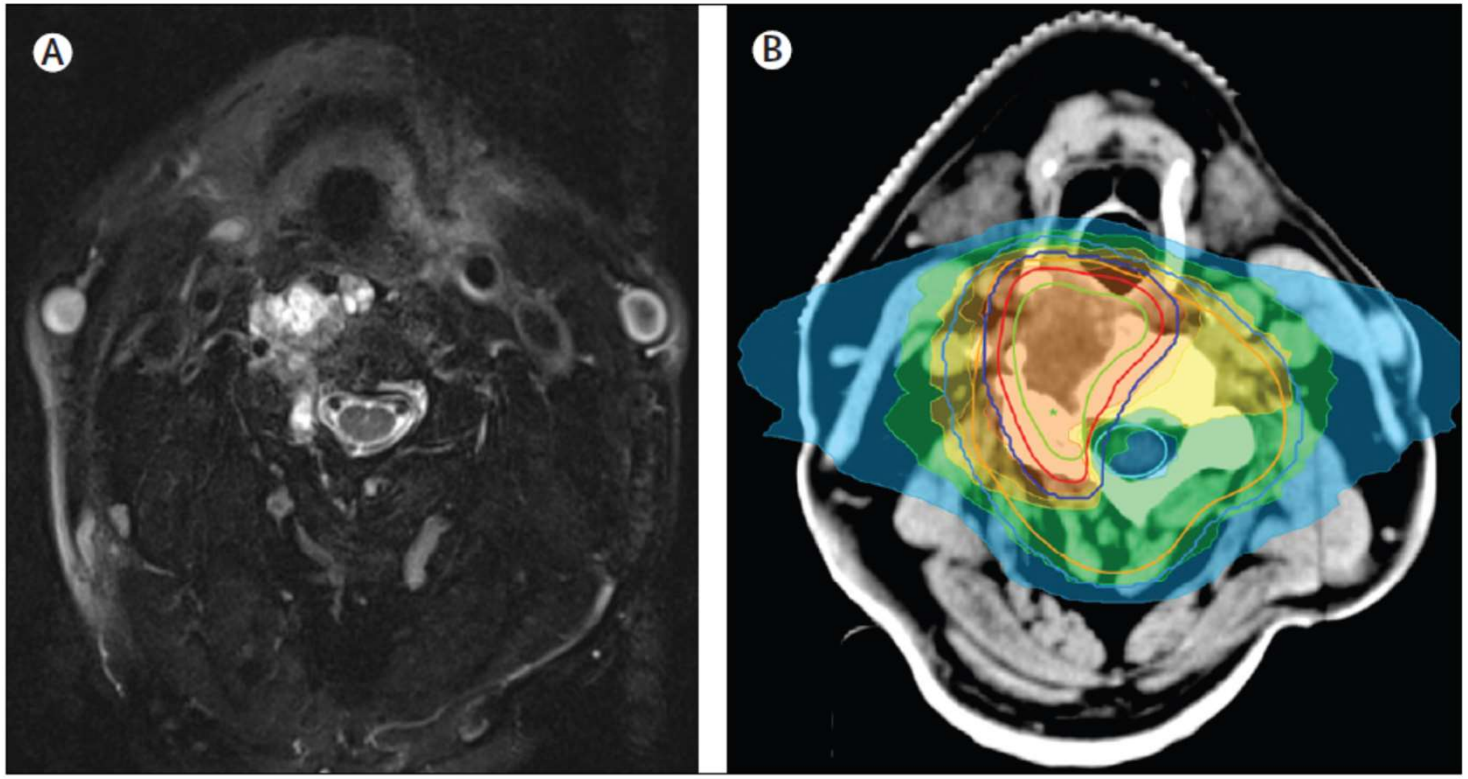
3 patients with grade 3 unilateral hearing loss.

Radiotherapy and Oncology 120 (2016) 169–174


%
108
95
90
80
70
60
50
40
0
T1Gd
26.02.07
Flair
26.02.07
T1Gd
26.09.07
T2 26.09.07

Chordoma - Carbon ion therapy

- Chordoma C3-5 - 66 GyE in 21# (≈ 82.5 Gy for a/b of 2)



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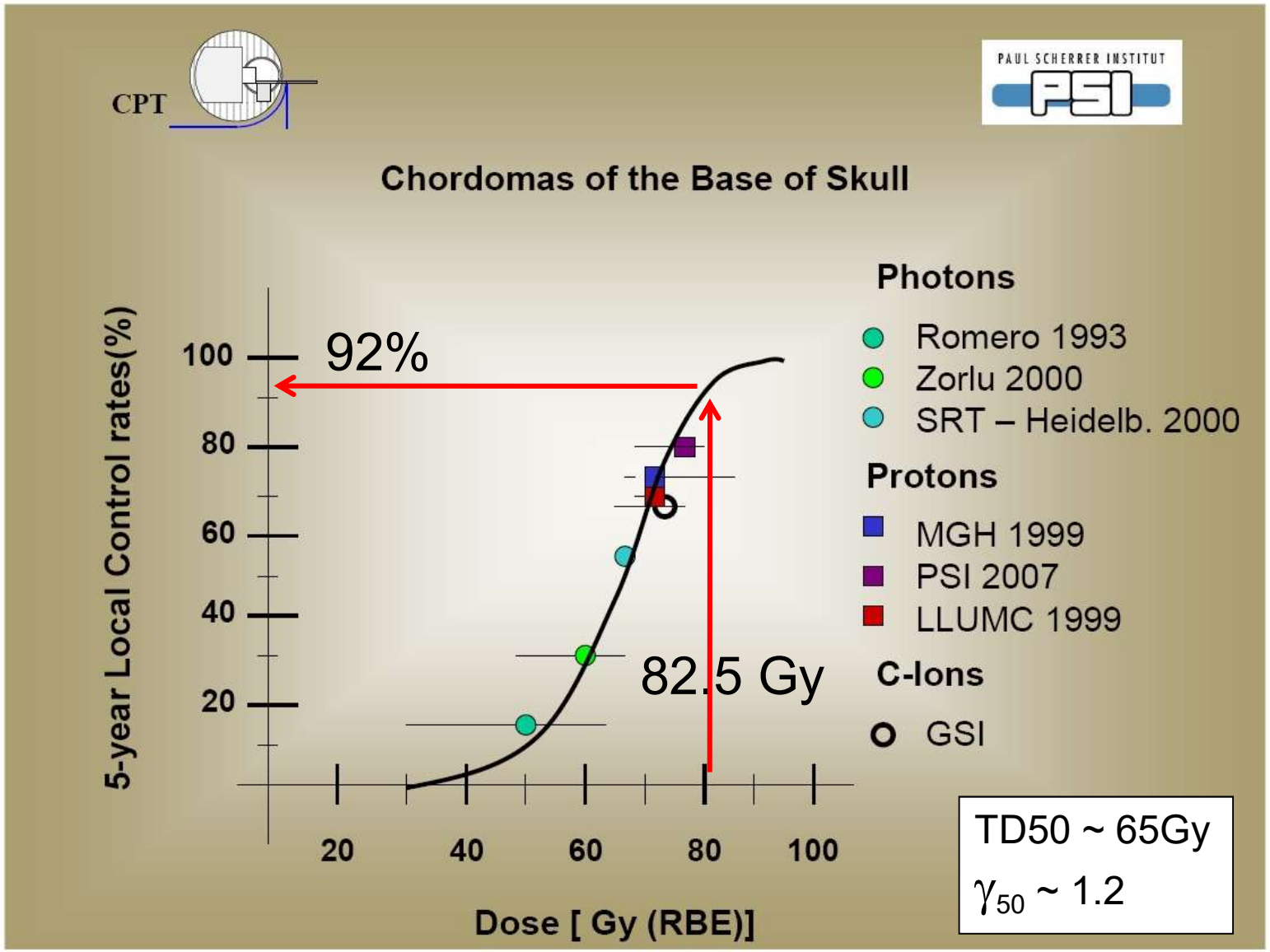
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Protons
MGH 1999
PSI 2007
LLUMC 1999
C-Ions
GSI
TD50 ~ 65Gy
γ_{50} ~ 1.2

Highly effective treatment of skull base chordoma with carbon ion irradiation using a raster scan technique in 155 patients: first long-term results.

N=155
Local control:
3-year 82%,
5-year 72%,
10-year 54%

Cancer. 2014120(21):3410-7.

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What can affect outcome

- Other factors affect outcome
  - Tumour volume
  - Brainstem compression
  - Metal

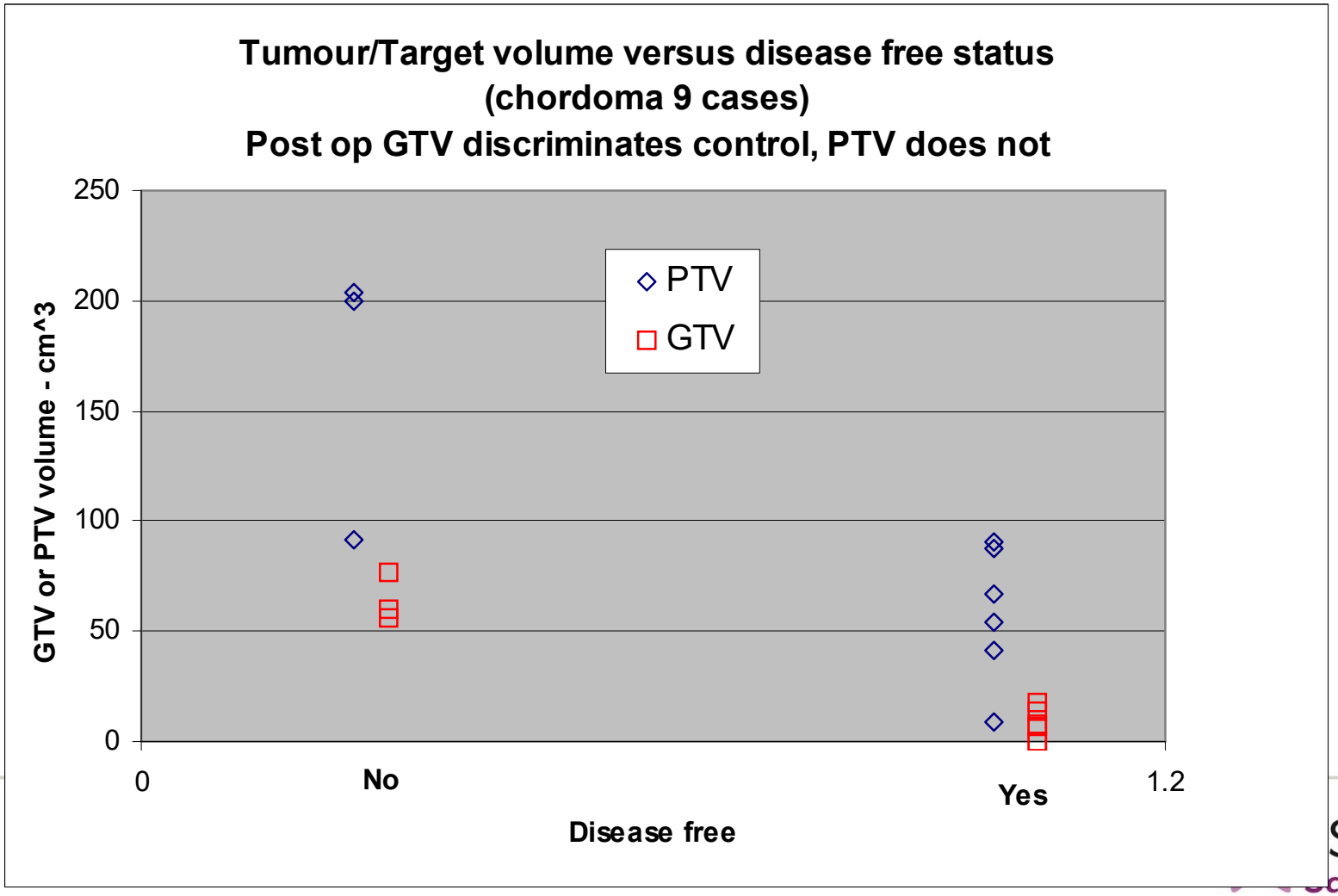
Outcome & Tumour volume

- PSI (mean 73.5 Gy) (Ares et al IJROBP 2009,
  - Local control at 5 years - 81%
  - GTV > 25 cm^3 worse – LC 78% vs 96%

- Cambridge (X-rays – 65 Gy)
  - GTV ≤ 18 cm^3 – LC in 6/6
  - GTV ≥ 60 cm^3 – LC in 0/3
  - Little relation with PTV

Tumour volume

- Cambridge experience



Univariate analysis of risk factors for local failure (LC) and death (OS) in 222 patients with skull base tumors treated with proton therapy. Significant *P* values ($P < 0.05$) are in bold

Prognostic factors		7-year LC (%) [95%CI]	*P* value*	7-Year OS (%)	*P* value*
Compression optic apparatus	Yes	64.6[51.4–81.2]	**0.003**	67.8[53.7–85.6]	**0.016**
	No	85.5[78.8–92.8]		88.3[82.1–95.0]	
Compression Brainstem	Yes	64.0[51.4–79.7]	**0.004**	69.4[56.4–85.5]	**0.008**
	No	86.2[79.3–93.7]		87.2[79.2–95.6]	
Any compression	Yes	67.1[56.8–79.2]	**0.0007**	73.7[63.1–86.0]	**0.025**
	No	92.3[86.9–98.0]		90.3[83.5–97.6]	
GTV	⩽25 cc	86.6[79.4–94.5]	**0.005**	86.2[77.8–95.5]	**0.01**
	>25 cc	65.6[51.2–84.2]		70.8[56.0–89.5]	
Histology	Chordoma	70.9[61.5–81.8]	**0.014**	72.9[62.3–85.3]	**0.014**
	ChSa	93.6[87.8–99.9]		94.1[87.7–100.0]	
Recurrent disease	Yes	72.8 [60.5–87.6]	0.052	82.5[68.6–99.3]	0.99
	No	79.8[71.6–89.0]		79.5[70.6–89.4]	
Number of weekly fractions	4	75.4[65.6–86.7]	0.42	76.8[67.1–87.8]	0.28
	5	81.9[73.1–91.8]		89.4[83.1–96.2]	
Gender	Female	72.8[61.4–86.5]	0.63	807[69.8–93.3]	0.79
	Male	83.1[75.7–91.2]		79.4[69.3–91.0]	
Age	⩽40 years	84.4[75.2–94.7]	0.27	89.5[82.2–97.5]	0.12
	>40 years	74.2[64.9-84.8]		72.5[60.9–86.3]	

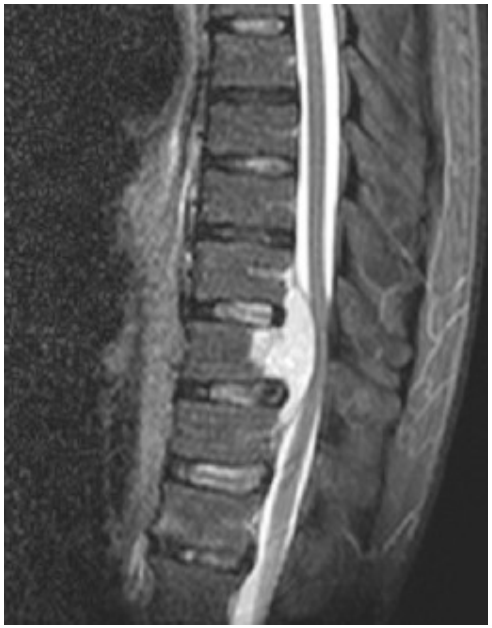
Tumour volume

- Implications for surgery
  - Major debulking important
  - Small remnant may be acceptable
    - Balance morbidity

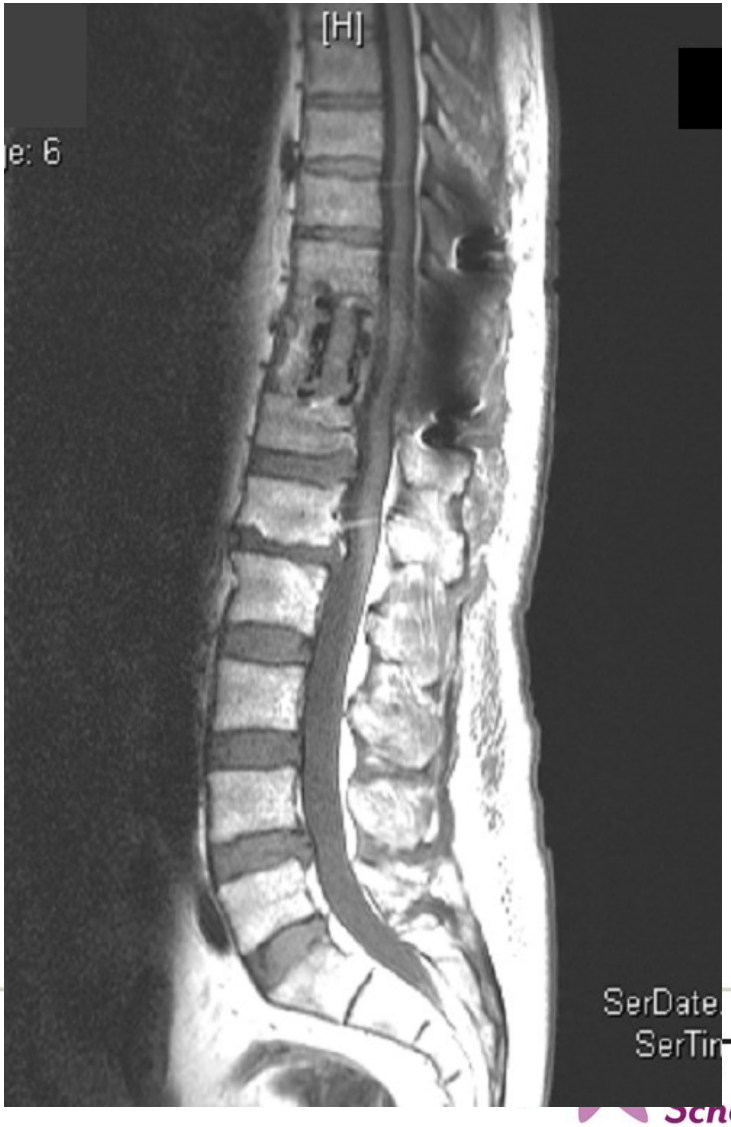
- PSI (mean 73.5 Gy)
- Brainstem/ON compression worse outcome
    - Relates to under-dose at ‘dangerous’ edge

Decompress

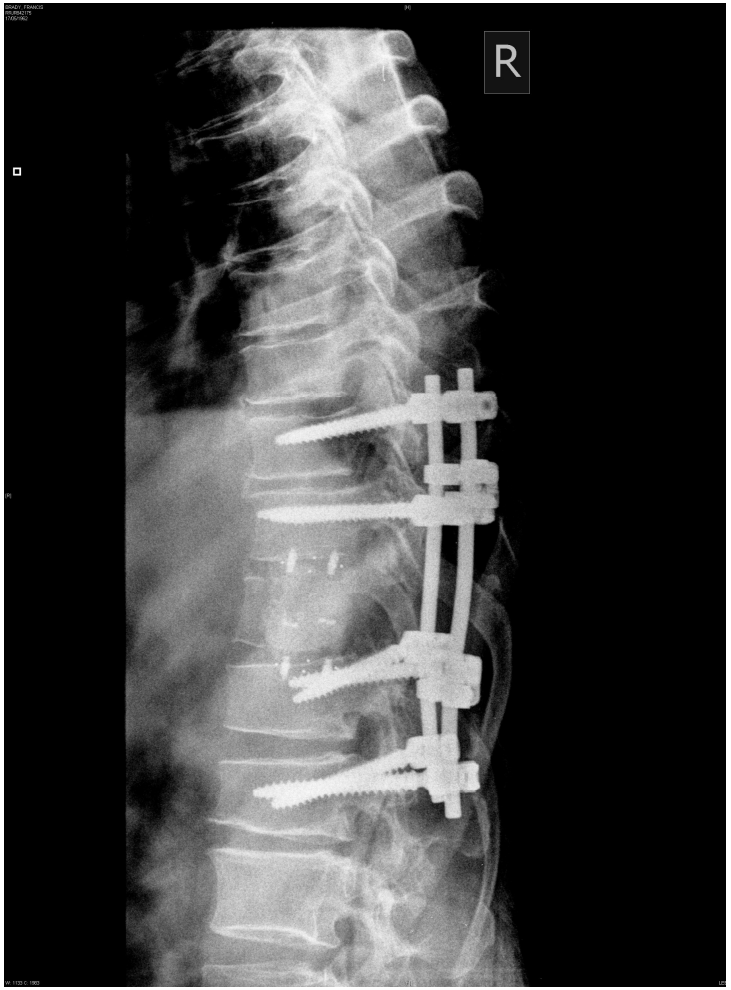
- T11

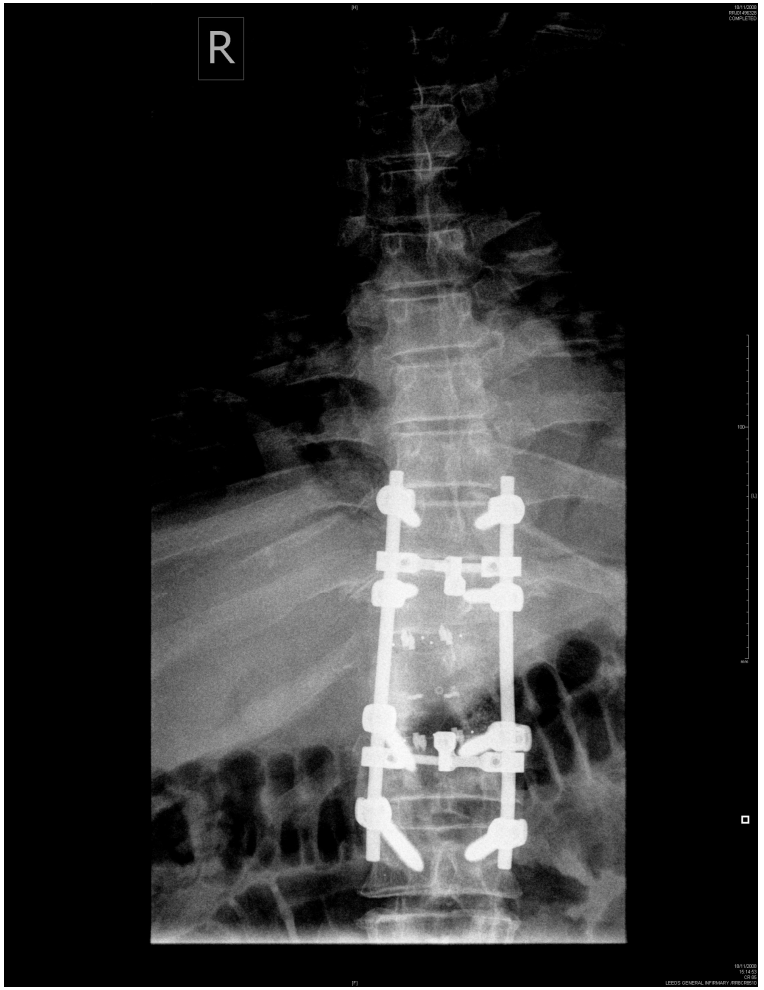


- Relief of compression essential
  - Clinical
  - Dose to target



Reconstruction





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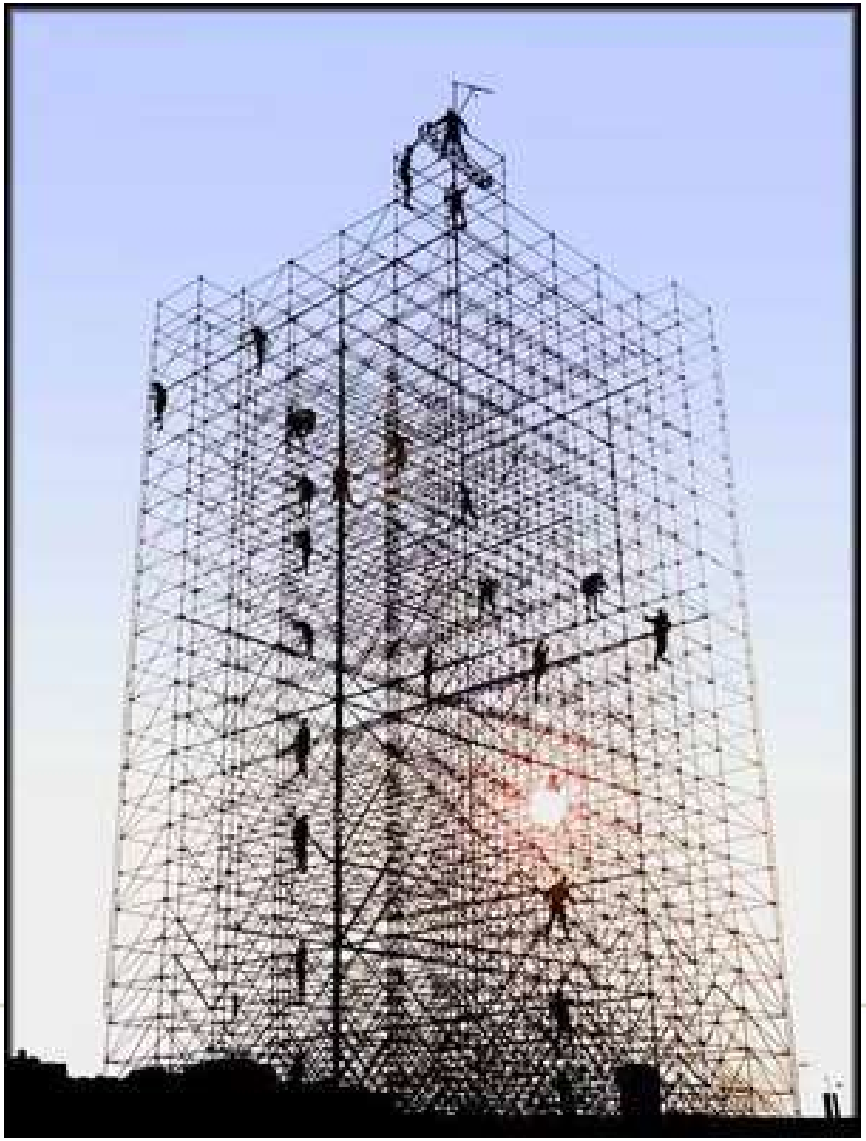
RT after metal reconstruction



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RT after metal reconstruction

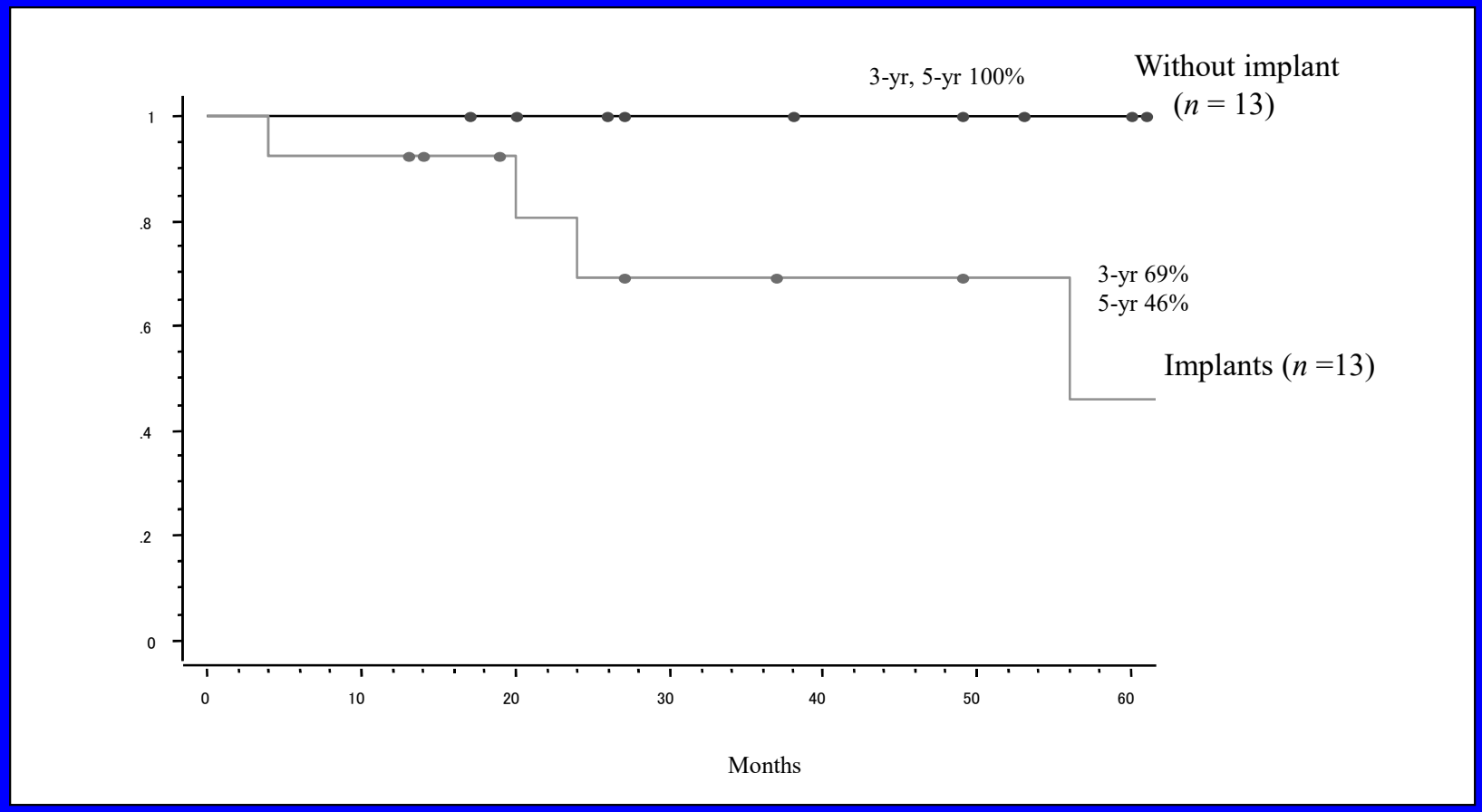
- Metal reduces local control with proton RT
  - Particularly important if metal within GTV
- Issue emerged during 2009
- Result of PSI review of outcomes

RT after metal reconstruction

- Local control at 5 years (PSI – 26 cases, spine)
  - With metal LC = 46%
  - No metal LC = 100%
- Metal reconstruction present in ~ 1/3 spine cases
  - Boston - Delaney et al IJROBP 2009
  - Numerically significant issue
- ? Bigger tumours need reconstruction

Clinical experience at PSI

Chordomas and chondrosarcomas of the spinal axis



Rutz et al 2009

Final Thought

If you always do what you always did,

You'll always get what you always got

Anon

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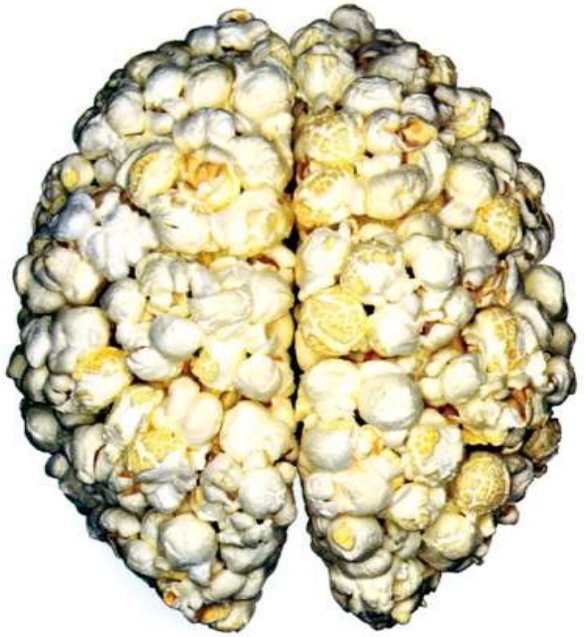
Management of benign tumours



Dr Sarah Jefferies

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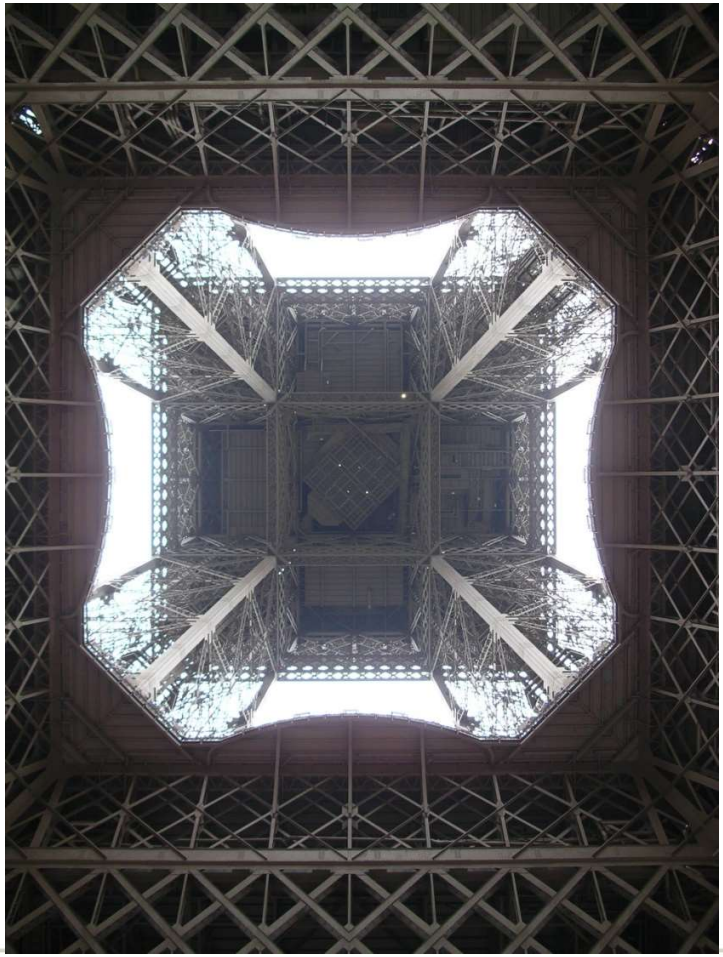
Perspective



Risks

Background

- Long natural history
- Often not life-threatening
- Radiotherapy can have a role

Which tumours?

- **Pituitary tumours**
- **Vestibular schwannoma**
- **Craniopharyngioma**
- **Glomus tumours**
- Meningioma

Requirements

- Understand
  - Natural history
  - Imaging
  - Other treatment modalities

Dose-fractionation-radiotherapy

- Fractionated 45-55Gy in 25-33#
- Hypo-fractionated 20-30Gy in 3-10#
- Single fraction (radiosurgery) 10-25Gy in 1#

Pituitary Adenoma

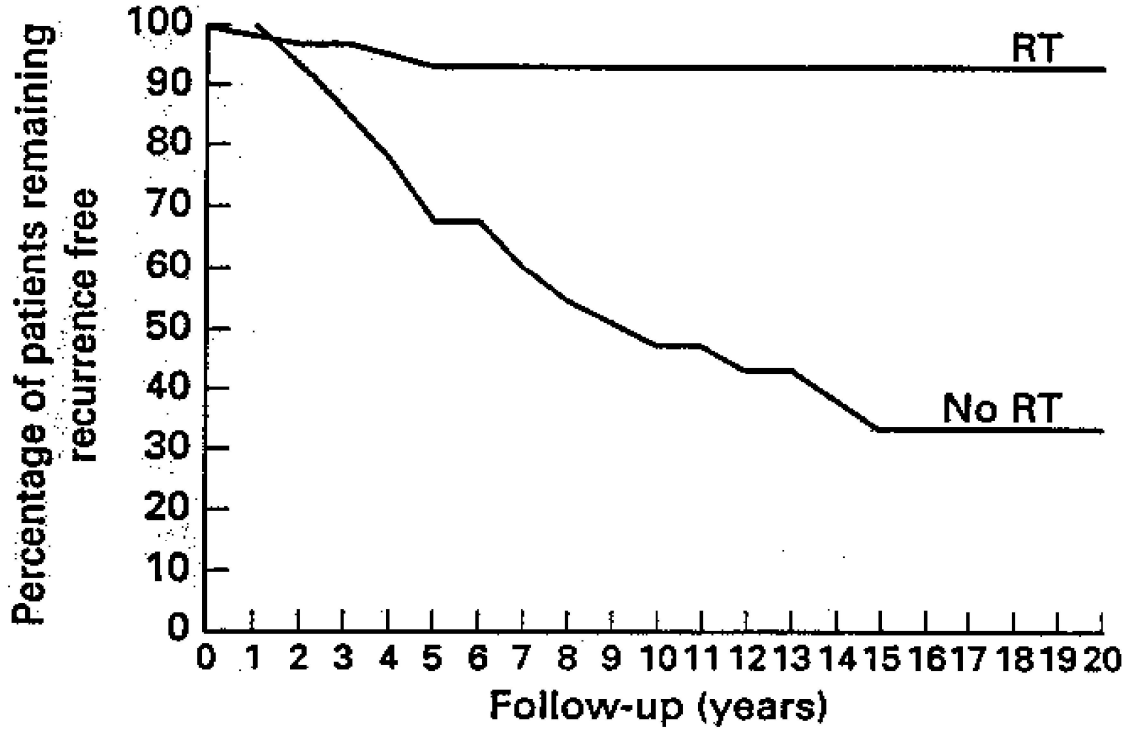
- Radiotherapy is used in patients:
  - with residual or recurrent secreting and nonfunctioning pituitary adenomas after surgery
  - resulting in a long-term tumour control of 80–97%
  - normalization of elevated hormone levels in 40–70% of patients

Int J Radiat Oncol Biol Phys 1995;**33**:307–14.

Clin Endocrinol (Oxf) 1993;**38**:571–8.

Non-functioning Pituitary Adenoma

No randomised data: 2 centre study – progression post surgery



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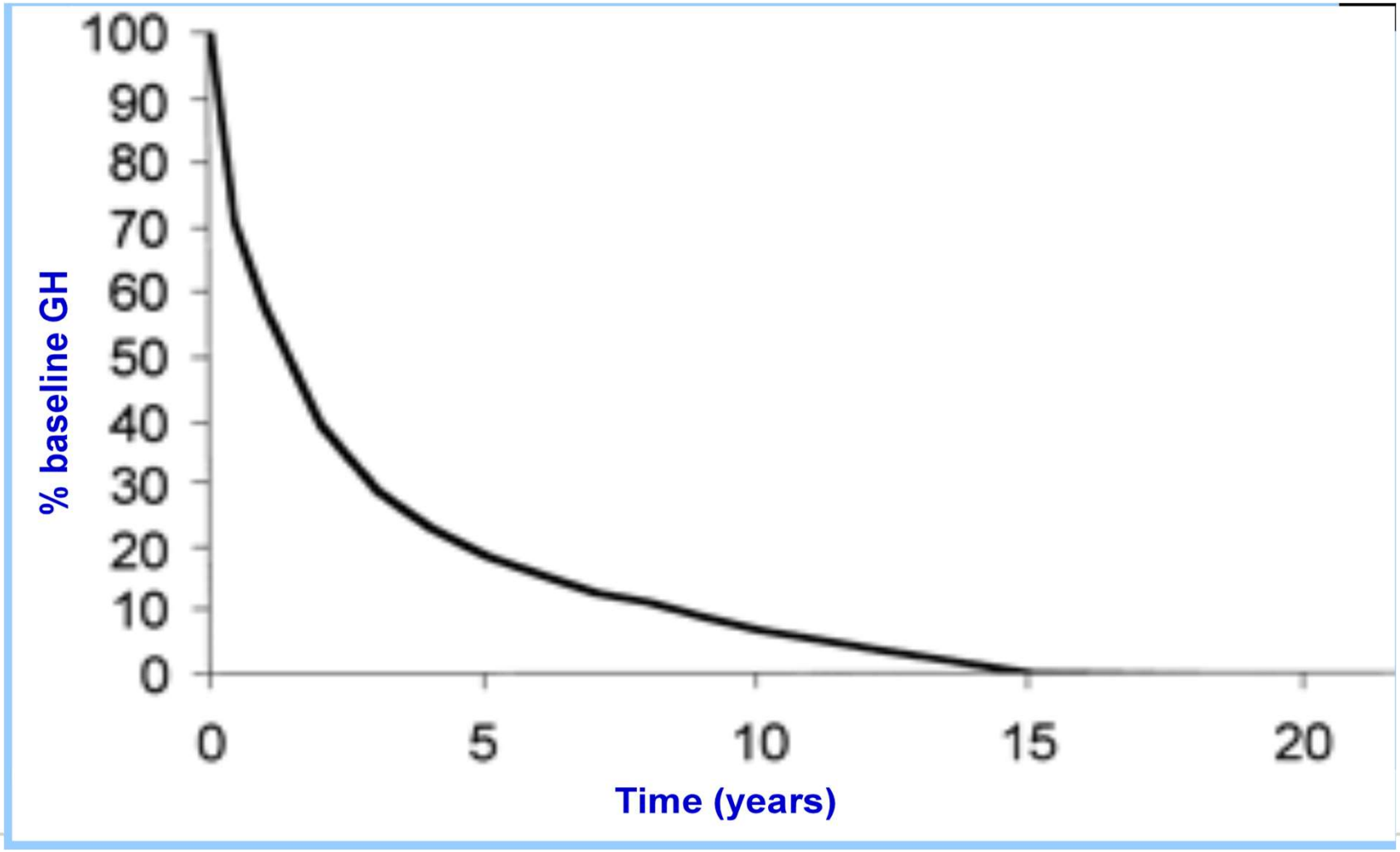
GH control - acromegaly



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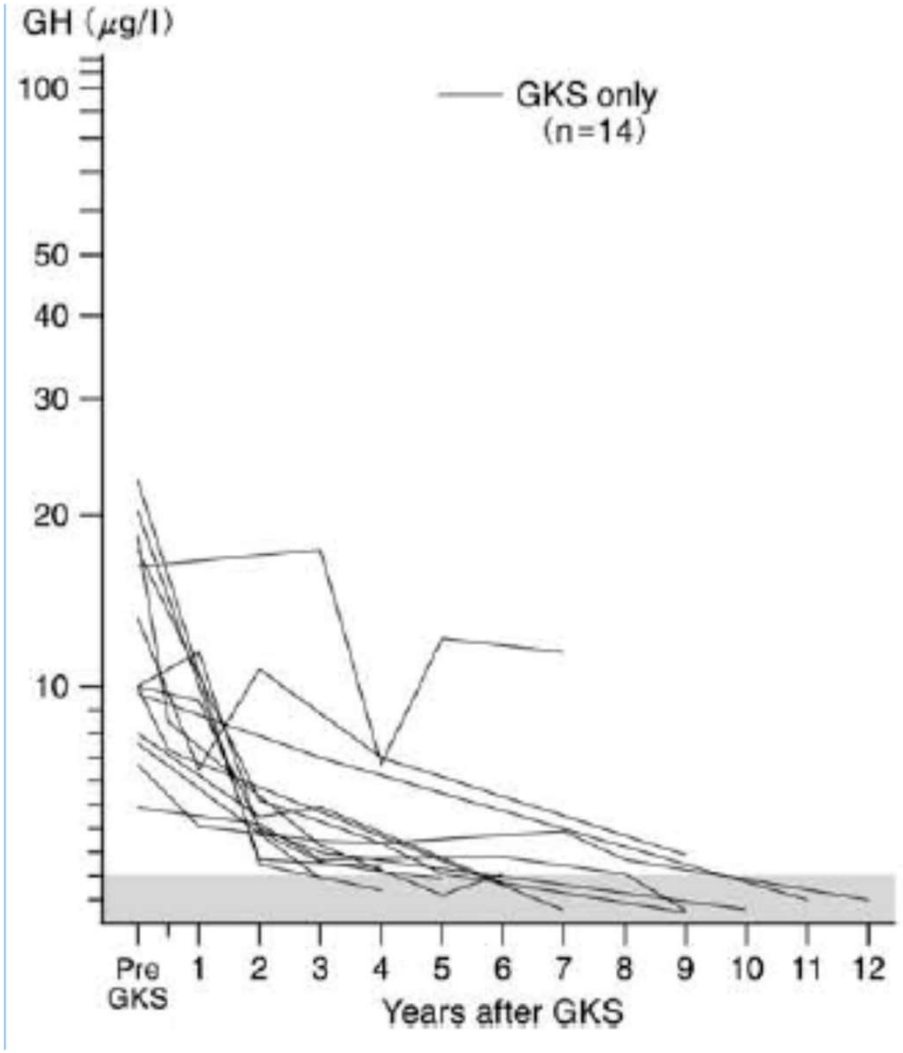
GH and IDH control after GK



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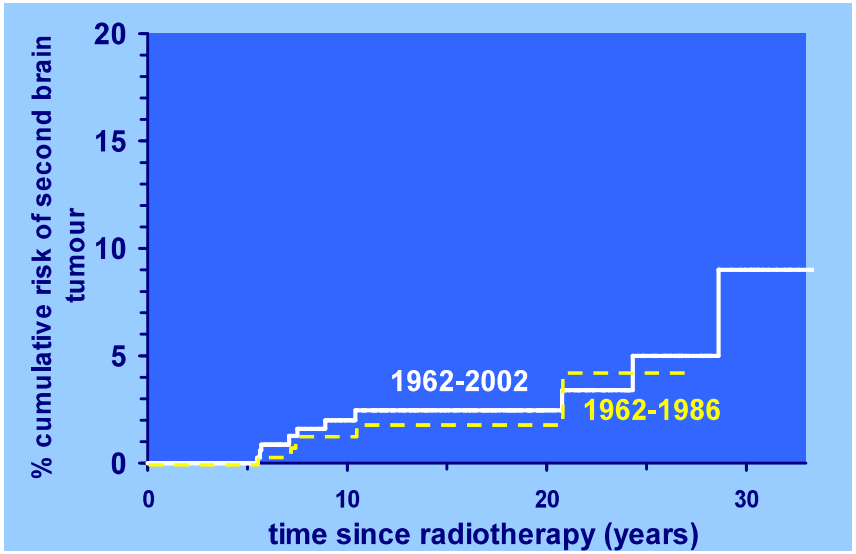
Risks of treatment

- Hypopituitism 30–60% in 5–10 years
- radiation-induced optic neuropathy
- cerebrovascular accidents
- second tumors 0–3%



J Clin Endocrinol Metab 2005;**90**:800–4.

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Which modality of RT to choose?

- SRS retrospective data
- incidence of radiation-induced optic neuropathy:
  - 2% for single doses of 8–12 Gy
  - >10% for doses of 12–15 Gy to the optic apparatus
- cranial nerves in the cavernous sinus:
  - maximum dose is 16–18 Gy
- brainstem
  - maximum dose of 12–13 Gy

Int J Radiat Oncol Biol Phys 2013;**87**:524–7

Table 1 – Summary of recent published results (2000–2014) on SRS for nonfunctioning pituitary adenomas.

Authors	Patients	Mean dose (Gy)	Follow-up (months)	Tumor control (%)	Late toxicity (%)	
					Visual	Hypopituitarism
Izawa et al., 2000	23	19.5	>6	NA	1	NA
Wowra and Stummer, 2002	45	16	55	93 at 3 years	0	14
Petrovich et al., 2003	56	15	36	94 at 3 years	4	NA
Pollock and Carpenter, 2003	33	16	43	97 at 5 years	0	41 at 5 years
Losa et al., 2004	56	16.6	41	88 at 5 years	0	24
Iwai et al., 2005	34	12.3	60	93 at 5 years	0	6.5
Mingione et al., 2006	100	18.5	45	92.2	0	25
Liscak et al., 2007	140	20	60	100	0	2
Pollock et al., 2008	62	16	64	95 at 5 years	0	27
Gopalan et al., 2011	48	18.4	95	83	0	39
Park et al., 2011	125	13	62	94 at 5 years	0.8	24
Starke et al., 2012	140	18	50	97 at 5 years	12.8	30.3
Runge et al., 2012	61	13	83	98	0	9.8
Wilson et al., 2012	51	14	50	100 at 5 years	0	NA
Sheehan et al., 2013	512	16	36	95 at 5 years	6.6	21
Lee et al., 2014	41	12	48	85 at 10 years	2.4	24.4

Authors	Patients	Dose (Gy)	Follow-up (months)	Tumor control (%)	Biochemical remission (%)	Late toxicity (%)	
						Visual	Hypopituitarism
Zhang et al., 2000	68	31	>12	100	40	NA	NA
Izawa et al., 2000	29	22.5	>6	93	41	0	0
Pollock et al., 2002	26	20	36	100	47	4	16%
Attanasio et al., 2003	30	20	46	100	23	0	6.3%
Jane et al., 2003	64	15	>18	NA	36	0	28
Castinetti et al., 2005	82	26	49.5*	NA	17	1.2	17
Gutt et al., 2005	44	23	22	100	48	NA	NA
Kobayashi et al., 2005	67	18.9	63	100	17	11	15
Jezkova et al., 2006	96	35	53.7	100	44 at 5 years	0	27.1
Voges et al., 2006	64	16.5	54.3	97	14 and 33 at 3 and 5 years	1.4	13 and 18 at 3 and 5 years
Pollock et al., 2007	46	20	63	100	11 and 60 at 2 and 5 years	0	33 at 5 years
Vik-Mo et al., 2007	53	26.5	67	100	58 and 86 at 5 and 10 years	3.8	10 at 5 years
Jagannathan et al., 2008	95	22	57	98	53	4	34
Losa et al., 2008	83	21.5	69	97	52 and 85 at 5 and 10 years	0	10 at 10 years
Ronchi et al., 2009	35	20	114	100	46 at 10 years	0	50
Wan et al., 2009	103	28	67	95	37	0	6
Hayashi et al., 2010	25	25	36	100	40	0	0
Iwai et al., 2010	26	20	84	96	17 and 47 at 5 and 10 years	0	8
Castinetti et al., 2009	43	28	96	100	42.0	0	23
Leenstra et al., 2010	31	20	32	100	NA	NA	45 at 5 years
Erdur et al., 2011	22	23.8	60	95.2	54.5	0	28.6
Sheehan et al., 2011	130	24	31	93.0	53	2.4	24.4
Sicignano et al., 2012	39	25	60	97.7	54	NA	12.3
Franzin et al., 2012	103	22.5	71	97.3	58.3 at 5 years	0	14
Liu et al., 2012	40	21	72	97.5	47.5	0	40
Zeiler et al., 2013	21	14.2	33*	100	30	3.9	13.2
Yan et al., 2013	22	23	98	95	68.2	0	22.7
Wilson et al., 2013	86	20	66	96	18.6	1.2	19.8

Table 3 – Summary of recent published results (2000–2014) on SRS for ACTH-secreting pituitary adenomas.

Authors	Patients	Mean dose (Gy)	Follow-up (months)	Tumor control (%)	Biochemical remission (%)	Late toxicity (%)	
						Visual	Hypopituitarism
Izawa et al., 2000	12	23	>6	100	17	NA	0
Sheehan et al., 2000	43	16.5	44	100	63	2.5	16
Hoybye et al., 2001	18	NA	180	100	83	0	66
Kobayashi et al., 2002	20	28.7	60	100	35	NA	NA
Devin et al., 2004	35	14.7	35	91	49	0	40
Castinetti et al., 2007	40	29.5	54	100	42.5	2.5	15
Jagannathan et al., 2007	90	23	45	96	54	5.5[a]	22
Pollock et al., 2008	8	20	73	100	87 at 4 years	0	26 at 4 years
Tinnel et al., 2008	12	25	37	83.3	50	0	50
Sicignano et al., 2012	15	23.8	60	97.7	64	NA	12.3
Wein et al., 2012	17	18	23	94.1	58.8	0	11.8
Zeiler et al., 2013	8	24.7	35	100	50	3.9	13.2
Grant et al., 2013	15	35	40.2	100	73	3.2	32
Sheehan et al., 2013	96	16	48	98	70	5	36
Wilson et al., 2014	36	20	66	97	25	0	13.9

Table 5 – Summary of recent published results (2000–2014) on FSRT for pituitary adenomas.

Authors	Type of adenoma	Patients	Mean dose (Gy)	Follow-up (months)	Tumor control (%)	Late toxicity (%)	
						Visual	Hypopituitarism
Milker-Zabel et al., 2001	NFA, SA	68	50.4	38	93 at 5 years	7.5	5
Milker-Zabel et al., 2004	GH	20	52.2	26	100 (92[a])	0	3
Paek et al., 2005	NFA, SA	68	50	30	98 at 5 years	3	6
Colin et al., 2005	NFA, SA	110	50.4	48	99 at 5 years	1.8	29 at 4 years
Minniti et al., 2006	NFA, SA	92	45	32	98 at 5 years	1	22
Kong et al., 2007	NFA, SA	66	50.4	36.7	97	0	27.3 at 5 years
Roug et al., 2010	GH	34	54	34	91 (30[a])	0	29 at 4 years
Schalin-Jantti et al., 2010	NFA, SA	30	45	64	100	0	40
Wilson et al., 2012	NFA	67	50	60.1	93 at 5 years	1.5	7
Kopp et al., 2013	NFA, SA	37	49.4	57	91.9	5	5
Kim et al., 2013	NFA, SA	76	50.4	80	97.1 at 7 years	0	48

What to do?

On the evidence available:

- no data to support the ***superiority*** of SRS over FSRT for patients with pituitary tumours
- Dose and fractionation should be chosen:
  - size
  - position of the pituitary adenoma
- single-fraction SRS at doses of 16–25 Gy ***small*** pituitary adenoma away from the optic chiasm
- FSRT is preferred over SRS for lesions >2.5–3 cm in size and/or involving the anterior optic pathway.

Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas

Giuseppe Minniti[a,b,*], *Enrico Clarke*[a], *Claudia Scaringi*[a], *Riccardo Maurizi Enrici*[a]

REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 21 (2016) 370–378

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Vestibular Schwannoma (VS)

- 6%– 8% of all intracranial tumours
- 80% of cerebellopontine angle tumours
- VSs may remain within the internal auditory canal (IAC) or extend into the CPA
- Symptoms are related to compression of:
  - adjacent cranial nerves
  - brain stem
  - posterior fossa (PF) structures

Differential Diagnosis

- facial nerve schwannoma
- meningioma
- metastasis
- epidermoid cyst
- arachnoid cyst
- aneurysm

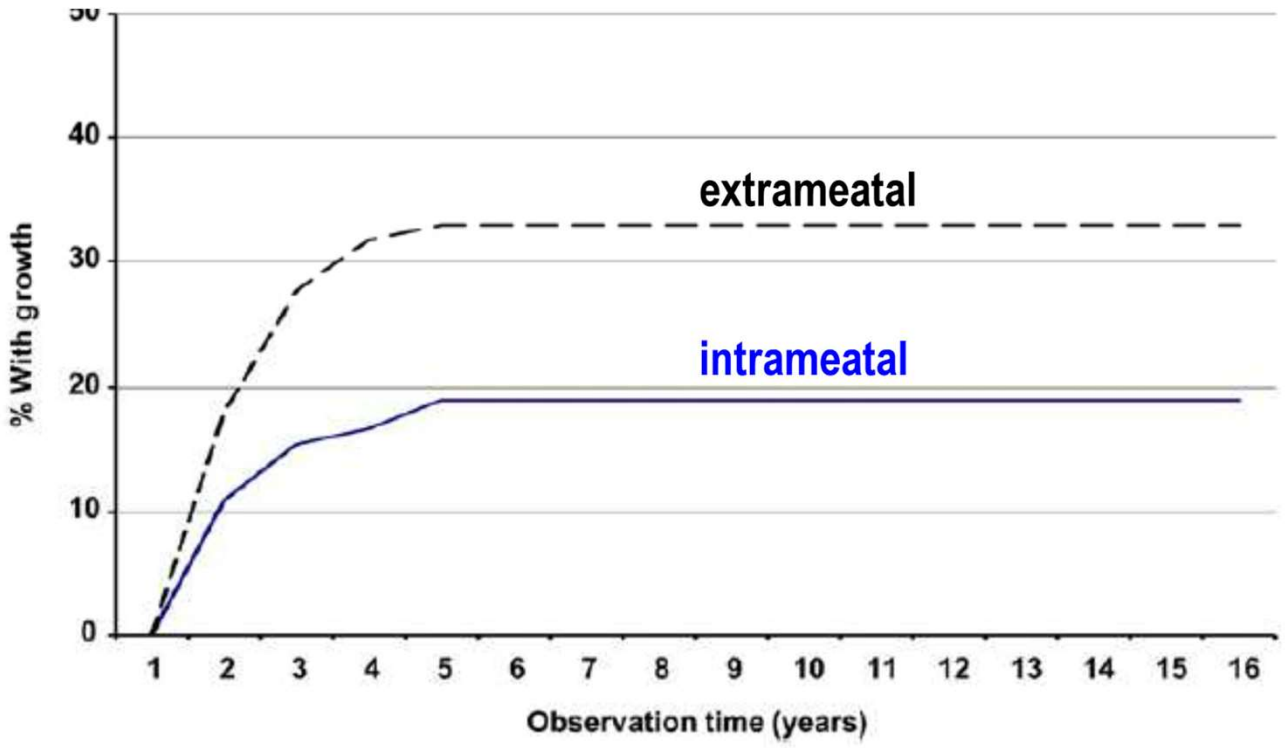
Treatment Options

- Depending on many factors including:
  - patient age
  - tumour size
  - tumour growth
  - and symptoms
- patients can choose:
  - surgery
  - radiation
  - conservative management.

