Definition of the clinical volumes in gliomas

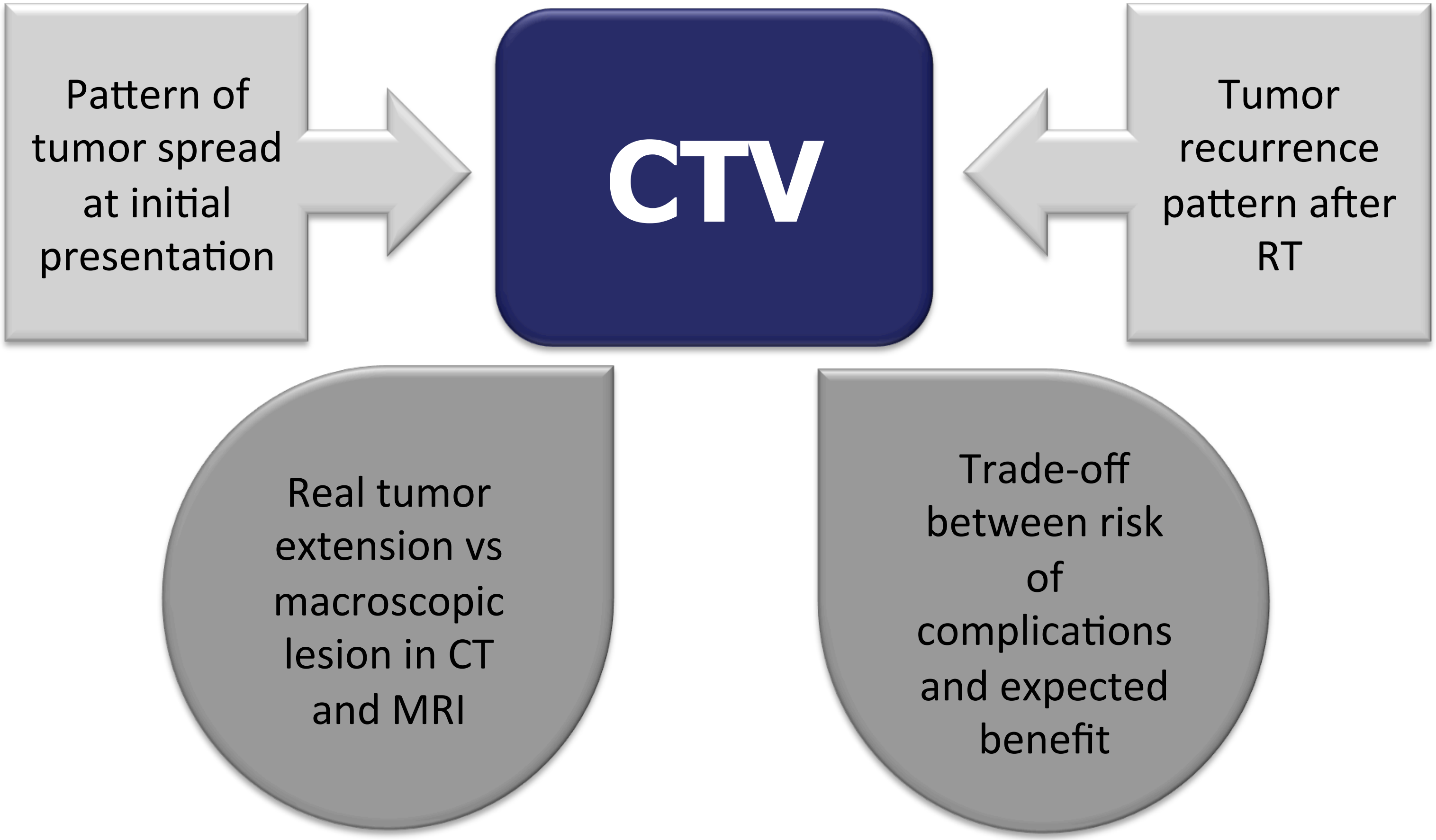
Silvia Scoccianti, Firenze

CTV definition in gliomas. Practical considerations

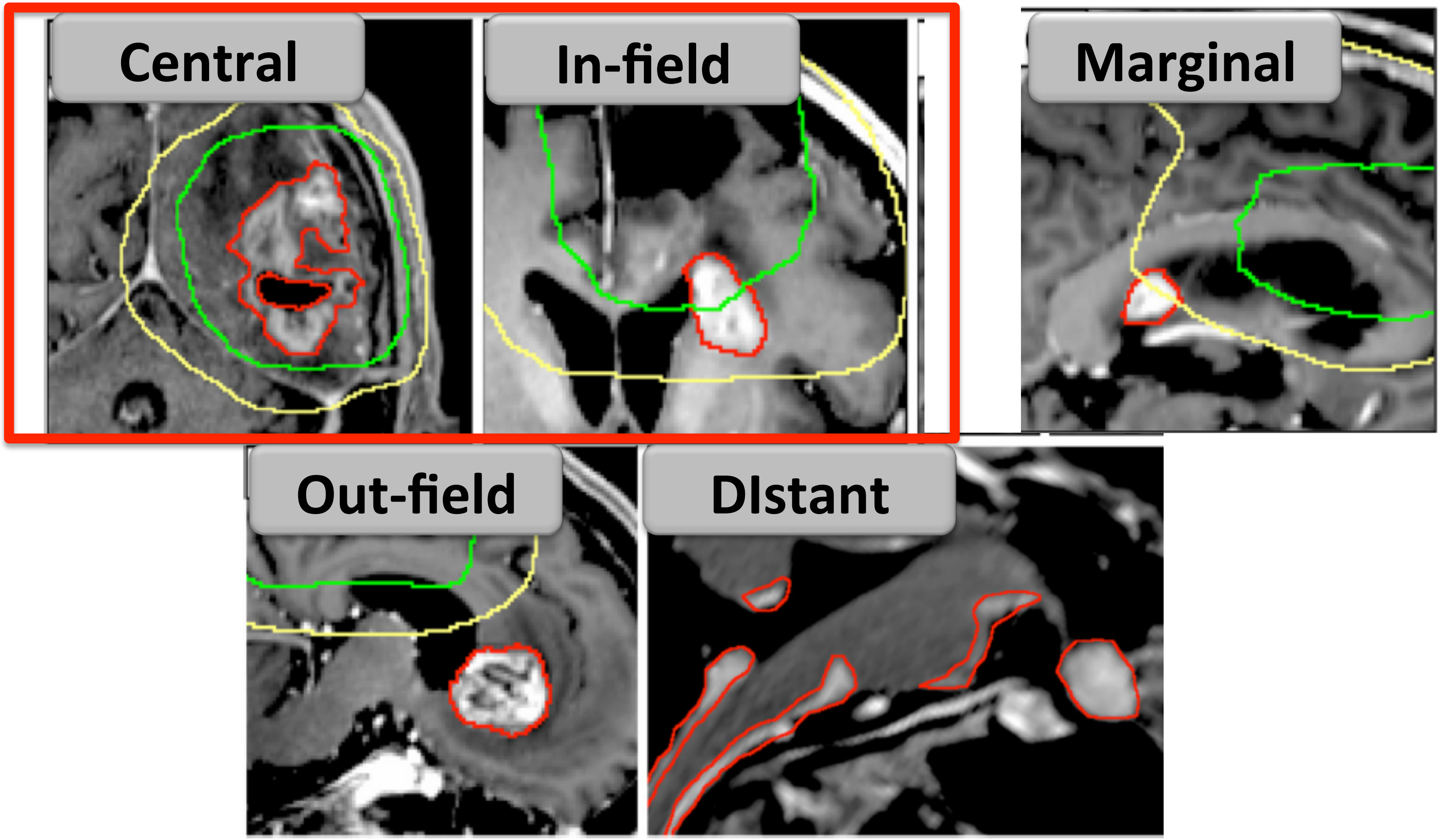
Use of advanced imaging for treatment planning purposes

Something new about OARs

Definition of the clinical volumes in GLIOBLASTOMA



patterns of relapse



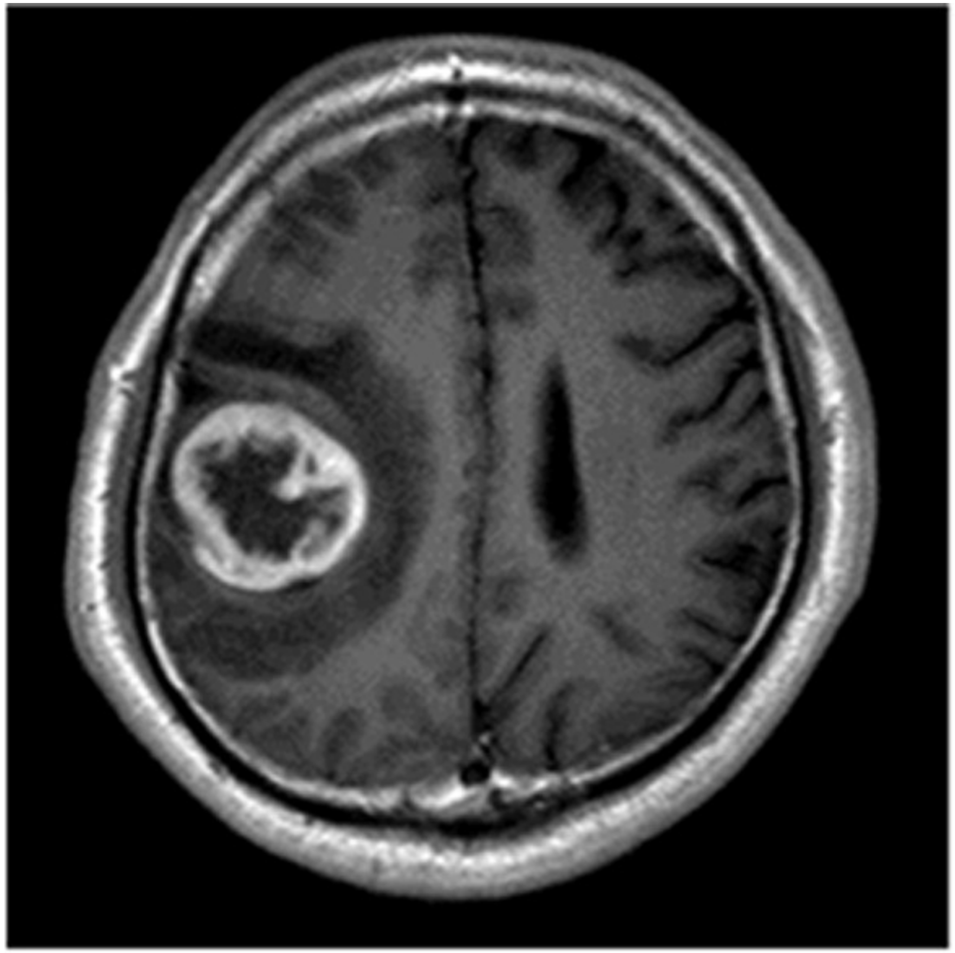
Ogura *et al. Radiation Oncology* 2013, **8**:97

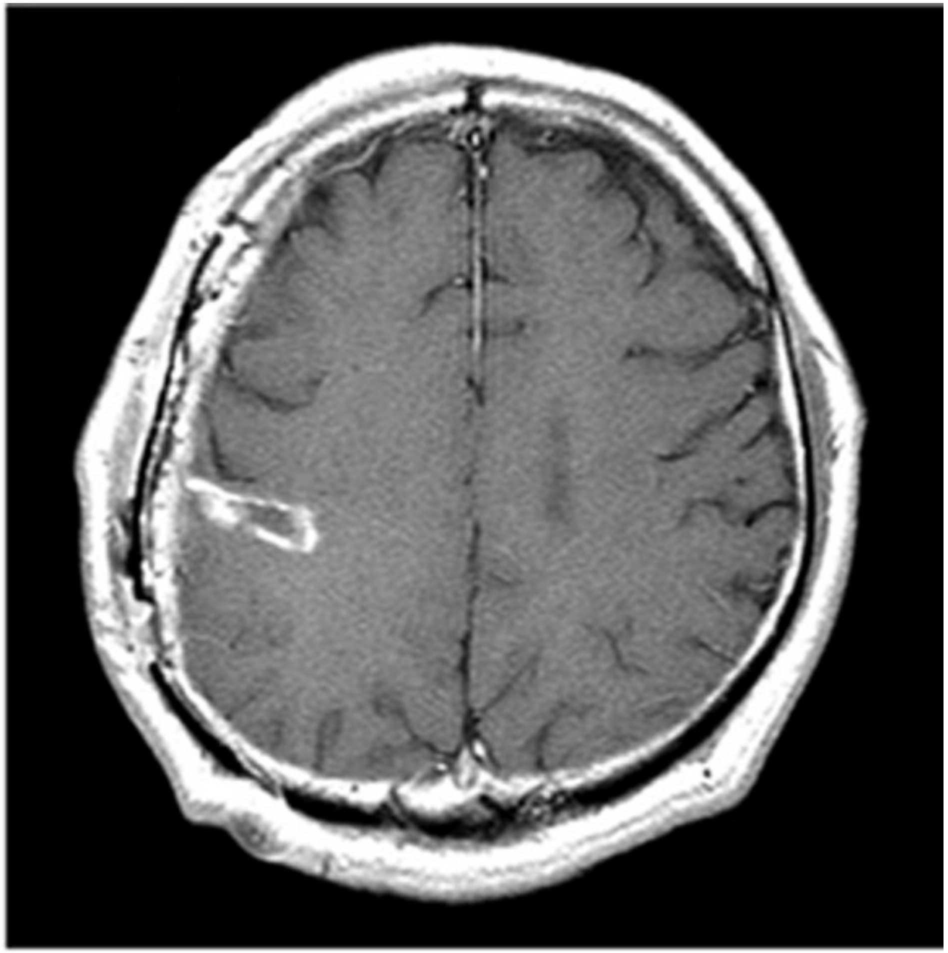
Table 5 Comparison of published data with regard to patterns of failure in patients with glioblastoma

Author	Year	Number	Treatment	Dose (Gy)	Margin (cm)	Recurrence sites			
						Central	In-field	Marginal	Distant
Nakagawa [7]	1998	38	3DCRT + ACNU	60–80	0–2	90%†			5%
				90	0–2	46%††			8%
Lee [5]	1999	36	3DCRT	70–80	1.5	72%	17%	8%	3%
Chan [6]	2002	34	3DCRT	90	0.5	78%	13%	9%	
Chang [3]	2007	48	3DCRT ± chemo*	60	1	83%	6%	6%	4%
Brandes [16]	2009	95	3DCRT + TMZ	60	2–3	72%		6%	22%
Milano [15]	2010	54	3DCRT + TMZ	60	2–2.5	92%§		15%	13%
Minniti [14]	2010	105	3DCRT + TMZ	60	1–2	79%	6%	6%	14%
McDonald [13]	2011	41	(IMRT or 3DCRT) ± TMZ	60	0.8	78%	15%	5%	2%
This study	2012	58	3DCRT ± (ACNU or TMZ)	60	1.5–2	69%	16%	12%	3%

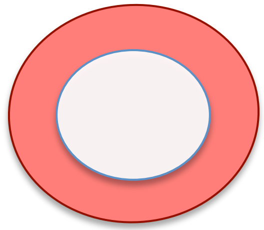
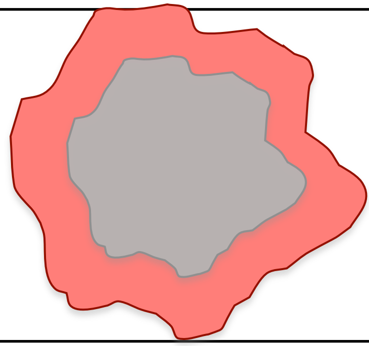
*21/48 patients received adjuvant or concurrent chemotherapy (carmustine, procarbazine, and temozolomide).
†5% were subependymal recurrences (did not apply to our classification method of recurrence sites).
††46% were subependymal recurrences (did not apply to our classification method of recurrence sites).
§Insufficient data to apply to our classification method of recurrence sites.

a)Preoperative or Postoperative MRI?
b)Inclusion of edema

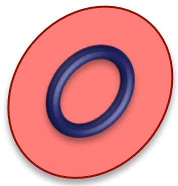
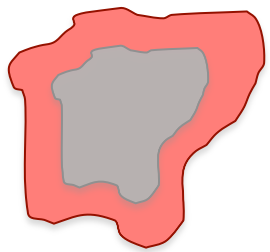




PREOPERATIVE scan

	Contrast enhancing lesion + margins
	Preoperative edema + margins

POSTOPERATIVE scan

	Surgical bed + any residual lesion + margins
	Postoperative edema + margins

Inclusion of edema: to be or not to be?

