Medical history

Medical history

Boy, born 2003 (10 years) (in Russia)

Visual disturbances since many years.
Since three months increasing motoric dysfunction both arms.
Since two months loss of appetite and weight loss (5 kg).
No neurofibromatosis.

Past medical history :
Shortly after birth enlargement of both lateral ventricles.
VP-shunt in July 2004. Delayed motoric development.

Ophthalmology
Hemianopsie both eyes

How do you proceed ?

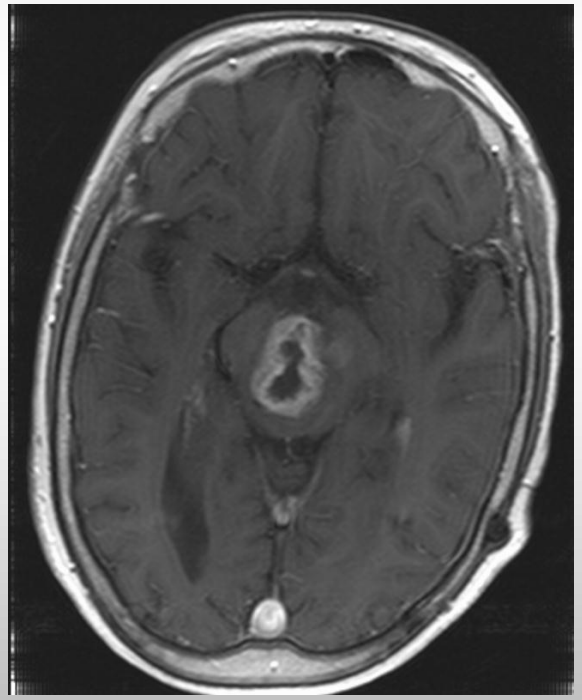
Is imaging indispensable ?

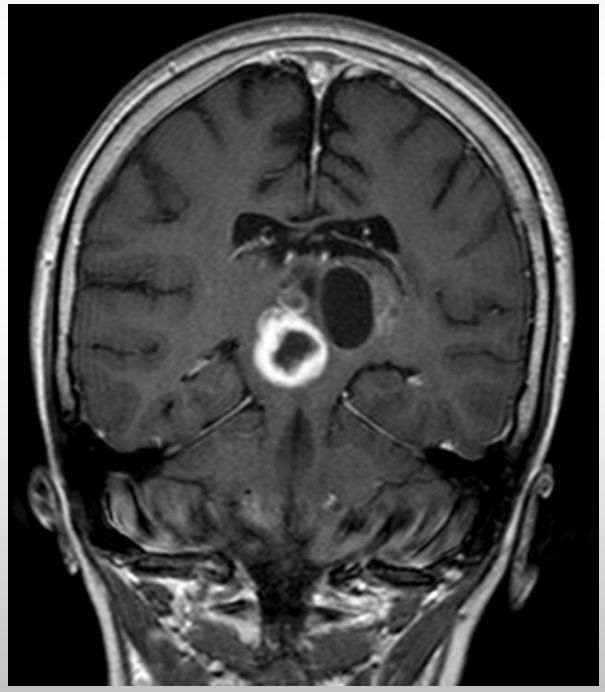
Where exactly do you suspect a (space occupying) lesion ?

Case / low grade glioma

MRI at diagnosis

22/10/2012 MRI: centrally localized space occupying lesion 3.3 x 2.9 x 2.6 cm extending into the left thalamus.
Marked contrast enhancement with centrally necrotic (cystic) areas.





What is your working hypothesis for diagnosis ?

Case / low grade glioma

Possible questions in general management

Benign process ?

**If you suspect a malignant lesion,
what will be your most likely diagnosis ?**

Differential diagnosis ?

Is a biopsy necessary ?

**Is a complete resection possible ?
Or would you ask the neurosurgeon to attempt
a complete resection ? If so why ?**

Case / low grade glioma

Diagnosis and further management

Diagnosis:
low grade glioma, localisation thalamus-mesencephalon left

Biopsy:
pilocytic astrocytoma WHO grade I.

Complete resection
is not possible without risking major neurological deficits

Case / low grade glioma

What would you do next ?

Case / low grade glioma

Further management

Is treatment necessary ?

If yes, would you recommend radiotherapy or chemotherapy or both ?

What is your rationale for treatment decision ?

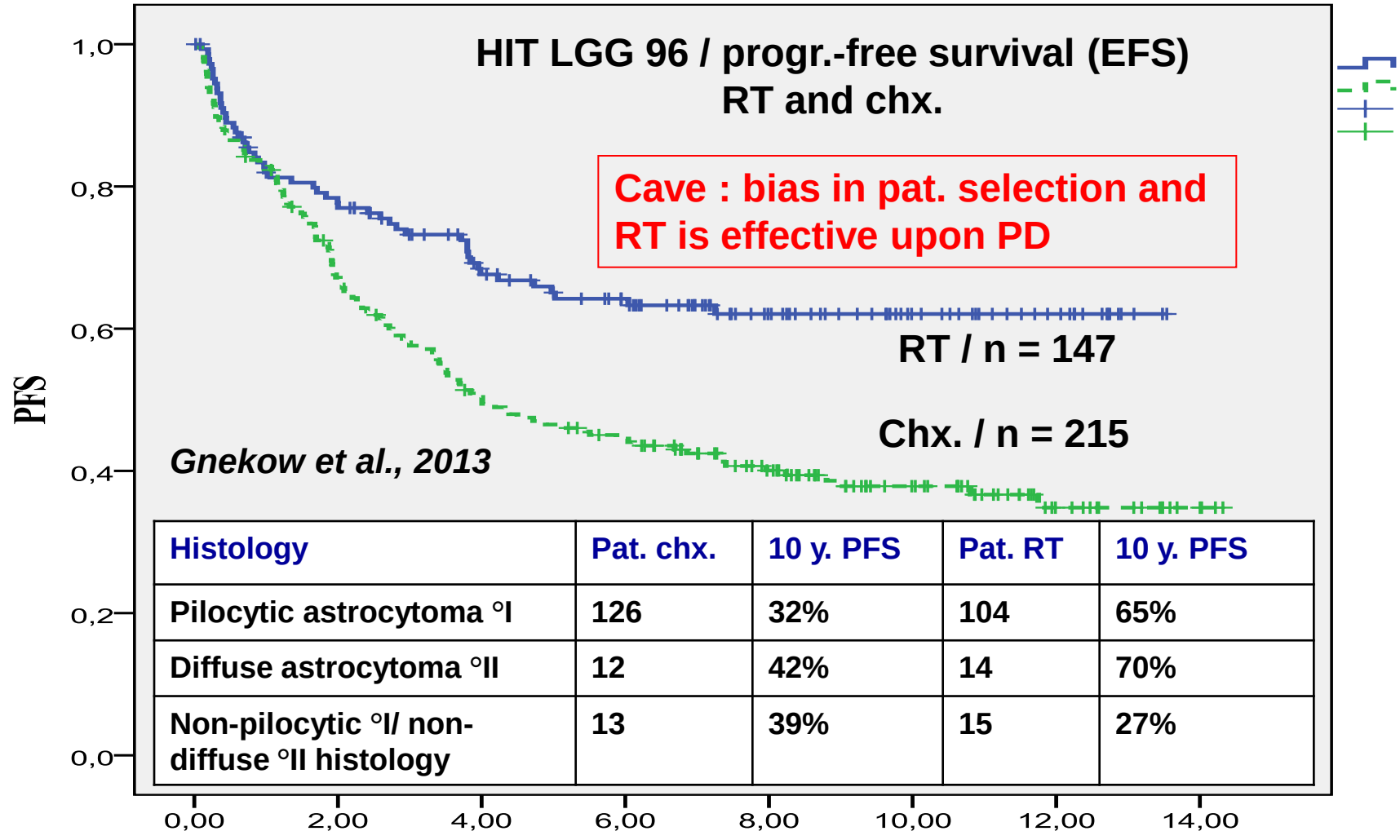
Case / low grade glioma

Radiotherapy of tumour site / outcome

Author	Dose prescription	Pat.	Results	F-up
Debus et al., 1999	Median 52.4 Gy/1.6-2.0 Gy	10	5 y. PFS: 90 %, 5 y. OS: 100 % No acute toxicities	12-72 mon.
Saran et al., 2002	Median 50-55 Gy/30-33 Fr.	14	3 y. PFS: 87 %, 3 y. OS: 100 % 1 relapse within GTV	33 mon.
Hug et al., 2002	Protons 50.4-63.0 CGE 1,8 Gy.	27	Local control survival Hemisph. 71 % 86 % Dienceph. 87 % 93 % Brain stem 60 % 60 %	3.3 years
Marcus et al., 2005	Ster. Conv RT Median 52,2 Gy/1,8Gy	81	5 y./8 y. PFS: 82.5 %/65 % 5 y./8 y. OS: 97.8 %/82 % 6 local	6.9 years
Combs et al., 2005	3D conformal RT Med. 52.2 Gy / 1.8Gy	15	3y. / 5 y. PFS : 92 % / 72 % 5 y. OS : 90 %	97 mon.
Merchant et al., 2009	3D conformal RT Median 54 Gy/1.8 Gy	78	5/10 y. EFS: 87.4 %/74.3 % 5 / 10 y. OS: 98.5 %/95.9 %	89 mon.
Paulino et al., 2013	IMRT 45-60 Gy	39	8 y. EFS/OS: 78.2 % and 93.7 %	n.a.
Muller et al., 2013	Conventional/3D planning Median 54 Gy/1.8 Gy Margin 1-2 cm	75	Pilocytic astrocytoma 5/10 y. PFS: 76.5 % 5/10 y. OS: 96.2 % Relapse pattern: n.a.	8.4 years

Case / low grade glioma

Radiotherapy / chemotherapy / outcome



Histology	Pat. chx.	10 y. PFS	Pat. RT	10 y. PFS
Pilocytic astrocytoma °I	126	32%	104	65%
Diffuse astrocytoma °II	12	42%	14	70%
Non-pilocytic °I/ non-diffuse °II histology	13	39%	15	27%

Case / low grade glioma

Which RT technology would you select ?

Case / low grade glioma

Further management

Conventional RT

3 D conformal RT

Brachytherapy

Protontherapy

Radiosurgery

?