Natural History

- >50% of all VS grow at an average of 2–4 mm/year
- 10% regress
- Extrameatal tumours are more likely to grow compared with intrameatal tumors
- VS of 2 cm is more likely to grow compared with a smaller VS
- Growth rates of 2 mm/year are associated with decreased rates of hearing preservation

VS - surveillance



Natural history of vestibular schwannoma. *Otol Neurotol* 2006;27:547–52

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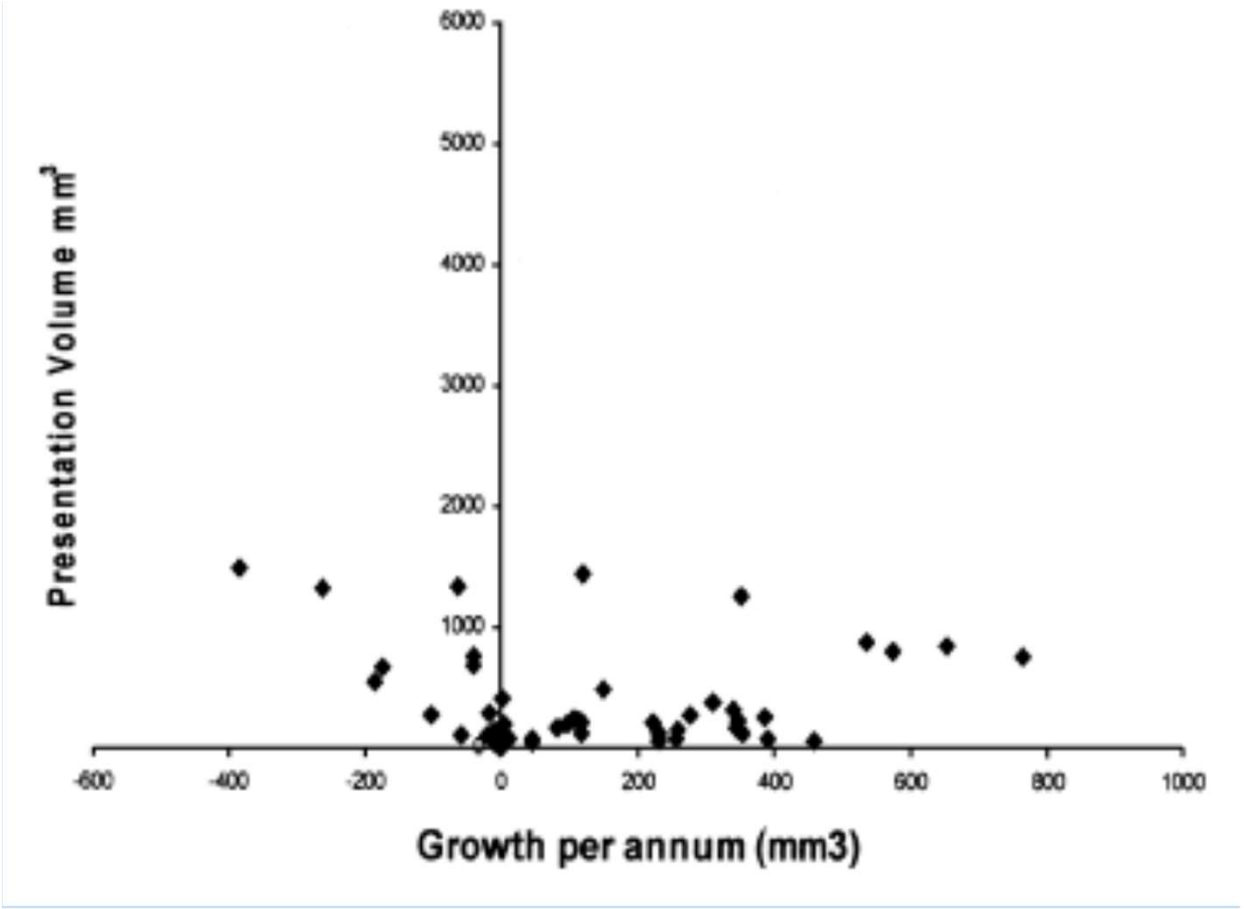
VS - surveillance



Acoustic neuroma growth: systematic review of the evidence. *Otol Neurotol* 2010; 31:478 – 85

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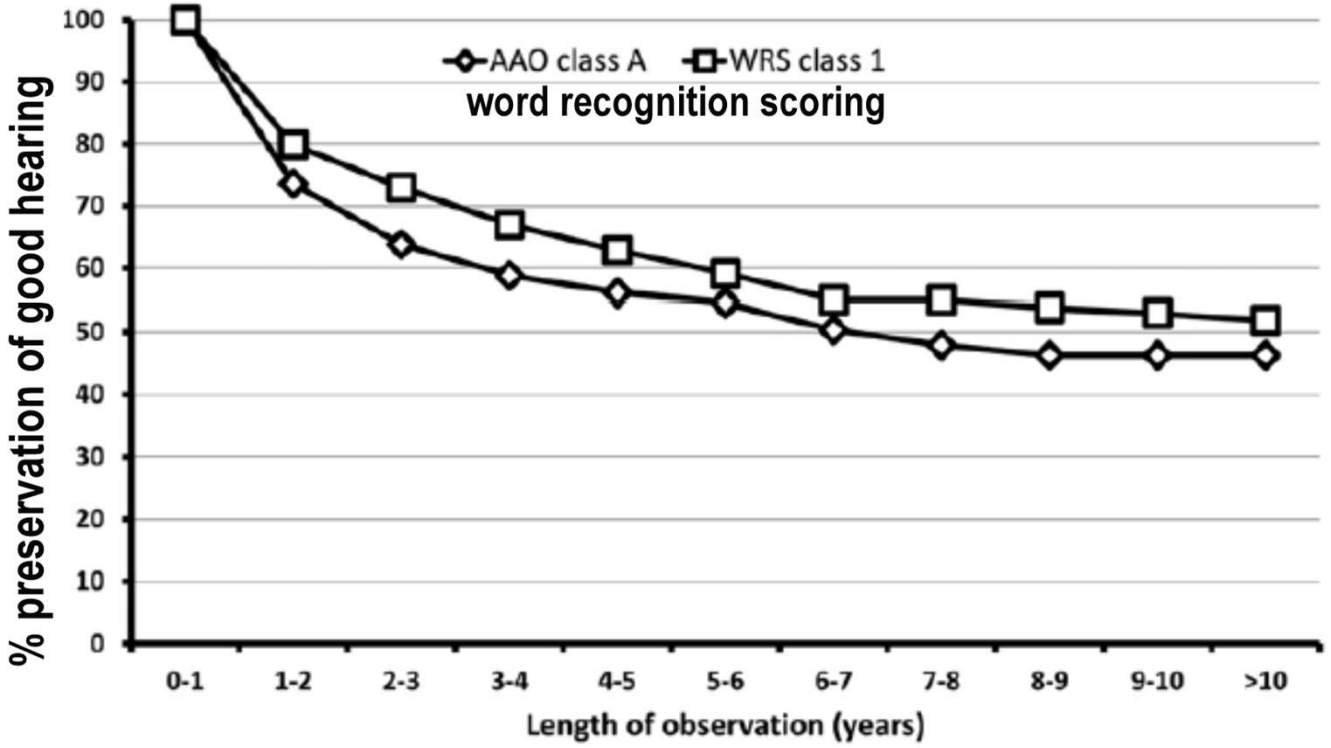
Hearing Loss – on surveillance

Danish Cohort Study <2cm VS



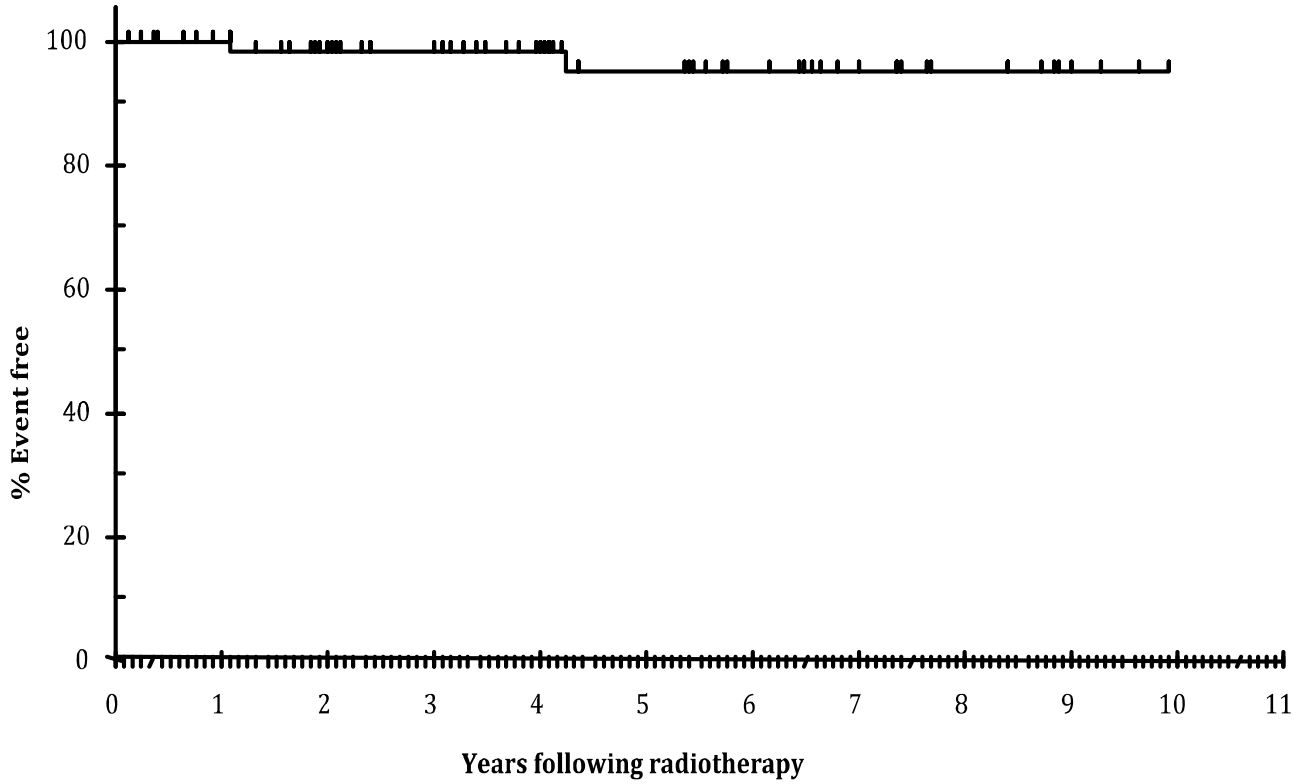
ESTRO School

Radiotherapy

- SRS – single
  - 11–12 Gy
  - 90% tumor control rates
  - 1% risk for permanent facial nerve palsies

- stereotactic fractionated radiation therapy 50/30# - for tumours too large for SRS and surgery not possible

Stereotactic RT



ESTRO School

Hearing

- Hearing preservation rates of 60%–70% initially reported
- Follow-up studies serviceable hearing was preserved in:
  - only 23%–24% patients at 10 years
- Risk Factors:
  - Older age,
  - Larger tumors
  - Poorer pretreatment hearing was found to be a risk factor for progressive post treatment hearing loss

Cystic VS

- 10% of VS are cystic
- Associated with higher degrees of hearing loss
- VS cysts are thought to arise from:
  - recurrent microbleeding or
  - osmosis-induced expansion of CSF trapped in arachnoid tissue
- Cystic VS may rapidly expand
- Surgery is favoured over SRS in the management of cystic VS
- In one study 6.4% of cystic VS treated with SRS required surgery

Neurosurg Rev 2005;28:209 –13

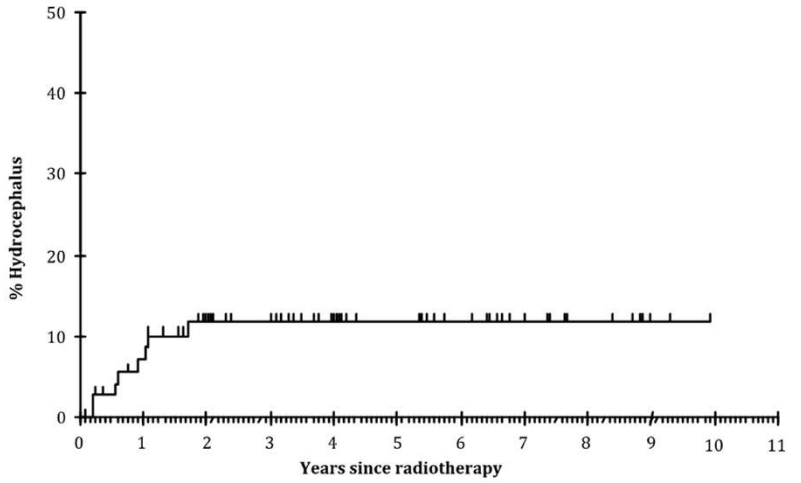
Follow-up

- Post SRS/FSRT the VS may increase in size due to intralesional oedema
- Some tumors will enlarge following SRS
- Most VS treated with SRS will subsequently:
  - decrease or
  - remain stable in size
  - takes time*

Dose and diameter relationships for facial, trigeminal, and acoustic neuropathies following acoustic neuroma radiosurgery. *Radiother Oncol* 1996;41: 215–19

Long-term Toxicity

- Hydrocephalus
- Cranial nerve palsies
- Second malignancy

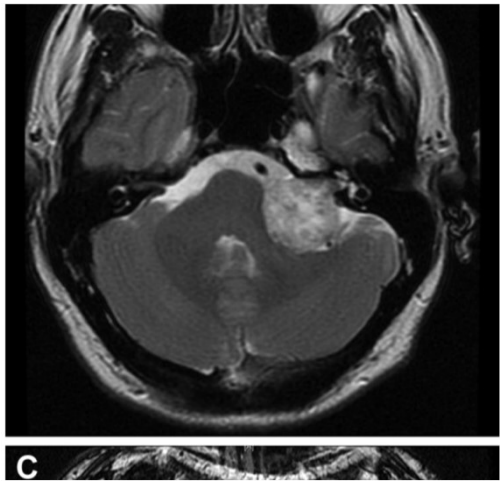


ESTRO School

Is there a place for hypofractionation?

The Outcome of Hypofractionated Stereotactic Radiosurgery for Large Vestibular Schwannomas

Mario Teo[1], Michael Zhang[1], Amy Li[1], Patricia A. Thompson[1], Armine T. Tayag[1], Jonathan Wallach[2], Iris C. Gibbs[2], Scott G. Soltys[2], Steven L. Hancock[2], Steven D. Chang[1]



N = 30
Over 3cm
8/30 cystic
6 NF

SRS 3 # in 3 days
median 18 Gy (18-25)
prescribed to median 80% (71-90)

WORLD NEUROSURGERY 93: 398-409, SEPTEMBER 2016

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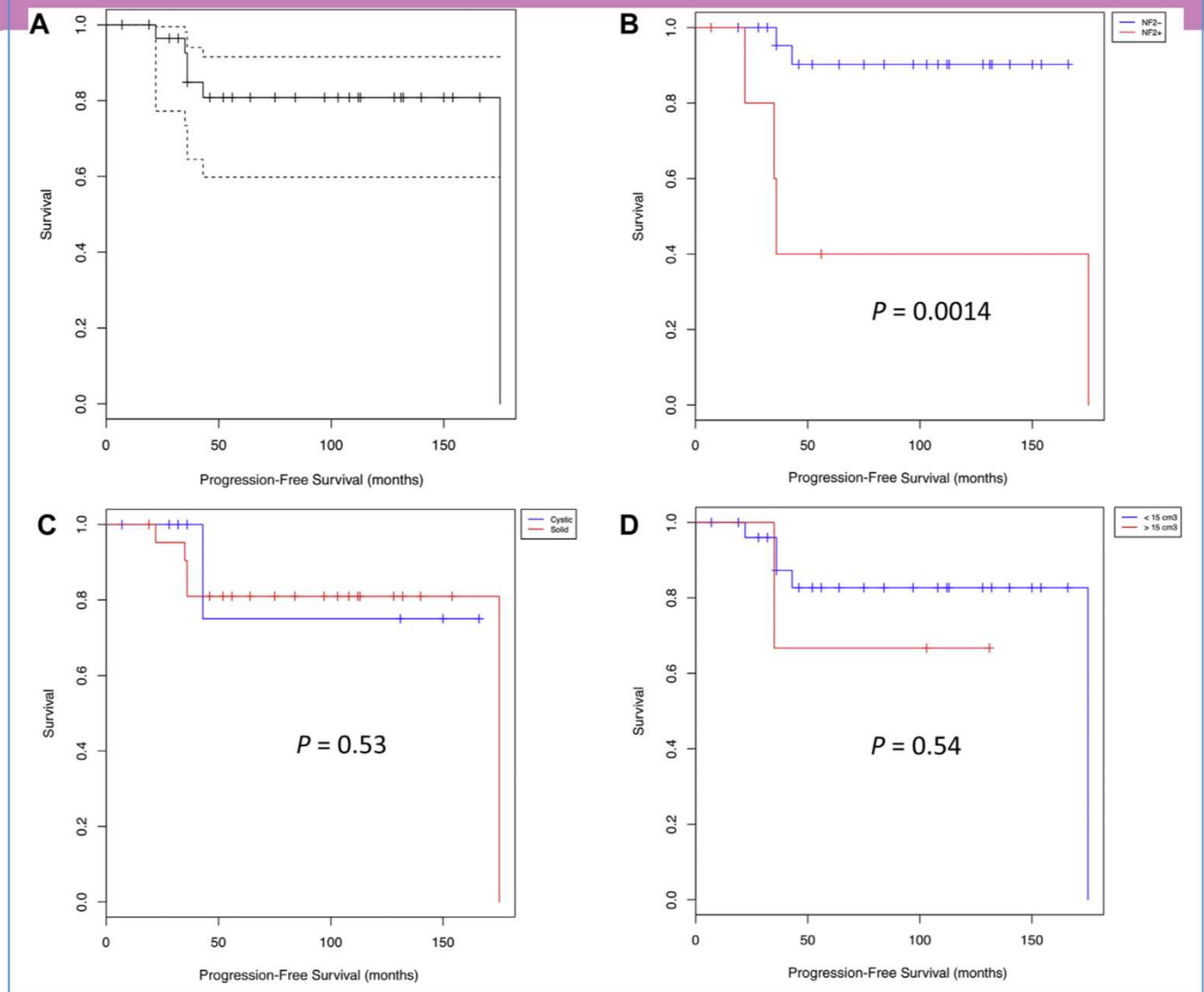
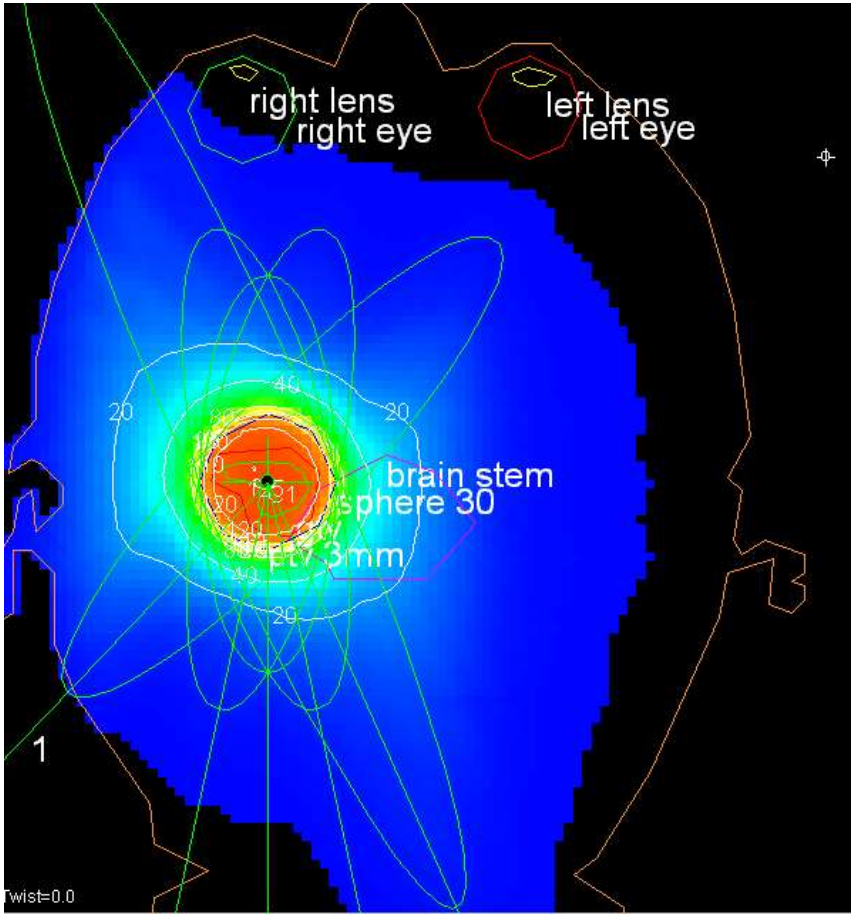


Figure 1. Kaplan-Meier curve for tumor control rate for (**A**) all patients, (**B**) neurofibromatosis 2 status, (**C**) tumor types (solid vs. cystic vestibular schwannoma), and (**D**) tumor volume (<15 cm^3, > 15cm^3).



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Craniopharyngioma

Long term results after fractionated stereotactic radiotherapy (FSRT) in patients with craniopharyngioma: maximal tumor control with minimal side effects

Semi B Harrabi[1,2*], Sebastian Adeberg[1], Thomas Welzel[1], Stefan Rieken[1], Daniel Habermehl[1], Jürgen Debus[1,2] and Stephanie E Combs[1]

N = 55

Median age 37 years (range 6–70) (8< 18 years)

RT was indicated:

- progressive disease after neurosurgical resection
- postoperatively after repeated resection or partial resection

Median dose of 52.2 Gy (50 – 57.6 Gy)

Median Follow-up 128 months (2-276)

Harrabi *et al. Radiation Oncology* 2014, **9**:203

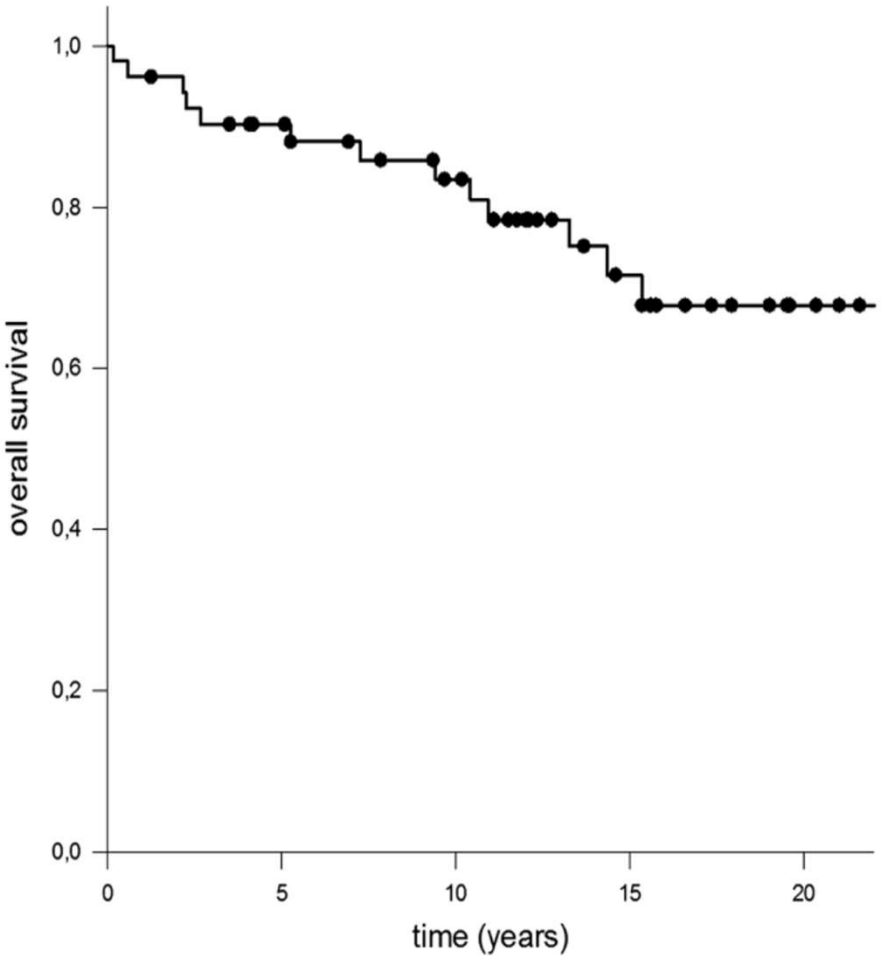

Figure 1 Median overall survival was 90.3% after 5 years respectively 83.3% (10 years) and 67.8% (20 years).

Harrabi *et al. Radiation Oncology* 2014, **9**:203

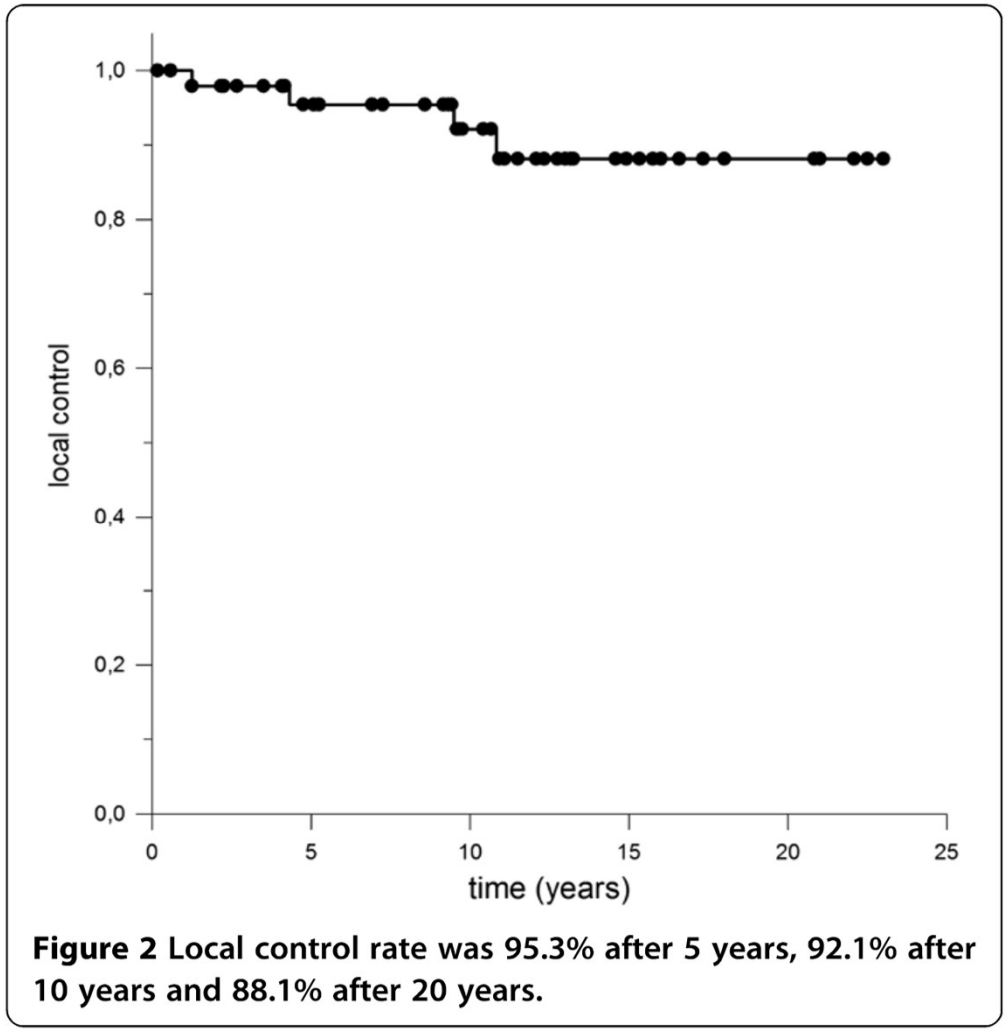

Figure 2 Local control rate was 95.3% after 5 years, 92.1% after 10 years and 88.1% after 20 years.

Harrabi *et al. Radiation Oncology* 2014, **9**:203

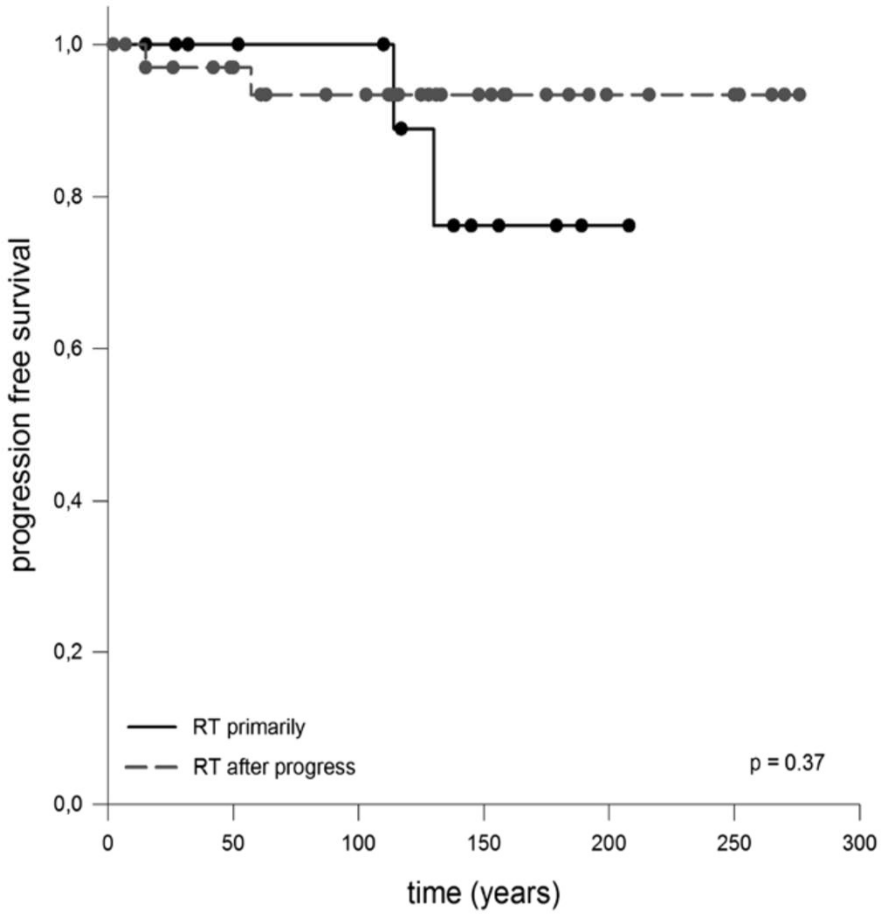

Figure 3 No significant difference was observed for progression free survival whether patients were treated early in the time course or received RT for tumor recurrence, p-value = 0.37.

1 patient – anosmia
1 patient worsening vision

Harrabi *et al. Radiation Oncology* 2014, **9**:203

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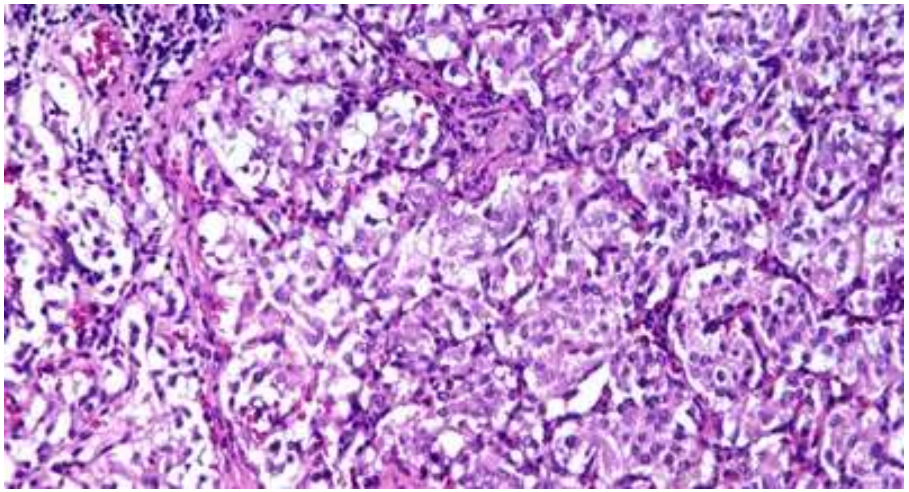
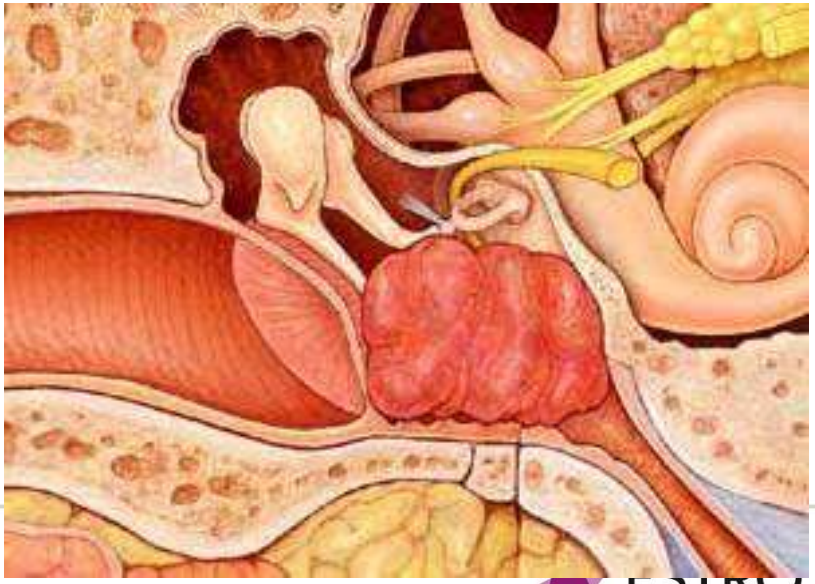
Craniopharyngioma

- Excellent outcomes from FSRT
- Management requires:
  - Dedicated high quality surgery
  - Support from ophthalmology/endocrinology
  - High quality imaging for planning
  - *alert for cystic enlargement if remnant present

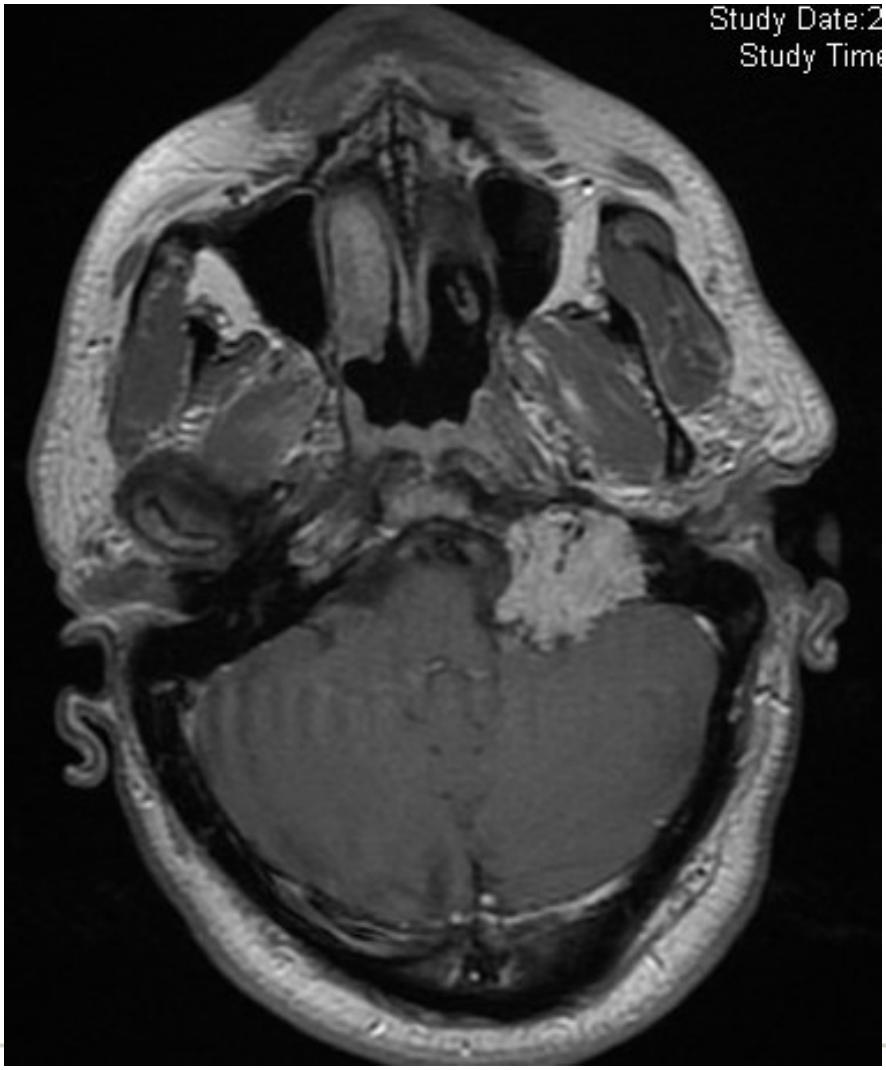
Paraganglioma





Paraganglioma

- Rare
- Need to exclude multiple tumours (SDHD mutations in 10%)
- Can secrete hormones
- Rarely metastasize



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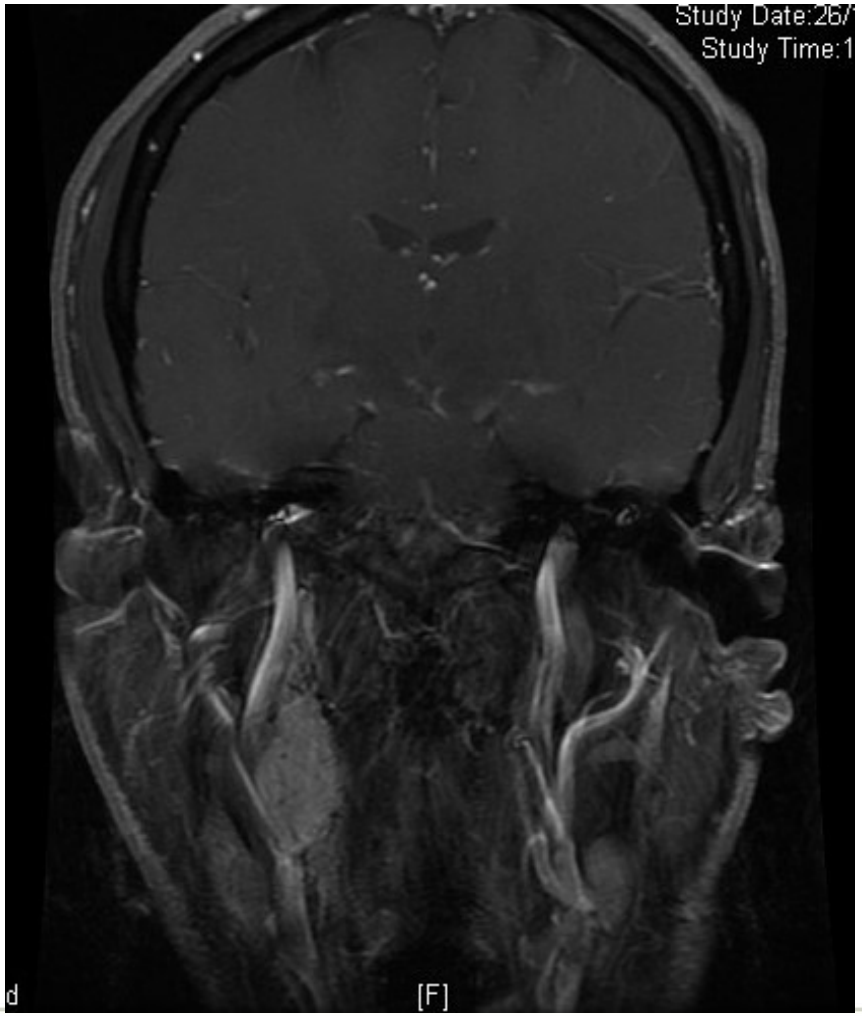
Paraganglioma

- Use optimal imaging
- Plan with radiologist
- Check for multiple tumours



Classification

Fisch

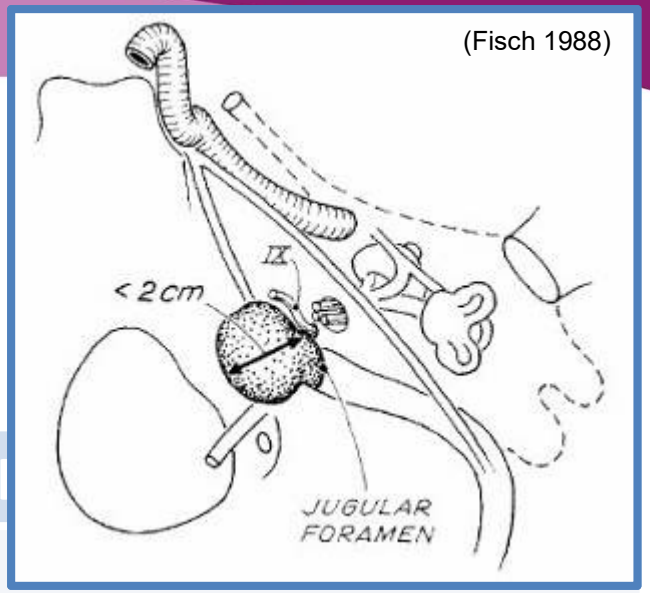
GLOMUS TUMORS

TYPE	CHARACTERISTICS
A	Limited to middle ear cleft
D	Intracranial involvement

TYPE	CHARACTERISTICS
D1	Intracranial extension less than 2cm
D2	Intracranial extension greater than 2cm

Classification

Fisch



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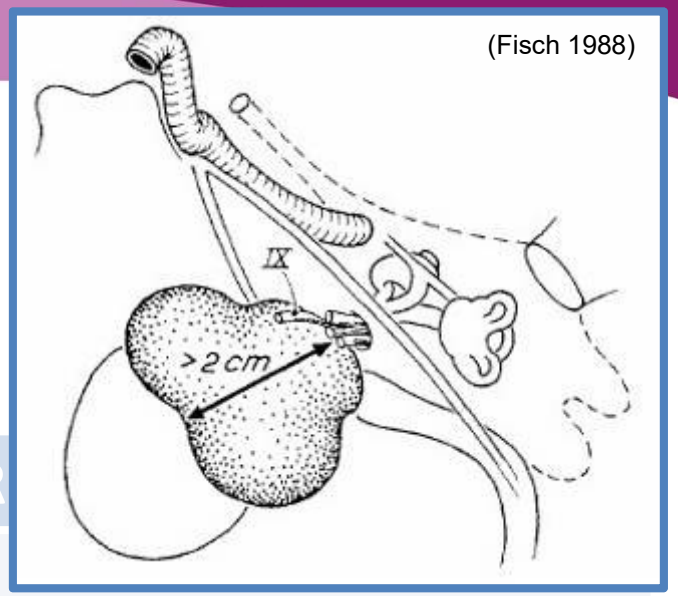
Classification

Fisch



GLOMUS TUMORS

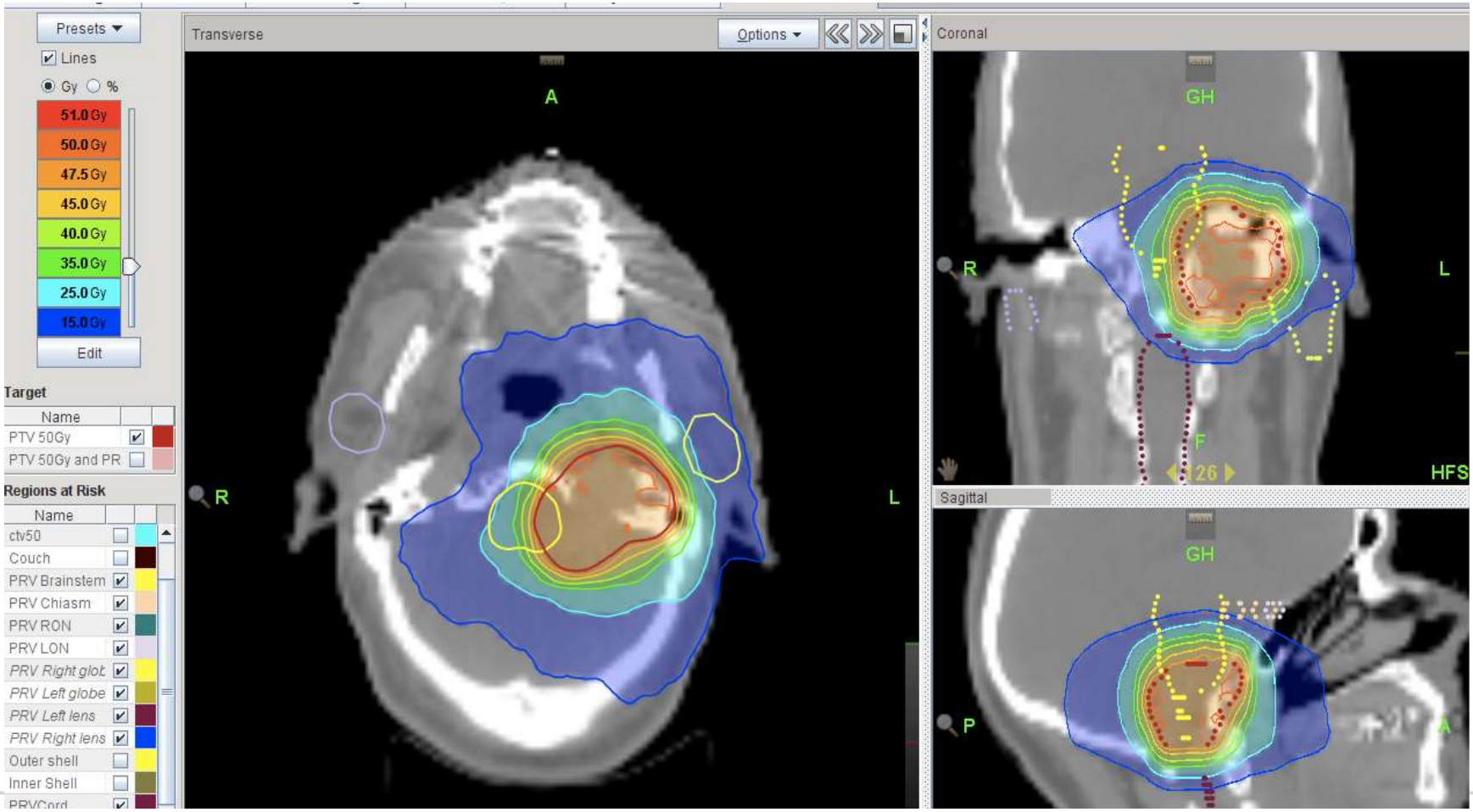
TYPE	CHARACTER
A	Limited to middle ear cleft
D	Intracranial involvement

TYPE	CHARACTERISTICS
D1	Intracranial extension less than 2cm
D2	Intracranial extension greater than 2cm

Paraganglioma

- IMRT +/- IGRT
- Treatment of choice if co-morbidities
- Also for the neurologically intact patients
- No difference in control if SDHD mutations

Paraganglioma



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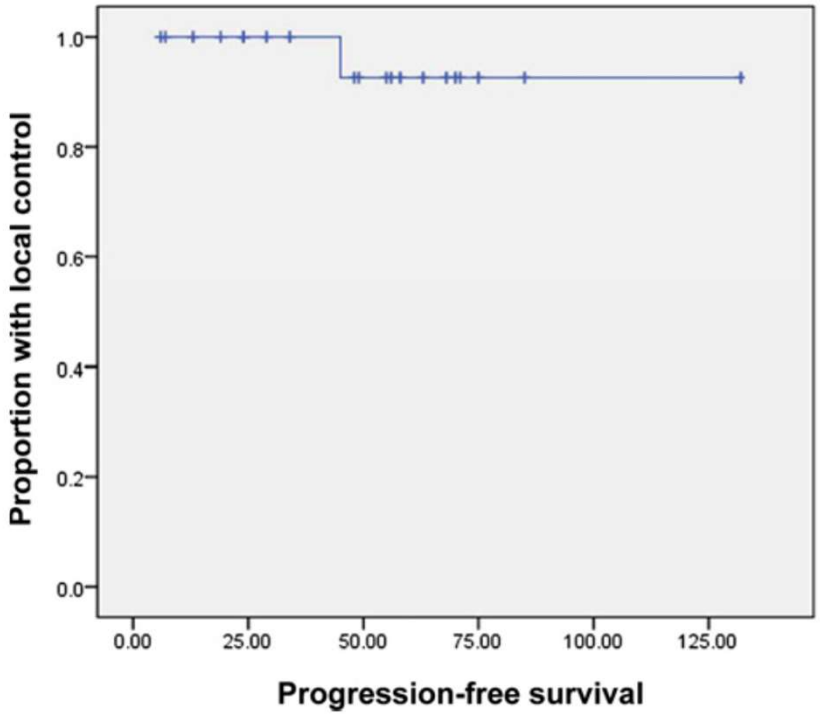
Paraganglioma



- 21 patients 1998-2008
- Median Follow-up 55 months (6 - 132)
- Mean age - 48.7 years (20-78)
- 2 SDHD mutations
- Median dose 50 Gy in 30 fractions

Clinical Oncology 22 (2010) 382–389

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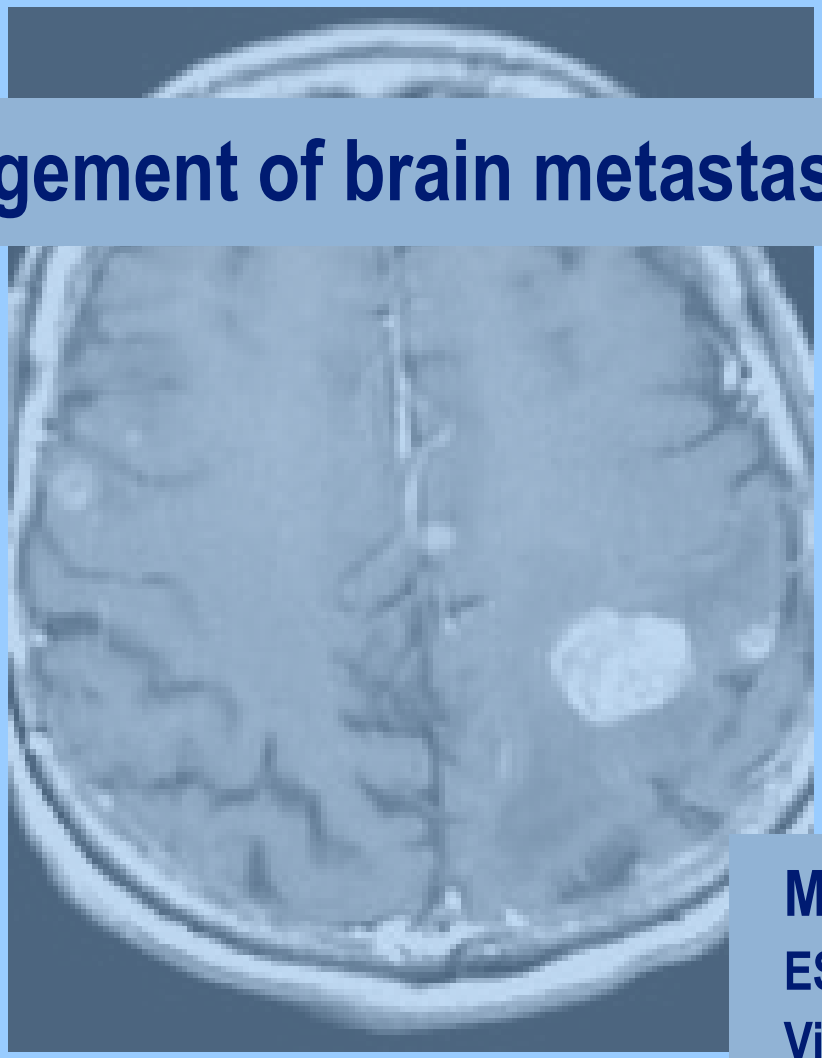
Benign tumours need a balanced approach

Management of brain metastases



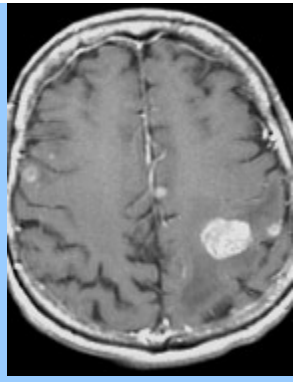
Michael Brada

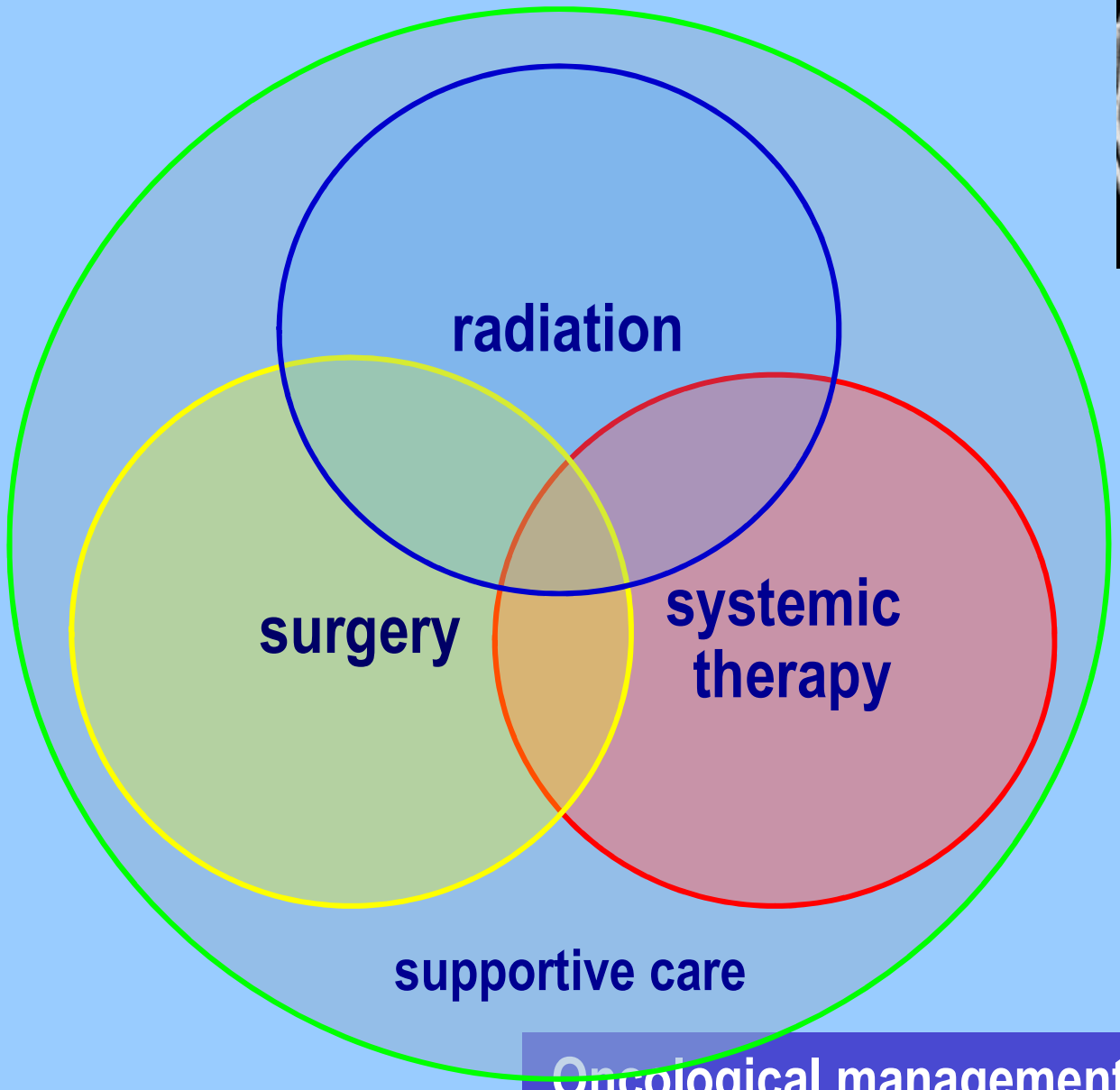
ESTRO BT course

Vienna 24 October 2017

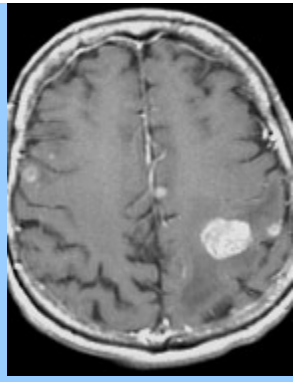
UNIVERSITY OF LIVERPOOL

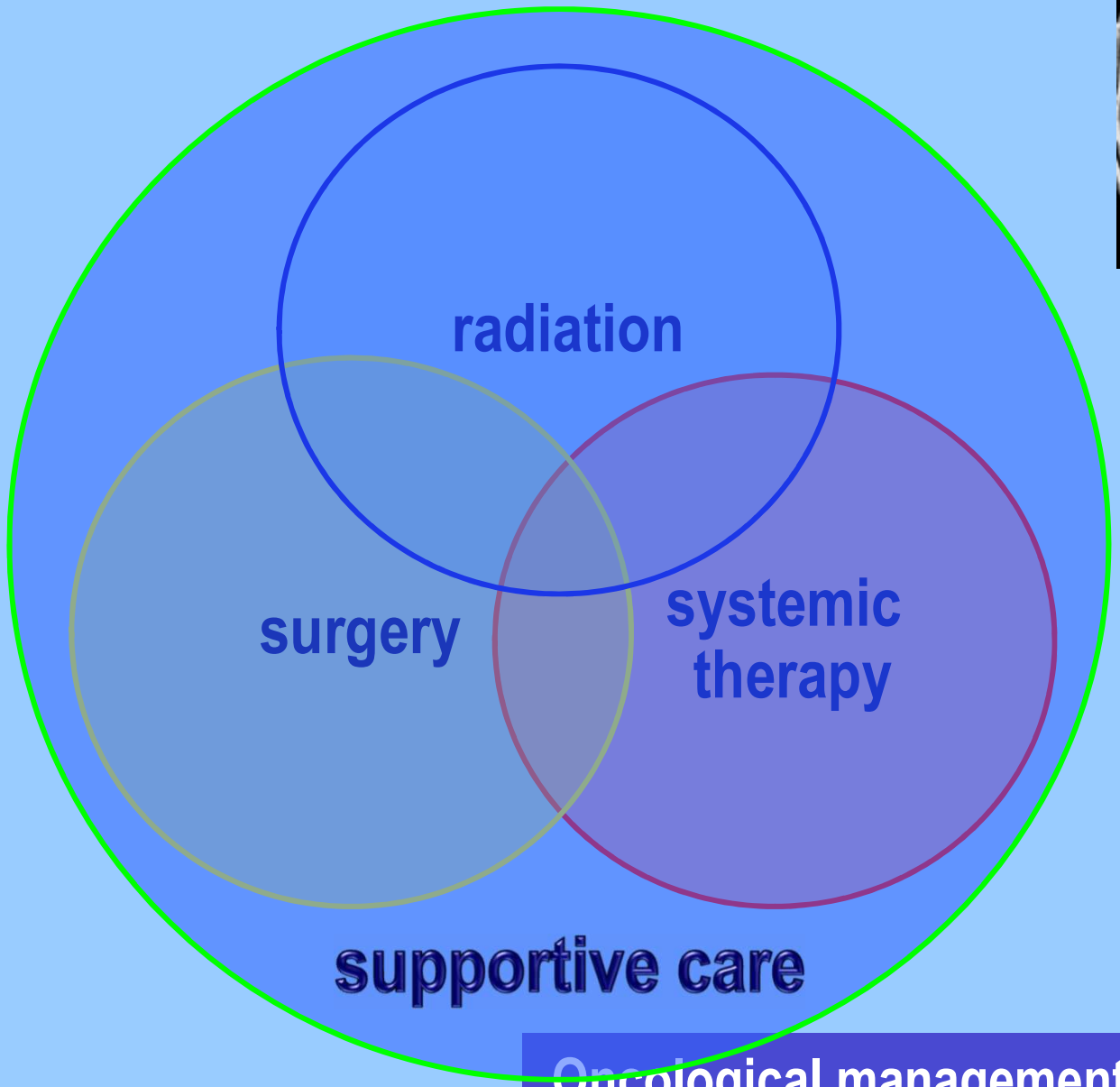
The Clatterbridge Cancer Centre NHS
NHS Foundation Trust