Yes → **Edema** ← **No**

- Burger, JNS 1983;
- Earnest, Radiology 1988;
- Halperin, IJROBP 1989;
- Kelly, Mayo Clin Proc 1987

Peritumoral edema is directly related to infiltrating tumors cells

Peritumoral edema is the result of mass effect and vascular permeability factors secreted by the tumor

-Stadlbauer, Neuroimage 2004;
-Ganslandt, NS 2005
- Farace, BJR 2011

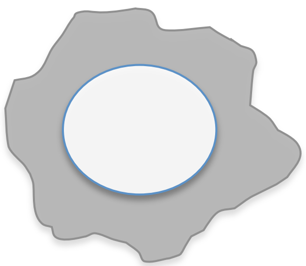
EVALUATION OF PERITUMORAL EDEMA IN THE DELINEATION OF RADIOTHERAPY CLINICAL TARGET VOLUMES FOR GLIOBLASTOMA

Eric L. Chang, M.D., Serap Akyurek, M.D., Tedde Avalos, C.M.D., Neal Rebueno, C.M.D., Chris Spicer, C.M.D., John Garcia, C.M.D., Robin Famiglietti, M.B.A., C.M.D., Pamela K. Allen, Ph.D., K. S. Clifford Chao, M.D., Anita Mahajan, M.D., Shiao Y. Woo, M.D., and Moshe H. Maor, M.D.

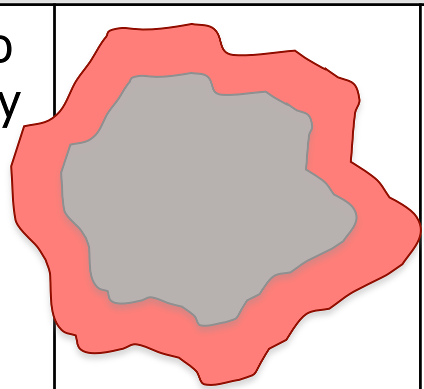
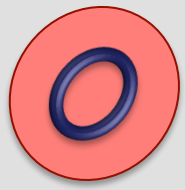
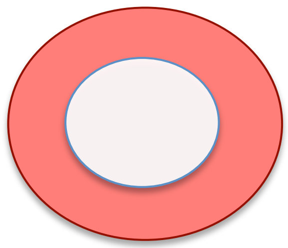
Department of Radiation Oncology, The University of Texas, M. D. Anderson Cancer Center, Houston, TX

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 1, pp. 144–150, 2007

Preoperative scan



Postoperative scan

Theoretical plans			Real plans		
Up to 46 Gy		Preoperative edema + 2 cm	Up to 50 Gy		Surgical bed + any contrast enhancing residual tumor + 2 cm
Boost 46 -> 60 Gy		Preoperative contrast ehnancing lesion + 2.5 cm	Boost 50 -> 60 Gy		Surgical bed + any contrast enhancing residual tumor

n=48

Most failures (90%) occurred with a central or in-field recurrence pattern.

	Theoretical plans	**Real plans**
Volume of brain irradiated in pts with large volumes of edema (>75cc)	p<0.001	

	Theoretical plans	**Real plans**
Failure in central and in-field localization	p=NS	

Despite the coverage of edema, three marginal and two distant recurrences failed to be covered by the theoretical 46-Gy isodose volume

Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide

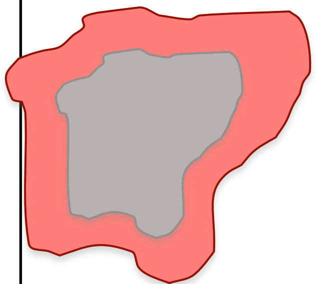
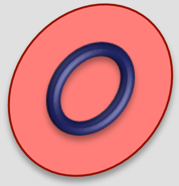
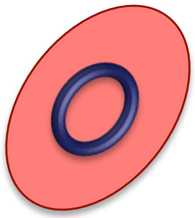
Giuseppe Minniti [a,b,*], Dante Amelio [c], Maurizio Amichetti [c], Maurizio Salvati [b], Roberta Muni [a], Alessandro Bozzao [d], Gaetano Lanzetta [b], Stefania Scarpino [e], Antonella Arcella [b], Riccardo Maurizi Enrici [a]

Radiotherapy and Oncology 97 (2010) 377–381

Postoperative scan

Edema

Surgical bed

Theoretical plans			Real plans		
Up to 46 Gy		Postoperative edema + 2 cm	Up to 60 Gy		Surgical bed + any contrast enhancing residual tumor + 2 cm
Boost 46 -> 60 Gy		Surgical bed any contrast enhancing residual tumor + 2.5 cm			

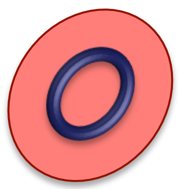
n=105

	Theoretical plans	Real plans
Volume of brain irradiated with 46 and 60 Gy	$p<0.001$	

Analysis of tumor recurrences in 105 patients with GBM.

Recurrence volume within radiation field	S'Andrea$_{plans}$	RTOG$_{plans}$
Central	79	80
In-field	6	7
Marginal	6	4
Outside	14	14

EORTC criteria

CTV		
Up to 60 Gy		Surgical bed + any contrast enhancing residual tumor + 2 cm

take home message!

EORTC Protocol CORE

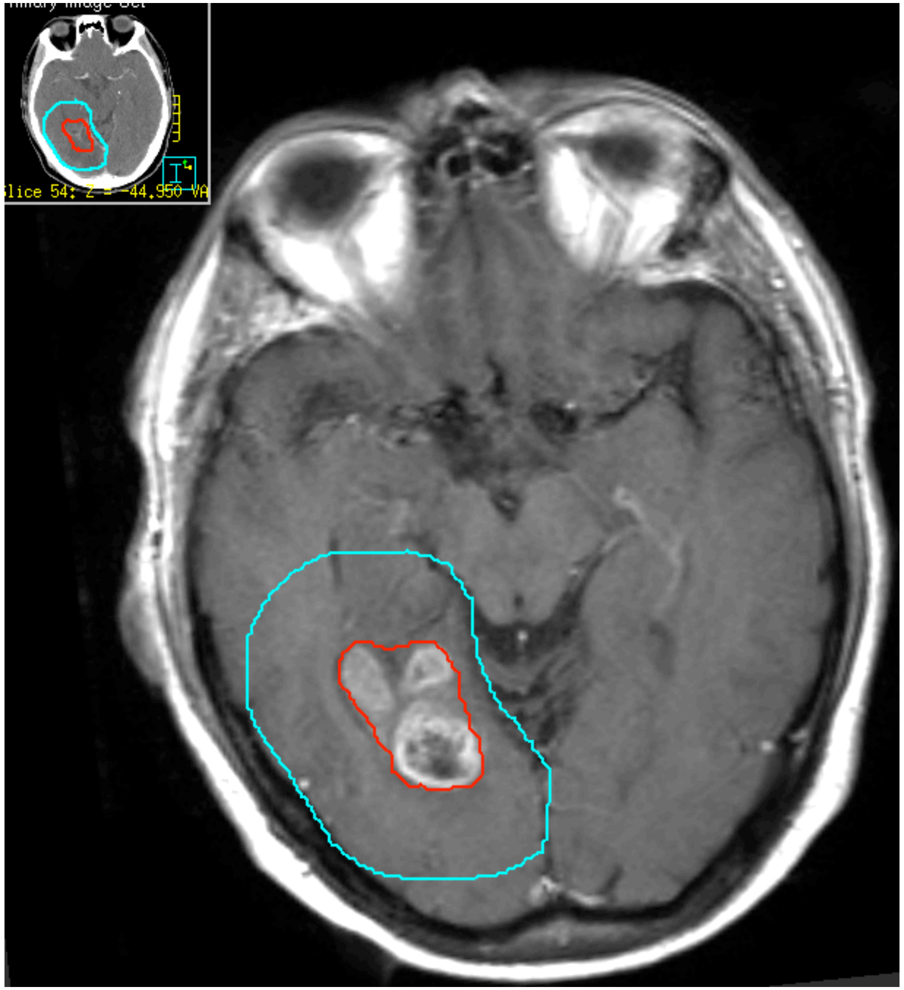
Contemporary planning is based on POSTOPERATIVE IMAGING

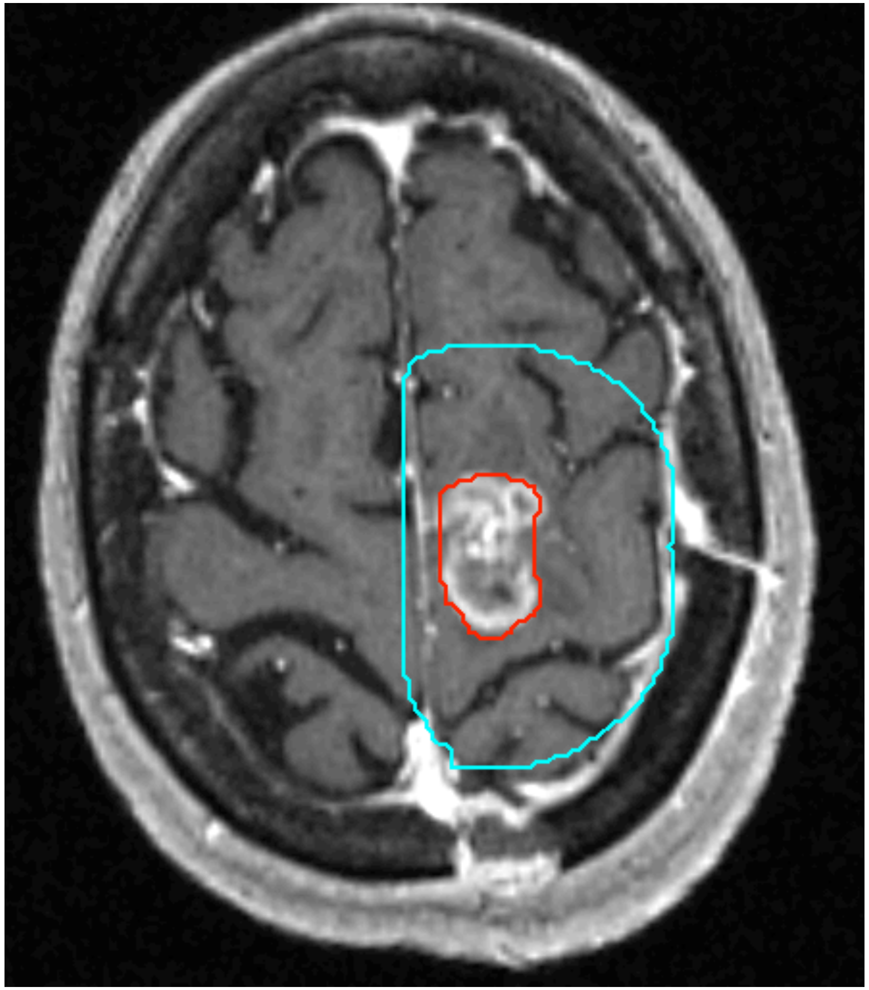
McDonald, IJROBP 2011

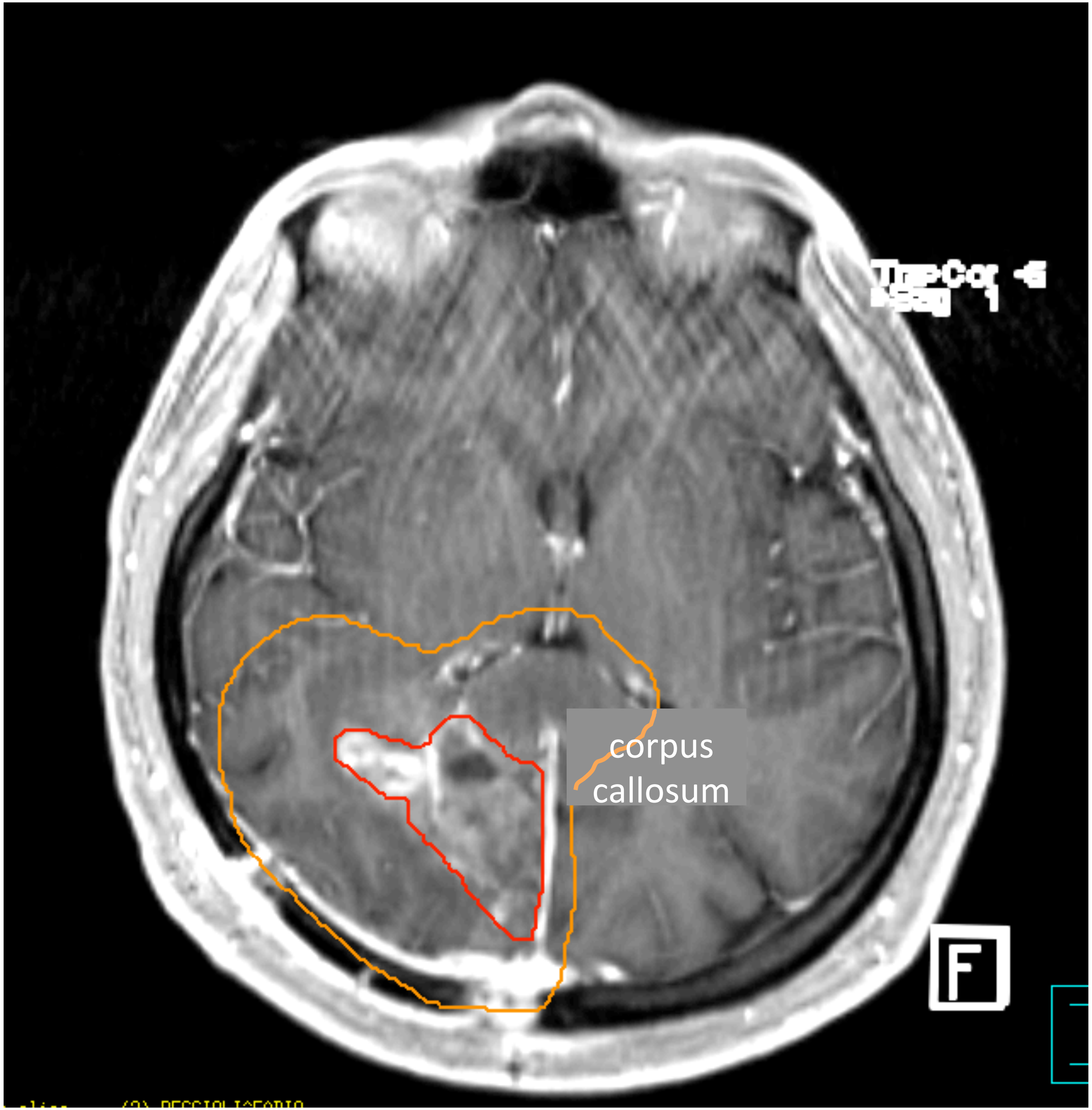
RTOG studies

Protocol		*CTV up to 46 Gy*	*CTV boost*
RTOG 9710 RTOG 8302 RTOG 8612 RTOG 9305	Rec IFN Hyperfract Iododeoxyuridine RS boost	Preoperative edema + 2 cm	Preoperative GTV + 2.5 cm
RTOG 0525 RTOG 0825 RTOG 0420	Dose intensive TMZ Bevacizumab Low dose TMZ + Irinotecan	Postoperative edema + 2 cm	Surgical bed + any contrast enhancing residual tumor + 2.5 cm
RTOG 9803	Dose escalation	Surgical bed + any contrast enhancing residual tumor + 1.5 cm	Surgical bed + any contrast enhancing residual tumor