Brachytherapy

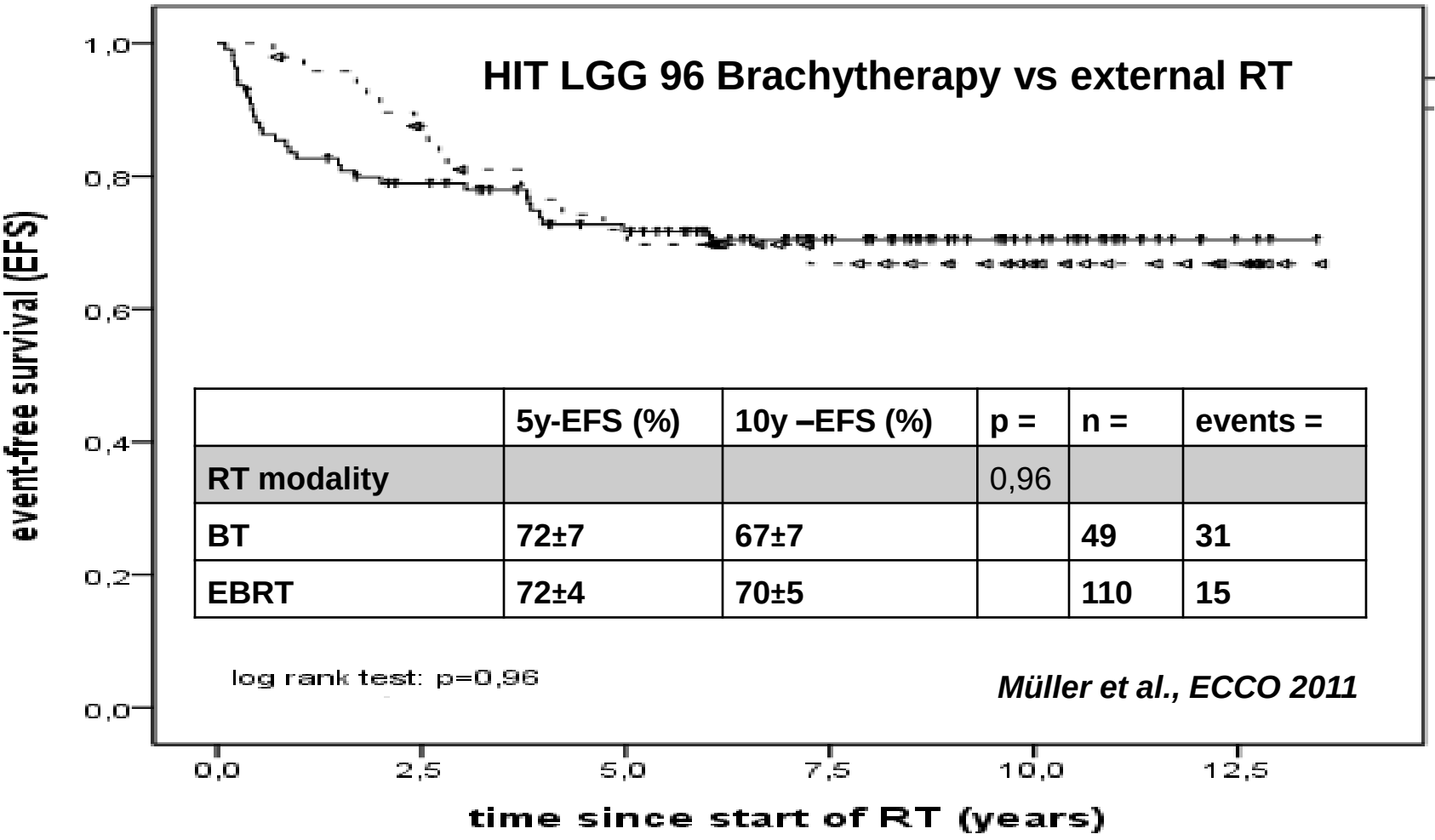
Case / low grade glioma

Outcome brachytherapy

Author	Technique	Patients	Outcome
Herrera et al. 2007	temporary iodine-125 seeds 60 Gy < 4 cm	n = 12 age range: 8-17 y. (median: 8.7 y.) pilocyt. A. only	OS: 83.3%
Peraud, Kreth et al. 2007	temporary iodine-125 seeds 54 Gy < 4 cm	N = 11 age: 11 m.-16 y. (median: 6.8 y.) astr. I: 6 Pat. Astr. II: 5 Pat.	Initial Vol.: 14.9 ml volume reduction CR: 4 pat. PR: 7 pat. OS: 100%
Korinthenberg et al. 2010	temporary iodine-125 seeds median dose 60 Gy < 5 cm, spherical shape	n = 94 age range: 1-19 y. median age: 9 y. WHO I + II	5y OS: 97 %, 10y OS: 92 % age, sex, histology, size, location, demarcation
Ruge et al., 2011	Permanent iodine-125 seeds. Median 50-65Gy <4-5cm, demarcated lesions	n = 147 age: 1.2-19.9 , median:10.7 years WHO I +II	5, 10, 15 years PFS: 92 %, 74 %, 67 %. OS: 98 %, 93 %, 82 %
Mueller et al., 2013	Permanent and temporay iodine-125 seeds	N= 42	5 years 10 years PFS 65 % 58 % OS 97 % 97 %

Case / low grade glioma

Outcome brachytherapy



	5y-EFS (%)	10y –EFS (%)	p =	n =	events =
RT modality			0,96		
BT	**72±7**	**67±7**		**49**	**31**
EBRT	**72±4**	**70±5**		**110**	**15**

Müller et al., ECCO 2011

Case / low grade glioma

Brachytherapy

Excellent tumour control rates

- reduction of integral dose to organs at risk
  (highly conformal even to irregular tumour shapes)
- excellent preservation of OAR‘s (steep dose gradient)
- excellent control of symtoms (high rate of improvements)
- identical tumour control rates (external RT)
  (explanation : dose escalation has no benefit)
- In trems of indication and application : surgery
- In terms of tumour control : radiotherapy

Disadvantages

- limited tumour volumes (< 4-5 cm)
- spherical shapes
- no RT in tumours of within the optic chiasm
- in tumour shrinkage while implant in position
  anatomical shift with high dose exposure to neighbouring OAR
  (hippocampus ?)
- no data concerning neurocognitive function

Further prospective evaluation of outcome necessary

Case / low grade glioma

Radiosurgery

Case / low grade glioma

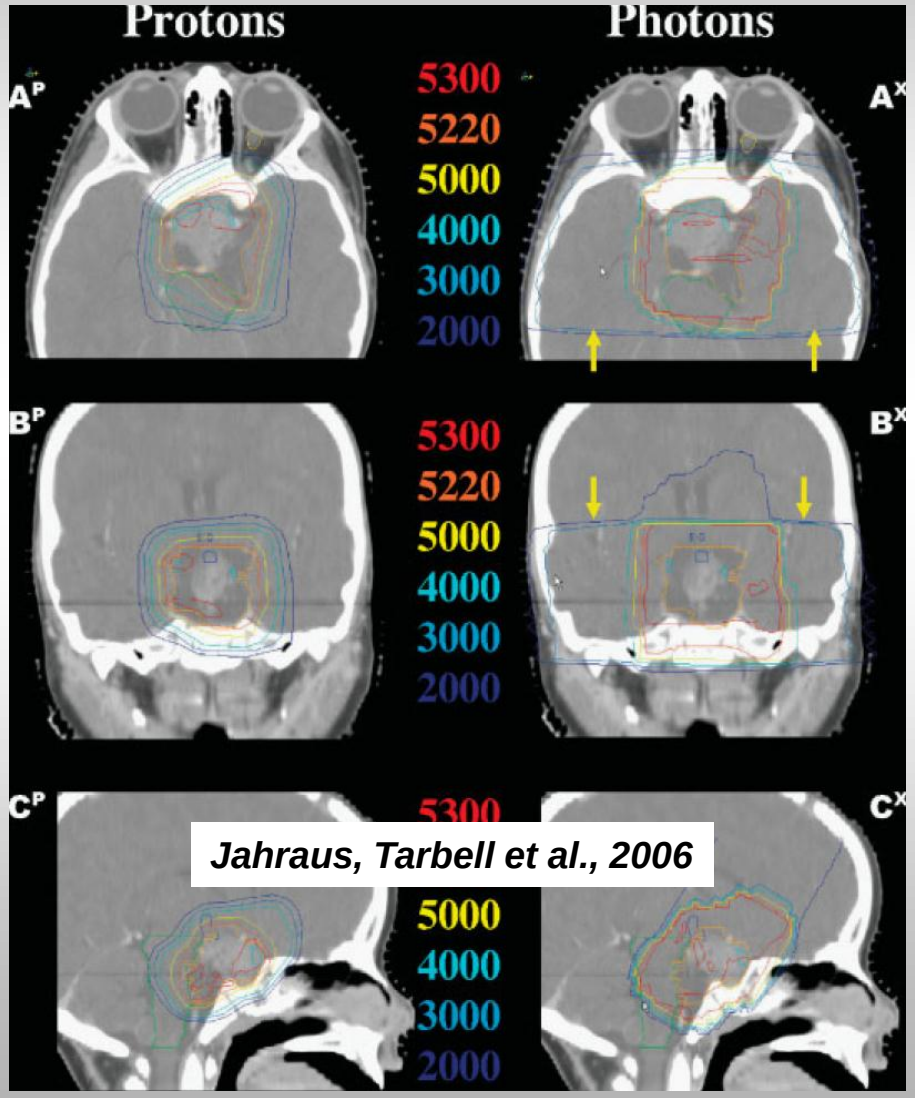
Radiosurgery / Gamma Knife

Author	*Dose*	*Patients*	*Outcome*	*Follow-up*
Ganz et al., 1994	12 Gy	7 pat. 8 tumours	No acute side effects 1 CR, 4 PR, 3 SD / OS 100%	21 mon.
Grabb et al., 1996	11-20 Gy	13	4 trans. Edema, 4 CR, 5 PR, 2 SD, 2 PD, OS 100%	21 mon.
Somaza et al., 1996	15 Gy	9	PFS 100% Overall survival 100%	19 mon.
Lim et al., 1996	12 – 14.4 Gy	2	No side effects, decrease tumour size both pat.	24 – 43 mon.
Kida et al., 2000	12 Gy	12 (Astro I)	PR :7, SD 4, PD 1	24.8 mon.
Boethius et al., 2002	10-12 Gy	19 (16 childr.)	Control : 18/19 pat. 85% vol.-reduction	5.7 years
Hadjipanais et al.,2002	15 Gy	37	CR 10, PR 8, SD 7 Delayed PD : 12 (32,4%)	28 mon.
Heppner et al.,2005	15 Gy	49 (21 pilocyt. A.)	5 year PFS : 41% 8/49 DOD (16.3%)	63 mon.

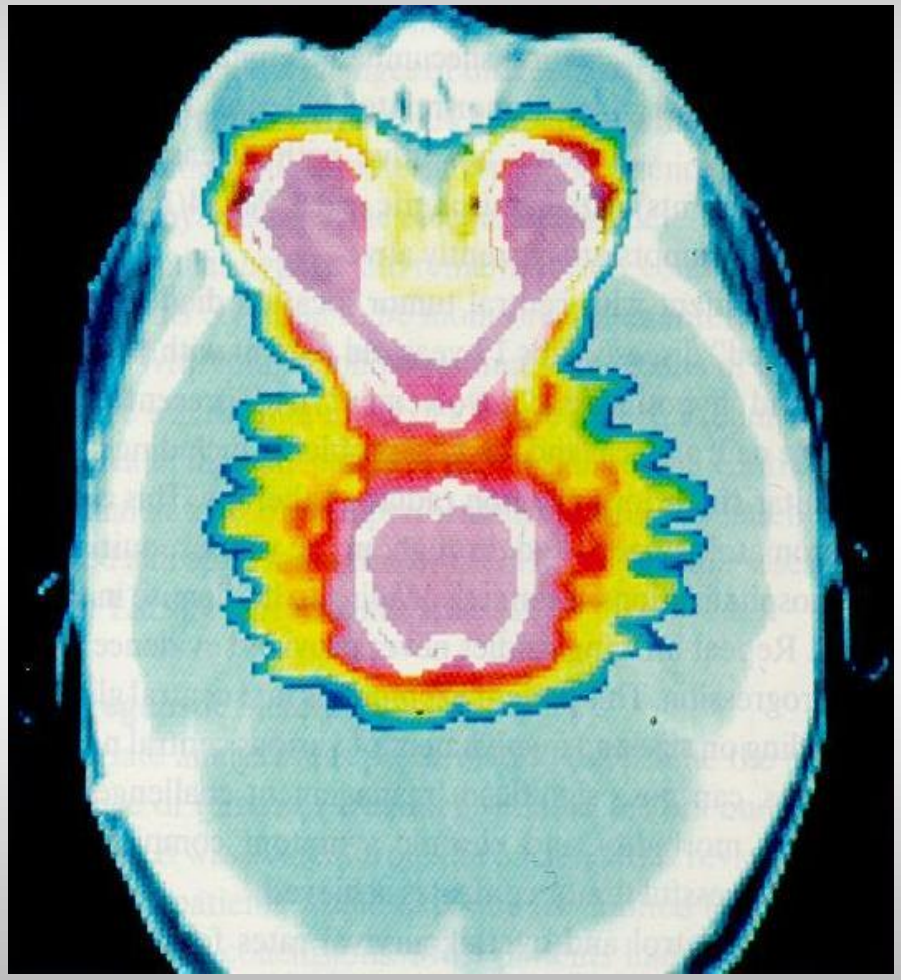
Protontherapy

Case / low grade glioma

Proton therapy



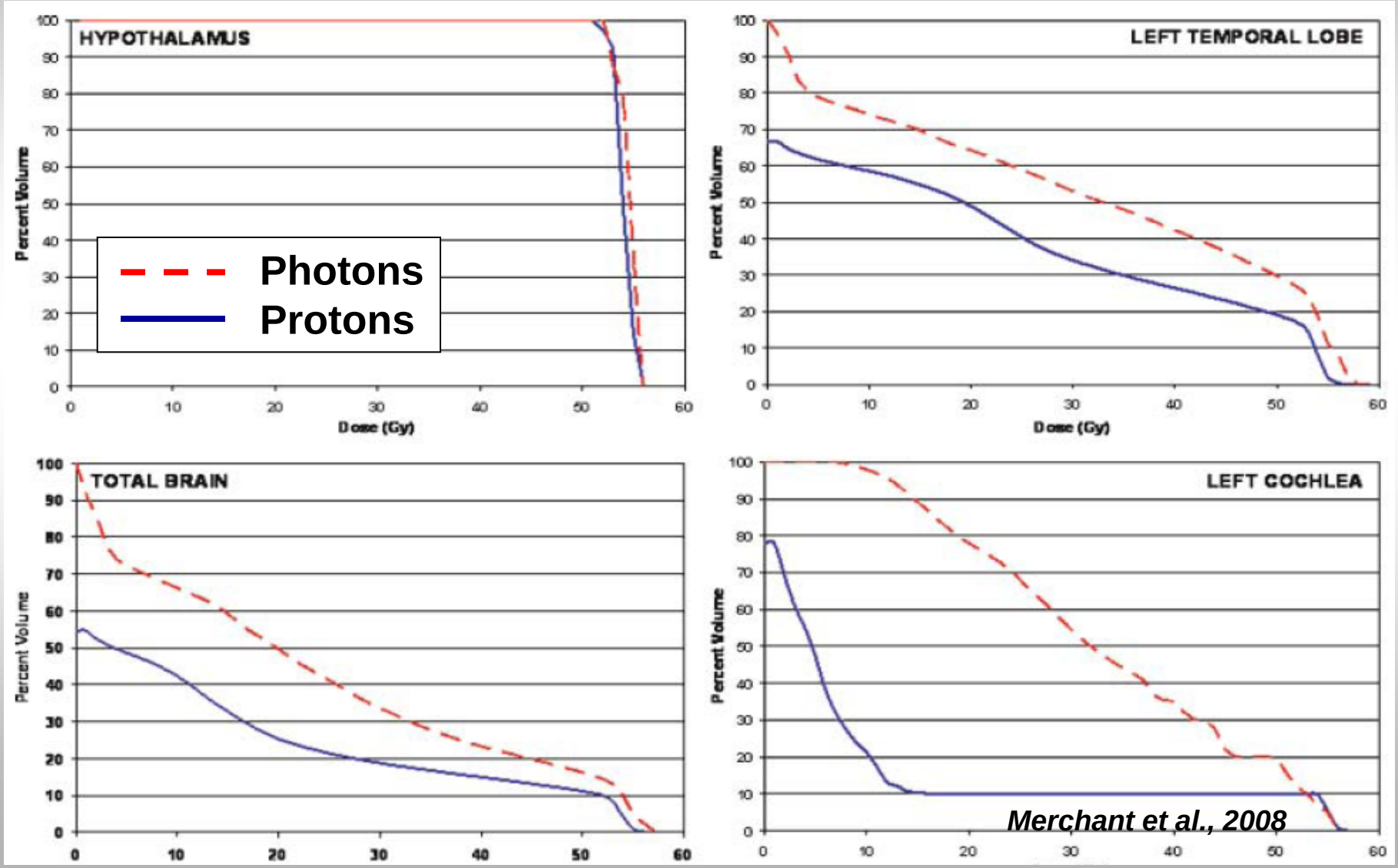
Jahraus, Tarbell et al., 2006



Hug et al., 2002

Case / low grade glioma

DVH comparison photons versus protons



Protontherapy

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

Case / low grade glioma

Which dose prescription would you select ?