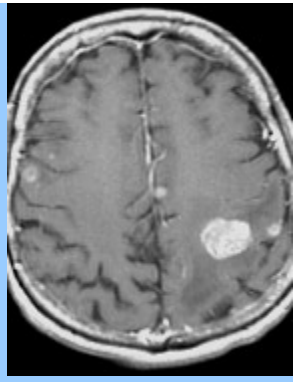


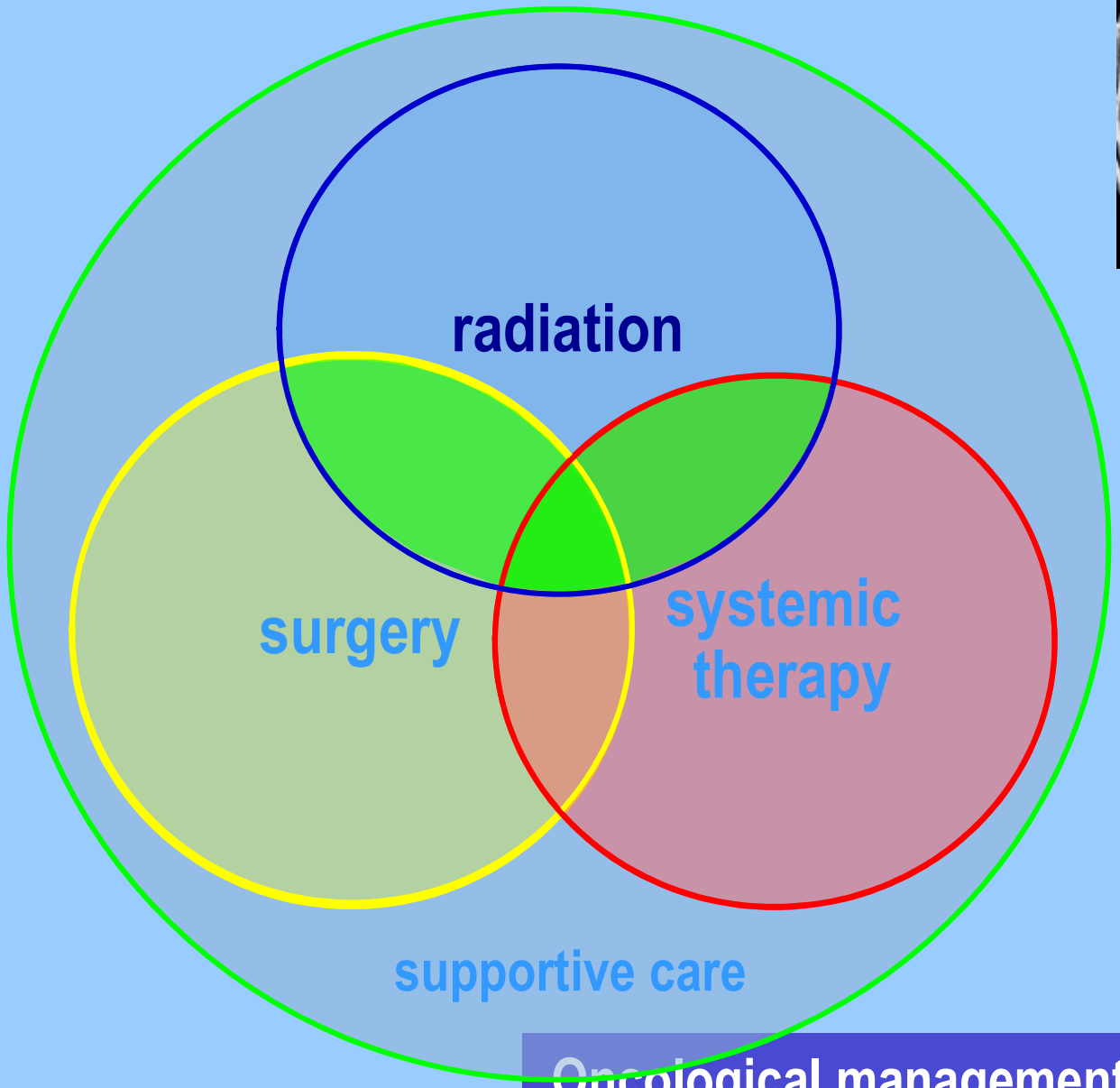
Oncological management options



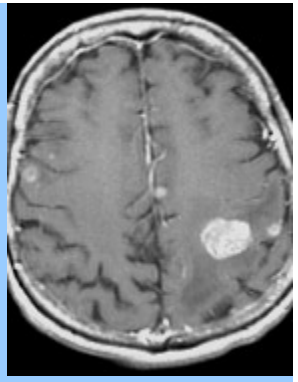


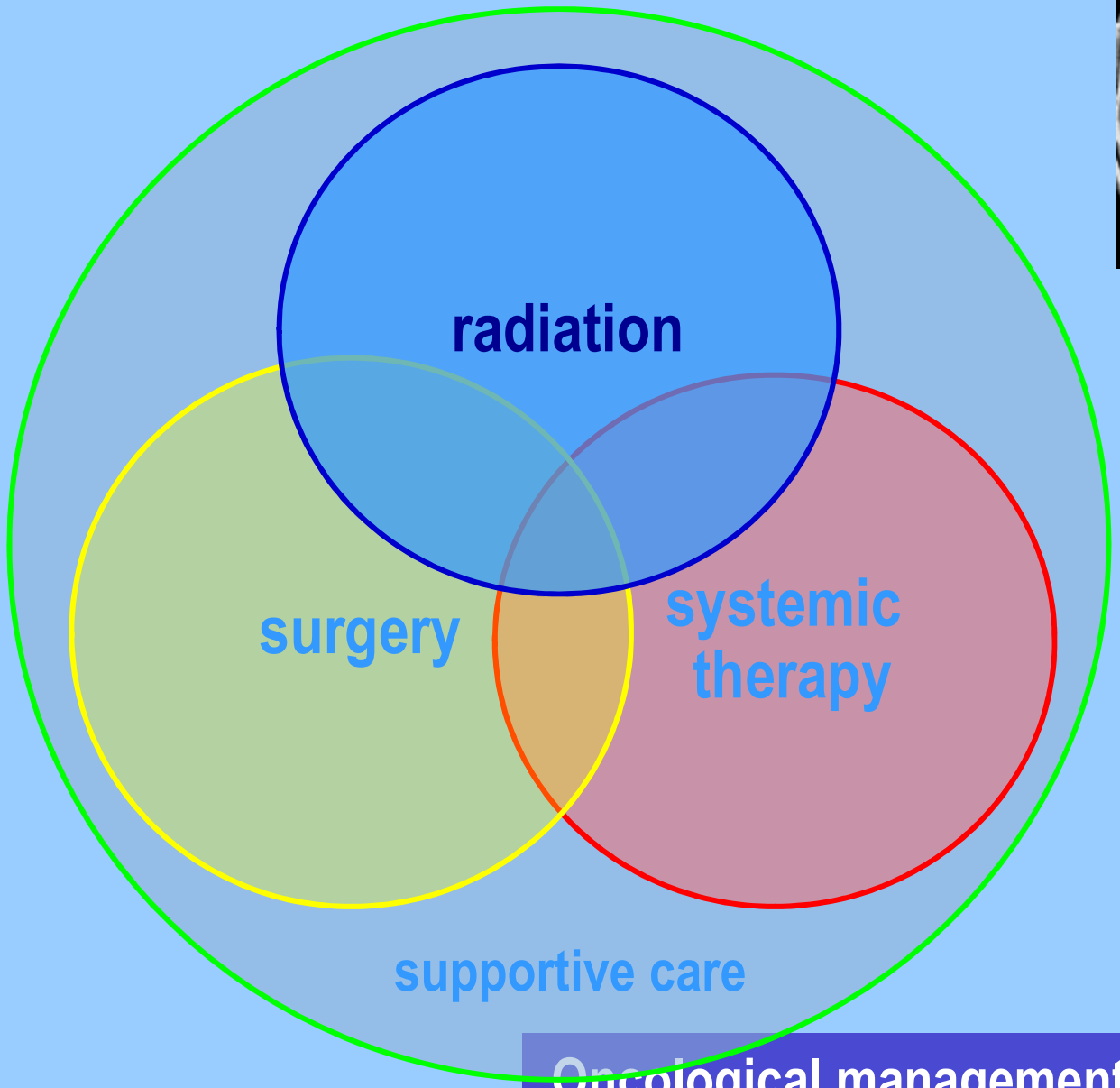
Oncological management options





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

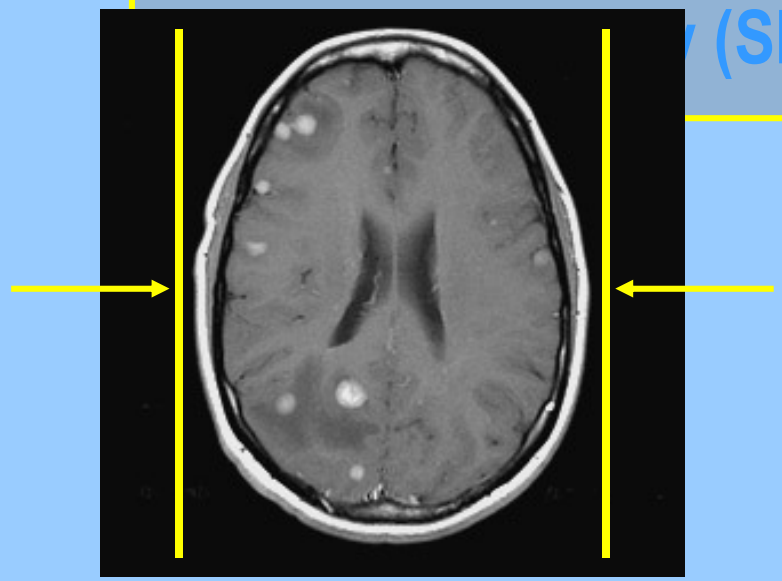
- whole brain radiotherapy (WBRT)
- partial brain radiotherapy (PBRT)
- focal radiotherapy (SRT) & radiosurgery (SRS)

Extent of irradiation

whole brain radiotherapy (WBRT)

partial brain radiotherapy (PBRT)

y (SRT) & radiosurgery (SRS)



Radiotherapy options

Extent of irradiation

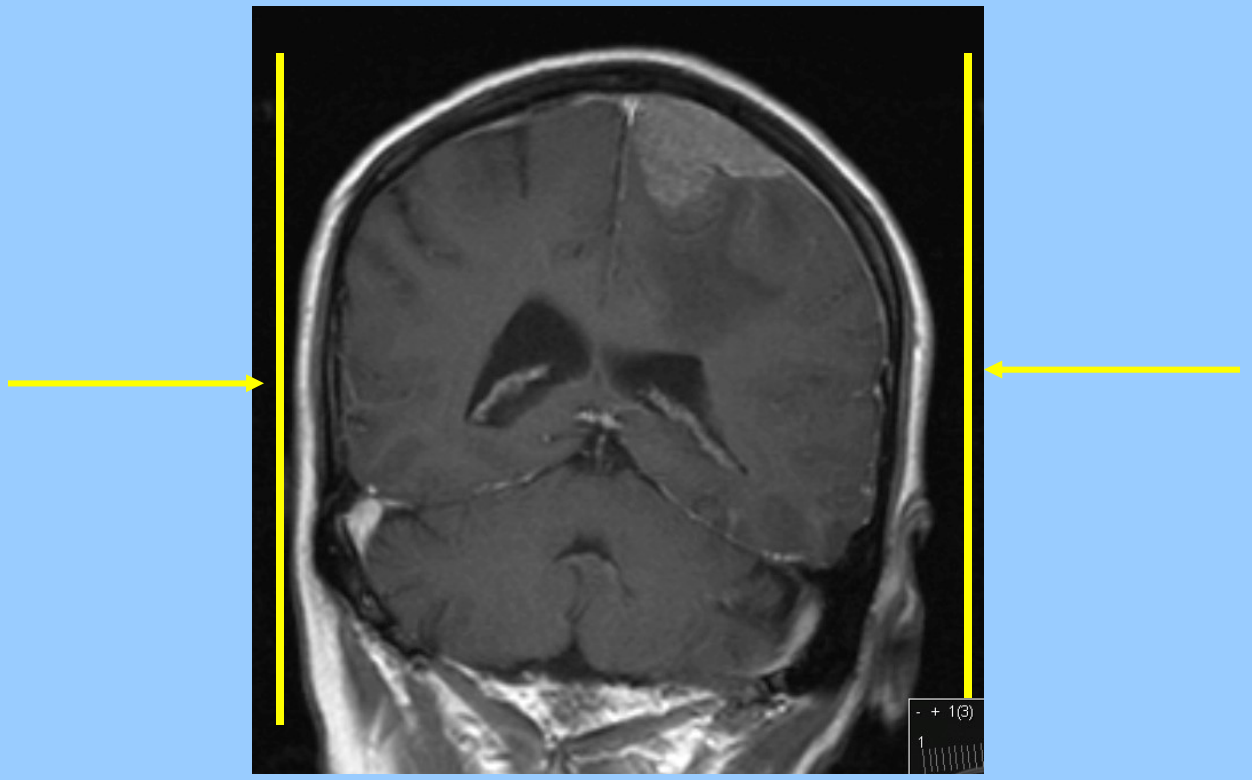
whole brain radiotherapy (WBRT)

partial brain radiotherapy (PBRT)

focal radiotherapy (SRT) & radiosurgery (SRS)

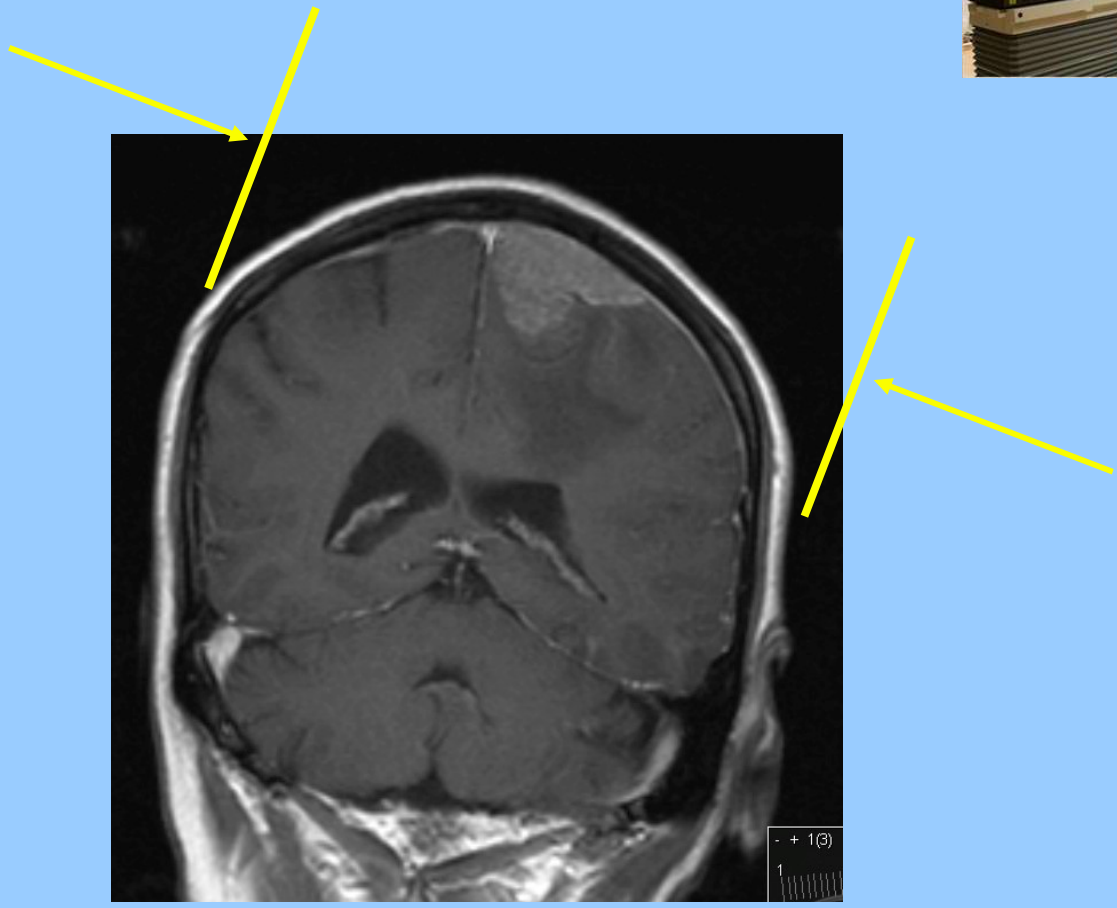
Radiotherapy options

whole brain radiotherapy



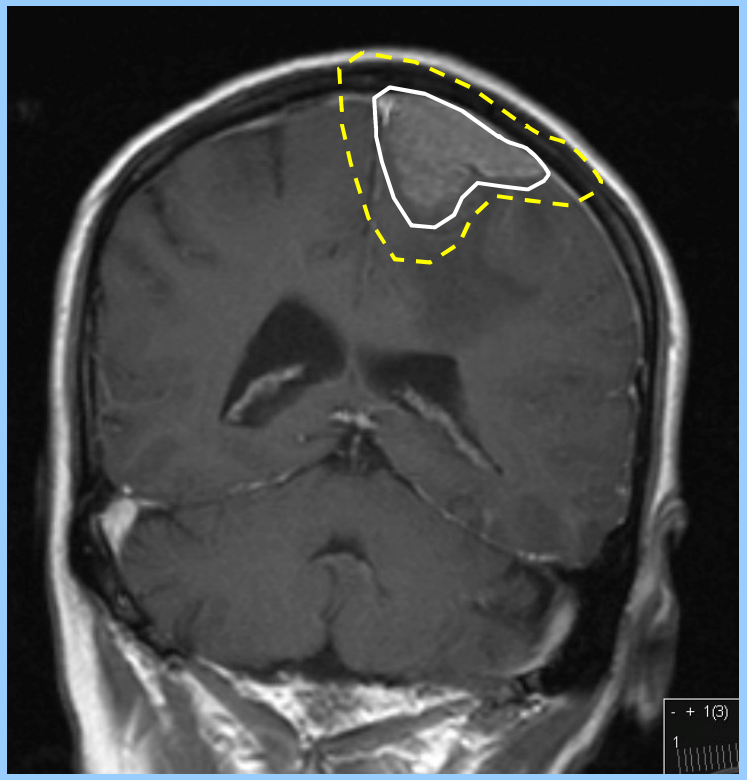
Radiotherapy options

partial brain radiotherapy



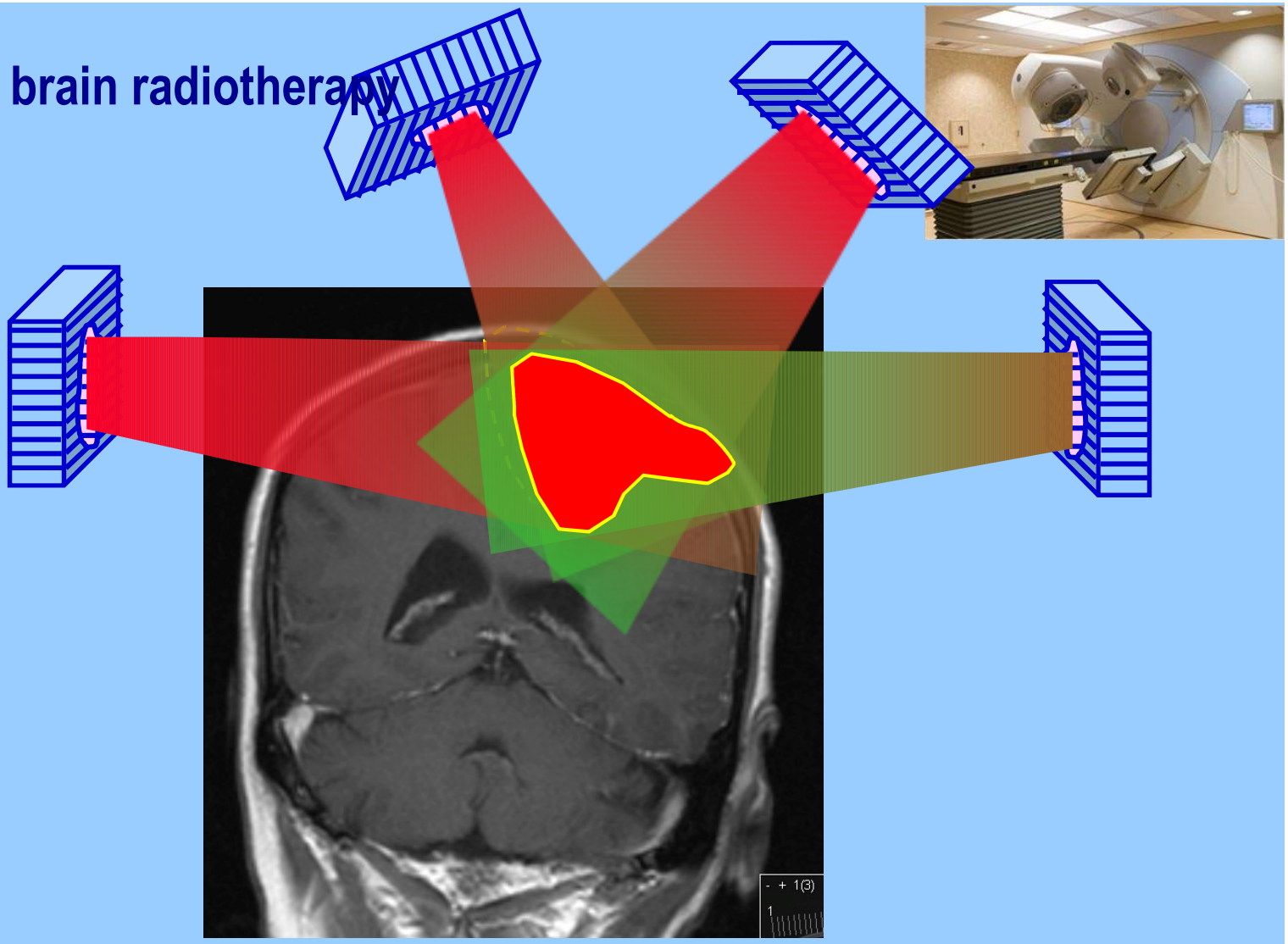
Radiotherapy options

partial brain radiotherapy



Radiotherapy options

partial brain radiotherapy



Radiotherapy options

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

Extent of irradiation

whole brain radiotherapy (WBRT)

partial brain radiotherapy (PBRT)

focal radiotherapy (SRT) & radiosurgery (SRS)

Radiotherapy options

Extent of irradiation

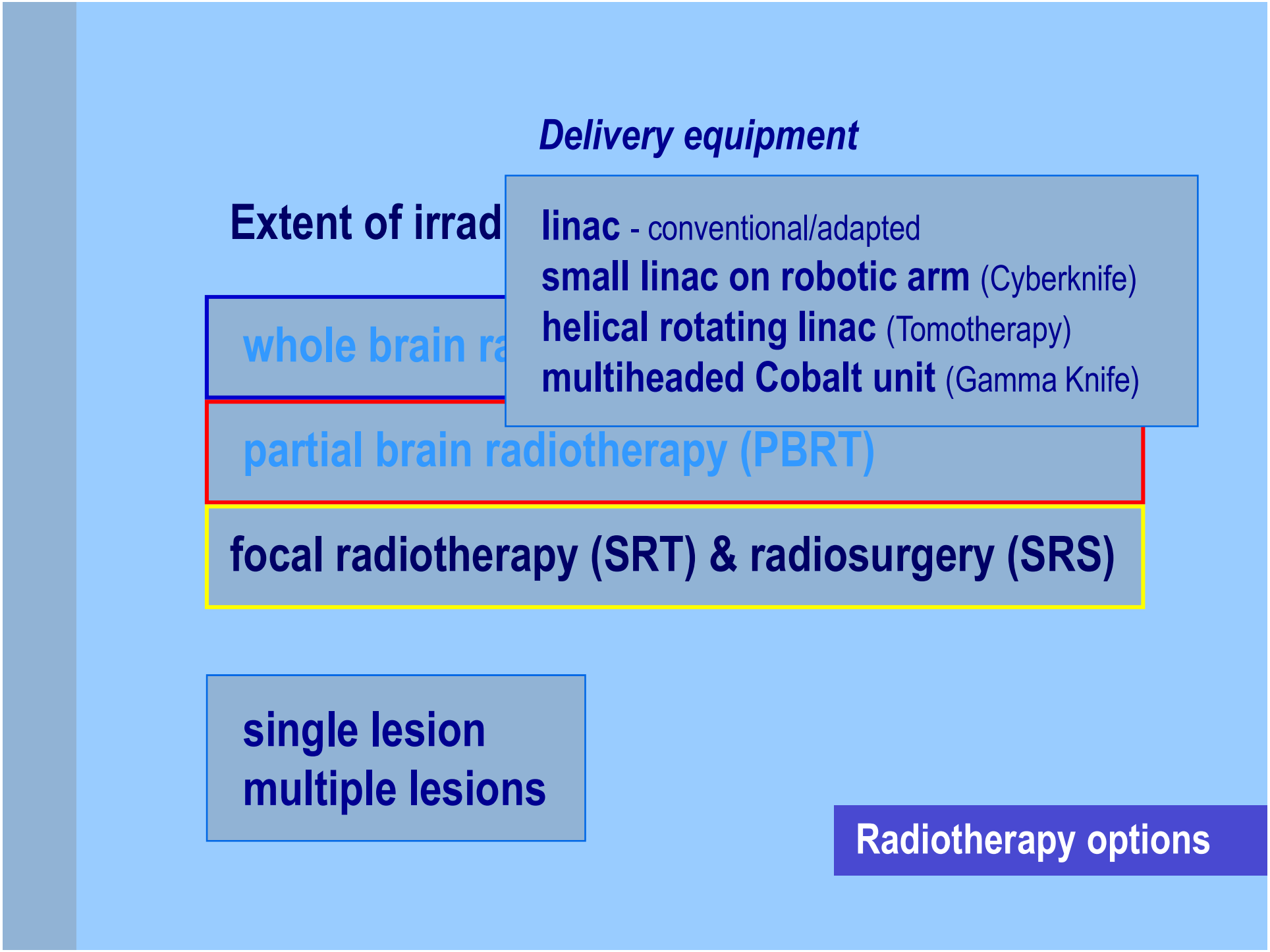
whole brain radiotherapy (WBRT)

partial brain radiotherapy (PBRT)

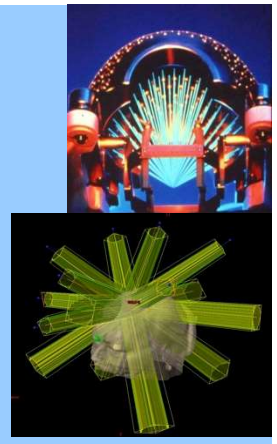
focal radiotherapy (SRT) & radiosurgery (SRS)

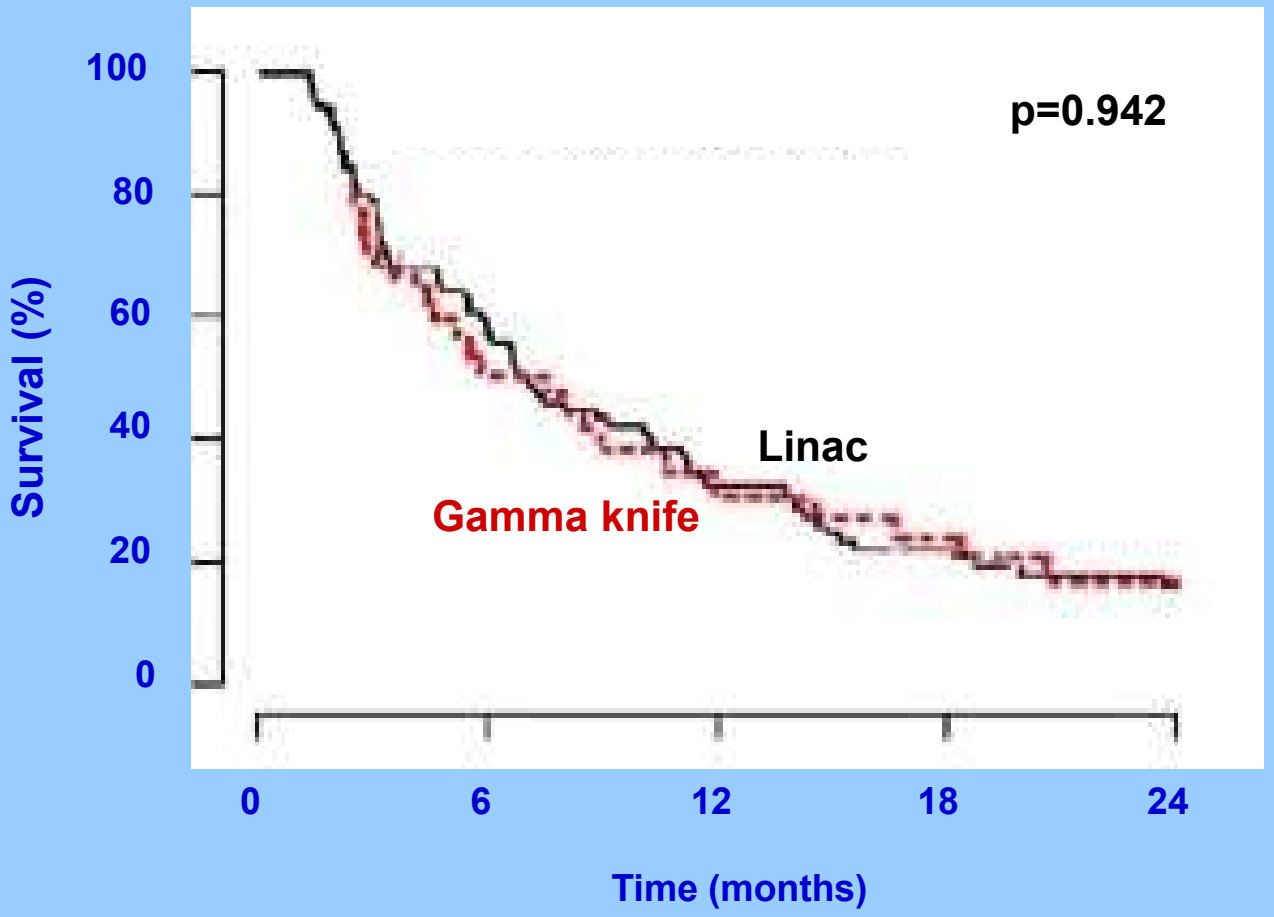
single lesion
multiple lesions

Radiotherapy options


Delivery equipment
Extent of irrad
linac - conventional/adapted
small linac on robotic arm (Cyberknife)
helical rotating linac (Tomotherapy)
multiheaded Cobalt unit (Gamma Knife)
whole brain ra
partial brain radiotherapy (PBRT)
focal radiotherapy (SRT) & radiosurgery (SRS)
single lesion
multiple lesions
Radiotherapy options

survival – by treatment unit





Radiosurgery for solitary brain metastases

Andrews et al 2004, Lancet 363: 1665–72

Delivery techniques

multiple conformal fixed fields
single or multiple/dynamic arcs +/- IMRT
single or multiple isocentres
multiple sources & isocentres (GK)
multiple small beams & isocentres (CK)

Extent of irra

whole brain

partial brain radiotherapy (PBRT)

focal radiotherapy (SRT) & radiosurgery (SRS)

single lesion
multiple lesions

Radiotherapy options

Delivery techniques

multiple conformal fixed fields
single or multiple/dynamic arcs +/- IMRT
single or multiple isocentres
multiple sources & isocentres (GK)
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Extent of irra

whole brain

partial brain radiotherapy (PBRT)

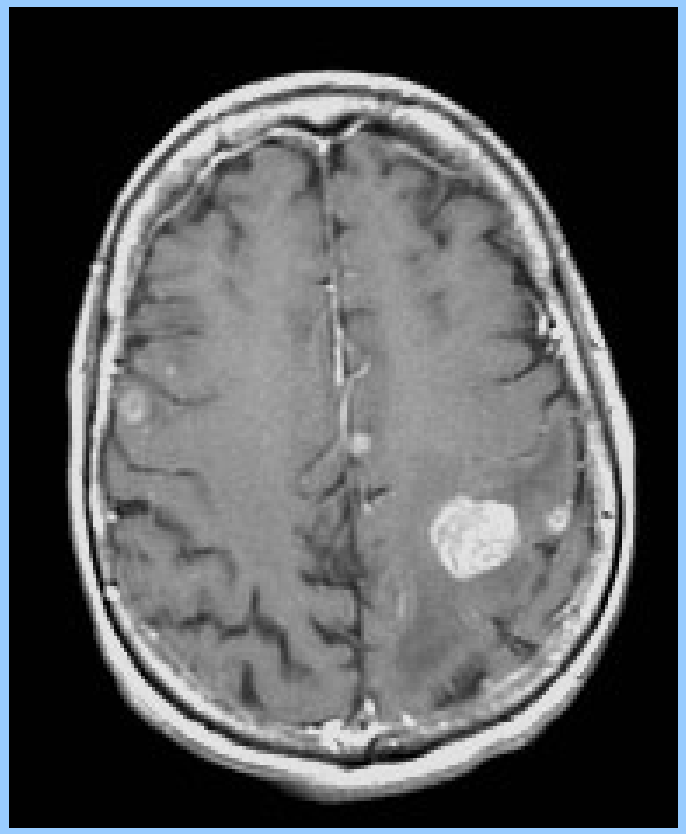
focal radiotherapy (SRT) & radiosurgery (SRS)

single lesion
multiple lesions

Radiotherapy options

whole brain RT

focal RT



Delivery techniques for multiple lesions

Techniques of RT for multiple lesions - focal vs whole brain

single isocentre dynamic conformal arc (SIDCA)

multiple isocentre dynamic conformal arc (MIDCA)

VMAT

whole brain radiotherapy

Comparison of delivery techniques for multiple lesions

Huang et al 2014, Radiother Oncol 112, 128–132

Techniques of RT for multiple lesions comparison of focal techniques

single isocentre dynamic conformal arc (SIDCA)

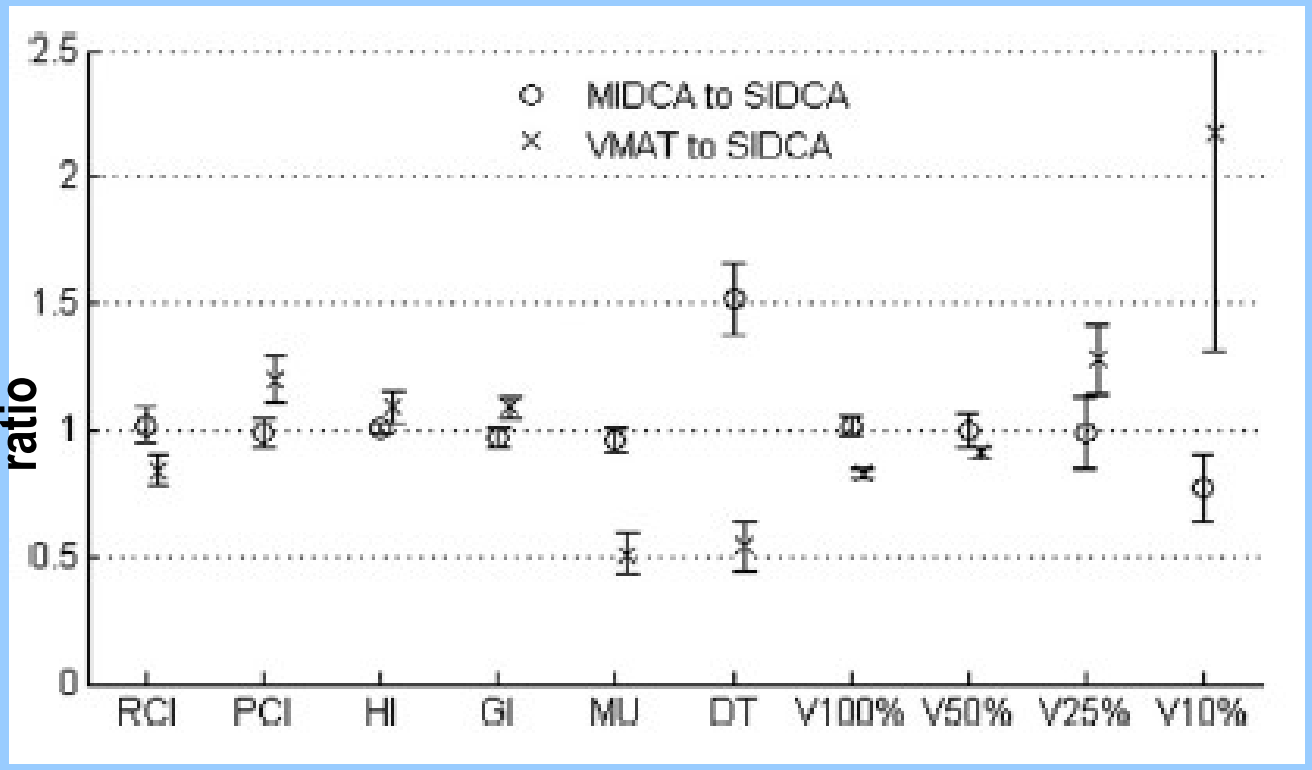
multiple isocentre dynamic conformal arc (MIDCA)

VMAT

Comparison of delivery techniques for multiple lesions

Huang et al 2014, Radiother Oncol 112, 128–132

Techniques of RT for multiple lesions comparison of focal techniques



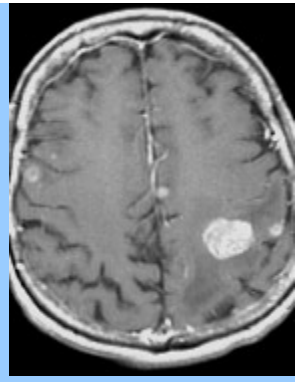
Comparison of delivery techniques for multiple lesions

Huang et al 2014, Radiother Oncol 112, 128–132

- Radiotherapy technologies
- **Context and endpoints**
- Clinical issues - evidence base

Radiotherapy in the treatment of brain metastases

Context



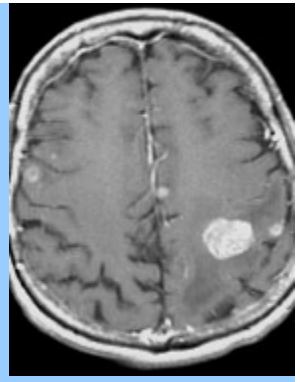
prognosis

primary tumour type

timing in the course of disease

Oncological management options

Context



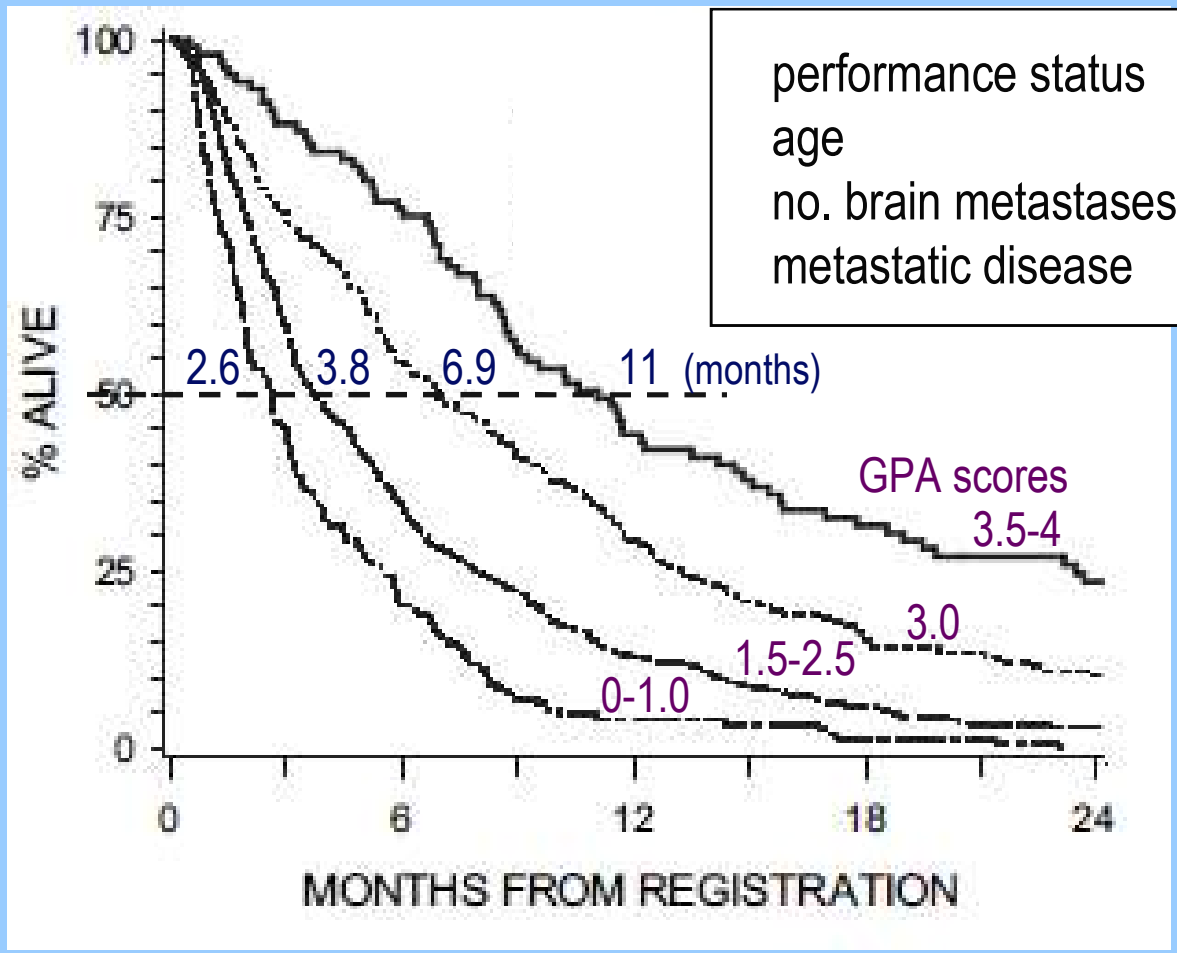
prognosis

primary tumour type

timing in the course of disease

Oncological management options

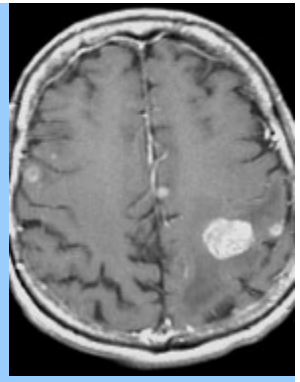
Graded prognostic assessment (GPA)



Prognosis in patients with brain metastases

Sperduto et al Int J Radiat Oncol Biol Phys 2008; 70: 510-514

Context



prognosis

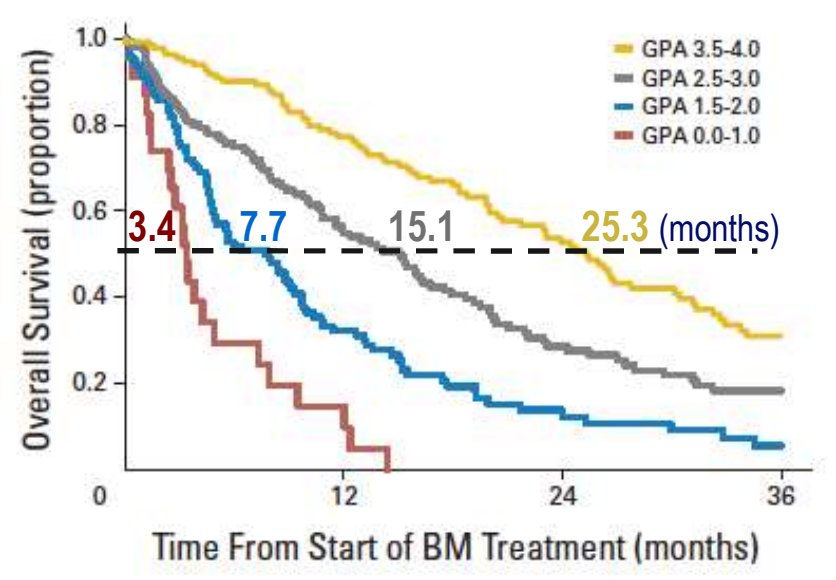
primary tumour type

timing in the course of disease

Oncological management options

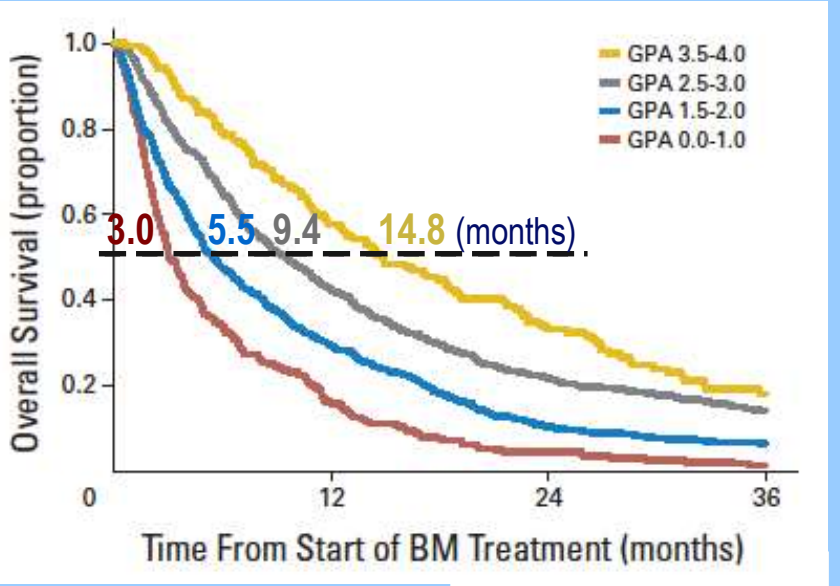
Graded prognostic assessment (GPA)

Breast



performance status
age
tumour subtype

NSCLC

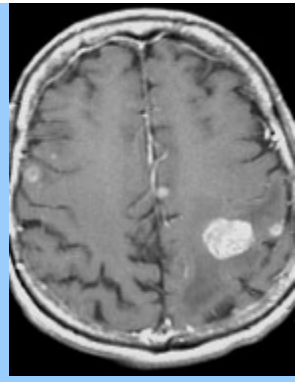


performance status
age
no. brain mets
metastatic disease

Prognosis in patients with brain metastases

Sperduto et al 2012 J Clin Oncol, 30: 419 - 425

Context



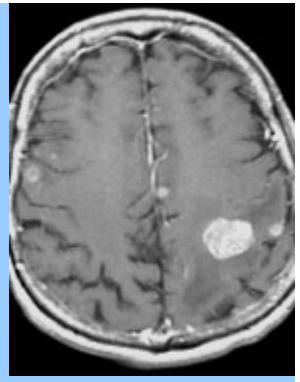
prognosis

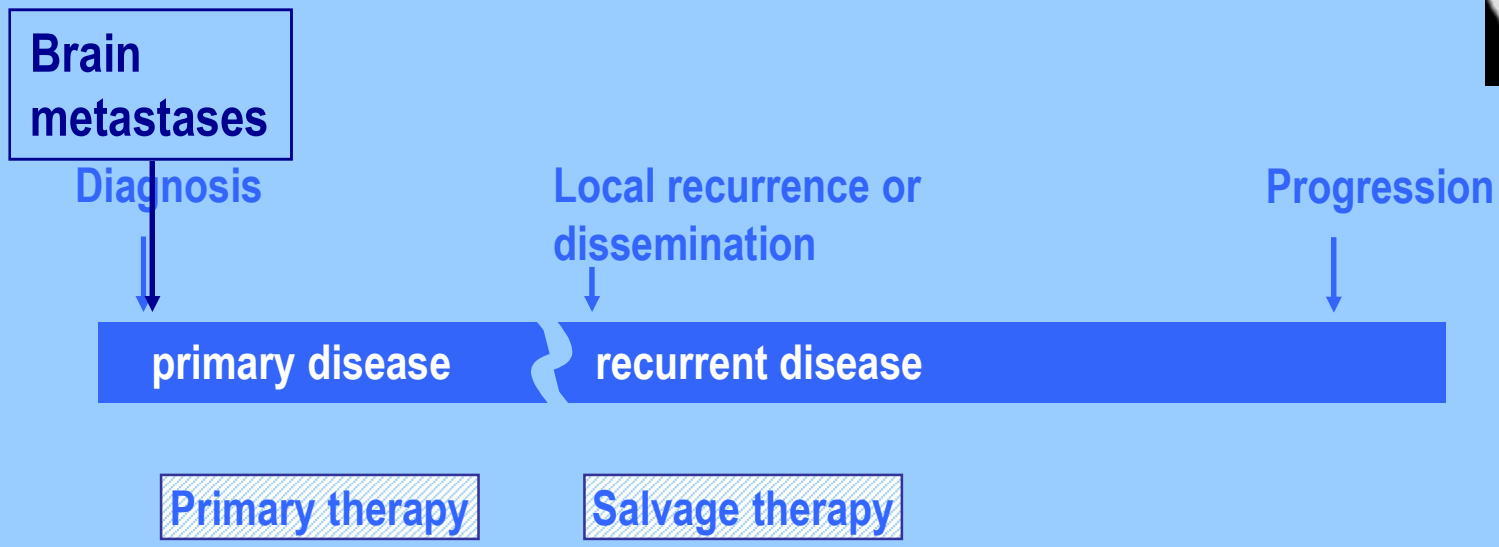
primary tumour type

timing in the course of disease

Oncological management options

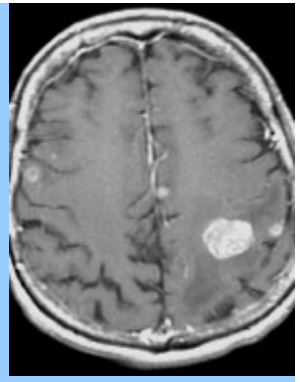
Course of malignant disease

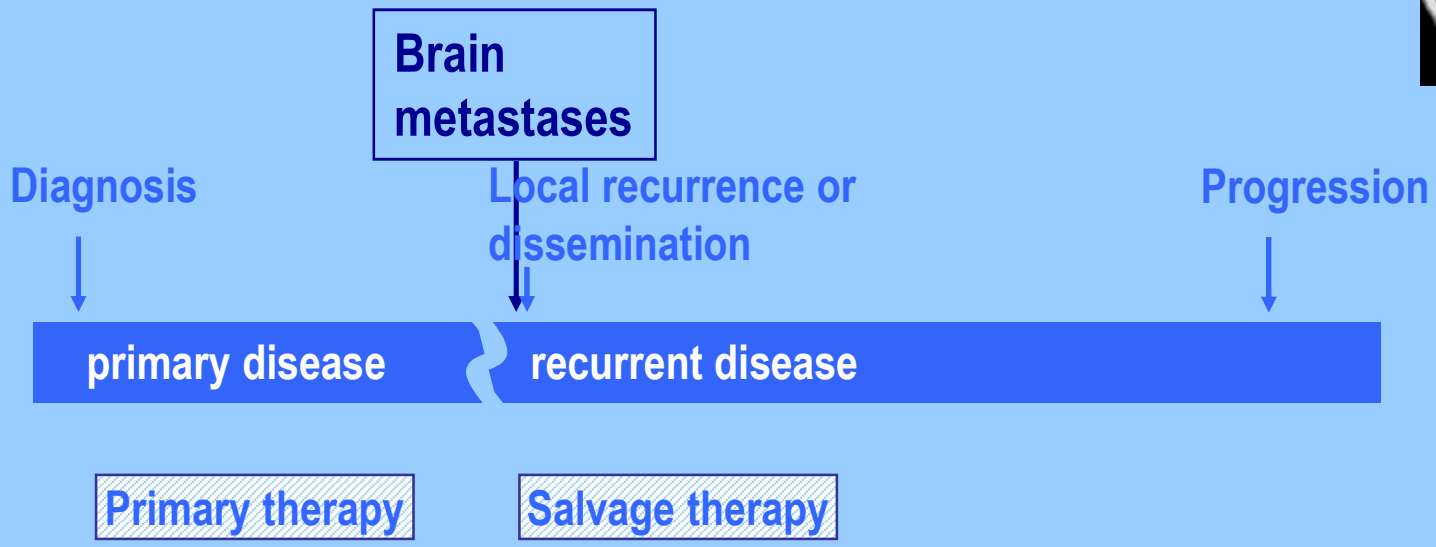




Brain metastases in malignancy

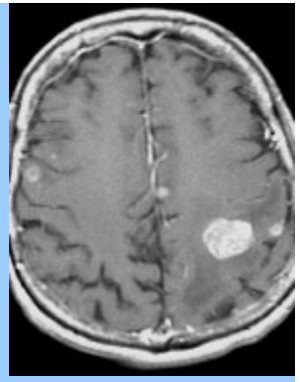
Course of malignant disease



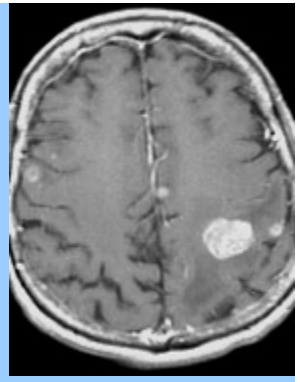


Brain metastases in malignancy

Course of malignant disease



Brain metastases in malignancy



Context

prognosis

primary tumour type

timing in the course of disease

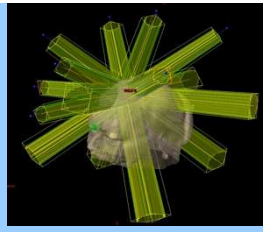
Endpoints

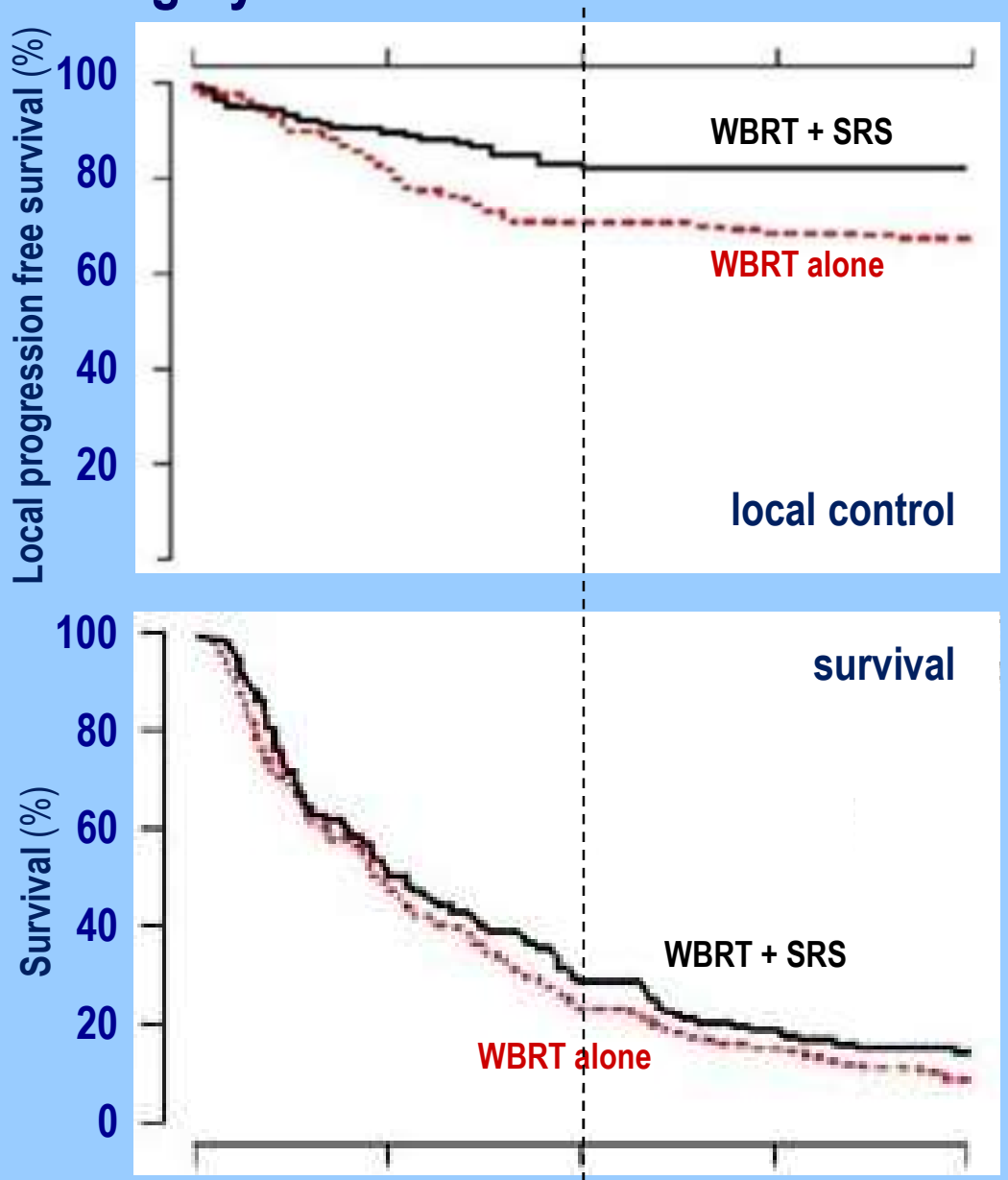
survival

quality of life

Oncological management options

WBRT +/- radiosurgery for brain metastases





RTOG 9508

Andrews et al 2004, Lancet; 363: 1665–72

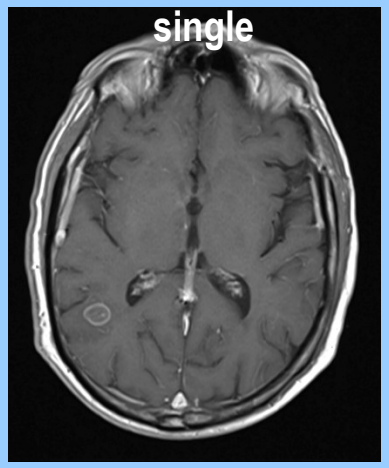
WBRT whole brain RT
SRS stereotactic radiosurgery

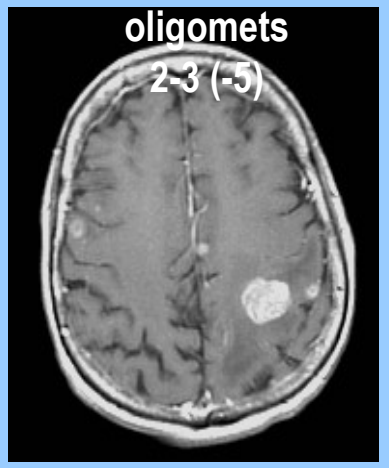
- Radiotherapy technologies
- Context and endpoints
- **Clinical issues - evidence base**