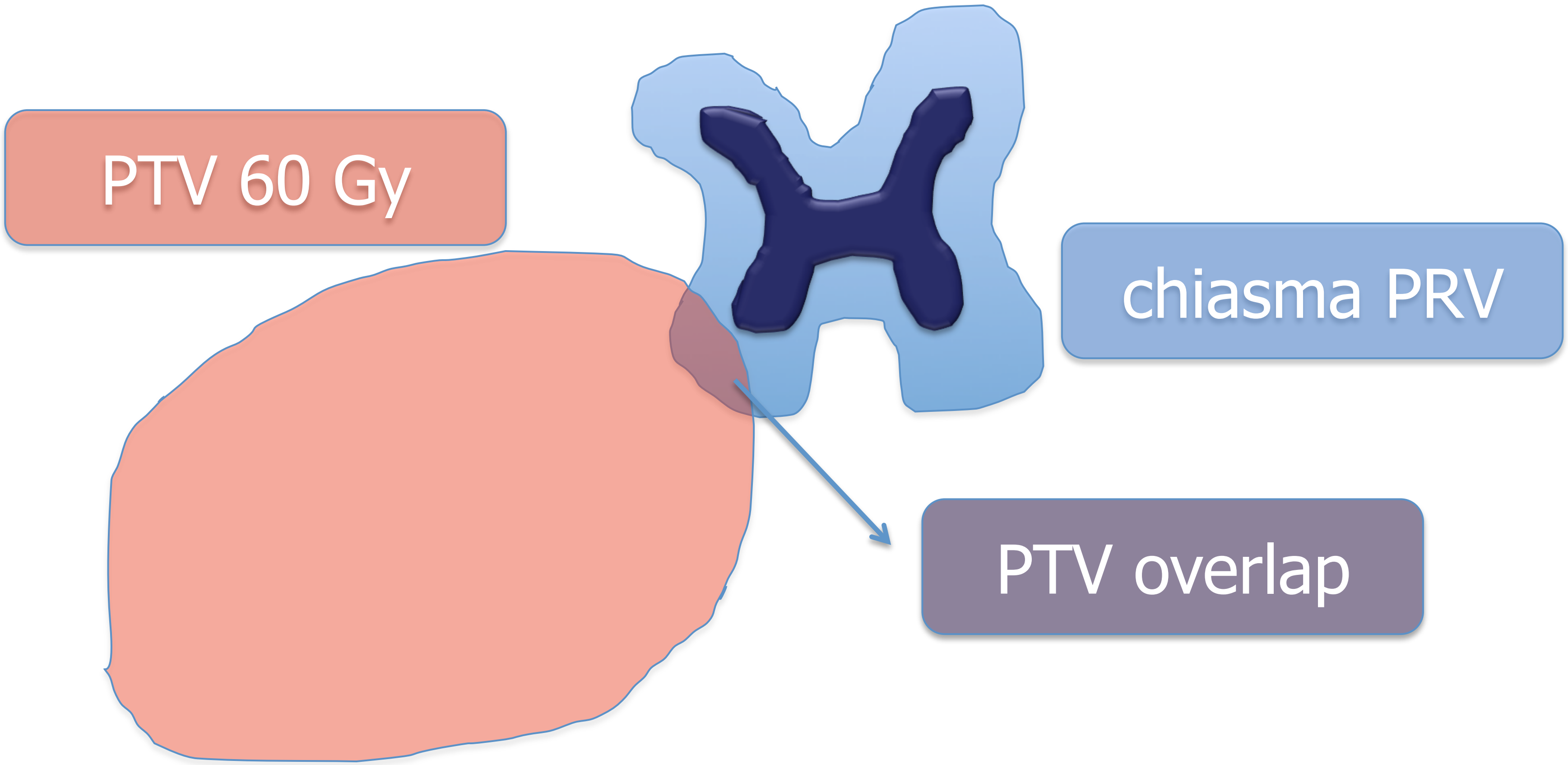
The CTV margin may be reduced to 0.5 cm around natural barriers to tumor growth

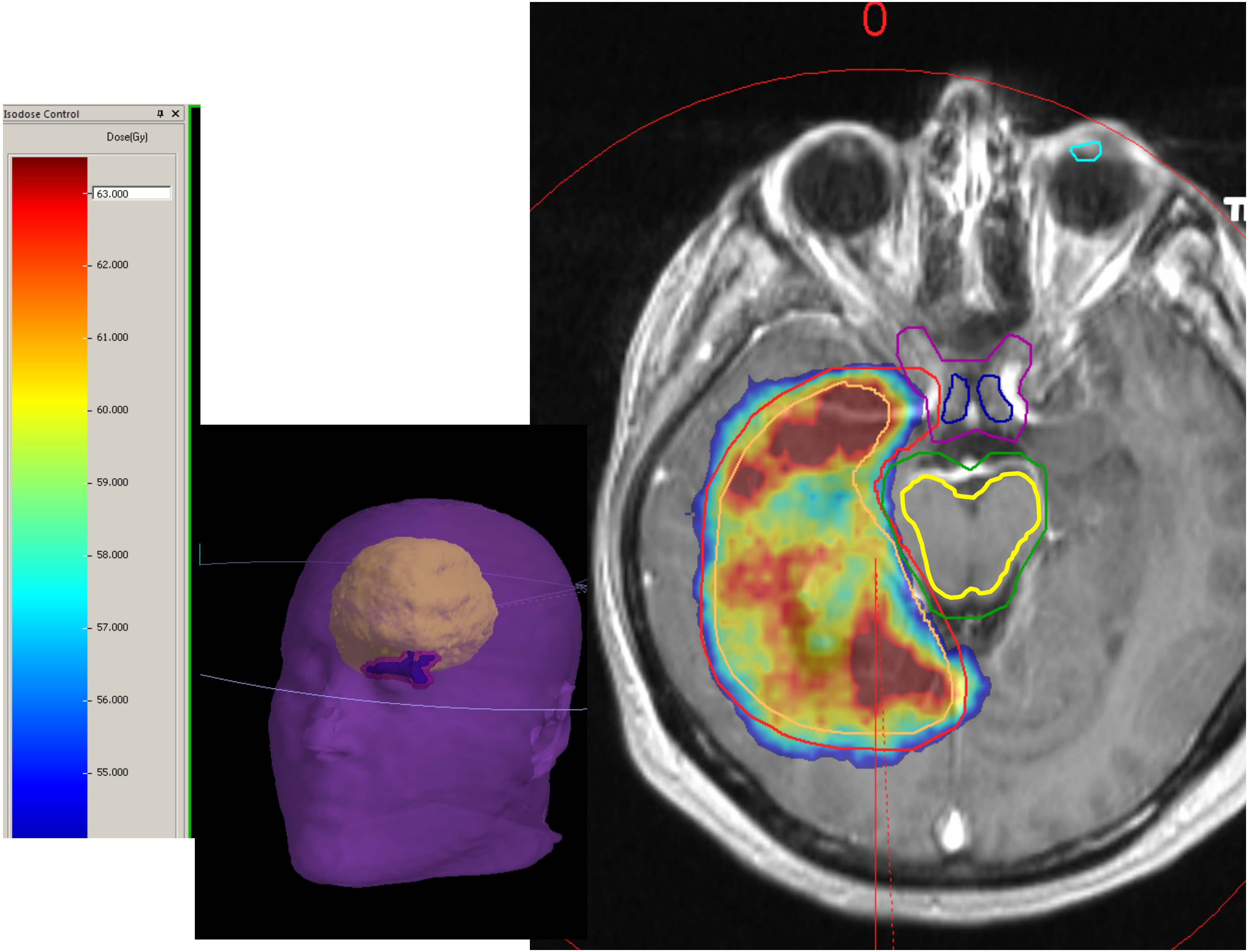





corpus
callosum
F

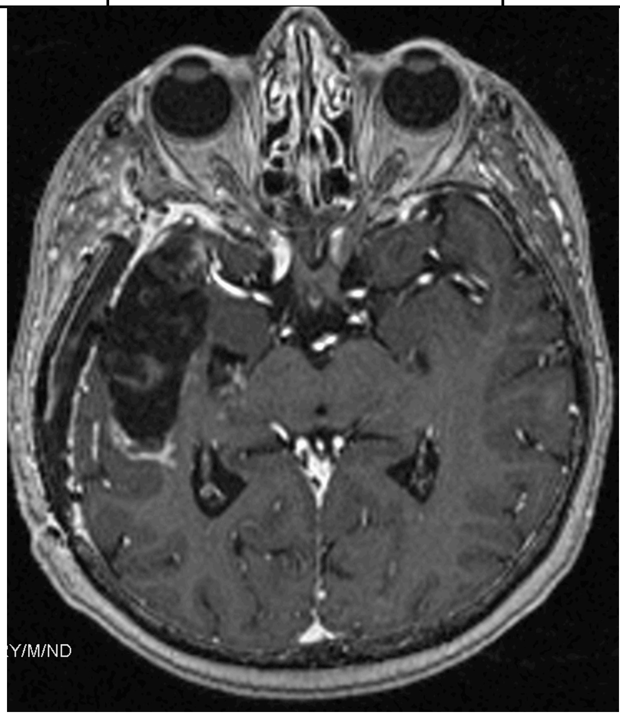
Proximity to OARs




Isodose Control
Dose(Gy)
63.000
62.000
61.000
60.000
59.000
58.000
57.000
56.000
55.000
0

Proximity to OARs

	CTV1		CTV2	
MDACC, Chang 2007	Up to 50 Gy	Surgical bed + any contrast enhancing residual tumor + 2 cm	50-60 Gy	Surgical bed + any contrast enhancing residual tumor



Definition of the clinical volumes in LOW GRADE GLIOMAS

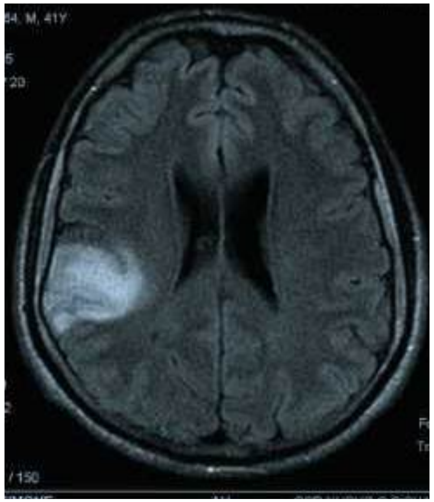
Radiotherapy and Oncology 103 (2012) 287–292

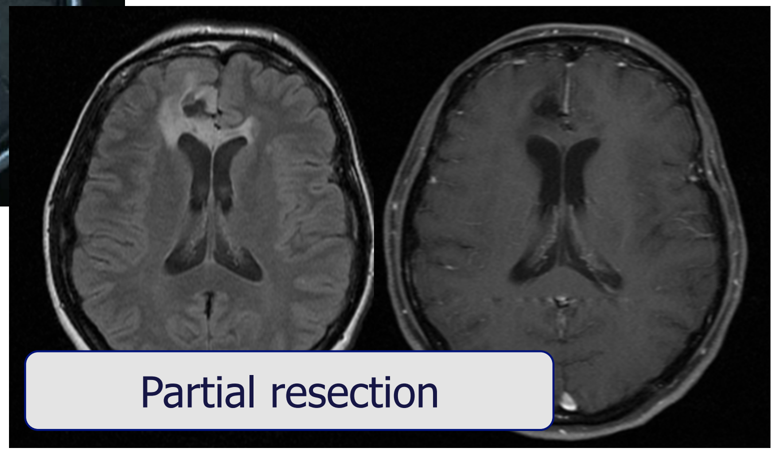
Quality assurance in the EORTC 22033–26033/CE5 phase III randomized trial for low grade glioma: The digital individual case review

Alysa Fairchild [a,b,*], Damien C. Weber [c], Raquel Bar-Deroma [d], Akos Gulyban [a,e], Paul A. Fenton [a,f], Roger Stupp [g], Brigitta G. Baumert [h]

Target volume – GTV	Region of high signal intensity on T2 or FLAIR–MRI corresponding to the hypodense area on CT, including any areas of CT enhancement; or operative cavity + any residual tumour
Target volume – CTV	GTV + 1–1.5 cm except at anatomic boundaries[a] where 5 mm is sufficient

take home message!





Reasons for volume deviations.

Volumes ($N = 57$)	CTV
Protocol compliant	30/57
Minor deviation	19/57 Crosses anatomic boundaries – 15/19 Margin incorrect – 3/19 Both – 1/19
Major deviation	8/57 No CTV – 4/8 Incorrect – 3/8 2 CTVs – 1/8

VOLUME 30 · NUMBER 25 · SEPTEMBER 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

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

GTV

Biopsy: any abnormality in T2 weighted images from the **preoperative** MRI scan

Surgical resection: resection cavity + any abnormality in T2 weighted images from the **postoperative** MRI scan

CTV= GTV plus a 2 cm margin.

VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Conformal Radiation Therapy for Pediatric Low-Grade Glioma

Thomas E. Merchant, Larry E. Kun, Shengjie Wu, Xiaoping Xiong, Robert A. Sanford, and Frederick A. Boop

n=78

Table 2. Pediatric Low-Grade Glioma Chemotherapy and Radiotherapy Series

Author by Type of Treatment	Year of Study	Treatment Regimen	No. of Patients	Event- or Progression-Free Survival (%)				
				2-Year	3-Year	5-Year	8-Year	10-Year
Chemotherapy								
Ater[21]	2008	CV	137			35		
		TPCV	137			48		
Gnekow[20]	2004	CV	198			61		
Massimino[19]	2002	CisVP	31		78			
Prados[18]	1997	TPCV	42	50				
Packer[17]	1997	CV	78		68			
Radiation therapy								
Marcus[27]	2005	52.2 Gy	50			82	65	
Saran[26]	2002	50-55 Gy	14		87			
Grabenbauer[29]	2000	45-60 Gy	25					69
Erkal[28]	1997	50 Gy	30			82		77
Merchant	2008	54 Gy	78			85		74

C, carboplatin; V, vincristine; T, thioguanine; P, procarbazine; Cis, cisplatin; VP, etoposide.

VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Late Effects of Conformal Radiation Therapy for Pediatric Patients With Low-Grade Glioma: Prospective Evaluation of Cognitive, Endocrine, and Hearing Deficits

Thomas E. Merchant, Heather M. Conklin, Shengjie Wu, Robert H. Lustig, and Xiaoping Xiong

Table 1. Models of Cognitive Effects After CRT for Pediatric Low-Grade Glioma

Evaluation	No. of Patients Who Had at Least Two Measures	Score* Baseline	Score* Change per Month	Score* Month 60	*P*†
IQ	55	98.9642	−0.0591	95.4182	
Math	55	96.9703	−0.0435	94.3603	
Reading	56	98.9448	−0.0989	93.0108	.0039
Spelling	56	98.2341	−0.1434	89.6301	.0014
Memory	53	47.5523	0.0164	48.5363	
Behavior problems‡	55	49.2340	−0.0556	45.8980	.0641
Externalizing‡	58	43.9829	−0.0099	43.3889	
Internalizing‡	58	51.5753	−0.0550	48.2753	.0248
Activities	55	43.2365	0.0031	43.4225	
School	53	41.8430	−0.0515	38.7530	.0479
Socialization	56	44.5348	−0.0084	44.0308	
Communication	57	94.6115	−0.1308	86.7635	.0041
Composite	57	94.4170	−0.1026	88.2610	.0433
Daily living	57	94.0500	−0.0635	90.2400	
Socialization	57	98.7889	−0.0559	95.4349	
Visual auditory learning	30	92.2834	0.1768	102.8914	< .0001

NOTE. Instruments for each evaluation are as follows: IQ, Bayley second edition; Wechsler Preschool and Primary Scale of Intelligence revised; Wechsler Intelligence Test for Children third edition or Wechsler Adult Intelligence Scale revised, as appropriate for age; math, reading, and spelling: Wechsler Individual Achievement Test; memory: California Verbal Learning Test: Child Version; behavior problems, externalizing, internalizing, activities, school, socialization: Child Behavior Checklist; communication composite, daily living, socialization: Vineland Adaptive Behavior Scale; and visual auditory learning: Woodcock Johnson revised, visual auditory learning subtest.

Abbreviations: CRT, conformal radiation therapy; IQ, intelligence quotient.

*Score = baseline + ([change per month] × time).

†*P* value for change per month.

‡Increasing scores represent worsening performance.

Five years after CRT, only the decline in spelling scores was clinically significant

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

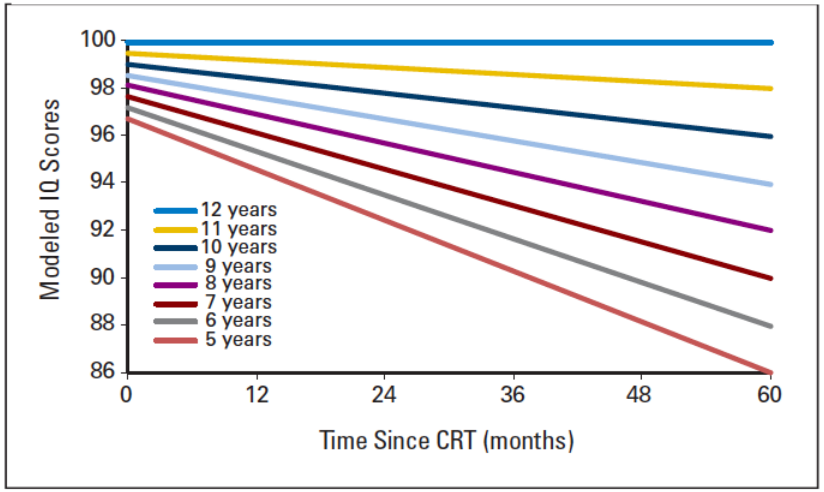


Fig 1. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age for pediatric low-grade glioma. Age is measured in years, and time is measured in months after the start of CRT.

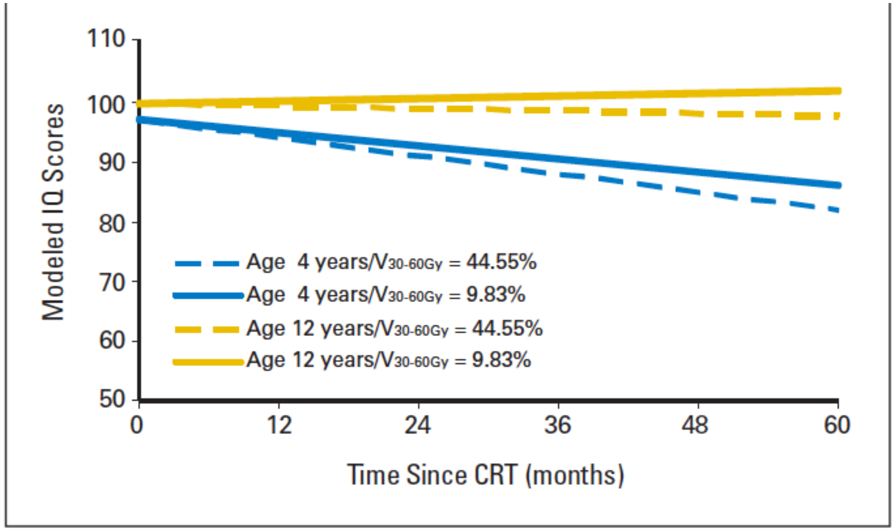


Fig 2. Modeled intelligence quotient (IQ) scores after conformal radiation therapy (CRT) by age and supratentorial brain dose-volume intervals for pediatric low-grade glioma. Age is measured in years, and time is measured in months after CRT. The dose-volume intervals $V_{0\text{-}30Gy}$ and $V_{30\text{-}60Gy}$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

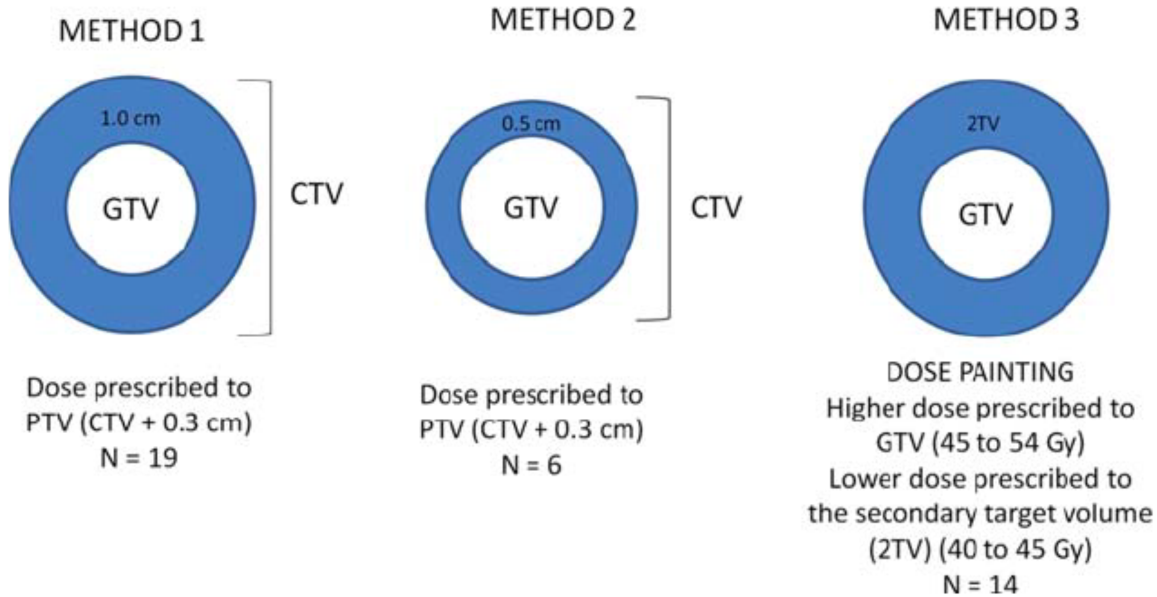
Cancer July 15, 2013

Intensity-Modulated Radiotherapy (IMRT) in Pediatric Low-Grade Glioma

Arnold C. Paulino, MD[1,2]; Ali Mazloom, MD[1]; Keita Terashima, MD[2]; Jack Su, MD[2]; Adekunle M. Adesina, MD, PhD[3]; M. Faith Okcu, MD, MPH[2]; Bin S. Teh, MD[1]; and Murali Chintagumpala, MD[2]

n=39

Margins Around GTV



8y-PFS rate 78.2%

Margins 1 cm added to the GTV may not be necessary, because excellent local control was achieved by adding a 0.5-cm margin and by dose painting

CTV definition in gliomas. Practical considerations

Use of advanced imaging for treatment planning purposes

Something new about OARs

Role of PET in neurooncology

- Differential diagnosis
- Biopsy- guidance
- **Evaluation of tumor extent in radiotherapy planning**
- Differentiation between relapse and pseudoprogression
- Differentiation between relapse and radionecrosis

Piroth, IJROBP 2011
Crippa, J Nucl Med Mol Imaging 2012
Gotz, Front Onc 2013

•^{11}C MET PET: ^{11}C-methionine PET

Miwa, J Neurol Neuros Psych 2004
Grosu, IJROBP 2005
Mahasittiwat, IJROBP 2008
Lee, IJROBP 2009
Matsuo, IJROBP 2012

•^{18}FET PET: ^{18}F-fluoroethyltyrosine PET

Weber, Rad Onc 2009
Piroth, Rad Onc 2011
Niyazi, Rad Onc 2011
Piroth, Strahlen Onkol 2012
Rieken, Radioth Oncol 2013

•^{18}F DOPA PET: ^{18}F dihydroxi-fluoro-phenylalanine PET

Pafundi, Neuro-oncology 2013

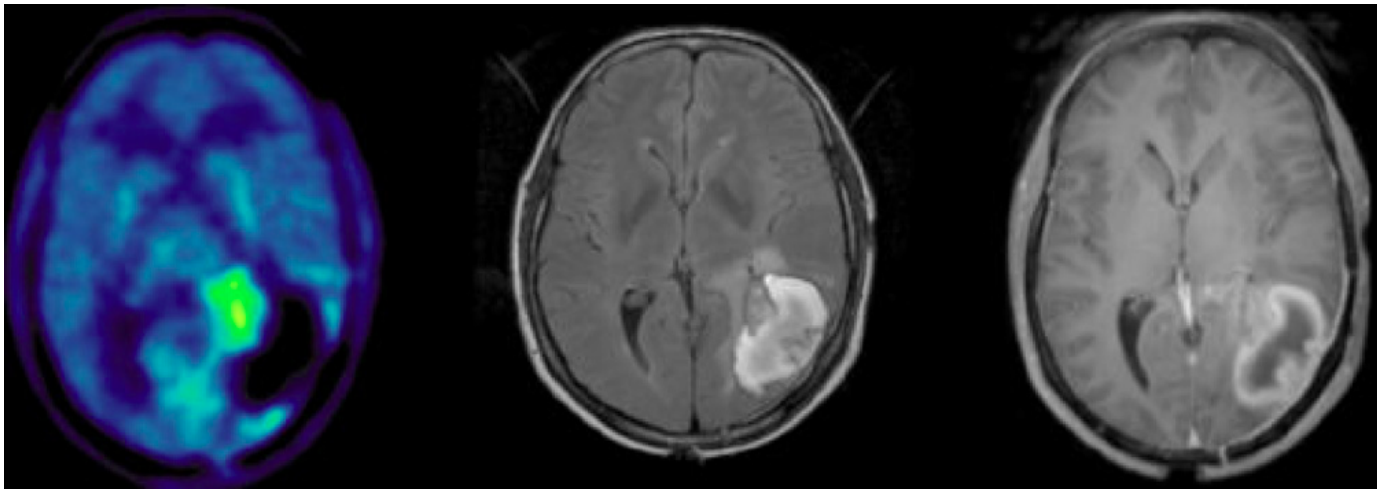
•^{11}C CHO PET: ^{11}C-choline PET

Li, Nuclear Medicine and Biology 2012

PET in the definition of tumor extent in radiotherapy

Analysis of discrepancies between pre-radiotherapy volumes (MRI-volume vs PET-volume)

Miwa, J Neurol NS Psych 2004
Mahasittiwat, IJROBP 2008
Lee, IJROBP 2009
Li, Nucl Med Bio 2012
Pafundi, NO, 2013
Rieken, Rad Onc 2013



Analysis of FET-PET imaging for target volume definition in patients with gliomas treated with conformal radiotherapy

Stefan Rieken [a,*], Daniel Habermehl [a], Frederik L. Giesel [b], Christoph Hoffmann [a], Ute Burger [a], Harald Rief [a], Thomas Welzel [a], Uwe Haberkorn [b], Jürgen Debus [a], Stephanie E. Combs [a]

[a] University Hospital of Heidelberg, Department of Radiation Oncology; [b] University Hospital of Heidelberg, Department of Nuclear Medicine, Germany

2013 41 pts

Planning target volumes (PTV)	Volume [ml]	*p*
PTV^{MRT} (all)	36.48 (±34.32)	
$PTV^{MRT+PET}$ (all)	61.96 (±50.94)	0.12
PTV^{MRT} (I/II)	68.05 (±38.87)	
$PTV^{MRT+PET}$ (I/II)	98.04 (±58.26)	0.18
PTV^{MRT} (III/IV)	35.62 (±33.84)	
$PTV^{MRT+PET}$ (III/IV)	53.1 (±48.73)	0.04*
PTV^{MRT} (initial RT)	44.51 (±35.36)	
$PTV^{MRT+PET\ T}$ (initial RT)	70.15 (±54.21)	0.02*
PTV^{MRT} (reirradiation)	23.86 (±26.83)	
$PTV^{MRT+PET}$ (reirradiation)	47.34 (±28.14)	0.28

Neuro-Oncology 15(8):1058–1067, 2013.
doi:10.1093/neuonc/not002
Advance Access publication March 3, 2013

NEURO-ONCOLOGY

Biopsy validation of ^{18}F-DOPA PET and biodistribution in gliomas for neurosurgical planning and radiotherapy target delineation: results of a prospective pilot study

Deanna H. Pafundi, Nadia N. Laack, Ryan S. Youland, Ian F. Parney, Val J. Lowe, Caterina Giannini, Brad J. Kemp, Michael P. Grams, Jonathan M. Morris, Jason M. Hoover, Leland S. Hu, Jann N. Sarkaria, and Debra H. Brinkmann

2013 10 pts

Table 4. Concordant and discordant volume percentages of threshold HGG ^{18}F-DOPA PET (T/N > 2.0) relative to the T1-CE gold standard and T2/FLAIR gold standard volumes

Patient	% Threshold T/N > 2.0 HGG PET Volume Outside T1-CE Volume	% Threshold T/N > 2.0 HGG PET Volume Inside T1-CE Volume	% T2/FLAIR Volume Outside Threshold T/N > 2.0 HGG PET Volume
FDOPA01[a]	100.0	0.0	99.9
FDOPA02[a]	100.0	0.0	96.1
FDOPA03	81.0	19.0	70.6
FDOPA04	35.8	64.2	87.5
FDOPA05[a]	100.0	0.0	91.7
FDOPA06	41.4	58.6	84.3
FDOPA07	63.2	36.8	84.5
FDOPA08[b]	N/A	N/A	N/A
FDOPA09	15.1	84.9	83.6
FDOPA10[a,b,c]	N/A	N/A	N/A

[a] No T1-CE.
[b] No high-grade disease per PET threshold.
[c] No PET uptake.