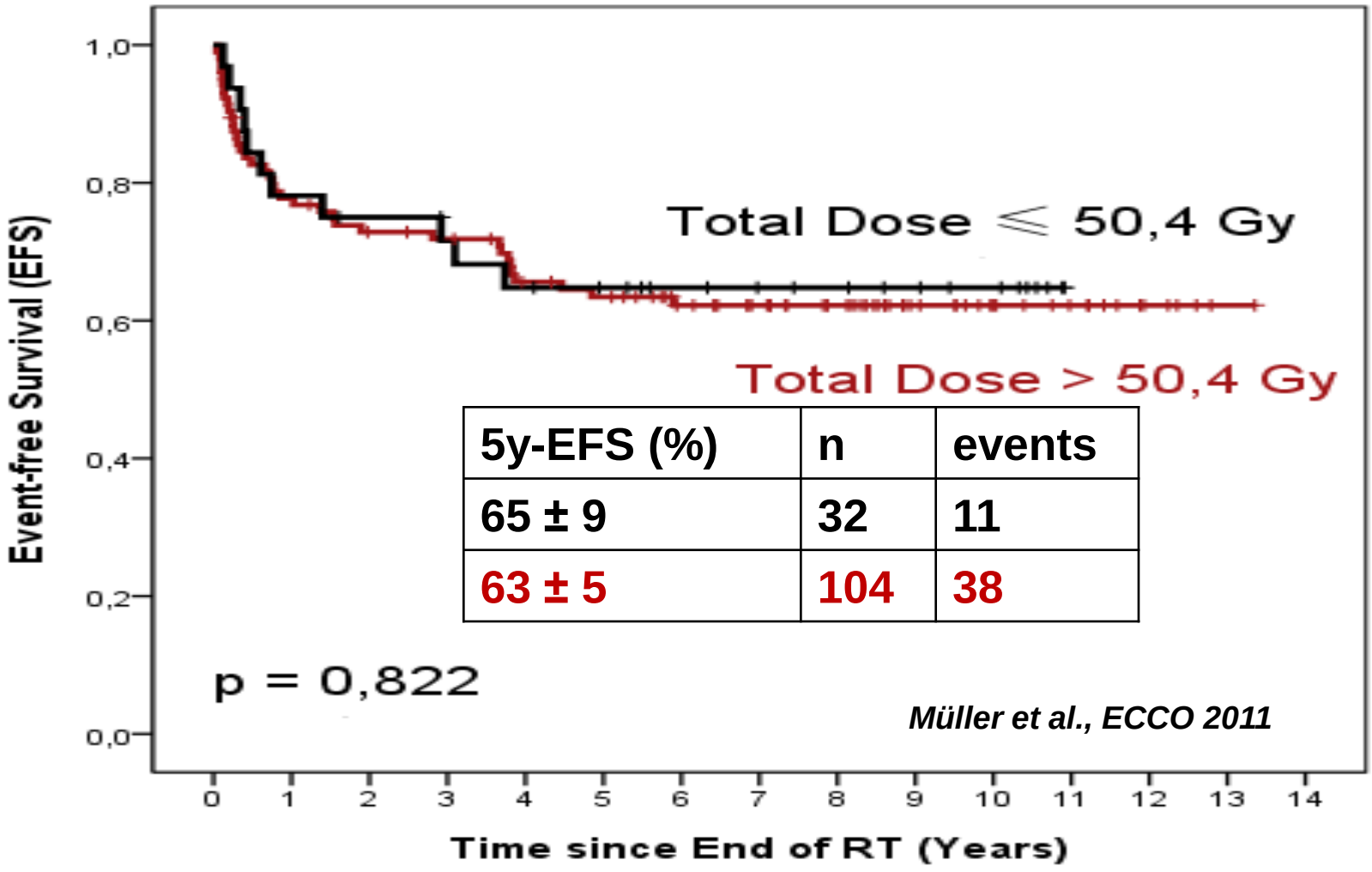
Case / low grade glioma

Dose – response relationship

Author	Patients	Total dose	Fractionated dose	PFS (5 y.)	PFS (10 y.)	p-value
Karim et al., 1996 (adults)	171 172	45.0 Gy 59.4 Gy	1.8 Gy	47 % 50 %	Not reached	p: n.s.
Montgomery et al., 1977	7 9	</= 42 Gy >/= 50 Gy	n.m.	Overall 43 % 100 %	n.m.	n.m.
Alvord et al., 1988	52 62	> 45.0 Gy < 45.0 Gy	n. m.	80 % 65 %	65 % 55 %	n. m.
Flickinger et al., 1988	12 12	> 45.0 Gy < 45.0 Gy	Calculation according NSD	100 % 75 %		P=0.045
Kovalic et al., 1990	3 30	< 40.0 Gy > 40.0 Gy	n. m.	0 90 %	0 % 79 %	<0.0001
Garcia et al., 1990	8 17	< 40 Gy =/> 40 Gy	n.m.	4/8 recurred 2/17 recurred	n.m.	n.m.
Jenkin et al., 1993	19 15	> 50.0Gy < 50.0 Gy	n. m.	88 % 72 %	88 % 57 %	0.37, n.s.
Grabenbauer et al., 2000	9 16	44-45 Gy 45.1-60 Gy	1.6-2.0 Gy	87 % 90 %	36 % 85 %	0.04
Paulino et al., 2013	29 10	</= 50.4 Gy >50.4 Gy	1.8 Gy	5 years 73.8 % 90.9 %	8 years 95.2 % 88.9%	0.37
Muller et al., 2013	13 52	</= 50.4 Gy >50.4 Gy	1.8Gy	77% 77%	77% 77%	0.941

Case / low grade glioma

HIT LGG 96 dose – response relationship / eventfree survival

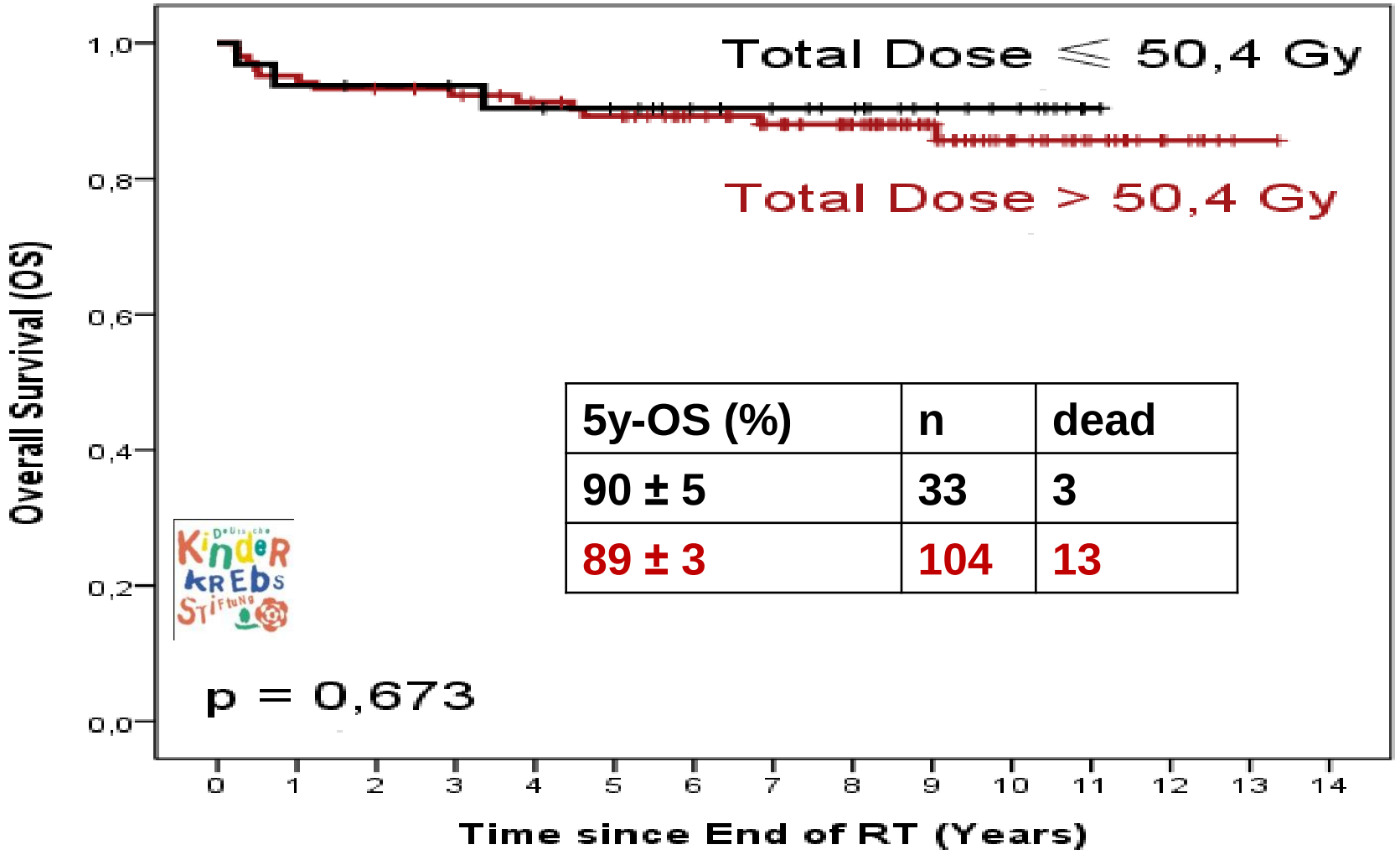


5y-EFS (%)	n	events
65 ± 9	32	11
63 ± 5	104	38

Müller et al., ECCO 2011

Case / low grade glioma

HIT LGG 96 dose – response relationship / overall survival



5y-OS (%)	n	dead
90 ± 5	33	3
89 ± 3	104	13

Case / low grade glioma

Which margin for CTV would you select ?