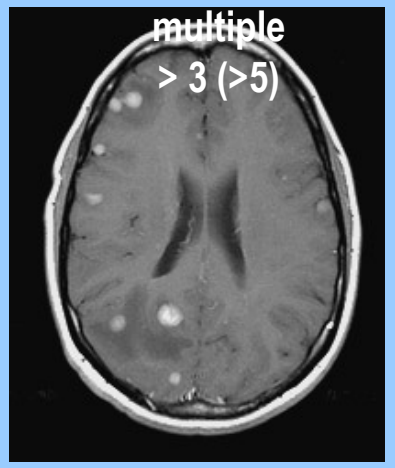
Radiotherapy in the treatment of brain metastases

radiotherapy options

- whole brain radiotherapy
- partial brain radiotherapy
- focal radiotherapy & radiosurgery



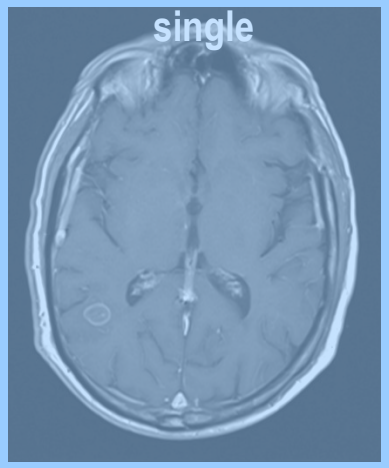


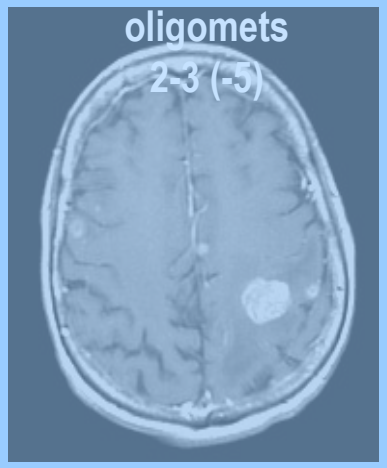


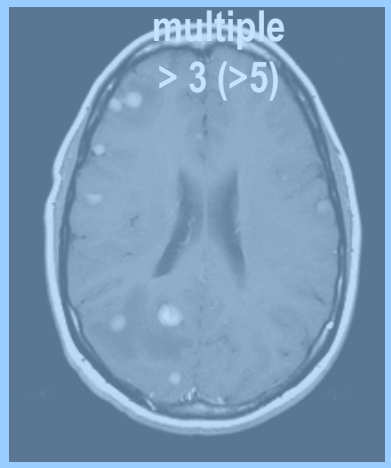
Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			



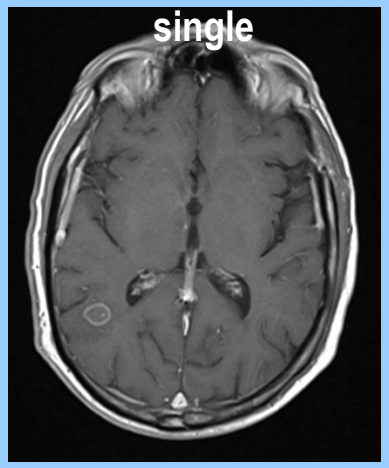




Evidence base for radiotherapy in the treatment of brain metastases

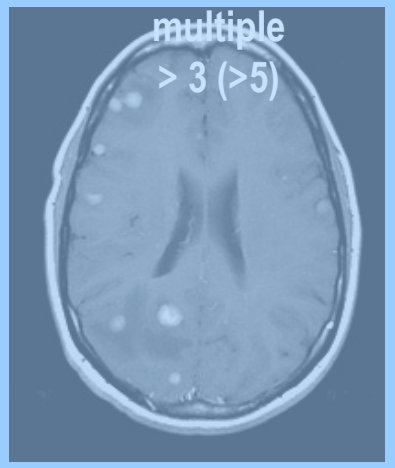
Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single	good	any	
oligomets			
multiple			



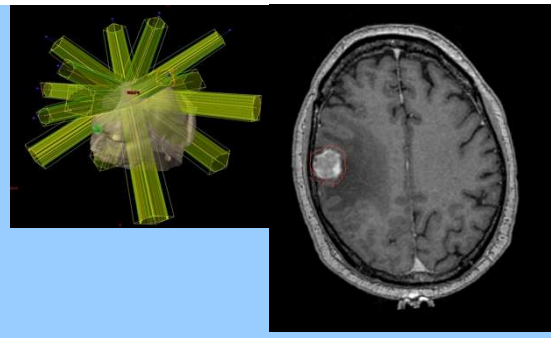
surgery

radiosurgery



Evidence base for radiotherapy in the treatment of brain metastases

RTOG trial 9508



1 - 3 brain metastases

oligometastases

randomise

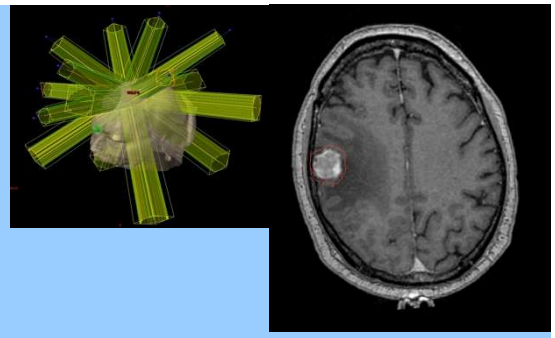
whole brain radiotherapy & radiosurgery (SRS)	**whole brain radiotherapy** (WBRT)
167 patients	**164 patients**

331 patients

Radiosurgery for “solitary” brain metastases

Andrews et al 2004, Lancet; 363: 1665–72

RTOG trial 9508



1 brain metastasis

randomise

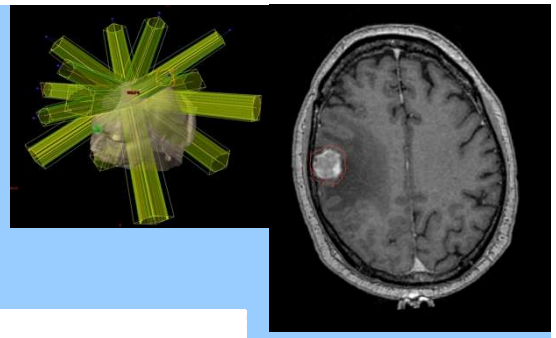
whole brain radiotherapy & radiosurgery (SRS)	whole brain radiotherapy (WBRT)
92 patients	94 patients

186 patients

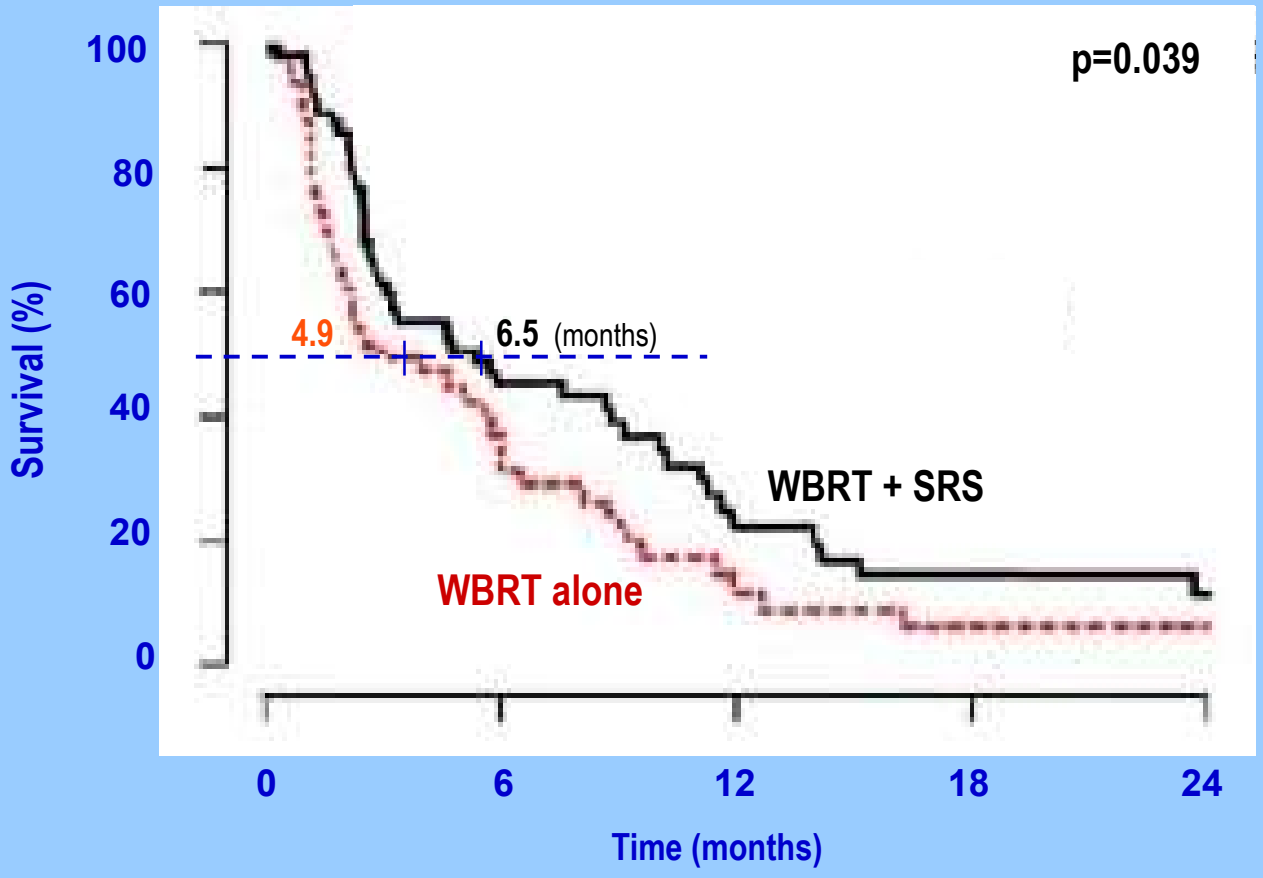
Radiosurgery for solitary brain metastases

Andrews et al 2004, Lancet; 363: 1665–72

RTOG trial 9508



survival – single brain metastases



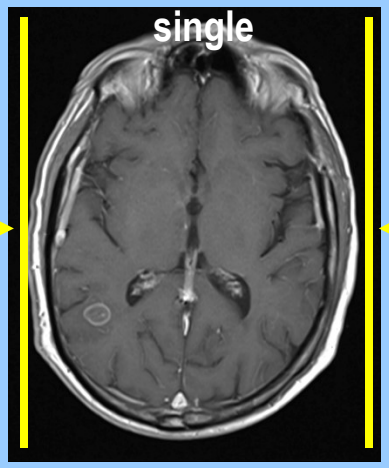
Radiosurgery for solitary brain metastases

Andrews et al 2004, Lancet; 363: 1665–72

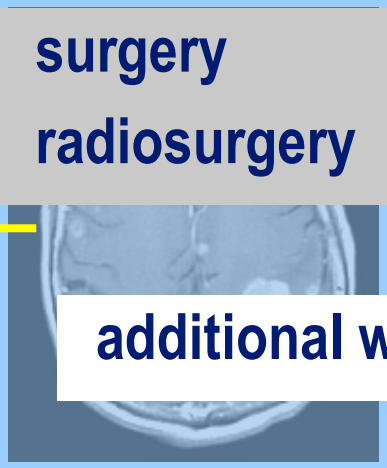
WBRT whole brain radiotherapy
SRS stereotactic radiosurgery

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single	good	any	
oligomets			
multiple			



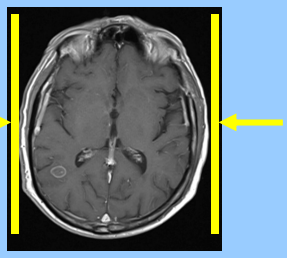
surgery
radiosurgery



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

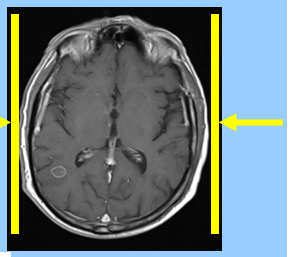
observation

132 patients

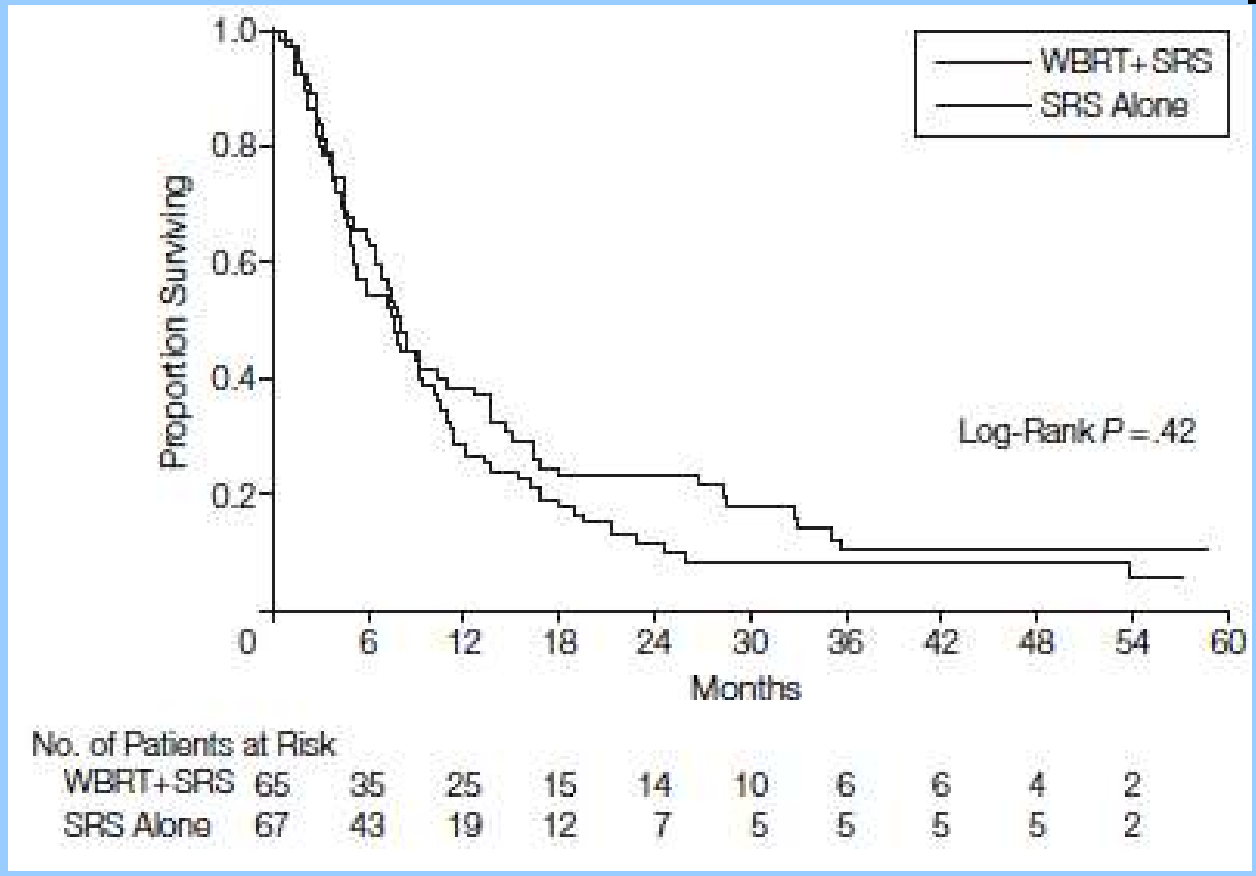
Whole brain radiotherapy following surgery or radiosurgery

Aoyama et al 2006, JAMA; 295: 2483-2491

Japanese Radiation Oncology Study Group (JROSG 99-1)



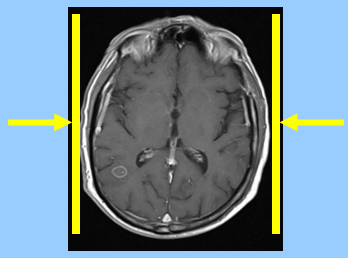
survival



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 — **180 patients**

observation — **179 patients**

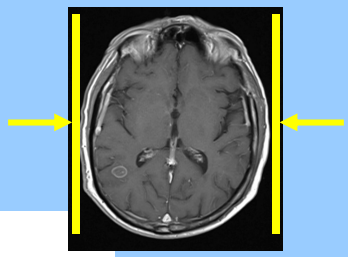
359 patients

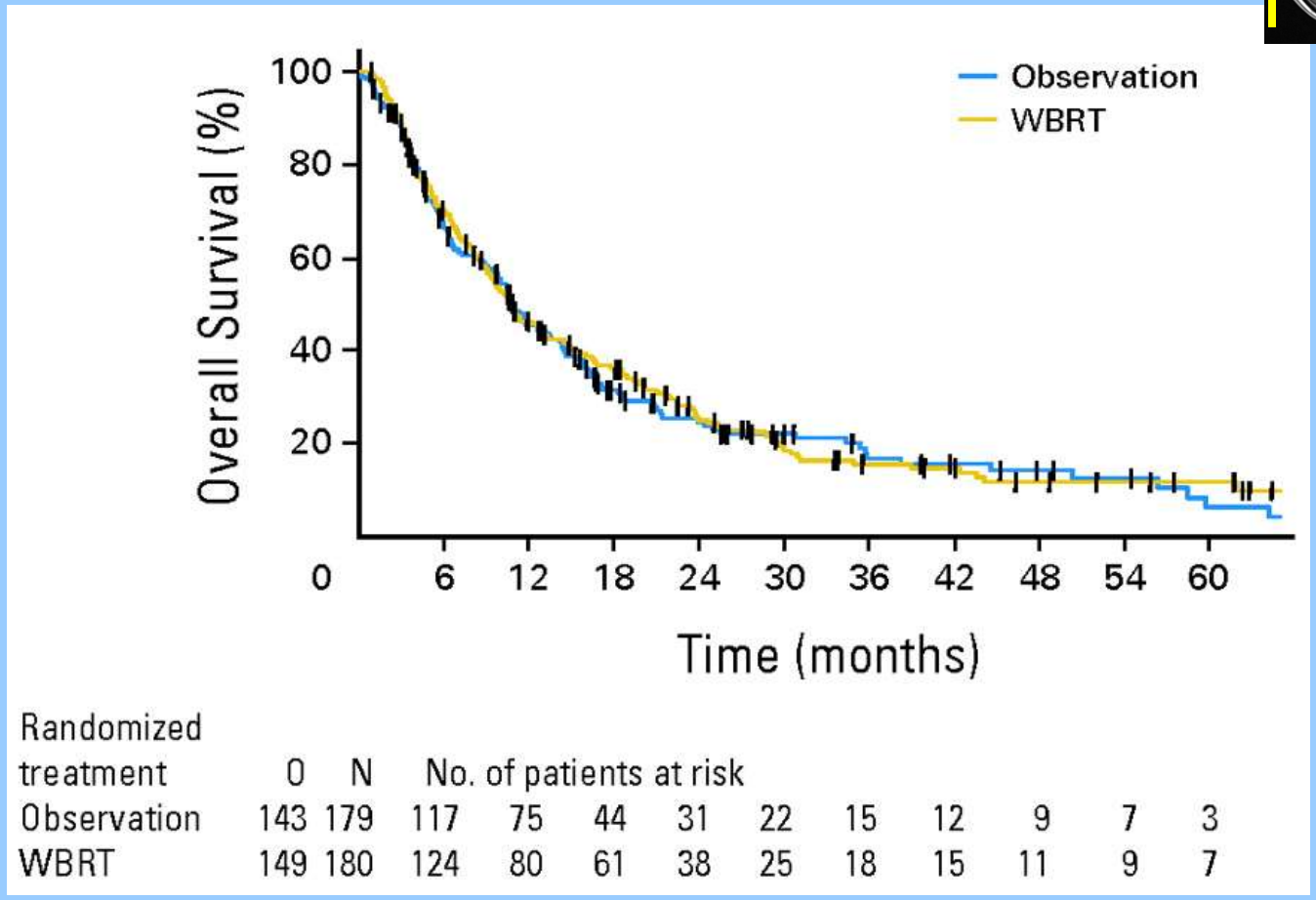
Whole brain radiotherapy following surgery or radiosurgery

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

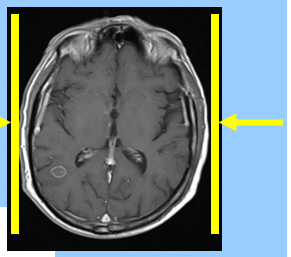
Whole brain radiotherapy following surgery or radiosurgery

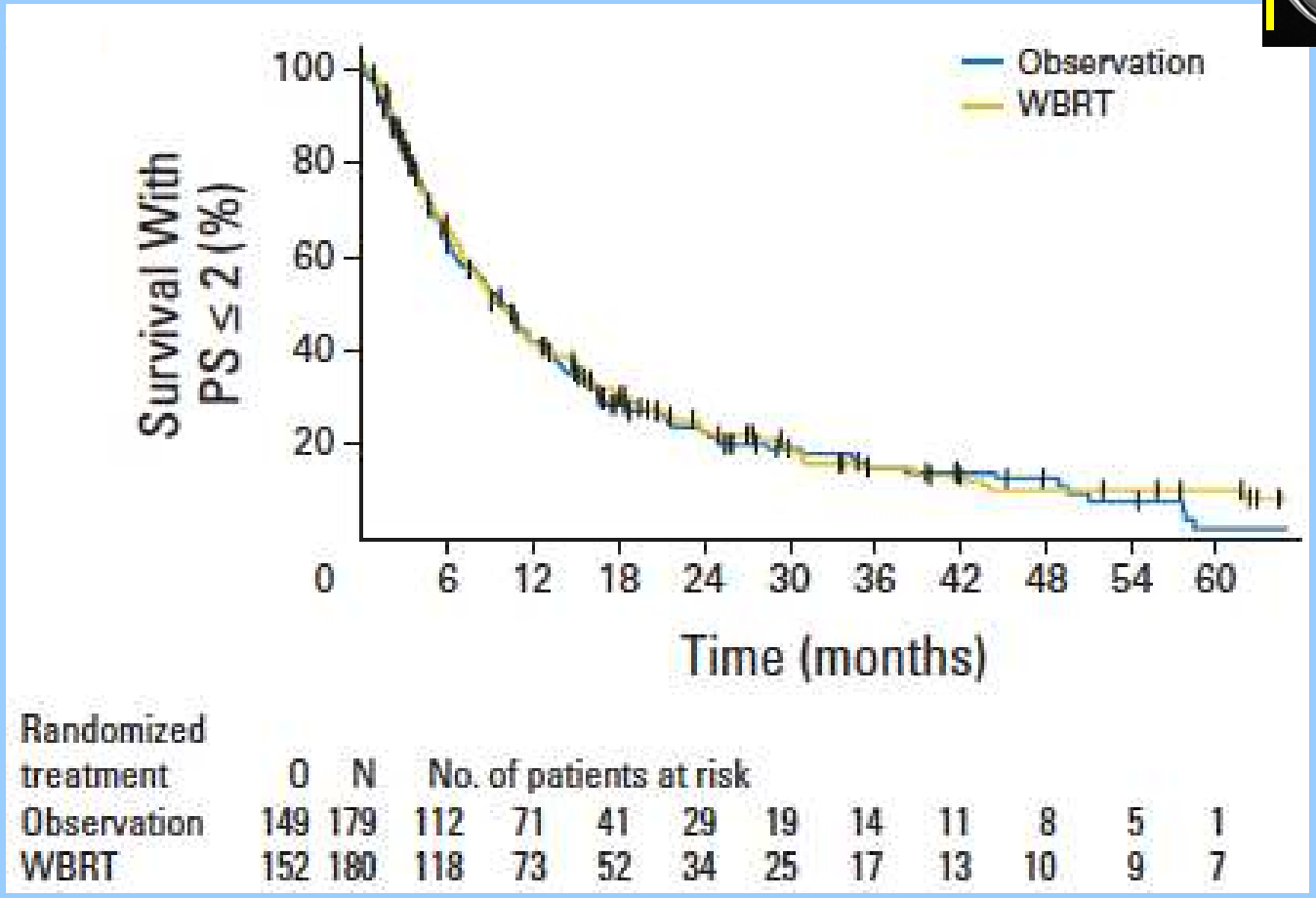
WBRT – whole brain radiotherapy

Kocher et al 2011 J Clin Oncol 29:134-141

EORTC 22952-26001

survival with good performance status





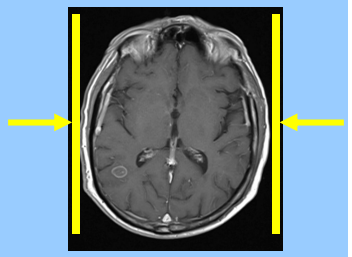
Randomized treatment	0	N	No. of patients at risk									
Observation	149	179	112	71	41	29	19	14	11	8	5	1
WBRT	152	180	118	73	52	34	25	17	13	10	9	7

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

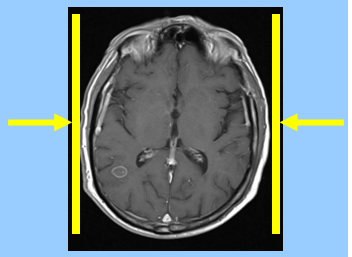
2° endpoint survival

Cognitive progression
cognitive function tests - drop in 1SD in one test

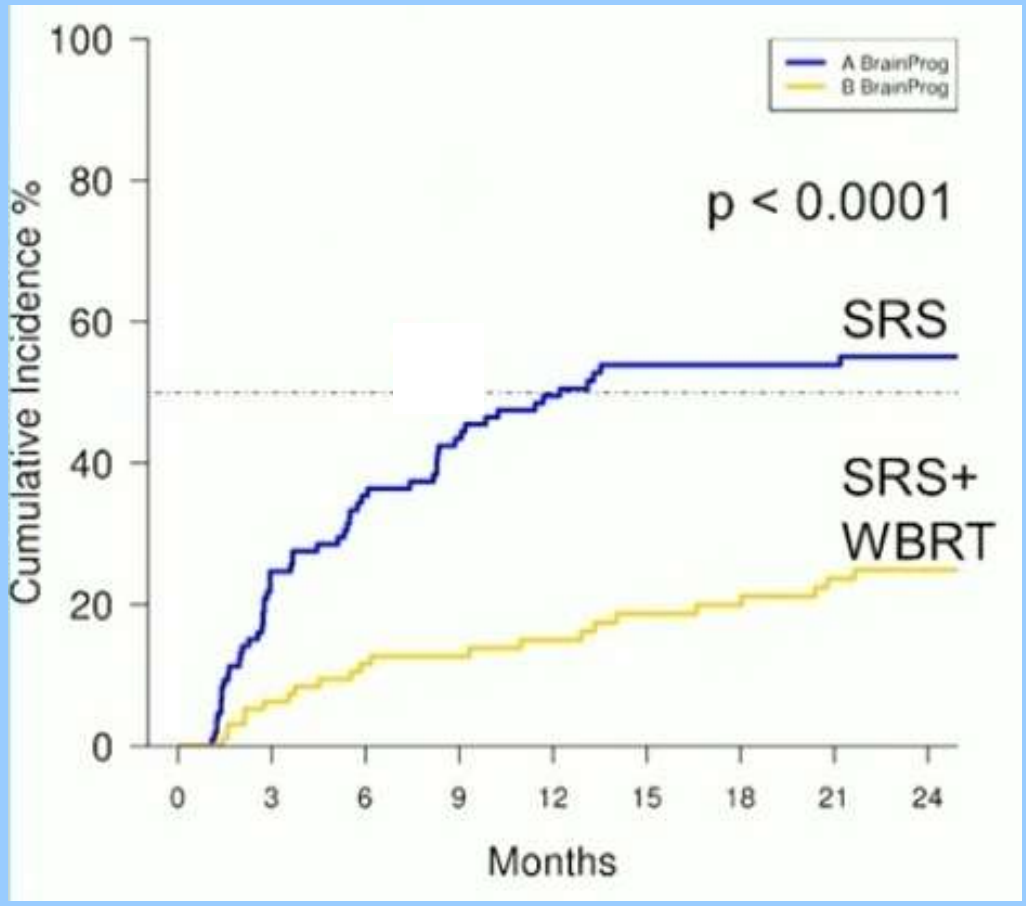
Whole brain radiotherapy following radiosurgery

Brown et al 2016 JAMA, 316, 401-409

NCCTG N0574 (Alliance) trial



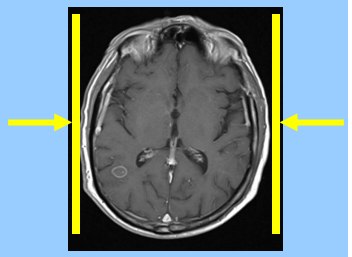
Intracranial progression



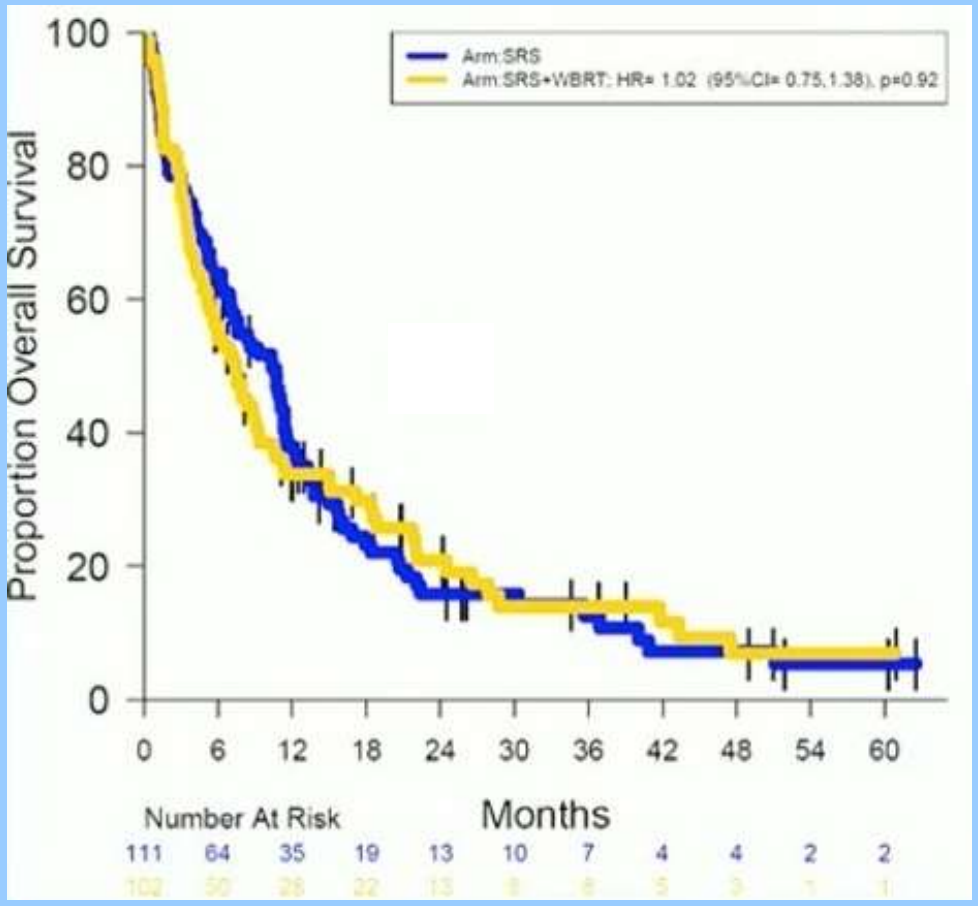
Whole brain radiotherapy following radiosurgery

Brown et al 2016 JAMA, 316, 401-409

NCCTG N0574 (Alliance) trial



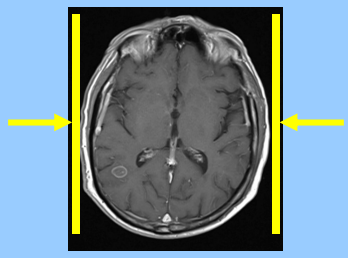
Survival



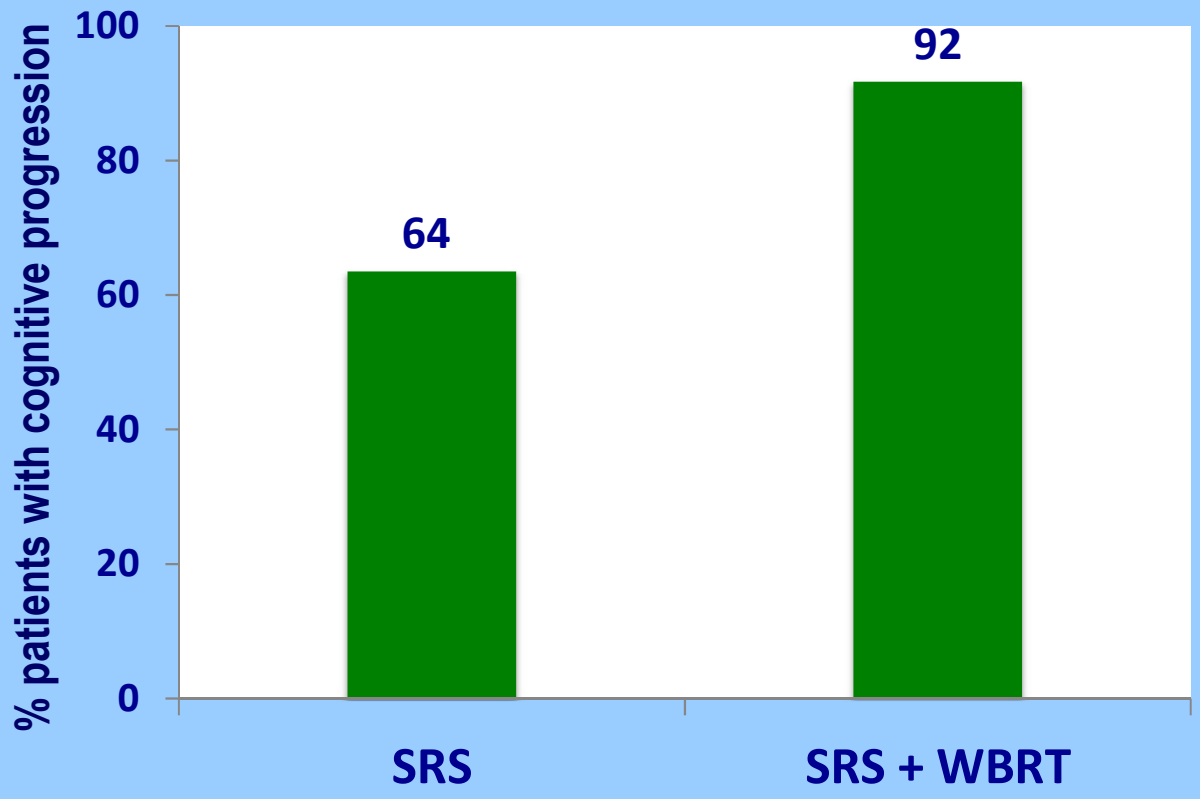
Whole brain radiotherapy following radiosurgery

Brown et al 2016 JAMA, 316, 401-409

NCCTG N0574 (Alliance) trial



Cognitive progression at 3 months

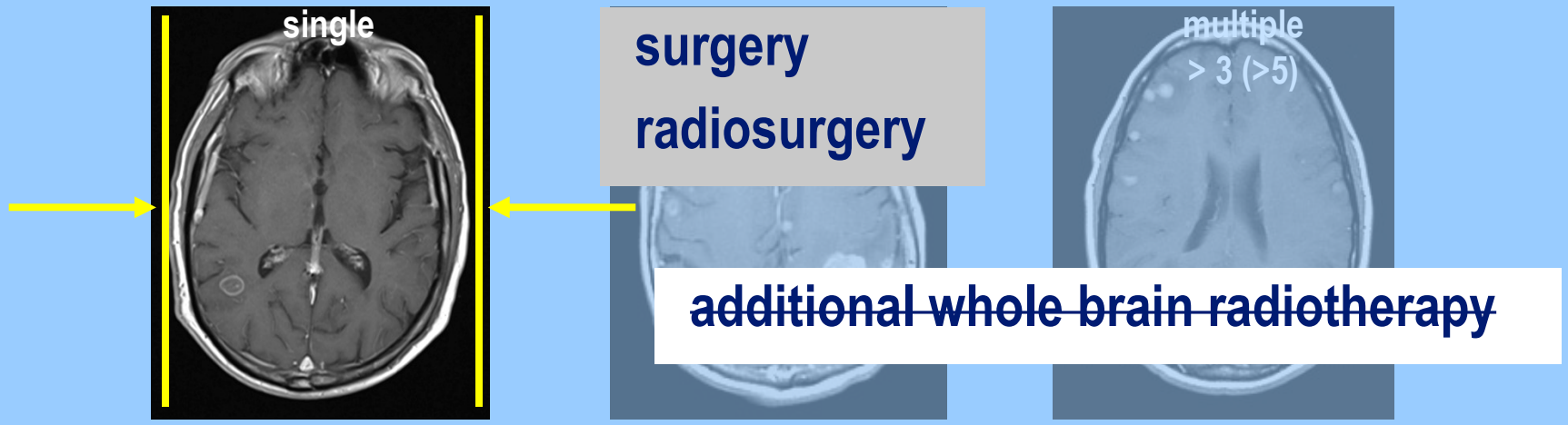


Whole brain radiotherapy following radiosurgery

Brown et al 2016 JAMA, 316, 401-409

Matrix - radiotherapy options

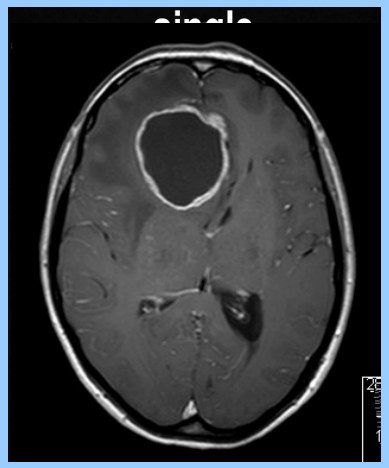
No. met's	prognosis	1^0 tumour	timing
single	good	any	
oligomets			
multiple			



Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single	good	any	
oligomets			
multiple			



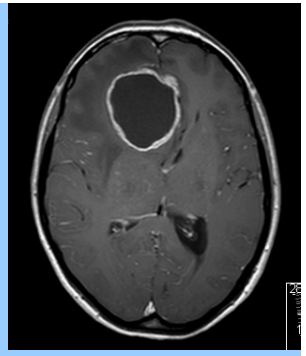
surgery

radiosurgery

additional radiosurgery ?

Radiotherapy in the management of brain metastases

NCCTG N107C/CEC·3



single brain metastasis
surgical resection

randomise

194 patients

radiosurgery

whole brain radiotherapy

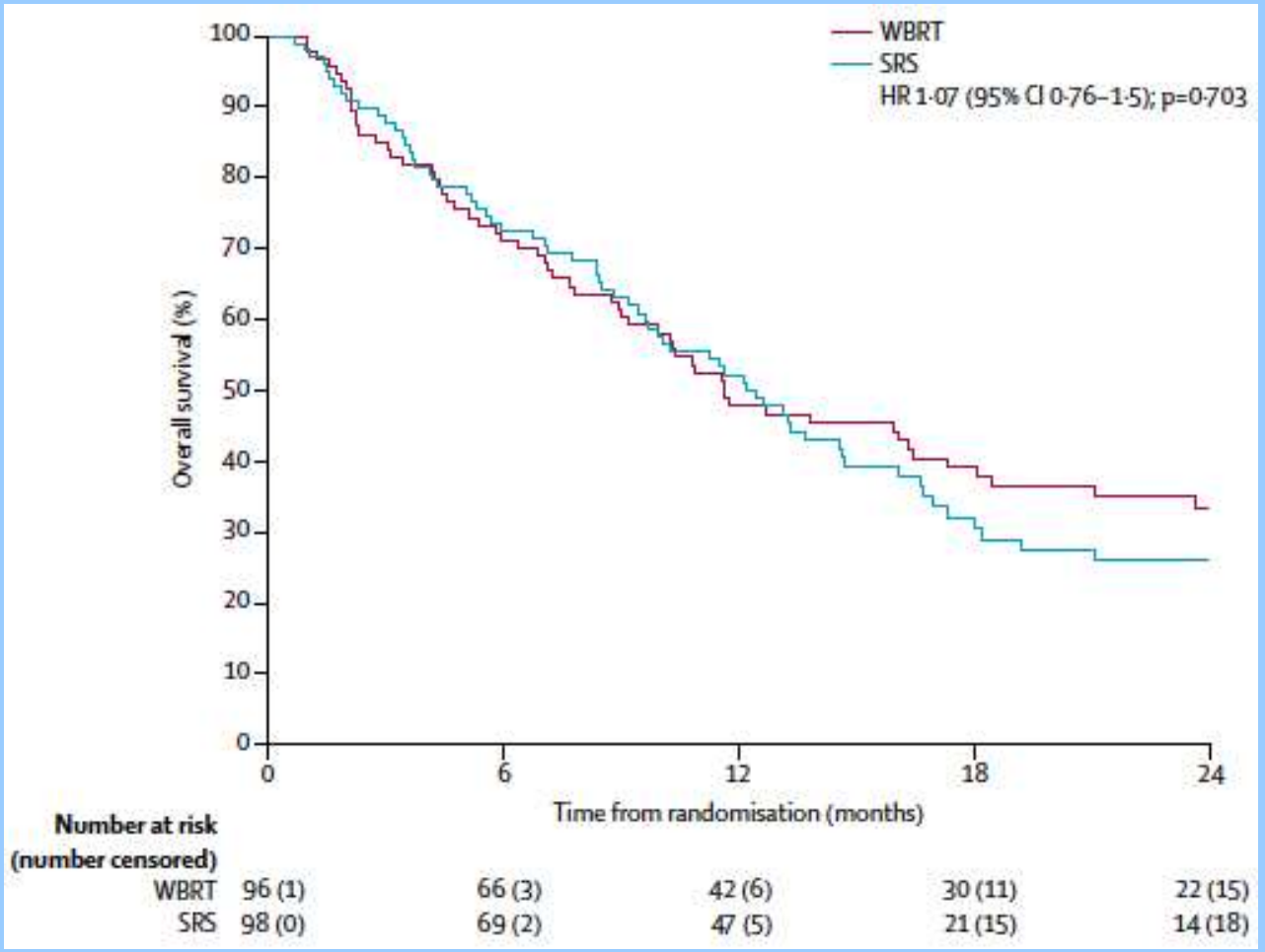
37.5Gy in 15F

WBRT vs radiosurgery following resection of solitary metastasis

Brown et al 2017 Lancet Oncol 2017; 18: 1049–60

NCCTG N107C/CEC·3

Survival

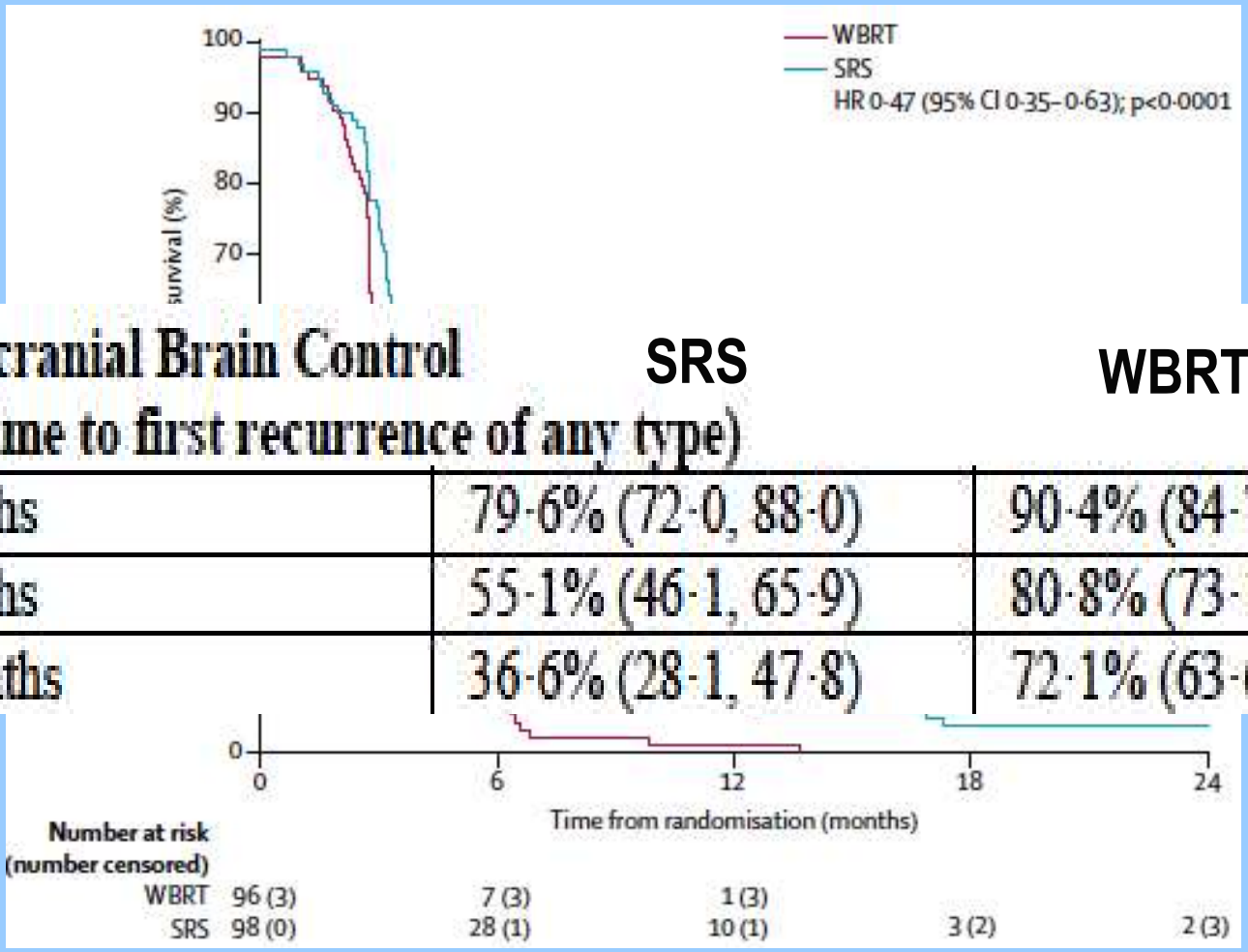


WBRT vs radiosurgery following resection of solitary metastasis

Brown et al 2017 Lancet Oncol 2017; 18: 1049–60

NCCTG N107C/CEC·3

Cognitive function



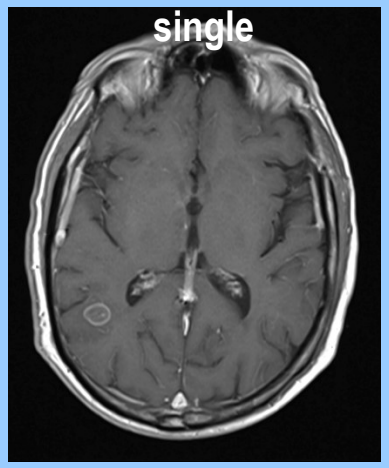
Total Intracranial Brain Control (based on time to first recurrence of any type)	SRS	WBRT
at 3 months	79·6% (72·0, 88·0)	90·4% (84·7, 96·6)
at 6 months	55·1% (46·1, 65·9)	80·8% (73·1, 89·2)
at 12 months	36·6% (28·1, 47·8)	72·1% (63·6, 81·8)

WBRT vs radiosurgery following resection of solitary metastasis

Brown et al 2017 Lancet Oncol 2017; 18: 1049–60

Matrix - radiotherapy options

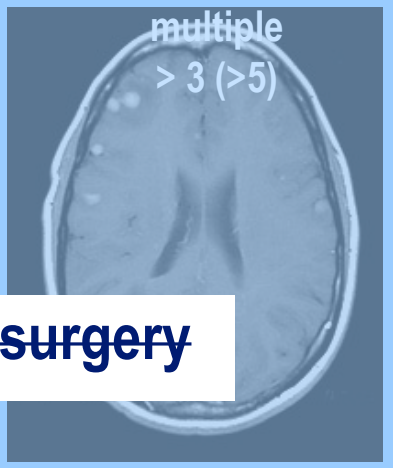
No. met's	prognosis	1^0 tumour	timing
single	good	any	
oligomets			
multiple			



surgery

radiosurgery

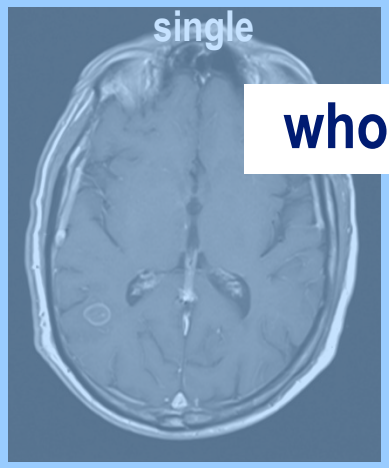
~~additional radiosurgery~~

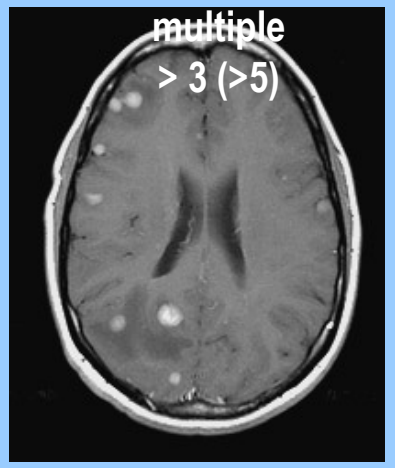


Radiotherapy in the management of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			

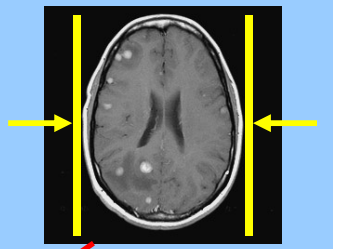




whole brain radiotherapy

Evidence base for radiotherapy in the treatment of brain metastases

whole brain radiotherapy and survival



patients with brain metastases

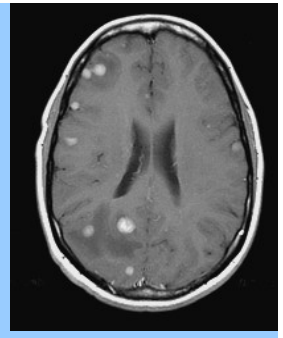
randomise

palliative radiotherapy & supportive care

supportive care alone

Effect of whole brain radiotherapy on survival

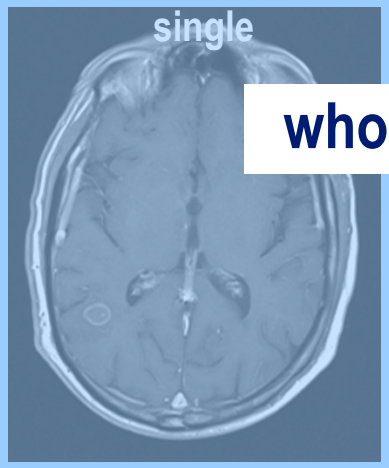
Course of malignant disease

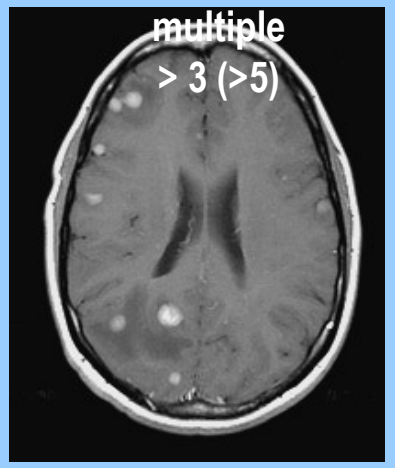


Brain metastases in malignancy

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple	poor		end stage



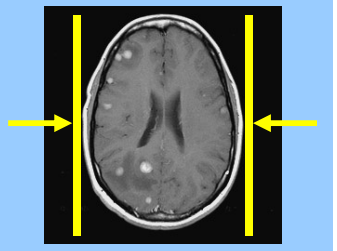


whole brain radiotherapy

Evidence base for radiotherapy in the treatment of brain metastases

QUARTZ trial

CR UK & TROG



brain metastases in NSCLC

& poor prognosis

randomise

palliative radiotherapy & supportive care

supportive care alone

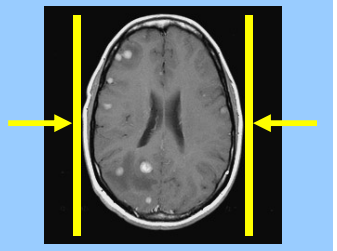
endpoints: **palliative efficacy (QOL, Barthel), survival free of neurological progression, survival**

Effect of whole brain radiotherapy on survival & QOL

Mulvenna et al 2016 Lancet Oncology; 388, 2004-2014

QUARTZ trial

CR UK & TROG



brain metastases in NSCLC

& poor prognosis

randomise

538

palliative radiotherapy & supportive care

269

supportive care alone

269

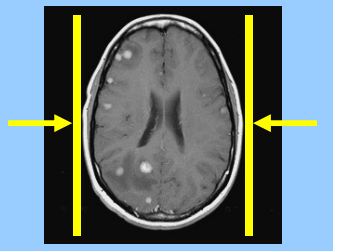
endpoints: palliative efficacy (QOL, Barthel), survival free of neurological progression, survival

Effect of whole brain radiotherapy on survival & QOL

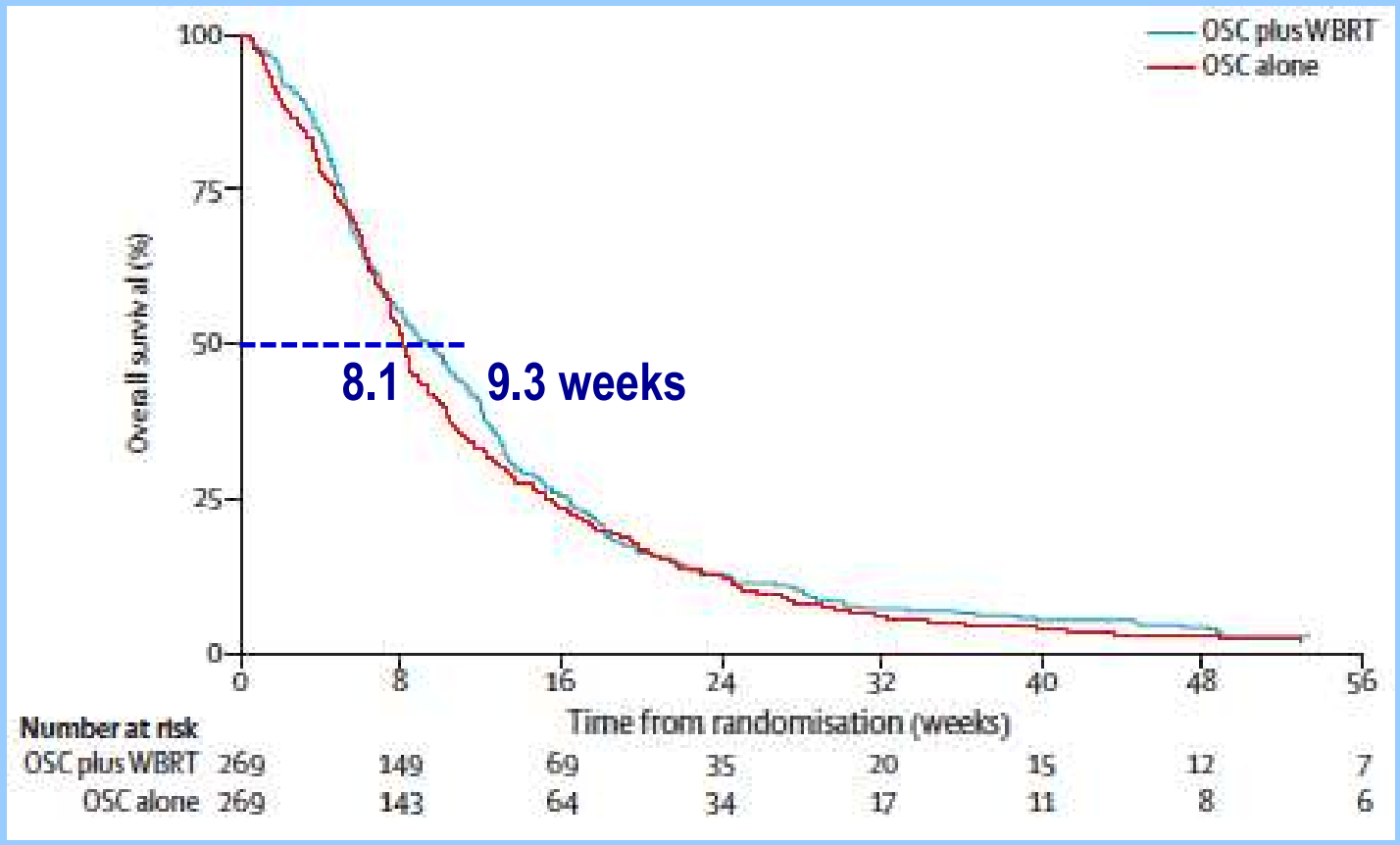
Mulvenna et al 2016 Lancet Oncology; 388, 2004-2014

QUARTZ trial

CR UK & TROG



survival



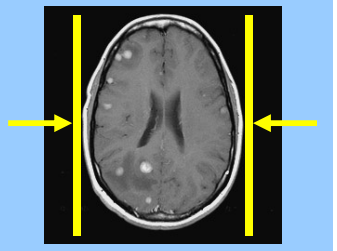
Effect of whole brain radiotherapy on survival & QOL