PET in the definition of tumor extent in radiotherapy

Use of PET for target definition

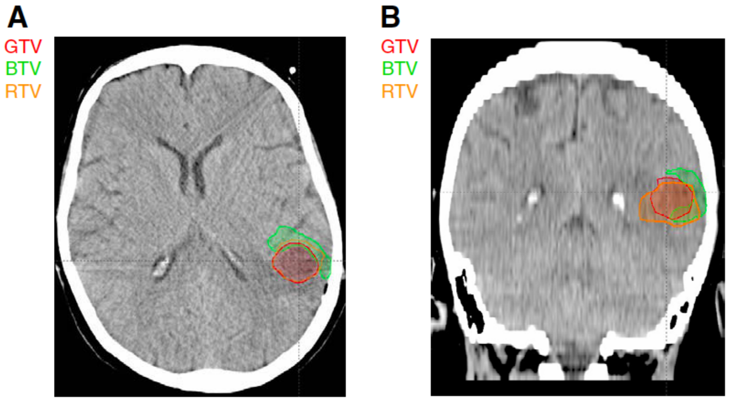
Weber, Rad Onc 2009
Piroth, Rad Onc 2011
Nizayi, Rad Onc 2011
Piroth, Strahlen Onkol 2012

Radiotherapy and Oncology 93 (2009) 586–592

Recurrence pattern after [(18)F]Fluoroethyltyrosine-Positron Emission Tomography-guided radiotherapy for high-grade glioma: A prospective study

Damien C. Weber [a,c,*], Nathalie Casanova [a], Thomas Zilli [a], Franz Buchegger [b], Michel Rouzaud [a], Philippe Nouet [a], Hansjorg Vees [a], Osman Ratib [b,c], Giovanna Dipasquale [a], Raymond Miralbell [a,c]

[a] Department of Radiation Oncology; and [b] Department of Nuclear Medicine, Geneva University Hospital, Switzerland;
[c] Department of Radiation Oncology, University of Geneva, Switzerland



n=41

CTV = (GTV ∪ BTV) + 1,5 cm

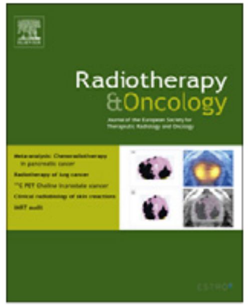
MRI-based PTVs miss 17% of FET-PET/CT-based GTVs

Table 2
Location and dosimetric characteristics of recurrences after chemo-radiotherapy using composite volumes (GTV U BTV; see text).

Patient #	RTV (cm^3)	RTV within the prescription 95% isodose surface (%)	RTV outside the prescription 95% isodose surface (cm^3)	Type of recurrence
1	45.3	100.0	0.00	Central
2	20.2	96.6	0.69	Central
3	20.7	95.0	1.02	Central
4	37.8	100.0	0.00	Central
5	18.2	100.0	0.00	Central
6	86.5	76.8	20.04	In-field
7	105.7	98.9	1.14	Central
8	8.5	100.0	0.00	Central
9	47.8	96.8	1.51	Central
10	3.9	98.3	0.07	Central

Abbreviations: GTV, gross tumour volume; BTV, biological tumour volume; RTV, recurrence tumour volume.

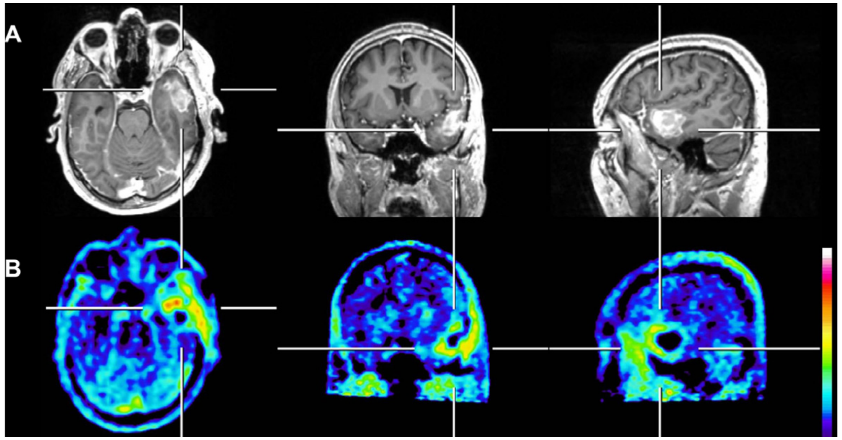
Radiotherapy and Oncology 99 (2011) 218–224



Prognostic impact of postoperative, pre-irradiation ^{18}F-fluoroethyl-L-tyrosine uptake in glioblastoma patients treated with radiochemotherapy

Marc D. Piroth [a,e,*], Richard Holy [a,e], Michael Pinkawa [a,e], Gabriele Stoffels [b,e], Hans J. Kaiser [c], Norbert Galldiks [b,d], Hans Herzog [b], Heinz H. Coenen [b,e], Michael J. Eble [a,e], Karl J. Langen [b,e]

[a] Department of Radiation Oncology, RWTH Aachen University Hospital, Germany; [b] Institute of Neuroscience and Medicine, Forschungszentrum Jülich, Germany; [c] Department of Nuclear Medicine, RWTH Aachen University Hospital, Germany; [d] Department of Neurology, University Hospital Cologne, Germany; [e] Jülich-Aachen Research Alliance (JARA) – Section JARA-Brain, Forschungszentrum Jülich, Germany



n=44
n=19 Focal dose escalation: SIB-IMRT 72 Gy in 30 fractions on GTV_{PET}

Multivariate analysis (Cox proportional hazards model).

	OS[*]		DFS[†]	
	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
RPA score[‡]				
III/IV				
vs. V	0.28 (0.08–0.97)	0.04	n.s.[&]	0.6
vs. VI	0.21 (0.06–0.68)		n.s.[&]	
Extent of resection[§]				
Gross total	n.s.[&]			
vs. Partial	n.s.[&]	0.5	n.s.[&]	0.1
vs. Biopsy			n.s.[&]	
$Vol_{TBR} \geqslant 1.6$[‖]				
⩾25 ml vs. <25 ml	6.46 (2.5–16.7)	<0.001	5.65 (2.17–14.7)	<0.001
$Vol_{TBR} \geqslant 2.0$[¶]				
⩾10 ml vs. <10 ml	6.46 (2.5–16.7)	<0.001	5.65 (2.17–14.7)	<0.001
MR Gd-volume[#]				
<10 ml	n.s.[&]	0.2	n.s.[&]	0.4
⩾10 ml	n.s.[&]		n.s.[&]	

Strahlentherapie und Onkologie
Journal of Radiation Oncology, Biology, Physics

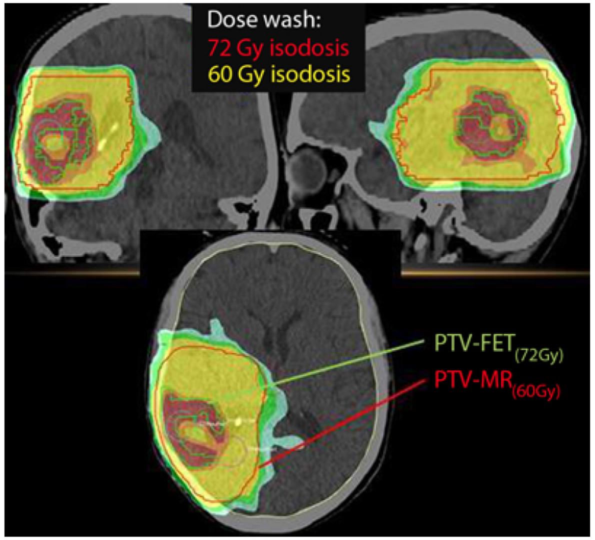
Integrated boost IMRT with FET-PET-adapted local dose escalation in glioblastomas

Results of a prospective phase II study

M.D. Piroth [1,5], M. Pinkawa [1,5], R. Holy [1,5], J. Klotz [1,5], S. Schaar [1,5], G. Stoffels [2,5], N. Galldiks [2,4], H.H. Coenen [2,5], H.J. Kaiser [3], K.J. Langen [2,5] and M.J. Eble [1,5]

n=22

SIB-IMRT 60 Gy in 30 fractions on PTV_{MRI}
72 Gy in 30 fractions on PTV_{PET}



No significative changes in neurocognitive performance and in quality of life
No increased toxicity

No survival benefit

Radiotherapy and Oncology 99 (2011) 44–48

FET–PET for malignant glioma treatment planning

Maximilian Niyazi[a], Julia Geisler[b], Axel Siefert[a], Silke Birgit Schwarz[a], Ute Ganswindt[a], Sylvia Garny[a], Oliver Schnell[c], Bogdana Suchorska[c], Friedrich-Wilhelm Kreth[c], Jörg-Christian Tonn[c], Peter Bartenstein[b], Christian la Fougère[b], Claus Belka[a,*]

[a] Department of Radiation Oncology; [b] Department of Nuclear Medicine; and [c] Department of Neurosurgery, Ludwig-Maximilians-University Munich, München, Germany

n=17

CTV_{morph} = GTV+2 cm

CTV_{biol} = BTV+2 cm

CTV_{final} = CTV_{morph} CTV_{biol}

Conformity Index =

$$\frac{CTV_{morph} \cap CTV_{biol}}{CTV_{morph} \cup CTV_{biol}} = 0.73 \pm 0.03$$

Data on tumor progression n=12

GTV_{MRI}		GTV_{PET}	
Inside	6	Inside	6
Marginal	3	Marginal	4
Outside	3	Outside	2

Tumour volumes. Measurement of different tumour volumes in 17 glioblastoma patients.

BTV [cc]	BTV + 2 [cc]	GTV [cc]	CTV [cc]
30.9	240.3	26.8	221.6
80.7	308.5	64	249.3
14.9	131.2	12.5	122.6
50.9	303.7	39.5	253.9
6.3	99.8	6	89.9
112.2	327.0	92.2	333
29.7	160.5	27.8	224.5
43.9	239.1	50.9	291.5
41.2	167.1	7.4	191.7
77.9	285.4	50.8	294.9
24.4	183.3	23.6	173.8
69.0	275.5	34.1	201.5
130.1	553.2	139.5	540.9
54.0	290.4	19	180.2
31.8	186.9	20.4	150.9
18.2	153.6	103	342.4
121.4	411.9	99.4	366.8
Median 43.9	**Median 240.3**	**Median 34.1**	**Median 224.5**

Role of advanced MRI in neurooncology

Differential diagnosis

Biopsy- guidance

Preoperative planning

Evaluation of tumor extent in radiotherapy planning

Differentiation between relapse and pseudoprogression

Differentiation between relapse and radionecrosis

- **MR spectroscopy (MRSI)**

Pirzkall, IJROBP 2004
Park , IJROBP2007
Narayana, BJR 2007
Einstein, IJROBP 2012

3D MRSI FOR RESECTED HIGH-GRADE GLIOMAS BEFORE RT: TUMOR EXTENT ACCORDING TO METABOLIC ACTIVITY IN RELATION TO MRI

Andrea Pirzkall, M.D.,* Xiaojuan Li, M.S.,† Joonmi Oh, Ph.D.,† Susan Chang, M.D.,‡ Mitchel S. Berger, M.D.,‡ David A. Larson, M.D., Ph.D.,*‡ Lynn J. Verhey, Ph.D.,* William P. Dillon, M.D.,† and Sarah J. Nelson, Dr.rer.nat.†

2004 30 pts

Correspondence of areas of new contrast enhancement with initial MRSI abnormalities in 8 of 10 non–contrast-enhancing patients

Patterns of Recurrence Analysis in newly diagnosed GBM following 3D Conformal Radiation Therapy with respect to Pre-RT MR Spectroscopic Findings

Ilwoo Park, BS[1,2], Gregory Tamai, BS[1], Michael C. Lee, Ph.D.[1], Cynthia F. Chuang, Ph.D.[3], Susan M. Chang, M.D.[4], Mitchel S. Berger, M.D.[4], Sarah J. Nelson, Ph.D.[1,2], and Andrea Pirzkall, M.D.[1,3,4]

2007 9 relapses in 23 pts

New or increased contrast-enhancement was within the pre-RT MRSI lesion in 89 % (8/9) of patients

The British Journal of Radiology, 80 (2007), 347–354

Use of MR spectroscopy and functional imaging in the treatment planning of gliomas

[1]A NARAYANA, MD, [2]J CHANG, PhD, [2]S THAKUR, PhD, [2,3]W HUANG, PhD, [3]S KARIMI, MD, [2,3]B HOU, PhD, [2]A KOWALSKI, MS, [2]G PERERA, MS, [3]A HOLODNY, MD and [4,5]P H GUTIN, MD

Departments of [1]Radiation Oncology, [2]Medical Physics, [3]Radiology and [4]Surgery, Memorial Sloan-Kettering Cancer Center and [5]Department of Neuro-Surgery, Weill Medical College of Cornell University, 1275 York Avenue, New York, NY 10021, USA

2007 12 pts

All the patients failed in MRSI defined volume which had high Cho:Cr ratio

Table 1. The grading system used to grade the choline: creatine (Cho:Cr) ratio for each MR spectroscopy voxel

	Grade	Clinical target volume	Dose painting
Cho:Cr <1	0		
Cho:Cr ≥1 but <2	1	CTV1	5400
Cho:Cr ≥2 but <3	2	CTV2	5940
Cho:Cr ≥3	3	CTV3	7000

Phase II Trial of Radiosurgery to Magnetic Resonance Spectroscopy—Defined High-Risk Tumor Volumes in Patients With Glioblastoma Multiforme

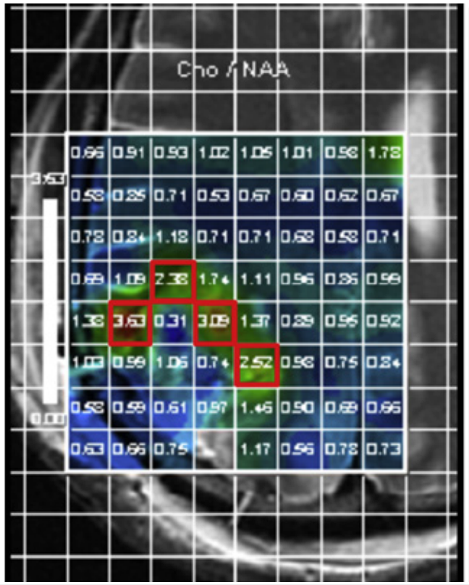
International Journal of
Radiation Oncology
biology • physics

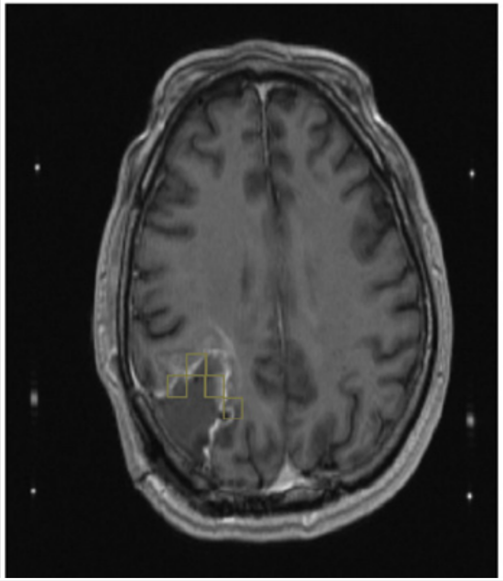
Douglas B. Einstein, M.D., Ph.D.,* Barry Wessels, Ph.D.,* Barbara Bangert, M.D.,†
Pingfu Fu, Ph.D.,§ A. Dennis Nelson, Ph.D.,† Mark Cohen, M.D.,‖
Stephen Sagar, M.D.,‡ Jonathan Lewin, M.D.,† Andrew Sloan, M.D.,¶
Yiran Zheng, M.S.,* Jordonna Williams, R.N.,* Valdir Colussi, Ph.D.,*
Robert Vinkler, R.T.T.,* and Robert Maciunas, M.D. M.P.H.¶

n=35

Boost toward areas of MRSI determined high biological activity (Cho/NAA ratio>2)
+
3DCRT 60 Gy