Case / low grade glioma

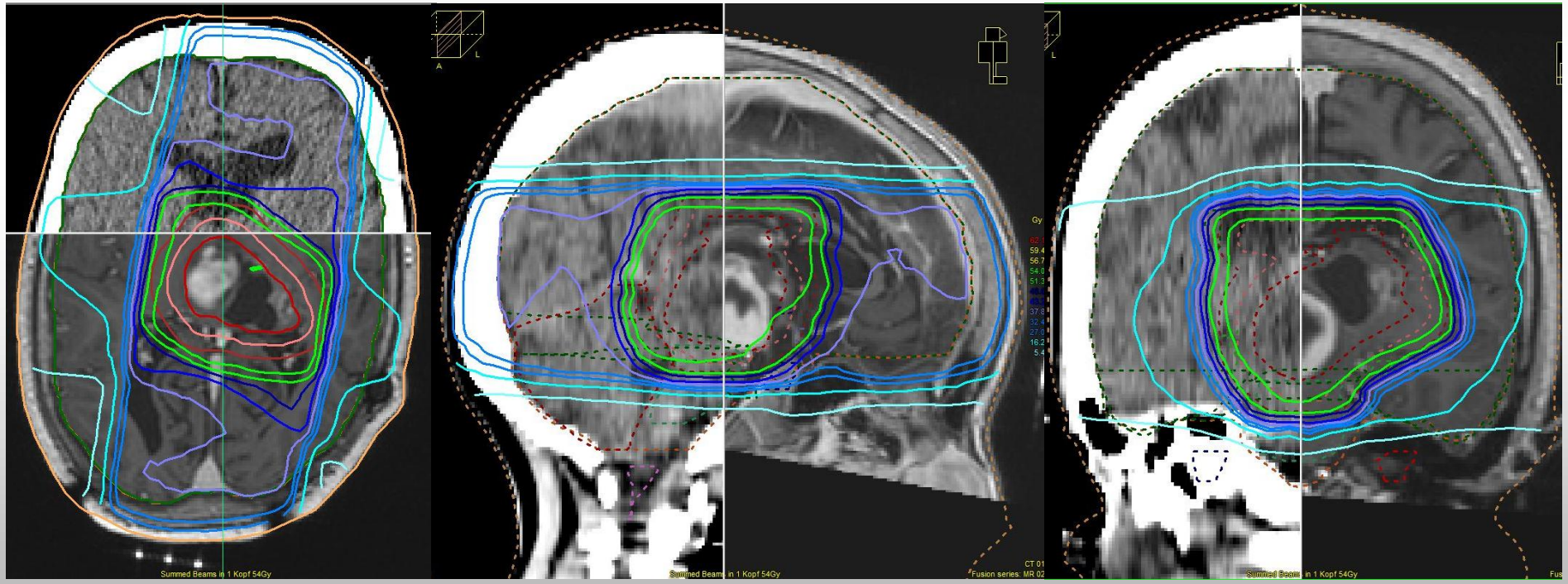
Outcome after RT with respect to margin / CTV

Author	Dose prescription	Pat.	Results	F-up
Debus et al., 1999	52.4 Gy/1.6-2.0 Gy Margin: 7 mm	10	5 y. PFS: 90 %, 5 y. OS: 100 %	12-72 mon.
Saran et al., 2002	50-55 Gy/30-33 Fr. Margin: 5 bis 10 mm	14	3 y. PFS: 87 %, 3 y. OS: 100 % 1 relapse within GTV	33 mon.
Marcus et al., 2005	Ster. Conv RT 52,2 Gy/1,8Gy Margin: 2 mm	81	5 y./8 y. PFS: 82.5 %/65 % 5 y./8 y. OS: 97.8 %/82 % 6 local relapses all within field	6.9 years
Combs et al., 2005	3D conformal RT 52.2 Gy / 1.8Gy Margin 5mm	15	3y. / 5 y. PFS : 92 % / 72 % 5 y. OS : 90 %	97 mon.
Merchant et al., 2009	3D conformal RT 54 Gy/1.8 Gy Margin: 15 mm	78	5/10 y. EFS: 87.4 %/74.3 % 5 / 10 y. OS: 98.5 %/95.9 % 13 relapses (8/13 within PTV) (1/13 margin) (4/14 CNS metast)	89 mon.
Paulino et al., 2013	IMRT45-60 Gy 5 – 10 mm	39	8 y. EFS/OS: 78.2 % and 93.7 % 7/7 failures in field	n.a.

Treatment plan

Case / low grade glioma

Image fusion with MRI T1 weighted with contrast and T2 weighted. 3 D conformal technique. Definition GTV on both MRI seq.
CTV = GTV plus 5 mm
PTV = CTV plus 5 mm
Dose prescription : 5 x 1.8 Gy, 54 Gy according to LGG 2004 protocol



Case / low grade glioma

Image fusion with MRI T1 weighted with contrast and T2 weighted. 3 D conformal technique. Definition GTV on both MRI seq.
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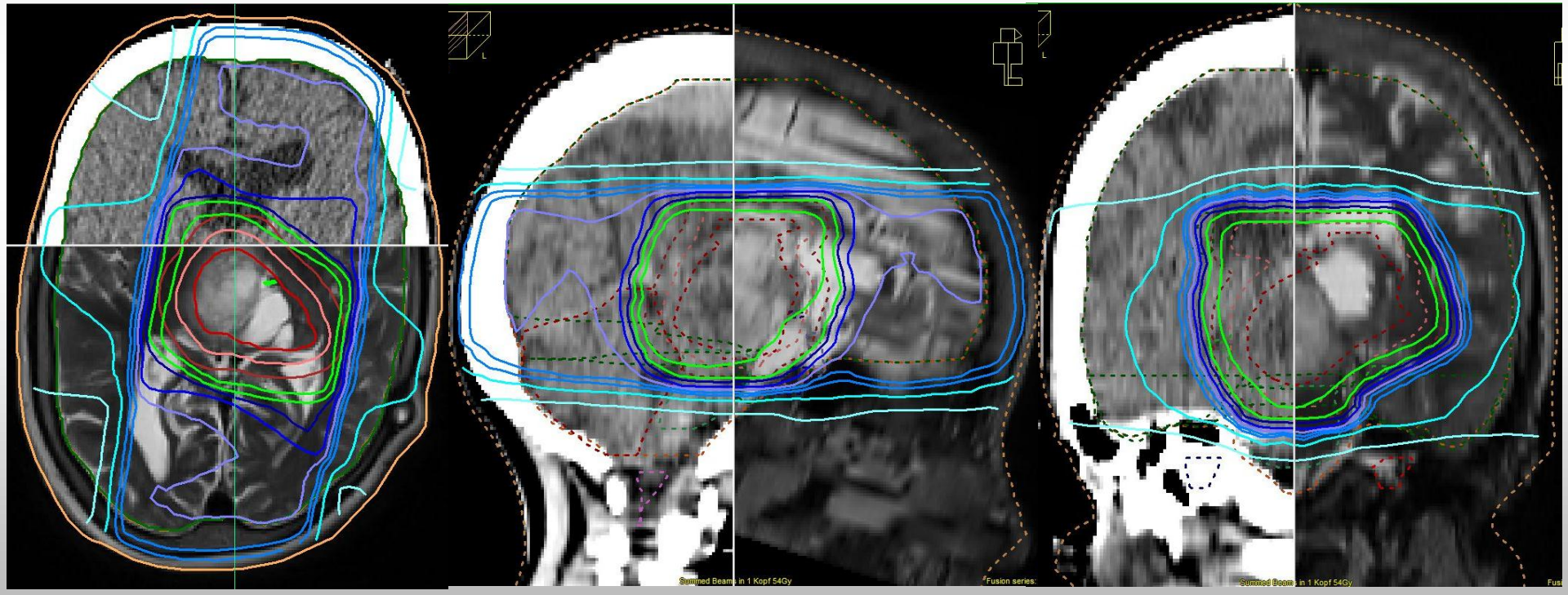
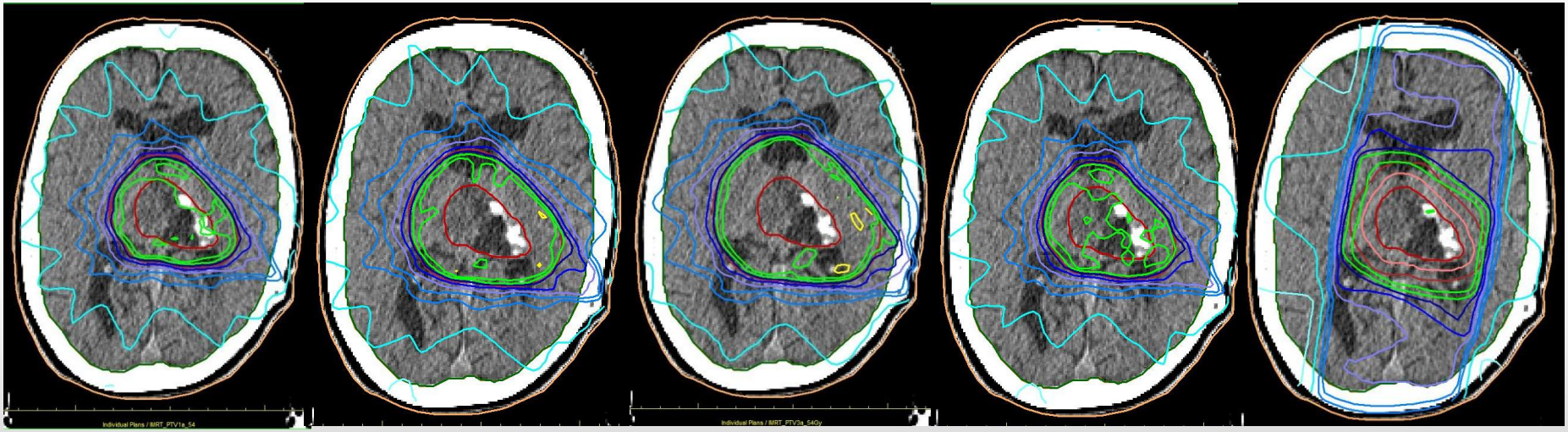


Case / low grade glioma

Impact of safety margin, treatment technology and dose constraints on dose distribution to organs at risk
Dose constraints : hippocampus / temporal lobe

IMRT 5mm with constr	IMRT 10mm with constr	IMRT 15mm with constr	IMRT 5mm no constr	3 D conf 5mm no constr

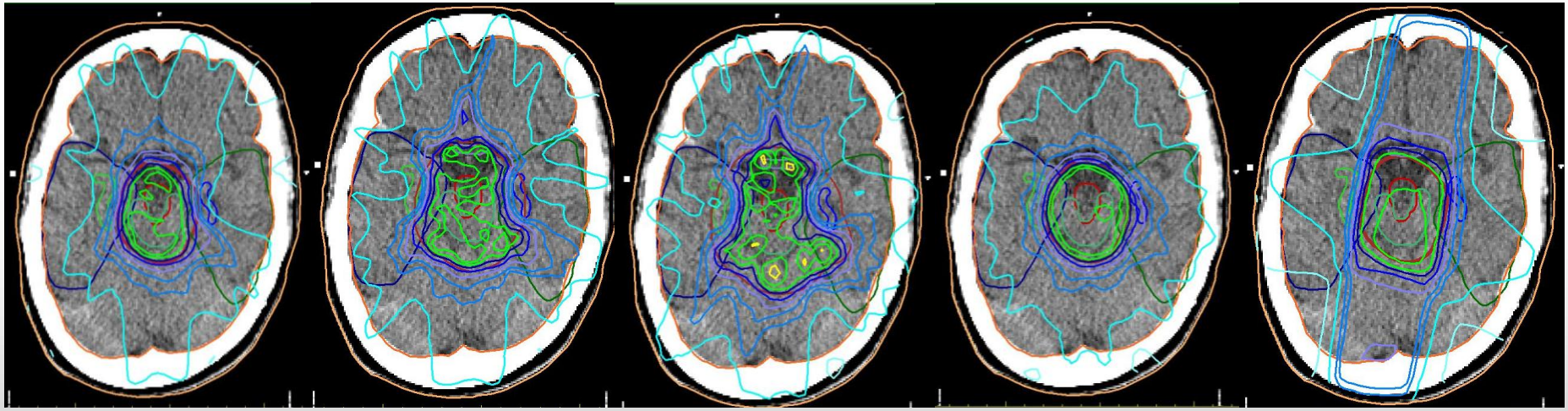


Central plane

Case / low grade glioma

Impact of safety margin, treatment technology and dose constraints on dose distribution to organs at risk
Dose constraints : hippocampus / temporal lobe

IMRT 5mm with constr	IMRT 10mm with constr	IMRT 15mm with constr	IMRT 5mm no constr	3 D conf 5mm no constr

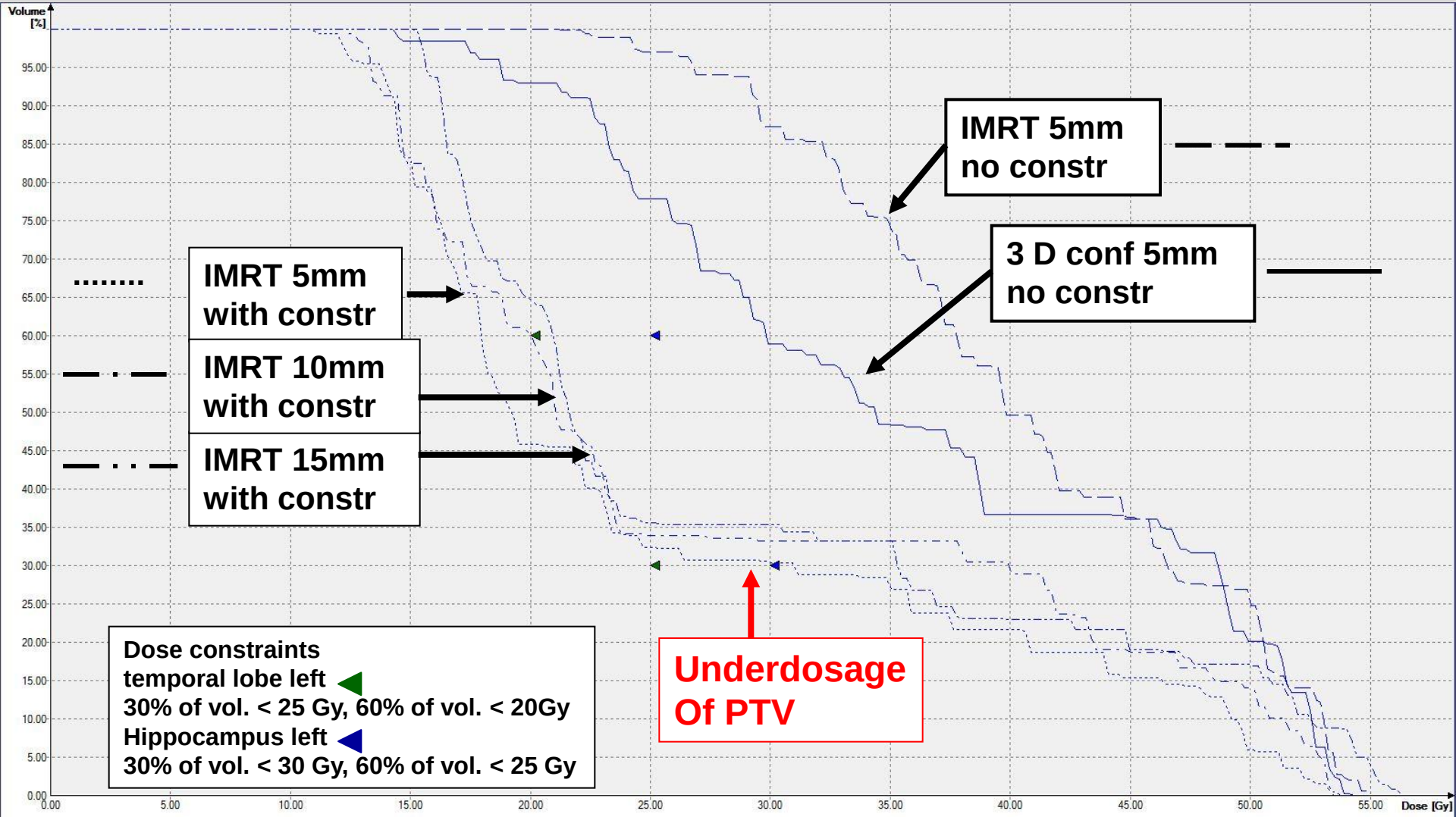


Off central plane / base of skull

Case / low grade glioma

Impact of safety margin, treatment technology and dose constraints on dose distribution to organs at risk