Mulvenna et al 2016 Lancet Oncology; 388, 2004-2014

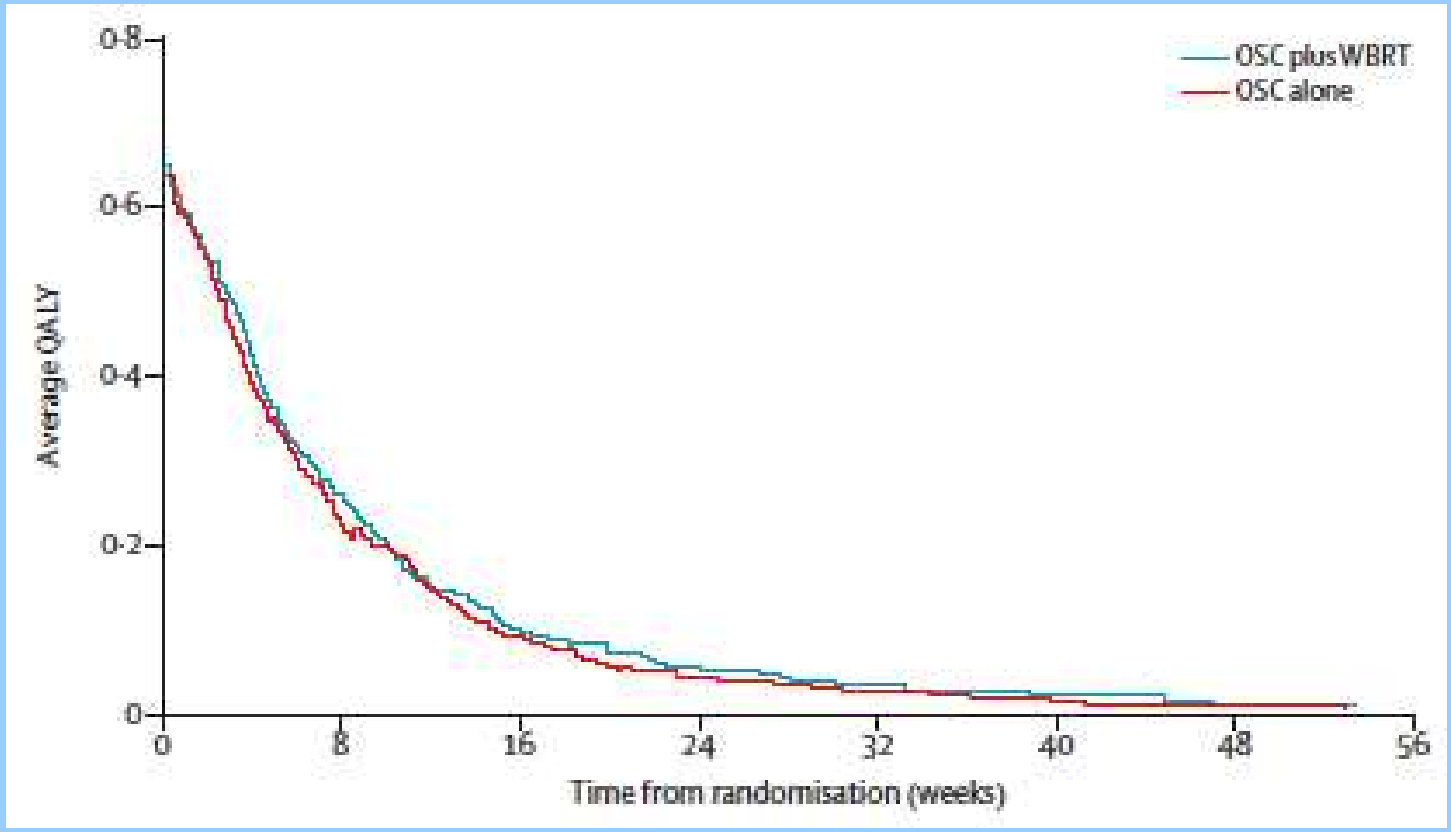
OSC optimum supportive care
WBRT whole brain radiotherapy

QUARTZ trial

CR UK & TROG



quality adjusted life years (QALY)



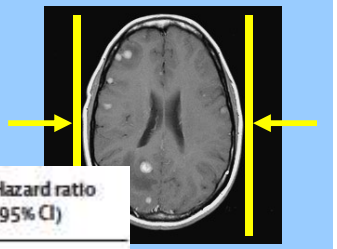
Effect of whole brain radiotherapy on survival & QOL

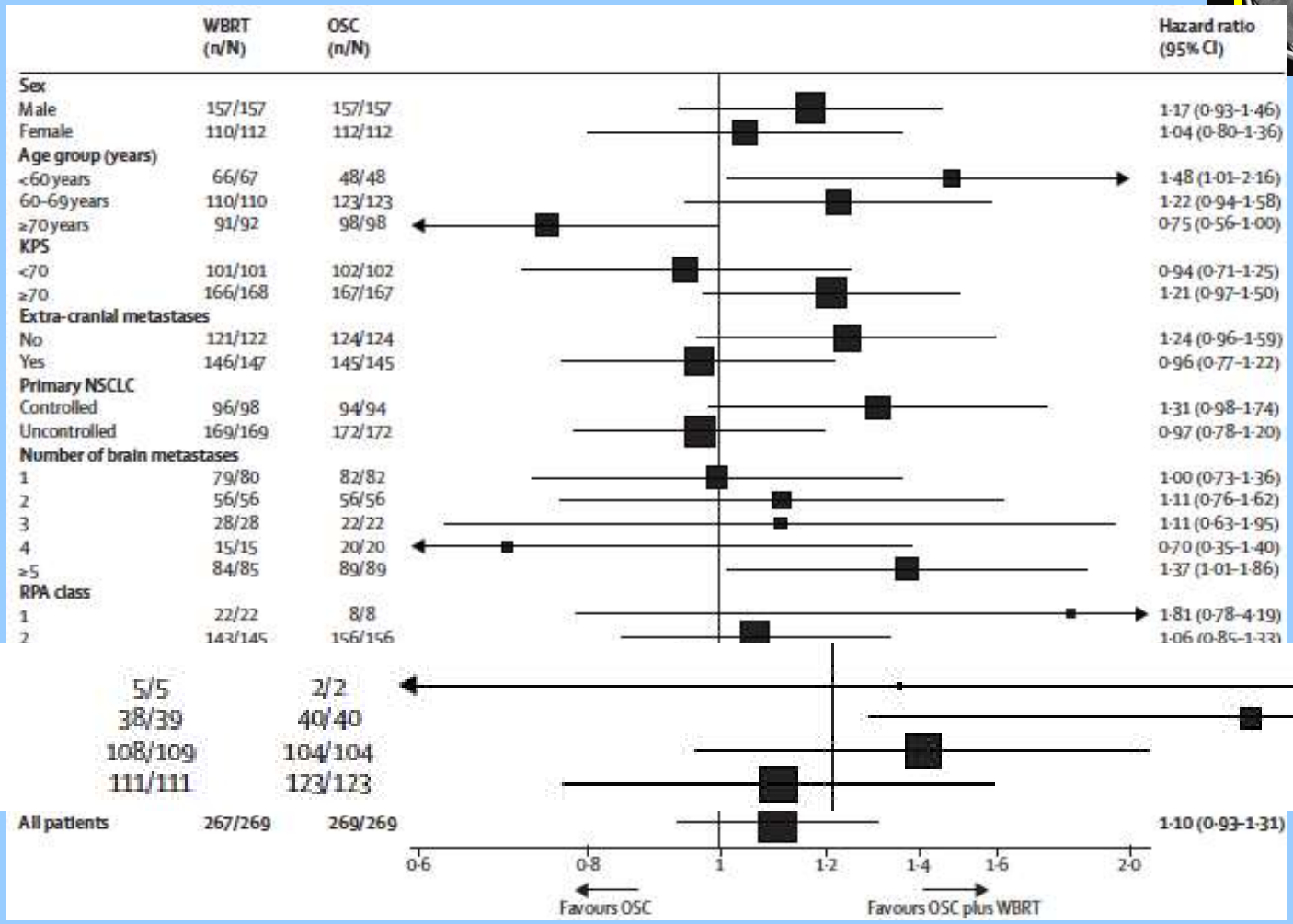
Mulvenna et al 2016 Lancet Oncology; 388, 2004-2014

OSC optimum supportive care
WBRT whole brain radiotherapy

QUARTZ trial

CR UK & TROG





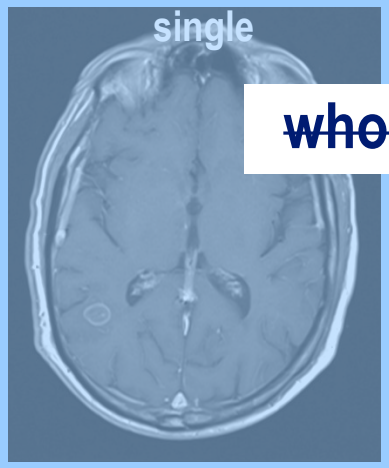
Effect of whole brain radiotherapy on survival & QOL

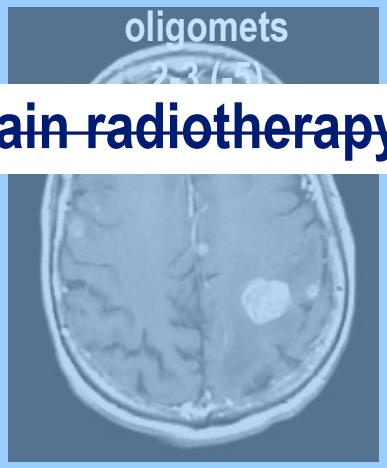
Mulvenna et al 2016 Lancet Oncology; 388, 2004-2014

OSC optimum supportive care
WBRT whole brain radiotherapy

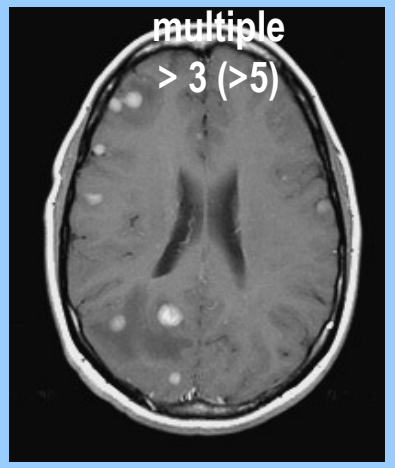
Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single oligomets			
multiple	poor		end stage





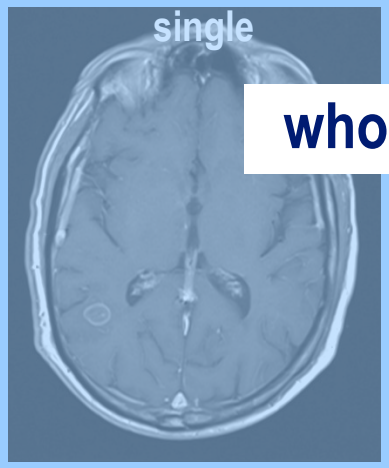
~~whole brain radiotherapy~~

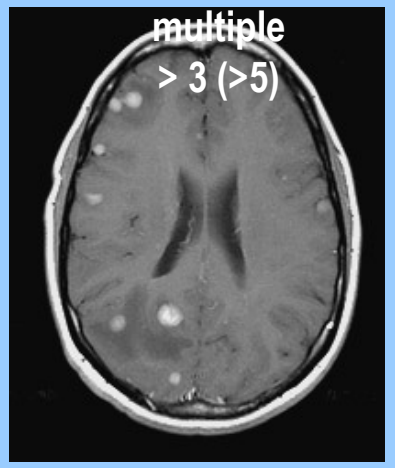


Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			



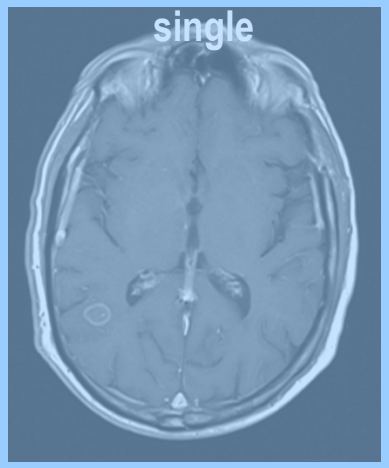


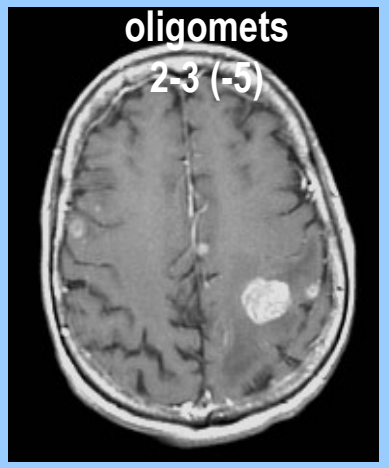
whole brain radiotherapy

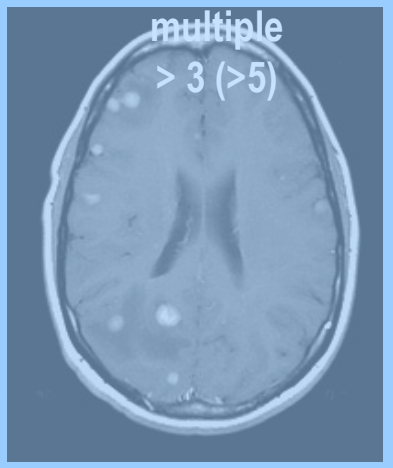
Evidence base for radiotherapy in the treatment of brain metastases

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets			
multiple			



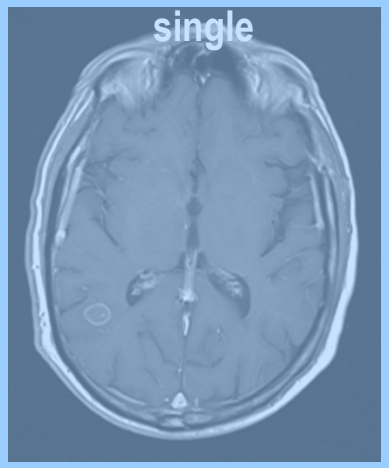


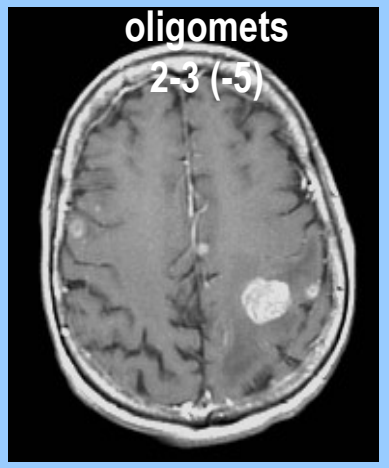


Evidence base for radiotherapy in the treatment of brain metastases

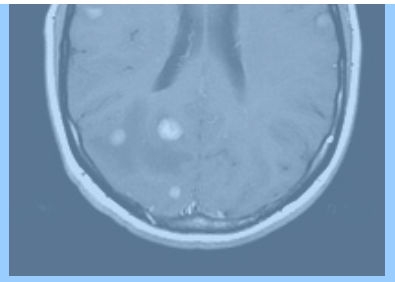
Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets	good		
multiple			



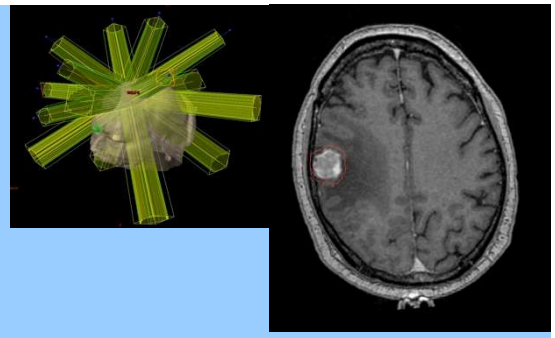


whole brain radiotherapy
or radiosurgery (or both)



Evidence base for radiotherapy in the treatment of brain metastases

RTOG trial 9508



1 - 3 brain metastases

oligometastases

randomise

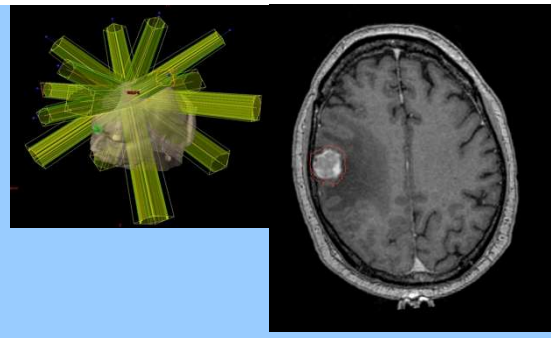
whole brain radiotherapy & radiosurgery (SRS)	**whole brain radiotherapy** (WBRT)
167 patients	**164 patients**

331 patients

Radiosurgery for “solitary” brain metastases

Andrews et al 2004, Lancet; 363: 1665–72

RTOG trial 9508



oligometastases
(2-3 mets)

randomise

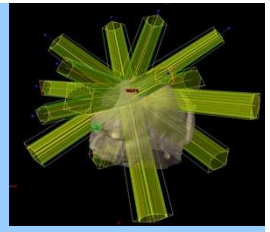
whole brain radiotherapy & radiosurgery (SRS)	**whole brain radiotherapy** (WBRT)
73 patients	**72 patients**

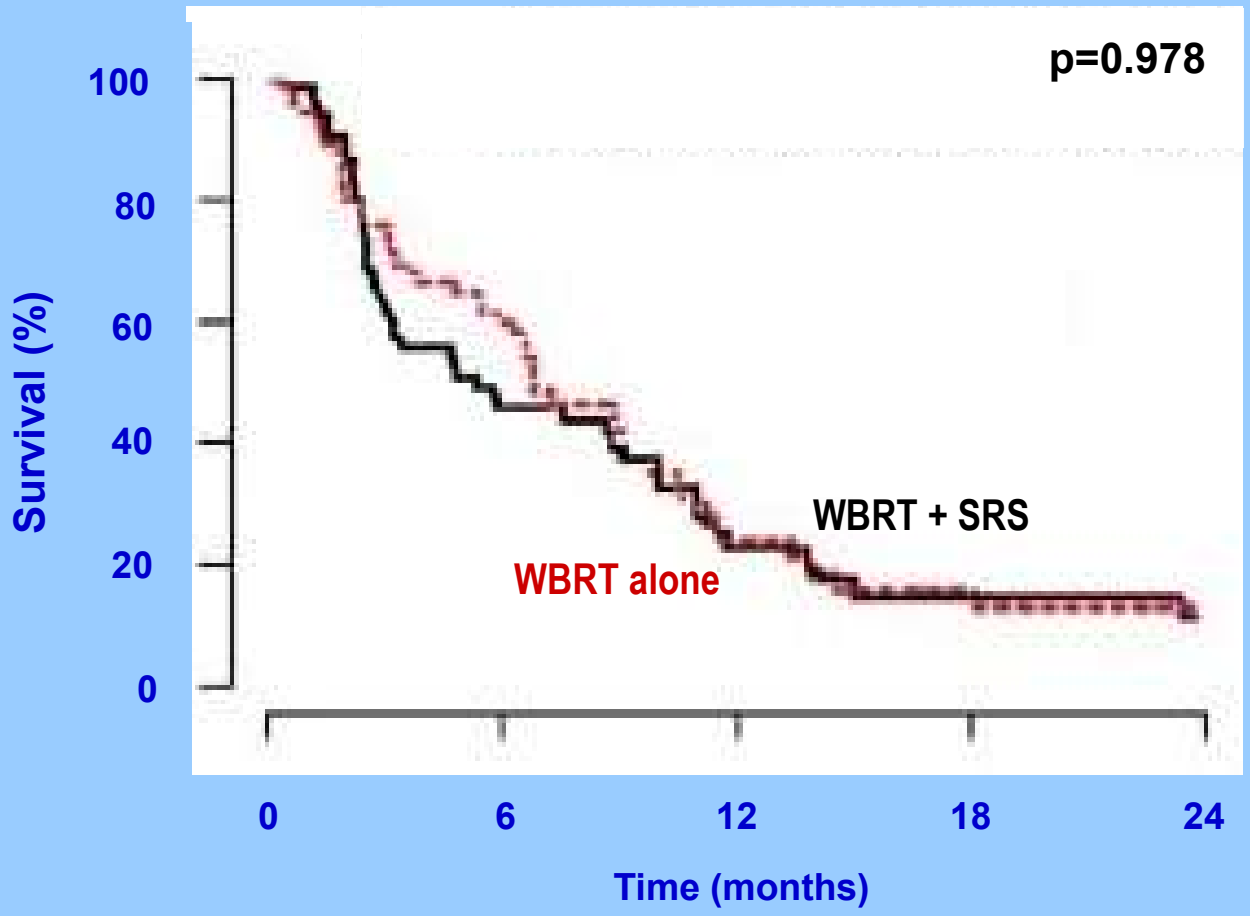
145 patients

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

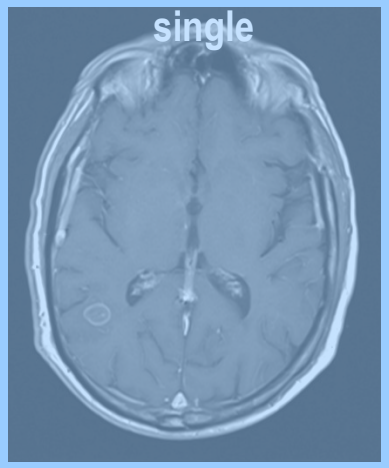
RTOG 9508

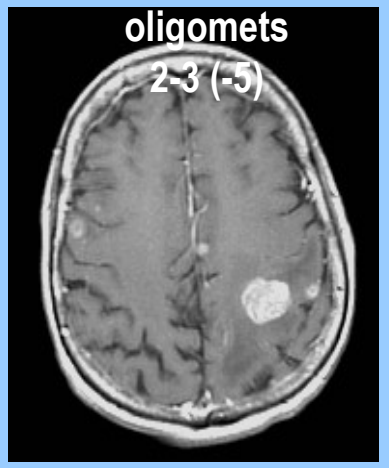
Andrews et al 2004, Lancet; 363: 1665–72

WBRT	whole brain radiotherapy
SRS	stereotactic radiosurgery

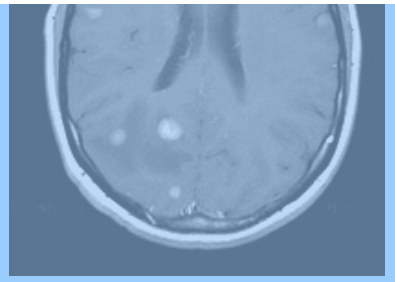
Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single			
oligomets	good		
multiple			



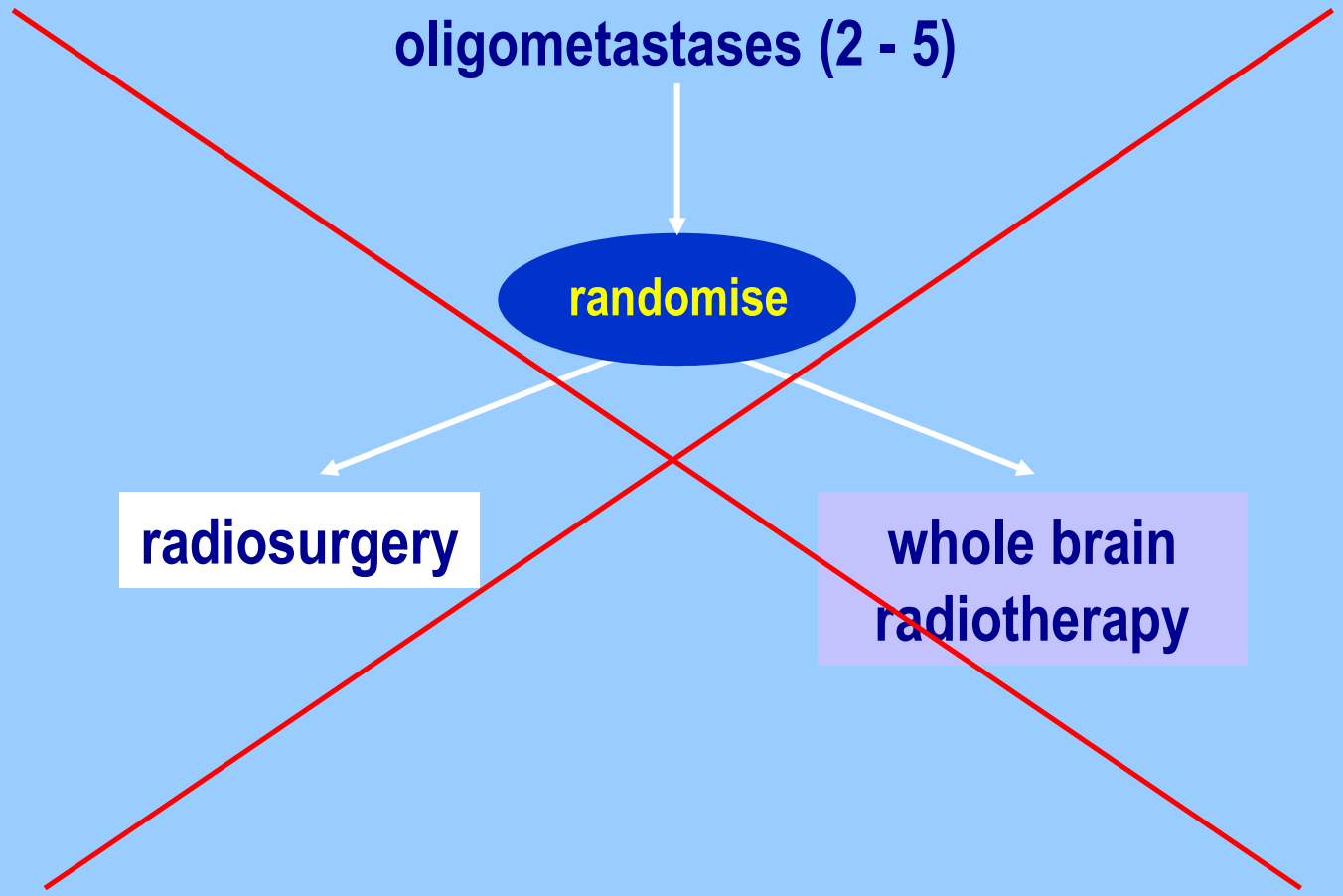


whole brain radiotherapy
or radiosurgery (or both)

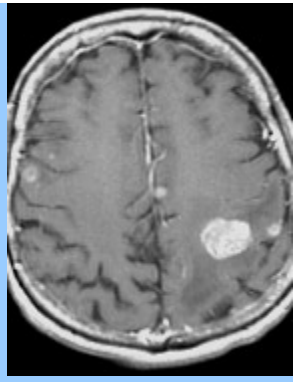


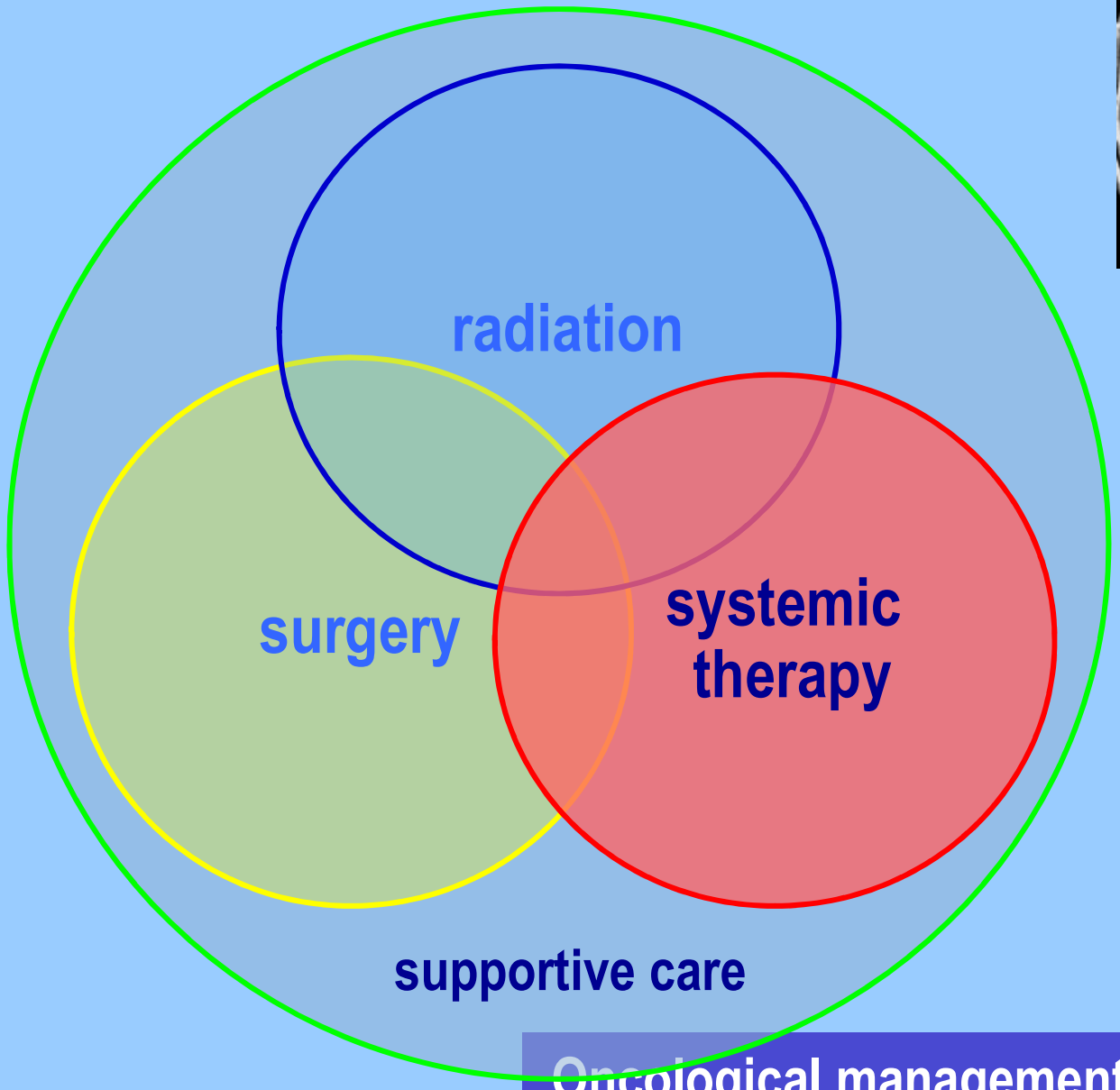
Evidence base for radiotherapy in the treatment of brain metastases

Oligometastases



Radiosurgery for oligometastases in the brain

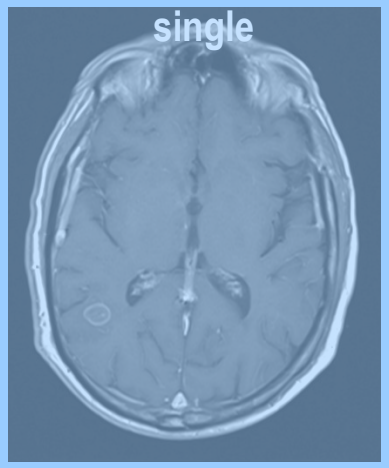


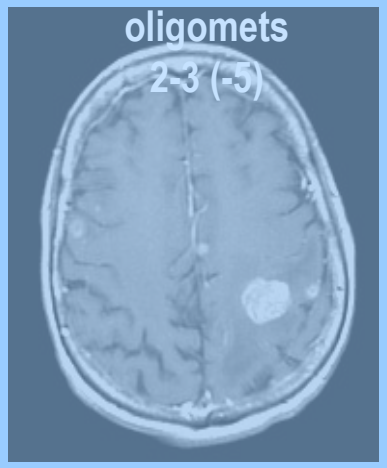


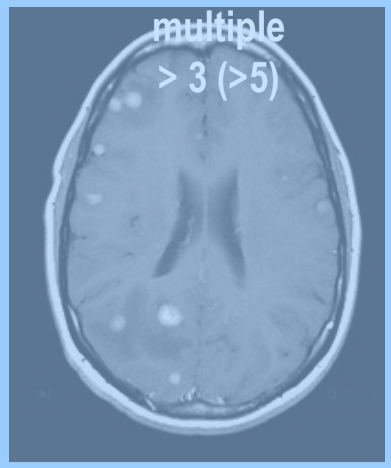
Oncological management options

Matrix - radiotherapy options

No. met's	prognosis 1^0 tumour timing
single oligomets multiple	responsive to systemic treatment

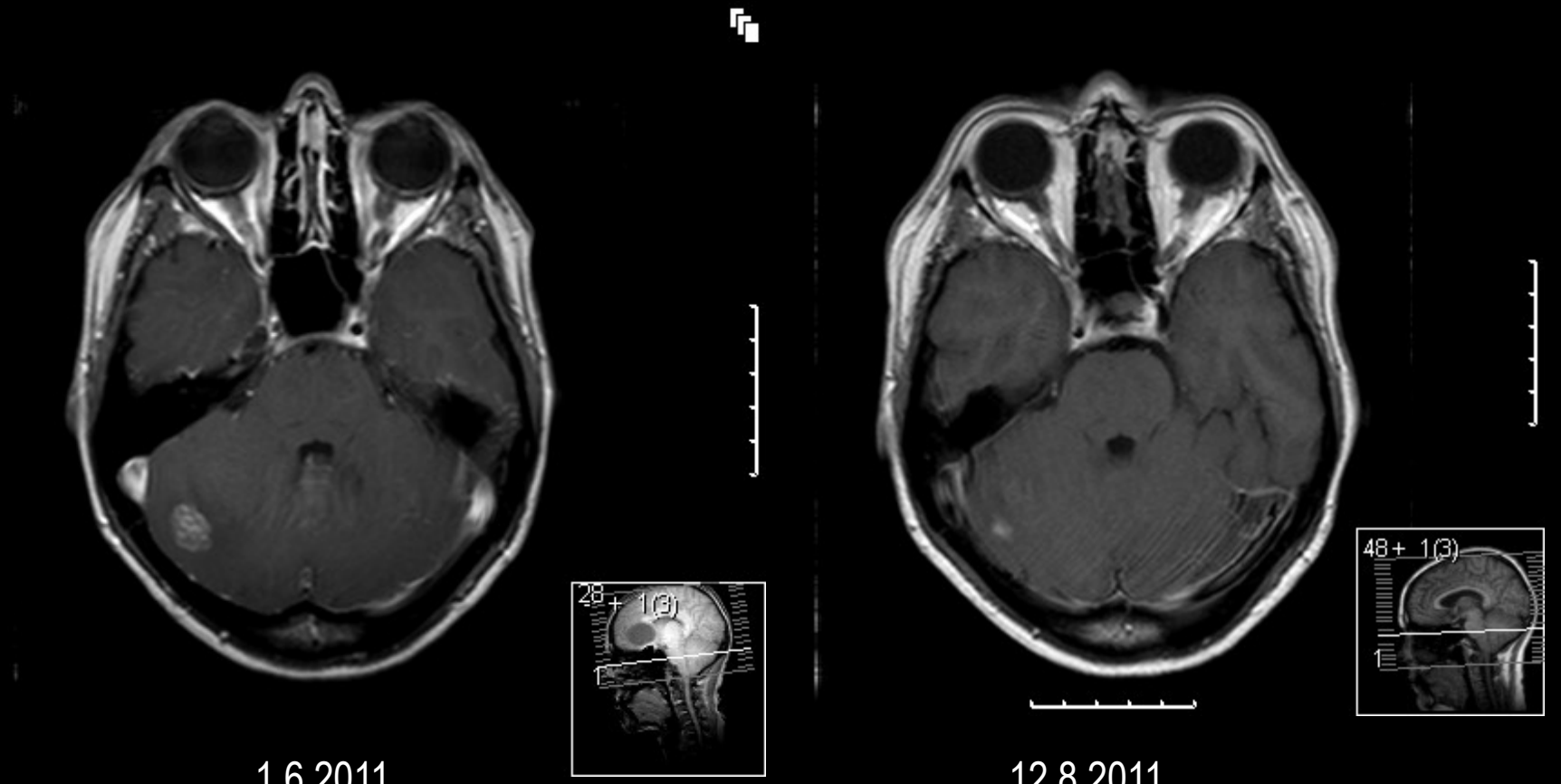






Evidence base for radiotherapy in the treatment of brain metastases

ER+ metastatic breast cancer

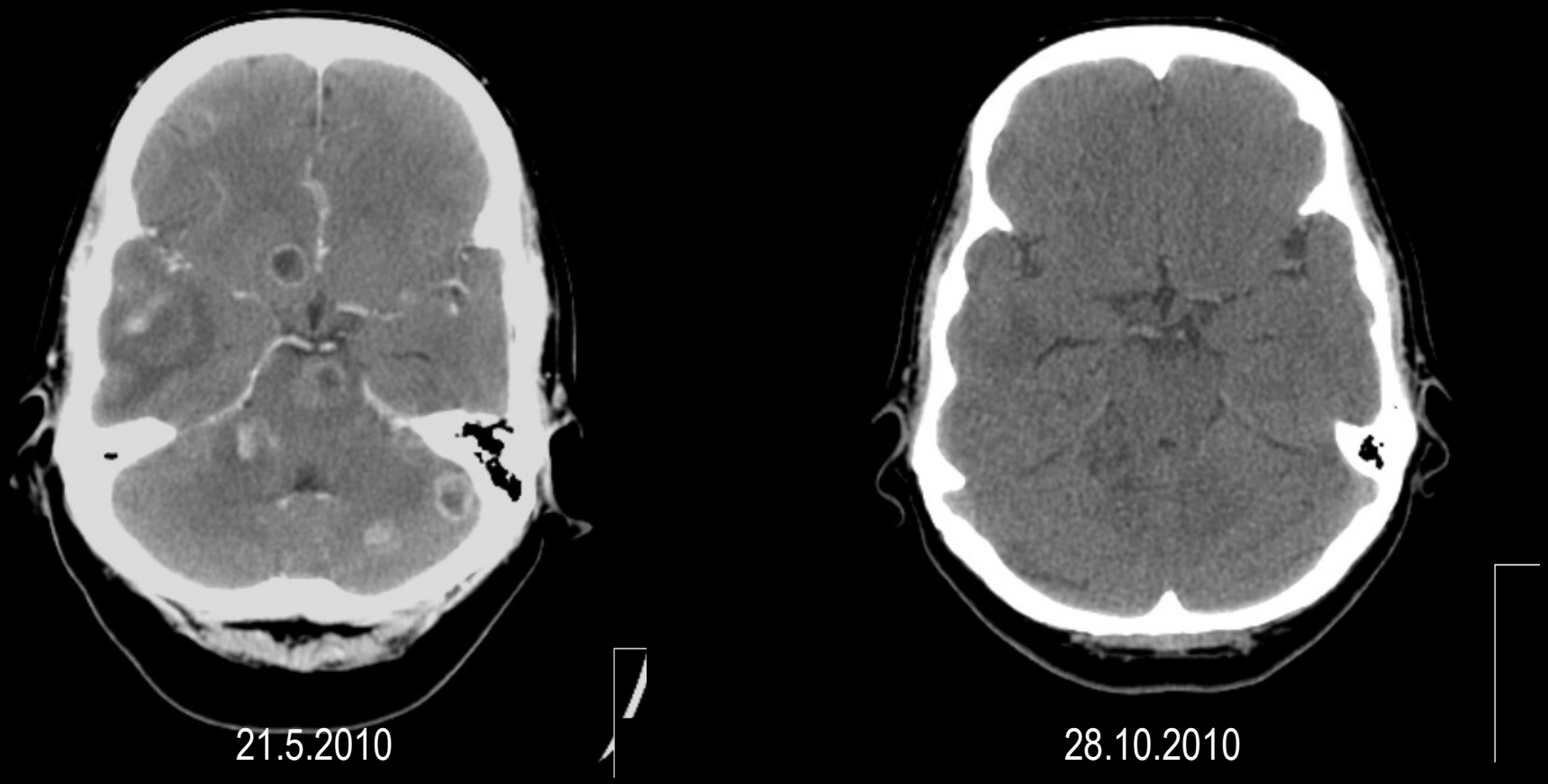


1.6.2011

12.8.2011

response to Anastrazole & Goserelin

lung adenocarcinoma with EGFR mutation



21.5.2010

28.10.2010

response to Erlotinib

Matrix - radiotherapy options

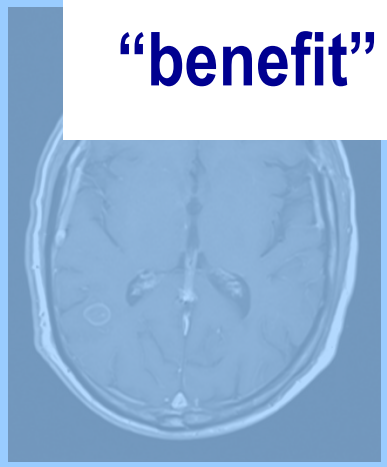
No. met's	prognosis	1^0 tumour	timing
single oligomets	responsive to systemic treatment		

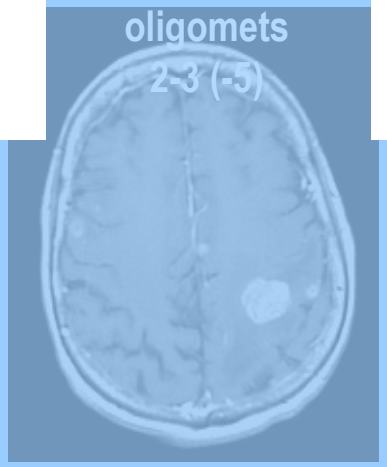
"activity"

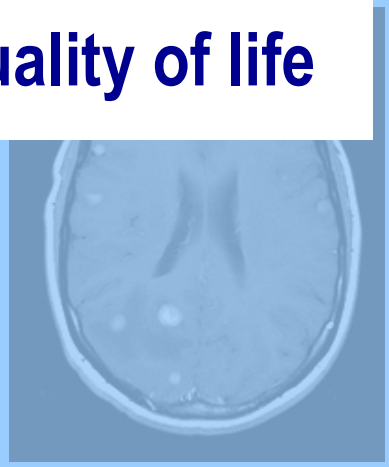
"benefit"

survival

quality of life







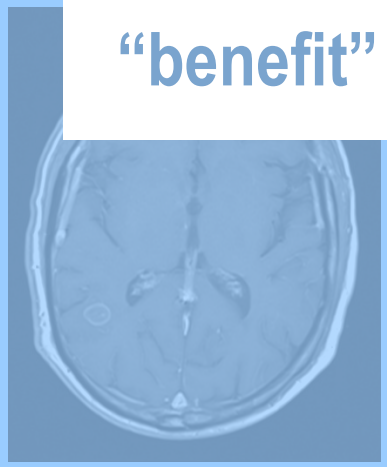
Systemic therapy endpoints

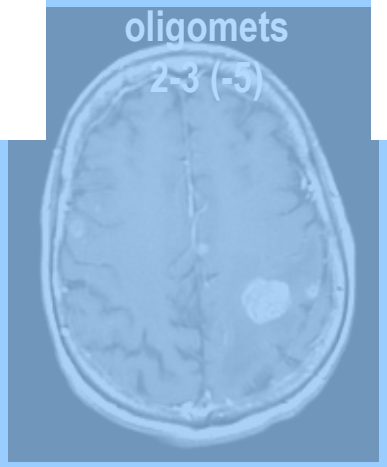
Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single oligomets	responsive to systemic treatment		

"activity"

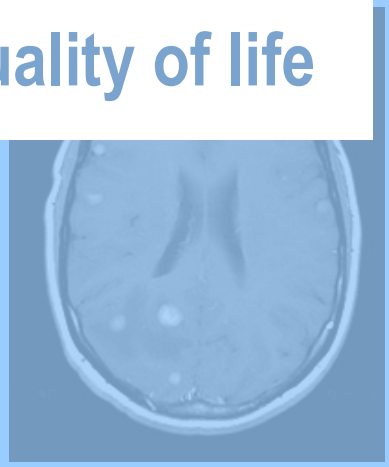
"benefit"





survival

quality of life



Systemic therapy endpoints

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single oligomets	responsive to systemic treatment		

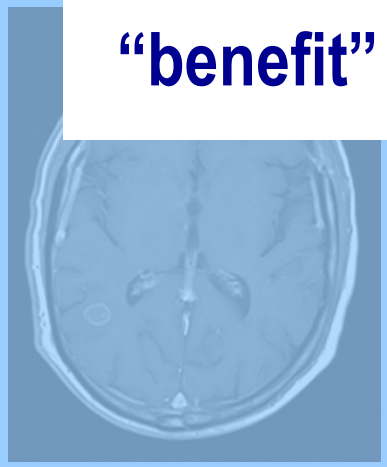
"activity"

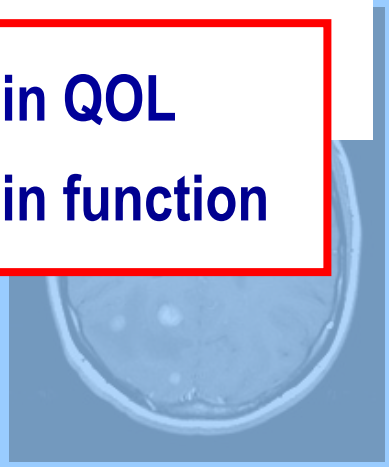
"benefit"

survival

improvement in QOL

improvement in function





Systemic therapy endpoints

Matrix - radiotherapy options

No. met's	prognosis	1^0 tumour	timing
single oligomets	responsive to systemic treatment		

"activity"

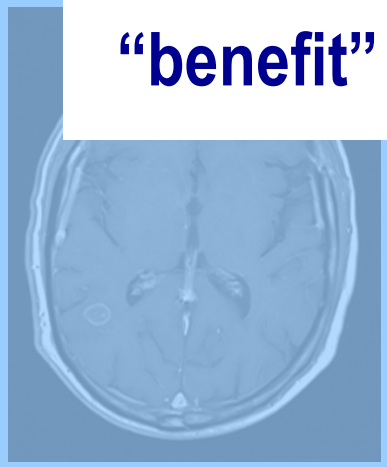
"benefit"

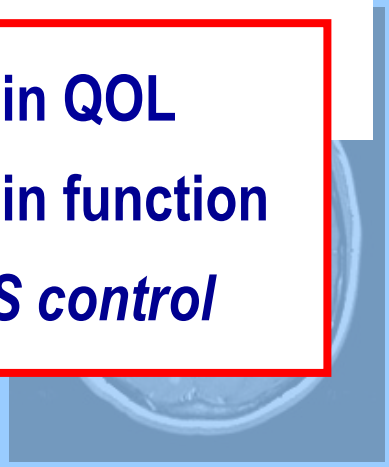
survival

improvement in QOL

improvement in function

long term CNS control

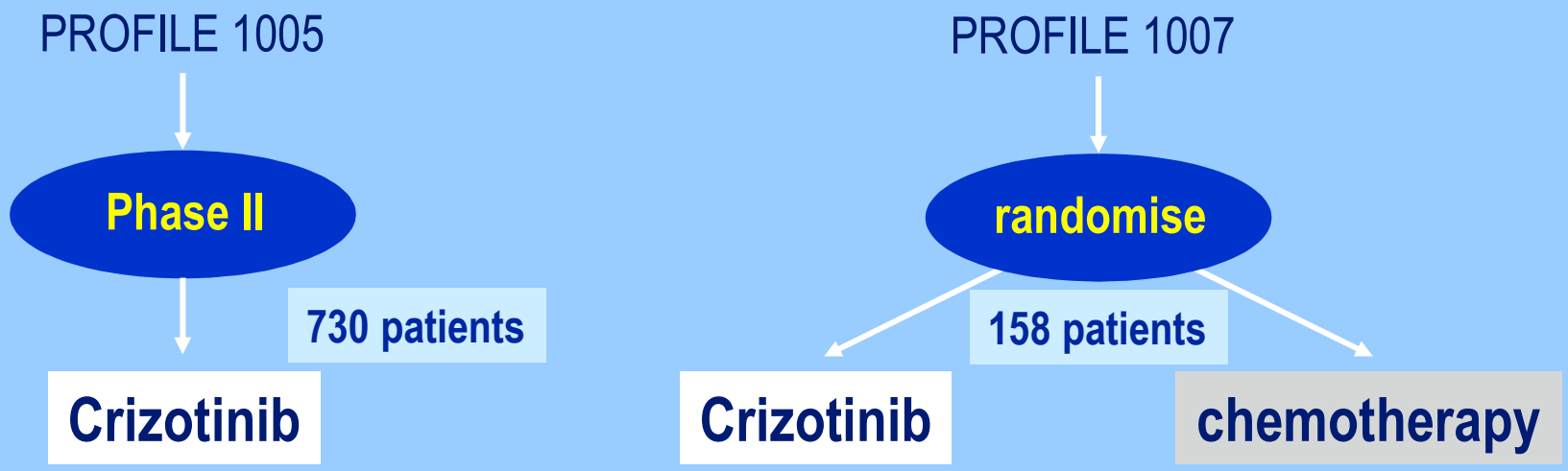




Systemic therapy endpoints

PROFILE trials

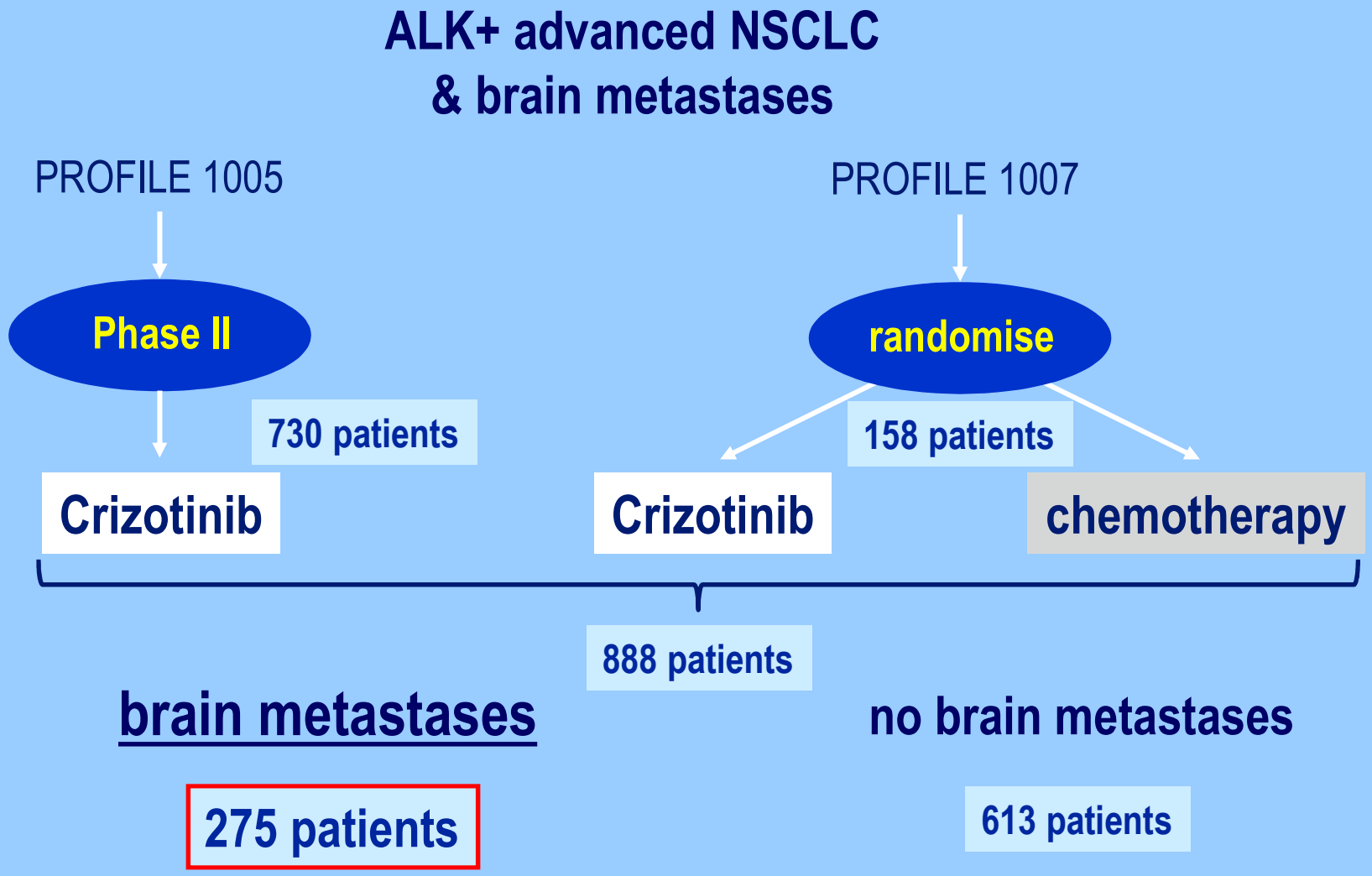
ALK+ advanced NSCLC



Brain metastases in patients with ALK-positive NSCLC

Costa et al 2015, J Clin Oncol; 33 (17): 1881-1888

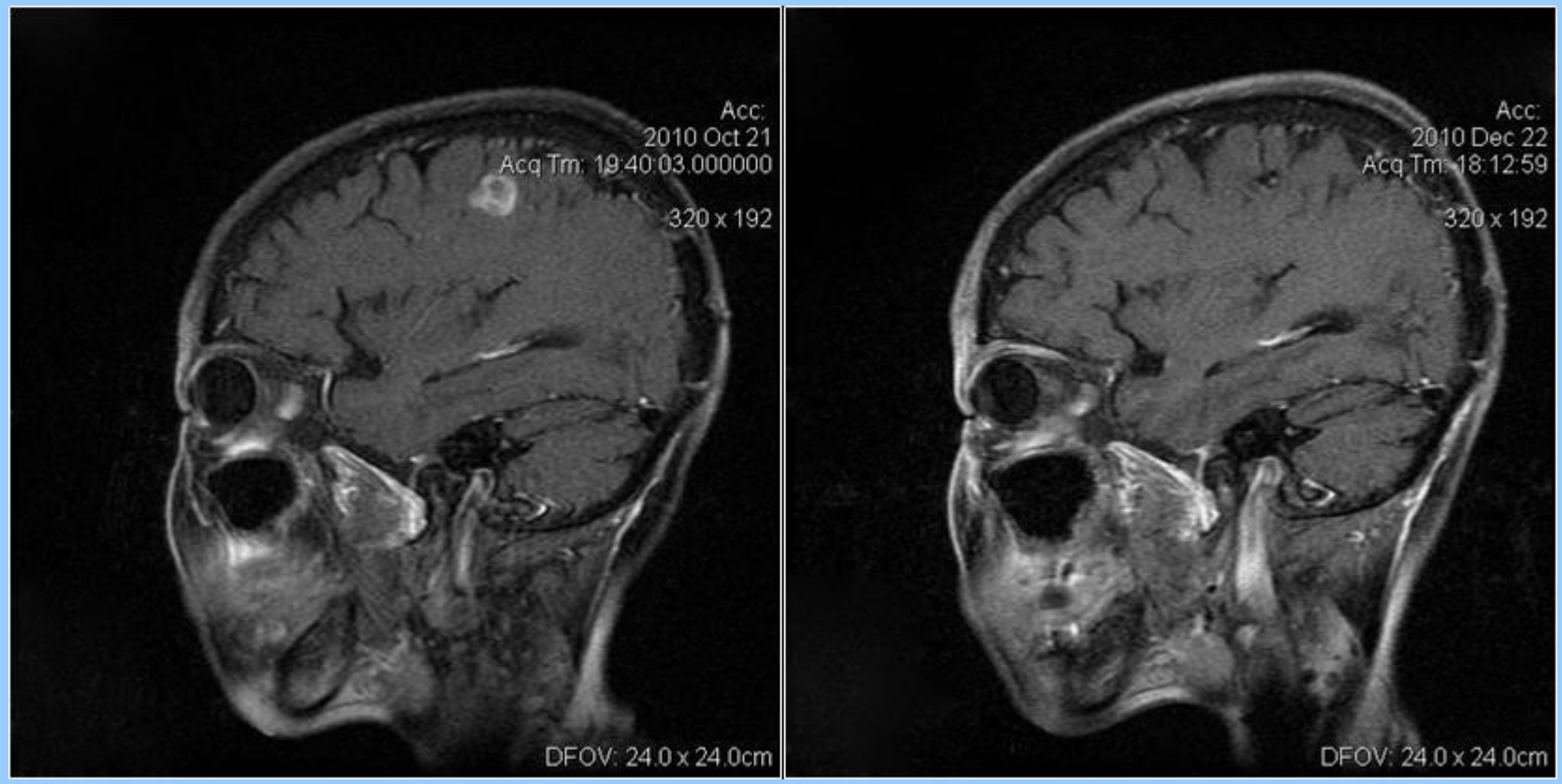
PROFILE trials



Brain metastases in patients with ALK-positive NSCLC

Costa et al 2015, J Clin Oncol; 33 (17): 1881-1888

PROFILE trials



Before initiation of crizotinib **6 weeks after crizotinib**

(provided by Pfizer, courtesy of J-Y Han, National Cancer Center, Goyang, South Korea)

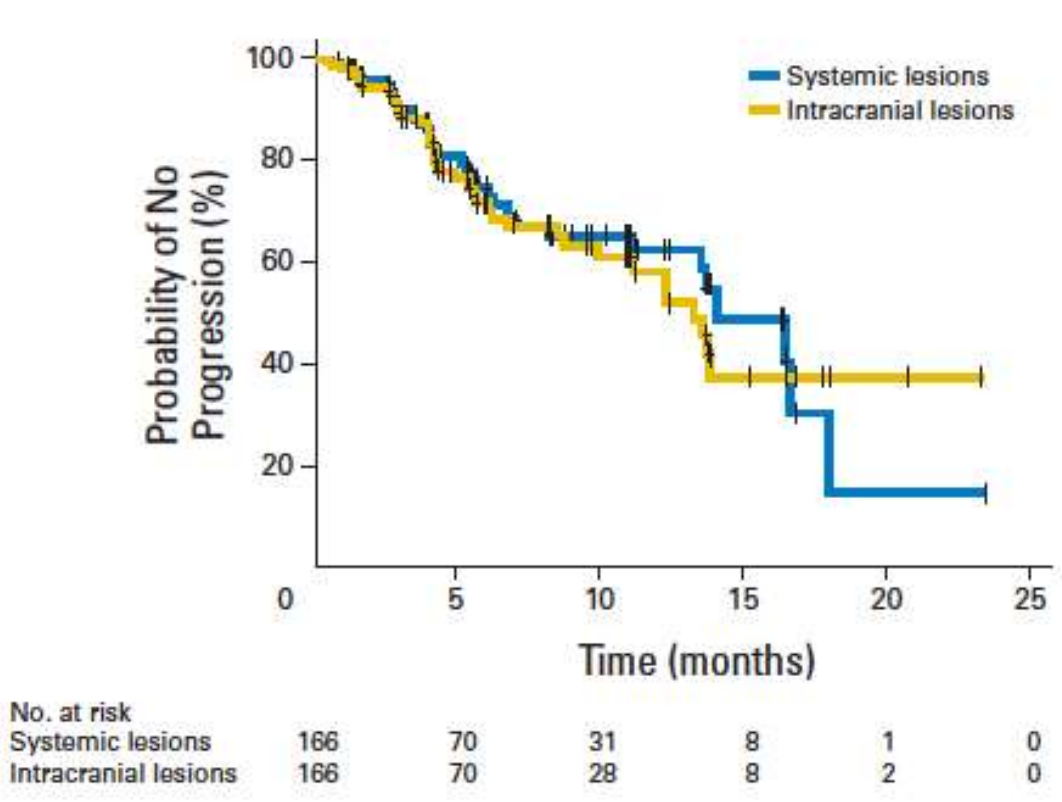
Brain metastases in patients with ALK-positive NSCLC

Costa et al 2015, J Clin Oncol; 33 (17): 1881-1888

PROFILE trials

asymptomatic previously untreated brain metastases (166)

progression free survival (systemic vs. intracranial)