Median OS entire cohort 15.8 months





		Survival time (mo)				
Classification	No. of patients	GK MRS median survival	RTOG historical control, XRT alone	Survival difference of GK MRS patients vs. historical control	EORTC historical control, XRT + temodar	Survival difference of GK MRS patients vs. historical control
RTOG RPA Class 3	4	>22*	17.9	4.1†	21.4	0.6†
RTOG RPA Class 4	13	18.7	11.1	7.6†	16.3	2.4†
RTOG RPA Class 5	16	12.9	8.9	4.0†	10.3	2.6†
Concurrent temozolomide	16	20.8	NA	NA	14.6	6.2†

CTV definition in gliomas. Practical considerations

Use of advanced imaging for treatment planning purposes

Something new about OARs

Differences in Brainstem Fiber Tract Response to Radiation: A Longitudinal Diffusion Tensor Imaging Study

Jinsoo Uh, PhD,* Thomas E. Merchant, DO, PhD,* Yimei Li, PhD,[†] Tianshu Feng, MS,[†] Amar Gajjar, MD,[‡] Robert J. Ogg, PhD,* and Chiaho Hua, PhD*

*Departments of *Radiological Sciences, [†]Biostatistics, and [‡]Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee*

Int J Radiation Oncol Biol Phys, Vol. 86, No. 2, pp. 292–297, 2013

International Journal of Radiation Oncology biology • physics

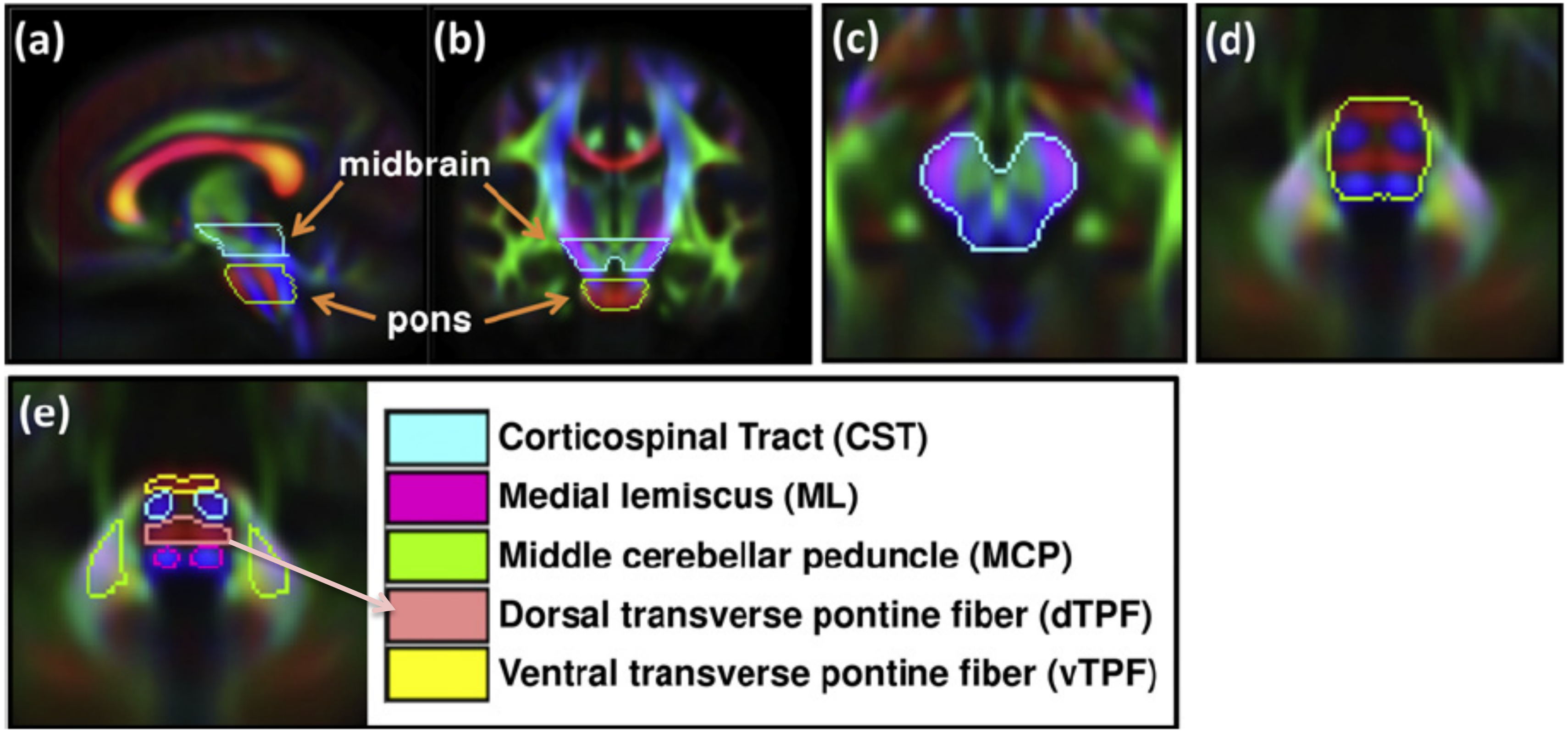
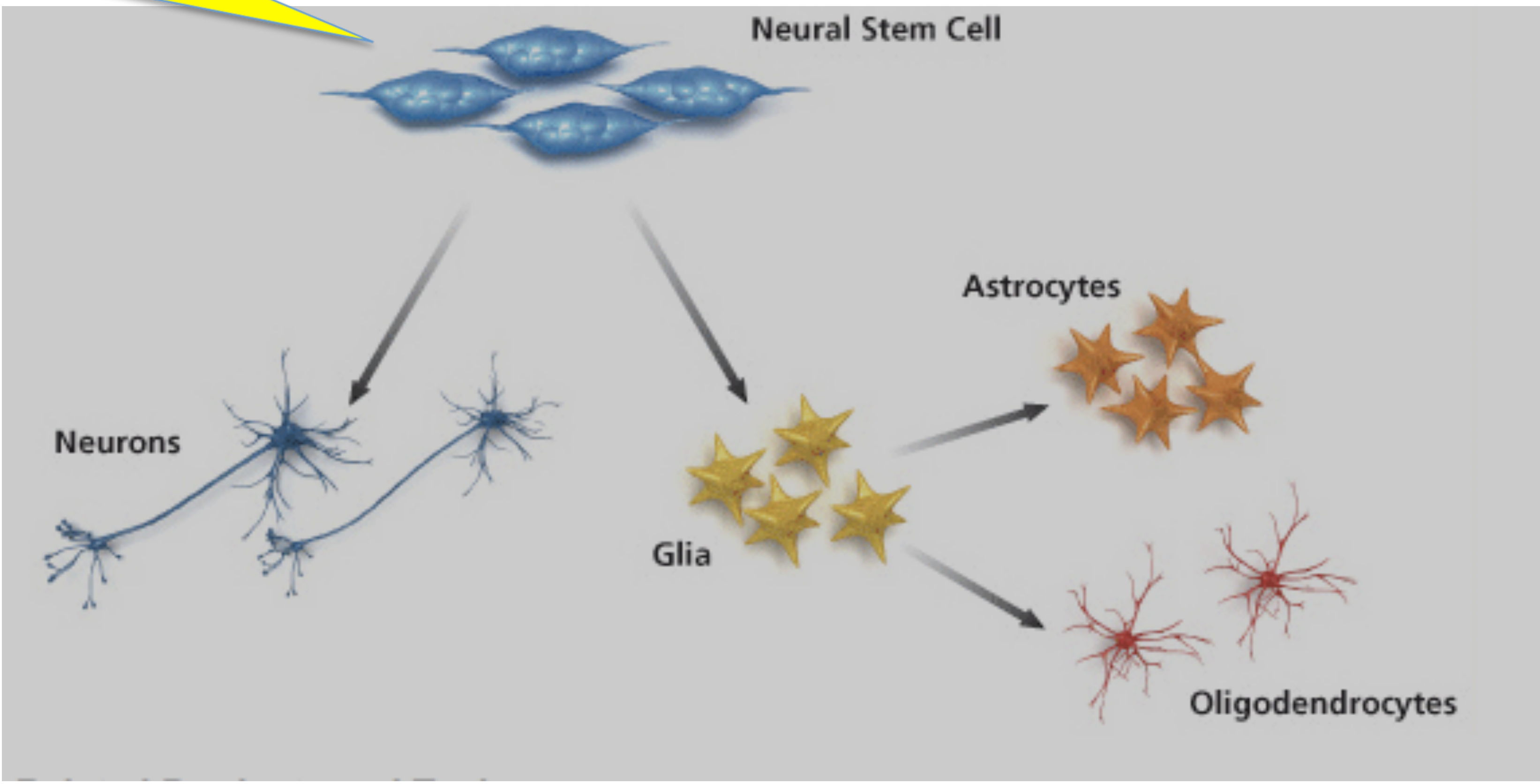


Fig. 1. Volumes of interest drawn on the standard color-coded fractional anisotropy map. (a, b) Sagittal and coronal views of midbrain and pons showing cranial-caudal locations of volumes of interest. (c, d) Axial views of midbrain and pons. (e) Substructures within brainstem.

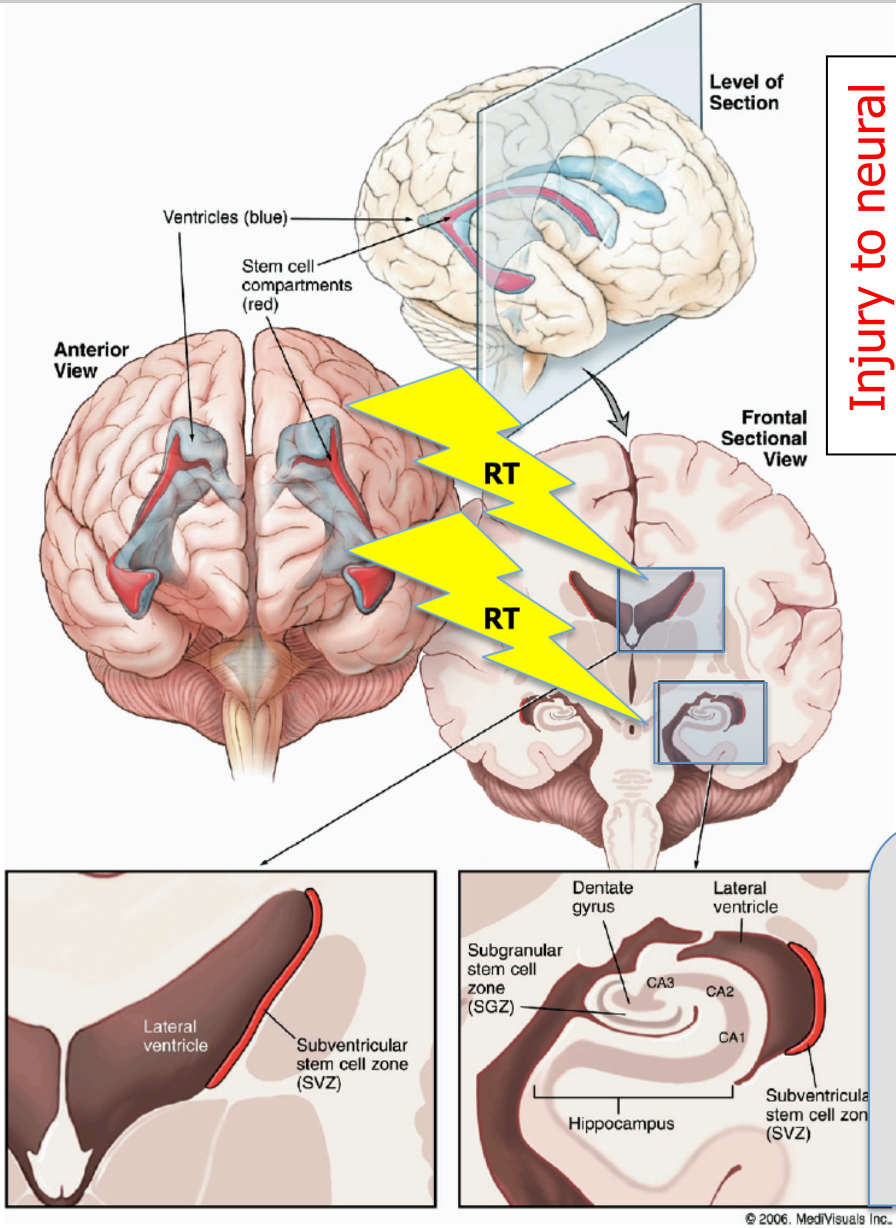
Radiation induced neurotoxicity

- Injury to neural stem cells

Tofilon, Radiat Res 2000;
Temple, Nature 2001
Song, Nature 2002;
Doetsch, Curr Opin Genet Dev 2003
Motomura, Neurosc Letters 2010



Radiation induced neurotoxicity



Injury to neural stem cells

Radiotherapy

Chemotherapy

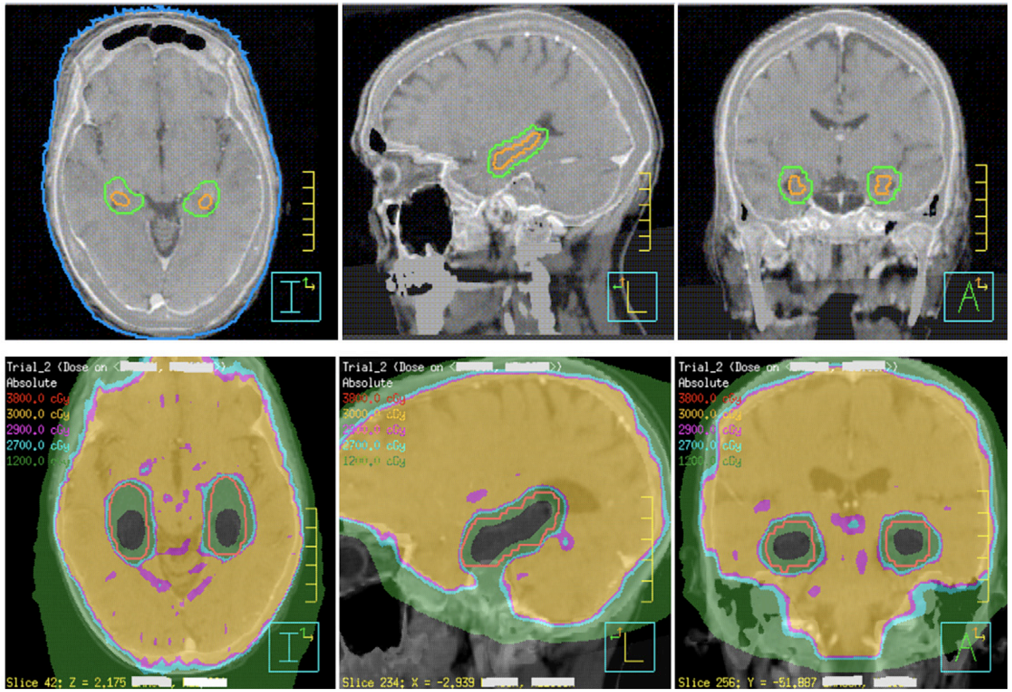
Shors, Nature 2001

Supportive care

Cameron, Neuroscience 1994

Tofilon, Radiation research 2000; van Praag, Nature 2002; Mohje, Curr Opin Neurol 2003; Monje, Science 2003; Rola, Exper Neurol 2004; Alvarez-Buylla, Neuron 2004;Byrne, Curr Opin Neuro 2005; Barani, IJROBP 2007