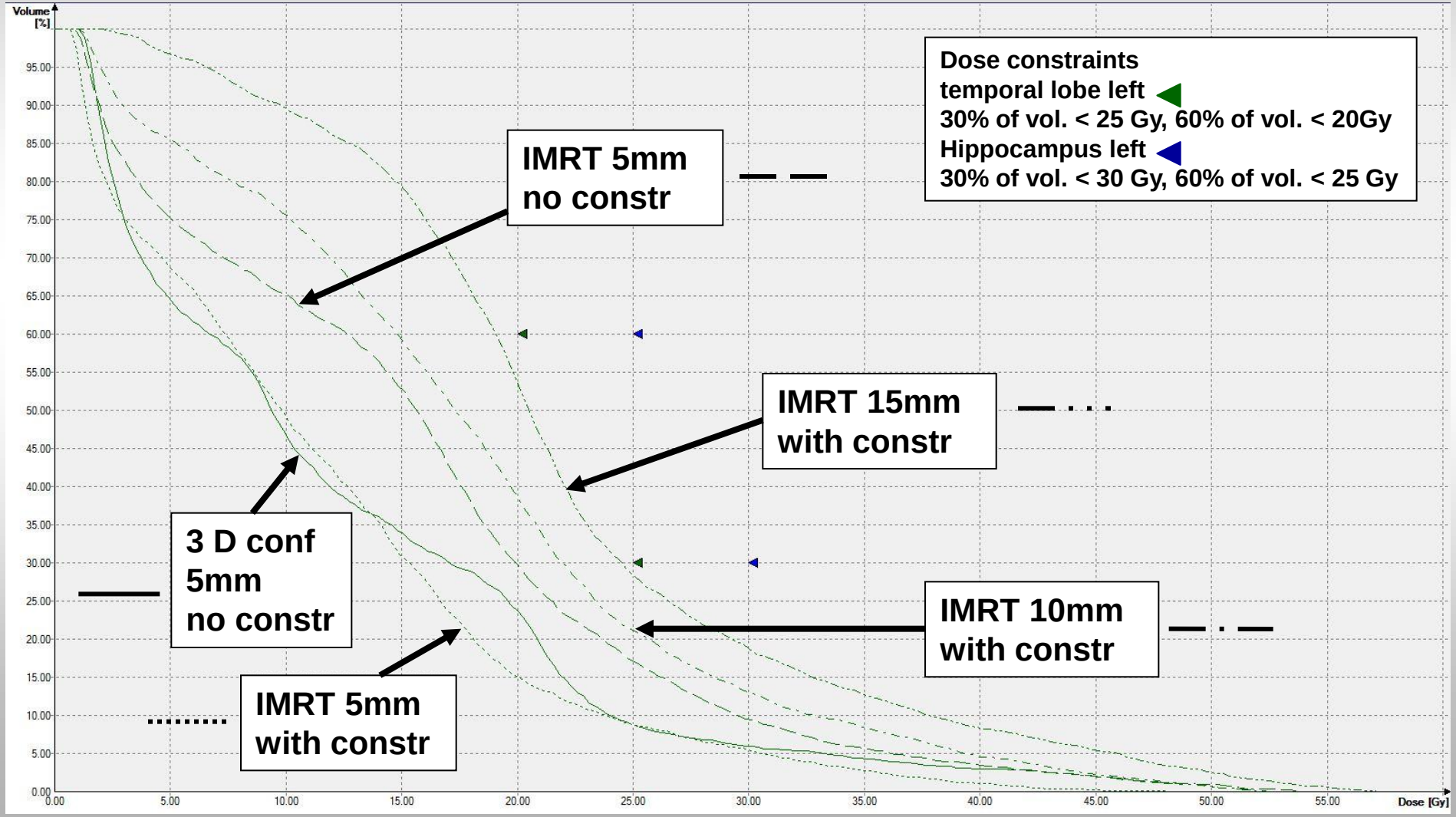
Dose constraints : hippocampus left / DVH



Case / low grade glioma

Impact of safety margin, treatment technology and dose constraints on dose distribution to organs at risk

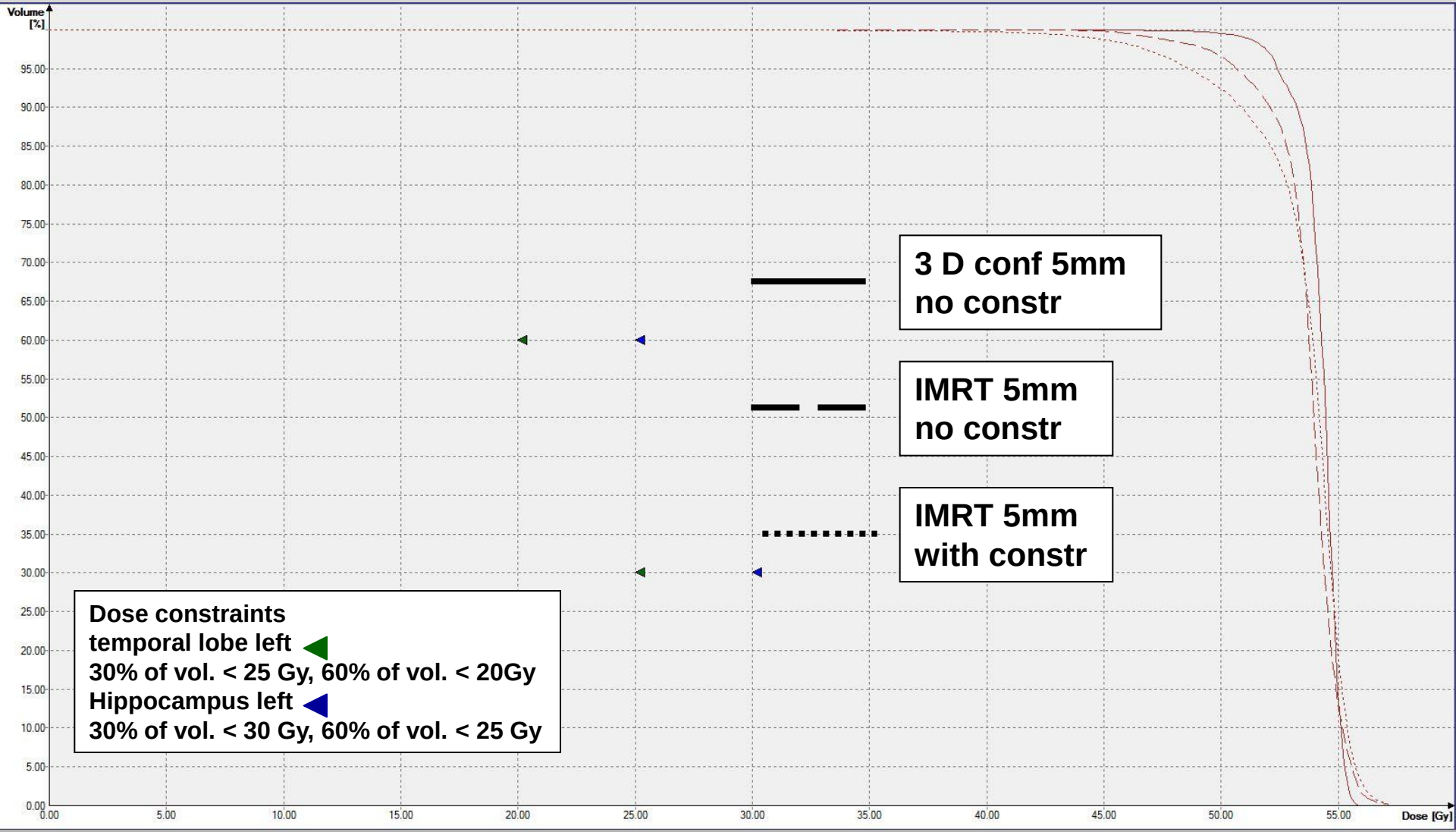
Dose constraints : temporal lobe left / DVH



Case / low grade glioma

Impact of safety margin, treatment technology and dose constraints on dose distribution to organs at risk

PTV / DVH



Case / low grade glioma

Impact of safety margin, treatment technology and dose constraints on dose distribution to organs at risk
Dose constraints : hippocampus / temporal lobe

Dose constraints in IMRT reduce integral dose to OAR, even if CTV is large
However, underdosage of PTV

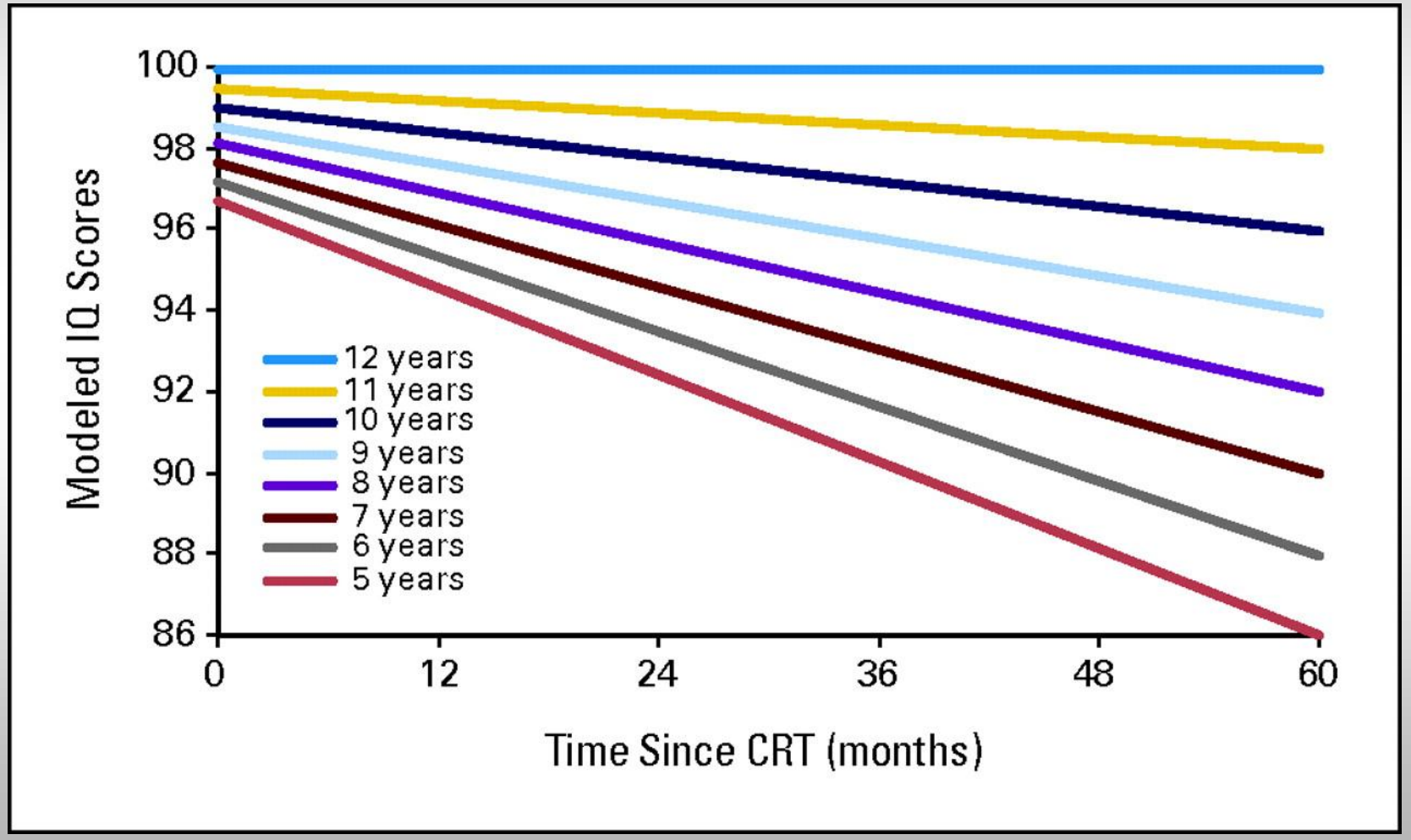
3 D conformal technique achieve a better preservation of OAR
as compared with IMRT without dose constraints
in OAR close to PTV