Brain metastases in patients with ALK-positive NSCLC

Costa et al 2015, J Clin Oncol; 33 (17): 1881-1888

PROFILE trials 1005 & 1007

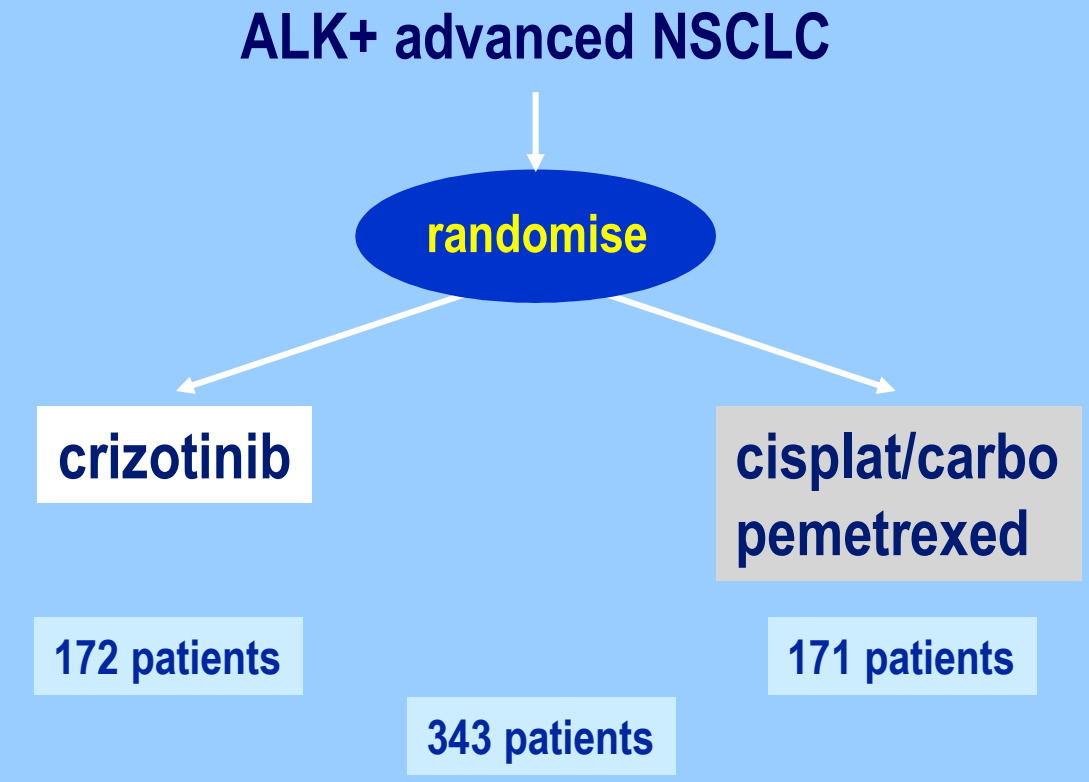
ALK+ advanced NSCLC & brain metastases

	brain mets previously untreated	no brain mets
no. pts	166	613
PFS median	**5.9m** (4.2-6.9)	**8.8m** (7.9-9.9)
6 m OS	**77%** (67-85)	**85%** (81-87)

Brain metastases in patients with ALK-positive NSCLC

Costa et al 2015, J Clin Oncol; 33 (17): 1881-1888

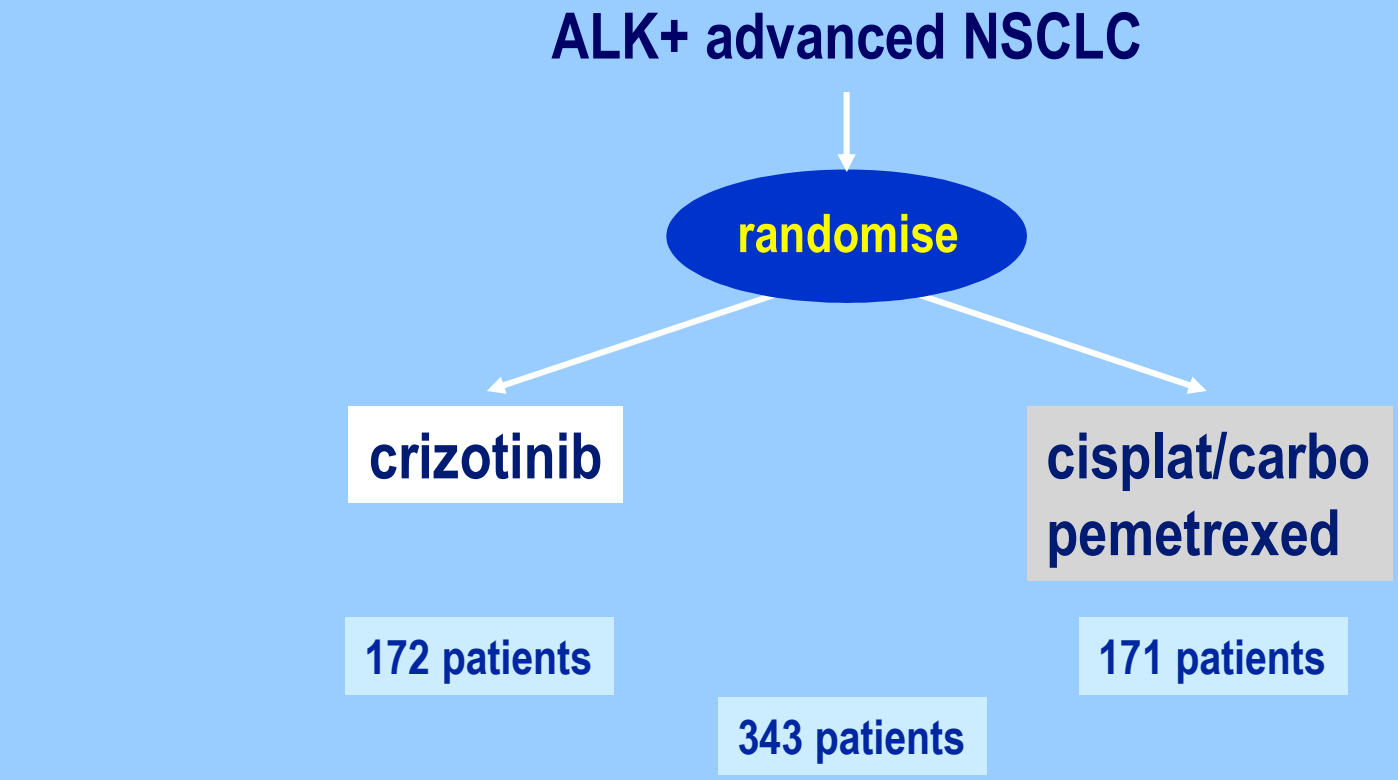
PROFILE trial 1014



Brain metastases in patients with ALK-positive NSCLC

Solomon et al 2016, J Clin Oncol; 34 (24), 2858-65

PROFILE trial 1014



crizotinib		cisplat/carbo pemetrexed	
BM present	BM absent	BM present	BM absent
39	132	40	131

brain metastases previously treated

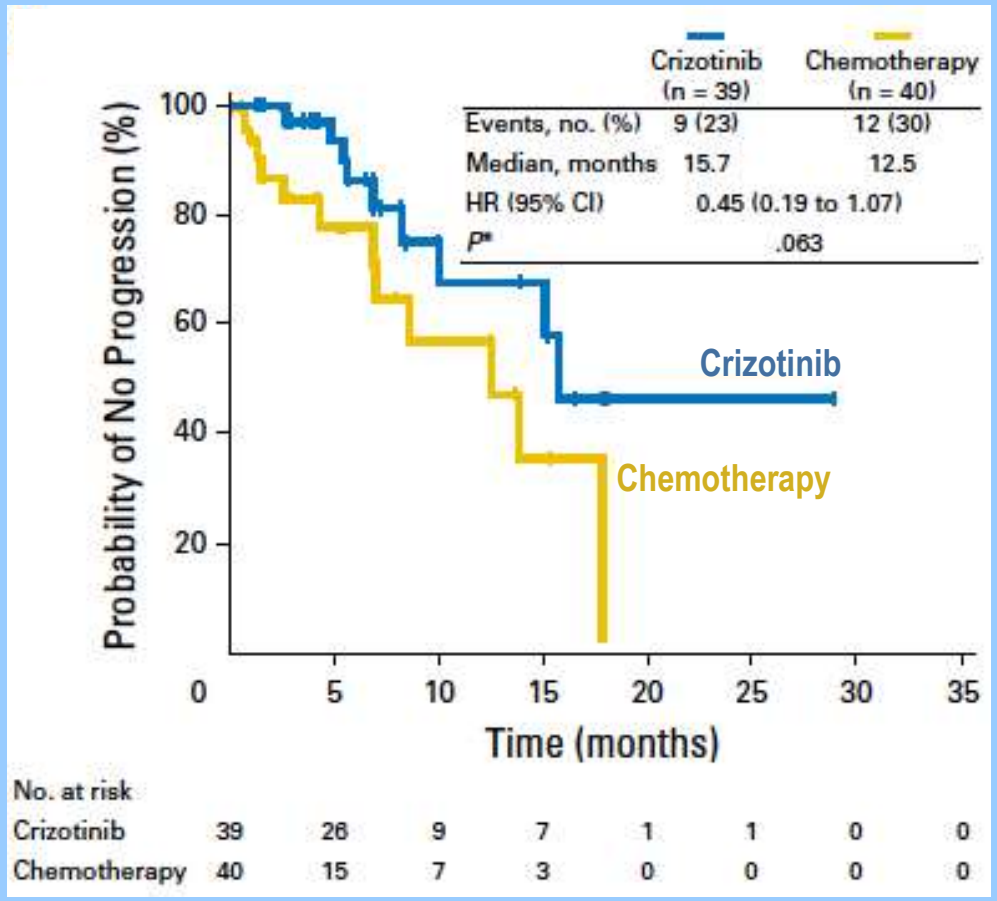
BM - brain metastases

Brain metastases in patients with ALK-positive NSCLC

Solomon et al 2016, J Clin Oncol; 34 (24), 2858-65

PROFILE trial 1014 (crizotinib vs chemotherapy)

intracranial progression free survival of pts with treated BM



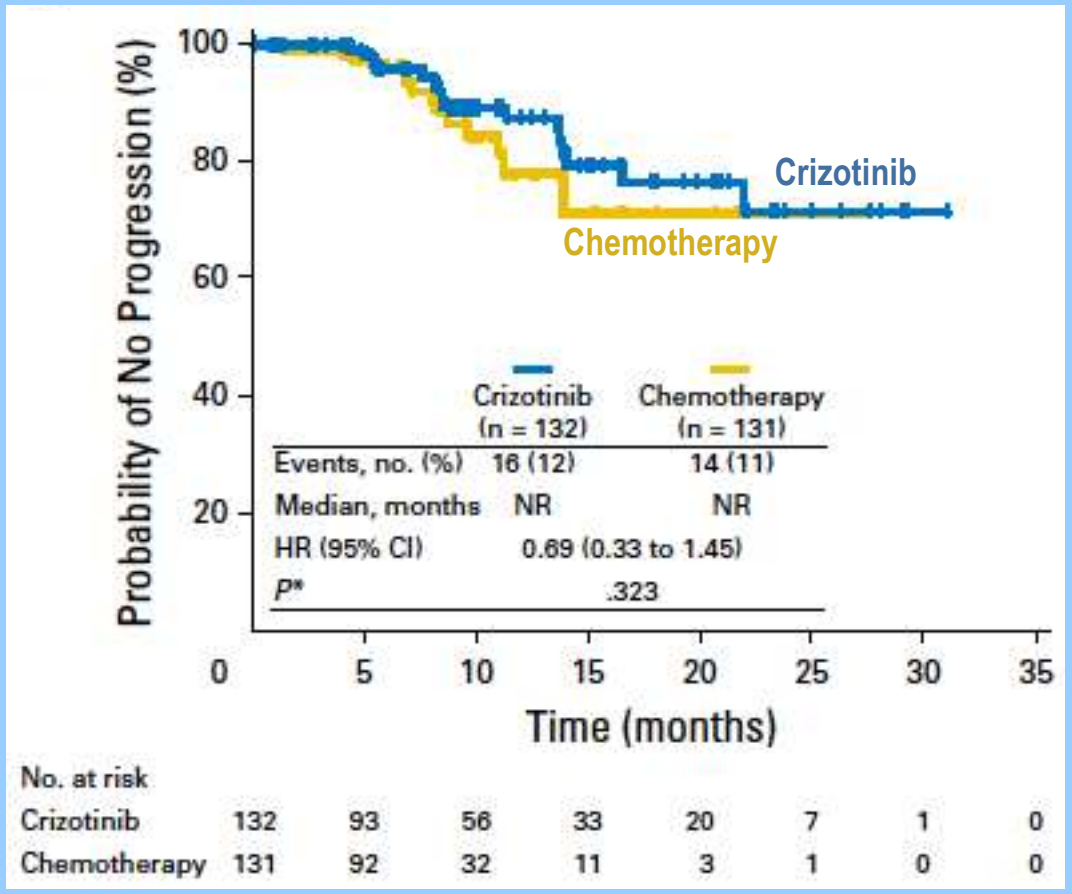
Brain metastases in patients with ALK-positive NSCLC

Solomon et al 2016, J Clin Oncol; 34 (24), 2858-65

BM - brain metastases

PROFILE trial 1014 (crizotinib vs chemotherapy)

intracranial progression free survival of pts without BM

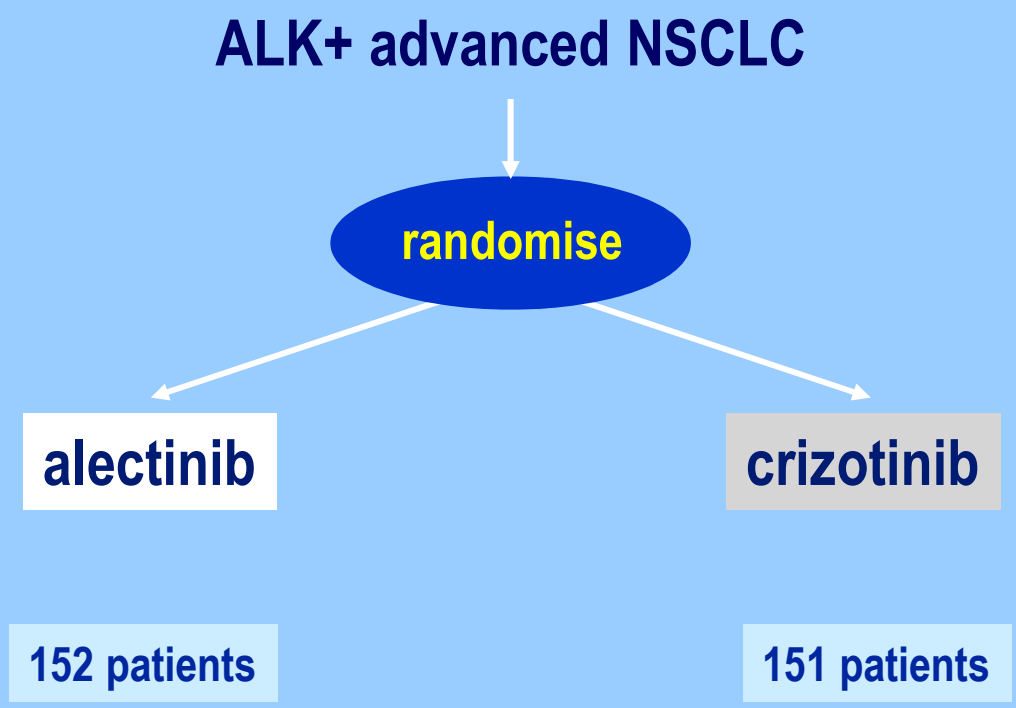


Brain metastases in patients with ALK-positive NSCLC

Solomon et al 2016, J Clin Oncol; 34 (24), 2858-65

BM - brain metastases

Alectinib vs Crizotinib trial

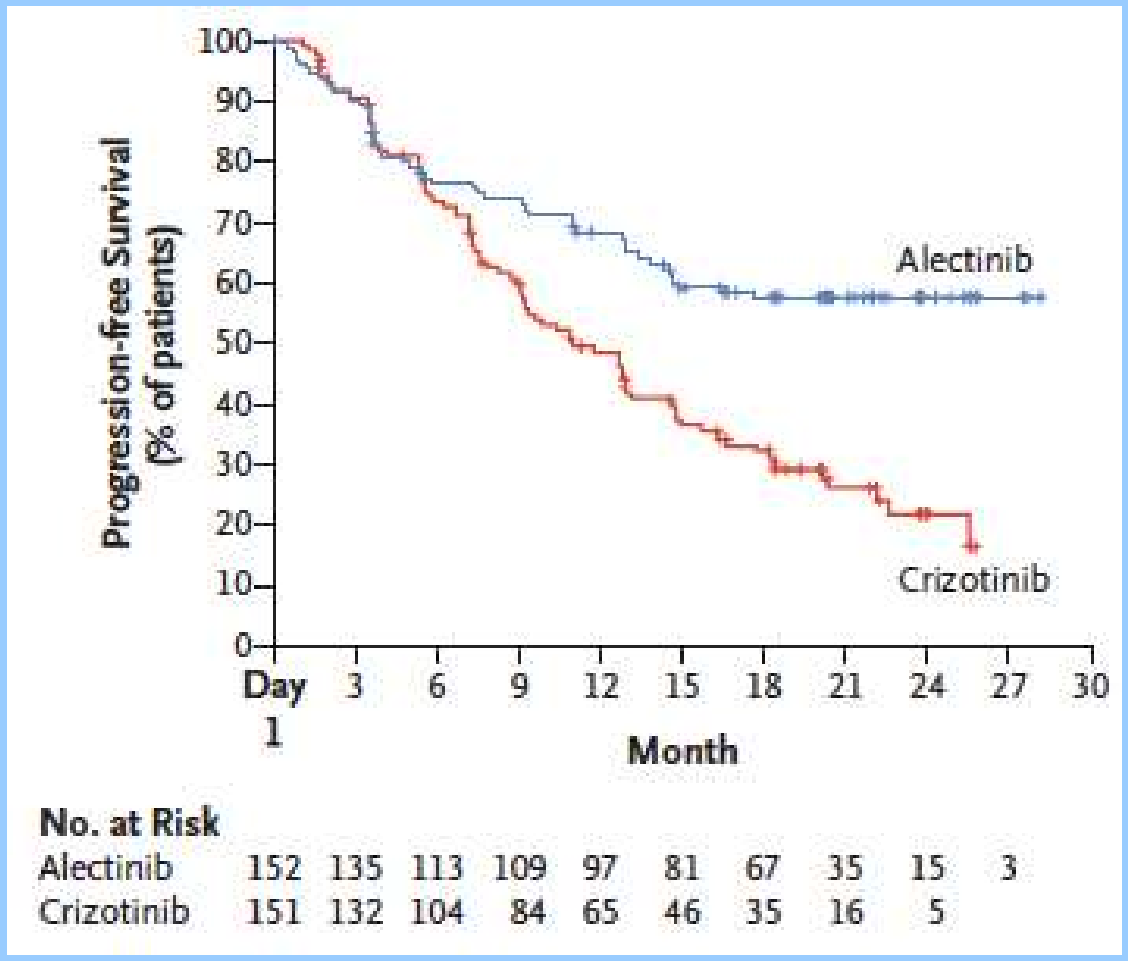


Brain metastases in patients with ALK-positive NSCLC

Peters et al 2017, N Engl J Med; 377: 829-38

Alectinib vs Crizotinib trial

progression free survival

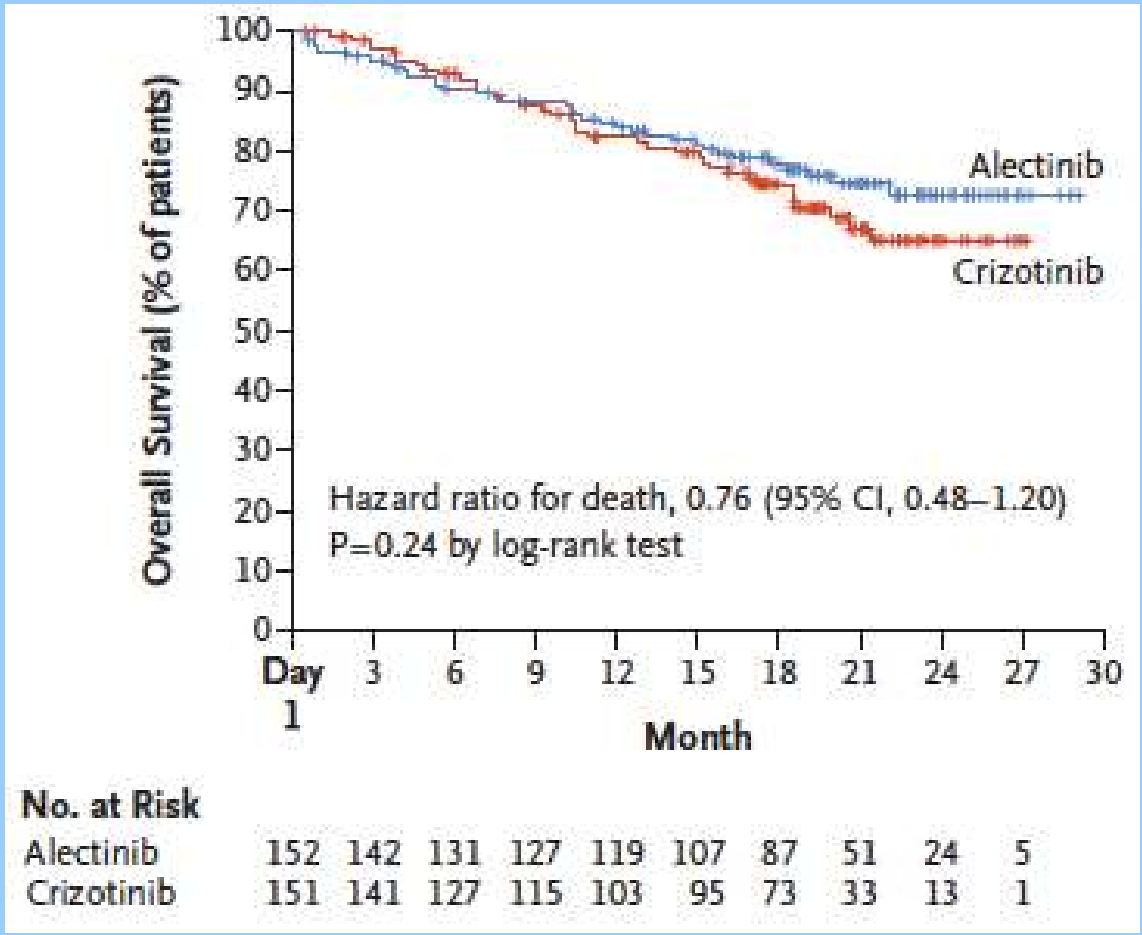


Brain metastases in patients with ALK-positive NSCLC

Peters et al 2017, N Engl J Med; 377: 829-38

Alectinib vs Crizotinib trial

survival

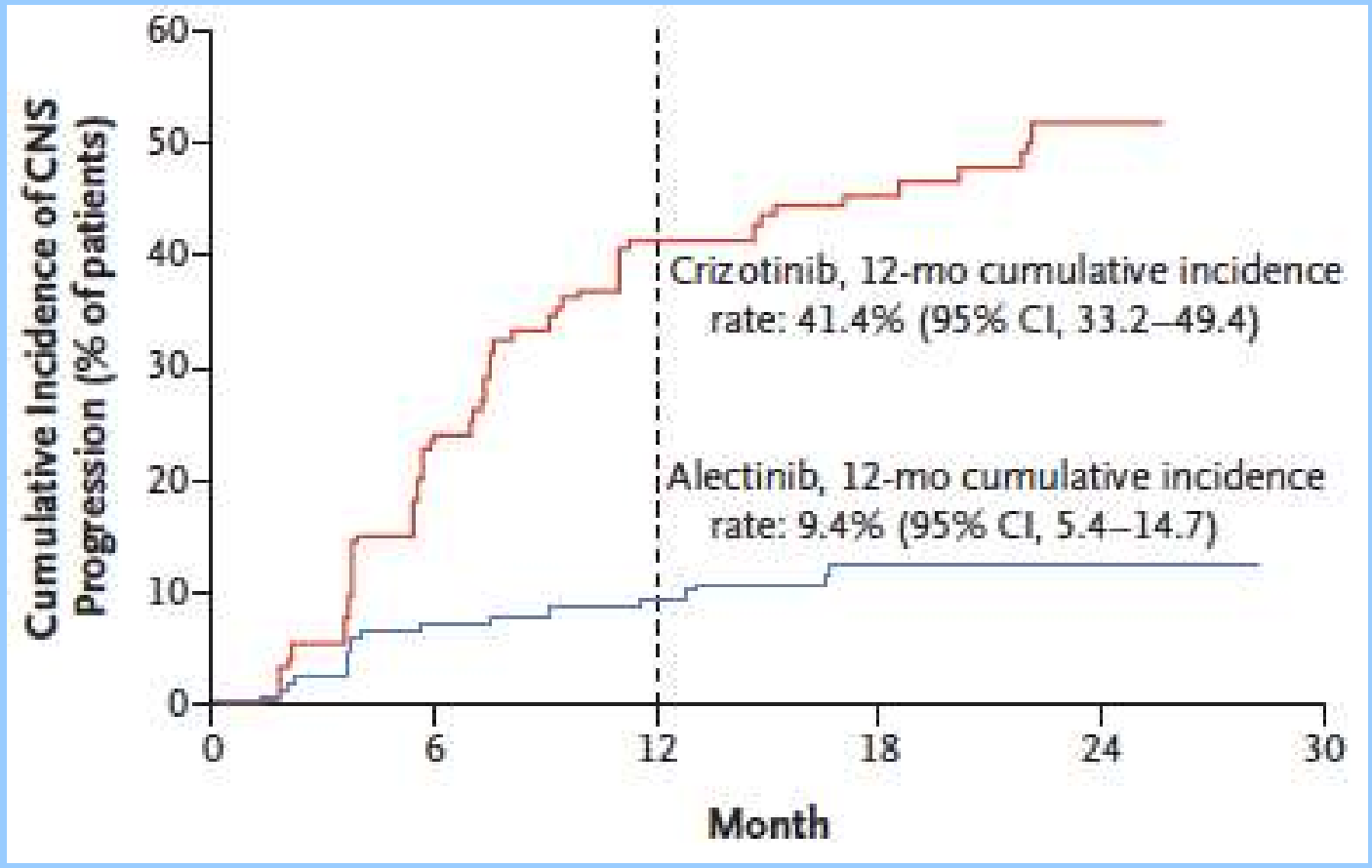


Brain metastases in patients with ALK-positive NSCLC

Peters et al 2017, N Engl J Med; 377: 829-38

Alectinib vs Crizotinib trial

cumulative incidence of CNS progression



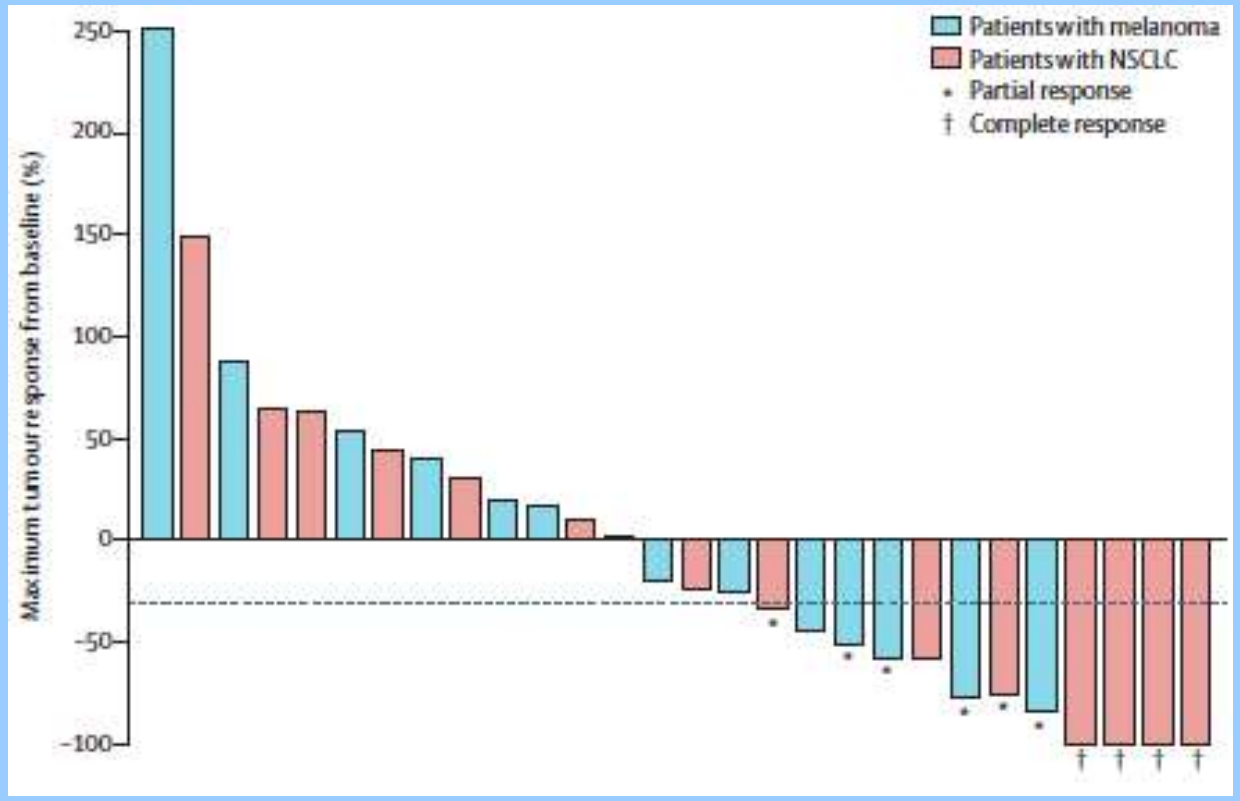
Brain metastases in patients with ALK-positive NSCLC

Peters et al 2017, N Engl J Med; 377: 829-38

Pembrolizumab in melanoma

Phase II study

patients with untreated brain metastases from melanoma (18) & NSCLC (34)



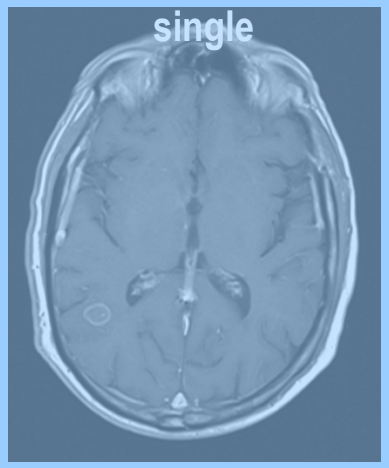
Immune checkpoint inhibitors in patients with brain metastases

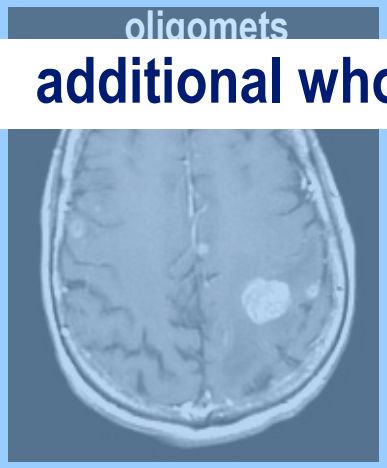
Goldberg et al 2016, Lancet Oncol; 17: 976–83

Evidence base

Matrix - radiotherapy options

No. met's	prognosis 1^0 tumour timing
single oligomets multiple	responsive to systemic treatment

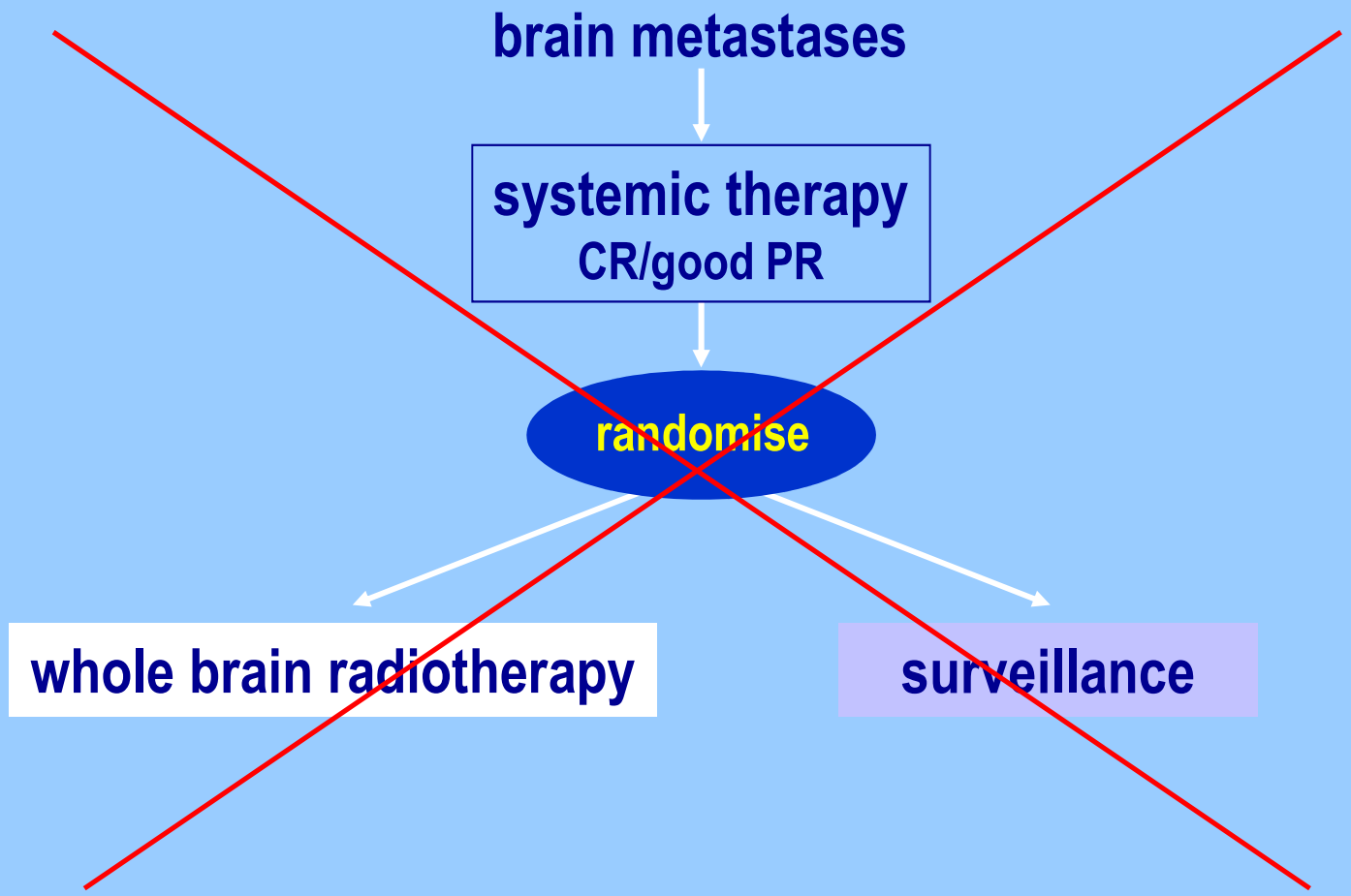




additional whole brain radiotherapy?

Radiotherapy in the management of brain metastases

Tumours responsive to systemic treatment

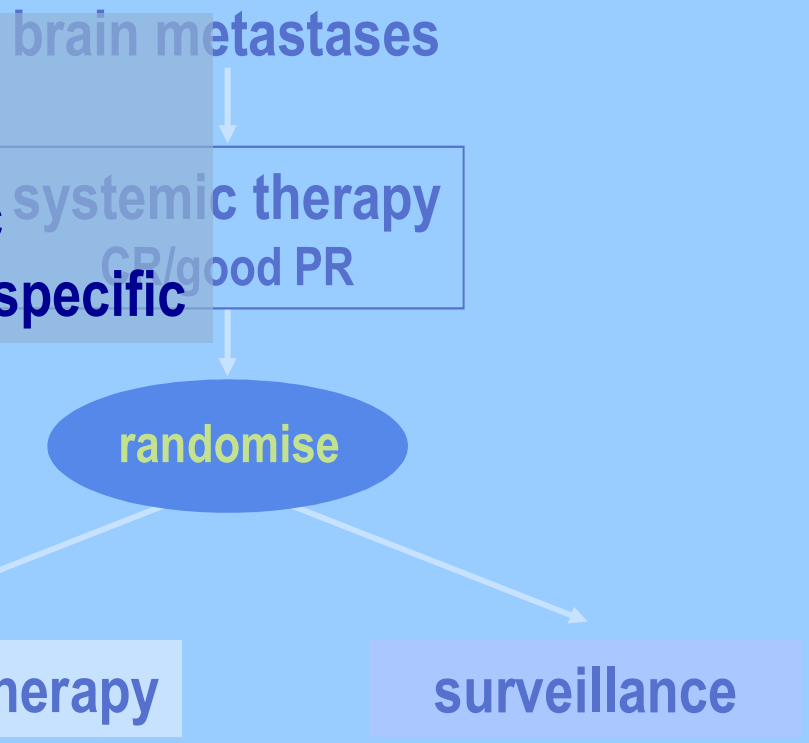


Role of radiotherapy in responsive tumours

Tumours responsive to systemic treatment

Potential trial design

- Tumour specific
- Biomarker specific
- Timing of disease specific

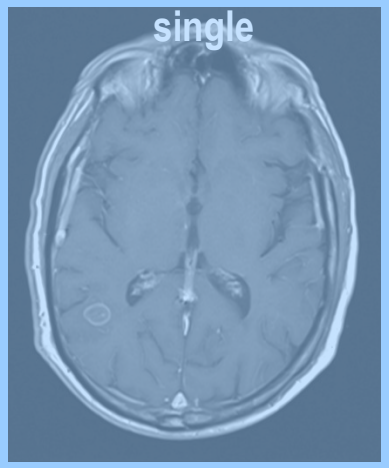


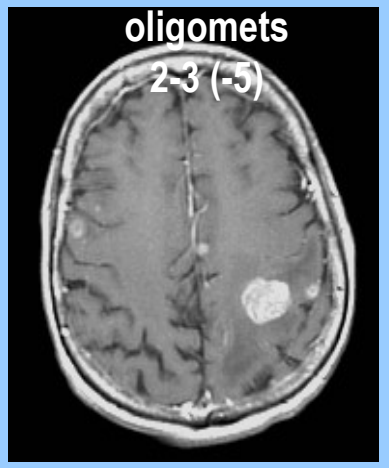
Role of radiotherapy in responsive tumours

Evidence base

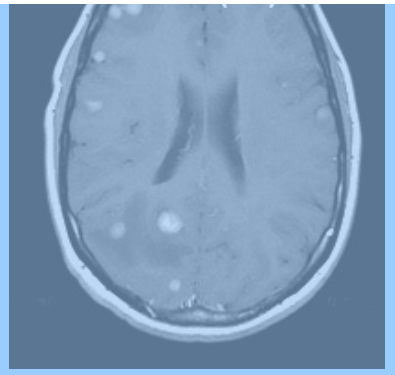
Matrix - radiotherapy options

No. met's	prognosis 1^0 tumour timing
single	
oligomets	responsive to systemic treatment
multiple	



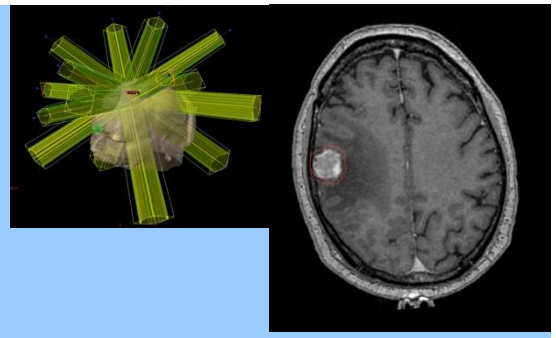


additional radiosurgery ?



Radiotherapy in the management of brain metastases

Synchronous oligometastases in non-small cell lung cancer



1 - 4 brain metastases

oligometastases

randomise

radiosurgery (SRS) (49)

chemotherapy

chemotherapy (49)

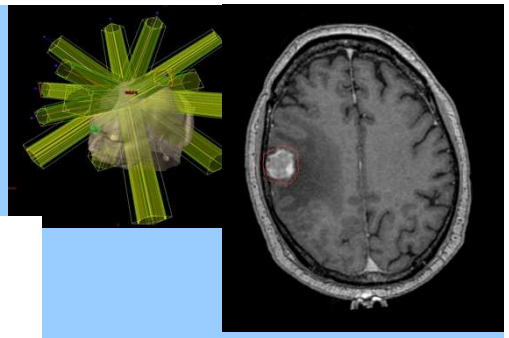
98 patients - synchronous asymptomatic brain metastases

Samsung Medical Centre, Seoul 2008 - 13

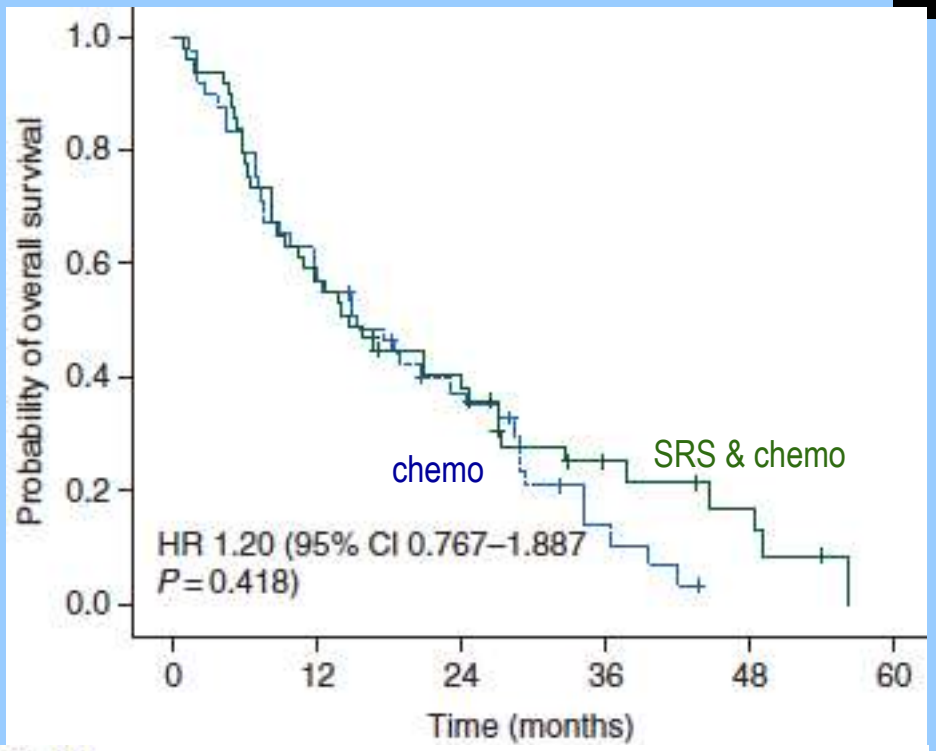
Radiosurgery for synchronous brain oligometastases

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

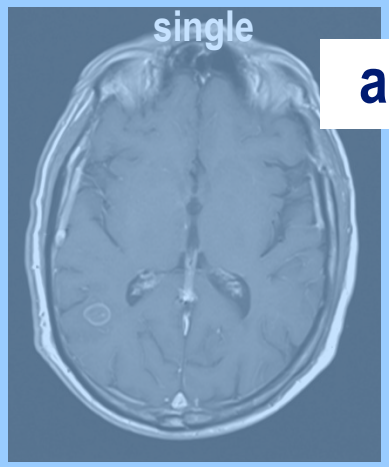
Radiosurgery for synchronous brain oligometastases

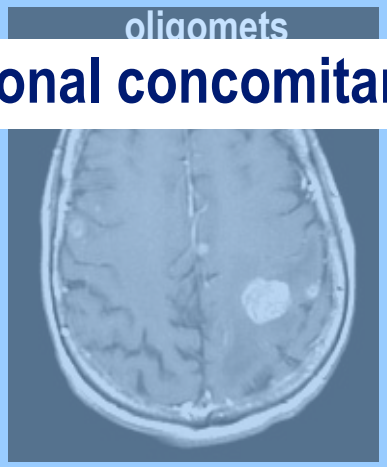
Lim et al 2015, Annals of Oncology 26: 762–768

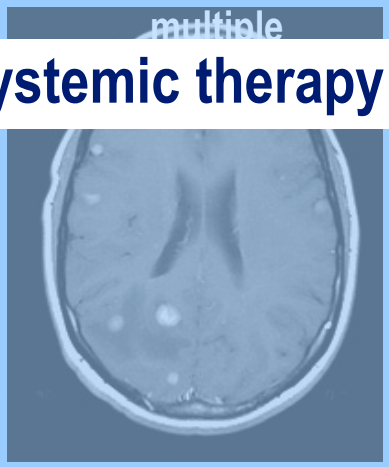
Evidence base

Matrix - radiotherapy options

No. met's	prognosis 1^0 tumour timing
single oligomets multiple	treated with radiotherapy



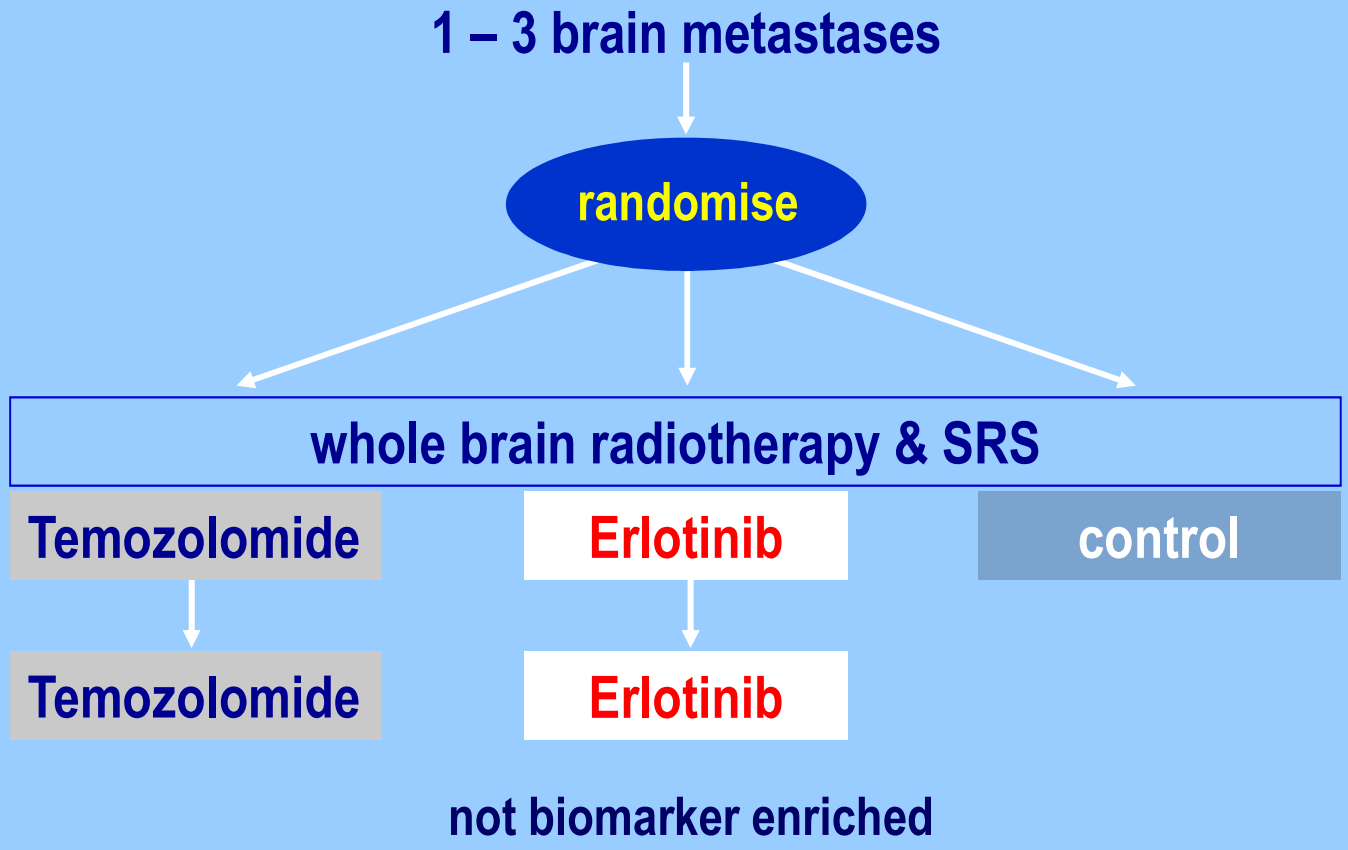




additional concomitant systemic therapy ?

Radiotherapy in the management of brain metastases

non-small cell lung cancer brain metastases
RTOG 0320

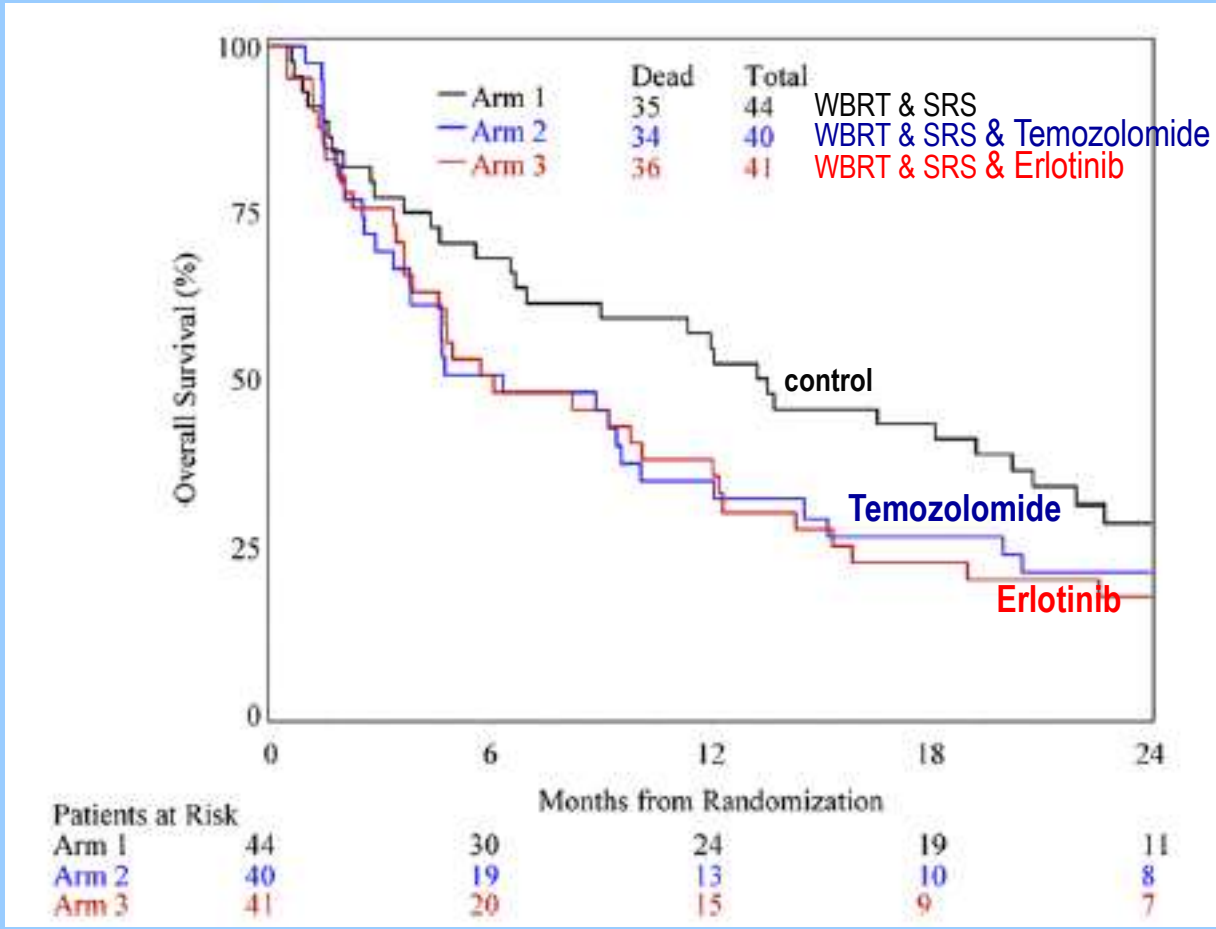


not biomarker enriched

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

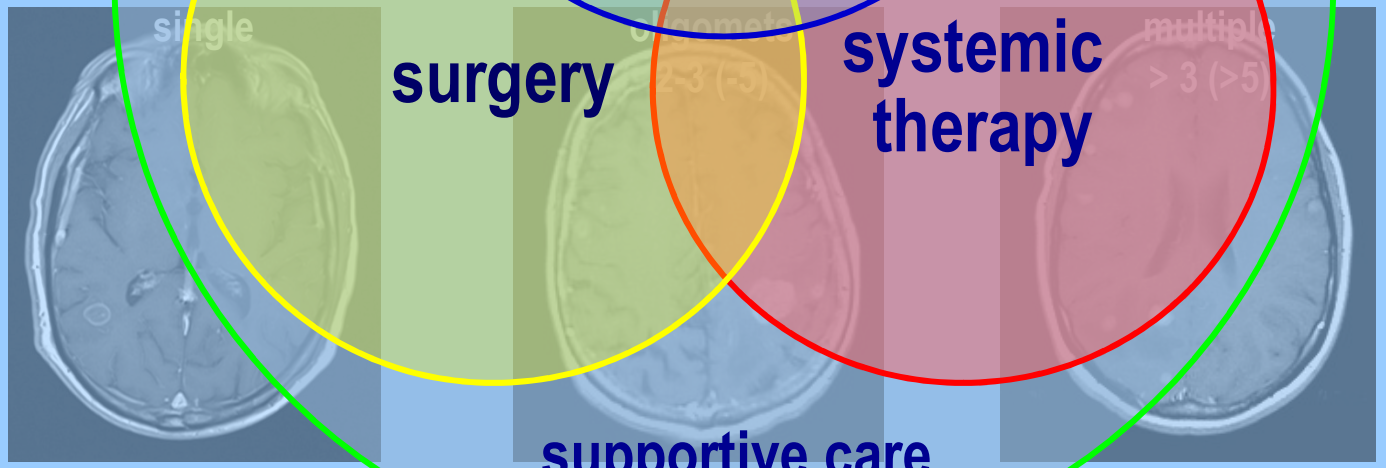


Additional systemic therapy in NSCLC brain metastases

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
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michael.brada@liverpool.ac.uk

UNIVERSITY OF LIVERPOOL

The Clatterbridge Cancer Centre NHS
NHS Foundation Trust

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

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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

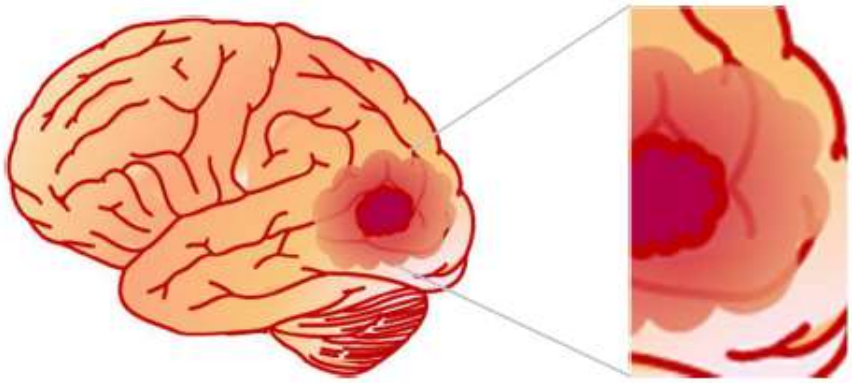
Epilepsy in brain tumor patients

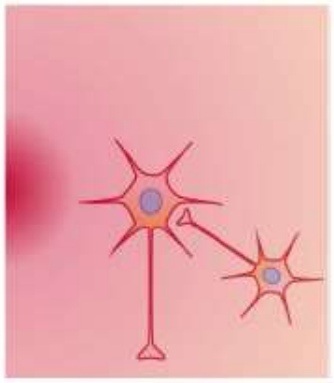
- Approx. 30-50% of all brain tumor patients are affected by seizures
  => frequently first clinical manifestation of a brain tumor

- Seizures are particularly common in slowly growing tumors and tumors of glial origin

• **DNET**	**100%**
• **Ganglioglioma**	**80-90%**
• **Low-grade glioma**	**70-80%**
• **Meningioma**	**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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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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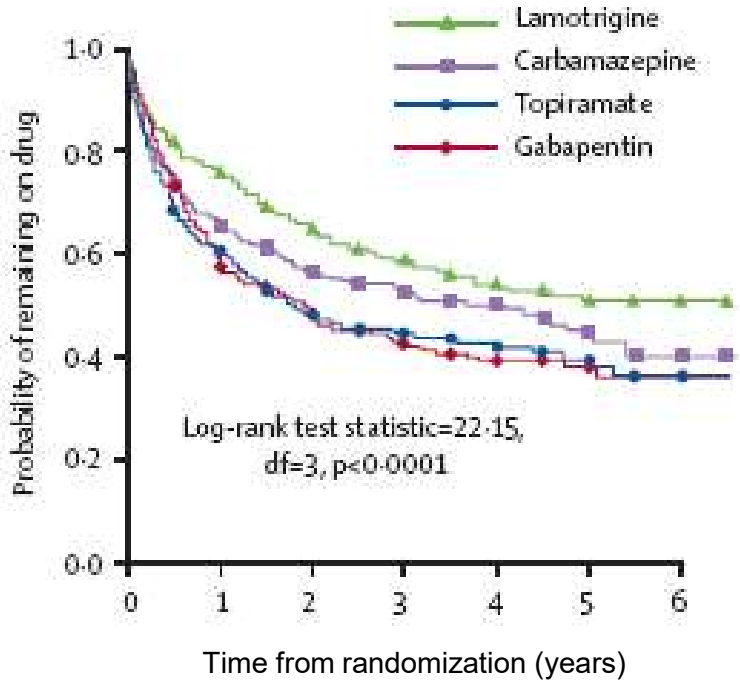
How to choose the best AED



„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

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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

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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):

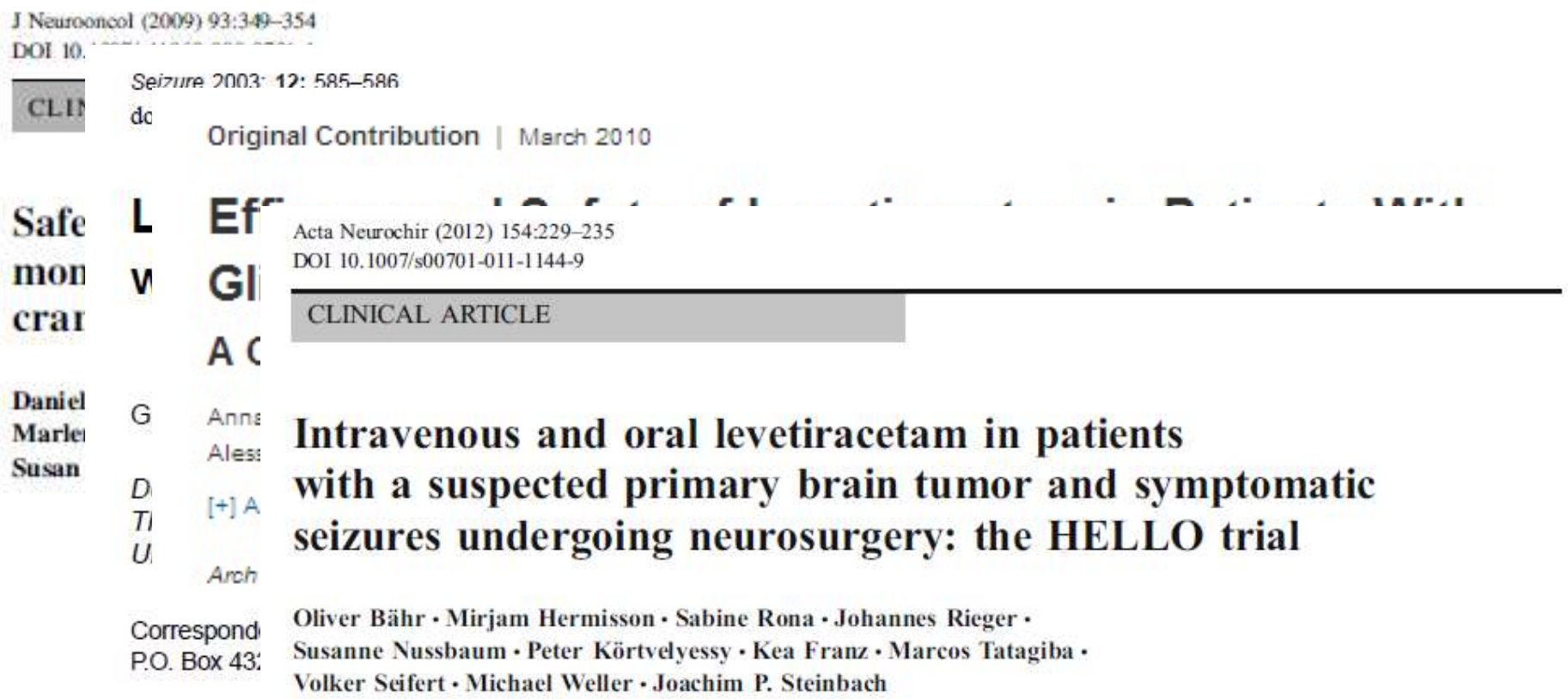
CBZ, GBP, LTG, LEV, OXC, Pb, PHT, PRM, TPM, VPA, ZON

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

Original Contribution | March 2010

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

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**: (very) active, moderate tolerability, teratogenicity!