Hippocampal avoidance



Review

Why avoid the hippocampus? A comprehensive review

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

Journal of Clinical Neuroscience xxx (2013) xxx–xxx

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Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Hippocampal-sparing radiotherapy: The new standard of care for World Health Organization grade II and III gliomas?

n=18

M.B. Pinkham [a,e,*], K.C. Bertrand [e], S. Olson [b], D. Zarate [f], J. Oram [b,c], A. Pullar [a,e], M.C. Foote [a,d,e]

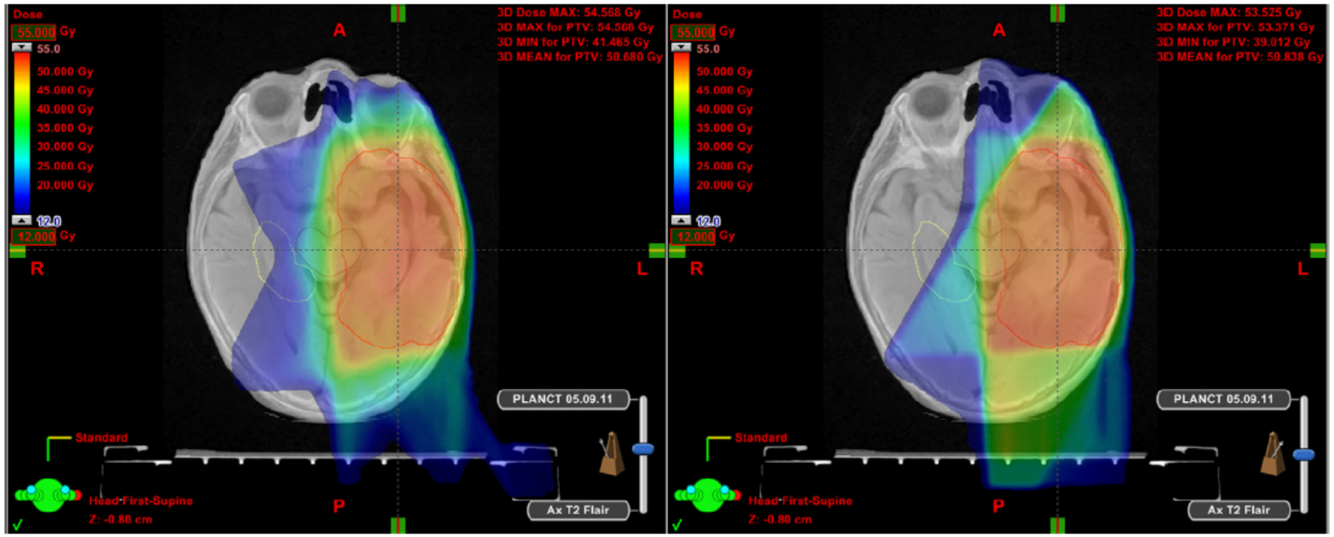


Fig. 1. Axial planning CT scans fused with T2-weighted fluid attenuated inversion recovery sequence MRI showing isodose distributions for a representative patient planned with intensity modulated radiotherapy (IMRT) (left) and conventional three-field three-dimensional conformal radiotherapy (right) techniques. The patient has a debulked World Health Organization grade II oligodendroglioma of the left temporal lobe and the dose prescribed to the planning target volume (red line) is 50.4 Gy in 28 fractions. The IMRT plan is more conformal and dose delivered in the intermediate range (25–45 Gy, cyan-green-yellow colourwash) is reduced, including that to the contralateral hippocampal avoidance volume (yellow line).

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

Vinai Gondi, M.D.,* Bruce P. Hermann, Ph.D.,† Minesh P. Mehta, M.D., FASTRO,¶ and Wolfgang A. Tomé, Ph.D., FAAPM*,‡,§

International Journal of Radiation Oncology biology • physics

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

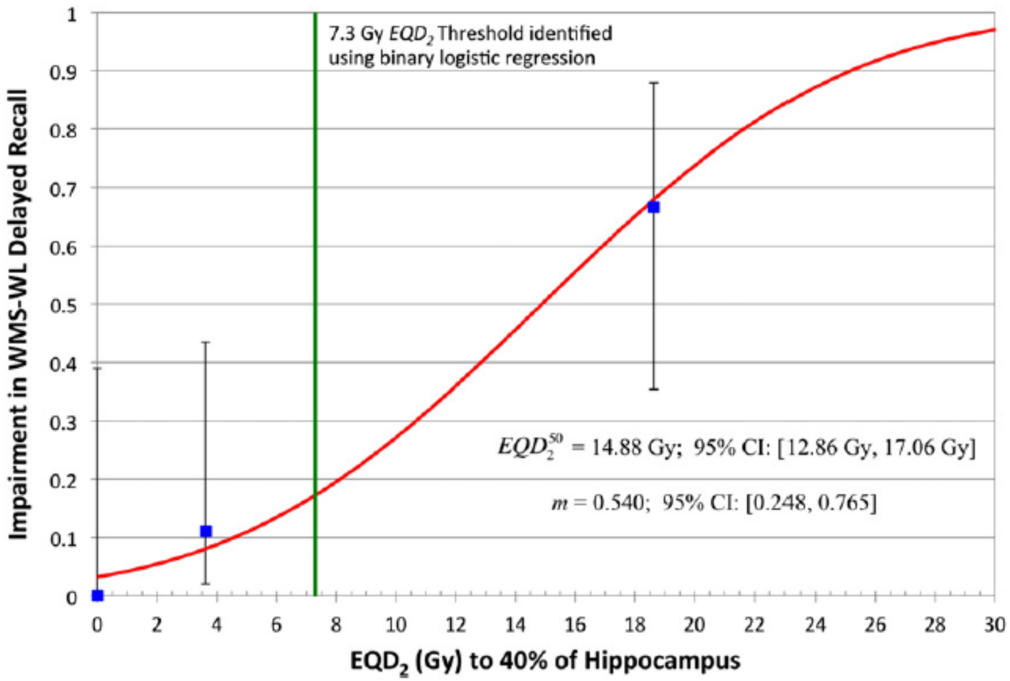


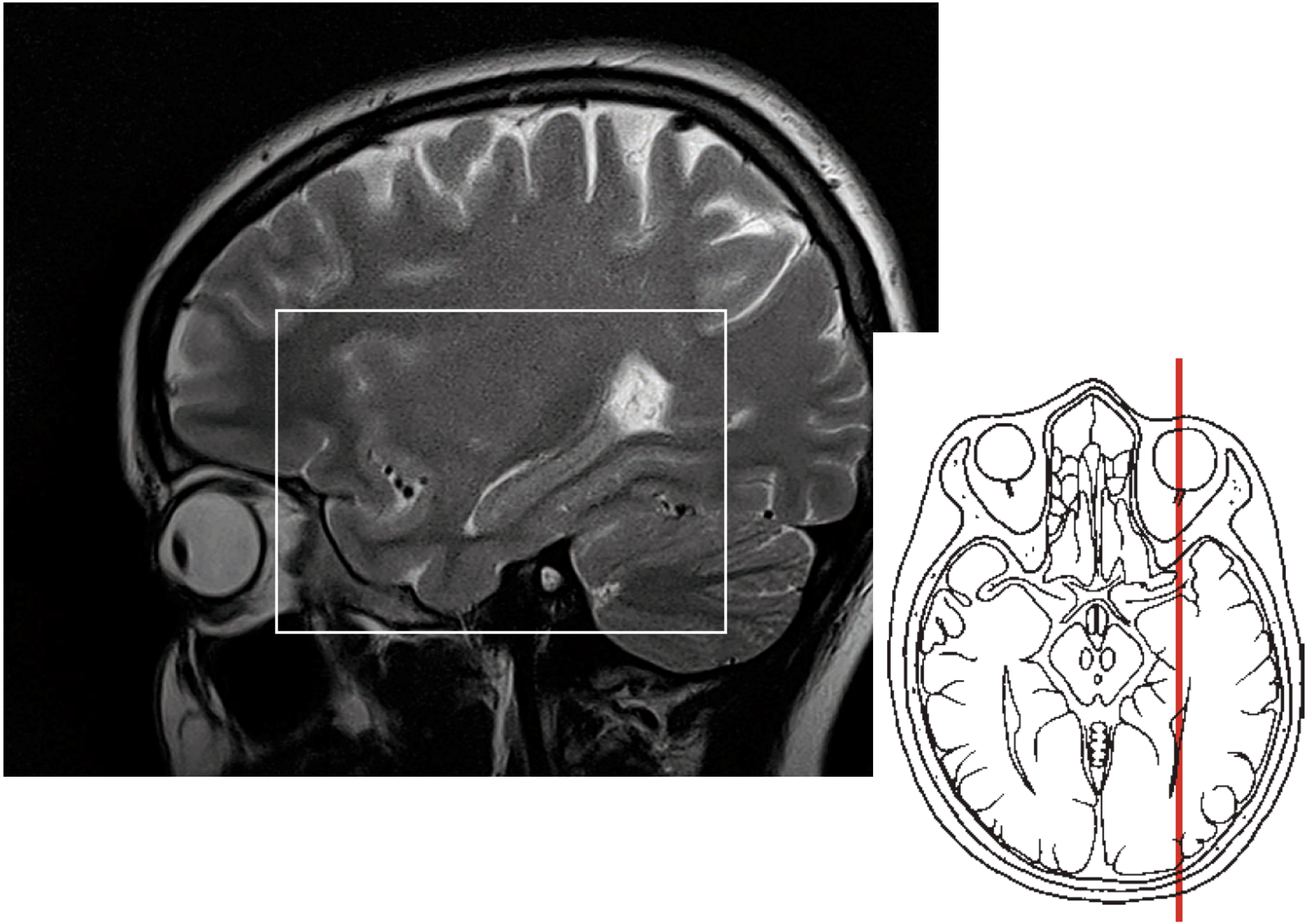
Table 4 Binary logistic regression analysis for risk of impairment in Wechsler Memory Scale-III Word Lists Delayed Recall at 18 months

Variable	Odds ratio	95% CI	p value
Age, y (≤50 vs. >50)	1.5	0.1–20.9	0.774
D40% of hippocampus >7.3 Gy	19.3	1.1–338.0	0.043
Age, y (≤50 vs. >50)	1.2	0.1–15.8	0.876
D100% of hippocampus >0.0 Gy	14.8	0.8–266.2	0.068

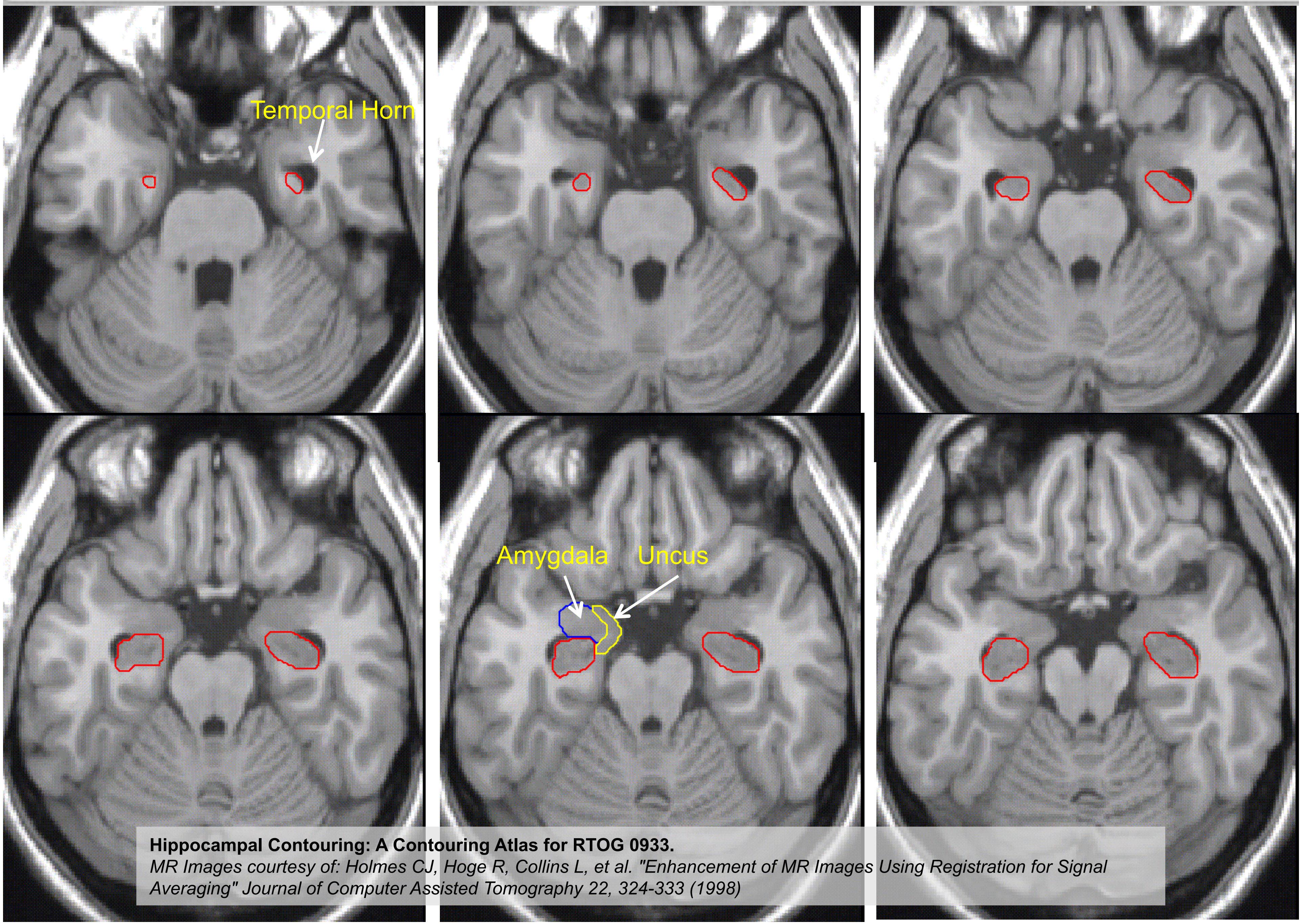
Abbreviations: D40% = equivalent dose in 2-Gy fractions (EQD_2) assuming α/β = 2 Gy to 40% of the structure volume; D100% = EQD_2 to 100% of the structure volume; CI = confidence interval.