The closer the OAR to PTV the higher the impact of dose constraints
on the reduction of dose to OAR

The extent of CTV impacts the integral dose to OAR

Case / low grade glioma

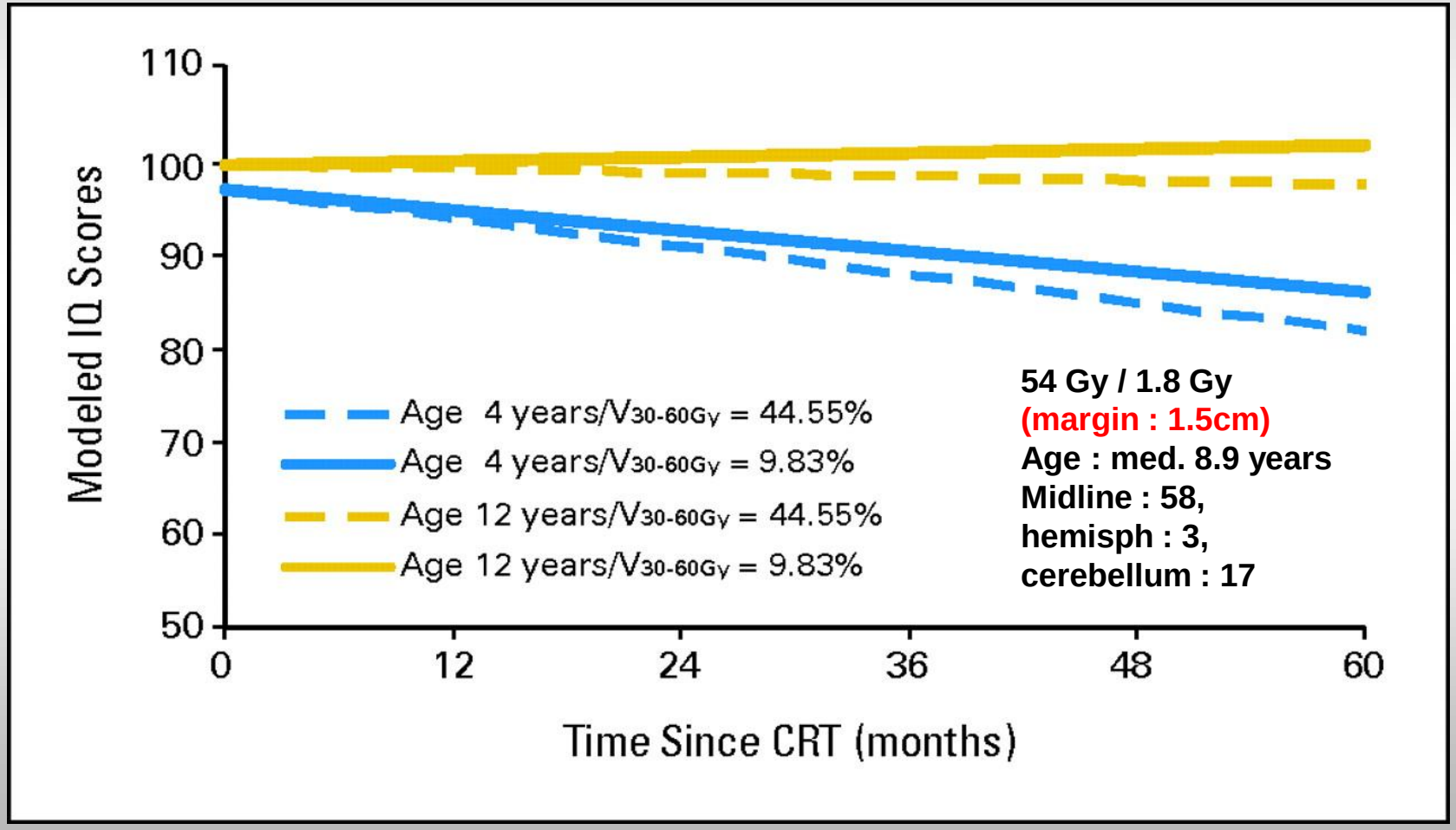
Modeled intelligence quotient (IQ) scores after conformal RT by age for pediatric low-grade glioma



Merchant, T. E. et al. J Clin Oncol; 27:3691-3697 2009

Case / low grade glioma

Modeled intelligence quotient (IQ) scores by age and supratentorial brain dose-volume intervals for pediatric low-grade glioma

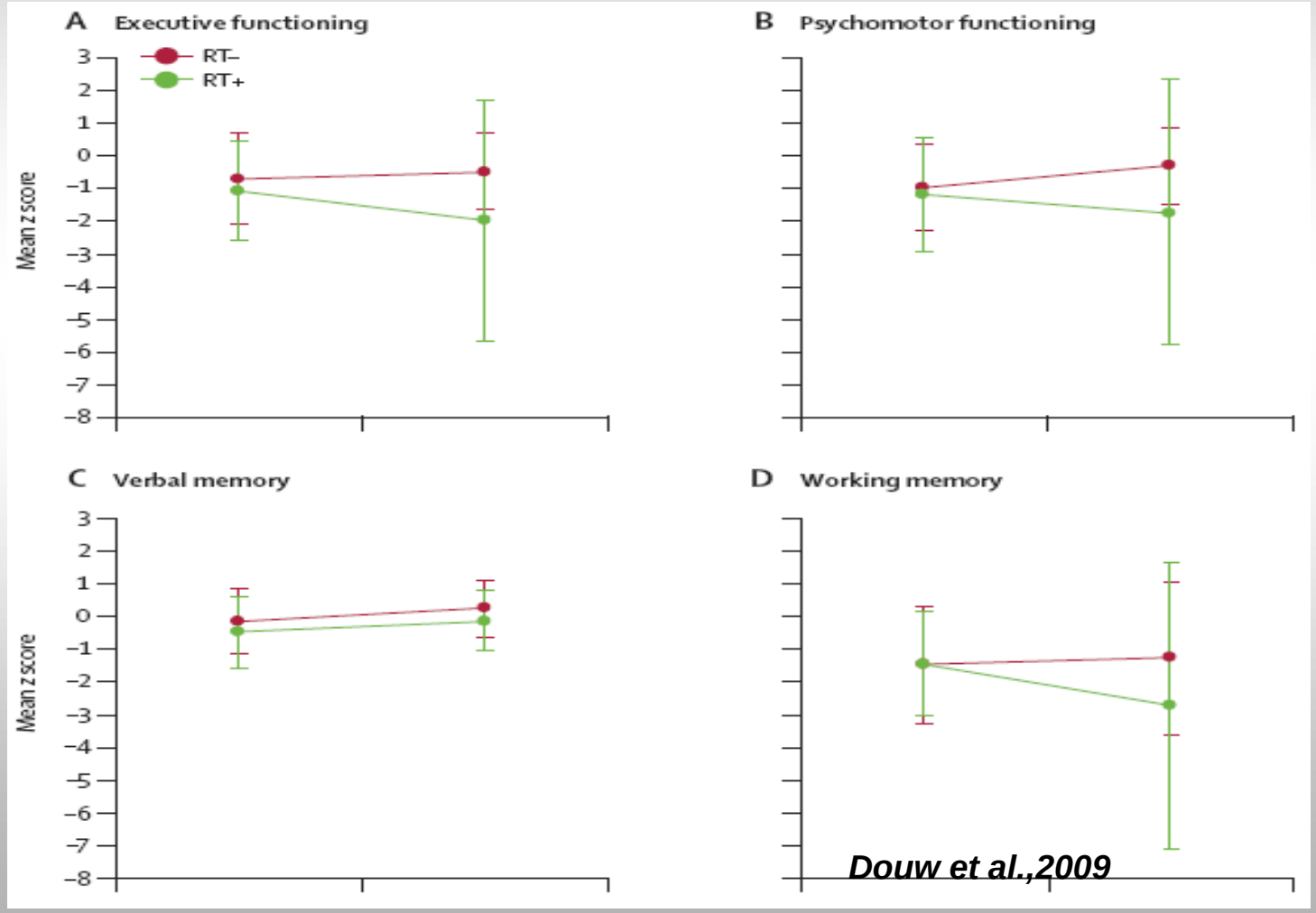


Merchant, T. E. et al. J Clin Oncol; 27:3691-3697 2009

Case / low grade glioma

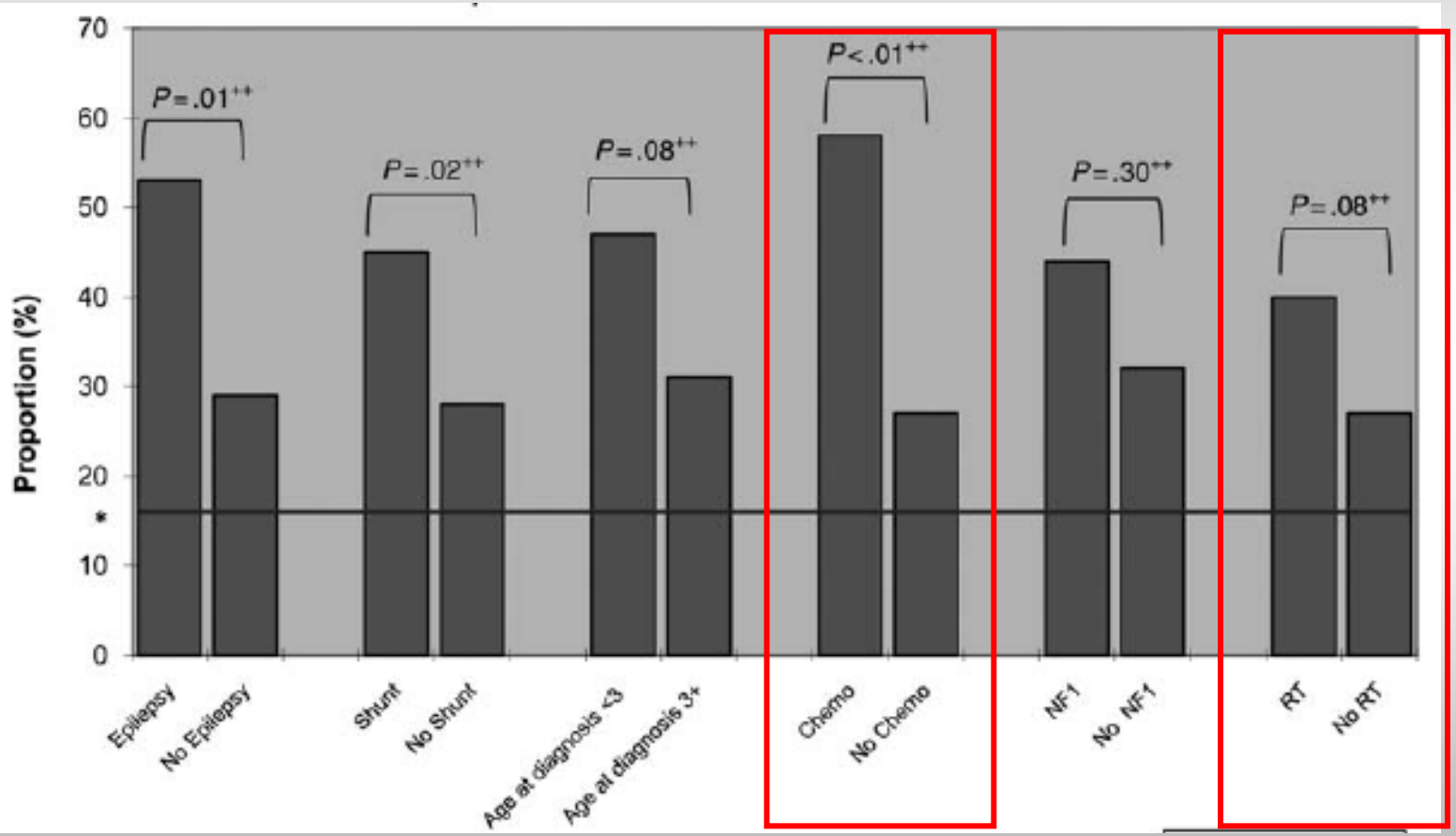
Neurocog. Function after RT (adults)

65 of 195 pat, age : not mentioned (mean 40 years ?) (32 RT, conv. techniques / margin 2 cm, dose : mean 56.6 Gy (30 (whole brain)-69 Gy)



Case / low grade glioma

Proportions of IQ score lower than 85 / Memphis series
Multivariate analysis : epilepsy, shunt, young age : neg. predictive