Overview

- Management of pain
- Antiemesis
- Treatment of seizures
- **Steroids for the treatment of tumor-associated edema**

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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

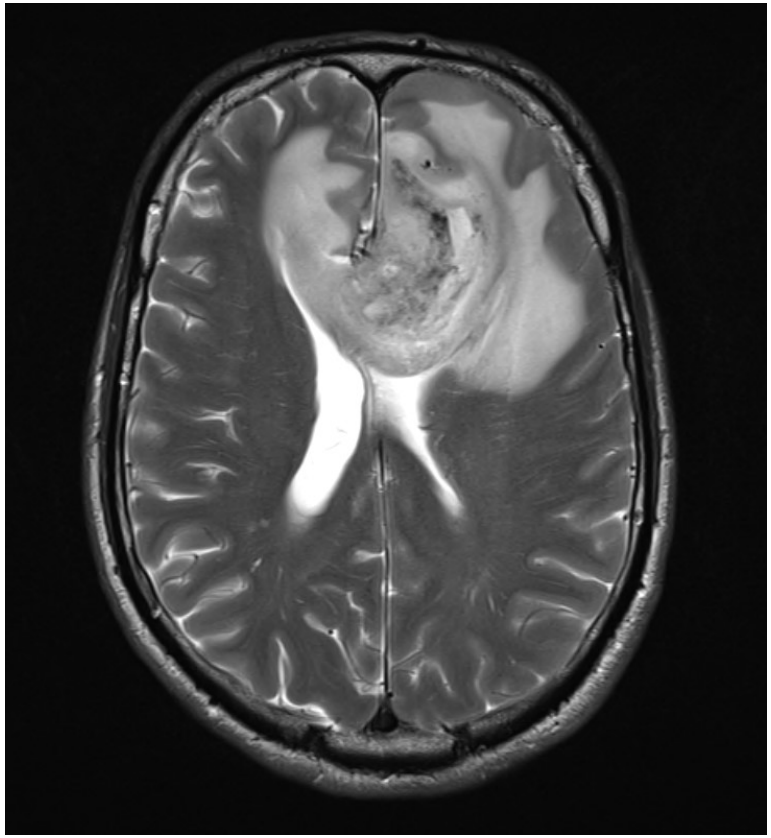
THE surgical management of craniopharyngiomas, whether radical or conservative, has always been hazardous. Gordy, Peet and Kahn[1] reported a series of 51 cases in which the operative mortality was 41 per cent, due principally to severe hypothalamic reactions incident to the surgical manipulation. Grant,[2] in summarizing the results of 40 operations on 30 patients, found a case mor-

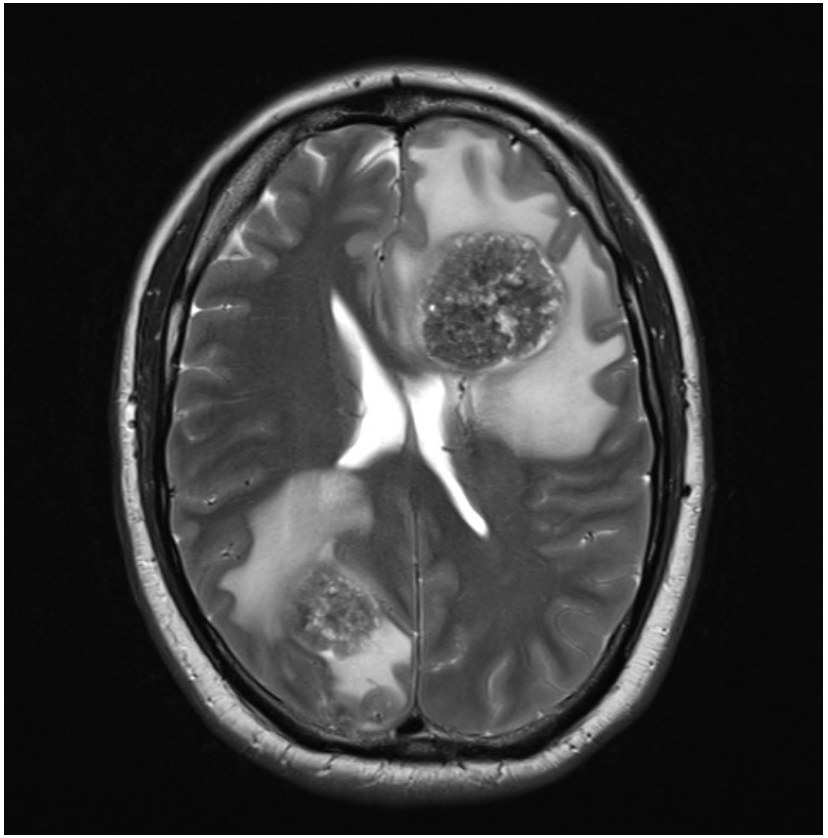
pacity of the pituitary adrenal system were, of course, not employed.

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





Anti-edematous therapy

- **70-100% of all brain tumor patients receive steroids during the course of the disease**

- **Commonly rapid effect on tumor-surrounding edema**

  => reduction of mass effect

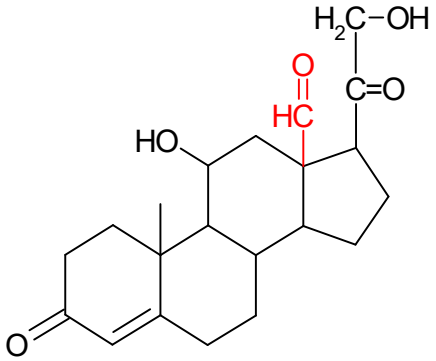
  => considerable clinical improvement is possible

  => maintenance of an acceptable quality-of-life

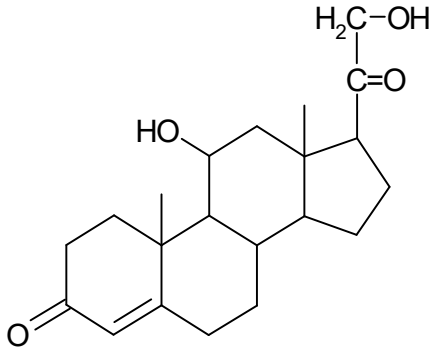
- **Steroid activity may decrease over time**

Physiological steroid hormones

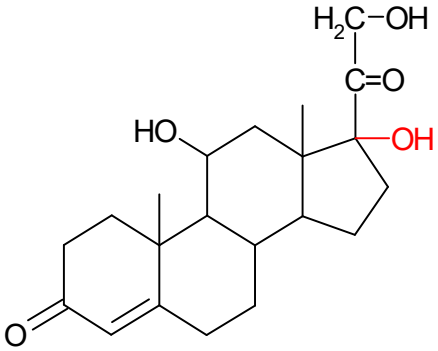
glucocorticoid activity



aldosterone



corticosterone



cortisol/hydrocortisone

mineralocorticoid activity

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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

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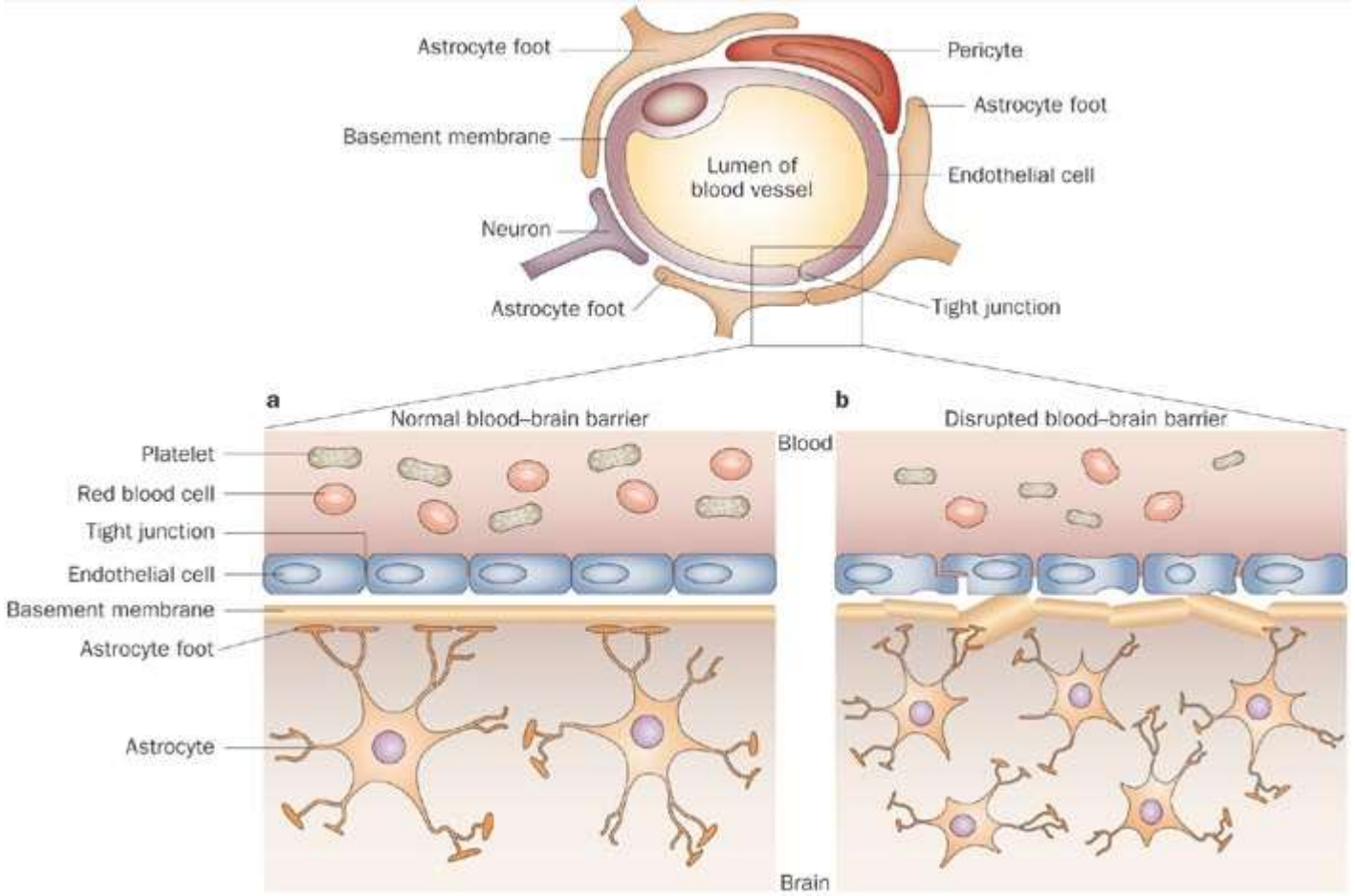
Brain tumors: vasogenic edema



Tumor-mediated mechanisms:

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

Gerstner et al. Nat Rev Clin Oncol 2009

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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

Steroids: side effects

- **Hyperglycemia ("steroid diabetes": > 50% of all patients)**

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JOURNAL OF CLINICAL ONCOLOGY

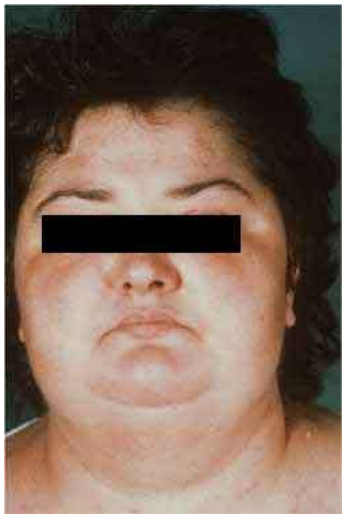
ORIGINAL REPORT

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**



ESTRO School

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

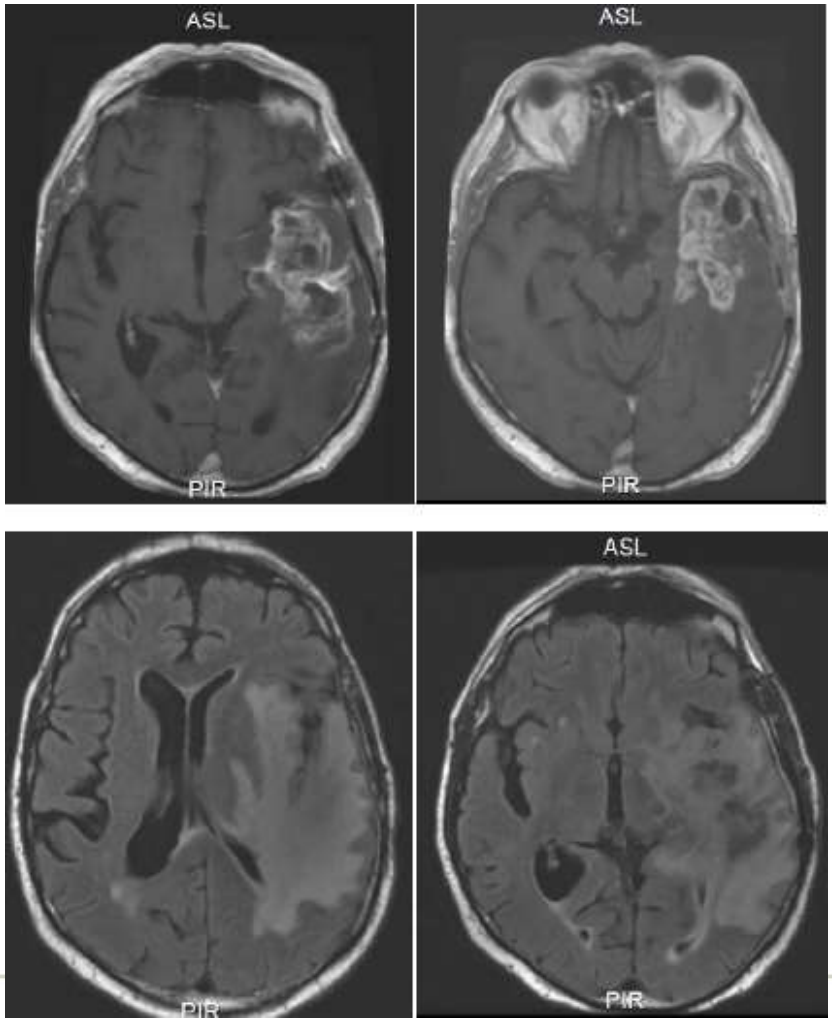
  => Watch for signs of hypocortisolism!

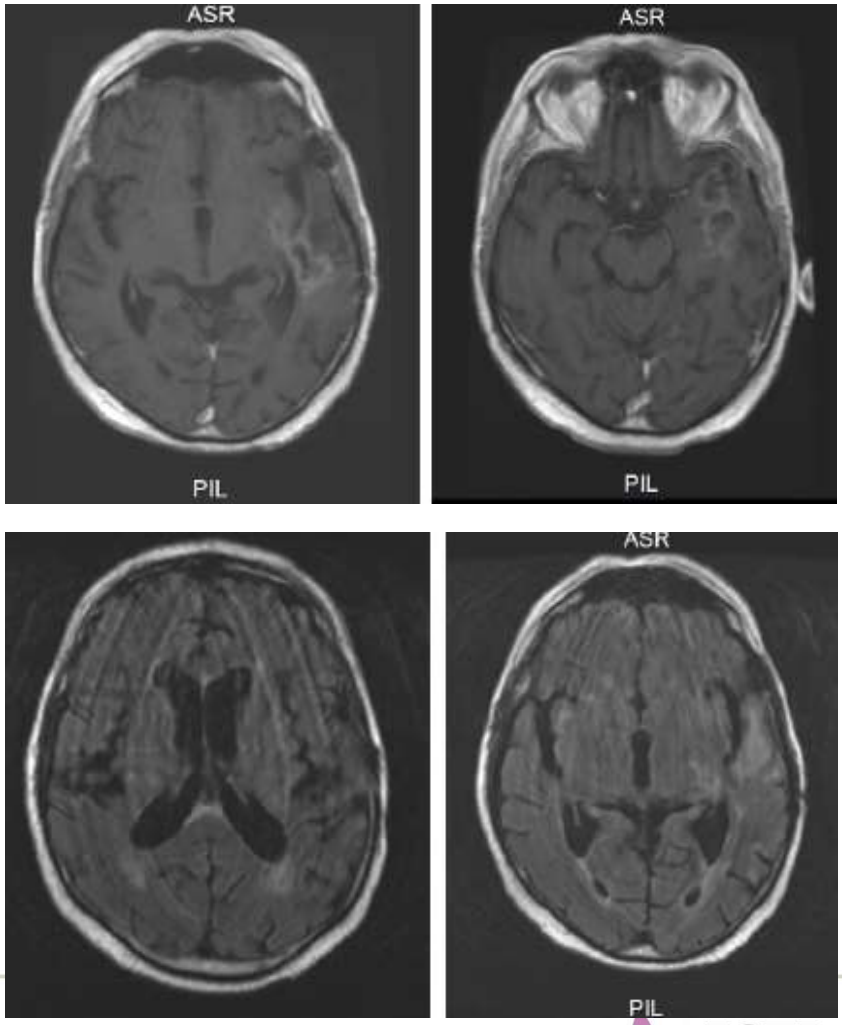
  - Nausea, vomiting, headaches
  - Myalgia, hypotension

- Manifest hypocortisolism: substitution with hydrocortisone

  => average daily dose: 20-30 mg

Bevacizumab





Recurrent glioblastoma

4 x Bev

ESTRO School

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]

VOLUME 31 · NUMBER 9 · MARCH 20 2013

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

ESTRO School

ESTRO School
Multidisciplinary management of brain tumours

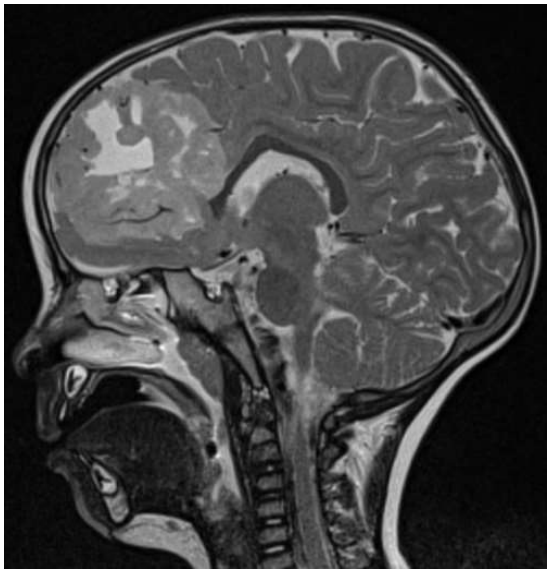
Cases

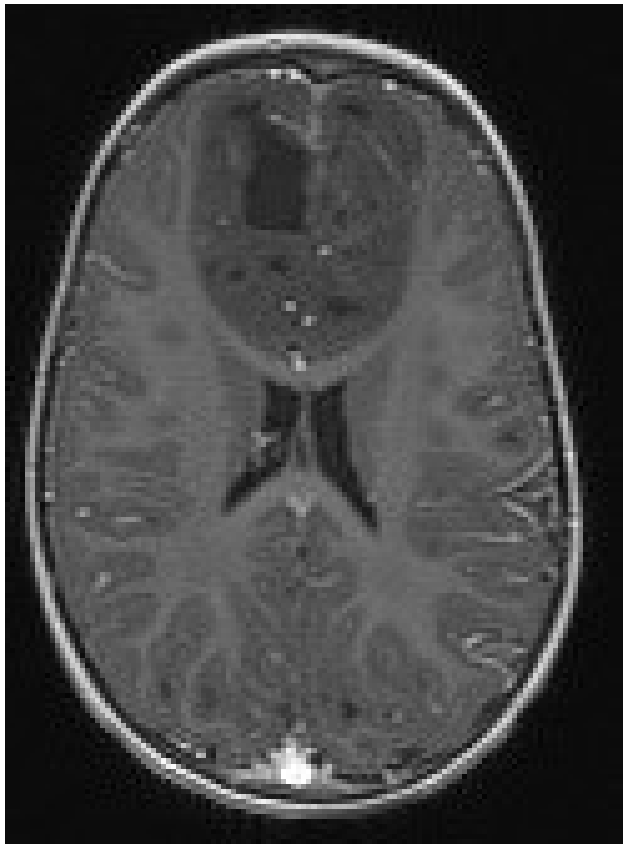
Karin Dieckmann, Radiation Oncologist

Johannes Gojo, Pediatric Oncologist

Case 1

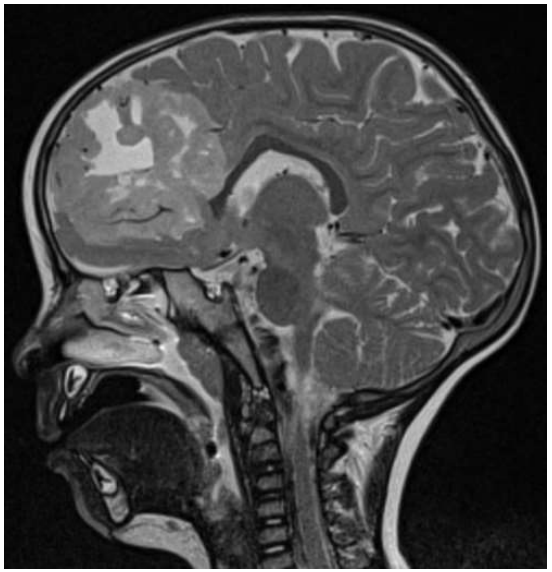
- female
- 2 years 2 months
- Seizure

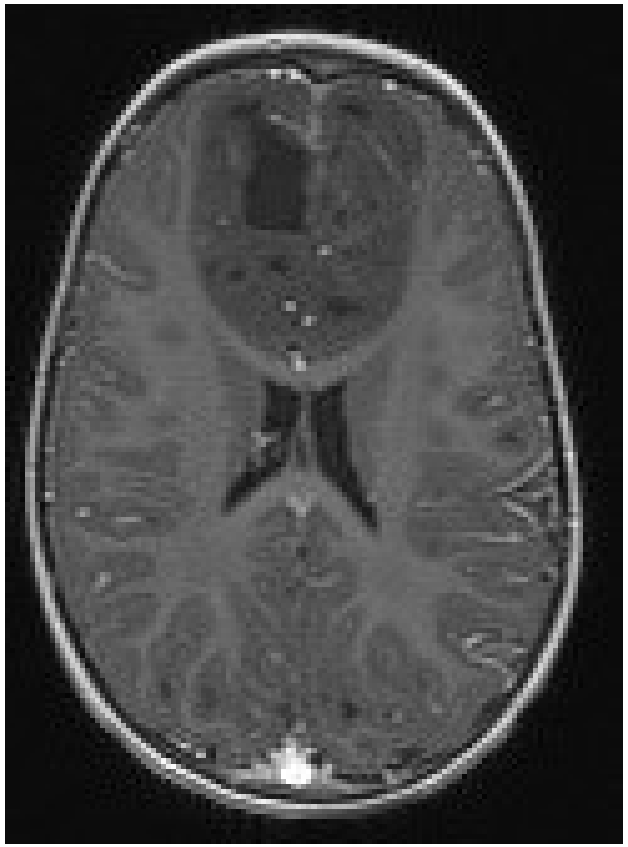




ETANTR/ETMR

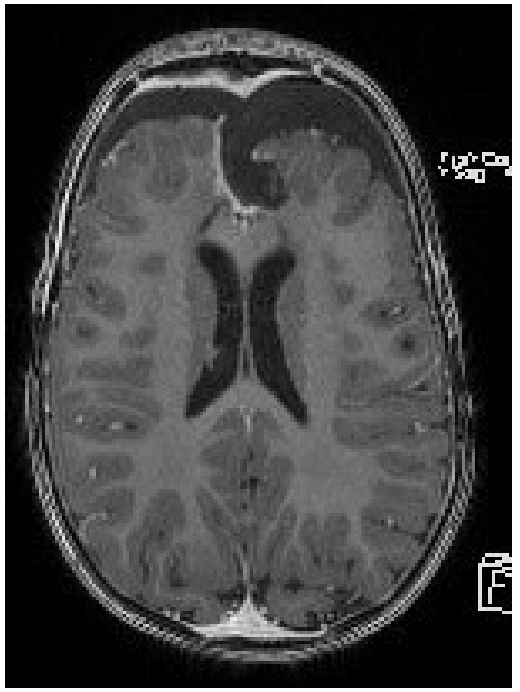
- ETMR = Embryonal tumors with multilayered rosettes
- Characteristic focal amplification of C19mC (chromosome 19)





ETANTR/ETMR

- Biopsy
- 2 blocks CTX :PEI
- gross total resection

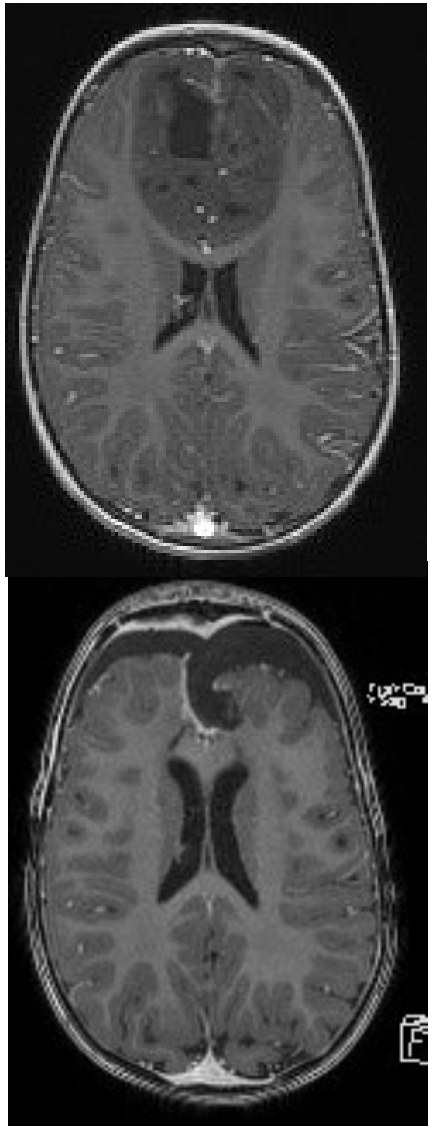


Mozes P., Hauser P., Hortobagyl T. et al., Evaluation of the good tumor response of embryonal tumor with abundant neuropil and true rosettes (ETANTR). J Neurooncol (2016) 126:99-105

ETANTR/ETMR

Proton therapy

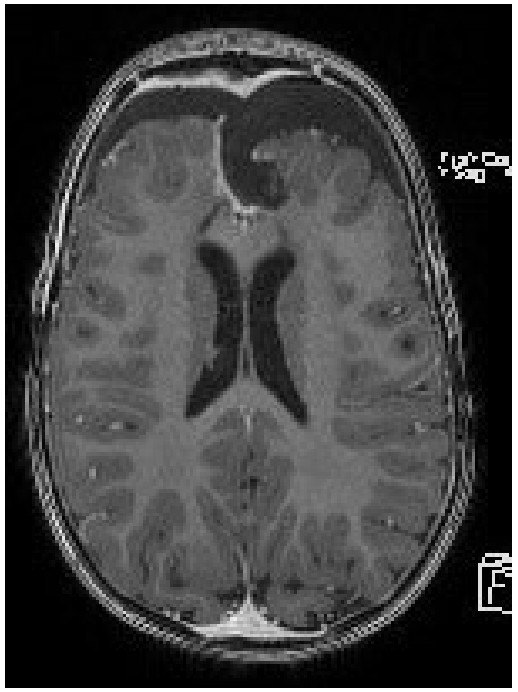
- Focal irradiation (54 Gy)
- concomitant temozolomide (75mg/m2)
- 12 cycles temozolomide (150-200mg/m2)
- + 4 weekly i.th. mit VP-16



Mozes P., Hauser P., Hortobagyl T. et al., Evaluation of the good tumor response of embryonal tumor with abundant neuropil and true rosettes (ETANTR). J Neurooncol (2016) 126:99-105

ETANTR/ETMR

- Biopsy -> 2 blocks CTX -> gross total resection



Proton therapy

- Focal irradiation (54 Gy)
- concomitant temozolomide (75mg/m2)
- 12 cycles temozolomide (150-200mg/m2)
- + 4 weekly i.th. mit VP-16

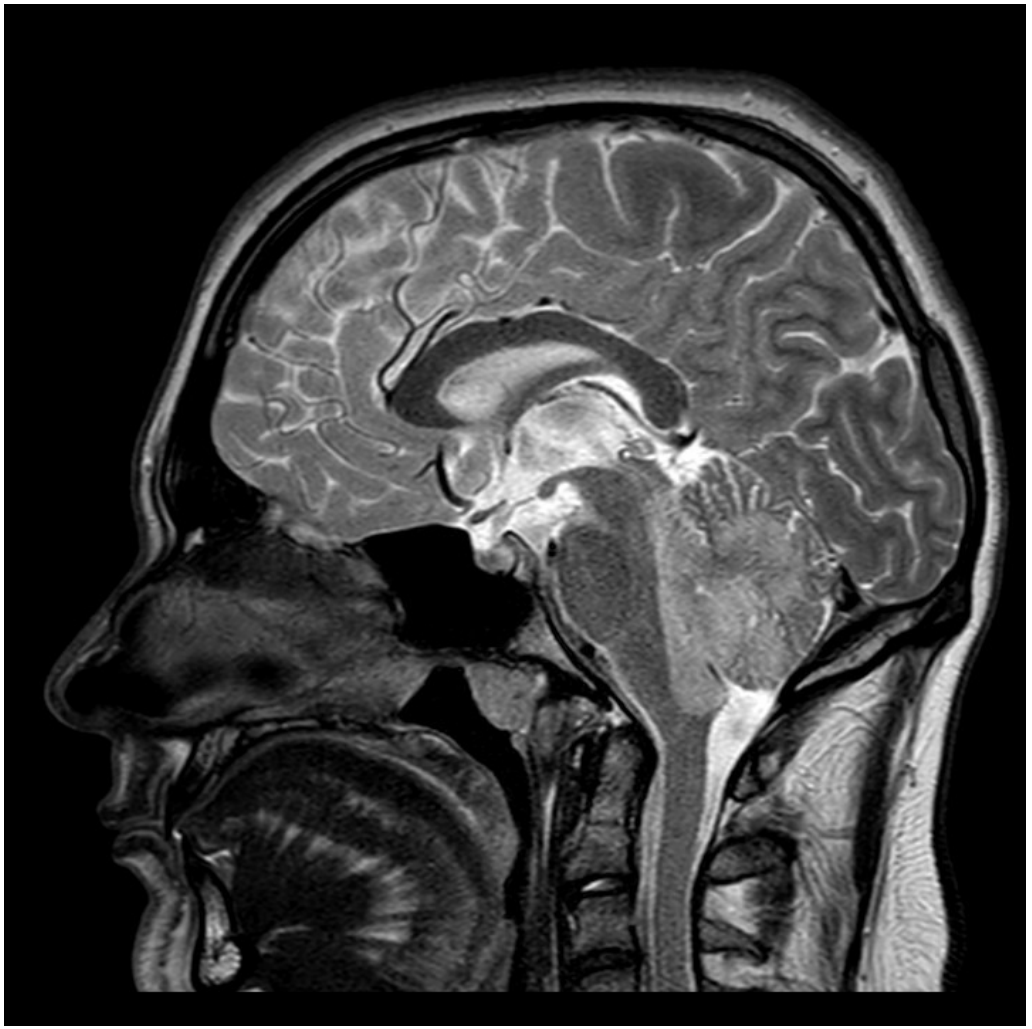
Still in remission after 18 months

visits kindergarten and shows adequate neurological development

Mozes P., Hauser P., Hortobagyl T. et al., Evaluation of the good tumor response of embryonal tumor with abundant neuropil and true rosettes (ETANTR). J Neurooncol (2016) 126:99-105

Medulloblastoma

- Male
- 16 years
- Nausea and vomiting

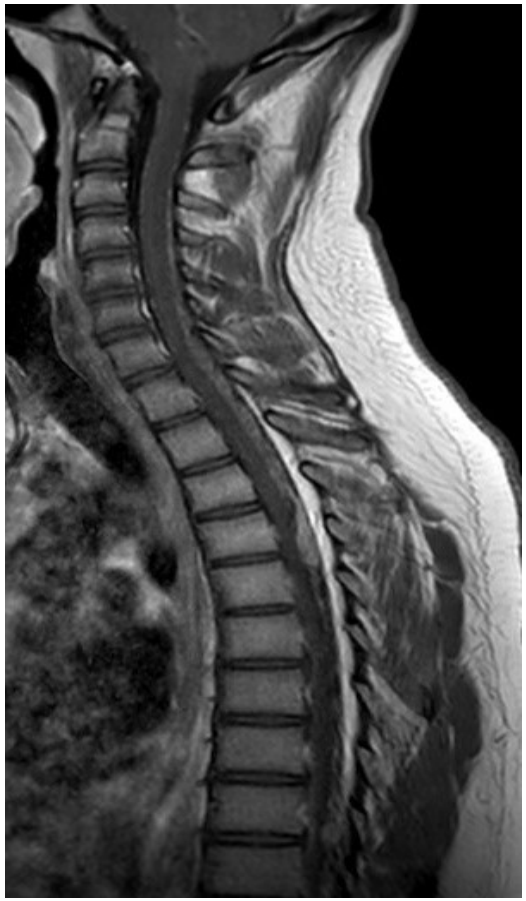


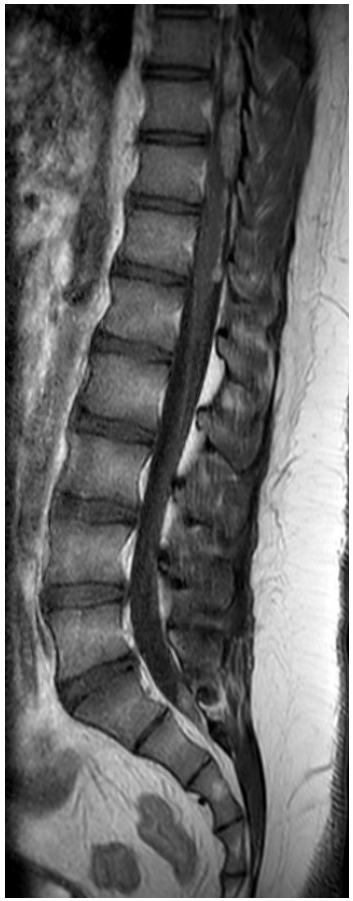
Medulloblastoma

Staging und Biology

- Metastases – M1-3
- Molecular Subgroup G4
- No MYC amplification

HIGH RISK

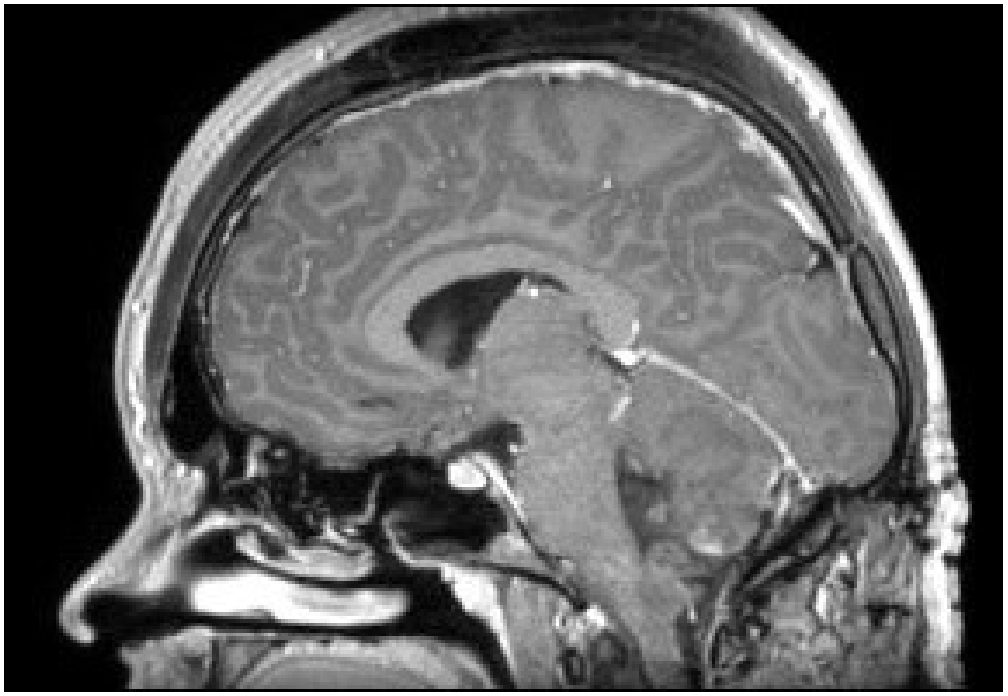




OP -> induction CTX -> RTX -> maintenance CTX

Medulloblastoma

- Resection of PF tumor
- Start with Chemotherapy
- intrathekal Chemotherapy



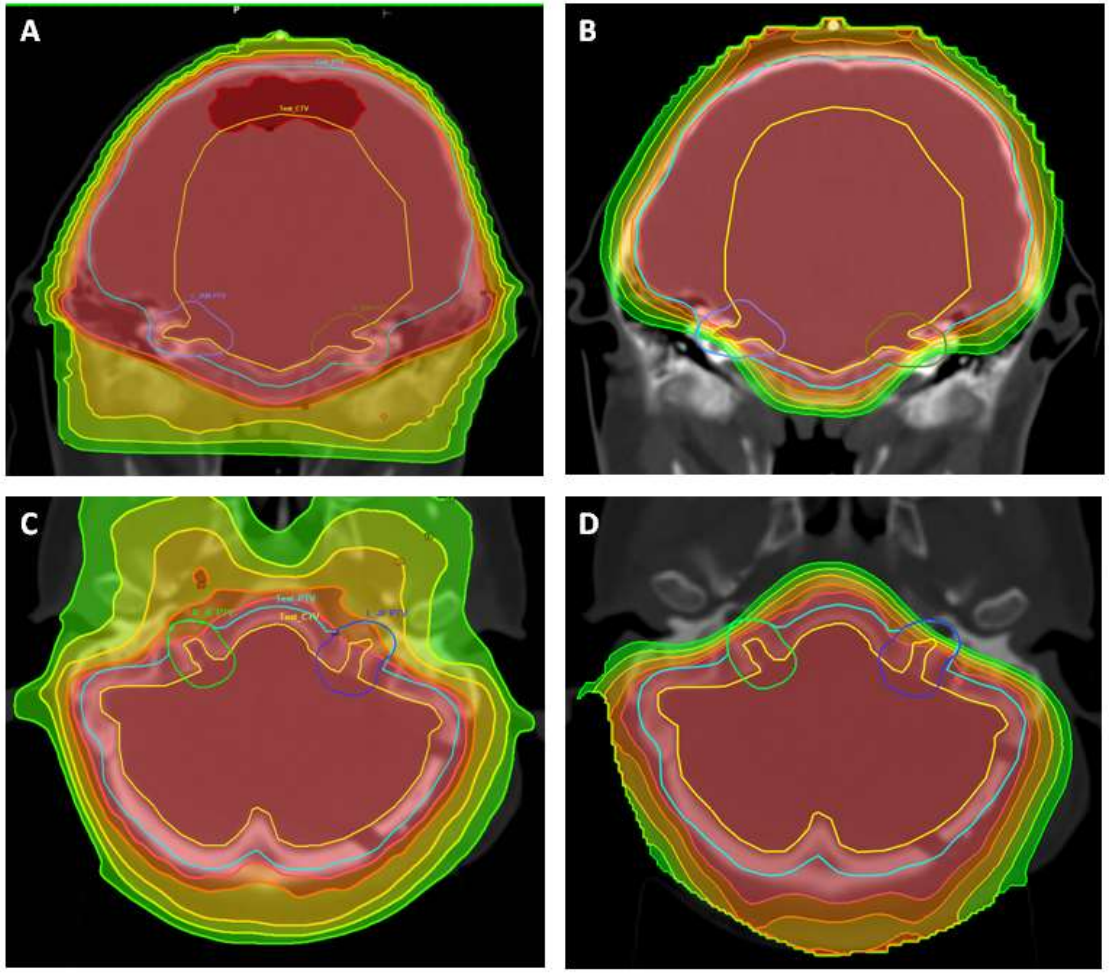
- Radiotherapy - CSI
- Proton therapy

- Less toxicity to vertebral bone marrow if in adolescents that have reached the final height the vertebral bodies can be spared from irradiation resulting in better tolerance of the chemotherapy (subsequent chemotherapy !)
- Less longterm toxicity on cervical/thoracic/abdominal organs

- **Highly Conformal Craniospinal Radiotherapy Techniques Can Underdose the Cranial Clinical Target Volume if Leptomeningeal Extension through Skull Base Exit Foramina is not Contoured.**

- Noble DJ, Ajithkumar T, Lambert J, Gleeson I, Williams MV, Jefferies SJ

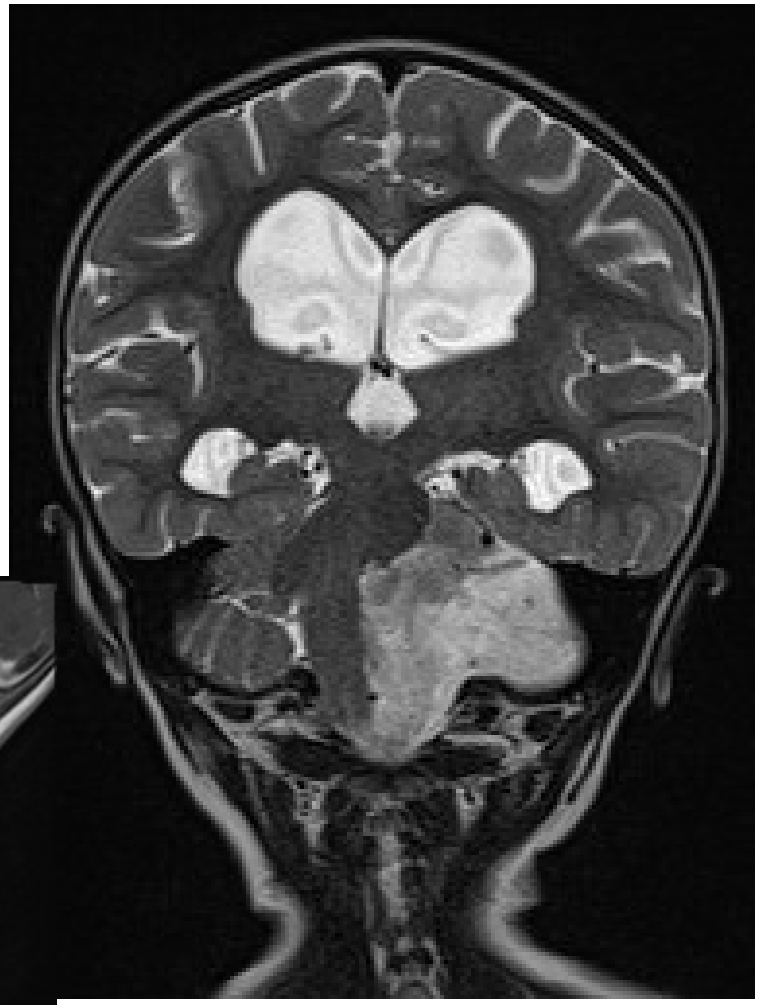
- Clin Oncol (R Coll Radiol). 2017;29(7):439-447

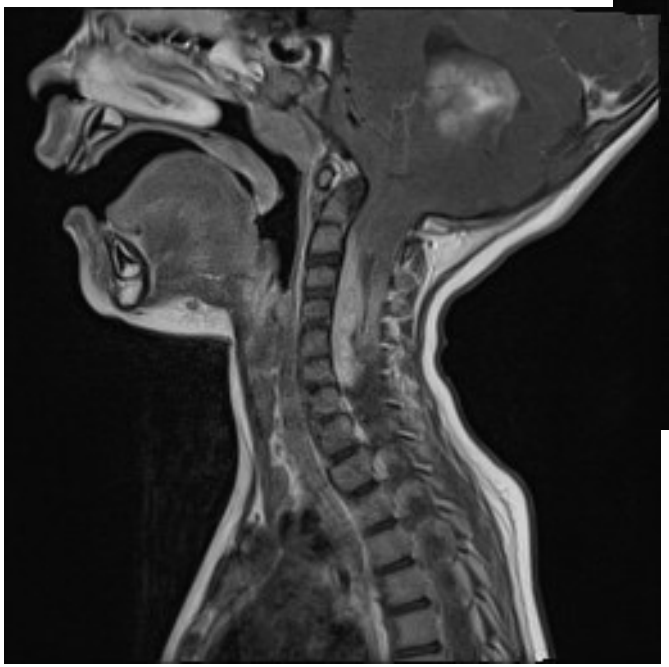


A = Field base, B = Proton, C= Tomotherapy, D = Proton

Ependymoma

- female
- 3 years 2 months
- long history of ataxia
- PF-EPN-A
- Staging: M0

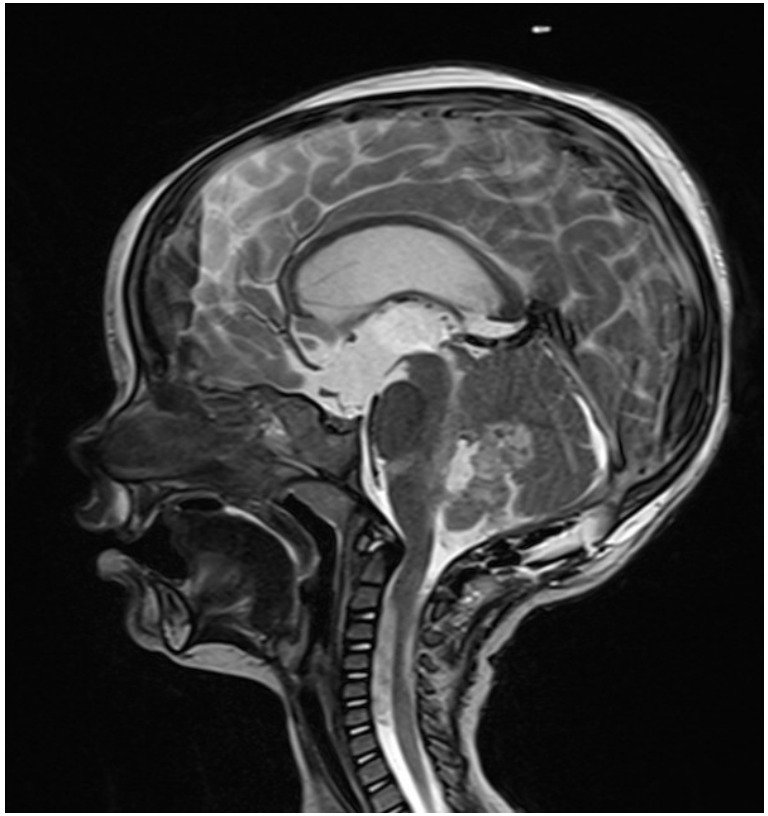


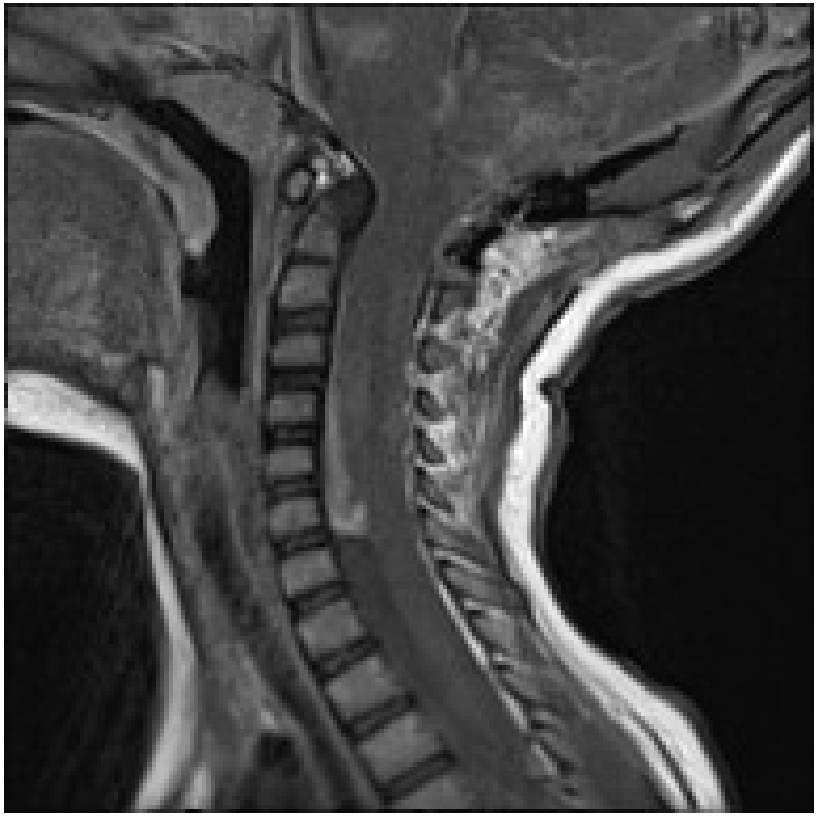


Ependymoma

Resection – postoperative residual tumor

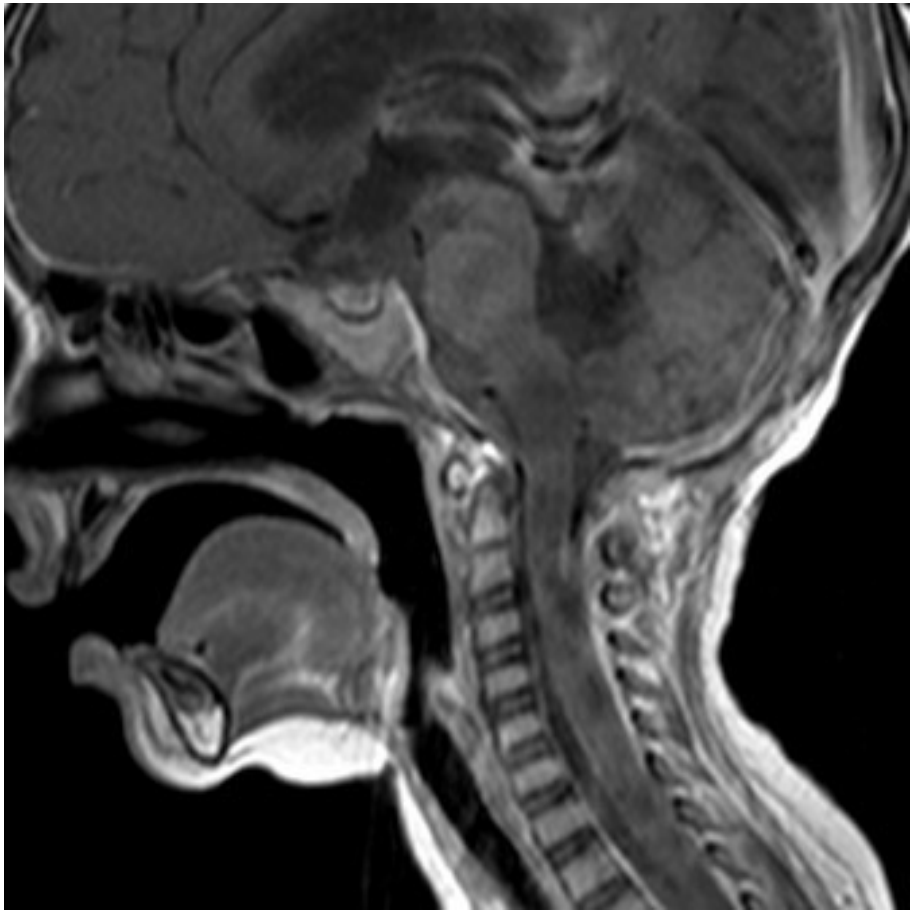
WHAT NEXT?