n=18

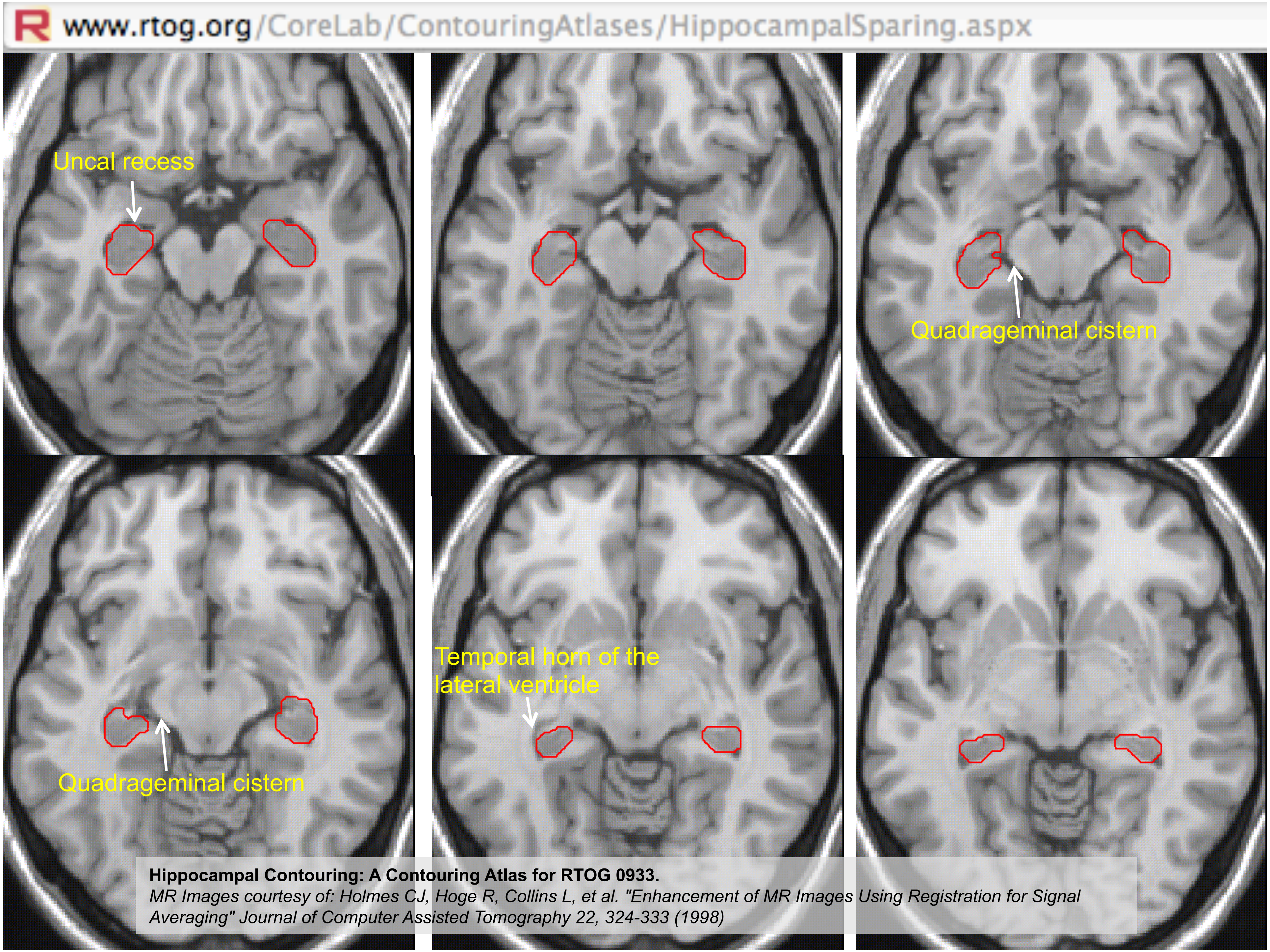
Equivalent dose in 2-Gy fractions to 40% of the bilateral hippocampi greater than 7.3 Gy is associated with long-term memory impairment.



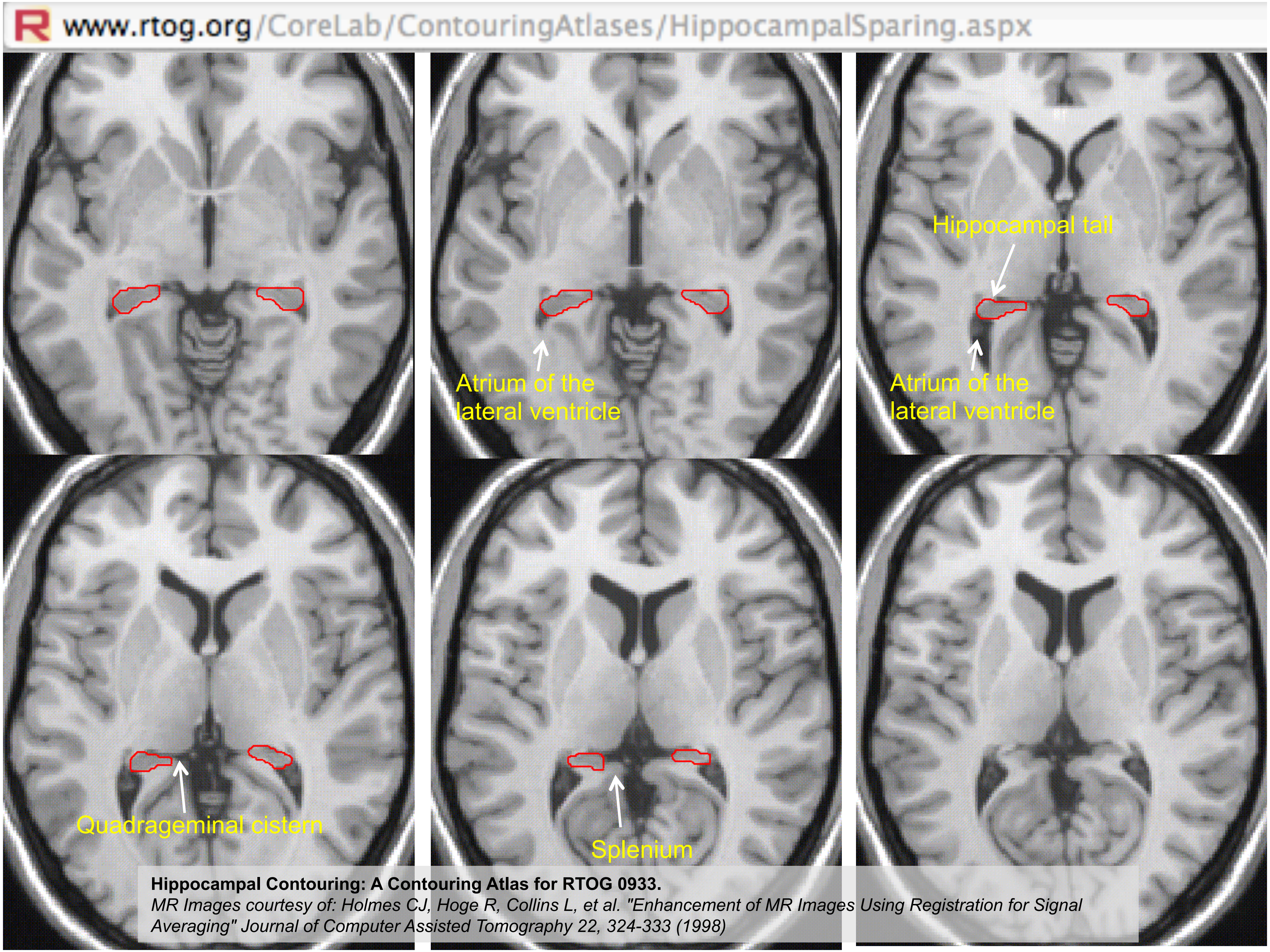
www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx



Hippocampal Contouring: A Contouring Atlas for RTOG 0933.
MR Images courtesy of: Holmes CJ, Hoge R, Collins L, et al. "Enhancement of MR Images Using Registration for Signal Averaging" Journal of Computer Assisted Tomography 22, 324-333 (1998)

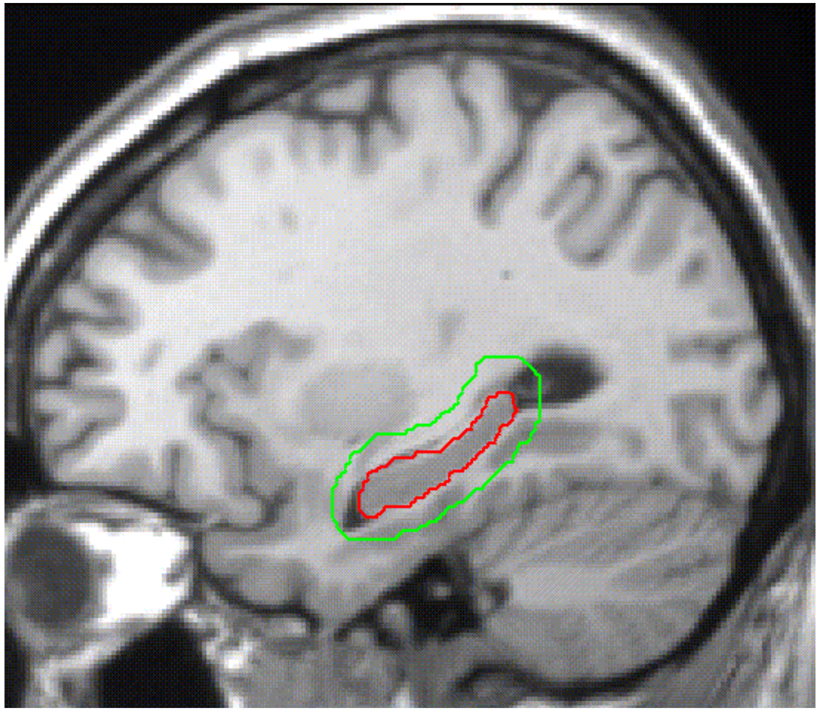


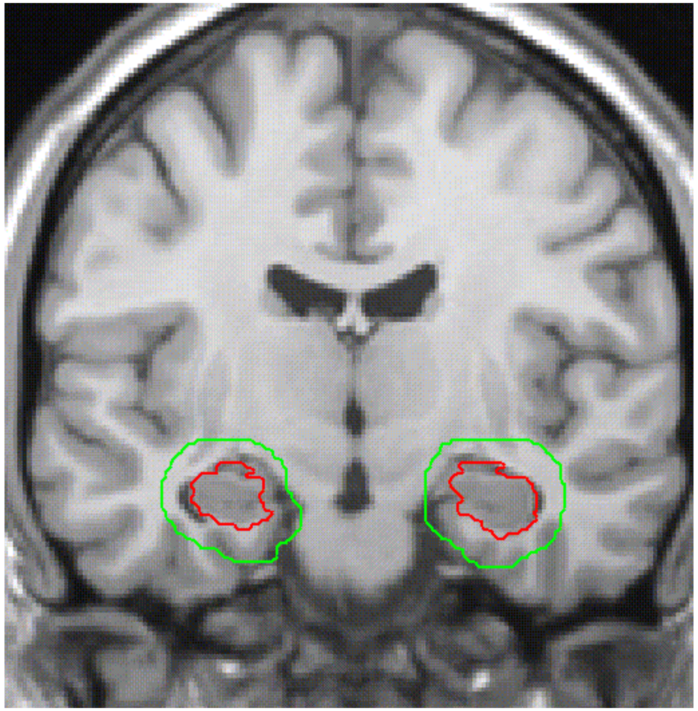
Hippocampal Contouring: A Contouring Atlas for RTOG 0933.
MR Images courtesy of: Holmes CJ, Hoge R, Collins L, et al. "Enhancement of MR Images Using Registration for Signal Averaging" Journal of Computer Assisted Tomography 22, 324-333 (1998)



Hippocampal Contouring: A Contouring Atlas for RTOG 0933.
MR Images courtesy of: Holmes CJ, Hoge R, Collins L, et al. "Enhancement of MR Images Using Registration for Signal Averaging" Journal of Computer Assisted Tomography 22, 324-333 (1998)

Red: Hippocampus
Green: Hippocampal Avoidance Zone





Generate the hippocampal avoidance zone using a 5mm volumetric expansion on the hippocampus.

Hippocampus	D_{max} <7.3-11	*Gondi, R&O 2010* *Gondi, IJROBP 2011*
	D_{max} <12-20	*Marsh, IJROBP 2010* *Marsh, J Med Imag Rad Onc 2011*
	D_{max} < 30	*Pinkham, J Cl Neurosc 2012*


take home message!

Definition of the clinical volumes in gliomas

Take-home messages

- GBM: Base your definition of CTV on postoperative MRI, t1-weighted images, without including edema. GTV+2 cm

- LGG: Base your definition of CTV on postoperative MRI, T2-weighted images. GTV +1/1,5 cm

- Remind to modify your CTV according to anatomical barriers

- Clinical benefit of PET or advanced MRI in radiotherapy planning is still to be confirmed

- Include among your OARs the hippocampus. Try to lower its dose below 15 Gy

Mise au point

Cancer/Radiothérapie 17 (2013) 434–443

Radiothérapie des tumeurs cérébrales : quelles marges ?

Radiotherapy for brain tumours: Which margins should we apply?

V. Martin[a,*], É. Moyal[b], M. Delannes[b], L. Padovani[c], M.-P. Sunyach[d], L. Feuvret[e], F. Dhermain[a], G. Noël[f], A. Laprie[b]

Glioblastomes (grade IV)	EORTC : T1 après injection de gadolinium + 2–3 cm corrigé au FLAIR RTOG CTV 1 = FLAIR + 2 cm CTV 2 = T1 après injection de gadolinium + 2 cm
Glioblastomes sujets âgés	EORTC : T1 après injection de gadolinium + 1,5–2 cm RTOG : idem sujets jeunes
Gliomes anaplasiques (grade III)	EORTC : T1 après injection de gadolinium et FLAIR + 1,5–2 cm RTOG CTV 1 = FLAIR + 2 cm CTV 2 = T1 après injection de gadolinium + 1,5 cm
Gliomes de grade II	FLAIR + 1–1,5 cm
Gliomes du tronc	FLAIR + 1,5–2 cm
Médulloblastomes	Volume cible anatomoclinique craniospinal Encéphale en totalité, 5 mm sous la lame criblée Axe médullaire, corps vertébraux et trous de conjugaison Cul-de-sac dural défini dur l'IRM *Boosts* selon l'âge et le stade Soit fosse postérieure Soit lit tumoral + 5mm ± résidu tumoral sans marge
PNET (*primitive neuroectodermal tumours*)	Irradiation craniopinale puis cavité opératoire + 0,5 cm Résidu tumoral sans marge
Épendymomes	Lit opératoire et résidu tumoral + 1–1,5 cm Irradiation craniospinale si métastatique
ATRT (*atypical teratoid rahbdoid tumours*)	Sous-tentorielles : lit opératoire/résidu + 1,5 cm Sus-tentorielles : idem + 1 cm Irradiation craniospinale si métastatique
Craniopharyngiomes	Lit tumoral ou tumeur en place (parties kystique et charnue) + 5 mm Replanification sur modifications du kyste en cours de traitement
Germinomes	Germinomes purs non secrétants PTV 1 = ventricules + 0,5 cm PTV 2 = tumeur primitive + 0,5 cm Irradiation craniospinale si métastatique Non germinomateuses CTV = GTV + 0,5 cm Irradiation craniospinale si métastatique
Lymphomes du système nerveux central	Encéphale en totalité jusqu'en C1-C2 ou C2-C3 ± *boost* = prise de contraste + 2 cm
Méningiomes de grade I	Volume tumoral macroscopique + 1 à 3 mm

Grazie per l’attenzione