Armstrong et al., 2010

Case / low grade glioma

Impact of RT on late effects / Memphis series
Multivariate analysis of clinical parameters including treatments

Multivariable models demonstrated radiation therapy to be a significant independent predictor of

- **hearing loss**
- **growth**
- **hormone deficiency**
- **abnormal thyroid function**
- **ACTH deficiency**

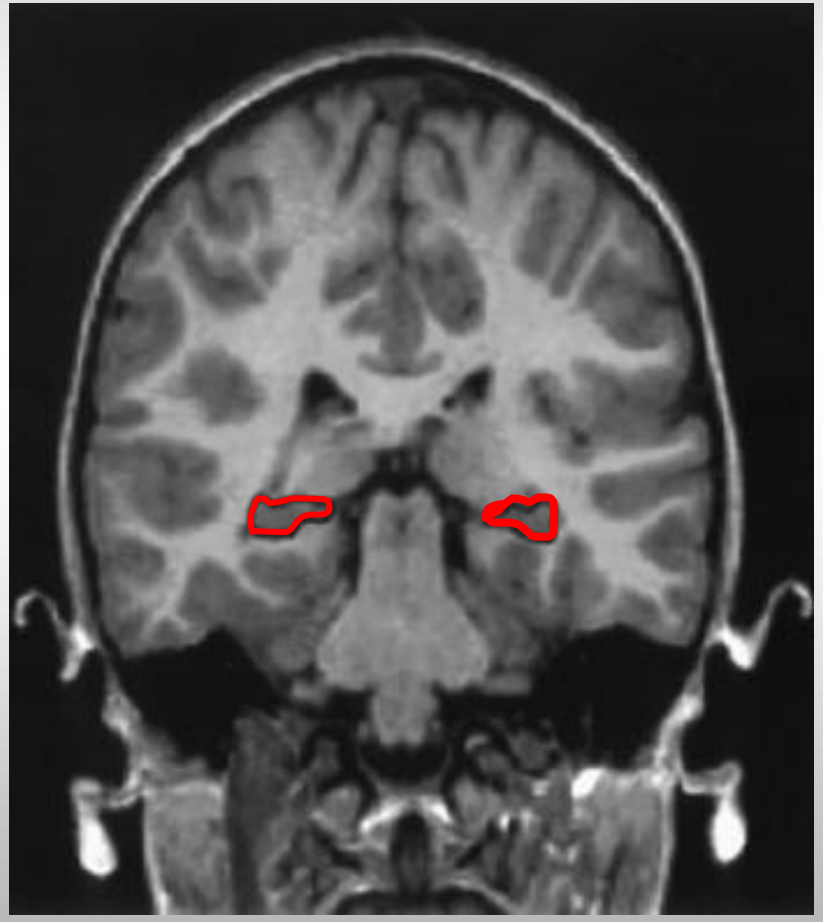
Treatments	n
Surgery only	165
Surgery + RT	83
Surgery + RT + chemo	56
Surgery + chemo	31

(but not neurocognitive function)
(vascular complications were not investigated)

Armstrong et al., 2010

Case / low grade glioma

Hippocampus



Major functions

Learning

Memory

Attention / executive functions

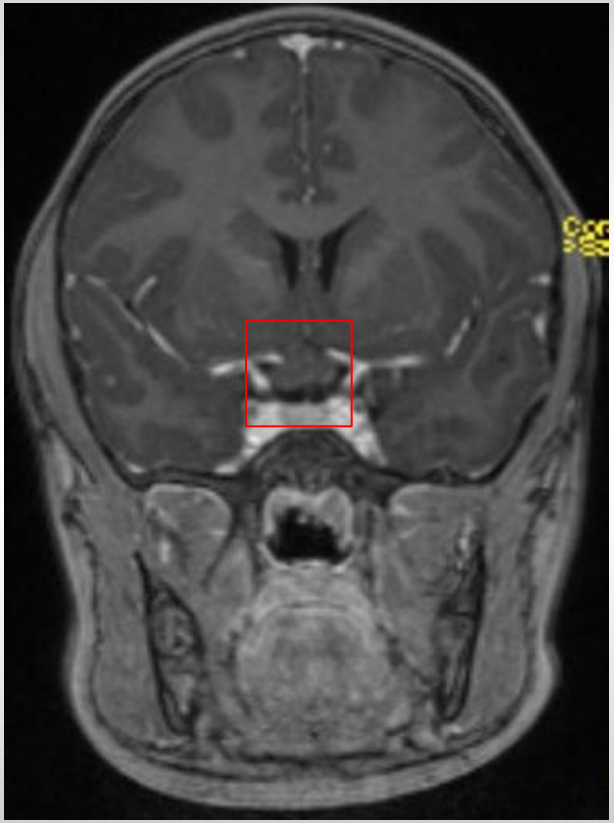
Neurogenesis

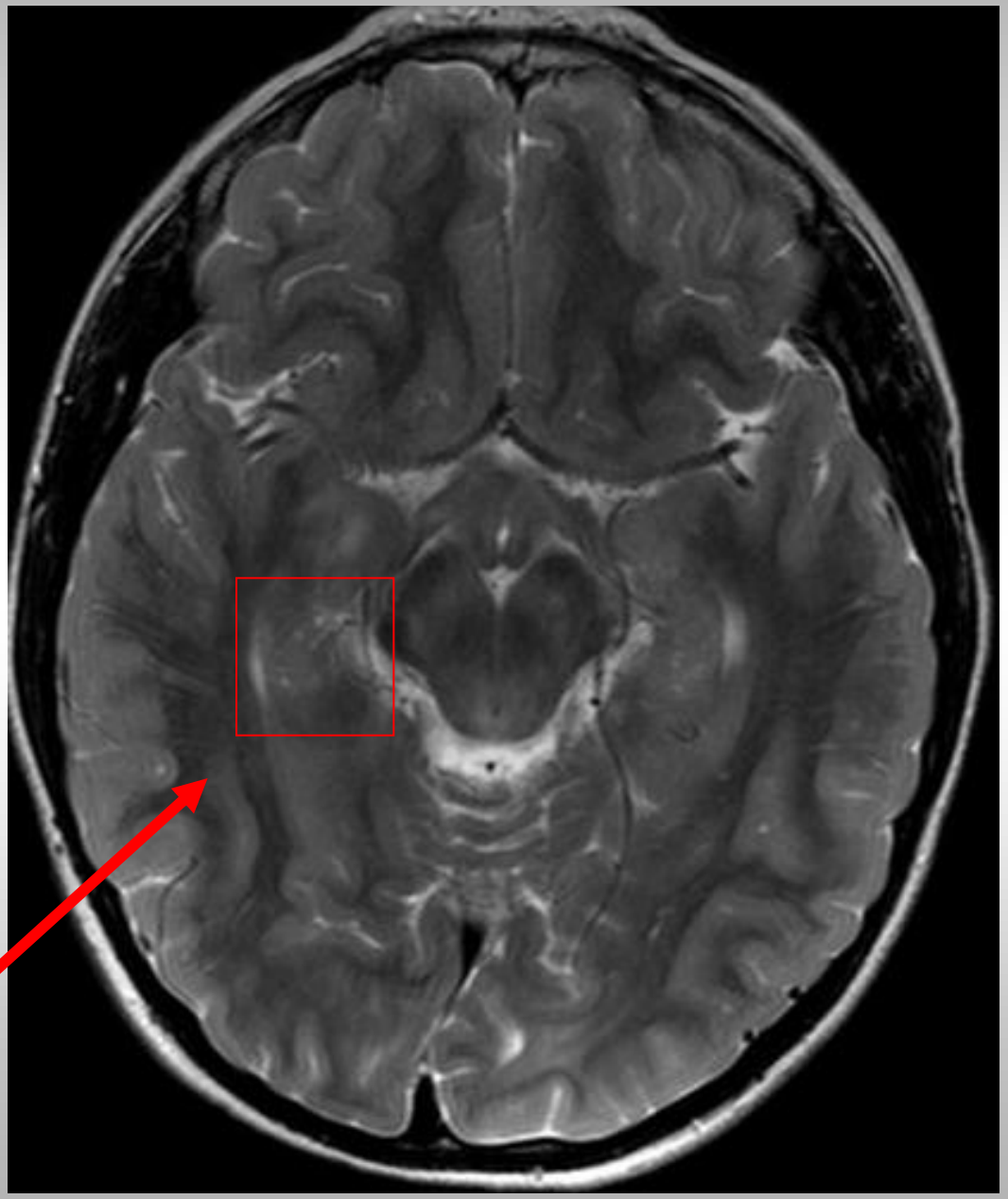
Development

repair

Case / low grade glioma

8 y. / glioma Optic chiasm in NF1
Heavy mental retardation

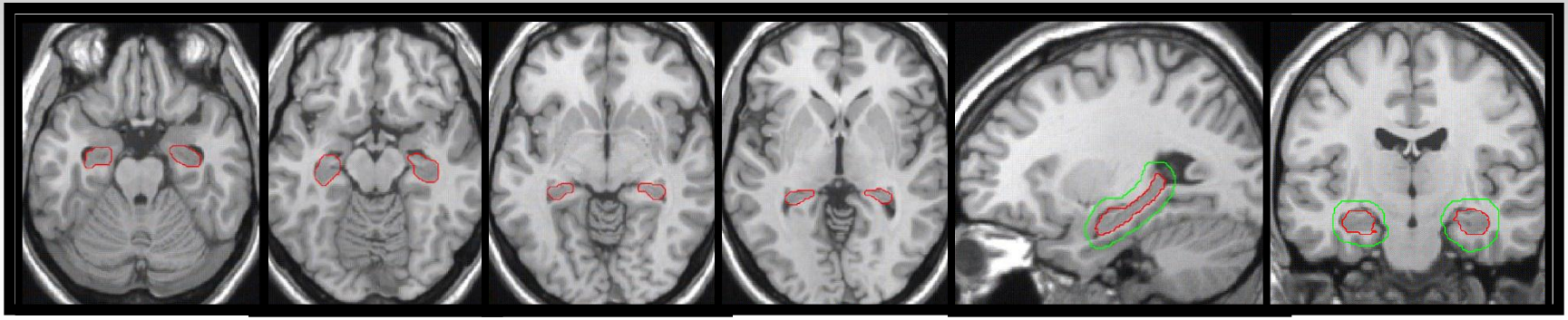


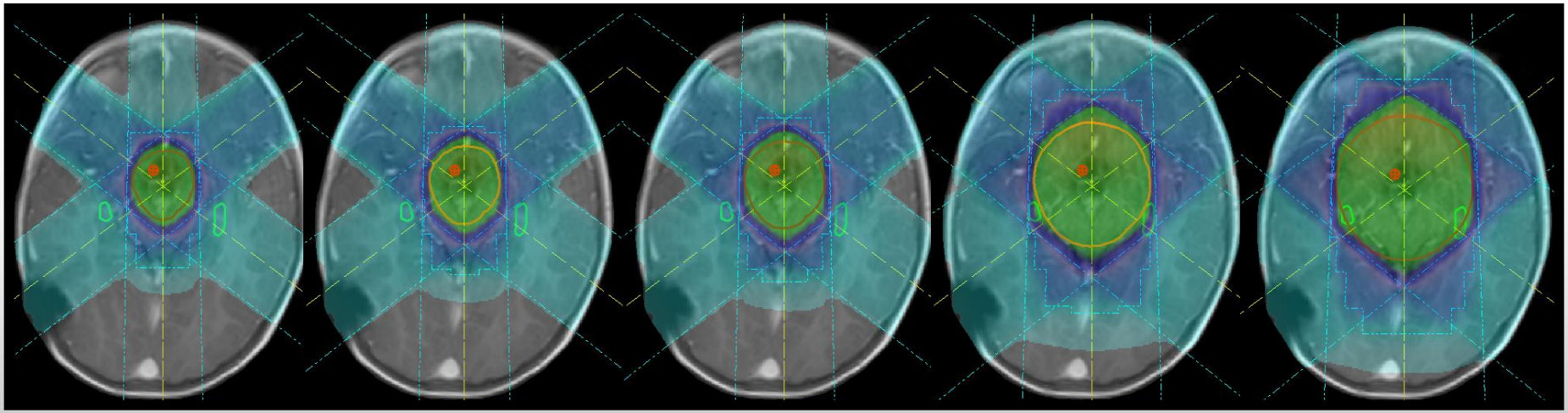


MRT:
In T2-weighted imaging multiple hyperintense white matter and hippocampal changes.