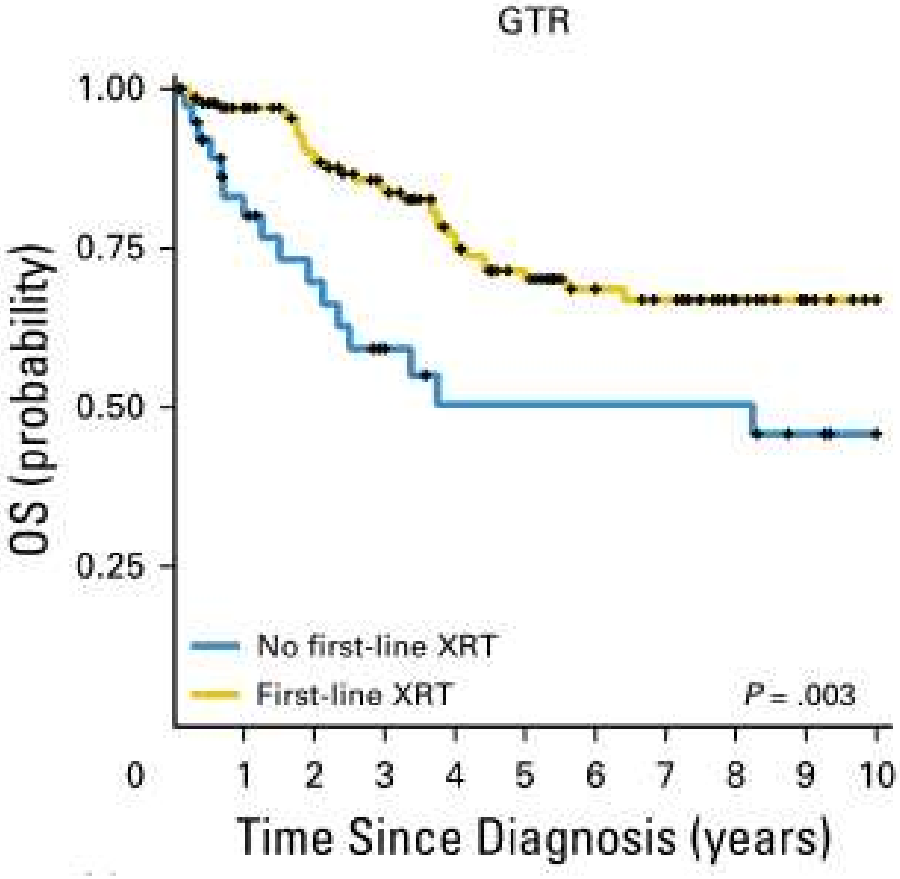


Ependymoma

2nd look surgery -> gross total resection



Ependymoma



No clear benefit of Chemotherapy

Ramaswamy et al., JCO 2016

Ependymoma

Photon therapy:

- local radiotherapy GHD 52,2 Gy in 1,8 Gy ED

- Subsequent chemotherapy 3cycles

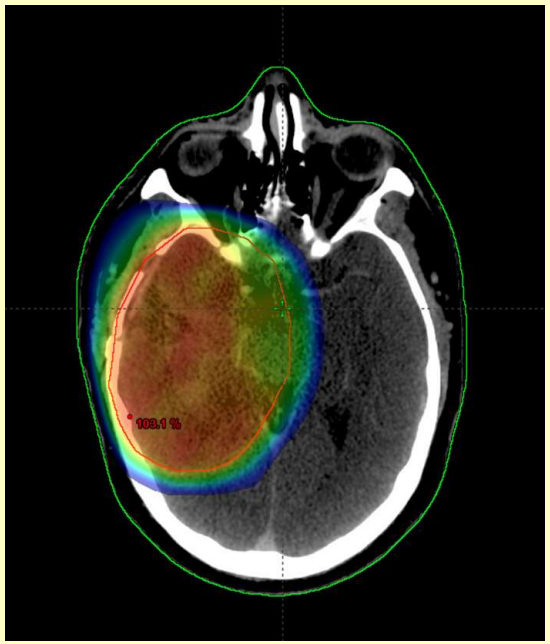
- Patient still in remssion 4 years after diagnosis

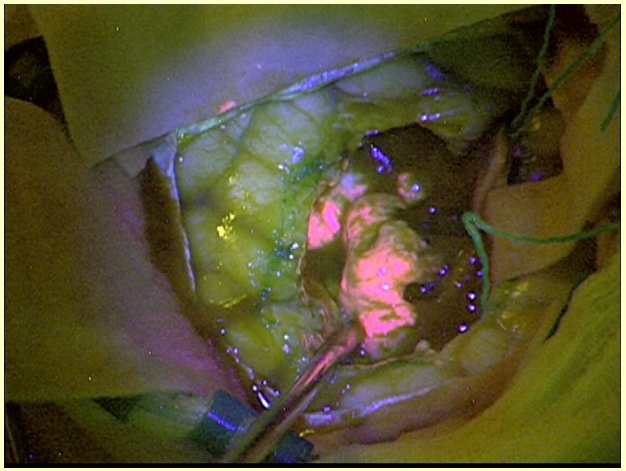
BUT

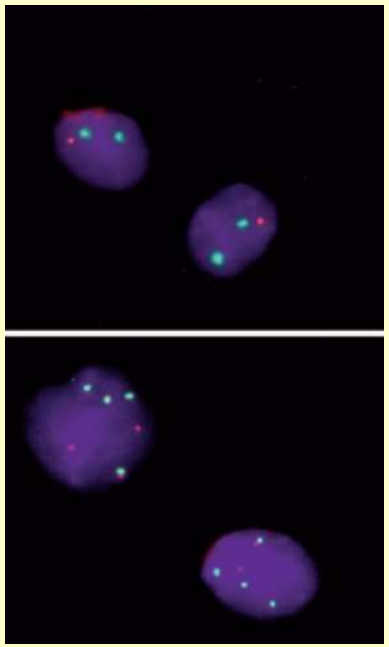
Hypothyroidism, growth hormone deficiency

Young patients with good outcome frequently experience longterm side effects

- Endocrinopathies, neuropsychological deficits, secondary tumors







Elderly patients with glioblastoma

ESTRO Brain Tumour Course

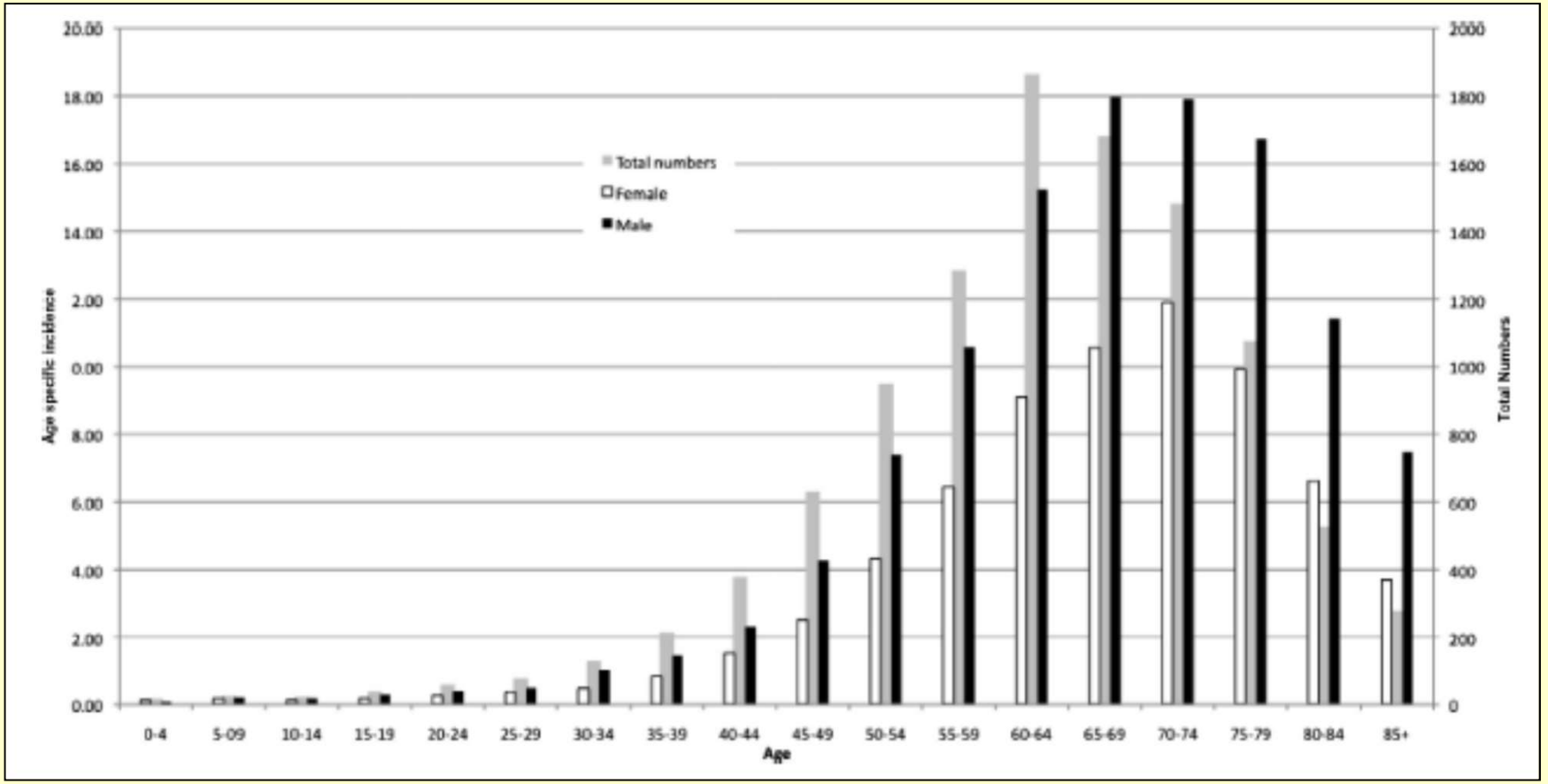
Vienna 2017

Anthony Chalmers

Chair of Clinical Oncology

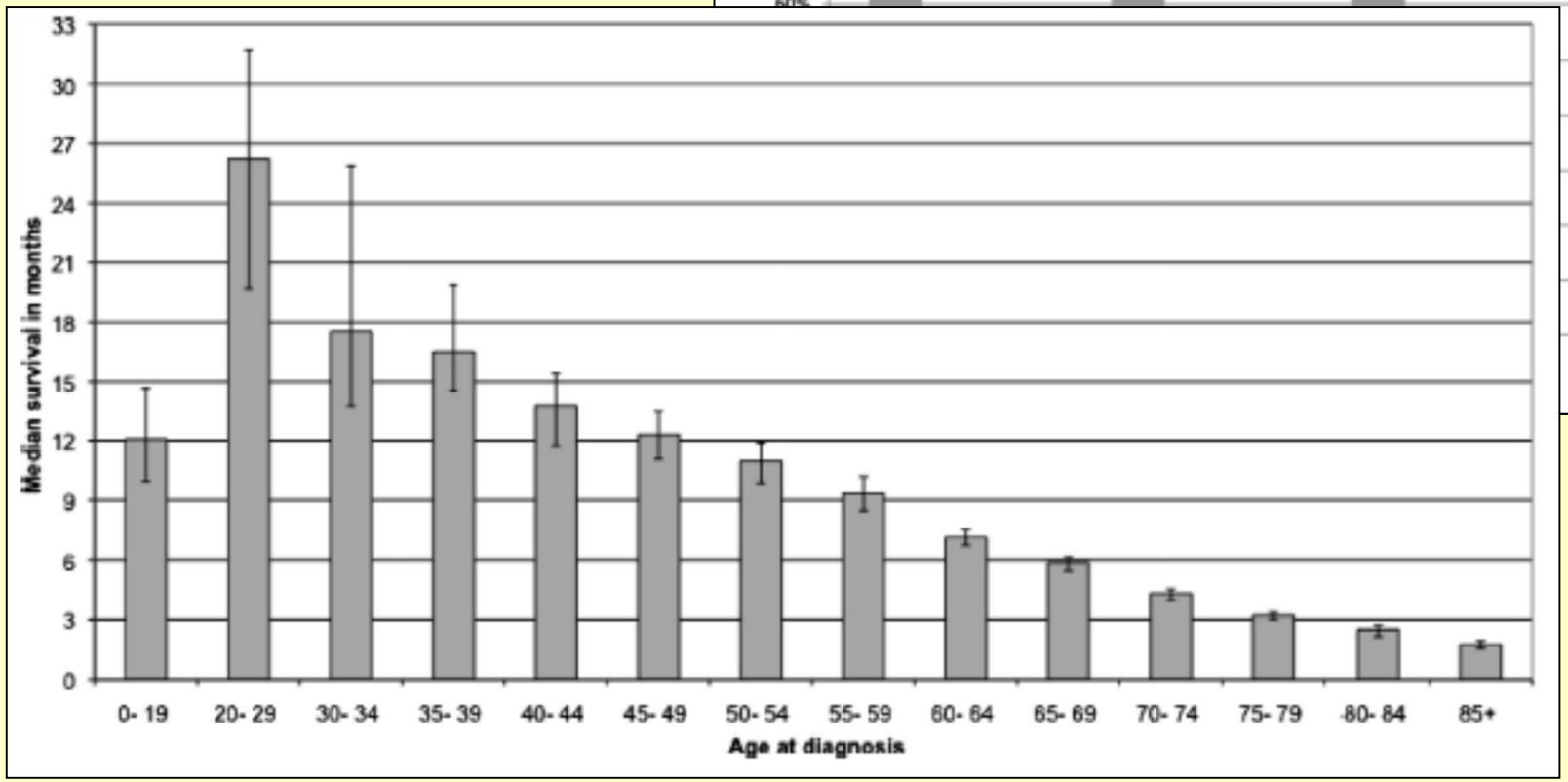
University of Glasgow

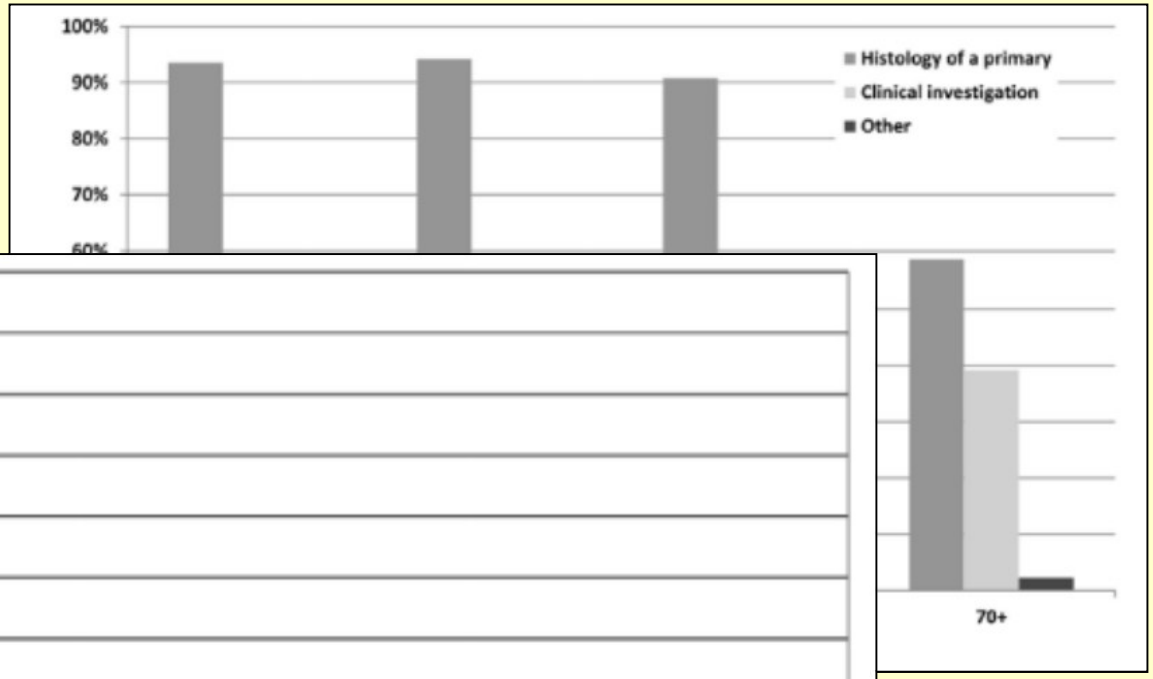
Age specific incidence of glioblastoma 2007-2011



Glioblastoma in England: 2007–2011

Andrew Brodbelt [a,*], David Greenberg [b], Tim Winters [c], Matt Williams [d], Sally Vernon [b], V. Peter Collins [e], on behalf of the (UK) National Cancer Information Network Brain Tumour Group





Glioblastoma in England: 2007–2011

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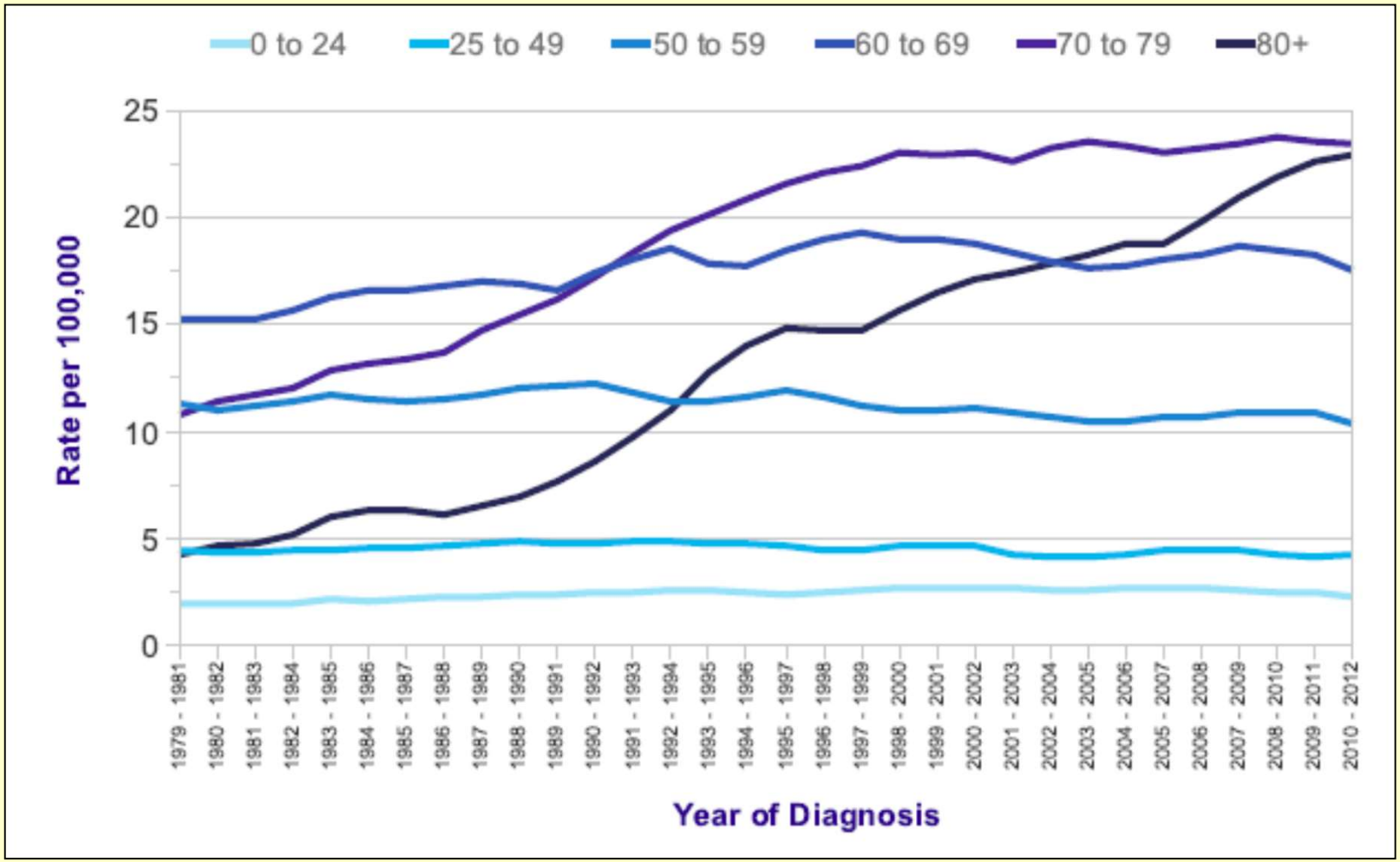
European age-standardised incidence rates of malignant brain tumours

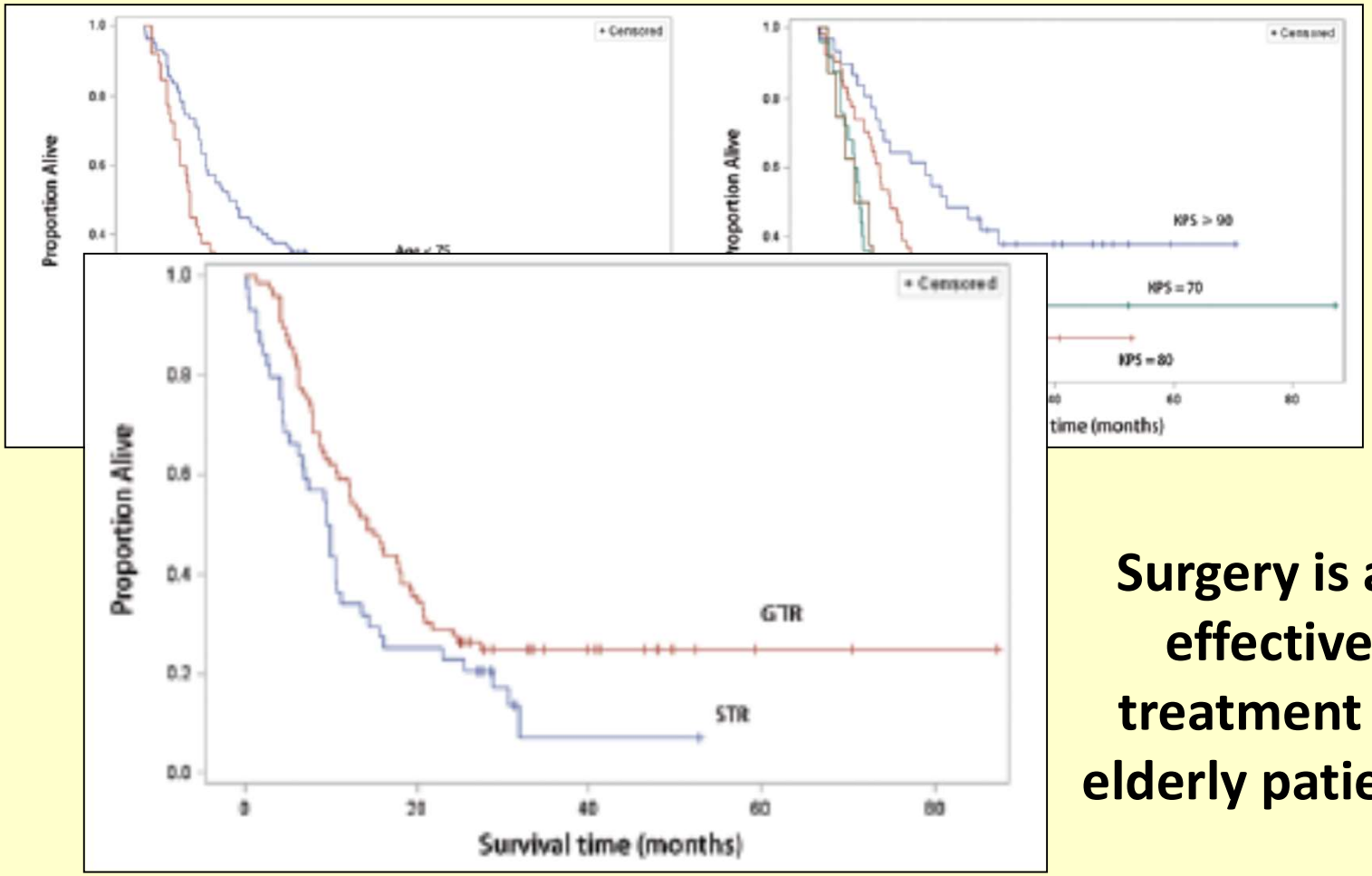


JNS

CLINICAL ARTICLE

Glioblastoma in the elderly: the effect of aggressive and modern therapies on survival

Ranjith Babu, MD, MS,[1] Jordan M. Komisarow, MD,[1] Vijay J. Agarwal, MD,[1]
Shervin Rahimpour, MD,[1] Akshita Iyer, BS,[1] Dylan Britt, BS,[1] Isaac O. Karikari, MD,[1]
Peter M. Grossi, MD,[1] Steven Thomas, MS,[2] Allan H. Friedman, MD,[1] and
Cory Adamson, MD, PhD, MPH, MHSc[1,3,4]



Surgery is an effective treatment in elderly patients

The Safety of Surgery in Elderly Patients with Primary and Recurrent Glioblastoma

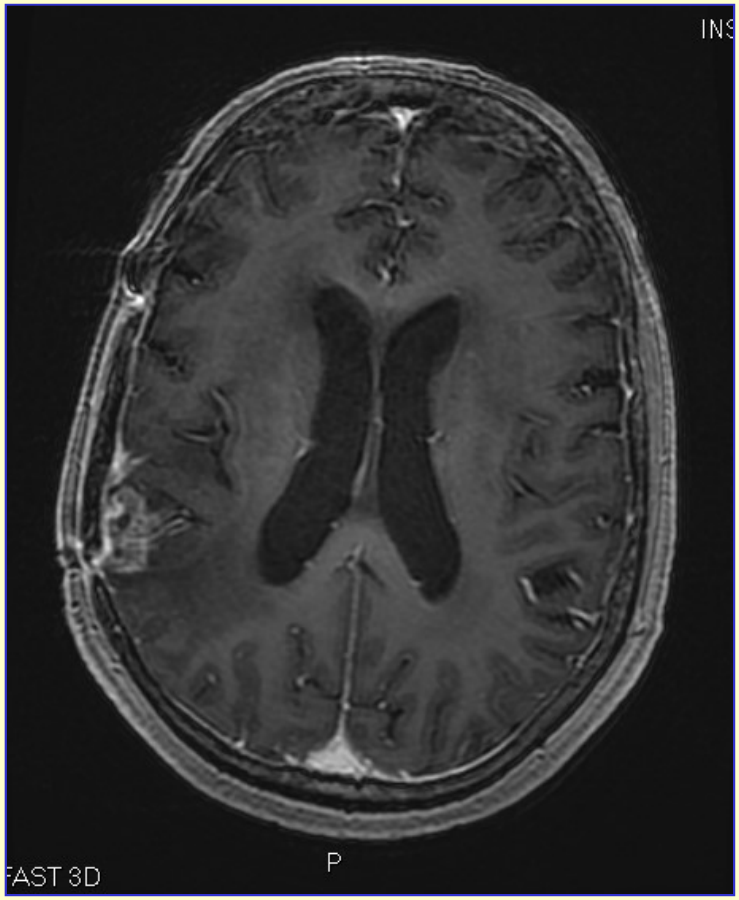
Randy S. D'Amico[1,2], Michael B. Cloney[1], Adam M. Sonabend[2], Brad Zacharia[2], Matthew N. Nazarian[1], Fabio M. Iwamoto[3], Michael B. Sisti[2], Jeffrey N. Bruce[1,2], Guy M. McKhann II[2]

Table 3. Postoperative Morbidity After Surgical Management of High-Grade Gliomas in Large Series Using Strict Reporting Criteria

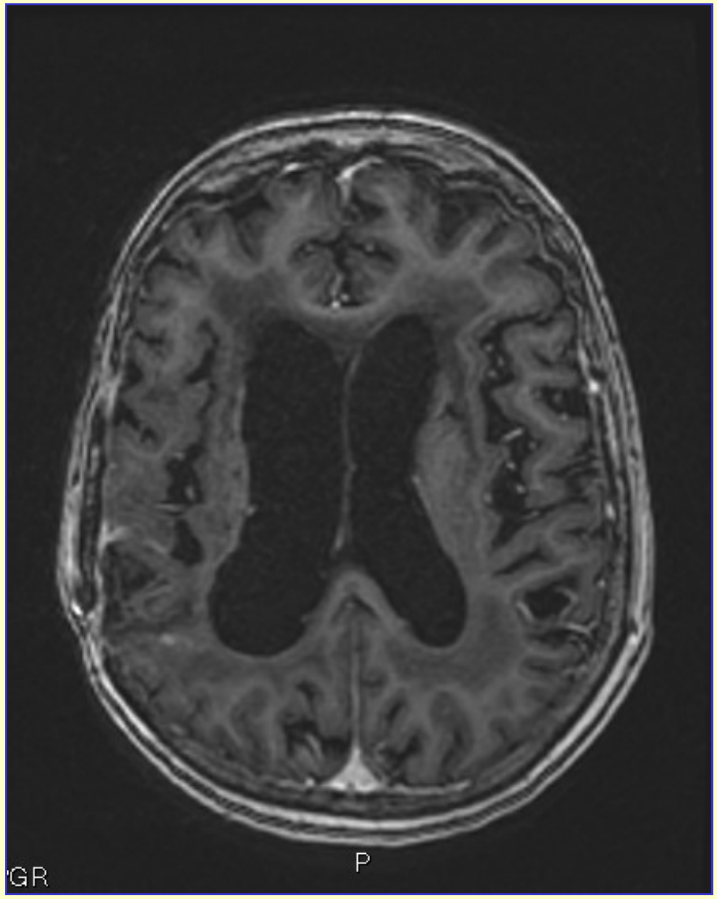
Authors/Year	Number of Patients	Median or Mean Age (years)	Number of Reoperations	% of Patients: Overall Complications	Neurological Complications	Regional Complications	Systemic Complications	Mortality
Chang et al., 2003 (9)								
Resection 1	408	55	—	24.2	8.1	10.0	9.2	1.5
Resection 2	91	50	91	32.6	18.0	13.0	8.7	2.2
Gulati et al., 2011 (17)	144	62	42	25.7	16.7	6.9	2.1	2.1
Tanaka et al., 2013 (43)	53	74.3	0	18.9	11.3 (3.8)*	7.6	3.8	0.0
D'Amico et al., 2014.								
Resection 1	243	73	—	21.9	6.5	8.4	7.3	1.5
Resection 2	31	72	31	25.8	6.5	9.7	9.7	0.0

Rates of postoperative morbidity across large series in elderly and nonelderly patients using morbidity reporting methodologies outlined in the Glioma Outcomes Project (9).

*Tanaka et al. (43) reported transient and permanent neurological deficits.



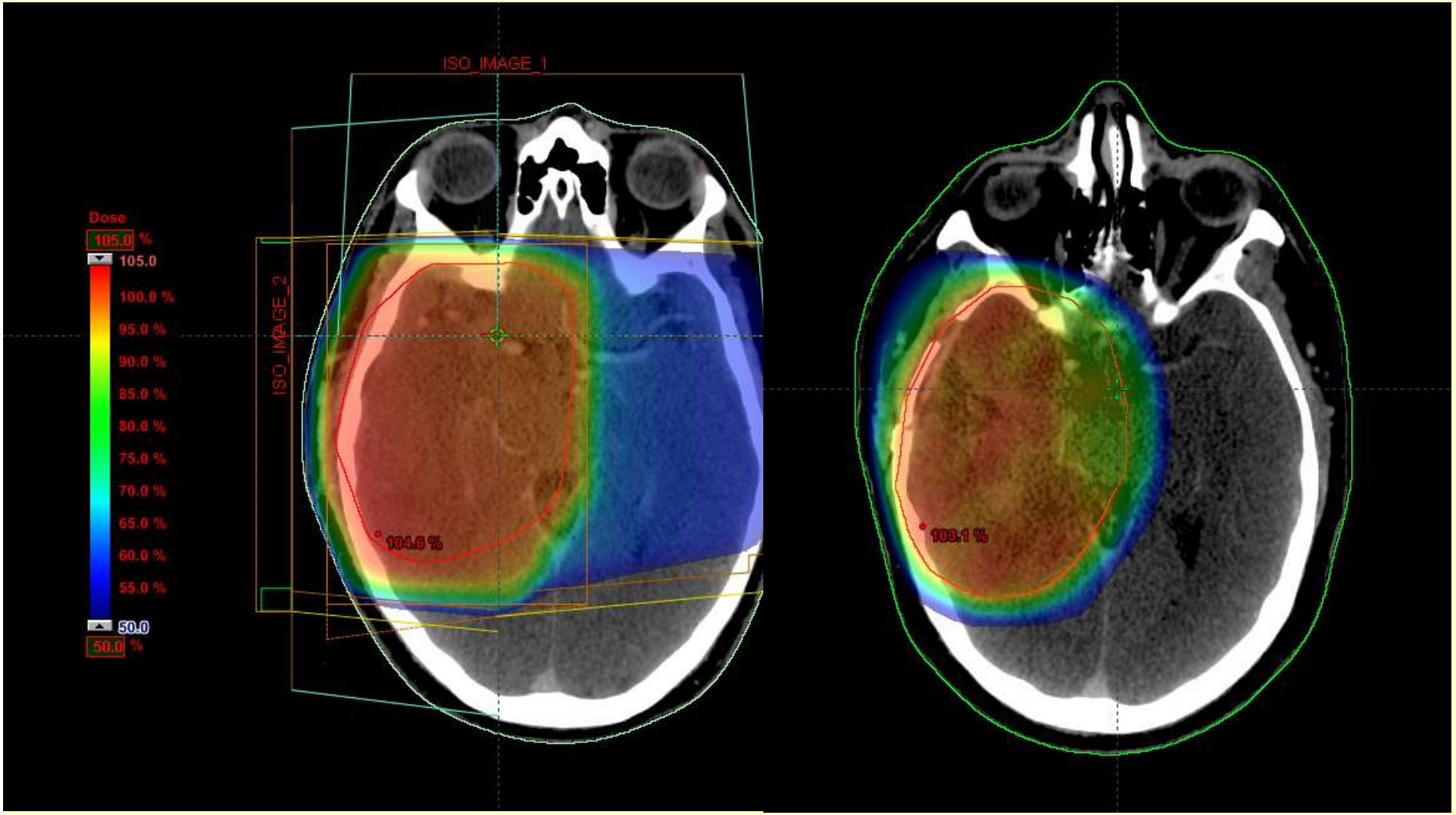
Pre-radiation



18 months
post-radiation

Conformal RT

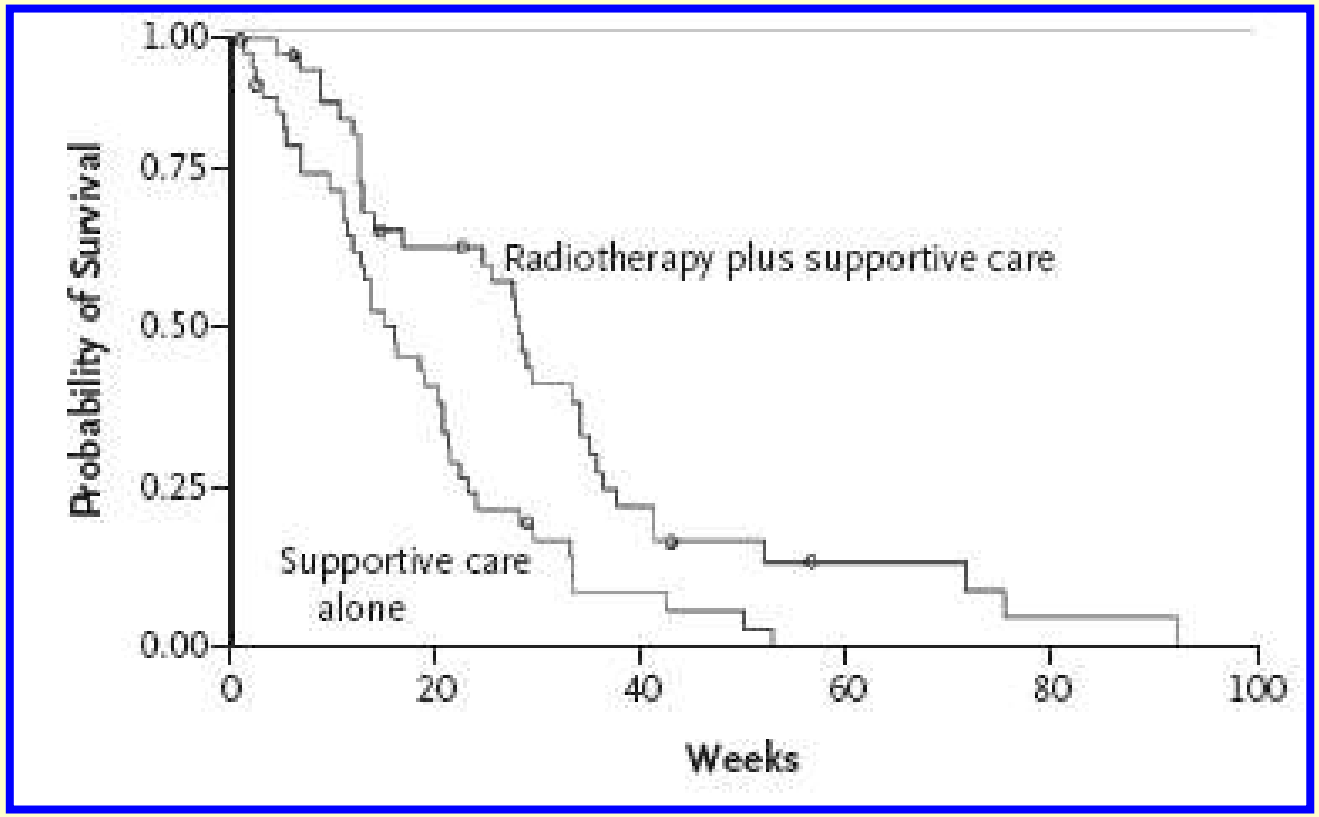
IMRT



ORIGINAL ARTICLE

Radiotherapy for Glioblastoma in the Elderly

Florence Keime-Guibert, M.D., Olivier Chinot, M.D., Luc Taillandier, M.D.,



50.4 Gy in 28 #

Age ≥70

N ENGL J MED 356;15 WWW.NEJM.ORG APRIL 12, 2007

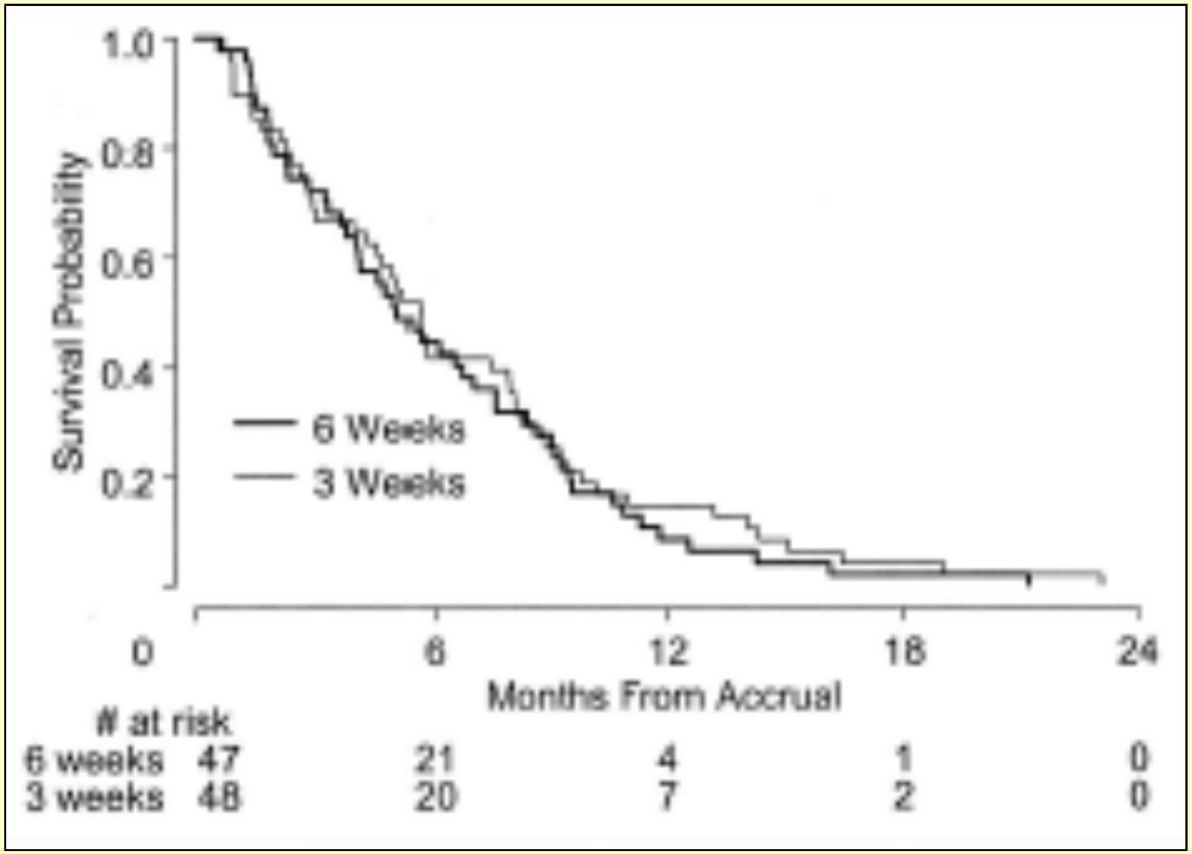
VOLUME 22 · NUMBER 9 · MAY 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial

W. Roa, P.M.A. Brasher, G. Bauman, M. Anthes, E. Bruera, A. Chan, B. Fisher, D. Fulton, S. Gulavita, C. Hao, S. Husain, A. Murtha, K. Petruk, D. Stewart, P. Tai, R. Urtasun, J.G. Cairncross, and P. Forsyth

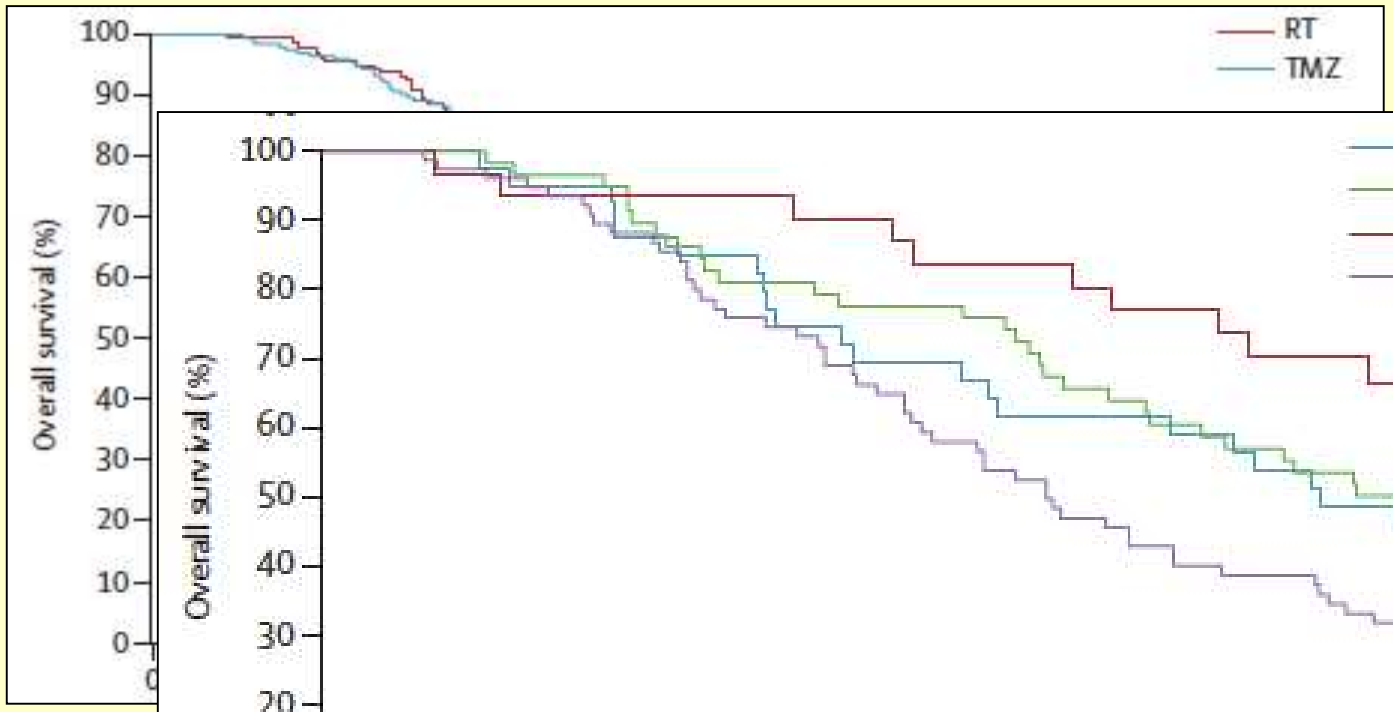


40 Gy in 15♯
equivalent to
60 Gy in 30♯

Age ≥60

Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

Wolfgang Wick, Michael Platten, Christoph Meisner, Jörg Felsberg, Ghazaleh Tabatabai, Matthias Simon, Guido Nikkhah, Kirsten Papsdorf, Joachim P Steinbach, Michael Sabel, Stephanie E Combs, Jan Vesper, Christian Braun, Jürgen Meixensberger, Ralf Ketter, Regine Mayer-Steinacker, Guido Reifenberger, Michael Weller, for the NOA-08 Study Group of the Neuro-oncology Working Group (NOA) of the German Cancer Society*



60 Gy in 30-

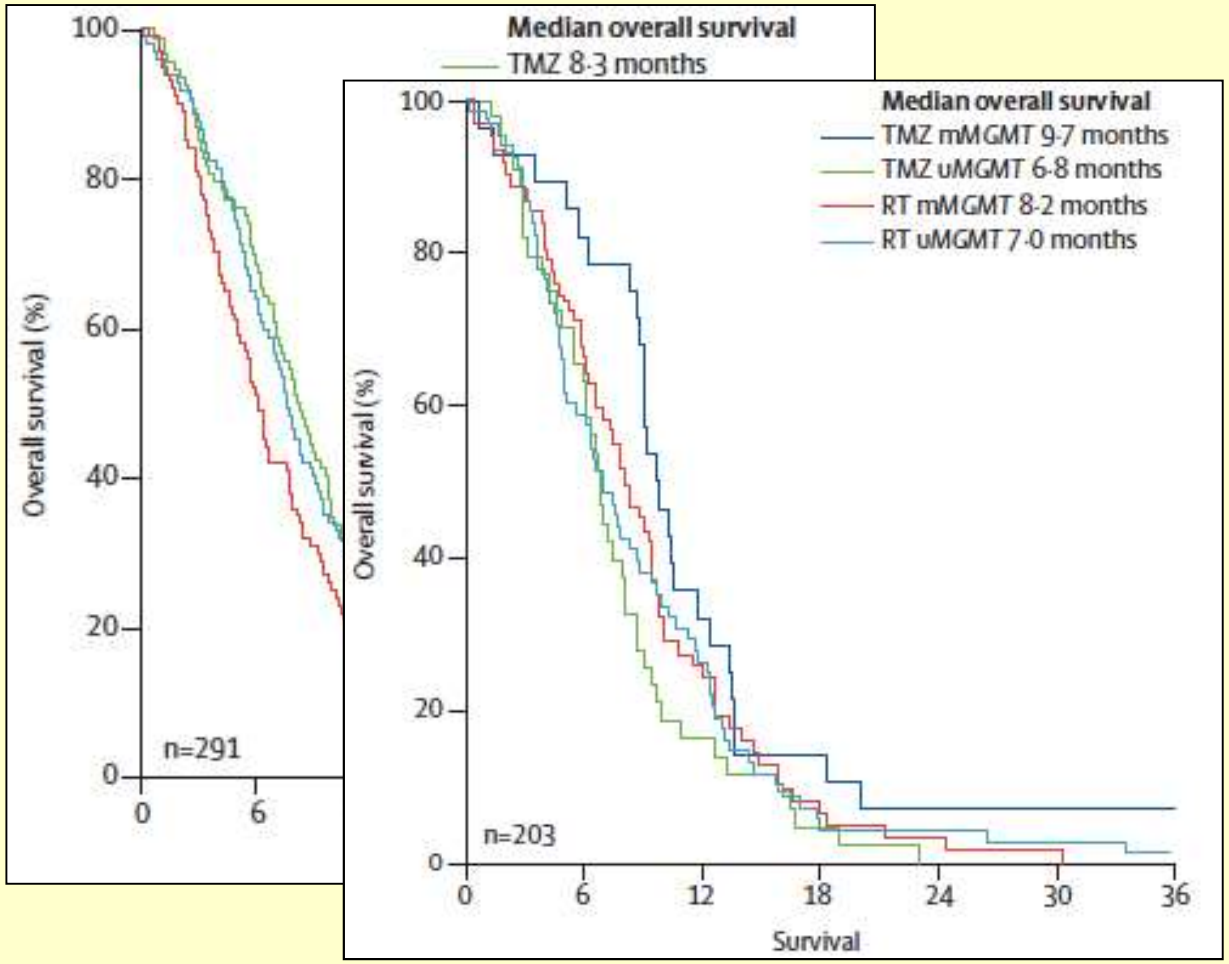
/m²

ys

65

Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

Annika Malmström, Bjørn Henning Grønberg, Christine Marosi, Roger Stupp, Didier Frappaz, Henrik Schultz, Ufuk Abacioglu, Björn Tavelin, Benoit Lhermitte, Monika E Hegi, Johan Rosell, Roger Henriksson, for the Nordic Clinical Brain Tumour Study Group (NCBTSG)



34 Gy in 10 #

v.

60 Gy in 30 #

v.

TMZ 200mg/m^2

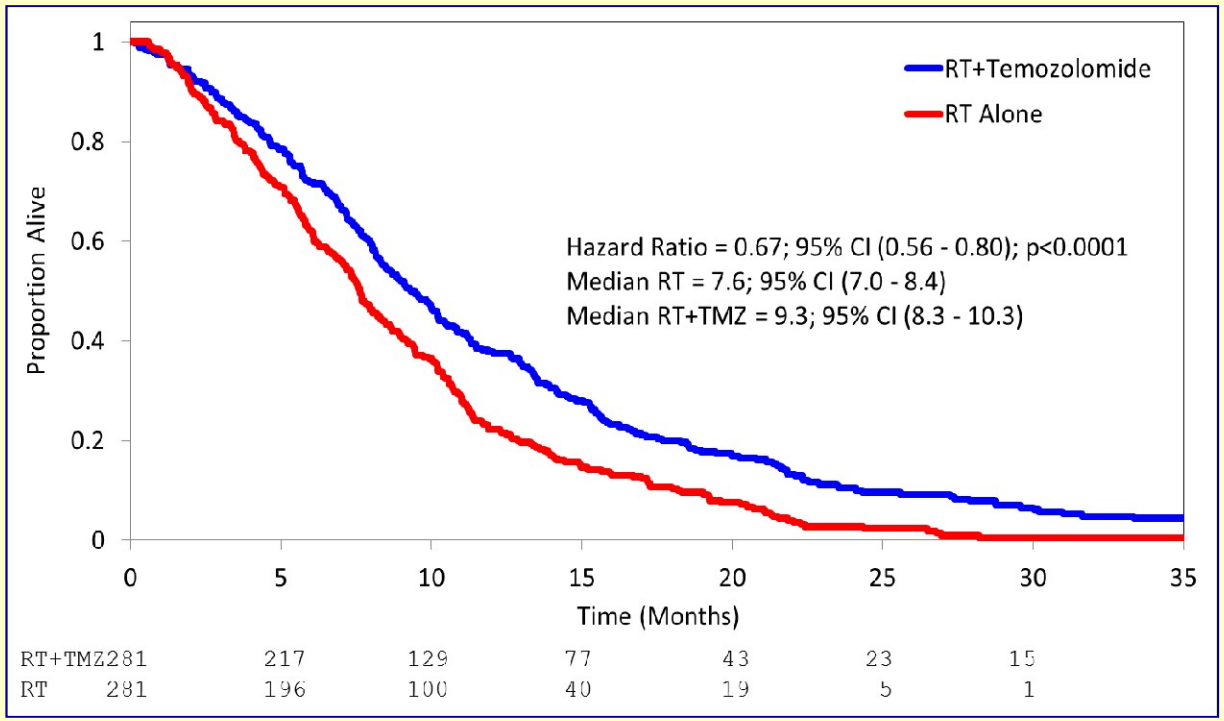
5/28 days

Age ≥60

ORIGINAL ARTICLE

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

James R. Perry, M.D., Normand Laperriere, M.D., Christopher J. O'Callaghan, D.V.M., Alba A. Brandes, M.D., Johan Menten, M.D., Claire Phillips, M.B., B.S., Michael Fay, M.B., Ch.B., Ryo Nishikawa, M.D., J. Gregory Cairncross, M.D., Wilson Roa, M.D., David Osoba, M.D., John P. Rossiter, M.B., B.Ch., Arjun Sahgal, M.D., Hal Hirte, M.D., Florence Laigle-Donadey, M.D., Enrico Franceschi, M.D., Olivier Chinot, M.D., Vassilis Golfinopoulos, M.D., Laura Fariselli, M.D., Antje Wick, M.D., Loic Feuvret, M.D., Michael Back, M.B., B.S., Michael Tills, M.B., B.S., Chad Winch, M.Sc., Brigitta G. Baumert, M.D., Wolfgang Wick, M.D., Keyue Ding, Ph.D., and Warren P. Mason, M.D., for the Trial Investigators*



Age ≥65

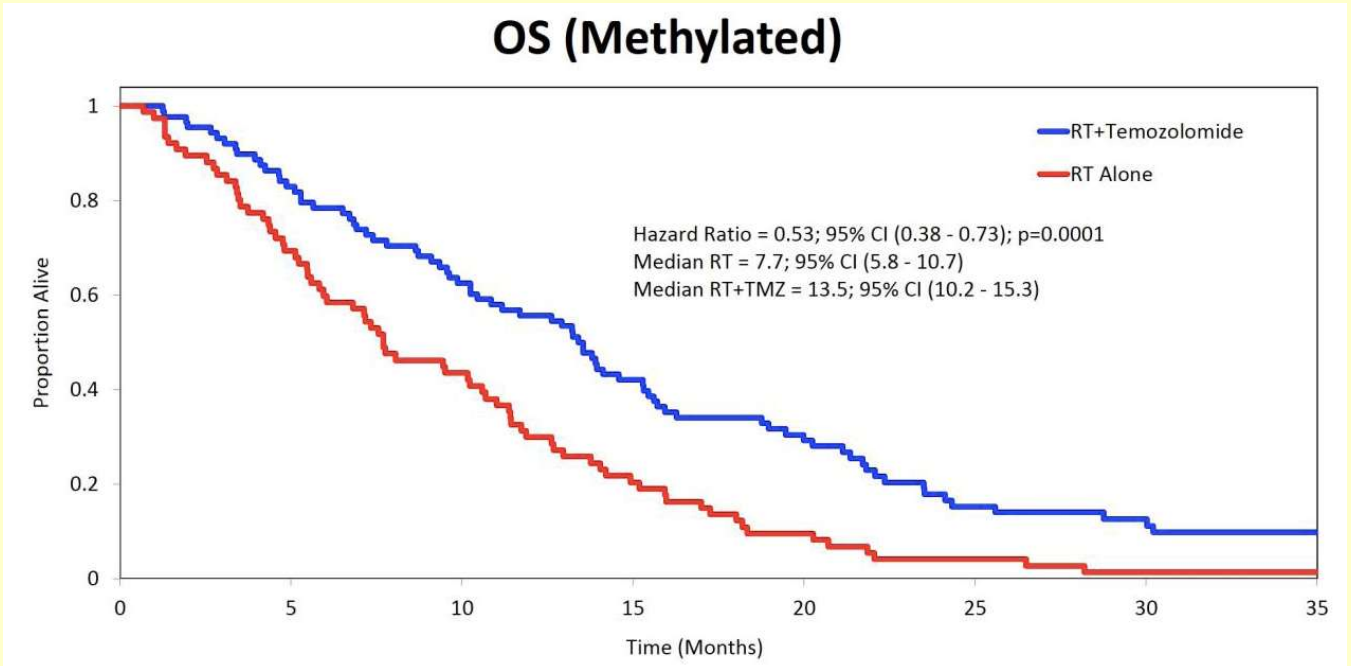
40 Gy in 15 ♯

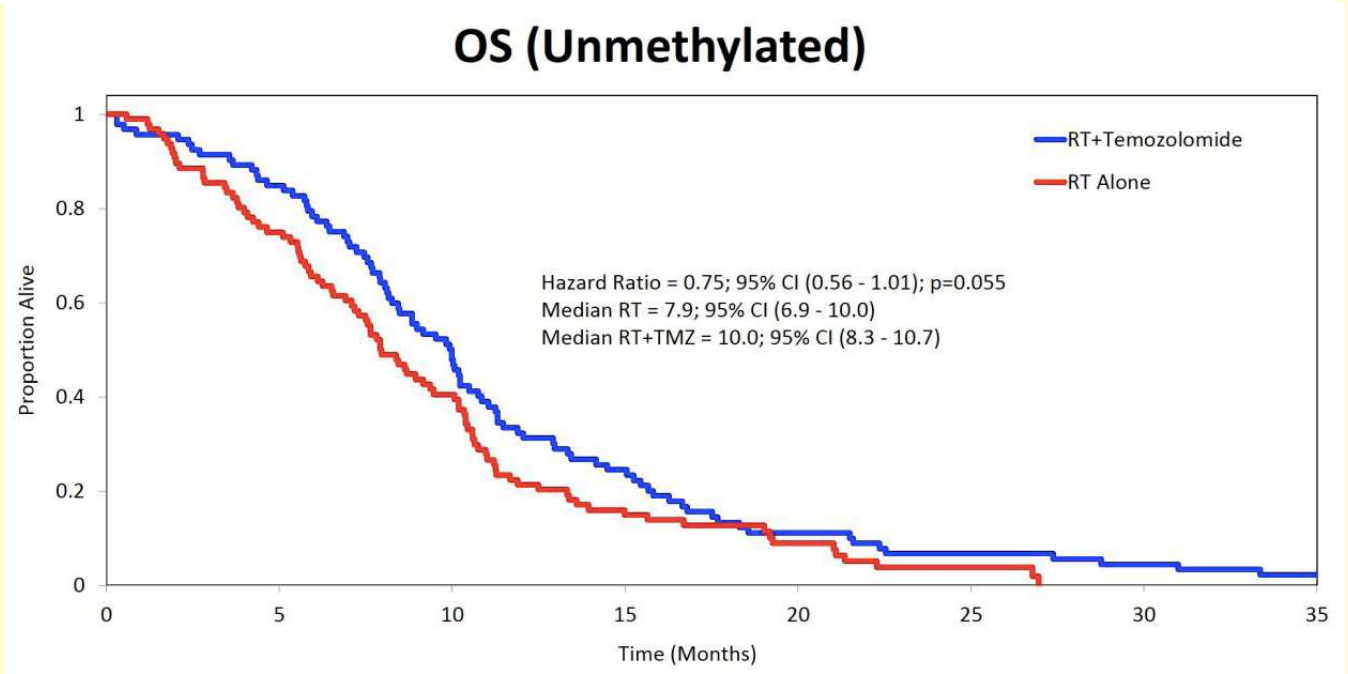
+/–

Concomitant and adjuvant TMZ

(median 5 cycles)

Perry et al NEJM 2017

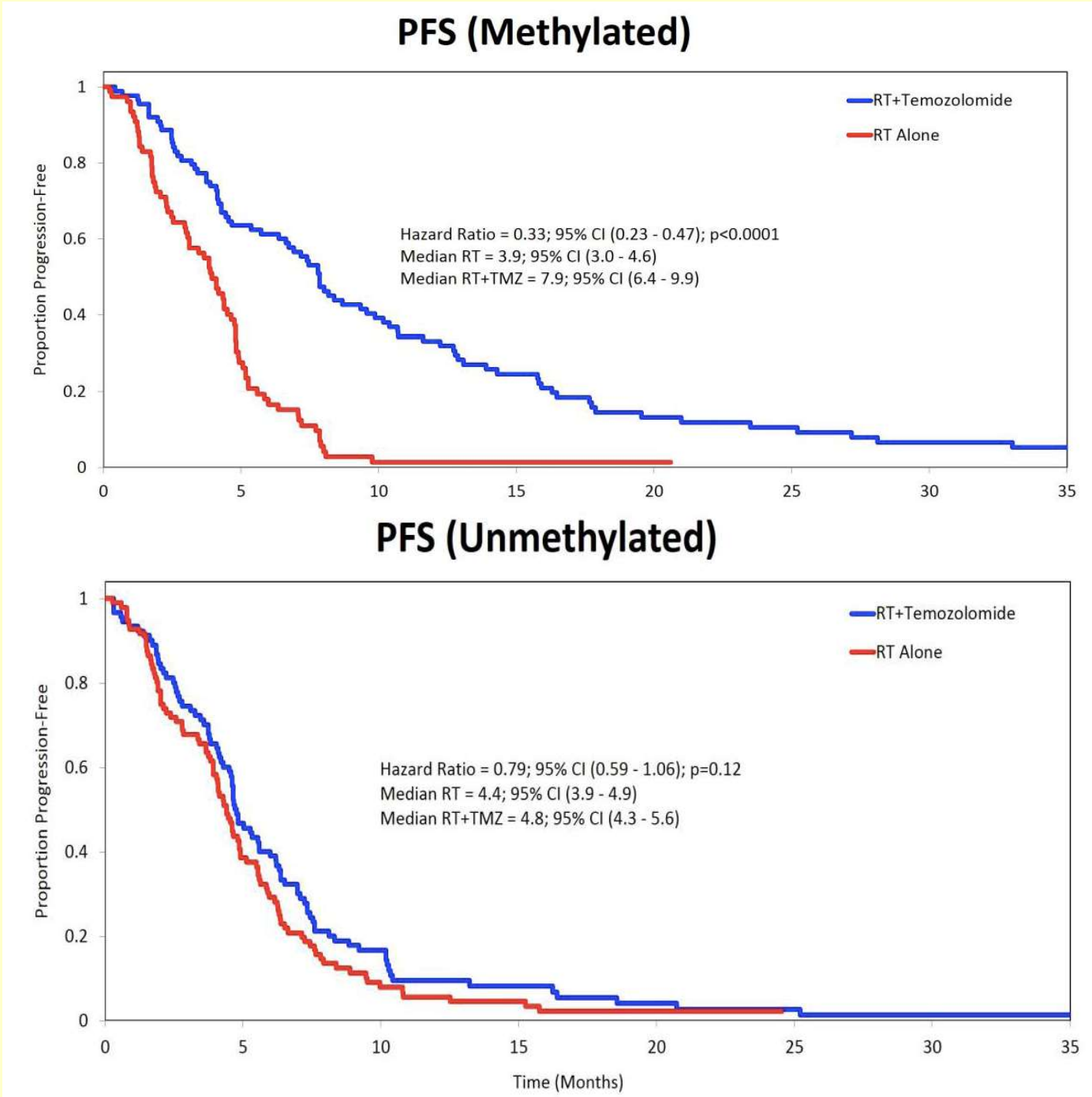




MGMT results available for 354 patients (62%)

47% methylated

53% unmethylated


PFS (Methylated)
Proportion Progression-Free
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
RT+Temozolomide
RT Alone
Hazard Ratio = 0.33; 95% CI (0.23 - 0.47); p<0.0001
Median RT = 3.9; 95% CI (3.0 - 4.6)
Median RT+TMZ = 7.9; 95% CI (6.4 - 9.9)
PFS (Unmethylated)
Proportion Progression-Free
1
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
Time (Months)
RT+Temozolomide
RT Alone
Hazard Ratio = 0.79; 95% CI (0.59 - 1.06); p=0.12
Median RT = 4.4; 95% CI (3.9 - 4.9)
Median RT+TMZ = 4.8; 95% CI (4.3 - 5.6)