Case / low grade glioma

3-D conformal treatment plan - craniopharyngioma





PTV 1
CTV = GTV
PTV = CTV +3mm
(=Boston)

PTV 2
CTV= GTV + 2 mm,
PTV = CTV+ 3mm

PTV 3
CTV= GTV + 2 mm,
PTV = CTV +5mm

PTV 4
CTV= GTV + 1.0cm
PTV = CTV plus 5mm
(=St. Jude)

PTV 5
CTV= GTV + 1.5 cm,
PTV = CTV + 5mm

Case / low grade glioma

3-D conformal treatment plan – craniopharyngioma
Dose to organs at risk (med and max dose)

	PTV 1-3 : high precision Stereotactic RT			PTV 4-5 : conventional 3-D- RT	
	PTV 1 med./max. Vol. : 18ml	PTV 2 med./max Vol.: 25 ml	PTV 3 med./max Vol.: 34 ml	PTV 4 med./max Vol.: 100 ml	PTV 5 med./max Vol.: 165 ml
Hippoc. left	16.0 / 20.4	16.7 / 25.2	17.4 / 32.5	48.7 / 52.9	52.7 / 53.3
right	15.6 / 16.0	16.2 / 17.2	17.0 / 19.2	48.3 / 50.3	52.8 / 53.2
Temp. left lobe	5.3 / 46.2	9.4 / 51.0	13.7 / 52.7	25.4 / 55.7	35.3 / 56.5
right	10.1 / 46.5	13.8 / 51.7	14.5 / 53.6	27.0 / 55.3	38.0 / 56.6
Supratent Brain	2.9 / 55.4	4.0 / 55.6	5.6 / 55.7	14.2 / 56.2	20.6 / 56.7

PTV 1
CTV = GTV
PTV = CTV +3mm

PTV 2
CTV= GTV + 2 mm,
PTV = CTV+ 3mm

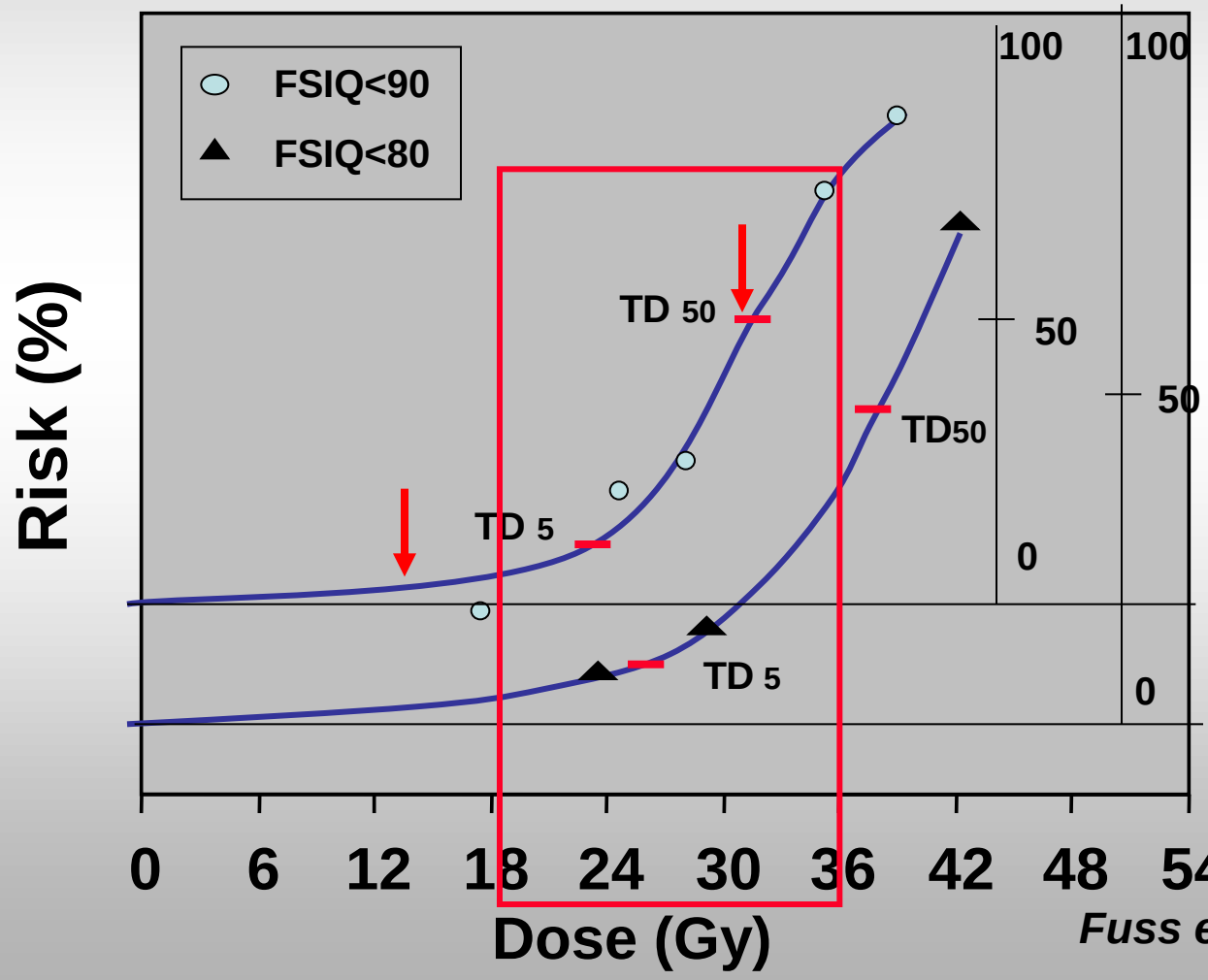
PTV 3
CTV= GTV + 2 mm,
PTV = CTV +5mm

PTV 4
CTV= GTV + 1.0cm
PTV = CTV plus 5mm

PTV 5
CTV= GTV + 1.5 cm,
PTV = CTV + 5mm

Case / low grade glioma

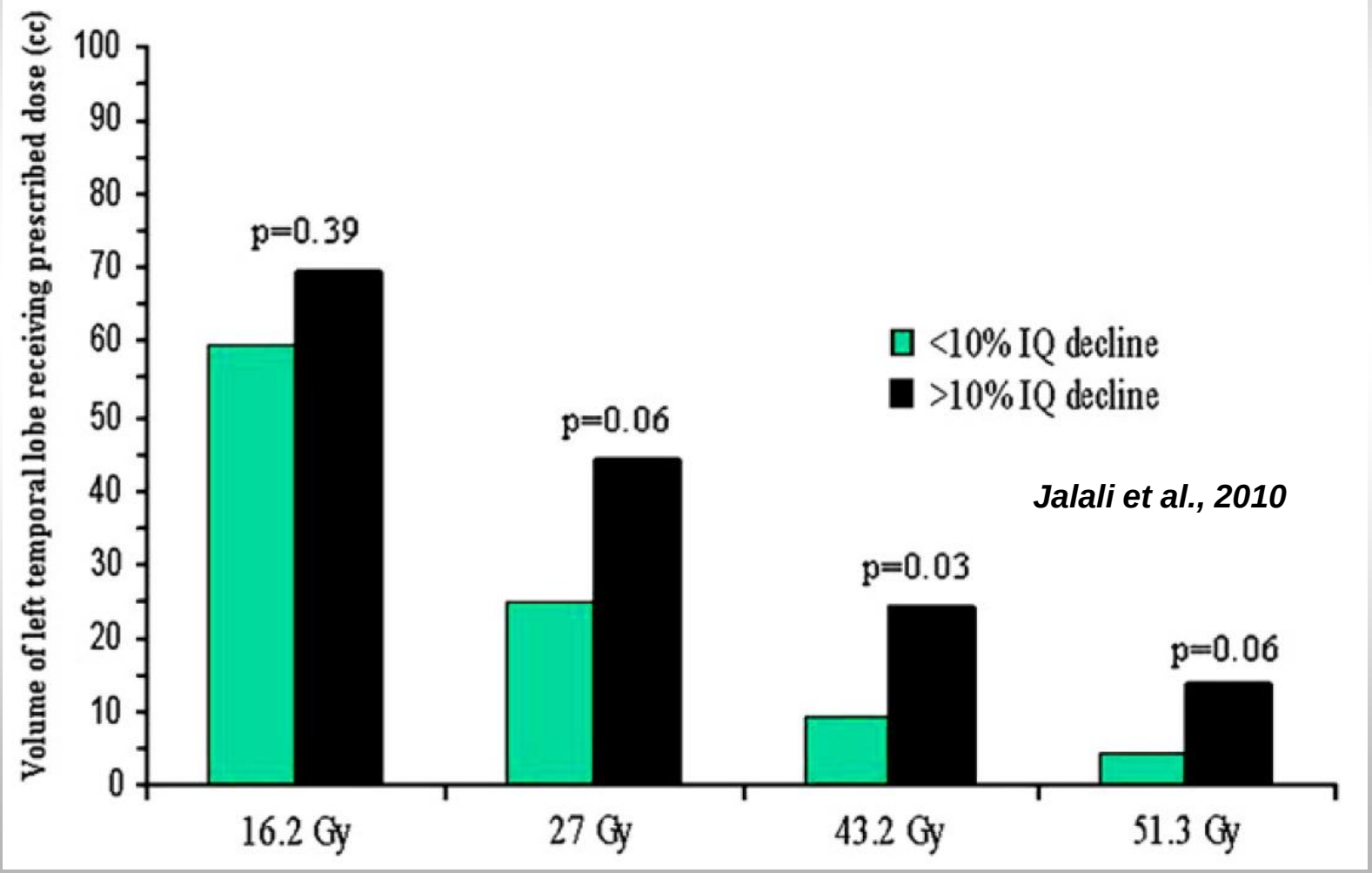
Dose response relationships, n=536, children
16 Publ. (ALL - + MTX)



Fuss et al., 2000

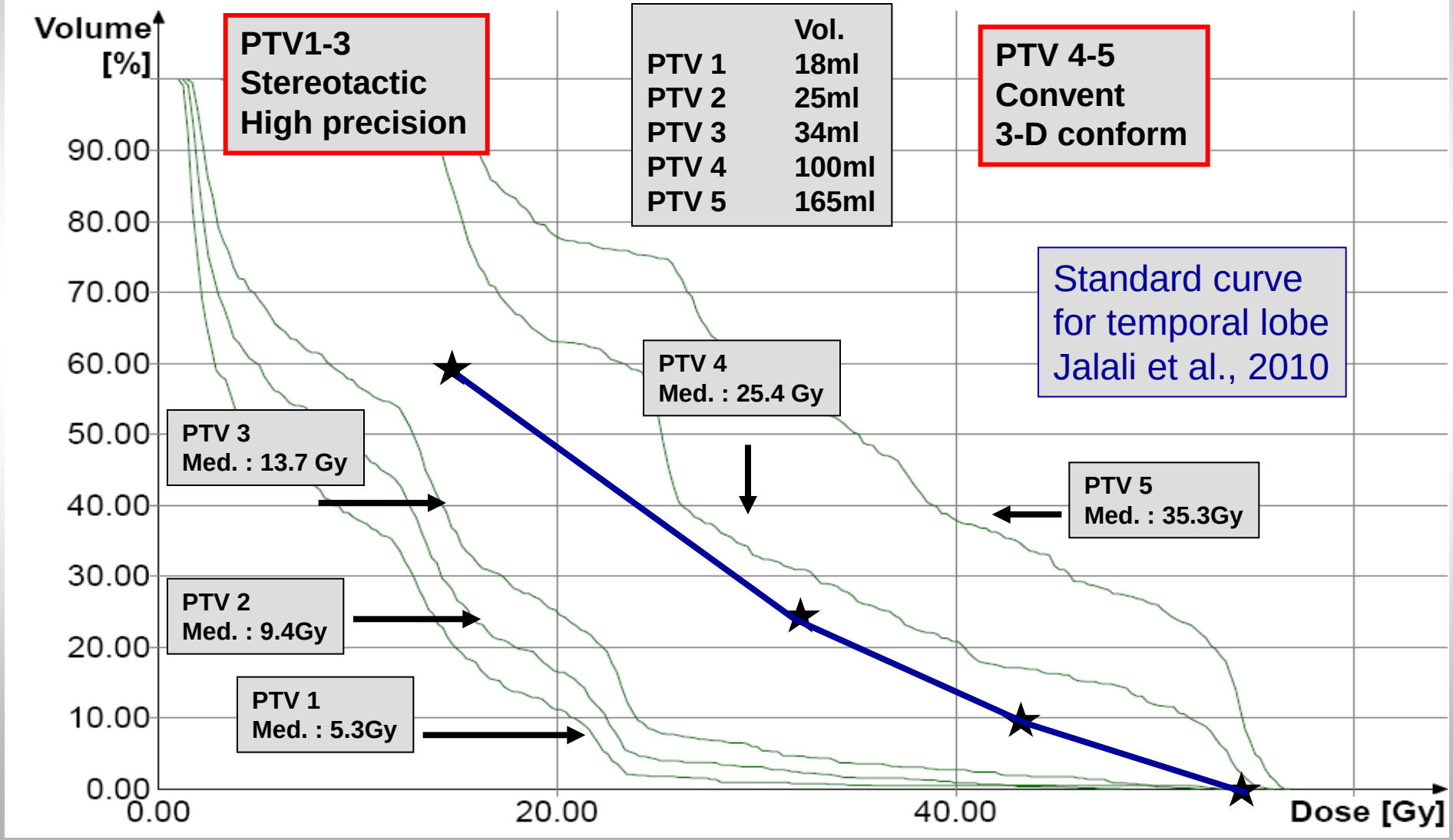
Case / low grade glioma

3-D conformal treatment plan – dose to temporal lobe
Integral dose distribution / decline in FSIQ



Case / low grade glioma

3-D conformal treatment plan – craniopharyngioma
DHV / temporal lobe left according to PTV volume / safety margin



Thank you very much for your attention

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